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Perioperative Medizin in der onkologischen Viszeralchirurgie
–
Eingriffsspezifische funktionelle Störungen und Komplikationen

Kumulative Habilitationsschrift
zur Erlangung der Lehrbefähigung für das Fach Viszeralchirurgie
im Fachbereich Medizin der Justus-Liebig-Universität Gießen

vorgelegt von
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Die vorliegende Habilitationsschrift widmet sich der Untersuchung operationsspezifischer funktioneller Störungen und Komplikationen in der perioperativen Medizin viszeralonkologischer Eingriffe. Ihr liegen die folgenden neun Originalarbeiten zugrunde, welche sich mit diesen Themen beschäftigt haben:

1. *Oxygenierungsstörungen und pulmonale Komplikationen nach abdomino-thorakaler Ösophagusresektion im Vergleich zu anatomischer Lungenresektion.*

   M. Reichert, M. Schistek, F. Uhle, C. Koch, J. Bodner, M. Hecker, R. Hörbelt, V. Grau, W. Padberg, MA. Weigand, A. Hecker: **Ivor Lewis esophagectomy patients are particularly vulnerable to respiratory impairment - a comparison to major lung resection.** *Scientific Reports*. 2019 Aug 14;9(1):11856. doi: 10.1038/s41598-019-48234-w.

2. *Oxygenierungsstörungen und pulmonale Komplikationen nach konventionell-offener im Vergleich zu hybrid-minimalinvasiver, laparoskopisch-assistierter abdomino-thorakaler Ösophagusresektion.*

   M. Reichert, M. Lang, M. Hecker, E. Schneck, M. Sander, F. Uhle, M. Weigand, W. Padberg, V. Grau, A. Hecker: **Early respiratory impairment and pneumonia after hybrid laparoscopically-assisted esophagectomy – a comparison with the open approach.** *Journal of Clinical Medicine*. 2020 Jun 17;9(6):1896. doi: 10.3390/jcm9061896.

3. *Einfluss der perioperativen Statinmedikation auf Oxygenierungsstörungen und pulmonale Komplikationen nach abdomino-thorakaler Ösophagusresektion.*

   M. Reichert, M. Lang, J. Pons Kühnemann, M. Sander, W. Padberg, A. Hecker: **Perioperative statin medication impairs pulmonary outcome after abdomino-thoracic esophagectomy.** *Perioperative Medicine (London)*. 2022 Sep 14;11(1):47. doi: 10.1186/s13741-022-00280-1.

4. *Vergleich konventionell-offener und minimalinvasiver Operationsverfahren zur Dekortikation des organisierten Pleuraempyems.*

   M. Reichert, B. Pösentrup, A. Hecker, E. Schneck, J. Pons-Kühnemann, F. Augustin, W. Padberg, D. Öfner, J. Bodner: **Thoracotomy versus video-assisted thoracoscopic surgery (VATS) in stage III empyema – an analysis of 217 consecutive patients.** *Surgical Endoscopy*. 2018 Jun;32(6):2664-2675. doi: 10.1007/s00464-017-5961-7.

5. *Lernkurve der minimalinvasiven, thorakoskopischen Dekortikation beim organisierten Pleuraempyem.*

   M. Reichert, B. Pösentrup, A. Hecker, W. Padberg, J. Bodner: **Lung decortication in phase III pleural empyema by video-assisted thoracoscopic surgery (VATS) – results of a learning curve study.** *Journal of Thoracic Disease*. 2018 Jul;10(7):4311-4320. doi: 10.21037/jtd.2018.06.72.

6. *Transhiatale Hernien nach Resektionen am oberen Gastrointestinaltrakt.*

   P.U. Oppelt, I. Askevold, R. Hörbelt, F.C. Roller, W. Padberg, A. Hecker, **M. Reichert**: **Transhiatal herniation following esophagectomy or gastrectomy: retrospective single-center experiences with a potential surgical emergency.** *Hernia.* 2022 Feb;26(1):259-278. doi: 10.1007/s10029-021-02380-1.

7. *Gastrointestinale Motilitätsstörungen nach Rechtshemikolektomie.*

   M. Hirschburger, R. Schneider, S. Kraenzlein, W. Padberg, A. Hecker, **M. Reichert**: **Right colectomy from open to robotic – a single-center experience with functional outcomes in a learning-curve setting.** *Langenbeck´s Archives of Surgery*. 2022 Nov;407(7):2915-2927. doi: 10.1007/s00423-022-02576-8.

8. *Postoperativer (paralytischer) Ileus nach onkologischer Rektumresektion mit protektiver Ileostomie.*

   M. Reichert, C. Weber, J. Pons-Kühnemann, M. Hecker, W. Padberg, A. Hecker: **Protective loop ileostomy increases the risk for prolonged postoperative paralytic ileus after open oncologic rectal resection.** *International Journal of Colorectal Disease*. 2018 Nov;33(11):1551-1557. doi: 10.1007/s00384-018-3142-3.

9. *Pharmakologische Prävention und Therapie postoperativer gastrointestinaler Motilitätsstörungen und des (paralytischen) Ileus nach gastrointestinaler Tumorresektion.*

   M. Reichert, F. Willis, S. Post, M. Schneider, T. Vilz, M. Willis, A. Hecker: **Pharmacologic prevention and therapy of postoperative paralytic ileus after gastrointestinal cancer surgery – systematic review and meta-analysis.** *International Journal of Surgery*. 2024 Jul 1;110(7):4329-4341. doi: 10.1097/JS9.0000000000001393.

Die dieser Habilitationsschrift zugrunde liegenden Originalarbeiten sind im Anhang in der Reihenfolge aufgeführt, in der sie im weiteren Verlauf behandelt werden.

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1 Einleitung

1.1 Präambel

Das Komplikationspotenzial nach viszeralchirurgischen Eingriffen ist vielseitig. Operationsspezifische funktionelle Störungen und Komplikationen stellen in der perioperativen Medizin insbesondere nach komplexer onkologischer Chirurgie für Patienten* und deren behandelnde Ärzte* häufige Herausforderungen dar.

Eine erhöhte perioperative Morbidität ist nicht nur ein Risikofaktor für eine erhöhte postoperative Letalität, sondern führt zu einer verlängerten Erholungsphase, einer längeren Krankenhausverweildauer, prolongierter Pflegebedürftigkeit, anhaltenden Behinderungen im Alltag und zu erheblichen kurz- und langfristigen Einschränkungen der Lebensqualität betroffener Patienten (1–10). In der onkologischen Chirurgie resultiert ein prolongierter postoperativer Verlauf bei Patienten mit schwerwiegenden Komplikationen zusätzlich in Verzögerung, Reduzierung oder sogar Verhinderung weiterführender, adjuvanter onkologischer Therapien (11). Dabei sind multimodale Konzepte – bestehend aus medizinischer Onkologie, Strahlenonkologie und onkologischer Viszeralchirurgie – in der Behandlung gastrointestinaler Karzinome entscheidend, um die Therapieeffektivität zu steigern und die Langzeitprognose der Patienten zu verbessern (1,3,4,11–17) .

In der onkologischen Viszeralchirurgie spielen postoperative Oxygenierungsstörungen und pulmonale Komplikationen, allen voran die Pneumonie, nach Eingriffen am oberen Gastrointestinaltrakt, wie der abdomino-thorakalen Ösophagusresektion, eine bedeutende Rolle (4,18–21). Nach onkologischen Eingriffen am unteren Gastrointestinaltrakt sind prolongierte gastrointestinale Motilitätsstörungen und der postoperative paralytische Ileus (POI) relevante Herausforderungen in der perioperativen Medizin (22–25).

Diese Arbeit untersucht Risikofaktoren, Pathophysiologie, Prävention und Therapie funktioneller Störungen und eingriffsspezifischer Komplikationen in der perioperativen Medizin der onkologischen Viszeralchirurgie am oberen und unteren Gastrointestinaltrakt.

* *Zur besseren Lesbarkeit wird im Folgenden das generische Maskulinum verwendet. Sämtliche Personenbezeichnungen gelten jedoch gleichermaßen für alle Geschlechter.*

1.2 Funktionelle Störungen und Komplikationen nach abdomino-thorakaler Ösophagusresektion

Komplikationen nach onkologischen Operationen am oberen Gastrointestinaltrakt, insbesondere nach abdomino-thorakaler Ösophagusresektion, sind komplex. Sie können sowohl im frühen sowie im mittel- und langfristigen postoperativen Verlauf auftreten und für die betroffenen Patienten schwerwiegende Folgen haben (4,18,21,26–31). Diese Arbeit untersucht das Auftreten von postoperativen Oxygenierungsstörungen ebenso wie weitere pulmonale, pleurale und diaphragmatische Komplikationen nach abdomino-thorakaler Ösophagusresektion. Im Fokus stehen dabei die Pathophysiologie und präventive Maßnahmen von Oxygenierungsstörungen und Pneumonien (Kapitel 3.1) im frühen postoperativen Verlauf, adäquate Therapiemodalitäten des organisierten Pleuraempyems (Kapitel 3.2) als mögliche pleurale Sekundärkomplikation im späteren postoperativen Verlauf sowie die transhiatale Hernie (Kapitel 3.3) als Langzeitkomplikation nach Ösophagusresektion.

1.2.1 Oxygenierungsstörungen und Pneumonien

Mit einer Gesamtinzidenz postoperativer Komplikationen von bis zu 60% selbst in erfahrenen Zentren (18,31–33) zählen – neben der Anastomoseninsuffizienz – pulmonale Komplikationen zu den häufigsten und relevantesten Problemen im früh-postoperativen Verlauf nach abdomino-thorakaler Ösophagusresektion (4,18–21,31,34–37). Mit einer Inzidenz von bis zu 46% stellen pulmonale Komplikationen ein zentrales postoperatives Risiko dar (32,38–45). Das Spektrum pulmonaler Komplikationen umfasst dabei unterschiedliche Pathologien, darunter Oxygenierungsstörungen mit respiratorischer Insuffizienz, deren Maximalform das *Acute Respiratory Distress Syndrome* ist, sowie pulmonalarterielle Embolien, bronchiale Schleimretention, Atelektasen und postoperative Pneumonien (19,37,38,46,47).

Postoperative pulmonale Komplikationen sind mit einer erheblichen Morbidität für die betroffenen Patienten verbunden: sie führen zu prolongiertem Aufenthalt auf der Intensivstation, prolongierter Hospitalisierung und erhöhter Pflegebedürftigkeit sowie zu einer gesteigerten postoperativen Letalität (4,21,54,55,31,44,48–53). Ihre Auswirkungen beschränken sich dabei nicht nur auf das unmittelbare postoperative

Outcome nach Ösophagusresektion, sondern führen auch zu einer deutlichen Kostensteigerung im Gesundheitswesen (12,21,50,56–58). Zudem beeinträchtigen sie mittel- bis langfristige onkologische Ergebnisse, da sie zur Verzögerung adjuvanter Therapien führen und somit eine potenziell schlechtere Prognose für die betroffenen Patienten bedingen können (4–6,29,30,53).

Trotz der hohen klinischen, onkologischen und ökonomischen Bedeutung bleibt weiterhin unklar, in welchem Ausmaß die verschiedenen unter dem Begriff der „postoperativen pulmonalen Komplikationen“ zusammengefassten Pathologien miteinander assoziiert sind. Zur Entstehung postoperativer pulmonaler Komplikationen werden folgende Faktoren diskutiert (43,48,59–64):

- Dauer der Ein-Lungenventilation und daraus resultierende intra- und postoperative Atelektasen,
- postoperative Schmerzen durch die Thorakotomie mit daraus resultierender Beeinträchtigung der Atemphysiologie,
- chirurgisches Trauma und postoperative Inflammation durch Manipulationen an Lunge, Pleura und Thoraxwand,
- Aspirationsrisiko durch die veränderte Anatomie im oberen Gastrointestinaltrakt infolge der Ösophagusresektion und mögliche Schädigungen des Nervus laryngeus recurrens im Rahmen der mediastinalen Präparation und Lymphknotendissektion.

In Kapitel 3.1 dieser Arbeit werden die Inzidenzen von früh-postoperativen Oxygenierungsstörungen und Pneumonien nach abdomino-thorakaler Ösophagusresektion untersucht.

1.2.2 Das organisierte Pleuraempyem – eine pleurale Komplikation nach Eingriffen am Ösophagus

Neben den pulmonalen Komplikationen im frühen postoperativen Verlauf stellt das Pleuraempyem ein relevantes klinisches Problem im mittelfristigen Verlauf nach Ösophagusresektion dar (7,65–70). Die Entwicklung eines Pleuraempyems kann durch verschiedene Risikokonstellationen begünstigt werden. Neben allgemeinen Risikofaktoren thorakaler Operationen, wie Atelektasen mit persistierendem Entfaltungsdefizit der Lunge, spielen vor allem postoperative Pneumonien mit

parapneumonischen Ergüssen sowie thorakale Anastomoseninsuffizienzen mit pleuraler Sepsis eine zentrale Rolle in der Pathogenese dieser sekundären chirurgischen Komplikation nach Ösophagusresektion (7,21,73–75,65–72).

Gemäß der Klassifikation der *American Thoracic Society* (ATS) wird das Pleuraempyem in verschiedene Stadien eingeteilt. Während sich das exsudative und fibropurulente Stadium I und II in der Regel konservativ durch Antibiose und Pleuradrainage behandeln lassen, stellt das organisierte Empyem im späten Stadium III eine Domäne der Chirurgie dar (71,72,76). Charakteristisch sind die fibrinöse Organisation und Fibrosierung der Pleurablätter mit Ausbildung der typischen Pleuraschwarte, wodurch die Lunge in ihrer Ausdehnungsfähigkeit eingeschränkt und regelrecht „gefesselt“ wird. Ziele der operativen Therapie sind daher die vollständige Dekortikation der Lunge, die Wiederherstellung ihrer Ausdehnungsfähigkeit sowie die Eradikation des septischen Fokus durch sorgfältiges Debridement der infizierten Pleurahöhle (71).

In Kapitel 3.2 wird untersucht, inwieweit die minimalinvasive Operationstechnik der video-assistierten Thorakoskopie bei diesen technisch anspruchsvollen Eingriffen effektiv eingesetzt werden kann und ob sich daraus Vorteile für betroffene Patienten ergeben.

1.2.3 Transhiatale Hernien

Innovative chirurgische Verfahren wie die hybrid-minimalinvasive oder total-minimalinvasive abdomino-thorakale Ösophagusresektion bieten unmittelbare postoperative Vorteile (19,20,36,77). Durch reduzierte Operationstraumata wird das Ausmaß von Adhäsionen verringert, was im Langzeitverlauf jedoch die Entstehung transhiataler Hernien begünstigen kann (26,78,87,88,79–86). Aufgrund der potenziellen Inkarzerationsgefahr mit schwerwiegenden respiratorischen und kardialen Symptomen stellt die transhiatale Hernie eine relevante Komplikation im späteren Verlauf nach Ösophagusresektion dar (26,84,89). Ihre Inzidenz nimmt mit der zunehmenden Anwendung minimalinvasiver Operationstechniken am oberen Gastrointestinaltrakt zu (26,78,87,88,79–86). Gleichzeitig bestehen offene Fragen zu präventiven Maßnahmen während der Primäroperation, zu Indikation und Technik der operativen Hernienversorgung insbesondere bei asymptomatischen oder oligosymptomatischen Patienten.

Kapitel 3.3 thematisiert die Dringlichkeit des Hernienverschlusses sowie der Versorgung prolabierter Organe. Die Indikationsstellung richtet sich dabei maßgeblich nach dem klinischen Erscheinungsbild der Patienten und den schnittbildgebenden Befunden der transhiatalen Hernien nach Eingriffen am oberen Gastrointestinaltrakt. Zudem werden verschiedene operative Techniken zur adäquaten Versorgung und zum Verschluss der hiatalen Lücke diskutiert.

1.3 Postoperative gastrointestinale Motilitätsstörungen und der paralytische Ileus in der onkologischen Viszeralchirurgie

Gastrointestinale Motilitätsstörungen sind zunächst physiologische Reaktionen auf abdominelle Operationen, die allerdings in bis zu 30 % in eine prolongierte gastrointestinale Paralyse und den postoperativen (paralytischen) Ileus (POI) übergehen (22–25,90–94).

Die klinischen Auswirkungen des POI sind für die betroffenen Patienten vielseitig. Der POI verursacht eine erhebliche klinische Symptomatik mit abdomineller Distension, Schmerzen, Übelkeit und Erbrechen (22,95). Als schwerwiegende klinische Komplikationen stehen Aspiration und Sepsis im Vordergrund. Diese führen nicht nur zu einem erhöhten Bedarf an intensivmedizinischen Ressourcen und einer verlängerten Hospitalisierung, sondern steigern die Letalität der betroffenen Patienten auf bis zu 28 % (22,90,93,95,96). Zusätzlich verschlechtert der POI indirekt das onkologische *Outcome* betroffener Patienten, indem die Initiierung einer weiterführenden, adjuvanten onkologischen Therapie verzögert oder sogar verhindert wird (13–16).

Pathophysiologisch tragen verschiedene perioperative Faktoren zur Genese prolongierter gastrointestinaler Motilitätsstörungen und des POI bei (22,93,97–101):

- altersassoziierte Komorbiditäten,
- das Ausmaß des chirurgischen Traumas und der Manipulation am Gastrointestinaltrakt,
- die postoperative Inflammation,
- eine Dysregulation des enterischen Nervensystems, einschließlich perioperativer sympathetischer Hyperreaktion,

- die perioperative Medikation, insbesondere eine opioidbasierte Schmerztherapie.

Wirksame präventive Maßnahmen gegen prolongierte gastrointestinale Motilitätsstörungen sind essenziell, um das postoperative *Outcome*, den Komfort und die Zufriedenheit der Patienten zu verbessern, die Krankenhausaufenthaltsdauer zu verkürzen und die Genesung nach Operationen im Rahmen von *Enhanced Recovery After Surgery* -Konzepten zu beschleunigten (98).

In Kapitel 3.4 werden chirurgisch-technische Maßnahmen und in Kapitel 3.5 wird die Evidenz pharmakologischer Ansätze zur perioperativen Prävention gastrointestinaler Motilitätsstörungen sowie zur Therapie des klinisch manifesten POI untersucht.

2 Zielsetzung

Ziel dieser kumulativen Habilitationsschrift ist es, moderne Ansätze zur Optimierung der perioperativen Versorgung von Patienten in der onkologischen Viszeralchirurgie darzustellen und kritisch zu bewerten. Die Arbeit bündelt wissenschaftliche Publikationen, die sich mit zentralen, bislang ungelösten Herausforderungen im Zusammenhang mit viszeralonkologischen Eingriffen befassen.

Im Fokus stehen funktionelle Störungen und Komplikationen nach onkologischen Operationen am oberen und unteren Gastrointestinaltrakt. Aus pathophysiologischer Sicht werden das operative Trauma sowie eingriffsspezifische (systemische) Inflammation in den Fokus gestellt. Daraus leitet diese Arbeit präventive und therapeutische Maßnahmen ab.

Im Rahmen abdomino-thorakaler Ösophagusresektionen werden folgende Themen behandelt:

- Pathogenese und klinische Relevanz postoperativer Oxygenierungsstörungen und Pneumonien (Publikation: *Ivor Lewis esophagectomy patients are particularly vulnerable to respiratory impairment - a comparison to major lung resection*).

- Bedeutung minimalinvasiver Operationstechniken und der postoperativen Inflammation für die Entstehung von postoperativen Oxygenierungsstörungen und Pneumonien (Publikationen: *Early respiratory impairment and pneumonia after hybrid laparoscopically-assisted esophagectomy – a comparison with the open approach* **und** *Perioperative statin medication impairs pulmonary outcome after abdomino-thoracic esophagectomy*).
- Effektivität und Sicherheit der minimalinvasiven Dekortikation zur Therapie des organisierten Pleuraempyems (Publikationen: *Thoracotomy versus video-assisted thoracoscopic surgery (VATS) in stage III empyema – an analysis of 217 consecutive patients* **und** *Lung decortication in phase III pleural empyema by video-assisted thoracoscopic surgery (VATS) – results of a learning curve study*).
- Adäquate Diagnostik und operative Versorgung transhiataler Hernien nach Resektionen am oberen Gastrointestinaltrakt (Publikation: *Trans-hiatal herniation following esophagectomy or gastrectomy: retrospective single-center experiences with a potential surgical emergency*).

Im Rahmen onkologischer Eingriffe am unteren Gastrointestinaltrakt werden folgende Themen behandelt:

- Einfluss der chirurgischen Technik auf Inflammation und Genese gastrointestinaler Motilitätsstörungen (Publikationen: *Right colectomy from open to robotic – a single-center experience with functional outcomes in a learning-curve setting* **und** *Protective loop ileostomy increases the risk for prolonged postoperative paralytic ileus after open oncologic rectal resection*).
- Evidenz zur medikamentösen Prävention postoperativer gastroinestinaler Motilitätsstörungen und Therapie des POI (Publikation: *Pharmacologic prevention and therapy of postoperative paralytic ileus after gastrointestinal cancer surgery – systematic review and meta-analysis*).

3 Ergebnisse eigener Arbeiten

Die in dieser kumulativen Habilitationsschrift zusammengefassten Studien beschäftigen sich mit häufigen, eingriffsspezifischen funktionellen Störungen und Komplikationen in der onkologischen Viszeralchirurgie des oberen und unteren Gastrointestinaltraktes.

3.1 Oxygenierungsstörungen und Pneumonien nach Ösophagusresektion

Zunächst werden Inzidenz, Pathophysiologie und präventive Ansätze früh-postoperativer Oxygenierungsstörungen sowie das Auftreten postoperativer Pneumonien nach Ösophagusresektion untersucht. Zur besseren Einordnung des pulmonalen *Outcome* erfolgte ein Vergleich mit Patientenkollektiven nach anatomischer Lungenresektion.

3.1.1 Vergleich der abdomino-thorakalen Ösophagusresektion mit der anatomischen Lungenresektion

M. Reichert, M. Schistek, F. Uhle, C. Koch, J. Bodner, M. Hecker, R. Hörbelt, V. Grau, W. Padberg, MA. Weigand, A. Hecker: **Ivor Lewis esophagectomy patients are particularly vulnerable to respiratory impairment - a comparison to major lung resection.** *Scientific Reports*. 2019 Aug 14;9(1):11856. doi: 10.1038/s41598-019-48234-w.

Postoperative Oxygenierungsstörungen und Pneumonien sind häufige funktionelle Probleme und Komplikationen im postoperativen Verlauf nach Eingriffen am thorakalen Ösophagus (4,18,38–47,19–21,32,34–37). Die zugrunde liegende Pathophysiologie ist jedoch nicht vollständig geklärt. Wie einleitend beschrieben, werden verschiedene allgemeine Aspekte wie perioperative Atelektasen, postoperative Schmerzen durch die Thorakotomie mit den daraus resultierenden Beeinträchtigungen in der Atemphysiologie sowie chirurgisches Trauma an Lunge, Pleura und Thorax pathophysiologisch diskutiert. Diese sind allerdings ebenso im Rahmen anderer thorakaler Eingriffe mit Zugang über eine Thorakotomie präsent (19,43,59–63).

Zur genaueren Untersuchung der Inzidenzen postoperativer Oxygenierungsstörungen und postoperativer Pneumonien wurden die klinischen Verläufe von 83 Patienten, die einer abdomino-thorakalen Ösophagusresektion per Laparotomie oder Laparoskopie

und Rechtsthorakotomie unterzogen wurden, mit 98 Patienten verglichen, bei denen eine rechtsseitige *major*-Lungenresektion im Sinne einer Lobektomie oder Bilobektomie per Rechtsthorakotomie erfolgte (102).

Als klinischer Parameter zur globalen Beurteilung perioperativer Oxygenierungsstörungen wurde das Verhältnis des arteriellen Sauerstoffpartialdrucks zur inspiratorischen Sauerstofffraktion (PaO_2/FiO_2, *Horovitz-Index*) verwendet. In Analogie zur *Berlin classification* des *Acute Respiratory Distress Syndrome* (103) galt die PaO_2/FiO_2-Ratio von < 300 mm Hg als Kriterium für eine Oxygenierungsstörung.

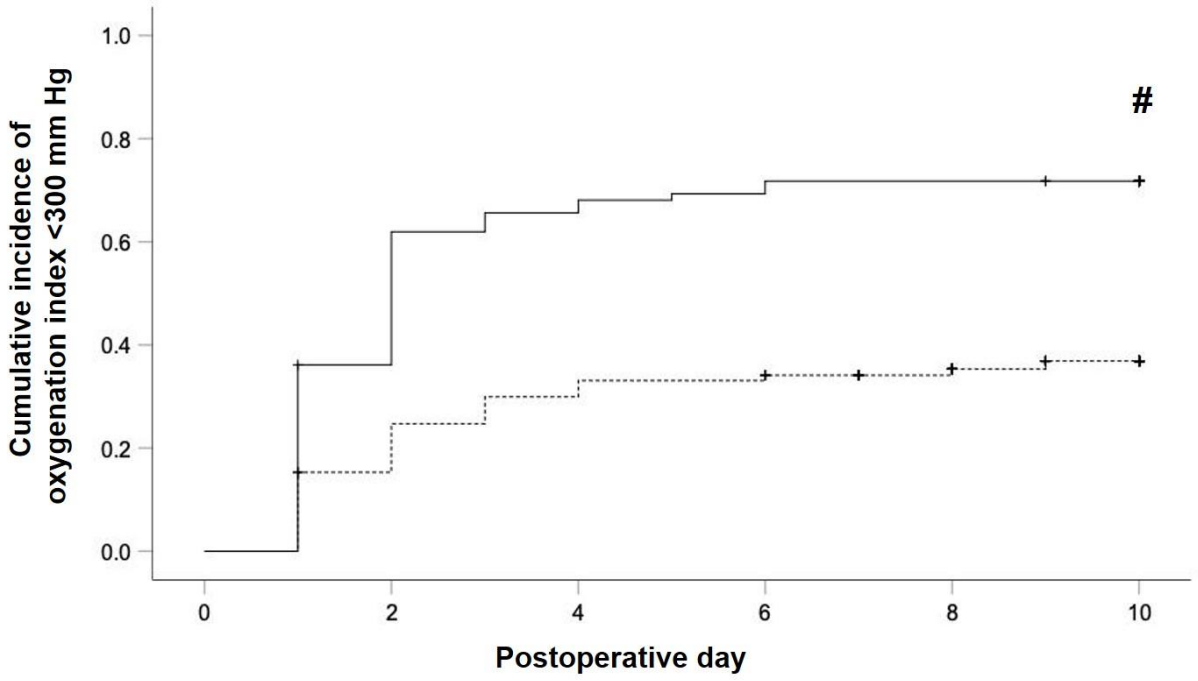


Abbildung 1: Kaplan-Meier-Kurven der kumulativen Inzidenz einer postoperativen PaO_2/FiO_2-Ratio von < 300 mm Hg: Ösophagusresektion versus Lungenresektion. Schwarze Linie: Patienten nach abdomino-thorakaler Ösophagusresektion, n = 83. **Gestrichelte Linie**: Patienten nach *major*-Lungenresektionen, n = 98. Patienten, die entlassen wurden, verstorben sind oder eine erneute (Revisions-)Operation benötigten, wurden ab dem Tag des Ereignisses aus der Analyse ausgeschlossen. Zensierte Daten sind in der Abbildung durch vertikale Striche markiert. Ein Oxygenierungsindex von < 300 mm Hg am Operationstag (postoperativer Tag 0; Ankunft auf der Intensivstation) wurde nicht als postoperatives Ereignis gewertet. **#** zeigt Unterschiede in der kumulativen Inzidenz einer postoperativen PaO_2/FiO_2-Ratio von < 300 mm Hg zwischen beiden Gruppen am postoperativen Tag 10 an ($p < 0{,}001$). Abbildung aus der Originalpublikation entnommen: M. Reichert, M. Schistek, F. Uhle, C. Koch, J. Bodner, M. Hecker, R. Hörbelt, V. Grau, W. Padberg, MA. Weigand, A. Hecker: Ivor Lewis esophagectomy patients are particularly vulnerable to respiratory impairment - a comparison to major lung resection. Scientific Reports. 2019 Aug 14;9(1):11856. doi: 10.1038/s41598-019-48234-w (102).

Obwohl Patienten mit Lungenresektionen häufiger an chronischen Lungenerkrankungen litten (35,7% versus 19,3%; p = 0,020) und bei den

anatomischen Resektionen beträchtliche Lungenvolumina entfernt wurden, war die Rate früh-postoperativer Oxygenierungsstörungen in der Patientengruppe der abdomino-thorakalen Ösophagusresektion vom 1. bis 10. postoperativen Tag – ebenso wie deren kumulative Inzidenz (Abbildung 1) – signifikant höher. Entsprechend der erhöhten Inzidenz der oxygenatorischen Störungen zeigten diese Patienten höhere Raten an Reintubationen und Tracheotomien, hatten längere (kumulative) postoperative Beatmungszeiten und eine prolongierte intensivstationäre Aufenthaltsdauer.

Postoperative Pneumonien wurden bis zum postoperativen Tag 30 mithilfe des international validierten *Uniform Pneumonia Score* erfasst (104). Die Diagnose wurde im Median am 6. postoperativen Tag nach abdomino-thorakaler Ösophagusresektion und am 3. postoperativen Tag nach pulmonaler Resektion gestellt. Die Pneumonierate war in der Patientenkohorte nach Ösophagusresektion signifikant höher als nach *major*-Lungenresektion (39,8% versus 20,4%; p = 0,0053). In den Kaplan-Meier-Kurven wurden die Unterschiede ab dem 10. postoperativen Tag deutlich (Abbildung 2).

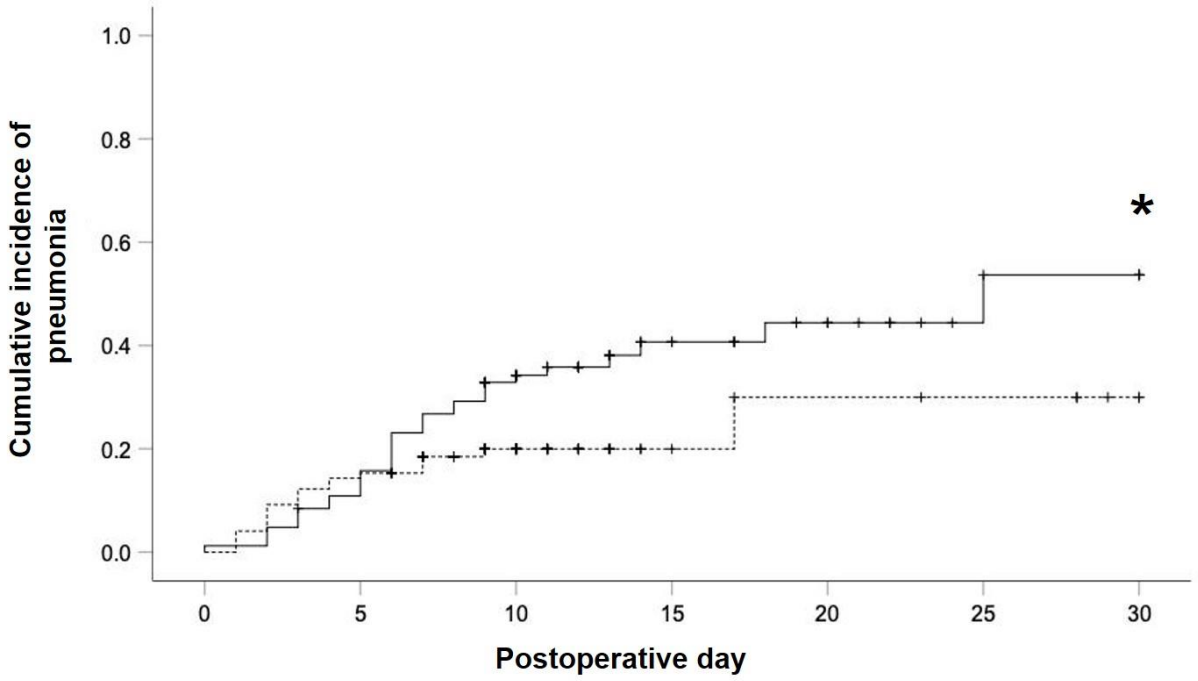


Abbildung 2: Kaplan-Meier-Kurven der kumulativen Inzidenz einer postoperativen Pneumonie: Ösophagusresektion versus Lungenresektion. Schwarze Linie: Patienten nach abdomino-thorakaler Ösophagusresektion, n = 83. **Gestrichelte Linie**: Patienten nach *major*-Lungenresektionen, n = 98. Patienten, die entlassen wurden oder zwischenzeitlich verstorben sind, wurden ab dem Tag des Ereignisses aus der Analyse ausgeschlossen. Zensierte Daten sind in der Abbildung durch vertikale Striche markiert. ***** zeigt Unterschiede in der kumulativen Inzidenz der postoperativen Pneumonie zwischen beiden Gruppen am postoperativen Tag 30 an (p = 0,042). Abbildung aus der Originalpublikation entnommen: M. Reichert, M. Schistek, F. Uhle, C. Koch, J. Bodner, M. Hecker, R. Hörbelt, V. Grau, W. Padberg, MA. Weigand, A. Hecker: Ivor Lewis esophagectomy patients are particularly vulnerable to respiratory impairment - a comparison to major lung resection. Scientific Reports. 2019 Aug 14;9(1):11856. doi: 10.1038/s41598-019-48234-w (102).

Fazit: Trotz ähnlichem thorakalem Trauma, bestehend aus rechts-anterolateraler Thorakotomie, Ein-Lungenventilation sowie Manipulationen an Lunge und Pleura, traten Oxygenierungsstörungen deutlich häufiger auf und das Pneumonierisiko war nach abdomino-thorakaler Ösophagusresektion signifikant höher als nach *major*-Lungenresektion.

Oxygenierungsstörungen und postoperative Pneumonien stellen damit spezifische und klinisch relevante Probleme in der perioperativen Medizin nach abdomino-thorakalen Ösophaguseingriffen dar. Die Kaplan-Meier-Kurven verdeutlichen dabei, dass funktionelle Oxygenierungsstörungen zunächst unabhängig von der Komplikation „postoperative Pneumonie“ betrachtet werden müssen: Während sich erstere typischerweise innerhalb der ersten beiden postoperativen Tage manifestierten, erfolgte die Diagnose der Pneumonie im Median erst am 6.

postoperativen Tag nach Ösophagusresektion. Die detaillierte Analyse der perioperativen Oxygenierungsparameter (Anlage 1, Tabelle 5) legt nahe, dass die Unterschiede erst im späteren postoperativen Verlauf auf die höhere Pneumonierate in der Ösophagusgruppe zurückgeführt werden können.

Ein relevanter operationstechnischer Unterschied zwischen beiden Eingriffsarten liegt im zusätzlichen abdominellen Operationsfeld der abdomino-thorakalen Ösophagusresektion. Dessen potenzieller Einfluss auf postoperative Oxygenierungsstörungen und Pneumonien wurde im Folgenden weiter untersucht (28).

3.1.2 Einfluss des abdominellen Operationszugangs

M. Reichert, M. Lang, M. Hecker, E. Schneck, M. Sander, F. Uhle, M. Weigand, W. Padberg, V. Grau, A. Hecker: **Early respiratory impairment and pneumonia after hybrid laparoscopically-assisted esophagectomy – a comparison with the open approach.** *Journal of Clinical Medicine*. 2020 Jun 17;9(6):1896. doi: 10.3390/jcm9061896.

Weder die Thorakotomie noch die Ein-Lungenventilation oder das chirurgische Trauma an Thoraxwand, Lunge und Pleura konnten als führende Ursache die hohe Rate früh-postoperativer Oxygenierungsstörungen und Pneumonien nach abdomino-thorakaler Ösophagusresektion identifiziert werden (102). In dieser Studie wurde nun der Einfluss des abdominellen Operationsfeldes untersucht – mit besonderem Fokus auf die Rolle der minimalinvasiven Operationstechnik hinsichtlich der Raten o.g. postoperativer pulmonaler Komplikationen (28).

Insgesamt wurden die Daten von 143 Patienten analysiert, die aufgrund eines Kardia- oder Ösophaguskarzinoms eine abdomino-thorakale oder abdomino-thorako-zervikale Ösophagusresektion erhielten. Dabei wurden 105 Patienten mit konventionell-offenem Vorgehen (Laparotomie und rechtsseitige Thorakotomie) mit 38 Patienten verglichen, bei denen eine hybrid-minimalinvasive, laparoskopisch-assistierte abdomino-thorakale Ösophagusresektion per Laparoskopie und rechtsseitiger Thorakotomie durchgeführt worden war.

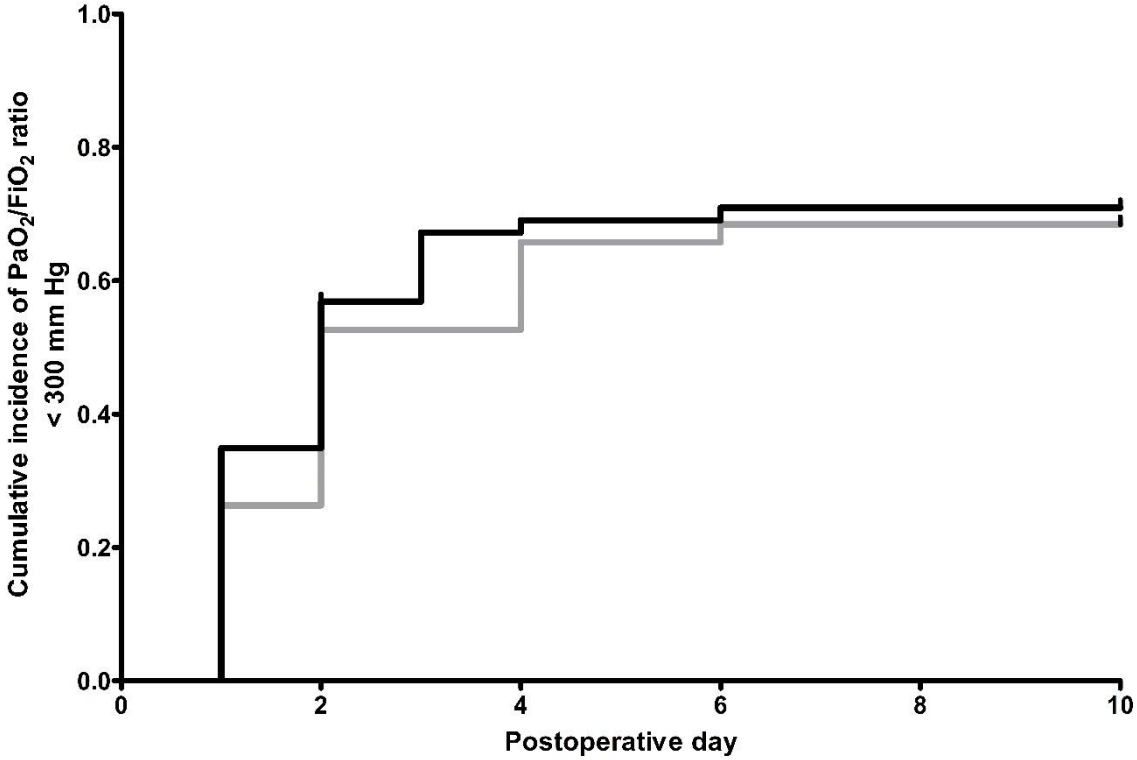


Abbildung 3: Kaplan-Meier-Kurven der kumulativen Inzidenz einer postoperativen PaO_2/FiO_2-Ratio von < 300 mm Hg: konventionell-offene versus hybrid-minimalinvasive Ösophagusresektion. **Schwarze Linie**: Patienten nach konventionell-offener abdomino-thorakaler Ösophagektomie, n = 105. **Graue Linie**: Patienten nach hybrid-minimalinvasiver, laparoskopisch-assistierter abdomino-thorakaler Ösophagektomie, n = 38. Patienten, die entlassen wurden, verstorben sind oder eine erneute (Revisions-) Operation benötigten, wurden ab dem Tag des Ereignisses aus der Analyse ausgeschlossen. Zensierte Daten sind in der Abbildung durch vertikale Striche markiert. Ein Oxygenierungsindex von < 300 mm Hg am Operationstag (postoperativer Tag 0; Ankunft auf der Intensivstation) wurde nicht als postoperatives Ereignis gewertet. Abbildung aus der Originalpublikation entnommen: M. Reichert, M. Lang, M. Hecker, E. Schneck, M. Sander, F. Uhle, M. Weigand, W. Padberg, V. Grau, A. Hecker: Early respiratory impairment and pneumonia after hybrid laparoscopically-assisted esophagectomy – a comparison with the open approach. Journal of Clinical Medicine. 2020 Jun 17;9(6):1896. doi: 10.3390/jcm9061896 (28).

Beide Gruppen zeigten ähnlich hohe kumulative Inzidenzen früh-postoperativer Oxygenierungsstörungen, bemessen anhand der PaO_2/FiO_2-Ratio von < 300 mm Hg (Abbildung 3), was dem charakteristischen Muster nach Ösophagusresektion entspricht, welches in Kapitel 3.1.1 bereits beschrieben wurde (102). Die Gesamtpneumonierate war jedoch in der Gruppe mit konventionell-offener Ösophagusresektion höher als in der Gruppe mit hybrid-minimalinvasiver Operationstechnik (45,7% versus 26,3%; p = 0,05). Abbildung 4 illustriert die kumulativen Inzidenzen postoperativer Pneumonien, deren Diagnose im Median am 5. postoperativen Tag nach konventionell-offener und am 8. postoperativen Tag nach

hybrid-minimalinvasiver, abdomino-thorakaler Ösophagusresektion gestellt wurde.

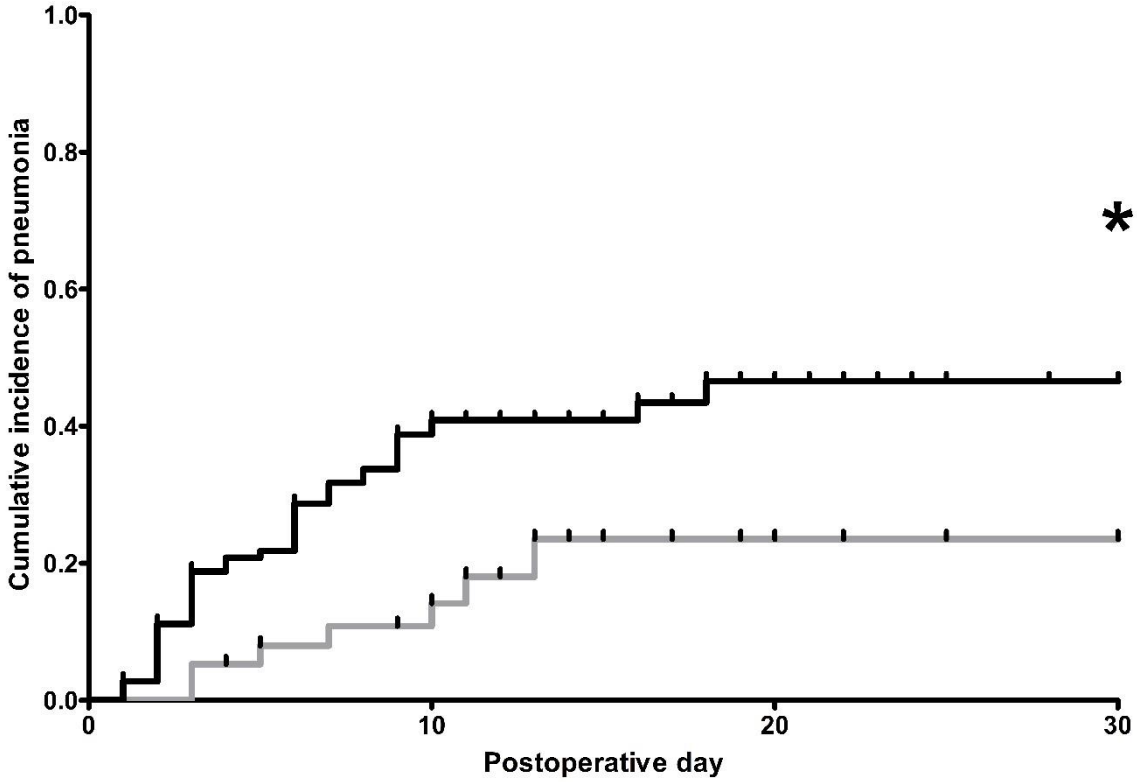


Abbildung 4: Kaplan-Meier-Kurven der kumulativen Inzidenz einer postoperativen Pneumonie: konventionell-offene versus hybrid-minimalinvasive Ösophagusresektion. Schwarze Linie: Patienten nach konventionell-offener abdomino-thorakaler Ösophagektomie, n = 105. **Graue Linie**: Patienten nach hybrid-minimalinvasiver, laparoskopisch-assistierter abdomino-thorakaler Ösophagektomie, n = 38. Patienten, die entlassen wurden, verstorben sind oder eine erneute (Revisions-) Operation benötigten, wurden ab dem Tag des Ereignisses aus der Analyse ausgeschlossen. Zensierte Daten sind in der Abbildung durch vertikale Striche markiert. ***** zeigt Unterschiede in der kumulativen Inzidenz der postoperativen Pneumonie zwischen beiden Gruppen am postoperativen Tag 30 an (p = 0,01). Abbildung aus der Originalpublikation entnommen: M. Reichert, M. Lang, M. Hecker, E. Schneck, M. Sander, F. Uhle, M. Weigand, W. Padberg, V. Grau, A. Hecker: Early respiratory impairment and pneumonia after hybrid laparoscopically-assisted esophagectomy – a comparison with the open approach. Journal of Clinical Medicine. 2020 Jun 17;9(6):1896. doi: 10.3390/jcm9061896 (28).

Hinsichtlich weiterer schwerwiegender Komplikationen, wie Anastomoseninsuffizienzen, Reoperationen oder Letalität, ergaben sich keine signifikanten Unterschiede zwischen beiden Gruppen. Die im späteren postoperativen Verlauf beobachteten Unterschiede in der PaO_2/FiO_2-Ratio (< 300 mmHg, Anlage 2, Tabelle 5) sowie die höheren Raten invasiver Beatmung ab dem 7. postoperativen Tag in der konventionell-offenen Patientengruppe ließen sich im Zusammenhang mit der erhöhten Pneumonierate interpretieren.

Fazit: Die vorliegenden Daten legen nahe, dass Oxygenierungsstörungen ein spezifisches, früh-postoperatives Problem nach Eingriffen am Ösophagus, unabhängig von der gewählten Operationstechnik, darstellen. Im Gegensatz dazu treten postoperative Pneumonien deutlich später auf und scheinen stärker durch chirurgisch-technische Faktoren beeinflusst zu werden. Beide postoperative pulmonale Komplikationen sollten daher zunächst unabhängig voneinander betrachtet werden.

Wie in Kapitel 3.1.1 beschrieben, ähnelte die Pneumonierate in der Laparoskopiegruppe dieser Studie jener von Patienten nach Lungenresektion (102). Daraus ergibt sich, dass die hohe Inzidenz postoperativer Pneumonien nicht ausschließlich durch den Eingriff am thorakalen Ösophagus erklärbar ist. Vielmehr haben zusätzliche operationstechnische Faktoren, wie die minimalinvasive Durchführung des abdominellen Teils, einen Einfluss auf das Auftreten postoperativer Pneumonien, selbst bei vergleichbaren chirurgischen Prinzipien (z.B. Lymphknotendissektion, Magenkonduitbildung).

Inwieweit postoperative Schmerzen nach Laparotomie im Vergleich zur Laparoskopie die Atemphysiologie, insbesondere den Hustenstoß, beeinträchtigen und somit die Entstehung von Pneumonien unterstützen, bleibt in der Retrospektive unbeantwortet und stellt eine Limitation dieser Untersuchung dar.

Das durch eine Laparotomie verursachte chirurgische Trauma führt im Vergleich zur hybrid-minimalinvasiven, laparoskopisch-assistierten Ösophagektomie zu einer ausgeprägteren systemischen Inflammation in der frühen postoperativen Phase, gemessen anhand eines erhöhten C-reaktiven Protein im Serum (Anlage 2, Tabelle 3). In der Literatur wird der Zusammenhang zwischen verstärkter bzw. verlängert erhöhter systemischer Inflammation und der Entstehung postoperativer Komplikationen – insbesondere von Pneumonien nach Ösophagusresektionen – diskutiert (62,63,105). In diesem Zusammenhang kommt minimalinvasiven Operationsverfahren eine wichtige präventive Rolle zu. Ob zusätzlich auch medikamentöse Ansätze, die in inflammatorische Prozesse eingreifen, zur Prävention pulmonaler Komplikationen nach abdomino-thorakaler Ösophagusresektion beitragen, wurde in der folgenden Arbeit weiter untersucht (106).

3.1.3 Einfluss der Statinmedikation

M. Reichert, M. Lang, J. Pons Kühnemann, M. Sander, W. Padberg, A. Hecker: **Perioperative statin medication impairs pulmonary outcome after abdomino-thoracic esophagectomy.** *Perioperative Medicine (London)*. 2022 Sep 14;11(1):47. doi: 10.1186/s13741-022-00280-1.

Weder der thorakale Zugangsweg noch das chirurgische Trauma an Lunge und Pleura oder die Ein-Lungenventilation konnten die hohe Inzidenz früh-postoperativer Oxygenierungsstörungen und Pneumonien nach abdomino-thorakalen Ösophagusresektionen vollständig erklären (102).

Beobachtungen aus Vorarbeiten zeigten, dass laparoskopisch-assistierte Operationsverfahren mit geringeren pulmonalen Komplikationsraten assoziiert waren (19,28,36,107,108). Dies kann zum Teil auf geringere postoperative Schmerzen nach Laparoskopie zurückgeführt werden (19,36,107,108). Darüber hinaus gehen minimalinvasive Verfahren mit einem reduzierten chirurgischen Trauma und einer geringeren intraabdominellen Manipulation einher, was in einer abgeschwächten postoperativen (systemischen) Inflammation resultiert (28). Indirekte Effekte der durch chirurgisches Trauma induzierten systemischen Inflammation auf die pulmonale Homöostase könnten wesentlich zur Entstehung von früh-postoperativen Oxygenierungsstörungen und postoperativen Pneumonien beitragen (28,62,63,105,109–112).

Bei Statinen handelt es sich um kompetitive Inhibitoren der 3-Hydroxy-3-Methylglutaryl-CoA-Reduktase. Sie zählen insbesondere bei den älteren Patientenkollektiven mit kardiovaskulären Komorbiditäten in der onkologischen Viszeralchirurgie, zu den häufig verabreichten Medikamenten. Ihre Gabe wird perioperativ zur Prophylaxe kardiovaskulärer Komplikationen in der Regel fortgesetzt (113–115). Darüber hinaus besitzen Statine immunmodulierende Eigenschaften und beeinflussen inflammatorische Prozesse, was über ihre bekannten lipidsenkenden und kardiovaskulären Effekte hinaus auch Auswirkungen auf die postoperative systemische Inflammation und das Infektionsgeschehen haben kann (116–122).

Vor diesem Hintergrund wurde der Einfluss einer perioperativen Statinmedikation auf die systemische Inflammation, postoperative Oxygenierungsstörungen und das Auftreten postoperativer Pneumonien nach abdomino-thorakaler Ösophagusresektion untersucht (106).

Initial wurden insgesamt 117 Patienten mit einem Kardia- oder Ösophaguskarzinom in die Analyse eingeschlossen. Aufgrund einer Dysbalance in den basalen Patientencharakteristika – Patienten unter Statinmedikation waren älter und wiesen im Vergleich zu statinnaiven Patienten ein höheres kardiovaskuläres Vorerkrankungsprofil auf – erfolgte ein *Propensity score matching*. Bei der Interpretation der Ergebnisse ist zu beachten, dass aufgrund dieser Methode vor allem ältere und komorbide Patienten miteinander gepaart wurden.

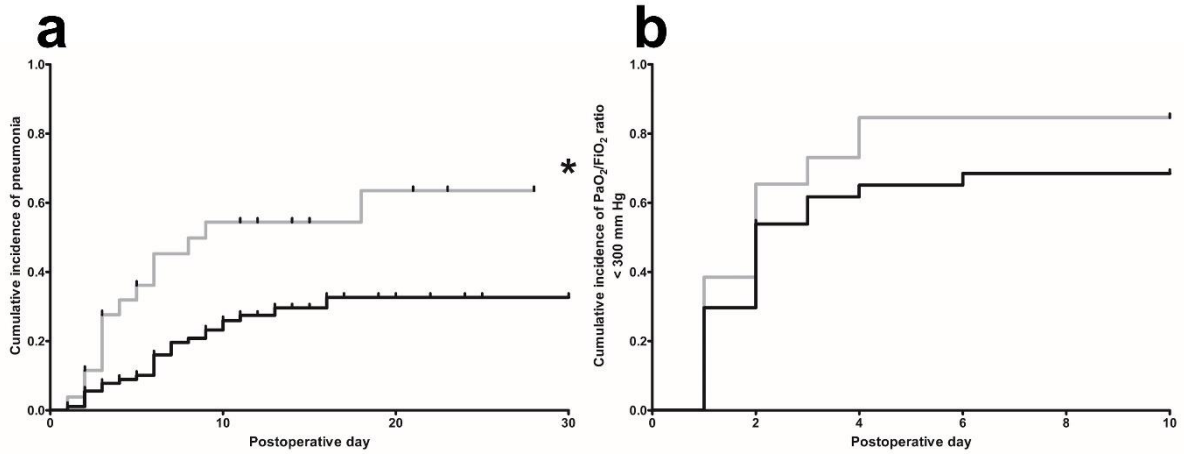
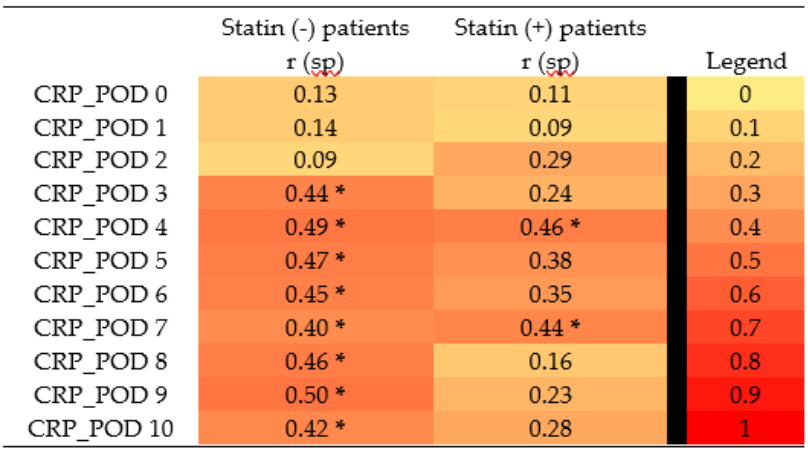


Abbildung 5: Kaplan-Meier-Kurven der kumulativen Inzidenz einer postoperativen Pneumonie und einer postoperativen PaO_2/FiO_2-Ratio von < 300 mm Hg: statinnaive Patienten versus Patienten unter Statinmedikation. Abgebildet sind die Kaplan-Meier-Kurven der Patienten nach *Propensity score matching*. **a.** Kumulative Inzidenzen der postoperativen Pneumonie. **b.** Kumulative Inzidenzen der PaO_2/FiO_2-Ratio von < 300 mm Hg. **Schwarze Linie**: Statinnaive Patienten, n=52. **Graue Linie**: Patienten unter perioperativer Statinmedikation, n=26. Patienten, die entlassen wurden, verstorben sind oder eine erneute (Revisions-) Operation benötigten, wurden ab dem Tag des Ereignisses aus der Analyse ausgeschlossen. Zensierte Daten sind in der Abbildung durch vertikale Striche markiert. * zeigt Unterschiede in der kumulativen Inzidenz der postoperativen Pneumonie zwischen beiden Gruppen am postoperativen Tag 30 an (p = 0,0468). Abbildung aus der Originalpublikation entnommen: M. Reichert, M. Lang, J. Pons Kühnemann, M. Sander, W. Padberg, A. Hecker: Perioperative statin medication impairs pulmonary outcome after abdomino-thoracic esophagectomy. Perioperative Medicine (London). 2022 Sep 14;11(1):47. doi: 10.1186/s13741-022-00280-1 (106).

Die Pneumonierate war in der Statin-Gruppe signifikant erhöht (65,4% versus 38,5%; p = 0,0317). Die kumulativen Inzidenzen bis zum 30. postoperativen Tag sind in Abbildung 5a dargestellt. In Übereinstimmung mit den Vorarbeiten (28,102) wurde die Pneumonie typischerweise zwischen dem 4. bis 6. postoperativen Tag diagnostiziert. Entsprechend waren sowohl die Dauer des Intensivaufenthalts als auch die gesamte stationäre Verweildauer in der Statin-Gruppe prolongiert.

Bezüglich postoperativer Oxygenierungsstörungen (PaO_2/FiO_2-Ratio < 300 mm Hg) zeigten sich in beiden Gruppen die erwarteten Inzidenzen nach Ösophagusresektion (28,102), ohne Unterschiede bis zum 10. postoperativen Tag (Abbildung 5b).

Trotz erhöhter Pneumonieraten ergab der Zweigruppenvergleich keine offensichtlichen Unterschiede im Serum-C-reaktiven Protein, dem laborchemischen Routinemarker der systemischen Inflammation. Allerdings zeigte sich in der statinnaiven Gruppe eine signifikante Korrelation zwischen der Höhe des C-reaktiven Proteins ab dem 3. postoperativen Tag und dem Auftreten postoperativer Pneumonien. Dieser Zusammenhang war in der Statin-Gruppe deutlich abgeschwächt (Abbildung 6).



	Statin (-) patients r (sp)	Statin (+) patients r (sp)	Legend
CRP_POD 0	0.13	0.11	0
CRP_POD 1	0.14	0.09	0.1
CRP_POD 2	0.09	0.29	0.2
CRP_POD 3	0.44 *	0.24	0.3
CRP_POD 4	0.49 *	0.46 *	0.4
CRP_POD 5	0.47 *	0.38	0.5
CRP_POD 6	0.45 *	0.35	0.6
CRP_POD 7	0.40 *	0.44 *	0.7
CRP_POD 8	0.46 *	0.16	0.8
CRP_POD 9	0.50 *	0.23	0.9
CRP_POD 10	0.42 *	0.28	1

Abbildung 6: Korrelationsanalyse der postoperativen Pneumonie mit der Höhe des postoperativen systemischen C-reaktiven Proteins bis zum 10. postoperativen Tag. Die Werte des C-reaktiven Proteins (CRP) nach abdomino-thorakaler Ösophagusresektion der durch das *Propensity score matching* gepaarten Patienten ohne [Statin(-), n = 52] und mit [Statin(+), n = 26] perioperativer Statinmedikation wurden mit dem Auftreten einer postoperativen Pneumonie mittels Spearman´s (Sp) Rangkorrelationsanalyse korreliert. Die *Heatmap* kodiert für keine Korrelation ($r_{Sp} = 0$) in gelb und starke Korrelation ($r_{Sp}=1$) in rot. * zeigt signifikante Werte an ($p < 0,05$). POD = postoperativer Tag. POD 0 entspricht dem ersten postoperativen Wert, bei Aufnahme auf Intensivstation. Abbildung aus der Originalpublikation entnommen: M. Reichert, M. Lang, J. Pons Kühnemann, M. Sander, W. Padberg, A. Hecker: Perioperative statin medication impairs pulmonary outcome after abdomino-thoracic esophagectomy. Perioperative Medicine (London). 2022 Sep 14;11(1):47. doi: 10.1186/s13741-022-00280-1 (106).

Fazit: Dieser fehlende Effekt der Pneumonie auf das systemische C-reaktive Protein in der Statin-Gruppe könnte auf die antiinflammatorische Wirkung der Statine zurückzuführen sein (117,118). Diese Immunsuppression auf Ebene des angeborenen Immunsystems könnte jedoch gleichzeitig zu einer inadäquaten Reaktion auf postoperative Inflammation und Infektionen führen – mit möglicher Beeinträchtigung pulmonaler Abwehrmechanismen. Gerade in dem hochvulnerablen Patientenkollektiv

nach abdomino-thorakaler Ösophagusresektion könnte dies zur Entstehung postoperativer Pneumonien beitragen (117,118,120–122).

3.2 Chirurgische Aspekte in der Therapie des organisierten Pleuraempyems

Inwieweit die Dekortikation und das pleurale Debridement beim organisierten Pleuraempyem im Stadium III minimalinvasiv thorakoskopisch sicher durchführbar ist und Vorteile für die betroffenen, teilweise kritisch kranken, septischen Patienten bringt, wurde in den beiden folgenden Studien untersucht (73,74). Die Anzahl der Prozeduren, die als Operateur durchgeführt werden müssen, um ausreichende operative Erfahrungen und Fertigkeiten für diese komplexen chirurgischen Eingriffe zu erlangen, wurde anhand einer operationszeiten- und *outcome*-basierten Lernkurvenanalyse evaluiert (73).

3.2.1 Konventionell-offene versus minimalinvasive Dekortikation

M. Reichert, B. Pösentrup, A. Hecker, E. Schneck, J. Pons-Kühnemann, F. Augustin, W. Padberg, D. Öfner, J. Bodner: **Thoracotomy versus video-assisted thoracoscopic surgery (VATS) in stage III empyema – an analysis of 217 consecutive patients.** *Surgical Endoscopy*. 2018 Jun;32(6):2664-2675. doi: 10.1007/s00464-017-5961-7.

Über einen Zeitraum von zwölf Jahren wurden aus einer Gesamtkohorte von insgesamt 217 Fällen 84 Patienten durch *Propensity score matching* gepaart und hinsichtlich des klinischen Verlaufs und *Outcome* analysiert. Die chirurgische Therapie des organisierten Pleuraempyems im Stadium III nach ATS erfolgte bei diesen Patienten entweder konventionell-offen (über eine Thorakotomie) oder minimalinvasiv (video-assistiert thorakoskopisch).

Es zeigten sich keine sicherheitsrelevanten Unterschiede zwischen der Thorakoskopie und der konventionell-offenen Operationstechnik: Weder Komplikationsraten noch die Liegedauer der Thoraxdrainagen unterschieden sich zwischen den Gruppen. Auch hinsichtlich der Effektivität, gemessen an Rezidiv- und Redrainageraten, ergaben sich keine Differenzen. Eine multiple lineare Regressionsanalyse, adjustiert für klinisch und statistisch relevante Störfaktoren, ergab eine signifikante Verkürzung der postoperativen Krankenhausverweildauer um durchschnittlich 0,836 Tage zugunsten des minimalinvasiven, thorakoskopischen Operationsverfahrens (Tabelle 1). Außerdem waren der intraoperative Blutverlust und die Rate an postoperativer mechanischer Ventilation in der Thorakotomiegruppe höher.

Fazit: Diese Studie bestätigt, dass die minimalinvasive video-assistierte Thorakoskopie eine sichere und effektive Methode zur chirurgischen Behandlung des organisierten Pleuraempyems darstellt. Darüber hinaus zeigte das minimalinvasive Operationsverfahren Vorteile in Bezug auf Blutverlust, Dauer der postoperativen Beatmung sowie eine beschleunigte Rekonvaleszenz mit früherer Entlassung in die ambulante Weiterbehandlung.

Model—after propensity score matching		Coefficients		*p* value	95.0% Confidence interval for B	
		B	Std. error		Lower bound	Upper bound
1	Independent variable:					
	Operation technique (Thoracotomy = 0, VATS = 1)	−0.042	0.111	0.705	−0.262	0.178
2	Independent variable:					
	Operation technique (Thoracotomy = 0, VATS = 1)	−0.179	0.083	0.032	−0.342	−0.016
	Confounder:					
	Pre-operative hospital stay (days)	0.005	0.004	0.211	−0.003	0.012
	C-reactive protein—maximum pre-operative (mg/l)	0.001	0.000	0.012	0.000	0.002
	ASA-Score pre-operative	0.096	0.066	0.148	−0.034	0.226
	Operation time (min)	0.002	0.001	0.001	0.001	0.003
	Post-operative stay on ICU (h)	0.001	0.000	0.000	0.001	0.001

Dependent variable: Length of post-operative hospital stay (days)

ASA American society of anesthesiologists classification of physical health (assessed pre-operatively), *ICU* Intensive care unit

Tabelle 1: Einfluss der Operationstechnik auf die Dauer des postoperativen Krankenhausaufenthaltes. Die Regressionsanalyse wurde in einem nicht-adjustierten Model (1) und in einem, um klinisch relevante Störfaktoren adjustierten Model (2) angewendet, um dein Einfluss der Operationstechnik (unabhängige Variable: konventionell-offene oder minimalinvasive, video-assistiert thorakoskopische Chirurgie) auf die Dauer des postoperativen Krankenhausaufenthaltes (abhängige Variable) zu untersuchen. Hierzu wurden die Daten der Patientenkohorte nach *Propensity score matching* verwendet. Der Regressionskoeffizient B = -0,179 der adjustierten Regressionsanalyse kann in eine Reduktion der postoperativen stationären Aufenthaltsdauer von $e^{-0,179}$ = 0,836 Tagen in der Thorakoskopie- verglichen mit der Thorakotomiegruppe übersetzt werden (p = 0,032). Tabelle aus der Originalpublikation entnommen: M. Reichert, B. Pösentrup, A. Hecker, E. Schneck, J. Pons-Kühnemann, F. Augustin, W. Padberg, D. Öfner, J. Bodner: Thoracotomy versus video-assisted thoracoscopic surgery (VATS) in stage III empyema – an analysis of 217 consecutive patients. Surgical Endoscopy. 2018 Jun;32(6):2664-2675. doi: 10.1007/s00464-017-5961-7 (74).

3.2.2 Lernkurve der thorakoskopischen Dekortikation

M. Reichert, B. Pösentrup, A. Hecker, W. Padberg, J. Bodner: **Lung decortication in phase III pleural empyema by video-assisted thoracoscopic surgery (VATS) – results of a learning curve study.** *Journal of Thoracic Disease*. 2018 Jul;10(7):4311-4320. doi: 10.21037/jtd.2018.06.72.

Die effektive und sichere Durchführbarkeit der minimalinvasiven Dekortikation bei Patienten mit Pleuraempyem im Stadium III wurde unter Punkt 3.2.1 gezeigt (74). Dabei bietet die thorakoskopische Dekortikation im Vergleich zur konventionell-offenen Chirurgie Vorteile hinsichtlich der Rekonvaleszenz, was sich in einer verkürzten postoperativen Krankenhausverweildauer widerspiegelt (74).

Bei der Etablierung innovativer chirurgischer Therapieverfahren, insbesondere in der minimalinvasiven Chirurgie, ist die Analyse der individuellen Lernkurve von besonderem Interesse. Das institutionelle Thorakoskopieprogramm (*video-assisted thoracoscopic surgery*, VATS) für komplexe Eingriffe, darunter anatomische Lungenresektionen oder Dekortikationen beim organisierten Pleuraempyem, wurde 2011 initiiert und von einem Thoraxchirurgen federführend durchgeführt. Die klinische und onkologische Sicherheit wurde fortlaufend im Vergleich zur offenen Chirurgie evaluiert, wobei relevante Ergebnisse regelmäßig wissenschaftlich publiziert wurden (74,102,123–127).

Vor Einführung des VATS-Programms wurde das organisierte Pleuraempyem im Stadium III primär konventionell-offen operiert. Ab 2011 erfolgte die Behandlung zunehmend minimalinvasiv thorakoskopisch: zwischen 2011 und 2015 wurden insgesamt 127 video-assistiert thorakoskopische Dekortikationen zur Behandlung dieser Erkrankung durchgeführt.

Bereits nach dem ersten Drittel dieser Eingriffe zeigte sich eine signifikante Reduktion der Operationszeit als Surrogatparameter für den Lernkurvenerfolg (Patient 1-43: 170,1 ± 73,6 min versus Patient 44-127: 141,6 ± 138,0 min; p = 0,0308). Mit zunehmender Erfahrung wurden auch komplexere Fälle thorakoskopisch versorgt, was sich u. a. in den Komorbiditäten der betroffenen Patienten (American Society of Anesthesiologists´ classification of physical health (ASA)-score der Patienten 1-43: 2,6 ± 0,6 versus ASA-score der Patienten 44-127: 2,9 ± 0,6; p = 0,0279), einer steigenden Rate präoperativer Drainagentherapie (Patient 1-43: 25,6% versus Patient 44-127: 44,0%; p = 0,0534) sowie der Ätiologie des Pleuraempyems (p = 0,0854; u.a. Zustand nach thorakaler Voroperation der Patienten 1-43: 7,0% versus der Patienten 44-127: 17,9%) widerspiegelte.

Trotz der zunehmenden Komplexität ergaben sich keine signifikanten Unterschiede hinsichtlich postoperativer Komplikationen, stationärer Aufenthaltsdauer oder Therapieerfolg, gemessen an Redrainage- und Rezidivraten.

Fazit: Die Lernkurve für video-assistiert thorakoskopische Dekortikationen bei organisierten Pleuraempyemen beträgt etwa 40 Eingriffe, um eine Verkürzung der Operationsdauer zu erreichen. Nach dieser initialen Phase zeigte sich kein signifikanter Einfluss mehr auf die Operationszeit.

3.3 Transhiatale Hernien nach Resektionen am oberen Gastrointestinaltrakt

P.U. Oppelt, I. Askevold, R. Hörbelt, F.C. Roller, W. Padberg, A. Hecker, **M. Reichert**: **Trans-hiatal herniation following esophagectomy or gastrectomy: retrospective single-center experiences with a potential surgical emergency.** *Hernia.* 2022 Feb;26(1):259-278. doi: 10.1007/s10029-021-02380-1.

In Kapitel 3.1.2 wurden die unmittelbaren postoperativen Vorteile der minimalinvasiven Chirurgie des Ösophaguskarzinoms beschrieben (28). In jüngerer Vergangenheit berichteten jedoch mehrere retrospektive Kohortenstudien über eine zunehmende Inzidenz transhiataler Hernien, insbesondere nach minimalinvasiver Ösophagusresektion. Hintergrund ist u.a. die steigende Lebenserwartung onkologischer Patienten infolge verbesserter multimodaler Therapieoptionen. Transhiatale Hernien stellen eine klinisch relevante und potenziell gefährliche Spätkomplikation nach Eingriffen am oberen Gastrointestinaltrakt dar (26,78,87–89,79–86).

Der Begriff „Hernie“ ist im eigentlichen Sinn nicht vollständig korrekt, da der transdiaphragmal prolabierte Bruchinhalt nicht von einem echten Bruchsack umgeben ist (84). Dennoch wird er in dieser Arbeit synonym verwendet.

Die Analyse des institutionellen Patientenkollektivs erfolgte hinsichtlich der Art der Voroperation und der Technik zur operativen Hernienversorgung (Abbildung 7).

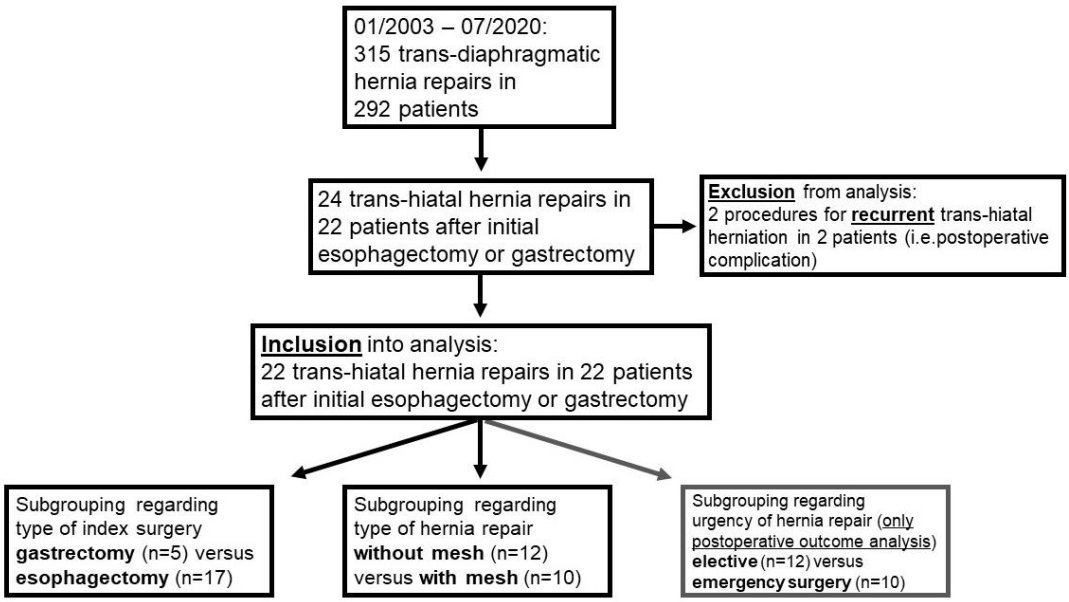


Abbildung 7: Zwerchfellhernienchirurgie im 18-Jahresverlauf. Lediglich 22 Prozeduren (7%) erfolgten wegen einer transhiatalen Hernie nach Resektionen am oberen Gastrointestinaltrakt. Abbildung aus der Originalpublikation entnommen: P.U. Oppelt, I. Askevold, R. Hörbelt, F.C. Roller, W. Padberg, A. Hecker, M. Reichert: Trans-hiatal herniation following esophagectomy or gastrectomy: retrospective single-center experiences with a potential surgical emergency. Hernia. 2022 Feb;26(1):259-278. doi: 10.1007/s10029-021-02380-1 (27).

Onkologische Resektionen am Ösophagus waren die häufigste Ursache dieser speziellen sekundären transhiatalen Hernien, die im Median etwa ein Jahr nach der Primäroperation diagnostiziert wurden.

Patienten, die eine transhiatale Hernie entwickelten, wiesen häufig einen komplikativen Verlauf nach Indexoperation auf, gemessen an einem *Comprehensive complication index* (128) im Median von 34,6. In der Subgruppe der Patienten nach Ösophagektomie (abdomino-thorakale Ösophagusresektion, transhiatale Ösophagusresektion mit Gastrektomie) erfolgte bei der Primäroperation meist eine Mitresektion der Zwerchfellschenkel. In dieser Kohorte war der bildgebende Herniendurchmesser größer als bei Patienten nach „einfacher“ Gastrektomie (Median [Minimum-Maximum]: 9,3 [6,0 – 12,8] cm versus 5,6 [4,4 – 9,4] cm; p = 0,04).

