



Salvage surgery for advanced stage head and neck squamous cell carcinoma following radiotherapy or chemoradiation

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Abstract

Purpose Salvage surgery for recurrent advanced stage head and neck squamous cell carcinoma (HNSCC) is known to result in poor prognosis. As there are only small and heterogeneous studies available with wide variety in outcome measures, our purpose was to select and pool literature according to specific criteria.

Methods Systematic review and meta-analysis of clinical outcome after salvage surgery for recurrent advanced stage HNSCC following primary radiotherapy or chemoradiation.

Results 16 of 3956 screened studies were included for analysis (729 patients). Pooled 5-year OS was 37% (95% CI 30–45%, 12 studies, 17 outcome measurements, 540 patients). Outcome was presented for larynx (6 studies, 397 patients), hypopharynx (2 studies, 47 patients), larynx and hypopharynx combined (3 studies, 69 patients) or separately (1 study, 134 patients), oral cavity (1 study, 11 patients), oropharynx (1 study, 34 patients) and multiple subsites combined (2 studies, 37 patients). There was no significant difference in survival outcome between subsites ($p_{\text{heterogeneity}} = 0.8116$). The pooled tumor-positive resection margin rate was 32% and pooled re-operation rate 17%. Complication rates from the pooled data were: fistulas 33%, wound infections 24% and flap failure 3%. Treatment-related mortality rate was 1% and mean hospital stay was 23 days.

Conclusions Salvage surgery for recurrent advanced stage head and neck squamous cell carcinoma after primary (chemo) radiotherapy is a good last resort curative treatment option, resulting in 37% overall survival at 5 years. As data from advanced stage non-laryngeal tumors were sparse, no solid conclusions can be drawn with regard to outcome differences between tumor subsites.

Keywords Head and neck squamous cell carcinoma · Radiotherapy · Salvage surgery · Advanced stage

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Introduction

In the United States and Europe, head and neck carcinoma accounts for 3–4 % of all malignancies [1, 2]. Worldwide, 380,000 patients die from head and neck carcinoma each year [3]. Radiotherapy with or without concurrent chemotherapy has been established as primary treatment for a variety of subsites and stages of head and neck squamous cell carcinoma (HNSCC), with salvage surgery as last resort treatment for residual or recurrent disease. Especially in advanced stage disease, salvage surgery may result in significant morbidity. However, data on clinical outcome are scarce and the reported 5-year overall survival rate varies widely between 6–70% [4, 5]. This broad range is explained by the following reasons. First, small retrospective studies have been published with heterogeneity in patient characteristics and primary treatment for the initial tumor, e.g. radiotherapy

with or without concurrent chemotherapy, or (partial) surgical resection with or without adjuvant treatment. These different primary treatment modalities affect disease control and complications after salvage surgery. Second, the type of salvage treatment differs between patients, as the term salvage is generally used for multiple treatment modalities such as re-irradiation, surgical resection and palliative chemotherapy [6]. Consequently, outcome of patients treated with different treatment modalities must be interpreted with care [7]. Finally, most studies specifically evaluating surgical salvage address partial laryngectomies for recurrent early stage larynx carcinoma [8–11], while data on advanced larynx carcinoma or other tumor subsites are scarce. As prognosis and toxicity primarily depend on tumor stage and type of treatment, our aim was to assess clinical outcome after salvage surgery for recurrent advanced stage HNSCC after radiotherapy (RT) or chemoradiation (CRT). We performed a systematic review and meta-analysis of disease control, survival and complications after (C)RT to help healthcare providers and patients in clinical decision-making in case of recurrent disease.

Materials and methods

Search strategy

A comprehensive systematic review was conducted according to PRISMA guidelines; PUBMED/MEDLINE, EMBASE-OVID and SCOPUS were used for computerized literature search. The search was limited to English literature published from January 1985 until July 2017. Search terms in title, abstract and MeSH were: salvage surgery, carbon dioxide (CO₂), laser, irradiation, radiotherapy, chemoradiation, failure, recurrent, recurrence, squamous cell carcinoma, laryngeal, oropharyngeal, glottic, oral cavity, hypopharyngeal, treatment outcome. Studies that focused on nasopharyngeal carcinoma, melanoma and re-irradiation were excluded. Relevant cross-references from other reviews or selected studies were considered. All procedures were performed in accordance with the ethical standards of the institutional research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Eligibility criteria

