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High-risk pathological features at the time of salvage surgery predict poor survival after definitive therapy in patients with head and neck squamous cell carcinoma

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ABSTRACT

Objectives: Salvage surgical resection is the preferred treatment for head and neck squamous cell carcinoma (HNSCC) patients who develop locally recurrent disease after failing primary therapy. However, salvage surgical resection is not always feasible, and survival outcomes for those that do undergo salvage remain poor. It is well known that patients with adverse pathological features (extracapsular extension (ECE) of lymph nodes (LN), positive margins, perineural invasion (PNI), lymphovascular invasion (LVI), and multiple LN metastases) at the time of primary surgical resection are likely to have relatively poor outcomes. However, the impact of adverse pathological features on outcomes in the salvage setting remains controversial.

Materials and Methods: We retrospectively analyzed 73 patients at a single institution from 2008 to 2017 who developed recurrence and subsequently underwent salvage surgery (SS) after definitive curative-intent therapy including radiation. Demographic and disease control outcomes were reviewed. Kaplan-Meier curves were used to estimate relapse free survival (RFS) and overall survival (OS).

Results: Median age at diagnosis was 61 years (range 40–86), 49/73 (67%) were male, and 55/73 (75%) had smoked. Patients with any adverse pathological features at SS had worse RFS (HR 3.15 $p = 0.0008$) and worse OS (3.97 $p = 0.0008$). Patients who relapsed < 6 months after initial therapy had worse OS (HR 2.96 $p = 0.004$).

Conclusions: Patients with adverse pathological features at time of salvage surgery as well as those who have an early recurrence after definitive treatment and salvage surgery have worse outcomes. Prospective studies are necessary to clarify which patients should receive more intense treatment at salvage.

Introduction

Head and neck squamous cell cancer (HNSCC) is the sixth most common cancer type worldwide, accounting for nearly 350,000 deaths annually [1,2]. Approximately 30–40% of patients with HNSCC present with either stage I or II (early) disease [3]. In general, these patients are cured with single modality therapy, either primary surgery or definitive radiation therapy (RT) [3]. However, patients who present with advanced stage disease (Stage III or IV) have a higher risk of both local recurrence and distant metastasis, posing a treatment challenge. Combined modality approaches (surgery, RT, and/or chemotherapy) are used as definitive therapy to optimize long-term disease control for patients with advanced stage disease. These combined modality approaches include primary surgery followed by postoperative RT or concurrent chemoradiotherapy (CRT), induction chemotherapy (the addition of chemotherapy prior to surgery and/or RT), concurrent CRT alone, or sequential therapy (induction chemotherapy followed by concurrent CRT) without surgery. In patients who undergo surgery as their initial definitive therapy, radiation is added for those who have any adverse pathological features at surgery including extracapsular

Abbreviations: SS, Salvage Surgery; ECE, extracapsular extension; LN, lymph nodes; PNI, perineural invasion; LVI, lymphovascular invasion

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extension (ECE) of lymph nodes (LN), positive margins, perineural invasion (PNI), lymphovascular invasion (LVI), and/or multiple LN metastases. The benefit of including systemic therapy using cisplatin based concurrent chemoradiation was borne out of two seminal studies which showed that the addition of cisplatin to radiation increased progression-free and overall survival in patients with high-risk features (ECE and positive margins) at surgery [4,5] but this survival benefit did not extend to patients with intermediate risk features (LVI and PNI, multiple LN metastases). Therefore, cisplatin, in addition to radiation, has become standard of care after primary surgery for only those patients with high-risk pathological features.

Despite advances in the treatment of locally advanced (Stage III or IV) HNSCC, approximately half of these patients (both with high and intermediate risk features) will develop locally recurrent disease [3]. In this setting, salvage surgery (SS) is considered the standard of care based on the Phase 3 GETTEC/GORTEC trial, which showed that SS alone resulted in similar overall survival compared to SS and chemoradiation [6]. The study also noted a significantly higher rate of toxicities at 2 years with chemoradiation when compared to surgery alone (39% versus 10%).