Die wenigsten Patienten waren bei Diagnosestellung symptomfrei; respiratorische, kardiale und gastrointestinale Symptome mit Ileuszeichen sowie abdominelle und thorakale Schmerzen standen klinisch im Vordergrund. In der Bildgebung fanden sich häufig das Kolon transversum und Anteile des Dünndarms nach links-thorakal prolabiert. Bei elf Patienten zeigten sich bildgebend Zeichen einer Inkarzeration (n = 11: Darmobstruktion / Ileus; n = 7: vaskuläre Strangulation), sodass in zehn Fällen eine Notfalloperation und in zwölf Fällen eine semielektive Versorgung notwendig war. Dank zügiger chirurgischer Intervention musste lediglich in einem Fall eine Darmresektion durchgeführt werden.

Bei zwölf Patienten erfolgte ein primärer Nahtverschluss durch Readaptation der Zwerchfellschenkel; bei zehn Patienten wurde ein Kunststoffnetz entweder zur Nahtaugmentation oder zum Verschluss des Hiatus durch Interposition implantiert. Ohne Netzeinlage erfolgte deutlich häufiger eine Pexie intraabdomineller Organe (allen voran Kolon transversum), um dadurch den Zugang zum Hiatus zu blockieren und einen erneuten Prolaps zu verhindern. Allerdings wurden Kunststoffnetze seltener in der Notfallsituation implantiert (p = 0,03). Die häufigste postoperative Komplikation war ein Pleuraerguss mit Drainagenotwendigkeit, insbesondere nach Netzimplantationen (p = 0,01).

Fazit: Transhiatale Hernien nach Ösophagusresektion stellen bei symptomatischen Patienten potenzielle chirurgische Notfälle dar. Zügiges operatives Handeln kann schwerwiegende Komplikationen und Morbidität verhindern. Der Nutzen eines *watchful waiting* -Konzepts bei oligo- oder asymptomatischen Hernien ist aktuell nicht

ausreichend belegt. In unserem Kollektiv erfolgte auch bei asymptomatischen Patienten eine elektive operative Versorgung.

Wie sowohl unsere Daten als auch unser systematisches Literaturreview retrospektiver, meist monozentrischer Fallserien zeigten, basieren die gewählten Techniken zum Verschluss transhiataler Hernien nach Resektionen am oberen Gastrointestinaltrakt weitgehend auf zentrumseigenen Erfahrungen und intraoperativen Gegebenheiten (Anlage 6, Tabelle 5). Der transabdominelle, primäre Nahtverschluss mittels Cruroplastik mit oder ohne Netzaugmentation sowie die Pexie des Kolons transversum zur mechanischen Blockade des Hiatus stellen sinnvolle operative Strategien dar. In Fällen mit größeren Defekten kann die Netzinterposition eine effektive Alternative zum Bruchlückenverschluss sein.

3.4 Gastrointestinale Motilitätsstörungen nach onkologischen Resektionen am unteren Gastrointestinaltrakt

Wie einleitend bereits erwähnt, stellen prolongierte postoperative gastrointestinale Motilitätsstörungen und der POI ein häufiges klinisches Problem nach onkologischer Viszeralchirurgie dar (22–24,98). Sie beeinträchtigen das Wohlbefinden und die Behandlungszufriedenheit der Patienten erheblich (22,95). Der klinisch manifeste POI erhöht darüber hinaus das Risiko schwerwiegender Komplikationen wie Aspiration und Sepsis. Er führt zu einer verlängerten intensivstationären sowie gesamtstationären Aufenthaltsdauer und verschlechtert das *Outcome* der betroffenen Patienten sowohl kurzfristig als auch im Langzeitverlauf (96,129–132).

3.4.1 Gastrointestinale Motilitätsstörungen nach Rechtshemikolekomie

M. Hirschburger, R. Schneider, S. Kraenzlein, W. Padberg, A. Hecker, **M. Reichert**: **Right colectomy from open to robotic – a single-center experience with functional outcomes in a learning-curve setting.** *Langenbeck´s Archives of Surgery*. 2022 Nov;407(7):2915-2927. doi: 10.1007/s00423-022-02576-8.

Onkologische Eingriffe am unteren Gastrointestinaltrakt, insbesondere am rechten Hemikolon, sind mit einem erheblichen Risiko für postoperative gastrointestinale Motilitätsstörungen assoziiert (25,94,133–139). Zur Analyse des Einflusses minimalinvasiver Techniken auf gastrointestinale Funktion und Rekonvaleszenz der Patienten wurden im Zehnjahresverlauf 117 konsekutive Patienten nach elektiver Rechtshemikolektomie untersucht. Die Operationsindikation

war in 97,4 % onkologisch, sodass in dieser Mehrzahl der Fälle eine komplette mesokolische Exzision mit zentraler Lymphknotendissektion durchgeführt wurde.

Die Patientenkohorte wurde auf Basis der Operationstechnik in drei konsekutive Phasen eingeteilt. Zunächst wurden die ersten 22 Patienten konventionell-offen über eine Medianlaparotomie operiert. Nach Implementierung eines viszeralchirurgischen Robotikprogramms wurden die folgenden 39 Eingriffe als roboter-assistierte Rechtshemikolektomien mit extrakorporaler Anlage einer Ileo-Transversostomie über eine Laparotomie im Oberbauch durchgeführt. Mit zunehmender Erfahrung wurde die minimalinvasive Technik weiterentwickelt, sodass die nächsten 56 Patienten total-robotisch mit intrakorporal, robotisch-handgenähter Ileo-Transversostomie operiert wurden. Die Bergung des Hemikolektomiepräparates erfolgte hierbei über eine limitierte Unterbauchlaparotomie nach Pfannenstiel.

Zwischen den Gruppen ergaben sich keine signifikanten Unterschiede in der onkologischen Resektionsqualität (R0-Resektion, Lymphknotenausbeute) oder hinsichtlich intraoperativer Komplikationen. Postoperative Wundinfektionen traten jedoch häufiger nach konventionell-offener ($n = 6$) und robotisch-assistierter ($n = 2$) Rechtshemikolektomie auf, verglichen mit der total-robotischen Technik, bei der keine Fälle dokumentiert wurden ($p < 0,0001$).

Zur Abschätzung der durch das chirurgische Trauma induzierten systemischen Inflammation wurde die Höhe des postoperativen C-reaktiven Proteins im peripheren Blut herangezogen. Trotz vergleichbarer Operationszeiten und analogen onkochirurgischen Prinzipien zeigte sich eine stufenweise Reduktion der systemischen Inflammation in Abhängigkeit vom Zugangsweg (konventionell-offen > robotisch-assistiert > total-robotisch; Abbildung 8).

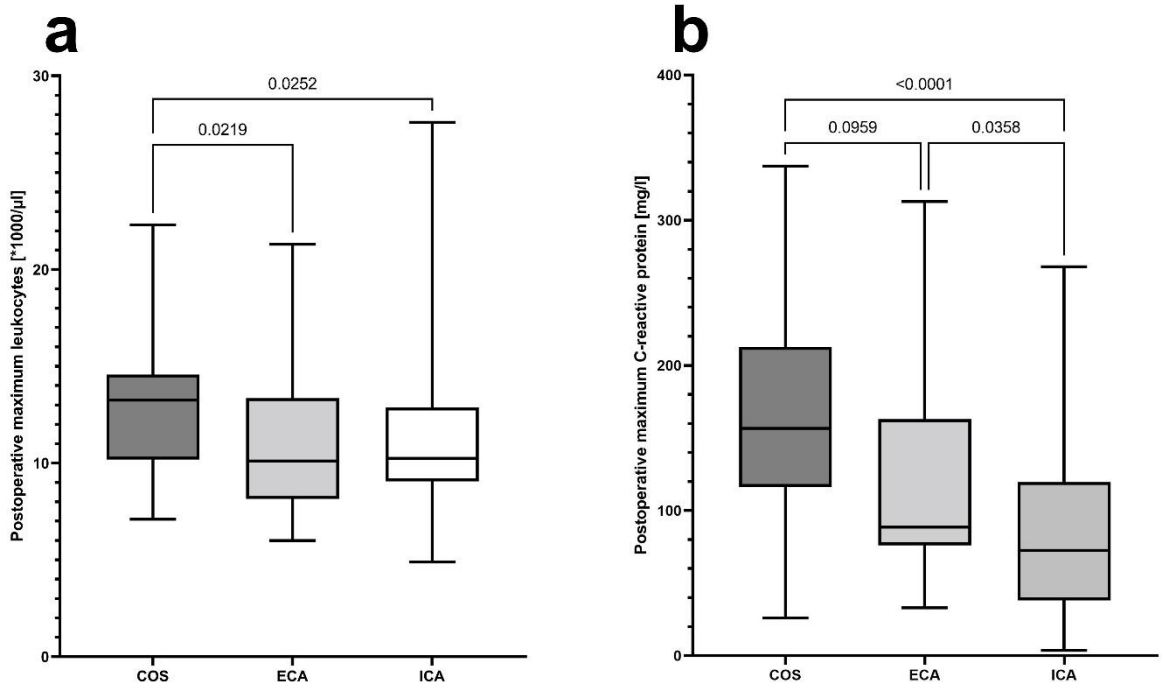


Abbildung 8: Einfluss der Operationstechnik auf die postoperative systemische Inflammation. Keine Unterschiede wurden in den präoperativen Leukozyten oder dem präoperativen C-reaktiven Protein im peripheren Blut zwischen den Gruppen nachgewiesen. **A:** Höchster Wert der Leukozyten im peripheren Blut an den postoperativen Tagen 1-3. Der Kruskall-Wallis Test zeigt hier globale Unterschiede zwischen den Gruppen (p = 0,014), sodass die einzelnen Gruppen untereinander mittels Dunn´s Test, der für multiple Vergleiche korrigiert wurde, *post hoc* verglichen wurden. Die entsprechenden Signifikanzen sind in der Abbildung angezeigt. **B:** Höchster Wert des C-reaktiven Proteins im peripheren Blut an den postoperativen Tagen 1-3. Der Kruskall-Wallis Test zeigt hier globale Unterschiede zwischen den Gruppen (p < 0,0001), sodass die einzelnen Gruppen untereinander mittels Dunn´s Test, der für multiple Vergleiche korrigiert wurde, *post hoc* verglichen wurden. Die entsprechenden Signifikanzen sind in der Abbildung angezeigt. COS = *conventional open surgery*; konventionell-offene Rechtshemikolektomie. ECA = *extracorporal anastomosis*; robotisch-assistierte Rechtshemikolektomie mit extrakorporaler Anlage einer (konventionell-handgenähten) Ileotransversostomie. ICA = *intracorporal anastomosis*; total robotische Rechtshemikolektomie mit intrakorporaler Anlage der (robotisch-handgenähten) Ileotransversostomie. Abbildung aus der Originalpublikation entnommen: M. Hirschburger, R. Schneider, S. Kraenzlein, W. Padberg, A. Hecker, M. Reichert: Right colectomy from open to robotic – a single-center experience with functional outcomes in a learning-curve setting. Langenbeck´s Archives of Surgery. 2022 Nov;407(7):2915-2927. doi: 10.1007/s00423-022-02576-8 (133).

Als Surrogatparameter für die gastrointestinale Rekonvaleszenz oder Dysfunktion wurde die Zeit bis zur ersten postoperativen Defäkation herangezogen. Auch hier zeigten sich klare Vorteile für das total-robotische Verfahren, was sich zusätzlich in einer verkürzten postoperativen Krankenhausverweildauer widerspiegelte Abbildungen 9).

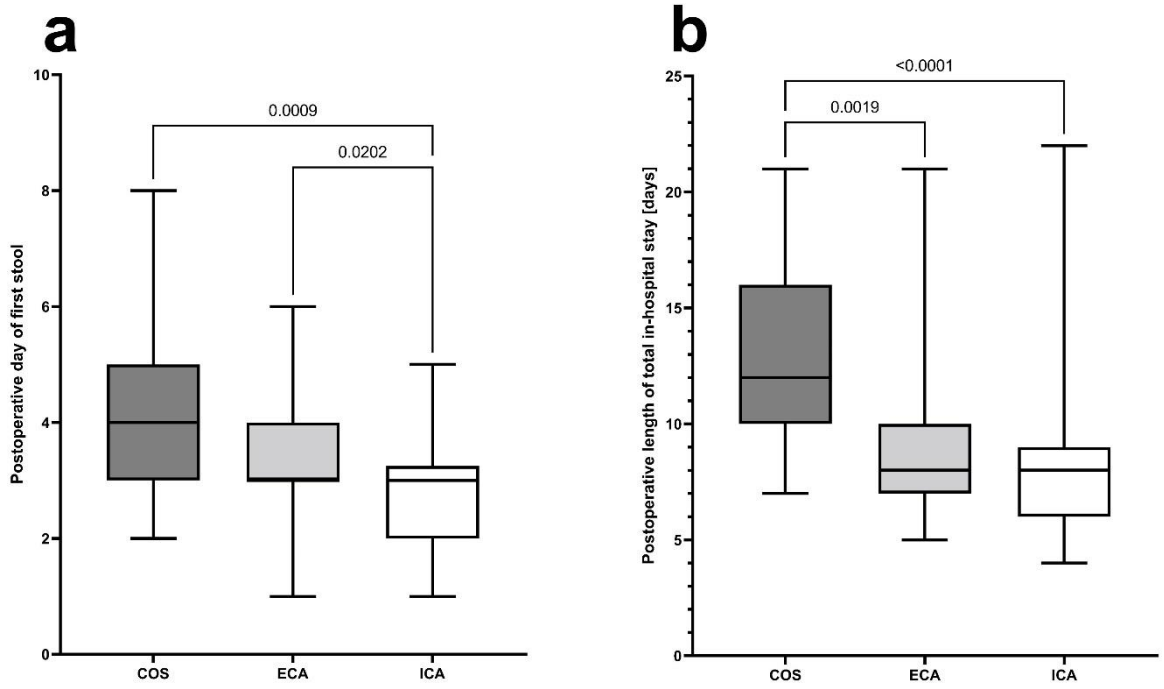


Abbildung 9: Einfluss der Operationstechnik auf postoperative Darmfunktion und Krankenhausverweildauer. A: Dauer bis zur ersten postoperativen Defäkation. Der Kruskall-Wallis Test zeigt hier globale Unterschiede zwischen den Gruppen (p = 0,0004), sodass die einzelnen Gruppen untereinander mittels Dunn´s Test, der für multiple Vergleiche korrigiert wurde, *post hoc* verglichen wurden. Die entsprechenden Signifikanzen sind in der Abbildung angezeigt. **B:** Dauer des postoperativen Krankenhausaufenthaltes. Der Kruskall-Wallis Test zeigt hier globale Unterschiede zwischen den Gruppen (p < 0,0001), sodass die einzelnen Gruppen untereinander mittels Dunn´s Test, der für multiple Vergleiche korrigiert wurde, *post hoc* verglichen wurden. Die entsprechenden Signifikanzen sind in der Abbildung angezeigt. COS = *conventional open surgery*; konventionell-offene Rechtshemikolektomie. ECA = *extracorporal anastomosis*; robotisch-assistierte Rechtshemikolektomie mit extrakorporaler Anlage einer (konventionell-handgenähten) Ileotransversostomie. ICA = *intracorporal anastomosis*; total robotische Rechtshemikolektomie mit intrakorporaler Anlage einer (robotisch-handgenähten) Ileotransversostomie. Abbildung aus der Originalpublikation entnommen: M. Hirschburger, R. Schneider, S. Kraenzlein, W. Padberg, A. Hecker, M. Reichert: Right colectomy from open to robotic – a single-center experience with functional outcomes in a learning-curve setting. Langenbeck´s Archives of Surgery. 2022 Nov;407(7):2915-2927. doi: 10.1007/s00423-022-02576-8 (133).

Dies wurde durch die lineare Regressionsanalyse bestätigt: dabei korrelierten das konventionell-offene Operationsverfahren und die damit verbundene höhergradige postoperative systemische Inflammation signifikant mit einer verlängerten Zeit bis zur ersten Defäkation sowie einer prolongierten postoperativen Krankenhausverweildauer (Abbildung 10).

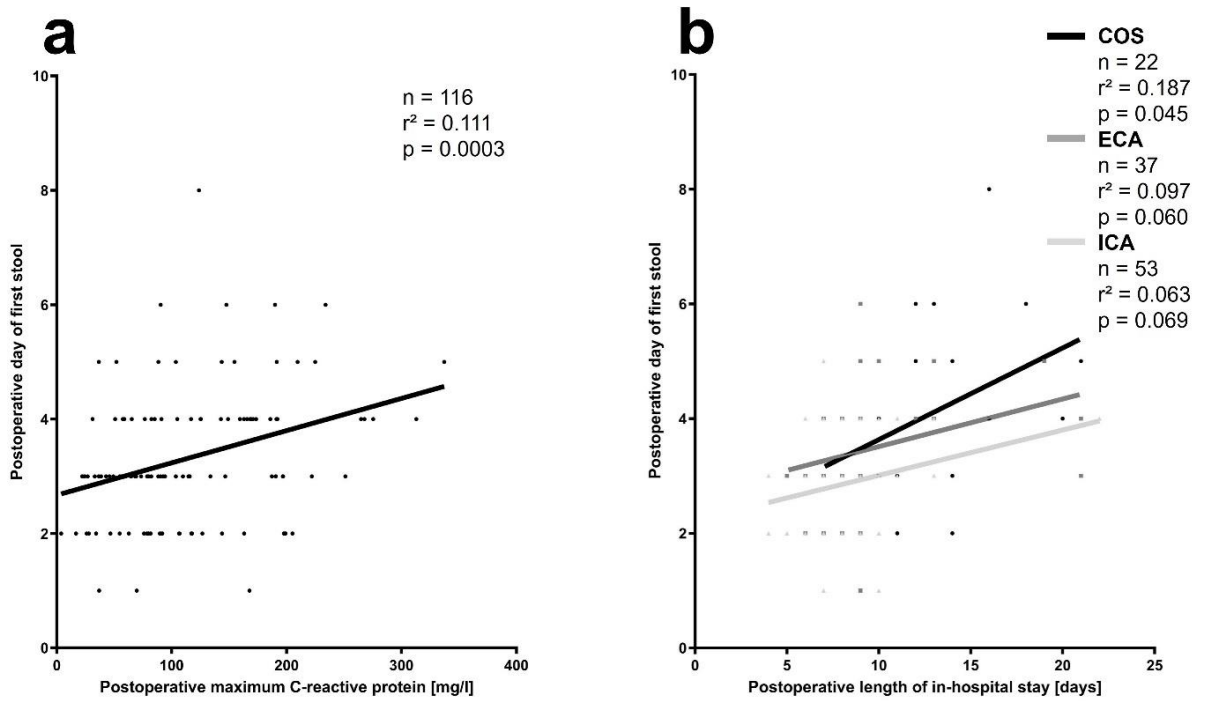


Abbildung 10: Einflussfaktoren auf die postoperative Darmfunktion in der linearen Regression.
A: Einfluss der postoperativen systemischen Inflammation, gemessen am postoperativen maximalen C-reaktiven Protein an den Tagen 1-3 nach Rechtshemikolektomie, auf die Dauer bis zur ersten postoperativen Defäkation. **B:** Einfluss der Dauer bis zur ersten postoperativen Defäkation als Ausdruck einer gastrointestinalen Motilitätsstörung nach Rechtshemikolektomie auf die Länge des postoperativen Krankenhausaufenthaltes in Abhängigkeit zur Operationstechnik. COS = *conventional open surgery*; konventionell-offene Rechtshemikolektomie. ECA = *extracorporal anastomosis*; robotisch-assistierte Rechtshemikolektomie mit extrakorporaler Anlage einer (konventionell-handgenähten) Ileotransversostomie. ICA = *intracorporal anastomosis*; total robotische Rechtshemikolektomie mit intrakorporaler Anlage einer (robotisch-handgenähten) Ileotransversostomie. Abbildung aus der Originalpublikation entnommen: M. Hirschburger, R. Schneider, S. Kraenzlein, W. Padberg, A. Hecker, M. Reichert: Right colectomy from open to robotic – a single-center experience with functional outcomes in a learning-curve setting. Langenbeck´s Archives of Surgery. 2022 Nov;407(7):2915-2927. doi: 10.1007/s00423-022-02576-8 (133).

Fazit: Diese Arbeit reflektiert die institutionelle Lernkurve von der konventionell-offenen über die robotisch-assistierte bis hin zur total-robotischen Rechtshemikolektomie. Die Ergebnisse zeigen eine deutliche Abhängigkeit der postoperativen Rekonvaleszenz und Krankenhausverweildauer von der Operationsmethode. Es konnte ein Zusammenhang zwischen dem Ausmaß des

chirurgischen Traumas, der postoperativen systemischen Inflammation und der Dauer einer gastrointestinalen Motilitätsstörung festgestellt werden.

Minimalinvasive Verfahren leisten durch ein geringeres Operationstrauma, reduzierte Manipulation am Gastrointestinaltrakt und verminderte postoperative Inflammation einen Beitrag zur Vermeidung gastrointestinaler Motilitätsstörungen. Allerdings bleiben weitere Aspekte der multifaktoriellen Pathogenese postoperativer gastrointestinaler Motilitätsstörungen (22,98,140,141), wie etwa postoperative Schmerzen und der Einsatz opioidbasierter Analgesie in der perioperativen Medizin, in dieser retrospektiven Analyse unberücksichtigt.

3.4.2 Das protektive Ileostoma als Risikofaktor für den postoperativen Ileus nach onkologischer Rektumresektion

M. Reichert, C. Weber, J. Pons-Kühnemann, M. Hecker, W. Padberg, A. Hecker: **Protective loop ileostomy increases the risk for prolonged postoperative paralytic ileus after open oncologic rectal resection.** *International Journal of Colorectal Disease*. 2018 Nov;33(11):1551-1557. doi: 10.1007/s00384-018-3142-3.

Wie bereits in Kapitel 3.4.1 dargestellt, treten gastrointestinale Motilitätsstörungen nach Resektionen am rechten Hemikolon außerordentlich häufig auf (133–139). Ihre genaue Pathophysiologie ist bislang nicht vollständig geklärt. Reduzierte chirurgische Traumata durch minimalinvasive Operationstechniken unterstützen jedoch die gastrointestinale Rekonvaleszenz und die Genesung der Patienten (133).

Inwieweit die alleinige ileozökale Manipulation zu der erhöhten Inzidenz des POI beiträgt, wurde in einem streng selektionierten Patientenkollektiv von 101 konventionell-offenen, sphinktererhaltenden, onkologischen, tief-anterioren Rektumresektionen mit kompletter mesorektaler Exzision und primärer Descendorektostomie untersucht (Tabelle 2). Zur Sicherstellung einer homogenen Studienpopulation wurden Patienten mit schwerer Herzinsuffizienz, laparoskopischen oder konvertierten Eingriffen, Diskontinuitätsresektionen, ausgedehnten Adhäsiolysen, multiviszeralen Resektionen sowie postoperativen *major*-Komplikationen ausgeschlossen. Letztere umfassten Anastomoseninsuffizienzen, Reinterventionen, intraabdominelle Abszesse, Nachblutungen und den postoperativen mechanischen Ileus.

Als objektives Kriterium für das Auftreten eines POI diente die intravenöse Gabe von Neostigmin innerhalb der ersten zehn postoperativen Tage. Mithilfe eines logistischen Regressionsmodells wurde das *Odds* Ratio für die Entwicklung eines POI in Abhängigkeit von der Ileostomieanlage berechnet. Das Geschlecht wurde als Störfaktor adjustiert, da es in der univariaten Analyse signifikant mit dem Auftreten eines POI korrelierte. Für andere potenziell relevante *Confounder* – darunter Adipositas, Diabetes mellitus, neoadjuvante Radiochemotherapie und Periduralanästhesie – ergab sich univariat kein signifikanter Einfluss.

Variable	Defunctioning loop ileostomy Yes	No	*p* value
n	62 (61.39%)	39 (38.61%)	
Male gender	37 (59.68%)	25 (64.1%)	0.68
Peridural anesthesia	32 (51.61%)	20 (51.28%)	1
Neoadjuvant radio-chemotherapy	19 (30.65%)	1 (2.56%)	0.0005
Diabetes mellitus	8 (12.9%)	7 (17.95%)	0.57
BMI ≥ 30 kg/m^2	6 (9.68%)	7 (17.95%)	0.24
Postoperative surgical re-intervention	1 (1.6%)	0	1

Tabelle 2: Charakteristika der Patienten mit und ohne protektive Ileostomie im Rahmen der onkologischen Rektumresektion. Diese unabhängigen Variablen wurden zunächst univariat auf das Auftreten eines postoperativen Ileus getestet. Hier zeigte sich lediglich das (männliche) Geschlecht mit dem postoperativen Ileus assoziiert, sodass dieses als Störfaktor in das logistische Regressionsmodell überführt wurde. BMI = Body mass index. Tabelle aus der Originalpublikation entnommen: M. Reichert, C. Weber, J. Pons-Kühnemann, M. Hecker, W. Padberg, A. Hecker: Protective loop ileostomy increases the risk for prolonged postoperative paralytic ileus after open oncologic rectal resection. International Journal of Colorectal Disease. 2018 Nov;33(11):1551-1557. doi: 10.1007/s00384-018-3142-3 (134).

Die logistische Regression zeigte, dass die protektive Ileostomie die Entwicklung eines POI nach onkologischer Rektumresektion signifikant beeinflusst (p = 0,047). Das *Odds* Ratio für den POI bei Patienten mit einer protektiven Ileostomie betrug 4,96 (95%-Konfidenzintervall 1,02 – 24,03).

Fazit: Die Anlage einer protektiven Ileostomie stellt eine etablierte Maßnahme im Rahmen von Rektumresektionen mit primärer Anastomose im mittleren und unteren Rektumdrittel dar. Sie hat ihre Vorteile in der Protektion schwerer septischer Komplikationen und Reoperationen im Falle von Anastomoseninsuffizienzen (142–145). In dieser retrospektiven Analyse zeigte sich jedoch, dass sie zugleich ein relevanter chirurgisch-technischer Risikofaktor für die Entwicklung eines POI ist.

Wie bereits im Rahmen der minimalinvasiven Rechtshemikolektomie vermutet, legen diese Ergebnisse nahe, dass bereits die Manipulation im Bereich des terminalen Ileums und ileozökalen Übergangs zur erhöhten Inzidenz des POI beitragen kann (133–138). Aus funktioneller Sicht sollte die Indikation zur Anlage eines protektiven Ileostomas daher individuell und differenziert geprüft werden.

3.5 Pharmakologische Prävention und Therapie postoperativer gastrointestinaler Motilitätsstörungen

M. Reichert, F. Willis, S. Post, M. Schneider, T. Vilz, M. Willis, A. Hecker: **Pharmacologic prevention and therapy of postoperative paralytic ileus after gastrointestinal cancer surgery – systematic review and meta-analysis.** *International Journal of Surgery*. 2024 Jul 1;110(7):4329-4341. doi: 10.1097/JS9.0000000000001393.

Die Pathophysiologie postoperativer gastrointestinaler Motilitätsstörungen und des POI ist multifaktoriell und komplex (22,98,140,141). Wie in den vorangegangenen Kapiteln dargestellt, beeinflussen chirurgisch-technische Aspekte die Entstehung prolongierter postoperativer gastrointestinaler Motilitätsstörungen. Minimalinvasive Verfahren mit reduziertem Zugangs- und Operationstrauma reduzieren dabei effektiv die Inzidenz gastrointestinaler Dysfunktionen und des POI (133,134). Zusätzlich wurden in der Literatur zahlreiche pharmakologisch wirksame Substanzen beschrieben, die an unterschiedlichen Punkten der Pathophysiologie ansetzen und entweder perioperativ zur Prophylaxe oder postoperativ zur Therapie des klinisch manifesten POI getestet wurden.

Nach einer vordefinierten und in einer internationalen Datenbank publizierten Strategie (*International prospective register of systematic reviews* – PROSPERO 2022 CRD42022351799) erfolgte durch eine systematische Literaturrecherche mit Metaanalyse die Synthese und Bewertung der aktuellen Evidenz zur pharmakologischen Prävention und Therapie des POI nach onkologischer Viszeralchirurgie aus Daten von prospektiv randomisiert-kontrollierten Studien (146). Die Ergebnisse dieser Arbeit bildeten die wissenschaftliche Grundlage für die Empfehlungen zur pharmakologischen Prävention und Therapie postoperativer gastrointestinaler Motilitätsstörungen (Kapitel 7.4.1) der S3-Leitlinie „Perioperatives Management bei gastrointestinalen Tumoren (POMGAT)“; Version 1.0 – November 2023; AWMF-Registernummer: 088-010OL aus dem Leitlinienprogramm Onkologie

der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), der Deutschen Krebsgesellschaft und der Deutschen Krebshilfe (99,147).

Eingeschlossen wurden prospektive randomisiert-kontrollierte Studien an Patienten während und/oder nach gastrointestinalen Tumorresektionen, in denen zugelassene Medikamente gegen Placebo oder Standardtherapie verglichen wurden. Studien ohne geeignete Vergleichsgruppe, ohne Patienten mit gastrointestinalen Tumorresektionen oder mit nicht von deutschen und/oder US-amerikanischen Behörden zugelassenen Medikamenten wurden aufgrund fehlender Relevanz für die klinische Routine ausgeschlossen.

Neben Parametern zur Patientensicherheit durch die pharmakologische Intervention wurden folgende Surrogatparameter zur Beurteilung der Effektivität erhoben:

- Dauer bis zum ersten postoperativen Flatus,
- Dauer bis zum ersten postoperativen Stuhlgang,
- Dauer bis zum vollständigen Kostaufbau,
- das *composite outcome* GI-2 (fasst die Dauer bis zum ersten Stuhlgang und die Dauer bis zur oralen Nahrungstoleranz zusammen) und
- die postoperative Krankenhausverweildauer.

Aufgrund unterschiedlicher Wirkmechanismen erfolgte die Stratifizierung der identifizierten Substanzen aus 55 Studien an 5078 Patienten in folgende effekt- bzw. wirkstoffbasierte Untergruppen:

- Reduzierung der peripheren Opioidwirkung durch peripheren Opioidantagonismus oder opioidsparende Analgesieverfahren,
- Reduktion der perioperativen sympathetischen Hyperreaktion,
- Parasympathomimetika,
- Prokinetika,
- Laxanzien, Stimulanzien und Adjuvanzien.

Opioidsparende Analgesieverfahren mit intravenösem Lidocain, peripherer Opioidantagonismus mit dem in Deutschland nicht zugelassenen, aber im anglo-amerikanischen Raum nach kolorektalen Resektionen mit primärer Anastomose etablierten oralen Alvimopan, sowie die Reduktion der perioperativen sympathetischen Hyperreaktivität durch den intravenös verabreichten Alpha-2-Rezeptoragonisten Dexmedetomidin, können wirksam zur Prävention einer gastrointestinalen

Motilitätsstörung beitragen. Diese Substanzen haben sich in der Metaanalyse als effektiv hinsichtlich verschiedener Aspekte der postoperativen gastrointestinalen Rekonvaleszenz erwiesen (Abbildung 11 zeigt diesbezüglich exemplarisch die Effekte einzelner Wirkstoffgruppen auf die Dauer bis zur postoperativen Defäkation) und verkürzten schließlich die Krankenhausaufenthaltsdauer (Abbildung 12).

Die nicht-opioiden Analgetika, Paracetamol und nicht-steroidale Antiphlogistika, zeigten ebenfalls Effekte in Bezug auf die Darmfunktion und die postoperative Krankenhausaufenthaltsdauer. Der frühzeitige Einsatz von Laxantien verkürzte die Dauer bis zum ersten Stuhlgang, hatte jedoch keinen Effekt auf postoperativen Kostaufbau und postoperative Hospitalisation.

Im Gegensatz zur pharmakologischen Prävention ist die Evidenz für die pharmakologische Therapie des klinisch manifesten POI limitiert. Lediglich eine Studie wies für intramuskulär appliziertes Neostigmin einen positiven Effekt auf Flatus und Defäkation nach, jedoch bei geringer methodischer Qualität (148). Auch Gastrografin, oral und *off-label* verabreicht, verkürzte die Dauer bis Flatus oder Stuhlgang, beeinflusste jedoch nicht den Kostaufbau oder die Krankenhausverweildauer.

Substanzen wie der selektive periphere μ-Opioidrezeptorantagonist Methylnaltrexon, der Betablocker Propranolol, der Serotonin-5-Hydroxytryptamin-4-Rezeptor-Agonist Prucaloprid, die Prokinetika Metoclopramid und Erythromycin, das Stimulans Simethicon sowie die phytotherapeutische japanische Formel Daikenchuto zeigten hingegen keine überzeugende oder konsistente Wirkung in den untersuchten Domänen.

Die Metaanalyse zeigte keine Unterschiede hinsichtlich relevanter Nebenwirkungen durch die unterschiedlichen perioperativen pharmakologischen Interventionen. Auch intravenös verabreichtes Lidocain erwies sich als sicher. Darüber hinaus fanden sich Hinweise auf eine Reduktion chirurgischer Komplikationen (> Grad 2 nach Clavien-Dindo (149)) sowie allgemein geringere Komplikationsraten durch die intravenöse Applikation von Lidocain (Anlage 9, Tabellen 1 und 2).

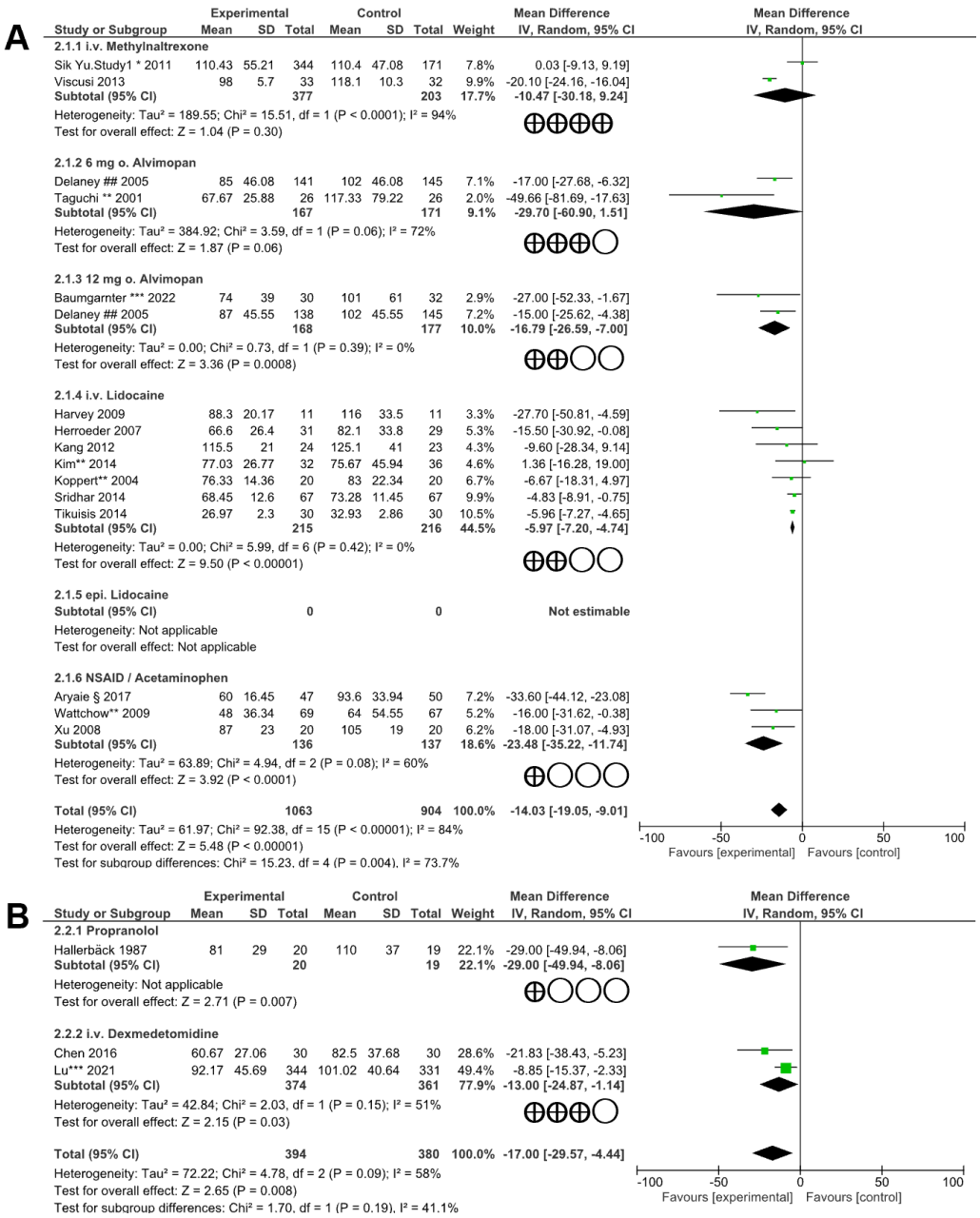


Abbildung 11: Effekte der verschiedenen Wirkstoffgruppen auf die Dauer bis zur ersten postoperativen Defäkation in Stunden, dargestellt in Forrest-Plots. Effekt der pharmakologischen Intervention auf die Dauer bis zum ersten Stuhlgang im Vergleich zur Kontrollgruppe. Die Ergebnisse werden als mittlere Differenz (*mean difference*) und 95% Konfidenzintervall (CI) angegeben. **A:** Periphere Opioidantagonisten und opioidsparende Analgetika. **B:** Reduktion der perioperativen sympathischen Hyperreaktion. ***** Daten wurden aus klinischen Studienregistern extrahiert. ****** Mittelwerte ± Standardabweichungen nach der Methode von Wan et al. abgeschätzt (150). ******* Daten direkt von den Studienautoren erhalten. ## Standardabweichungen der Mittelwerte durch den RevMan Calculator nach dem Cochrane Handbuch abgeschätzt. **§** Dauer bis zum ersten Flatus oder bis zur ersten Defäkation. i.v. = intravenös. NSAID = nicht-steroidale Antiphlogistika. o = per os. epi. = epidural. i.m. = intramuskulär. Das Vertrauen in die Evidenz wurde durch das *Cochrane Collaboration's risk-of-bias tool-2* und das GRADE-Verfahren (Grading of Recommendations, Assessment, Development and Evaluation; GRADE software GRADEpro GDT; www.gradepro.org) bestimmt: sehr niedrig ⊕, niedrig ⊕⊕, moderat ⊕⊕⊕, hoch ⊕⊕⊕⊕**.** Abbildung aus der Originalpublikation entnommen: M. Reichert, F. Willis, S. Post, M. Schneider, T. Vilz, M. Willis, A. Hecker: Pharmacologic prevention and therapy of postoperative paralytic ileus after gastrointestinal cancer surgery – systematic review and meta-analysis. International Journal of Surgery. 2024 Jul 1;110(7):4329-4341. doi: 10.1097/JS9.0000000000001393 (146).

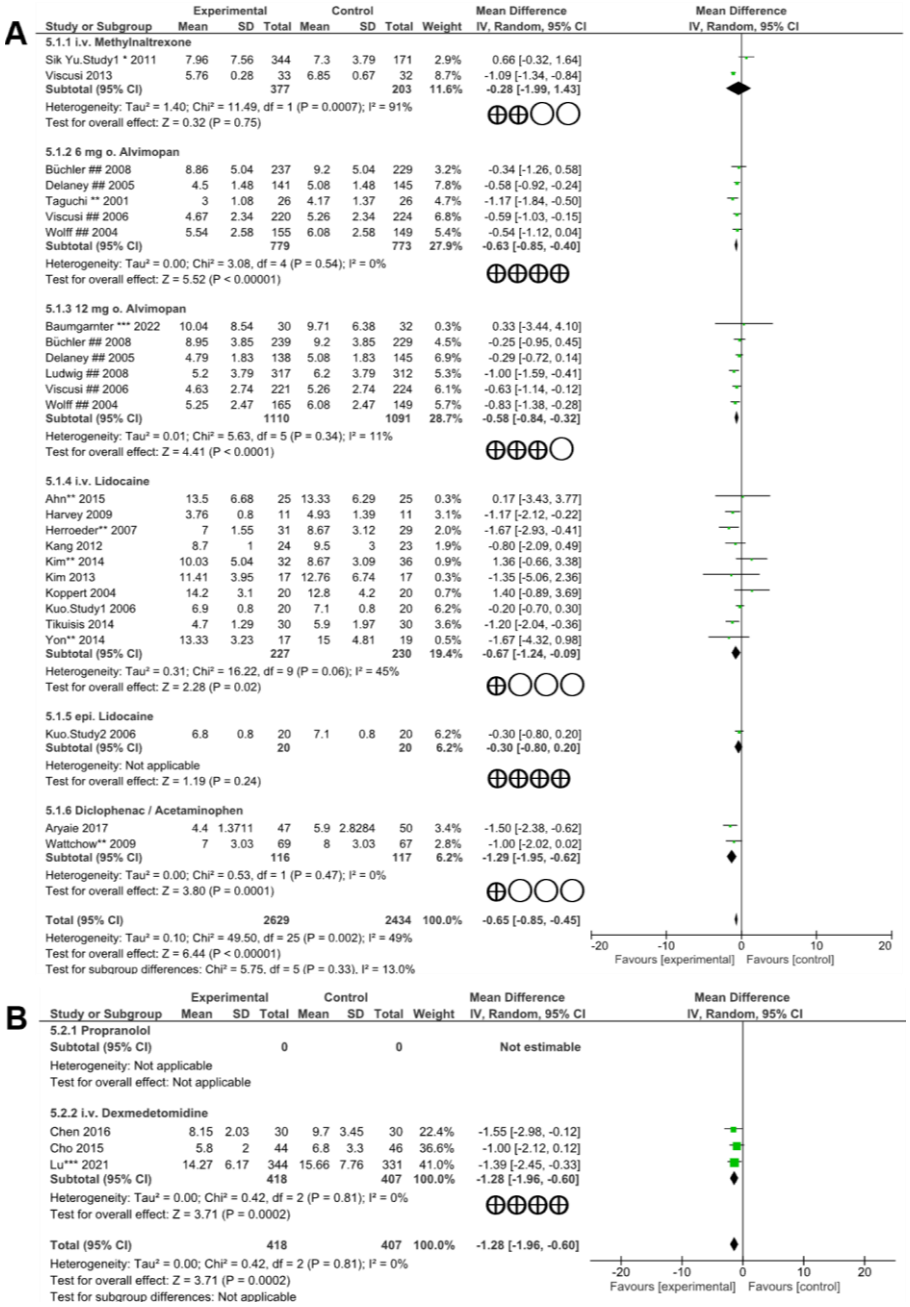


Abbildung 12: Effekte der verschiedenen Wirkstoffgruppen auf die Dauer des postoperativen Krankenhausaufenthaltes in Tagen, dargestellt in Forrest-Plots. Effekt der pharmakologischen Intervention auf die Dauer des postoperativen Krankenhausaufenthaltes im Vergleich zur Kontrollgruppe. Die Ergebnisse werden als mittlere Differenz (*mean difference*) und 95% Konfidenzintervall (CI) angegeben. **A:** Periphere Opioidantagonisten und opioidsparende Analgetika. **B:** Reduktion der perioperativen sympathischen Hyperreaktion. ***** Daten wurden aus klinischen Studienregistern extrahiert. ****** Mittelwerte ± Standardabweichungen nach der Methode von Wan et al. abgeschätzt (150). ******* Daten direkt von den Studienautoren erhalten. ## Standardabweichungen der Mittelwerte durch den RevMan Calculator nach dem Cochrane Handbuch abgeschätzt. i.v. = intravenös. o = per os. epi. = epidural. Das Vertrauen in die Evidenz wurde durch das *Cochrane Collaboration's risk-of-bias tool-2* und das GRADE-Verfahren (Grading of Recommendations, Assessment, Development and Evaluation; GRADE software GRADEpro GDT; www.gradepro.org) bestimmt: sehr niedrig ⊕, niedrig ⊕⊕, moderat ⊕⊕⊕, hoch ⊕⊕⊕⊕. Abbildung aus der Originalpublikation entnommen: M. Reichert, F. Willis, S. Post, M. Schneider, T. Vilz, M. Willis, A. Hecker: Pharmacologic prevention and therapy of postoperative paralytic ileus after gastrointestinal cancer surgery – systematic review and meta-analysis. International Journal of Surgery. 2024 Jul 1;110(7):4329-4341. doi: 10.1097/JS9.0000000000001393 (146).

Fazit: Postoperative gastrointestinale Motilitätsstörungen und der POI als deren Maximalform stellen relevante postoperative funktionelle Störungen und Komplikationen dar. Sie beeinträchtigen nicht nur das individuelle Wohlbefinden der Patienten, sondern führen auch zu verlängerten Krankenhausverweildauern, erhöhter Morbidität und erheblichen Kosten im Gesundheitssystem (92,96,99,151,152). An die Pathophysiologie adaptierte medikamentöse Interventionsstrategien insbesondere zur Prophylaxe des POI werden für die klinische Routine nach viszeralchirurgischen Resektionen dringend benötigt (22,98). Die derzeitige Evidenzlage für in Deutschland zugelassene Medikamente und in der klinischen Routine etablierte Substanzen ist jedoch unzureichend. Auch die positiven Effekte von intravenösem Lidocain sind nur eingeschränkt belastbar, da diese auf sekundären Endpunkten aus 12 kontrollierten Studien zur perioperativen Schmerztherapie an inhomogenen Patientenkollektiven basieren (153).

Ein vielversprechender neuer Ansatz ergibt sich aus der Gabe des Alpha-2-Rezeptoragonisten Dexmedetomidin. In der Metaanalyse von vier asiatischen Studien zeigte sich bei moderater bis hoher Evidenzqualität eine signifikante Verkürzung der Zeit bis zur ersten Defäkation, zum vollständigen Kostaufbau sowie eine Reduktion der Krankenhausverweildauer. Auch die Patientenzufriedenheit war verbessert. Allerdings weist die S3-Leitlinie „Perioperatives Management bei gastrointestinalen Tumoren (POMGAT)“ kritisch darauf hin, dass diese Studien an heterogenen asiatischen Patientenkollektiven durchgeführt wurden, weshalb direkte Rückschlüsse auf westeuropäische Populationen derzeit nicht möglich sind (99). Daraus ergibt sich ein dringender Forschungsbedarf: Eine valide, populationsspezifische Prüfung der Wirksamkeit und Sicherheit von Dexmedetomidin in der onkologischen Viszeralchirurgie ist notwendig (99). In der Metaanalyse konnten keine Sicherheitsbedenken hinsichtlich Dosierung oder perioperativer Anwendung von Dexmedetomidin identifiziert werden. Künftige Studien müssen den Nutzen dieser sympatholytisch, antiinflammatorisch und analgetisch wirksamen Substanz systematisch bei unterschiedlichen chirurgischen Indikationen und im Rahmen verschiedener perioperativer Behandlungskonzepte untersuchen (99).

4 Diskussion

Die onkologische Viszeralchirurgie umfasst hochkomplexe Eingriffe, die mit einem erheblichen Risiko für postoperative Komplikationen einhergehen. Angesichts der hohen Vulnerabilität der betroffenen Patientenkollektive ist die kontinuierliche Weiterentwicklung effizienter Präventions- und Behandlungsstrategien von zentraler Bedeutung. Diese beeinflussen nicht nur die postoperative Morbidität, sondern auch das langfristige onkologische *Outcome* maßgeblich.

Im vorangegangenen Abschnitt wurden die klinischen Ergebnisse zu onkologischen Eingriffen am oberen und unteren Gastrointestinaltrakt vorgestellt, mit Fokus auf häufige funktionelle Störungen, eingriffsassoziierte Komplikationen und deren pathophysiologische Zusammenhänge. Im Zentrum standen dabei:

- postoperative Oxygenierungsstörungen und Pneumonien im frühen Verlauf nach abdomino-thorakaler Ösophagusresektion,
- das organisierte Pleuraempyem und die transhiatale Hernie als relevante Spätkomplikationen in der Ösophaguschirurgie,
- gastrointestinale Motilitätsstörungen und der POI nach Eingriffen am unteren Gastrointestinaltrakt sowie
- die systematische Aufarbeitung der Evidenz auf Basis prospektiv-randomisierter Studien zur pharmakologischen Prävention und Therapie gastrointestinaler Motilitätsstörungen nach onkologischer Viszeralchirurgie.

Im Folgenden werden die wesentlichen Ergebnisse zu chirurgischen und pharmakologischen Ansätzen zur Prävention und Therapie dieser funktionellen Störungen und Komplikationen im Kontext der onkologischen Viszeralchirurgie eingehend diskutiert.

4.1 Oxygenierungsstörungen und Pneumonien nach abdomino-thorakaler Ösophagusresektion

Die Analysen zumeist sekundärer Endpunkte von prospektiven, teils multizentrisch durchgeführten Studien zeigten hohe Raten postoperativer pulmonaler Komplikationen nach Ösophagusresektion (19,34–36). Besonders infektiöse Komplikationen sowie postoperative Oxygenierungsstörungen gelten in diesem Zusammenhang als klinisch relevant. Allerdings bleibt der Sammelbegriff

„postoperative pulmonale Komplikation“ unspezifisch, da er heterogene Krankheitsbilder mit unterschiedlicher Ätiologie und Pathophysiologie zusammenfasst (19). Somit gingen in die postoperativen pulmonalen Komplikationsraten sowohl funktionelle Störungen, wie die respiratorische Insuffizienz und deren Maximalform, das *Acute Respiratory Distress Syndrome*, als auch spezifische Entitäten wie postoperative Pneumonien, bronchiale Schleimretentionen und pulmonale Embolien ein (19,37).

Vor diesem Hintergrund befassten sich die hier vorgestellten Arbeiten insbesondere mit der Pathophysiologie der postoperativen Pneumonie sowie dem Phänomen früh-postoperativer Oxygenierungsstörungen mit respiratorischer Insuffizienz nach abdomino-thorakaler Ösophagusresektion (28,102,106).

Die detaillierte Analyse perioperativer Blutgaswerte ergab, dass Oxygenierungsstörungen – definiert als PaO_2/FiO_2-Ratio < 300 mm Hg analog zur *Berlin classification* des *Acute Respiratory Distress Syndrome* (103) – ein häufiges funktionelles Problem im früh-postoperativen Verlauf nach Ösophagusresektionen darstellen (102). In den untersuchten Kohorten lagen die kumulativen Inzidenzen innerhalb der ersten 2 – 4 postoperativen Tage bei bis zu 80 % (28,102,106). Diese Oxygenierungsdefizite im früh-postoperativen Verlauf nach abdomino-thorakaler Ösophagusresektion konnten weder chirurgisch-technisch noch medikamentös beeinflusst werden (28,106).

Im Gegensatz dazu wurden postoperative Pneumonien nach abdomino-thorakaler Ösophagusresektion deutlich später diagnostiziert – im Median am 6. postoperativen Tag (102). Daher ist eine pathogenetische Trennung beider Entitäten erforderlich: Oxygenierungsstörungen als frühfunktionelle Störung und Pneumonien als spezifische Komplikation des späteren postoperativen Verlaufs. Lediglich die im weiteren postoperativen Verlauf beobachteten Oxygenierungsstörungen sowie die erhöhten Reintubations- und Tracheotomieraten lassen sich mit einer gesteigerten Pneumonierate in Verbindung bringen (28,102,106). Die prolongierte Intensivpflichtigkeit und verlängerte postoperative Krankenhausverweildauer in den Patientenkollektiven mit erhöhter Pneumonierate nach abdomino-thorakaler Ösophagusresektion (102,106) verdeutlichen die klinische Relevanz sowie die gesundheitsökonomische Belastung durch diese postoperative Komplikation (4,5,53–58,6,12,44,48–52). In einer trizentrischen europäischen Studie führten postoperative

infektiöse Komplikationen, u.a. die Pneumonie, nahezu zu einer Verdopplung der Behandlungskosten nach Ösophagusresektion (21).

In der Literatur wurden verschiedene allgemeine perioperative Risikofaktoren für postoperative pulmonale Komplikationen beschrieben (43,48,59–64). Der Einfluss der Ein-Lungenventilation sowie des chirurgischen Traumas an Thorax, Lunge und Pleura wurde in einer direkten Vergleichsstudie zwischen abdomino-thorakaler Ösophagusresektion und *major*-Lungenresektionen untersucht (102). Trotz ähnlicher Zugangstechniken (anterolaterale Thorakotomie) und längerer thorakaler Operationsdauer mit konsekutiv längerer Ein-Lungenventilation bei den Lungenresektionen zeigte sich eine höhere Inzidenz von postoperativen Oxygenierungsstörungen und Pneumonien nach Ösophagusresektion. Diese Beobachtungen stimmen mit den publizierten Inzidenzen überein: Pneumonieraten von bis zu 40 % und *Acute Respiratory Distress Syndrome* -Raten von bis zu 25 % nach Ösophagusresektion stehen etwa 10 % bzw. 5 % nach Lungenresektionen gegenüber (19,34,157,158,35,36,41,48,49,154–156). Diese Ergebnisse stellen die bisherige Annahme infrage, dass insbesondere der thorakale Teil der Operation maßgeblich die Entstehung pulmonaler Komplikationen nach Ösophagusresektion beeinflusst (43,59–63). Vielmehr muss hier differenziert werden: Oxygenierungsstörungen sind als eigenständiges funktionelles Problem im frühen Verlauf zu werten, Pneumonien hingegen als spezifische Komplikation des späteren postoperativen Verlaufes nach Ösophagusresektionen. Unsere Arbeit legt nahe, dass funktionelle, atemphysiologische und schmerzbedingte Aspekte, wie sie im Zusammenhang mit dem chirurgischen Zugangsweg über die Thorakotomie diskutiert werden können, sowie das intraoperative Trauma an Thorax und Lunge nicht die alleinigen Ursachen für die hohen Inzidenzen von Oxygenierungsstörungen und Pneumonien nach Ösophagusresektionen sind.

Ein möglicher pathophysiologischer Mechanismus betrifft die hoch-thorakale vagale Denervierung. Wie von Weijs et al. dargelegt (159), führt einerseits die Durchtrennung der Speiseröhre oberhalb der Vena azygos – als Standard während der Ösophagusresektion, andererseits zusätzlich die systematische mediastinale Lymphknotendissektion im Rahmen des onkologischen Eingriffs zu einer (sub-)totalen vagalen Denervierung von Lunge und Bronchialsystem (159,160). Diese kann die

Entstehung eines pulmonalen (neurogenen) Lungenödems begünstigen, die pulmonale *Clearance* stören und inflammatorische Prozesse verstärken (161–166).

Damit könnten früh-postoperative Oxygenierungsstörungen durch die Bildung eines neurogenen Ödems erklärt werden, während die gestörte bronchiale *Clearance* und die Dysregulation lokal inflammatorischer Prozesse durch die Vagotomie die Genese späterer Pneumonien beeinflussen könnten. Diese Hypothese wird durch die tierexperimentellen Studien von Janssen et al. gestützt, die den Einfluss des Nervus vagus auf das postoperative pulmonale *Outcome* betonen. (112). Sie diskutieren den Einfluss der Radikalität einer Vagotomie während der Ösophagusresektion auf das postoperative pulmonale *Outcome*. Janssen et al. interpretieren ihre Ergebnisse dahingehend, dass eine gezielte Stimulation des Nervus vagus als potenzielle Intervention in Betracht gezogen werden kann, um das Auftreten postoperativer pulmonaler Komplikationen nach einer Ösophagusresektion zu verringern (112).

In diesem Zusammenhang wurden vagus-schonende Operationstechniken des Ösophagus entwickelt, die zu niedrigeren Raten von postoperativen Pneumonien, des *Acute Respiratory Distress Syndrome* und auch zur Reduktion der verzögerten Magenpassage (*Delayed Gastric Emptying*, eine funktionelle Störung, die aufgrund eines Pylorospasmus infolge der trunkalen Schädigung des Nervus vagus entsteht) führten (159,160,167–173). Aufgrund der reduzierten Radikalität und des Fehlens einer systematischen mediastinalen Lymphknotendissektion haben diese Verfahren jedoch derzeit keinen Stellenwert in der onkologischen Chirurgie des Ösophagus (159,160). Direkte Nachweise vagaler Effekte auf postoperative pulmonale Komplikationen sollten in zukünftigen Studien weiter untersucht werden.

4.2 Chirurgisch-technische Aspekte in der Prävention der postoperativen Pneumonie nach abdomino-thorakaler Ösophagusresektion

Ein weiterer relevanter operationstechnischer Unterschied zwischen Lungen- und Ösophagusresektionen ist das zusätzliche abdominelle Operationsfeld bei der abdomino-thorakalen Ösophagusresektion. Während die *ROMIO* Studie (35) keinen Unterschied bei „infektiösen thorakalen Komplikationen“ feststellen konnte, zeigten frühere randomisiert-kontrollierte Studien eine deutliche Reduktion postoperativer pulmonaler Komplikationen durch den Einsatz minimalinvasiver Operationsverfahren im Rahmen der abdomino-thorakalen Ösophagusresektion (19,37). Zu

berücksichtigen ist jedoch, dass diese Komplikationen hier lediglich als sekundäre Endpunkte erfasst wurden. Dennoch deuten die Ergebnisse darauf hin, dass insbesondere die minimalinvasive Durchführung des abdominellen Teils die Inzidenz postoperativer pulmonaler Komplikationen senken kann (19,20,34,38,47). Der spezifische Einfluss auf postoperative Oxygenierungsstörungen und Pneumonien wurde in der vorliegenden Arbeit näher untersucht (28).

Die unter 3.1.2 dargestellte Analyse des konventionell-offenen versus hybrid-minimalinvasiven Zugangs bestätigt, dass früh-postoperative Oxygenierungsstörungen ein spezifisches Problem der Ösophagusresektion selbst darstellen – unabhängig vom Operationsverfahren. Diese Beobachtung stützt die zuvor diskutierte Hypothese eines vagalen Einflusses auf die pulmonale Homöostase (102,112,159). Oxygenierungsstörungen treten bereits im früh-postoperativen Verlauf auf, während Pneumonien in der Regel erst nach mehreren Tagen diagnostiziert werden. Auch die Ergebnisse dieser Arbeit unterstreichen die Notwendigkeit, beide Entitäten zunächst als voneinander unabhängige postoperative pulmonale Komplikationen zu betrachten (28).

Die vergleichbare Inzidenz postoperativer Pneumonien der laparoskopisch operierten Ösophagektomiepatienten mit jener nach Lungenresektion (siehe Kapitel 3.1.1 (102)) legt nahe, dass die hohe Pneumonierate nicht allein durch den Eingriff am thorakalen Ösophagus zurückzuführen ist. Vielmehr beeinflussen operationstechnische Aspekte wie die minimalinvasive Chirurgie des abdominellen Teils der Ösophagusresektion das Auftreten postoperativer Pneumonien zusätzlich. Nachdem der Einfluss des thorakalen chirurgischen Traumas bereits diskutiert wurde, betonen Brietz et al. und Berlth et al. die Bedeutung reduzierter postoperativer abdomineller Schmerzen durch minimalinvasive Operationstechniken und multimodale postoperative Analgesieverfahren. Sie berichten, dass diese Maßnahmen mit einer niedrigeren Rate pulmonaler Komplikationen nach Ösophagusresektion assoziiert sind (19,36,107). Auch Mariette et al. greifen diese Diskussion auf und führen die niedrigere pulmonale Komplikationsrate in ihrer prospektiv-randomisierten Studie zur konventionell-offenen versus hybrid-minimalinvasiven, laparoskopisch-assistierten abdomino-thorakalen Ösophagusresektion darauf zurück (19). Während diese Ergebnisse in der prospektiv-randomisierten *ROMIO* Studie nicht reproduziert werden konnten (35), bleibt in unserer retrospektiven Arbeit offen, inwieweit postoperative Schmerzen die

Atemphysiologie und insbesondere den Hustenstoß beeinträchtigen. Dies stellt eine Limitation unserer Studie dar.

Der konventionell-offene Zugang führt darüber hinaus zu einer verstärkten systemischen Inflammation. Dies spiegelte sich in unseren Daten in erhöhten früh-postoperativen Werten des C-reaktiven Proteins wider (28,102).

Eine ausgeprägte systemische Inflammation könnte die ohnehin vulnerable Lunge zusätzlich belasten, somit pulmonale Komplikationen begünstigen und zu der hohen Inzidenz postoperativer Pneumonien nach konventionell-offener, abdomino-thorakaler Ösophagusresektion beitragen. In diesem Zusammenhang konnten mehrere Arbeiten einen Zusammenhang zwischen der Höhe des postoperativen C-reaktiven Proteins und dem Auftreten pulmonaler Komplikationen nachweisen (62,63,109,112). Babic et al. betonten hierbei den Nutzen minimalinvasiver Verfahren und identifizierten das früh-postoperative systemische C-reaktive Protein als Prädiktor für postoperative, insbesondere pulmonale Komplikationen (105).

Zusammenfassend bestätigt unsere Arbeit, dass Oxygenierungsstörungen im früh-postoperativen Verlauf ein charakteristisches Problem nach Ösophagusresektion darstellen und in der perioperativen Medizin der Ösophaguschirurgie berücksichtigt werden sollten. Pneumonien hingegen sind als eigenständige Komplikation zu betrachten, deren Inzidenz durch minimalinvasive Techniken reduziert werden kann (19,34,36,37). Inwieweit moderne Entwicklungen – etwa die total-minimalinvasive oder robotisch-assistierte Ösophagusresektion – zu einer weiteren Reduktion in chirurgischem Trauma, traumaassoziierter Inflammation, Schmerzen und pulmonaler Komplikationen beitragen, ist Gegenstand aktueller klinischer Forschung (174).

4.3 Statine in der Genese der postoperativen Pneumonie nach abdomino-thorakaler Ösophagusresektion

Wie unter Punkt 4.2 diskutiert, könnten indirekte Effekte der durch Trauma induzierten systemischen Inflammation, insbesondere nach konventionell-offenen, abdomino-thorakalen Ösophagusresektionen, mitverantwortlich für das Auftreten früh-postoperativer pulmonaler Komplikationen sein (28,62,63,105,109–112).

Statine sind kompetitive Inhibitoren der 3-Hydroxy-3-Methylglutaryl-CoA-Reduktase und gerade in älteren Patientenkollektiven mit kardiovaskulären Komorbiditäten häufig

verabreichte Medikamente, deren Gabe zur Prophylaxe kardiovaskulärer Komplikationen perioperativ in der Regel fortgesetzt wird (113–115). Allerdings haben Statine das Potenzial, neben ihrer lipidsenkenden Wirkung, Inflammation und Immunfunktion zu beeinflussen (116,117). Diese Effekte sind vielfältig und deren Interferenz mit (lokalen) inflammatorischen Prozessen spielen eine Schlüsselrolle in der Plaquestabilisierung bei atherosklerotischen Patienten. Sie können jedoch auch die systemische Inflammation beeinflussen und somit eine Rolle in der Pathogenese postoperativer Komplikationen spielen (117–122). So konnte in der Studie von Krivoy et al. die systemische Konzentration des C-reaktiven Proteins durch die Applikation von hoch-dosiertem Atorvastatin nach aortokoronarer Bypasschirurgie gesenkt werden (119). Die randomisiert-kontrollierte Studie von Shyamsundar et al. zeigte, dass eine hochdosierte perioperative Simvastatinintervention zwar die Marker für systemische Inflammation reduzierte, jedoch keinen Einfluss auf die Rate postoperativer Oxygenierungsstörungen hatte (175). Pneumonien als pulmonale Komplikationen wurden hier nicht dezidiert und gesondert erfasst. Inwieweit die chronische und perioperativ fortgesetzte Statintherapie einen Einfluss auf systemische Inflammation, postoperative Oxygenierungsstörungen und insbesondere das Auftreten postoperativer Pneumonien hat, wurde an dem Patientenkollektiv nach abdomino-thorakaler Ösophagusresektion untersucht (106).

Zusammenfassend zeigte sich in unserer Analyse erneut die hohe kumulative Inzidenz postoperativer Oxygenierungsstörungen, gemessen anhand einer PaO_2/FiO_2-Ratio < 300 mm Hg, was die spezifische Anfälligkeit der Lunge für diese früh-postoperativen funktionellen respiratorischen Störungen nach abdomino-thorakalen Ösophagusresektionen unterstreicht (28,102). Auffällig war jedoch, dass die Inzidenz postoperativer Pneumonien im Patientenkollektiv, welches mit Statinen behandelt wurde, höher als bei statinnaiven Patienten war. Da die Patientencharakteristika mittels *Propensity score matching* ausgeglichen waren, bieten Korrelationsanalysen einen möglichen Erklärungsansatz hierfür: dort fehlte unter Statinmedikation der pneumoniebedingte Effekt auf die systemische Inflammation, gemessen am C-reaktiven Protein im Serum.

Wie Koushki et al. in ihrer Übersichtsarbeit ausführlich darlegen, interferieren Statine mit der Expression von Adhäsionsmolekülen und der Rekrutierung von Immunzellen (117). Zudem reduzieren Statine die Produktion proinflammatorischer Zytokine und

Akute-Phase-Proteine, darunter die Vertreter der lokalen Inflammation Interleukin-1, Interleukin-6, Tumornekrosefaktor-α und das C-reaktive Protein als Vertreter der systemischen Inflammation (117,120). Diese antiinflammatorischen Eigenschaften sind für die Plaquestabilisierung und die konsekutive Prophylaxe thrombembolischer Ereignisse verantwortlich, beeinflussen jedoch auch systemisch die angeborene Immunität (117,118,120–122).

Obwohl diese immunmodulatorischen Eigenschaften vorteilhaft bei überschießenden und fehlgeleiteten Immunreaktionen, wie chronischen Entzündungserkrankungen, Autoimmunerkrankungen oder der Transplantatabstoßung sein können (121,176,177), könnte eine solche antiinflammatorische Wirkung die Abwehr bakterieller Infektionen schwächen (117). Die komplexen und teils widersprüchlichen Effekte von Statinen auf das Immunsystem, insbesondere in Bezug auf perioperative Inflammation und deren Assoziation mit postoperativen Komplikationen, sind nicht vollständig verstanden. Die Ergebnisse unserer Studie weisen jedoch auf eine gestörte Immunreaktion hin, die schließlich zur erhöhten Inzidenz postoperativer Pneumonien beiträgt.

Ob Patienten nach abdomino-thorakaler Ösophagusresektion von einer vorübergehenden Unterbrechung ihrer Statinmedikation profitieren, muss in prospektiven Studien weiter untersucht werden. Dabei sollten die individuellen Indikationen und das individuelle Risiko für thrombembolische Ereignisse sorgfältig abgewogen werden, da der perioperative Nutzen einer fortgesetzten Statintherapie in Bezug auf die Reduktion kardiovaskulärer Morbidität bereits belegt ist (113–115).

4.4 Die video-assistierte Thorakoskopie zur Therapie des organisierten Pleuraempyems

Obwohl die minimalinvasive Thoraxchirurgie mit der video-assistierten Thorakoskopie bereits in den 1990er Jahren etabliert und insbesondere im anglo-amerikanischen Raum in der thoraxchirurgischen Onkologie kontinuierlich weiterentwickelt wurde (123,178,179), blieb ihre Verbreitung in Deutschland zunächst begrenzt, wie eine eigene deutschlandweite Umfrage aus den Jahren 2014/15 zeigte (124). In der Behandlung des nicht-kleinzelligen Bronchialkarzinoms, insbesondere im Frühstadium, konnte die Thorakoskopie vergleichbare onkologische bei gleichzeitig verbesserten postoperativen funktionellen Ergebnissen und geringerer Morbidität im Vergleich zur konventionell-offenen Chirurgie erzielen (123,156,157,180).

Im Gegensatz dazu lagen für benigne, insbesondere entzündliche Erkrankungen, deutlich weniger Erfahrungen mit der Thorakoskopie vor (124). Gründe hierfür sind die technisch anspruchsvolleren Bedingungen, die bei entzündlichen Prozessen durch Adhäsionen, Neovaskularisationen, vulnerablem Lungenparenchym und hilären Lymphadenopathien entstehen (125,181,182). Eine Analyse unseres eigenen Patientenkollektivs bestätigte diese höhere Komplexität, zeigte jedoch, dass anatomische Resektionen auch bei benignen entzündlichen pulmonalen Erkrankungen minimalinvasiv sicher durchgeführt werden können (125). Allerdings waren diese Eingriffe mit längerer Operationszeit, prolongierter Drainagedauer sowie einer verlängerten intensiv- und gesamtstationären Verweildauer im Vergleich zu anatomischen Lungenresektionen wegen nicht-kleinzelligen Bronchialkarzinomen im Frühstadium assoziiert (125).

Operationen wegen eines Pleuraempyems, insbesondere im organisierten Stadium III, sind häufig durch unübersichtliche anatomische Verhältnisse geprägt und erfordern ein hohes Maß an chirurgischer Erfahrung. Die aktuelle Evidenzlage zur Operationsmodalität (konventionell-offen versus minimalinvasiv) bei Pleuraempyemen bleibt weiterhin begrenzt und basiert überwiegend auf retrospektiven Fallserien aus spezialisierten Zentren (71,183–185). Diese zeigten, dass die Thorakoskopie bei gemischten Patientenkollektiven mit Stadium II und III Pleuraempyemen sicher durchführbar ist (183–185). Unsere eigene Arbeit, die ausschließlich streng selektionierte Patienten mit organisiertem Pleuraempyem (Stadium III) und Notwendigkeit zur vollständigen Dekortikation einer fibrösen Pleuraschwarte einschloss, bestätigte die Effektivität, Sicherheit und ökonomischen Vorteile der minimalinvasiven chirurgischen Therapie (74,183–185).

Ähnlich berichteten Ricciardi et al. in ihrem Kollektiv von 719 Patienten mit einem Stadium II/III Pleuraempyem über eine hohe Erfolgsrate, kürzere Hospitalisationsdauer und geringere Morbidität nach minimalinvasiver Chirurgie (183). Chambers et al. wiesen in einem systematischen Review auf weitere postoperative Vorteile wie reduzierte Schmerzen und geringere Luftfistelraten hin, welche schließlich in reduzierter Hospitalisierung resultierten (185). Diese Ergebnisse unterstreichen, dass die minimalinvasive Thoraxchirurgie auch abseits klassischer onkologischer Indikationen sicher sowie effektiv einsetzbar ist und postoperative Vorteile im Vergleich zur konventionell-offenen Chirurgie bietet (180).

Mit zunehmender Erfahrung in der minimalinvasiven Thoraxchirurgie in den vergangenen Jahren befürworten Autoren wie Steen et al. die video-assistierte Thorakoskopie frühzeitig in der Therapie des Pleuraempyems einzusetzen und sie auch bei organisiertem Pleuraempyem im Stadium III als chirurgische Therapieoption zumindest in Erwägung zu ziehen (184,186). Unsere Studie zeigt, dass komplexe Eingriffe, wie die video-assistiert thorakoskopische Dekortikation, mit zunehmender Expertise routinemäßig und sicher im klinischen Alltag durchgeführt werden können (73,123,125).

Die Lernkurve für minimalinvasive Dekortikationen bei organisierten Pleuraempyemen ähnelt der anderer komplexer thoraxchirurgischer Operationen, etwa der thorakoskopischen Lobektomie beim Bronchialkarzinom, bei der 30–50 Eingriffe notwendig sind, um eine Plateauphase in der Effizienz zu erreichen (124,178,187,188). Operationen bei chronischen entzündlichen Erkrankungen sind zum Teil technisch schwieriger (125), dennoch zeigte sich in unserem Kollektiv für die video-assistierte Dekortikation eine Verkürzung der Operationszeit nach etwa 40 Eingriffen, ohne weitere Reduktion hiernach (73).

Ein Pleuraempyem kann nach thorakalen Eingriffen wie der Ösophagusresektion als sekundäre Komplikation infolge von Pneumonien oder Anastomoseninsuffizienzen auftreten (7,21,65–72). Wie unsere Ergebnisse belegen, ist die minimalinvasive chirurgische Therapie auch im organisierten Stadium III bei entsprechender Erfahrung sicher möglich (73,74). In diesen speziellen Fällen muss bei der chirurgischen Dekortikation und dem pleuralen Debridement besonders auf die Schonung der intestinalen Rekonstruktion im hinteren Mediastinum geachtet werden, um eine Gefährdung des Magenkonduits zu vermeiden.

4.5 Die transhiatale Hernie im Kontext der abdomino-thorakalen Ösophagusresektion

Die aktuelle Literatur beschreibt eine zunehmende Inzidenz transhiataler Hernien nach chirurgischen Eingriffen am oberen Gastrointestinaltrakt, insbesondere nach abdomino-thorakaler Ösophagusresektion, bei der die Integrität des Hiatus oesophagei kompromittiert wird (26,78,87–89,79–86). Wie in Abbildung 7 dargestellt, ist die chirurgische Behandlung dieser komplexen Komplikation selbst für erfahrene Zentren herausfordernd. Mehrere Faktoren tragen zum Auftreten dieser klinisch

bedeutsamen und potenziell gefährlichen Spätkomplikation bei (26,78,87,189–192,79–86):

- zunehmender Einsatz neoadjuvanter Therapiekonzepte mit konsekutiver Beeinträchtigung der Wundheilung,
- verbesserte Überlebensraten und längere Nachsorgezeiträume,
- bildgebungsbasierte Nachsorgeprogramme,
- Einsatz minimalinvasiver Operationstechniken.

Die genannten Risikofaktoren und die daraus abgeleiteten Schlussfolgerungen beruhen auf Beobachtungen aus retrospektiven, teilweise multizentrischen Kohortenstudien (26,78,87,189–192,79–86).

Durch Fortschritte in der onkologischen Therapie mit multimodalen Behandlungskonzepten für das Ösophaguskarzinom sowie das Adenokarzinom des ösophagogastralen Übergangs konnten die *Response*raten sowie die lokale und systemische Tumorkontrolle verbessert werden, was das Langzeitüberleben der Patienten deutlich steigert (193–195). Gleichzeitig führt die verlängerte Überlebenszeit zu einer höheren Lebenszeitinzidenz transhiataler Hernien nach Ösophagusresektion (27,79–81,85–87), sodass durch den vermehrten Einsatz bildgebender Verfahren in der Tumornachsorge zunehmend auch asymptomatische oder oligosymptomatische Hernien detektiert werden (27,82,86,189).

Wie bereits detailliert dargelegt, bietet die minimalinvasive Chirurgie am oberen Gastrointestinaltrakt wesentliche postoperative Vorteile wie geringere pulmonale Komplikationsraten, reduzierte postoperative Schmerzen und eine beschleunigte Rekonvaleszenz (19,28,34,36,37,107). Allerdings führt das reduzierte chirurgische Trauma zu vergleichsweise geringeren (intraabdominellen) Adhäsionen, wodurch der transhiatale Prolaps von abdominellen Organen langfristig begünstigt wird (26,78,87,88,79–86). Die Leber und Verwachsungen an der Klammernaht des Schlauchmagenkonduits sichern den Hiatus nach rechts-thorakal, was die Präferenz des Organprolapses in den linken Hemithorax erklärt (27).