Retrospective cohort studies and prospective trials both with > 10 patients were amendable for inclusion. Only advanced stage tumors were of interest, as defined by the American Joint Committee on Cancer (AJCC) staging manual 7th edition [12]. We accepted all studies with at least 90% of patients enduring advanced disease. We

agreed beforehand that less than 10% early stage disease would be acceptable, considering the fact that excluding all studies with a heterogeneous case mix would result in loss of potentially valuable data. Since disease stage was mostly described at primary treatment or at recurrence (and not both), we accepted studies with > 90% of patients with stage III–IV disease at primary radiotherapy and/or at the time of salvage surgery. For primary treatment, we solely focused on definitive radiotherapy, with or without cisplatin or cetuximab. For secondary treatment, studies concerning salvage surgery for loco(regional) disease with or without post-operative re-irradiation were included. Studies were excluded if neck dissections for isolated regional recurrences were included and not separately described. To warrant homogeneity, we excluded studies if patients were treated for second primary tumors, received planned neck dissection following radiotherapy or neoadjuvant radiotherapy followed by planned surgery and when intraoperative brachytherapy or adjuvant systemic therapy was administered.

Quality assessment

Two reviewers independently selected and reviewed literature (JE and LV) according to PRESS criteria [13]. All papers were screened by title and abstract, and subsequently assessed on quality by the Newcastle–Ottawa Scale for cohort studies (Table A1, Electronic Supplementary Material) [14]. Studies were judged on eight items and categorized into three groups: (1) the selection of the study groups, (2) the comparability of the groups and (3) the ascertainment of either the exposure or outcome of interest. Points were awarded for each quality item. We modified some of the criteria for a more specific assessment of cohort studies concerning salvage surgery (see Table 1 footnote, Electronic Supplementary Material). A maximum of 8 points per study could be allocated. The more points, the better the results reflect our outcomes of interest. Systematic difference between studies of higher and lower precision, and publication bias was shown by funnel plot for 5-year OS.

Outcome measures

Our primary endpoints were locoregional control (LRC), disease-free survival (DFS) and overall survival (OS). For locoregional control data, studies with a clear description of follow-up time were included. For data pooling, we used 2-year and 5-year proportions. To compare study outcomes, we included studies for DFS data pooling only if OS data were also reported. Complications and duration of hospital stay were secondary objectives.

Table 1 Tumor and treatment characteristics; per study

	N	Previous treatment	Advanced stage (%)		Tumor site	Salvage type, local	Neck dissection (%)
			Primary	Recurrence			
Alcock 1992	15	RT	100	x	Larynx	TLE	x
Andrews 2011	13	RT, CRT	100	x	Multiple	TLE, mandibulectomy	x
Chen 2013	33	CRT	x	91	Hypopharynx	LPE	x
Hilly 2015	57	RT, CRT	x	100	Larynx	TLE	63
Kadota 2010	14	CRT	x	100	Hypopharynx	LPE	86
Klozar 2012	13	RT, CRT	100	x	Larynx, Hypopharynx	TLE	x
Koss 2014	54	RT, CRT	46	96	Larynx	PLE (4), TLE	85
Leon 2015	24	BRT, CRT	100	38	Multiple	Multiple	x
Li 2013	28	RT, CRT	100	71	Larynx	PLE (4), TLE	89
Patel 2016	34	RT, CRT	94	x	Oropharynx	Multiple	x
Relic 2009	16	CRT	94	100	Larynx, Hypopharynx	PLE (1), TLE	100
Stankovic 2015	134	RT, CRT	x	95	Larynx, Hypopharynx	TLE	89
Weber 2003	76	RT, CRT	100	x	Larynx	TLE	59
Wulff 2017	40	RT, CRT	100	x	Larynx, Hypopharynx	TLE	x
Yuen 1995	167	RT	x	100	Larynx	TLE	25
Yuen 1997	11	RT ± Brachy	x	100	Oral cavity	Glossectomy	100

x not reported/not further specified for (sub)group, *LPE* laryngopharyngectomy, *PLE* partial laryngectomy, *TLE* total laryngectomy

Statistical analysis

Disease control and survival rates were estimated by read out on Kaplan–Meier curves or calculated using SPSS 22 when data were tabularly presented per individual patient. A Freeman–Tukey transformation was applied to normalize and stabilize variance of the proportions sampling distribution. The transformed values were used in all meta-analyses; results were transformed back to show the pooled estimates. Pooled studies were analyzed with random effects models to account for heterogeneity between studies. For meta-analysis, R software version 3.2.1 was used.

