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# Prognostic factors and selection criteria in the retreatment of head and neck cancers

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ABSTRACT

*Objectives:* To determine predictors of treatment selection, outcome, and survival, we examined a cohort of previously irradiated head and neck squamous cell carcinoma (HNSCC) patients.

*Materials and methods:* We retrospectively analyzed 100 patients at our institution who were treated for recurrent or second primary (RSP) HNSCC, focusing on subgroups receiving reirradiation (ReRT) alone and those undergoing surgical salvage (SS) with or without post-operative reirradiation therapy (POReRT). Logistic regression modeling was performed to identify factors predictive of retreatment modality. Cox regression modeling was used to determine prognostic factors for progression free survival (PFS) and overall survival (OS).

*Results:* ReRT alone was less likely in current smokers and neck recurrences, with reirradiation more likely in primary site recurrences. POReRT was significantly more likely in patients with positive surgical margins (PSM), neck dissection, or organ dysfunction. POReRT omission negatively impacted PFS when PSM (HR: 8.894, 95% CI: 1.742–45.403) and perineural invasion (PNI) (HR: 3.391, 95% CI: 1.140–10.089) were present. Tracheostomy was associated with worse OS, but ReRT alone and POReRT improved OS. PSM correlated with worse OS, regardless of whether POReRT was given (HR: 14.260, 95% CI: 2.064–98.547).

*Conclusion:* This analysis confirms known factors for predicting outcome and shows nonsmoking status and primary site recurrence as predictors for ReRT alone. POReRT for PSM and PNI improves PFS. Tracheostomy patients are more likely to have ReRT due to acute toxicity not limiting treatment and POReRT improves OS compared to surgery alone. The presence of PSM negatively impacts survival which cannot be overcome by POReRT.

## Introduction

Head and neck squamous cell carcinomas (HNSCC) present with a wide spectrum of disease manifestation and multimodal treatment options. Many patients will experience good outcomes with surgery or radiation therapy (RT), either alone, combined, or with the addition of chemotherapy, with five-year overall survival rates of over 60% [1]. Due to the aggressive nature of these tumors, regardless of primary therapy, recurrence occurs in 15–50% of HNSCC patients, and further management becomes more difficult [2].

If feasible, surgical resection of recurrence is recommended, though this frequently presents a clinical challenge depending on the extent of recurrence and the resultant requirements for postoperative reconstruction [3]. When recurrence is detected early, surgical salvage (SS) can provide a moderate chance of cure, however, a majority of this patient population will be not be surgical candidates, with only 20–30% eligible for curative resection [4]. For those patients ineligible for SS who had received prior radiation therapy, chemotherapy alone was historically the primary modality for retreatment of recurrent and inoperable head and neck cancer, however, with modern regimens

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median overall survival is still less than one year [5].

Reirradiation (ReRT) has now become an accepted modality for the treatment of recurrent head and neck cancer, with 2 year survival rates of 10–30% [6]. Prospective randomized trials demonstrated reirradiation with concurrent chemotherapy as feasible and tolerable, with improved overall survival compared to chemotherapy alone [7,8]. Recent multi-institutional comparisons have demonstrated efficacy and safety of reirradiation using stereotactic body radiation therapy (SBRT) and intensity modulated radiation therapy (IMRT) [9,10]. We examined a cohort of patients retreated for head and neck cancer after previous irradiation to determine whether particular characteristics would emerge as predictors of survival, treatment selection, and outcome, and if these provide utility in treatment decision making.

## Materials & methods

### *Patients*

Patients were evaluated retrospectively using an IRB-approved database compiled with waiver of informed consent from our institutional multidisciplinary head and neck cancer clinic. The recruitment and follow up period was from February 2006 through July 2016. Patients with recurrent or second primary (RSP) head and neck cancer who had previously received external beam radiation therapy (EBRT) as part of their original cancer treatment were selected, with further subgroup analysis performed based on the retreatment modality. All patients had previously received full course radiation therapy, with or without chemotherapy either definitively or after surgery prior to evaluation for RSP. To identify factors affecting selection for either surgery or reirradiation, we first subdivided our cohort into those receiving reirradiation (ReRT) alone versus any SS. We divided the surgical group between those who received surgical salvage (SS) alone and those who underwent post-operative re-irradiation therapy (POReRT) to further evaluate outcomes and assess for factors affecting survival.