Unsere Analyse verdeutlicht, dass chirurgisch-technische Aspekte und ein komplikationsreicher Verlauf nach den komplexen Primäreingriffen das *Outcome* der Patienten nicht nur unmittelbar postoperativ, sondern auch im Langzeitverlauf beeinflussen können. Die Genese einer transhiatalen Hernierung kann durch eine

unzureichende Rekonstruktion des Hiatus oesophagei während der Primäroperation begünstigt werden (196). Inwieweit der Hiatus insbesondere nach Resektionen der Zwerchfellschenkel im Rahmen von Ösophagusresektionen verschlossen werden sollte, bleibt unklar; Empfehlungen zur Hernienprävention basieren hauptsächlich auf zentrumseigenen Erfahrungen (26,80,199–201,81,82,84,85,190,191,197,198). Bei der Rekonstruktion des Hiatus muss sorgfältig zwischen einer ausreichenden Sicherung gegen Herniation und dem Erhalt der Nahrungspassage sowie der Perfusion des Magenkonduits abgewogen werden (80,81,203–205,83–85,89,198–200,202). Auch sind mögliche Konduiterosionen durch eingebrachtes Netzmaterial gefürchtete Komplikationen (80,81,205,83,84,89,198,199,202–204).

Wie das systematische Literaturreview der überwiegend retrospektiven, monozentrischen publizierten Fallserien zeigte, stehen verschiedene Techniken zum Hiatushernienverschluss nach Resektionen am oberen Gastrointestinaltrakt zur Verfügung (Anlage 6, Tabelle 5). Der transabdominelle primäre Nahtverschluss über eine Cruroplastie mit oder ohne Netzaugmentation sind sinnvolle Verschlussmöglichkeiten der hiatalen Bruchlücke. Im Falle großer Defekte kann die Netzinterposition zum Bruchlückenverschluss eine Option sein. Zusätzlich kann eine Pexie des Kolon transversums vor dem Hiatus durchgeführt werden, um den Verschluss mechanisch zu stabilisieren.

Aufgrund der potenziellen Inkarzerationsgefahr der prolabierten Organe und der möglichen respiratorischen sowie kardialen Symptome stellt die transhiatale Hernie eine bedeutende Komplikation nach Ösophagusresektion dar (26,84,89). Die Symptomatik ist jedoch variabel und oft unspezifisch, was die Diagnosestellung erschwert (27). Trotz der klinischen Relevanz bleiben viele Fragen offen. Diese betreffen einerseits effektive präventive Maßnahmen während der Primäroperation zur Wiederherstellung der Integrität des Hiatus oesophagei und andererseits die Indikationsstellung zur operativen Versorgung transhiataler Hernien bei asymptomatischen oder oligosymptomatischen Patienten.

Die Indikation zur zügigen Revision einer transhiatalen Hernie im frühen postoperativen Verlauf ist eindeutig, da diese Patienten häufig eine kritische Symptomatik aufweisen (26,79,80,82,85,206). Im längeren postoperativen Verlauf wird die Indikation zur operativen Versorgung einer transhiatalen Hernie in der Literatur hingegen differenzierter diskutiert, insbesondere im Hinblick auf die Symptomatik der

Patienten und die potenzielle Inkarzerationsgefahr (81,84,190,206). Unsere Arbeit unterstreicht die Notwendigkeit einer operativen Intervention bei transhiatalen Hernien nach Eingriffen am oberen Gastrointestinaltrakt, abhängig vom klinischen Erscheinungsbild und den Befunden der Schnittbildgebung. Bei Nachweis pulmonaler, kardialer oder gastrointestinaler Symptome und/oder bildgebender Hinweise auf eine Inkarzeration ist eine rasche operative Versorgung erforderlich, wie es auch zahlreiche andere Publikationen nahelegen (26,81,84). Inwieweit Patienten mit oligo- oder asymptomatischen transhiatalen Hernien von einer Operation oder *watchful waiting* Konzepten profitieren, hängt maßgeblich von der Lebenszeitinzidenz schwerwiegender Komplikationen, wie Inkarzeration oder der Entwicklung gravierender kardialer und/oder respiratorischer Symptome ab. Hier besteht ein dringender Bedarf an weiteren Studien in größeren, prospektiv beobachteten Patientenkollektiven im onkologischen Langzeitverlauf nach Ösophagusresektion.

4.6 Prolongierte gastrointestinale Motilitätsstörungen nach onkologischer Viszeralchirurgie

Gastrointestinale Motilitätsstörungen stellen zunächst eine kurzfristige, physiologische Reaktion auf das chirurgische Trauma nach onkologischer Viszeralchirurgie dar (22,141,207). Der Übergang von einer vorübergehenden Störung hin zum pathologischen Zustand einer prolongierten Paralyse ist jedoch fließend. Der POI erhöht schließlich die Morbidität der Patienten sowie die Behandlungskosten erheblich (92,96,151,152). Trotz der klinischen Relevanz ist seine Definition in der aktuellen Literatur heterogen, unspezifisch und häufig subjektiv (91,92,140,208–210), was die Vergleichbarkeit von Studien erschwert und die Evidenzlage für Prävention und Therapie schwächt.

Die Inzidenz prolongierter gastrointestinaler Motilitätsstörungen nach onkologischer Viszeralchirurgie beträgt etwa 30 % (22–24,90–93). Neben Einschränkungen des postoperativen Wohlbefindens führen prolongierte Motilitätsstörungen zu erhöhter Morbidität, verlängerter Intensiv- und Krankenhausverweildauer sowie damit verbundener Zunahme der Pflegebedürftigkeit (12–16,129). Obwohl die Letalität, die allein durch eine prolongierte gastrointestinale Motilitätsstörung verursacht wird, nicht exakt ermittelt werden kann, wurde eine verdoppelte Inzidenz schwerer postoperativer Komplikationen in Patientenkohorten mit POI beobachtet (96). Bei Patienten nach

kolorektalen Resektionen stieg demnach die Letalitätsrate bei Auftreten eines POI von 4 % auf bis zu 28 %, wenn zusätzliche schwerwiegende Komplikationen wie Aspirationspneumonie und Sepsis auftraten (96).

Epidemiologische Daten der *Global Burden of Disease* Studie von 2016 belegen zudem die weltweite Bedeutung des paralytischen Ileus und der Darmobstruktion mit über 25 Millionen Todesfällen und einem Verlust von 757 Millionen Lebensjahren (131). Aufgrund altersassoziierter Risikofaktoren wurde bereits in den vergangenen Jahren eine Zunahme der Inzidenz des POI beobachtet. In einer alternden Gesellschaft ist weiterhin mit einer steigenden Inzidenz, einer daraus resultierenden höheren Morbidität sowie einer zunehmenden ökonomischen Belastung des Gesundheitswesens durch den POI zu rechnen (97,129–132). Durch den gesteigerten Bedarf an Ressourcen aufgrund von postoperativer Morbidität, Intensivbehandlung und verlängerter Krankenhausverweildauer sowie durch langfristige Gesundheitsbeeinträchtigungen und Pflegebedürftigkeit wurde kalkuliert, dass der POI die Gesamtbehandlungskosten um mindestens 57 % nach elektiver kolorektaler Chirurgie erhöht (151,152,211). Allein in den USA wurde die wirtschaftliche Belastung durch den POI auf bis zu 12 Milliarden Dollar pro Jahr geschätzt (130,212).

Neben den postoperativen klinischen und gesundheitsökonomischen Folgen verschlechtern postoperative Komplikationen im Allgemeinen und der POI im Besonderen zusätzlich die langfristigen onkologischen Ergebnisse (12–16,129). Prolongierte gastrointestinale Motilitätsstörungen führen zu höheren Raten schwerer Komplikationen, verlängerter Hospitalisierung sowie verzögerter Genesung (151,152,211) und beeinträchtigen oder verhindern dadurch die zeitgerechte Einleitung adjuvanter Therapien, die für das Langzeitüberleben bei gastrointestinalen Tumorerkrankungen entscheidend sind (11,13–16).

Diese Daten verdeutlichen die klinische, onkologische und ökonomische Bedeutung effektiver Strategien zur Prävention prolongierter gastrointestinaler Motilitätsstörungen und Therapie des POI.

4.6.1 Chirurgisch-technische Aspekte in der Prävention prolongierter gastrointestinaler Motilitätsstörungen

Wie bereits einleitend beschrieben, tragen verschiedene perioperative Faktoren pathophysiologisch zur Entstehung prolongierter gastrointestinaler Motilitätsstörungen und des POI bei (22,97–99). Im Rahmen der dieser Habilitationsschrift zugrunde liegenden Arbeiten wurden chirurgisch technische Maßnahmen zur Reduktion der Manipulation am Gastrointestinaltrakt und des chirurgischen Traumas untersucht (133,134).

Resektionen am rechten Hemikolon gehen im Vergleich zu linksseitigen Eingriffen mit einem höheren Risiko für postoperative Motilitätsstörungen und prolongierte gastrointestinale Paralyse einher (135,136,139). Zwar sind die genauen Ursachen hierfür noch nicht abschließend geklärt, doch zeigte unsere Analyse von 117 überwiegend onkologischen Rechtshemikolektomien, dass eine zunehmende Minimalinvasivität die Dauer der postoperativen Paralyse bis zum ersten Stuhlgang verkürzen und die Krankenhausverweildauer reduzieren konnte. Zudem korrelierte die Anwendung minimalinvasiver Operationstechniken mit einer geringeren postoperativen systemischen Inflammation, die als ein zentraler pathophysiologischer Mechanismus des POI gilt (22). Unsere Ergebnisse werden durch die aktuelle Literatur gestützt, die eine verkürzte Rehabilitation und eine geringere Hospitalisationsdauer für die total-robotische Operationstechnik bei Wahrung onkologischer Standards im Rahmen der Rechtshemikolektomie beschreibt (213–218).

Inwieweit das reduzierte chirurgische Trauma mit einer verminderten sympathischen Aktivierung, reduzierten postoperativen Schmerzen und einem geringerem Opioidbedarf zur Prävention des POI beiträgt, bleibt in unserer retrospektiven Fallserie offen. Ergebnisse aus prospektiv-randomisierten Studien stützen jedoch die Hypothese, dass total-minimalinvasive Verfahren im Vergleich zur extrakorporalen Anastomose mit geringeren postoperativen Schmerzen, reduziertem Opioidverbrauch und einer niedrigeren Inzidenz prolongierter gastrointestinaler Motilitätsstörungen nach minimalinvasiver Rechtshemikolektomie assoziiert sind (219,220).

Ergänzend wurde der Einfluss des protektiven Ileostomas als chirurgisch-technischer Risikofaktor für die Entwicklung eines POI nach onkologischen Rektumresektionen untersucht. Das doppelläufige Ileostoma hat eine etablierte Indikation zur Vermeidung septischer Komplikationen und zur Reduktion der Reoperationsrate bei

Anastomoseninsuffizienzen nach Rektumresektionen (142–144). Zudem wird ein protektiver Effekt auf die Anastomosenheilung diskutiert (142,145). Allerdings sind mit der Anlage eines Ileostomas auch spezifische Komplikationen verbunden, darunter persistierende Flüssigkeits- und Elektrolytverluste sowie die Entstehung von Hernien (221,222). Durch strenge Patientenselektion und Ausschluss von potenziellen Störfaktoren konnte unsere Analyse zeigen, dass das protektive Ileostoma die Inzidenz des POI nach onkologischer Rektumresektion signifikant erhöht (134). Ähnliche Assoziationen wurden auch in anderen retrospektiven Studien festgestellt (93,223), wobei Limitationen in der Heterogenität der Definitionen des POI und im retrospektiven Studiendesign bestehen (93,140,208,209,223). Eine umfassende Metaanalyse von Du et al., die unter anderem zwei randomisiert-kontrollierte Studien einschloss, bestätigte zudem höhere Raten des POI nach Ileostomie im Vergleich zur Kolostomie im Rahmen der Rektumresektion (221,224).

Zusammenfassend kann konstatiert werden, dass das protektive Ileostoma zur multifaktoriellen Entstehung des POI beiträgt, wobei die exakten pathophysiologischen Mechanismen weiterhin nicht gänzlich aufgeklärt sind. Erfahrungen aus rechtsseitigen Hemikolektomien, bei denen eine höhere Inzidenz postoperativer gastrointestinaler Motilitätsstörungen im Vergleich zu linksseitigen Resektionen beobachtet wurde (133–139), legen nahe, dass Manipulationen im Bereich des terminalen Ileums eine Rolle spielen könnten (134). Vor diesem Hintergrund sollten chirurgische Manipulationen am Gastrointestinaltrakt möglichst minimiert, kolorektale Resektionen bevorzugt minimalinvasiv durchgeführt und die Indikation zur Anlage eines protektiven Ileostomas im Rahmen der onkologischen Rektumresektion individuell und risikoadaptiert abgewogen werden.

4.6.2 Pharmakologische Prävention und Therapie prolongierter gastrointestinaler Motilitätsstörungen

Neben chirurgisch-technischen Maßnahmen in der Prävention des POI, insbesondere der minimalinvasiven Chirurgie mit Vorteilen wie reduziertem Trauma, geringerer postoperativer Inflammation und verminderten Schmerzen, existiert eine Vielzahl prospektiv, randomisiert-kontrollierter Studien, die sich mit der präventiven oder therapeutischen pharmakologischen Intervention postoperativer gastrointestinaler Motilitätsstörungen beschäftigen (146,225).

Durch unsere systematische Literaturrecherche wurden 55 randomisierte Studien extrahiert und in die Metaanalyse eingeschlossen, bei denen – im Gegensatz zu dem älteren, umfangreichen *Cochrane Review* von Traut et al. (225) – pharmakologische Interventionen bei Patienten getestet wurden, die einer gastrointestinalen Tumorresektion unterzogen wurden (PROSPERO 2022 CRD42022351799).

Die einzelnen Substanzen wurden nach ihrem Wirkmechanismus in Gruppen eingeteilt und systematisch hinsichtlich ihrer Effektivität in der Prävention oder Therapie des POI sowie in Bezug auf Nebenwirkungen und Medikamentensicherheit analysiert (146). Dadurch konnte die Effektivität spezifischer, an die Pathophysiologie des POI adaptierter Wirkmechanismen beurteilt werden.

Wie die Analyse der Endpunkte zeigt, unterschieden sich die verwendeten Definitionskriterien und Endpunkte des POI zwischen den Studien erheblich. Da nicht in allen Studien alle klinisch relevanten Domänen des POI – wie Zeit bis zum ersten Flatus, Stuhlgang, orale Nahrungstoleranz und Krankenhausverweildauer – systematisch erfasst wurden, war ein vollständiger Vergleich der Wirksamkeit aller untersuchten Substanzen über alle Domänen hinweg nicht möglich. Diese Heterogenität stellt eine wesentliche Limitation der aktuellen Evidenzlage aus den randomisierten Studien dar.

Während frühere Arbeiten meist einzelne Wirkstoffe oder Substanzgruppen isoliert analysierten (24,153,226), verfolgte unser Ansatz eine an pathophysiologischen Mechanismen orientierte Systematik: Durch die Gruppierung pharmakologischer Interventionen nach ihrem gezielten Eingreifen in zentrale pathogenetische Kaskaden werden Rückschlüsse auf die Effektivität ganzer Wirkmechanismen ermöglicht. Dieser umfassendere Ansatz erlaubt eine differenzierte Evidenzsynthese und schafft die Grundlage für praxisnahe Empfehlungen zur Prophylaxe und Therapie des POI (146).

Im Zusammenhang mit minimalinvasiven Operationstechniken wurden in Kapitel 4.6.1 bereits die positiven Effekte einer reduzierten Inflammation, geringerer postoperativer Schmerzen und eines reduzierten Bedarfs an opioidbasierter Analgesie diskutiert. Analog dazu erwiesen sich pharmakologische Konzepte, die gezielt die periphere Opioidwirkung, die postoperative Inflammation oder die sympathetische Hyperreaktion reduzieren, als besonders wirksam in der Prophylaxe des POI sowie der Förderung der postoperativen Rekonvaleszenz. Für in Deutschland zugelassene Medikamente bedeutet dies, dass opioidsparende Analgesieverfahren, wie der perioperative Einsatz

von systemisch verabreichtem Lidocain, perioperativem Dexmedetomidin sowie Laxantien sicher und sinnvoll in die multimodale perioperative Medizin integriert werden können. Jedoch müssen die bisherigen, in unserer Metaanalyse zusammengefassten, positiven Ergebnisse aus sekundären Endpunkten kontrollierter Studien zur opioidsparenden postoperativen Analgesie mittels perioperativ verabreichtem Lidocain im Licht der rezent publizierten *ALLEGRO* Studie kritisch bewertet werden: in dieser großen randomisierten Multizenterstudie konnte bei Patienten, die sich einer elektiven minimalinvasiven kolo-rektalen Resektion unterzogen, kein Unterschied zwischen intravenösem Lidocain und Placebo hinsichtlich des primären Endpunkts GI-3 (kombiniert orale Nahrungstoleranz und erster Flatus oder Stuhlgang) innerhalb von 72 Stunden sowie weiterer sekundärer Endpunkte der postoperativen (gastrointestinalen) Rekonvaleszenz festgestellt werden (227). Allerdings erfolgte die medikamentöse Intervention nur unter kontinuierlicher kardialer Überwachung und war auf maximal 12 Stunden postoperativ begrenzt.

Teile dieser umfangreichen Arbeit wurden in die evidenzbasierten Empfehlungen der 2023 publizierten deutschen S3-Leitlinie *Perioperatives Management bei gastrointestinalen Tumoren (POMGAT)* aufgenommen (99,147). Besonders hervorgehoben wurde hier der perioperative Einsatz von Dexmedetomidin, einem Alpha-2-Rezeptoragonisten mit sympatholytischen, analgetischen und antiinflammatorischen Eigenschaften (99,146,226,228–232). Dexmedetomidin adressiert damit multiple pathophysiologische Aspekte postoperativer gastrointestinaler Motilitätsstörungen und des POI (22,98).

Obwohl unsere Metaanalyse die Sicherheit der perioperativen Anwendung von Dexmedetomidin als Adjuvans zur Allgemeinnarkose bestätigt, bestanden Bedenken hinsichtlich potenzieller kardiopulmonaler Nebenwirkungen wie Bradykardien, Hypoxämien und einer erhöhten Langzeitletalität (99). Diese resultieren aus Studien zur Langzeitsedierung kritisch kranker Intensivpatienten sowie zur opioidfreien Anästhesie, etwa von Shehabi et al. und Beloeil et al. (233–235). Allerdings ist zu berücksichtigen, dass Dexmedetomidin in diesen Studien in deutlich höheren (kumulativen) Dosierungen, über längere Zeiträume und bei anderen Patientenkollektiven eingesetzt wurde. Wie auch in der Forschungsfrage der *POMGAT* Leitlinie betont wird, erscheinen die bisherigen Ergebnisse von Dexmedetomidin aus

kontrollierten Studien zur Prophylaxe des POI vielversprechend (99). Eine direkte Übertragbarkeit dieser Studienergebnisse, die überwiegend an asiatischen Patientenkollektiven gewonnen wurden, auf westeuropäische Populationen ist jedoch nicht möglich, sodass weitere randomisierte Studien erforderlich sind, um Sicherheit und Wirksamkeit von Dexmedetomidin in unseren Patientenkollektiven fundiert bewerten zu können (99).

5 Zusammenfassung

Operative Strategien und perioperative Medizin bilden zentrale Säulen einer modernen multimodalen onkologischen Therapie. Im Fokus dieser Arbeit stehen onkologische Radikalität, perioperative Sicherheit und minimalinvasive Konzepte. Besonders im Kontext minimalinvasiver chirurgischer Verfahren konnte gezeigt werden, dass die Inzidenz eingriffsspezifischer funktioneller Störungen und Komplikationen – wie Pneumonien nach Ösophagusresektion oder gastrointestinale Paralyse nach kolorektaler Resektion – deutlich gesenkt werden kann. Pathophysiologisch spielen dabei das chirurgische Trauma, die perioperative (systemische) Inflammation und die Kontrolle postoperativer Schmerzen eine zentrale Rolle. Inwieweit moderne minimalinvasive und robotisch-assistierte Operationstechniken in der onkologischen Viszeralchirurgie die Häufigkeit dieser relevanten funktionellen Störungen und Komplikationen künftig weiter reduzieren, bleibt Gegenstand aktueller klinischer Forschung. Ergänzend hierzu wurde die Rolle medikamentöser Strategien in der Prävention und Therapie funktioneller Störungen und eingriffsspezifischer Komplikationen untersucht. Während Statine, die mit inflammatorischen Prozessen interferieren, keinen protektiven Effekt auf postoperative Oxygenierungsstörungen zeigten und die Inzidenz von Pneumonien nach Ösophagusresektion sogar erhöhten, lieferte der Alpha-2-Rezeptoragonist Dexmedetomidin – mit sympatholytischen, antiinflammatorischen und analgetischen Eigenschaften – vielversprechende Ergebnisse in der Prävention gastrointestinaler Motilitätsstörungen bei Patienten nach onkologischer Viszeralchirurgie in randomisiert-kontrollierten Studien. Darüber hinaus erwiesen sich pharmakologische Ansätze zur Reduktion peripherer Opioidwirkungen sowie der Einsatz von Laxantien im Rahmen multimodaler perioperativer Konzepte als vorteilhaft für die postoperative (gastrointestinale) Rekonvaleszenz.

Zusammenfassend zeigen chirurgisch-technische und pharmakologische Strategien zur multimodalen, opioidsparenden perioperativen Medizin sowie zur Reduktion der postoperativen systemischen Inflammation großes Potenzial, funktionelle Störungen und eingriffsspezifische Komplikationen nach onkologischen Eingriffen am Gastrointestinaltrakt wirksam zu verringern. Diese Ansätze sollten künftig weiter präzisiert und durch hochwertige klinische Studien validiert werden, um das kurz- und langfristige *Outcome* von Patienten nach onkologischer Viszeralchirurgie stetig zu verbessern.

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8 Abkürzungen

ASA	American Society of Anesthesiologists´ classification of physical health
ATS	American Thoracic Society
BMI	Body mass index
CI	Konfidenzintervall
COS	Conventional open surgery; konventionell-offene Rechtshemikolektomie
CRP	C-reaktives Protein
ECA	Extracorporal anastomosis; robotisch-assistierte Rechtshemikolektomie mit extrakorporaler Anlage einer (konventionell-handgenähten) Ileotransversostomie
epi.	Epidural
GI-2	*Composite outcome* aus Dauer bis zum ersten Stuhlgang und Dauer bis zur oralen Nahrungstoleranz
GI-3	*Composite outcome* aus Dauer bis zum ersten Flatus oder Stuhlgang und Dauer bis zur oralen Nahrungstoleranz
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
i.m.	Intramuskulär
i.v.	Intravenös
ICA	Intracorporal anastomosis; total robotische Rechtshemikolektomie mit intrakorporaler Anlage einer (robotisch-handgenähten) Ileotransversostomie
NSAID	Nicht-steroidale Antiphlogistika
o.	Per os

PaO_2/FiO_2	Verhältnis des arteriellen Sauerstoffpartialdrucks zur inspiratorischen Sauerstofffraktion, *Horovitz-Index*
POD	Postoperativer Tag
POI	Postoperativer (paralytischer) Ileus
POMGAT	S3-Leitlinie „Perioperatives Management bei gastrointestinalen Tumoren“
rSp	Korrelationskoeffizient aus Spearman´s Rangkorrelation
Sp	Spearman´s Rangkorrelation
VATS	V*ideo-assisted thoracoscopic surgery*

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11 Anlagen

11.1 Anlage 1

M. Reichert, M. Schistek, F. Uhle, C. Koch, J. Bodner, M. Hecker, R. Hörbelt, V. Grau, W. Padberg, MA. Weigand, A. Hecker: **Ivor Lewis esophagectomy patients are particularly vulnerable to respiratory impairment - a comparison to major lung resection.** *Scientific Reports*. 2019 Aug 14;9(1):11856. doi: 10.1038/s41598-019-48234-w.

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Ivor Lewis esophagectomy patients are particularly vulnerable to respiratory impairment - a comparison to major lung resection

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Pulmonary complications and a poor clinical outcome are common in response to transthoracic esophagectomy, but their etiology is not well understood. Clinical observation suggests that patients undergoing pulmonary resection, a surgical intervention with similarities to the thoracic part of esophagectomy, fare much better, but this has not been investigated in detail. A retrospective single-center analysis of 181 consecutive patients after right-sided thoracotomy for either Ivor Lewis esophagectomy (n = 83) or major pulmonary resection (n = 98) was performed. An oxygenation index <300 mm Hg was used to indicate respiratory impairment. When starting surgery, respiratory impairment was seen more frequently in patients undergoing major pulmonary resection compared to esophagectomy patients (p = 0.009). On postoperative days one to ten, however, esophagectomy caused higher rates of respiratory impairment (p < 0.05) resulting in a higher cumulative incidence of postoperative respiratory impairment for patients after esophagectomy (p < 0.001). Accordingly, esophagectomy patients were characterized by longer ventilation times (p < 0.0001), intensive care unit and total postoperative hospital stays (both p < 0.0001). In conclusion, the postoperative clinical course including respiratory impairment after Ivor Lewis esophagectomy is significantly worse than that after major pulmonary resection. A detailed investigation of the underlying causes is required to improve the outcome of esophagectomy.

Esophageal cancer is one of the leading cancer diagnoses with a high cancer-related mortality and a rapidly growing incidence over the past years world-wide[1]. The only curative treatment option in earlier, limited stages (Union internationale contre le cancer (UICC) – stages I and II) as well as in selected cases with a locally advanced disease (UICC stage III) is the subtotal resection of the esophagus, frequently following neoadjuvant and accompanied by adjuvant oncologic treatment modalities[1]. Nevertheless, the surgical therapy is challenging for the patients since it is associated with high rates of postoperative complications and morbidity. Overall, up to 60% of the patients experience any type of postoperative complication and the mortality rate of up to 14% after transthoracic esophagectomy for esophageal cancer is unacceptably high[2,3]. Especially pulmonary complications including atelectasis, pneumonia, pulmonary embolism, respiratory failure and acute respiratory distress syndrome (ARDS) are overrepresented after esophagectomy with an incidence ranging between 20% and 40% and consequently

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Variables	ILE	MPR	p-value
Male gender	68 (81.9%)	65 (66.3%)	0.019
Age [years]	63.0 (41–80)	62.0 (26–82)	0.631
BMI [kg/m²]	24.2 (15.6–41.3)	26.5 (15.9–39.0)	0.041
ASA			0.431
1	6 (7.2%)	9 (9.2%)	
2	40 (48.2%)	37 (37.8%)	
3	33 (39.8%)	49 (50.0%)	
4	4 (4.8%)	3 (3.1%)	
Chronic lung disease	16 (19.3%)	35 (35.7%)	0.020
Chronic kidney disease	6 (7.2%)	10 (10.2%)	0.602
Induction therapy			
Chemo	42 (50.6%)	8 (8.2%)	<0.0001
Radio	20 (24.1%)	2 (2.0%)	<0.0001
Indication			0.007
Malignancy	82 (98.8%)	87 (88.8%)	
Primary Tumor	82 (100%)	81 (93.1%)	
Metastasis	0	5 (5.7%)	
Lymphoma	0	1 (1.1%)	
Benign disease	1 (1.2%)	11 (11.2%)	

Table 1. Patient characteristics. ILE = Ivor Lewis esophagectomy. MPR = major pulmonary resection. BMI = body mass index. ASA = American society of Anesthesiologist's classification of physical health score.

contribute to postoperative morbidity and even mortality[3–8]. After transthoracic esophagectomy, pneumonia, respiratory failure and ARDS rates accounted for 22%, 6% and 1.5%, respectively, in a large patient cohort reported by Zingg *et al.*[3]. As published recently, pulmonary complications after esophagectomy negatively impact not only on short-term clinical but also on long-term oncological patient outcome[3,9,10]. Pulmonary complications increase the time spent on the intensive care unit (ICU) and in the hospital, thus raising the overall health care costs after esophageal resections[3,9,11,12]. As it has been discussed by Molena *et al.*, development of postoperative respiratory complications after esophagectomy is a multifactorial process[9]. Different hypotheses have been published on the pathophysiology of exceptional high pulmonary complication rates after esophagectomy with all kinds of consecutive respiratory impairment[9,13,14].

However, these factors should resemble the pulmonary complication rates after conventional (open) major pulmonary resection (MPR). Similar to Ivor Lewis transthoracic esophagectomy (ILE), thoracotomy is used to access the thoracic cavity and single-lung ventilation is performed during MPR. Pulmonary complication rates after conventional open MPR are, however, considerably lower than those after esophagectomy[15,16].

We conducted a single-center analysis to compare patients after right-sided thoracotomy for ILE with those after MPR, primarily focusing on the pulmonary outcome.

Results

Patients. Patient characteristics of both groups were similar regarding physical status, indicated by the 'American society of Anesthesiologist's classification of physical health' (ASA) score, however, patients from the MPR-group suffered more frequently from chronic lung diseases (19.3% vs. 35.7%, $p = 0.020$). In contrast to the MPR-group, patients awaiting ILE underwent more frequently induction therapy of any kind ($p < 0.0001$). Indication for ILE was mainly primary malignancy (carcinoma of the esophagus in 98.8%). MPR was performed for malignancy in 88.8% (predominantly primary lung cancer) and benign diseases in 11.2% of the patients (lung volume reduction for emphysema (n = 1), inflammatory destroyed pulmonary lobe (n = 2), aspergilloma or tuberculoma (n = 4), and sequestration (n = 2), Table 1).

Surgery. The rate of intraoperative lymph node dissection was higher in the ILE-group (98.8% vs. 88.8%, $p = 0.007$), as was the total duration of the surgical procedure compared with patients from the MPR-group (306 (177–635) min vs. 180.5 (78–356) min, $p < 0.0001$) – although the rates of extended surgical procedures did not differ between both groups. Of note, the duration of the thoracic part of the two-stage ILE procedure was significantly shorter compared to the total duration of surgery in the MPR-group (142 (48–423) min vs. 180.5 (78–356) min, $p < 0.0001$, Table 2).

Inflammation. Blood leukocytes on POD 0–2 were higher in patients of the MPR-group compared to the ILE-group. Later on POD 8-9, there was a tendency towards slightly higher leukocyte counts in ILE patients ($p < 0.1$). No differences in serum C-reactive protein (CRP) values were observed on POD 0-1. CRP levels tended higher after ILE compared to MPR on POD 2 and POD 5 ($p < 0.1$), whereas on POD 3-4 and POD 6-10 these differences between both patient groups were statistically significant (Table 3).

Variables	ILE	MPR	p-value
Main procedure	Laparoscopy: 31 (37.3%) Laparotomy: 52 (62.7%) Gastric tube: 79 (95.2%) Colon interposition: 4 (4.8%)	Upper lobectomy: 45 (45.9%) Middle lobectomy: 5 (5.1%) Lower lobectomy: 33 (33.7%) Upper bilobectomy: 7 (7.1%) Lower bilobectomy: 8 (8.2%)	
Lymph node dissection	82 (98.8%)	87 (88.8%)	0.007
Relevant abdomino/thoracic extended procedures (additional to main procedure)	n = 17 (20.5%) Major lung resection: 3[#] Minor lung resection: 5[#] Lung decortication: 1 Minor liver resection: 3 Multivisceral resection: 1 Jejunum catheter: 3 Cholezystectomy: 1 Colon resection: 1 Others: 3[§]	n = 26 (26.5%) Sleeve resections, bronchoplasty: 11 Sublobar resection: 12[&] Pleurectomy: 3 Decortication: 2 Chest wall resection: 1	0.3836
Duration of the thoracic part of Ivor Lewis procedure [min]	142 (48–423)[$]		<0.0001
Total duration of surgery [min]	306 (177–635)	180.5 (78–356)	<0.0001
Blood loss [ml]	600 (50–4800)*	500 (50–3000)	0.221
Peridural anesthesia	57 (68.7%)	49 (50%)	0.015

Table 2. Procedure characteristics. ILE = Ivor Lewis esophagectomy. MPR = major pulmonary resection. [#]Including 3 lobectomies and 5 wedge resections. [&]Including 3 segmentectomies and 9 wedge resections. [§]Including appendectomy, resection of a soft tissue tumor and hemithyroidectomy. [$]Not available retrospectively in 9 patients. *Not available retrospectively in 2 patients.

Respiratory impairment. The cumulative duration of perioperative mechanical ventilation (invasively and non-invasively) and cumulative postoperative stay on the ICU was longer in patients after ILE (both $p < 0.0001$). Accordingly, the rates of postoperative ventilation ($p < 0.05$ at POD 1-10), re-intubation ($p = 0.0058$) (independently from re-do surgery making re-intubation necessary), therapy with nitric oxide ($p = 0.095$), and of tracheotomy ($p = 0.013$) were higher in patients of the ILE-group indicating higher rates of severe respiratory impairment (Tables 4 and 5). Even higher rates of pneumonia defined by the 'Uniform Pneumonia Score'[17] (39.8% vs. 20.4%, $p = 0.0053$) and aspiration (10.8% vs. 1%, $p = 0.006$) were found in patients from the ILE-group (Table 5). These factors lead to higher rates of mechanical ventilation on POD 1-10 as well as longer cumulative duration of mechanical ventilation in patients after ILE compared to MPR (ILE-group: 17.93 (5–2280) h vs. MPR-group: 9.16 (3–701) h, $p < 0.0001$). Markedly, there were no differences in the rates of early postoperative mechanical ventilation (POD 0) as well as initial extubation success (during initial 12 h after surgery) between both groups (Tables 4, 5). The same holds true for intra- and early postoperative OI, where no obvious differences were found between both groups. However, since the rate of reduced OI (<300 mm Hg) was significantly higher initially in patients awaiting right-sided MPR (ILE: 17 patients vs. MPR: 38 patients, $p = 0.009$), the rates of reduced OI vice versa were significantly higher on all POD 1-10 in patients after ILE (overall 59 patients (71.1%) from the ILE-group and 35 patients (35.7%) from the MPR-group suffered from an OI < 300 mm Hg at least once during the observational period on POD 1-10, $p < 0.0001$, Table 5). Nevertheless, there was no difference concerning the clinical diagnosis of ARDS between both groups (ILE: 3 patients vs. MPR: 1 patient, $p = 0.334$).

As revealed by the Spearman's Rho test, a correlation between total duration of surgery and early postoperative OI (POD 1-3), as well as cumulative duration of perioperative mechanical ventilation can be excluded (Table 6).

Kaplan-Meier analysis was performed to compare the cumulative incidences of postoperative pneumonia as well as postoperative respiratory impairment (OI < 300 mm Hg) over time. Pneumonia was more prevalent after ILE during POD 0–30 compared to right-sided thoracotomy for MPR ($p = 0.042$). This difference occurs beyond POD 10 (Fig. 1). In line with the differences observed in postoperative rates of reduced OI between both groups (Table 5), the cumulative incidence of respiratory impairment (OI < 300 mm Hg) differed significantly among the groups ($p < 0.001$) from POD 3 onwards (Fig. 2).

Discussion

Respiratory complications are one major clinical problem in thoracic surgery, leading to unacceptably high rates of morbidity, disability and mortality[3–9,11]. Several studies have shown extraordinary high rates of pulmonary complications, especially of up to 40% pneumonia and up to 25% ARDS after ILE[7,12,18,19]. Perioperative atelectasis due to single-lung ventilation, postoperative pain after thoracotomy impairing respiratory physiology, manipulation and injury of the thoracic cavity and the lung during surgery, as well as potential laryngeal nerve injury caused by extended lymph node dissection or cervical esophageal preparation with an increased postoperative risk for aspiration were suggested to contribute to high pulmonary complication rates[9,13,14]. Except the obviously higher rate of aspiration due to delayed gastric emptying and a loss of the functional esophago-gastric junction in ILE-patients (10.8%, $p = 0.006$), these factors apply not only to ILE, but also to MPR with conventional thoracotomy. However, the previously reported pulmonary complication rates, especially for pneumonia (up to 6%[20–22]) and ARDS (approximately 4% in the early phase after anatomic lung resection[20,23]) are considerably lower after MPR compared with ILE, although – as shown in the present study – the rate of preexisting chronic pulmonary diseases is obviously higher in MPR patients.

Variables	ILE		MPR		
Leukocytes [giga/l]		**missing values**		**missing values**	**p-value**
POD 0 (on arrival at ICU)	8.6 (2.9–29.6)	1	13.1 (0.9–31.9)	3	<0.0001
POD 1	10.1 (3.6–71.0)	1	12.3 (4.2–30.3)	0	0.0001
POD 2	11.3 (1.8–24.6)	0	12.2 (3.8–114.0)	33	0.0488
POD 3	9.7 (1.9–34.1)	8	10.3 (3.6–21.3)	34	0.271
POD 4	8.3 (1.0–106.0)	14*	9.8 (2.5–22.9)	42	0.3052
POD 5	7.8 (3.9–21.5)	22*	9.5 (2.5–25.0)	52*	0.135
POD 6	9.3 (3.6–26.10)	26#	10.0 (3.8–21.5)	53*	0.992
POD 7	10.2 (2.9–29.0)	24#	10.4 (3.4–74.0)	47*	0.6968
POD 8	11.3 (3.4–33.3)	30#	9.7 (3.6–28.5)	61*	0.0927
POD 9	12.5 (4.5–49.7)	30#	10.8 (3.4–31.5)	68#	0.0747
POD 10	13.6 (4.2–38.7)	38#	11.65 (5.7–45.7)	74#	0.4021
C-reactive protein [mg/l]		**missing values**		**missing values**	
POD 0 (on arrival at ICU)	6.35 (0–80.1)	3	6.6 (0–238.7)	9	0.592
POD 1	92.79 (31.6–226.2)	1	87.25 (15.4–300.2)	0	0.24
POD 2	211.3 (82.7–359.4)	0	194.5 (46.8–390.7)	33	0.098
POD 3	219.2 (68.5–403.9)	8	166.7 (31.5–453.6)	34	0.001
POD 4	196.2 (30.1–410.0)	14*	153.4 (37.1–348.7)	43	0.019
POD 5	158.8 (37.1–539.1)	22*	109.1 (33.7–413.0)	52*	0.0776
POD 6	137.7 (24.1–423.2)	25#	74.4 (17.6–338.2)	53*	0.004
POD 7	147.7 (12.1–445.1)	24#	66.2 (3.9–408.8)	48*	0.0002
POD 8	152.8 (12.0–491.9)	31#	85.37 (22.9–270.2)	61*	0.002
POD 9	182.1 (19.0–446.9)	32#	73.1 (8.5–385.1)	68#	0.0008
POD 10	184.3 (4.9–387.3)	38#	97.8 (20.4–239.4)	74#	0.0111

Table 3. Perioperative leukocyte counts and C-reactive protein levels. ILE = Ivor Lewis esophagectomy. MPR = major pulmonary resection. *Including 1 death. #Including 2 deaths.

In the present study, the complication rates after ILE correspond to those of previously reported patient cohorts[7]. Especially the rate of postoperative respiratory insufficiency leading to re-intubation of ILE patients is similar or even lower than those reported in the recent literature[7,24]. Nevertheless, pneumonia was assessed retrospectively through the "Uniform Pneumonia Score"[17]. The revised scoring system by Weijs *et al.*[17] was herein applied in a slightly modified version with regard to the current "International Guidelines for the Management of Severe Sepsis and Septic Shock 2012"[25] by using a body temperature $\geq$38.0 °C or $\leq$36.0 °C. This resulted in a high sensitivity of the scoring system for retrospective assessment of pneumonia in our patient cohort and a slightly higher rate of postoperative pneumonia of ILE and MPR patients (39.8% and 20.4%, respectively) than those reported in the recent literature[7,15,16,24].

In addition to the clinical diagnoses of pneumonia and ARDS, the Horovitz OI (PaO_2/FiO_2) below 300 mm Hg was used as a sensitive indicator of respiratory impairment, irrespective of the underlying pulmonary disease[26]. Of note, the clinical diagnosis of ARDS (acute onset, bilateral pulmonary infiltrates, reduced OI[26]) was made in only a minority of our patients with an OI < 300 mm Hg. To the best of our knowledge, we are the first to describe an extraordinarily high cumulative incidence of respiratory impairment during POD 1–10 after ILE that is significantly higher than that of MPR patients ($p < 0.001$). In the light of a higher preoperative prevalence of preexisting chronic lung disease in MLR patients that is reflected by the first intraoperative OI value, the poor lung function of ILE patients on POD 1 and thereafter is even more striking. However, in both surgical approaches (ILE or MPR) the access to the thoracic cavity was the same standardized right-sided anterolateral thoracotomy and all patients underwent single-lung ventilation as well as most patients underwent disease-specific mediastinal lymph node dissection.

Development of postoperative respiratory complications after ILE and MPR is certainly a multifactorial process[9]: surgical tissue damage leads to an extensive inflammatory response, which may increase pulmonary endothelial permeability. Vascular leakage was previously suspected to contribute to acute lung injury and respiratory impairment after esophagectomy[27–30]. This would explain the early postoperative onset of ARDS after esophagectomy reported by Howells *et al.*[12]. However, pulmonary vascular leakage was not directly investigated in our study.

Among the various factors that can lead to respiratory impairment, transfusion-related acute lung injury is not expected to be responsible for the differences between ILE and MPR, because transfusion rates did not differ. The duration of single-lung ventilation was reported as a significant contributing factor for postoperative ARDS in the study by Tandon *et al.*[21], while it did not seem to contribute to postoperative ARDS in the study by Morita *et al.*[31]. In our study, the total surgical procedure of ILE lasted longer than that of MPR. However, in contrast to the results of Tandon *et al.*[21], the duration of the thoracic part of ILE was significantly shorter compared to MPR in our study ($p < 0.0001$). Hence, we can also exclude that differences in the duration of single-lung ventilation are responsible for the differences in respiratory impairment between ILE and MPR.

Variables	ILE	MPR	p-value
Total postoperative hospital stay [d][$]	16 (9–68)	10 (6–87)	<0.0001
Cumulative postoperative stay on ICU [d]	4.64 (1–140)	0.95 (0–66)	<0.0001
Cumulative perioperative mechanical ventilation [h]	17.93 (5–2280)	9.16 (3–701)	<0.0001
Rate of postoperative ventilation[&]			
POD 0 (on arrival at ICU)	66 (79.5%)	66 (67.3%)	0.093
Invasive	64	66	
Non-invasive	2	0	
POD 1	45 (54.2%)	23 (23.5%)	<0.0001
Invasive	41	22	
Non-invasive	4	1	
POD 2	17 (20.5%)	7 (7.1%)	0.0142
Invasive	9	5	
Non-invasive	8	2	
POD 3	19 (22.9%)	8 (8.2%)	0.0065
Invasive	13	7	
Non-invasive	6	1	
POD 4	20 (24.4%)	9 (9.2%)	0.0077
Invasive	16	7	
Non-invasive	4	2	
POD 5	19 (23.2%)	6 (6.2%)	0.0019
Invasive	16	4	
Non-invasive	3	2	
POD 6	20 (24.7%)	7 (7.2%)	0.0015
Invasive	18	5	
Non-invasive	2	2	
POD 7	24 (29.6%)	7 (7.2%)	0.0001
Invasive	20	5	
Non-invasive	4	2	
POD 8	22 (27.2%)	6 (6.2%)	0.0001
Invasive	20	5	
Non-invasive	2	1	
POD 9	19 (23.5%)	4 (4.2%)	0.0002
Invasive	18	3	
Non-invasive	1	1	
POD 10	21 (25.9%)	4 (4.2%)	<0.0001
Invasive	17	3	
Non-invasive	4	1	
Blood transfusion*	18 (21.7%)	18 (18.4%)	0.582
Postoperative catecholamine therapy[§,&]			
POD 0	29 (34.9%)	17 (17.3%)	0.0098
POD 1	30 (36.1%)	14 (14.3%)	0.0009
POD 2	21 (25.3%)	6 (6.1%)	0.0003
POD 3	22 (26.5%)	8 (8.2%)	0.0012
POD 4	17 (20.7%)	7 (7.1%)	0.0086
POD 5	14 (17.1%)	4 (4.1%)	0.0053
POD 6	13 (16.0%)	5 (5.2%)	0.0232
POD 7	17 (21.0%)	4 (4.1%)	0.0007
POD 8	15 (18.5%)	4 (4.1%)	0.0027
POD 9	16 (19.8%)	2 (2.1%)	<0.0001
POD 10	17 (21.0%)	1 (1.0%)	<0.0001
Return to ICU	16 (19.3%)	12 (12.2%)	0.22
Re-do (revision) surgery	12 (14.5%)	6 (6.1%)	0.0811
Bronchial stump insufficiency after MPR/Anastomotic complications after ILE[ß]	13 (15.7%)	1 (1.0%)	
Organ Failure			
Liver	4 (4.8%)	1 (1.0%)	0.181
Kidney	5 (6.0%)	5 (5.2%)	1

Continued

Variables	ILE	MPR	p-value
Dialysis	5 (6.0%)	1 (1.0%)	0.095
In-hospital mortality[§]	11 (13.3%)	5 (5.1%)	0.07

Table 4. Perioperative results. ILE = Ivor Lewis esophagectomy. MPR = major pulmonary resection. POD = postoperative day. ICU = intensive care unit. $ excluding patients, who suffered from in-hospital mortality. *Within the first 24 hours after surgery, including blood transfusions, thrombocyte concentrates and fresh frozen plasma. [§]Including arterenol and/or dobutamine. & Patients who died during POD 0–10 (n = 4, two in each group) were excluded from further analysis after their death. ß anastomotic complications, i.e. insufficiency and/or gastric tube necrosis requiring therapy (i.e. stent, endo-vacuum therapy or re-do surgery). § even exceeding 30-day mortality. The 30-day in-hospital mortality was 8.4% in the ILE-group and 5.1% in the MPR-group.

Also, the extent of tissue damage and the resulting release of pro-inflammatory damage-associated molecular patterns have to be considered. ILE is expected to generally cause more tissue damage compared to MPR, because, in addition to the surgical manipulations in the thorax, extensive surgery is performed in the abdominal cavity. However, MPR patients had higher leukocyte counts until POD 2, which might be explained by preoperative inflammation in this patient group. Further, CRP levels were similar on POD 1 and POD 2 and started to be higher in ILE patients as late as POD 3. Hence, the increased CRP levels in ILE patients are probably not directly related to differences in the extent or localization of surgery-associated trauma. However, we cannot fully exclude differences in trauma-associated inflammation, because unfortunately no pro-calcitonin or cytokine data were available in this retrospective study. Inflammatory markers should be carefully investigated in future prospective studies. In addition to trauma-associated inflammation caused by a more extensive surgery, the second operation site (laparotomy or laparoscopy) in ILE procedures could also contribute to pulmonary complications by increasing postoperative pain. For trans-thoracic procedures it is well known that minimally-invasive approaches result in reduced postoperative pain and lower pulmonary complication rates compared to conventional open thoracic surgery[16,31–33]. This has not only been shown for totally but also for hybrid minimally-invasive ILE procedures[34–37]. Briez *et al.* found that a hybrid minimally-invasive approach with laparoscopy for ILE procedures as well as pain management with epidural anesthesia are independent factors predicting against major postoperative pulmonary complications[35]. Also in a recently published well-controlled multicenter trial, Mariette *et al.* discussed reduced pain in response to their laparoscopic, hybrid minimally-invasive approach to ILE as the reason for a decreased rate of major pulmonary complications[36]. Further studies are needed to clarify this potential protective effect, especially with regard to perioperative oxygenation indexes.

The rate of neoadjuvant treatment clearly differed between both groups. The role of multimodal therapeutic approaches and especially induction therapies prior to ILE as a cause for an increased rate of postoperative pulmonary complications is still disputed. Reynolds *et al.* reported a higher rate of postoperative septic and pulmonary complications in patients, who underwent esophagectomy after induction therapy[38], whereas Zingg *et al.* did not identify neoadjuvant treatment as a risk factor for postoperative pulmonary complications in their large patient cohort[3]. If alterations of the lung parenchyma including radiation pneumonitis and lung fibrosis, which can be observed in patients after irradiation of thoracic carcinomas[39], play a role in the pathogenesis of perioperative respiratory impairment and postoperative pulmonary complications remains to be elucidated. However, an increased inflammatory status in ILE patients following radio-chemo induction should be reflected in an early elevation of leukocyte counts and CRP levels, which was obviously not the case.

Furthermore, the role of anastomotic complications in the development of respiratory impairment remains unclear. In this patient cohort only two patients of the ILE-group presented respiratory insufficiency (OI < 300 mm Hg) synchronously with the clinical diagnosis of anastomotic leakage requiring treatment. The other ILE patients either developed no respiratory impairment postoperatively (n = 1), presented a reduced OI (<300 mm Hg) metachronously (≥three days before anastomotic leakage, n = 4 patients) or were excluded from the Kaplan Meier analysis for a cumulative incidence of reduced postoperative OI due to re-do surgery. If the OI is sufficient to predict postoperative (pulmonary) complications in abdomino-thoracic surgery had – to the best of our knowledge – never been investigated before and should be evaluated in lager patient cohorts.

The surgical access route by thoracotomy is, however, notoriously a cause for postoperative pain, impairing postoperative breathing and respiratory physiology[9]. Previous reports have shown not only a reduction in pulmonary complications and pneumonia rates in patients undergoing (hybrid) minimally-invasive approaches for ILE or MPR as discussed above but also for abdominal-only transhiatal approaches for distal esophagectomy[3,13,14,32,33,40–43]. Especially after transhiatal esophagectomy, the rate of pulmonary complications is lower compared with the transthoracic approach[12–14,40]. However, the extent of mediastinal lymph node dissection and the location regarding the thoracic height of intrathoracic resection margins of the esophagus itself is technically limited by transhiatal esophageal surgery.

Nevertheless, the localization of esophageal resection margins with regard to the mediastinal level after transthoracic or transhiatal esophagectomy could explain the reported high rate of respiratory impairment in ILE patients as well as the observed major differences between both groups: some kind of neurogenic pulmonary damage has to be considered and discussed as a possible cause for the high rate of respiratory impairment after ILE. A dysbalance in the autonomic nervous system with a sympathetic hyperreaction is well-known in patients after brain damage, including the medulla and hypothalamic injury leading to neurogenic derived pulmonary edema formation by pulmonary vasculature constriction and pressure overload[44–46]. Vice versa, it had been shown in animal experiments that formation of pulmonary edema was either caused by bilateral (cervical) vagotomy[44] or

Variables	ILE		MPR		p-value
Pneumonia rate	33 (39.8%)		20 (20.4%)		0.0053
Pneumonia - diagnosis on POD	6 (0–25)[§]		3 (1–17)		0.0052
Tracheotomy	10 (12.0%)		2 (2.0%)		0.013
ECMO	4 (4.8%)		1 (1.0%)		0.181
NO therapy	3 (3.6%)		0		0.095
Aspiration	9 (10.8%)		1 (1.0%)		0.006
Initial extubation during first 12 h postoperatively	66 (79.5%)		88 (89.8%)		0.0614
Initial extubation ≥ POD 10	4 (4.8%)		1 (1.0%)		0.1809
Re-intubation[§]	22 (26.5%)		10 (10.2%)		0.0058
Oxygenation Index		**missing values**		**missing values**	
First intraoperative	416.8 (76.32–749.2)	1	425.8 (68.35–1219)	2	0.572
<300 mm Hg [n patients]	17 (20.7%)	1	38 (39.6%)		0.009
PEEP [mm Hg]	5 (1–12)		5 (0–13)		0.3
Last intraoperative	290.6 (55.79–655.7)		252.6 (43.33–637.9)		0.84
<300 mm Hg [n patients]	46 (55.4%)		56 (57.1%)		0.8808
PEEP [mm Hg]	5 (0–12)		5 (0–8)		0.207
POD 0 (on arrival at ICU)	381.6 (87.33–870.0)	0	401.4 (103.0–828.9)	5	0.188
<300 mm Hg [n patients]	27 (32.5)		18 (18.4%)		0.0379
POD 1	325.3 (113.8–843.3)	0	395.0 (128.0–1020)	14	0.0003
<300 mm Hg [n patients]	30 (36.1%)		15 (15.3%)		0.0017
POD 2	264.7 (83.17–685.0)	20	297.2 (112.3–483.3)	74	0.195
<300 mm Hg [n patients]	39 (47.0%)		13 (13.3%)		<0.0001
POD 3	259.9 (65.5–523.3)	38	263.3 (160.8–556.7)	80	0.784
<300 mm Hg [n patients]	29 (34.9%)		12 (12.2%)		0.0003
POD 4	236.0 (65.8–642.9)	44*	260.7 (110.7–646.7)	78	0.671
<300 mm Hg [n patients]	26 (31.7%)		17 (17.3%)		0.0346
POD 5	236.1 (101.9–642.0)	50*	284.1 (106.3–560.0)	83*	0.392
<300 mm Hg [n patients]	22 (26.8%)		10 (10.3%)		0.0057
POD 6	235.0 (106.6–419.5)	54[#]	317.7 (193.7–476.7)	84*	0.002
<300 mm Hg [n patients]	25 (30.9%)		6 (6.2%)		<0.0001
POD 7	227.1 (108.9–666.7)	59[#]	320.0 (158.0–790.5)	85*	0.0095
<300 mm Hg [n patients]	20 (24.7%)		6 (6.2%)		0.0006
POD 8	189.6 (95.33–685.0)	59[#]	420.0 (120.3–642.9)	87*	0.0042
<300 mm Hg [n patients]	22 (27.2%)		5 (5.2%)		<0.0001
POD 9	218.1 (75.29–533.2)	60[#]	219.9 (115.1–350.0)	91[#]	0.883
<300 mm Hg [n patients]	19 (23.5%)		6 (6.3%)		0.0019
POD 10	218.8 (80.32–523.3)	60[#]	238.7 (104.9–389.2)	91[#]	0.922
<300 mm Hg [n patients]	19 (23.5%)		6 (6.3%)		0.0019

Table 5. Pulmonary outcome. ILE = Ivor Lewis esophagectomy. MPR = major pulmonary resection. POD = postoperative day. ECMO = extracorporal membrane oxygenation. NO = nitric oxide. [§]One patient suffered from preoperative pneumonia. [§]Independently from re-do (revision) surgery. Missing values for the postoperative oxygenation index come into account through discharge from ICU or death. The oxygenation index of patients intraoperatively as well as staying postoperatively on ICU is given in median(range). Patients not staying postoperatively on ICU are considered not to have any respiratory impairment (oxygenation index ≥300 mm Hg). *Including 1 death. [#]Including 2 deaths.

prevented by sympathetic denervation[46]. During ILE, surgeons usually transect the vagus nerve at the level, where the azygos vein joins the vena cava, which results in extensive or even complete vagal denervation of the lung[47]. Vagal branches carrying all parasympathetic and the vast majority of sensory fibers to the lung emerge from the vagal main trunk distally from this transection site down to the inferior margin of the main bronchus, so that this pathway is interrupted by cutting the vagus nerve more cranially[47]. Contrastingly, the sympathetic fibers innervating pulmonary structures, together with a few spinal sensory fibers, derive from the paravertebrally located sympathetic trunk, take a route along the bronchial artery[47,48] and are obviously not injured to the same extent as parasympathetic and vagal sensory fibers during surgery. A vagus-sparing esophagectomy technique previously showed reductions in the rate of postoperative pneumonia, ARDS and delayed gastric emptying. This technique was, however, not combined with mediastinal lymph node assessment and is not suitable for oncologic surgical purposes with regard to oncological radicality[47,49]. A frequent and well-known postoperative clinical manifestation of bilateral truncal vagotomy during ILE is delayed gastric emptying and gastric outlet obstruction through

		Oxygenation index				
	Cumulative perioperative mechanical ventilation [h]	First intraoperative [mm Hg]	Last intraoperative [mm Hg]	POD 1 [mm Hg]	POD 2 [mm Hg]	POD 3 [mm Hg]
Total duration of surgery [min]						
ILE-group						
Correlation coefficient	0.186	0.118	0.084	−0.095	−0.171	−0.089
p-value (two-sided)	0.092	0.29	0.45	0.394	0.182	0.563
missing data	0	1	0	0	20	38
Total duration of surgery [min]						
MPR-group						
Correlation coefficient	0.141	0.02	0.94	−0.041	0.295	−0.053
p-value (two-sided)	0.166	0.849	0.358	0.712	0.162	0.836
missing data	0	2	0	14	74	80

Table 6. Results of Spearman's Rho rank correlation. ILE = Ivor Lewis esophagectomy. MPR = major pulmonary resection. The cumulative duration of mechanical ventilation as well as perioperative oxygenation indexes were independent from the duration of surgery.

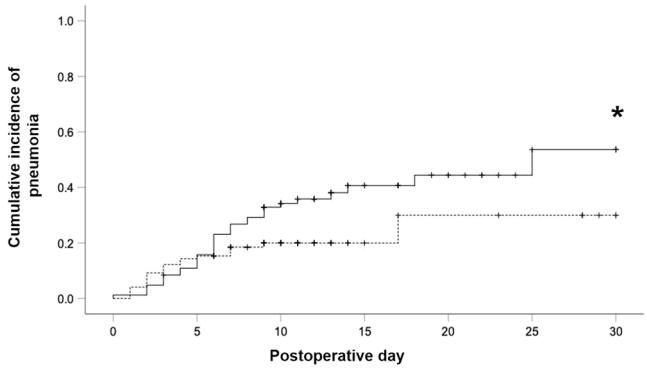


Figure 1. Kaplan-Meier estimation of cumulative incidence of postoperative pneumonia. Black line: Ivor Lewis esophagectomy (ILE)-group, n = 83 patients. Dashed line: Major pulmonary resection (MPR)-group, n = 98 patients. Patients who were discharged or died were censored from the analysis of cumulative incidence of postoperative pneumonia since the day of the event. Censored data are indicated in the figure by vertical ticks. *Indicates differences in the cumulative incidence of postoperative pneumonia between both groups at postoperative day 30 (p = 0.042).

pyloric denervation and consecutive spasm[50]. Even the high rate of postoperative atrial fibrillation after ILE might be partially caused by similar imbalances in the autonomic nervous system through higher mediastinal denervation[41,48,51]. We hypothesize, that a classical ILE with high thoracic esophageal resection margins and mediastinal lymph node dissection even leads to parasympathetic and sensory denervation of trachea, bronchi and pulmonary vasculature (especially pulmonary arteries) by vagotomy, the consecutive dysbalance of the autonomic nervous system innervating pulmonary structures would result in a higher sympathetic drive and thus may impair respiratory function and gas exchange widely analogous to the situation of neurogenic pulmonary edema.

Retrospectively conducted patient analyses like this study are only suited to generate hypotheses, which should be further tested in larger prospectively conducted trials with a high standardization of surgical procedures. Based on our findings, respiratory impairment beyond pulmonary complications after ILE need to be further evaluated, because these will have a major negative impact on the outcome of affected patients and prevention of postoperative pulmonary impairment is mandatory. This study shows, that beyond the surgical access route and the necessity of single-lung ventilation during surgery or inflammatory marker profile, other causes of lung function impairment after ILE must be considered. The impact of a dysbalanced autonomic nervous system on the perioperative pulmonary and cardiac function caused by ILE due to the concomitant vagotomy should therefore be examined in further prospectively trials, that should include e.g. a perioperative monitoring of heart rate variability, pulmonary arterial wedge pressure, pulmonary edema formation and immunological parameters.

Materials and Methods

Patients. The study was performed in accordance to the latest version of the Declaration of Helsinki and was approved by the local ethics committee of University of Giessen (AZ214/15). As this study was conducted retrospectively using routine patient data and as patient data were evaluated fully anonymized, written informed consent of the retrospectively included patients was waived by the local ethics committee in accordance to local legislation. 181 consecutive patients who underwent right-sided anterolateral thoracotomy for either ILE (n = 83)

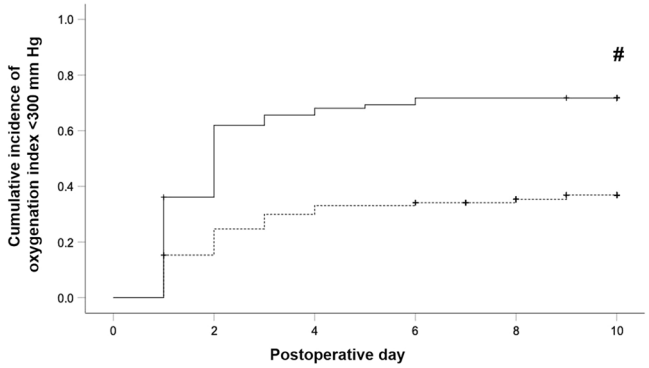


Figure 2. Kaplan-Meier estimation of cumulative incidence of postoperative oxygenation index <300 mm Hg indicating respiratory impairment. Black line: Ivor Lewis esophagectomy (ILE)-group, n = 83 patients. Dashed line: Major pulmonary resection (MPR)-group, n = 98 patients. Patients who were discharged, died or suffered from re-do (revision) surgery were censored from the analysis of cumulative incidence of postoperative reduced oxygenation index (<300 mm Hg) since the day of the event. Censored data are indicated in the figure by vertical ticks. An oxygenation index of <300 mm Hg on postoperative day 0 (arrival on ICU) was not judged as postoperative event. #Indicates differences in the cumulative incidence of postoperative respiratory impairment (oxygenation index <300 mm HG) between both groups at postoperative day 10 ($p < 0.001$).

or MPR (lobectomy and bi-lobectomy, n = 98) were retrospectively identified during a seven-year period and included into this single-center analysis. Patients who underwent ILE together with any kind of pulmonary resection were included in the ILE-group. Patients who underwent left-sided thoracic surgery, right-sided anterolateral thoracotomy with minor lung resection (less than lobectomy: segmentectomy or (multiple) wedge resection) or pneumonectomy as well as patients who underwent transhiatal esophagectomy without thoracotomy were excluded from the analysis. All patients were treated according to the institutional standard-of-care. Patient data were analyzed retrospectively from the prospectively maintained institutional database. Patient data were analyzed during the first ten postoperative days (POD 0–10) regarding the Horovitz oxygenation index (OI), a key parameter to evaluate perioperative pulmonary function. OI-values were available for patients staying on ICU. Patients on a normal ward were excluded from analysis of OI-values and indicated in the tables as "missing values". Consequently, discharge from the ICU was interpreted as absence of respiratory impairment or failure and an OI ≥ 300 mm Hg was assumed.

As described previously[26], the OI was calculated as the ratio of the arterial pressure of oxygen (PaO_2) and the fraction of inspired oxygen (FiO_2) (PaO_2/FiO_2) at the beginning of mechanical ventilation (in most cases under double-lung ventilation), at the end of surgery, upon arrival at the ICU (POD 0), and on POD 1–10. If the PaO_2 and FiO_2 were assessed more than once a day, the first measurement of the day was used. According to the *Berlin classification*, an OI ≤ 300 mm Hg is an important criterion for the clinical definition of ARDS (mild: 201–300 mm Hg, moderate: 101–200 mm Hg and severe: ≤100 mm Hg)[26]. For mechanically ventilated patients (either invasively or non-invasively) the FiO_2 was available. Patients who were not mechanically ventilated (invasively or non-invasively), a FiO_2 of 30% was anticipated. An OI < 300 mm Hg was considered to indicate respiratory impairment or failure.

Surgery. Right-sided anterolateral thoracotomy in the 4th or 5th intercostal space was the standard procedural access to the thoracic cavity for ILE as well as right-sided MPR. Regarding the local clinical standard ILE was performed as a synchronous two-stage procedure with laparotomy or laparoscopy for gastric tube building and gastric pull-up followed by an anterolateral thoracotomy on the right side to complete the subtotal esophagectomy and reconstruct the esophago-gastric continuity. Two-field lymph node dissection was performed as the standard procedure during oncologic esophagectomy, except in cases of cervical anastomosis, lymph node dissection was completed as a three field procedure following international recommendations[1]. The decision for laparoscopy or laparotomy was made based on the surgeon's preferences and tumor stages. In cases of colon reconstruction, patients underwent primary laparotomy. Gastric tube was stapled from the small gastric curvature and anastomosis was usually made by using circular stapler devices. The time of the thoracic incision or of the intraoperative rearrangement of the patients into a lateral decubitus position for thoracotomy, respectively, was used to estimate retrospectively the time spent for of the transthoracic part of ILE, indicating the duration of single-lung ventilation during two-stage ILE.

For right-sided anatomic MPR a standard anterolateral thoracotomy in the 4th or 5th intercostal space was performed. Hilar structures were dissected and individually ligated, sutured or stapled. Systematic lymph node dissection in patients undergoing MPR for primary lung cancer was performed according to international recommendations[52,53]. Principles of the institutional standard in systematic lymph node dissection during lung cancer surgery were described previously in more detail in a patient cohort undergoing minimally-invasive oncologic pulmonary surgery by video-assisted thoracoscopy[54].

In the postoperative phase, patients were treated by principles of an "enhanced recovery after surgery" protocol with extubation as soon as possible, early enteral nutrition and mobilization at the earliest convenience[55].

Usually, patients were monitored at the ICU after ILE or MPR for at least for one day (POD 1) and – if cardiorespiratorily stable – discharged from the ICU. One important clinical criterion for discharge from the ICU to a normal ward after major thoracic surgery is an adequate respiratory function. Patients on normal ward are classified as "normal oxygenation" with an OI $\geq$ 300 mm Hg ("no respiratory impairment" according to the ARDS definition[26]) to make them comparable to patients on ICU with regard to the rate of postoperative respiratory impairment or failure (OI $<$ 300 mm Hg). Pneumonia was assessed and defined retrospectively in this study during the hospital stay using the "Uniform Pneumonia Score" introduced initially by van der Sluis *et al*. and revised by Weijs *et al*. as a standardized methodology to define pneumonia after esophagectomy[17,56]. However, apart from the revised "Uniform Pneumonia Score", but according to current "International Guidelines for the Management of Severe Sepsis and Septic Shock 2012" we decided to use a body temperature $\geq$38.0 °C or $\leq$36.0 °C, respectively, as the threshold for pneumonia scoring in our study[17,25].

Statistical analyses. Statistical analyses were performed using GraphPad Prism (Version 5.00 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com) for two group comparisons and SPSS (IBM SPSS Statistics for Windows, Version 24.0).

For descriptive statistics, data of both groups were analyzed using Fisher's exact or Pearson's X^2 test for categorical data in cross-tabulation. Two group comparisons were performed by Mann-Whitney-U test. Patients who died were censored from analysis upon the day of death (indicated in the tables).

To determine statistical dependence, the total duration of surgery was correlated with the duration of cumulative (perioperative) mechanical ventilation as well as the intraoperative and postoperative (POD 1–3) OI by Spearman's Rho rank correlation coefficient.

Cumulative incidences of postoperative pneumonia during POD 0–30 and postoperative respiratory impairment or failure (defined by an OI $<$ 300 mm Hg) during POD 1–10 of patients after ILE or MPR were analyzed by Kaplan-Meier estimator. Patients who were discharged or died were censored from the analysis of cumulative incidences of postoperative pneumonia since the day the event. Patients who were discharged, died or underwent re-do surgery were censored from the analysis of cumulative incidences of postoperative reduced OI ($<$300 mm Hg) since the day of the event. Censored data are indicated in the figures by vertical ticks. An OI $<$ 300 mm Hg on POD 0 (arrival on ICU) was not judged as postoperative event.

Data are given in tables as median and ranges; p-values $\leq$ 0.05 were considered to indicate statistical significance.

Compliance with ethical standards. The data are collected, the manuscript is written and submitted in accordance to the COPE guidelines.

The acquisition of data and the study was formally approved by the local ethics committee of University of Giessen (AZ214/15). As this is a retrospective, fully anonymized patient data analysis, for this type of study formal written consent from the patients is waived by the local ethics committee in accordance to local legislation. All patients were treated by the current local standard of care. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Author Contributions

M.R., F.U., C.K., M.W. and A.H. made substantial contributions of the conception and design of the work. M.R. and M.S. obtained the data. M.R. and F.U. analyzed the data. M.R., J.B., M.H., R.H., V.G., W.P., M.W. and A.H. interpreted and discussed the data substantially. M.R. and F.U. drafted the work. C.K., J.B., M.H., R.H., V.G., W.P., M.W. and A.H. revised the work substantively. All authors read and approved the final manuscript.

Additional Information

Competing Interests: The authors declare no competing interests.

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11.2 Anlage 2

M. Reichert, M. Lang, M. Hecker, E. Schneck, M. Sander, F. Uhle, M. Weigand, W. Padberg, V. Grau, A. Hecker: **Early respiratory impairment and pneumonia after hybrid laparoscopically-assisted esophagectomy – a comparison with the open approach.** *Journal of Clinical Medicine*. 2020 Jun 17;9(6):1896. doi: 10.3390/jcm9061896.

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Early Respiratory Impairment and Pneumonia after Hybrid Laparoscopically Assisted Esophagectomy—A Comparison with the Open Approach

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Abstract: Patients undergoing esophageal cancer surgery are at high risk of developing severe pulmonary complications. Beneficial effects of minimally invasive esophagectomy had been discussed recently, but the incidence of perioperative respiratory impairment remains unclear. This is a retrospective single-center cohort study of patients, who underwent open (OE) or laparoscopically assisted, hybrid minimally invasive abdomino-thoracic esophagectomy (LAE) for cancer regarding respiratory impairment (PaO_2/FiO_2 ratio (P/FR) < 300 mmHg) and pneumonia. No differences were observed in the cumulative incidence of reduced P/FR between OE and LAE patients. Of note, until postoperative day (POD) 2, P/FR did not differ among both groups. Thereafter, the rate of patients with respiratory impairment was higher after OE on POD 3, 5, and 10 ($p \leq 0.05$) and tended being higher on POD 7 and 9 ($p \leq 0.1$). Although the duration of LAE procedure was slightly longer (total: $p = 0.07$, thoracic part: $p = 0.004$), the duration of surgery (Spearman's rank correlation coefficient (r_{sp}) = −0.267, $p = 0.006$), especially of laparotomy (r_{sp} = −0.242, $p = 0.01$) correlated inversely with respiratory impairment on POD 3 after OE. Pneumonia occurred on POD 5 (1–25) and 8.5 (3–14) after OE and LAE, respectively, with the highest incidence after OE ($p = 0.01$). In conclusion, respiratory impairment and pulmonary complications occur frequently after esophagectomy. Although early respiratory impairment is independent of the surgical approach, postoperative pneumonia rate is reduced after LAE.

Keywords: abdomino-thoracic esophagectomy; Ivor Lewis esophagectomy; respiratory complication; Horovitz index; oxygenation; pulmonary function; pulmonary function index; pneumonia; lung injury; vagal nerve

1. Introduction

Esophageal carcinoma is a common cancer with a growing incidence over the past years and a major cause for cancer-related mortality worldwide [1]. Subtotal resection of the esophagus also as part of a multimodal treatment strategy is the gold-standard for early stage cancer and for selected locally advanced tumors [1]. If the tumor is localized in the thoracic part of the esophagus, the abdomino-thoracic Ivor Lewis procedure for an intrathoracic anastomosis or three-incision McKeown procedure for a cervical anastomosis are adequate surgical techniques for resection [1]. These procedures allow the resection of the tumor-bearing esophagus, mediastinal and perigastric lymph node dissection, and reconstruction of the intestinal passage that is routinely performed as gastric pull-up. Nevertheless, abdomino-thoracic esophagectomies are high-risk surgical procedures, facing high rates of postoperative morbidity and mortality, even in high-volume surgical centers [2–10]. Apart from anastomotic complications, high rates of postoperative respiratory complications, especially pneumonia, are reported after abdomino-thoracic esophagectomy that cause a high postoperative morbidity, a frequent need for critical care, and poor postoperative short-term as well as unsatisfactory long-term oncological outcomes [2,4–9,11–15]. Multiple factors were proposed to contribute to the pathogenesis of postoperative pulmonary complications like perioperative atelectasis after single-lung ventilation, post-thoracotomy pain affecting respiratory physiology, as well as intraoperative injury to the thoracic cavity and the lung [10,15–20].

Several minimally invasive approaches to esophagectomy were introduced into clinical practice: total minimally invasive and hybrid minimally invasive procedures including laparoscopy combined with thoracotomy or thoracoscopy combined with laparotomy [1,21–28]. If minimally invasive thoracoscopy is superior to thoracotomy in the context of esophagectomy, is still a matter of debate [23,25,27,29,30]. However, ample evidence including the prospectively conducted randomized MIRO trial reported considerably higher incidences of major pulmonary complications after open esophagectomy (OE) compared to hybrid minimally invasive laparoscopically assisted esophagectomy (LAE) [21,22,24,29–32]. This might be due to reduced abdominal pain and trauma in comparison to open surgery [15,17–20,22,31,33–35]. As the trauma-associated release of danger-associated molecular patterns (DAMPs) is expected to directly cause pulmonary barrier dysfunction [17,19,20], a better early postoperative lung function should be expected in patients undergoing minimally invasive surgery. This is, however, not yet systematically investigated.

Previously, we compared the pulmonary impairment in patients, who underwent Ivor Lewis abdomino-thoracic esophagectomy with right-sided thoracotomy, to patients, who underwent conventional open right-sided major pulmonary resection [5]. Herein, the esophagectomy group included both, OE and LAE [5]. Although the thoracic part of the surgical procedure is largely similar among both groups, the pneumonia rate after esophagectomy amounted to almost 40% and was considerably higher than after pulmonary resection [5]. We further analyzed the time course of the Horovitz index (i.e., PaO_2/FiO_2 ratio (P/FR)), which is a highly sensitive indicator of any kind of respiratory impairment [5,36]. As expected, the first intraoperative P/FR was worse in the pulmonary resection group. However, already at postoperative day (POD) 0, the situation reversed and esophagectomy patients suffered more frequently from a reduced P/FR than patients after pulmonary resection [5]. This striking result led us to the conclusion that neither thoracotomy with injury to the thoracic cavity and to the lung during surgery nor single lung ventilation are the main culprits for the high rate of respiratory impairments and complications after abdomino-thoracic esophagectomies [5]. We hypothesized that partial or complete vagal denervation of the lung, bronchi, and pulmonary vasculature, that is typical for oncologic esophagectomies, causes a dysbalance of the autonomic nervous system innervating pulmonary structures and eventually impairs gas exchange [5]. Another possible explanation is the abdominal part of the esophagectomy that is associated with additional surgical trauma and more pain [15,17–20,22,31,33–35].

We conducted this retrospective single-center analysis to compare the pulmonary outcome of patients after a conventional OE to patients, who underwent a hybrid minimally invasive LAE.