Notably, closer examination of this heterogeneous class of malignancies suggests the possibility of good outcomes that may depend on the sources of the original tumor, papilloma virus status, specific pathological features, age of the patient and other factors [7]. For example, patients with recurrent oropharyngeal cancers may have survival rates of up to 50% at 5 years [8]. However, the prognostic significance of various tumor and patient attributes has not been rigorously studied in any prospective trials, and available current literature provides conflicting results due to the heterogeneity of patients analyzed. Therefore, treatment decisions are frequently determined by extrapolating from the primary definitive setting. Currently, the use and choice of systemic therapy at the time of recurrence is largely physician and institution dependent, often determined through multidisciplinary consensus [9], and not evidenced-based.

The goal of this retrospective study was to determine if identification of prognostic factors that predict outcomes after salvage surgery could be used to establish evidence-based adjuvant therapy in the recurrent setting for the individual patient.

Methods

Patient selection

The Institutional Review Board at University of Cincinnati approved this study under Protocol# 2016–6434. Patients (de-identified for this analysis) who had recurrent locally advanced, non-metastatic, HNSCC after receiving definitive therapy (defined as either chemo-radiotherapy (CRT), radiation (RT) alone or surgery and RT) from 2008 to 2017 and underwent salvage resection at University of Cincinnati were identified for potential retrospective analysis. Patients were excluded if diagnosed with a local recurrence > five years after their initial diagnosis or had undergone surgery for palliative intent. Using electronic medical records, eligible subjects post SS had the following characteristics extracted: age at diagnosis, gender, race, and environmental exposures (HPV, smoking, and alcohol), HPV status (defined by increased p16 expression by immunohistochemistry performed as standard of care by our clinical pathology laboratory), co-morbidities using the Charlson Comorbidity Index, type of surgical procedure, surgical complications defined as minor or major, time-to-relapse from primary therapy as well as time-to-relapse after salvage surgery (stratified by ≥ 6 or < 6 months) and adverse risk pathological features (high or intermediate). Based on previous adjuvant trials [4,5] after definitive resection, high-risk features were defined as extracapsular extension of lymph nodes (ECE), and/or positive margins, whereas intermediate risk features included close margins (< 5 mm from ink), lymphovascular invasion (LVI), perineural invasion (PNI), and/or involvement of more than two lymph nodes.

Statistical analysis

Relapse free survival (RFS) after salvage resection was defined as the time from salvage resection to recurrence or death from any cause; overall survival (OS) was defined as time to death from any cause from initial date of diagnosis. Time-to-relapse after initial definitive therapy was defined as time from diagnosis to time of first relapse and time-to-relapse after SS was defined as time from salvage surgery to subsequent relapse. RFS and OS were analyzed with Kaplan-Meier survival curves. The survival interval was calculated from the diagnosis date to first event (death or relapse).

Comparisons of Kaplan-Meier survival data between different subgroups (with or without high risk, any adverse risk; relapse within or more than 6 months) were conducted by the log-rank test. Univariate analysis was performed to check the significance of the predictors. For RFS and OS data, Cox proportional hazard regression model was conducted with single predictor (with or without high risk; with or without any risk; co-morbidities; type of surgical procedure; surgical complications; and relapse time within or more than 6 months).

Multivariate analysis was performed in order to adjust for confounding factors such as age, gender, and race. For RFS and OS data, Cox proportional hazard regression model was performed. All statistical analyses were performed using R software (The R project for statistical computing), version 3.3.3 with $p < 0.05$ considered to be significant.

Results

Demographic data

We identified 73 patients that met inclusion/exclusion criteria. The clinical characteristics and patient characteristics are summarized in Table 1. The median age at diagnosis was 61 years (range 40–86), 49/73 (67%) were male, 66/73 (90%) were white, 55/73 (75%) patients had smoking history, and p16 status was available for 44 patients of which 17 patients were positive.

Primary tumors were located in the larynx in 23/73 (32%), oral cavity in 28/73 (38%), and oropharynx in 22/73 (30%). Initial staging (classified by AJCC 7th edition) revealed that 60% had either Stage III (16%) or Stage IV (44%) disease. Amongst the 73 patients who required salvage surgery 21/73 (29%) and 29/73 (40%) had intermediate risk features and high-risk features respectively on pathology while 23/73 had no intermediate or high-risk features.

