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Review

Evolution in the management of oropharyngeal squamous cell carcinoma: systematic review of outcomes over the last 25 years

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Abstract

The treatment of oropharyngeal squamous cell carcinoma (SCC) has evolved over the last 25 years, from open surgery to combined chemoradiotherapy, and now to the development of minimally invasive procedures, but evidence for the best treatment is lacking. We therefore did a systematic search of the MEDLINE database for studies published between 1992 and 2017 that reported oncological or functional outcomes, or both. Predefined inclusion and exclusion criteria were used for screening and selection, and 45 studies were chosen. Only one was a randomised controlled trial, all the rest were prospective or retrospective case series. The heterogeneities in their characteristics made meta-analysis impossible and only qualitative analysis was feasible. We found no conclusive evidence to suggest the advantage of one therapeutic approach over another, so we still cannot offer patients the "ideal" treatment. We have, however, raised the possibility of there being two different entities: human papillomavirus (HPV)-positive and HPV-negative disease.

Keywords: Oropharyngeal Squamous Cell Carcinoma; Management; Treatment; Outcomes; Systematic Review

Introduction

The incidence of oropharyngeal squamous cell carcinoma (SCC) is rising throughout the developed world, particularly in North America, Northern Europe, and Taiwan.[1,2]

In 2007, the International Agency for Research on Cancer (IARC) reported that the human papillomavirus (HPV) type16 was a cause of both oropharyngeal and oral cavity cancer[3] (until then, the main causes had been thought to be consumption of tobacco and alcohol). Recent studies have shown that HPV causes more than 5% of cancers worldwide, including all cervical, and an increasing proportion of oropharyngeal cancers.[4] The incidence of oropharyngeal SCC has been predicted to surpass that of cervical cancer in some developed countries,[5] and currently, the number of patients with the disease worldwide affects the resources that are available because so many cases are now attributed to the virus.

The oropharynx should be considered as a separate entity from the rest of the head and neck because of its distinctive anatomical and histological features. A recent American epidemiological study that included four decades of data (1973–2012) confirmed that cancers of the oral cavity and pharynx do not have a single cause. It showed that the incidence of most cancers of the oral cavity (vestibular cancers,

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and those of the lip, gum, floor of the mouth, hard palate, and buccal mucosa) had declined considerably as a result of a reduction in smoking in the United States, but that the incidence of oropharyngeal cancers and cancers of the tongue had increased to a similar extent in both sexes. Age-period-cohort analyses have shown increases in the incidence of oropharyngeal cancers and those of the tongue, but the greatest increase was in oropharyngeal cancers.[6]

The prevalence of HPV in oropharyngeal SCC has also increased considerably in the European population. A 2016 multicentre cross-sectional retrospective study on patients diagnosed between 2002 and 2011 in the United Kingdom showed that although the number of cases had nearly doubled, the proportion of those without HPV remained at roughly 50%.[7] Results were similar in East Germany (1998–2011). Compared with the United States, the epidemiological shift over recent decades in European countries from HPV-negative to HPV-positive disease seems to have been delayed because of minor behavioural changes (consumption of alcohol and tobacco smoking).[8] According to the conclusions of these studies, however, the rapid increase in the incidence of oropharyngeal SCC cannot be attributed solely to the influence of HPV.

The oropharynx comprises the base of the tongue, soft palate, palatine tonsillar fossa, and pharyngeal wall. The palatine and lingual tonsils, together with the pharyngeal (adenoid) and tubal tonsils of the nasopharynx, form a circular area of mucosa-associated lymphoid tissue (MALT) known as Waldeyer's tonsillar ring.

Histologically, the mucosa of this region is distinct from other mucosal surfaces, as it is composed of lymphoepithelium, a reticulated epithelium with a discontinuous basement membrane. The palatine tonsils have the most convoluted and deep crypts, followed by the lingual tonsils. The adenoids and tubal tonsils contain less of this lymphoid tissue.

SCC accounts for more than 95% of tumours of the oropharynx. The lack of a consistent basement membrane in the palatine and lingual tonsils precludes the possibility of the disease being restricted by their surfaces (SCC in situ tends to occur only in the soft palate and pharyngeal wall), and more than 60% of patients with SCC of the oropharynx (notably of the tonsil and base of the tongue) present with involved cervical lymph nodes. Between 10% and 15% have distant metastases.[9]

Anatomically, the oropharynx is the intersection between the airway and digestive tract, and it has a strategic role in the swallowing process. Surgery and radiological interventions for oropharyngeal SCC can damage the pharyngeal tissues and result in obstruction, xerostomia, stenosis, or lack of muscular coordination, and will eventually lead to dysphagia.[10]

The ultimate goal of treatment is to cure, prevent secondary tumours or recurrence, preserve function (speech, swallowing, and taste), and minimise complications. To achieve this, management has evolved, and the Veterans Affairs Laryngeal Cancer Study in 1991, which showed the effectiveness of chemoradiotherapy to preserve the larynx in cases of advanced cancers (stage III or IV),[11] established the conversion from surgical management to organ preservation. This new approach resulted in the adoption of combined chemoradiotherapy alone as the first-line treatment for oropharyngeal SCC despite a lack of studies and evidence.

Currently, when operation is the first method of treatment, minimal access techniques such as transoral laser microsurgery or transoral robotic surgery (TORS) are used. Two-dimensional radiotherapy has evolved into less toxic intensity-modulated radiotherapy (IMRT), and new de-escalations in protocols for chemoradiation have been studied to reduce complications.[12]

Decisions about the best approach should take these changes into account.

We know of no recommended published guideline that compares the effectiveness of different treatments in terms of oncological and functional outcomes. The purpose of this systematic review therefore was to establish whether these changes in the treatment and management of oropharyngeal SCC over the last 25 years have improved outcomes in terms of disease control, maintenance of function, and reduction in toxicity.

Aim

All patients studied were treated with curative intent. We compared the results of the different treatments (conventional and minimally-invasive surgery, radiotherapy, chemotherapy, or a combination) and used the oncological and functional outcomes as benchmarks for success. Our main objective was to find out which, if any, is the most effective.

Material and methods

Electronic search strategy

For this systematic study, we developed a detailed search strategy in collaboration with a specialist librarian. We searched the MEDLINE database in May 2017 for all original studies published between 1992 and 2017 using the following search terms: "oropharyngeal", "squamous cell carcinoma", "management", "treatment", "surgery", "minimally invasive surgery", "minimally invasive procedures", "outcomes", "salvage", "response to treatment", "neoadjuvant chemotherapy", "induction chemotherapy", "chemoradiation", "radiotherapy", "radiation therapy", "intensity-modulated radiation therapy", "target therapy", and "targeted drugs".

