*The Laryngoscope*


# Benefit of Postoperative Radiotherapy for Early Tumors With Single Ipsilateral Lymph Node Metastasis

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**Objectives/Hypothesis:** Indication for postoperative radiotherapy in patients with locally circumscribed tumors (pT1–pT2) and a single ipsilateral lymph node metastasis (pN1) is debatable. The aim of this study was to evaluate the oncological long-term outcome of patients with pT1-pT2 pN1 squamous cell carcinoma (SCC) of the oral cavity, the oropharynx, and the hypopharynx without extracapsular spread (ECS) after a margin-negative surgical resection, who either received or did not receive postoperative (chemo)radiotherapy.

**Study Design:** Retrospective case series.

**Methods:** The oncological outcome of patients with pT1-pT2 pN1 SCC without ECS was evaluated retrospectively. All patients underwent primary tumor resection that included transoral laser microsurgery and neck dissection at an academic tertiary referral center.

**Results:** Of 65 identified patients treated between 1986 and 2015 (18 oral cavity, 30 oropharynx, 17 hypopharynx), 21 (32%) received postoperative radiotherapy, and 44 (68%) were treated by surgery alone. The group of patients receiving postoperative treatment showed a significantly superior 5-year disease-specific (94.4% vs. 73.2%, $P = .029$) and recurrence-free survival (85.2% vs. 43.2%, $P = .002$), as well as a higher local control rate (90.2% vs. 64.9%, $P = .042$). The overall survival was 71.4% vs. 62.6% ($P = .53$). The mean follow-up was 80.7 months.

**Conclusions:** Patients with locally circumscribed carcinomas and a single ipsilateral ECS-negative lymph node metastasis seem to benefit from postoperative radiotherapy.

**Key Words:** Postoperative radiotherapy, head and neck cancer, early tumor, single lymph node metastasis, multimodal treatment concept.

**Level of Evidence:** 4

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## INTRODUCTION

Minimally invasive transoral laser microsurgery (TLM) is an effective therapeutic option for locally circumscribed squamous cell carcinoma (SCC) of the oral cavity, the oropharynx, and the hypopharynx, and is often completed with a selective neck dissection (ND).[1–3] Postoperative (chemo)radiotherapy (PORT) is well established in cases of advanced neck disease and/or adverse features like extracapsular tumor spread (ECS) as well as positive surgical margins.[4–7] Nevertheless, it is debatable for patients with locally circumscribed primaries (pT1–pT2) with a single ipsilateral lymph node metastasis (pN1) and without the previously mentioned adverse features.[6,8] One reason is that no results of prospective randomized trials addressing this topic are available. Only a few retrospective studies[9–14] provide data upon which therapeutic recommendations and rational clinical decision making can be based.

The aim of the study was to provide a detailed presentation of long-term oncological results of this rare patient group that either received or did not receive PORT.

## MATERIALS AND METHODS

### *Patients and Therapy*

A retrospective analysis was conducted of patients with pT1–pT2 pN1 M0 categorized SCC of the oral cavity (OSCC), oropharynx (OPSCC), and hypopharynx (HPSCC) without ECS, who received primary surgical treatment at an academic tertiary referral center. Time span of inclusion was between August 1986 and October 2015, with subsequent systematic follow-up. Cases were identified, and data were obtained from the hospital's cancer database and original medical records. This study was approved by the institutional review board (Ethics Committee of the University Medical Center Göttingen) according to the national regulation.

Cases with non-SCC, previous or simultaneous secondary malignancies, simultaneous distant metastases, primaries treated primarily in another hospital, and/or those treated by



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conventional surgery, flap reconstruction, primary (chemo-)radiotherapy, and with palliative intent were excluded. Of the remaining 807 patients who received primary $CO_2$ TLM for pT1–pT4a oral, oropharyngeal, or hypopharyngeal carcinomas, 430 (53.3%) were diagnosed with pT1–pT2 tumors. Among these, 76 (17.7%) revealed a single ipsilateral lymph node metastasis after histopathological assessment. From this group, 11 cases with ECS were excluded. Finally, 65 patients met the inclusion criteria. Data of some patients were partially evaluated in previous studies.[1,2,9,15] Laryngeal SCC were excluded, because only four patients met the inclusion criteria.

### *Staging and Surgical Treatment*

Preoperative staging to evaluate tumor burden and to detect regional and distant metastasis or synchronous primary tumors was performed as described previously.[2] Diagnosis was confirmed by histopathological assessment. Disease was staged in accordance with the seventh edition of classification of the Union for International Cancer Control[16] and the American Joint Committee on Cancer.[17]

Details on surgical technique were described previously by Steiner et al.[18–20] In all cases, negative-margin resection status (R0) was ensured by histopathological assessment.

### *Treatment of the Neck*

Neck dissections were described based on the standardized terminology.[21,22] Indications for a selective ND comprised a carcinoma's infiltration depth of ≥3 mm and/or suspicious lymph nodes detected in the course of preoperative diagnostic assessment. In general, a bilateral ND was performed in cases of a midline localization of the local primary and/or clinically suspicious lymph nodes bilaterally.

