

Efficacy, outcomes, and complication rates of different surgical and nonsurgical treatment modalities for recurrent/residual oropharyngeal carcinoma

Jayaram, Sharan Chakkyath; Muzaffar, Sayed Jameel; Ahmed, Ikhlaaq; Dhanda, Jagtar; Paleri, Vinidh; Mehanna, Hisham

DOI:
[10.1002/hed.24531](https://doi.org/10.1002/hed.24531)

License:
Creative Commons: Attribution (CC BY)

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Jayaram, SC, Muzaffar, SJ, Ahmed, I, Dhanda, J, Paleri, V & Mehanna, H 2016, 'Efficacy, outcomes, and complication rates of different surgical and nonsurgical treatment modalities for recurrent/residual oropharyngeal carcinoma: A systematic review and meta-analysis', *Head & Neck*. <https://doi.org/10.1002/hed.24531>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Efficacy, outcomes, and complication rates of different surgical and nonsurgical treatment modalities for recurrent/residual oropharyngeal carcinoma: A systematic review and meta-analysis

Sharan Chakkyath Jayaram, FRCS (ORL-HNS), Sayed Jameel Muzaffar, MRCS (ENT), Ikhlmaq Ahmed, PhD, Jagtar Dhanda, PhD, Vinidh Paleri, FRCS (ORL-HNS), Hisham Mehanna, PhD, FRCS (ORL-HNS)*

Institute of Head and Neck Studies and Education (InHANSE), University of Birmingham, Birmingham, West Midlands, United Kingdom.

Accepted 6 May 2016

Published online 00 Month 2016 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/hed.24531

ABSTRACT: *Background.* Treatment of recurrent oropharyngeal cancer is widely thought to have poor outcomes. Justification for treatment, especially in advanced cases, can be difficult.

Methods. A systematic search of MEDLINE, Embase, and Cochrane databases was conducted. Included studies reported specific recurrent oropharyngeal cancer survival data.

Results. Twenty-two retrospective studies were included. Pooled 3-year overall survival (OS) was 26% (95% confidence interval [CI] = 22% to 29%; I squared = 40.7%; $p = .057$). Pooled 5-year OS was 23% (95% CI = 20% to 27%; I squared = 73.9%; $p = .000$). Surgical treatment was superior to radiation (5-year OS 26% vs 16%, respectively; $p <$

.001). The 5-year OS improved over time: 18% in the pre-2000 cohort; 35% in the mixed pre-2000 and post-2000 group; and 51% in the post-2000 cohort ($p < .001$).

Conclusion. Outcomes have improved considerably over the last 2 decades, resulting in approximately 50% overall 5-year survival. Human papillomavirus (HPV) status, patient selection, and improvements in care may explain this. © 2016 The Authors Head & Neck Published by Wiley Periodicals, Inc. *Head Neck* 00: 000–000, 2016

KEY WORDS: oropharynx, malignancy, cancer, surgery, radiotherapy

INTRODUCTION

The treatment of oropharyngeal cancer recurrence is widely thought to have poor outcomes, with a previous systematic review reporting the 5-year overall survival (OS) rate of 26%¹ for all pharyngeal cancers including nasopharyngeal, oropharyngeal, and hypopharyngeal. Questions have therefore been raised about the justification for such treatment, especially in advanced recurrence cases,¹ and consequently patients are usually offered palliative treatment or best supportive care.^{2,3}

The management of oropharyngeal cancer recurrence has gained more prominence recently because of the rapid rise in the incidence of oropharyngeal cancer⁴ over the past decade. There has also been a change in causation, with an increasing proportion caused by the human papillomavirus (HPV). HPV-related oropharyngeal cancer seems to be a distinct disease entity with a different molecular mechanism and significantly improved prognosis compared to HPV-negative oropharyngeal cancer.⁵

Very recently, a study has suggested that HPV-positive recurrence also demonstrates better 2-year survival rates than HPV-negative tumors, and that this was especially evident in patients who were treated surgically.⁶ Confirmation of these findings could result in a reappraisal of the paradigms of the management of oropharyngeal cancer recurrence.

We therefore aimed to conduct a systematic review and meta-analysis of the effectiveness of treatments of local/locoregional recurrence of oropharyngeal squamous cell carcinoma over time, and to explore the possible causes of these trends through assessing HPV status and complication rates (as a surrogate for improved surgical techniques).

