Salvage surgery for recurrence after radiotherapy for squamous cell carcinoma of the head and neck

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Salvage Surgery for Recurrence after Radiotherapy for Squamous Cell Carcinoma of the Head and Neck

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Abstract

Objective. Most studies that report on salvage surgery after primary radiotherapy for head and neck squamous cell carcinoma (HNSCC) are small and heterogeneous. Subsequently, some relevant questions remain unanswered. We specifically focused on (1) difference in prognosis per tumor subsite, corrected for disease stage, and (2) differences in prognosis after salvage surgery for local, regional, and locoregional recurrences.

Study Design. Retrospective analysis.


Subjects and Methods. Patients treated with salvage surgery for HNSCC recurrence after (chemo)radiotherapy.

Results. In total, 189 patients were included. Five-year overall survival (OS) was 33%, and median OS was 18 (95% confidence interval [CI], 11-26) months. Treatment-related mortality was 2%. Larynx carcinoma was associated with more favorable local (adjusted hazard ratio [HR] = 4.02; 95% CI, 1.46-11.10; \( P = .007 \)) and locoregional control (adjusted HR = 5.34; 95% CI, 1.83-15.61; \( P = .002 \)) than pharyngeal carcinoma. American Society of Anesthesiologists (ASA) score (\( 3 \) vs \( 1-2 \): adjusted HR = 3.04; 95% CI, 1.17-7.91; \( P = .023 \)), pT stage (\( 3-4 \) vs \( 1-2 \): adjusted HR = 4.41; 95% CI, 1.65-11.82; \( P = .003 \)), and salvage surgery for locoregional recurrences (locoregional vs local: adjusted HR = 3.81; 95% CI, 1.13-11.82; \( P = .021 \)) were independent predictors for disease-free survival (DFS).

Conclusion. Salvage surgery for larynx carcinoma, regardless of disease stage and other prognostic factors, results in more favorable loco(regional) control but not favorable DFS than pharyngeal carcinoma. The observed difference in DFS between salvage surgery for local and regional recurrences was not significant after correction for confounders. However, survival following salvage surgery for locoregional disease is significantly worse. For this subgroup, we propose to consider T status and comorbidity for clinical decision making, as high pT stage and ASA score are independent predictors for worse DFS.

Keywords
salvage surgery, head and neck squamous cell carcinoma, radiotherapy, chemoradiation

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In the United States and Europe, head and neck squamous cell carcinoma (HNSCC) accounts for 3% to 4% of all malignancies.1,2 Worldwide, 380,000 patients die of HNSCC each year.3 Radiotherapy with or without concurrent chemotherapy has been established as primary treatment for a variety of subsites and stages. However, loco(regional) failure occurs in up to 50% of patients.4 For these patients, salvage surgery is considered the best treatment option.
possible curative treatment. Most studies regarding salvage surgery are small and heterogeneous, still leaving some clinically relevant questions unanswered. First, salvage surgery for laryngeal tumor recurrence is believed to result in better survival compared to other subsites, partly because recurrences from other subsites may be more difficult to resect due to nearby anatomical structures (eg, carotid artery and skull base). Therefore, we aimed to investigate which variable (eg, tumor site, tumor stage, and R0 dissection) is key for clinical outcome after salvage surgery for advanced disease. After reviewing literature, we found that patient and tumor subgroups are frequently presented by stage or by subsite often without correcting for these factors as being confounders. Hence, it remains to be determined whether the difference in prognosis per tumor subsite remains significant after adjusting for prognostic factors such as stage of disease. Second, outcome after salvage surgery is commonly reported by combining local and regional tumor recurrence data together. However, both type of recurrences are different entities that require different therapeutic approaches; hence, a comparison of prognosis is warranted. To address these topics, we performed a retrospective analysis of all patients treated with salvage surgery for tumor recurrence in our institute between 2000 and 2016. To minimize heterogeneity, we only selected patients who received salvage surgery after primary curative radiotherapy or chemoradiation as index treatment.