### *Histological Assessment*

For patients with OPSCC, especially in the early years, molecular diagnostics of human papillomavirus (HPV) status or p16 expression was not performed routinely. Thus, if sufficient

TABLE I.
Patient and Disease Characteristics and Follow-up Data Stratified by Treatment Group.

| Characteristic | PORT, n = 21 | No PORT, n = 44 | *P* Value* | Total, N = 65 |
|---|---|---|---|---|
| All patients, no. (%) | 21 (32.3%) | 44 (67.7%) | | 65 (100%) |
| Year of initial diagnosis | | | | |
| 1986–2000 | 14 (66.7%) | 32 (72.7%) | .615 | 46 (70.8%) |
| 2001–2015 | 7 (33.3%) | 12 (27.3%) | | 19 (29.2%) |
| Gender | | | | |
| Male | 17 (81.0%) | 36 (81.8%) | .933 | 53 (81.5%) |
| Female | 4 (19.0%) | 8 (18.2%) | | 12 (18.5%) |
| Age, yr, mean ± SD | 57.7 ± 7.5 | 55.9 ± 8.1 | | 56.5 ± 7.9 |
| Median (minimum–maximum) | 59.1 (42.8–68.3) | 55.3 (39.0–77.3) | | 57.0 (39.0–77.3) |
| <57 | 8 (38.1%) | 25 (56.8%) | .158 | 33 (50.8%) |
| >57 | 13 (61.9%) | 19 (43.2%) | | 32 (49.2%) |
| Main localizations | | | | |
| OSCC | 4 (19.0%) | 14 (31.8%) | .069 | 18 (27.7%) |
| OPSCC | 14 (66.7%) | 16 (36.4%) | | 30 (46.2%) |
| p16 positive | 3 (21.4%) | 6 (37.5%) | .569 | 9 (30.0%) |
| p16 negative | 2 (14.3%) | 2 (12.5%) | | 4 (13.3%) |
| p16 undetermined | 9 (64.3%) | 8 (50.0%) | | 17 (56.7%) |
| HPSCC | 3 (14.3%) | 14 (31.8%) | | 17 (26.2%) |
| T categorization | | | | |
| pT1 | 8 (38.1%) | 20 (45.5%) | .575 | 28 (43.1%) |
| pT2 | 13 (61.9%) | 24 (54.5%) | | 37 (56.9%) |
| Histopathologic differentiation | | | | |
| High | 1 (4.8%) | 0 (0.0%) | .285 | 1 (1.5%) |
| Moderate | 14 (66.7%) | 34 (77.3%) | | 48 (73.8%) |
| Poor | 6 (28.6%) | 10 (22.7%) | | 16 (24.6%) |
| Tumor size within the lymph node, n = 44 | | | | |
| Micrometastasis | 1 (7.7%) | 9 (29.0%) | .123 | 10 (22.7%) |
| Macrometastasis | 12 (92.3%) | 22 (71.0%) | | 34 (77.3%) |
| Follow-up, mo | | | | |
| Mean ± SD | 93.4 ± 48.5 | 74.6 ± 51.2 | | 80.7 ± 50.7 |
| Median (minimum–maximum) | 88.3 (10.3–208.5) | 64.4 (12.5–190.7) | | 75.7 (10.3–208.5) |

*Pearson $\chi^2$ test.
HPSCC = hypopharyngeal squamous cell carcinoma; OPSCC = oropharyngeal squamous cell carcinoma; OSCC = oral squamous cell carcinoma; PORT = postoperative (chemo)radiotherapy; SD = standard deviation.

formalin-fixed paraffin embedded tissue was still available, immunohistochemistry was performed to examine p16 expression to at least consider this surrogate marker for oncogenic HPV infection.[23,24] Therefore, the visualization system EnVision FLEX+, Mouse, High pH (Link) (Dako, Agilent Technologies, Santa Clara, CA; reference number K8002) combined with monoclonal p16 antibodies (Santa Cruz Biotechnology, Dallas, TX; Cat# sc-56330, RRID: AB_785018) (1:50; pH 9) were applied. Only OPSCCs that exhibited strong (≥75%) nuclear and cytoplasmic staining were classified p16 positive.[23,24]

### *Postoperative Therapy*

Due to the retrospective design of this study and the long inclusion period, the reason for application and nonapplication of PORT in the individual case could not be identified. Moreover, from 1986 to 2015, standardization of recommendations for PORT were just evolving. In general, treatment decisions were influenced by tumor- and patient-associated factors, such as by the primary carcinoma's extent, its histologically proven infiltration depth, histopathological grade, main localization, and moreover the patient's individual risk factors and the patient's individual decision following informed consent.