METHODS

Search strategy

A systematic computer-based search was performed of the following databases: MEDLINE, Embase, and the Cochrane collaboration. No limit was placed on the year of publication. The following search terms were used: [Neoplasm OR Cancer OR Tumor OR Tumor OR Malignancy] AND [Recurrent OR Residual OR Treatment failure OR Salvage] AND [Oropharynx OR Oropharyngeal OR Tonsil OR Tongue base OR Base of tongue OR Soft palate]. Reference lists of articles retrieved and previous reviews were screened for further suitable studies. A full review protocol is available on request.

*Corresponding author: H. Mehanna, Institute of Head and Neck Studies and Education (InHANSE), School of Cancer Sciences, University of Birmingham, Birmingham, B15 2TT, United Kingdom. E-mail: G.jones@bham.ac.uk

Additional Supporting Information may be found in the online version of this article.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

Inclusion and exclusion criteria

Two trained reviewers (S.C.J. and S.J.M.) independently reviewed abstracts in accordance with a priori criteria, and selected suitable studies for further evaluation of the full manuscript. Abstracts were selected if they reported management of recurrent or residual oropharyngeal cancers.

Studies were included in the review if they fulfilled the following a priori criteria: reported survival data specific to recurrent oropharyngeal cancer, the minimal data that had to be reported for inclusion was 2-year, 3-year, or 5-year OS data taken from the date of management of local/locoregional oropharyngeal recurrences; studies that reported other subsites were included only if oropharynx-specific survival data was either reported separately or could be extracted via Kaplan–Meier curves or individual patient data.

Studies dealing with isolated residual or recurrent nodal disease were excluded. Studies were also excluded if not published in English or in a language suitable for Optical Character Recognition and translation software (Google Translate; Google, Mountain View, CA). Both prospective and retrospective studies of cross-sectional, cohort, and randomized designs were included.

Data extraction and study outcomes

A data extraction sheet (Excel; Microsoft, Redmond, WA) was piloted using 10 studies. After amendment, this was then used for collection of data from all included studies. The 2 reviewers (S.C.J. and S.J.M.) independently extracted data from selected articles. Data were collected on the country of origin, study and patient characteristics, dates of recruitment of patient cohort, initial and recurrent treatment, complications, feeding, and survival outcomes. HPV status was recorded where available. Where there were discrepancies that were not resolved by discussion between the 2 reviewers, adjudication was undertaken by the senior author (H.M.).

Quality and risk of bias appraisal

Study quality and risk of bias were independently assessed by the 2 reviewers. As all studies were non-randomized, the Methodological Index for Non-Randomized Studies⁷ tool was used. Noncomparative studies were assessed for the following criteria: clearly stated aim; inclusion of consecutive patients; prospective data collection; appropriate endpoints; unbiased evaluation of endpoints; appropriate length of follow-up; and loss to follow-up not exceeding 5%. If studies were comparative, they were also assessed for: control group having the gold standard intervention; having contemporary groups; baseline equivalence of groups; prospective calculation of sample size; and statistical analysis adapted to the study design.

Statistical analysis

All statistical analyses were performed in Stata 12.1. An estimation approach was used to calculate the 95% confidence intervals (CIs). By regarding the survival rates as a binomial proportion, using p as the survival rate and n (the number of patients), it was possible to calculate the 95% CIs using Jeffreys interval (recommended by Brown

et al⁸). To estimate the CI when n is small, and is reported to be comparable to other methods when n is large. A random-effect meta-analysis was performed and a forest plot was generated for 3-year and 5-year OS rates. Meta-regression was used to obtain a p value for the difference in subgroups. Any p values $< .05$ are considered statistically significant.

Heterogeneity was assessed using the I^2 index statistic, which estimates the percentage of variability that is due to heterogeneity rather than error in sampling (chance).

RESULTS

Search results and study selection

Using the search strategy described, we identified 1280 abstracts. We found 13 additional records by screening reference lists of articles and previous reviews. We undertook a full review of 138 articles. Of these, 116 articles were excluded. The reasons for exclusion are stated in Supplementary Figure S1, online only (Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram).

Characteristics of selected studies and treatment modalities

Twenty-two articles were selected for inclusion and analysis in the study (Table 1).^{6,9–29} The studies reported on 1105 patients, a mean of 50 patients (range, 5–163) per study, published between 1976 and 2014. Because some of the studies included several cohorts for different treatment modalities, data were collected on 27 cohorts. Among these, 21 cohorts reported on the outcomes of salvage surgery, 5 on salvage brachytherapy, 1 on reirradiation +/- chemotherapy. Seventeen studies that reported either 3-year OS or 5-year OS were included in the quantitative meta-analysis.