Multiple variables were assessed to determine factors predictive of disease progression or death, as well as elucidate potential selection criteria for those patients who received SS and those who would derive a benefit from reirradiation. Patient variables included age, race, biological sex, Charlson comorbidity index score, Karnofsky Performance Status (KPS) at retreatment, current smoking status, pack-years smoking history, primary tumor site, surgery for primary treatment, area of recurrence (primary site or neck), new primary versus recurrence, retreatment modality, and organ dysfunction (defined as presence of tracheostomy or feeding tube at recurrence). Pathological factors known to predispose to recurrence were evaluated for impact on treatment decision making and outcome, and included surgical margin (SM) status (positive or negative), presence of lymphovascular space invasion (LVSI) or perineural invasion (PNI), and whether lymph node dissection (LND) was performed.

### *Statistics*

Univariate and multivariable analyses were performed to assess odds ratios for retreatment modality (logistic regression) and hazard ratios for progression free survival (PFS) and overall survival (OS; Cox proportional hazards). Because incidence of locoregional recurrence (LRR) was low in our sample (20%), PFS was chosen as an endpoint and defined as any recurrence or death.

Univariate logistic regressions compared patient, disease, and primary treatment factors between the groups receiving reirradiation alone versus those who were offered surgery. The surgical subgroups of surgery alone and surgery with post-operative radiation therapy were compared with the reirradiation alone group using univariate multinomial logistic regressions to further evaluate treatment decision making based upon patient variables. Univariate Cox proportional hazard models tested whether traditional pathologic factors predictive of recurrence served as significant independent risk factors for poorer PFS. Then multivariable models tested surgical variables and ReRT together with their interaction terms.

To evaluate PFS and OS outcomes, univariate Cox proportional hazard models tested each patient and pathologic variable as an independent predictor of OS, then multivariable Cox proportional hazard models tested significant predictors and variables predictive of increased likelihood of reirradiation or any operative procedure together with their interaction terms. Kaplan-Meier curves were then generated to depict survival differences between subgroups. All analyses were performed using SPSS v. 25 (IBM; Aramonk, NY) with alpha = 0.05 using two-tailed tests.

## Results

### *Patient population*

The cohort consisted of 100 patients who underwent treatment for RSP of the head and neck. Of these, 61 underwent SS and 39 received ReRT alone. Of the patients who received surgery, 45.9% (n = 28) received POReRT, with the remainder receiving surgery alone. The majority (85%, n = 57) of reirradiated patients received IMRT, with 9% receiving 3D conformal RT (n = 2 ReRT, n = 4 POReRT) and the remaining 6% receiving SBRT (n = 1 ReRT, n = 3 POReRT). The clinical and pathological characteristics of the patients are reported in Tables 1 and 2. The mean interval between the two treatment courses was 32.7 months for the entire cohort, with a mean of 19.1 (3.1–96.8) months and 120.3 (8.2–237.6) months for patients with recurrent disease and second primaries, respectively.

### *Factors affecting treatment selection*

The SS group was compared with the ReRT alone group using univariate analysis (UVA) to identify factors that affected the likelihood of a patient being offered surgery. When comparing groups receiving ReRT alone versus surgery with or without POReRT, current smokers were significantly more likely to undergo surgery than ReRT (OR 3.879, CI: 1.485–10.135, p = 0.006). Patients with neck recurrences were also found to have a significantly higher likelihood of undergoing surgical salvage (OR 4.512, CI: 1.888–10.787, p = 0.001), but there was no significant difference in treatment between the ReRT and SS group when comparing new primaries to recurrences (OR 0.830, CI: 0.264–2.607, p = 0.750).

