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HEAD & NECK

Outcomes of salvage surgery for the oropharynx and larynx: a contemporary experience in a UK Cancer Centre

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Abstract

Introduction The purpose of this study was to review our recent experience of salvage surgery, comparing larynx and oropharynx recurrence patterns.

Methods A single centre, retrospective review of salvage surgery for recurrent head and neck cancer including patients between 2008 and 2016.

Results 61 patients were identified, 36 underwent salvage laryngectomy and 25 received oropharyngeal resections. The median overall survival of oropharyngeal recurrent tumors was 26 months (95% CI 15–118 months) and for laryngeal tumors was 23 months (95% CI 11–38 months), $p=0.1008$. There was a significant overall survival benefit in patients with negative resection margin. The median survival in the negative margin group was 38 months (95% CI 25–108 months) compared to the positive margin group, 9 months (95% CI 5–15 months), $p<0.0001$.

Conclusion Survival results following surgical salvage in the larynx and oropharynx appear to be similarly poor. Those patients with clear margins appear to have a significantly better prognosis.

Keywords Oropharynx cancer · Larynx cancer · Salvage surgery · Recurrent head and neck cancer

Introduction

The management of recurrent head and neck cancer represents a major challenge for all the members of the head and neck cancer multidisciplinary team. A significant majority of patients in modern cohorts with early or advanced stage cancers of the larynx and oropharynx receive non-surgical/organ preserving treatment modalities [1–4]. Despite this being an effective treatment, the incidence of local failure in the larynx has been reported between 19 and 33% [5]. In the oropharynx, the incidence of local failure has been reported as 10.2% [6] by a European single center and 11.8% by a large center in the USA [7]. Therefore, the management of locally recurrent disease is usually focused on the management of recurrence after radiotherapy or chemo-radiotherapy [8].

Recurrence after treatment for head and neck cancer is associated with a poor prognosis, particularly in high-stage recurrences [9] or even poorer if untreated [10]. The treatment options can include surgery, re-irradiation, palliative care or enrollment onto a clinical trial such as immunotherapy. Surgery in the salvage setting is complicated by the previous oncological treatment. The tissue quality after radiotherapy is often poor, which affects healing, a multifocal pattern of recurrence in an irradiated field makes resection challenging and the general health of the patient following their previous treatment is often compromised. Salvage surgery, therefore, has a higher risk of complications, longer hospital admissions and long-term effects on swallowing and airway competence [11]. However, salvage surgery is often the patient's best chance at a cure and long-term survival [9].

The management of recurrent laryngeal squamous cell carcinoma (LSCC) has traditionally contrasted that of recurrent oropharyngeal squamous cell carcinoma (OPSCC). Conventionally recurrent LSCC is thought to be more amenable to salvage surgery. In a cohort of 109 primary laryngeal cancers treated with organ preservation, salvage surgery for recurrence disease was performed in 89% (39/44) of the

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recurrences [12]. A high proportion of salvage surgery was also performed in this cohort of glottis cancer recurrences, 88.5% (23/26) of recurrences received salvage surgery after definitive non-surgical treatment [13].

However, in patient cohorts of OPSCC the use of salvage surgery is much lower. In a series of 170 patients with OPSCC initially treated with chemo radiotherapy, 31.4% (11/35) of the recurrences received salvage surgery [14]. In a larger series reviewing 1681 OPSCC patients there were 199 patients with locally recurrent tumors and 20.6% received salvage surgery [7].

The patient population receiving treatment for OPSCC has changed over the last decade. These patients are younger and have less comorbidities. The incidence of HPV associated OPSCC is now recognized to have caused the large increase in OPSCC and the associated change in characteristics of the patient population [15]. With exponential increases in the incidence of OPSCC [16], the need for salvage surgery in OPSCC maybe be increasing.

The objectives of this study were to review surgical salvage cases of LSCC and OPSCC at our institution. In modern practice, are OPSCC still poorer salvage surgery candidates?

Method

Setting

Tertiary Head and Neck Cancer referral centre.

Patients

Institutional approval was granted for a retrospective study of patients that received salvage surgery at our institution for squamous cell cancers of the larynx and oropharynx. Patients between January 2008 and January 2016 were identified to give a contemporary cohort of patients and their outcomes.

Treatment

Treatment was provided within a tertiary head and neck cancer center. All patients were discussed by a multi-disciplinary team (MDT) consisting of head and neck surgeons, clinical oncologist, dedicated head and neck radiologists and allied health professionals. Treatment was guided by UK national guidelines, the most recent document published in 2016 [17].