In contrast to the above mentioned studies from other authors [21,22,24,29–32], we included the highly sensitive P/FR that enables us to investigate pulmonary impairment in the early postoperative phase [5]. We critically scrutinize the common hypothesis that the minimally invasive LAE causes less pulmonary damage compared to OE because of reduced intraoperative trauma [17–20,35].

2. Material and Methods

2.1. Patients

This retrospective single-center cohort study was performed in accordance to the latest version of the Declaration of Helsinki and was approved by the local ethics committee of University of Giessen (approval No. 214/15 and 253/16). The data are collected, the manuscript is written and submitted in accordance to the COPE guidelines. All patients were treated according to the institutional standard-of-care.

From 01/2007 to 12/2017, all consecutive patients who underwent the two-staged, abomino-thoracic (Ivor Lewis) or three-incision, abdomino-thoraco-cervical (McKeown) esophagectomy for cancer were retrospectively evaluated. All patients underwent right-sided, anterolateral thoracotomy for the thoracic part and laparotomy (OE group) or laparoscopy (LAE group) for the abdominal part of the esophagectomy procedure. To focus on abdomino-thoracic procedures for esophagectomy, patients were excluded from the study, who underwent a transhiatal surgical approach to the lower thoracic esophagus. To generate homogenous cohorts of oncologic abdomino-thoracic esophagectomies, patients were excluded from the study, who underwent re-do surgery for recurrent esophageal carcinoma (n = 2) or multivisceral abdominal surgery with pancreatic resection for locally advanced carcinoma of the esophago-gastric junction (n = 2) as well as abdomino-thoracic esophagectomy for benign disease or esophageal perforation (n = 3), abdomino-cervical esophagectomy without a trans-thoracic part of the operation (n = 2), and cervical esophagectomy for carcinoma of the larynx or hypopharynx (n = 2). Patients were divided into two groups: patients who underwent either conventional open surgery for abdomino-thoracic esophagectomy (OE) or a hybrid minimally invasive approach with laparoscopic surgery for the abdominal part of esophagectomy (LAE). Patients who underwent conversion from the initially intended laparoscopic to conventional open abdominal surgery were assigned to the OE group. Overall, 10 patients underwent conversion from the laparoscopic approach to OE: n = 2 due to bleeding, n = 5 due to dense adhesions, n = 3 due to technical considerations.

Patient data were analyzed retrospectively from the prospectively maintained institutional database during the first ten postoperative days (POD 0–10) regarding the P/FR, a key parameter to evaluate perioperative pulmonary function. P/FR values were available for patients staying on intensive care unit (ICU). An important general clinical criterion for discharge of patients from the ICU to a normal ward after major surgery is adequate respiratory function. Consequently, discharge from ICU was interpreted as absence of respiratory impairment (or failure). For patients on the normal ward a "normal oxygenation" was anticipated and a P/FR ≥ 300 mm Hg was assumed. As described previously [36], the P/FR was calculated as the ratio of the arterial pressure of oxygen (PaO_2) and the fraction of inspired oxygen (FiO_2) (PaO_2/FiO_2) at the beginning of mechanical ventilation (in most cases under double-lung ventilation), at the end of surgery, upon arrival at the ICU (POD 0), and on POD 1–10 [5]. If the PaO_2 and FiO_2 were measured more than once a day, the first values of the day were used. For mechanically ventilated patients (either invasively or non-invasively) the FiO_2 was available. For patients who were not mechanically ventilated (invasively or non-invasively), a FiO_2 of 30% was anticipated. Postoperative re-intubations were assessed independently from re-do surgery, to focus on acute respiratory insufficiency making a re-intubation necessary. According to the *Berlin classification*, a P/FR ≤300 mm Hg is an important criterion for the clinical definition of ARDS (mild: 201–300 mm Hg, moderate: 101–200 mm Hg and severe: ≤ 100 mm Hg) [36], thus a P/FR <300 mm Hg was considered in this work to indicate respiratory impairment [5].

The rate of pneumonia during the first 30 postoperative days (POD 1–30) after esophagectomy was assessed as the second key parameter of the study. For the retrospective assessment of postoperative pneumonia the "Revised Uniform Pneumonia Score," introduced and validated for patients after esophagectomy by Weijs et al. was used [37]. The postoperative day of retrospective pneumonia diagnosis was recorded for two-group comparison as well as cumulative incidence calculation. As described previously, although resulting in slightly higher pneumonia rates compared to the current literature, the scoring system was minimally modified according to current "International Guidelines for the Management of Severe Sepsis and Septic Shock 2012," and we decided to use a body temperature ≥ 38.0 °C or ≤ 36.0 °C, respectively, as the threshold for pneumonia scoring in our study [5,37,38].

Postoperative pneumonia and perioperative P/FR were investigated as the main outcome parameters of the present study. The following secondary outcome parameters were assessed: characteristics of patients, tumors as well as surgical procedures, perioperative markers of inflammation (leukocyte count and C-reactive protein (CRP) in peripheral blood obtained from routine laboratory examinations), postoperative pulmonary outcome parameters (duration of mechanical ventilation, rates of mechanical ventilation during POD 0–10, reintubation and tracheotomy rates), and major general patient outcome parameters (duration of stay at the ICU and duration of total in-hospital stay, rates of anastomotic complications, re-do surgery, and overall mortality). Duration of postoperative stay data were stratified into initial postoperative stay at the ICU, cumulative postoperative stay at the ICU, and total postoperative in-hospital stay. The "cumulative postoperative stay at the ICU" variable was calculated for patients who underwent repeated referrals to the ICU during the postoperative in-hospital stay.

2.2. Surgery

Abdomino-thoracic esophagectomy for esophageal malignoma or cancer of the esophago-gastric junction is a widely used standard surgical procedure. The institutional technique was described previously [5]. Briefly, a median laparotomy from the xiphoid to the umbilicus was performed for the open abdominal part of Ivor Lewis as well as McKeown esophagectomy. For the hybrid minimally invasive approach we used a minilaparotomy for the camera access and a four-port technique for laparoscopic surgery. Basically, the technique of gastric mobilization and tube building as well as perigastric, abdominal lymph node dissection was the same for OE and LAE. All abdomino-thoracic esophagectomy patients underwent a right-sided, anterolateral thoracotomy in the 4 th or 5 th intercostal space as the standard access to the thoracic cavity for the thoracic part of the operation. In line with the local clinical standard, abdomino-thoracic esophagectomy was performed as a two-stage procedure in one surgical intervention. In most cases the thoracic part followed the abdominal part of surgery. Reasons for a thorax-first approach were the determination of local resectability in cases of suspected infiltration of neighboring thoracic organs. The subtotal esophagectomy and reconstruction the esophago-gastric continuity was completed trans-thoracally by gastric pull-up. Only in one case included into this study the continuity was restored by colonic interposition following esophago-gastrectomy. Two-field lymph node dissection was performed as the standard procedure during oncologic esophagectomy, except in cases of abdomino-thoraco-cervical esophagectomies with cervical anastomoses, lymph node dissection was completed as a three-field procedure following international recommendations [1]. The decision for OE or LAE was based on the surgeon's preferences and tumor stages. OE was preferred, especially when perigastric lymph node metastases were suspected and in cases of locally advanced tumors of the esophago-gastric junction. Gastric tube was stapled from the small gastric curvature and the anastomosis was done using circular stapler devices. The duration of the thoracic part of the surgical procedure was estimated by the duration of single-lung ventilation or the time of the thoracic incision, respectively.

In the postoperative phase, patients were treated by principles of a "fast track" protocol with extubation as soon as possible, early enteral nutrition and mobilization at the earliest convenience [39].

Usually, patients were monitored at the ICU after abdomino-thoracic esophagectomy for at least until POD 1 and—if cardiac and respiratory functions were stable—discharged from the ICU.

2.3. Statistical Analysis

Statistical analyses were performed using GraphPad Prism (Version 5.00 for Windows, GraphPad Software, San Diego, CA, USA, www.graphpad.com). For descriptive statistics, data of both groups were analyzed using Fisher's exact or Pearson's X^2 test for categorical data in cross-tabulation. Two group comparisons of continuous variables were performed by Mann-Whitney-U test. Patients who died were censored from analysis upon the day of death (indicated in the tables).

To determine a statistical dependence, the duration of surgery (total, thoracic part, abdominal part) was correlated with the last intraoperatively assessed P/FR as well as P/FR on POD 0–3 by Spearman's Rho rank correlation. If P/FR were not available on POD 1–3 due to the reasons mentioned before, a P/FR = 300 mm Hg was assumed for the calculation. Results are given as the Spearman's rank correlation coefficient (r_{sp}).

Cumulative incidences of postoperative pneumonia during POD 1–30 and postoperative respiratory impairment (defined by a P/FR < 300 mm Hg) during POD 1–10 of patients after OE or LAE were calculated by Kaplan-Meier estimation. Log-rank test was used to compare Kaplan-Meier curves. Patients who were discharged, died, or underwent re-do surgery were censored from the analysis of cumulative incidences. Censored data are indicated in the figures by vertical ticks. A P/FR <300 mm Hg on POD 0 (arrival on ICU) was not judged as postoperative event.

Data are given in tables as medians and minimum to maximum ranges for continuous variables as well as *n* (%) for categorical variables; *p*-values ≤ 0.05 were considered to indicate statistical significance.

Post hoc power calculations and sensitivity analysis was performed using the freely available software G*Power 3.1 [40].

3. Results

3.1. Patients

In total, 143 patients, who underwent abdomino-thoracic surgery for esophageal malignancy, were included in this study. Among them, 105 patients underwent OE and 38 patients LAE. Except for the rate of arterial hypertension, which was more prevalent in the OE group ($p = 0.02$), preoperative patient characteristics resembled in both groups regarding body mass index, American society of Anesthesiologist's classification of physical health (ASA) score as well as chronic cardiac and pulmonary diseases. Even tumor characteristics and the rate of induction therapies (chemo- or radio-chemo-therapy) embedded in multimodal treatment strategies were similar between both groups (Table 1).

Table 1. Patient characteristics.

Variables	Conventional Open Esophagectomy (*n* = 105)	Laparoscopically Assisted Esophagectomy (*n* = 38)	*p*-Value
Male gender (*n*)	86 (81.9%)	33 (86.8%)	0.62
Age (years)	64 (40–86)	62.5 (42–77)	0.34
BMI (kg/m^2)	24.5 (15.6–41.3)	24.1 (16.2–31.7)	0.35
ASA (median)	3 (1–4)	2 (1–3)	0.43
1 (*n*)	5	2	
2 (*n*)	44	18	
3 (*n*)	52	18	
4 (*n*)	4	0	
History of malignancy (*n*)	19 (18.1%)	5 (13.2%)	0.62
Arterial hypertension (*n*)	67 (63.8%)	16 (42.1%)	0.02
Coronary artery disease (*n*)	18 (17.1%)	7 (18.4%)	0.81
Chronic lung disease (*n*)	19 (18.1%)	7 (18.4%)	1
Chronic kidney failure (*n*)	7 (6.7%)	3 (7.9%)	0.73

Table 1. *Cont.*

Variables	Conventional Open Esophagectomy (n = 105)	Laparoscopically Assisted Esophagectomy (n = 38)	p-Value
Induction therapy (n)	57 (54.3%)	22 (51.9%)	0.85
Chemo	22	9	
Radio–Chemo	35	13	
Indication (n)			
Malignancy	100%	100%	
Adenocarcinoma	62 (59.0%)	24 (63.2%)	0.65
Squamous cell carcinoma	40 (38.1%)	12 (31.6%)	
Other	3 (2.9%) *	2 (5.3%) #	
Pathological tumor stage (n) §			
T 0	13 (12.6%)	7 (19.4%)	0.71
T 1	13 (12.6%)	3 (8.3%)	
T 2	30 (29.1%)	11 (30.6%)	
T 3	46 (44.7%)	14 (38.9%)	
T 4	1 (1.0%)	1 (2.8%)	
N 0	52 (50.5%)	18 (50%)	1
N +	51 (49.5%)	18 (50%)	
M + $	11 (10.7%)	1 (2.3%)	0.3

* Including neuroendocrine carcinoma and gastrointestinal stromal tumor (each n = 1) as well as one salvage esophagectomy for suspected malignant stenosis after primary radio-chemo-therapy 14 years before. # Including sarcoma and mucosal melanoma. § including adenocarcinoma and squamous cell carcinoma, regarding the current UICC-classification. $ intraoperatively detected oligo-metastatic disease in all patients.

3.2. Surgical Procedure

During surgery, the intestinal continuity was restored by a cervical anastomosis in 12 patients of the OE group and in one patient of the LAE group (p = 0.19). Furthermore, 36 patients from the OE group and 10 patients from the LAE group underwent an extended surgical procedure (p = 0.42), while one patient of the OE group underwent esophagogastrectomy with colonic interposition. The surgical procedure was most frequently extended to minor lung or liver resections as well as to cholecystectomy or omentectomy (Table 2).

Table 2. Procedure characteristics.

Variables	Conventional Open Esophagectomy (n = 105)	Laparoscopically Assisted Esophagectomy (n = 38)	p-Value
Main procedure			0.19
Thoracic anastomosis	93 (88.6%)	37 (97.4%)	
Cervical anastomosis	12 (11.4%)	1 (2.6%)	
Lymph node dissection	100%	100%	1
	n patients = 35 (33.3%)	n patients = 10 (26.3%)	0.54
	esophagogastrectomy: 1 (1.0%) *	esophagogastrectomy: 0	1
	Major lung resection: 1 (1.0%)	Major lung resection: 1 (2.6%)	0.46
	Minor lung resection: 7 (6.7)	Minor lung resection: 4 (10.5%)	0.48
Relevant abdomino/thoracic extended procedures (additional to main procedure) (n)	Minor liver resection: 13 (12.4%)	Minor liver resection: 1 (2.6%)	0.11
	Jejunum catheter: 4 (3.8%)	Jejunum catheter: 0	0.57
	Cholecystectomy: 3 (2.9%)	Cholecystectomy: 1 (2.6%)	1
	Colon resection: 1 (1.0%)	Colon resection: 2 (5.3%)	0.17
	Appendectomy: 2 (1.9%)	Appendectomy: 0	1
	Omentectomy: 4 (3.8%)	Omentectomy: 1 (2.6%)	1
	Left adrenalectomy: 2 (1.9%)	Left adrenalectomy: 0	1
	Other minor resections: 3 (2.9%)	Other minor resections: 2 (5.3%)	0.61
Duration of the thoracic part of Ivor Lewis procedure (min) #	118 (45–304) §	146.5 (86–423)	0.004
Total duration of surgery (min)	288 (177–537)	315 (190–635)	0.07
IO Blood loss (mL)	600 (100–4800)	432.5 (50–2500)	0.01
IO transfusion (n patients) &	28 (26.7%)	7 (18.4%)	0.38
Peridural anesthesia (n)	76 (72.4%)	30 (78.9%)	0.52

* One patient underwent esophago-gastrectomy with colon interposition. # Duration of single-lung ventilation or total duration of the thoracic part of esophagectomy, depending on retrospective availability of data. § Not available retrospectively in 2 patients. & Including packed red blood cells and fresh frozen plasma. IO = intraoperative.

The total duration of surgery ($p = 0.07$), the duration of the thoracic part of esophagectomy and hence, also the duration of single-lung ventilation was longer in LAE patients ($p = 0.004$, Table 2). Of note, the remaining time needed for the abdominal part of the procedure and for intraoperative re-positioning did not differ between both groups (OE: 161 (82–408) min vs. LAE: 170 (90–276) min, $p = 0.66$), indicating that the laparoscopic approach for the abdominal part of surgery was not more time consuming than the open abdominal approach.

3.3. Inflammation

Leukocyte counts and C-reactive protein (CRP) levels in peripheral blood showed a peak on POD 2 after esophagectomy. While perioperative leukocyte counts did not differ among both groups, perioperative CRP levels, were slightly higher on POD 0 ($p = 0.05$) and tended to be higher on POD 1 ($p = 0.07$) in patients, who underwent OE compared to the LAE group (Table 3).

Table 3. Perioperative leukocyte counts and C-reactive protein levels.

Variables	Conventional Open Esophagectomy ($n = 105$)		Laparoscopically Assisted Esophagectomy ($n = 38$)		p-Value
Leukocytes (giga/L)		missing values		missing values	
pre–operatively	6.6 (2.0–16.4)	–	6.7 (3.6–15.5)	–	0.83
POD 0 (on arrival at ICU)	9.3 (3.0–29.6)	–	7.8 (4.3–28.9)	1	0.54
POD 1	10.5 (4.0–23.6)	–	10.2 (6.2–19.1)	1	0.72
POD 2	11.4 (1.8–21.9)	–	11.4 (3.7–24.6)	–	0.85
POD 3	9.5 (1.9–34.1)	4	9.0 (5.5–21.5)	4	0.57
POD 4	8.1 (2.7–106.0)	12 *	7.9 (3.9–17.9)	6	0.37
POD 5	7.8 (3.4–22.0)	20 *	7.8 (3.9–16.3)	9	0.46
POD 6	9.1 (3.4–26.1)	24 #	9.0 (4.8–17.6)	14	0.4
POD 7	9.9 (3.0–29.0)	26 #	9.3 (5.4–23.0)	13	0.72
POD 8	11.0 (4.1–33.3)	32 #	10.0 (5.9–22.5)	17	0.41
POD 9	12.3 (4.5–49.7)	29 #	10.4 (5.3–30.2)	16	0.37
POD 10	12.6 (4.7–38.7)	36 § &	10.4 (4.2–36.7)	18 €	0.29
at discharge	8.1 (3.1–19.0)	13 $	6.9 (4.2–15.7)	2 #	0.07
C–reactive protein (mg/L)		missing values		missing values	
pre–operatively	3.8 (0.5–159.1)	–	2.4 (0.5–124.4	–	0.53
POD 0 (on arrival at ICU)	6.8 (0–256.0)	5	3.1 (0.5–76.6)	2	0.05
POD 1	94.4 (31.6–226.2)	–	78.0 (31.2–205.2)	1	0.07
POD 2	199.2 (55.3–359.4)	–	192.9 (97.7–329.3)	–	0.6
POD 3	185.7 (26.3–403.9)	4	161.3 (69.2–359.5)	4	0.26
POD 4	159.8 (30.1–410.0)	12 *	129.0 (64.0–391.0)	6	0.15
POD 5	136.4 (25.4–539.1)	20 *	135.6 (32.7–287.7)	9	0.5
POD 6	129.8 (14.1–423.2)	23 #	119.7 (26.6–281.4)	14	0.66
POD 7	123.1 (8.3–445.1)	26 #	121.9 (27.4–333.4)	13	0.74
POD 8	144.5 (6.0–491.9)	33 #	131.5 (30.4–361.7)	17	0.72
POD 9	141.9 (5.6–446.9)	30 #	138.0 (27.1–283.6)	18	0.97
POD 10	153.4 (8.1–393.9)	36 § &	109.3 (4.9–302.2)	18 €	0.19
at discharge	32.0 (1.4–145.1)	13 $	34.4 (4.9–144.9)	2 #	0.31

* including 1 death. # including 2 deaths. § including 3 deaths. & including 2 patients who were discharged on postoperative day 9. € including 4 patients who were discharged on postoperative day 9. $ including 13 deaths.

3.4. General Outcome

No statistically significant differences were observed between both groups regarding the initial and cumulative postoperative stays on the ICU as well as the total postoperative duration of hospitalization. Patients, who died during hospitalization, were excluded from calculation of postoperative lengths of stays. No differences were observed concerning the rates of perioperative catecholamine administration, re-do surgery (during POD 1–30), anastomotic complications requiring an intervention, and 30-day or total in-hospital mortality (Table 4).

Table 4. Perioperative results.

Variables	Conventional Open Esophagectomy (n = 105)	Laparoscopically Assisted Esophagectomy (n = 38)	p-Value
PO hospital stay Total (d) *	18 (9–141)	14.5 (9–75)	0.14
Initial PO stay at the ICU (d) *	5 (1–76)	4 (1–35)	0.15
Return to ICU (n patients)	17 (16.2%)	6 (15.8%)	1
Cumulative PO stay at the ICU (d) *	5.5 (1–84)	5 (1–35)	0.16
Cumulative perioperative mechanical ventilation (h)	17.3 (4.8–2280)	12.6 (5.3–26.3)	0.05
Rate of invasive PO ventilation (n) #			
POD 0 (on arrival at ICU)	83 (79.0%)	32 (84.2%)	0.64
POD 1	46 (43.8%)	17 (44.7%)	1
POD 2	12 (11.4%)	2 (5.3%)	0.35
POD 3	18 (17.1%)	1 (2.6%)	0.03
POD 4	20 (19.2%) §	3 (7.9%)	0.13
POD 5	21 (20.2%) §	3 (7.9%)	0.13
POD 6	21 (20.4%) $	3 (7.9%)	0.13
POD 7	26 (25.2%) $	1 (2.6%)	0.001
POD 8	23 (22.3%) $	2 (5.3%)	0.02
POD 9	20 (19.4%) $	1 (2.6%)	0.01
POD 10	20 (19.6%) &	2 (5.3%)	0.04
PO catecholamine administration (n patients) # €			
POD 0	48 (45.7%)	14 (36.8%)	0.45
POD 1	46 (43.8%)	10 (26.3%)	0.08
POD 2	32 (30.5%)	9 (23.7%)	0.53
POD 3	29 (27.6%)	6 (15.8%)	0.19
POD 4	22 (21.2%) §	5 (13.2%)	0.34
POD 5	17 (16.3%) §	4 (10.5%)	0.59
POD 6	16 (15.5%) $	4 (10.5%)	0.59
POD 7	20 (19.4%) $	3 (7.9%)	0.13
POD 8	16 (15.5%) $	2 (5.3%)	0.16
POD 9	16 (15.5%) $	2 (5.3%)	0.16
POD 10	19 (18.6%) &	3 (7.9%)	0.19
Re–do (revision) surgery during POD 1–30	17 (16.2%)	3 (7.9%)	0.28
Anastomotic complications (n patients) ¶	20 (19.0%)	5 (13.2%)	0.47
PO in–hospital mortality (n) ¥	13 (12.4%)	2 (5.3%)	0.36

* Patients who suffered from in-hospital mortality were excluded from analysis of postoperative ICU and total hospital stays. # Patients who died during POD 0–10 (n = 4, two in each group) were excluded from further analysis after their death: § including 1 death. $ including 2 deaths. & including 3 deaths. € including arterenol and/or dobutamine. ¶ anastomotic complications, i.e., insufficiency and/or gastric tube necrosis requiring therapy (i.e., stent, endo-vacuum therapy or re-do surgery). ¥ indicating the in-hospital mortality, even exceeding the 30-day mortality. The overall 30-day mortality rate was 7.0% (n = 10 patients). PO = postoperative. ICU = intensive care unit, includes medium care unit. POD = postoperative day.

3.5. Pulmonary Outcome

Cumulative incidences of postoperative pneumonia between POD 1–30, which was adjusted to re-do surgery, mortality and discharge from hospital, were significantly different among the OE and LAE group (p = 0.01, Figure 1). The overall rate of postoperative pneumonia, regardless of re-do surgery, death or discharge, was 45.7% and 26.3% among patients from the OE and LAE group, respectively (p = 0.05, Table 5). To evaluate this result, we conducted a post hoc power analysis (by G*Power 3.1 [40]) based on our data. With an alpha error probability of 5%, the analysis yielded a moderate power of 0.61 and an actual alpha value of 0.032. Vice versa, a sample size of 159 respectively 57 patients (therewith maintaining the reported group proportion) would have been needed to achieve a power of 0.8 (with

alpha error probability of 0.05), assuming the reported effect size. A subsequent sensitivity analysis based on sample size and alpha error probability further showed that a proportion of 51% pneumonia would have increased the actual power to 0.8.

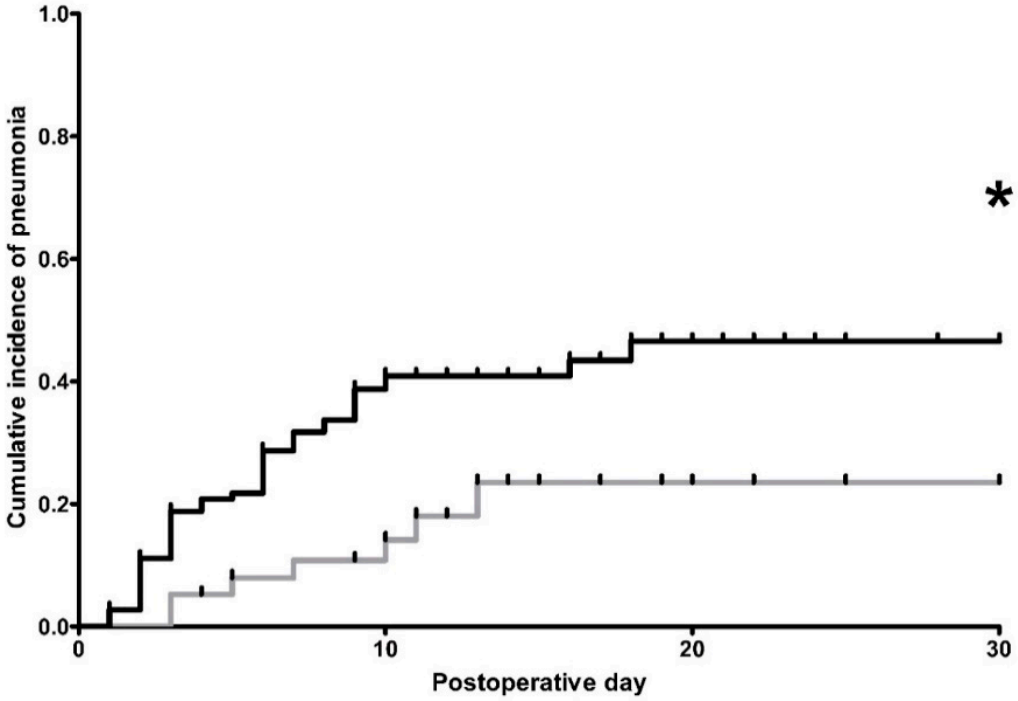


Figure 1. Kaplan-Meier estimation of cumulative incidences of postoperative pneumonia. Black line: conventional open abdomino-thoracic esophagectomy (OE)-group, n = 105 patients. Gray line: hybrid minimally invasive, laparoscopically assisted abdomino-thoracic esophagectomy (LAE)-group, n = 38 patients. Patients, who were discharged, died, or suffered from re-do (revision) surgery were censored from the analysis of cumulative incidences since the day of the event. Censored data are indicated in the figures by vertical ticks. * indicates differences in the cumulative incidence of postoperative pneumonia between both groups at postoperative day 30 (p = 0.01).

Table 5. Pulmonary outcome.

Variables	Conventional Open Esophagectomy (n = 105)	Laparoscopically–Assisted Esophagectomy (n = 38)	p-Value
Pneumonia (n patients) *	48 (45.7%)	10 (26.3%)	0.05
Pneumonia diagnosis on POD	5 (1–25)	8.5 (3–14)	0.03
Tracheotomy (n patients)	19 (18.1%)	2 (5.3%)	0.06
Initial extubation during first 12 h postoperatively (n patients)	82 (78.1%)	30 (78.9%)	1
Re–intubation (n patients) #	31 (29.5%)	5 (13.2%)	0.05
Perioperative PaO_2/FiO_2 < 300 mm Hg (n patients) § $			
Overall during POD 1–10	78 (74.3%)	32 (84.2%)	0.27
First intraoperative	25 (24.0%) &	5 (13.2%)	0.25
Last intraoperative	61 (58.7%) &	25 (65.8%)	0.56
POD 0 (on arrival at ICU)	39 (37.1%)	10 (26.3%)	0.32
POD 1	38 (36.2%)	10 (26.3%)	0.32
POD 2	50 (47.6%)	14 (36.8%)	0.34
POD 3	44 (41.9%)	7 (18.4%)	0.01
POD 4	30 (28.8%) ß	8 (21.1%)	0.4
POD 5	29 (27.9%) ß	4 (10.5%)	0.04
POD 6	28 (27.2%) €	7 (18.4%)	0.38
POD 7	27 (26.2%) €	4 (10.5%)	0.07
POD 8	26 (25.2%) €	7 (18.4%)	0.5

Table 5. *Cont.*

Variables	Conventional Open Esophagectomy (n = 105)	Laparoscopically–Assisted Esophagectomy (n = 38)	p-Value
POD 9	24 (23.3%) €	4 (10.5%)	0.1
POD 10	23 (22.5%) ¶	3 (7.9%)	0.05

* Overall pneumonia rate, irrespectively from re-do surgery. Pneumonia was retrospectively assessed by the "Revised Uniform Pneumonia score" by Weijs et al. using the body temperature ≥38.0 °C or ≤36.0 °C [37] during postoperative days 1–30. # re-intubation because of acute respiratory insufficiency during the hospital stay, independently from re-do (revision) surgery making re-intubation necessary. § Irrespectively from re-do surgery. $ Patients who died during POD 0–10 (n = 3 in the open esophagectomy group) were excluded from further analysis after their death. & Not available retrospectively in 1 patient. ß excluding one death, € excluding 2 deaths, ¶ excluding 3 deaths. POD = postoperative day. ICU = intensive care unit.

Only rarely, a P/FR < 300 mm Hg was measured at the beginning of surgery. However, the majority of patients from both groups had a reduced P/FR (<300 mm Hg) during POD 1–10 after esophagectomy (74.3% and 84.2% of the patients from the OE and LAE group, respectively, p = 0.27). This indicates a high rate of respiratory impairment after surgery, with a peak on POD 2 in both groups (Table 5). Consequently, no differences were observed in the cumulative incidences of reduced P/FR during POD 1–10 between the OE and LAE group (p = 0.54, Figure 2). Not surprisingly, post hoc analysis computes a low power of 0.27 for this comparison.

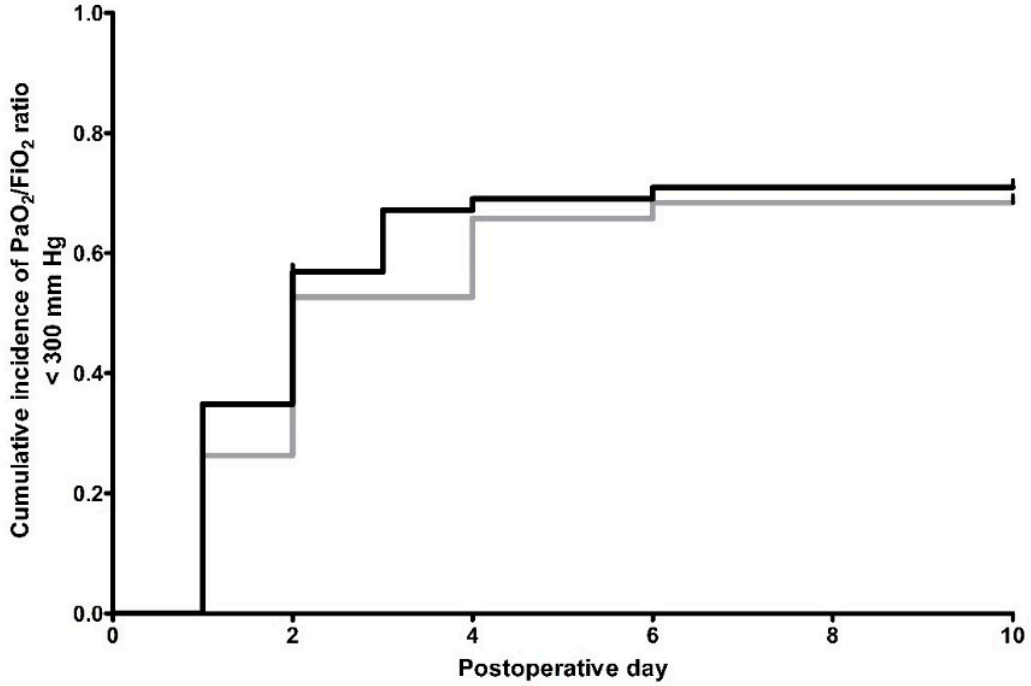


Figure 2. Kaplan-Meier estimation of PaO_2/FiO_2 < 300 mm Hg, indicating respiratory impairment. Black line: conventional open abdomino-thoracic esophagectomy (OE)-group, n = 105 patients. Gray line: hybrid minimally invasive, laparoscopically assisted abdomino-thoracic esophagectomy (LAE)-group, n = 38 patients. Patients, who were discharged, died, or suffered from re-do (revision) surgery were censored from the analysis of cumulative incidences since the day of the event. Censored data are indicated in the figures by vertical ticks. An PaO_2/FiO_2 of <300 mm Hg on postoperative day 0 (arrival on intensive care unit) was not judged as postoperative event.

No differences between both groups have been observed in the initial extubation success and in the direct comparison of rates of reduced P/F ratios during the early postoperative phase (POD 0–2). By contrast, a reduced P/FR was more frequently observed on POD 3, 5, and 10 ($p \leq 0.05$) in patients from the OE group and this respiratory impairment tended to persist on POD 7 and 9 ($p \leq 0.1$, Table 5).

This may reflect the higher rate of invasive mechanical ventilation on POD 7–10 ($p < 0.05$) as well as higher rate of acute respiratory insufficiency necessitating re-intubation independent of re-do surgery ($p = 0.05$). Accordingly, a longer duration of cumulative perioperative mechanical ventilation ($p = 0.05$) was seen in the OE group (Tables 4 and 5).

Interestingly, although the duration of surgery tended to be longer in LAE patients, we found negative correlations between the total duration of surgery and P/F ratios on POD 2 and 3 in the OE group ($r_{Sp} = -0.194$, $p = 0.05$ and $r_{Sp} = -0.267$, $p = 0.006$, respectively). This also holds true for the correlation of the duration of the abdominal part of surgery and P/FR in OE patients on POD 3 ($r_{Sp} = -0.242$, $p = 0.01$, Table 6).

Table 6. Results of Spearman´s Rho rank correlation.

	PaO_2/FiO_2 Ratio				
	Last IO (mm Hg)	**POD 0 (mm Hg)**	**POD 1 (mm Hg)**	**POD 2 (mm Hg)**	**POD 3 (mm Hg)**
Total duration of surgery (min) OE-group					
Correlation coefficient	0.042	−0.017	−0.146	−0.194	−0.267
p-value (two-sided)	0.67	0.87	0.14	0.05	0.01
Total duration of surgery (min) LAE-group					
Correlation coefficient	−0.079	0.116	−0.047	−0.028	−0.187
p-value (two-sided)	0.64	0.49	0.78	0.87	0.26
Duration of the thoracic part (min) OE-group					
Correlation coefficient	−0.014	−0.017	−0.136	−0.128	−0.205
p-value (two-sided)	0.89	0.87	0.17	0.20	0.04
Duration of the thoracic part (min) LAE-group					
Correlation coefficient	−0.253	0.003	−0.050	−0.115	−0.008
p-value (two-sided)	0.13	0.98	0.77	0.49	0.96
Duration of the abdominal part (min) OE-group					
Correlation coefficient	0.017	−0.035	−0.098	−0.114	−0.242
p-value (two-sided)	0.86	0.72	0.32	0.25	0.01
Duration of the abdominal part (min) LAE-group					
Correlation coefficient	0.085	0.117	0.064	0.165	−0.178
p-value (two-sided)	0.61	0.48	0.70	0.32	0.29
IO blood loss (mL) OE-group					
Correlation coefficient	0.201	0.117	−0.062	−0.076	−0.209
p-value (two-sided)	0.04	0.23	0.53	0.44	0.03
IO blood loss (mL) LAE-group					
Correlation coefficient	0.073	0.011	−0.039	−0.045	0.056
p-value (two-sided)	0.66	0.95	0.81	0.79	0.74
IO transfusion (*n* patients) OE-group					
Correlation coefficient	0.137	0.164	0.190	0.086	−0.090
p-value (two-sided)	0.17	0.09	0.05	0.38	0.36
IO transfusion (*n* patients) LAE-group					
Correlation coefficient	0.170	0.160	0.245	0.121	0.174
p-value (two-sided)	0.31	0.34	0.14	0.47	0.30

OE = open abdomino-thoracic esophagectomy. LAE = minimally-invasive, laparoscopically-assisted abdomino-thoracic esophagectomy. (Spearman's rank) Correlation coefficient = r_{Sp}. IO = intraoperative. POD = Postoperative day. PaO_2/FiO_2 ratio on postoperative day 3 correlated inversely with the duration of surgery in patients after open esophagectomy.

4. Discussion

Respiratory complications, mainly pneumonia, are a severe problem after esophageal surgery and at least in part responsible for the frequent need for postoperative critical care as well as for the high morbidity and mortality [2,4–9,11–20]. A better understanding of the presumably multifactorial pathogenesis of postoperative pulmonary impairment [15] is mandatory for the development of new preventive and therapeutic strategies that are urgently needed.

The present study that compares OE to LAE is a relatively small, retrospective single-center analysis with all known inherent draw-backs and limitations. Apart from the retrospective character of the study, the assumption of a FiO_2 = 30% for the P/FR calculation of patients, who were not ventilated as well as the assumption of a P/FR = 300 mm Hg for patients on the normal ward without respiratory impairment are further limitations of this study. For patients, who did not obtain any kind of ventilation on the ICU but frequently receive nasal oxygen supply the FiO_2 was set to 30% in our calculation. Patients with missing information regarding PaO_2 and FiO_2 usually stayed on the normal ward without respiratory impairment. Thus, for the calculation of r_{sp} the P/FR was set to 300 mm Hg, which corresponds to the lower limit of a normal oxygenation [36]. Hence, our data should be interpreted with utmost care, and no firm conclusions can be drawn. However, our study allows the creation of testable hypotheses. Our results suggest that the pathogenesis of pulmonary morbidity in response to esophagectomy is even more complex than expected.

Our study suggests that two distinct phases of postoperative pulmonary impairment can be discerned: (i) during POD 0–2, the rate of patients with a P/FR < 300 mm Hg is high, irrespective of OE or LAE. Rates of reduced P/F ratios in the early postoperative phase (POD 0–2) were not caused by pneumonia or anastomotic complications [5]. (ii) Later on (POD 3, 5, 7, 9, and 10) a higher prevalence of a P/FR < 300 mm Hg is seen in OE patients, which presumably reflects the higher incidence of pneumonia in this group. This time-line is important for the treating physicians, especially regarding discharge considerations of esophagectomy patients from the intensive care unit to a normal ward.

We confirm the result of numerous studies including the recent prospective randomized MIRO trial, that the cumulative incidence of major postoperative pulmonary complications, especially pneumonia is significantly higher after OE compared to LAE [21,22,24,29,30,34,41]. In comparison to these studies, we observed slightly higher rates of postoperative pneumonia, presumably because we used the minorly modified "Revised Uniform Pneumonia Score" by Weijs et al. for the retrospective assessment of pneumonia [37]. The threshold of the body temperature was adjusted according to the current "International Guidelines for the Management of Severe Sepsis and Septic Shock 2012" [38], which in turn lead to a higher pneumonia rate than that reported in the recent literature.

However, our observation that the P/FR, a sensitive marker of pulmonary dysfunction, does not differ among both patient groups early after surgery (POD 0–2), argues against the common interpretation, that the higher incidence of pneumonia in the OE group was directly due to an increased surgical trauma, to more postoperative pain or to a higher incidence of surgery-induced basal lung damage [10,15–21]. The effects of these factors would be expected to be visible early after surgery, which was obviously not the case in our study. We hypothesize that the rate of early impairment of pulmonary function after esophagectomy, that is surprisingly similar in the LAE and in the OE group, is not importantly influenced by the extent of the trauma and even pain caused by the laparotomy during the abdominal part or injury of the thoracic cavity by the thoracic part of the esophagectomy procedure.

We reported before, that especially the early postoperative pulmonary impairment of patients undergoing Ivor Lewis esophagectomy is more pronounced than that of patients undergoing lung resection [5]. A possible explanation is that the thoracic part of esophagectomy results in pulmonary dysfunction due to an imbalance in the autonomous nervous system caused by vagal denervation of the lung [5,42]. This imbalance might cause an early postoperative situation resembling neurogenic pulmonary edema [5,43,44]. Indeed, an extended damage of vagal nerve fibers to pulmonary structures due to mediastinal lymph node dissection and the transthoracic esophagectomy itself as well as the

technical feasibility of vagus-sparing techniques during abdomino-thoracic esophagectomy have been previously described [42,45–49]. However, vagus-sparing techniques bare the much feared risks of a lower oncological radicality [42,45,50]. Nevertheless, in some small case series a reduced prevalence of complications driven by vagal damage as well as pulmonary complications after esophagectomy was reported if care was taken for the vagal nerve during surgery [42,45–49]. If damage to the vagal nerve is the major threat for the lung in the context of esophagectomy, it is conceivable that the early postoperative P/F ratios are similar in the OE and in the LAE group. Vagus-sparing techniques should be carefully evaluated in prospective multi-center studies, because they might reduce respiratory impairment and pneumonia rates after LAE below those observed after pulmonary resection.

Nevertheless, we still need to explain, why the incidence of postoperative pneumonia beyond POD 3 is much higher in the OE group compared to the LAE group. As the cumulative incidence of pneumonia in the LAE group is close to that of patients, who underwent pulmonary resection [5], the damage associated with laparotomy but not with laparoscopy seems, at least in part, to be responsible for the increased incidence of pneumonia after esophagectomy compared to pulmonary resection. As discussed above, a direct effect of a trauma-induced release of DAMPs is unlikely, although the elevated CRP levels at POD 0 suggest that more DAMPs were released in OE patients. However, the negative correlation of the duration of surgery in the OE group and the P/FR on POD 3 would be in favor of the idea that lager amounts of DAMPs released during prolonged major abdominal surgery increase the risk to acquire pneumonia [51–53]. We speculate that a more severe initial DAMP-induced systemic inflammation might have impaired host defense against pneumonia-associated pathogens. If this holds true, LAE should be favored whenever possible. Similar conclusions can be drawn from the recent study by Babic et al. [54]. Here the open esophagectomy approach resulted in higher levels of inflammatory markers (CRP and blood leukocytes) during the first two postoperative days compared to minimally invasive approaches including the hybrid one. In the their analysis Babic et al. evaluated high early postoperative CRP values as positive predictive factors for the development of postoperative overall as well as pulmonary complications [54]. Another variable, which was significantly different between both the OE and LAE group in the present study, was intraoperative blood loss. The most probable explanations for respiratory impairment due to an extensive intraoperative blood loss are volume overload or transfusion-associated lung injury, but the intraoperative rate of blood product transfusion and respiratory impairment did not correlate. However, blood loss negatively correlated with P/FR on POD 3 in the OE group (see Table 6). In our study, POD 3 seems to be the day with the highest risk for developing lung injury following OE and the immunological impact of intraoperative blood loss and perioperative transfusion should be further investigated. Another trivial explanation for the higher incidence of pneumonia in the OE group might be respiratory impairment due to larger painful operation scars, although our center attaches much importance to an appropriate pain management. Besides that, Klevebro et al. evaluated higher pneumonia and pulmonary complication rates in patients with cardiorespiratory co-morbidities, especially in patients with lung diseases after neoadjuvant therapies, in their multicentric analysis of 1590 esophagectomies [14]. Although one could suspect, that because of the retrospective and non-randomized nature of the current study, the OE procedure was preferentially performed in patients with preoperatively suspected more advanced tumor stages and a higher general morbidity, our data speak against this theory: both study groups are widely balanced concerning the (local) tumor stages and showed only differences in pre-existing arterial hypertension—not in chronic lung or cardiac diseases. Differences in irradiation-induced lung pathology, that might foster postoperative pneumonia [2,55,56], can also be excluded in our study, as the rate of neoadjuvant therapy did not differ between both groups of the present study. Although, other factors might contribute to the incidences of pneumonia as well as reduced P/FR after abdomino-thoracic esophagectomy, we decided not to perform a multivariable analysis in order to focus on the results of two-group comparisons, incidence analyses and rank correlations and to avoid statistical overstatement in the present work.

5. Conclusions

In summary, our study suggests that an early phase of postoperative pulmonary impairment that starts immediately after surgery is inherent to the open thoracic part of the esophagectomy procedure but largely independent of the extent of abdominal trauma. Prospective randomized clinical studies are warranted to improve the pulmonary outcome of esophagectomy and to decide if a minimally invasive approach to the thoracic part, a vagus-sparing technique or both is of advantage. The slightly delayed development of pneumonia is most likely driven by the initial pulmonary damage after OE and LAE. It is less likely that the laparotomy itself is responsible for the increased postoperative pneumonia rate.

Author Contributions: All authors made substantial work on the data and manuscript. All authors agreed that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors made substantial contribution to the work and gave important intellectual content. Data curation, M.L., M.R., and F.U.; formal analysis, M.H., E.S., and M.A.W.; project administration, M.S., W.P., and A.H.; software, I.A.; writing—original draft, M.R.; writing—review and editing, W.P., V.G., and A.H. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest: All authors declare no conflicts of interest related to the present work.

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11.3 Anlage 3

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Perioperative Medicine

RESEARCH

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Perioperative statin medication impairs pulmonary outcome after abdomino-thoracic esophagectomy

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Abstract

Background: Although surgery is the curative option of choice for patients with locally advanced esophageal cancer, morbidity, especially the rate of pulmonary complications, and consequently mortality of patients undergoing abdomino-thoracic esophagectomy remain unacceptably high. Causes for developing post-esophagectomy pulmonary complications are trauma to the lung and thoracic cavity as well as systemic inflammatory response. Statins are known to influence inflammatory pathways, but whether perioperative statin medication impacts on inflammatory response and pulmonary complication development after esophagectomy had not been investigated, yet.

Methods: Retrospective analysis and propensity score matching of patients, who either received perioperative statin medication [statin(+)] or not [statin(−)], with regard to respiratory impairment ($PaO_2/FiO_2 < 300$ mmHg), pneumonia development, and inflammatory serum markers after abdomino-thoracic esophagectomy.

Results: Seventy-eight patients who underwent abdomino-thoracic esophagectomy for cancer were included into propensity score pair-matched analysis [statin(+): $n = 26$ and statin(−): $n = 52$]. Although no differences were seen in postoperative inflammatory serum markers, C-reactive protein values correlated significantly with the development of pneumonia beyond postoperative day 3 in statin(−) patients. This effect was attenuated under statin medication. No difference was seen in cumulative incidences of respiratory impairment; however, significantly higher rate (65.4% versus 38.5%, $p = 0.0317$, OR 3.022, 95% CI 1.165–7.892) and higher cumulative incidence ($p = 0.0468$) of postoperative pneumonia were seen in statin(+) patients, resulting in slightly longer postoperative stay on intensive care unit ($p = 0.0612$) as well as significantly prolonged postoperative in-hospital stay ($p = 0.0185$).

Conclusions: Development of pulmonary complications after abdomino-thoracic esophagectomy is multifactorial but frequent. The establishment of preventive measures into the perioperative clinical routine is mandatory for an improved patient outcome. Perioperative medication with statins might influence pneumonia development in the highly vulnerable lung after abdomino-thoracic esophagectomy. Perioperative interruption of statin medication might be beneficial in appropriate patients; however, further clinical trials and translational studies are needed to prove this hypothesis.

Keywords: Esophagectomy, Esophageal cancer, Statin, Pneumonia, Ivor Lewis, Perioperative medication

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Background

Esophageal cancer is one of the leading cancer diagnoses worldwide and esophageal resection is frequently decided as the curative option of choice (Pennathur

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et al. 2013). Thereby, esophageal cancer surgery is a high-risk procedure resulting in high postoperative complication and mortality rates being up to 60% and 14%, respectively (Zingg et al. 2011; McCulloch et al. 2003). Apart from anastomotic leakages, frequently observed postoperative complications are of pulmonary origin including respiratory distress and pneumonia (Reichert et al. 2020, 2019). The rates of postoperative pulmonary complications (PPC) range between 20 and 40%, and vice versa PPC majorly contribute to postoperative morbidity and mortality of the affected patients (Zingg et al. 2011; Avendano et al. 2002; Ferguson and Durkin 2002; Law et al. 2004; Blencowe et al. 2012; Seesing et al. 2018). Explanations for these high rates of PPC are vague. Perioperative atelectasis due to single-lung ventilation, postoperative pain after thoracotomy impairing the respiratory physiology, manipulation and injury of the thoracic cavity and the lung during surgery, and potential laryngeal nerve injury caused by extended lymph node dissection or cervical approaches to the esophagus resulting in an increased postoperative risk for aspiration were suggested to contribute to high PPC rates (Molena et al. 2014; Boshier et al. 2011; Bhayani et al. 2013). However, it has been observed that patients are significantly more vulnerable for impairments in pulmonary gas exchange and for development of PPC, especially pneumonia, after surgical approaches to the thoracic esophagus compared with major lung surgery, although both procedures result in a comparable operative trauma to the chest (Reichert et al. 2019).

Strategies to prevent postoperative pulmonary morbidity are almost lacking but are urgently needed. Hence, some authors advocate minimally invasive surgical approaches, especially to the abdominal cavity for gastric mobilization during abdomino-thoracic or abdomino-thoraco-cervical esophagectomy, resulting in improved postoperative pulmonary outcomes including lower pneumonia rates (Reichert et al. 2020; Mariette et al. 2019; Briez et al. 2012; Glatz et al. 2017). In the recent literature, this observation had been mainly attributed to lower abdominal pain levels after laparoscopic compared with open abdominal surgery (Mariette et al. 2019; Briez et al. 2012; Berlth et al. 2018; Sluis et al. 2019). In a previous work, we concluded that neither thoracotomy with surgical injury to the lung and to the thoracic cavity nor single-lung ventilation is mainly responsible for the high rates of respiratory impairment as well as PPC development after abdomino-thoracic esophagectomies (Reichert et al. 2019). However, a more indirect effect of trauma-induced systemic inflammation after (prolonged) conventional open abdominal surgery in comparison with hybrid minimally invasive, laparoscopically assisted esophagectomy might impair lung physiology and increases the risk to acquire pneumonia postoperatively (Reichert et al. 2020; D'Journo et al. 2010; Okamura et al. 2015; Katsuta et al. 1998; Babic et al. 2020). Considering this, some daily medication has the potential to influence inflammatory pathways and the immune reaction of surgical patients majorly, which, vice versa, may have an impact on postoperative patient outcome after major surgery. Statins, formally known as competitive inhibitors of the 3-hydroxy-3-methyl-glutaryl-CoA reductase, are a widely used every-day medication for hyperlipidemic and atherosclerotic patients, with a previously proven safety profile (Lemos et al. 2004). Beneath lipid-lowering and beneficial effects on atherosclerosis and subsequently on cardiovascular morbidity, statins are known to influence inflammatory pathways as recently reviewed by Koushki and colleagues (Koushki et al. 2020). Statins interfere with the expression of adhesion molecules and recruitment of inflammatory cells as well as decrease inflammasome activity and pro-inflammatory cytokine or acute phase protein production including interleukin (Il)-1, Il-6, tumor necrosis factor (TNF)-α, and C-reactive protein (CRP) (Koushki et al. 2020). These effects on inflammation are multifaceted and play a key role in plaque stabilization in atherosclerotic patients, but these effects may also play a role in other cases of systemic inflammation or infection (Koushki et al. 2020; Meyer et al. 2020; Krivoy et al. 2008; Meng et al. 2020; Jesus Oliveira et al. 2020; Oliveira et al. 2020). However, the influence of statins on perioperative inflammatory reaction and patient outcome, especially on postoperative pulmonary outcome in esophagectomy patients, has been poorly investigated until now. The present work aims to investigate the effect of perioperative statin medication on postoperative respiratory dysfunction as well as pneumonia rates following abdomino-thoracic esophagectomy.

Methods

Patients

This retrospective single-center cohort study was formally approved by the local ethics committee of the medical faculty of the University of Giessen (approval no. 214/15 and 253/16). The study was performed in accordance with the latest version of the Declaration of Helsinki. The data are collected and the manuscript is written and submitted in accordance with the COPE guidelines. All patients were treated according to the institutional standard of care.

From 01/2009 to 12/2017, all consecutive patients who underwent abomino-thoracic (Ivor Lewis) or abdomino-thoraco-cervical (McKeown) esophagectomy for cancer were included in the data analysis. Patients, who underwent a transhiatal surgical approach to the esophagus or who underwent re-do surgery for local

recurrent esophageal carcinoma, were excluded from the study. Further exclusion criteria were multivisceral abdominal surgery with pancreatic resection for locally advanced carcinoma of the esophago-gastric junction, benign disease or esophageal perforation necessitating esophageal resection, abdomino-cervical esophagectomy without a trans-thoracic part of the procedure, and cervical esophagectomy for carcinoma of the larynx or hypopharynx.

Patient data were analyzed retrospectively from the prospectively maintained institutional database regarding general patient characteristics and surgical procedure characteristics, general postoperative patient outcome and more specifically regarding perioperative blood leukocyte counts and C-reactive protein (CRP) values from routine laboratory examinations, postoperative pulmonary outcome including duration of invasive mechanical ventilation through endotracheal tube or tracheotomy, re-intubation and tracheotomy rates, postoperative pneumonia, and perioperative oxygenation indices. The patient cohort was divided with regard to perioperative statin medication, which was obtained from medical records.

The rate of pneumonia was assessed retrospectively until postoperative day 30 (POD 1–30) after abdomino-thoracic or abdomino-thoraco-cervical esophagectomy. Therefore, the "Revised Uniform Pneumonia Score," which had been previously validated for patients after esophagectomy, was used (Weijs et al. 2016). The postoperative day of retrospective pneumonia diagnosis was recorded for pairwise comparisons as well as cumulative incidence calculation. As described previously, the scoring system was minimally modified: we decided a body temperature ≥ 38.0 °C or ≤ 36.0 °C, respectively, as the threshold for pneumonia scoring in the present study according to the current "International Guidelines for the Management of Severe Sepsis and Septic Shock 2012" (Reichert et al. 2020, 2019; Weijs et al. 2016; Hecker et al. 2019).

The oxygenation index (i.e., PaO_2/FiO_2 ratio or P/FR) is a well-known parameter for the evaluation of pulmonary function. P/FR values were regularly available for patients staying in the intensive care unit (ICU) and adequate respiratory function is an important general clinical criterion for discharge of patients from the ICU to the normal ward after major surgery. Thus, discharge from the ICU was consequently interpreted as the absence of respiratory impairment (or failure) in this study and a "normal oxygenation" with a P/FR ≥ 300 mm Hg was anticipated for patients on the normal ward. In the present work, P/FR was calculated as the ratio of the arterial pressure of oxygen (PaO_2) and the fraction of inspired oxygen (FiO_2) (PaO_2/FiO_2) as described previously (Ranieri et al. 2012) at different time points: at the beginning of mechanical ventilation (under double-lung ventilation), upon arrival at the ICU (POD 0), and on POD 1–10 (Reichert et al. 2020, 2019). If the PaO_2 and FiO_2 were measured more than once a day, the first values of the day were used. According to the Berlin classification, a P/FR ≤ 300 mmHg is an important criterion for the clinical definition of acute respiratory distress syndrome (Ranieri et al. 2012); thus, a P/FR < 300 mmHg was considered to indicate respiratory impairment or failure (Reichert et al. 2020, 2019). For mechanically ventilated patients (either invasively or non-invasively), the FiO_2 was available. For patients, who were not mechanically ventilated (invasively or non-invasively) in the ICU, a FiO_2 of 30% was assumed to globally take nasal oxygen supply into consideration in these patients immediately following extubation. To focus on acute respiratory insufficiency making re-intubation necessary, we assessed postoperative re-intubations independently from re-do surgery.

Surgery and perioperative patient care

Two-incision, abomino-thoracic esophagectomy (Ivor Lewis) for lower- or mid-esophageal malignoma or cancer of the esophago-gastric junction or three-incision, abdomino-thoraco-cervical (McKeown) esophagectomy for higher located esophageal malignoma are widely used standard surgical procedures (Pennathur et al. 2013). The institutional technique was described previously (Reichert et al. 2020, 2019). All patients included in this study underwent right-sided, anterolateral thoracotomy for the thoracic part and either laparotomy or laparoscopy for the abdominal part of the esophagectomy procedure. Patients who underwent conversion from an initially intended hybrid, minimally invasive, laparoscopically assisted approach to laparotomy were attributed to conventional open surgery.

All patients underwent either a two-field or a three-field lymph node dissection dependent on the extent of surgery (abdomino-thoracic or abdomino-thoraco-cervical esophagectomy) following international recommendations (Pennathur et al. 2013). All abdomino-thoracic or abdomino-thoraco-cervical esophagectomy procedures reported in this study were performed in one surgical intervention. In most cases, the thoracic part followed the abdominal part of the surgery. Reasons for a thorax-first approach were the determination of local resectability. The (subtotal) esophagectomy and reconstruction of the esophago-gastric continuity were regularly completed trans-thoracally by gastric pull-up. In one case included in this study, esophago-gastrectomy was performed. In this case, the continuity was restored by colonic interposition.

The duration of the thoracic part of the surgical procedure was calculated by the duration of single-lung ventilation or the time of the thoracic incision upon retrospective availability of data, respectively.

Postoperatively, patients were treated by principles of a "fast track" protocol including early extubation, early enteral nutrition, and early mobilization (Rubinkiewicz et al. 2019; Low et al. 2019; Moorthy and Halliday 2021). Patients were monitored at the ICU for at least until POD 1 and—if cardiac and respiratory functions were stable—discharged from the ICU.

Statistical analyses

The patient cohort was divided into either group of patients who received a statin medication perioperatively [statin(+)] or who did not [statin-naïve or statin(−)].

Statistical analyses were performed using GraphPad Prism (version 5.00 for Windows, GraphPad Software, San Diego, CA, USA, www.graphpad.com). Categorical data of both groups were analyzed using Fisher's exact or Pearson's X^2 test. Mann–Whitney U test was used to perform two-group comparisons of continuous variables. Patients who died were excluded from the analysis upon the day of death.

Odds ratios (OR) and 95% confidence intervals (95% CI) were used to calculate the effect size of perioperative statin medication on postoperative pneumonia development by the Baptista-Pike method.

Cumulative incidences of postoperative pneumonia during POD 1–30 and postoperative respiratory impairment (defined by a P/FR < 300 mmHg) during POD 1–10 of statin-naïve and statin(+) patients were calculated by Kaplan–Meier estimation, as described previously (Reichert et al. 2020, 2019). P/FR on POD 0 (arrival on ICU) was not included in the cumulative incidence calculation. Kaplan–Meier curve comparisons were performed by log-rank test. Patients who were discharged, died, or underwent re-do surgery were censored from the analysis of cumulative incidences. Vertical ticks in the figures indicate censored data.

To obtain a better comparability of both groups regarding patient characteristics, 1:2 [statin(+) patients: statin(−) patients] propensity score pair matching (PSM) with a match tolerance = 0.0 was performed by the package "MatchIt" with "R" (version 4.0.3) followed by a repeat of the analyses as described above. The propensity score of the patients was calculated including relevant variables of preoperative patient characteristics and relevant characteristics of the surgical procedure [American Society of Anesthesiologist's classification of physical health (ASA) score, chronic pulmonary diseases, Charlson Comorbidity Index (CCI) and conventional open or hybrid minimally invasive, laparoscopically assisted surgery].

Finally, to determine statistical dependences between perioperative statin medication and postoperative pneumonia as well as postoperative pneumonia and postoperative leukocyte counts and C-reactive protein values, Spearman's rho rank correlation was used. Results are given as Spearman's rank correlation (r_{sp}) and respective significances.

Data are given in tables as medians with minimum to maximum ranges for continuous variables as well as n (%) for categorical variables; p-values ≤ 0.05 indicate statistical significance. Because of the exploratory character of the study, no adjustments of p-values were performed.

Results

General characteristics of the unmatched patient cohort

Between 2009 and 2017, 117 patients, who underwent Ivor Lewis (abdomino-thoracic) or McKeown (abdomino-thoraco-cervical) esophagectomy for oncologic purposes, were included into the data analysis. The patient cohort was subdivided into the group of patients who received a statin medication perioperatively [statin(+): $n = 26$, 22.2%] or not [statin(−): $n = 91$, 77.8%]. Patient characteristics of both native, unmatched groups are shown in Table 1. Overall, 87 (95.6%) statin-naïve patients and all patients from the statin(+) group preoperatively had evidence of chronic diseases ($p = 0.5739$). Of note, patients from the statin(+) group were at baseline significantly older and suffered from more severe chronic diseases including arterial hypertension, coronary artery diseases, and (by tendency) chronic lung diseases, which is reflected by higher ranks in the ASA score. Higher rates of co-morbidities in the characteristics of patients from the statin(+) group and vice versa might cause higher rates of primary surgery without previous induction therapies, although these patients had evidence for locally more advanced histo-pathological tumor stages ($p = 0.0084$), accordingly for locally more extended esophageal surgery [McKeown procedure with cervical anastomosis was performed in 3.3% of statin(−) and 23.7% of statin (+) patients, $p = 0.0037$] and these patients were approached by tendency less frequently by a hybrid minimally invasive, laparoscopically assisted approach ($p = 0.0758$, Tables 1 and 2). However, no differences were observed in additional procedures to the esophagectomy, nor in the duration of surgery and intraoperative blood loss (Table 2).

Outcome analysis of the unmatched patient cohort

Although no differences were observed in the most relevant postoperative outcome parameters [initial extubation success, duration of mechanical ventilation or

Table 1 Patient characteristics

Variable	All patients			Propensity score-matched patients		
	Statin (−) patients (*n* = 91)	Statin (+) patients (*n* = 26)	*p* value	psmStatin (−) patients (*n* = 52)	psmStatin (+) patients (*n* = 26)	*p* value
Type of statin [*n*]	-		-	-		-
Lipophilic						
Simvastatin		19 (73.1%)			19 (73.1%)	
Atorvastatin		4 (15.4%)			4 (15.4%)	
Hydrophilic						
Pravastatin		3 (11.5%)			3 (11.5%)	
Male gender [*n*]	72 (79.1%)	23 (88.5%)	0.3970	39 (75.0%)	23 (88.5%)	0.2371
Age [years]	64.0 (40.0–85.0)	67.5 (53.0–86.0)	0.0224	63.5 (40.0–85.0)	67.5 (53.0–86.0)	0.0536
BMI [kg/m^2]	24.2 (15.6–41.3)	25.0 (20.3–37.6)	0.0841	24.1 (16.0–41.3)	25.0 (20.3–37.6)	0.1407
ASA [median]	2 (1–4)	3 (2–4)	< 0.0001	3 (2–4)	3 (2–4)	0.2336
1 [*n*]	3 (3.3%)	0		0	0	
2 [*n*]	47 (51.6%)	3 (11.5%)		11 (21.2%)	3 (11.5%)	
3 [*n*]	39 (42.9%)	21 (80.8%)		39 (75.0%)	21 (80.8%)	
4 [*n*]	2 (2.2%)	2 (7.7%)		2 (3.8%)	2 (7.7%)	
History of malignancy [*n*]	14 (15.4%)	6 (23.1%)	0.3817	10 (19.2%)	6 (23.1%)	0.7690
Abuse [*n*]						
Alcohol	19 (20.9%)	5 (19.2%)	1	11 (21.2%)	5 (19.2%)	1
Smoking	33 (36.3%)	12 (46.2%)	0.3709	18 (34.6%)	12 (46.2%)	0.3365
Arterial hypertension [*n*]	50 (54.9%)	22 (84.6%)	0.0062	34 (65.4%)	22 (84.6%)	0.1093
Coronary artery disease [*n*]	10 (11.0%)	10 (38.5%)	0.0024	9 (17.3%)	10 (38.5%)	0.0524
Chronic lung disease [*n*]	17 (20.9%)	10 (38.5%)	0.0617	12 (23.1%)	10 (38.5%)	0.1867
Chronic kidney failure [*n*]	6 (6.6%)	4 (15.4%)	0.2259	5 (9.6%)	4 (15.4%)	0.4713
Previous abdominal surgery [*n*]	28 (30.8%)	5 (19.2%)	0.3262	12 (23.1%)	5 (19.2%)	0.7783
Induction therapy [*n*]	63 (69.2%)	11 (42.3%)	0.0199	36 (69.2%)	11 (42.3%)	0.0285
Indication [*n*]						
Malignancy			0.9162			1
Adenocarcinoma	56 (61.5%)	15 (57.7%)		30 (57.7%)	15 (57.7%)	
SCC	31 (34.1%)	10 (38.5%)		20 (38.5%)	10 (38.5%)	
Others	4[a] (4.4%)	1[b] (3.8%)		2[c] (3.8%)	1[b] (3.8%)	
Pathological tumor stage[d]						
T 0	19[e] (21.6%)	0	0.0084	11[e] (21.6%)	0	0.0428
T 1	9 (10.2%)	4 (16.0%)		7 (13.7%)	4 (16.0%)	
T 2	23 (26.1%)	9 (36.0%)		15 (29.4%)	9 (36.0%)	
T 3	37 (42.1%)	10 (40.0%)		18 (35.3%)	10 (40.0%)	
T 4	0	2 (8.0%)		0	2 (8.0%)	
N 0	53 (58.2%)	13 (50.0%)	0.5055	30 (57.7%)	13 (50.0%)	0.6305
N +	38 (41.8%)	13 (50.0%)		22 (42.3%)	13 (50.0%)	
M+[f]	5 (5.5%)	1 (3.8%)	1	4 (7.7%)	1 (3.8%)	0.6598

Data are given in median and minimum to maximum ranges or *n* (%).[a]Including one salvage esophagectomy after primary radio-chemo-therapy as well as sarcoma, neuroendocrine carcinoma, and gastrointestinal stromal tumor (each *n* = 1). [b]I.e., mucosal melanoma. [c]Including one salvage esophagectomy after primary radio-chemo-therapy and one gastrointestinal stromal tumor. [d]Postoperative pathological "T" stage of primary adenocarcinoma and squamous cell carcinoma of the esophagus [concerning *n* = 88 statin (−) patients or *n* = 51 psmStatin (−) patients, respectively, and *n* = 25 statin (+) patients], regarding the current UICC classification. [e]Including the one salvage esophagectomy. [f]Oligo-metastatic disease detected intraoperatively in all patients. *psm* Propensity score matched, *BMI* Body mass index, *ASA* American Society of Anesthesiologist's classification of physical health score, *SCC* Squamous cell carcinoma

evidence for acute (re-intubation, independently from re-do surgery) or chronic (tracheotomy) respiratory insufficiency, the need for re-do surgery as well as anastomotic complications], patients from the statin(+) group had significantly higher rates of postoperative pneumonia [statin(−) patients: *n* = 30, 33.0% versus statin(+) patients: *n* = 17, 65.4%, *p* = 0.0057, OR 3.841, 95% CI 1.510–8.944]. This difference in postoperative pneumonia

Table 2 Characteristics of the surgical procedure

Variable	All patients			Propensity score-matched patients		
	Statin (−) patients (*n* = 91)	Statin (+) patients (*n* = 26)	*p* value	psmStatin (−) patients (*n* = 52)	psmStatin (+) patients (*n* = 26)	*p* value
Main procedure						
COS	63[a] (69.2%)	23 (88.5%)	0.0758	41 (78.8%)	23 (88.5%)	0.3633
LAE	28 (30.8%)	3 (11.5%)		11 (21.2%)	3 (11.5%)	
Thoracic anastomosis	88[a] (96.7%)	20 (76.9%)	0.0037	50 (96.2%)	20 (76.9%)	0.0145
Cervical anastomosis	3 (3.3%)	6 (23.1%)		2 (3.8%)	6 (23.1%)	
Lymph node dissection	91 (100%)	26 (100%)	1	52 (100%)	26 (100%)	1
Relevant abdomino/thoracic extended procedures (additional to esophagectomy) [*n*]	Major lung resection: 1	Major lung resection: 1		Major lung resection: 0	Major lung resection: 1	
	Minor lung resection: 4	Minor lung resection: 2		Minor lung resection: 4	Minor lung resection: 2	
	Minor liver resection: 9	Minor liver resection: 2		Minor liver resection: 4	Minor liver resection: 2	
	Jejunum catheter: 3	Jejunum catheter: 1		Jejunum catheter: 2	Jejunum catheter: 1	
	Cholecystectomy: 4	Cholecystectomy: 0		Cholecystectomy: 2	Cholecystectomy: 0	
	Colon resection: 2	Colon resection: 1		Colon resection: 0	Colon resection: 1	
	Appendectomy: 2	Appendectomy: 0		Appendectomy: 1	Appendectomy: 0	
	Omentectomy: 3	Omentectomy: 1		Omentectomy: 1	Omentectomy: 1	
	Left adrenalectomy: 1	Left adrenalectomy: 0		Left adrenalectomy: 0	Left adrenalectomy: 0	
	Other minor resections: 4	Other minor resections: 2		Other minor resections: 1	Other minor resections: 2	
n patients	27 (29.7%)	9 (34.6%)	0.6366	13 (25.0%)	9 (34.6%)	0.4286
Duration of the thoracic part of esophagectomy procedure [min]	126 (67–423)	127.5 (45.0–228.0)[b]	0.2078	119.5 (67.0–304.0)	127.5 (45.0–228.0)[b]	0.5955
Total duration of surgery [min]	297 (177–635)	296 (191–537)	0.9556	285.5 (177.0–534.0)	296.0 (191.0–537.0)	0.7829
Blood loss [ml]	500 (50–2500)	600 (200–4800)	0.3454	505 (100–2500)	600 (200–4800)	0.4501
IO transfusion [*n* pat]	24 (26.4%)	5 (19.2%)	0.6084	16 (30.8%)	5 (19.2%)	0.4172
PO transfusion [*n* pat]	24 (26.4%)	12 (46.2%)	0.0898	16 (30.8%)	12 (46.2%)	0.2156
Peridural anesthesia	69 (75.8%)	18 (69.2%)	0.6109	35 (67.3%)	18 (69.2%)	1

Data are given in median and minimum to maximum ranges or *n* (%). [a]Esophago-gastrectomy with colon interposition in one case. [b]Not available retrospectively in 2 patients. *psm* Propensity score matched, *COS* Conventional open surgery (i.e., laparotomy/thoracotomy, including patients who underwent conversion from an initially intended LAE to open surgery), *LAE* hybrid minimally invasive, laparoscopically assisted esophagectomy (i.e., laparoscopy/thoracotomy), *IO* Intraoperative, *PO* Postoperative

rates of the two groups was confirmed by the Kaplan–Meier curve comparison with log-rank test adjusted by postoperative discharge, re-do surgery, and mortality: Fig. 1a shows the difference of cumulative postoperative pneumonia incidence at POD 30 ($p = 0.0030$), whereas no differences in cumulative incidences of postoperative respiratory impairment, indicated by reduced oxygenation index (PF/R < 300 mmHg), were observed ($p = 0.1063$, Fig. 1b). In line, patients from the statin(+) group presented with significantly longer duration of postoperative stay on ICU as well as longer total duration of postoperative hospitalization (Tables 3 and 4).