We considered only studies in the English language and those on human subjects.

All the papers included focused on the oncological or functional outcomes, or both, of treatments for oropharyngeal SCC. They reported original research including randomised trials, cohort studies, case control studies, retrospective and prospective observational studies, and case series of more

than 10 patients. Overviews, reviews, meta-analyses, and papers that did not focus on the treatment and outcomes of patients with oropharyngeal SCC, together with those that included fewer than 10 patients, or patients with tumours in other sites (nasopharynx, hypopharynx, larynx, or oral cavity), were excluded.

Search for other resources

We also searched the references of the papers included and other reviews of the treatment of oropharyngeal SCC (not included in the study) to identify further relevant papers.

Review process

Two reviewers assessed the titles and abstracts for relevance. If the abstract did not clearly state the site of the tumour, the full text was screened. Full texts of all the papers included were retrieved, and two authors reviewed them independently for relevance. Any disagreements were resolved by discussion with the third author. The review was conducted according to the Prisma extension statement for the reporting of systematic reviews.[13] No ethics approval was required.

Data extraction and management

The data were extracted independently by both reviewers and stored on a Microsoft Excel spread sheet. In each case we recorded the year of publication, period and design of the study, site and type of treatment, stage of disease, number of patients, follow up, oncological outcome (overall and disease-free survival, and locoregional control), functional outcome (including method of assessment), and complications.

Details of the studies are shown in Table 1.[14–59]

Quality assessment

Table 2 summarises the methodological quality of evidence of each study based on the levels published by the Oxford Centre for Evidence–based Medicine.[60]

Results

Fig. 1 shows the search strategy. A total of 46 papers (45 studies) were finally included. Two papers reported the outcomes of one study (Holsinger et al[44] reported functional outcomes, and Laccourreye et al[45] oncological outcomes).

Study characteristics

Only one of the studies was randomised.[34] Twelve were prospective case series.[34,37,40,46–50,53,54,56,57] All the rest were retrospective case series,[14–33,35,36,38,39,41–45,51,52,55,58,59] of which three were matched for stage of disease.[43,52,55] A total of 27 papers considered all four subsites of the oropharynx,[21–24,27,31,32,34,36–43,47–50,52,53,55–59] ten focused on the tonsil,[15–18,26,33,35,44,45,54] eight on the base of the tongue,[14,19,20,25,29,30,46,51] and one on the lateral wall.[28]

Twenty-one compared different treatments[15–17,20,21,23,25,31,34–38,42,43,52,54–57,59] while 25 did not.[14,18,19,22,24,26–30,32,33,39–41,44–51,53,58]

A total of 27 papers considered all stages of disease.[14–19,23,25,27,28,31–33,36,37,39,44–47,50–53,55,57,59] The rest considered only early[21,22,24,30,40,48,54,56,58] or advanced cancer.[20,26,29,34,35,38,41–43,49] All studies reported different follow-up rates.

A total of 30 papers reported overall survival,[14,15,18,19,22,24–26,28–32,34–36,38,39,41–46,49,51,52,54,57,58] and of them, 19 reported it at five years. A total of 20 reported locoregional control (13 at five years),[15,16,24,25,30–36,38,39,44–46,49,51,57,58] and 23 disease-free survival (15 at five years).[16,17,19,26,28–36,38,39,42,46,49,51,54,55,57,58]

A total of 24 objectively assessed functional outcomes and quality of life.[20–23,27,28,37,40,42–54,56,58,59] Table 3 shows the questionnaires that were used, and Table 4 the objective assessments. In one publication a multivariate analysis had been done to assess the ability to swallow solids, pastes, and liquids.[27]

Complications were reported in 32 publications.[14,15,17–19,21,22,27–29,32–36,38–47,49,51–54,57,58]

We had planned to use the data for statistical analysis, but the heterogeneities in the studies' characteristics (different comparisons and outcome measures) made it impossible.

The data, however, provide an overview of the changes in management during the last 25 years, and to show this, we have grouped the publications chronologically according to approach: conventional surgery, organ preservation, and minimally-invasive surgery.

Conventional surgery

The first retrospective studies from 1993 and 1994 supported aggressive surgery for oropharyngeal cancers, and reported good survival and local control in patients with SCC of the base of the tongue[14] and tonsil.[15] Resection was done through a transoral approach, mandibular osteotomy, partial mandibulectomy, or pharyngotomy. In both studies, adjuvant treatment was suggested only in advanced stages (III and IV) to improve locoregional control. The most common complications were wound infections, partial flap necrosis, and pulmonary compromise. Outcomes for speech and swallowing were satisfactory, but no objective measures were used.[14,15]

In 1998, a retrospective study on tonsillar SCC showed that radiation was a valid alternative to operation for local disease (stage I/II). In cases of advanced disease (stage III/IV), however, five-year local control with radiotherapy alone was

Table 1
Study characteristics.

First author, year, and reference	Group	Site	Management	Stage	No. of patients	Follow up (months)	Oncological outcome			Functional outcome/QoL objective measurement	Reported complications
							Overall survival	Locoregional control	Disease-free survival		
Kraus 1993[14]	1979–1989	BoT	Operation +/− RT	T1,T2,T3,T4	100	Median 39.6	5-year I/II 77%, III 64%, IV 59%	NR	NR	NR	Yes
Foote 1994[15]	1970–1988	Tonsil	Operation cf operation + RT	T1,T2,T3,T4	72 (56 cf 16)	Minimum 42	5-year III 56% cf 100%, IV 43% cf 78%	5-year I 77% cf 78%, II 70% cf 83%, III/IV75% cf 44%	NR	NR	Yes
Hicks 1998[16]	1971–1991	Tonsil	Operation alone cf RT alone	T1,T2,T3,T4	76 (56 cf 20)	Median 42	NR	5-year 75% cf 60%	5-year 61% cf 37%	NR	No
Perez 1998[17]	1959–1991	Tonsil	RT cf preRT + operation cf operation + post RT	T1,T2,T3,T4	384 (154 cf 144 cf 86)	Median 111.6	NR	NR	5-year I 50% cf 50%, II 23% cf 60% cf 50%, III 50% cf 57% cf 62%, IV 58% cf 50% cf 50%	NR	Yes
Galati 2000[18]	1981–1995	Tonsil	Operation +/− RT	T1,T2,T3,T4	162	Minimum 24	5-year I 89%, II 91%, III 79%, IV 52%	NR	NR	NR	Yes
Gourin 2001[19]	1980–1997	BoT	Operation +/− RT	T1,T2,T3,T4	87	Median 38	5-year 49%	NR	5-year I 100%, II 86%, III 62%, IV 48%	NR	Yes
Perlmutter 2002[20]	1976–2000	BoT	Operation cf no operation	T3,T4	61 (43 cf 18)	Median 38.5	NR	NR	NR	3 questionnaires: PSSHN, UW-QoL, history of treatment	No
Pourel 2002[21]	1992–1998	OP	Surgery + RT cf BT +/− EBRT cf EBRT alone	T1,T2,T3	113 (27 cf 49 cf 37)	Median 62	NR	NR	NR	2 questionnaires: EORTC QLQ C30, EORTC H&N35	Yes
Watkinson 2002[22]	1993–2000	OP	Operation + RT	T1,T2	18	Median 45,6	2-year 100%, 5-year 92%	NR	NR	2 questionnaires: EORTC QLQ C30, GHQ-12	Yes
Allal 2003[23]	1981–1998	OP	Operation + RT cf RT +/− CT	T1,T2,T3,T4	60 (20 cf 40)	Median 78 cf 27	NR	NR	NR	2 questionnaires: PSSHN, EORTC QLQ C30	No
Cosmidis 2004[24]	1995–2000	OP	Operation alone	T1,T2 N0	53	Up to 60	1-year 100%, 3-year 94.6%, 5-year 73%	1-year 96.22%, 3-year 92.45%, 5-year 88.68%	NR	NR	No