**Methods**

**Patients**

We retrospectively analyzed all patients treated in the Netherlands Cancer Institute between 2000 and 2016. The study had official institutional research board approval (Medisch-Ethische Toetsingscommissie van Stichting Nederlands Kankerinstituut–Het Antoni van Leeuwenhoek Ziekenhuis [METC-AVL]); all procedures were in accordance with the 1964 Helsinki declaration and its later amendments. Amendable patients received salvage surgery (with or without postoperative reirradiation) with curative intent for local, regional, or locoregional HNSCC recurrence after primary curative radiotherapy or chemoradiation. We excluded patients treated with salvage surgery in combination with photodynamic therapy (PDT, n = 5) and patients with oral cavity carcinoma (n = 17), as radiation is not standard of care for these patients. Also, those patients with no vital tumor in the resection specimen (n = 31) were excluded. Last, patients who received salvage surgery for second primary tumors were excluded (n = 2), defined as tumor recurrence more than 5 years after index treatment. In total, 194 patients were included. In 5 patients, the tumor was irresectable during surgery. These R2 resections were also excluded, leaving 189 patients for final analysis. We defined tumor <1 mm relative to ink as an R1 resection.5,6 We did not consider a margin containing dysplasia a positive margin. When initial frozen-section margins were positive for tumor and further resection resulted in negative frozen-section margins, this was considered a negative resection margin. We sampled the frozen section from the surgical bed rather than from the main specimen. When possible, the preraditherapy margin was resected. Physical status was scored according to American Society of Anesthesiologists (ASA) and World Health Organization (WHO) performance score. All patients were staged (both at initial and recurrent stage) based on clinical examination, ultrasonography, and computed tomography (CT) or magnetic resonance imaging (MRI) and according to the American Joint Committee on Cancer (AJCC) staging as they were at the time of diagnosis. After 2007, FDG-PET scan was gradually introduced.

**Outcome Measures**

Primary outcome measures were locoregional control (LRC), disease-free survival (DFS), and overall survival (OS). We specifically focused on comparison of the outcome between subgroups: residual vs recurrent disease, local vs regional vs locoregional recurrences, larynx vs pharyngeal carcinoma, and early vs advanced disease. Outcomes were evaluated from the date of salvage surgery.

**Statistical Methods**

Survival curves were calculated with the Kaplan-Meier method and compared between subgroups using the log-rank test. Bivariable Cox models were used to find confounders (ie, covariates that changed the tumor subsite and recurrence localization comparison univariable hazard ratios by more than 10%) and prognostic factors (ie, covariates with P < .10). All potential variables are listed in the corresponding tables for multivariate analysis. Final multivariable models included all prognostic factors and confounders. Patients with missing covariate information were excluded from the models. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS, Inc, an IBM Company, Chicago, Illinois).

**Results**

**Demographics**

In total, 189 patients were included (Table 1). Mean age was 61 years, and 148 (78%) were male. Ninety-nine patients (52%) had larynx carcinoma and 26 had hypopharynx carcinoma (14%). Eleven of 64 oropharynx carcinoma were human papillomavirus (HPV) related. In 71% of patients, tumors were advanced stage at diagnosis. The median follow-up of patients alive was 63 (95% confidence interval [CI], 56-70) months. Two patients (1%) were lost to follow-up (LTFU) after a median of 1 and 13 months (Table 2).

**Treatment**

In total, 116 patients (61%) were treated with radiotherapy alone as index treatment, 69 patients (37%) received concurrent cisplatin, and 4 patients (2%) had concurrent epidermal growth factor receptor (EGFR) inhibition with
etuximab. Radiotherapy consisted of an elective dose of 46 Gy in 23 fractions (sequential) or 54.25 Gy in 35 fractions (concomitant) followed by a boost on the primary tumor and involved nodes, resulting in a total dose of 70 Gy. All patients received the prescribed dose.

