

Original Research Article

Defining failure patterns and dynamics in locally advanced pharyngeal and laryngeal SCC following radiotherapy: Real-World Insights in the modern Era!

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ABSTRACT

Introduction: We aimed to evaluate the prevalence and patterns of locoregional recurrence (LRR), outcome and prognostic factors in patients with locally advanced squamous cell carcinoma of the oropharynx, hypopharynx, and larynx treated with intensity-modulated or volume-modulated arc therapy definitive radiotherapy (RT) with or without systemic therapy.

Methods: Of the 213 reviewed patients treated between 2016 and 2023, 177 met the inclusion criteria. LRR was defined as recurrence in the primary tumor region or regional nodes. Failure patterns were classified based on a recurrence model, including central high-dose (A), peripheral high-dose (B), central elective (C), peripheral elective (D), and out-of-field recurrence (E).

Results: LRR was observed in 50/177 (28.2%) patients and 81 recurrent lesions. Most recurrences occurred within the first year after RT (39/177, 22.0%), predominantly in HPV-negative patients. The majority of failures were within the high-dose target volume (65% type A, 14% type C), with marginal recurrences (types B and D) occurring in 22% of cases and type E in 5% of patients. HPV-positive patients had fewer LRR (16.0% vs. 34.4% in HPV-negative patients).

Multivariate analysis identified HPV status as a significant prognostic factor for OS, PFS and LRR. The occurrence of distant metastases showed a negative impact on OS, PFS and LRR. LRR showed a trend toward worse OS ($p = 0.072$). Chemotherapy had a significant effect on PFS and LRR.

Conclusion: LRR remains a challenge, especially in HPV-negative patients. Most failures occurred centrally, but marginal and extra-field recurrences highlight the need for improved target delineation and adaptive RT strategies. Further research is needed to optimize treatment in high-risk patients.

Introduction

The current estimated incidence of squamous cell carcinoma of the head and neck (HN-SCC) in Europe is approximately 21.8 per 100,000 with a mortality rate of approximately 15.6 per 100,000 [1]. Radiotherapy (RT) in combination with chemotherapy (CT) or immunotherapy (IT) along with upfront surgery represents a cornerstone in the

curative setting treatment of locally advanced HNC. Human papillomavirus (HPV) occurrence in patients with oropharyngeal cancer represents a favorable prognosis in these individuals, while hypopharyngeal cancer patients have the poorest prognosis compared to other HNC [2,3].

Modern RT techniques, including intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT), in the treatment

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of HNC, have allowed for dose escalation while simultaneously reducing the side effects of therapy after application of high dose to the tumor region and a prophylactic dose in the locoregional lymph nodes [4]. However, locoregional recurrence remains the major cause of failure in locally advanced HNC, affecting approximately 15–50 % of patients each year following radiotherapy [5].

Relatively little is known about patterns of treatment failure and post-relapse outcomes after definitive RT using modern radiation techniques. Recurrence patterns are significantly influenced by variations in RT quality, which may confound results from multicenter trials. An analysis of large series of HN-SCC patients treated with RT reported that overall survival (OS) after recurrence is influenced by primary tumor subsite and HPV or p16 status, as well as surgical and systemic interventions [5]. In the era of personalized medicine, the study of local recurrence patterns will help to better define both tumor and prophylactic volumes, taking into account biological factors such as HPV and technical factors such as dose distribution and image guidance with cone beam computed tomography (CBCT).

The aim of the current study was to investigate the prevalence and patterns of loco regional recurrence of recurrence in a series of patients with locally advanced SCC of the oropharynx, hypopharynx, and larynx treated with definitive RT with or without associated systemic therapy. Clinical outcomes and risk factors were compared and evaluated between recurrent patients and nonrecurrent patients.

Materials and methods

Patients' characteristics

We retrospectively reviewed the medical records of 213 consecutive patients with primary squamous cell carcinoma (SCC) of the oropharynx, hypopharynx, or larynx who were scheduled to receive definitive RT at our Department between 2016 and 2023. A series of patients with the following characteristics was selected: histologically confirmed SCC, locally advanced stage (cT3/4 and/or N +), tumor located in the oropharynx or hypopharynx or larynx, completion of definitive radiotherapy at the planned dose, and sufficient follow-up data. Exclusion criteria were as follows: distant metastases at the time of RT, non-SCC histology, oral cavity or lateralized tumors, and conversion to palliative RT.

After applying the inclusion and exclusion criteria, 213 patients were identified. Of the 213 patients, 177 patients were included in the current retrospective study (see [Supplementary 1/ Fig. 1](#)). The demographic data and clinical parameters of the entire cohort, including age, sex, lifestyle factors (smoking, alcohol), comorbidities, TNM stage [American Joint Committee on Cancer (AJCC) 7th edition staging system], tumor site, p16 and HPV status, combined therapy and treatment modality are summarized in [Supplementary 2/ Table 1](#). Although toxicities were not the focus of this study, they were nonetheless collected and reported in [Supplementary 2/ Table 2](#).