Outcome analysis after propensity score matching

The 26 patients from the statin(+) group were matched with 52 statin-naïve patients by propensity score, which was calculated by relevant variables of preoperative patient or procedure characteristics. Thereafter, relevant characteristics of the study groups were widely balanced (Tables 1 and 2). The main results of the native two-group comparison were confirmed by the analysis of the matched patient cohorts. Even after PSM, postoperative pulmonary outcome was significantly impaired in patients from the statin(+) group reflected by both a significantly higher postoperative pneumonia rate in the two-group comparison ($p = 0.0317$, OR 3.022, 95% CI 1.165–7.892, Tables 3 and 4) as well as a higher cumulative pneumonia incidence calculated by Kaplan–Meier estimation and log-rank test ($p = 0.0468$, Fig. 2a), whereas still no differences in cumulative incidences of postoperative respiratory impairment, indicated by reduced oxygenation

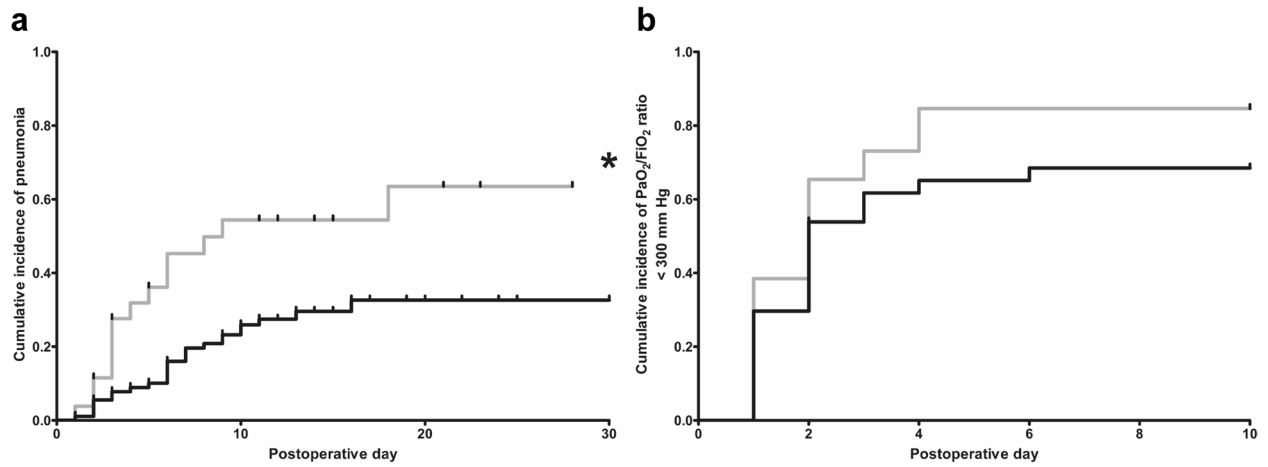


Fig. 1 Cumulative incidences of postoperative pneumonia and postoperative reduced oxygenation index (< 300 mmHg) of the unmatched patient cohort. Black line: statin-naïve patients [statin(−) group, $n=91$]. Gray line: patients with perioperative statin medication [statin(+) group, $n=26$]. Patients, who were discharged, died, or suffered from re-do (revision) surgery were censored from the analysis of cumulative incidences since the day of the event. Vertical ticks indicate censored data. **a** Kaplan–Meier estimation of cumulative incidences of postoperative pneumonia of all unmatched patients. Asterisk indicates significant differences in the cumulative incidence of postoperative pneumonia between both groups at postoperative day 30 ($p=0.0030$). **b** Kaplan–Meier estimation of cumulative incidences of reduced oxygenation index ($PaO_2/FiO_2 < 300$ mmHg) of all unmatched patients. No difference between both groups was observed at postoperative day 10 ($p=0.1063$)

Table 3 Postoperative C-reactive protein values and leukocyte counts in peripheral blood

Variable	All patients					Propensity score-matched patients				
	Statin (−) patients ($n=91$)		Statin (+) patients ($n=26$)		*p* value	psmStatin (−) patients ($n=52$)		psmStatin (+) patients ($n=26$)		*p* value
Leukocytes [giga/l]		MV		MV			MV		MV	
POD 0 (on arrival at ICU)	9.2 (3.6–29.6)	1	8.9 (3.0–24.6)	0	0.5736	9.5 (3.7–29.6)	1	8.9 (3.0–24.6)	0	0.5180
POD 1	10.4 (4.0–23–6)	1	10.7 (5.3–23.1)	0	0.4664	10.2 (4.4–23.6)	0	10.7 (5.3–23.1)	0	0.5076
POD 2	11.2 (1.8–24.6)	0	11.5 (6.7–19.0)	0	0.4607	10.4 (1.8–24.6)	0	11.5 (6.7–19.0)	0	0.4297
POD 3	8.9 (4.4–34.1)	8	9.5 (1.9–17.9)	0	0.9010	8.9 (4.4–34.1)	2	9.5 (1.9–17.9)	0	0.8652
POD 4	7.6 (3.9–106.0)	14	8.4 (2.7–18.2)	1	0.5285	7.4 (3.9–106.0)	7	8.4 (2.7–18.2)	1	0.5728
POD 5	7.7 (3.4–21.5)	23	8.4 (3.9–16.7)	2	0.5572	7.7 (3.4–16.6)	13	8.4 (3.9–16.7)	2	0.7989
POD 6	8.7 (3.4–23.1)	26	9.9 (5.8–15.2)	5	0.2070	9.3 (3.4–19.2)	12	9.9 (5.8–15.2)	5	0.5286
POD 7	9.4 (3.0–29.0)	25	10.7 (5.4–15.8)	5	0.2578	9.8 (3.0–29.0)	16	10.7 (5.4–15.8)	5	0.4923
POD 8	11.0 (4.1–33.3)	36	11.0 (5.9–22.4)	5	0.8800	10.7 (4.1–31.5)	17	11.0 (5.9–22.4)	5	0.8990
POD 9	11.6 (4.5–49.7)	30	11.5 (6.2–22.3)	3	0.8923	12.3 (4.9–40.7)	17	11.5 (6.2–22.3)	3	0.8115
POD 10	13.0 (4.2–38.7)	37	11.3 (7.1–28.2)	5	0.7101	12.4 (4.7–37.8)	18	11.3 (7.1–28.2)	5	0.7950
C-reactive protein [mg/l]		MV		MV			MV		MV	
POD 0 (on arrival at ICU)	5.2 (0–256.0)	1	5.2 (0.5–106.7)	2	0.7730	8.7 (0.0–256.0)	0	5.2 (0.5–106.7)	2	0.6670
POD 1	93.4 (31.2–226.2)	1	88.4 (48.9–155.3)	0	0.8296	94.4 (35.4–226.2)	0	88.4 (48.9–155.3)	0	0.7385
POD 2	202.8 (55.3–359.4)	0	211.0 (110.7–329.3)	0	0.2472	194.0 (55.3–359.4)	0	211.0 (110.7–329.3)	0	0.2091
POD 3	185.1 (68.5–365.4)	8	234.1 (26.3–403.9)	0	0.1290	186.3 (68.5–365.4)	2	234.1 (26.3–403.9)	0	0.0683
POD 4	156.9 (30.1–405.8)	14	194.3 (85.8–410.0)	1	0.0557	156.9 (51.4–405.8)	7	194.3 (85.8–410.0)	1	0.0931
POD 5	138.1 (25.4–348.0)	23	150.1 (40.7–539.1)	2	0.4632	139.9 (25.4–345.2)	13	150.1 (40.7–539.1)	2	0.4748
POD 6	124.5 (6.0–423.2)	25	148.8 (36.8–390.9)	5	0.3188	123.8 (14.1–423.2)	12	148.8 (36.8–390.9)	5	0.3351
POD 7	122.5 (8.3–445.1)	25	135.4 (19.9–316.4)	5	0.4019	133.7 (8.3–445.1)	16	135.4 (19.9–316.4)	5	0.6611
POD 8	147.1 (6.0–431.8)	36	213.6 (12.0–491.9)	5	0.4714	147.1 (6.0–431.8)	17	213.6 (12.0–491.9)	5	0.6116
POD 9	138.2 (5.6–412.9)	32	153.2 (22.1–446.9)	3	0.3319	138.2 (5.6–412.9)	17	153.2 (22.1–446.9)	3	0.4550
POD 10	148.7 (4.9–393.9)	37	159.8 (22.9–310.5)	5	0.3018	127.2 (8.1–393.9)	18	159.8 (22.9–310.5)	5	0.2638

Data are given in median and minimum to maximum ranges. *MV* Missing values, including patients who died during postoperative day 0–10, *psm* Propensity score matched, *POD* Postoperative day

Table 4 Postoperative outcome

Variable	All patients			Propensity score-matched patients		
	Statin (−) patients (*n* = 91)	Statin (+) patients (*n* = 26)	*p* value	psmStatin (−) patients (*n* = 52)	psmStatin (+) patients (n = 26)	*p* value
PO hospital stay						
Total [d][a]	17 (9–141)	25 (11–75)	0.0068	16.5 (9–141)	25 (11–75)	0.0185
Initial PO stay on ICU [d][a]	4 (1–76)	6 (2–58)	0.0729	5 (1–76)	6 (2–58)	0.2556
Return to ICU [n patients]	17 (18.7%)	3 (11.5%)	0.5578	8 (15.4%)	3 (11.5%)	0.7429
Cumulative PO stay on ICU [d][a]	5 (1–84)	11.5 (2–58)	0.0221	5 (1–84)	11.5 (2–58)	0.0612
Initial postoperative extubation [h]	0 (0–11)	0 (0–4)	0.8171	0 (0–11)	0 (0–4)	0.8666
Cumulative perioperative mechanical ventilation [h]	12.6 (4.8–2280)	13.5 (5.2–788.3)	0.5184	12.7 (5.3–876.9)	13.5 (5.2–788.3)	0.6146
Pneumonia[b]	30 (33.0%)	17 (65.4%)	0.0057	20 (38.5%)	17 (65.4%)	0.0317
Pneumonia diagnosis on POD	6 (1–25)	4 (1–18)	0.1390	6 (1–25)	4 (1–18)	0.2507
Tracheotomy	13 (14.3%)	7 (26.9%)	0.1462	10 (19.2%)	7 (26.9%)	0.5619
Extubation in the operating room	22 (24.2%)	6 (23.1%)	1	12 (23.1%)	6 (23.1%)	1
Initial extubation during the first 12 h postoperatively	75 (82.4%)	21 (80.8%)	0.7808	42 (80.8%)	21 (80.8%)	1
Re-intubation[c]	22 (24.2%)	10 (38.5%)	0.2111	15 (28.9%)	10 (38.5%)	0.4453
Perioperative oxygenation index < 300 mm Hg [*n* patients][d]						
First intraoperative	21 (23.1%)	6 (23.1%)	1	14 (26.9%)	6	0.7891
POD 0 (on arrival at ICU)	32 (35.2%)	8 (30.8%)	0.3429	22 (42.3%)	8	0.4594
POD 1	27 (29.7%)	10 (38.5%)	0.4743	19 (36.5%)	10	1
POD 2	37 (40.7%)	14 (53.9%)	0.2667	20 (38.5%)	14	0.2312
POD 3	28 (30.8%)	14 (53.9%)	0.0382	17 (32.7%)	14	0.0889
POD 4	19* (21.1%)	12 (46.2%)	0.0215	10* (19.6%)	12	0.0187
POD 5	17* (18.9%)	10 (38.5%)	0.0624	11* (21.6%)	10	0.1752
POD 6	21* (23.3%)	7* (28.0%)	0.6087	12* (23.5%)	7*	0.7795
POD 7	19* (21.1%)	10* (40.0%)	0.0695	14* (27.5%)	10*	0.3015
POD 8	20* (22.2%)	10* (40.0%)	0.1201	12* (23.5%)	10*	0.1799
POD 9	19* (21.1%)	7* (28.0%)	0.5890	12* (23.5%)	7*	0.7795
POD 10	17* (18.9%)	7** (29.2%)	0.2730	10* (19.6%)	7**	0.3860
Re-do (revision) surgery during POD 1–30	12 (13.2%)	9 (34.6%)	0.2278	10 (19.2%)	6 (34.6%)	0.7690
Anastomotic complications[e]	18 (19.8%)	6 (23.1%)	0.7842	11 (21.2%)	6 (23.1%)	1
PO 30-day mortality [*n*]	6 (6.6%)	3 (11.5%)	0.4139	5 (9.6%)	3 (11.5%)	1

Data are given in median and minimum to maximum ranges or *n* (%). [a]Patients who suffered from in-hospital mortality were excluded from the analysis of postoperative length of stays. [b]Overall pneumonia rate, irrespectively from re-do surgery. [c]Re-intubation due to acute respiratory insufficiency excluding re-intubations due to re-do (revision) surgery. [d]Irrespectively from re-do surgery; patients who died during POD 0–10 were excluded from the analysis upon their death: asterisks (* and **) indicate the number of deaths on the respective postoperative day. [e]Anastomotic complications, including insufficiency and/or gastric tube necrosis requiring therapy (stent, endo-vacuum therapy, or re-do surgery). *psm* Propensity score matched; *PO* Postoperative, *ICU* Intensive care unit, includes medium care unit; *POD* Postoperative day

index (PF/R < 300 mmHg), were observed ($p = 0.2980$, Fig. 2b).

Correlations between statin medication, postoperative pneumonia, and markers of inflammation

Perioperative statin medication correlated significantly with the pneumonia rate of both the unmatched ($r_{sp} = 0.275$, $p = 0.0027$) as well as propensity score-matched patient cohorts ($r_{sp} = 0.254$, $p = 0.0247$, Table 5). Although no obvious differences were observed between the unmatched and matched patient groups regarding perioperative markers of inflammation, pneumonia vice versa results in positive correlations with postoperative CRP values and leukocyte counts beyond postoperative days 3 or 4, respectively (Tables 4 and 5). However, this effect was attenuated in statin(+) patients (Table 5).

Discussion

Postoperative pulmonary outcome

Patients after abdomino-thoracic esophagectomy are highly vulnerable for the development of postoperative respiratory impairment as well as pulmonary

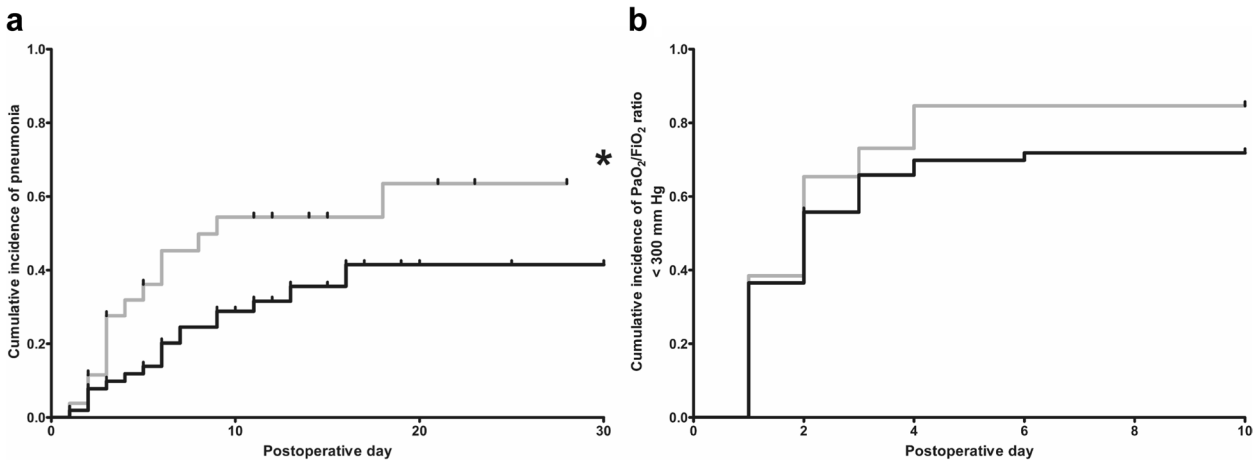


Fig. 2 Cumulative incidences of postoperative pneumonia and postoperative reduced oxygenation index (< 300 mmHg) of the matched patient cohort by propensity score. Black line: statin-naïve patients [statin(−) group, $n = 52$]. Gray line: patients with perioperative statin medication [statin(+) group, $n = 26$]. Patients who were discharged, died, or suffered from re-do (revision) surgery were censored from the analysis of cumulative incidences since the day of the event. Vertical ticks indicate censored data. **a** Kaplan–Meier estimation of cumulative incidences of postoperative pneumonia of matched patients. Asterisk indicates significant differences in the cumulative incidence of postoperative pneumonia between both groups at postoperative day 30 ($p = 0.0468$). **b** Kaplan–Meier estimation of cumulative incidences of reduced oxygenation index ($PaO_2/FiO_2 < 300$ mmHg) of matched patients. No difference between both groups was observed at postoperative day 10 ($p = 0.2980$)

Table 5 Correlation analysis

	Statin (-) patients r (sp)	Statin (+) patients r (sp)		Statin (-) patients r (sp)	Statin (+) patients r (sp)	Legend
CRP_POD 0	0.13	0.11	Leuk_POD 0	0.32 *	0.03	0
CRP_POD 1	0.14	0.09	Leuk_POD 1	0.28 *	0.30	0.1
CRP_POD 2	0.09	0.29	Leuk_POD 2	0.15	0.28	0.2
CRP_POD 3	0.44 *	0.24	Leuk_POD 3	0.12	0.16	0.3
CRP_POD 4	0.49 *	0.46 *	Leuk_POD 4	0.21	0.41 *	0.4
CRP_POD 5	0.47 *	0.38	Leuk_POD 5	0.37 *	0.70 *	0.5
CRP_POD 6	0.45 *	0.35	Leuk_POD 6	0.22	0.55 *	0.6
CRP_POD 7	0.40 *	0.44 *	Leuk_POD 7	0.31	0.35	0.7
CRP_POD 8	0.46 *	0.16	Leuk_POD 8	0.32	0.19	0.8
CRP_POD 9	0.50 *	0.23	Leuk_POD 9	0.56 *	0.29	0.9
CRP_POD 10	0.42 *	0.28	Leuk_POD 10	0.41 *	-0.03	1

Values of the propensity score-matched patient cohorts were included in Spearman's rho rank correlation analysis (i.e., $n = 52$ statin-naïve and $n = 26$ patients, who received statin medication perioperatively). Correlations between postoperative pneumonia and postoperative C-reactive protein (CRP) values as well as postoperative leukocyte (Leuk) counts in peripheral blood immediately after surgery (POD0) and during postoperative days (POD) 1–10 are presented by the heatmap with no correlation ($r_{sp} = 0$) in yellow to strong correlation ($r_{sp} = 1$) in red. Asterisks indicate statistical significance (p value ≤ 0.05)

complications (Reichert et al. 2020, 2019). Development of PPC after abdomino-thoracic esophagectomy is caused by a multifactorial pathogenesis and impairs patient outcome dramatically (Molena et al. 2014); hence, investigation and modulation of factors contributing to postoperative pneumonia are mandatory to sustainably improve perioperative patient care after this type of high-risk surgery. The results of the present work are in line with the hypothesis, whether statin medication has an influence on postoperative pulmonary outcome concerning pneumonia development in patients after abdomino-thoracic esophagectomy. These effects were shown in unmatched patient cohorts and were constantly confirmed after PSM of statin-naïve patients with the statin(+) patient cohort. Thereby, patients under perioperative statin medication were investigated with an impaired pulmonary outcome by increasing pneumonia rates after abdomino-thoracic esophagectomy. This harmful effect in statin(+) patients was shown in the absence of other factors, which had been previously evaluated as possible contributors to pulmonary morbidity, including rates of conventional open or hybrid minimally invasive,

laparoscopically assisted surgery, the duration of the abdominal part of abdomino-thoracic esophagectomy or preoperative induction (chemo-irradiation-) therapy (Reichert et al. 2020, 2019; Mariette et al. 2019; Schroder et al. 2019; Reynolds et al. 2006).

Potential effects of statin medication on the development of postoperative pneumonia

Concerning initial dysbalances in patient characteristics between both the statin(−) and statin(+) patient cohorts, one has to be aware that statin medication is indicated for the primary as well as secondary prophylaxis of thromboembolic cardiovascular events in lipidemic and atherosclerotic patients. This might be the reason why patients from the statin(+) group were older and suffered more frequently from chronical illness and it must be noted that the slightly sicker patients were filtered out of the group of statin-naïve patients by propensity score for comparison. Whether the statin effect on pulmonary outcome after esophagectomy might be also evident in younger and more healthy patients at the time of surgery remains elusive from the present data analysis. Apart from the lipid-lowering effect of statins through the competitive inhibition of 3-hydroxy-3-methyl-glutaryl-CoA reductase (Lemos et al. 2004), these drugs have some properties that interfere with inflammatory responses. Statins suppress the expression of adhesion molecules and consecutively inhibit the activation and recruitment of inflammatory cells and decrease inflammasome activity as well as production of pro-inflammatory cytokines including Il-1, Il-6, TNF-α, and CRP in vitro as well as in vivo (Koushki et al. 2020; Meng et al. 2020). Thereby, some of the anti-inflammatory effects of statins are mainly responsible for plaque stabilization in atherosclerotic diseases (Koushki et al. 2020), but statins also systemically affect innate immunity and host defense (Koushki et al. 2020; Meyer et al. 2020; Meng et al. 2020; Jesus Oliveira et al. 2020; Oliveira et al. 2020). The role of statins in the regulation of inflammasome activation, especially NLRP3 and consecutively the interleukin-1 release, remains controversial; however, statins suppress Toll-like receptor 4 signaling and NF-*k*B pathway, which are key players in innate immunity (Koushki et al. 2020; Meyer et al. 2020). In line with these findings, atorvastatin affects peripheral blood mononuclear cells with reduced production of pro-inflammatory cytokines, including TNF-*a* and interleukin-6 (Oliveira et al. 2020). Nevertheless, the actions of statins on the immune system are complex and multifaceted and by now their anti-inflammatory effects and their role in innate immunity are not completely understood (Koushki et al. 2020). Especially the impact of statin medication on perioperative inflammation and postoperative complication development has been poorly investigated until now. Notably, in the present study, the most commonly used statins were lipophilic including simvastatin and atorvastatin (23 of 26 patients). Slight differences in their pleiotropic effects had been reported in the literature, but even hydrophilic statins as pravastatin [used in the remaining three statin(+) patients] have similar effects on inflammatory pathways (Koushki et al. 2020). In the past, Krivoy et al. showed a reduction of systemic CRP levels during high-dosage therapy with atorvastatin after coronary artery bypass graft surgery (Krivoy et al. 2008). However, the statin dosages within the therapeutic ranges applied in patients of the present study were much lower compared with those being effective on postoperative systemic CRP levels in the experimental setting reported by Krivoy and colleagues (Krivoy et al. 2008). But the findings with a suppressed CRP response upon inflammatory stimuli go in line with correlation analyses from our study. In correlation analyses, we found a rather strong and significant correlation between development of postoperative pneumonia, an infectious complication, which is regularly diagnosed during the early postoperative phase (Reichert et al. 2020, 2019), and postoperative CRP values in statin(−) patients. This CRP response corresponding to pneumonia development was attenuated in statin(+) patients, although the rate of postoperative pneumonia correlated significantly with statin medication. The latter might be a detrimental result of an impaired host defense in patients under statin medication driven by the interruption of various pro-inflammatory pathways. Also, Meyer et al. recently described the impact of statin medication on perioperative systemic inflammatory reaction after lung cancer surgery (Meyer et al. 2020). Although they found no impact of perioperative statin medication on postoperative markers of systemic inflammation in their overall results, they investigated a gender-specific effect of statin-naïve and statin-taking patients on postoperative systemic CRP levels (Meyer et al. 2020). Furthermore, they confirmed their clinical results by a translational research approach and pronounced that statin medication the other way around leads to a more pro-inflammatory phenotype upon (surgical) trauma on a monocytic level in their experimental setting (Meyer et al. 2020).

These immunomodulatory actions of statins might be beneficial in diseases caused by chronic inflammation or autoimmunity, e.g., rheumatoid arthritis and multiple sclerosis, or an overwhelming and misdirected immune reaction, e.g., in the early phase of sepsis (Jesus Oliveira et al. 2020; Patel et al. 2012) as well as allograft rejection after transplantation (Johnson et al. 2003). However, immunomodulation to an anti-inflammatory phenotype might be harmful and impairs host defense under

infectious conditions. The results of the present study show significantly higher rates of postoperative pneumonia in patients under statin medication after esophagectomy, a surgical procedure which results in an extended surgical trauma to the chest and a highly vulnerable lung (Reichert et al. 2020, 2019). Although no differences were observed in the postoperative systemic inflammatory response in the reported patient cohorts, indicated by systemic CRP levels, the extraordinarily high rate of postoperative pneumonia development in statin(+) compared with statin-naïve patients after abdomino-thoracic esophagectomy might be a result of the anti-inflammatory or — in cases of impaired host defense against bacterial infection by suppression of TLR4 pathways — immunosuppressive effects through perioperative statin medication. Impaired systemic host defense against bacterial infection of the lung as well as the inadequate reaction of local, pulmonary monocytes upon surgical trauma-induced CRP as interpreted from the work by Meyer et al. (Meyer et al. 2020) may result in high pneumonia rates, impaired oxygenation on postoperative days 3 and 4, impaired systemic inflammatory response to pneumonia investigated in the correlation analyses, prolonged postoperative critical illness, and prolonged length of postoperative stay at the intensive care unit as well as longer duration of total hospitalization in statin(+) patients.

By contrast, some authors reported beneficial effects of statin use in patients who underwent non-cardiac surgery. Recently, Komatsu and colleagues published a data bank analysis and reported slightly reduced rates of postoperative respiratory complications, reduced in-hospital mortality, and shorter duration of hospitalization in statin users after non-cardiac surgery (Komatsu et al. 2020). Also, London and Berwanger and their colleagues found a reduction of risk for complications, especially of cardiovascular morbidity in patients under perioperative statin medication from their large propensity score-matched data bank analyses of non-cardiac surgery (London et al. 2017; Berwanger et al. 2016), as well as in the meta-analysis by Ma et al., the reduction of postoperative cardiovascular complications was confirmed for statin users after non-cardiac surgery (Ma et al. 2018). However, in the prospectively randomized controlled LOAD trial, these beneficial cardiovascular effects were not reproduced under medication with atorvastatin (Berwanger et al. 2017). Nevertheless, in these studies, major thoracic surgery, especially abdomino-thoracic esophagectomy is highly underrepresented (Berwanger et al. 2016, 2017); thus, a generalization and transfer of the results to perioperative patient care and complication rates after esophagectomies might not be suitable. In a prospectively randomized controlled trial including 31 patients by Shyamsundar et al., perioperative high-dosage treatment with simvastatin compared with placebo resulted in deceased levels of systemic inflammatory markers, but did not influence on the rate of PPC (Shyamsundar et al. 2014).

Nevertheless, as abdomino-thoracic esophagectomies are surgical procedures with an extraordinarily high risk for severe, especially pulmonary complications, the results of the present study should be noted with utmost care. In a previous work, we have shown high rates of impairments in pulmonary function measured by reduced P/F ratios after abdomino-thoracic esophagectomy and compared them with other types of major thoracic surgery, even those including major trauma to the chest cavity and single-lung ventilation during surgery (Reichert et al. 2019). Herein, we investigated dramatic impairments of lung physiology and pulmonary function (objectified by P/FR perioperatively) after esophagectomy (Reichert et al. 2019). Therefore, the rate of early impairment of pulmonary function after esophagectomy is not mainly influenced by the extent of the trauma and even pain caused by the laparotomy during the abdominal part nor injury of the thoracic cavity and the lung during the thoracic part of the esophagectomy procedure (Reichert et al. 2020). Nevertheless, the incidence of postoperative pneumonia beyond POD 3, which seems to be the day with the highest vulnerability of the lung and consecutively highest risk for developing lung injury following esophagectomy, might be associated with the surgical trauma-induced release of danger-associated molecular patterns (DAMP) which then indirectly harm the lung and consecutively increase the risk to acquire pneumonia (Reichert et al. 2020; D'Journo et al. 2010; Okamura et al. 2015; Katsuta et al. 1998). Thus, a more severe initial DAMP-induced systemic inflammation might have impaired host defense against pneumonia-associated pathogens (Reichert et al. 2020; Babic et al. 2020). We speculate that alterations of local inflammatory response in the lung against pneumonia-associated pathogens upon statin medication lead to a local anti-inflammatory or more specifically immunosuppressive phenotype which then impairs local host defense. This harmful statin effect would result in the higher rate of postoperative pneumonia with a consecutively impaired postoperative patient outcome and prolonged postoperative hospitalization in statin(+) patients of the present study.

Causal role of statins in the development of postoperative pneumonia

According to Bradford Hill's criteria (Hill 1965), the present work investigates a causal role of perioperative statin medication in the development of postoperative pneumonia after abdomino-thoracic esophagectomy.

The strength effect size of perioperative statin medication on postoperative pneumonia development was demonstrated by the OR 3.022 in the analysis of the PSM-matched patient cohorts. Thereby, the significant differences in postoperative pneumonia between both the highly specific statin(−) and statin(+) patient cohorts were consistently observed by the different statistical methods performed. As coherently discussed above, the literature provides plausible explanations of the extent to which statins influence inflammatory pathways and thus favor the development of postoperative pneumonia after esophagectomy. However, further experimental and clinical studies are necessary to investigate confounding factors in patient characteristics, different types of statins, and dose–response relationships, which might influence the effect size of perioperative statin medication on postoperative pneuomonia development.

Limitations of the present study and future aspects

Although relevant patient characteristics, which might influence on postoperative pulmonary outcome after abdomino-thoracic esophagectomy including chronic cardiovascular and pulmonal diseases, were balanced between both groups after PSM, the retrospective character with a relatively small sample size is the strongest limitation of the present study. Hence, no firm conclusions should be drawn from the results, but the present study allows the creation of testable hypotheses for larger-scaled retrospective patient data analyses or prospectively conducted trials regarding the effects of perioperative statin medication to develop strategies that make esophageal surgery safer for our patients.

Conclusion

In conclusion, the pathogenesis of pulmonary morbidity in response to esophagectomy is complex and our results suggest that statin medication might contribute to postoperative pneumonia development. Because the main indication for statin medication is prophylaxis of cardiovascular events for atherosclerotic patients in the long term and although some retrospective studies have shown beneficial effects of statin medication on cardiovascular morbidity after non-cardiac surgery, the results of the present study might support the conclusion to interrupt statin medication perioperatively in appropriate patients with a low risk for severe cardiovascular morbidity undergoing esophagectomy and to prevent them from exceptionally high rates of postoperative pulmonary morbidity. Therefore, this hypothesis generated from our retrospective study needs to be further investigated by prospectively conducted trials.

Abbreviations

ASA: Anesthesiologist's classification of physical health score; CCI: Charlson Comorbidity Index; CRP: C-reactive protein; FiO_2: Fraction of inspired oxygen; ICU: Intensive care unit; Il: Interleukin (Il); NF-*k*B: Nuclear factor *k*B; P/FR: Oxygenation index (i.e., PaO_2/FiO_2 ratio); PaO_2: Arterial pressure of oxygen; POD: Postoperative day; PPC: Postoperative pulmonary complications; PSM: Propensity score pair matching; r_{sp}: Spearman's rank correlation coefficient; TNF-α: Tumor necrosis factor-α.

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Authors' contributions

All authors substantially contributed to the manuscript, and all authors were involved in drafting the work, manuscript writing, or revising it critically for important intellectual content. All authors have read the final version of the manuscript and gave final approval of the version to be published. All authors agree to be accountable for the author's own contributions and to ensure that questions related to the integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. Conception and design of the work: MR, JPK, and WP. Acquisition of data: MR, ML, and MS. Analysis of data: MR and JPK. Interpretation of data: MR and AH. Writing the original draft of the manuscript: MR, ML, and JPK. Substantial revision of the manuscript: MS, WP, and AH.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This retrospective study was performed in accordance with the latest version of the Declaration of Helsinki and was approved by the local ethics committee of the Medical Faculty of the University of Giessen (approval no. 214/15 and 253/16). The data are collected and the manuscript is written and submitted in accordance with the COPE and STROBE guidelines. All patients were treated according to the institutional standard of care.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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11.4 Anlage 4

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Thoracotomy versus video-assisted thoracoscopic surgery (VATS) in stage III empyema—an analysis of 217 consecutive patients

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Abstract

Background Pleural empyema is an infectious disease of the chest cavity, with a high morbidity and mortality. According to the American Thoracic Society, pleural empyema gets graduated into three stages, with surgery being indicated in intermediate stage II and chronic stage III. Evidence for the feasibility of a minimally-invasive video-assisted thoracoscopic approach in stage III empyema for pulmonary decortication is still little.

Methods Retrospective single-center analysis of patients conducted to surgery for chronic stage III pleural empyema from 05/2002 to 04/2014 either by video-assisted thoracoscopic surgery (VATS, $n=110$) or conventional open surgery by thoracotomy ($n=107$). Multiple regression analysis and propensity score matching was used to evaluate the influence of operation technique (thoracotomy versus VATS) on the length of post-operative hospitalization.

Results Operation time was longer in the thoracotomy-group ($p=0.0207$). Conversion rate from VATS to open surgery by thoracotomy was 4.5%. Post-operative complication- (61 patients in thoracotomy- and 55 patients in VATS-group), recurrence- (3 patients in thoracotomy- and 5 in VATS-group) and mortality-rates (6.5% in thoracotomy- and 9.5% in VATS-group) did not differ between both groups; the length of (post-operative) stay at intensive care unit was longer in the VATS-group ($p=0.0023$). Duration of chest tube drainage and prolonged air leak rate were similar among both groups, leading to a similar overall and post-operative length of hospital stay in both groups. Adjusted to clinically and statistically relevant confounders, multiple regression analysis showed an influence of the surgical technique on length of post-operative stay after pair matching of the patients ($n=84$ in each group) by propensity score ($B=-0.179$ for thoracotomy $=0$ and VATS $=1$, $p=0.032$) leading to a reduction of 0.836 days after a VATS-approach compared to thoracotomy.

Conclusions VATS in late stage (III) pleural empyema is feasible and safe. The decrease in post-operative hospitalization demonstrated by adjusted multiple regression analysis may indicate the minimally-invasive approach being safe, more tolerable for patients, and more effective.

Keywords Video-assisted thoracoscopic surgery · VATS · Thoracotomy · Pleural empyema · Empyema thoracis · Pleural infection

Pleural empyema is an infectious disease of the pleural space with bacterial pneumonia as the most common cause, when bacteria invade the pleural cavity [1]. Other common causes for pleural empyema are previous operation, other thoracic interventions, esophageal diseases, and abdominal sepsis

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[1]. Pleural empyema is associated with high morbidity and mortality, regardless of the underlying disease [1].

In 1962, pleural empyema was classified by the American Thoracic Society (ATS) into three stages, whereby the earlier stage migrates into the next one, when therapy is insufficient: early exudative (I), fibropurulent (II), and late (chronic) organized stage (III) [2]. In late stage (III) pleural empyema, the lung gets gradually restricted by a rigid fibrous cortex which hinders the lung to re-expand even after evacuation of all pleural fluid collections [2]. Therapy is stage-dependent and focuses on controlling the infectious focus, evacuation of fluid and pus, and on re-expansion of the lung: chest tube drainage in early stages, intrathoracic fibrinolysis as well as surgery for evacuation of septated fluid collections in intermediate stage and surgery for decortication (=removing the rigid fibrous cortex from the visceral pleura of the lung, the diaphragm, the chest wall, and the mediastinum) in the late organized stage [2, 3]. The by far most common approach for decortication in stage III empyema is conventional open surgery (COS) by thoracotomy. Since video-assisted thoracoscopic surgery (VATS) was gradually applied also in more complex thoracic surgical procedures, some few studies have focused on minimally-invasive pleural decortication in stage III empyema. A both high conversion-to-open surgery rate as well as complication rate were reported in the current literature and the acceptance of VATS for late stage (III) empyema has remained poor so far [3].

This study analyzes the influence of the surgical approach (thoracotomy versus VATS) on the length of post-operative hospital stay after surgery for late stage (III) pleural empyema.

Materials and methods

Two-hundred-seventeen patients were operated for lung decortication in stage III pleural empyema between May 2002 and April 2014 and were included into this retrospective analysis. Until February 2011, operations were performed by an open approach by thoracotomy ($n=107$), thereafter, pleural decortications were approached minimal-invasively by VATS ($n=110$).

Patients were treated according to the institutional standard of care. Patient data were analyzed retrospectively from the prospectively maintained institutional database. Inclusion criterium was a stage III pleural empyema with a restrictive pleural scar tissue/fibrous cortex overlying the visceral pleura of the lung as well as the parietal, mediastinal, and diaphragmatic pleura, thus requiring decortication. Bilateral diseases ($n=6$) were not included in this study, recurrent disease after surgical therapy (overall 10 recurrences in 8 patients) was classified as a complication. Patients in who the initial VATS-approach was converted intra-operatively to an open approach by thoracotomy were excluded from further outcome evaluation and regression analysis and conversion from VATS to thoracotomy was classified as an intra-operative complication.

The retrospective collection of data and the study was approved by the local ethics committee (AZ 114/13 and AZ 242/13).

Surgical technique

Patients underwent general anesthesia with a double-lumen endotracheal tubus allowing for selective single-lung ventilation. Surgery was performed in lateral decubitus position. An antero-lateral muscle-sparing thoracotomy in the 4th or 5th intercostal space was applied for COS and usually led to the rupture of the fibrotic empyema capsule immediately on entering the pleural cavity. Thus, evacuation of the fluid components of the empyema was the first step, followed by freeing the lung from its fibrotic capsule (=decortication) as well as dissecting the empyema's capsule off the parietal, mediastinal, and diaphragmatic pleura.

VATS decortication was performed via a three port anterior approach without rib-spreading using a 30 degree camera. In contrast to the standardized sites of the thoracocenteses for anatomic lung resections (two centeses—anterior and posterior axillary line—in the eighth and a third one in the fourth intercostal space, respectively) [4, 5], centeses for VATS decortications were positioned individually and strictly according to the patients' computed tomography scans in order to initially enter the pleural cavity in an area not affected by the empyema but where the lung was in direct contact to the chest wall. In most of the cases, this was cranially and anteriorly on the chest wall, in the area of the 4th intercostal space, anterior axillary line. In uniportal technique, the lung was then gradually mobilized by taking down its adhesions to the chest wall bluntly with an endo-kittner or using the cautery hook as a dissector. Once the mobilization was completed caudally to the diaphragm, two additional basal centeses were set and the operation was continued in a three port technique with the camera put into the antero-basal centesis. Proceeding the dissection latero-dorsally, caution was taken to keep the fibrous scar layer separating the lung from the fluid empyema components intact by peeling the lung off its cortex without entering the empyema "cavity". Having the lung partially or even fully inflated by the anesthetists via the double-lumen tubus usually facilitated this step. Once the lung was completely mobilized not only from the chest wall, the diaphragm, and the mediastinum but also off the empyema's fibrotic capsule, empyemectomy was performed by dissecting the corresponding parts of the capsule off the diaphragm, the chest wall, and the (mainly posterior) mediastinum. However, if

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not done even earlier, the fibrotic capsule quite regularly ruptured during this maneuver and the leaking fluid empyema components were controlled with a large sucker before removal of the capsule was fully completed.

In all patients of both the VATS- and thoracotomy-group, 1–3 chest tubes were placed at the end of the operation and negative pressure was usually applied for at least 2 days and/or until chest X-ray confirmed complete re-expansion of the lung. Chest tubes were removed gradually after air-leakage had stopped and fluid collection was below 300 ml per day.

After surgery, patients were extubated and discharged from Intensive Care Unit (ICU) as soon as possible; once oral alimentation and complete mobilization were achieved, they were discharged home at their earliest convenience for enhanced recovery and return to normal physical activity.

Statistical analysis

Two-group comparisons were performed using GraphPad Prism (Version 5.00 for Windows, GraphPad Software, San Diego California USA, http://www.graphpad.com). Regression analysis as well as propensity score matching was performed using SPSS (IBM SPSS Statistics for Windows, Version 24.0). For descriptive analysis, data of both groups were analyzed using Fisher´s exact or Pearson's χ^2 test for categorical data in cross-tabulation. Normal distribution was tested by Shapiro–Wilk test—all analyzed data were not normally distributed. Man-Whitney-*U* test was used for two-group comparisons of non-parametric data.

Univariate linear regression analysis was used for further evaluating the influence of operation technique (independent variable: thoracotomy = 0 or VATS = 1) on the dependent variable (Y) "length of post-operative hospital stay" (Table 4: model 1). To obtain normal distribution of the dependent variable, data of "length of post-operative hospital stay" were logarithmized. In the first step, univariate linear regression analysis was performed for selected independent variables (Table 5). Those with a high clinical relevance, a significant influence (tested by the previous step), a high regression coefficient (B), and a low correlation (correlation coefficient) amongst each other, tested by Spearman´s Rho, were considered as confounders for adjusting the multiple linear regression analysis (Table 4: model 2) to receive a high adjusted coefficient of determination (r^2). The result of the multiple regression analysis is given as the regression coefficient (*B*).

To obtain a better comparability of both groups regarding pre-operative patient characteristics, propensity score matching of patients from both groups (1:1 pair matching with a match tolerance = 0.05) was performed, followed by a repeat of the regression analysis as described above. Patients ($n = 5$) underwent intra-operative conversion from VATS to open surgery by thoracotomy were initially excluded from this step. To calculate the propensity score of the patients, variables of pre-operative patient characteristics (gender, age, body mass index (BMI), chronic diseases, abuse, operation side, pre-operative hospital stay, pre-operative drainage therapy) were included into a logistic regression model.

p values ≤ 0.05 were considered to indicate statistical significance.

Results

Patient characteristics

Patients in the VATS-group were significantly older and had higher BMI, but otherwise both groups were widely balanced regarding co-morbidities and subsequently pre-operatively assessed ASA-score. A major difference in patients' characteristics was the underlying cause of the pleural empyema (Table 1). The patients' length of stay in hospital prior to surgery as well as the rate and duration of pre-operative drainage/fibrolytic therapy were similar in both groups. However, the rate and duration of pre-operative antibiotic therapy were significantly higher and longer in patients from the VATS- compared with those from the thoracotomy-group, respectively (Table 2).

Operative data

VATS for empyema evacuation and pleural decortication was performed via an anterior approach using ≤ 3 thoracocenteses (less than 3 thoracocenteses in 24 (21.8%) cases). Operative times were significantly shorter in the VATS- compared with the thoracotomy-group ($p = 0.0207$) and were longest ($p = 0.0018$) in those patients who underwent conversion from VATS to an open approach by thoracotomy (operative times in patients converted from VATS to COS: median (range) = 226 (213–314)min; mean ± SD = 241.8 ± 41.3 min). In the thoracotomy-group, more extended procedures (pulmonary (wedge or lobe) resections for pulmonary abscesses and/or inflammatory destroyed lung parenchyma and/or lymph node dissections) were performed and intra-operative blood loss was higher ($p = 0.0018$); however, the rate of blood transfusions was similar between both groups. No significant differences were observed with regard to intra-operative complications. Reasons for conversion from VATS to an open approach by thoracotomy ($n = 5$, 4.5%) were lack of surgical progress in three and pulmonary arterial bleedings in two cases, respectively. In four patients of the thoracotomy-group, a thoracostoma (Clagett window) was primarily performed. The number of chest tubes placed per patient was higher in the VATS-group (Tables 2, 3).

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Table 1 Patient characteristics

Variable	Thoracotomy			Video-assisted thoracoscopic surgery			*p* value
	n (%)	Mean ± SD	Median (range)	*n* (%)	Mean ± SD	Median (range)	
Gender (*n*)							0.6219
Male	82 (76.6%)			88 (80.0)			
Female	25 (23.4%)			22 (20.0)			
Age (years)		54.2 ± 15.9	57 (1–78)		61.3 ± 15.6	63 (13–88)	0.0009
BMI (kg/m^2)		24.4 ± 4.9	23.6 (13.2–36.7)		25.9 ± 4.8	25.2 (17.3–39.9)	0.0311
Chronic diseases (*n* patients)							
COPD	9 (8.4%)			17 (15.5%)			0.1419
Emphysema	3 (2.8%)			3 (2.7%)			1
AH	25 (23.4%)			48 (43.6%)			0.0017
CAD	12 (11.2%)			20 (18.2%)			0.1811
DM	16 (15%)			20 (18.2%)			0.5861
Abuse (*n* patients)							
Nicotin	21 (19.6%)			17 (15.5%)			0.4768
Alcohol	12 (11.2%)			7 (6.4%)			0.2363
Drugs (i.v.)	5 (4.7%)			1 (1%)			0.1157
Previous thoracic surgery (*n* patients)	25 (23.4%)			24 (21.8%)			0.8713
ASA[a]							0.4726
1	3 (2.8%)			2 (1.8%)			
2	39 (36.4%)			30 (27.3%)			
3	55 (51.4%)			66 (60%)			
4	10 (9.3%)			12 (10.9%)			
Side (*n*)							0.4152
Right	55 (51.4%)			63 (57.3%)			
Left	52 (48.6%)			47 (42.7%)			
Etiology (*n* patients)							0.0067
Parapneumonic	24 (22.4%)			45 (40.9%)			
Pneumothorax	4 (3.7%)			3 (2.7%)			
Post-interventional							
Thoracic operation	11 (10.3%)			17 (15.5%)			
Thoracic drainage	5 (4.7%)			7 (6.4%)			
Post-traumatic	21 (19.6%)			6 (5.5%)			
Cancer	14 (13.1%)			10 (9.1%)			
Chronic pleural fluid collection	28 (26.2%)			22 (20.0%)			

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *AH* arterial hypertension, *CAD* coronary artery disease, *DM* diabetes mellitus, *ASA* American society of anesthesiologists classification of physical health (assessed pre-operatively)

[a]pre-operatively assessed

Post-operative outcome

Overall and post-operative lengths of hospital stay as primary endpoints of this study were equal in both groups (Table 2). Post-operative length of stay on ICU was longer in the VATS-group, caused by higher rates of vasoconstrictive therapy as well as of prolonged post-operative mechanical ventilation (Table 2). Rate of post-operative complications did not differ within both groups (115 and 100 post-operative complications in 61 and 55 patients in the thoracotomy- and VATS-group, respectively) nor did the mortality-rate (Table 3). Length of post-operative antibiotic therapy was significantly longer in patients of the VATS-group, although germ detection on intra-operatively obtained samples was equally low in both groups (24.3%). Rate of prolonged air leaks (≥ 7 days) as well as duration of chest tube drainage were similar among both groups (Table 3).

Multiple regression analysis

Linear regression analysis was used to determine the influence of the operation technique (thoracotomy = 0 and

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Table 2 Peri-operative outcome

Variable	Thoracotomy			Video-assisted thoracoscopic surgery			*p* value
	n (%)	Mean ± SD	Median (range)	*n* (%)	Mean ± SD	Median (range)	
Hospital stay (days)[a]							
Total		28.6 ± 25.5	21 (7–214)		28.1 ± 30.7	19.5 (5–232)	0.1528
Pre-operative		11.6 ± 13.5	7 (1–86)		9.8 ± 12.1	5 (2–75)	0.3153
PO		17.0 ± 20.5	12 (2–193)		18.3 ± 26.8	10 (3–230)	0.0811
Stay on ICU (h)[a]							
Total		145.8 ± 317.2	22.4 (0–1517)		319.2 ± 768.2	32.7 (0–5534)	0.0023
PO		114.6 ± 241.0	22.4 (0–1339)		238.4 ± 660.2	30.4 (0–5517)	0.0044
PO mechanical ventilation (*n* patients)[ba]	62 (57.94%)			31 (29.52%)			< 0.0001
Duration (h)[a]		71.4 ± 216.9	7.2 (1.3–1339)		371.0 ± 1025	69.3 (1.7–5517)	< 0.0001
Prolonged (> 120 h) (*n* patients)[ba]	7 (6.54%)			12 (11.42%)			0.0051
Catecholamine on ICU[ca]							
Total (*n* patients)	16 (16.16%)			29 (27.62%)			0.0628
0–24 h PO							
Patients (*n*)	14			29			0.0250
Volume (µg/kgBW/min)		0.129 ± 0.261	0.02 (0.003–0.753)		0.151 ± 0.249	0.079 (0.003–1.249)	0.0639
24–48 h PO							
Patients (*n*)	8			22			0.0103
Volume (µg/kgBW/min)		0.261 ± 0.484	0.089 (0.022–1.443)		0.199 ± 0.534	0.041 (0.002–2.503)	0.3605
48–72 PO							
Patients (*n*)	8			14			0.2638
Volume (µg/kgBW/min)		0.229 ± 0.337	0.118 (0.005–1.016)		0.228 ± 0.527	0.041 (0.001–2.004)	0.4325
Operation time (min)[a]		172.4 ± 70.72	160 (53–386)		152.6 ± 68.14	140 (41–385)	0.0207
Additional surgical procedures[a] (*n* patients)	31 (28.97%)			7 (6.67%)			< 0.0001
Pulmonary (wedge/major) resection (*n* patients)	29			6			
Lymph node assessment (*n* patients)	4			3			
IO blood loss (ml)[a]		779.9 ± 837.4	500 (0–5500)		494.3 ± 477.2	300 (0–2200)	0.0018
Blood transfusion[ad]							
Total (*n* patients)	53 (52.48%)			46 (43.81%)			0.2645
IO (*n* patients)	33 (32.67%)			31 (29.52%)			0.6537
PO (*n* patients)	42 (41.58%)			30 (28.57%)			0.0580
Total EC							
IO (n EC)	83			69			0.3656
PO (n EC)	130			130			0.1532
Antibiotic treatment							
Pre-operative (*n* patients)	67 (62.6%)			84 (76.4%)			0.0384
Pre-operative (days)		7.5 ± 12.5	1 (1–86)		9.2 ± 12.4	1 (1–75)	0.0083
PO (*n* patients) [a]	78 (72.9%)			86 (81.9%)			0.1403
PO (days)[a]		10.2 ± 14.6	6 (1–85)		15.5 ± 28.8	7 (1–230)	0.0172

ICU intensive care unit, *PO* post-operative, *IO* intra-operative, *BW* body weight, *EC* erythrocyte concentrate

[a]Excluding those 5 patients who underwent conversion from VATS to open surgery by thoracotomy

[b]Prolonged mechanical ventilation, acute respiratory insufficiency, and re-intubation were classified as complications

[c]Not available retrospectively in 8 patients of the thoracotomy-group

[d]Not available retrospectively in 6 patients of the thoracotomy-group

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Table 3 Complications and drainage management

Variable	Thoracotomy			Video-assisted thoracoscopic surgery			*p* value
	n (%)	Mean ± SD	Median (range)	*n* (%)	Mean ± SD	Median (range)	
IO complications							
Total (*n*)	16 (15.0%)			14 (12.7%)[a]			0.6964
Conversions (*n*)	–			5 (4.5%)			
Total PO complications (*n* patients)[b]	61 (57.0%)			55 (52.4%)			0.5811
Grade I (*n*) [c]	12			9			
Grade II (*n*)[c]							
Bleeding[d]	5			6			
Pneumonia	13			8			
GI infection	2			2			
TAA	3			2			
Prolonged PO chest drainage therapy ≥ 10days	21			20			
Others	3			5			
Grade IIIa (*n*)[c]							
Re-drainage	12			8			
Bronchoscopy	5			3			
Others	0			3			
Grade IIIb (*n*)[c]							
Recurrent empyema	3			5[e]			
Others[f]	17			8			
Grade IVa (*n*)[c]							
Acute respiratory insufficiency	6			2			
Chronic respiratory insufficiency	9			12			
Acute renal failure	3			4			
Others	1			3			
Mortality (*n* patients) [gb]	7 (6.5%)			10 (9.5%)			0.4588
Pre-operative drainage therapy (*n* patients) [b]	50 (46.7%)			41 (39.0%)			0.2703
Duration (days) [b]		11.1 ± 9.4	10 (1–49)		11.2 ± 13.2	8 (1–73)	0.6008
Number of IO placed chest tubes[khb]							< 0.0001
0 (*n* patients)	2 (1.9%)			0			
1 (*n* patients)	19 (17.8%)			22 (21.0%)			
2 (*n* patients)	81 (75.7%)			61 (58.1%)			
3 (*n* patients)	2 (1.9%)			22 (21.0%)			
PO chest tube duration (days) [bk1]		6.6 ± 3.4	6 (1–17)		6.8 ± 4.2	6 (2–22)	0.7210
≥ 7 days (*n* patients)[jb]	39 (38.6%)			37 (35.6%)			0.6671
> 10 days (*n* patients) [jb]	16 (15.8%)			18 (17.3%)			0.8520

IO intra-operative, *PO* post-operative, *GI* gastro-intestinal, *TAA* tachyarrhythmia absoluta

[a]Including the 5 conversions-to-open surgery

[b]Excluding those 5 patients who underwent conversion from VATS to open surgery by thoracotomy

[c]According to the Dindo-Clavien classification of surgical complications [6]

[d]Requiring blood transfusion

[e]5 patients in the VATS-group suffered from 7 recurrences

[f]Beside redo-procedures for recurrent empyema, 11 patients in the thoracotomy-group underwent 17 operative redo-procedures (including re-thoracotomy for persistent air-leakage ($n=1$), organized hemothorax ($n=1$), destroyed pulmonary lobe ($n=2$), bronchial stump insufficiency ($n=5$ in 4 patients), bleeding ($n=4$) after empyema surgery), and 7 patients in the VATS-group underwent 8 operative redo-procedures (including re-thoracotomy/re-VATS for persistent air-leakage ($n=1$), organized hemothorax ($n=3$), bleeding ($n=1$), recurrent malignant effusion ($n=2$) after empyema surgery)

[g]30 day and in-hospital mortality (according to grade V complications), including sepsis and multi-organ failure (according to grade IV complications) leading to death

[k]Means the duration of the primarily (intra-operatively) placed chest tube/s. Chest tube re-insertion et cetera was classified as a complication. Four patients in the thoracotomy-group were primarily treated with a Clagett window—two with and two without intra-operative placement of a chest tube

[h]No information retrospectively about intra-operative chest tube insertion in three patients of the thoracotomy-group

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Table 3 (continued)

[i]Not available retrospectively in 4 patients of the thoracotomy-group and in 1 patient of the VATS-group who was discharged with a chest tube and a Heimlich valve

[j]Prolonged chest tube duration was considered as indicating a persistent air leak (prolonged parenchyma fistula) and/or high effusion drainage

Table 4 Results of the unadjusted (model 1) and adjusted (model 2) regression analysis (before propensity score matching) testing the influence of operative approach (independent variable: conventional open surgery by thoracotomy = 0 or video-assisted thoracoscopic surgery (VATS) = 1) on the dependent variable (Y) natural logarithm of the "length of post-operative hospital stay"

Model		Coefficients		*p* value	95.0% Confidence interval for B	
		B	Std. error		Lower bound	Upper bound
1	Independent variable:					
	Operation technique (Thoracotomy = 0, VATS = 1)	−0.090	0.098	0.362	−0.284	0.104
2	Independent variable:					
	Operation technique (Thoracotomy = 0, VATS = 1)	−0.148	0.076	0.051	−0.297	0.001
	Confounder:					
	Pre-operative hospital stay (days)	0.004	0.003	0.214	−0.002	0.010
	C-reactive protein—maximum pre-operative (mg/l)	0.001	0.000	0.016	0.000	0.001
	ASA-score pre-operative	0.084	0.059	0.156	−0.032	0.201
	Operation time (min)	0.003	0.001	0.000	0.001	0.004
	Post-operative stay on ICU (h)	0.001	0.000	0.000	0.001	0.001

Dependent variable: Length of post-operative hospital stay (days)

ASA American society of anesthesiologists classification of physical health (assessed pre-operatively), *ICU* Intensive care unit

VATS = 1) on the "length of post-operative hospital stay". In the unadjusted univariate linear regression analysis, an influence of the operation technique (thoracotomy = 0 and VATS = 1) on the dependent variable (Y) "length of post-operative hospital stay" was not detected: regression coefficient (B) = − 0.090, p = 0.362 and r^2 = − 0.001 (Table 4: model 1).

The variables given in Table 5 were considered as clinically and statistically relevant to influence the dependent variable "length of post-operative hospital stay" and thus were chosen for adjusting the multiple linear regression analysis (Table 4: model 2) as confounders. The independent variable "extubation in operating room" was excluded for adjusting the multiple regression analysis due to an high correlation coefficient, "pre-operative drainage therapy" and "post-operative mechanical ventilation" were excluded due to low regression coefficients and low clinical relevance compared to the other independent variables summarized in Table 5. The adjusted regression model resulted in a higher r^2 (= 0.477) and a regression coefficient (B) = − 0.148 (p = 0.051) (Table 4: model 2). This indicates that the dependent variable "length of post-operative hospital stay" decreases by the factor $e^{-0.148}$=0.862 days in the VATS- compared to the thoracotomy-group (p = 0.051, 95% confidence interval: $e^{-0.297}$, $e^{0.001}$).

Propensity score matched analysis

168 patients were evaluated (84 patients in each the VATS- and thoracotomy-group) by propensity score matching and included into further analyses. Propensity score matching led to homogeneity between patients of both groups regarding the pre-operative data and patient characteristics (Table 6). Even after patient matching, the post-operative length of hospital stay was equal between the two groups, but post-operative length of stay on ICU was longer and the rate of vasoconstrictive therapy was higher in the VATS-group in two-group comparisons. After propensity score matching, the rate of patients suffered from prolonged post-operative mechanical ventilation (> 120 h) did not significantly differ (Table 6).

As in the unmatched analysis, an influence of the operation technique (thoracotomy = 0 and VATS = 1) on the dependent variable (Y) "length of post-operative hospital stay" was not even observed in the unadjusted univariate linear regression analysis after propensity score matching: regression coefficient (B) = −0.042, p = 0.705 and r^2 = −0.005 (Table 7: model 1).

The model of the adjusted multiple linear regression analysis was repeated using the propensity score matched data (Table 7: model2). In comparison to the unmatched

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Table 5 Results of univariate linear regression analysis of selected independent variables to evaluate those with a high regression coefficient (*B*) for adjusting the multiple regression analysis before (left columns) and after (right columns) propensity score matching

Independent variable	Before propensity score matching					After propensity score matching				
	Coefficients		*p* value	95.0% Confidence interval for B		Coefficients		*p* value	95.0% Confidence interval for B	
	B	Std. error		Lower bound	Upper bound	B	Std. error		Lower bound	Upper bound
Operation time (min)	0.003	0.001	0.000	0.001	0.004	0.002	0.001	0.012	0.000	0.004
Post-operative stay on ICU (h)	0.001	0.000	0.000	0.001	0.001	0.001	0.000	0.000	0.001	0.001
Extubation in operating room	−0.467	0.093	0.000	−0.651	−0.283	−0.441	0.106	0.000	−0.651	−0.232
Post-operative mechanical ventilation (h)	0.001	0.000	0.000	0.001	0.001	0.001	0.000	0.000	0.001	0.001
ASA-score pre-operative	0.274	0.071	0.000	0.135	0.414	0.287	0.08	0.000	0.128	0.446
C-reactive protein—maximum pre-operative (mg/l)	0.001	0.000	0.008	0.000	0.002	0.001	0.000	0.008	0.000	0.002
Pre-operative drainage therapy (days)	−0.002	0.007	0.818	−0.016	0.013	−0.003	0.008	0.726	−0.018	0.012
Pre-operative hospital stay (days)	0.009	0.004	0.015	0.002	0.017	0.01	0.005	0.043	0.000	0.019

Dependent variable: Length of post-operative hospital stay (days)

ICU Intensive care unit, *ASA* American society of anesthesiologists classification of physical health (assessed pre-operatively)

analysis, the r^2 (=0.485) stayed nearly similar, the regression coefficient (B) = −0.179 changed slightly, but the p value decreased to p = 0.032 (Table 7: model 2). This indicates that the dependent variable "length of post-operative hospital stay" decreases by the factor $e^{-0.179}$=0.836 days in the VATS- compared with the thoracotomy-group after propensity score matching (p = 0.032, 95% confidence interval: $e^{-0.342}$, $e^{-0.016}$).

Discussion

Adequate therapy of pleural empyema is stage-dependent with surgery being considered whenever antibiotic therapy and fluid drainage alone do not achieve sustained infection control and re-expansion of the lung [7].

In intermediate stage II empyema, it has been appraised controversially, if and when surgical therapy is more efficient than prolonged drainage therapy with intra-pleural fibrinolysis [3, 8]. However, it is widely accepted, that VATS is the approach of choice, once decision for surgery has been made [3]. VATS for evacuation of separated fluid components as well as for debridement of the pleural cavity has been shown to be safe and feasible with good peri-operative results and long-term outcomes at least equivalent when compared to the open approach by thoracotomy in an intermediate stage II pleural empyema [3, 8].

In contrast, in late stage III empyema, the need for surgery to control the disease is indisputable; however, it is the surgical approach—thoracotomy versus VATS—which has remained being debated. Until recently, the feasibility of complete decortication of the lung by means of VATS has been questioned, even by experienced thoracic surgeons. In fact, decortication of the visceral pleura allowing the lung to fill up the pleural cavity completely is the by far most important demand in empyema surgery. Any remaining cavity inevitably causes recurrence of pleural effusion, thus bearing the risk of persistent or recurrent infection of the pleural space. So far, the evidence for the feasibility of a minimally-invasive surgical approach in organized stage III pleural empyema is still low [3, 7].

As recently reviewed by an expert consensus statement by Scarci et al., prospective studies in the field of empyema surgery are lacking [3]. Besides, the majority of studies include mixed populations with both stage II and stage III pleural empyema, only the vast minority—three retrospective case series—described a study group of isolated late, organized stage (III) pleural empyema [3, 9–11]. Of those, only two compared the impact of the surgical approach (VATS versus open surgery by thoracotomy) [3, 10, 11]. Since the progression of pleural empyema from an earlier to a later stage is fluent, stratification by stage is subjective, depending on the surgeon's judgment and experience [7].

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Table 6 Patient characteristics and post-operative outcome after propensity score matching ($n = 84$ matched patients in both the VATS- and thoracotomy-group)

Variable	Thoracotomy			Video-assisted thoracoscopic surgery			*p* value
	n (%)	Mean ± SD	Median (range)	*n* (%)	Mean ± SD	Median (range)	
Gender (*n*)[a]							1
Male	66 (78.6%)			65 (77.4%)			
Female	18 (21.4%)			19 (22.6%)			
Age (years)[a]		58 ± 13	61 (26–78)		60 ± 16	61 (13–88)	0.3607
BMI (kg/m^2)[a]		25.2 ± 4.8	25.2 (16.5–36.7)		25.1 ± 4.7	24.5 (17.3–39.9)	0.7319
Chronic diseases (*n* patients)[a]							
COPD	9 (10.7%)			8 (9.5%)			1
Emphysema	2 (2.4%)			2 (2.4%)			1
AH	25 (29.8%)			30 (35.7%)			0.5110
CAD	12 (14.3%)			11 (13.1%)			1
DM	15 (17.9%)			13 (15.5%)			0.8363
ASA							0.2543
1	2 (2.4%)			2 (2.4%)			
2	33 (39.3%)			21 (25.0%)			
3	42 (50.0%)			51 (60.7%)			
4	7 (8.3%)			10 (11.9%)			
Side (*n*)[a]							1
Right	45 (53.6%)			46 (54.8%)			
Left	39 (46.4%)			38 (45.2%)			
Hospital stay (days)							
Total		27 ± 25	19 (7–214)		30 ± 33	22 (5–232)	0.9720
Pre-operative[a]		10 ± 10	6 (1–50)		11 ± 13	6 (2–75)	0.9480
PO		17 ± 22	11 (5–193)		19 ± 29	11 (3–230)	0.3690
PO stay on ICU (h)		115.78 ± 258.06	21.88 (3.07–1339.40)		264.35 ± 712.60	40.63 (0–5517.48)	0.0040
Operation time (min)		167 ± 63	159 (53–386)		157 ± 67	148 (43–385)	0.1700
IO blood loss (ml)		718 ± 660	500 (0–4000)		511 ± 477	315 (0–2200)	0.0110
PO mechanical ventilation (*n* patients)	51 (60.7%)			28 (33.3%)			0.0006
Prolonged (> 120 h) (*n* patients)	5 (6.0%)			12 (14.3%)			0.1228
Catecholamine on ICU[b]							
Total (*n* patients)	11 (13.9%)			22 (26.2%)			0.0782
0–24 h PO (*n* patients)	9 (11.4%)			22 (26.2%)			0.0175
24–48 h PO (*n* patients)	5 (6.3%)			18 (21.4%)			0.0066
48–72 PO (*n* patients)	7 (8.9%)			11 (13.1%)			0.4586
Total PO complications (*n* patients)	38 (45.2%)			38 (45.2%)			1
Mortality (*n* patients)[c]	3 (3.6%)			9 (10.7%)			0.1314
Pre-operative drainage therapy (*n* patients)[a]	37 (44.0%)			36 (42.9%)			1
Duration (days)		11.35 ± 10.05	10 (1–49)		11.33 ± 14.10	7.5 (1–73)	0.5323
PO chest tube duration (days)[de]		6.53 ± 3.41	5 (2–17)		6.95 ± 4.24	6 (2–22)	0.8896
> 10 days (*n* patients)[fe]	12 (15.0%)			17 (20.5%)			0.4158

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *AH* arterial hypertension, *CAD* coronary artery disease, *DM* diabetes mellitus, *ASA* American society of anesthesiologists' classification of physical health (assessed pre-operatively), *PO* post-operative, *ICU* intensive care unit, *IO* intra-operative

[a]Variables used for patient matching by propensity score

[b]Not available retrospectively in 5 patients of the thoracotomy-group

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Table 6 (continued)

[c]30 day and in-hospital mortality (according to grade V complications), including sepsis and multi-organ failure (according to grade IV complications) leading to death

[d]Means the duration of the primarily (intra-operatively) placed chest tube/s. Chest tube re-insertion et cetera was classified as a complication. Two patients in the thoracotomy-group were primarily treated with a Clagett window—both without intra-operative placement of a chest tube

[e]Not available retrospectively in 4 patients of the thoracotomy-group and in 1 patient of the VATS-group who was discharged with a chest tube and a Heimlich valve

[f]Prolonged chest tube duration was considered as indicating a persistent air leak (prolonged parenchyma fistula) and/or high effusion drainage

Table 7 Regression analysis after propensity score matching—Results of the unadjusted (model 1) and adjusted (model 2) regression analysis testing the influence of operative approach (independent variable: conventional open surgery by thoracotomy = 0 or video-assisted thoracoscopic surgery (VATS) = 1) on the dependent variable (Y) natural logarithm of the "length of post-operative hospital stay"

Model—after propensity score matching		Coefficients		*p* value	95.0% Confidence interval for B	
		B	Std. error		Lower bound	Upper bound
1	Independent variable:					
	Operation technique (Thoracotomy = 0, VATS = 1)	−0.042	0.111	0.705	−0.262	0.178
2	Independent variable:					
	Operation technique (Thoracotomy = 0, VATS = 1)	−0.179	0.083	0.032	−0.342	−0.016
	Confounder:					
	Pre-operative hospital stay (days)	0.005	0.004	0.211	−0.003	0.012
	C-reactive protein—maximum pre-operative (mg/l)	0.001	0.000	0.012	0.000	0.002
	ASA-Score pre-operative	0.096	0.066	0.148	−0.034	0.226
	Operation time (min)	0.002	0.001	0.001	0.001	0.003
	Post-operative stay on ICU (h)	0.001	0.000	0.000	0.001	0.001

Dependent variable: Length of post-operative hospital stay (days)

ASA American society of anesthesiologists classification of physical health (assessed pre-operatively), *ICU* Intensive care unit

In this present study, strict criteria were set in order to concentrate on a homogeneous group of real stage III pleural empyema patients. The study period of 12 years enabled for the so far largest cohorts to compare a video-assisted thoracoscopic with an open approach by thoracotomy for surgery in chronic stage III pleural empyema. A selection bias with regard to minimally-invasive or open decortication is excluded to the greatest possible extent because of the metachrone adaption of the two different approaches: after the implementation of a VATS-program for complex thoracic surgical procedures in 02/2011, 93.2% of the patients were primarily conducted to the thoracoscopic approach with a conversion rate of 4.5%. Prior to that surgical treatment of late stage pleural empyema was intended by thoracotomy in 99% of the cases.

The parameter "length of post-operative hospital stay" was used as the primary endpoint for measuring patient outcome after surgery. Multiple regression analysis focused on this same parameter as it is directly influenced by post-operative outcome and thus by chest tube duration, chest tube re-insertion rate and post-operative complications. Confounders for multiple regression analysis were chosen with respect to clinical relevance and statistical correlation amongst each other: post-operative stay at ICU directly influences the length of post-operative hospitalization. The pre-operatively assessed ASA-score reflects co-morbidities of the patients and was chosen for adjusting the regression analysis, thus respecting the recent finding that not age but multi-morbidity is relevant for worse outcome in all surgically treated pleural empyema patients regardless of ATS-stage [12]. The length of pre-operative hospital stay was chosen in order to include the duration of medical treatment before surgery. The operative procedure was repeatedly shown being more challenging, with high conversion rates of a VATS-approach whenever patients got belatedly referred for surgery [13–15]. Furthermore, the post-operative stay after a primarily intended VATS-approach was reported to be longer whenever surgery was delayed by a prolonged conservative/medical treatment attempt [13–15].

It is to note, that this study did not find an obvious difference in the length of post-operative hospital stay between both the VATS- and the thoracotomy-group in two-group comparisons, although post-operative length of stay at ICU was significantly longer and the rate of prolonged mechanical ventilation was higher in VATS-patients (Table 2). The significances in post-operative prolonged mechanical ventilation, prolonged vasoconstrictive therapy, and the consecutive prolonged post-operative length of stay at ICU might

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be a result of higher age and higher rate of co-morbidities (body mass index and chronic diseases) of patients in the VATS-group before patient propensity score matching. Nevertheless, the unmatched adjusted multiple regression analysis (Table 4: model 2) showed a decrease in length of post-operative hospital stay by the factor 0.862 for patients after a VATS-approach when compared to thoracotomy. The results of two-group comparisons regarding post-operative length of stay on ICU and post-operative vasoconstrictive therapy as well as the adjusted regression analysis for the evaluation of differences in the lengths of post-operative hospital stay in dependence to the operation technique (thoracotomy versus VATS) were verified by a (1:1) propensity score matching (Tables 6, 7: model 2). Propensity score matching of the patients not only led to a significance of the adjusted multiple regression analysis ($p = 0.032$) but also confirmed previous results and thus showed a decrease in length of post-operative hospital stay by the factor 0.836 for patients after a VATS-approach. This suggests VATS for lung decortication in stage III pleural empyema not only being equal to but even revealing (slightly) better results compared with the open surgical approach which confirms previous retrospective studies on smaller case series and/or cohorts including patients with mixed stage II and III pleural empyema [3, 10, 11]. The sofar only two published studies dealing with VATS versus thoracotomy for chronic stage III pleural empyema, both revealed a reduction of operation time [10], a shorter post-operative chest tube duration [11], and a shorter length of post-operative hospital stay [10] in the VATS-groups. Other studies on mixed populations of stage II and III pleural empyema demonstrated less pain, fewer post-operative complications, a higher patients' satisfaction with regard to the cosmetic result as well as a faster recovery, and return to work after the VATS-approach [13, 16–18]. An anterior (two- or three port) VATS-approach for chronic pleural empyema similar to the one applied in the present study was reported already before [9–11, 16]; however, then with a quite high conversion-to-open surgery rate of up to 61.6% (0–61.6%) in mixed patient cohorts with stage II and III pleural empyema [3]. The conversion rate as well as the overall result of a minimally-invasive surgical treatment was found to be dependent on the experience of the surgeons [10].

In conclusion, based on the results of the present study, VATS is safely feasible in organized, late stage III pleural empyema, and should thus be considered as the preferred approach as long as complete pulmonary decortication is achieved, which is a prerequisite for complete re-expansion of the lung. The parameter "length of post-operative hospital stay" reflects post-operative outcome data and co-morbidities of patients conducted to surgery for stage III pleural empyema. A decrease in post-operative hospitalization in the adjusted multiple regression analysis of patients after a VATS-approach compared with thoracotomy for late stage pleural empyema may indicates that the minimally-invasive approach is safe, more tolerable for patients and more effective.

Compliance with ethical standards

Disclosures Martin Reichert, Bernd Pösentrup, Andreas Hecker, Emmanuel Schneck, Jörn Pons-Kühnemann, Florian Augustin, Winfried Padberg, Dietmar Öfner, and Johannes Bodner have no conflicts of interest or financial ties to disclose.

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11.5 Anlage 5

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Original Article

Lung decortication in phase III pleural empyema by video-assisted thoracoscopic surgery (VATS)—results of a learning curve study

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Background: Pleural empyema (PE) is a devastating disease with a high morbidity and mortality. According to the American Thoracic Society it is graduated into three phases and surgery is indicated in intermediate phase II and organized phase III. In the latter, open decortication of the lung via thoracotomy is the gold standard whereas the evidence for feasibility and safety of a minimally-invasive video-assisted thoracoscopic approach is still poor.

Methods: Retrospective single-center analysis of patients undergoing surgery for phase III PE from 02/2011 to 03/2015 [n=138, including n=130 VATS approach (n=3 of them with bilateral disease) and n=8 open approach]. The learning curve was assessed by grouping those 127 patients with unilateral disease who underwent a video-assisted thoracoscopic approach into two groups: VATS-1 (03/2011 to 06/2012, n=43) and VATS-2 (06/2012 to 03/2015, n=84).

Results: ASA-scores (P=0.0279) and rate of pre-operative drainage therapy (P=0.0534) were higher in VATS-2 patients. Operating times were longer in VATS-1 (P=0.0308), intra-operative complication as well as conversion to open surgery rates did both not differ. Rates of post-operative vasoconstrictive therapy (P=0.0191) and prolonged mechanical ventilation (P=0.0560) were both higher in VATS-2, however, post-operative length of stay (LOS) at intensive care unit, overall post-operative LOS and post-operative complication rate were similar in both groups.

Conclusions: Video-assisted thoracoscopic surgery is feasible for evacuation and decortication in late phase III PE. A learning curve of approximately 40 cases is sufficient to gain procedure-specific surgical skills and thus reduce the operating times sufficiently.

Keywords: Video-assisted thoracoscopic surgery (VATS); learning curve; pleural empyema (PE); lung decortication

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Introduction

Pleural empyema (PE) is an infectious condition of the pleural cavity (1). The most frequent cause of PE is pneumonia, when a pre-existing parapneumonic effusion gets superinfected by bacteria, often due to perforation of a subpleural pulmonary abscess (2,3). Other common causes are previous thoracic surgery or other invasive thoracic interventions, esophageal diseases, trauma, sub-diaphragmatic infections and sepsis (3,4). PE itself is associated with high morbidity and mortality rates

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independently from the underlying disease (4). According to the American Thoracic Society (ATS) PE is classified into three phases: the early exudative (phase I), the intermediate fibroproliferative (phase II) and the late organized phase III (1). If therapy is insufficient the earlier phase of PE merges into the next one and the disease gets more complicated (1,3). Therapy is stage dependent and should focus on controlling the infectious focus (i.e., antibiotics), evacuation of fluid and pus collections (needle aspiration, chest tube insertion or surgery), re-expansion of the lung and re-establishment of the physiologic respiratoric chest mobility (degradation of fibrinous septa and removal of fibrotic capsules from the lung's surface, the diaphragm, mediastinum and chest wall either by fibrinolytic agents or by surgery) (1,5).

In organized phase III empyema conventional open surgery (COS) via thoracotomy has remained the most established, gold standard approach for decortication. So far, only little experience exists on decortication in late phase PE via a minimally-invasive video-assisted thoracoscopic surgery (VATS) approach (5,6). However, those few so far published retrospective case series suggest principal feasibility and safety of VATS for pulmonary decortication (5,6).

We herein report an institutional experience with the VATS approach for lung decortications in organized phase III PE with a particular focus on the learning curve.

Methods

At Department of General, Visceral, Transplant and Thoracic Surgery at Giessen University Hospital a VATS-program for more complex thoracic surgical procedures was started in 02/2011. Initially, all complex VATS-procedures (anatomic lung resections, mediastinal tumor resections, decortications in phase III PE) were taken care of by one single experienced senior thoracic surgeon either as the performing surgeon or the teaching assistant.

Only patients with documented ATS-phase III PE with a restrictive pleural scar tissue/fibrous cortex overlying and constraining the visceral pleura were included in this retrospective study. Patients were treated by the institutional standard of care. Patient data were retrospectively analyzed from the prospectively maintained institutional database.

In order to analyze the learning curve of minimally-invasive VATS decortication in organized phase III PE in a cohort as homogenous as possible, patients with bilateral PE and patients primarily conducted to COS for phase III PE were excluded. Conversions from an initial VATS approach to COS were classified as intra-operative complications and the respective patients were excluded from further outcome analysis. Recurrent disease indicating a redo-operation was classified as post-operative complication and the respective re-VATS or re-COS procedures were not included into the outcome analysis. For assessing the learning curve the cohort of patients was divided into two groups based on operation date [VATS-1: from 03/2011 to 06/2012, n=43 (33.9%) and VATS-2: from 06/2012 to 03/2015, n=84 (66.1%)].

The retrospective acquisition of data was formally approved by the local ethics committee of the medical faculty, Justus-Liebig-University of Giessen, Germany (AZ 114/14 and AZ 242/13). As this is a retrospective patient data analysis, all patients were treated by the present local standard of care.

Operation technique

Patients were placed in lateral decubitus position and underwent general anesthesia with a double-lumen endotracheal tube for selective single-lung ventilation. An anterior VATS-approach with a 30 degree camera without rib-spreading was used for minimally-invasive empyema evacuation and lung decortication. The thoracocenteses were positioned according to the expansion of the PE based on the patients' pre-operative computed tomography scans. Strict focus was put on initially entering the pleural cavity at an area, where the lung was in direct contact to the chest wall preferably without any empyema lying in between. In most cases the first thoracocentesis was placed in the area of the fourth intercostal space, anterior axillary line; initially in a uniportal approach the lung was gradually mobilized by taking down its adhesions to the chest wall. Dissection was performed mainly bluntly using an endo-Kittner or the cautery hook as a dissector. Once the lung was freed anteriorly all the way down to the diaphragm, two additional basal thoracocenteses were placed to continue the operation in a three port technique. The anterobasal thoracocentesis was used as the camera port. The dissection/lung decortication was processed laterodorsally by peeling the lung's visceral pleura off the fibrous cortex encapsulating the empyema. Thereby care was taken to keep the empyema sac, separating the lung from and surrounding the fluid empyema components, intact. This step was usually facilitated by partial or complete ventilation of the lung via the double-lumen endotracheal tube. After complete mobilization of the lung, empyemectomy was

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performed by dissecting the corresponding parts of the empyema capsule off the diaphragm, the chest wall and the (mainly posterior) mediastinum. However, the fibrotic capsule no seldom ruptured during this maneuver—or even earlier—and the leaking liquid empyema components were controlled with a sucker.