Further analysis then focused on three subgroups of patients receiving ReRT alone, SS alone, or surgery with POReRT. Univariate multinomial regression evaluated treatment decision factors in these 3 groups. Odds ratios of receiving reirradiation with corresponding confidence intervals are shown in Table 3. Building on the above findings, current smokers continued to be less likely to be irradiated, even postoperatively. The remaining patient characteristics did not significantly affect the treatment received. There was no significant interaction between groups regarding site of the tumor or whether the patient underwent surgery during their first cancer treatment. Presence of tracheostomy was predictive of an increased likelihood to receive POReRT (OR: 14.000, 95% CI: 1.841–106.465, p = 0.011) with absence correlating with decreased likelihood of POReRT. The increased likelihood of POReRT was seen in the population with feeding tube at recurrence as well (OR: 5.000, 95% CI: 1.448–17.271, p = 0.011).

As reflected in the analysis between the ReRT alone and SS groups, RSP in the anatomical site of the original primary were more likely to receive reirradiation alone (OR: 7.00, 95% CI: 2.455–19.957, p < 0.001). If these patients did undergo surgery, there was an increased likelihood of POReRT (OR: 4.500, 95% CI: 1.523–13.296, p = 0.007). Patients with RSP occurring in the cervical lymphatic chain were more likely to receive surgery than reirradiation (OR: 0.379, 95% CI: 0.189–0.759, p = 0.006) and less likely to receive POReRT (OR:

**Table 1**
Baseline clinicopathologic characteristics.

| | Reirradiation alone (ReRT) (n = 39) n (%) | Surgical salvage alone (SS) (n = 33) n (%) | Post-operative reirradiation (POReRT) (n = 28) n (%) | Total (n = 100) n (%) |
|---|---|---|---|---|
| *Race* | | | | |
| Non-Hispanic white | 34 (87.2) | 32 (97.0) | 26 (92.9) | 92 (92.0) |
| Other | 5 (12.8) | 1 (3.0) | 2 (7.1) | 8 (8.0) |
| Biological sex | | | | |
| Male | 28 (71.8) | 27 (81.8) | 11 (78.6) | 77 (77.0) |
| Female | 11 (28.2) | 6 (18.2) | 6 (21.4) | 23 (23.0) |
| *Charlson comorbidity index* | | | | |
| 0 | 15 (38.5) | 8 (24.2) | 6 (21.4) | 29 (29.0) |
| 1 | 12 (30.8) | 12 (36.4) | 15 (53.6) | 39 (39.0) |
| 2 | 10 (25.6) | 11 (33.3) | 6 (21.4) | 27 (27.0) |
| 3 | 2 (5.1) | 2 (6.1) | 1 (3.6) | 5 (5.0) |
| *Karnofsky Performance Scale (KPS)* | | | | |
| 100 | 1 (2.6) | 5 (15.12) | 0 (0.0) | 6 (6.1) |
| 90 | 12 (30.8) | 9 (27.3) | 7 (25.9) | 28 (28.3) |
| 80 | 17 (43.6) | 18 (54.5) | 18 (66.7) | 53 (53.5) |
| 70 | 7 (17.9) | 1 (3.0) | 2 (7.4) | 10 (10.1) |
| 60 | 2 (5.1) | 0 (0.0) | 0 (0.0) | 2 (2.0) |
| *Current smoker (at RSP diagnosis)* | | | | |
| Yes | 7 (17.9) | 26 (78.8) | 2 (7.1) | 35 (35.0) |
| No | 32 (82.1) | 7 (21.2) | 26 (92.9) | 65 (65.0) |
| *Site of primary diagnosis* | | | | |
| Oropharynx | 15 (38.5) | 9 (27.3) | 8 (28.6) | 32 (32.0) |
| Oral cavity | 7 (17.9) | 8 (24.2) | 7 (25.0) | 22 (22.0) |
| Larynx | 13 (33.3) | 15 (45.5) | 10 (35.7) | 38 (38.0) |
| Nasal Cavity/ Sinus | 4 (10.3) | 1 (3.0) | 3 (10.7) | 8 (8.0) |
| *Treatment at primary diagnosis* | | | | |
| Chemotherapy | 18 (46.2) | 17 (51.5) | 16 (57.1) | 51 (51.0) |
| Surgery | 16 (41.0) | 8 (24.2) | 7 (25.0) | 31 (31.0) |
| *Site of recurrence* | | | | |
| Primary site | 28 (71.8) | 4 (12.1) | 18 (64.3) | 50 (50.0) |
| Neck | 11 (28.2) | 29 (87.9) | 10 (35.7) | 50 (50.0) |
| *Recurrence vs second primary* | | | | |
| Recurrence | 33 (84.6) | 31 (93.9) | 22 (78.6) | 86 (86.0) |
| New primary | 6 (15.4) | 2 (6.1) | 6 (21.4) | 14 (14.0) |
| *Organ dysfunction* | | | | |
| Tracheostomy | 4 (10.3) | 1 (3.0) | 14 (50.0) | 19 (19.0) |
| Feeding tube | 9 (23.1) | 3 (9.1) | 15 (53.6) | 27 (27.0) |
| Local recurrence | 9 (23.1) | 8 (24.2) | 3 (10.7) | 20 (20.0) |
| Death | 25 (64.1) | 12 (36.4) | 19 (67.9) | 56 (56.0) |
| Pathologic factors | | | | |
| PSM | – | 2 (6.1) | 9 (32.1) | 11 (11.0) |
| LVSI | – | 5 (15.2) | 9 (32.1) | 14 (14.0) |
| PNI | – | 7 (21.2) | 12 (42.9) | 19 (19.0) |
| LND at recurrence | – | 5 (15.2) | 16 (57.1) | 21 (21.0) |