Patients' information including clinical records, imaging and follow up data were reviewed from electronic medical records to identify patients with locoregional recurrence.

Assessment and treatment

Most cases were analyzed using the VisionArray HPV Chip 1.0 (Zytomed Systems, Germany), which detects 41 HPV subtypes by targeting the L1 region via GP5+/GP6 + primers, with DNA quality confirmed by amplification of the HLA-DQA1 gene. Signal detection and analysis were performed using the VisionArray Detection Kit and Analysis Package. This method has a detection limit of approximately 50 genome equivalents. In earlier cases (before 2021), HPV detection was performed using a validated PCR-hybridization assay targeting the E1 region with the AID HPV DNA-Array (Analytik Jena), with DNA integrity confirmed by GAPDH amplification [6]. All testing was conducted in

accredited pathology laboratories in accordance with national quality assurance protocols.

All patients underwent planning computed tomography (CT) with thermoplastic mask immobilization. The primary tumor and involved lymph nodes were included in the gross tumor volume (GTV). Based on all clinical information, two levels of radiation target volumes were delineated according to our institutional selective neck irradiation policy: high-risk clinical target volume (HR-CTV) and low-risk clinical target volume (LR-CTV), including the elective lymph node stations, delivered over 28–30 fractions. The prescribed dose was 1.6–2.2 Gy/fraction/day, administered 5 days per week. The HR tumor sites received a median dose of 70.2 Gy (range 67.5–72 Gy) and the LR neck sites received a median dose of 57.6 Gy (range 50.4–57.6 Gy). Planning target volumes (PTVs) were created by automatically expanding all clinical target volumes (CTVs) by 3 to 5 mm to account for setup errors. The same target delineation and dose prescription guidelines were applied regardless of HPV status, according to the discretion of the treating radiation oncologist [7,8].

Normal structures including the parotid glands, spinal cord, brain-stem, optic nerves, and optic chiasm were also contoured on the treatment plan. Treatment was planned using IMRT or VMAT at 6 MV for all patients. Cone beam computed tomography (CBCT) was performed at least once to twice weekly in approximately 86 % of patients.

Overall, 91.0 % (n = 161) of the patients received combined systemic therapy as follows: 50.8 % (n = 90) cisplatin weekly, 18.1 % (n = 32) cisplatin + 5-fluorouracil (5-FU), 6.2 % (n = 11) 5-FU + mitomycin C, 2.8 % (n = 5) cisplatin switched to carboplatin due to intolerance, 3.8 % (n = 6) carboplatin, and 9.6 % (n = 17) cetuximab (see [Supplementary 2/ Table 1](#)).

Locoregional recurrence and survivals definition

Follow-up after treatment was performed by magnetic resonance imaging (MRI) and/or CT with contrast and/or positron emission tomography (PET)-CT. Imaging studies of relapsed patients were reviewed by an expert in the field. Diagnostic images were then fused with planning CT images to identify patterns of recurrence. Local recurrence refers to the return or further progression of cancer in the same area where it originally started. Locoregional recurrence refers to the recurrence of cancer both in the original area and in nearby tissues or neck lymph nodes. Regional recurrence refers to the recurrence of cancer in neck lymph nodes, but not at the site of the primary tumor.

Recurrence patterns are defined according to Mohamed et al. [9] as follows: Group A – recurrence in the central SIB/high-dose volume included in the 95 % isodose; Group B – recurrence in the peripheral high-dose volume; Group C – recurrence in the central elective node volume included in the 95 % isodose of the prophylactic dose; Group D – recurrence in the peripheral elective node volume; Group E – recurrence outside the irradiated volume but still within the head and neck region (see [Fig. 1](#)). We further subdivided groups A and B to report detailed information on local recurrence: A1 and B1 for recurrence within or adjacent to the primary region, respectively, and A2 and B2 for recurrence within or adjacent to the irradiated involved node region, respectively.

We evaluated the prevalence, timing, and pattern of locoregional recurrence after definitive radiotherapy, whether or not associated with systemic therapy. Possible relevant variables (Karnofsky index, HPV status, p16 status, frequency of CBCTs per week during Radiotherapy, cT/N status, primary tumor site, combination to systemic therapy, occurrence of recurrence, and occurrence of distant metastases), survival outcome and toxicity profile were also investigated. Overall survival (OS) was defined as the time from the last date of RT to death or last follow-up. Progression-free survival (PFS) was defined as the time from the last RT date to progression or death, and cancer-specific survival (CSS) was defined as the time from the last RT date to death from HN cancer or last follow-up.