Barrett 2004[25]	1992–1998	BoT	Operation + RT cf RT cf RT + interstitial RT	T1,T2,T3,T4	53 (17 cf 16 cf 20)	Median 31	5-year 44% cf 24% cf 33%	5-year 74% cf 25% cf 87%	NR	NR	No
Bachar 2010[26]	1970–1990	Tonsil	Salvage operation after RT	NR	175	Up to 60	5-year 23%	NR	5-year 40%	NR	No
Buiret 2011[27]	1998–2003	OP	Operation +/− RT+/− chemotherapy	T1,T2,T3,T4	254	Up to 120	NR	NR	NR	Alimentation multivariate model analysis, NGT dependence, weight loss	Yes
Diaz-Molina 2011[28]	1990–2008	Lateral wall	Operation +/− RT	T1,T2,T3,T4	155	Median 39	5-year 33%	NR	5-year 43%	Tracheotomy duration; NGT dependence	Yes
Rodrigo 2011 [29]	1990–2007	BoT	Transhyoid operation +/− RT	II,III,IV	84	Median 19	5-year 19%	NR	5-year 31%	NR	Yes
Iyer 2013[30]	1985–2005	BoT	Operation +/− CRT	T1,T2	128	Median 68	5-year 60%	5-year 70%	5-year 61%	NR	No
Iyer 2015[31]	1985–2005	OP	Operation +/− RT P16 + OPC cf P16 - OPC	T1,T2,T3,T4	201 (106 cf 95)	Up to 60	5-year 60% (74% cf 44%)	5-year 89%	5-year 76% (84% cf 66%)	NR	No
Fein 1996[32]	1964–1991	OP	RT +/− neck dissection +/− salvage surgery	T1,T2,T3,T4	490	Minimum 24	5-year 44%	5-year 85%	5-year 77%	NR	Yes
Mendenhall 2000[33]	1964–1997	Tonsil	RT +/− neck dissection	T1,T2,T3,T4	400	Minimum 24	NR	5-year T1 83%,T2 81%,T3 74%,T4 60%	5-year I 100%, II 86%, III 82%, IVa 63%, IVb 22%	NR	Yes
Denis 2004[34]	1994–2001	OP	RT cf CRT	III,IV	226 (113 cf 109)	Median 66	5-year 15.8% cf 22.4%	5 year 24.7% cf 47.6%	5-year 14.6% cf 26.6%	NR	Yes
Shirazi 2006[35]	1994–2002	Tonsil	CRT cf operation	T3,T4	74 (38 cf 36)	Median 34.8	4-year 41% cf 71%	4-year 48% cf 71%	4-year 86% cf 94%	NR	Yes

Table 1 (*Continued*)

First author, year, and reference	Group	Site	Management	Stage	No. of patients	Follow up (months)	Oncological outcome			Functional outcome/QoL objective measurement	Reported complications
							Overall survival	Locoregional control	Disease-free survival		
Hodge 2007[36]	1995–2005	OP	IMRT cf RT cf RTpreIMRTera	T1,T2,T3,T4	195 (52 cf 38 cf 105)	Median 30.4	3-year 88.2% cf 81.1% cf 67.7%	3-year 96.1% cf 78.1% cf 88.1%	3-year 97.7% cf 83.5% cf 79.9%	NR	Yes
Yao 2007[37]	1997–2005	OP	IMRT cf conventional RT	T1,T2,T3,T4	53 (26 cf 27)	12	NR	NR	NR	Questionnaire: HNCI HRQoL	No
Rusthoven 2008[38]	1998–2007	OP	3D-CRT cf AFRT-CB cf IMRT	III, IV	87 (23 cf 32 cf 32)	Median 24	2-year 77.3%	2-year 86,4%	2-year 69.5%	NR	Yes
Mendenhall 2010[39]	2001–2007	OP	IMRT	T1,T2,T3,T4	130	Median 42	5-year 76%	5-year 87%	5-year 93%	NR	Yes
Cartmill 2012[40]	2006–2009	OP	AFRT-CB	T1,T2,T3	12	24	NR	NR	NR	Questionnaire: MDADI	Yes
Self 2013[41]	2005–2010	OP	CT without operation	T2,T3,T4	139	24	13.0 months haemorrhages cf 50.0 months haemorrhage	NR	NR	NR	Yes
Lohia 2014[42]	2000–2009	OP	IMRT cf 3D-CRT	T2,T3,T4	159 (103 cf 56)	Median 34.8 cf 57.5	2-year 62% cf 71%	NR	2-year 59% cf 66%	ECOG performance status; NGT dependence;Weight loss	Yes
Dobrosotskaya 2014[43]	2000–2002	OP	CRT carboplatin and cisplatin + RT cf weekly carboplatin + RT	T3,T4	70 (35 cf 35)	36	3-year 71% cf 88%	NR	NR	NGT dependence 26% cf 6%	Yes
Holsinger 2005[*,44] Laccourreye 2005[*,45]	1978–1998	Tonsil	TLO +/− induction CT or RT +/− post RT	T1,T2,T3,T4	191	Mean 120	1-year 87.5%, 3-year 66.2%, 5-year 56.2%	1-year 91.2% 3-year 82.1%, 5-year 82.1%	NR	NGT dependence; tracheotomy duration; hospital stay duration	Yes
Grant 2006[46]	1997–2005	BoT	TLM +/− RT	T1,T2,T3,T4	59	Mean 31	2-year T192%,T2 91%,T3100%,T4 75%, 5-year T1 58%, T2 91%,T3 75%, T4 38%	2-year and 5-year T1 100%,T2 87%,T3 100%,T4 69%	2-year and 5-year: 84%	FOSS, CS	Yes
Moore 2009[47]	2007–2008	OP	TORS +/− CRT	T1,T2,T3,T4	45	1	NR	NR	NR	FOSS, CS	Yes
Sinclair 2011[48]	2007–2010	OP	TORS +/− CRT	T1,T2	42	Median 17	NR	NR	NR	Questionnaire: MDADI	No
Haughey 2011[49]	1996–2006	OP	TLM + neck dissection +/− CRT	III,IV	204	Mean 49	2-year 89%, 3-year 86,5%, 5-year 78%	NR	2-year 85%, 3-year 82%, 5-year 74%	NGT dependence; FOSS, hospital stay duration	Yes