Results

Search results and quality assessment

The PRISMA flowchart is presented in Fig. 1. After duplicates were removed, 3956 studies (out of 8801 studies between January 1985 and July 2017) were screened on title and abstract. After 304 studies were assessed for eligibility, 16 studies were included. The main reason for exclusion was advanced stage disease in <90% of patients (92 studies) and not exclusively radiotherapy or chemoradiation as primary treatment (39 studies). In Table A1 (Electronic Supplementary Material), individual study quality and comparability is described. In 10 of 16 studies, 6–7 points were allocated (out of an 8 point maximum) indicating acceptable quality and

comparability. A funnel plot for transformed overall survival proportions at 5 years is shown in Figure A1. Although the plot is relatively symmetrical around the pooled estimate, 5 of 16 studies were outside the triangular region, indicating considerable publication bias.

Patient, tumor and treatment characteristics

Sixteen studies (729 patients) were included for qualitative analysis. Tumor and treatment characteristics per study are summarized in Table 1. Authors presented age either by median (57–67 years in seven studies [5, 15–20]) or mean (57–69 years in four studies [4, 21–23]) with range and standard deviation as descriptive measures. In five studies, we could not obtain the age of our population of interest [24–28].

Nine studies reported on advanced disease in 100% of patients, in the other studies at least 90% of patients were treated for advanced disease at primary treatment or recurrence. Out of 729 patients from 16 studies, there were 27 patients with early stage disease in the primary setting and 11 patients in the recurrent setting. That accounts for only 1–3% of all included patients. Disease control or overall survival was given specifically for larynx carcinoma in six studies ($n=397$) [4, 15, 17, 19, 20, 24], hypopharynx carcinoma in two studies ($n=47$) [21, 22] and both for larynx ($n=79$) and hypopharynx carcinoma ($n=55$) separately in one study [26]. In three studies [23, 25, 27], disease control was presented for both larynx and hypopharynx carcinoma

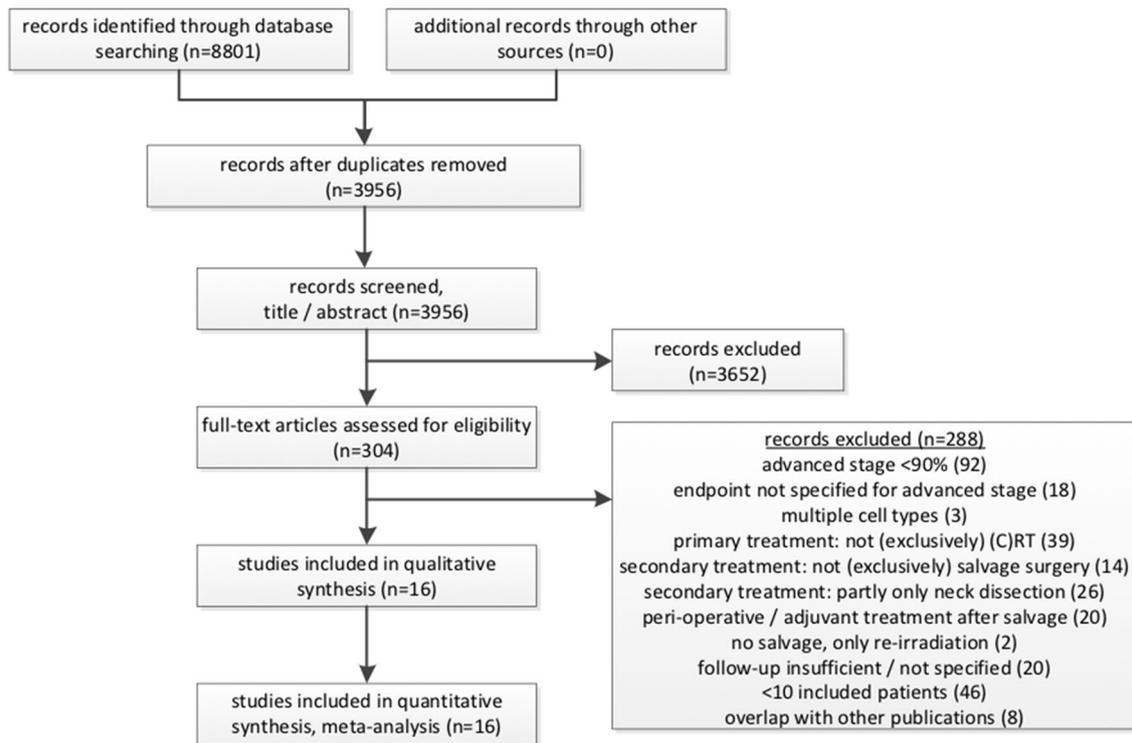


Fig. 1 Literature search (PRISMA flow chart)