Following histological confirmation of cancer, clinical and radiological staging, primary radiotherapy or chemo radiotherapy was used as definitive treatment. IMRT was used to deliver a treatment dose of 65–70 Gy to the primary tumor volume and 55–60 Gy to the at-risk areas. Early stage glottis tumors received a narrow field radiotherapy dose to 55 Gy. Cisplatin was used in concomitant chemo-radiotherapy in three cycles as first-line treatment. Indications for chemotherapy included oncological stage 3 and 4 disease in patients less than 70 years old without a major comorbidity.

Patients received a 3-month post-treatment PET scan and routine clinical follow-up every 2–3 months for the first 2 years after treatment. All patient with recurrent disease were reassessed and restaged by the MDT. The decision to offer salvage surgery was made by the MDT, in patients without evidence of distant metastasis. An ablative and reconstructive team performed simultaneous resection and reconstruction.

Data collection

Patients receiving salvage surgery were identified from the institution's head and neck cancer database. Salvage surgery was defined as definitive surgery with curative intent after radiotherapy or chemo-radiotherapy to a previous head and neck squamous cell cancer. Patients treated with palliative chemotherapy, sequential chemotherapy or palliative re-irradiation were excluded from this study.

Patient demographical information, tumor staging information of the primary and recurrent tumor and clinical outcomes were collected from the electronic patient record and paper notes where needed. This was stored on an institutional networked database.

The histopathologic slides were reviewed by a dedicated head and neck histo-pathologist. A positive margin after salvage surgery was defined as the presence of tumor at a cut margin. All cancers were staged according to the 7th edition of TNM classification [18]. Overall survival and follow-up were calculated from the day of salvage surgery.

Statistical analysis

Unadjusted univariate analysis using the Chi-square test of proportions was used to compare clinical and histopathological factors of patients with oropharynx and larynx tumor subsites. Multivariate analysis was not possible because the number of events was too small to support a robust multivariate model. Survival analysis used the Kaplan–Meier method and the log ranks statistic to compare groups. By convention $p < 0.05$ was deemed the level of statistical significance. Statistical analysis was performed using STATA (StataCorp. 2017).

Results

Between January 2008 and January 2016 there were 61 patients that met the inclusion criteria for this study. There were 36 laryngeal recurrences and 25 oropharyngeal

recurrences that received salvage surgery. The median age was 71 years old with a range of 55–89 years. 44 (72.1%) of the patients were male with 23 (63.9%) in the larynx groups being male and 21 (84.0%) in the oropharynx group being male. There was no statistical difference between these groups, (Table 1). At initial diagnosis 12 (19.7%) of tumors were T1, 33 (54.1%) were T2, 12 (19.7%) were T3 and 4 (6.6%) were T4. There was no statistical difference between the larynx and oropharynx groups in the distribution of T stages at initial diagnosis. 10 (16.4%) of patients received concomitant chemo-radiotherapy and 51 (83.6%) received radiotherapy alone. There was no statistical difference between the larynx and oropharynx groups in the use of chemotherapy.

The T classification at recurrence for all patients showed there were 4 (6.6%) T1, 11 (18%) T2, 19 (31.5%) T3 and 27 (44.3%) T4 tumors. There was a higher proportion of T4 recurrences in the larynx group with 20 (55.6%) T4 recurrences compared to the oropharynx group which had 7 (28.0%), $p=0.005$ (Table 2). At recurrence, the majority, 45 (73.8%) of the tumors presented with a more advanced T classification than the initial classification (Fig. 1). In the oropharyngeal recurrences, 60% (15/25) presented with a more advanced tumor. In the larynx group 83.3% (30/36) presented with a more advanced tumor.

The neck stage at the time of recurrence of the primary tumor showed no difference between the larynx and oropharynx groups with 41 (67.2%) of patients having a N0 neck, 15 (24.1%) having a N1 neck and 5 (8.2%) having a N2 neck. Extra capsular spread was seen in 16 (26.2%) of patients, with no difference between the groups.

A positive surgical resection margin was seen in 17 (27.9%) of cases, with 13 (36.1%) of larynx resections having a positive margin and 4 (16%) of oropharynx also having a positive margin, $p=0.085$. The majority of positive margins occurred in patients with T4 recurrent tumors 13/27 (48.1%).