At the end of the procedure 1–3 chest tubes were placed and negative pressure was usually applied for at least 2 days and/or until chest X-ray confirmed complete (re-) expansion of the lung. Chest tubes were removed consecutively as soon as air leakage had stopped and/or fluid collection was below 300 mL per day.

Statistical analysis

Statistical analysis was performed using GraphPad Prism version 5.00 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com. Normally distribution was tested by Shapiro-Wilk test. Two-tailed Mann-Whitney U-test or two-tailed, un-paired Student's T test was used for two-group comparisons of non-parametric or normally distributed data, respectively. Normally distributed data are denoted within the tables. Fisher's exact or Pearson's χ^2 test was applied for comparisons of categorical data in cross-tabulation.

P values <0.05 were considered to indicate statistical significance. Data are given in mean ± SEM as well as in median (range).

Results

Between 02/2011 and 03/2015 one-hundred-thirty-eight patients were conducted to surgery for late organized phase III PE. Within those, 3 patients had bilateral disease and 8 patients were primarily treated by COS. The remaining 127 (94.1%) patients conducted to minimally-invasive surgical (VATS-approach) empyema evacuation and lung decortication were included into this study.

In 5 patients the initially intended VATS approach was converted to COS and the respective patients were excluded from further outcome analysis. In 8 patients 10 redo-interventions for recurrent disease were performed after initial VATS decortications and those 10 respective redo-procedures were classified as post-operative complications and not included into this primary outcome analysis.

Although patient characteristics within both the VATS-1 and VATS-2 group were widely balanced, male gender was over-represented among patients from VATS-2 and patients from VATS-2 pre-operatively were more multi-morbid reflected by a significantly higher ASA- (American society of anesthesiologists' classification of physical health) score. By tendency more (P=0.0534) patients from VATS-2 (n=37) were treated by pre-operative drainage therapy, indicating a prolonged medical treatment prior to and a delay of surgery (*Table 1*). However, no differences were observed in the length of pre-operative hospital stay between both groups

Table 1 Patient characteristics

Variable	VATS-1	VATS-2	P value
Gender (n patients)			0.0117
Male	30 (69.8%)	75 (89.3%)	
Female	13 (30.2%)	9 (10.7%)	
Age (years)	61.9±12.9; 63.0 (range, 27.0–86.0)	62.3±17.0; 65.0 (range, 13.0–88.0)	0.5175
BMI (kg/m²)	25.3±5.2; 24.5 (range, 17.3–37.1)	26.3±4.6; 26.3 (range, 14.2–39.9)	0.1226
Chronic diseases (n patients)			
Pulmonary	22 (51.2%)	37 (44.0%)	0.4592
COPD	8 (18.6%)	11 (13.1%)	0.4378
Emphysema	2 (4.7%)	1 (1.2%)	0.2645
Cardio-vascular	23 (53.5%)	58 (69.0%)	0.1181
Arterial hypertension	15 (34.9%)	43 (51.2%)	0.0927
Coronary arterial disease	5 (11.6%)	21 (25.0%)	0.1039

Table 1 (*continued*)

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Table 1 (*continued*)

Variable	VATS-1	VATS-2	P value
Diabetes mellitus	4 (9.3%)	18 (21.4%)	0.1356
Oncologic	13 (30.2%)	17 (20.2%)	0.2699
Neurologic	6 (14.0%)	23 (27.4%)	0.1181
Gastro-intestinal	9 (20.9%)	27 (32.1%)	0.2162
Nephrologic	3 (7.0%)	16 (19.0%)	0.1127
Abuse (n patients)			
Nicotin	7 (16.3%)	12 (14.3%)	0.7959
Alcohol	2 (4.7%)	5 (6.0%)	1
Drugs (i.v.)	0	2 (2.4%)	0.5686
Previous thoracic surgery (n patients)*	7 (16.3%)	21 (25.0%)	0.366
ASA (n patients)	2.6±0.6; 3 (range, 1–4)	2.9±0.6; 3 (range, 1–4)	0.0279
1	1 (2.3%)	1 (1.2%)	
2	16 (37.2%)	18 (21.4%)	
3	24 (55.8%)	55 (65.5%)	
4	2 (4.7%)	10 (11.9%)	
Side (n patients)			0.0386
Right	30 (69.8%)	42 (50.0%)	
Left	13 (30.2%)	42 (50.0%)	
Etiology (n patients)			0.0854
Parapneumonic	17 (39.5%)	41 (48.8%)	
Pneumothorax	2 (4.7%)	1 (1.2%)	
Post-interventional			
Thoracic operation	3 (7.0%)	15 (17.9%)	
Thoracic drainage	4 (9.3%)	2 (2.4%)	
Post-traumatic	3 (7.0%)	3 (3.6%)	
Cancer/paraneoplastic	6 (14.0%)	4 (4.8%)	
Chronic pleural fluid collection	8 (18.6%)	18 (21.4%)	
Pre-operative drainage therapy (n patients)	11 (25.6%)	37 (44.0%)	0.0534
Duration (d)	9.8±6.0; 10 (range, 1.0–22.0)	11.8±13.8; 8.0 (range, 1.0–73.0)	0.7734
Pre-operative oral temperature >38 ℃ (n patients)#	11 (27.5%)	29 (35.8%)	0.4155
Pre-operative oral temperature (℃)§	37.6±1.0; 37.7 (range, 36.0–39.8)	37.6±0.9; 37.5 (range, 35.8–40.3)	0.8699

*, previous thoracic surgery in the VATS-1 group (7 patients): VATS (n=5), aortocoronary bypass surgery (n=2). Previous thoracic surgery in the VATS-2 group (21 patients: 3 patients underwent 2 thoracic surgical procedures previously): thoracotomy (n=4), VATS (n=13), aortocoronary bypass surgery (n=7). #, not available retrospectively in 3 patients of both the VATS-1 and the VATS-2 group. §, normally distributed data. BMI, body mass index; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists' classification of physical health.

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(*Table 2*).

Operating times were significantly longer (P=0.0308) among the first third of patients (VATS-1) compared to the following two thirds (VATS-2). Nevertheless, no differences were seen in the rate of intra-operative complications or conversions to open surgery as well as the intra-operative blood loss (*Tables 2,3*).

Both the overall length of stay (LOS) at intensive care unit (ICU) as well as the post-operative LOS at ICU was similar between both groups (*Table 2*). However, rates of prolonged post-operative mechanical ventilation as well as catecholamine therapy were higher in patients from VATS-2. The rate of delayed (>10 d) post-operative chest tube removal indicating a prolonged post-operative air leakage and/or a prolonged post-operative high chest tube output was slightly (P=0.0702) higher in patients from VATS-2. No differences were observed in post-operative complication rates and post-operative in-hospital LOS among both groups (*Tables 2,3*).

Discussion

Complete decortication, i.e., removal of all fibrotic tissue constricting the lung is of utmost importance for the success of surgical therapy in phase III PE. Any remaining cortex on the lung's surface preventing its complete re-expansion and thus leaving an empty space within the pleural cavity leads to recurrent pleural effusion which is of high risk for getting re-infected; mainly when the—most often—underlying pneumonia is usually not fully recovered at time of surgery.

Lung decortication is a challenging and time-consuming procedure. Meticulous dissection is mandatory in order to peel the sticking fibrotic cortex off the visceral pleura without causing too many lesions consequently leading to prolonged air leaks. The most established surgical approach for lung decortication in late phase PE is COS and the minimally-invasive VATS approach has been evaluated quite delayed (when compared to other complex thoracic procedures like anatomic lung resections) for this particular procedure.

The feasibility of evacuation and decortication in phase III PE via a VATS approach initially was suggested in various retrospective analysis: their validity was limited by rather small and mostly inhomogeneous cohorts mixing up both phase II and III PE patients (5,8). However, those series suggested that the benefits [with regard to post-operative pain, post-operative complication rate, LOS, pulmonary function, quality of life (9-13)] of a VATS over a COS approach known in oncologic thoracic surgery come to effect also in empyema surgery (5,14-17). Thus, in its recent expert consensus statement the European Association for Cardio-Thoracic Surgery (EACTS) has recommended a primary VATS-approach for the surgical management even for organized phase III PE (5).

Overall, reported post-operative morbidity, mortality and re-intervention rates (up to 25.1%, 7.6% and 23.8%, respectively) of VATS decortications in phase III PE are rather high (5) and a limited experience in thoracic surgery is reported to be one risk factor for intra-operative conversion to COS as well as for treatment failure after surgery (5,8). Thus, the surgeons' experience and technical skills seem to be a major factor influencing the outcome in VATS empyema surgery. For VATS pulmonary lobectomies a number of 30 to 50 procedures was quoted as the required learning curve numbers of an averaged talented trainee and 20 cases per year were recommended to preserve the technical skills constantly (18-21). Compared to lobectomies for early (I) stage non-small cell lung cancer (NSCLC), thoracic surgery in chronic inflammatory/infectious conditions is technically even more challenging due to severe adhesions and fibrotic changes, neovascularization and lymph node reactions (22-25). Visualization and anatomic orientation are impaired, which bears the risk for significant bleeding by injuring hilar structures during mobilization of the lung. This study aimed to determine a realistic learning curve volume for VATS decortications in phase III PE by evaluating operative time, peri-operative complication and morbidity rates. Hypothesizing the learning curve to be at least the same or even higher than known in minimally-invasive anatomic lung resections (18-21), outcomes of the first, assumed "learning curve" third of patients (n=43) were compared to those of the second two thirds of patients (n=84). Severity of disease was similar between both groups although in VATS-2 patients both higher pre-operative CRP-values and pre-operative body temperature indicated severer inflammatory reactions and a longer pre-operative drainage therapy indicated a potentially delayed decision for surgery (*Tables 1,3*) (14,26,27). However, operative times as the most relevant outcome parameter for the learning curve was significantly longer among VATS-1 compared to VATS-2 patients. Post-operative LOS at ICU, chest tube duration and post-operative overall LOS were chosen as secondary outcome parameters in this study. Interestingly, despite shorter operative times in VATS-2 and a similar LOS at ICU among both groups, both the rates of

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Table 2 Peri-operative outcome

Variable	VATS-1	VATS-2	P value
Operation time (min)	170.1±73.6; 155.0 (range, 41.0–378.0)	141.6±61.1; 138.0 (range, 43.0–385.0)	0.0308
Hospital stay (d)			
Total	22.2±14.2; 15.0 (range, 9.0–57.0)	30.4±35.3; 20.0 (range, 5.0–232.0)	0.5746
Pre-operative*	8.6±8.9; 5.0 (range, 2.0–45.0)	9.9±12.8; 5.0 (range, 2.0–75.0)	0.608
PO	13.9±10.0; 9.0 (range, 4.0–45.0)	20.3±30.7; 10.0 (range, 3.0–230.0)	0.7384
Stay on ICU (h)			
Total	124.2±231.2; 25.0 (range, 0.0–1,339.0)	410.3±897.5; 42.9 (range, 0.0–5,534.0)	0.1104
PO	99.3±190.2; 25.0 (range, 0.0–1,079.0)	306.3±763.2; 41.9 (range, 0.0–5,517.0)	0.1471
PO mechanical ventilation (n patients)[€]	9 (22.0%)	24 (29.6%)	0.3978
Duration (h)	35.5±83.5; 8.4 (range, 1.65–260.8)	469.8±1,148.0; 128.1 (range, 3.1–5,517.0)	0.0034
Prolonged (>120 h) (n patients)[€]	1 (2.4%)	12 (14.8%)	0.056
Catecholamine on ICU			
Total (n patients)	4 (9.8%)	29 (35.8%)	0.0023
0–24 h PO			
Patients (n)	4 (9.8%)	29 (35.8%)	0.0023
Volume (µg/kgbw/min)	0.20±0.24; 0.10 (range, 0.06–0.56)	0.13±0.04; 0.08 (range, 0.003–1.25)	0.3075
24–48 h PO			
Patients (n)	3 (7.3%)	21 (25.9%)	0.0158
Volume (µg/kgbw/min)	0.04±0.02; 0.03 (range, 0.02–0.06)	0.21±0.55; 0.04 (range, 0.002–2.50)	0.8614
48–72 PO			
Patients (n)	1 (2.4%)	14 (17.3%)	0.0191
Volume (µg/kgbw/min)	0.05	0.23±0.53; 0.03 (range, 0.001–2.00)	Small sample
Additional surgical procedures (n patients)			
Pulmonary (wedge/major) resection	4 (9.8%)	4 (4.9%)	0.44
Lymph node assessment	2 (4.9%)	1 (1.2%)	0.2611
Number of thoracenteses (n patients)			0.0344
1	3 (7.3%)	0	
2	9 (22.0%)	14 (17.3%)	
3	29 (70.7%)	67 (82.7%)	
IO blood loss (mL)	490.7±423.2; 400.0 (range, 40.0–2,000.0)	545.4±561.0; 300.0 (range, 0.0–2,600.0)	0.9027
Blood transfusion			
Total (n patients)	14 (34.1%)	37 (45.7%)	0.2485
IO (n patients)	13 (31.7%)	23 (28.4%)	0.8338
IO (No. of EC)	2.0±1.3; 2 (range, 1–6)	2.4±2.6; 2 (range, 1–13)	0.6277
PO (n patients)	5 (12.2%)	30 (37.0%)	0.0054
PO (No. of EC)	2.8±2.2; 2 (range, 1–6)	4.3±3.1; 4 (range, 1–14)	0.293

*, including those patients (2 patients in VATS-1 and 3 patients in VATS-2) underwent conversion to open surgery; [€], mechanical ventilation of patients not being extubated after surgery, acute respiratory insufficiency and re-intubation were classified as complications. PO, post-operative; ICU, intensive care unit; BW, body weight; IO, intra-operative; EC, erythrocyte concentrate.

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Table 3 Peri-operative complications and drainage management

Variable	VATS-1	VATS-2	P value
IO complications (n)			
Total*	6 (14.0%)	11 (13.1%)	1
Conversions[¶]	2 (4.7%)	3 (3.6%)	1
Total PO complications (n patients)			0.7037
n (%)	21 (51.2%)	38 (46.9%)	
Grade I[€]	3	5	
Grade II[€]			
Bleeding	2	5	
Pneumonia	2	6	
GI infection	1	1	
TAA	0	2	
Prolonged PO chest drainage therapy ≥10 d	5	18	
Others	0	5	
Grade IIIa[€]			
Re-drainage	3	6	
Bronchoscopy	2	1	
Others	0	3	
Grade IIIb[€]			
Recurrent empyema	3	5[&]	
Others[µ]	4	4	
Grade IVa[€]			
Acute respiratory insufficiency	1	1	
Chronic respiratory insufficiency	1	12	
Acute renal failure	2	2	
Others	0	3	
Mortality (n patients)[$]	2 (4.9%)	9 (11.1%)	0.3314
No. of IO placed chest tubes (n patients)			<0.0001
1	10 (24.4%)	12 (14.8%)	
2	11 (26.8%)	66 (81.5%)	
3	20 (48.8%)	3 (3.7%)	
PO chest tube duration (d)[¥]	6.15±3.02; 6.0 (range, 2.0–16.0)	7.01±4.45; 5.0 (range, 2.0–22.0)	0.7035
≥7 d (n patients)[£]	14 (34.1%)	30 (37.0%)	0.8428
>10 d (n patients)[£]	3 (7.3%)	17 (21.0%)	0.0702
Blood leucocytes			
Elevated pre-operative (n patients)*	30 (69.8%)	51 (60.7%)	0.337

Table 3 (*continued*)

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Table 3 (*continued*)

Variable	VATS-1	VATS-2	P value
Highest value pre-operative (giga/L)*	15.23±8.01; 14.0 (3.2–38.6)	14.50±8.91; 11.9 (range, 4.6–54.2)	0.3131
Elevated POD 3–6 (n patients)[#]	9 (22.0%)	20 (24.7%)	0.8227
Highest value POD 3–6 (giga/L)[#]	8.41±3.48; 7.8 (2.2–19.6)	9.06±6.75; 8.0 (range, 2.9–61.5)	0.9418
Elevated at discharge (n patients)	16 (39.0%)	23 (28.4%)	0.3043
Value at discharge (giga/L)	10.35±4.52; 9.6 (3.3–25.0)	9.42±5.29; 8.4 (range, 2.9–42.1)	0.0833
C-reactive protein			
>10 mg/L pre-operative (n patients)*	38 (88.4%)	83 (98.8%)	0.0168
Highest value pre-operative (mg/L)*	162.2±152.0; 110.0 (range, 5.3–532.2)	156.6±120.1; 134.0 (range, 0.6–485.5)	0.8344
Highest value POD 3–6 (mg/L)[#]	89.94±47.24; 84.6 (range, 5.9–263.3)	102.1±48.29; 98.8 (range, 0.5–260.6)	0.1272
Value at discharge (mg/L)[^]	81.68±72.81; 81.3 (range, 0.5–424.9)	72.24±50.68; 68.3 (range, 0.5–212.5)	0.5972

*, including those patients underwent conversion to open surgery. [¶], the two conversions in the VATS-1 group were due to technical reasons in 1 case and due to bleeding in 1 case. The three conversions in VATS-2 were due to technical reasons in 2 cases and due to bleeding in 1 case. [€] according to the Dindo-Clavien classification of surgical complications (7). [&], 5 patients from VATS-2 suffered from 7 recurrences after surgery. [µ], beside (operative) redo-procedures for empyema recurrences, 3 patients in VATS-1 and 4 patients in VATS-2 underwent 4 operative redo-procedures in each group [including re-VATS for organized hemothorax (n=1) and malignant pleural effusion (n=2) as well as re-thoracotomy for persistent air leak (n=1) in VATS-1 and re-VATS for organized hemothorax (n=2) and re-thoracotomy for bleeding (n=1) in VATS-2]. [$], 30-day and in-hospital mortality [according to grade V complications regarding the Clavien-Dindo classification of surgical complications (7)] as well as septic multi-organ failure [according grade IV complications regarding the Clavien-Dindo classification of surgical complications (7)] leading to death. [¥], means the duration of the primarily (intraoperative) placed chest tube/s. Chest tube re-insertion et cetera was classified as a complication. One patient of the VATS-1 group died before chest tube removal and one patient from VATS-2 was discharged with a chest tube and a Heimlich valve. [£], prolonged chest tube duration was considered to indicate persistent air leak (prolonged parenchyma fistula) and/or high fluid losses. [#], not available retrospectively in 2 patients of the VATS-1 and 4 patients of the VATS-2 group. [^], not available retrospectively in 2 patients of the VATS-2 group. IO, intra-operative; PO, post-operative; GI, gastro-intestinal; TAA, tachyarrhythmia. POD, post-operative day.

prolonged post-operative mechanical ventilation and of prolonged vasoconstrictive therapy were higher in VATS-2. This may be explained by the impaired physical status and a higher peri-operative risk of the respective patients reflected by significantly higher pre-operative ASA-scores in VATS-2 (28). The constantly rising ASA-score over the study period might indicate that with growing surgical experience even severer cases and sicker patients were operated on.

The LOS at ICU as well as the duration of chest tube insertion are both parameters significantly influencing the overall post-operative LOS (29). A prolonged air leak and/or a prolonged high volume output are frequent post-operative complications inducing a delayed (>10 days) chest tube removal (29-31). The rate of prolonged chest tube duration was slightly higher in VATS-2 (P=0.0702), which might, however, be based on the fact that fewer tubes were inserted in patients of this subgroup; thus, delayed removal eventually could have been prevented by a more extensive (3 *vs.* 2 tubes) initial drainage of the pleural cavity at the end of operation, thereby facilitating an immediate complete re-expansion of the lung. The higher rate of patients who underwent mechanically over-pressure ventilation post-operatively may explain the higher rate of prolonged air leaks in VATS-2.

In conclusion, a VATS approach for empyema evacuation and lung decortication in phase III PE has shown to be feasible and safe with an acceptable rate of peri-operative morbidity in this study. A significant reduction of operative times between the two subgroups suggests a learning curve volume of approximately 40 cases as being sufficient in order to develop relevant procedure specific surgical skills and experience.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The retrospective acquisition of data was formally approved by the local ethics committee of the medical faculty, Justus-Liebig-University of Giessen, Germany (AZ 114/14 and AZ 242/13).

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11.6 Anlage 6

P.U. Oppelt, I. Askevold, R. Hörbelt, F.C. Roller, W. Padberg, A. Hecker, **M. Reichert**: **Trans-hiatal herniation following esophagectomy or gastrectomy: retrospective single-center experiences with a potential surgical emergency.** *Hernia.* 2022 Feb;26(1):259-278. doi: 10.1007/s10029-021-02380-1.

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ORIGINAL ARTICLE

Trans-hiatal herniation following esophagectomy or gastrectomy: retrospective single-center experiences with a potential surgical emergency

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Abstract

Purpose Trans-hiatal herniation after esophago-gastric surgery is a potentially severe complication due to the risk of bowel incarceration and cardiac or respiratory complaints. However, measures for prevention and treatment options are based on a single surgeon´s experiences and small case series in the literature.

Methods Retrospective single-center analysis on patients who underwent surgical repair of trans-hiatal hernia following gastrectomy or esophagectomy from 01/2003 to 07/2020 regarding clinical symptoms, hernia characteristics, pre-operative imaging, hernia repair technique and perioperative outcome.

Results Trans-hiatal hernia repair was performed in 9 patients following abdomino-thoracic esophagectomy (40.9%), in 8 patients following trans-hiatal esophagectomy (36.4%) and in 5 patients following conventional gastrectomy (22.7%). Gastrointestinal symptoms with bowel obstruction and pain were mostly prevalent (63.6 and 59.1%, respectively), two patients were asymptomatic. Transverse colon (54.5%) and small intestine (77.3%) most frequently prolapsed into the left chest after esophagectomy (88.2%) and into the dorsal mediastinum after gastrectomy (60.0%). Half of the patients had signs of incarceration in pre-operative imaging, 10 patients underwent emergency surgery. However, bowel resection was only necessary in one patient. Hernia repair was performed by suture cruroplasty without ($n = 12$) or with mesh reinforcement ($n = 5$) or tension-free mesh interposition ($n = 5$). Postoperative pleural complications were most frequently observed, especially in patients who underwent any kind of mesh repair. Three patients developed recurrency, of whom two underwent again surgical repair.

Conclusion Trans-hiatal herniation after esophago-gastric surgery is rare but relevant. The role of surgical repair in asymptomatic patients is disputed. However, early hernia repair prevents patients from severe complications. Measures for prevention and adequate closure techniques are not yet defined.

Keywords Trans-hiatal herniation · Trans-hiatal hernia · Esophagectomy · Gastrectomy · Hiatal hernia repair · Emergency surgery

Introduction

Esophago-gastric surgery bears an extraordinary high risk for postoperative complications, which consecutively contribute majorly to postoperative morbidity and mortality even in high-volume, well-experienced operative centers [1, 2]. Vice versa, postoperative complications not only impair short- but also (oncologic) long-term outcomes of the affected patients [1–3]. Especially pulmonary complications, including pneumonia, respiratory failure and respiratory distress, as well as anastomotic complications, predominantly leakages, become critically apparent immediately after surgery [4–6]. Furthermore,

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anastomotic stenosis, reflux disease, malnutrition and even tumor recurrencies after oncologic esophagectomy or gastrectomy are well-known clinical problems in the long-run after surgery. Nevertheless, these complex surgical approaches for esophagectomy or gastrectomy bear the risk for some other, rather uncommon surgical complications, which might appear during both the short-term as well as long-term follow-up of the patients. Thereby, it is well known that an early and correct diagnosis as well as early and appropriate therapy of severe and potentially life-threatening complications after esophago-gastric surgery, reduce further morbidity and mortality of the patients and is one of the main differences between the high-volume and lower-volume centers for upper gastrointestinal surgery [1, 2]. One of these rare but feared complications is trans-hiatal herniation of abdominal viscera following gastrectomy or esophagectomy [7]. Already in 2016 Crespin and colleagues entitled post-esophagectomy hiatal hernia (HH) as "an underreported complication" with a cumulative incidence even in asymptomatic patients being up to 26% [8, 9]. HH after esophago-gastric surgery might cause severe, life-threatening complications and critical illness in a high percentage of the affected symptomatic patients [7, 10]. However, clear evidence for strategies on "how to approach the hiatus" during the initial surgery to prevent patients from trans-hiatal herniation following esophago-gastric surgery are not yet established [7, 8, 10–22]. Furthermore, symptoms of the patients reported in mainly small case series in the literature vary strongly [7, 16] and, although surgery is the only therapeutic solution, guidelines or recommendations from the respective medical societies for adequate diagnosis and surgical hernia repair addressing the question "when, why and how" are currently missing [7]. Thus, the knowledge about symptoms, adequate diagnosis and imaging techniques as well as appropriate surgical treatment is only based on a single surgeon's experiences as well as case reports and small retrospective case series from the current literature without providing sufficient long-term follow-up [23]. Questions may arise, when and why to operate even asymptomatic patients with an incidental finding of trans-hiatal herniation after esophago-gastric surgery considering the high risk for incarceration, how to perform the surgery for hernia repair and by which technique to close the hiatal defect considering the size and the consecutive risk for recurrency: suture cruroplasty, additional mesh augmentation or tension-free mesh interposition? Therefore, it seems to be important to improve the evidence by providing single institutional experiences along with our patient cohort and presenting a systematic review of case series on trans-hiatal hernia repair after esophago-gastric surgery from the current literature.

Materials and methods

Patients and study design

We retrospectively evaluated adult patients who underwent repair of trans-hiatal hernia from 01/2003 to 07/2020 at the University Hospital of Giessen with a special focus on patients, who were operated on HH following previous esophago-gastric surgery. The retrospective data acquisition was formally approved by the local ethics committee of the medical faculty of the University of Giessen (approval numbers: 214/15, 253/16 and 97/19). Each patient was treated by the local standard-of-care.

Inclusion criteria were adult patients (≥ 18 years of age) with trans-hiatal herniation (i.e. prolapse of abdominal contents into the chest cavities or the posterior mediastinum) following gastrectomy, trans-hiatal esophagectomy or abdomino-thoracic esophagectomy in the patients´ history. Other types of trans-diaphragmatic hernia and even re-do surgeries for recurrent HH without previous gastrectomy and/or esophagectomy as well as HH after bariatric surgery were excluded from the analysis.

Outcome parameters were symptoms of the patients, preoperative diagnostic modalities and findings, indication for surgery, character of surgery (emergency versus elective), surgical technique and modalities of hernia repair (primary suture with or without mesh augmentation and mesh interposition), duration of surgery and postoperative stay on intensive care unit (ICU), total postoperative in-hospital stay as well as postoperative complications. The latter were assessed during the postoperative in-hospital stay or during the initial 30 postoperative days. Patient data and patient characteristics were evaluated retrospectively from the prospectively maintained institutional database.

After a primary analysis of patient data, patients were divided into one group who initially had undergone gastrectomy and another group who initially had undergone esophagectomy (including both trans-hiatal and abdomino-thoracic esophagectomy) to compare differences by the initial surgical procedure. Secondly, the patients were divided according to the surgical closure technique of the HH: patients who underwent either "only" primary suture for hernia repair or patients who underwent mesh-repair, including mesh augmentation (after suture cruroplasty) or tension-free mesh interposition. Results of both analyses are presented in the tables. Furthermore, for a better understanding of therapeutic decision making and perioperative patient outcome evaluation, postoperative outcome parameters were compared regarding the urgency of surgery: elective versus emergency hernia repair (Fig. 1 gives an overview of the patient cohort and subgrouping).

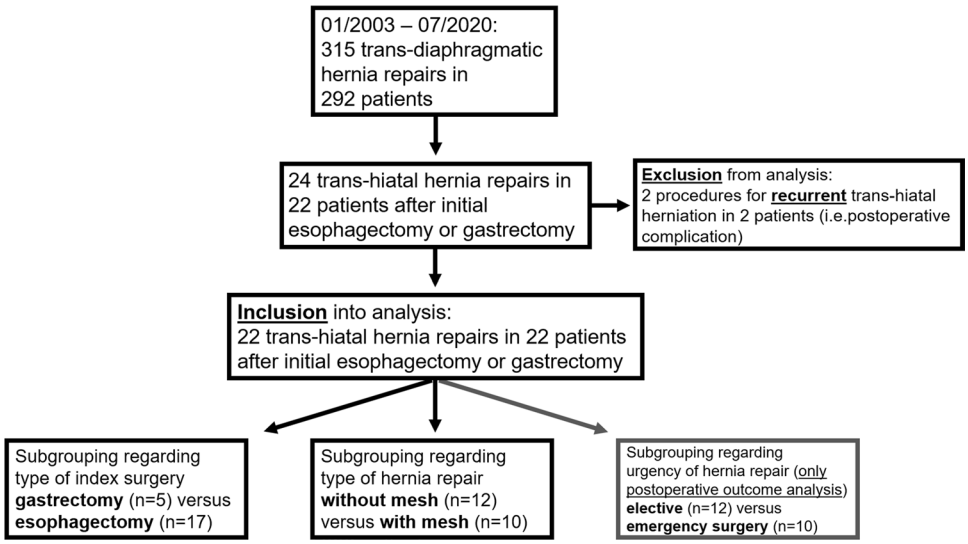


Fig. 1 Patient cohort and subgrouping

Statistical analyses were performed using GraphPad Prism (Version 5.00 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com). Two-group comparisons (regarding initial surgery: gastrectomy versus esophagectomy, hernia closure technique: with versus without mesh, or the urgency of hernia repair: elective versus emergency) were analyzed using Mann–Whitney-U test for continuous data or Pearson's X^2 test for categorical data in cross-tabulation. Data are given as *n* (%) or medians and ranges (i.e. minimum–maximum); *p* values ≤ 0.05 were considered to indicate statistical significance.

Surgical technique

Basically, the institutional surgical techniques approaching diaphragmatic hernia had been described previously [24]. Abdominal approaches play the leading role for HH repair after esophago-gastric surgery. Patients who undergo open surgical hernia repair are placed in the supine position and a median laparotomy is used to access the epigastric region under general anesthesia. Hernia contents are gently reduced and retrieved into the abdominal cavity as the first step. In cases of classical HH repair, excision and resection of the hernia sac is the standard procedure in our institution, however, there is usually no hernia sac present surrounding the prolapsed organs in cases of trans-hiatal hernia after esophago-gastric surgery [10]. The hiatal defect is closed by cruroplasty primarily with thick, non-resorbable, interrupted sutures. If a mesh is used to buttress the cruroplasty, the size of the mesh is considered to overlap the repair site approximately 5 cm beyond the edges of the defect. Single sutures or endo-staplers are used for the fixation of the mesh. If primary cruroplasty is not possible, due to the large size of the defect, a mesh interposition is inserted anteriorly from the diaphragm to the gastric conduit after esophagectomy or the jejunal limb to the anastomosis after trans-hiatal esophagectomy with gastrectomy, thus the conduit is located dorsally.

In laparoscopic, minimally invasive surgery for HH repair we basically follow the same principles as in open surgery. Here, patients are placed in reverse Trendelenburg position. The mesh for reinforcement of the cruroplasty is fixed in laparoscopic surgery by using endo-stapling devices. The institutional operation technique for laparoscopic hernia repair with mesh augmentation of trans-hiatal herniation after esophago-gastric surgery is adopted from the clinical standard of classical HH repair.

Literature review

To improve the evidence and the discussion of manuscript data, a systematic literature review on the repair of trans-hiatal hernia following gastrectomy, trans-hiatal or abdomino-thoracic (-cervical) esophagectomy was performed. English literature in Medline was systematically searched in September 2020. Original case series published from 01/2005 to 09/2020 containing ≥ 5 adult cases, who underwent surgery for trans-hiatal hernia repair after an initial esophagectomy or gastrectomy were included. Reports on HH repair following esophago-gastric resections containing < 5 surgical procedures, para-hiatal hernia or HH repair following bariatric surgery including gastric bypass or sleeve gastrectomy were excluded from the literature review.

Results

General characteristics of the patient cohort

Between 01/2003 and 07/2020 three-hundred-fifteen surgical procedures were performed in 292 patients for any type of

trans-diaphragmatic hernia. Amongst them, 24 operations, i.e. 7.6% of the total procedures, were performed for trans-hiatal hernia in 22 patients following abdomino-thoracic esophagectomy ($n = 9$, 40.9%), trans-hiatal esophagectomy ($n = 8$, 36.4%) or conventional gastrectomy ($n = 5$, 22.7%) and met the inclusion criteria. The remaining 2 procedures in 2 patients were performed for repeated repair of recurrent post-esophagectomy trans-hiatal herniation and were classified as a short- or long-term complication, respectively, in the patient outcome analysis of the present study (Fig. 1). The patients, included in this study, had undergone index surgeries between the years 1998 and 2018; twenty of the patients had undergone esophagectomy or gastrectomy initially at our institution, thus detailed information on the initial procedure was available. All patients of the esophagectomy group initially had undergone resection for oncologic purposes, including carcinoma of the thoracic esophagus or gastro-esophageal junction (GEJ) in 16 of 17 patients. Among them, conventional open trans-hiatal esophagectomy with gastrectomy and Roux-Y reconstruction had been performed in 7 patients and trans-hiatal esophagectomy with fundectomy and gastric conduit reconstruction had been performed in one patient. In the remaining 9 patients abdomino-thoracic esophagectomy had been performed with gastric conduit for reconstruction (conventional open surgery in 6 patients and a hybrid minimally invasive, laparoscopically assisted approach in 3 patients). Two patients from the gastrectomy group initially had undergone oncologic resection for gastric carcinoma, three patients initially had undergone gastrectomy for incarcerated paraesophageal hernia. Notably, in 9 patients of the esophagectomy group, especially in those with a carcinoma of the GEJ, resection of diaphragmatic crura had been performed during initial surgery versus in none of the gastrectomy patients ($p = 0.03$, Table 1). The size of the hernial orifice was extensively in patients with crus resection during index surgery [9.7 (6.7–12.8) cm versus patients without crus resection: 6.8 (4.4–9.7) cm, $p < 0.01$]. All of the patients, who suffered from trans-hiatal prolapse of abdominal contents into the chest immediately [i.e. in median 6 (6–13) days] after index surgery, underwent resection of diaphragmatic crura during the initial trans-hiatal ($n = 3$) or abdomino-thoracic esophagectomy ($n = 2$). Two of these patients who developed the hernia early post-esophagectomy suffered from herniation into both sides of the chest. Clinically, three patients with developing the hernia immediately suffered from severe cardiac ($n = 2$: tachyarrythmia and $n = 1$: cardiac arrest) and respiratory symptoms ($n = 2$) prior to hernia repair. Bowel incarceration was detected in two of these patients by preoperative computed tomography (CT). Four of these patients underwent emergency surgery. Hernia were repaired by simple sutures without mesh reinforcement in all five patients.

In one patient, who initially had undergone an abdomino-thoracic esophagectomy, the hernia was electively approached by laparoscopy (Table 1). Thereby, the contents of the hernia (intraoperatively assessed in this case: transverse colon and omentum majus) were reduced and the orifice was closed by single suture cruroplasty with mesh augmentation. Of note, signs of incarceration, including bowel obstruction or vascular strangulation, were not detected in the preoperative CT in this case (Table 2). One patient after an initial abdomino-thoracic esophagectomy underwent again an abdomino-thoracic approach for hernia repair with left-sided antero-lateral thoracotomy for lysis of the hernia contents out of the left chest (herniation of transverse colon and subtotal herniation of the small bowel). The large hiatal defect was closed in this case with mesh interposition during the abdominal part of the surgery.

Symptoms of the patients and radiographic diagnosis

Preoperative symptoms varied strongly among the patients. Gastrointestinal symptoms with bowel obstruction as well as abdominal and/or thoracic pain were mostly prevalent (63.6 as well as 59.1%, respectively). In the group of patients who underwent primary suture (without mesh repair) cardiac symptoms were more frequently prevalent ($p = 0.04$) and these patients underwent more frequently emergency surgery for hernia repair ($p = 0.03$, Tables 1, 2). Notably, two patients, who suffered from severe abdominal pain, presented with serological and radiological signs of acute pancreatitis as well as signs of cholestasis. In both patients the biliodigestive limb after an initial trans-hiatal esophagectomy with gastrectomy and Roux-Y reconstruction was affected and consecutively obstructed by the HH, resulting in a surgical emergency.

In 95.5% of the patients, cross-sectional imaging with CT was sufficient for preoperative diagnosis of trans-hiatal herniation after esophago-gastric surgery. In one single case pre-operative imaging was limited to conventional chest X-ray, which confirmed extensive small bowel herniation into the left chest (Table 2). Additional diagnostic tools played a minor role in the preoperative work-up. Therefore, endoscopy ($n = 4$) and barium swallow imaging study ($n = 1$) were applied for a more functional evaluation of the upper gastrointestinal tract, e.g. for diagnosis of reflux and dysphagia (both in two different patients) or to exclude local recurrencies after an initial oncologic esophagectomy or gastrectomy. These "extended" pre-operative diagnostic work-up did not play a role in the emergency setting; all of these five patients with an

Table 1 Patient characteristics

Variables	All patients	Subgroup analysis					
	($n = 22$)	Initial surgery			Mesh repair		
		Gastrectomy	Esophagectomy	*p*-value	Without mesh	With mesh	*p*-value
		($n = 5$)	($n = 17$)		($n = 12$)	($n = 10$)	
Male gender	16	3	13	0.47	9	7	0.79
Age (years)	66.5 (26–81)	69 (26–78)	65 (45–81)	0.94	64 (26–79)	72 (48–81)	0.2
Body mass index (kg/m^2)	21.6 (15.8–34.7)	22.0 (15.8–29.4)	21.1 (18.0–34.7)	0.85	21.6 (15.8–34.7)	22.5 (19.0–29.4)	0.58
Chronic diseases	17	3	14	0.29	9	8	0.78
Cardiac	12	1	11		6	6	
Pulmonal	6	1	5		4	2	
Renal	1	1	0		0	1	
Symptoms							
None	2	1	1	0.33	1	1	0.89
Dyspnoe	5	1	4	0.87	3	2	0.78
Cardiac	4[#]	0	4	0.23	4	0	0.04
Gastrointestinal	14	4	10	0.37	7	7	0.57
Ileus	7	2	5	0.66	3	4	0.54
Dysphagia	3	0	3	0.31	0	3	0.04
Reflux disease*	2	1	1	0.33	1	1	0.89
Pain	13	3	10	0.96	7	6	0.94
Thoracic	4	1	3	0.9	2	2	0.84
Abdominal	11	3	8	0.61	7	4	0.39
Characteristics of initial surgery							
Oncologic indication	19	2 [ß]	17	< 0.01	11	8	0.43
Conventional gastrectomy	5	5	–		3	2	0.78
Trans-hiatal esophagectomy with gastrectomy (Roux-Y reconstruction)	7	–	7		4	3	
Trans-hiatal esophagectomy (with gastric conduit reconstruction)	1	–	1		1	0	
Abdomino-thoracic esophagectomy (with gastric conduit reconstruction)	9	–	9		4	5	
Additional procedures during initial surgery [n patients][¶]	8	2	6	0.85	6	2	0.15
Minor surgery [n procedures]	9	1	8		7	2	
Major surgery [n procedures]	4	2[§]	2[&]		3[@]	1 €	
Crus resection during initial surgery [n patients][¶]	9	0	9	0.03	7	2	0.07
Comprehensive complication index after initial surgery[µ]	34.6 (0–99.9)	35.9 (22.6–47.4)	33.5 (0–99.9)	0.73	39.5 (0–99.9)	21.1 (0–54.2)	0.43
Duration from initial surgery to							
Hernia diagnosis [d]	320 (6–3884)	748 (285–2624)	143 (6–3884)	0.1	81 (6–2624)	619.5 (143–3884)	0.01
Hernia surgery [d]	368 (6–3891)	751 (289–2650)	171.5 (6–3891)	0.15	81 (6–2650)	751 (242–3891)	0.01
Duration of symptoms or time from diagnosis to hernia surgery ≤ 1 day [n patients]	10	2	8	0.78	8	2	0.03
Elective surgery	12	3	9	0.78	4	8	0.03
Emergency surgery	10	2	8		8	2	

[*] Including recurrent acid aspiration in both patients. # including cardiopulmonary resuscitation in 1 case

§ Splenectomy in both cases

& Including resection of the right upper pulmonary lobe in one case and laryngectomy in one case

¶ Unknown in one case with an initial trans-hiatal esophagectomy with gastrectomy from the group of patients who underwent mesh repair of the hernia.

€ Including the laryngectomy

Table 1 (continued)

@ Including splenectomy in two cases and resection of the right upper pulmonary lobe in one case

ß Three gastrectomies performed for incarcerated up-side down stomach or paraesophageal hernia. µ postoperative complications after index surgery were not available retrospectively in 3 patients (one from the gastrectomy and two from the esophagectomy group as well as one from the mesh- and two from the mesh + group, respectively); please be aware, that trans-hiatal hernia occurred immediately after index surgery (during the initial hospital stay or initial 30 postoperative days) in 5 patients (all from the esophagectomy group)

"extended" pre-operative diagnostic work-up underwent elective surgery for hernia repair.

Hernia repair

There were some discrepancies between the localization of the herniation between patients, who initially had undergone a gastrectomy versus esophagectomy: whereas patients after gastrectomy suffered more frequently from an "axial" herniation into the posterior mediastinum (60%) containing parts of the small bowel, patients after esophagectomy suffered most commonly from an extensive trans-hiatal herniation into the left thoracic cavity (76.5%) or both sides (11.8%). Small bowel (in most cases subtotal proportion of the small bowel) and transverse colon most commonly prolapsed into the chest, but also the pancreatic tail and parts of the liver were found as hernia contents in preoperative CT. However, some discrepancies between preoperative imaging by CT and intraoperative findings during hernia repair concerning the hernia contents as well as sings of incarceration were observed, as shown in Table 2. After reducing the hernia contents gently into the abdominal cavity, the orifice of the hernia was repaired in 12 patients by suture cruroplasty without the usage of meshes. In the remaining 10 patients, meshes were used for hernia repair ($n = 5$: mesh augmentation after suture cruroplasty and $n = 5$: tension-free mesh interposition). In patients without the application of meshes abdominal viscera (especially transverse colon) were fixed surgically by sutures more frequently in the abdominal cavity to prevent re-herniation compared with patients who underwent any kind of mesh repair ($p = 0.02$, Table 2). Interestingly, patients underwent more frequent hernia repair by simple suture cruroplasty without mesh augmentation or mesh interposition during emergency surgery ($p = 0.03$, Table 1).

Perioperative outcome

Higher peripheral blood leucocytes and serum C-reactive protein values prior to hernia repair might be an expression of the emergency character due to bowel incarceration in the group of patients, who underwent surgery without mesh implantation (Table 3). Basically, differences in postoperative inflammatory markers as indicators for surgical trauma or infectious complications as well as in the overall incidence for severe postoperative complications (≥ grade 3 concerning the Clavien-Dindo classification of surgical complications [25]) were not observed after hernia repair with regard to index surgery (≥ grade 3 after initial gastrectomy versus esophagectomy: $p = 0.61$), usage of meshes (≥ grade 3 after hiatal hernia repair with versus without mesh: $p = 0.39$, Table 4) or the urgency of hernia repair (≥ grade 3 after emergency versus elective surgery for hernia repair: $p = 1$). However, a pleural fluid drainage was placed in seven patients (all from the group of patients, who initially had undergone esophagectomy) at the end of hernia repair surgery into the affected thoracic cavity. Postoperatively, pleural complications including recurrent pleural fluid collections and re-drainage of the thoracic cavity were the most frequently observed complications. Although the number of patients, who developed recurrent pleural fluid collections, was not significantly different between the subgroups ($p = 0.09$), pleural re-drainage was necessary more frequently in patients after mesh repair of the hernia ($p = 0.01$, Table 4)—regardless of the urgency of surgery ($p = 0.28$). Furthermore, two patients from the esophagectomy group suffered from severe or fatal complications, indicated by an extraordinary high comprehensive complication index [26]. One of these patients died on the 12th postoperative day due to cerebral hemorrhage after infarction following cardiac arrest immediately after hernia repair. Three patients developed recurrency: two of them underwent again surgical repair for recurrent trans-hiatal hernia (Table 4).

Discussion

Esophagectomy and gastrectomy, especially for cancer, are high-risk procedures bearing the potential for postoperative severe and life-threatening complications [1–3]. Short-term outcome, lengths of hospital stay and health care costs are determined by the development of postoperative, especially pulmonary, cardiac and anastomotic complications [1–6, 27]. Severe complications, thereby, have not only the potential to dramatically increase early postoperative mortality rate but also to impair even long-term and oncological outcomes, thus an early recognition and adequate therapy of the complication is mandatory for the affected patients [1–3]. A currently underreported complication is the development of trans-hiatal herniation, which can occur during both the

Table 2 Hernia characteristics

Variables	All patients ($n=22$)	Subgroup analysis					
		Initial surgery			Mesh repair		
		Gastrectomy	Esophagectomy	*p*-value	Without mesh	With mesh	*p*-value
		($n=5$)	($n=17$)		($n=12$)	($n=10$)	
Localization				0.02			0.61
Dorsal mediastinum, i.e. "axial"	4	3	1		2	2	
Left-sided enterothorax	14	1	13		7	7	
Right-sided enterothorax	2	1	1		1	1	
Both-sided enterothorax	2	0	2		2	0	
Imaging[$]: Contents of the hernia							
Transverse colon	10	1	9[#]	0.19	5[#]	5	0.7
Small intestine[§]	15	4	11	0.52	9	6	0.45
Pancreas*	2	0	2	0.42	0	2	0.1
Liver	1	0	1	0.58	1	0	0.35
Omentum majus	3	0	3	0.31	0	3	0.04
CT: Signs of incarceration	11	3	8	0.61	8	3	0.09
Bowel obstruction/ileus	11	3	8	0.61	8	3	0.09
Vascular strangulation	7	2	5	0.66	5	2	0.28
Ileus + vascular strangulation	7	2	5	0.66	5	2	0.28
IO: Contents of the hernia							
Transverse colon	12	0	12[ß]	0.01	7	5	0.7
Small intestine	17	5	12	0.17	9	8	0.78
Esophagojejunostomy	2	2	–		1	1	0.89
Pancreas*	1	0	1	0.58	0	1	0.26
Liver	0	0	0	1	0	0	1
Omentum majus	2	0	2	0.42	0	2	0.1
IO							
Signs of vascular strangulation	5	1	4	0.87	4	1	0.19
Bowel ischemia[€]	1	0	1	0.58	1	0	0.35
Bowel fixation/pexy of abdominal contents	5	3	2	0.02	5	0	0.02
Hernia closure technique							
Primary suture cruroplasty	12	3	9	0.78	12	–	
Mesh augmentation[¶]	5	2	3	0.29	–	5	
Mesh interposition	5	0	5	0.17	–	5	
Lateral diameter of the hernial orifice in pre-operative CT-scan [cm][&]	7.9 (4.4–12.8)	5.6 (4.4–9.4)	9.3 (6.0–12.8)	0.04	8.7 (4.4–12.0)	7.7 (6.0–12.8)	0.82

CT Computed tomography, *IO* intraoperative

[$] Computed tomography in 21 patients, conventional chest X-ray in 1 patient from the esophagectomy group

Subtotal colonic herniation in 5 cases

§ Most commonly subtotal small intestine herniation

* Herniation of the pancreatic corpus and tail

¶ After suture cruroplasty. ß Subtotal colonic herniation in 3 cases

€ Irreversible ischemia with bowel gangrene and consecutive right hemicolectomy in one case

& The largest lateral diameter of the hernial orifice from both diaphragmatic crura was measured after adjusting the CT-scan by the axis of the hernia; not available in two patients from the esophagectomy/hernia repair with mesh interposition group: one patient did not receive CT-scan before surgery and in one patient the pre-operative CT-scan was not available retrospectively. No differences were observed regarding the orificial sizes from patients who underwent suture cruroplasty with or without mesh augmentation [7.9 (4.4–12.0)] versus closure with tension-free mesh interposition [8.2 (6.0–12.8), $p=0.67$]

short- and long-term follow-up after esophago-gastric surgery [7, 8, 10, 17, 28]. Therefore, Oor et al. described in their meta-analysis from 2016 lower pooled incidences of HH being 1.0% after conventional open and quite higher (4.5%) after minimally-invasive esophagectomy [29], which might be dramatically underestimated since structured upper

Table 3 Perioperative inflammatory marker profile

Variables	All patients ($n = 22$)	Subgroup analysis					
		Initial surgery			Mesh augmentation		
		Gastrectomy ($n = 5$)	Esophagectomy ($n = 17$)	p-value	Without mesh ($n = 12$)	With mesh ($n = 10$)	p-value
Perioperative leucocytes [giga/l]							
Preoperative	8.3 (3.7–26.5)	9.5 (3.7–20.3)	7.9 (4.7–26.5)	0.97	9.6 (5.2–26.5)	6.2 (3.7–12.6)	0.04
POD 1	11.2 (0.1–30.5)#	12.2 (9.6–18.5)	11.2 (0.1–30.5)#	0.46	11.4 (0.1–30.5)	11.2 (8.1–18.5)#	0.62
POD 3–5*	8.4 (4.6–27.3)	8.1 (6.3–15.6)	8.6 (4.6–27.3)	0.97	10.6 (4.6–27.3)	8.0 (6.3–16.1)	0.6
POD 5–15*	9.7 (3.2–59.2)#	9.7 (6.3–15.1)	10.5 (3.2–59.2)#	0.8	10.4 (3.2–59.2)	9.7 (5.1–14.6)#	0.48
Perioperative CRP [mg/l]							
Preoperative	6.3 (0.5–156.0)	6.9 (0.8–80.6)	5.7 (0.5–156.0)	0.88	49.3 (0.5–156.0)	1.5 (0.5–71.2)	0.04
POD 1	68.5 (0.8–182.3)	48.0 (9.2–92.5)	72.9 (0.8–182.3)	0.24	78.9 (0.8–182.3)	67.7 (11.6–82.7)	0.49
POD 3–5*	119.0 (37.4–479.1)	81.2 (43.6–160.8)	152.2 (37.4–479.1)	0.09	138.1 (68.6–269.5)	110.2 (37.4–479.1)	0.53
POD 5–15*	77.5 (17.3–585.6) #	61.2 (22.0–114.0)	89.4 (17.3–585.6)#	0.34	101.7 (22.0–246.6)	96.4 (17.3–585.6)#	0.17

POD postoperative day, *CRP* C-reactive protein

* Highest value at postoperative day 3–5 or 5–15, respectively

Not available in one patient retrospectively

Table 4 Perioperative outcome

Variables	All patients ($n = 22$)	Subgroup analysis					
		Initial surgery			Mesh augmentation		
		Gastrectomy ($n = 5$)	Esophagectomy ($n = 17$)	p-value	Without mesh ($n = 12$)	With mesh ($n = 10$)	p-value
Duration of hernia surgery [min]	103 (47–461)	152 (47–239)	102 (47–461)	0.97	95.5 (47–276)	129 (66–461)	0.12
Postoperative in-hospital stay [d]							
ICU	2.5 (0–157)	1 (0–12)	3 (0–157)	0.14	3 (0–157)	1.5 (0–12)	0.55
Total	9.5 (4–157)	8 (6–20)	10 (4–157)	0.58	10 (6–157)	8.5 (4–20)	0.49
Postoperative complications§							
Comprehensive complication index	23.56 (0–43.8)	20.9 (8.7–42.6)	33.5 (0–100)	0.69	20.9 (0–99.9)	42.6 (0–100)	0.49
≥ Grade 3*	11	2	9	0.61	5	6	0.39
Recurrent pleural fluid collections	11	2	9	0.61	4	7	0.09
Pleural re-drainage	7	1	6	0.52	1	6	0.01
Recurrency of hernia	3	1$	2¶	0.63	1$	2¶	0.43

ICU Intensive care unit

§ Complications during the postoperative hospital stay or during the initial 30 postoperative days after the hernia repair * regarding the Clavien-Dindo classification of surgical complications [25] as well as expressed by the comprehensive complication index [26]

$ recurrent trans-hiatal hernia into the dorsal mediastinum occurred after an initial gastrectomy in the long-run (7 months) after suture cruroplasty and was decided for non-operative management due to the absence of symptoms and worse clinical condition of the patient

¶ Two patients after initial esophagectomy (one trans-hiatal, one abdomino-thoracic), who underwent mesh repair (one augmentation and one interposition). Both patients underwent surgery for the recurrent hernia again: one patient after an initial abdomino-thoracic esophagectomy with resection of the diaphragmatic crura and left-sided trans-hiatal enterothorax, who underwent mesh interposition due to a large hiatal orifice two years after index surgery, developed hernia recurrency on postoperative day one due to tear out of the mesh with consecutive surgical revision. The other patient underwent suture cruroplasty with mesh augmentation for trans-hiatal herniation into the left chest 10 years after trans-hiatal esophagectomy and developed symptomatic recurrency of the hernia five months later with consecutive hernia repair by suture cruroplasty

gastrointestinal cancer surveillance with cross-sectional imaging especially in patients without symptoms is almost lacking [8, 30, 31]. Furthermore, (asymptomatic) patients who underwent non-operative management of HH after esophagectomy are underreported within predominantly surgical articles (Table 5). But, most importantly, only the vast minority of post-esophagectomy HH were reported initially by radiologists upon the CT scans [8, 30, 31]. Thus, in the very recent literature some authors depicted the "true" incidence of post-esophagectomy HH beeing unequally higher (up to 26% after minimally invasive esophagectomy) [8–10, 17, 19, 28]. However, as proven by our presented data as well as literature review in Table 5, only little experience with trans-hiatal hernia repair after esophagectomy or gastrectomy exists even in higher-volume centers for upper gastrointestinal surgery.

Minimally-invasive esophago-gastric index surgery as a risk factor for trans-hiatal herniation due to decreased formation of abdominal adhesions, which has been repeatedly reported in the literature [11, 17, 19, 28, 30, 32, 33], seems to be underrepresented in the patient cohort of the present study. This might be due to the fact that the institutional standard for gastrectomy and trans-hiatal esophagectomy (with gastrectomy) was conventional open surgery and abdomino-thoracic esophagectomy was approached hybrid minimal-invasively in approximately one third of the patients in the past as published previously [5]. Nevertheless, minimally invasive surgery, especially for trans-hiatal and Ivor Lewis esophagectomy as well as structured surveillance with cross-sectional imaging are both increasingly provided to patients with esophago-gastric cancer. Furthermore, long-term survival is improved in upper gastrointestinal cancer patients due to better multimodal treatment strategies, thus trans-hiatal herniation after oncologic esophago-gastric surgery will become increasingly relevant in the future (note the rising number of reports in the more recent literature, Table 5) [11, 17, 19, 28, 30, 32]. However, evidences derived from the current literature or recommendations from medical societies clearing the questions on "how to approach the hiatus during esophago-gastric surgery " and "when, why and how" to repair trans-hiatal herniation after esophagectomy or gastrectomy are not yet defined.

The most frequently prolapsed organ is transverse colon into the left chest (literature review in Table 5). Therefore, some risk factors for trans-hiatal hernia development after esophagectomy or gastrectomy can be found in the present patient cohort, including pre-existing hiatal hernia (which were present in three of five patients from the gastrectomy group), iatrogenic enlargement of the hiatus and diaphragmatic crus incision—especially of the left one, without resection, violence to the left pleura and higher tumor stages, especially of carcinoma of the esophago-gastric junction making crus resection necessary [7, 10, 11, 13–19, 21–23, 28–32, 34–37]. These lead consecutively to a loss of functional anatomy of the hiatus. Additionally, a lower BMI (< 25 kg/m^2) or excessive weight loss after index surgery facilitates the mobility of intra-abdominal viscera and diabetes as well as neoadjuvant therapy impair wound healing [10, 11, 14, 17, 22, 30, 32, 36]. However, several measures have been described in the literature to restore hiatal function during index surgery in the hope to reduce the incidence of HH after esophago-gastric surgery, but data on their efficacy are still lacking: direct closure of the diaphragmatic defect anteriorly (because the conduit lies posteriorly) and/or posteriorly, fixation of the conduit to the crura, mesh interposition, colopexy or omentopexy in front of the hiatus [9–11, 13, 15–19, 34, 37, 38].

The most common symptoms of patients with trans-hiatal hernia after esophagectomy or gastrectomy are abdominal and/or thoracic pain as well as signs of bowel obstruction [7, 19]. The current literature agrees, that patients with severe and acute onset of symptoms should undergo urgent or emergency surgery for hernia repair [7, 10, 17]. Thereby, CT is an adequate technique in the elective as well as emergency situation for diagnosis of the hernia and assessment of possible hernia-associated complications of the prolapsed contents such as incarceration, strangulation or perforation [10, 11, 14, 30, 31, 36]. Fuchs et al. and Sutherland et al. described hernia-associated bowel complications in approximately one-third of the patients [10, 37]. This is relevant to know, as reflected by data of the present study reported in Table 2, if CT estimates ischemic bowel complications, rapid surgical therapy prevents patients from bowel resection (only necessary in one of seven patients with signs of hernia-associated vascular strangulation in preoperative CT). Approximately one-third of the affected patients develop post-esophagectomy HH early after index surgery, i.e. during the first 90 postoperative days due to lack of adhesions holding abdominal viscera in place [7, 8, 11, 19, 20, 28]. These patients suffered more frequently from severe, acute respiratory and cardiac symptoms compared with patients, who developed HH in the long-run after index surgery [7, 11, 14, 19, 21]. Both are reflected in the current study by the group of patients who underwent hernia repair without the use of meshes (Tables 1 + 2) as well as results of their large multicentric study by Gust and colleagues [7]. The latter reported high rates for emergency post-esophagectomy HH repair of being 76% during the first 90 days and 41% beyond the first year after esophagectomy [7]. Therefore, the indication for surgical correction of trans-hiatal hernia after esophago-gastric surgery in moderate to severe symptomatic patients remains undoubtedly, whereas, whether asymptomatic to mild symptomatic patients should undergo either elective hernia repair or clinical observation with a "wait-and-see" strategy is controversially discussed in the current literature (literature review in Table 5) [10, 14, 17, 20]. In

Table 5 Systematic literature review on trans-hiatal herniation following gastrectomy and esophagectomy

Author [Reference number]	Reference	Study information, Observational period	General characteristics of the study cohort, *n* patients	Symptoms, Most commonly observed hernia content, Surgical hernia closure technique
Vallböhmer et al. [21]	Diaphragmatic Hernia After Conventional or Laparoscopic-Assisted Transthoracic Esophagectomy	Retrospective, Monocentric, 1997–2007	355 trans-thoracic esophagectomies, 9 (2.5%) patients were diagnosed with HH 8 (0.3–30) months after index surgery, 7 patients underwent HH repair	Asymptomatic: $n = 2$ (of the operated patients) Colon + small bowel: all patients Emergency surgery: $n = 5$ Laparotomy: all patients **Type of repair:** Suture repair: $n = 6$ Mesh repair: $n = 1$* Recurrency: n/a
Kent et al. [42]	Revisional Surgery After Esophagectomy: An Analysis of 43 Patients	Retrospective, Monocentric, 1995–2007	24 patients developed HH $n = 7$ after open trans-hiatal esophagectomy $n = 1$ after open ILE $n = 2$ after MI-ILE $n = 14$ after MIE with cervical anastomosis 32 months (46 days-7 years) after index surgery, 22 patients underwent HH repair	Asymptomatic: $n = 4$ (of all patients) Colon: $n = 92\%$ Small bowel: $n = 21\%$ Emergency surgery: $n = 4$ Laparotomy: $n = 7$ (conversion: $n = 2$) Laparoscopy: $n = 15$ **Type of repair:** Suture repair (+ Pexy of the conduit to the diaphragm): $n = 22$ Direct suture + mesh reinforcement: $n = 9$ Recurrency: $n = 6$
Sutherland et al. [37]	Postoperative incidence of incarcerated hiatal hernia and its prevention after robotic transhiatal esophagectomy	Retrospective, Monocentric, 2007–2009	36 trans-hiatal robot-assisted total esophagectomies with gastric conduit and cervical anastomosis, 7 (19.4%) patients underwent HH repair for incarceration: < POD 30: $n = 1$ POD 30–60: $n = 1$ POD 60–120: $n = 3$ > POD 120: $n = 2$	Asymptomatic: $n = 0$ Most common hernia content: n/a Emergency surgery: $n = 6$ Surgical approach: n/a **Type of repair:** Direct suture + mesh reinforcement: $n = 7$ Recurrency: $n = 2$
Price et al. [40]	Hiatal Hernia After Esophagectomy: Analysis of 2,182 Esophagectomies From a Singe Institution	Retrospective, Monocentric 1988–2008	2182 esophagectomies, 15 (0.69%) patients developed HH and underwent hernia repair 1 year 9 months (3 days – 12 years) after index surgery $n = 9$ (0.92%) after ILE $n = 5$ (0.83%) after trans-hiatal esophagectomy $n = 1$ after substernal colonic interposition	Asymptomatic: $n = 2$ Colon: $n = 6$ Colon + small bowel: $n = 4$ Small bowel: $n = 5$ Emergency surgery: $n = 2$ Trans-abdominal approach: $n = 14$ Laparotomy/Laparoscopy: n/a Trans-thoracic approach: $n = 1$ **Type of repair:** Suture repair: $n = 13$ Mesh repair: $n = 2$* Recurrency: $n = 2$

Table 5 (continued)

Author [Reference number]	Reference	Study information, Observational period	General characteristics of the study cohort, *n* patients	Symptoms, Most commonly observed hernia content, Surgical hernia closure technique
Erkmen et al. [18]	Laparoscopic repair of Hiatal Hernia After Esophagectomy	Retrospective, Monocentric, 2011–2017	Total number of esophagectomies: n/a 5 patients underwent surgery for intended hiatal repair* 24 (10–36) months post-esophagectomy [#] in one patient with carcinomatosis diagnosed during laparoscopy hernia repair was aborted!	Asymptomatic: $n = 0$ Colon: $n = 2$ Colon + small bowel: $n = 2$ Small bowel: $n = 0$ Emergency surgery: n/a Laparoscopy: $n = 5^{\#}$ **Type of repair[#]:** Direct suture: $n = 3$ Mesh interposition: $n = 1$ Recurrency: $n = 1$
Ganeshan et al [30]	Diaphragmatic Herniation After Esophagectomy in 440 Patients With Long-Term Follow-up	Retrospective, Monocentric, 2001–2007	440 esophagectomies, retrospective assessment of CT scans 67 (15%) patients developed HH 2 years (47 days–9.35 years) after esophagectomy $n = 32$ (12%) after ILE $n = 7$ (17%) after McKewon esophagectomy $n = 25$ (24%) after trans-hiatal esophagectomy $n = 3$ (10%) after MIE 9 patients underwent HH repair	Asymptomatic: $n = 2$ (of the operated patients) Colon: $n = 28$ (all patients; $n = 6$ of the operated patients) Colon + small bowel: $n = 4$ (all patients; $n = 2$ of the operated patients) Small bowel: $n = 1$ (all / operated patient) Emergency surgery: $n = 5$ Laparotomy: $n = 8$ Laparoscopy: $n = 1$ **Type of repair:** n/a Recurrency: $n = 4$
Bronson et al. [16]	The Incidence of Hiatal Hernia after Minimally Invasive Esophagectomy	Retrospective, Monocentric, 2003–2011	114 MIE, 9 (8%) patients developed hernia 13.7 (1.8–55.6) months after MIE and underwent repair $n = 2$ after trans-hiatal MIE $n = 7$ after McKeown MIE	Asymptomatic: $n = 5$ Colon: $n = 5$ Colon + small bowel: $n = 2$ Small bowel: $n = 1$ Emergency surgery: $n = 2$ Laparotomy: $n = 2$ Laparoscopy: $n = 7$ **Principles of repair** in all patients *: Reclosure of the crura, Biologic mesh placement and Colopexy Recurrency: $n = 1$
Narayanan et al. [23]	Treatment of Diaphragmatic Hernia Occurring After Transhiatal Esophagectomy	Retrospective, Monocentric, 2000–2013	199 esophagectomies, 10 (5%) patients developed HH in median 2.4 years after esophagectomy and underwent repair $n = 9$ after trans-hiatal esophagectomy $n = 1$ after McKeown esophagectomy 1 patient excluded	Asymptomatic: $n = 3$ Most common hernia content: n/a Emergency surgery: $n = 3$ Laparotomy: all patients **Type of repair:** Mesh interposition: all patients Recurrency: $n = 0$

Table 5 (continued)

Author [Reference number]	Reference	Study information, Observational period	General characteristics of the study cohort, *n* patients	Symptoms, Most commonly observed hernia content, Surgical hernia closure technique
Benjamin et al. [41]	Diaphragmatic hernia post-minimally invasive esophagectomy: a discussion and review of literature	Retrospective, Monocentric, 2006–2013,	120 MIE, 7 (5.8%) patients developed hernia 3.4 (1–45) months after MIE 5 patients underwent hernia repair 2 patients were asymptomatic and did not undergo hernia repair	Asymptomatic: $n = 0$ (of the operated patients) Colon: $n = 6$ Small bowel: $n = 1$ Emergency surgery: $n = 1$ Laparoscopy: all patients **Type of repair:** Direct suture (anterior cruropasty): $n = 3$ Direct suture + mesh reinforcement: $n = 2$ Recurrency: $n = 1$
Messenger et al. [19]	Symptomatic diaphragmatic herniation following open and minimally invasive oesophagectomy: experience from a UK specialist unit	Retrospective, Monocentric, 1996–2012	273 esophagectomies (205 COS, 68 MIE), 11 patients developed HH 3.2 months (2 days–44 months) after esophagectomy and underwent hernia repair $n = 9$ after MIE $n = 2$ after open trans-hiatal esophagectomy	Asymptomatic: $n = 0$ Colon: $n = 6$ Colon + small bowel: $n = 4$ Small bowel: $n = 1$ Emergency surgery: $n = 5$ Laparotomy: $n = 4$ (conversion: $n = 1$) Laparoscopy: $n = 7$ **Type of repair:** Direct suture: $n = 6$ Direct suture + mesh reinforcement: $n = 4$ No closure, only omentopexy: $n = 1$ (discrepancies between text and table in the manuscript) Recurrency: $n = 2$
Crespin et al. [8]	Hiatal Herniation After Transhiatal Esophagectomy: an Underreported Complication	Retrospective, Monocentric 2004–2013	192 laparoscopic-assisted trans-hiatal esophagectomies, retrospective assessment of CT scans 22 patients developed HH (cumulative incidence over two years 14%) 7.5 months (2 days–97 months) after index surgery < POD 11: $n = 5$ 3–97 months: $n = 17$ 15 patients were asymptomatic (non-operative management), 7 patients were symptomatic and underwent HH repair	Asymptomatic: $n = 0$ (of the operated patients) Most common hernia content: n/a Emergency surgery: $n = 2$ Laparotomy: $n = 4$ Laparoscopy: $n = 3$ **Type of repair:** Suture repair: $n = 3$ Mesh repair: $n = 4$* Recurrency: $n = 1$

Table 5 (continued)

Author [Reference number]	Reference	Study information, Observational period	General characteristics of the study cohort, *n* patients	Symptoms, Most commonly observed hernia content, Surgical hernia closure technique
Kanamori et al. [33]	Diaphragmatic herniation after thoracolaparoscopic esophagectomy for carcinoma of the esophagus: a report of six cases	Retrospective, Monocentric 2010–2014	150 total MIE (abdomino-thoracic) 6 (4%) patients developed HH 1–8 month after MIE, 5 patients were symptomatic and underwent HH repair, 1 patient was asymptomatic	Asymptomatic: $n = 0$ (of the operated patients) Colon: $n = 2$ Colon + small bowel: $n = 4$ Emergency surgery: $n = 4$ Laparotomy: $n = 4$ Laparoscopy: $n = 1$ **Type of repair:** Suture repair (+ pexy of the conduit to the diaphragm): $n = 5$ Recurrency: $n = 1$
Matthews et al. [28]	Diaphragmatic herniation following esophagogastric resectional surgery: an increasing problem with minimally invasive techniques?	Retrospective, Monocentric 2001–2015	631 esophagectomies, Hernia incidence (overall 5.5%): $n = 4/221$ (2%) after open 2 or 3 stage esophagecomy $n = 22/212$ (10%) after LAE $n = 5/73$ (7%) after total MIE $n = 4/125$ (3%) after total gastrectomy Hernia development: < POD 7: $n = 6$ POD 7–90: $n = 6$ POD 90–365: $n = 10$ > POD 365: $n = 13$ 31 patients underwent hernia repair	Asymptomatic: $n = 1$ Colon: $n = 18$ Colon + small bowel: $n = 12$ Small bowel: $n = 4$ Emergency surgery: $n = 20$ Laparotomy: $n = 20$ (conversion: $n = 8$) Laparoscopy: $n = 11$ **Type of repair:** Suture repair: $n = 24$ Mesh repair: $n = 7$ Recurrency: $n = 7$
Severino et al. [15]	Laparoscopic repair of hiatal hernia after minimally invasive esophagectomy	Retrospective, Monocentric 2000–2013	390 LAE, 32 (8.2%) patients developed HH 10 months (3 days–96 months) after LAE	Asymptomatic: $n = 10$ Colon: $n = 29$ Small bowel: $n = 4$ Emergency surgery: $n = 6$ Laparotomy: $n = 11$ (conversion: $n = 6$) Laparoscopy: $n = 19$ Thoracoabdominal approach: $n = 1$ (information for one patient missing in the manuscript) **Type of repair:** Suture repair: $n = 12$ Mesh interposition: $n = 20$ Recurrency: $n = 6$

Table 5 (continued)

Author [Reference number]	Reference	Study information, Observational period	General characteristics of the study cohort, *n* patients	Symptoms, Most commonly observed hernia content, Surgical hernia closure technique
Andreou et al. [32]	Incidence and Risk Factors of Symptomatic Hiatal Hernia Following Resection for Gastric and Esophageal Cancer	Retrospective, Monocentric 2005–2012	471 esophagectomies and gastrectomies, 13 (2.8%) had symptomatic HH and underwent repair 15 (0.1–57) months after index surgery Incidences: 0.7% after gastrectomy 6.1% after extended gastrectomy 2.7% after trans-thoracic esophagectomy	Asymptomatic: $n = 0$ Most common hernia content: n/a Emergency surgery: $n = 8$ Laparotomy: $n = 13$ **Type of repair:** Direct suture: $n = 10$ Direct suture + mesh augmentation: $n = 3$ Recurrency: n/a
Brenkman et al [14]	Hiatal Hernia After Esophagectomy for Cancer	Retrospective, Bicentric 2000–2014	657 (432 MIE, 225 COS) trans-hiatal, 2 and 3 stage esophagectomies, HH was diagnosed in 45 patients 20 (0–101) months after index surgery $n = 12$ after COS $n = 33$ after MIE 26 patients underwent HH repair 14 patients underwent emergency surgery at time of HH diagnosis 17 symptomatic patients of whom 10 initially underwent elective HH repair 14 asymptomatic patients with "wait-and-see" concept "Wait-and-see" successful in 19/21 patients	Asymptomatic: $n = 0$ of the patients at time of surgery ($n = 14$ initially) Colon: $n = 37$ Small bowel: $n = 19$ Emergency surgery: $n = 16$ Laparotomy: $n = 17$ (conversion: $n = 1$) Laparoscopy: $n = 9$ **Type of repair:** Suture repair: $n = 21$ Direct suture + mesh augmentation: $n = 5$ Recurrency: $n = 4$
Gooszen et al. [11]	Incidence and Treatment of Symptomatic Diaphragmatic Hernia After Esophagectomy for Cancer	Retrospective, Monocentric 2005–2015	851 esophagectomies (345 MIE and 506 OE, both including THE, Ivor Lewis and McKeown esophagectomies) Symptomatic HH was diagnosed in 21 (2.5%) patients 172 (1–1031) days after index surgery All patients underwent HH repair: 4.3% after MIE (highest incidence with 9.4% after MI-ILE) 1.2% after OE	Asymptomatic: $n = 0$ Hernia contents not available in the manuscript Emergency surgery: $n = 71.4\%$ Laparotomy: $n = 11$ (Conversion: $n = 1$) Laparoscopy: $n = 10$ **Type of repair:** Direct suture: $n = 10$ Direct suture + mesh reinforcement: $n = 11$ Conduit fixation to the crus: all patients Recurrency: $n = 4$
Gust et al. [7]	Hiatal hernia after oesophagectomy: a large European survey	Retrospective, Multicentric, 2000–2016	6608 esophagectomies (including THE, Ivor Lewis and McKeown esophagectomies), HH was diagnosed in 79 (1.2%) patients 78 patients [$n = 49$ (62%) after laparoscopy and $n = 29$ (37%) after laparotomy for the abdominal approach during index surgery, respectively] underwent hernia repair < POD 90: $n = 17$ POD 90–365: $n = 21$ > POD 365: $n = 41$	Asymptomatic: $n = 11$ Most common hernia content: n/a Emergency surgery: $n = 43$ Laparotomy: $n = 35$ (conversion: $n = 3$) Laparoscopy: $n = 19$ Thoracic approach: $n = 24$ **Type of repair:** Direct suture ± mesh reinforcement: $n = 63$ Mesh interposition: $n = 12$ Mesh-repair (n/a): $n = 3$ Recurrency: $n = 8$

Table 5 (continued)

Author [Reference number]	Reference	Study information, Observational period	General characteristics of the study cohort, *n* patients	Symptoms, Most commonly observed hernia content, Surgical hernia closure technique
Gong et al. [36]	Diaphragmatic Hernia After Totally Laparoscopic Total Gastrectomy for Gastric Cancer	Retrospective, Monocentric, 2011–2017	490 laparoscopic total gastrectomies, 8 (1.63%) patients underwent emergency surgery for hernia repair 7.3 (3.4–12.8) months after gastrectomy	Asymptomatic: $n = 0$ Most common hernia content: n/a Emergency surgery: $n = 8$ Laparotomy: $n = 3$ Laparoscopy: $n = 5$ **Type of repair:** Direct suture: $n = 6$ Mesh-repair (n/a): $n = 2$ Recurrency: n/a
Urabe et al. [13]	Diaphragmatic herniation following total gastrectomy: review of the long-term experience of a tertiary institution	Retrospective, Monocentric, 1985–2013	1361 total gastrectomies, 5 patients underwent surgery for HH repair 78.1 (2.9–189.0) months after gastrectomy $n = 2$ after laparoscopic gastrectomy $n = 3$ after COS	Asymptomatic: $n = 0$ Colon: $n = 2$ Colon + small bowel: $n = 1$ Small bowel: $n = 2$ Emergency surgery: $n = 4$ Laparotomy: $n = 2$ Laparoscopy: $n = 1$ Left-thoracoabdominal approach: $n = 2$ **Type of repair:** Direct suture: $n = 4$ Mesh interposition: $n = 1$ Recurrency: $n = 0$
Takeda et al. [39]	Diaphragmatic Hernia Repair After Esophagectomy: Technical Report and Lessons After a Series of Cases	Retrospective, Monocentric 2009–2019	328 esophagectomies, 8 (2.4) patients were diagnosed with HH 18 months (7 days–39 months) after MIE and underwent hernia repair	Asymptomatic: $n = 1$ Colon: $n = 4$ Colon + small bowel: $n = 4$ Emergency surgery: n/a Laparotomy: $n = 1$ Laparoscopy: $n = 7$ **Type of repair:** Suture repair: $n = 3$ Mesh repair (n/a): $n = 5$ Recurrency: $n = 1$
Hanna et al. [17]	Hiatal Hernia after Esophagectomy: An Underappreciated Complication?	Retrospective, Monocentric, 2011–2017	258 of 310 esophagectomies analyzed, 79 (31%) patients had evidences of hiatal hernia, 44 of 79 had symptoms, 17 of 79 underwent hernia repair between < 1 and 39 months after index surgery	Asymptomatic: $n = 35$ of all patients Colon: $n = 4$ Colon + small bowel: $n = 4$ Small bowel: $n = 9$ Emergency surgery: $n = 8$ Surgical approach: n/a **Type of repair:** Direct suture: $n = 14$ Mesh repair: $n = 3$ Recurrency: $n = 5$

Table 5 (continued)

Author [Reference number]	Reference	Study information, Observational period	General characteristics of the study cohort, *n* patients	Symptoms, Most commonly observed hernia content, Surgical hernia closure technique
Fuchs et al. [10]	Transdiaphragmatic herniation after transthoracic esophagectomy: an underestimated problem	Retrospective, Monocentric, 2003–2017	39 patients underwent HH repair 259 (1–1467) days after hybrid Ivor Lewis esophagectomy	Asymptomatic: $n = 3$ Colon: $n = 34$ Small bowel: $n = 19$ Emergency surgery: $n = 20$ Laparotomy: $n = 29$ Laparoscopy: $n = 10$ **Type of repair:** Hiatoplasty: all patients (but, technique not described) Pexy of prolapsed organs to the diaphragm: $n = 10$ Recurrency: $n = 3$
Lubbers et al. [20]	Hiatal Hernia with Acute Obstructive Symptoms After Minimally Invasive Oesophagectomy	Retrospective, Monocentric, 2011–2018	307 total MIE (Ivor Lewis or McKeown) 8 (2.6%) patients underwent hernia repair 262 (1–1830) days after index surgery	Asymptomatic: $n = 0$ Colon: $n = 3$ Colon + small bowel: $n = 3$ Small bowel: $n = 2$ Emergency surgery: $n = 8$ Laparotomy: $n = 3$ (conversion: $n = 2$) Laparoscopy: $n = 5$ (additional thoracoscopy: $n = 1$) **Type of repair:** Direct suture: $n = 5$ Direct suture + mesh reinforcement: $n = 3$ Recurrency: $n = 3$

Terms used for the systematic review of English literature in *Medline* published from 01/2005–09/2020 reporting ≥ 5 surgical cases: "hiatal hernia" OR "hiatal herniation" OR "transdiaphragmatic herniation" OR "transdiaphragmatic hernia" OR "diaphragmatic hernia" OR "diaphragmatic herniation" OR "herniation" OR "hernia" OR "enterothorax" OR "cruroplasty" OR "hiatoplasty" AND "esophagectomy" OR "oesophagectomy" OR "gastrectomy". * not further specified in the manuscript

n/a = not available in the manuscript, *HH* = hiatal hernia, *ILE* Ivor Lewis esophagectomy, *MI* minimally invasive, *POD* postoperative day. MIE = minimally invasive esophagectomy, *LAE* laparoscopically-assisted esophagectomy, *COS* conventional open surgery, *THE* trans-hiatal esophagectomy, *OE* open esophagectomy

the present study two of the patients, who underwent hernia repair, were asymptomatic. This goes in line with several reports in the current literature, which reported hernia repair even in patients without or with only mild symptoms, where the hernia had been found incidentally. This strategy follows the hypotheses, that the hernia may be progressive in size and symptoms, thus symptoms may arise in initially asymptomatic patients and an early elective hernia repair might prevent patients from severe cardiac, pulmonary and bowel complications as well as the fatal risk of incarceration with obstruction or perforation in the emergency situation [10, 15, 17, 30, 31]. By that way, no predictors are known for an unfavorable outcome of conservative "wait-and-see" strategies, thus a great proportion of patients require emergency surgery although an initially intended "wait-and-see" concept [14, 28, 30, 39]. Thereby, it is known that not only morbidity rates of the patients (up to 60%) with consecutively longer hospital stays but also mortality rates (up to 20%) are dramatically increased after hernia repair in the emergency situation [11, 14, 15, 20, 28, 29, 40].