Survival analysis

Patients in this cohort had a median RFS (Fig. 1A) of 14.23 months (95% CI 8.07–28.95) and a median OS (Fig. 1B) of 60.3 months (95% CI 42.1–97.6).

Prognostic predictors of RFS and OS after salvage surgery

Patients with adverse pathological features at salvage surgery had worse RFS (Fig. 2). Patients with high-risk features at surgery (ECE + or positive/close margins) had shorter RFS in comparison to those who did not have high-risk features (Fig. 2A) with a median RFS of 5.5 months versus 24.6 months ($p = 0.002$). Similarly, patients with any adverse features at surgery (which included either intermediate or high risk features) also recurred earlier (Fig. 2B) compared to those who had no adverse features with a median RFS of 6.7 months versus 43.7 months ($p < 0.001$).

Patients who had high-risk features at salvage resection had a statistically ($p = 0.001$) significant shorter OS (39.9 months) compared to those with no high-risk features (74.5 months) (Fig. 3A). Patients who had any adverse feature at resection (Fig. 3B) also had a significantly

Table 1
Demographics and tumor characteristics.

Characteristic	(N = 73)
Age	
Median -yr	61
Range - yr	40–86
Sex- no. (%)	
Male	49 (67)
Female	24 (33)
Smoking - no. (%)	
Yes	55 (75)
No	18 (25)
Racial or Ethnic Group - no (%)	
White	66 (90)
Black	7 (10)
Site of tumor - no (%)	
Larynx	23 (32)
Oral cavity	28 (38)
Oropharynx	22 (30)
T Stage	
Tx	2 (3)
T1	12 (16)
T2	32 (44)
T3	11 (15)
T4	16 (22)
N Stage	
Nx	4 (5)
N0	35 (48)
N1	10 (14)
N2a	3 (4)
N2b	13 (18)
N2c	6 (8)
N3	2 (3)
Pathological risk - no. (%)	
Intermediate	21 (29)
High	29 (40)
None	23 (32)
p16 status - no. (%)	
Positive	17 (23)
Negative	27 (37)
Unknown	29 (40)

shorter survival compared with patients without any adverse features (median OS of 39.9 months versus not reached ($p = 0.004$)). Although early relapse after definitive therapy (Fig. 4A) had a shorter OS, it was not statistically significant (53.7 months versus 67.9 months ($p = 0.129$)). However, for those undergoing salvage, patients who recurred early (< 6 months) after salvage surgery did have a shorter OS (95.9 versus 26.1 months, $p < 0.001$).

We assessed for common patient factors known to influence survival in patients undergoing salvage therapy including comorbidities using Charlson Comorbidity Index [10], minor and major surgical complications [11], adjuvant treatment including radiation after salvage, and type of salvage surgery performed. The average Charlson Comorbidity Score was 4.5 with a median score of 4. A total of 15 patients developed major surgical complications with the most common being infection, fistula formation and clotting events. 26 patients developed minor complications. Only 7 patients received adjuvant radiation. The most common salvage surgical procedures were pharyngectomy, total laryngectomy and wide local excision with no patients receiving TORS at salvage. Using Cox proportional multivariate analysis, none of these patient factors were found to significantly affect RFS or OS (Table 2) with the exception of comorbidities on OS in our study. HPV positive status and stage II disease (compared to stage III/IV) at diagnosis on multivariate analysis were also found to be important prognostic factors for OS (data not shown) which is congruent with previous studies.

Multivariate analysis adjusting for race, gender, age, smoking, and alcohol (Table 3) suggested that the strongest predictor of relapse after SS was any type of adverse pathological features at surgery (HR = 3.15 $p = 0.0008$). Moreover, adverse pathological features at surgery and relapse < 6 months after initial treatment were the two risk factors that were the strongest predictors for death after salvage surgery (Table 3).