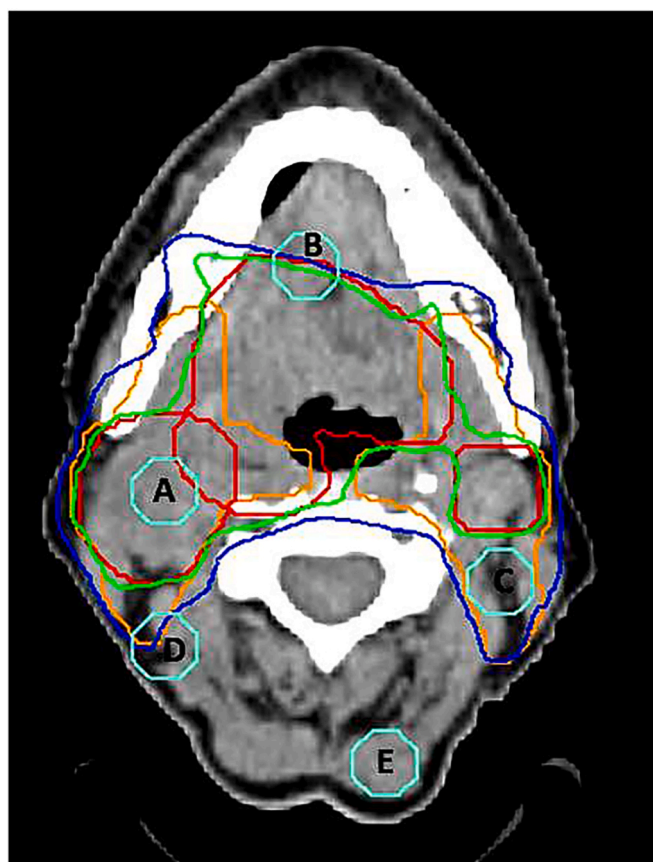


Fig. 1. Patterns of locoregional relapse (n = 81 lesions) according to Mohamed et al.: Group A – occurrence of relapse in the central SIB/high-dose volume, included in the 95 % isodose; Group B – occurrence of relapse in the peripheral high-dose volume; Group C – occurrence of relapse in the central elective node volume, included in the 95 % isodose of the prophylactic dose; Group D – occurrence of relapse in the peripheral elective node volume; Group E – occurrence of relapse outside the irradiated volume but still in the head and neck region.

Statistical analysis

Categorical variables were compared using Fisher's exact test, while continuous variables were analyzed using the Mann-Whitney *U* test. Kaplan-Meier survival analyses were performed to determine survival after initial and salvage treatment. Survival curves were tested for differences between groups using the log-rank test. Univariate and multivariate Cox proportional hazards model analyses were used to identify potential risk factors associated with locoregional recurrence, progression-free survival (PFS), and overall survival (OS). Hazard ratios (HRs) and 95 % confidence intervals (CIs) were calculated. Statistical significance was defined as *p*-value < 0.05. Statistical analysis was performed with R software (version 4.4.2).

Ethics

The study was conducted in accordance with the tenets of the Declaration of Helsinki, version 2013. All patients signed an informed consent form, and the study was approved by our internal review board at the Justus-Liebig-University of Giessen (ethics approval AZ 73/24).

Results

Outcomes of recurrent patients and patterns of recurrence

LRR was observed in 50/177 (28.2 %) patients with 81 recurrent lesions after definitive Radiotherapy with or without systemic therapy. Most of LRR patients presented with T3-4 and N2 stage at; 38/136 (28 %) were male and 12/41 (29.2 %) were female. The primary tumor entity was oropharynx in 33/113 (29.2 %) patients, hypopharynx in 10/33 (30.3 %) patients, and larynx in 7/31 (22.5 %) patients. Most of these patients were HPV negative (84 %). Characteristics of patients with locoregional recurrence are summarized in Table 1.

Median time to LRR was 7 months (range 4–11 months): 39/177 (22 %) patients relapsed in the first year (n = 7 HPV + and n = 32 HPV –), 8/177 (5 %) patients in the second year, and 3/177 (2 %) patients

Table 1

Characteristics of patients with locoregional recurrence after definitive radiotherapy (n = 50).