Radiotherapy was applied as described previously.[25] From August 1986 until December 1993 (11 patients), the schedule of radiotherapy comprised two daily fractions separated by 6-hour intervals. Over 6 weeks as a split-course regimen, maximum fractions of 2.1 Gy (1.25 MV 60Co) were applied, with a total radiation dose of 56 and 70 Gy to the neck bilaterally and primary tumor, respectively. From January 1994 to December 2004 (seven patients), normofractionated radiotherapy (2 Gy/d, five times per week) was delivered by the application of parallel, opposed lateral portals matched to a single anterior portal encompassing the primary tumor and associated nodal drainage sites up to a maximum dose of 50 Gy. One anterior portal was used to cover the lower neck and supraclavicular node with applying a dosage of 50 Gy at a 3 cm depth. Finally, the three-dimensional (3D) conformal external beam radiotherapy technique was used for the boost to achieve a total dose of 60 Gy. Since January 2005 (three patients), normofractionated (2 Gy/d, five times per week), 3D conformal external beam radiotherapy was administered from the beginning of radiotherapy. In the first phase, a dose of 50 Gy was administered to the primary tumor, the involved lymph node, and to the potential drainage sites on both sides of the neck, including the supraclavicular region, followed by a boost of up to 64 Gy covering the primary tumor and involved lymph node. For the effect of radiosensitization provided by additional platinum-based chemotherapy, this concomitant treatment was administered as described previously.[25]

### *Follow-up*

Postoperatively, all patients were examined according to a previously described follow-up regime.[2] After five years without recurrence, a patient was considered as cured. However, for 58.8% of all patients (n = 38), follow-up examinations continued after 5 years.

### *Statistics*

Descriptive analysis of observed values or quantities was denoted by the respective mean value and corresponding standard deviation, median and/or absolute, and relative frequencies. Pearson $\chi^2$ test was used to analyze frequency distributions. Applying the Kaplan-Meier method,[26] overall survival (OS), disease-specific survival (DSS), recurrence-free survival (RFS), and the local control rate (LCR) were calculated starting from the date of primary surgery.

Regarding OS, death for any reason was considered as an event, and patients alive at the last follow-up were censored. Concerning DSS, death related to the primary tumor was exclusively considered as an event, and all other causes of death were counted as censored. With regard to RFS, events were defined as local and/or regional recurrences, occurrence of distant metastasis, or death related to primary diagnosis, whereas death from any other cause and patients alive without any disease manifestation were included as censored observations. Calculating LCR, local recurrences were considered as events. In the present study, 5-year estimates are stated. Statistical differences between groups were calculated by the log-rank test. The level of significance was determined at 5%. Regarding statistical analysis and to create graphics, the software Dell Statistica version 13.3 (Dell, Round Rock, TX; RRID:SCR_014213) was used. Final editing was performed with the software Adobe Illustrator CC version 18.1 (Adobe Systems, San José, CA; RRID:SCR_010279).

## RESULTS

### *Patients*

Sixty-five patients diagnosed with pT1–pT2 pN1 M0 malignancies were included in the study. Reagrding tumor location, 27.7% (n = 18) were located in the oral cavity, 46.2% (n = 30) in the oropharynx, and 26.2% (n = 17) in the hypopharynx.

### *Therapy*

All patients received resection of the local primary tumor by TLM and selective ND. ND was performed unilaterally in 70.8% (n = 46) and bilaterally in 29.2% (n = 19) of all patients. Level II and III were completed in all patients, except for one (98.5%, n = 64). Additionally,

TABLE II.
Oncologic Outcomes Stratified by Treatment Group.

| | PORT, n = 21 | No PORT, n = 44 | Total, N = 65 |
|---|---|---|---|
| Status at Last Follow-up | | | |
| Alive without index cancer | 8 (38.1%) | 18 (40.9%) | 26 (40.0%) |
| Cancer-related death | 1 (4.8%) | 12 (27.3%) | 13 (20.0%) |
| Death related to secondary primary | 2 (9.5%) | 3 (6.8%) | 5 (7.7%) |
| Intercurrent death | 10 (47.6%) | 11 (25.0%) | 21 (32.3%) |
| Local, locoregional, or regional recurrences | | | |
| No | 19 (90.5%) | 20 (45.5%) | 39 (60.0%) |
| Yes | 2 (9.5%) | 24 (54.5%) | 26 (40.0%) |
| Time initial surgery until recurrence, mo, mean ± SD | 17.7 ± 13.3 | 16.7 ± 13.9 | 17.5 ± 13.3 |
| Distant metastasis | | | |
| No | 20 (95.2%) | 37 (84.1%) | 57 (87.7%) |
| Yes | 1 (4.8%) | 7 (15.9%) | 8 (12.3%) |
| Time initial surgery until distant disease, mo, mean ± SD | 27.2 ± 0.0 | 36.7 ± 33.7 | 35.5 ± 31.4 |

PORT = postoperative (chemo)radiotherapy; SD = standard deviation.