Abbreviations: RSP – Recurrent or second primary, PSM – Positive surgical margins, LVSI – Lymphovascular space invasion, PNI – perineural invasion, LND – Lymph node dissection.

0.345, 95% CI: 0.168–0.708, p = 0.004).

When analyzing those who received SS, there was a statistically significant likelihood of receiving POReRT when surgical margins were positive (OR: 7.342, 95% CI: 1.431–37.666, p = 0.017) and when a lymph node dissection was performed (OR: 7.467, 95% CI: 2.225–25.056, p = 0.001). Presence of PNI approached but did not reach significance in increasing the likelihood of receiving POReRT (OR 2.786, 95% CI: 0.908–8.547, p = 0.73).

*Importance of postoperative reirradiation*

Next, we evaluated variables where POReRT may provide a survival benefit in the SS group. UVA did not show significant correlation for SM, LVSI, PNI, or LND as independent risk factors for poorer PFS between the SA and POReRT groups, but on multivariable analysis (MVA), a significant detriment to PFS was seen in patients with PSM (HR: 8.894, 95% CI: 1.742–45.403, p = 0.009) or PNI (HR: 3.391, 95% CI: 1.140–10.089, p = 0.028) when POReRT was not given. Additionally, patients who received POReRT when neither of these factors were present trended toward worse PFS although this was not significant. These results are shown in Fig. 1. There was no improvement in survival with POReRT seen when PNI was positive, but there was a statistically significant detriment to PFS when RT was omitted with positive PNI (HR: 3.391, 95% CI: 1.140–10.089, p = 0.028). Presence of LVSI after SS did not significantly predict for POReRT.

*Prognostic factors*

The mean overall survival was 3.6 months, with a range of 0.30–20.40 months. Univariate Cox proportional hazard models tested clinicopathologic variables as independent predictors of survival. KPS was predictive of improved OS as would be expected (HR = 0.970, CI: 0.941–1.000, p = 0.047). Patients who were diagnosed with a second primary rather than a recurrence of original disease had improved OS, with a HR of 0.269 (95% CI: 0.100–0.723, p = 0.009). OS was not affected by tumor location, surgery at first diagnosis, or organ dysfunction as defined by presence of tracheostomy or feeding tube. On MVA, presence of a feeding tube at recurrence did not significantly affect OS, but worse outcomes were seen in those patients with a tracheostomy. Additionally, those with a tracheostomy who received ReRT (HR: 0.123, 95% CI: 0.029–0.520, p = 0.004) or POReRT (HR: 0.176, 95% CI: 0.047–0.658, p = 0.010) did better from a survival standpoint than tracheostomy patients undergoing SS alone (Fig. 2A).