Variable	Value or No. Patients (%)
Age, years	
- Median (range)	65 (47–89)
Gender	
- Male	38 (76 %)
- Female	12 (24 %)
Karnofsky Index (%)	
- > 80	28 (56 %)
- 80–70	18 (36 %)
- 60	4 (8 %)
Smoke	
- never	6 (12 %)
- quit	6 (12 %)
- current	27 (54 %)
- unknown	11 (22 %)
Alcohol	
- yes	20 (40 %)
- no	10 (20 %)
- unknown	20 (40 %)
Primary tumor site	
- Oropharynx	33 (66 %)
- Hypopharynx	10 (20 %)
- Larynx	7 (14 %)
T-stage	
- T1	3 (6 %)
- T2	5 (10 %)
- T3	19 (38 %)
- T4	23 (46 %)
N-Stage	
- N0	14 (28 %)
- N1	6 (12 %)
- N2	29 (58 %)
- N3	1 (2 %)
Human papilloma virus-status	
- positive	8 (16 %)
- negative	42 (84 %)
- p16 positive	7 (14 %)
Combined systemic therapy	
- Chemotherapy	38 (76 %)
- Immunotherapy	4 (8 %)
- None	8 (16 %)
Systemic therapy schemata	
- Cisplatin + 5 FU	10 (20 %)
- Cisplatin weekly	22 (44 %)
- Carboplatin	4 (8 %)
- 5FU + MMC	2 (4 %)
- Cetuximab	4 (8 %)
RT prescribed dose (Gy)	
- Elective (median)	57,6 Gy
- igh dose (median)	70,2 Gy
CBCT	
- Once a week	19 (38 %)
- Twice a week	24 (48 %)
- Daily	7 (14 %)

RT: radiotherapy; CBCT: cone beam computed tomography.

thereafter (see Fig. 2). Twenty-nine patients developed LRR alone, 21 patients had both distant (mainly lung) and locoregional, and other 16 patients had only distant metastases mainly to the lungs.

Local recurrence rates were different in HPV-positive and HPV-negative patients: 16 % (8/50 patients) in HPV-positive and 34.4 % (42/127) in HPV-negative patients. Patterns of locoregional failure after definitive RT were as follows: 52 lesions in the central SIB/high-dose volume (34 primary lesions and 18 nodal recurrences); 14 lesions in the peripheral high-dose volume (8 primary lesions and 6 nodal recurrences); 11 lesions in the central elective nodal volume; 4 recurrent lesions in the peripheral elective nodal volume; and 4 lesions outside the irradiated volume but still in the head and neck region. Patterns of LRR are detailed in Table 2 and Fig. 3.

Of the 50 patients with LRR, 43 patients underwent further salvage treatment and 7 patients refused any further procedures. Thirteen patients underwent salvage surgery: 7 patients unilateral and 3 patients bilateral neck dissection. Of the 13 patients who underwent surgery, 3 also received postoperative high-dose reirradiation. Seven patients received high-dose reirradiation in the salvage setting. Overall, CT or IT was administered in 27 patients; systemic therapy was administered as maintenance therapy in 2 patients after salvage surgery and, associated to re-irradiation in 3 patients.

Outcome after definitive radiotherapy

Mean follow-up for the entire series was 24 months $\pm$ 20 months (SD). At the time of analysis, 52 patients were deceased (mean follow-up 17.4 months $\pm$ 19.1 months) and 125 patients were alive (mean follow-up 25.6 months $\pm$ 19.5 months). Death occurred due to tumor progression in 30 patients and other causes in 22 patients. Among patients with locoregional recurrence: 26 patients were alive, and 24 patients died, mainly due to local progression.

Median OS for the entire cohort was 5.8 years, and OS at 2, 3 and 5 years were 70.6 %, 65.4 % and 56.5 %, respectively. Median PFS was 5 years, and 2-, 3-, and 5-year PFS were 60 %, 55.7 %, and 48.3 %, respectively. The median CSS was 1.2 years, and the 2-, 3-, and 5-year CSS were 70.6 %, 65.4 %, and 56.5 %, respectively (Supplementary 3/

Table 2
Locoregional recurrence patterns (n patients = 50) according to Mohamed et al.

Patterns of relapse N = 81 lesions			
	HPV pos		HPV neg
			Overall
Group A (central high dose volume)	7	45	52
- 1 (primary tumor)	5	29	34
- 2 (positive nodes)	2	16	18
Group B (marginal high dose volume)	2	12	14
- 1 (primary tumor)	1	7	8
- 2 (positive nodes)	1	5	6
Group C (central elective volume)	2	9	11
Group D (marginal elective volume)	0	4	4
Group E (outside of RT volume in head and neck region)	2	2	4

HPV: human papilloma virus.

Fig. 2a-c).

The median OS in LRR patients was 1.7 years, compared to 6.5 years in patients without LRR vs. patients without LRR ($p < 0.01$). The median OS in HPV-negative patients was significantly shorter than in HPV-positive patients (3.5 vs. 6.5 years; $p < 0.01$) (see Fig. 4). The time from diagnosis up to radiotherapy start did not significantly affect OS or PFS between LRR and non-LRR patients (median 46 vs. 43 days, $p = 0.399$ and median 45 vs. 42 days, $p = 0.614$) (see Supplementary 2/ Table 4).