The question on "how to sufficiently repair" trans-hiatal herniation after esophagectomy or gastrectomy cannot be adequately answered from case reports and small case series published in the literature. Surgical closure techniques depend on surgeons´ expertise and on characteristics of the hernia. Nearly all authors report a trans-abdominal approach for the hernia repair, with laparoscopy being safely feasible, especially in patients, who had undergone minimally-invasive approaches for index surgery, considering conversion rates up to 42% [7, 16, 28]. Vice versa, in emergency cases the preferred approach for hernia repair is conventional laparotomy [7, 14, 16]. However, surgeons should be prepared to undertake a thoracic approach, if dense intra-thoracic adhesions prevent the reduction of the prolapsed contents into the abdominal cavity [19, 21, 40, 41]. After reduction of prolapsed contents, essential steps during post-esophagectomy or post-gastrectomy trans-hiatal hernia repair are: assessment of the gastric conduit or jejunum to the anastomosis, assessment of herniated bowel viability, closure of the diaphragmatic defect around the conduit or jejunal limb, respectively, and thereby recreate a functional hiatus [18].

No consensus or broad experiences exit for the adequate repair technique resulting in extraordinary high recurrence rates reported in the literature. Surgeons have to be aware of different closure techniques of the hiatal orifice. However, our data show that the native size of the hernial orifice obtained from preoperative diagnostic imaging is not an adequate predictor of the appropriate closure technique especially regarding the intraoperative option for mobilization and reapproximation of the diaphragmatic crura followed by suture cruroplasty with or without mesh augmentation versus the need for tension-free mesh interposition (Table 2). In some cases anterior and posterior suture cruroplasty—the conduit lies dorsal –might be sufficient for hernia repair. Kent et al. recommend preservation of the peritoneal lining and dorsal mobilization of the crura for tension-free adaptation [40, 42]. Additional mesh augmentation can be performed after suture cruroplasty of larger defects similar to paraesophageal hernia repair [8, 16, 39, 43, 44]. Furthermore, some authors recommend the fixation of the conduit to the crus or pexy of abdominal organs, especially of the transverse colon as the most often prolapsed organ as an additional measure [10, 14, 16, 19, 32, 40]. Interestingly, the latter was done in our patient cohort more frequently in patients who underwent suture cruroplasty without the use of meshes. If tension is too strong for primary suturing, closure of the hiatal defect can be achieved by mesh as an inlay patch anteriorly from the conduit to the diaphragm with no approximation of the crural muscles [15, 23, 32, 40]. Nevertheless, most articles in the current literature report a mixture of these techniques for hernia repair resulting in high recurrence rates, up to 38%, which, however, might be independently from mesh buttressing of suture cruroplasty [17, 19, 20, 28, 42]. Thereby care has to be taken on the blood supply of the jejunal limb or the gastric conduit from the right gastroepiploic artery after gastrectomy or esophagectomy, respectively, and not to obstruct the passage, which both can increase the risk for conduit necrosis and anastomotic leakages especially in cases of hiatal hernia repair in the early phase after gastrectomy or esophagectomy [9–11, 13, 16–21, 34]. The use of meshes to restore the integrity of the hiatus during the index surgery is still disputed due to the additional feared risk of erosion of the conduit [9, 10, 13, 16–19, 34].

Limitations of the former case series describing treatment modalities and outcome of patients with post-esophagectomy or post-gastrectomy HH from the current literature are even reflected by the present study (Table 5). The present data analysis narratively reviews the institutional experience with the hernia repair, however, the current study was not designed to evaluate incidences of HH development after esophagectomy or gastrectomy. Thus, the retrospective character of the study, the missing information regarding incidences of HH development after index surgery and the lack of an institutional structured follow-up protocol after HH surgery might be the strongest limitation. The long observational period with a small sample size on the one hand, the lack of evidence-based standard protocols for post-esophagectomy or post-gastrectomy HH repair on the other hand have to be stated as limitations as well. Regarding the latter, it remains unclear, why patients underwent more frequently crural repair by simple suture without mesh usage in an emergency situation. This might be due to the fear of mesh-related complications by local peritonitis through initially incarcerated bowel or due to single surgeon´s preferences and even expertise in the emergency setting. Both might be prone to bias in the current data analysis. Finally,

the inhomogeneous patient collective regarding index surgeries leads to some differences in hernia characteristics and thus should be interpreted as a minor limitation. Thereby, the current literature reveals the lowest incidence for trans-hiatal herniation after conventional gastrectomy [13, 28, 32, 36], since in these cases other types of internal hernia, like Peterson´s hernia or herniation through the jejunojejunostomy mesenteric defect after Roux-Y reconstruction, are more frequent [13, 36, 45–47]. Thus, the group of patients, who initially underwent total gastrectomy with Roux-Y reconstruction, seems a bit overrepresented in our cohort. However, principles of HH repair remain the same for post-gastrectomy as well as for post-esophagectomy HH. These factors surely limit the evidence regarding considerations of therapeutic strategies (emergency versus elective hernia repair versus "wait and see" concepts) as well as modalities of hernia repair surgery (primary suture cruroplasty versus primary suture cruroplasty with mesh augmentation versus tension-free mesh interposition) from the current study. However, firm conclusions should generally not be drawn from retrospective case series for clinical practice.

In conclusion, surgeons should be aware of trans-hiatal hernia, which is certainly an underestimated problem after esophagectomy or gastrectomy. Experiences with the disease and expertise in surgical repair techniques are low, even in high-volume centers for upper gastrointestinal surgery. Referring to high recurrence and morbidity rates, guidelines or expert recommendations are urgently needed, clearing the open questions regarding appropriate surveillance or the role of hernia repair in asymptomatic patients and principles of the adequate hernia repair technique. In our opinion, surgical repair should be offered to all patients with post-esophagectomy or post-gastrectomy trans-hiatal herniation. Patients with acute onset of especially pulmonary and cardiac symptoms, clinical signs of bowel obstruction or radiological signs of incarceration should undergo emergency surgery.

Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Philip Ulrich Oppelt, Martin Reichert and Fritz Christian Roller. The first draft of the manuscript was written by Martin Reichert and Andreas Hecker. Ingolf Askevold performed the statistical analysis, Winfried Padberg and Rüdiger Hörbelt interpreted the data and contributed to further drafts of the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interests All authors declare that they have nothing to disclose. Philip Ulrich Oppelt, Ingolf Askevold, Rüdiger Hörbelt, Fritz Christian Roller, Winfried Padberg, Andreas Hecker and Martin Reichert declare that they have no conflicts of interests regarding this article.

Statement of human rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Ethics committee of the medical faculty of the University of Giessen) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

All patients of this retrospective conducted patient data analysis were treated following the current local standard of care.
The retrospectively conducted analysis of patient data and the study was formally approved by the local ethics committee of the medical faculty of the University of Giessen (Approval Numbers: 214/15, 253/16 and 97/19).

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11.7 Anlage 7

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ORIGINAL ARTICLE

Right colectomy from open to robotic — a single-center experience with functional outcomes in a learning-curve setting

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Abstract

Purpose Right colectomy (RC) is a frequently performed procedure. Beneath standard conventional open surgery (COS), various minimally invasive techniques had been introduced. Several advantages had recently been described for robotic approaches over COS or conventional laparoscopy. Nevertheless, novel minimally invasive techniques require continuous benchmarking against standard COS to gain maximum patient safety. Bowel dysfunction is a frequent problem after RC. Together with general complication rates postoperative bowel recovery are used as surrogate parameters for postoperative patient outcome in this study.

Methods Retrospective, 10-year single-center analysis of consecutive patients who underwent sequentially either COS ($n=22$), robotic-assisted (ECA: $n=39$), or total robotic surgery (ICA: $n=56$) for oncologic RC was performed.

Results The conversion from robotic to open surgery rate was low (overall: 3.2%). Slightly longer duration of surgery had been observed during the early phase after introduction of the robotic program to RC (ECA versus COS, $p=0.044$), but not anymore thereafter (versus ICA). No differences were observed in oncologic parameters including rates of tumor-negative margins, lymph node-positive patients, and lymph node yield during mesocolic excision. Both robotic approaches are beneficial regarding postoperative complication rates, especially wound infections, and shorter length of in-hospital stay compared with COS. The duration until first postoperative stool is the shortest after ICA (COS: 4 [2–8] days, ECA: 3 [1–6] days, ICA: 3 [1–5] days, $p=0.0004$). Regression analyses reveal neither a longer duration of surgery nor the extent of mesocolic excision, but the degree of minimally invasiveness and postoperative systemic inflammation contribute to postoperative bowel dysfunction, which prolongs postoperative in-hospital stay significantly.

Conclusion The current study reflects the institutional learning curve of oncologic RC during implementation of robotic surgery from robotic-assisted to total robotic approach without compromises in oncologic results and patient safety. However, the total robotic approach is beneficial regarding postoperative bowel recovery and general patient outcome.

Keywords Right colectomy · Complete mesocolic excision · Robot · Intracorporal anastomosis · Bowel dysfunction · Ileus

Introduction

Right colectomy (RC) with complete mesocolic excision (CME) for carcinoma of the ascending colon is a frequently performed standard procedure in general surgery. Several different techniques are known for oncologic RC with CME, ranging from conventional open surgery (COS) to hybrid or total minimally invasive approaches with different variants of extracorporal or intracorporal techniques for the ileo-colic anastomosis, respectively [1–3]. Thereby, numerous studies have proven the non-inferiority of minimally invasive surgery in colorectal cancer concerning oncological long-term results compared with COS as the benchmark [4–7].

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Although conventional laparoscopy had broadly been applicated as standard in surgery of the left colon and rectum over the last decades, minimally invasive approaches using conventional laparoscopy are sparsely introduced into clinical routine practice for oncologic resections of the right colon [8–11]. However, through increasing numbers and availability of robotic programs, growing experiences with, further development in as well as technical advantages of robotic-assisted surgery over conventional laparoscopy [2, 8, 12–16], minimally invasive robotic approaches for RC are constantly evolving and progressively established in the clinical routine [9, 11, 16–18]. Although costs of minimally invasive approaches, especially of robotic surgery, are considerably higher compared with COS [11, 17, 19, 20], some evidences exist in the current literature concerning improved postoperative short-term outcome and morbidity, respectively, of patients after minimally invasive RC with CME [11, 17, 18, 20–24]. Particularly the total minimally invasive approach with intracorporal anastomosis is beneficial considering postoperative pain [25], surgical site infections [22, 26], and complications urging re-interventions [22, 26, 27] and finally results overall in a shorter recovery and decreased postoperative length of hospital stay [22, 25–29]. After this had been extensively shown in studies and confirmed by systematic reviews and metaanalyses for conventional laparoscopic apporaches [30], current literature reveals further improvements of intraoperative visualization resulting in higher lymph node yield and postoperative patient outcome with growing experiences in minimally invasive robotic surgery for RC with CME [8, 24, 30, 31]. Nevertheless, the beneficial impact of robotic-assisted or total robotic surgery in comparison with COS as the benchmark approach for oncologic RC with CME on postoperative outcome, especially including systemic inflammation, functional bowel recovery, and their association with duration of hospitalization, currently remains elusively. While postoperative bowel dysmotility and paralysis is a temporary physiologic reaction after abdominal surgery, a prolonged state of bowel dysfunction and paralytic ileus is an extraordinary frequent clinical problem in patients after surgery of the right hemicolon [24, 32]. Nonetheless, their pathophysiology is currently not fully understood, but delayed postoperative return to normal bowel function is a major threat for patients, which frequently results in high risk for harmful acid aspiration, impaired patient comfort, and general postoperative outcome and prolongs hospital stay as well as recovery of affected patients and consequently increases public health costs [33–35].

We herein report the experiences with oncologic RC including CME from a nation-wide benchmark center for robotic colorectal surgery [36] with regard to postoperative bowel recovery and patient outcome. Before implementation of the robotic program at that institution, RC was approached by COS. During the learning curve of robotic surgery, the complex procedure of oncologic RC with CME was initially performed by a robotic-assisted approach with extracorporal ileo-colic anastomosis and was finally converted to total minimally invasive robotic surgery with intracorporal anastomosis, giving the opportunity to compare both minimally invasive approaches with standard COS in the era of robotic surgery.

Material and methods

Patients

This retrospective single-center cohort study was formally approved by the local ethics committee of the Landesaerztekammer Rheinland-Pfalz (approval No. 2019–14732-retrospektiv). The study was performed in accordance with the latest version of the Declaration of Helsinki. The data are collected, and the manuscript is written and submitted in accordance with the COPE guidelines. All patients were treated according to the institutional standard of care.

All consecutive 117 patients who underwent elective oncological RC with CME due to preoperative concerns or histologically proven malignancy were included into the data analysis from 01/2013 to 03/2022. Through implementation of a robotic surgery program at the institution, the surgical technique was converted from a conventional open surgical approach (COS: 01/2013–12/2014, $n = 22$ patients) to minimally invasive robotic surgery as clinical standard for oncological RC with CME during the 10-year observational period. Thereby the robotic approach by itself underwent some evolution from robotic-assisted RC with extracorporal (ECA: 01/2015–12/2017, $n = 39$ patients) to total minimally invasive robotic technique with intracorporal hand-sewn ileo-colic anastomosis (ICA: 01/2018–03/2022, $n = 56$ patients).

Patient data were analyzed retrospectively from the prospectively maintained institutional database regarding general patient characteristics and surgical procedure characteristics, general postoperative patient outcome, and more specifically regarding postoperative day of first stool as the surrogate parameter for postoperative bowel recovery or dysfunction. Perioperative peripheral blood leukocyte counts and C-reactive protein (CRP) values were obtained from routine laboratory examinations. The highest values of leukocytes and CRP on POD 1–3 were used as markers for interpreting surgical trauma-induced systemic inflammation.

Surgery and perioperative patient care

All patients received mechanical bowel preparation at the day before surgery and antibiotic single-shot prophylaxis

with ceftriaxone (2 g iv) and metronidazole (500 mg iv) immediately before surgery. Median laparotomy was used for COS. Mobilization of the right colon and CME were approached by a lateral-to-medial approach with central ligation of the ileo-colic vessels and consecutive dissection of the lymph nodes across the CME plain. Transverse colon and ileum were transected by a stapling device and the bowel continuity was restored by side-to-side ileo-colic hand-sewn running suture anastomosis.

For robotic procedures the Da Vinci Si system was used from 01/2015 to 12/2017. From 01/2018 all procedures were performed with the Da Vinci Xi system (Intuitive Surgical, Sunnyvale, CA, USA). As shown in Fig. 1a, three-port robotic technique with one assistant port was used for surgery of the right colon. The 12-mm "assistant" port was introduced through a minilaparotomy in the left lower abdomen. After establishing the pneumoperitoneum at 15 mm Hg three "robotic" ports (two 8 mm and one 12 mm) were placed in the left midclavicular line between the symphysis and the costal arch under vision. Surgery was performed in slight Trendelenburg position (~ 10–15°) to the left (~ 10°). Robotic oncologic RC followed the principles of COS. The CME was performed by a medial-to-lateral approach with central ligation of the ileo-colic vessels and lymph node dissection. Transverse colon and ileum were transected by stapling devices. In the ECA group the specimen was retrieved and the ileo-colic anastomosis was performed by the COS technique through a 7–10-cm transverse laparotomy in the right upper abdomen. In the ICA group, ileum and transverse colon were positioned side-to-side. Ileum and colon were opened by an incision with the robotic monopolar scissors and the side-to-side ileo-colic anastomosis was performed by bidirectional running suture with Stratafix™ (3/0). Finally, the specimen was retrieved through a 5-cm Pfannenstiel incision. At the end of the procedure the gastric tube was removed and the patients started drinking on the day of surgery and were on liquid diet until the first postoperative day.

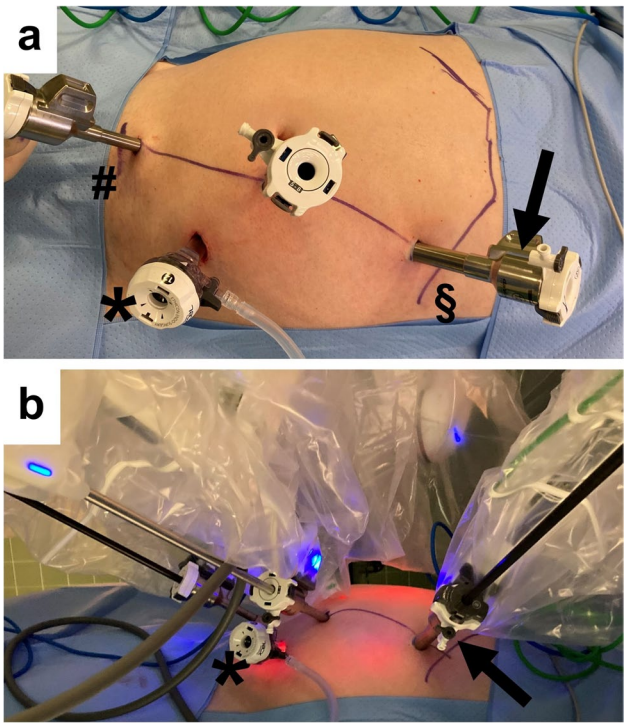


Fig. 1 Port placement for right colectomy with the Da Vinci ® Xi system (Intuitive Surgical, Sunnyvale, CA, USA). Three robotic ports and one assistant port (*) were used. **a** The 12-mm assistant port (*) is placed in the left lower abdomen by means of a minilaparotomy. Thereafter, the three robotic ports are introduced under vision on a line between the symphysis (#) and the left costal arch (§) on the midclavicular line (two 8-mm ports and one 12-mm port [→]). Care has to be taken on the assistant port, which should be placed in a triangle between the two lower robotic ports to have optimal access. For the later Pfannenstiel minilaparotomy the access of the lowest robotic port above the symphysis is used. **b** The lowest robotic port above the symphysis is used for bipolar instrument. The middle robotic port is used for the camera and the upper port in the left upper abdomen beneath the costal arch (→) is used for monopolar scissors, stapler devices, and in case of intracorporal anastomosis for the needle holder

Statistical analysis

The patient cohort was subdivided into three groups regarding the surgical approach: (1) conventional open surgery (COS group, $n = 22$ patients), (2) the either group of patients who underwent a robotic-assisted, minimally invasive approach with extracorporal anastomosis (ECA group, $n = 39$ patients), and (3) the other group of patients who underwent a total minimally invasive, robotic approach with intracorporal anastomosis (ICA group, $n = 56$ patients).

Statistical analyses were performed using GraphPad Prism (Version 9 for Windows, GraphPad Software, San Diego, CA, USA; www.graphpad.com). For descriptive statistics, categorical data were analyzed using Fishers exact test or Pearson's χ^2 test. Group comparisons of continuous variables were performed by Kruskal–Wallis test for global effects and, if applicable (i.e. $p_{KW} \leq 0.05$), followed by Dunn's test (corrected for multiple comparisons) for pairwise multiple comparisons.

Simple linear regression analysis was used to predict significant dependencies between relevant variables.

Data are given in median and minimum to maximum ranges for continuous variables as well as n (%) for categorical data. Bars in the boxplots, shown in the figures, depict medians. Whiskers indicate minimum to maximum ranges. The boxes extend from the 25th to 75th percentiles and indicate the interquartile ranges.

The p-values ≤ 0.05 were considered to indicate statistical significance. Because of the exploratory character of the study no adjustments of p-values were performed.

Results

Basic characteristics of patients and procedures

Basic patient characteristics and relevant chronic diseases were widely balanced between the three groups of patients (Table 1). The overall conversion rate in the robotic cohort from an initially intended robotic approach to COS for RC was low (3.2%). Two patients from the ECA group and one patient from the ICA group underwent conversion to COS due to dense adhesions, bleeding, and unclear definition of the tumor site during minimally invasive surgery, respectively (ECA: 5.1% and ICA: 1.8%, $p = 0.566$). These patients, who underwent conversion to open surgery, were excluded from further (postoperative) outcome analyses.

Although all procedures were intended as oncological RC with complete mesocolic excision due to preoperative concerns or histologically proven malignancy, colon carcinoma was postoperatively histopathologically confirmed in 18 (81.8%), 22 (59.5%), and 47 (85.5%) of the cases from the COS, ECA, and ICA groups, respectively ($p = 0.055$). However, no differences were observed regarding tumor sizes (T-factor), rates of tumor-negative resection margins (R-factor), rates of nodal positive patients (N-factor), and the numbers of retrieved lymph nodes between the groups as important parameters for radical oncologic surgery (Table 2; Fig. 2). Notably, the duration of surgery was only slightly longer compared with COS during the ECA phase immediately after introduction of the robotic program for RC (COS: 140 [68–240] min versus ECA: 161 [95–235] min, $p = 0.044$). This effect was abandoned later on in ICA patients (151 [110–250] min, $p = 0.154$ versus COS; Fig. 2).

Perioperative C-reactive protein and leukocytes

The highest postoperative CRP values and leukocyte counts during POD 1–3 were used to estimate the extent of surgical trauma. No differences were observed between the three groups in preoperative CRP values and leukocyte counts; however, these markers of systemic inflammation were the highest postoperatively in the group of patients who underwent primary conventional open RC (Fig. 3).

Postoperative outcome and recovery of bowel function

More patients from the COS group suffered from any postoperative complication, resulting in the highest ranks of comprehensive complication indexes in this group of patients (Fig. 4). Especially the rate of surgical site infections was the highest in the open RC group (COS: 27.3% vs. ECA: 5.4% vs. ICA: 0, $p < 0.0001$; Table 2). The duration until first postoperative defecation was used as the surrogate parameter

Table 1 Patient characteristics

Variable	Conventional open surgery ($n = 22$)	Robotic surgery		p-Value
		ECA ($n = 39$)	ICA ($n = 56$)	
Male gender (*n patients*)	14	19	25	0.317
Age (*years*)	73 (44–89)	71 (39–87)	74 (41–90)	0.268
BMI (kg/m^2)	26.7 (20.7–41.1)	26.8 (17.2–39.5)	25.1 (16.7–39.5)	0.167
ASA (*score*)	2 (2–3)	2 (1–3)	2 (1–4)	0.165
Chronic diseases (*n patients*)	22	32	47	0.113
Arterial hypertension	18	24	37	0.254
Coronary artery disease	2	4	11	0.320
Chronic pulmonal disease	2	2	11	0.097
Diabetes mellitus	3	4	7	0.913
Chronic kidney disease	4	5	2	0.093
Systemic immunosuppression	0	4	7	0.229
Neurologic disease	2	6	10	0.627
Previous malignoma (*n patients*)	6	6	10	0.505
Active smoking (*n patients*)	5	9	6	0.214
Active alcohol abuse (*n patients*)	0	0	1	0.577
Previous abdominal surgery (*n patients*)	11	13	24	0.414

BMI body mass index, *ASA* American Society of Anaesthesiologists physical status classification, *ECA* hybrid minimally invasive, robotic-assisted right colectomy with extracorporal hand-sewn anastomosis, *ICA* total minimally invasive, robotic right colectomy with intracorporal hand-sewn anastomosis

Table 2 Perioperative results and outcome

Variable	Conventional open surgery ($n=22$)	Robotic surgery		*p*-Value
		ECA ($n=39$)	ICA ($n=56$)	
Final diagnosis[*]				
Divertikulitis	0	2	1	0.055
Large adenoma	4	13	7	
Carcinoma	18	22	47	
pT 1	3	4	13	0.785
pT 2	2	6	9	
pT 3	11	10	21	
pT 4	2	2	4	
pN +	5	4	9	0.704
Local pR0	All patients	All patients	All patients	1
Adhesiolysis	10	15	18	0.528
Intraoperative complications	1[µ]	1[µ]	0	0.333
Intraoperative conversion[#]	-	2	1	0.566
Intraoperative transfusion	1	1	1	0.786
Intraoperative drainage	5	2	0	0.0007
Postoperative complications (*n* patients)[¶]	13	6	5	< 0.0001
Surgical site infections	6	2[§]	0	< 0.0001
Pneumonia	2	0	1	
Intraluminal bleeding	1	0	3	
Intraabdominal bleeding	1	1[£]	0	
Anastomotic leakage	2[&]	1	1[£]	0.262
Internal hernia	1[¥]	0	0	
Abdominal re-do surgery	2	2	1	
Other	1	1	0	
CCI	8.7 (0–34.8)	0 (0–42.4)	0 (0–100)	< 0.0001
Grade I (*n* complications)[€]	6	2	0	
Grade II (*n* complications)[€]	6	2	1	
Grade IIIa (*n* complications)[€]	0	0	3	
Grade IIIb (*n* complications)[€]	2	2	1	
Grade IVa (*n* complications)[€]	0	1	0	
Grade IVb (*n* complications)[€]	0	0	0	
Mortality	0	0	2	$p=0.336$
Postoperative return to ICU (*n* patients)	2[Ω]	1[ΩΩ]	3[ΩΩΩ]	0.537
Postoperative bowl stimulation (*n* patients)	7	12	21	0.553
Neostigmin	0	1	0	
Laxantives	4	5	2	
Movicol	1	7	16	
Klysma	6	2	2	

Patients who underwent conversion from an initially intended minimally invasive approach to conventional open surgery ($n=3$) were excluded from perioperative outcome analysis. All procedures were performed due to preoperative concerns or histologically proven malignancy

[*]The "final" histopathologically confirmed diagnosis; patients who underwent intraoperative conversion to open surgery were excluded

[#]Overall conversion rate was 3.2%

[µ]Bleeding in both cases; in the ECA group leading to conversion to open surgery. Reasons for conversion to open surgery from an initially intended minimally invasive approach were dense adhesions and bleeding in the ECA group and unclear definition of the tumor site in the ICA group

[¶]Postoperative complications during the postoperative day 30 were included

[§]One deep organ space surgical site urging re-do surgery

[&]One anastomotic insufficiency urging re-do surgery. The other anastomotic insufficiency in the COS group as well was the anastomotic insufficiency from the ECA group were covered and did not require re-interventional therapy

[£]Urging re-do surgery

[¥]Internal hernia causing ileus and urging re-do surgery

[€]Regarding the Clavien-Dindo classification of surgical complications [60]. Ω Due to re-do surgery in both cases, Ω Ω due to acute kidney injury and Ω Ω Ω due to pneumonia ($n=1$), intraluminal bleeding ($n=1$), and intraluminal bleeding at postoperative day 6 and severe prolonged sepsis after re-do surgery for anastomotic leakage ($n=1$). *CCI* comprehensive complication index [61], *ICU* intensive care unit, *ECA* hybrid minimally invasive, robotic-assisted right colectomy with extracorporal hand-sewn anastomosis, *ICA* total minimally invasive, robotic right colectomy with intracorporal hand-sewn anastomosis

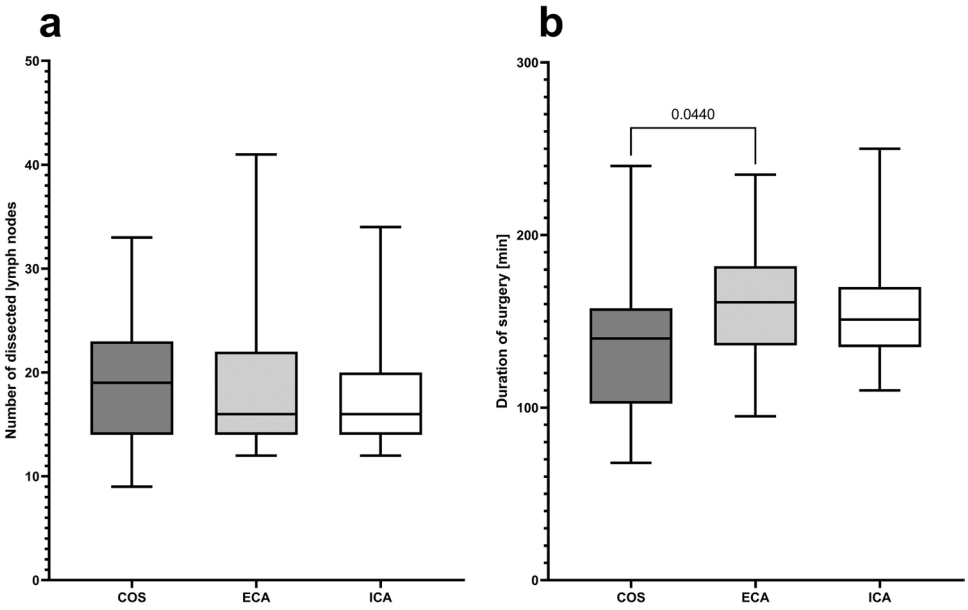


Fig. 2 Surrogate outcomes of the surgical procedure. **a** Numbers of harvested lymph nodes during oncological right colectomy with complete mesocolic excision (p [Kruskal–Wallis test] = 0.570) and **b** duration of surgery (p [Kruskal–Wallis test] = 0.047). *COS* conventional open surgery; *ECA* hybrid minimally invasive, robotic-assisted right colectomy with extracorporal hand-sewn anastomosis; *ICA* total minimally invasive, robotic right colectomy with intracorporal hand-sewn anastomosis

for postoperative bowel recovery or dysfunction after RC. Although no differences were observed in the rates of postoperative bowel stimulation among the groups, duration until postoperative first stool was the shortest in the ICA group (COS: 4 [2–8] days vs. ECA: 3 [1–6] days vs. ICA: 3 [1–5] days, $p_{KW} = 0.0004$). Longer duration of postoperative bowel recovery and higher rates of postoperative complications as well as higher ranks of comprehensive complication indexes in the COS group resulted in longer postoperative stay at intensive care unit (COS: 0.5 [0–3] days vs. ECA: 0 [0–1] day vs. ICA: 0 [0–4] days, $p_{KW} = 0.0006$) as well as longer postoperative total in-hospital stay of these patients (COS: 12 [7–21] days vs. ECA: 8 [5–21] days vs. ICA: 8 [4–22] days, $p_{KW} < 0.0001$) (Table 2; Fig. 4). However, we complained two patients from the ICA group, who suffered from postoperative mortality (overall mortality rate in the study cohort: 1.7%, $p = 0.336$ for COS [0%] versus ECA [0%] versus ICA [3.6%]): one patient died on postoperative day 3 after ICA due to severe pulmonary embolism, and the other polymorbid patient died on postoperative day 11 after ICA due to prolonged severe sepsis after re-do surgery for anastomotic leakage.

Linear regression analyses

Linear regression analyses basically confirm the results from group comparisons. The postoperative elevation of CRP values and leukocyte counts, the postoperative day of first stool, and the length of postoperative in-hospital stay correlate significantly with the surgical approach (i.e., COS > ECA > ICA; Fig. 5a and b).

Further factors were evaluated that might influence on postoperative bowel dysfunction, independently from the surgical approach. The day of postoperative first stool was dependent on the height of postoperative inflammatory markers, but not on the duration of surgery or numbers of retrieved lymph nodes (Fig. 6). Consequently, a longer duration of postoperative bowel dysfunction indicated by first postoperative stool as well as postoperative complications resulted in a longer postoperative in-hospital stay after RC. This effect was mostly obvious and significant in the COS group (Fig. 5c and d).

Discussion

The present study describes beneficial effects of the total robotic approach on postoperative bowel recovery and general patient outcome during the learning curve of robotic RC with CME. Since implementation of the robotic surgery program, the institution had been evolved to a nationwide benchmark center for robotic colorectal surgery [36]. However, we came from conventional open surgery as the generally accepted standard procedure and went directly to robotic surgery for oncologic RC without taking the detour via conventional laparoscopy. Hence, a comparison of conventional laparoscopy directly with robotic surgery was not performed herein, which might be a weak limitation of the present study. However, as our experience and data from the recent literature proof as well as nationwide research in medical care show, robotic surgery allows consistent results even for surgeons with no prior experience in minimally invasive, conventional laparoscopic surgery after adequate and structured training [4–7, 9, 11, 16, 37]. Although non-inferiority was proven by randomized trials early in 2005 and 2007 for laparoscopic compared with conventional open colorectal resections for cancer,

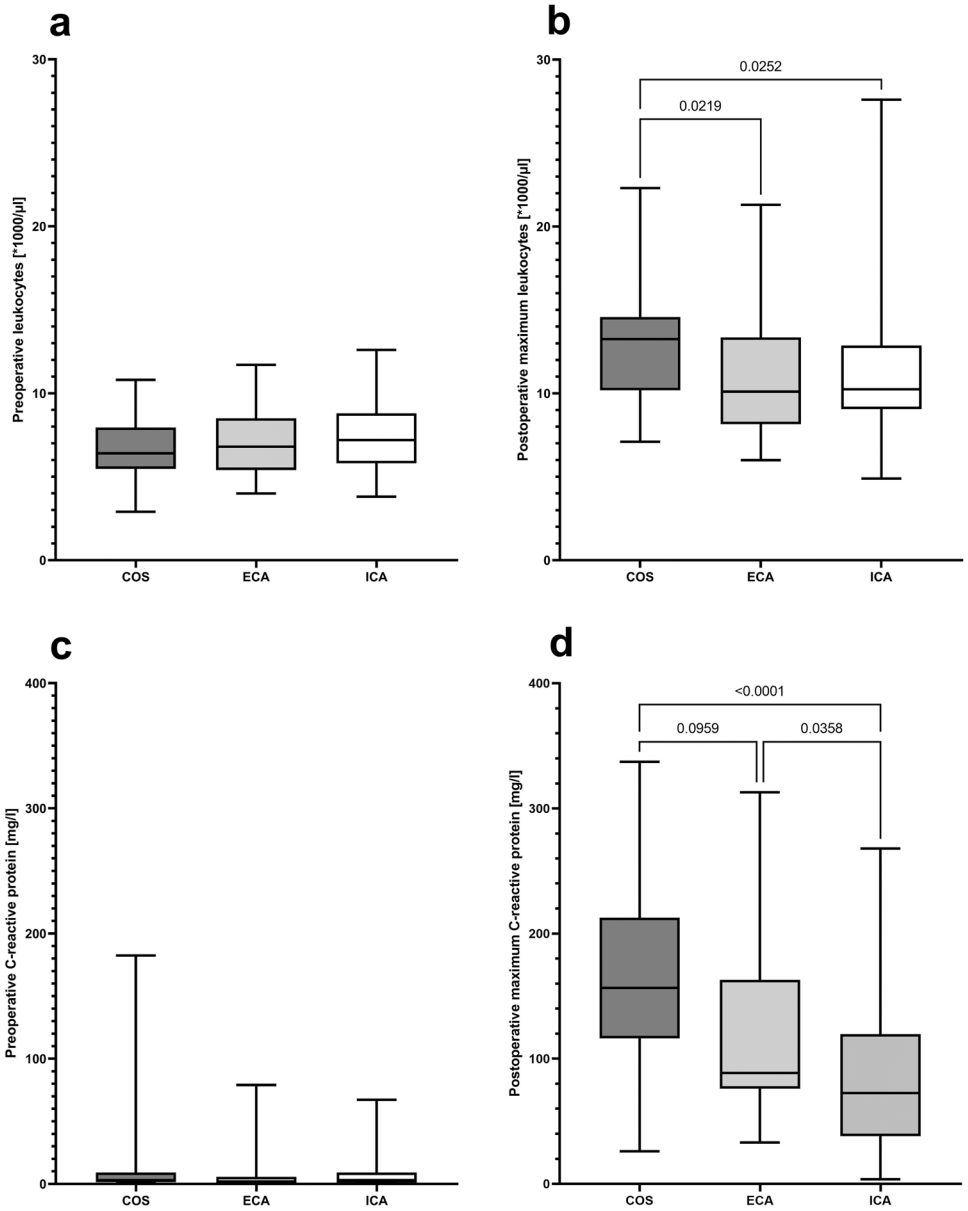


Fig. 3 Perioperative markers for systemic inflammation. **a** Preoperative leukocyte counts in peripheral blood (p [Kruskal–Wallis test] = 0.411) and **b** highest leukocyte counts in peripheral blood during postoperative days 1–3 (p [Kruskal–Wallis test] = 0.014). **c** Preoperative C-reactive protein values in peripheral blood (p [Kruskal–Wallis test] = 0.408) and **d** highest C-reactive protein values in peripheral blood during postoperative days 1–3 (p [Kruskal–Wallis test] < 0.0001). *COS* conventional open surgery; *ECA* hybrid minimally invasive, robotic-assisted right colectomy with extracorporal hand-sewn anastomosis; *ICA* total minimally invasive, robotic right colectomy with intracorporal hand-sewn anastomosis

conventional laparoscopic approaches did not reach general acceptance in many European countries [4–7, 9, 37]. Especially the rate of laparoscopically performed right colectomies remains low [9] with an overall increasing trend towards robotic surgery [11, 16]. This reflects the situation in many surgical departments, as ours: the decision is made between COS or robotic surgery, but conventional laparoscopy is not considered for oncologic RC. Thereby, the literature reveals for patients after robotic surgery some impactful advantages with respect to relevant clinical outcome parameters moreover laparoscopy [11, 16, 24, 31], including higher lymph node yield during CME and shorter intracorporal hand-sewn anastomosis time due to improvements in ergonomics, handling, and visualization through the robot [8, 12, 31, 38].

Procedure times seem to be an aspect of economic disadvantages of robotic surgery. Although the literature proofs shorter time for intracorporal suturing of the anastomosis during robotic surgery [12, 38], the duration of the total robotic procedure is — in contrast to the data of the present ICA group — supposed being longer compared with conventional laparoscopy and COS [11, 39, 40]. But, there is currently no standardized definition available which data should be recorded for the operation time of robotic surgery and most publications on robotics do not discriminate between port setup time, time-consuming docking, robot time, or assisted time, which includes creation and closure of the minilaparotomy, extraction of the specimen, or different steps of surgery, for example, the time for extracorporal anastomosis as well [8, 41]. Nevertheless, slightly

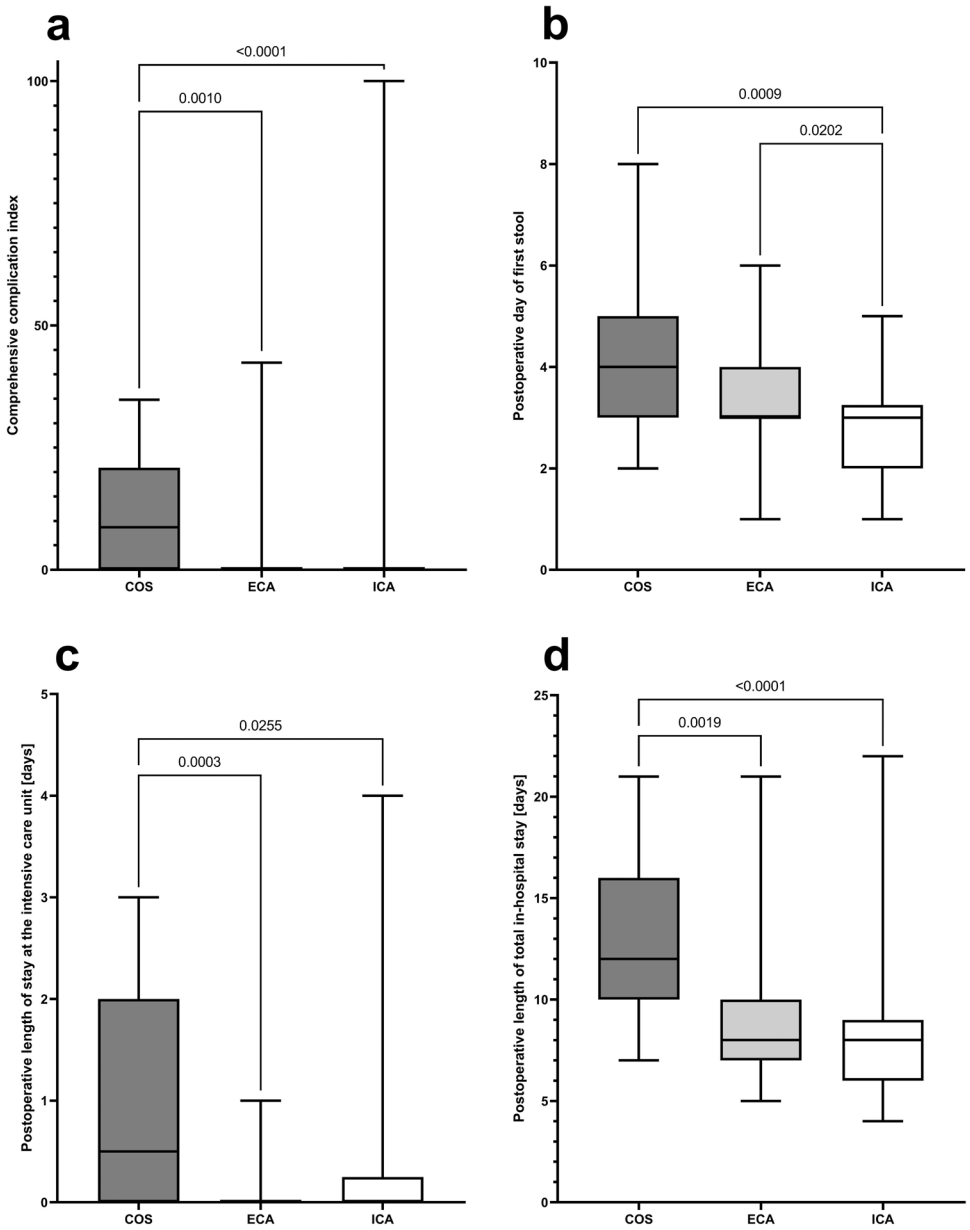


Fig. 4 Surrogate parameters of postoperative patient outcome. **a** Postoperative comprehensive complication index summarizes postoperative complications classified by the Clavien-Dindo classification of surgical complications [60, 61] (p [Kruskal–Wallis test] < 0.0001). **b** Postoperative day of first stool (p [Kruskal–Wallis test] = 0.0004). **c** Initial postoperative length of stay at the intensive care unit (p [Kruskal–Wallis test] = 0.0006). **d** Postoperative length of total in-hospital stay (p [Kruskal–Wallis test] < 0.0001). *COS* conventional open surgery; *ECA* hybrid minimally invasive, robotic-assisted right colectomy with extracorporal hand-sewn anastomosis; *ICA* total minimally invasive, robotic right colectomy with intracorporal hand-sewn anastomosis

longer operation times in comparison with standard COS ($p = 0.044$) were only observed in the present study during the initial ECA phase, immediately after introduction of robotic surgery to oncological RC, but not thereafter. Though the operative time was defined in the present study as the continuum from the first incision to complete skin closure and consecutively includes all the previously mentioned surgical steps. Hence, these quite short operation times especially after these initial (ECA) cases might be an effect of the strong two-step learning curve setting described in here. Increases in surgeon experiences and team training are essential to improve performance in robotic surgery [8, 41, 42]. In the present study we started the program with the robotic-assisted approach; thereby the ileo-colic anastomosis was sewn by hand in the conventional manner through a transverse laparotomy (ECA patients). This first step allowed us to get in touch with robotics and to gain sufficient experiences with mobilization of the colon and appropriately approaching the CME, a crucial and difficult-to-perform step in minimally invasive RC [8]. Thereafter we went to the total minimally invasive approach with intracorporal hand-swen anastomosis (ICA patients), which can be safely performed by experienced robotic surgeons [3], as the next step. Although we only saw slight differences in operation times in direct group comparison between COS and ECA, learning curve analysis confirmed these results impressively: significant decrease over time during initial ECA patients, but not anymore thereafter (ECA: $r^2 = 0.107$, $p = 0.048$; ICA:

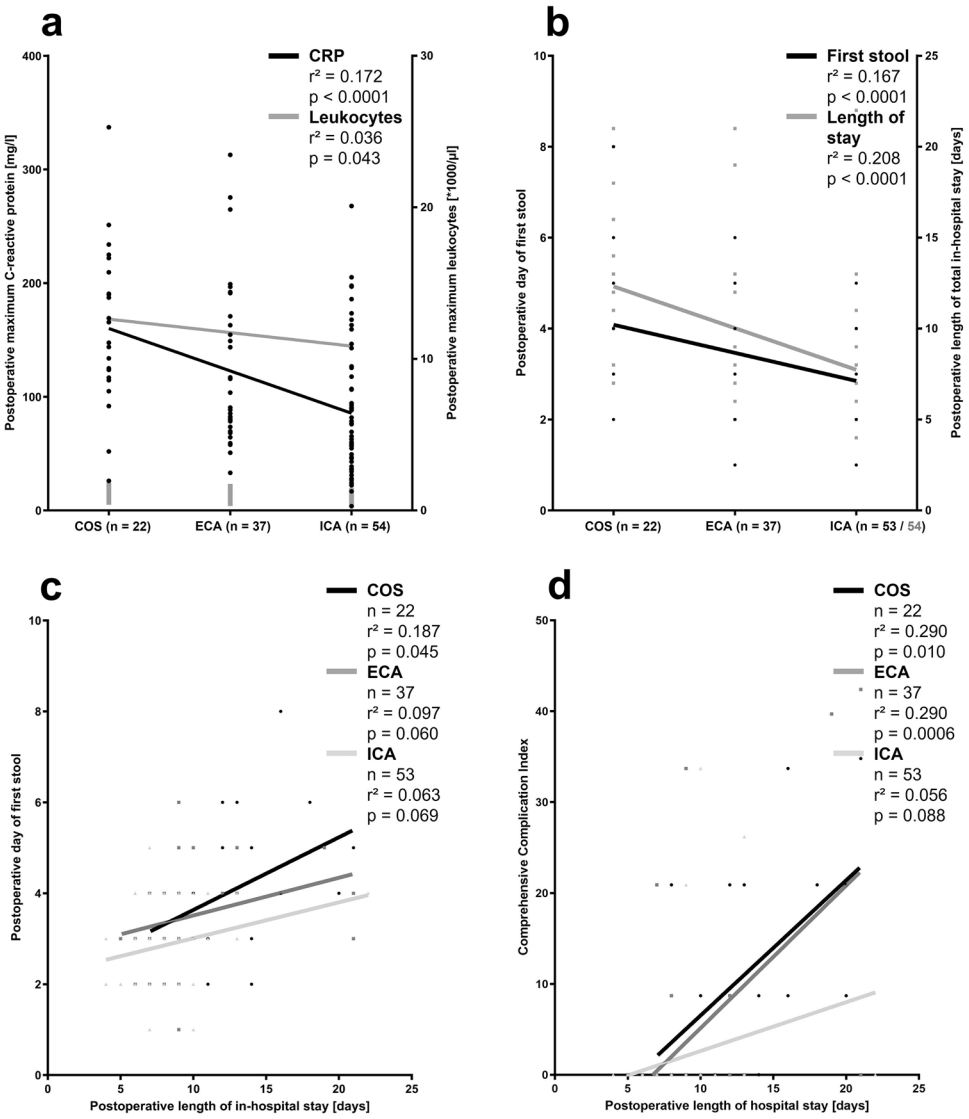


Fig. 5 Linear regression analysis in response to the surgical approach. **a** Linear regression of highest C-reactive protein values in peripheral blood during postoperative days 1–3 (left *Y*-axis, black line and dots) and highest leukocyte counts in peripheral blood during postoperative days 1–3 (right *Y*-axis, grey line and dots) against the surgical approach. **b** Linear regression of postoperative bowel dysfunction, i.e. duration until first postoperative stool (left *Y*-axis, black line and dots) and postoperative length of total in-hospital stay (right *Y*-axis, grey line and dots) against the surgical approach. **c** and **d** Linear regression of the length of postoperative total in-hospital stay against postoperative day of first stool and comprehensive complication index differentiated by the three surgical approaches. *COS* conventional open surgery; *ECA* hybrid minimally invasive, robotic-assisted right colectomy with extracorporal hand-sewn anastomosis; *ICA* total minimally invasive, robotic right colectomy with intracorporal hand-sewn anastomosis

$r^2 = 0.002$, $p = 0.755$; data not shown). However, the duration of operation times in COS patients might reflect a minor limitation of the study through the fact that in the present patient cohort open right colectomies were performed by different surgical teams, including different surgeons ($n = 8$) at different training levels. Thereby the open procedures were performed together with a well-experienced senior surgeon at least as the first assistant. In contrast, robotic surgeries were performed exclusively by two well-experienced senior surgeons in an experienced team. Nevertheless, by the decrease over time, we conclude that procedure durations approximate the standard COS approach for RC after the initial learning phase. This was the situation for the ICA cohort and, together with the low conversion to open surgery rate in ICA patients ($n = 1/56$, 1.8%), these data proved the sufficiency of our learning curve setting. However, this learning curve effect was not observed in total lymph node yield through CME over time as a global parameter for oncologic quality of surgical approaches. Both the decrease in operation time and constant lymph node yield over time indicate the efficacy of our learning curve setting, which was accordingly completed during the initial observational period of the present study [8, 14] and allows for the conclusion that the institutional development from COS via ECA to ICA had neither impaired oncologic quality during surgery nor patient safety.

The advantages concerning short-term outcomes of minimally invasive surgery over COS in colorectal surgery are obviously evident and had been extensively shown in the current literature for RC by laparoscopic approaches, whereby oncological outcomes were not inferior [1, 43]. Although operation times of minimally invasive routes were considerably longer in previous literature, beneficial effects of minimally invasive surgery for RC were also reproduced by the robotic approaches in the present study: rate of major morbidity including re-operations, postoperative bleeding,

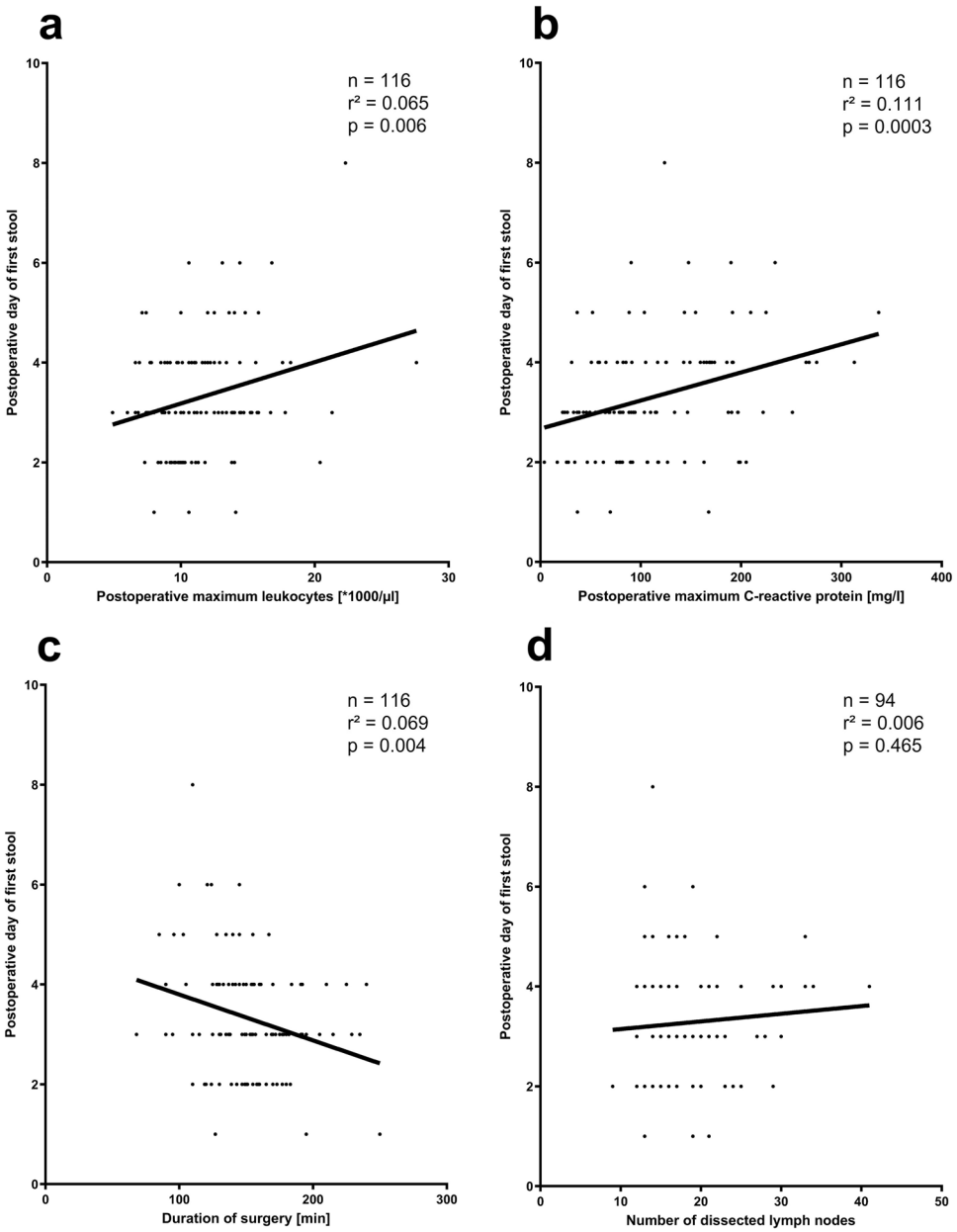


Fig. 6 Evaluation of factors that might influence on postoperative bowel dysfunction independently from the surgical approach by linear regression analysis

anastomotic complications, and rates of surgical site infections, reflected by longer length of postoperative hospitalization and higher rates in CCI in the COS group [10, 11, 16, 17, 30, 31, 44]. In the recent literature no differences have been shown regarding anastomotic complications, i.e., leackages and bleeding, in comparsion of different types of anastomoses (intracorporal versus extracorporal or handsewn versus stapling, et cetera) [3, 45–48]. Vice versa, the intraabdominal creation of the anastomosis itself, including shorter incision length [49–51] and alternatives of the extraction site, i.e., Pfannenstiel versus midline or pararectal incisions [26, 50–52], correlate with reduced rates of surgical site infections [26, 27, 31, 53] and incisional hernia [51, 54] during short-term and long-term follow-up after RC. Furthermore, a lower pain level [50], a shorter duration until normalization of bowel function including a faster food tolerance, and time to passage of first postoperative flatus and stool contribute to improved patient comfort, enhanced patient recovery, and result in shorter length of postoperative hospital stay in patients after total minimally invasive RC with intracorporal anastomosis [26, 27, 49, 50, 52, 55].

Prolonged postoperative bowel dysfunction and ileus observed in up to 30% of the patients are frequent pathologies after RC [24] and cause prolonged food intolerance, significant dyscomfort, and potential severe morbidity for the affected patients [33–35]. Time to first stool was decided as the surrogate parameter of postoperative bowel recovery in the present study, which allows for comparison with the

literature; however core outcome sets for defining postoperative gastrointestinal recovery or prolonged bowel dysfunction and ileus had not been described, yet [56]. Postoperative gastrointestinal dysmotility is a physiologic and temporary reaction following abdominal surgery, but usually returns to normal function rapidly [33, 57]. The pathophysiology of prolonged postoperative bowel dysfunction is uncertainly multifactorial but currently not fully understood [58]. Although the literature previously suggests that intracorporal anastomoses are beneficial regarding the duration of postoperative bowel recovery, our data give some important insights in the pathophysiology of prolonged gastrointestinal dysfunction: neither duration of surgery nor extent of CME with central lymph node harvesting but greater extent of ileocolic manipulation, higher trauma to the abdominal cavity, and more severe systemic inflammatory response, both might trigger opioid-based pain therapy, contribute to prolonged gastrointestinal dysfunction in the COS and ECA groups ($p = 0.0009$ and $p = 0.020$ versus ICA, respectively) [33, 57, 59]. Furthermore, regression analyses clearly demonstrate the harmful effect of gastrointestinal dysfunction on patient outcome: delayed postoperative bowel dysfunction contributes to longer postoperative in-hospital stay especially in patients who underwent COS ($r^2 = 0.187$, $p = 0.045$) for oncologic RC. This was comparable with other severe postoperative complications. These results reveal that the ICA procedure is clinically more effective with regard to postoperative bowel recovery and length of postoperative hospitalization.

Nevertheless, higher initial and running costs, stronger investment in surgical instruments and consumables, and longer operation times lead to ongoing debate if the benefits of robotic surgery justify economic concerns, especially competing with conventional laparoscopy [1, 11, 21, 24]. Aspects, which might finally overcome initial economic burdens, include the optimization of the surgical procedure by decreasing the duration over time through surgical team formation and strong adherence to the learning curve as well as the use of more cost-effective techniques and materials (hand-sewn instead of stapler anastomosis, conventional laparoscopic instead of robotic staplers, reduction of robotic ports). However, the most powerful impact from a clinical and economic view have lower complication rates, faster recovery, and shorter length of in-hospital stay after robotic compared with both COS and laparoscopic RC [11, 16, 20, 24]. Thus, in our study robotic surgery let to a significant reduction in cost-intensive postoperative complications, duration at the intensive care unit, and length of postoperative in-hospital stay by one third from median 12 (COS) to 8 days (both robotic approaches: ECA and ICA, $p < 0.01$ each in comparison with COS). This might all together turn initial economic disadvantages into a potential benefit and increases the revenue for robotic cases.

Conclusion

In conclusion, the results of this single-center experience demonstrate that implementation of a robotic program for right colectomies with CME is safely feasible even without experiences in conventional laparoscopic surgery in that field. Beginning the learning curve with the robotic-assisted approach and extracorporal anastomosis is appropriate; conversion to total-robotic surgery with intracorporal anastomosis after enough experiences and surgical skills had been acquired provides excellent outcome for the patients. Especially the effects of total minimally invasive robotic surgery on postoperative functional bowel recovery and wound complications positively impact on length of hospitalization and patient comfort. This might overcome economic concerns regarding robotic surgery.

Authors' contributions Study conception and design: M. H., M. R. Acquisition of data: R. S., S. K. Analysis and interpretion of data: M. H., A. H., M. R. Drafting of manuscript: M. H., M. R. Critical revision of manuscript: R. S., S. K., W. P., A. H.

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Declarations

Competing interests Dr. Hirschburger reports personal fees from Proctor for Intuitive surgical, personal fees from lectures for Intuitive surgical, both outside the submitted work.

Rolf Schneider reports non-financial support from Intuitive surgical, outside the submitted work.
Andreas Hecker received honoraria from KCI and MSD, independently from the content of this work.
Sophie Kraenzlein, Winfried Padberg, and Martin Reichert have nothing to declare.

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11.8 Anlage 8

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ORIGINAL ARTICLE

Protective loop ileostomy increases the risk for prolonged postoperative paralytic ileus after open oncologic rectal resection

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Abstract

Purpose Postoperative gut dysmotility is a physiologic and frequent temporary reaction after major abdominal surgery. If paralysis merges into a prolonged ileus state, it causes significant morbidity and subsequently worse outcome and discomfort for the patients. Pathophysiology of pathologic prolonged postoperative paralytic ileus remains multifactorial.

Methods We present a retrospective single-center analysis of patients, who underwent a primary open oncologic anterior rectal resection with primary anastomosis with or without defunctioning loop ileostomy during a 43-month period of observation. Primary endpoint was the rate of prolonged postoperative paralytic ileus, defined by the intravenous administration of neostigmine. Confounders for regression analysis were assessed by univariate analysis and correlations between confounders were examined. Odds ratio for prolonged postoperative paralytic ileus in patients with defunctioning loop ileostomy was estimated by a logistic regression model.

Results Of 101 patients (62 male), 62 (61.39%) received defunctioning loop ileostomy. In univariate analysis, male gender and patients with ileostomy showed more frequently prolonged paralysis by tendency (both $p = 0.07$). Logistic regression analysis proves the influence of a defunctioning ileostomy on the development of prolonged postoperative paralytic ileus after oncologic rectal resection ($p = 0.047$). Odds ratio for prolonged postoperative paralytic ileus in patients with ileostomy was 4.96 [95% CI 1.02–24.03].

Conclusions Although the construction of defunctioning loop ileostomies during rectal resection is a safe, uncomplicated surgical procedure, they can cause significant postoperative morbidity for the patients. High fluid and electrolyte loss are well-known complications, but herewith we raise the evidence for prolonged gut paralysis in patients with defunctioning loop ileostomy.

Keywords Rectal resection · Oncology · Ileostomy · Ileus · Paralysis

Introduction

Colorectal carcinoma is one of the leading cancer diagnoses and cause for cancer-related death worldwide [1, 2]. Depending on tumor location and stage regarding the Union international contre le cancer (UICC) criteria, surgery is the crucial element of modern tumor therapy both as a single treatment and as the key element in multimodal treatment approaches [3]. Especially for rectal carcinoma, primary resection in early or limited stage (UICC stage I) or multimodal therapy with surgery after neoadjuvant radio-chemotherapy in locally advanced tumor stages (UICC stages II and III) can be considered as curative treatment options [4]. Depending on location of the carcinoma, a primary anastomosis by descendo-rectostomy should be applied to the patients. The protective diverting/defunctioning loop ileostomy is one routine surgical procedure, which can be considered during low anterior rectal resection, depending on intraoperative findings (e.g., height of the anastomosis ab ano, perfusion, and tension of the anastomosis), preoperative induction therapy, and at least patient's characteristics (e.g., immunosuppression, vascular status, and other comorbidities).

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There is striking evidence that a defunctioning ileostomy is basically useful to prevent patients from septic complications in cases of anastomotic leakages [5, 6]. Nevertheless, the defunctioning loop ileostomy by itself can be responsible for postoperative complications like high fluid and electrolyte loss, parastomal hernia, prolapse, and skin irritations [7–9]. In the current literature, some weak evidence exists regarding a higher rate of prolonged postoperative gut paralysis and paralytic ileus in patients, who underwent large bowel and rectal resection with primary anastomosis with a defunctioning loop ileostomy versus patients without the defunctioning ileostomy [10, 11]. Thereby, postoperative gut dysmotility, paralysis, and ileus are quite a physiologic, temporary reaction due to the tissue trauma after abdominal surgery [12]. Typically, the entire gut recovers completely within 3–5 days—the small intestine returns to normal function at first within 24 h after surgery, and function of the stomach and colon recovers within 24–48 h and 48–72 h after surgery, respectively [12, 13]. However, a delayed postoperative return to normal gut function can frequently be responsible for reduced patient comfort, worse postoperative outcome, and longer hospital stay and thus affects patient's recovery and causes higher public health costs [13–17].

We herein describe our institutional experience with prolonged postoperative paralytic ileus in a selected patient collective, who underwent oncologic open anterior rectal resection with complete mesorectal excision for rectal carcinoma in patients with or without a protective diverting ileostomy within a period of 43 months. Contributing factors for postoperative gut paralysis were excluded to the greatest extent due to formally focusing on isolated rectal resections as well as due to evaluating possible confounders in univariate analysis for a logistic regression model.

Material and methods

One hundred one patients were conducted to elective open anterior rectal resection with complete mesorectal excision and primary anastomosis by descendo-rectostomy with or without protective defunctioning loop ileostomy for rectal carcinoma within a period of 43 months. Patient data were retrospectively analyzed from the prospectively maintained institutional database. Each patient was treated by the institutional standard of care. The acquisition of data was approved by the local ethics committee (AZ 131/14).

Patients, who underwent primary intended and isolated open sphincter-preserving anterior rectal resection with complete mesorectal excision for rectal carcinoma with primary anastomosis by descendo-rectostomy, were included into this study. To obtain a homogeneous study population, exclusion criteria from this retrospective analysis were (1) severe cardiac insufficiency (≥ NYHA 3), (2) laparoscopic or converted-to-open rectal resection as well as Hartman procedure, (3) extended adhesiolysis and/or multi-visceral resections, (4) peritoneal carcinomatosis, and (5) postoperative major complications including anastomotic leakage, intraabdominal abscess, massive bleeding, and postoperative mechanical ileus.

Patients were divided into two groups: anterior rectal resection (1) with and (2) without a protective diverting loop ileostomy and the rate of postoperative paralytic ileus, determined by the intravenous administration of neostigmine during the first 10 days after surgery, was assessed as the primary endpoint of the study. The institutional standard of care was to stimulate gut motility stepwise, initially by conservative therapy (e.g., maintenance of fluid and electrolyte balance) and enteral laxatives on postoperative days 2 and 3. Neostigmine was given intravenously, when evidence for adequate gastrointestinal motility was lacking thereafter. The intraoperative decision for or against a diverting ileostomy was usually made by the surgeon during the operation as usual. Patients were basically treated using an "enhanced recovery after surgery" (ERAS) protocol postoperatively, including early mobilization, oral nutrition as soon as possible, and multimodal pain therapy.

Patient data (gender, age, body mass index (BMI), obesity, diabetes mellitus, peridural anesthesia, ileus-related re-intervention rate, and rate of neoadjuvant radio-chemotherapy) were proceeded to statistical analysis. Statistical analysis was performed using SAS V9.2 (SAS Institute, Cary, NC, USA). For univariate analysis, Fisher's exact test was applied for two-group comparisons of categorical data in cross-tabulation as well as Wilcoxon rank-sum test for continuous variables. Spearman's rho test was used for correlation analysis. Finally, a logistic regression model was used for estimating the odds ratio for prolonged postoperative paralytic ileus in patients after open oncologic rectal resection with protective defunctioning loop ileostomy.

Results

One hundred one patients (62 male, 39 female) were included into the study. The median (range) age and BMI of the study cohort were 63 (35–85) years and 25.65 (17.01–37.20) kg/m^2, respectively. The overall incidence of postoperative paralytic ileus, defined retrospectively through the intravenous administration of neostigmine, was 13.86% ($n = 14$ patients). Figure 1 shows the remaining patient characteristics of the study cohort.

Sixty-two (61.39%) of the patients received protective defunctioning loop ileostomy during open rectal resection. No differences were observed in gender (male, 37 (59.68%) in the group with ileostomy and 25 (61.1%) in the group without ileostomy, $p = 0.68$), age (patients with ileostomy, 63.00 (39.00–85.00) years, patients without ileostomy, 64.00

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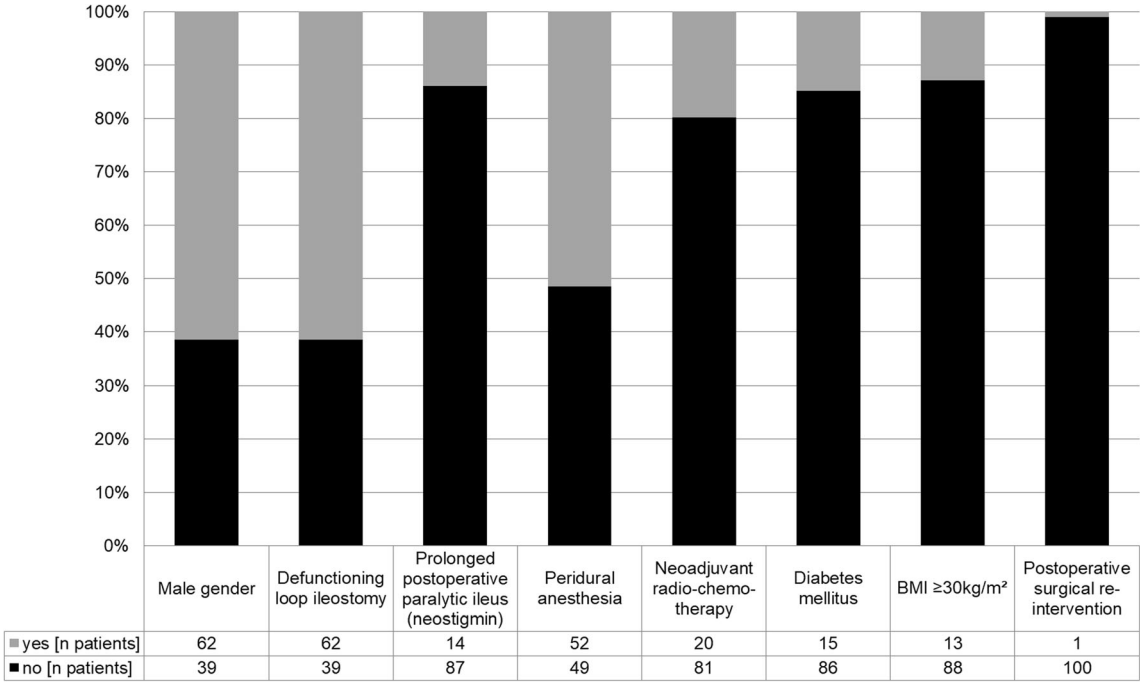


Fig. 1 Characteristics of the patient cohort of this study. BMI, body mass index

(35.00–85.00) years, $p = 0.83$), and BMI (of patients with ileostomy, 25.09 (18.75–32.85) kg/m^2, of patients without ileostomy, 26.42 (17.01–37.20) kg/m^2, $p = 0.4$) between both groups. Significant differences were obtained regarding the rate of neoadjuvant radio-chemotherapy prior to surgery between patients with and without defunctioning loop ileostomy: more patients of group 1 (with ileostomy) received neoadjuvant radio-chemotherapy (19 (30.65%) patients versus 1 (2.56%) patient, $p = 0.0005$—see Table 1). Notably, male patients developed prolonged gut paralysis postoperatively more frequently by tendency ($p = 0.07$—see Table 2). Results of univariate analysis are shown in Table 2 and the supplemental material.

Finally, a logistic regression model was used to estimate the odds ratio for the development of prolonged postoperative paralytic ileus in patients with a defunctioning loop ileostomy after oncologic open rectal resection. Due to an influence by tendency of the independent variable "gender" on the dependent variable "postoperative paralytic ileus" in univariate analysis (Table 2), the variable "gender" of the patients was used as a confounder for the regression model. For all other clinically relevant possible confounders, no influence was detected and no evidence for correlation among them was found. Logistic regression analysis showed that a defunctioning loop ileostomy during oncologic open rectal resection influences the development of prolonged postoperative paralytic ileus ($p = 0.047$). Odds ratio for prolonged postoperative paralytic ileus in patients after oncologic open rectal resection with a protective defunctioning loop ileostomy was 4.96 (95% confidence interval 1.02–24.03).