Pathologic factors predictive of recurrence also failed to demonstrate an independent effect on OS, but on MVA with treatment group, positive margins significantly predicted death regardless of treatment received (HR: 14.260, 95% CI: 2.064–98.547, p = 0.007). Patients who had positive surgical margins did worse than those with negative margins even when receiving POReRT (Fig. 2B).

## Discussion

*Factors in treatment selection*

*Smoking*

The first goal of our analysis was to identify factors affecting treatment selection. Treatment options for patients with RSP HNSCC are more limited than at first diagnosis, and treatment allocation in a multidisciplinary setting will carry inherent physician bias. We found that smoking status and site of recurrent disease are statistically significant predictors of the type of salvage procedure offered to a patient. Current smokers were nearly four times more likely to undergo surgery than ReRT, and were even less likely to receive POReRT. Smoking is shown to negatively impact outcomes in HNSCC patients receiving radiation, which may contribute to a hesitancy to recommend ReRT [11].

*Pre-existing organ dysfunction*

Presence of tracheostomy or feeding tube are surrogates for organ dysfunction of the airway or swallowing mechanics respectively and have been shown to portend a poorer prognosis in the setting of retreatment [10,12,13]. We found the presence of tracheostomy or feeding tube at time of diagnosis of RSP significantly increased the likelihood of receiving POReRT, and in turn, the absence of these factors decreased the likelihood POReRT. The increased likelihood of receiving POReRT when a tracheostomy or feeding tube likely reflects

**Table 2**
Patient characteristic and dose information.

| | ReRT | | | SS | | | POReRT | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Med | Range | Mean | Med | Range | Mean | Med | Range | Mean | Med | Range |
| Age | 63 | 65 | 38–85 | 63 | 63 | 40–81 | 64 | 63 | 47–85 | 63 | 65 | 38–85 |
| KPS | 81 | 80 | 60–100 | 85 | 80 | 70–100 | 82 | 80 | 70–100 | 83 | 80 | 60–100 |
| Initial RT dose (cGy) | 6612 | 6996 | 5000–7200 | 6405 | 6800 | 3960–8160 | 6756 | 7000 | 5000–7400 | 6584 | 7000 | 3960–8160 |
| Retreat dose (cGy) | 5367 | 6000 | 1500–7200 | – | – | – | 5126 | 5750 | 3000–7000 | 5266 | 6000 | 1500–7200 |

Abbreviations: KPS – Karnofsky Performance Score, RT – Radiation therapy, ReRT – Reirradiation alone, SS – Surgical salvage, POReRT – Postoperative reirradiation.

that as these patients already have organ dysfunction, they are less impacted by the adverse effects of radiation therapy that could preclude completion of a full treatment course, and thus the treating radiation oncologist may be less weary of more aggressive treatment. While mucositis is a major toxicity of radiation for HNSCC, the resultant dysphagia and poor nutritional intake are the major sequelae of this adverse effect, with pretreatment weight loss negatively impacting survival [14]. Likewise, laryngeal edema and mechanical dysfunction can result in airway compromise or aspiration which can lead to life threatening consequences. In these patients with baseline organ dysfunction, the pretreatment presence of tracheostomy places them at less risk for laryngeal aspiration and a feeding tube allows for the receipt of enteral nutrition despite acute toxicity in the more distal digestive tract. While the above studies demonstrate worse outcomes for these patients after ReRT as demonstrated by nomograms and recursive partitioning analysis, pre-existing tracheostomy or feeding tube may contribute to the decision to offer POReRT, due to the perception that acute toxicity may not be a treatment limiting factor.