Eighty patients (42%) received salvage surgery for resid-ual disease (ie, within 6 months after radiotherapy). The other 109 patients (58%) received salvage surgery for recurrent disease within 6 months to 5 years after radiotherapy. For salvage treatment, 123 patients (65%) received local surgery. A neck dissection was performed in 148 patients (89 selective and 59 modified radical neck dissections). Sixty-six patients (35%) received a transposition flap for reconstruction. After surgery, 10 patients (5%) received postoperative reirradiation.

### Table 1. Patient, Tumor, and Treatment Characteristics at Date of Diagnosis or Salvage Surgery.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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</thead>
<tbody>
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</tr>
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<td>0-1</td>
<td>152 (80)</td>
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<td>2-3</td>
<td>36 (19)</td>
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<tr>
<td>WHO performance</td>
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### Table 2. Tumor Recurrence at the End of Follow-up and Cause of Death.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Variable</th>
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</thead>
<tbody>
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<td>Loco(regional) recurrence localization</td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>29 (15)</td>
</tr>
<tr>
<td>Regional</td>
<td>31 (16)</td>
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<tr>
<td>Locoregional</td>
<td>12 (6)</td>
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<tr>
<td>Distant metastasis</td>
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<tr>
<td>No</td>
<td>155 (82)</td>
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<tr>
<td>Yes</td>
<td>34 (18)</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td></td>
</tr>
<tr>
<td>Isolated</td>
<td>21 (62)</td>
</tr>
<tr>
<td>Plus local(regional) recurrence</td>
<td>13 (38)</td>
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<tr>
<td>Patient status</td>
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<tr>
<td>Alive</td>
<td>55 (29)</td>
</tr>
<tr>
<td>Diseased</td>
<td>132 (70)</td>
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<tr>
<td>LTFU</td>
<td>2 (1)</td>
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<tr>
<td>Cause of death</td>
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</tr>
<tr>
<td>Recurrent disease</td>
<td>90 (68)</td>
</tr>
<tr>
<td>Second primary (local and distant)</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Intercurrent disease\textsuperscript{b}</td>
<td>19 (14)</td>
</tr>
<tr>
<td>Treatment complication\textsuperscript{c}</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (7)</td>
</tr>
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</table>

Abbreviation: LTFU, lost to follow-up.
\textsuperscript{a}Not all percentages sum up exactly to 100% due to rounding errors.
\textsuperscript{b}Known disease, not tumor related.
\textsuperscript{c}Aspiration pneumonia (n = 1) and blowout (n = 2).

Cetuximab. Radiotherapy consisted of an elective dose of 46 Gy in 23 fractions (sequential) or 54.25 Gy in 35 fractions (concomitant) followed by a boost on the primary tumor and involved nodes, resulting in a total dose of 70 Gy. All patients received the prescribed dose.

Eighty patients (42%) received salvage surgery for residual disease (ie, within 6 months after radiotherapy). The other 109 patients (58%) received salvage surgery for recurrent disease within 6 months to 5 years after radiotherapy.

For salvage treatment, 123 patients (65%) received local surgery. A neck dissection was performed in 148 patients (89 selective and 59 modified radical neck dissections). Sixty-six patients (35%) received a transposition flap for reconstruction. After surgery, 10 patients (5%) received postoperative reirradiation. Table 1 illustrates a detailed overview of treatment characteristics.

**Loco(regional) Control**

Overall, 72 patients were diagnosed with local, regional, or locoregional recurrence after salvage surgery. The locoregional control (LRC) rate at 5 years was 57% (Figure 1). After controlling for prognostic and confounding factors (Table 3), larynx carcinoma was associated with a more favorable locoregional control than pharyngeal carcinoma.
(adjusted hazard ratio [HR] = 5.34; 95% CI, 1.83-15.61; \( P = .002 \)). We found salvage surgery for locoregional recurrences (adjusted HR = 4.01; 95% CI, 1.15-14.03; \( P = .030 \)) associated with worse LRC compared to salvage for only local or regional recurrences.