considering the total amount of 84 treated neck sides, level I was included in 32.1% (n = 27), level IV in 27.4% (n = 23), and level V in 11.9% (n = 10). In all cases, histopathological assessment revealed malignant cells in a single ipsilateral lymph node without ECS. The location of the lymph node metastasis for oral cavity tumors was 27.8% (n = 5) in level I, 27.8% (n = 5) in level II, 33.3% (n = 6) in level II–III, and 5.6% (n = 1) in level III. It could not be specified in one case (5.6%, level I–IV en block ND specimen). The lymph node metastasis of oropharyngeal tumors was located in 26.7% (n = 8) in level II and in 50.0% (n = 15) level II–III. It was not further specified in seven cases (23.3%), in which en bloc ND specimens comprise three to five levels. For hypopharyngeal tumors it was 35.3% (n = 6) level II, 11.8% (n = 2) level III, and 41.2% (n = 7) level II–III. It was not specified for two cases (11.8%) that received a level II–IV neck dissection.

Postoperative radiotherapy was implemented in the treatment of 32.3% (n = 21 of 65) patients. By main localizations, 22.2% (n = 4) of 18 patients with OSCC, 46.7% (n = 14) of 30 patients with OPSCC, and 17.6% (n = 3) of 17 patients with HPSCC received this postoperative treatment. It was combined with concomitant chemotherapy in 57.1% of the cases (n = 12). No patient received chemotherapy without radiotherapy.

The mean follow-up time until death (or lost to follow-up) was 80.7 ± 50.7 months with a maximum of 208 months. Stratified by treatment group (PORT, no PORT, and complete cohort), patients and disease characteristics, as well as follow-up data are presented in Table I. The analyzed characteristics were not significantly different distributed