Quality and heterogeneity of included studies

The quality assessment of the included studies is detailed in Supplementary Table S1, online only. All the 22 studies were retrospective studies. The median quality assessment score of the studies according to the Methodological Index for Non-Randomized Studies checklist was 11 of a maximum of 16 (range, 8–12). Overall, a low level of heterogeneity ($I^2 < 40\%$; $p > .05$) was seen across the studies, but significant heterogeneity was identified in the reporting of 5-year survival data ($I^2 = 73.9$; $p = .00$).

Overall survival rates

The pooled overall 3-year survival rate was 26% (95% CI = 22% to 29%) ($I^2 = 40.7\%$; $p = .057$; see Figure 1). The pooled overall 5-year survival rate was 23% (95% CI = 20% to 27%; $I^2 = 73.9\%$; $p = .000$; see Figure 2).

Effect of treatment modality

We compared the outcomes of salvage surgery to non-surgical treatment modalities of oropharyngeal cancer recurrence (brachytherapy/reirradiation). Patients undergoing surgical salvage demonstrated a trend to better 3-

TABLE 1. Study characteristics.

Authors	Study identifiers		Subject details			Survival data				
	Year of publication	Treatment modality	Type of study	Subjects, total	Time period	2-y DFS	3-y DFS	2-y OS	3-y OS	5-y OS
Andrews et al ⁹	2010	Surgery	Retrospective cohort	5	(1993–2004)	40%	30%	40%	20%	20%
Bachar et al ¹⁰	2009	Surgery	Retrospective cohort	175	(1970–1990)				23%	
Bussi et al ¹¹	1991	Surgery	Retrospective cohort	21	(1980–1988)			40%		24%
Brunin et al ¹²	1999	Surgery	Retrospective cohort	21	(1960–1992)	29%			21%	
Gehanno et al ¹³	1993	Surgery	Retrospective cohort	50	(1978–1985)				38%	24%
Grant et al ¹⁴	2008	Surgery	Retrospective cohort	52	(1996–2006)	55%	55%	55%	40%	40%
Fakhry et al ⁶	2014	Surgery	Retrospective cohort	49	(2002–2009)			61% overall 72% p16-pos 45% p16-neg		
Kaplan et al ¹⁵	1976	Surgery	Retrospective cohort	8	(1964–1971)	37.50%				49%
Kostrzewa et al ¹⁶	2010	Surgery	Retrospective cohort	36	(2001–2008)					19%
Maulard et al ¹⁷	1994	Brachytherapy	Retrospective cohort	28	(1981–1990)			25%	19%	14%
Mazoner et al ¹⁸	1987	Brachytherapy	Retrospective cohort	70	1971–1980			36%		43%
Nichols et al ¹⁹	2010	Surgery	Retrospective cohort	29	(1991–2008)	64.5%	22%			
Omura et al ²⁰	2014	Surgery	Retrospective cohort	18	(2001–2011)					
Puthawala et al ²¹	1985	Brachytherapy	Retrospective cohort	47	(1974–1982)	42%			20%	10%
Regueiro et al ²²	1995	Brachytherapy	Retrospective cohort	17	(1964–1989)				50%	50%
Reynolds et al ²³	2013	Surgery (TLM)	Retrospective cohort	6	(2002–2010)		20%	50%	22%	16%
Rodrigues et al ²⁴	1996	Surgery	Retrospective cohort	163	(1970–1990)					
Roosli et al ²⁵	2009	Surgery	Retrospective cohort	18	(1990–2006)				25%	
(prev CRT/DXT + surgery)									40%	
Roosli et al ²⁵	2009	Surgery	Retrospective cohort	15	(1990–2006)					
(prev surgery + DXT)									20%	
Roosli et al ²⁵	2009	Surgery	Retrospective cohort	15	(1990–2006)					
(prev surgery alone)										
Viani et al ²⁶	1991	Surgery	Retrospective cohort	47	(1963–1990)					31%
White et al ²⁷	2013	Surgery (open)	Retrospective cohort	64	(2003–2011)		74%			
White et al ²⁷	2013	Surgery (TORS)	Retrospective cohort	64	(2003–2011)		43%			
Wilson et al ²⁸	2014	Surgery	Retrospective cohort	28	(2004–2013)					54%
Zafereo et al ²⁹	2009	Surgery	Retrospective cohort	41	(1998–2005)		26%		42%	28%
Zafereo et al ²⁹	2009	Reirradiation	Retrospective cohort	18	(1998–2005)				32%	32%

Abbreviations: DFS, disease-free survival; OS, overall survival; TLM, transoral laser microsurgery; CRT, chemoradiotherapy; DXT, Radiotherapy; TORS, transoral robotic surgery.