We separately analyzed local control for those 122 patients (65%) receiving salvage surgery for local tumor recurrence, with or without synchronous lymph node metastases. In this group, local control rate at 5 years was 72%. After controlling for prognostic factors and confounders (Table 3), pharyngeal carcinoma again showed worse local control than larynx carcinoma (adjusted HR = 4.02; 95% CI, 1.46-11.10; \( P = .007 \)), and receiving adjuvant reirradiation after salvage surgery (because of pathological risk factors for recurrence) was associated with worse local control in comparison to no reirradiation (adjusted HR = 9.08; 95% CI, 1.16-71.20; \( P = .036 \)).

In total, 99 patients (52%) received a neck dissection for regional recurrence, with or without synchronous local recurrence. Regional control rate at 5 years was 61%. There were no significant predictors for regional control in multivariable analysis (data not shown).

**Disease-Free Survival**

Overall, the 5-year DFS rate was 32% (Figure 1). As shown in Figure 2, subgroup analysis resulted in significant differences between DFS curves (all \( P \leq .03 \)).

The 5-year DFS rates for larynx and pharyngeal carcinoma were 38% and 26%, respectively. When controlling for prognostic and confounding factors, we found high ASA score (≥3) at salvage surgery (adjusted HR = 3.04; 95% CI, 1.17-7.91; \( P = .023 \)), T3 to T4 tumors at recurrence (adjusted hazard ratio [HR] = 5.34; 95% CI, 1.83-15.61; \( P = .002 \)), and receiving adjuvant reirradiation after salvage surgery (because of pathological risk factors for recurrence) was associated with worse local control in comparison to no reirradiation (adjusted HR = 9.08; 95% CI, 1.16-71.20; \( P = .036 \)).

**Table 1.** (continued)

<table>
<thead>
<tr>
<th>Variable</th>
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</thead>
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<td>47 (25)</td>
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<td>65 (34)</td>
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<td>4</td>
<td>72 (38)</td>
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<td>RT</td>
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<tr>
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<td>TTRc</td>
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<td>Mean (SD), mo</td>
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<td>Residual</td>
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<tr>
<td>Recurrent</td>
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<tr>
<td>Recurrence localization after RT</td>
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<td>Local</td>
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<td>Transoral excision</td>
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<td>TLE</td>
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<td>TLE + (partial) glossectomy</td>
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<tr>
<td>TLE + (partial) pharyngectomy</td>
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<td>Composite resection</td>
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<td>No local resection</td>
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<tr>
<td>Surgery, regional neck dissection</td>
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<td>Selective</td>
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<tr>
<td>Flap reconstruction</td>
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<td>Free radial forearm flap</td>
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<td>Gastric pull-up</td>
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<td>Free fibula flap</td>
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<td>M. rectus abdominis flap</td>
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<td>M. lattissimus dorsi flap</td>
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<td>10 (5)</td>
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*Values are presented as number (%) unless otherwise indicated. Not all percentages sum up exactly to 100% due to rounding errors.
*Abbreviations: AJCC, American Joint Committee on Cancer; ASA, American Society of Anesthesiologists; BRT, bioradiotherapy with cetuximab; CRT, chemoradiotherapy; HPV, human papillomavirus; PLE, partial laryngectomy; RT, radiotherapy; TLE, total laryngectomy; TTR, time to recurrence; WHO, World Health Organization.
*Based on pathology report.
*Calculated from end of radiotherapy until first recurrence. Residual: <6 months; recurrent: 6 months to 5 years.
*Defined as tumor <1 mm relative to ink from the resection margin.
Table 3. Multivariate Analysis for Loco(regional) Control.

<table>
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<td>P Value</td>
<td>HR (95% CI)</td>
<td>P Value</td>
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<td>≥3</td>
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(continued)
Table 3. (continued)

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<td>Reirradiation</td>
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<td>.036</td>
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</table>

Abbreviations: AJCC, American Joint Committee on Cancer; ASA, American Society of Anesthesiologists; BRT, bioradiotherapy with cetuximab; CI, confidence interval; CRT, chemoradiotherapy; ECE, extracapsular extension; HPV, human papillomavirus; HR, hazard ratio; RT, radiotherapy; TTR, time to recurrence; WHO, World Health Organization; —, all other variables (see footnote “a”).