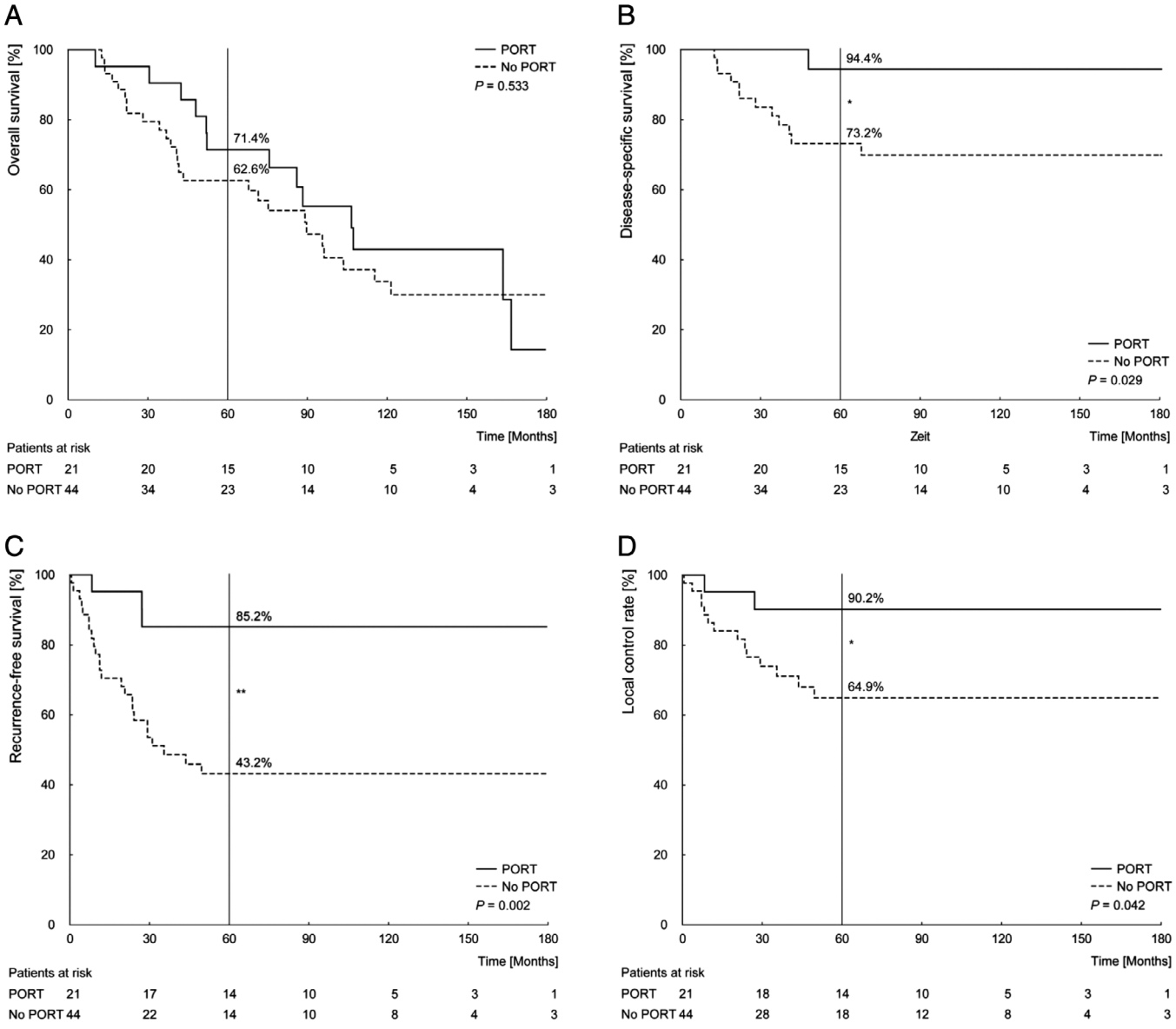


Fig. 1. Five-year Kaplan-Meier estimates of overall survival (A), disease-specific survival (B), recurrence-free survival (C), and local control rate (D) stratified by treatment group. *P* values calculated by log-rank test. PORT = postoperative (chemo)radiotherapy.

TABLE III.
Overview of Studies Evaluating Five-Year Oncologic Outcomes for Patients With pT1-pT2 pN1 Categorized Head and Neck Squamous Cell Carcinoma Treated With or Without Postoperative (Chemo)Radiotherapy.

| Study | Data Source | Inclusion Time | ECS, R+ Excluded | No. of Patients | Tumor Localizations Included | PORT | pT1, No. (%) | pT2, No. (%) | OS (%) | DSS (%) | RFS (%) | LCR (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Present study complete cohort | Single institution | 1986–2015 | Yes | 65 | 27.2% OSCC, 46.2% OPSCC, 26.2% HPSCC | Yes | 8 (28.6) | 13 (35.1) | 71.4 | 94.4* | 85.2* | 90.2* |
| | | | | | | No | 20 (71.4) | 24 (64.9) | 62.6 | 73.2* | 43.2* | 64.9* |
| | | | | | | All | 28 (100) | 37 (100) | 65.5 | 80.0 | 56.9 | 73.4 |
| pT1 subgroup | | | | 28 | 28.6% OSCC, 46.4% OPSCC, 25.0% HPSCC | Yes | 8 (28.6) | Excluded | 87.5 | 100 | 100* | 100 |
| | | | | | | No | 20 (71.4) | | 69.1 | 89.7 | 48.5* | 65.9 |
| | | | | | | All | 28 (100) | | 74.4 | 92.7 | 63.7 | 76.7 |
| pT2 subgroup | | | | 37 | 27.0% OSCC, 45.9% OPSCC, 27.0% HPSCC | Yes | Excluded | 13 (35.1) | 61.5 | 90.0 | 75.5* | 83.9 |
| | | | | | | No | | 24 (64.9) | 57.2 | 59.9 | 38.5* | 64.2 |
| | | | | | | All | | 37 (100) | 58.6 | 70.3 | 51.3 | 71.1 |
| OSCC subgroup | | | | 18 | 100% OSCC | Yes | 2 (25.0) | 2 (20.0) | 100 | 100 | 100 | 100 |
| | | | | | | No | 6 (75.0) | 8 (80.0) | 47.6 | 64.9 | 54.4 | 70.7 |
| OPSCC subgroup | | | | 30 | 100% OPSCC | Yes | 5 (38.5) | 9 (52.9) | 64.3 | 91.7 | 77.4* | 85.1 |
| | | | | | | No | 8 (61.5) | 8 (47.1) | 62.5 | 62.5 | 31.3* | 65.7 |
| | | | | | | All | 13 (100) | 17 (100) | 63.3 | 75.6 | 52.2 | 74.9 |
| HPSCC subgroup | | | | 17 | 100% HPSCC | Yes | 1 (14.3) | 2 (20.0) | 66.7 | 100 | 100 | 100 |
| | | | | | | No | 6 (85.7) | 8 (80.0) | 76.9 | 92.3 | 48.2 | 61.1 |
| Kadletz et al. 2018* | Multicenter | 2000–2012 | Yes | 31 | 100% OPSCC | Yes | 15 (48.4) | Excluded | 92.9 | Not stated | 100* | Not stated |
| | | | | | | No | 16 (51.6) | | 100 | | 44.9* | |
| Chen et al. 2016* | | | | | | | | | | | | |
| OSCC subgroup | Database | 2004–2013 | Yes | 1467 | 100% OSCC | Yes | 332 (45.4) | 408 (55.5) | 58.8* | Not stated | Not stated | Not stated |
| | | | | | | No | 400 (54.6) | 327 (44.5) | 54.4* | | | |
| OPSCC subgroup | | | | 790 | 100% OPSCC | Yes | 263 (57.3) | 186 (56.2) | 85.1* | Not stated | Not stated | Not stated |
| | | | | | | No | 196 (42.7) | 145 (43.8) | 74.7* | | | |
| Shrime et al. 2010* | | | | | | | | | | | | |
| Complete cohort | Database | 1983–2004 | No | 1539 | 100% OSCC | Yes | 442 (78.2) | 767 (78.7) | 54.2* | 72.1 | Not stated | Not stated |
| | | | | | | No | 123 (21.8) | 207 (21.3) | 41.4* | 64.3 | | |
| pT1 subgroup | | | | 565 | 100% OSCC | Yes | 442 (78.2) | Excluded | 63.4 | 76.6 | Not stated | Not stated |
| | | | | | | No | 123 (21.8) | | 56.5 | 75.3 | | |
| pT2 subgroup | | | | 974 | 100% OSCC | Yes | Excluded | 767 (78.7) | 48.8* | 69.5* | Not stated | Not stated |
| | | | | | | No | | 207 (21.3) | 32.5* | 57.0* | | |