Discussion

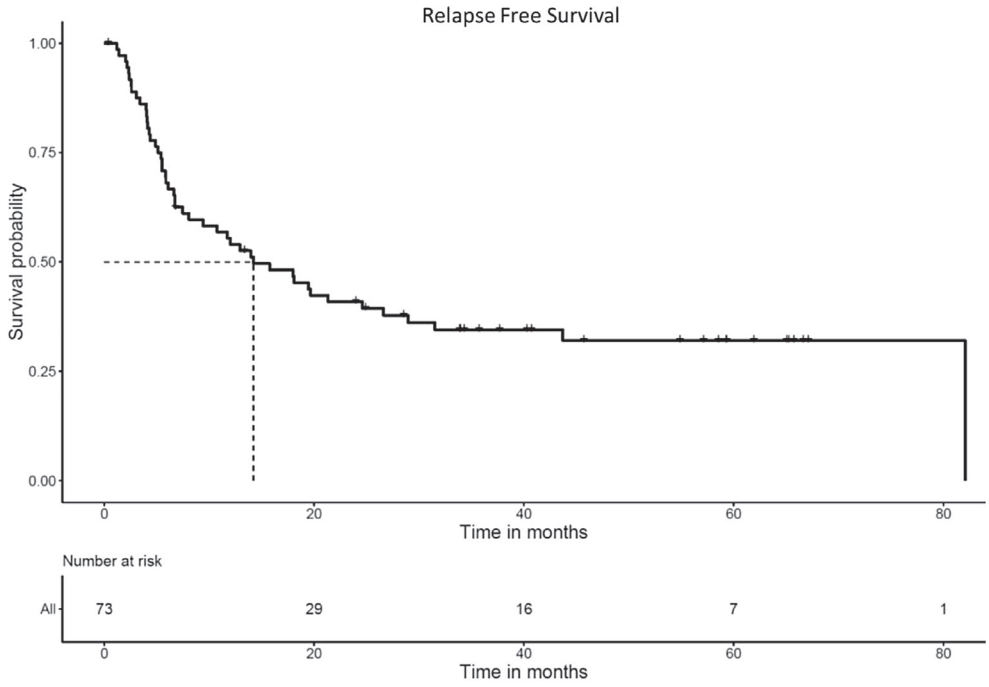
Although SS is the preferred option for curative treatment patients with locally recurrent HNSCC after initial definitive therapy, survival rates continue to remain at only 40% at 5 years [12]. In this retrospective study, we aimed to examine the natural history following SS to establish useful predictors for patient survival outcomes. We found that SS patients' poorer outcomes were observed when pathological features at SS considered to be "high-risk" were present. These high-risk features were defined in our study based on previous trials examining recurrence predictors at the time of the initial definitive therapy (EORTC 22931 [4] and RTOG 9501) which included ECE and positive margins [5]. Importantly, both those who relapsed within 6 months after salvage surgery as well as after initial definitive therapy were at unusually higher risk for poor survival. Importantly, these results suggest that patients who have an early relapse or are at risk for having adverse pathology at surgery need to be considered for more aggressive intervention than is currently standard.

Impact of adverse prognostic features on pathology

The prognostic importance of adverse pathological features after initial surgery (primary setting) in newly diagnosed HNSCC has been well established in two seminal studies, EORTC 22931 [4] and RTOG 9501 [5]. In these two studies, the addition of cisplatin-based chemoradiation in patients with high-risk adverse pathological features at surgery (ECE, or positive margins) led to improved outcomes compared to radiation alone [4,5]. However, these studies also found that patients with intermediate pathological features did not benefit from the addition of cisplatin chemotherapy to radiation therapy despite poor outcomes compared to patients with no risk factors.