\(^a\)Only prognostic covariates \(P < .10\) in univariate analysis or confounding covariates that changed the treatment group recurrence localization hazard ratio by more than 10% were further included in multivariate analysis. Patients with missing covariate information were excluded from the models. All statistically significant variables in multivariate analysis were highlighted in bold.

\(^b\)Analyzed as a continuous variable. For categorical variables, the first category is the reference category.

\(^c\)Calculated from end of radiotherapy until first recurrence. Residual: <6 months; recurrent: 6 months to 5 years.

\(^d\)Defined as tumor <1 mm relative to ink from the resection margin.

Within 100 days after end of treatment, 3 patients (2%) died of treatment-related complications. One patient died of respiratory insufficiency after severe aspiration during postoperative brachytherapy reirradiation (after the 16th fraction of 3 Gy). Two other patients died of arterial blow-out 27 to 45 days after surgery, despite pectoralis major (PM) flap reconstruction. All patients who died of treatment-related toxicity were ASA-II. One patient was WHO 1; the other 2 patients were WHO 0.

**Discussion**

The current study is one of the largest cohort studies describing prognostic features related to salvage surgery after primary radiotherapy or chemoradiation for HNSCC. In a cohort of 189 patients, the 5-year OS rate was 33% and the treatment-related mortality was 2%. Our aim was to focus on 2 key parameters for guidance in clinical decision making, which we further discuss in the next paragraphs. First, we have shown that salvage surgery for larynx carcinoma, when corrected for other variables (eg, disease stage), results in a more favorable loco(regional) control than for other HNSCC subsites. Second, salvage surgery for local tumor recurrence results in improved crude DFS in comparison to regional recurrences. However, this difference was not statistically significant after adjusting for prognostic and confounding factors. Survival following salvage surgery for locoregional recurrences is significantly worse than for local or regional recurrences. For this subgroup, we suggest to offer treatment only to highly motivated patients or patients with low additional risk for recurrence. We propose to consider T status and comorbidity for clinical decision making, as high pT stage and ASA score are independent predictors for worse DFS.

In our research, salvage surgery for larynx carcinoma results in a favorable locoregional control but not favorable survival compared to pharyngeal carcinoma. This might suggest that tumor subsite is of less importance when all prognostic factors (eg, tumor stage) are taken into account.
### Table 4. Multivariate Analysis for Disease-Free Survival.a

<table>
<thead>
<tr>
<th>Variable</th>
<th>2 Year, %</th>
<th>5 Year, %</th>
<th>Univariable P Value</th>
<th>Multivariable Model</th>
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<td>HR (95% CI)</td>
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consideration. However, with 189 patients included, our sample size may still be too small to reveal a significant survival difference. Our data are in agreement with results from a prospective study of 109 patients by Goodwin,7 who also found no significant difference in DFS. Moreover, Clark et al8 showed extracapsular extension (ECE) but not the tumor site to be a significant negative predictor for disease specific survival (DSS). Wulff et al9 and Woodard et al10 both found pharyngeal carcinoma associated with unfavorable OS than larynx carcinoma in univariable but not in multivariable analysis. Three other groups did find significant unfavorable survival for hypopharynx carcinoma but included both primary and recurrent tumors.11 did not describe the statistical significance,12 or included only 2 hypopharynx carcinomas and 1 oropharynx carcinoma.13 Specifically, for oropharyngeal carcinoma, we evaluated the impact of HPV on outcome and found no prognostic effect. In the primary treatment setting, outcome clearly depends on HPV status, but whether this also goes for recurrent tumors in the salvage surgery setting remains unclear. In a study by Patel et al14 concerning salvage surgery for locally recurrent oropharyngeal cancer, 19 of 32 evaluable oropharynx carcinomas (59%) were HPV positive. Interestingly, the authors also did not find HPV status associated with either OS or DFS.