A non-coherent invasive front was the most frequent invasive tumor pattern occurring in 40 (65.6%) of tumors. Peri-neural invasion (PNI) was seen in 10 (27.8%) of larynx tumors and 3 (12%) of oropharynx tumors, $p=0.139$. Lympho-vascular invasion (LVI) was seen in 5 (13.9%) of larynx tumors and 2 (8%) oropharynx tumors, $p=0.478$. Of the 25 cases of oropharyngeal cancer treated with salvage surgery, HPV testing was available on 18. HPV positivity determined using FISH was detected in only 2/18 (11%) of these cases.

The median follow-up was 22 months (range 2–154). There were 41 deaths with 26 deaths in the larynx group and 15 deaths in the oropharynx group.

The median overall survival of oropharyngeal recurrent tumors after salvage surgery was 26 months (95% CI 15–118 months) and for laryngeal tumors was 23 months (95% CI 11–38 months), (Fig. 2). There was no statistical difference in survival between the tumor sites, $p=0.1008$. There was a significant overall survival benefit in patients that had a negative resection margin at salvage surgery (Fig. 3). The median survival in the negative margin group was 38 months (95% CI 25–108 months) compared to the positive margin group, 9 months (95% CI 5–15 months), $p<0.0001$. Patients with recurrent T4 staged tumors had a poorer survival than the other less advanced tumors, (see Fig. 4). T4 tumors had a median survival of 15 months (95% CI 8–25), $p=0.0086$.

Table 1 Demographics of patients and initial tumor information

	Total ($N=61$) Freq (%)	Larynx ($N=36$) Freq (%)	Oropharynx ($N=25$) Freq (%)	p value
Age (years)				
Median	71	71	71	N/A
Max	89	89	82	
Min	55	57	55	
Sex				
Male	44 (72.1)	23 (63.9)	21 (84.0)	0.085
Female	17 (27.9)	13 (36.1)	4 (16.0)	
T Stage for initial tumor				
T1	12 (19.7)	4 (11.1)	8 (32.0)	0.174
T2	33 (54.1)	21 (58.3)	12 (48.0)	
T3	12 (19.7)	9 (25.0)	3 (12.0)	
T4	4(6.6)	2 (5.6)	2 (8.0)	
Initial treatment				
Radiotherapy	51 (83.6)	31 (86.1)	20 (80.0)	0.526
Chemo-radiotherapy	10 (16.4)	5 (13.9)	5 (20.0)	

Table 2 Recurrent tumor clinico-pathological features (*ECS* extra capsular spread, *PNI* perineural invasion, *LVI* lymphovascular invasion)

	Total ($N=61$) Freq (%)	Larynx ($N=36$) Freq (%)	Oropharynx ($N=25$) Freq (%)	*p* value
T Stage for recurrent tumor				
T1	4 (6.6)	1 (2.8)	3 (12.0)	0.005
T2	11 (18.0)	2 (5.6)	9 (36.0)	
T3	19 (31.5)	13 (36.1)	6 (24.0)	
T4	27 (44.3)	20 (55.6)	7 (28.0)	
N Stage for recurrent tumor				
N0	41 (67.2)	22 (61.1)	19 (76.0)	0.415
N1	15 (24.6)	10 (27.8)	5 (20.0)	
N2 (A, B and C)	5 (8.2)	4 (11.1)	1 (4.0)	
ECS present in lymph nodes				
Yes	16 (26.2)	11 (30.6)	5 (20.0)	0.357
No	45 (73.8)	25 (69.4)	20 (80.0)	
Surgical resection margin				
Positive	17 (27.9)	13 (36.1)	4 (16.0)	0.085
Negative	44 (72.1)	23 (63.9)	21 (84.0)	
Invasive front				
Infiltrative	4 (6.6)	3 (8.3)	1 (4.0)	0.632
Non-cohesive	40 (65.6)	22 (61.1)	18 (72.0)	
Cohesive	17 (27.9)	11 (30.6)	6 (24.0)	
PNI				
Present	13 (21.3)	10 (27.8)	3 (12.0)	0.139
Absent	48 (78.7)	26 (72.2)	22 (88.0)	
LVI				
Present	7 (11.5)	5 (13.9)	2 (8.0)	0.478
Absent	54 (88.5)	31 (86.1)	23 (92.0)	
HPV Status by FISH				
Positive	N/A	N/A	2 (8.0)	N/A
Negative			16 (64.0)	
Missing			7 (28.0)	
Follow up				
Median	22	21	26	N/A
Min	2	2	3	
Max	154	60	154	
Outcome				
Alive at last F/U	20 (32.8)	10 (27.8)	10 (40.0)	N/A
Dead	41 (67.2)	26 (72.2)	15 (60.0)	

Free flap reconstruction was used in all cases of oropharyngeal resection (25 patients). 28 out of 36 salvage laryngectomy procedures utilized free flap reconstruction. There was a change in clinical practice to use free flap reconstruction in all salvage cases after an initial experience of fistula after primary closure of the pharyngeal defect.