combined ($n = 13$, $n = 16$ and $n = 40$). One study [28] evaluated salvage for recurrent oral cavity tumors ($n = 11$) and one study for oropharynx tumors ($n = 34$). In the latter, 19 of 32 evaluable oropharynx carcinomas (59%) were HPV positive. In the remaining two studies ($n = 13$ and $n = 24$), primary endpoints were presented for tumors originating from multiple subsites, with no further description of HPV status [5, 18]. Tumor and treatment characteristics per patient are depicted in Table 2.

Clinical outcome

The pooled 2-year OS after salvage surgery for advanced stage disease was 55% at 2 years (95% CI 44–66%, 8 studies, 12 outcome measurements, 439 patients) and 37% at 5 years (95% CI 30–45%, 12 studies, 17 outcome measurements, 540 patients). At 5 years, larynx carcinoma-specific overall survival was 37% and was not significantly different from oropharynx (5-year OS, 25%), hypopharynx (5-year OS, 52%) and oral cavity (5-year OS, 38%) ($p_{\text{heterogeneity}} = 0.8116$). See Fig. 2 for 5-year overall survival rates.

Pooled disease-free survival after salvage surgery for advanced stage disease (data not shown) was 53% at 2 years (95% CI 37–69%, three studies, five outcome measurements, 187 patients) [4, 15, 20] and 41% at 5 years (95% CI 30–52%, seven studies, ten outcome measurements, 305

patients) [4, 15, 16, 20, 21, 27, 28]. Two studies were not included for DFS data pooling as no overall survival data were presented. Kadota and colleagues found a 5-year DFS of 57% in patients with recurrent advanced hypopharynx carcinoma [22]. Stankovic et al. found a 5-year DFS of 42% and 45% for advanced hypopharynx carcinoma and 48% and 54% for advanced larynx carcinoma after salvage surgery following radiotherapy and chemoradiation, respectively [26].

Locoregional control data were not pooled, as all but one author described the proportion of control after a certain follow-up time instead of 2- or 5-year estimates. Kadota et al. found a 5-year LRC rate of 79% in 14 patients [22]. Locoregional control was reported in six other studies (334 patients) and varied between 19 and 90% after 1–181 months of follow-up [16–20, 23].

Overall, the pooled microscopically tumor-positive surgical resection margin rate was 32% (95% CI 13–54%, three studies, three outcome measurements, 74 patients) [5, 16, 23]. In these studies, larynx carcinomas were also included. Multivariate analysis (MVA) was described in three studies. Leon et al. found no significant predictors [5], whereas Hilly found increased recurrent T stage to be associated with a decrease in DFS ($p = 0.006$) and OS ($p < 0.001$) [4], and the performance of an elective neck dissection associated with improved DFS ($p = 0.009$) and OS ($p = 0.001$). Chen et al.

Table 2 Tumor and treatment characteristics; per patient

		Salvage surgery, local	
Subsite			
Larynx	496	Total laryngectomy	600
Oropharynx	39	Partial laryngectomy	9
Hypopharynx	106	Laryngopharyngectomy	47
Oral cavity	11	Mandibulectomy	35
Multiple	77	Glossectomy	12
Stage, primary		Unknown	26
I	13	Neck dissection	
II	14	Unilateral	25
III	107	Bilateral	29
IV	82	Radical	64
III/IV	92	Selective	55
Unknown	421	NOS	178
Stage, recurrence		None	230
I	1	Unknown	148
II	11	Transposition flap	
I + II	8	Gastric pull up	53
III	83	Pectoralis major	47
II + III	15	Anterior lateral thigh	46
IV	343	Jejunal transfer	14
III/IV	77	Free radial forearm	11
Unknown	191	Latissimus dorsi	1
Primary treatment		Deltpectoralis	1
RT	395	Fibula	1
CRT	203	Rectus abdominis	1
RT/CRT	107	NOS	21
iCRT	16	None	15
BRT	8	Unknown	518

iCRT induction chemotherapy, followed by chemoradiotherapy, *BRT* bioradiotherapy with cetuximab, *NOS* not otherwise specified

found that a high number of tumor-positive lymph nodes was predictive for worse OS ($p=0.04$) [21]. All three studies included a selected number of key variables in MVA, and did not evaluate for instance smoking status. In one study, 19 of 32 evaluable oropharynx carcinomas (59%) were HPV positive [16]. Interestingly, HPV status was not associated with either OS or DFS. Other studies reporting on multiple subsites did not include HPV-status.