Leonhardt 2012[50]	2007–2008	OP	TORS +/− CRT	T1,T2,T3,T4	38	12	NR	NR	NR	2 questionnaires: PSSHN, SF-8 health survey	No
Canis 2013[51]	1986–2007	BoT	TLM +/− CRT	I,II,III,IV	82	Median 51	5-year I–II 70%, III 44%, IV 58%	5-year I–II 94%, III 78%, IV 81%	5-year I–II 86%, III 54%, IV 69%	NGT dependence	Yes
White 2013[52]	2003–2011	OP	Salvage surgery: TORS cf open surgery	T1,T2,T3,T4	128 (64 cf 64)	24	2-year 74% cf 43%	NR	NR	NGT dependence; tracheotomy duration; hospital stay duration	Yes
Dziegielewski 2013[53]	2008–2012	OP	TORS	T1,T2,T3,T4	81	Mean 22.7	NR	NR	NR	Questionnaire: HNCI HRQoL; NGT dependence; hospital stay duration	Yes
Lee 2014 [54]	2008–2011	Tonsil	TORS cf conventional surgery	T1,T2,T3	57(27 cf 30)	Mean 20.3	2-year 100% cf 96.7%	NR	2-year 95,6% cf 91,6%	2 questionnaires: VHI 10, MDADI; NGT dependence	Yes
Ford 2014[55]	2004–2012	OP	TORS cf open surgery	T1,T2,T3,T4	130 (65 cf 65)	36	NR	NR	1-year 94% cf 85%, 2-year 91% cf 75%, 3-year 89% cf 73%	NR	No
O'Hara 2015[56]	2011–2013	OP	TLM +/− CRT cf CRT	T1,T2,T3	56 (23 cf 33)	3	NR	NR	NR	Questionnaire: MDADI; Normalcy of Diet Scale (subsection of PSSHN); WST time	No
Smith 2015[57]	2000–2009	OP	TORS + neck dissection cf CRT	T1,T2,T3,T4	70 (42 cf 38)	33	3-year 83% cf 57%	3-year 90% cf 74%	3-year 94% cf 85%	NR	Yes
Chauhan 2015[58]	2010–2014	OP	TLM	T1,T2	12	Median 15	1-year 82%	1-year 100%	1-year 100%	NGT dependence	Yes
Zevallos 2016[59]	2010–2011	OP	TORS cf non-robotic transoral surgery	T1,T2,T3,T4	514 (369 cf 145)	1	NR	NR	NR	30 days readmission	No

cf = compared with; QoL = quality of life; BoT = base of tongue; RT = radiotherapy; NR = not reported; PSSHN = performance status scale for head and neck cancer patients; UW-QoL, University of Washington quality of life instrument; OP = oropharynx; BT = brachytherapy; EBRT = external beam radiotherapy; EORTC = European Organisation for Research and Treatment of Cancer; GHQ = General Health Questionnaire; CT = chemotherapy; NGT = nasogastric tube; CRT = chemoradiotherapy; OPC = oropharyngeal cancer; IMRT = intensity-modulated radiotherapy; HNCI HRQoL = Head and Neck Cancer Inventory health-related quality of life; 3D-CRT = 3-dimensional conformal radiotherapy; AFRT-CB = accelerated fractionation radiotherapy with concomitant boost; MDADI = MD Anderson Dysphagia Inventory; ECOG = Eastern Cooperative Oncology Group; TLO = transoral lateral oropharyngectomy; TLM = transoral laser microsurgery; FOSS = Functional Outcome Swallowing Scale; CS = Communication Scale; TORS = transoral robotic surgery; S = short form; VHI = Voice Handicap Index; WST = water swallow test.

* Holsinger et al[44] and Laccourreye et al[45] reported outcomes from the same study.

Table 2
Methodological quality of evidence based on the Oxford Centre for Evidence–based Medicine.

First author and reference	Year	Study design	Level of evidence
Kraus[14]	1993	Retrospective	4
Foote[15]	1994	Retrospective	4
Hicks[16]	1998	Retrospective	4
Perez[17]	1998	Retrospective	4
Galati[18]	2000	Retrospective	4
Gourin[19]	2001	Retrospective	4
Perlmutter[20]	2002	Retrospective	4
Pourel[21]	2002	Retrospective	4
Watkinson[22]	2002	Retrospective	4
Allal[23]	2003	Retrospective	4
Cosmidis[24]	2004	Retrospective	4
Barrett[25]	2004	Retrospective	4
Bachar[26]	2010	Retrospective	4
Buiret[27]	2011	Retrospective	4
Diaz-Molina[28]	2011	Retrospective	4
Rodrigo[29]	2011	Retrospective	4
lyer[30]	2013	Retrospective	4
Iyer[31]	2015	Retrospective	4
Fein[32]	1995	Retrospective	4
Mendenhall[33]	2000	Retrospective	4
Denis[34]	2004	Prospective randomised	3B
Shirazi[35]	2005	Retrospective	4
Hodge[36]	2007	Retrospective	4
Yao[37]	2007	Prospective non-randomised	4
Rusthoven[38]	2008	Retrospective	4
Mendenhall[39]	2010	Retrospective	4
Cartmill[40]	2011	Prospective non-randomised	4
Self[41]	2013	Retrospective	4
Lohia[42]	2014	Retrospective	4
Dobrosotskaya[43]	2014	Retrospective matched	4
Holsinger*,[44]	2005	Retrospective	4
Laccourreye*,[45]			
Grant [46]	2006	Prospective non-randomised	4
Moore [47]	2009	Prospective non-randomised	4
Sinclair[48]	2011	Prospective non-randomised	4
Haughey[49]	2011	Prospective non-randomised	4
Leonhard[50]	2012	Prospective non-randomised	4
Canis[51]	2013	Retrospective	4
White[52]	2013	Retrospective matched	4
Dziegielewski[53]	2013	Prospective non-randomised	4
Lee[54]	2014	Prospective non-randomised	4
Ford[55]	2014	Retrospective matched	4
O'Hara[56]	2015	Prospective non-randomised	4
Smith[57]	2015	Prospective non-randomised	4
Chauhan[58]	2015	Retrospective	4
Zevallos[59]	2016	Retrospective	4