*Neck vs primary site recurrence*

SS is the standard of care for RSP when technically feasible, with reirradiation recommended in cases of unresectable disease or as an adjuvant to surgery based on pathologic factors [3]. Likelihood of receiving either surgery or ReRT was not significantly different when comparing patients with new primaries versus those with recurrence; however a significant difference was seen based upon the site of recurrence. Surgical management of disease recurrence at the primary site can be complicated by any combination of altered anatomy from previous operations, resectability of new disease, and previous irradiation of the surgical field. Thus, resection of a cervical nodal recurrence generally is more feasible and less technically challenging than further surgery at the primary site which is supported by our analysis.

Those patients whose recurrence manifested in a cervical lymph node were more likely to receive SS versus ReRT, and were less likely to receive POReRT. Those failing at the primary site were more likely to receive ReRT, though if they did receive surgery they were more likely to receive POReRT. This is likely explained by difficulty of resection in a previously treated field, due to the aggressiveness of the local recurrence and subsequent ability to obtain adequately clear margins in an effort to maintain an acceptable functional outcome. Neck recurrences may have represented failures in areas which did not receive LND or radiation during the initial treatment course, which would facilitate a resection with adequate margins and explain the decreased likelihood of these patients receiving POReRT.

*Importance of reirradiation*

Presence of PSM, PNI, and LVSI are known risk factors for recurrence in HNSCC and carry recommendations for postoperative RT [15,16]. Our sample size did not provide enough power to significantly demonstrate an effect of these factors on PFS on UVA, but on MVA we showed a significant detriment to PFS when radiation is omitted in the setting of positive margins or PNI, with a slightly greater effect demonstrated for positive surgical margins, in concordance with historical series showing PSM as a detriment to OS [17].

Presence of PNI approached but did not reach significance in

**Table 3**
Factors influencing likelihood of receiving reirradiation. Univariate multinomial logistic regressions tested each variable separately to determine its impact on treatment group assignment.

| Variable | | Treatment group | Odds ratio (Ref = SA) | 95% Confidence interval | p-value |
|---|---|---|---|---|---|
| Smoking status | Non | ReRT | **4.571** | 2.018–10.375 | < **0.001** |
| | | POReRT | **3.714** | 1.612–8.557 | **0.002** |
| | Current | ReRT | **0.269** | 0.117–0.620 | **0.002** |
| | | POReRT | **0.077** | 0.077–0.018 | < **0.001** |
| Recurrence site | Primary | ReRT | **7.000** | 2.455–19.957 | < **0.001** |
| | | POReRT | **4.500** | 1.523–13.296 | **0.007** |
| | Neck | ReRT | **0.379** | 0.189–0.759 | **0.006** |
| | | POReRT | **0.345** | 0.168–0.708 | **0.004** |
| Organ dysfunction | Tracheostomy | ReRT | 4.000 | 0.447–35.788 | 0.215 |
| | | POReRT | **14.000** | 1.841–106.465 | **0.011** |
| | No Tracheostomy | ReRT | 1.094 | 0.677–1.766 | 0.714 |
| | | POReRT | **0.438** | 0.233–0.820 | **0.010** |
| | Feeding tube | ReRT | 3.000 | 0.812–11.081 | 0.099 |
| | | POReRT | **5.000** | 1.448–17.271 | **0.011** |
| | No Feeding tube | ReRT | 1.000 | 0.603–1.659 | 1.000 |
| | | POReRT | **0.433** | 0.226–0.831 | **0.012** |
| Pathologic factors | Positive margins | POReRT | **7.342** | 1.431–37.666 | **0.017** |
| | LVSI | POReRT | 2.653 | 0.769–9.155 | 0.123 |
| | PNI | POReRT | 2.786 | 0.908–8.547 | 0.073 |
| | LND | POReRT | **7.467** | 2.225–25.056 | **0.001** |

Abbreviations: ReRT – Reirradiation alone, POReRT – Postoperative reirradiation, LVSI – Lymphovascular space involvement, PNI – Perineural invasion, LND – Lymph node dissection.