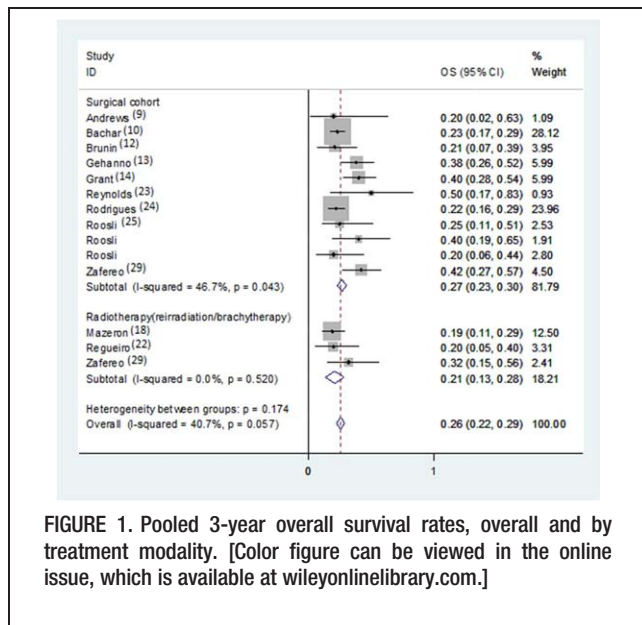


FIGURE 1. Pooled 3-year overall survival rates, overall and by treatment modality. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

year OS rate (27%) compared to brachytherapy/reirradiation (21%; see Figure 1), but the difference was not statistically significant ($p = .057$). Overall, heterogeneity between the groups was low ($I^2 = 37.3%$; $p = .072$).

Surgical treatment demonstrated a statistically significant higher 5-year OS rate compared to brachytherapy and reirradiation (26% vs 16%, respectively; $p < .001$; see Figure 2). The 5-year surgical cohort exhibited significant heterogeneity ($I^2 = 76.1%$; $p = .000$).

Survival trends over time

We also analyzed the results of treatment by the time-period of patient recruitment to assess trends in survival rates over time. We used the year 2000 as a cutoff. Because there were some studies that reported on patients recruited both before and after 2000 together, we included these studies in a third group. Therefore, we had 3 groups: (1) pre-2000; (2) pre-2000 and post-2000; (3) and post-2000.

Overall, there was a statistically significant improvement in 5-year survival over time: 18% in the pre-2000 cohort; 35% in the mixed pre-2000 and post-2000 group; and 51% in the post-2000 cohort ($p < .001$; see Figure 3). On comparing 5-year OS for the surgical cohort, the survival rate had significantly increased from 20% (pre-2000) to 35% (pre-2000 and post-2000) to 51% (post-2000; $p < .001$). In the radiotherapy cohort, there were only 2 groups (pre-2000 and pre-2000 and post-2000) because no study post-2000 had recruited patients for radiotherapy alone. Although 5 survival rates had improved in this cohort from 14% to 32%, the difference was not statistically significant ($p = .093$).

For the 3-year OS, there were only 2 studies examining patients exclusively post-2000. We therefore combined the last 2 groups (ie, pre-2000, and post-2000 and post-2000) for meta-analysis. Overall, the 3-year OS rate had improved from 23% to 35% (p value = .005; see Figure 4). The 3-year OS rate for the surgical cohort had improved from 24% to 35% (p value = .007), whereas

for the radiotherapy cohort, it had improved from 19% to 32% (p value = .237).

Treatment-related mortality and complications

In the 19 studies that reported treatment-related mortality data specific for oropharyngeal cancer recurrences, 27 (2.9%) treatment-related deaths were reported in 936 patients. On comparing the pooled data by time period of patient recruitment, treatment-related mortality had reduced from 4.5% pre-2000 to 0.7% in the combined (pre-2000 and post-2000) group, and no treatment-related deaths in the studies recruiting patients post-2000.