Complications

In Table 3, pooled complication rates are presented. The pooled tube feeding rate was 27% (95% CI 9–50%, five studies, five outcome measurements, $n=187$), all following salvage surgery for larynx and pharyngeal carcinoma. In the study by Chen et al., all except four patients (12.1%) achieved oral intake of varying degree with 29 patients (60.6%) being completely independent from tube feeding [21]. The mean interval to start oral intake was 15.1 days. In the study of Kadota et al., all patients achieved oral intake

without tube feeding within a mean interval of 13 days [22]. Stankovic et al. reported nasogastric tube feeding for a median of 16.5 days (range 16–27) after salvage TLE for both larynx and hypopharynx carcinoma [26]. The pooled free flap failure rate was 3% (95% CI 0–9%, three studies, three outcome measurements, $n=81$). In these three studies, tissue flaps were used during salvage surgery for 82% [16] and 100% of patients [21, 22]. In addition, four studies reported mean duration of hospital stay. Corrected for the total number of patients included in each individual study, the calculated weighted mean duration of hospital stay in days was 23 days (range 21–40 days) [5, 16, 21, 26].

Discussion

Salvage surgery for recurrent head and neck squamous cell carcinoma (HNSCC) after radiotherapy is considered a last resort curative treatment option. After an extensive search and meta-analysis of available literature specifically focusing on advanced stage disease, we found a pooled 55% overall survival at 2 years and 37% at 5 years. These results are higher than we expected, probably due to adequate selection of patients who were suitable for surgery. Larynx recurrences are more often resectable than other subsites, mainly because of anatomical and functional reasons. As a consequence, most patients in our study were treated for larynx carcinoma. Moreover, even when salvage surgery for non-laryngeal tumors is feasible, survival is still considered inferior. Interestingly, we found no statistical significant survival difference between tumor subsites. Our data suggest that the prognostic value of subsite is limited in the setting of advanced stage resectable tumors following radiotherapy. However, these results have to be interpreted with care, since only few and small case series on non-laryngeal tumors could be included in our analysis. The lack of available literature on this group of patients urges further investigation for guidance in clinical decision-making and proper informed consent.

Our findings are in agreement with Davidson et al., who published one of the few studies regarding salvage surgery for advanced larynx carcinoma. In a cohort of 108 patients, the complication rate was 27% and 3-year OS rate only 22% [29], suggesting that salvage surgery for advanced larynx carcinoma results in unfavorable disease control than generally expected. In addition, Goodwin et al. performed a meta-analysis and found a 5-year OS of 36.7% after salvage surgery for advanced larynx carcinoma [30]. The authors also performed a prospective study of 109 patients who underwent salvage surgery for all HNSCC subsites and stages, and found no significant difference in outcome between tumor subsites. Moreover, Clark et al. showed extra capsular extension (ECE) but not tumor site to be a significant negative

Fig. 2 Forrest plot for overall survival at 5 years. The pooled transformed-back estimates and confidence intervals calculated with a random effects model. *T3 and T4* T stage, *ND* neck dissection, *BRT* bioradiation, *CRT* chemoradiation, *multiple* overall outcome presented for multiple tumor subsites combined