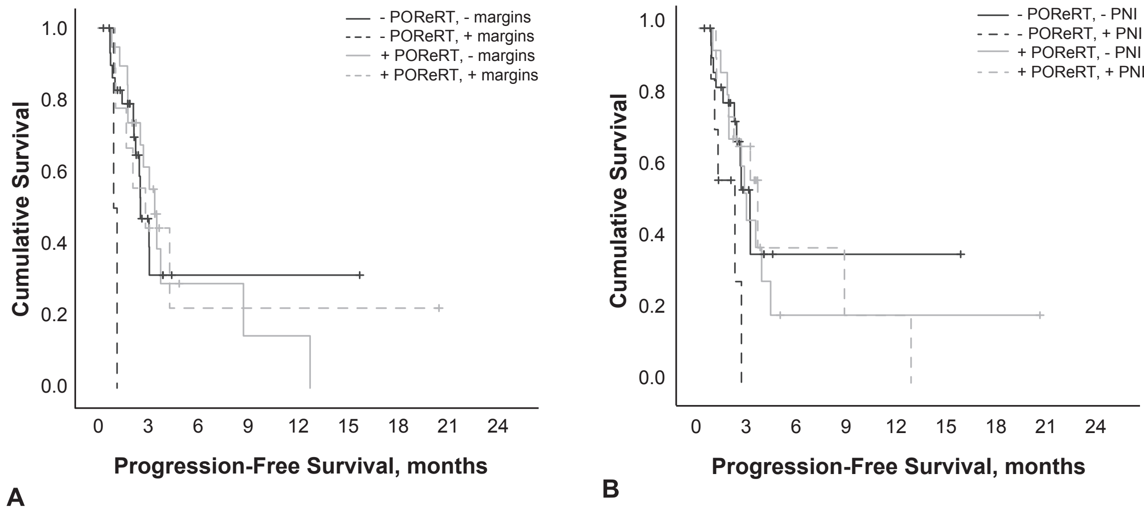


**Fig. 1.** Importance of postoperative reirradiation therapy. Kaplan-Meier curves demonstrating progression free survival in the cohort receiving postoperative reirradiation in the setting of surgical margin status (A) and perineural invasion (B). Abbreviations: POReRT – Postoperative reirradiation therapy, PNI – Perineural invasion.

increasing the likelihood of receiving POReRT (OR 2.786, 95% CI: 0.908–8.547, p = 0.73). There was no improvement in survival with POReRT seen when PNI was positive, but there was a statistically significant detriment to PFS when RT was omitted with positive PNI (HR: 3.391, 95% CI: 1.140–10.089, p = 0.028), likely due to improved local control. We would therefore suggest careful consideration of POReRT in those patients who receive SS with PNI present on final pathology, while all patients with PSM be referred for evaluation of POReRT.

In terms of treatment selection, when patients underwent SS, there was a significantly increased likelihood of receiving POReRT when pathology revealed PSM or when a LND was performed. POReRT for PSM is warranted, based on the discussion above. Elective LND for recurrence after previous irradiation is controversial, with some groups advocating for the practice due to improved local control [18,19], and others against it due to increased toxicity without improvement in outcomes [20]. Therefore, patients who underwent LND likely had cervical involvement, either as a contralateral neck failure of a well lateralized tumor, an ipsilateral failure after treatment of a small localized primary, or locally advanced recurrent disease. Further adverse pathologic factors likely prompted POReRT, as irradiation of elective nodal volumes in RSP has not been shown to have clear benefit [20].