Outcome and variables associated with LRR

The 1-year and 2-year OS of patients with LRR were 75 % and 40 %, respectively. There was no significant difference ($p = 0.32$) in median survival between HPV + and HPV- patients with LRR (not reached vs. 1.7 years) (see Supplementary 3/Fig. 3). In patients with LRR, the 2-year survival in patients without distant progression was 50 % compared to 28 % in those patient with additional distant metastases, without achieving statistical significance ($p = 0.089$) (see Supplementary 3/ Fig. 4). Median survival after LRR was 12.4 months in patients without

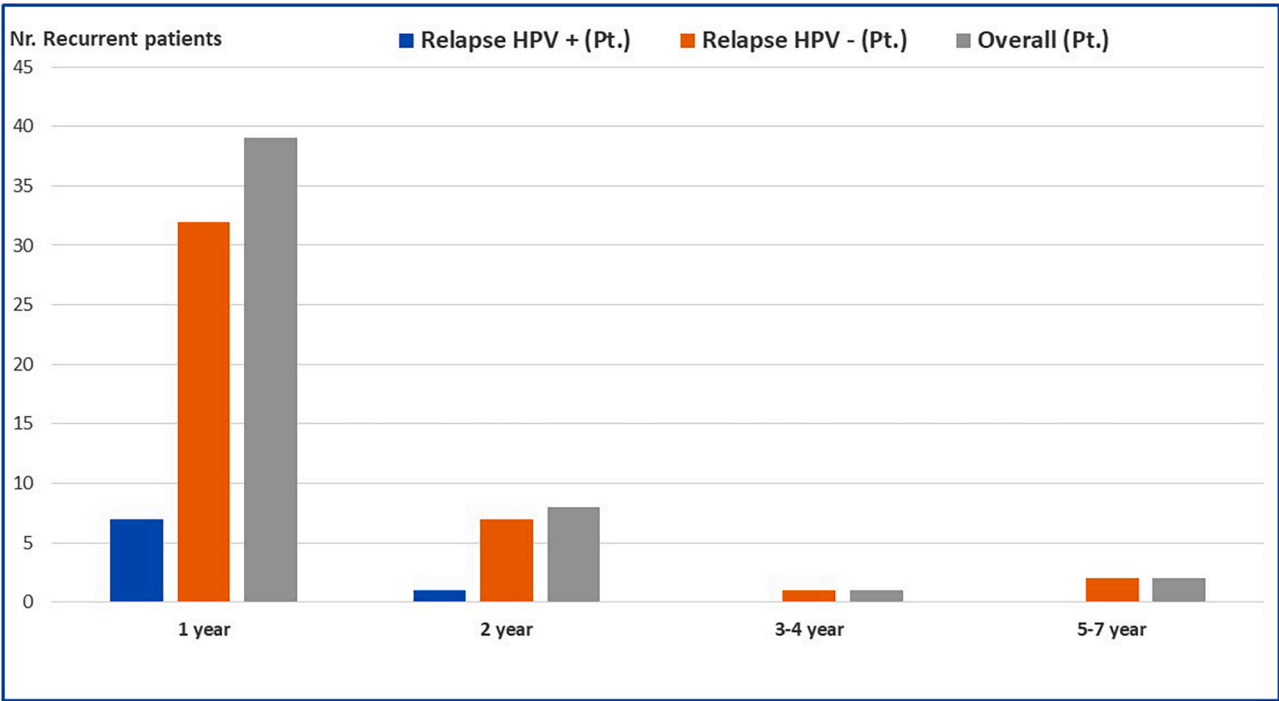


Fig. 2. Timing of locoregional recurrence in HPV positive and negative patients with oropharynx, hypopharynx and larynx cancer after definitive radiotherapy.