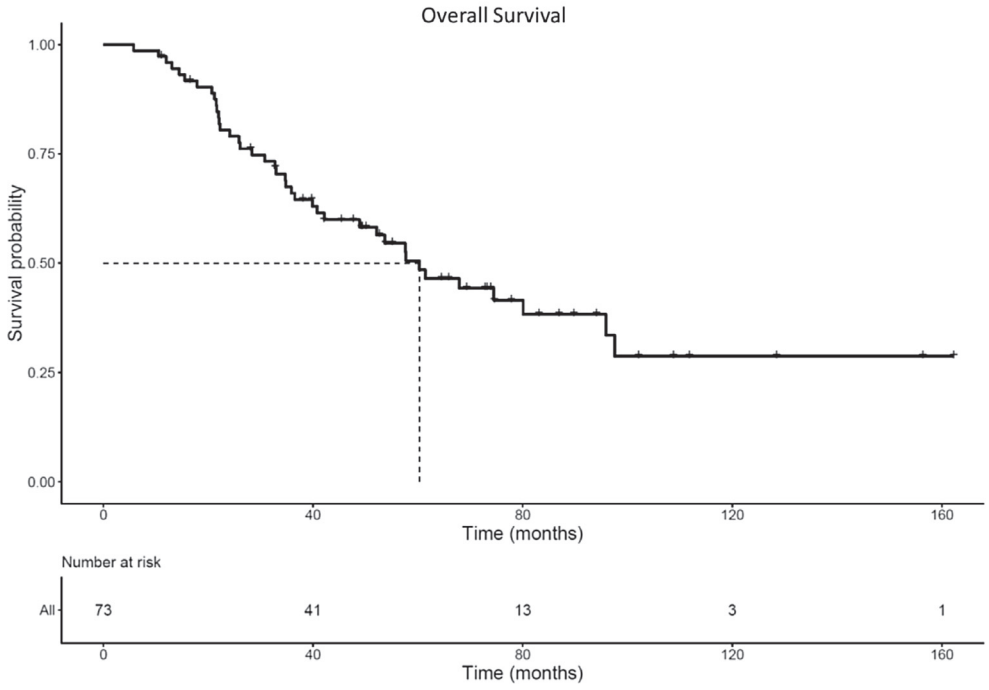
Our comprehensive analysis confirms that any adverse pathological features at the time of salvage surgery are also strong predictors of poorer outcomes. Results from this study are largely consistent with other reported literature in the salvage setting. Sweeny et al. analyzed outcomes after salvage resection in 69 patients who had recurrent oropharyngeal cancer and found that although PNI, and cervical lymph node metastases did not correlate with a second recurrence, patients who had cervical lymph node metastases at SS had worse 2 year overall survival (30% versus 57% $p = 0.02$) and 5 year overall survival (6% versus 36% $p = 0.008$) [13]. Another analysis of 86 oropharyngeal cancer patients showed that positive surgical margins was a highly significant predictor of worse disease free survival after salvage surgery with a HR of 8.43 (95% CI 1.99–35.70 $p = 0.04$) [14]. Moreover, Righini et al. demonstrated that multiple lymph node involvement led to inferior outcomes in patients who underwent salvage resection for oropharyngeal cancers [15] and other published data have demonstrated that positive margins, and ECE were associated with poorer outcomes [10,16]. Interestingly, however, Wulff et al. conducted a retrospective analysis of 142 patients who underwent salvage laryngectomy across tertiary centers in Denmark and showed that, while patients with tumor free margins had a better 5 year survival, this did not reach statistical significance in comparison to those who had close (defined as 1– < 5 mm) or involved margins (< 1 mm) (42.8 versus 23.7% $p = 0.059$) [17]. The finding from this analysis is somewhat surprising as positive margins have consistently demonstrated to be a very important predictor for recurrence and death but could be explained by the potentially different nature of laryngeal tumors and technical advances in surgery in this more recent study from Denmark. In fact, a study by Hamoir et al. [18], in which 109 patients with

A)



Median RFS: 14.23 months (95% CI 8.07 – 28.95)

B)