Thirteen studies reported the incidence of major complications, with a total of 72 reported complications (14.8%) in 485 patients. On analyzing results by time period of patient recruitment, the incidence of major treatment-related complications showed a steady decline from 22.8% pre-2000 to 15.2% in the combined (pre-2000 and post-2000) group to 5.3% in the post-2000 group.

Effect of human papillomavirus

Only 2 studies reported the HPV status of patients.^{6,20} Neither of these could be included in the quantitative meta-analysis because of lack of 3-year or 5-year OS data. The study by Omura et al²⁰ reported 3-year disease-free survival (DFS) rates, but included only 4 patients who were HPV-positive. As most of the patients who underwent salvage surgery were HPV-negative, he concluded that HPV status was of little relevance in his study.

In a recent study, Fakhry et al⁶ reported on their analysis of 49 patients with documented p16 status. The 29 patients with p16-positive disease who underwent salvage surgery had significantly better 2-year OS rates after salvage surgery (72% vs 45%; $p = .004$) compared with p16-negative patients.

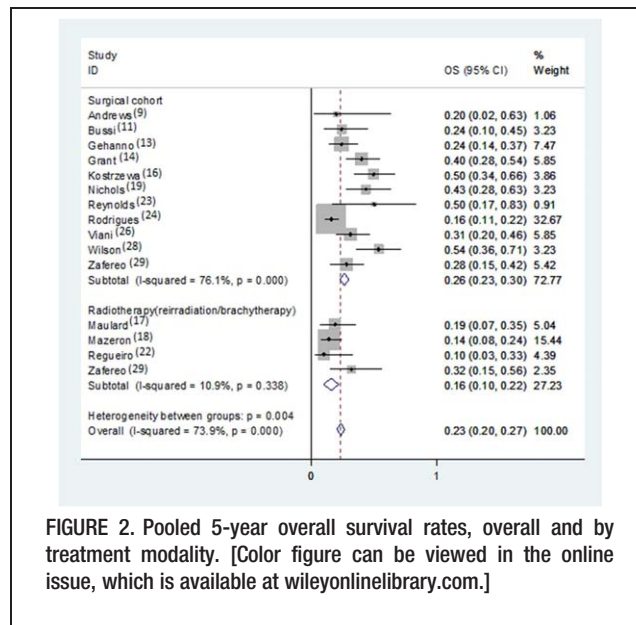


FIGURE 2. Pooled 5-year overall survival rates, overall and by treatment modality. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

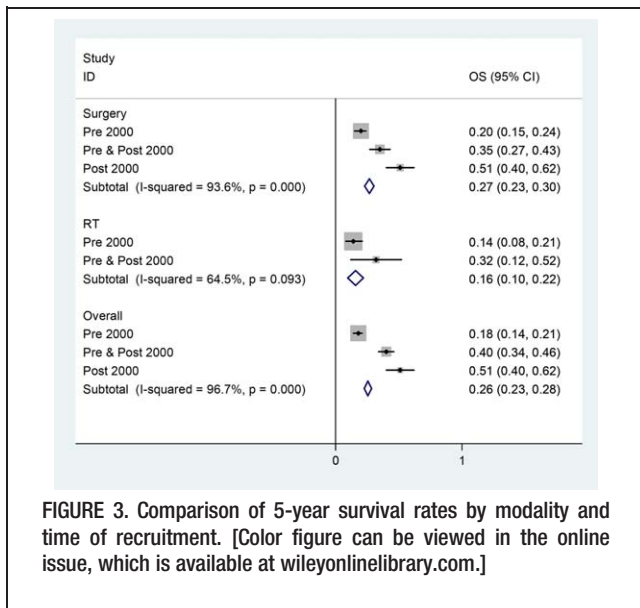


FIGURE 3. Comparison of 5-year survival rates by modality and time of recruitment. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Functional outcomes

Eight studies reported functional outcomes, with 209 of 339 patients (61.6%) able to return to an oral diet after treatment.

Prognostic factors

Although various studies assessed the significance of prognostic factors determining success of surgical salvage/reirradiation, only 3 studies separated oropharyngeal cancers from other head and neck subsites.

Bachar et al¹⁰ found that increasing T classification and N classification were significant predictors of time to death.

Nichols et al¹⁹ reported that the ability to completely resect the tumors and obtain negative margins was significantly associated with improved survival ($p < .01$). History of alcohol abuse was also associated with poorer survival. None of the other factors that they analyzed (including age, sex, subsite, recurrent T and N classifications, smoking, and perineural invasion) were statistically significant.