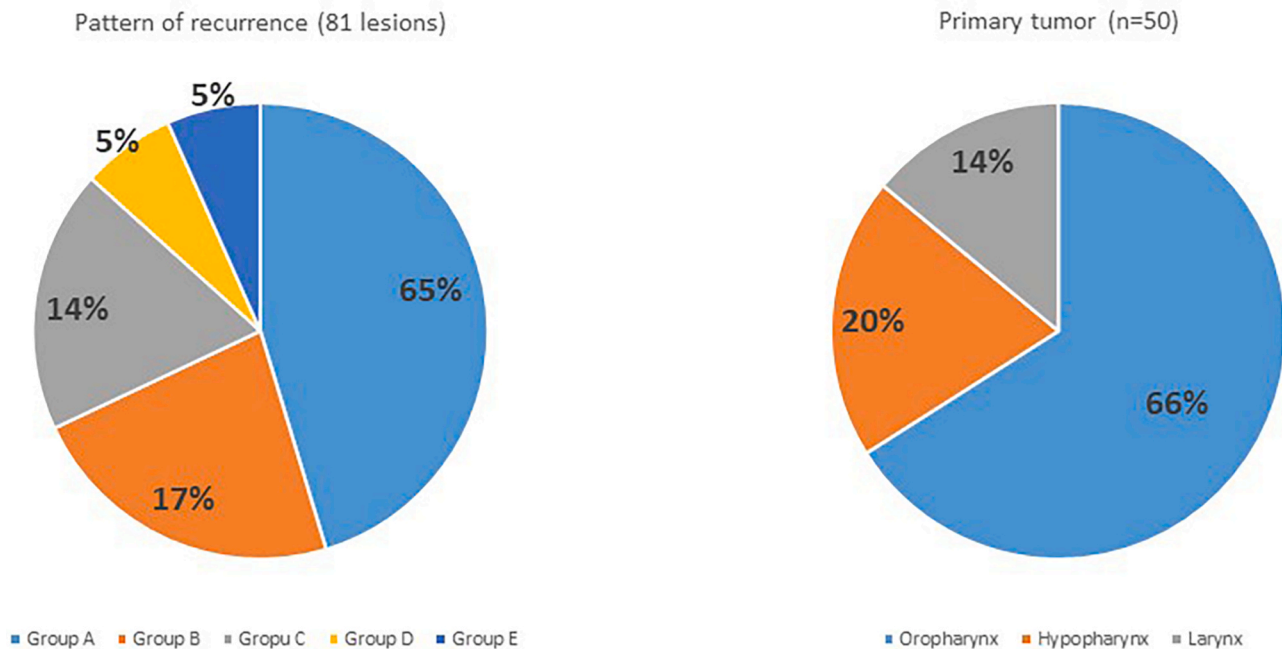


Fig. 3. Patterns of locoregional relapse (n = 81 lesions) according to Mohamed et al. and to primary tumor site (n = 50 patients).

distant metastases and 8.9 months in patients with distant metastases ($p = 0.32$) (see [Supplementary 3/Fig. 5](#)). Distant progression occurred earlier in the LRR patients (320 vs. 504 days, $p = 0.029$) (see [Supplementary 2/Table 4](#)).

Stratification and multivariate analysis

No statistically significant differences in OS, PFS, or LRR were observed between the subsites. A subsite-specific stratification by HPV status was thus only feasible for HPV-negative tumors (see [Fig. 5](#)). There were no significant differences between tumor subsites within the HPV-negative subgroup (data not shown).

The co-variables such as Chemotherapy, HPV status, T2-stage, LRR and distant metastases were found to be significantly correlated with the OS, PFS and LRR in the univariate analysis for the entire series and were then included in the multivariate analysis.

Chemotherapy combined with definitive Radiotherapy showed a significant positive impact on PFS and the occurrence of LRR, while the presence of HPV showed a significant benefit in OS, PFS and LRR. The occurrence of distant metastases showed a negative impact on OS, PFS and LRR. LRR had a trend toward worse OS ($p = 0.072$), but was not statistically significant. Chemotherapy had no impact on OS and cT2 was not found to be significant for OS, PFS and LRR (see [Table 3](#)).

Notably, primary tumor site was not significantly correlated with local and regional recurrence, OS, PFS and MFS in either univariate or multivariate Cox regression analyses of our series (data not shown).

Discussion

The current study evaluated the prevalence of locoregional recurrence and the patterns of relapse in a series of patients with locally advanced SCCs of the pharynx and larynx treated with definitive RT using a validated method taking into account the point-based and volume-based recurrence classification developed by Mohamed et al. [9].

In our analysis, LRR occurred mainly within the first year following radiotherapy, predominantly in HPV-negative patients, regardless of the primary tumor site (larynx, hypopharynx, or oropharynx) in agreement with the results reported in the literature [10]. Sometimes, LRR occurred

with multiple lesions within the head and neck region, with a notable incidence of marginal LRR, particularly Types B (17 % of the lesions) and D (5 % of the lesions). This represents a challenge for definitive RT, even with modern techniques such as VMAT and IMRT, which may require further refinement to optimize local control [11]. Recently, Trada et al. reported peripheral local recurrence rates of Type B and Type D in 18 % and 14 % respectively among HPV-negative oropharyngeal cancer patients, compared to 3 % and 3 % in HPV-positive patients, respectively [12]. In the current study, HPV-positive patients showed no Type D pattern, while the Type E pattern was present in 5 % of lesions including both HPV-positive and HPV-negative patients. Other studies have reported slightly higher rates of Type E LRR, ranging from 0 % to 13 % depending on HPV-status [9,10]. Our patients experienced mainly central failures (65 % Type A, 14 % Type C), primarily at the primary tumor site, with similar patterns in HPV-positive and negative groups. Tandon et al. [13] reported a total of 69 % Type A and 5 % Type C failures, while Mohamed et al. [9] found 82 % Type A and 8 % Type C. Chen et al. [14], studying only HPV-associated OPSCC, reported 41 % of locoregional recurrences as “in-field,” though their volume-based approach may have misclassified failures as peripheral. Our findings and existing data suggest a significant portion of recurrences occur in high-dose central regions also in HPV-positive patients, urging caution in RT dose de-escalation without better predictive biomarkers [15]. Moreover, adaptive planning can adjust for anatomical changes and better tumor delineation could reduce recurrences, with potential benefits from higher doses to high-risk nodal regions [16,17].