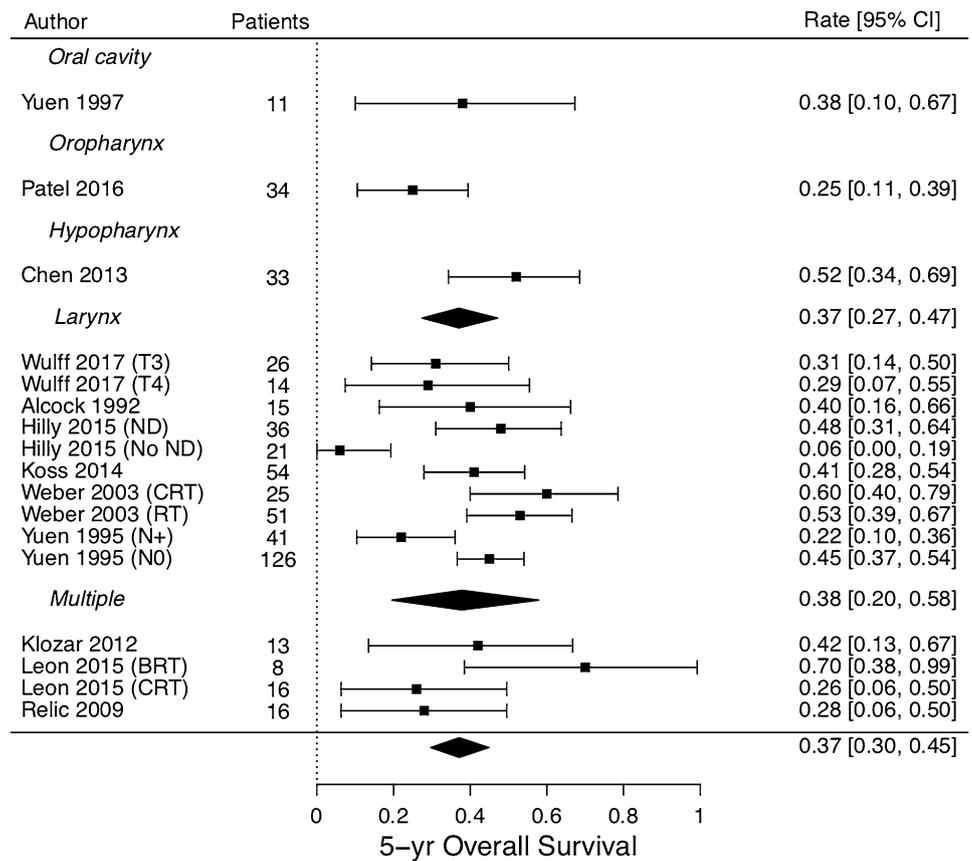


Table 3 Complications after salvage surgery for advanced recurrent HNSCC

Outcome	Studies	Patients	Outcome (%)	95% CI
Fistula ^{a,b,c}	6	306	33	0.20 0.47
Strictures ^b	2	47	17	0.03 0.36
Infection ^{a, b, c}	6	458	24	0.10 0.40
Tube-feeding ^{b, c}	5	187	27	0.09 0.50
Re-operation ^{a, b}	2	57	17	0.08 0.29
Dysphagia ^c	2	210	19	0.05 0.34
Haemorrhage ^{a, b, c}	4	167	3	0.01 0.07
Free Flap failure ^{a, b}	3	81	3	0.00 0.09
Mortality, treatment related ^{a, b, c, d}	9	506	1	0.00 0.04

Pooled transformed-back outcomes calculated with random effects models when number of studies > 1

^a‘Multiple’ treatments, for multiple tumor subsites together presented in one study

^b(Laryngo)pharyngectomy

^cLaryngectomy

^dMandibulectomy

predictor for DSS [31]. On the other hand, Wulff and Woodward et al. both found pharyngeal carcinoma associated with unfavorable OS than larynx carcinoma in univariable, but not in multivariable analysis [27, 32]. Three other groups did find significant unfavorable survival for hypopharynx carcinoma, but included both primary and recurrent tumors [33], did not describe the statistical significance [34], or included only two hypopharynx and one oropharynx carcinoma [35]. Following salvage surgery for oropharynx carcinoma, Zafereo et al. reported a remarkable 3-year overall survival rate of 48.7% [36]. Nevertheless, Gehanno et al. found worse actuarial survival of 38% after 3 years and 24% after 5 years after salvage surgery for tonsil carcinoma [37]. The authors ascribed this result to a high post-operative mortality (8%) rate, which is substantially higher than the pooled 1% mortality rate from nine studies in our study. Our reported mortality rate is also lower than the 5% observed by Goodwin et al. [30], possibly because most of the included studies in our review were published more recently, with an increased standard of care concerning surgery with reconstruction flaps, perioperative care and pre-treatment radiotherapy techniques. We searched for literature published from 1985 until present as we anticipated finding few data. In this broad time frame, not only treatment techniques but also the AJCC staging system has changed. We, therefore,

verified disease stage according to the AJCC 7th edition. However, we found no correlation between publication date and clinical outcome.