*(Continues)*

TABLE III.
Continued

| Study | Data Source | Inclusion Time | ECS, R+ Excluded | No. of Patients | Tumor Localizations Included | PORT | pT1, No. (%) | pT2, No. (%) | OS (%) | DSS (%) | RFS (%) | LCR (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Chen et al. 2010* | | | | | | | | | | | | |
| Complete cohort | Single institution | 1980–2002 | No | 59 | 100% OSCC (100% tongue) | Yes | 12 (44.4) | 16 (50.0) | 77.0 | 81.2* | Not stated | Not stated |
| | | | | | | No | 15 (55.6) | 16 (50.0) | 70.5 | 53.0* | | |
| Subgroup without adverse features | | | Yes | 39 | 100% OSCC (100% tongue) | Yes | 20 (51.3) | | 92.3* | 95.0* | Not stated | Not stated |
| | | | | | | No | 19 (48.7) | | 54.9* | 54.7* | | |
| Jäckel et al. 2008* | Single institution | 1986–2002 | Yes | 55 | 20% OSCC, 38.2% OPSCC, 34.5% HPSCC, 3.6% supraglottis, 3.6% glottis | Yes | 5 (25.0) | 11 (31.4) | 63.6 | Not stated | Not stated | Not stated |
| | | | | | | No | 15 (75.0) | 24 (68.6) | 60.7 | | | |

Five-year OS, RFS, DSS, LCR, LRC estimates in percentages, calculated via Kaplan-Meier method.
*Significant group differences ($P < .05$).
DSS = disease-specific survival; ECS = extracapsular spread; HPSCC = hypopharyngeal squamous cell carcinoma; LCR = local control rate; OPSCC = oropharyngeal squamous cell carcinoma; OS = overall survival; R+ = positive surgical resection margins; RFS = recurrence free survival.

between both treatment groups (for $P$ values of the Pearson $\chi^2$ test see Table I).

### *Oncological Results*

Treatment failures occurred in 9.5% (n = 2) of patients with PORT, whereas 54.5% (n = 24) of the unirradiated patients experienced recurrence. Of those patients, 11.4% (n = 5) later developed a second recurrence, whereas no patient treated by PORT had a second recurrence. Moreover, unirradiated patients were more frequently diagnosed with distant metastases (15.9% vs. 4.8%, Pearson $\chi^2$ test: $P = .201$). Out of eight cases in total with distant metastases, one occurred in a postoperatively irradiated patient who developed neither local nor regional recurrence, but was diagnosed with multiple distant metastasis after 27.2 months of initial surgical resection. The remaining seven cases occurred in unirradiated patients after a mean time of $36.7 \pm 33.7$ months following initial surgical resection. Prior to the distant disease, all of those unirradiated patients were diagnosed with a local or a regional recurrence. The occurrence of secondary primary tumors in the head and neck was comparable within both treatment groups (14.3% [n = 3] of the irradiated vs. 13.6% [n = 6] of unirradiated patients, Pearson $\chi^2$ test: $P = .943$). Details of oncological outcomes stratified by treatment group are depicted in Table II.

The complete study group's 5-year OS, DSS, RFS, and LCR was 65.5%, 80.0%, 56.9%, and 73.4%, respectively. In an analysis of the oncological outcome estimates of patients with or without PORT by log-rank test, no significant difference of OS was observed (71.4% vs. 62.6%, $P = .533$). With regard to DSS as well as RFS, irradiated patients showed a significant superiority over the unirradiated ones (DSS: 94.4% vs. 73.2%, $P = .029$; RFS: 85.2% vs. 43.2%, $P = .002$). Moreover, the LCR was significantly higher in patients who underwent PORT (90.2% vs. 64.9%, $P = .04$). Figure 1 illustrates the Kaplan-Meier curves for OS, DSS, RFS, and the LCR stratified by treatment groups. When comparing the survival rates of patients with chemotherapy-enhanced PORT (n = 12) versus PORT alone (n = 9), no statistically significant differences were observed (data not shown).

### *Subgroup Analyses*

***pT category.*** To analyze potential differences with regard to local tumor extent, patients were stratified according to the pT category. Within the subset of 28 patients with pT1 carcinomas, 28.6% (n = 8) underwent PORT. Comparing the survival estimates of irradiated patients to those who did not receive PORT (71.4%, n = 20), there was no significant difference between the OS and DSS, even though results were higher for the PORT group. Regarding RFS, a significant superiority of this subgroup's irradiated patients was evident (100% vs. 48.5%, $P = .013$). Additionally, a trend toward an improved LCR was observed (100% vs. 65.9%, $P = .06$).