Local and regional tumor recurrences are different entities that require different surgical approaches and may consequently result in a different outcome. We therefore compared outcome after salvage surgery for local vs regional recurrences and found no significant difference when adjusted for prognostic and confounding factors. However, those patients receiving salvage surgery for locoregional disease (either residual or recurrent) had a disappointing median survival of 8 months. After 2 and 5 years, only 23% and 13% of these patients were alive and disease free, respectively. These results are disappointing, especially because salvage surgery may be accompanied by significant morbidity. We therefore suggest that treatment in this setting should be offered only to a limited group of patients who are really fit for surgery and/or have a low additional risk for treatment recurrence (eg, large local tumors and high comorbidity, based on our multivariable analysis for DFS). Altogether, patients requiring salvage surgery for advanced stage recurrent disease after radiotherapy have limited chances of success and may benefit from novel treatment options. Currently, we are running an immunotherapy trial for advanced stage primary and recurrent HNSCC. In this study, anti-PD1 with or without anti-CTLA4 is given 2 times in a 2-week interval prior to primary and salvage surgery (NCT03003637). By combining immunotherapy with standard of care, we aim to improve both locoregional control and survival for patients urgently in need for better treatment options.

Resection margins after salvage surgery are reported tumor positive in up to 18% to 56% of patients,14-16 possibly because recurrent disease is typically multifocal and can spread with microscopic deposits.17 Positive resection margins are therefore predictive for decreased DFS, OS, and DSS9,18,19 Consequently, in our institute, reirradiation is always considered in those cases. In our patient cohort, we evaluated the influence of reirradiation on treatment outcome and found that adjuvant reirradiation after salvage surgery was associated with worse local control in comparison to no reirradiation. First, this paradoxical finding is because only those patients with extremely poor pathological prognostic risk factors were treated with reirradiation. Second, there were 28 patients with an R1 resection, and only 10 patients received reirradiation. We are very cautious in applying reirradiation, as this may be accompanied by significant morbidity.20 This treatment heterogeneity, more specifically the absence of reasons given for the indication or not for reirradiation, resulted in a considerable

Table 4. (continued)

<table>
<thead>
<tr>
<th>Variable</th>
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<th>5 Year, %</th>
<th>Univariable P Value</th>
<th>Multivariable Model</th>
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<td>Year of treatmentb</td>
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Abbreviations: AJCC, American Joint Committee on Cancer; ASA, American Society of Anesthesiologists; BRT, bioradiotherapy with cetuximab; CI, confidence interval; CRT, chemoradiotherapy; ECE, extracapsular extension; HPV, human papillomavirus; HR, hazard ratio; RT, radiotherapy; TTR, time to recurrence; WHO, World Health Organization; —, all other variables (see footnote “a”).

Only prognostic covariates P < .10 in univariate analysis or confounding covariates that changed the treatment group recurrence localization hazard ratio by more than 10% were further included in multivariate analysis. Patients with missing covariate information were excluded from the models. All statistically significant variables in multivariable analysis were highlighted in bold.

aDefined as tumor <1 mm relative to ink from the resection margin.

bAnalyzed as a continuous variable. For categorical variables, the first category is the reference category.

cCalculated from end of radiotherapy until first recurrence. Residual: <6 months; recurrent: 6 months to 5 years.
confidence interval surrounding the hazard ratio of reirradiation on local control (1.16-71.20). Altogether, we believe reirradiation may positively influence treatment outcome and should be weighed against significant morbidity by both patient and physician.