* Holsinger et al[44] and Laccourreye et al[45] reported outcomes from the same study.

not satisfactory when compared with operation (five-year disease-specific survival was 47% in the operation group and 27% in the radiation group).[16]

In the same year, Perez et al reported long-term oncological outcomes (five and 10 years) of 32 years' experience (1959–1991) of radiotherapy alone, preoperatively, and postoperatively. They thought that radiotherapy was the treatment of choice in patients with stage T1–T2 carcinoma of the tonsillar fossa. In those with T3–T4 tumours who were in a good general condition, operation and postoperative irradiation offered better control than a single method of treatment and preoperative irradiation, but with greater morbidity. Complications in patients who had postoperative radiotherapy were severe dysphagia, oropharyngeal fistulas, and rupture of the carotid artery that resulted in death.[17]

More recently, a study of 53 patients treated between 1992 and 1998 for SCC of the base of the tongue, compared three different treatments: surgical resection combined with radiotherapy, radiotherapy alone, and radiotherapy plus interstitial radiation. Five-year survival and local control was lowest in patients treated with radiotherapy alone, but they had the best speech and swallowing outcomes.[25]

In a retrospective analysis of the surgical treatment of 87 patients with SCC of the base of the tongue in 2001, Gourin and Johnson[19] found that operation was effective for early disease. However, as a result of postoperative complications in those with advanced disease, they suggested organ-preserving protocols using radiotherapy or chemoradiation instead.

On the other hand, Galati et al[18] supported the use of operation for tonsillar SCC (even in patients with advanced lesions) to enable the biological staging of cancers that require adjuvant treatment. They emphasised the problems radiotherapy can cause (xerostomia, dysphagia, pain, difficulty in speaking, and dental caries), and the need for dental assessment before treatment to reduce the risk of osteoradionecrosis.

In their study of 18 patients (published in 2002) from Birmingham, UK, Watkinson et al supported combination treatment to improve five-year survival and quality of life in patients with T1 and T2 lesions.[22]

In 2003, Cosmidis et al[24] reported that operation alone had an essential role in patients with T1/T2, N0 disease, and they stated that the oncological results were similar to those of classic radiotherapy in terms of locoregional control and survival because it avoided the complications and aftereffects of radiotherapy. In cases of recurrence, they found that operations in non-irradiated areas resulted in lower morbidity and mortality. Postoperative radiotherapy could also be more effective.

To our knowledge, the first study that reported functional outcomes and quality of life (QoL) objectively after treatment of advanced SCC of the base of the tongue, was published in 2002. It included 61 patients (43 treated by operation and 18 by radiotherapy, with or without chemoradiotherapy or brachytherapy) with stage III and IV disease, and used three independent questionnaires. The first was the Performance Status Scale for Head and Neck Cancer Patients, which considered three areas of function: eating in public, understandability of speech, and normality of diet. The second was The University of Washington Quality of Life (UW-QoL) instrument, and the third, a questionnaire developed by the authors to evaluate the history of treatment. Statistical analysis showed that xerostomia was significantly worse with

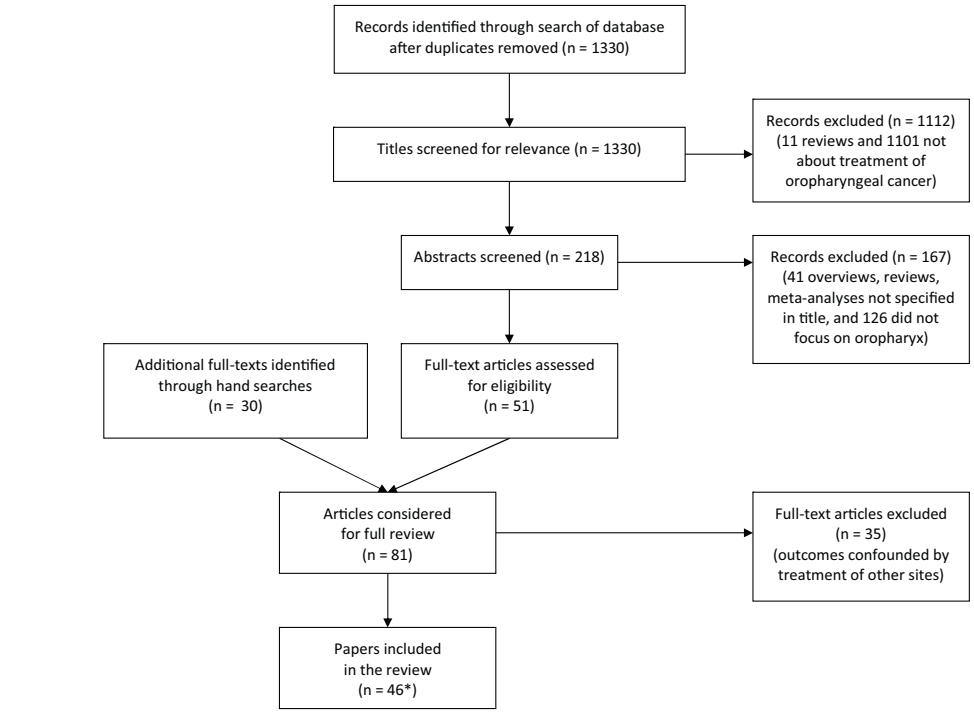

Fig. 1. Flow diagram of the search strategy.

Table 3
Questionnaires used.

Questionnaire and reference
Performance Status Scale for Head and Neck cancer Patients (PSSHN)[20,23,50]
University of Washington Quality of Life (UW-QoL)[20]
European Organisation for Research and Treatment of Cancer (EORTC) QLQ C30[21–23]
Head and Neck (H&N)35[21]
General Health Questionnaire (GHQ)12[22]
MD Anderson Dysphagia Inventory (MDADI)[40,48,54,56]
Head and Neck Cancer Inventory Health-Related Quality of Life (HNCI HRQoL)[37]
Short Form (SF) 8 Health Survey[50]
Voice Handicap Index (VHI)[54]

Table 4
Objective assessments used in the studies.