### *Survival*

KPS and new primaries were associated with improved OS. This is expected in those with better KPS and is consistent with previous data [21]. Previous work has demonstrated better outcomes for patient undergoing reirradiation when more time has passed since the initial radiation course, and this was seen in our cohort as well [22]. It is understandable that patients treated for a new HNSCC would face less complications related to the local effects of previous definitive treatment than those with recurrent disease. Though these findings did not persist on MVA, we did find associations with OS when analyzing treatment group with positive surgical margins and tracheostomy presence. Patients with negative margins receiving POReRT fared worse than those who did not have negative margins, likely representing toxicity from further treatment without the benefit of disease control. While smoking status and anatomic location of RSP were significant predictors of treatment selection as mentioned above, when interaction between these variables and treatment group was tested on MVA, there

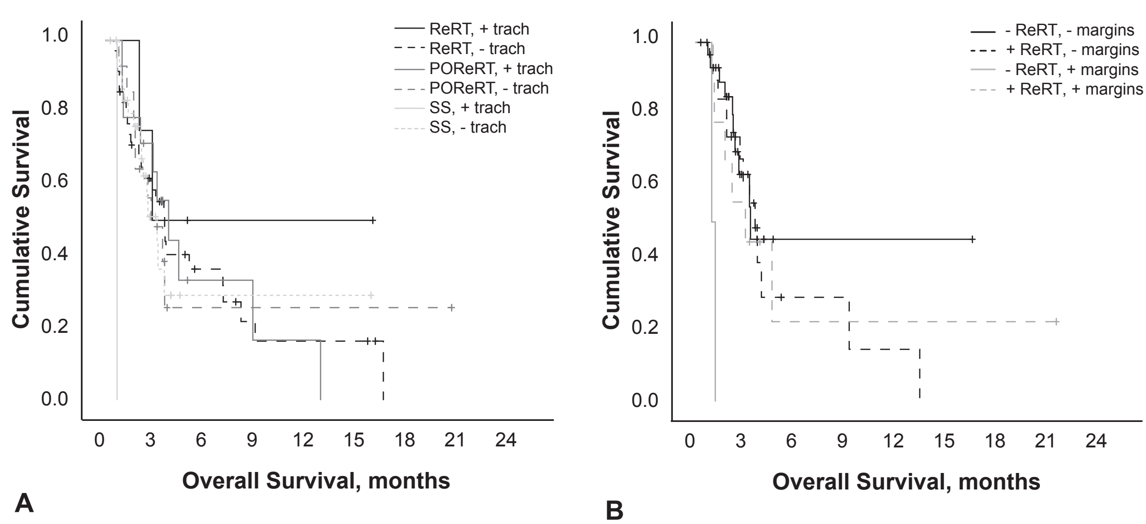


**Fig. 2.** Factors affecting overall survival. Kaplan-Meier curves demonstrating overall survival for all 3 cohorts in the presence or absence of tracheostomy (A) and for the cohort receiving postoperative reirradiation in the setting of surgical margin status (B). Abbreviations: ReRT – Reirradiation therapy, POReRT – Postoperative reirradiation therapy, SS – Surgical salvage, Trach – Tracheostomy.

was no significant correlation with survival.

As with all retrospective analyses, our study does come with limitations. The patient database did not provide HPV status which is a known prognostic factor for HNSCC [23], nor did it include detailed data on chemotherapy or extent of surgery. Selection bias is a known limitation of retrospective studies and we sought to identify factors leading to this, but this could have affected our outcome analysis as well, with treatment decisions made before publication of recent multi-institutional recommendations for ReRT. While previous studies show agreement with the indications for postoperative radiation therapy for PNI and positive surgical margins, an accurate assessment of the true benefit of POReRT in these situations can only be clarified in the setting of a prospective randomized clinical trial. Additionally, these patients were treated before current trends of adjuvant immunotherapy in RSP HNSCC so the predictive value of the analysis may change as this becomes more widespread.

## Conclusion

Our analysis confirms a predilection for ReRT alone in current nonsmokers and patients with primary site recurrence, likely due to concern over impaired wound healing and difficulty with further SS, respectively. Patients found to have LVSI and PSM are more likely to receive POReRT. PFS is improved with POReRT in those undergoing SS found to have PSM and PNI and adjuvant ReRT should always be considered in these groups. Patients with tracheostomy had an increased likelihood of ReRT, and when undergoing SS had an OS benefit when receiving POReRT. PSM portends worse survival, which can be improved but not negated with POReRT.


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## Conflicts of interest disclosure

None.

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