Among the 37 patients with pT2 carcinomas, 35.1% (n = 13) underwent PORT. Regarding OS and LCR, there was no significant difference between irradiated and unirradiated patients, even though results were higher for

TABLE IV.
Distribution of Treatment Failures Stratified by Main Localization and Treatment Group.

| | OSCC | | OPSCC | | HPSCC | | All Localizations | |
|---|---|---|---|---|---|---|---|---|
| | PORT, n = 4 | No PORT, n = 14 | PORT, n = 14 | No PORT, n = 16 | PORT, n = 3 | No PORT, n = 14 | PORT, n = 21 | No PORT, n = 44 |
| Recurrence | | | | | | | | |
| Local | 0 | 4 | 1 | 3 | 0 | 5 | 1 | 12 |
| Locoregional | 0 | 0 | 1 | 2 | 0 | 0 | 1 | 2 |
| Regional | 0 | 2 | 0 | 6 | 0 | 2 | 0 | 10 |
| Total | 0 (0%) | 6 (42.9%) | 2 (14.3%) | 11 (68.8%) | 0 (0%) | 7 (50.0%) | 2 (9.5%) | 24 (54.5%) |
| Distant metastasis | 0 (0%) | 1 (7.1%) | 1 (7.1%) | 3 (18.8%) | 0 (0%) | 3 (21.4%) | 1 (4.8%) | 7 (15.9%) |

HPSCC = hypopharyngeal squamous cell carcinoma; OPSCC = oropharyngeal squamous cell carcinoma; OSCC = oral squamous cell carcinoma; PORT = postoperative (chemo)radiotherapy.

the PORT group. Concerning DSS, the group with PORT exhibited a trend toward an improved survival (90.0% vs. 59.9%, $P = .053$). Furthermore, RFS was significantly higher in patients with PORT (75.5% vs. 38.5%, $P = .04$).

Supporting Figure 1 illustrates the Kaplan-Meier curves of OS, DSS, RFS, and LCR for the pT1 and pT2 cohort stratified by treatment groups. Oncological results of the studies' complete cohort as well as of subgroup analysis are presented in Table III.

***OPSCC subsite.*** Most of the included patients were diagnosed with OPSCC (46.2%, n = 30). Demonstrating a relatively equal distribution of 14 (46.7%) patients with and 16 (53.3%) without PORT, a subset analysis of oncological long-term outcomes was performed. Occurrence of treatment failures and distant metastasis stratified by treatment group are presented in Table IV with regard to each of the three main localizations (oral cavity, oropharynx, and hypopharynx).

Analyzing the differences of oncological results between the two treatment groups with OPSCC, the PORT group showed a significant superiority for RFS and a statistical trend toward higher DSS (RFS: 77.4% vs. 31.3%, $P = .011$; DSS: 91.7% vs. 62.5%, $P = .06$). No statistically significant difference in OS and LCR was observed, even though results were higher for the PORT group. Supporting Figure 2 illustrates the Kaplan-Meier curves, and Table III illustrates the 5-year estimates of OS, DSS, RFS, and LCR for the subanalyses of OSCC, OPSSC, and HPSCC patients stratified by treatment groups.

In 43.3% (n = 13) of OPSCC cases, the p16 status could be determined. It was relatively equally distributed between both treatment groups (Pearson $\chi^2$ test: $P = .569$; Table I). The 5-year estimates of p16-positive (n = 9) versus p16-negative (n = 4) cases were as follows: OS: 88.9% vs. 50.0%, DSS: 88.9% vs. 66.7%, RFS: 55.6% vs. 33.3%, and LCR: 76.2% vs. 100%. Estimates stratified by treatment group were not calculated due to the small sample sizes.

## DISCUSSION

This study presents a retrospective analysis of patients with locally circumscribed head and neck SCC (pT1–pT2) and a single ipsilateral lymph node metastasis (pN1) without ECS. The benefit of postoperative radiotherapy in these patients has been controversially discussed to this day.[6] Studies addressing this topic are scarce and exclusively of retrospective nature.[9–14] Additionally, the described disease constellation is relatively rare. Out of 807 patients who received primary TLM for OSCC, OPSCC, or HPSCC, and whose outcome was reviewed previously,[1,2,15] only 65 (8.1%) met these criteria. Patients treated between 1986 and 2015 were included in this study. Throughout this time period, knowledge leading to more standardized recommendations for PORT was still evolving. Therefore, patients exist who received or did not receive this additional treatment. Their data provide the opportunity to evaluate the differences of long-term oncological outcome between, in particular, those two treatment groups retrospectively.