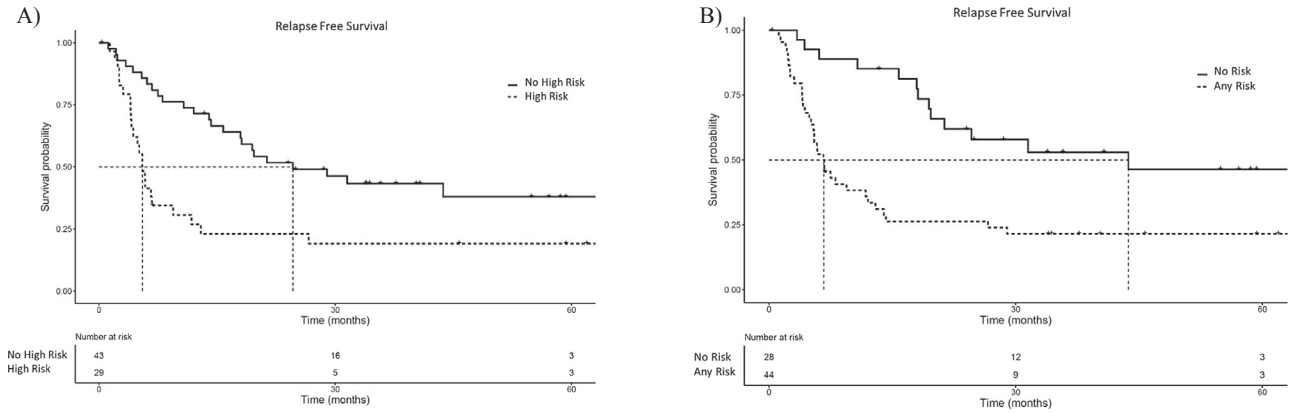
Median OS: 60.3 months (95% CI 42.1 – 97.6).

Fig. 1. Kaplan-Meier survival curves and median survival of entire cohort. (A) Relapse free survival. (B) Overall survival.

recurrent HNC were assessed, non-laryngeal cancers did have poorer outcomes. Like our study and others, they confirmed that high risk features at salvage predicted a poorer survival. They also showed that primary therapy and post-operative complications had an impact on DFS for which our study did not demonstrate, possibly due to fewer number of patients.

Time to recurrence after initial therapy

Early recurrence after initial therapy for HNSCC has been validated as an important predictor for poor outcomes [19–21] and, like other analyses, our findings confirm that early relapse (< 6 months) following initial primary treatment was an important predictor for such



High Risk Features	Median RFS *
No high risk features	24.62months
High Risk Features	5.51 months

* p = 0.002

Adverse Risk Features	Median RFS *
None	43.7 months
Any adverse risk features	6.67 months

* p < 0.001

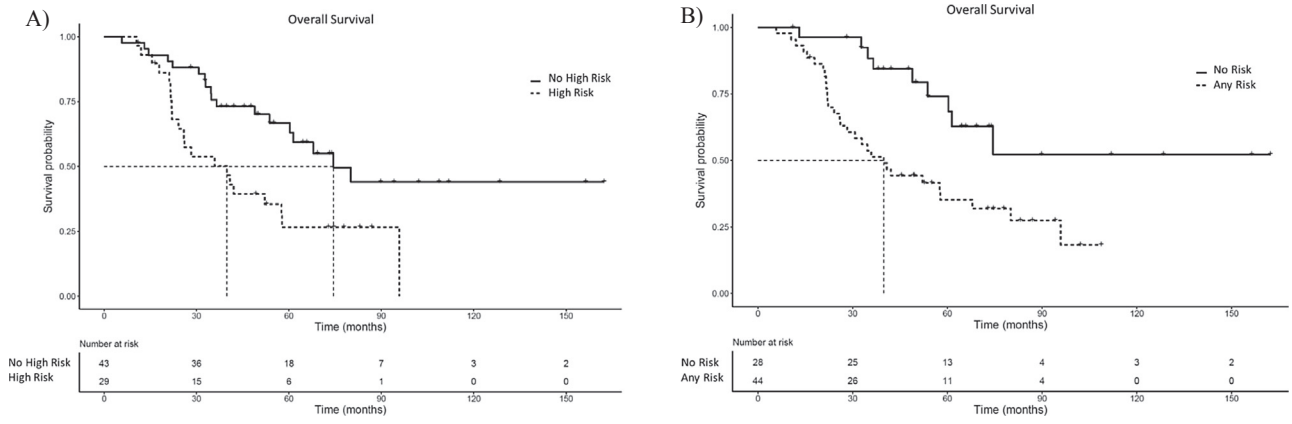
Fig. 2. Impact of adverse pathological features on relapse free survival (RFS) after salvage surgery. (A) Kaplan Meier (KM) survival curves and (RFS) tables for patients who had high-risk pathological features versus no high-risk features. High-risk features included those who had a positive margin or extracapsular extension. (B) Median RFS and KM survival curves for patients who had no adverse pathological features on pathology versus those patients who did. Adverse risk features included high risk features as above as well as perineural invasion, lymphovascular invasion, > 2 lymph nodes involvement.