Our analysis highlights the significant impact of locoregional recurrence (LRR) on survival outcomes while demonstrating that distant metastases do not independently influence post-recurrence survival. Importantly, within the LRR subgroup, patients with and without distant metastases exhibited similar survival durations post-recurrence. The median survival after LRR was 12.4 months for those without distant metastases and 8.9 months for those with distant spread, with no statistically significant difference ($p = 0.32$). This suggests that the development of distant metastases after LRR may not further compromise survival, potentially due to the already aggressive nature of LRR itself. Cause of death was often attributed to local progression, while distant metastases did not significantly impact overall survival. Patients with LRR experienced significantly shorter time to recurrence and

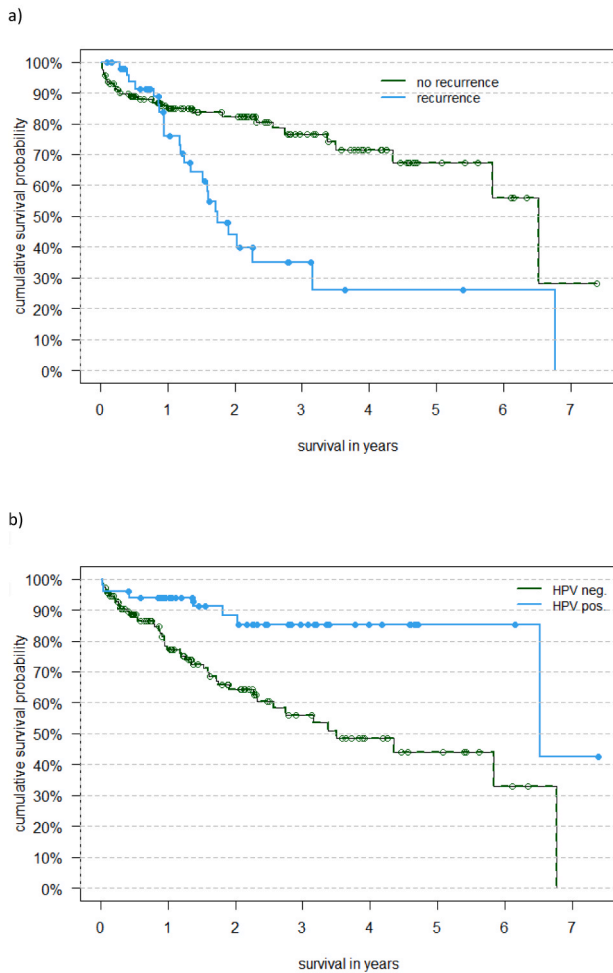


Fig. 4. Overall survival in patients with locoregional recurrence vs. patients without locoregional recurrence (a), and HPV positive vs. HPV negative patients (b).

progression-free survival compared to non-LRR patients ($p < 0.001$). These findings underscore the aggressive nature of LRR and its contribution to overall disease progression and also the need for early intervention and close monitoring in high-risk patients. Despite the observed differences in survival metrics, overall survival (OS) did not significantly differ between LRR and non-LRR patients ($p = 0.092$). While a trend toward shorter OS in LRR patients was noted, this result suggests that factors beyond LRR alone may play a role in determining long-term

survival.

Data in the literature regarding prognostic factors are inconsistent. In a retrospective multicenter study including oropharyngeal cancer patients, HPV-negative status and locoregional recurrence had a negative impact on OS in multivariate analysis, as did distant metastases [18]. On the other hand, Sweeny et al. reported no difference in OS rates when stratified by HPV status or smoking, but found tumor stage and gastrostomy dependence significantly affected OS in oropharyngeal cancer patients [18]. In addition, cervical lymph node metastasis, clinical stage, and solitary versus multisite recurrence were identified as key survival factors [19,20]. In another recent study by Choi et al, neither p16 status nor site of recurrence affected OS [21].

In our analysis, the concurrent application of Chemotherapy improved PFS and reduced LRR, while HPV positivity benefited OS, PFS, and LRR. Distant metastases negatively impacted all outcomes, and LRR showed a trend toward worse OS but was not statistically significant.