Objective assessment
Functional Outcome Swallowing Scale (FOSS)[46,47,49]
Communication Scale (CS)[46,47]
Normalcy of Diet Scale (subsection of the PSSHN)[56]
Weight loss[27,42]
Timed water swallowing test (WST)[56]
Duration of need for nasogastric tube[27,28,42–45,49,51–54,58]
Duration of need for tracheotomy[28,44,45,52]
Duration of hospital stay[44,45,49,52,53]
Readmission[59]

non-operative treatment, and that operation was associated with a longer hospital stay.[20]

Another study used two questionnaires, the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 core questionnaire and the specific head-and-neck cancer module (H&N35), to evaluate 113 patients two years after treatment for T1–T3 oropharyngeal SCC in two French cancer centres. Patients had brachytherapy with or without external beam radiotherapy, operation plus radiotherapy, or external beam radiotherapy only. The authors found that operation plus radiotherapy, as the initial treatment, favourably influenced scores for emotional function, but that brachytherapy had a negative influence on QoL.[21]

The first study we found that came to different conclusions in terms of functional outcome was done at the University Hospital of Geneva. The QoL of 60 patients had been assessed with the Performance Status Scale for Head and Neck Cancer Patients, and the EORTC QLQ-C30 questionnaire after radiotherapy with or without chemotherapy, or after radical surgery with or without radiotherapy. Functional outcomes for early disease were equivalent in the operation and radiotherapy groups, but in cases of advanced disease, the results were better in the radiotherapy group. As a result, the authors decided to move away from radical surgery to radical non-surgical treatment for all patients with advanced oropharyngeal cancers and, despite the ongoing movement in this direction, suggested that a prospective study with a larger sample size was essential.[23]

Conversely, in 2013, Iyer et al[30] reported successful five-year oncological outcomes in 128 patients who had primary conventional operations for T1/T2 SCC of the base of the tongue. The study period was from 1985 to 2005. Two

years later, the same team published a retrospective study of oropharyngeal SCC in patients who had primary operations with curative intent, and found that prognosis was better in those who were HPV-positive than in those who were not (five-year overall survival was 74% in the HPV-positive group and 44% in the HPV-negative group).[31]

Rodrigo et al reported good oncological and functional results at five years after a mandible-sparing approach using transhyoid surgery in patients with stages I, II, and III SCC of the base of the tongue.[29]

Diaz-Molina et al reported the results of conventional operations in patients with SCC of the lateral wall.[28] Intraoral, transpharyngeal, and transmandibular approaches, followed by radiotherapy in those with early and moderately advanced stages (I–III) resulted in good oncological and functional outcomes. In those with stage IV disease, morbidity was low and function preserved, but five-year oncological outcomes were poor, and patients were considered for concurrent chemoradiotheray.

Buiret et al[27] reported long-term functional outcomes (five and 10 years) in terms of alimentation in 254 patients who were treated surgically for oropharyngeal SCC (if operable) and radiotherapy with or without chemotherapy. To assess the impact of treatment on swallowing, the authors analysed the patients' weight, use of a nasogastric tube, and ability to eat solids, pastes, and liquids. Although 25.9% had surgical complications (infection, bleeding, pharyngostoma, cervical haematoma, pneumonia, orostoma, fever with an unknown cause, disunion of the flap, hepatic failure, acute delirium, and lymphorrhea), the authors stated that they preferred operation followed by radiotherapy to radiotherapy alone because of the potential long-term side effects of radiation (despite the lack of significant evidence).

In their study of 175 patients with recurrent tonsillar SCC after radical radiotherapy, Bachar et al[26] supported the use of operation when radiotherapy failed. They reported five-year overall survival of 23% and disease-free survival of 40%.

Organ-preservation

In 1996, Fein et al published the findings of 30 years' experience of the treatment of oropharyngeal SCC with radiotherapy alone at the primary site, with or without neck dissection. A total of 490 patients were treated between 1964 and 1991 with follow up of at least two years. Local control was achieved in 73% of patients with radiotherapy alone, overall local control after salvage was 78%, and 2.6% had severe complications (defined as those that required surgical intervention, inpatient stay, or resulted in death). The authors concluded that tumour control and survival after radiotherapy were comparable to the rates achieved with combined irradiation and operation, but with less morbidity.[32] Mendenhall et al[33] reached similar conclusions five years later. They reported good five-year oncological outcomes in their series of 400 patients treated for tonsillar SCC, and the incidence of severe complications was 5%.

In their comparison of organ-preservation and operation for advanced tonsillar SCC, Shirazi et al[35] found no significant difference in four-year overall survival and recurrence. The incidence of complications was similar in both groups: 26% after operation (serious wound infection, failed free flap, wound dehiscence, orocutaneous fistula) and 25% after organ-preservation treatment (haematological toxicity in those treated with chemotherapy, and xerostomia and osteonecrosis in those treated with radiotherapy). The authors therefore recommended organ-preservation treatment for patients with stage III–IV disease.

In 2004 the results were published of a French randomised prospective study that compared radiotherapy alone with concomitant chemoradiotherapy in patients with stages III and IV oropharyngeal SCC and no evidence of distant metastases. Five-year overall survival and locoregional control was better in the concomitant chemoradiotherapy group but there were more complications (56%) than in the radiotherapy group (30%). Anaemia was the most important prognostic factor for survival.[34]

Cartmill et al[40] reported ongoing problems with swallowing and salivary function two years after altered fractionation radiotherapy with concomitant boost (AFRT-CB). Patients' diets were restricted and they had not regained the weight they had lost.

The popularity of organ-preservation treatment grew after the introduction of IMRT, which improved locoregional control and survival when compared with conventional radiotherapy. These findings were published in a 2007 study that compared the three-year oncological outcomes of patients treated with IMRT with those treated before its introduction.[36] In 2010 Mendenhall et al[39] reported similar oncological results at five years in 130 patients. IMRT reduced the mean irradiation dose to the parotids and consequently the risk of long-term xerostomia.

Yao et al[37] compared the health-related quality of life (HRQoL) of patients who had IMRT with that of those who had conventional radiotherapy. At 12 months, eating, speech, aesthetics, and social disruption, were better in the IMRT group than in the radiotherapy group. However, at three months, both groups had a considerable reduction in the eating domain, and at six months, function had started to improve in the IMRT group, but was continuing to deteriorate in the other.