poor outcomes. For example in the salvage setting, Kim et al. demonstrated that recurrence free period of < 6 months after initial definitive therapy was an independent risk factor for death at one year after salvage surgery (RR 5.61 p = 0.003) [10]. Another large retrospective analysis of 272 recurrent HNSCC patients was conducted to identify a predictive marker that would identify those who would ideally benefit from SS. The results showed that late relapse after initial therapy (defined as > 10 months) was associated with better disease free and OS; the authors concluded that SS was most beneficial in those who had a late relapse [22]. In addition to poor outcomes for early relapse after definitive therapy, we also found that early relapse after salvage surgery also resulted in poor survival.

Implications for management of SS patients

Our study suggests that patients with any adverse pathologic features at the time of SS are at high risk for recurrence and, therefore, should be considered for additional interventions such as re-irradiation. However, most studies combining chemotherapeutic agents with radiation have also not resulted in a survival advantage with a median OS ranging from 9 to 16 months [6,23]. For example, Janot et al. used full-dose irradiation and chemotherapy (with fluorouracil and hydroxyurea) after salvage resection in 132 patients with HNSCC and found that adjuvant chemoradiation improved DFS (HR of 1.68 95% CI 1.13–2.50 p = 0.01) but did not improve OS (p = 0.5) [6].

Different radiation techniques are also being investigated in both resectable and non-resectable disease. Brachytherapy is one such



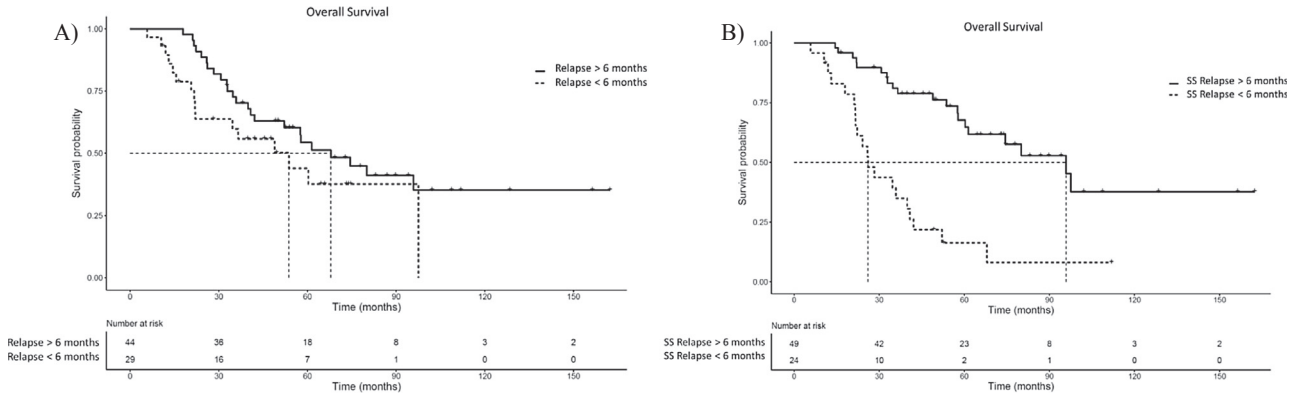
Features	Median OS *
No High Risk Pathological Features	74.5 months
High risk Pathological features	39.9 months

*p = 0.005

Adverse Risk Features	Median OS *
None	NR
Any adverse risk features	39.9 months

* p = 0.004

Fig. 3. Impact of adverse pathological features on overall survival (OS). (A) Kaplan Meier survival Curves and median OS tables for patients who had high-risk pathological features versus no high-risk features. (B) Median OS and KM survival curves for patients who had no adverse risk features on pathology.



Time to Relapse	Median OS *
Relapse > 6 months	67.9 months
Relapse < 6 months	53.7 months

* p = 0.129

Time to Relapse	Median OS *
SS Relapse > 6 months	95.9 months
SS Relapse < 6 months	26.1 months

P < 0.001

Fig. 4. Impact of timing of relapse on patient outcomes. (A) Kaplan-Meier survival curve compares median and overall survival curves for patients who relapsed in less than 6 months versus those who relapsed after 6 months after definitive therapy. (B) Median OS and KM survival curves for patients who relapsed after salvage surgery in less than 6 months versus those who relapsed after 6 months after salvage surgery.