In the study by Zafereo et al,²⁹ a disease-free interval of >12 months ($p < .01$) and younger age ($p = .03$) were associated with higher OS rates. Patients with recurrent T3 or T4 tumors and patients showed a trend toward lower 3-year OS rates compared to T1 or T2, however, the difference was not statistically significant ($p = .07$). Similarly, patients with recurrent neck disease had a lower 3-year survival rate than patients without recurrent neck disease, but this difference was also not statistically significant ($p = .47$).

DISCUSSION

Traditionally, the treatment of patients with oropharyngeal recurrence is considered to have a poor prognosis and considerable morbidity, and, as a result, patients are often offered palliative or supportive care. Our results indicate that the outcomes of treatment of recurrent oropharyngeal cancer seem to have improved considerably

over the last 2 decades, now resulting in OS of up to 50% over 5 years. Complications after treatment seem to have reduced significantly over the past 2 decades, and are now relatively low. In addition, deaths from treatment of recurrence seem to be similar to those expected from the treatment of primary cancers. These remarkable improvements in the outcomes of treatment of recurrent oropharyngeal cancer in recent years suggest the need for reappraisal of the perception that outcomes of salvage treatment are poor. Our findings point to the possible need for a paradigm shift in the consideration of the treatment options and counseling offered to patients with oropharyngeal recurrence in the future, with appropriately selected patients being offered the option of treatments with a curative intent more frequently.

Overall, salvage surgery seems to have better survival outcomes compared to nonsurgical treatment (reirradiation). However, when adjusted for the period of recruitment of patients, it would seem that the apparent superiority of surgery may be due to the fact that the included surgical studies were more recent than the radiotherapy studies. Because more recent studies reported better outcomes, surgery shows an apparent overall better outcome than radiotherapy. On closer inspection, the efficacy of surgery seems to be better than radiotherapy only in cohorts recruited before the year 2000. In those studies that include a mixture of patients recruited before and after the year 2000, pooled overall 5-year survival seem to be very similar between surgery and radiotherapy (35% vs 32%, respectively). As for studies with patients recruited after 2000, only surgical studies are included in the meta-analysis, and so a comparison with radiotherapy cannot be made. Therefore, we cannot conclude that surgery is better than radiotherapy for the treatment of recurrent oropharyngeal cancer. Nevertheless, these surgical studies show a remarkable improvement to 5-year OS of 51%. Similarly, a recent study examining oropharyngeal cancer recurrence outcomes reported that surgical salvage was strongly and independently associated with improved survival after recurrence on multivariable analysis.⁶

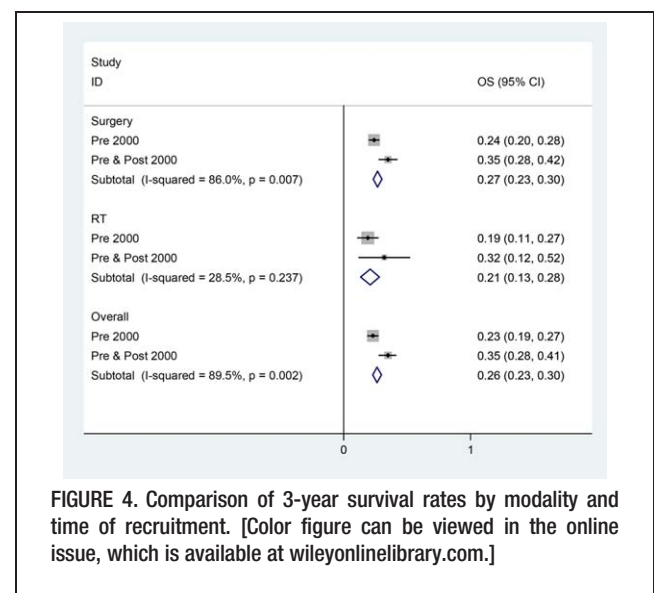


FIGURE 4. Comparison of 3-year survival rates by modality and time of recruitment. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Therefore, surgical salvage may be the best overall curative option for appropriately selected patients.