In comparison with 3-dimensional conformal radiotherapy (3D-RT) and accelerated fractionation with concomitant boost (AFxCB), IMRT was more effective and resulted in less skin and mucosal toxicity in patients treated for stage III and IV oropharyngeal SCC.[38]

Lohia et al[42] found that when compared with 3-dimensional conformal radiotherapy, IMRT improved outcomes related to toxicity (effect on skin and mucous membranes) and the need for a percutaneous endoscopic gastrostomy (PEG) tube.

Self et al[41] studied the risk of oropharyngeal haemorrhage, a life-threatening complication associated with chemora-

diotherapy alone. The most important determinant for its occurrence was advanced T stage (nodal disease was not a risk factor), and it occurred in patients with recurrent or persistent disease, or both, or those with radiation necrosis.

Different combinations of chemoradiotherapy have been used to minimise morbidity without compromising the oncological results. Dobrosotskaya et al[43] found that in locally advanced SCC, three-year survival in patients treated weekly with chemotherapy plus radiotherapy was similar to that in those treated with high-dose chemotherapy plus radiotherapy, but was better tolerated.

Minimally-invasive surgery

A prospective study published in 2006 by Grant et al[46] presented the functional and oncological outcomes of all patients treated with transoral microsurgery for SCC of the base of the tongue (1997–2005) at the Mayo Clinics in Jacksonville, Florida, and Scottsdale, Arizona. The authors concluded that it was a promising alternative to conventional surgery, with or without radiotherapy, and resulted in favourable local control and survival, with fewer functional side-effects.

Seven years later, in a similar study on SCC of the base of the tongue, Canis et al[51] came to a similar conclusion about the effectiveness of primary transoral microsurgery, but they had combined it with radiotherapy with or without chemotherapy.

Holsinger et al[44] and Laccourreye et al[45] reported the use of transoral lateral oropharyngectomy as a conservative alternative to radiation therapy. These two studies reported 20 years' retrospective analysis of the same 191 patients, and stated that the approach, which allowed en bloc resection of the mucosa and muscle through a non-invaded peripharyngeal space, could be used safely in patients with T1 or T2 SCC of the tonsil without posterior anatomical spread. The authors thought that it was oncologically superior to direct transoral resection with the superior constrictor at the deep margin, as described by Galati et al,[18] and piecemeal resection as described by Watkinson et al.[22] They reported an incidence of complications of 6.3%, and good functional and oncological outcomes that were comparable to radiotherapy.[44,45]

In a United States multicentre prospective study of the functional and oncological outcomes of 204 patients with advanced oropharyngeal SCC, Haughey et al[49] found that transoral microsurgery was a highly effective primary treatment, particularly in those with HPV. They found that, although adjuvant treatment improved survival and local control, the addition of chemotherapy was not associated with significantly better oncological outcomes when compared with radiotherapy alone. The good functional and oncological outcomes offered by this approach were also noted by Chauhan et al[58] in a minor single-centre Irish study.

Moore et al[47]reported good preliminary functional outcomes in 45 patients treated by TORS for oropharyngeal SCC. Function was evaluated four weeks after operation or three months after completion of radiotherapy or chemotherapy. The mean (range) follow up of 12.3 (1–16) months was insufficient to show adequate oncological control, but functional results were promising. Speech was normal in all patients postoperatively and there were no life-threatening complications. Orocutaneous fistulas developed in three.

Leonhardt et al[50] used two questionnaires to evaluate QoL one year after treatment. They found that TORS plus radiotherapy resulted in better functional outcomes than TORS plus chemoradiotherapy. According to Dziegielewski et al,[53] speech was only moderately affected by TORS.

Sinclair et al[48] used the MD Anderson Dysphagia Inventory (MDADI) to objectively assess patient-perceived dysphagia in 42 patients treated by TORS and adjuvant radiotherapy and chemoradiotherapy for T1 or T2 disease. One third reported a reduction in swallowing function that improved over the time. Adjuvant chemotherapy required prolonged dependence on a gastrostomy tube.

Lee et al[54] compared TORS with conventional surgery through a transoral approach or mandibulotomy for tonsillar SCC. They used the Voice Handicap Index, the MD Anderson Dysphagia Inventory, and dependence on nasogastric feeding, to show the better functional outcomes achieved with TORS. Complications occurred only in the mandibulotomy group (one flap revision, one malunion, and one case of osteoradionecrosis).

Ford et al[55] confirmed that survival at three years after TORS was better than that after open operation (89% compared with 73%, respectively). They found that oncological outcomes after a combination of treatments were better in patients with HPV.

In a retrospective matched study on salvage surgery, White et al[52] compared TORS with open surgical approaches and recorded operative (blood loss, operating time, status of the margins, and complications) and functional (duration of hospital stay, use of a tracheostomy, and use of a feeding tube) outcomes. Generally, patients treated by TORS lost 6.7 times less blood, operations were shorter by about one third, and the hospital stay was reduced by 50%. Outcomes for speech and swallowing, and two-year survival, were considerably better in the TORS group (74% compared with 43%, respectively). More margins were invaded in the open operation group. The incidence of final invaded margins in the TORS group was lowered by further resection in outpatients. This would not have been possible in the open operation group.

Zevallos et al,[59] who based their study on the American National Cancer Database, compared the perioperative outcomes of TORS with the non-robotic transoral approaches used between 2010 and 2011 in 514 patients with oropharyngeal SCC. The primary outcome measure was the final report on the surgical margin, and secondary outcomes were duration of hospital stay, rates of conversion to open operation, 30-day unplanned readmissions, and 30-day mortality. Patients treated by TORS had significantly lower rates of invaded margins than those treated by non-robotic transoral surgery. Rates for conversion to open surgery

were higher in the non-robotic group than in the TORS group. Overall rates of unplanned readmissions were 3.1% and the difference between the groups was not significant. The results of the study suggested that the selection of patients and the surgeon's experience were more important predictors of negative margins than the type of transoral approach.

Smith et al compared the outcomes of TORS with primary chemoradiotherapy in a prospective non-randomised study that was matched for tumour stage. Results showed a survival benefit in the TORS group with three-year overall survival of 83% compared with 57%, and disease-specific survival of 94% compared with 85%. The authors found that primary surgical management of oropharyngeal SCC with TORS together with neck dissection provided accurate staging of patients in case of the need for further treatment.[57]

O'Hara et al[56] concluded that primary transoral laser microsurgery affected swallowing less than primary chemoradiotherapy even in cases of stage III and IV oropharyngeal SCC. Their study used the MD Anderson Dysphagia Inventory, the Performance Status Scale, and a timed water swallow test to analyse functional outcomes before, and three months after, treatment.