The overall complication rates are modest due to the nature of salvage surgery. The PEG dependence at 12 months was 29.5% (18 patients) and fistula formation rate was 25.0% (15 patients). There was a 10% (6 patients) rate of long-term tracheostomy and 20% (12 patients) incidence of osteoradionecrosis.

Discussion

The epidemic of HPV-related OPSCC has caused a significant change in the population receiving treatment for head and neck cancers [15]. The incidence and the total number of patients with OPSCC is increasing exponentially [16]. In general, HPV-related head and neck cancer has a favorable prognosis but local failure still occurs and the number of patients being considered for salvage surgery of the oropharynx is likely to increase with the projected exponential increase in numbers of OPSCC. In a series of 108 patients combining two large North American institutions detailing salvage surgery outcomes for OPSCC, 80 (74%) patients were HPV positive [19].

Traditionally OPSCC recurrences have not been treated with surgical salvage surgery as frequently as recurrent LSCC. The aim of this study was to compare salvage surgery outcomes in larynx and oropharynx recurrences at our institution to provide a perspective on the treatment of oropharyngeal recurrences in a modern cohort.

This study identified 61 patients that received salvage surgery between 2008 and 2016 at our institution. There were 36 laryngeal salvage surgeries and 25 oropharyngeal salvage surgeries in the cohort. When these groups were compared for age, sex, initial tumor stage and the treatment received there were no differences between the groups. The available evidence for salvage treatments is mostly from single institution reports [8] and highlights the differences in the use of salvage surgery between oropharyngeal and laryngeal recurrences. A study of 109 primary LSCC showed salvage surgery for recurrence disease was performed in 89% (39/44) of the recurrences [12]. Salvage surgery was also performed in 88.5% (23/26) of recurrences in a series of glottis tumors [13]. There are some larger oropharyngeal series reflecting the increasing incidence of this disease. In a series of 170 patients with OPSCC, 31.4% (11/35) of the recurrences received salvage surgery [14]. A larger series reviewing 1681 OPSCC patients had 199 patients with locally recurrent tumors and 41 (20.6%) received salvage surgery [7].

A potential reason for OPSCC receiving less salvage surgery is because recurrent disease can be hard to detect clinically [20]. The oropharynx is more difficult to examine, recurrence can be deep in the tissue and may not be associated with significant symptoms until it presents at large T stage. However, the regular use of PET scanning may allow

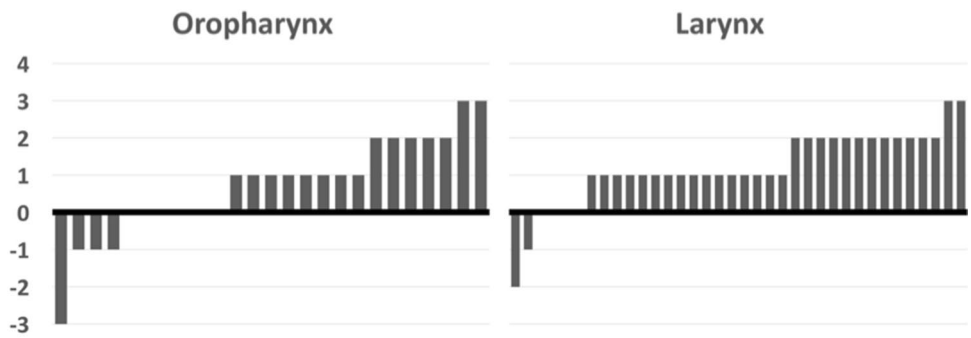
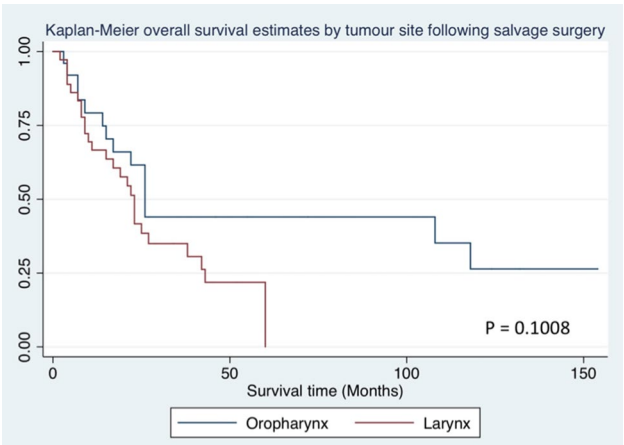
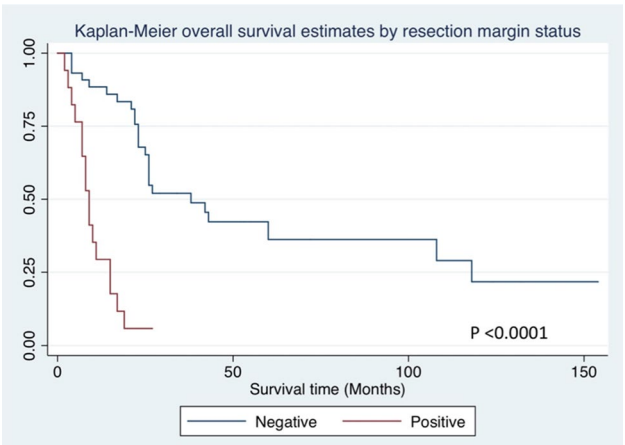