There may be several reasons for the marked improvement in the outcomes of treatment of recurrent oropharyngeal cancer with time. Improvements in surgical techniques with better reconstruction and better intraoperative and postoperative care, as well as improvement in radiotherapy techniques and quality assurance¹⁹ may have been partly responsible for this improvement in outcomes. The relatively low mortality rate and the remarkable reduction in complication rates reported over time lend support to this hypothesis. The realization of poor overall outcomes of salvage surgery in the past, as well as publication of data suggesting prognostic factors for better outcomes, may have led to improved selection of patients. It could be postulated that this better selection, as well as increased multidisciplinary working and centralization of services in some countries, may have also led to better outcomes. Importantly, the increase in the incidence of HPV-related oropharyngeal cancer may also have a significant role. Primary HPV-associated head and neck cancer has significantly better outcomes than HPV-negative head and neck cancers. The recent study by Fakhry et al⁶ suggests that the improved prognosis may also apply to patients with HPV-positive recurrence. In addition, the study reported that patients who were p16-positive and received surgery demonstrated significantly better survival rates compared with p16-negative patients who had surgery (72% vs 45% 2-year survival; $p = .004$). It is likely that a combination of all the above factors has contributed to this remarkable increase in OS.

The reporting of prognostic factors determining success of salvage treatment was limited with only 3 studies, all of which reported factors determining success of salvage surgery. These studies reported different factors to be statistically significant – including T classification,¹⁰ N classification,¹⁰ complete resection with negative margins, alcohol abuse,¹⁹ disease-free interval²⁹ and mean age at presentation.²⁹

Limitations of the study

There was a lack of uniformity in the presentation and reporting of data by studies. We could not include a few large studies of mixed head and neck sites because it was not possible to extract or obtain oropharyngeal specific survival data separate to other data.^{30–33} Some of the studies included in the qualitative analysis could not be included in the meta-analysis because of absence of either 3-year or 5-year OS data.^{6,15,20,21,27} Furthermore, reported prognostic data were limited and disparate and could not be subjected to meta-analysis.

Implications for research and practice

Research regarding the management of recurrent oropharyngeal cancers is of relatively low quality and quantity. Because outcomes seem to be improving considerably, it is important that this area is studied more and that the quality of studies is improved. It is recommended that, in the future, authors should adhere to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines³⁴ for reporting studies and pres-

ent point estimates of data and its measure of variability. Furthermore, because of the low number of patients being treated for recurrent oropharyngeal cancer, national databases should be set up to examine outcomes of these patients and to explore better predictors of improved outcome and patient selection. In addition, harmonization of the definitions of the different predictive factors to be studied would be of great benefit in the long term.

Furthermore, HPV status should be documented for all patients, and its effect on the outcomes of patients with oropharyngeal cancer recurrence should be explored further. Finally, more research on functional and quality of life outcomes and treatment cost in the management of oropharyngeal recurrence are needed.