In general, more advanced tumors may require the addition of concurrent chemotherapy with radiotherapy. It has been reported that surgery after chemoradiation leads to even two times more wound fistulae compared to surgery after radiotherapy alone [38, 39]. However, in a review by Lee and colleagues, disease control and complication rate after salvage surgery were not statistically different between chemoradiation and radiotherapy alone, but correlated with disease stage [40]. We could not compare complication rates between patients that received salvage surgery following radiotherapy versus chemoradiation, as outcome was not presented separately in most studies.

We also could not evaluate time to recurrence (TTR) as a prognostic variable. In the prospective analysis published by Goodwin et al., there was no difference in outcome after salvage surgery for residual versus recurrent disease [30]. However, it is generally believed that a short disease-free interval after radiotherapy implies a more aggressive tumor behavior. In line with this, others have found a short disease-free interval to negatively correlate with survival [36, 41, 42]. Of note, it is currently under debate whether the initial or recurrent tumor stage is of more prognostic value [29, 30, 41, 43, 44].

We found a considerable tumor-positive resection margin rate of 32% (pooled data from three studies, all subsites), partly because recurrent disease is typically infiltrative and multifocal that spreads broadly in microscopic deposits [45]. Interestingly, Jones et al. already demonstrated that 34% of patients with positive margins at salvage surgery did not develop primary site recurrence, possibly because excisions are typically carried out with a diathermy which may kill remaining cancer cells [46]. However, positive resection margins are predictive for decreased survival [27, 47, 48]. Therefore, adjuvant re-irradiation is traditionally considered in case of R1 resections, despite significant morbidity [49]. Interestingly, none of our included patients received re-irradiation after salvage surgery.

Limitations

Interpretation of our results must be tempered by recognition of substantial bias. First, all except two of the included studies were retrospective case series, which are prone to selection bias. The included studies reflect only those patients considered operable and fit for salvage surgery. Consequently, our results cannot directly be extrapolated to all patients with recurrent advanced stage disease. Second, tumors other than larynx carcinoma were relatively under-represented as these recurrences are less often

resectable. Therefore, no solid conclusions can be drawn from differences in outcome between tumor subsites. We have considered to solely focus on recurrent laryngeal cancer to offer more focused data. However, as we performed a systematic review of literature, the lack of sufficient data itself is a key finding from our work. In addition, salvage surgery should be considered for all different subsites, thus an overview of available data would be valuable. Therefore, we did not exclude the less represented anatomic subsites, but performed a subgroup analysis and described clinical outcome separately. Third, our results reflect a heavily selected study group, as only well-documented studies with a clear denotation of our inclusion criteria and primary endpoints were included. Specifically, we only evaluated salvage surgery after primary radiotherapy or chemoradiation, so one could argue the generalizability of our findings. Fourth, the reported disease control and survival rates may be positively skewed as we accepted studies if < 10% of patients had early stage of disease. However, out of 729 patients from 16 studies, there were 27 patients with early stage disease in the primary setting and 11 patients in the recurrent setting. That accounts for only 1–3% of all included patients. We consider this acceptable, given the fact that excluding all studies with a heterogeneous case mix would result in unacceptable loss of available data. Last, although the studies were of acceptable quality and reflected our outcomes of interest as scored by the Newcastle–Ottawa Scale, the differences in outcome between single studies were considerable. Although the funnel plot was relative symmetrical around the pooled estimate, 5 of 16 studies were outside the triangular region indicating significant publication bias. Altogether, despite very strict selection, heterogeneity within and between studies appeared to be unavoidable.

Conclusion

Salvage surgery for recurrent advanced stage head and neck squamous cell carcinoma (HNSCC) following radiotherapy should be considered a good curative treatment option, as 37% of patients are still alive 5 years after surgery. These encouraging results might be attributed to adequate selection of salvageable patients who are offered surgery. Although we found no statistical significant survival difference between tumor subsites, solid conclusions cannot be drawn as data from advanced stage non-laryngeal tumors were sparse. More research studies are warranted specifically on this group of patients to identify and guide those who will benefit from surgery.

Funding None.

Compliance with ethical standards

Conflict of interest The authors declare that there is no competing interest.

Ethical standards The present study is a systematic review of literature and in that sense did not involve human participants. However, all procedures we performed were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent This study does not fall under the scope of the Medical Research Involving Human Subjects Act (WMO), which means that no informed consent had to be obtained.

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