Fig. 1 A waterfall plot of Oropharynx and Larynx squamous cell cancers showing the stage change between the presenting primary tumour T stage and the recurrent primary tumour T stage at consideration for treatment. A positive number indicates an increase in T stage



	Deaths	Total	Median survivals 95% (CI)
Oropharynx	15	25	26 (15-118)
Larynx	26	36	23 (11-38)

Fig. 2 Kaplan–Meier plot of overall survival following salvage surgery for recurrent Larynx and Oropharynx tumors by primary tumor site with median survivals and 95% confidence interval (CI)



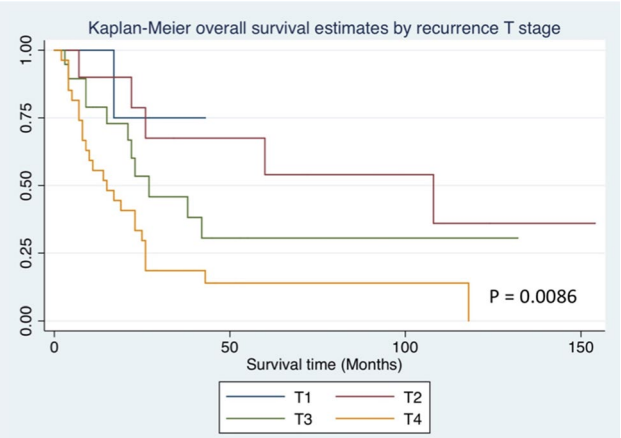
	Deaths	Totals	Median survivals 95% (CI)
Negative	25	44	38 (25- 108)
Positive	16	17	9 (5-15)
All	41	61	23 (17 – 38)

Fig. 3 Kaplan–Meier plot of overall survival following salvage surgery for recurrent Larynx and Oropharynx by resection margin status. Median survivals and 95% confidence interval (CI) shown by margin status

for OPSCC recurrences to be identified earlier [21, 22]. In a study with patients included between 1998 and 2005, 76.2% of OPSCC recurrent cancers presented with T stage 3 or 4 disease at recurrence [7]. PET scanning of the recurrence disease in the oropharynx allows for a good assessment of disease response [23] and gives data that allows for a resection to be planned. Previously, without PET scanning being as available, this was more difficult, and therefore, less patients may have received salvage surgery. The potential for better identification of OPSCC recurrences, with imaging used more frequently in OPSCC compared to LSCC might have caused an increase in patient with OPSCC being considered for salvage surgery. This may explain our high stage of recurrent larynx cancers compared to oropharynx. Our unit also offers partial laryngeal surgery and these patients are not represented in this study.

Our study suggests recurrences present at later stages than the initial tumor and a large proportion of these are advanced T4 cancers, with those occurring more often in LSCC. 27/61 (44.3%) presented with T stage 4 recurrent disease with 20/36 (55.6%) occurring in the LSCC recurrences and 7/25 (28.0%) occurring in the OPSCC recurrences. The impact of advanced stage recurrence had a large negative association with overall survival in our study, with T4 stage recurrence having an estimated 15-month median survival. An association between higher T-stage recurrences and poorer surgical salvage outcomes was described in a retrospective study of 175 patients [24]. Zafereo et al. also noted that increasing T stage had an important association with a poorer outcome [7].