Discussion

A high number of patients suffer from rectal carcinoma worldwide [2] and undergo rectal surgery. Thus, it is of great

Table 1 Characteristics of patients of the two groups: (1) with and (2) without defunctioning loop ileostomy. BMI, body mass index

Variable	Defunctioning loop ileostomy Yes	No	*p* value
n	62 (61.39%)	39 (38.61%)	
Male gender	37 (59.68%)	25 (64.1%)	0.68
Peridural anesthesia	32 (51.61%)	20 (51.28%)	1
Neoadjuvant radio-chemotherapy	19 (30.65%)	1 (2.56%)	0.0005
Diabetes mellitus	8 (12.9%)	7 (17.95%)	0.57
BMI ≥ 30 kg/m^2	6 (9.68%)	7 (17.95%)	0.24
Postoperative surgical re-intervention	1 (1.6%)	0	1

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Table 2 Results of univariate analysis. *p* values of continuous variables of both age and body mass index (BMI) were assessed by Spearman's rho correlation

Variable	Postoperative paralytic ileus (neostigmine)		
	No	Yes	*p* value
Gender			0.07
Male	50 (80.65%)	12 (19.35%)	
Female	37 (94.87%)	2 (5.13%)	
Age [years]			0.33
Median (range)	63 (35–85)	62.5 (48–71)	
Diverting ileostoma			0.07
No	37 (94.87%)	2 (5.13%)	
Yes	50 (80.65%)	12 (19.35%)	
Peridural anesthesia			0.78
No	43 (87.76%)	6 (12.24%)	
Yes	44 (84.62%)	8 (15.38%)	
Neoadjuvant radio-chemotherapy			1
No	70 (86.42%)	11 (13.58%)	
Yes	17 (85.0%)	3 (15.0%)	
Diabetes mellitus			1
No	74 (86.05%)	12 (13.95%)	
Yes	13 (86.67%)	2 (13.33%)	
BMI ≥ 30 kg/m^2			1
No	76 (86.36%)	12 (13.64%)	
Yes	11 (84.62%)	2 (15.38%)	
BMI [kg/m^2]			0.82
Median (range)	25.68 (17.01–37.2)	25.41 (22.28–30.86)	

importance to optimize surgical therapy and postoperative care to preserve those numerous patients from morbidity, worse postoperative outcome, and subsequently from mortality. Postoperative complications after major abdominal surgery, especially colorectal surgery, are not only relevant for the patients during the immediate postoperative hospital stay, but also delay the onset of adjuvant therapies and/or rehabilitation of the patients and thereby impair clinical and oncological outcomes as well as increase hospital and consecutively public health costs [13–15, 18]. The role of a defunctioning or diverting temporary loop ileostomy in reducing the rate of postoperative anastomotic failure after rectal resection with primary anastomosis is discussed diversely in the current literature [5–7]. Nevertheless, it has been well described that fecal diversion by a defunctioning loop ileostomy during anterior rectal resection with primary anastomosis per se is a safe surgical procedure and prevents patients from severe septic complications and re-operation in cases of anastomotic leakages [5–7]. Compared to colostomy, the reconstruction of the intestinal continuity in patients with a defunctioning loop ileostomy is less complicated, and the rate of surgical site infections, prolapse, and incisional hernias is reduced [7–9]. A whole bundle of studies suggests that a temporary defunctioning loop ileostomy is a considerable uncomplicated adjunctive surgical procedure following oncologic rectal resection [7]. Well-known and frequently observed complications of loop ileostomies are impairments in kidney function through high stomal output with consecutive high fluid and electrolyte loss [7]. Nevertheless, some studies raise the evidence for an increased risk of the development of prolonged postoperative paralytic ileus following bowel resection with ileostomy [10, 11].

The present study focused on patients, who underwent isolated open oncologic rectal resection with a primary rectal—not anal—anastomosis with or without a diverting ileostomy, showing a widely uneventful postoperative hospital stay: patients with anastomotic leakages as well as re-do procedures were primarily excluded from the data analysis. The primary endpoint of the study was the intravenous administration of the parasympathomimetic drug neostigmine as an objective measure for giving the hardest evidence for intestinal paralysis in the present retrospective study. Basically, temporary gut dysmotility after uncomplicated colorectal surgery due to the surgical trauma is frequently observed with an average duration to functional recovery of 3–5 days [10, 13, 14]. Although the duration, when a physiologic postoperative gut dysmotility becomes a pathologic prolonged postoperative paralytic ileus, is not clearly defined [19]. However, a prolonged dysmotility or postoperative paralytic ileus following bowel resection has to be discriminated from the former

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physiologic condition. Postoperative paralytic ileus causes nausea, vomiting, abdominal distension, and pain, delay in intestinal passage as well as in physiologic enteral nutrition, and thus impairs wound healing, immune response, surgical outcome, as well as patient comfort, and prolongs hospital stay [10, 14, 17–20]. These circumstances lead to a significant increase in ileus-related morbidity and subsequently mortality for the patients following open bowel resection [10, 16–18, 20]. The incidence for prolonged postoperative paralytic ileus after bowel resection given in the current literature ranges between 3 and 32% [17, 21]. Thereby, the progress from physiologic postoperative gut dysmotility to pathologic prolonged dysmotility or postoperative paralytic ileus is fluent and the definition of postoperative paralytic ileus after major colorectal surgery is significantly heterogeneous and weak in the current literature [21]: the absence of adequate bowel function on a certain postoperative day [10], the presence of nausea and vomiting [19], prolonged use of nasogastric tubes, and intolerability of oral nutrition [11, 19, 22]. These criteria for defining postoperative paralytic ileus after bowel surgery are subjective, unspecific [19], and not useful for retrospective patient data analysis. Therefore, in the present study, not these clinical and subjective data but the intravenous administration of the prokinetic drug neostigmine during the first 10 days after surgery was used to record the incidence of prolonged postoperative paralytic ileus retrospectively in this patient cohort.

The pathogenesis of prolonged postoperative gut dysmotility and paralytic ileus is multifactorial and complex [19]. In the past, risk factors for the development of postoperative paralytic ileus after bowel resection had been identified and concepts had been evaluated for preventing or even reducing the duration of (prolonged) postoperative gut dysmotility and postoperative paralytic ileus, e.g., minimally invasive laparoscopic surgery, multimodal analgesic concepts including spinal anesthesia, early postoperative mobilization, and early enteral nutrition of the patients [17, 21–25]. However, postoperative prolonged gut dysmotility and paralytic ileus following bowel resection is still a clinical problem and still affects patients even when applying the above-mentioned measures [10]. In the present study, the application of epidural anesthesia did not influence significantly the frequency of prolonged postoperative paralytic ileus (see Table 2). Previously known influencing factors of postoperative paralytic ileus after bowel resection were widely excluded due to the inclusion criteria of the present retrospective analysis, e.g., high preoperative ASA score (≥ III) [10, 18], cardiac disorders [10], minimally invasive surgery [17, 21, 22, 24, 25], or intraoperative conversion-to-open surgery [24, 25], postoperative anastomotic failure [17], or otherwise paralysis-nonrelated higher-grade complications [26]. Subsequently, gender seems to be a contributing factor ($p = 0.07$) for the development of postoperative paralytic ileus after open oncologic rectal resection in the present study in univariate statistical analysis (see Table 2). Male gender had been described as a risk factor for postoperative paralytic ileus in previous studies [11, 18]. Furthermore, the construction of a protective defunctioning loop ileostomy during oncologic rectal resection with primary anastomosis showed a tendency ($p = 0.07$) to increase the incidence of postoperative paralytic ileus in the present study in univariate analysis. This was continuously proven by a logistic regression model, which resulted in a significant influence of the development of prolonged postoperative paralytic ileus after oncologic rectal resection by defunctioning loop ileostomy ($p = 0.047$) and a high odds ratio (= 4.96) for prolonged postoperative paralytic ileus in patients with loop ileostomy after oncologic rectal resection.

The evidence for the influence of (prolonged) postoperative paralytic ileus by defunctioning loop ileostomy in patients, who underwent colorectal surgery, is weak since only a small number of mainly retrospective studies evaluate and focus on the issue. In the current literature, Millan et al. used intolerance to oral nutrition and gut dysmotility on postoperative day 6 for the definition of prolonged postoperative ileus and also observed ileostomy as a significant independent risk factor in univariate as well as multivariate analysis with an odds ratio of 1.97 in their retrospective review of 773 patients that underwent surgery for colorectal cancer [10]. With 20.1%, they observed the highest incidence of prolonged postoperative ileus in the group of patients that underwent low anterior rectal resection [10]. Interestingly, based on the results of their multivariate analysis, Millan et al. calculated that the incidence of prolonged postoperative ileus is increased to 38.3% in male patients with preoperative evidence of chronic obstructive lung disease and ileostomy as a part of surgery [10]. In a retrospective analysis of 2400 patients, also, Chapuis et al. observed an odds ratio of 1.4 for postoperative prolonged ileus in patients that underwent colorectal resections with the construction of any stoma [11]. Although prospectively conducted studies are still lacking, the presence of a defunctioning stoma seems to contribute to the multifactorial pathogenesis of prolonged gut paralysis after bowel resection.

An explanation for this observation is not clearly noticed in the current literature. A higher extent of surgical tissue trauma or inflammation or postoperative pain—all of them being well-known factors contributing to postoperative paralytic ileus [12]—due to the construction of a defunctioning ileostomy during large bowel surgery might not account for these findings as the construction of a defunctioning ileostomy is a relatively atraumatic optional part of the surgical procedure during oncologic rectal resection. Other surgery-related factors—potentially promoting intra- and/or postoperative complications like difficult surgery of the male pelvis as well as the size and infiltration of neighboring organs due to the rectal tumor, height of the anastomosis, and difficulty in splenic flexure mobilization for an adequate extent in

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colonic lengthening during the reconstructive part of the operation—are quite difficult to investigate retrospectively and, however, had to the best of our knowledge never been evaluated and discussed within the context of prolonged postoperative gut paralysis and paralytic ileus so far. Also, metabolic complications driven from the ileostomy itself like high fluid and electrolyte loss, hypokalemia, and acidosis [12] due to high output through the stoma might not be responsible for postoperative prolonged gut paralysis in those patients with defunctioning ileostomy. Although more patients in the ileostomy group received neoadjuvant radio-chemotherapy ($p = 0.0005$), preoperative induction therapy had no impact on the rate of postoperative paralytic ileus in univariate analysis of this study cohort ($p = 1$). Also, the current literature gives no evidence that preoperative pelvic irradiation increases the rate of postoperative paralytic ileus [25, 27]. However, inspired by clinical experiences, compared with left-sided procedures, a slow return to normal bowel function and higher incidence of postoperative paralytic ileus is frequently observed in patients undergoing right hemicolectomy [17, 28–32]; thus, prolonged paralytic ileus in patients with defunctioning loop ileostomy after oncologic rectal resection might be contributed by ileocolic manipulation.

In conclusion, we herein report on the first study evaluating the development of prolonged postoperative paralytic ileus as the primary outcome measure in patients after primary open oncologic anterior rectal resection with the simultaneous construction of a defunctioning loop ileostomy. The group of patients in this study is highly selected, due to presenting a widely uneventful postoperative hospital stay, to exclusively focus on the influence of the defunctioning ileostomy on postoperative prolonged paralytic ileus. For defining postoperative paralytic ileus, we retrospectively evaluated the intravenous application of neostigmine as an objective primary outcome measure within the first 10 days following surgery. A standardized and homogeneous definition as well as consensus for the management of postoperative prolonged paralytic ileus is currently not established in the literature. Endpoints of former studies focusing on postoperative prolonged ileus after bowel resection are inconsistent and almost subjective. Prolonged gut dysmotility after bowel surgery is a frequent postoperative problem and results in increased morbidity and prolonged hospital stay for the patients as well as higher costs for public health. In the present retrospective analysis, defunctioning ileostomy was proven as a contributor for and to dramatically increase the incidence of prolonged postoperative paralytic ileus. The influence of loop ileostomies on prolonged postoperative paralytic ileus after bowel surgery has to be proven in larger retrospective patient cohorts and further prospective trials. Especially, the hypothesis that ileocolic manipulation during the formation of defunctioning ileostomies influences prolonged postoperative gut dysmotility as well as whether the construction of any colostomy would be more beneficial within this context might be further investigated as this could majorly impact on clinical practice in the future. But, nevertheless, surgeons have to accurately consider the advantages—regarding the prevention of septic complications in patients with anastomotic failure—and disadvantages—regarding high fluid and electrolyte loss as well as prolonged postoperative paralytic ileus—of a defunctioning loop ileostomy in patients undergoing oncologic rectal resection.

Compliance with ethical standards

As this was a retreospective analysis, all patients included were initially treated by the local standard of care. The local ethics committee gave approval to retrospectively analyze these patient data.

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11.9 Anlage 9

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Systematic Review and/or Meta-analysis

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Pharmacologic prevention and therapy of postoperative paralytic ileus after gastrointestinal cancer surgery: systematic review and meta-analysis

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Background: Postoperative paralytic ileus (POI) is a significant concern following gastrointestinal tumor surgery. Effective preventive and therapeutic strategies are crucial but remain elusive. Current evidence from randomized-controlled trials on pharmacological interventions for prevention or treatment of POI are systematically reviewed to guide clinical practice and future research.

Materials and methods: Literature was systematically searched for prospective randomized-controlled trials testing pharmacological interventions for prevention or treatment of POI after gastrointestinal tumor surgery. Meta-analysis was performed using a random effects model to determine risk ratios and mean differences with 95% CI. Risk of bias and evidence quality were assessed.

Results: Results from 55 studies, involving 5078 patients who received experimental interventions, indicate that approaches of opioid-sparing analgesia, peripheral opioid antagonism, reduction of sympathetic hyperreactivity, and early use of laxatives effectively prevent POI. Perioperative oral Alvimopan or intravenous administration of Lidocaine or Dexmedetomidine, while safe regarding cardio-pulmonary complications, demonstrated effectiveness concerning various aspects of postoperative bowel recovery [Lidocaine: – 5.97 (– 7.20 to – 4.74)h, $P < 0.0001$; Dexmedetomidine: – 13.00 (– 24.87 to – 1.14)h, $P = 0.03$ for time to first defecation; Alvimopan: – 15.33 (– 21.22 to – 9.44)h, $P < 0.0001$ for time to *GI-2*] and length of hospitalization [Lidocaine: – 0.67 (– 1.24 to – 0.09)d, $P = 0.02$; Dexmedetomidine: – 1.28 (– 1.96 to – 0.60)d, $P = 0.0002$; Alvimopan: – 0.58 (– 0.84 to – 0.32)d, $P < 0.0001$] across wide ranges of evidence quality. Perioperative nonopioid analgesic use showed efficacy concerning bowel recovery as well as length of hospitalization [– 1.29 (– 1.95 to – 0.62)d, $P = 0.0001$]. Laxatives showed efficacy regarding bowel movements, but not food tolerance and hospitalization. Evidence supporting pharmacological treatment for clinically evident POI is limited. Results from one single study suggest that Neostigmine reduces time to flatus and accelerates bowel movements [– 37.06 (– 40.26 to – 33.87)h, $P < 0.0001$ and – 42.97 (– 47.60 to – 38.35)h, $P < 0.0001$, respectively] with low evidence quality.

Conclusion: Current evidence concerning pharmacological prevention and treatment of POI following gastrointestinal tumor surgery is limited. Opioid-sparing concepts, reduction of sympathetic hyperreactivity, and laxatives should be implemented into multimodal perioperative approaches.

Keywords: alvimopan, bowel recovery, cancer surgery, dexmedetomidine, gastrointestinal atony, gastrointestinal surgery, lidocaine, postoperative Ileus, surgical oncology

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Introduction

Gastrointestinal dysmotility following abdominal surgery is to certain extents a physiological response. Patients undergoing gastrointestinal tumor resections are particularly susceptible, with up to 30%, experiencing prolonged gastrointestinal dysmotility and postoperative (paralytic) ileus (POI)[1,2]. POI leads to significant discomfort, increased morbidity, and prolonged hospital stay[2]. Consecutively, it imposes substantial costs and thus is a financial burden on healthcare systems[1,2]. Given these factors, effective preventive measures and prompt initiation of suitable therapeutic interventions against clinically evident POI are essential to improve patient outcomes.

Beyond the transient physiological gastrointestinal paralysis that occurs shortly after major abdominal surgery, the development of prolonged postoperative gastrointestinal dysmotility is influenced by multiple factors[3–5]. Perioperative neurogenic dysregulation and inflammatory processes play pivotal roles in the pathogenesis of POI[2,6]. Additionally, medications administered in the perioperative phase, such as opioids, potentially exacerbate postoperative gastrointestinal atony[2,6]. Alongside technical considerations involving minimally invasive surgical techniques that mitigate the inflammatory response and postoperative opioid consumption by minimizing surgical trauma[2,4–6], pharmacological interventions gain importance in clinical practice for both primary prevention and secondary treatment of POI within, '*enhanced recovery after surgery*' concepts[6]. Due to the multifactorial pathogenesis, numerous pharmacological strategies have been explored in clinical trials resulting in a broad spectrum of perioperative pharmacological options[2,6,7]. Approximately 100 substances have been tested for either preventing or treating postoperative gastrointestinal dysmotility[6]. The scientific landscape is diverse due to inconsistent trial quality, inhomogeneous patient collectives, varying endpoints, absence of well-defined '*core outcome sets*' for POI, and the wide range of pharmaceuticals investigated as interventions[7,8]. Moreover, some drugs tested for prophylaxis or targeted therapy of POI bear the risk of potential serious side effects. These factors pose challenges in implementing focused pharmacological interventions in clinical practice and make the translation of extensive literature into practical application complex. Nonetheless, surgeons and treating physicians must be acquainted with potential agents amidst a myriad of tested drugs that hold promise for sufficiently preventing or effectively treating POI.

In order to address this, we have systematically reviewed current evidence from randomized-controlled trials (RCT), which tested substances for their potential in either the prevention or treatment of postoperative gastrointestinal dysmotility and POI. Our focus is on substances that are globally available and can be safely administered in clinical routine. Due to the limited availability of high-quality evidence supporting specific pharmacological interventions against postoperative gastrointestinal dysmotility and POI using widely accessible pharmaceuticals, results of the meta-analysis will be subsequently discussed in terms of their practical relevance in the perioperative setting and their implications for further research within the field.

HIGHLIGHTS

- Evidence for pharmacological prevention of postoperative paralytic ileus following gastrointestinal tumor surgery is limited.
- Postoperative opioid-sparing analgesia, perioperative peripheral opioid antagonism and perioperative reduction of sympathetic hyperreactivity are promising approaches for enhancing bowel recovery.
- Oral Alvimopan or intravenous Lidocaine or Dexmedetomidine, respectively, showed the highest effectiveness in various domains of postoperative bowel as well as overall recovery and prevention of postoperative ileus.
- Evidence for pharmacologic intervention for the therapy of clinically evident postoperative paralytic ileus is much worse; intravenous Neostigmine and oral Gastrografin have demonstrated some benefits regarding bowel movements, but the efficacy in other domains of bowel recovery remain elusive.
- Inadequate pharmacological preventive measures for postoperative paralytic ileus lead to increased morbidity and prolonged hospitalization.
- Further research is urgently needed for improvements in patient recovery.

Methods

The study was prospectively registered in the *International Prospective Register of Systematic Reviews* (PROSPERO; unique identifying number: PROSPERO 2022 CRD42022351799; hyperlink: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022351799). Systematic review and meta-analysis were performed and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Supplemental Digital Content 1, http://links.lww.com/JS9/C227) 2020 statement[9] and Assessing the methodological quality of systematic reviews (AMSTAR-2) guidelines[10]. The overall quality of this work has been rated as high by AMSTAR-2 (see AMSTAR-2 checklist in the Digital Supplement, Supplemental Digital Content 2, http://links.lww.com/JS9/C228).

Systematic literature search and data extraction

English or German literature was screened in MEDLINE, CENTRAL, as well as information were extracted from ClinicalTrials.gov. Prospective randomized-controlled trials investigating pharmacologic options for either the prevention or therapy of gastrointestinal dysmotility and POI after gastrointestinal tumor surgery were identified using a predefined search strategy (Supplement 1, Supplemental Digital Content 3, http://links.lww.com/JS9/C229). Final searches were performed on 15 August 2023.

Eligibility criteria for inclusion in the meta-analysis required that the study data be sourced from RCTs involving patients who had undergone gastrointestinal tumor resections, including resections of the esophagus, stomach, pancreas, liver, small and/or large bowel. Additionally, the drug under investigation must have been tested against placebo, standard therapy, or no therapy. Studies lacking suitable comparators– for example, comparison with another pharmacologic intervention, studies failing to include patients undergoing gastrointestinal tumor resections, or studies examining drugs not approved by German and / or U.S. American drug administration authorities, mainly due to safety

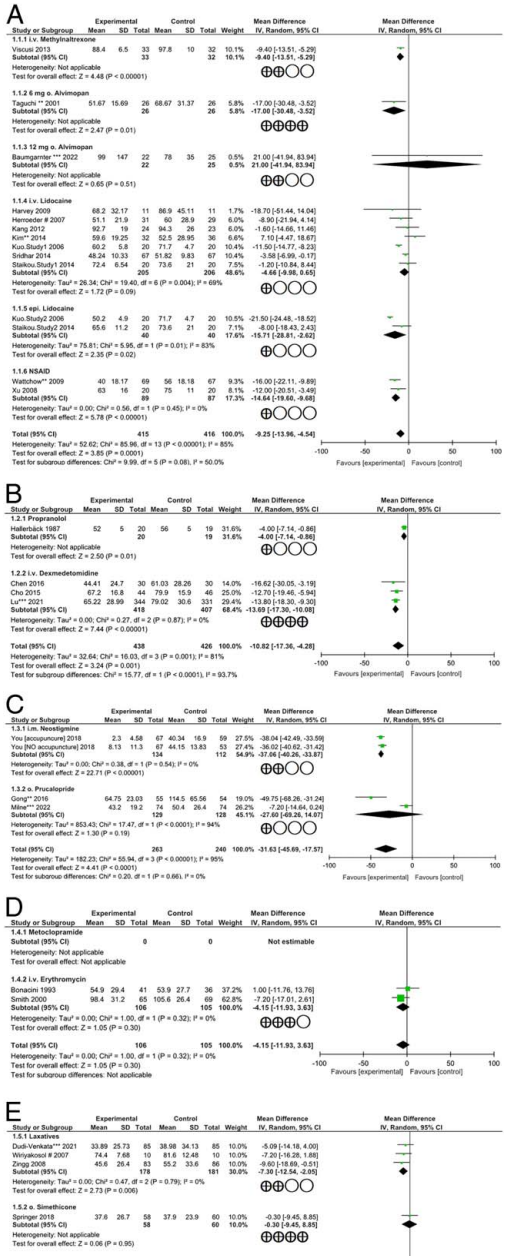


Figure 1. Duration until first flatus [h]. Effect of pharmacologic intervention on duration until first flatus versus comparator. Results are given as mean difference and 95% CI. A, Reduction of peripheral opioid effects and opioid-sparing approaches. B, Reduction of perioperative sympathetic hyperreaction. C, Parasympathomimetic agents. D, Prokinetic drugs. E, Laxatives, stimulants and adjuncts. ** Estimation of mean ± SD using the method described by Wan *et al*.[12]. *** Data were obtained directly from the study authors. # data estimated from publication graphs. i.v., intravenous; NSAID, non-steroidal anti-inflammatory drugs; o., per os; epi., epidural; i.m., intramuscular. Certainty of evidence is indicated for each calculation as very low ⨁, low ⨁⨁, moderate ⨁⨁⨁, high ⨁⨁⨁⨁.

concerns, were excluded from the meta-analysis. Administrative approval of pharmaceuticals by the German and/or U.S. American health care system served as the benchmark for assessing overall treatment efficacy and safety. The absence of such approval from these evidence-based health care systems indicates limited global accessibility and applicability, translating to a lack of relevance in the context of perioperative medicine.

The mean outcomes for gastrointestinal recovery were: time to first flatus and time to first bowel movement (TTF, TTM; Figs 1, 2). Other continuous outcome parameters were time to (solid) diet tolerance (TTD; Fig. 3), time to achieve the GI-2 composite outcome criterion (GI-2 combines TTM and TTD; Fig. 4) and length of hospital stay (LOS; Fig. 5). Secondary outcomes were: Nasogastric tube (re-) insertion rate, postoperative (total, cardiac, pulmonary, surgical, i.e. > grade II regarding the Clavien–Dindo classification of surgical complications[11]) complication rates (Tables 1, 2) and patient satisfaction.

Two reviewers independently screened the titles and abstracts of studies retrieved using the search strategies outlined above and those from additional sources for potential inclusion. Full texts of potentially eligible studies were retrieved and again independently assessed for final inclusion into the meta-analysis by two reviewers (see PRISMA flow diagram in Supplement 2, Supplemental Digital Content 4, http://links.lww.com/JS9/C230). Data for quality assessment and evidence synthesis were extracted from the studies and included into a standardized form by two reviewers. At any stage disagreements between the two primary reviewers were resolved by an independent third party.

If relevant data were missing from the published manuscript or other sources, these were requested from study authors. Other potential sources for obtaining comprehensive datasets were open registries for clinical studies. Otherwise, if only the median was provided or SD of means were lacking, conversion from median to mean and SD was carried out using the method by Wan *et al*.[12] or SD of means were estimated following the Cochrane Handbook (Cochrane Handbook for Systematic Reviews of Interventions. Version 6.4, 2023. www.training.cochrane.org/handbook) and using the RevMan Calculator (www.training.cochrane.org/resource/revman-calculator), respectively.

Data synthesis and statistical analysis

When comparable data from multiple RCTs were available, data synthesis and statistical analysis were performed using the Cochrane Collaboration's Review Manager (RevMan Version 5.4). Heterogeneity of included studies was tested using Cochran's Q statistic and I^2 test ($I^2 = 0$–40%: low; $I^2 = 41$–74%: moderate; $I^2 = 75$–100%: high).

For dichotomous outcomes, risk ratios (RR) were calculated. RR < 1 is in favor of the experimental pharmacologic intervention. For continuous parameters, mean differences (MD) between two groups were calculated. If studies report on time-to-event data, the logarithmically transformed hazard ratios were synthesized to obtain an overall estimate of the treatment effect. Random effects modeling was used for analysis due to considerable heterogeneity among studies concerning modalities of intervention and comparator, sample sizes, patient population, types of surgery, and results in I^2 tests. Results are reported in forest plots with 95% CI. Funnel Plots in Supplement 3 (Supplemental Digital Content 5, http://links.lww.com/JS9/C231) indicate

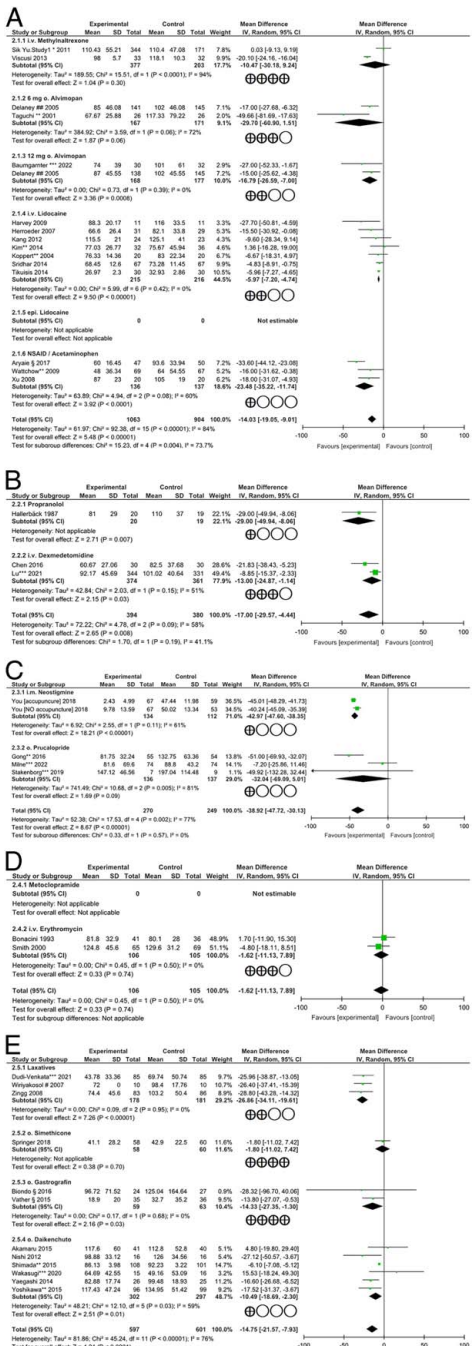


Figure 2. Duration until first defecation [h]. Effect of pharmacologic intervention on duration until first bowel movement versus comparator. Results are given as mean difference and 95% CI. A, Reduction of peripheral opioid effects and opioid-sparing approaches. B, Reduction of perioperative sympathetic hyperreaction. C, Parasympathomimetic agents. D, Prokinetic drugs. E, Laxatives, stimulants and adjuncts. *data were extracted from clinical trial registries. **Estimation of mean ± SD using the method described by Wan *et al*.[12]. ***Data were obtained directly from the study authors. # data estimated from publication graphs. ## SD of means estimated using RevMan Calculator regarding the Cochrane Handbook. § Studies did not isolate the variables 'time to first flatus' and 'time to first bowel movement' as separate variables but recorded the 'time to first flatus or bowel movement' as the outcome. i.v., intravenous; NSAID, non-steroidal anti-inflammatory drugs; o., per os; epi., epidural; i.m., intramuscular. Certainty of evidence is indicated for each calculation as very low ⨁, low ⨁⨁, moderate ⨁⨁⨁, high ⨁⨁⨁⨁.

publication bias among different studies with various interventional pharmacologic treatment modalities regarding the continuous outcomes analyzed. If no meta-analysis could be calculated due to missing data or clinical or statistical heterogeneity, results of the individual studies are reported narratively.

Assessment of bias and quality of evidence

Risk of bias was assessed independently for each outcome of interest of each study included into the meta-analysis by two investigators and a third party, if necessary, using the Cochrane Collaboration's risk-of-bias tool-2 (available at: www.methods.cochrane.org; version from 22 August 2019; Supplement 4, Supplemental Digital Content 6, http://links.lww.com/JS9/C232 depicts results of risk of bias assessment). Quality of evidence was assessed using 'Grading of Recommendations, Assessment, Development and Evaluations' (GRADE software GRADEpro GDT; available at: www.gradepro.org). The respective certainty of evidence (CoE) is given at each calculation: very low ⨁, low ⨁⨁, moderate ⨁⨁⨁, high ⨁⨁⨁⨁.

Results

Results from 55 RCTs with 5078 patients having undergone experimental intervention versus 3857 patients having undergone placebo, standard care (three studies) or no therapy (five studies), respectively, were included into the meta-analysis (Supplement 5, Supplemental Digital Content 7, http://links.lww.com/JS9/C233).

Reduction of peripheral opioid effects and opioid-sparing approaches

Three RCTs tested the selective μ-opioid receptor antagonist methylnaltrexone intravenously at different dosages against placebo for the prevention of POI in patients, who underwent oncologic colorectal resections with primary anastomosis[13,14]. Sik Yu *et al*. summarize the results of two RCTs with similar study designs in their publication[14]. Herein, 12 mg or 24 mg of methylnaltrexone was given repetitively after surgery until gastrointestinal recovery. Owing to an incompatible published data set and unavailability of source data, continuous data from the second RCT reported by Sik Yu *et al*. (NCT00387309) were excluded from the meta-analysis[14]. Nevertheless, findings regarding the effects of methylnaltrexone on gastrointestinal recovery from both studies summarized by Sik Yu *et al*. are basically consistent[14]. A similar study design with intravenous 0.3 mg/kg of methylnaltrexone was tested against placebo by Viscusi *et al*.[13]. Although some benefits of methylnaltrexone on gastrointestinal recovery were observed in the small RCT by Viscusi *et al*., these could not be confirmed in larger patient cohorts by Sik Yu *et al*.[13,14]. Even no significant differences in effectiveness were observed between the groups receiving different dosing strategies and the placebo group were described by Sik Yu *et al*.[14]. Thus, in the meta-analysis, methylnaltrexone failed to have an effect on LOS [MD −0.28 (−1.99–1.43]d, $P = 0.75$; Fig. 5A) or on the prevention of gastrointestinal dysmotility as indicated by both relevant outcome parameters, TTM [MD −10.47 (−30.18–9.24)h, $P = 0.30$; Fig. 2A] and achievement of the composite outcome GI-2 [MD −18.89 (−48.43–10.65)h, $P = 0.21$; Fig. 4A]. GI-2 combines TTM and TTD. The latter was

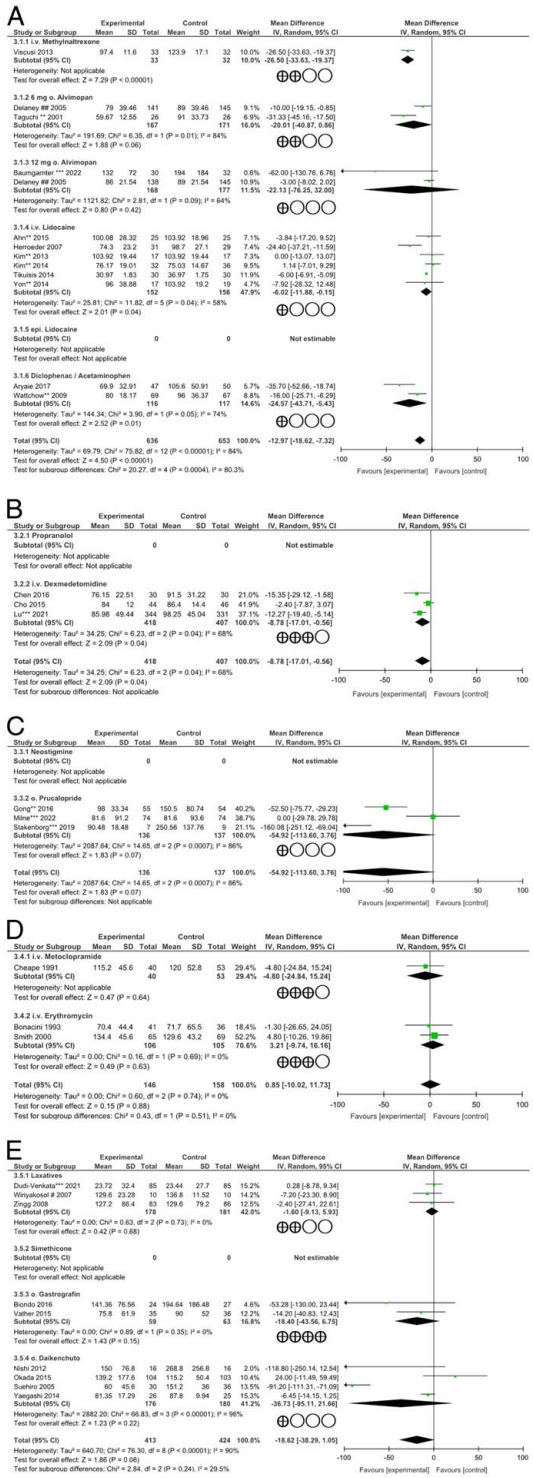


Figure 3. Duration until food tolerance [h]. Effect of pharmacologic intervention on duration until (solid) food tolerance versus comparator. Results are given as mean difference and 95% CI. A, Reduction of peripheral opioid effects and opioid-sparing approaches. B, Reduction of perioperative sympathetic hyperreaction. C, Parasympathomimetic agents. D, Prokinetic drugs. E, Laxatives, stimulants and adjuncts. **Estimation of mean ± SD using the method described by Wan *et al*.[12]. ***Data were obtained directly from the study authors. # data estimated from publication graphs. ## SD of means estimated using RevMan Calculator regarding the Cochrane Handbook. i.v., intravenous; o., per os; epi., epidural. Certainty of evidence is indicated for each calculation as very low ⨁, low ⨁⨁, moderate ⨁⨁⨁, high ⨁⨁⨁⨁.

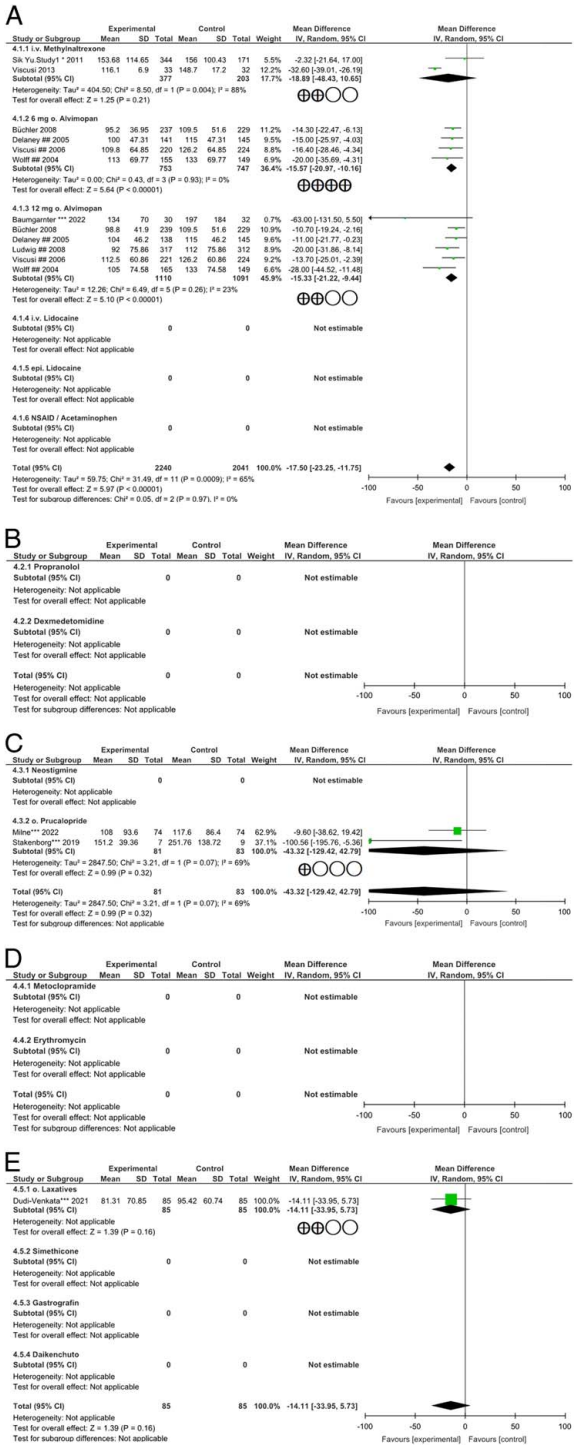


Figure 4. Duration until achievement of the composite outcome GI-2 [h]. Effect of pharmacologic intervention on duration until achievement of the composite outcome GI-2 versus comparator. GI-2 includes first bowel movement and oral intake tolerance. Results are given as mean difference and 95% CI. A, Reduction of peripheral opioid effects and opioid-sparing approaches. B, Reduction of perioperative sympathetic hyperreaction. C, Parasympathomimetic agents. D, Prokinetic drugs. E, Laxatives, stimulants and adjuncts. *data were extracted from clinical trial registries. ***Data were obtained directly from the study authors. ## SD of means estimated using RevMan Calculator regarding the Cochrane Handbook. i.v., intravenous; NSAID, non-steroidal anti-inflammatory drugs; o., per os; epi., epidural. Certainty of evidence is indicated for each calculation as very low ⨁, low ⨁⨁, moderate ⨁⨁⨁, high ⨁⨁⨁⨁.

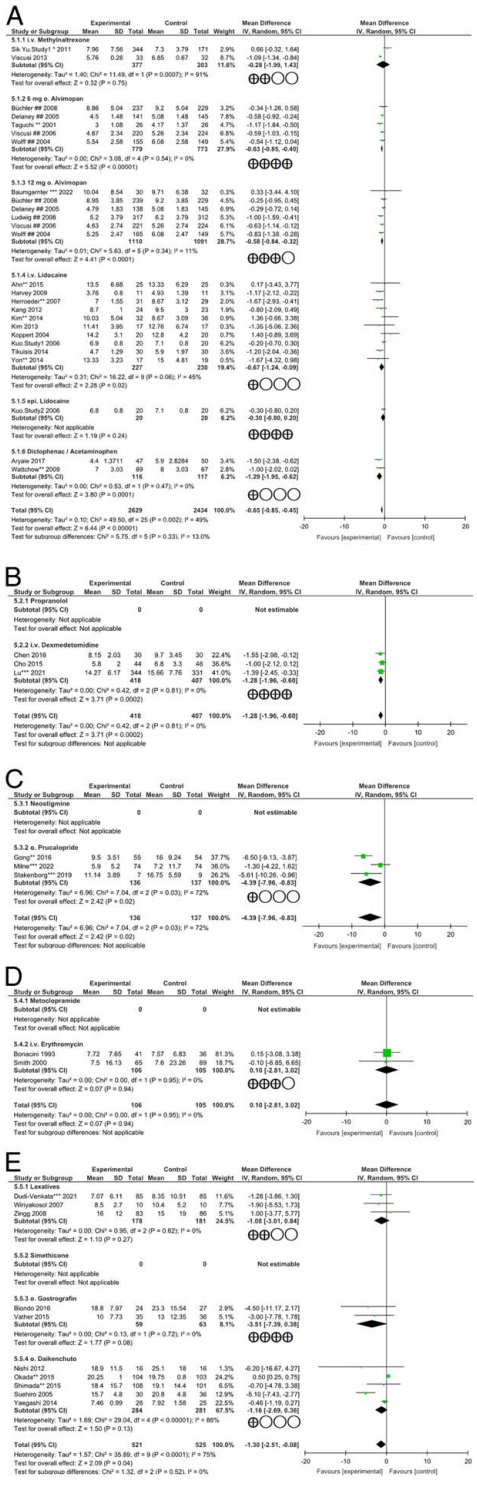


Figure 5. Length of hospital stay [d]. Effect of pharmacologic intervention on length of hospital stay versus comparator. Results are given as mean difference and 95% CI. A, Reduction of peripheral opioid effects and opioid-sparing approaches. B, Reduction of perioperative sympathetic hyperreaction. C, Parasympathomimetic agents. D, Prokinetic drugs. E, Laxatives, stimulants, and adjuncts. *data were extracted from clinical trial registries. **Estimation of mean ± SD using the method described by Wan *et al*.[12]. ***Data were obtained directly from the study authors. ## SD of means estimated using RevMan Calculator regarding the Cochrane Handbook. i.v., intravenous; o., per os; epi., epidural. Certainty of evidence is indicated for each calculation as very low ⊕, low ⊕⊕, moderate ⊕⊕⊕, high ⊕⊕⊕⊕.

reported as a single parameter only by Viscusi *et al*., thus potentially introducing bias regarding methylnaltrexone's efficacy in reducing the time to solid diet tolerance reported by Viscusi *et al*. Consequently, this leads to a low CoE. Seven RCTs investigated the efficacy of perioperative oral alvimopan, even a peripherally acting μ-opioid receptor antagonist, on postoperative bowel recovery. Alvimopan was administered once before surgery until postoperative day seven or reaching the endpoint of bowel recovery or discharge. The patient cohorts and administration protocols were reasonably homogeneous across studies. The four earliest studies included patients undergoing small or large bowel resection with primary anastomosis or hysterectomy[15–18], while Ludwig *et al*. and Büchler *et al*. focused on patients undergoing bowel resections with primary anastomosis[19,20]. Baumgartner *et al*. included patients with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy[21]. In the initial RCT by Taguchi *et al*., 1 mg or 6 mg of alvimopan versus placebo was evaluated[15], while more recent RCTs tested 12 mg against placebo[19,21]. Other studies investigated two dosing strategies, either 6 mg or 12 mg, against placebo[16–18,20] (Supplement 5, Supplemental Digital Content 7, http://links.lww.com/JS9/C233). As Taguchi *et al*. did not observe differences with 1mg alvimopan versus placebo[15] (Supplement 6, Supplemental Digital Content 8, http://links.lww.com/JS9/C234), a detailed presentation of these individual single study results in the respective figures is omitted. Regarding the dosage with 6 mg and 12 mg, the studies reported varying efficacy between individual dosing strategies, which were analyzed separately in the meta-analysis. The statistics of continuous outcomes primarily relied on time-to-event analyses reported in the included studies[16–20]. Means and SD were estimated according to the Cochrane Handbook and incorporated into the meta-analysis. Supplement 6 (Supplemental Digital Content 8, http://links.lww.com/JS9/C234) provides the synthesis of original hazard ratios for published continuous outcomes. The pooled data from various dosing strategies did not reveal differences in safety outcomes, exhibiting low CoE (Table 1). Although the analysis of individual outcomes did not show clear significance within different dosages of oral alvimopan, the meta-analysis highlights significant efficacy of higher-dose alvimopan (6 mg or 12 mg) on relevant outcomes for gastrointestinal and overall recovery, GI-2 and LOS (Figs 4A, 5A). These synthesized results of GI-2 and LOS were consistent with the meta-analysis of hazard ratios obtained from the primary published data, as presented in Supplement 6 (Supplemental Digital Content 8, http://links.lww.com/JS9/C234). Furthermore, the meta-analysis of results from four RCTs heterogeneously shows a reduced nasogastric tube (re-) insertion rate upon intervention with alvimopan [RR 0.58 (0.43–0.78), $P < 0.001$; Table 1].

Due to their opioid-sparing, analgesic and anti-inflammatory properties, NSAIDs, and selective cyclooxygenase-2 inhibitors have been tested regarding their effects on postoperative gastrointestinal dysmotility in several smaller RCTs. While the latter have some serious safety concerns and do not hold general approval, two RCTs testing twice perioperative applications of 1 mg/kg i.v. Flurbiprofen or perioperative 50 mg oral Diclofenac, twice daily for seven days, against placebo were identified[22,23]. One RCT evaluated the postoperative opioid-sparing effects of i.v. 1000 mg Acetaminophen administered perioperatively every 6 h for a maximum of five postoperative days following colorectal resections[24]. In the meta-analysis, these opioid-

sparing approaches had an effect on parameters indicating bowel recovery, including TTF [MD −14.64 (−19.60 to −9.68)h, $P<0.0001$; Fig. 1A], TTM [MD −23.48 (−35.22 to −11.74)h, $P<0.0001$; Fig. 2A] and TTD [MD −24.57 (−43.71 to −5.43)h, $P=0.01$; Fig. 3A] as well as on LOS [MD −1.29 (−1.95 to −0.62)d, $P=0.0001$; Fig. 5A]. However, the CoE is very low.

We identified 12 RCTs investigating effects of intravenous[25–36] or epidural[26,34] lidocaine with varying dosages and administration protocols (detailed information are given in Supplement 5, Supplemental Digital Content 7, http://links.lww.com/JS9/C233), and addressing their impact on gastrointestinal recovery following gastrointestinal tumor surgery as secondary endpoints. Meta-analysis of study data demonstrated positive effects of intravenous lidocaine on TTM [MD −5.97 [−7.20 to −4.74)h, $P<0.0001$; Fig. 2A], TTD [MD −6.02 (−11.88 to −0.15)h, $P=0.04$; Fig. 3A] and LOS [MD −0.67 (−1.24 to −0.09)d, $P=0.02$; Fig. 5A], as well as a trend towards shorter TTF [MD −4.66 (−9.98–0.65)h, $P=0.09$; Fig. 1A]. The meta-analysis of results from three studies[28,33,35] revealed higher patient satisfaction scores under intervention [MD 1.12 (0.60–1.64), $P<0.0001$; $I^2=0\%$]. Epidurally administered lidocaine had an effect on TTF [MD −15.71 (−28.81 to −2.62)h, $P=0.02$; Fig. 1A] but not on LOS. No further relevant outcomes were available in the epidural context.

No differences were observed concerning the risk of complications upon intervention with both selective μ-opioid receptor antagonists, NSAIDs, or Acetaminophen. Although one study explicitly reported one adverse event with intravenous lidocaine[28], the meta-analysis did not identify unfavorable complication rates upon administration of lidocaine. By contrast, the meta-analysis provides some evidence that relevant surgical complications occurred less frequently in the lidocaine groups [RR 0.35 (0.13–0.97), $P=0.04$; Table 1].

Reduction of perioperative sympathetic hyperreaction

Therapy with β-adrenoreceptor antagonists and α2-receptor agonists aims to downregulate perioperative sympathetic hyperactivity, thus disrupting the contribution of the enteric nervous system to postoperative gastrointestinal paralysis and POI[37,38]. Perioperative use of β-adrenoreceptor blockers for prophylaxis of postoperative ileus in patients undergoing colorectal resections was investigated in one RCT[37]. Either 4 mg or 10 mg of intravenous Propranolol were administered twice daily, and escalated to 40 mg or 80 mg per os after surgery. Both Propranolol regimens resulted in shorter TTF and TTM (Figs 1B, 2B). This effect was particularly evident in older patients (>60 years) and those who underwent left-sided colon resections. Propranolol led to a reduction in heart rate, but without notable cardiovascular side effects. However, the mixed patient cohort and unclear blinding results in very low CoE. Furthermore, this study does not include alternative readouts of gastrointestinal recovery after colorectal resections, such as diet tolerance or LOS.

Recent studies have focused on the α2-receptor agonist Dexmedetomidine, which has sympatholytic, sedative and analgesic effects, thereby promoting opioid-sparing benefits[38,39]. In three studies, Dexmedetomidine was administered perioperatively as an adjuvant to general anesthesia: loading doses (0.5 μg/kg–1μg/kg) before anesthesia induction and maintenance with 0.2 μg/kg/h–0.4 μg/kg/h during surgery[38,40,41]. In the study by Xin *et al.*, Dexmedetomidine was administered via *patient controlled analgesia* with 0.04 μg/h for 48 h in addition to postoperative opioid-based pain management[42]. Although Dexmedetomidine led to lower heart rates and blood pressures, it did not result in critical bradycardia, hypotension, or higher rates of clinically evident hemodynamic instability (Table 1). With a moderate to high CoE, the meta-analysis proves beneficial effects of perioperative i.v. Dexmedetomidine on TTF [MD −13.69 (−17.30 to −10.08)h, $P<0.0001$; Fig. 1B], TTM [MD −13.00 (−24.87 to −1.14)h, $P=0.03$; Fig. 2B], TTD [MD −8.78 (−17.01 to −0.56)h, $P=0.04$; Fig. 3B], and LOS [MD −1.28 (−1.96 to −0.60)d, $P=0.0002$; Fig. 5B]. Additionally, Xin *et al.* reported higher patient satisfaction, lower pain levels, subsequently reduced supplementary analgesic use, and lower incidence of nausea under *patient controlled analgesia* supplemented with dexmedetomidine[42].

Parasympathomimetic agents

Parasympathomimetics enhance intestinal smooth muscle tone. Two RCTs tested the efficacy of neostigmine in treatment of clinically evident POI following gastrointestinal tumor resections. Myrhoj *et al.*[43] defined paralysis as absence of flatus or stool on postoperative day two, with patients receiving either placebo or 0.5 mg Neostigmine intramuscularly in 3 h intervals. However, no significant effect of Neostigmine on gastrointestinal recovery was observed[43]. Because of inappropriate data format, these results were not suitable for inclusion into the meta-analysis. Similar inclusion criteria were employed by You *et al.*[44] in their four-arm RCT among patients after oncologic gastrectomy. Notably, bilateral injection of 0.5 mg Neostigmine at the ST36 acupuncture point was particularly effective and reduced TTF [MD −37.06 (−40.26 to −33.87)h, $P<0.0001$; Fig. 1C] and TTM [MD −42.97 (−47.60 to −38.35)h, $P<0.0001$; Fig. 2C]. Additionally, sole intramuscular injection of 1 mg Neostigmine outperformed both sole acupuncture and standard therapy[44]. However, CoE in this regard is low due to lack of blinding and heterogeneity of study results. Care has to be taken since complications, especially those of cardiovascular origin, are rarely reported.

Serotonin-5-hydroxytryptamine-4 receptor agonists unfold prokinetic activity through neuronal acetylcholine release in myenteric plexus, and exert local anti-inflammatory effects[6]. Three RCTs evaluated oral Prucalopride (2 mg, orally up to the 7th postoperative day)[45–47], which is approved in Germany for salvage therapy of chronic constipation[48]. Other drugs from this substance group including cisapride and mosapride are not generally approved, as described above, due to some severe cardiac side effects. The meta-analysis did not reveal any effects of oral Prucalopride on postoperative gastrointestinal recovery (Figs 1C–4C). Nevertheless, Prucalopride demonstrated some advantage in terms LOS [MD −4.39 (−7.96 to −0.83)d, $P=0.02$; Fig. 5C] with a very low CoE.

Prokinetic drugs

Two RCTs evaluated the effect of postoperative administration of 10 mg metoclopramide either intramuscularly or intravenously on prevention of postoperative gastrointestinal dysmotility[49,50]. Although some advantages regarding postoperative nausea and vomiting were observed in the small patient cohort reported by Davidson *et al.*, no relevant effects of metoclopramide were seen regarding TTD or rate of nasogastric tube reinsertion (Fig. 3D, Table 2).

Table 1

Summary of findings from dichotomous outcomes regarding opioid-sparing approaches and pharmacologic reduction of perioperative sympathetic hyperreaction.

Experimental pharmacologic intervention	Total complications	Cardiac complications	Pulmonary complications	Surgical complications > CD II°	Naso-gastric tube reinsertion
Reduction of peripheral opioid effects and opioid-sparing approaches					
i.v. Methylnaltrexone	↔ RR 1.0 95% CI 0.9–1.1 *P* = 0.93	↔ RR 1.25 95% CI 0.90–1.73 *P* = 0.18	↔ RR 0.79 95% CI 0.21–2.96 *P* = 0.73	—	—
CoE	⊕⊕⊕◯	⊕⊕⊕⊕	⊕⊕⊕◯	—	—
Number of RCTs	2 RCTs	3 RCTs	2 RCTs		
Heterogeneity	I^2 = 66%	I^2 = 0%	I^2 = 74%		
o. Alvimopan	↔ RR 0.97 95% CI 0.80–1.17 *P* = 0.73	↔ RR 0.81 95% CI 0.62–1.05 *P* = 0.11	↔ RR 3.00 95% CI 0.13–71.61 *P* = 0.50	↔ RR 0.79 95% CI 0.44–1.42 *P* = 0.43	↑ RR 0.58 95% CI 0.43–0.78 *P* < 0.001
CoE	⊕◯◯◯	⊕⊕◯◯	⊕⊕◯◯	⊕◯◯◯	⊕⊕⊕⊕
Number of RCTs	2 RCTs	5 RCTs	1 RCT	4 RCTs	4 RCTs
Heterogeneity	I^2 = 86%	I^2 = 0%	I^2 = n.a.	I^2 = 58%	I^2 = 0%
o. Diclophenac	—	↔ RR 0.49 95% CI 0.05–5.23 *P* = 0.55	—	—	—
CoE	—	⊕⊕◯◯	—	—	—
Number of RCTs		1 RCT			
Heterogeneity		I^2 = n.a.			
i.v. Lidocaine	↔ RR 0.71 95%CI 0.13–3.97 *P* = 0.69	↔ RR 7.00 95%CI 0.38–127.32 *P* = 0.19	—	↑ RR 0.35 95%CI 0.13–0.97 *P* = 0.04	↔ n.e.
CoE	⊕◯◯◯	⊕⊕⊕◯	—	⊕◯◯◯	⊕⊕◯◯
Number of RCTs	2 RCTs	4 RCTs		4 RCTs	1 RCT
Heterogeneity	I^2 = 82%	I^2 = n.a.		I^2 = 0%	I^2 = n.a.
epi. Lidocaine	—	↔ n.e.	—	—	↔ n.e.
CoE	—	⊕⊕⊕◯	—	—	⊕⊕◯◯
Nnumber of RCTs		2 RCT			1 RCT
Heterogeneity		I^2 = n.a.			I^2 = n.a.
Reduction of perioperative sympathetic hyperreaction					
i.v. / o. Propranolol	—	—	↔ n.e.	—	—
CoE	—	—	⊕⊕◯◯	—	—
Number of RCTs			1 RCT		
Heterogeneity			I^2 = n.a.		
i.v. Dexmedetomidine	—	↔ RR 0.86 95% CI 0.65–1.14 *P* = 0.29	—	↔ RR 0.42 95% CI 0.09–2.04 *P* = 0.28	—
CoE	—	⊕⊕⊕⊕	—	⊕⊕⊕⊕	—
Number of RCTs		2 RCTs		1 RCT	
Heterogeneity		I^2 = 0%		I^2 = n.a.	

Effect of experimental pharmacologic intervention on dichotomous outcomes versus comparator (no effect: ↔; ↑ = positive effect through experimental intervention, indicated by decreasing risk ratio; ↓ = negative effect through experimental intervention, indicated by increasing risk ratio). - = outcome not assessed in the respective studies. n.a., not applicable; n.e., not estimable; CD, Clavien–Dindo classification of surgical complications[11]. i.v., intravenous; o., oral; epi., epidural; CoE, certainty of evidence regarding GRADE (Grading of Recommendations, Assessment, Development and Evaluations, GRADE software GRADEpro GDT; available at: www.gradepro.org). Certainty of evidence is indicated for each calculation as very low ⊕, low ⊕⊕, moderate ⊕⊕⊕, high ⊕⊕⊕⊕. RCT, randomized-controlled trial; RR, risk ratio.

The macrolide antibiotic erythromycin, which acts as a prokinetic agent especially in the upper gastrointestinal tract through motilin receptors, was tested in two RCTs against placebo. 200 mg–250 mg erythromycin, administered repetitively intravenously after surgery showed no effect in the prevention of postoperative gastrointestinal dysmotility including TTF, TTM, or TTD (Figs 1D–3D) in the meta-analysis of two RCTs[51,52].

Table 2

Summary of findings from dichotomous outcomes regarding parasympathomimetics, prokinetics, laxatives, and stimulants.

Experimental pharmacologic intervention	Total complications	Cardiac complications	Pulmonary complications	Surgical complications > CD II°	Naso-gastric tube reinsertion
Parasympathomimetic agents					
i.m. Neostigmine	—	—	—	—	—
o. Prucalopride	↔ RR 1.15 95% CI 0.77–1.70 $P = 0.50$	↔ RR 0.95 95% CI 0.33–2.76 $P = 0.93$	↔ RR 2.0 95% CI 0.19–21.58 $P = 0.57$	↔ RR 1.05 95% CI 0.56–1.95 $P = 0.88$	↔ RR 0.75 95% CI 0.40–1.39 $P = 0.36$
CoE	⨁⨁⨁⨁	⨁⨁⨁◯	⨁⨁⨁⨁	⨁⨁⨁⨁	⨁⨁⨁⨁
Number of RCTs	1 RCT	2 RCTs	1 RCT	2 RCTs	2 RCTs
Heterogeneity	I^2 = n.a.	I^2 = 41%	I^2 = n.a.	I^2 = 0%	I^2 = 0%
Prokinetic drugs					
i.v. Metoclopramide	—	—	—	—	↔ RR 0.88 95%CI 0.27–2.92 $P = 0.84$
CoE	—	—	—	—	⨁⨁⨁◯
Number of RCTs					1 RCT
Heterogeneity					I^2 = n.a.
i.v. Erythromycin	↔ RR 0.82 95% CI 0.39–1.73 $P = 0.60$	↔ RR 0.10 95% CI 0.01–1.71 $P = 0.11$	↔ RR 1.76 95% CI 0.17–18.57 $P = 0.64$	—	↔ RR 1.27 95% CI 0.41–3.97 $P = 0.68$
CoE	⨁⨁⨁◯	⨁⨁⨁◯	⨁⨁⨁⨁	—	⨁⨁⨁◯
Number of RCTs	1 RCT	1 RCT	1 RCT		1 RCT
Heterogeneity	I^2 = n.a.	I^2 = n.a.	I^2 = n.a.		I^2 = n.a.
Laxatives, stimulants, and adjuncts					
Laxatives	↔ RR 0.86 95% CI 0.41–1.79 $P = 0.69$	↔ RR 1.26 95% CI 0.35–4.60 $P = 0.73$	↔ RR 2.39 95% CI 0.85–6.77 $P = 0.10$	↔ RR 1.52 95% CI 0.85–2.72 $P = 0.36$	↔ RR 0.94 95% CI 0.65–1.36 $P = 0.75$
CoE	⨁⨁◯◯	⨁⨁◯◯	⨁⨁◯◯	⨁⨁◯◯	⨁⨁◯◯
Number of RCTs	2 RCTs	3 RCTs	3 RCTs	3 RCTs	2 RCTs
Heterogeneity	I^2 = 11%	I^2 = 0%	I^2 = 10%	I^2 = 1%	I^2 = 0%
o. Simethicone	↔ RR 1.10 95% CI 0.63–1.91 $P = 0.75$	—	—	↔ RR 0.52 95% CI 0.05–5.55 $P = 0.59$	—
CoE	⨁⨁⨁⨁	—	—	⨁⨁⨁⨁	—
Number of RCTs	1 RCT			1 RCT	
Heterogeneity	I^2 = n.a.			I^2 = n.a.	
o. Gastrografin	↔ RR 0.99 95% CI 0.82–1.19 $P = 0.93$	—	↔ RR 0.56 95% CI 0.05–5.82 $P = 0.63$	↔ RR 0.81 95% CI 0.06–10.37 $P = 0.87$	↔ RR 0.88 95% CI 0.70–1.10 $P = 0.26$
CoE	⨁⨁⨁⨁	—	⨁⨁⨁⨁	⨁⨁⨁◯	⨁⨁⨁⨁
Number of RCTs	2 RCTs		1 RCT	2 RCTs	2 RCTs
Heterogeneity	I^2 = 0%		I^2 = n.a.	I^2 = 73%	I^2 = 0%
o. Daikenchuto	↔ RR 0.93 95% CI 0.69–1.24 $P = 0.61$	—	↔ RR 0.37 95% CI 0.10–1.47 $P = 0.16$	↔ RR 0.81 95% CI 0.39–1.65 $P = 0.56$	↔ RR 0.99 95% CI 0.06–15.62 $P = 0.99$
CoE	⨁⨁◯◯	—	⨁⨁◯◯	⨁◯◯◯	⨁⨁◯◯
Number of RCTs	8 RCTs		5 RCTs	5 RCTs	1 RCT
Heterogeneity	I^2 = 15%		I^2 = 8%	I^2 = 45%	I^2 = n.a.

Effect of experimental pharmacologic intervention on dichotomous outcomes versus comparator (no effect: ↔; ↑ = positive effect through experimental intervention, indicated by decreasing risk ratio; ↓ = negative effect through experimental intervention, indicated by increasing risk ratio). - = outcome not assessed in the respective studies. n.a., not applicable; CD, Clavien–Dindo classification of surgical complications[11]. i.v., intravenous; o., oral; i.m., intramuscular; CoE, certainty of evidence regarding GRADE (Grading of Recommendations, Assessment, Development and Evaluations, GRADE software GRADEpro GDT; available at: www.gradepro.org). Certainty of evidence is indicated for each calculation as very low ⨁, low ⨁⨁, moderate ⨁⨁⨁, high ⨁⨁⨁⨁. RCT, randomized-controlled trial; RR, risk ratio.

Laxatives, stimulants, and adjuncts

Beneath their osmotic effects, laxatives increase colonic motility. Two RCTs were identified in which colorectal cancer patients perioperatively received laxatives orally including 10 mg bisacodyl or a multimodal mixture versus placebo or standard therapy, respectively[53,54]. One further study assessed rectal application 10 mg bisacodyl once at postoperative day 3 for the treatment of clinically manifest POI[55]. Laxatives were administered repetitively until reaching the respective study endpoints (bowel movement or GI-2). The meta-analysis demonstrated beneficial effects of laxatives, both in the prevention of gastrointestinal dysmotility and treatment of POI following colorectal resections, with regard to TTF [MD – 7.30 (– 12.54 to – 2.05)h, $P = 0.006$; Fig. 1E] and TTM [MD – 26.86 (– 34.11 to – 19.61)h, $P < 0.0001$; Fig. 2E]. In the smaller study by Zingg *et al.*[53] bisacodyl shortened the time to reach the composite outcome GI-3, which combines TTD and TTM or TTF. In the report of their larger trial, Dudi-Venkata *et al.*[54] also noted a significantly shorter duration until achieving the composite criterion GI-2. However, this effect could not be replicated in the present analysis of the primary data provided by the authors [MD – 14.11 (– 33.95–5.73)h, $P = 0.16$; Fig. 4E]. Thereby perioperative therapy with laxatives is safe as complication rates did not differ between the investigated groups (Table 2). However, no effect was observed with regard to TTD or LOS (Figs 3E, 5E).

In contrast, simethicone (160 mg oral, four times daily) did not yield an effect on prevention of gastrointestinal dysmotility following colorectal resections in one RCT[56]. Concerning the osmotically active radiographic contrast agent Gastrografin (100 ml oral at diagnosis of POI) the meta-analysis of two RCTs revealed some advantages regarding TTF or TTM [MD – 14.33 (– 27.35 to – 1.30)h, $P = 0.03$; Fig. 2E] for therapy of clinically manifest POI[57,58]. Both RCTs summarized TTF or TTM into a single outcome measure, which is a relevant limitation. No other benefits were observed by Vather *et al.*[58], neither regarding time to resolution of POI, nor regarding any other parameters including nausea and vomiting. Even the meta-analysis of other surrogate parameters for resolution of POI, including TTD or LOS showed no further benefits of Gastrografin in the treatment of clinically manifest POI (Figs 3E, 5E).

Daikenchuto (DKC) is a phytotherapeutic formula derived from traditional Japanese medicine and consists of the herbal components Japanese pepper, dried ginger, ginseng root, and maltose powder[59]. DKC is attributed with stool-regulating and anti-inflammatory properties[60–62]. Eleven RCTs were identified, wherein the perioperative oral administration of DKC was tested with varying dosages and administration protocols (detailed information are given in Supplement 5, Supplemental Digital Content 7, http://links.lww.com/JS9/C233) against placebo or no treatment for its impact on postoperative gastrointestinal motility in the context of gastrointestinal tumor resections[59–69]. Although effects were observed in the meta-analysis for DKC concerning TTF [MD – 9.91 (– 19.15 to – 0.67)h, $P = 0.04$; Fig. 1E] and TTM [MD – 10.49 (– 18.69 to – 2.30]h, $P = 0.01$; Fig. 2E], DKC failed to demonstrate efficacy in relation to other parameters of gastrointestinal recovery, including the rate of nasogastric tube reinsertion, TTD and LOS (Figs 3E, 5E, Table 2). Four of the RCTs provide insight into quality of life and patient satisfaction across various dimensions, with all consistently reporting no differences between DKC and their control groups[60,61,64,65]. However, CoE regarding TTF and TTM remains very low due to the use of diverse comparators across various RCTs, high risk of bias among the studies and inconsistency in results.

Discussion

The presented meta-analysis evaluates evidence from RCTs that have focused on the pharmacological prophylaxis or treatment of POI following major oncologic gastrointestinal surgery. The systematic review with meta-analysis included data from 5078 patients in the intervention groups. Across the various RCTs reviewed here, a total of 17 substances were tested. These were categorized into five subgroups regarding their mechanisms of action. Single RCTs that evaluated choline citrate[70] and glutamin[71] were not included in the meta-analysis. These studies did not show any relevant effects on postoperative gastrointestinal dysmotility and bowel recovery in their reported results.

The selection of medications limited to those approved by German and/or U.S. American drug administration authorities underscores the stringent evidence-based criteria regarding efficacy and safety driving pharmaceutical authorization. However, it is crucial to note that this approach does not diminish the broader applicability of our findings beyond the German or U.S. American healthcare context, as the inclusion process of studies in the meta-analysis largely pertains to globally available medications. Furthermore, our deliberate focus on medications approved within these rigorously evidence-based healthcare systems does not imply restrictions on the general validity of our results. This selection process purposefully excludes therapeutic strategies relying on limited evidence, ensuring the comprehensive evaluation of treatments demonstrating both efficacy and safety within a well-established healthcare setting. Certain substances tested in RCTs for POI were excluded from the meta-analysis. This exclusion was attributed to significant safety concerns, coupled with a lack of general approval in both health care systems. Consequently, these substances exhibit limited global applicability in the perioperative setting. The excluded substances encompass selective cyclooxygenase-2 inhibitors, cholecystokinin-like acting drugs, ghrelin agonists, dihydroergotamine, and the serotonin-5-hydroxytryptamine-4 receptor agonists cisapride and mosapride. However, their benefit in preventing POI is uncertain and evidence for most of these substances does not substantially go beyond the results of the meta-analyses by Traut *et al.*[7] from 2008 and Milne *et al.*[1] from 2018.

The evidence for pharmacological treatment of clinically manifest POI is very limited, but the results from one single study suggest, that neostigmine is particularly effective[44]. In the prophylaxis of POI, especially opioid-sparing analgesic techniques, reduction of peripheral opioid effects and approaches that reduce sympathetic hyperreactivity, along with early use of laxatives, should be considered. In particular, the perioperative oral administration of alvimopan or intravenous administration of lidocaine or dexmedetomidine demonstrated effectiveness in various domains of postoperative bowel recovery and LOS, with dexmedetomidine showing the strongest effects regarding LOS as the surrogate parameter for postoperative overall recovery. However, it remains unclear which surgical cancer patients would benefit most from the perioperative administration of

dexmedetomidine. Furthermore, regarding the sympatholytic and analgesic effects of dexmedetomidine, it is unclear whether pharmacological therapy with dexmedetomidine is at least equivalent or more effective compared to the widely used practice of epidural anesthesia in abdominal surgery, or to what extent its effects can be potentiated by spinal analgesic techniques. However, when considering the indications and dosing of dexmedetomidine in the perioperative setting, it is important to take into account the adverse events reported by Beloeil *et al*. and Shehabi *et al*. These authors reported increasing cardiac complications and long-term mortality, albeit at substantially higher doses, longer duration of administration and in different settings and patient populations[72–74]. Even in the context of long-term use of alvimopan for chronic opioid-induced constipation, severe cardiac side effects have been observed[75]. Consequently, despite not being approved in Germany, the indication for alvimopan by the American Food and Drug Administration is strictly limited to the perioperative setting, specifically for patients who have undergone bowel resections with primary anastomosis[75]. Nevertheless, in contrast to Methylnaltrexone, another representative of the class of peripherally acting μ-opioid receptor antagonists, our meta-analysis demonstrated good effectiveness in the assessed domains of postoperative bowel and overall recovery after perioperative administration of 6 mg or 12 mg alvimopan versus placebo. No differences in the safety profile of perioperative alvimopan were observed in our meta-analysis. Vice versa, inadequate pharmacological preventive measures for POI lead to increased postoperative morbidity and longer LOS. This is demonstrated by the results of the present meta-analysis concerning lidocaine, dexmedetomidine, and alvimopan.

Despite these findings, our study has some limitations primarily rooted in the published data and heterogeneous study populations. The pathophysiology of POI is multifactorial, and beyond the pathways addressed by the proposed pharmacological treatment options, further factors contribute to an increased risk of POI. There is some evidence available for nonpharmacological, adjunctive interventions for patients after gastrointestinal surgery to prevent POI, such as early use of coffee or chewing gum and in general early mobilization[76–78]. Nevertheless, these were not the focus of our systematic review and meta-analysis. However, they can be applied as safe and cost-effective adjuvant interventions in clinical practice. Moreover, procedure-specific and surgical-technical aspects are relevant in the development of POI, such as surgical site, minimally invasiveness as well as factors like operation, and anesthesia duration or patient-specific characteristics such as general physical condition. However, these factors are inadequately addressed within the scope of the meta-analysis since the patient cohorts reported in the current literature exhibit heterogeneity. The absence of subgroup analyses in individual publications and the lack of available or published primary data impede the synthesis of data for secondary subgroup analyses. Consequently, meaningful identification of patient subgroups that particularly benefit from specific pharmacological interventions remains elusive based on the available data. This underscores the need for further clinical research, especially regarding the most promising pharmacological approaches for preventing POI identified in our meta-analysis. These include opioid-sparing approaches, peripheral opioid antagonism through perioperative administration of lidocaine or alvimopan and alpha-2 agonism through dexmedetomidine.

Conclusion

In summary, effective prevention as well as adequate therapeutic pharmacologic options against prolonged gastrointestinal dysmotility and POI is important to enhance outcome of patients after oncologic gastrointestinal surgery as well as to reduce healthcare resource utilization and length of hospital stays. However, considering the current state of research, evidence for pharmacological intervention for either prevention of postoperative gastrointestinal dysmotility or therapy of POI following gastrointestinal tumor resections is limited. The findings from our meta-analysis can be used to generate hypotheses for further studies in this field.

Ethical approval

Not applicable.

Consent

Not applicable.

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Author contribution

All the authors have made a substantial contribution to the concept or design of the study, or the acquisition, analysis or interpretation of data, and to drafting the work or revising it critically for important intellectual content. S.P., T.V., and M.W.: study concept; M.R., T.V., M.W., and A.H.: data collection; M.R., M.W., and A.H.: data analysis; M.R., F.W., M.S., M.W., and A.H.: data interpretation; M.R., M.W., and A.H.: writing – first draft; F.W., S.P., M.S., and T.V.: writing – critical revision.

Conflicts of interest disclosure

No conflicts of interests to be declared concerning this article.

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Data availability statement

Any datasets generated during and/or analyzed during the current study are available upon reasonable request from the corresponding author.

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12 Erklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit bzw. die mir zuzuordnenden Teile im Rahmen einer kumulativen Habilitationsschrift, selbstständig und ohne zulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Alle Textstellen, die wörtlich oder sinngemäß aus veröffentlichten oder nichtveröffentlichten Schriften entnommen sind, und alle Angaben, die auf mündlichen Auskünften beruhen, sind als solche kenntlich gemacht. Ich versichere, dass ich für die nach §2 (3) der Habilitationsordnung angeführten bereits veröffentlichten Originalarbeiten als Erst- oder Seniorautor fungiere, da ich den größten Teil der Daten selbst erhoben habe, für das Design der Arbeiten verantwortlich bin und die Manuskripte maßgeblich gestaltet habe. Für alle von mir erwähnten Untersuchungen habe ich die in der „Satzung der Justus-Liebig-Universität zur Sicherung guter wissenschaftlicher Praxis“ niedergelegten Grundsätze befolgt. Ich versichere, dass alle an der Finanzierung der Arbeiten beteiligten Geldgeber in den jeweiligen Publikationen genannt worden sind. Ich versichere außerdem, dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Weise einer anderen Prüfungsbehörde vorgelegt wurde oder Gegenstand eines anderen Prüfungsverfahrens war. Mit der Überprüfung meiner Arbeit durch eine Plagiatserkennungssoftware bzw. ein internetbasiertes Softwareprogramm erkläre ich mich einverstanden.

Dr. med. Martin Reichert