REFERENCES

- Goodwin WJ Jr. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means? *Laryngoscope* 2000;110(3 Pt 2 Suppl 93):1–18.
- Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008;359:1116–1127.
- Kowalski LP, Carvalho AL. Natural history of untreated head and neck cancer. *Eur J Cancer* 2000;36:1032–1037.
- Mehanna H, Beech T, Nicholson T, et al. Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer – systematic review and meta-analysis of trends by time and region. *Head Neck* 2013;35:747–755.
- Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010;363:24–35.
- Fakhry C, Zhang Q, Nguyen-Tan PF, et al. Human papillomavirus and overall survival after progression of oropharyngeal squamous cell carcinoma. *J Clin Oncol* 2014;32:3365–3373.
- Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg* 2003;73:712–716.
- Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. *Stat Sci* 2001;16:101–117.
- Andrews G, Lango M, Cohen R, et al. Nonsurgical management of oropharyngeal, laryngeal, and hypopharyngeal cancer: the Fox Chase Cancer Center experience. *Head Neck* 2011;33:1433–1440.
- Bachar GY, Goh C, Goldstein DP, O'Sullivan B, Irish JC. Long-term outcome analysis after surgical salvage for recurrent tonsil carcinoma following radical radiotherapy. *Eur Arch Otorhinolaryngol* 2010;267:295–301.
- Bussi M, Giordano C, Carlevato MT, Ferrero V, Farri A, Orecchia R. Recurrence after radiotherapy and/or surgery of carcinoma of the oropharynx and the pharynx. Possibilities of salvage surgery [in Italian]. *Radiol Med* 1990;82:137–142.
- Brunin F, Mosseri V, Jaulerry C, Point D, Cosset JM, Rodriguez J. Cancer of the base of the tongue: past and future. *Head Neck* 1999;21:751–759.
- Gehanno P, Depondt J, Guedon C, Kebaili C, Koka V. Primary and salvage surgery for cancer of the tonsillar region: a retrospective study of 120 patients. *Head Neck* 1993;15:185–189.
- Grant DG, Salassa JR, Hinni ML, Pearson BW, Hayden RE, Perry WC. Transoral laser microsurgery for recurrent laryngeal and pharyngeal cancer. *Otolaryngol Head Neck Surg* 2008;138:606–613.
- Kaplan R, Million RR, Cassisi NJ. Carcinoma of the tonsil: results of radical irradiation with surgery reserved for radiation failure. *Laryngoscope* 1977;87(4 Pt 1):600–607.
- Kostrzewa JP, Lancaster WP, Iseli TA, Desmond RA, Carroll WR, Rosenthal EL. Outcomes of salvage surgery with free flap reconstruction for recurrent oral and oropharyngeal cancer. *Laryngoscope* 2010;120:267–272.
- Maulard C, Housset M, Delanian S, et al. Salvage split course brachytherapy for tonsil and soft palate carcinoma: treatment techniques and results. *Laryngoscope* 1994;104(3 Pt 1):359–363.
- Mazoner JJ, Langlois D, Glaubiger D, et al. Salvage irradiation of oropharyngeal cancers using iridium 192 wire implants: 5-year results of 70 cases. *Int J Radiat Oncol Biol Phys* 1987;13:957–962.
- Nichols AC, Kneuert PJ, Deschler DG, et al. Surgical salvage of the oropharynx after failure of organ-sparing therapy. *Head Neck* 2011;33:516–524.
- Omura G, Saito Y, Ando M, et al. Salvage surgery for local residual or recurrent pharyngeal cancer after radiotherapy or chemoradiotherapy. *Laryngoscope* 2014;124:2075–2080.
- Puthawala AA, Syed AM, Gates TC. Iridium-192 implants in the treatment of tonsillar region malignancies. *Arch Otolaryngol* 1985;111:812–815.
- Regueiro CA, de la Torre A, Valcárcel FJ, Magallón R, Aragón G. Salvage brachytherapy and salvage surgery for recurrent oropharyngeal carcinoma following radiotherapy. *J Laryngol Otol* 1995;109:45–48.

23. Reynolds LF, Rigby MH, Trites J, Hart R, Taylor SM. Outcomes of transoral laser microsurgery for recurrent head and neck cancer. *J Laryngol Otol* 2013;127:982–986.
24. Rodriguez J, Point D, Brunin F, Jaulerry C, Brugère J. Surgery of the oropharynx after radiotherapy [in French]. *Bull Cancer Radiother* 1996;83:24–30.
25. Rööslä C, Studer G, Stoeckli SJ. Salvage treatment for recurrent oropharyngeal squamous cell carcinoma. *Head Neck* 2010;32:989–996.
26. Viani L, Dammeijer P, Jones AS, Dalby JE, Stell PM. Recurrence of oropharyngeal carcinoma after radiotherapy. *J Laryngol Otol* 1991;105:24–28.
27. White H, Ford S, Bush B, et al. Salvage surgery for recurrent cancers of the oropharynx: comparing TORS with standard open surgical approaches. *JAMA Otolaryngol Head Neck Surg* 2013;139:773–778.
28. Wilson L, Enepekides D, Higgins K. Management of oropharyngeal cancer: a cross-sectional review of institutional practice at a large Canadian referral centre. *J Otolaryngol Head Neck Surg* 2014;43:19.
29. Zafereo ME, Hanasono MM, Rosenthal DI, et al. The role of salvage surgery in patients with recurrent squamous cell carcinoma of the oropharynx. *Cancer* 2009;115:5723–5733.
30. Agra IM, Carvalho AL, Ulbrich FS, et al. Prognostic factors in salvage surgery for recurrent oral and oropharyngeal cancer. *Head Neck* 2006;28:107–113.
31. Chen YJ, Kuo JV, Ramsinghani NS, Al-Ghazi MS. Intensity-modulated radiotherapy for previously irradiated, recurrent head-and-neck cancer. *Med Dosim* 2002;27:171–176.
32. Kupferman ME, Morrison WH, Santillan AA, et al. The role of interstitial brachytherapy with salvage surgery for the management of recurrent head and neck cancers. *Cancer* 2007;109:2052–2057.
33. Temam S, Pape E, Janot F, et al. Salvage surgery after failure of very accelerated radiotherapy in advanced head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys* 2005;62:1078–1083.
34. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;370:1453–1457.