The ability to achieve a negative margin resection may be more technically difficult in tumors of the oropharynx, and therefore, may be a barrier to salvage surgery in the past. The surgical management would typically include a mandibulotomy or mandibulectomy and free flap reconstruction. In a study of 29 patients undergoing salvage surgery, a negative



	Deaths	Totals	Median survivals 95% (CI)
T1	1	4	NR
T2	5	11	108 (7 – NR)
T3	11	19	27 (15 –NR)
T4	24	27	15 (8- 25)

Fig. 4 Kaplan–Meier plot of overall survival following salvage surgery for recurrent Larynx and Oropharynx by T stage at time of salvage surgery. Median survivals and 95% confidence interval (CI) shown by margin status (*NR* not reached)

margin was achieved in 17 (58.6%) patients [25]. Similar findings were seen in a study from Toronto, in which 12 patients (35.3%) had negative margins, 16 patients (47.1%) had close margins (< 5 mm), and 6 patients (17.6%) had a positive margin [26].

In our study 44/61 (72.1%) had a negative resection margin following salvage surgery. A negative resection margin was also seen in 52% (14/27) of patients with T4 tumors. There was no statistical difference in achieving a negative margin between the two tumor sites. A negative margin was achieved in 63.9% of patients with laryngeal tumors and in 84% of patients with oropharyngeal tumors, $p = 0.085$. The increased availability of free flap reconstruction allowed for a two-team approach in the more recent cases and may be a reason for the improved negative margin rate in the latter cases, as it allowed the ablative team more confidence to perform the resection. A negative resection margin was associated with an improved overall survival, with a median survival of 38 months in patients with negative resection compared to a median of 9 months in patients with a positive margin, $p < 0.0005$.

In our study, both larynx and oropharynx median survival outcomes were similar at 23 and 26 months respectively, $p = 0.1008$. This is in contrast to some reports of the effect of tumor site on outcome after salvage surgery. It has previously been described that non-laryngeal sites have worse outcomes after salvage surgery [27].

Previous studies have shown surgery to be an effective intervention in this difficult disease, in which a small subset of patients can achieve long-term survival. In a Toronto series of 34 patients treated with salvage surgery for recurrent OPSCC survival at 2, 3 and 5 years was 62%, 41%, and 25% [26]. They reported no difference in outcomes between HPV positive and negative tumors but also highlighted the importance of negative margin resection. In a review of recurrent OPSCC at John Hopkins hospital in Baltimore, 108 recurrent tumors were studied and they reported that both HPV positive and negative tumors benefited from surgical salvage [19]. These survival outcomes are universally poor but the reported outcomes in other studies are similar to the findings in our study [9]. Our experience suggests that OPSCC can be treated with salvage surgery and can be as successful as salvage surgery for larynx recurrences. The importance and prognostic effect of achieving a negative margin is shown, although it is more difficult in T4 disease. However, in 52% of T4 disease we achieved a negative margin and this should not be a contraindication for surgery, but stimulate a case by case decision. Recurrent OPSCC is expected to become an increasing problem for the head and neck surgeon and all cases should be considered for salvage with an understanding of the higher risk for complications, gastrostomy and tracheostomy dependences.

The use of adjuvant treatments in the salvage setting was not utilized for patients in this study. These tumors are thought to be radio-resistant as they have recurred following radiotherapy treatment, and therefore, re-irradiation was not indicated at our institution. However, the overall poor long-term outcome rates in these patients may indicate a role for adjuvant therapy in the future.

This is a retrospective study, and therefore, suffers from the deficiencies of retrospective data collection. The patients that underwent surgery are likely to have been selected to undergo surgical salvage and this should be recognized when assessing the generalizability of this study.

Conclusion

In this single-center retrospective study of salvage surgery for head and neck cancer, the patterns of failure and outcomes after salvage surgery have been assessed in detail. This study is unique as it includes a large number of salvage oropharyngeal cancers, a site of recurrence that has not been regularly salvaged with surgery. In the era of the oropharyngeal cancer epidemic it offers a new perspective, showing a similar overall survival can be seen in recurrent OPSCC compared to recurrent LSCC and highlights the importance of achieving clear margins.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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