Table 2
Cox proportional hazard model for Relapse free survival and overall survival.

Relapse free survival	Hazard ratio	2.50% CI	97.50% CI	P-value
Comorbidities	1.060	0.855	1.313	0.595
Pharyngectomy	0.569	0.182	1.783	0.333
Total laryngectomy	0.706	0.254	1.968	0.506
Wide local excision	1.300	0.584	2.895	0.521
Adjuvant radiation	1.567	0.628	3.908	0.335
Major complications	1.653	0.710	3.852	0.244
Minor complications	1.369	0.678	2.764	0.381
Overall survival				
Comorbidities	1.311	1.046	1.644	0.019
Pharyngectomy	0.911	0.281	2.948	0.876
Total laryngectomy	0.830	0.268	2.571	0.747
Wide local excision	1.104	0.452	2.695	0.828
Adjuvant radiation	2.109	0.774	5.747	0.145
Major complications	2.089	0.844	5.174	0.111
Minor complications	1.428	0.701	2.907	0.326

Table 3
Adjusted HR tables to identify predictors of recurrence and death after salvage resection.

Risk factors RFS	Hazard ratio (HR)	p value
Any adverse pathology features	3.15	0.0008
Relapse < 6 months from definitive therapy	0.96	0.915
Risk factors OS		
Any adverse pathology features	3.97	0.0008
Relapse < 6 months from definitive therapy	2.96	0.004

modality, which allows for more focal delivery of radiation. A small re-irradiation study (n = 25) utilizing high dose brachytherapy (32 Gy–40 Gy) reported local control rates of 85% and OS of 46% at 4 years but 40% of patients reported ≥grade 3 toxicities [24]. Proton therapy has also been utilized in this setting given its advantage in sparing normal tissue [25,26]. For example, a retrospective analysis of 60 patients by Phan et al. showed local control rates of 68% at 1 year with 30% of patients experiencing a grade 3 toxicity [25].

Immunotherapy, including checkpoint inhibitors, has also emerged as a potential treatment option and is being evaluated in an ongoing trial at our institution (NCT03355560). Checkpoint inhibitors have proven to be active in the metastatic setting for HNSCC [27,28]. In particular, nivolumab was shown to improve OS in comparison to standard chemotherapy [27] and has been approved by the FDA in this setting. As a result, there are many trials underway examining its role in patients with newly diagnosed HNSCC.

Our analysis, similar to most retrospective analyses, is limited by its sample size and single institution analysis; this limits its predictive ability. Furthermore, significant heterogeneity of head and neck sites is almost always a challenge for interpretation. Another limitation of our study was that p16 (HPV) status was not available in many of our patients. However, HPV status was a predictor for OS on multivariate analysis (data not shown).

Our results, coupled with the existing literature, suggests that patients who are eligible for SS should be considered for more a personalized approach and should have recommendations from a head and neck cancer team that includes surgeons, medical and radiation oncologists. For example, a more aggressive approach could be proposed if a patient has adverse tumor pathology at surgery. This could entail either the most advanced surgical techniques and tissue sparing focus radiation or novel immunologic treatment and clinical trials. However, it could also be argued that given the morbidity of SS, if novel tissue sparing options and clinical trials are unavailable, then palliative measures are more appropriate depending on clinician and patient preference. In contrast, SS may be the only intervention needed in those patients who have no adverse features on pathology or who have had a long disease-free interval from their initial therapy.

Conclusion

Our study found that patients undergoing salvage surgery have markedly worse outcomes if any adverse pathological feature is present at the time of salvage surgery and if time to recurrence following initial definitive treatment or after salvage surgery is < 6 months. This is largely consistent with previous studies on HNSCC and has important implications for personalized therapy decision making for this patient population. As new modalities such as those harnessing the immune system are increasingly available, we would argue that it is now possible to identify better those patients eligible for more aggressive and/or experimental therapies. Prospective studies will be required to confirm these findings.

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Conflict of interests

None declared.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2018.11.010.

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