Salvage treatment remains a critical issue. In our series, most patients received Immunotherapy, with two patients experiencing grade 5 pneumonia from nivolumab. Reirradiation was feasible in only seven patients, further emphasizing the challenges in effective salvage treatment options.

These findings highlight the need for improved therapeutic strategies targeting LRR, given its clear association with poorer disease control. Future research should focus on identifying predictive markers for recurrence and optimizing treatment approaches to prolong survival in high-risk patients. Additionally, further studies with larger cohorts are necessary to validate these results and refine clinical management strategies for patients experiencing LRR.

Conclusion

LRR is a major challenge, occurring mostly within the first year post-RT, particularly in HPV-negative patients. Distant metastases do not significantly affect survival after LRR, with local progression being the main cause of death. Marginal LRR remains a concern, emphasizing the need for improved imaging, such as daily image-guidance. However, salvage options are limited, with modest immunotherapy benefits and reirradiation feasibility in selected cases. Considering HPV's prognostic significance, personalized treatment strategies are essential for enhancing patient outcomes.

Human ethics and consent to participate declarations

Not applicable.

Ethics

The study was performed in accordance with the Declaration of Helsinki Version 2013. The current study was approved from our

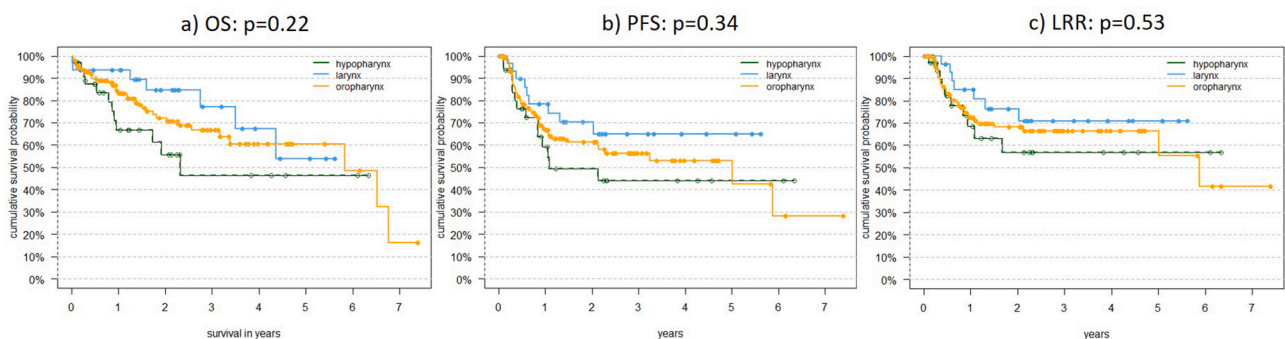


Fig. 5. Subsite-specific Kaplan-Meier analyses based on the tumor subsites (oropharynx, larynx, hypopharynx) regarding (a) overall survival (OS: $p = 0.22$), (b) progression free survival (PFS: $p = 0.34$) and (c) locoregional recurrence (LRR: $p = 0.53$).

Table 3

Multivariate analysis with Cox regression model to identify potential risk factors associated with locoregional recurrence, progression-free survival (PFS), and overall survival (OS).

Cox-regression	OS			PFS			LRR		
Variables	p-value	CI	HR	p-value	CI	HR	p-value	CI	HR
Combined Chemotherapy	NS			0.001	−1.17	0.31	0.001	−1.86	0.31
HPV status	0.010	−1.09	0.34	0.028	−0.87	0.42	0.021	−0.91	0.40
cT2 stage	NS			NS			NS		
Distant metastases	0.002	0.94	2.55	0.000	1.34	3.82	0.000	0.75	3.82
Locoregional recurrence	0.072	0.55	1.73	—			—		

OS: overall survival; PFS: progression-free survival; LRR: locoregional recurrence; HPV: human papilloma virus; NS: not significant.

internal review board of Justus-Liebig University of Giessen (ethic approval AZ 73/24 – Ethik-Kommission des Fachbereiches Medizin).

Permission notes

We did not use any material in the manuscript that is not original content.

CRedit authorship contribution statement

Linda Agolli: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Visualization, Writing – original draft. **Luise Reinhard:** Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Visualization, Writing – original draft. **Christine Langer:** Resources, Validation, Writing – review & editing. **Christoph Arens:** Methodology, Resources, Validation, Writing – review & editing. **Gabriele A. Krombach:** Resources, Supervision, Writing – review & editing. **Sebastian Harth:** Resources, Supervision, Writing – review & editing. **Andreas Lurtz:** Data curation, Project administration, Resources, Software. **Ann-Katrin Exeli:** Data curation, Project administration, Resources, Software. **Stefan Gattenlöhner:** Resources, Validation, Writing – review & editing. **Daniel Habermehl:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctro.2025.101026>.

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