In the present study, PORT was associated with a significant superior DSS, RFS, and LCR. Regarding OS, it was 71.4% for patients receiving PORT and 62.6% for those treated by surgery alone. Nevertheless, albeit close, the difference was not statistically significant. On the one hand, 40% of the patients died by other causes not related to the primary disease or in association with a second malignancy, whereas on the other hand, the limited statistical power to reach significance was most probably owed due to the disease's rareness in a single center, thus resulting in a smaller cohort. Based on larger study populations derived from the Surveillance, Epidemiology, and End Results Database[11] or the National Cancer Database,[12] two studies reported a significant improvement of OS for patients who underwent PORT. However, in an approach more comparable to the present study of a single-center retrospective study, Chen et al. reported significantly superior OS estimates of 20 irradiated patients over those of 19 unirradiated patients with pT1–pT2 pN1 ECS-negative tongue SCC as well.[10] Concerning DSS, the present results are in accordance with the studies mentioned above,[10,11] where it was found to be significantly higher for patients with PORT. Unfortunately, the study investigating the results of the National Cancer Database does not provide DSS at all.[12] Moreover, the present analysis exhibited significant higher RFS for patients with PORT. Only one other study investigated RFS in this context. Even though it was limited to pT1 carcinomas, it also reported a significant difference.[14] Furthermore,

according to our knowledge, the present study is currently the only one considering 5-year LCR as an endpoint. It was significantly higher in the subgroup of PORT-treated patients. Taken together, the current study as well as previous studies in the literature suggest better oncological outcome for patients with pT1–pT2 pN1 carcinomas treated additionally with PORT. Overall, the present study evaluated ECS-negative patients alone in contrast to the heterogenic cohort of Shrime et al., who was unable to exclude patients with ECS because the reviewed database did not provide this information.[11]

Benefit of adding platinum-based chemotherapy to postoperative radiotherapy was demonstrated with level 1 evidence for cases with extracapsular tumor spread and/or microscopically involved surgical margins.[5,27,28] In our center for the effect of radiosensitization provided by additional chemotherapy, this concomitant treatment was applied generously, even in cases without the major risk factors mentioned above. In due consideration of the small number of cases and therefore limited statistical conclusions, survival of patients treated with chemotherapy-enhanced PORT versus PORT alone did not differ in the current study.

To investigate the influence of local tumor extent, subgroups with either pT1 or pT2 carcinomas were analyzed separately. Superior 5-year estimates were calculated for the group of irradiated patients compared to those of the unirradiated ones. For RFS, this difference was statistically significant in the pT1 and pT2 subgroups, respectively. Consequently, PORT appeared beneficial in cases of a single ipsilateral lymph node metastasis independently of local tumor extent. Whereas for a pT2 subgroup, significantly improved OS and DSS were reported in other studies, this was not significant within their pT1 subgroup.[11,12] In line with the present study, for pT1 carcinomas, Kadletz et al. described significantly higher RFS estimates for patients who received PORT as well.[14]

Most of the previous studies focused on patients with OSCC[10–13] and/or OPSCC.[12,14] In the present study, carcinomas localized in the oral cavity, oropharynx, and hypopharynx were included and analyzed together as well as separately. These subset analyses exhibited comparable results. An overview about studies evaluating long-term oncological results is given in Table III.

HPV-associated (p16 positive) OPSCC are often related to a more favorable prognosis.[29] Due to the long timespan of inclusion, neither HPV nor p16 diagnostics were included to the routine pathological assessment for the whole cohort. Therefore, we performed p16 immunohistochemistry for those cases in which tissue was still available. Among both treatment groups, the p16 status was relatively equally distributed. Due to the small sample size with a known p16 status, statistical analysis stratified by treatment group (with or without PORT) was not performed. According to our knowledge, there is currently no study available assessing the association between PORT and the long-term oncological outcome for a homogenous cohort of patients with pT1–T2 pN1 OPSCC that takes into account the carcinoma's p16 status. Only Kadletz et al. addressed this topic without providing data for the pT1 pN1 subgroup. Moreover, this study did not include pT2 pN1 carcinomas.[14] Thus, a potential prognostic impact of p16/HPV needs to be addressed in future studies.

The relevance of the present study is emphasized by the lack of detailed high-evidence data for postoperative radiotherapy in patients with the rare disease constellation of pT1–pT2 pN1 ECS negative R0-resected head and neck SCC. This is reflected by a paucity of published data, with only five retrospective studies addressing this topic at all.[9–12,14] A considerable limit in data quality and a high risk of bias inherent to retrospective studies need to be considered in the present study. However, we faced this limitation by strict inclusion criteria and detailed data deriving from the original patients' charts as well as surgical and pathological reports. This enabled us to present detailed long-term oncological outcome information for patients with and without PORT, and therefore provide data that will potentially aid clinical decision making as well as generate hypotheses for future prospective research. Because no information with regard to side effects and health-related quality of life was available for the current analysis, this needs to be addressed in future investigations.

## CONCLUSION

Our results support the potential benefit of PORT for patients after a margin-negative surgical resection of locally circumscribed carcinomas with a single, ipsilateral, ECS negative lymph node metastasis.


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