It is generally known that a short disease-free interval after radiotherapy implies a more aggressive tumor behavior and is associated with unfavorable treatment outcome. Therefore, we evaluated time to recurrence (TTR) as a prognostic variable for treatment outcome. In daily clinics, tumors are often considered residual (0-6 months) or recurrent (6 months to 5 years) after index treatment. When we analyzed TTR as a categorical variable, we found residual tumors to be correlated with worse DFS than recurrent tumors (data not shown). This is in line with findings already made by others who analyzed TTR as a categorical variable.\textsuperscript{21-23} Interestingly, when we analyzed TTR as a continuous variable in our multivariate analysis, we lost evidence to prove a significant effect on prognosis. Of note, in agreement, there was also no significant impact of time to presalvage recurrence on disease-free survival after salvage surgery in the prospective analysis published by Goodwin.\textsuperscript{7}

**Limitations**

The results presented in this study are subject to several limitations. On one hand, data were extracted retrospectively and therefore prone to selection bias. Since we included only patients suitable for salvage surgery, results cannot be extrapolated to inoperable recurrences or reoperation for secondary tumors. On the other hand, our findings may be skewed toward a more beneficial clinical outcome, as patients with larynx carcinoma were relatively

---

**Figure 2.** Disease-free survival (DFS). Differences between survival curves were tested by log-rank test. (A) Residual vs recurrent disease: 5-year rate 26% vs 37%, \( P = .003 \). (B) Local vs regional vs locoregional recurrence: 5-year rate 43% vs 27% vs 13%, \( P < .001 \). (C) Laryngeal vs pharyngeal tumors: 5-year rate 38% vs 26%, \( P = .034 \). (D) Early vs advanced disease (at recurrence): 5-year rate 62% vs 22%, \( P < .001 \).
overrepresented. Moreover, missing data are inherent to retrospective studies. Toxicity and functional outcome were underreported and therefore not presented in this study. Also, we were not able to evaluate quality of life (QoL) as no validated questionnaires at baseline were taken. For future research, prospective toxicity scores and evaluation of the impact of salvage surgery on quality of life are recommended. Furthermore, we used ASA and WHO performance score as a surrogate for physical status, as the anesthesiologist routinely scored both before surgery. However, neither ASA nor WHO performance are the best measures of comorbidity. We acknowledge that it is better to include, for instance, the Charlson Comorbidity Index or Adult Comorbidity Evaluation 27, and severity of comorbidity has been adequately shown to affect outcomes in the salvage setting.24 However, in an attempt to extract comorbidity data from clinical chart review, we encountered considerable missing and conflicting information. Given the retrospective nature of this study, we did not feel confident enough about the available data. Last, although we report on a relatively large number of patients, the subgroups by site are quite small for stage correction in each category. This might explain why the difference in DFS between tumor subsites was not statistically significant in the multivariable model.

Conclusions
Salvage surgery for larynx carcinoma, regardless of disease stage and other confounding factors, results in more favorable locoregional control but not favorable DFS compared to pharyngeal carcinoma. We found no difference between outcome after salvage surgery for local and regional recurrences after correction for confounders. However, survival following salvage surgery for locoregional disease is significantly worse. For this subgroup, we propose to consider T status and comorbidity for clinical decision making, as high pT stage and ASA score are independent predictors for worse DFS.

Author Contributions
Joris B. W. Elbers, design of the work, analysis, interpretation of data, drafting and revising, final approval, and accountability for the work; Abraham Al-Mamgani, design of the work, interpretation of data, acquisition, drafting and revising, final approval, and accountability for the work; Michiel W. M. van den Brekel, interpretation of data, revising, final approval, and accountability for the work; Katarzyna Joźwiak, design of the work, analysis, revising, interpretation of data, drafting and revising, final approval, and accountability for the work; J. P. de Boer, acquisition, interpretation of data, revising, final approval, and accountability for the work; Peter J. F. M. Lohuis, acquisition, interpretation of data, revising, final approval, and accountability for the work; Stefan M. Willems, interpretation of data, revising, final approval, and accountability for the work; Marcel Verheij, interpretation of data, revising, final approval, and accountability for the work; Charlotte L. Zuur, design of the work, interpretation of data, acquisition, drafting and revising, final approval, and accountability for the work.

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