Complications

The complications reported in the studies are presented in Table 5.

Discussion

Histologically, the oropharynx is a distinct anatomical entity with a discontinuous basement membrane. HPV directly involves the immune system, and a patient's status in this regard influences and modifies the behaviour of oropharyngeal SCC.[6,7] HPV vaccination seems to reduce the prevalence of HPV, but we know of no trials to validate the effect of vaccination to prevent infection and HPV-positive oropharyngeal SCC.[61] Local infiltration of immune cells and innate systemic inflammation have already been studied in this disease.[62,63] Immunotherapy will probably be the subject of future studies, but as yet, these findings have had no impact on current treatments.

The purpose of this review was to show how treatments have evolved in the last 25 years and to assess how accurately we can recommend a treatment in a multidisciplinary team meeting.

Although the studies reflect the developments in clinical practice, most of them reported series without randomisation so the choice of treatment was based on personal preference. The differences in the treatments and functional outcome measures made comparison difficult, and the low level of evidence for the decisions made reflects the lack of certainty about which would be best.

All health professionals who treat patients with cancer of the head and neck will have seen the transition from conventional primary surgery to organ-preservation treatment after publication of the preliminary results of the Veterans Affairs

Table 5
Overall complications by type of treatment.

Conventional surgery	Chemoradiotherapy	Minimally-invasive surgery
Wound infections[14,15,27,28,29,35]	Dysphagia[14,18,32,33,36,40]	Pulmonary compromise/aspiration pneumonia[44,45,51]
Fistula/pharyngostoma/orostoma[14,15,19,27,35]	Xerostomia[18,36,38,39,40,47]	Rhinolalia[44,45]
Partial flap necrosis/flap disunion[14,27]	Difficulty speaking[18]	Chyle leak[44,45]
Pulmonary compromise/aspiration pneumonia[14,19,28,29]	Stiff neck[40]	Seroma[44,45]
Upper airway oedema[19]	Loss of appetite[40]	Cervical abscess/sepsis[44,45]
Malocclusion[15]	Agneusia[34]	Wound breakdown[58]
Fatal rupture of carotid artery in salvage operation[17]	Dental caries[18,36,40]	Cerebrovascular event[44,45]
Temporary dysphagia[18]	Aspiration pneumonia[32,33]	Dysphagia[44,45,51]
Temporary paresis of hypoglossal nerve[19]	Skin toxicity[32,40,42,43]	Postoperative bleeding/cervical haematoma[44,45,46,49,51,53,57,58]
Paralysis of phrenic nerve[19]	Mucosal toxicity[32,40,42,43]	Orocutaneous fistula[47,53,58]
Pneumointestinalis coli[19]	Facial oedema[36]	Trismus[47]
Postoperative haemorrhage/haematoma[27,29,52]	Oesophageal stenosis[49]	Oral ulceration[47]
Seroma[29]	Tracheal fibrosis[36]	Shoulder pain[47]
Chyle leak[27]	Laryngeal necrosis[32]	Paresis of hypoglossal nerve[49]
Hepatic failure[27]	Necrosis of the pharynx and parapharyngeal space[49]	Velopharyngeal incompetence [49]
Acute delirium[27]	Osteonecrosis[18,19,32,36,33,39]	
	Neurological toxicity[34,43]	
	Ototoxicity[34]	
	Gastrointestinal toxicity[43]	
	Weight loss[34,42]	
	Haematological toxicity [34,43]	
	Haemorrhage[41]	
	Fatigue/weakness[43]	

Study[11] in 1991, which was based on the management of laryngeal SCC.[64,65]

We included studies that were published after 1992. Cohort studies after 2000 showed that operation alone was no longer an option, as the paradigm had shifted in favour of primary radiotherapy alone or with chemotherapy.

Organ-preservation treatment based on chemoradiotherapy avoided the surgical complications that were mainly the result of invasive approaches (Table 5). Most occurred immediately postoperatively (pulmonary compromise, infection, formation of a fistula, failure of the flap) and a higher incidence of those that were fatal were seen in patients who had had preoperative radiotherapy and needed salvage surgery. The complications after salvage surgery were breakdown of the wound, orocutaneous fistula, fatal rupture of the subclavian artery, and mandibular fracture. The blame should be placed largely on radiation.[17]

As the success of radiotherapy began to be seen, its complications also became evident. The most common was xerostomia, which reduced patients' QoL. A combination of chemotherapy and radiotherapy improved oncological outcomes but increased the complications, and a French study, the only randomised trial we found, [34] showed that late toxicity was more common after chemoradiotherapy than after radiotherapy alone (56% compared with 30%, respectively).

Compared with operation, the adverse effects of chemoradiotherapy were more silent, and toxicity, such as osteonecrosis, stenosis, and fibrosis, appeared late and were difficult to treat (Table 5). IMRT seemed to reduce xerostomia more than classic radiotherapy[38] and, compared with conventional chemoradiotherapy, also improved overall survival[36] and QoL.[37]

We included two studies by Mendenhall et al that were published 10 years apart (2000 and 2010). The first reported treatment with conventional radiotherapy[33] and the second with IMRT.[39] Although lower doses to the salivary glands with IMRT reduced xerostomia, the authors still reported osteonecrosis that required segmental mandibulectomy, as well as soft tissue necrosis and haemorrhage.

Iyer et al[31] showed that surgical outcomes were better in HPV-positive patients, and this group also responded better to chemoradiotherapy.[43] One should, however, question whether there are two types of disease: HPV-positive and HPV-negative. Viral infections affect the immune system, and the good response in younger patients with HPV supports this hypothesis.

Minimally-invasive techniques have developed exponentially over the last decade.

The complications related to transoral microsurgery were not as severe as those for conventional operations (Table 5), but adjuvant treatment increased the number that were serious. These included late-radiation-induced oesophageal stenosis, and necrosis of the pharynx and parapharyngeal space,[49] to name but a few. Long-term dependence on percutaneous feeding (PEG) has been seen in patients who had adjuvant radiotherapy,[46] and late-onset muscular fibrosis can cause difficulty in swallowing.

Operations that cause no neurological trauma and leave the anatomy intact may have better outcomes than organ-preservation treatment with its associated complications. Two randomised controlled trials are currently comparing minimally invasive surgery with radiotherapy or chemotherapy. The first, a phase II trial, is comparing primary radiotherapy with TORS (ORATOR) for small-volume primary T1, T2, N0-2, early-stage SCC of the oropharynx. The second is the European Organisation for Research and Treatment of Cancer 1420 (EORTC 1420-HNCG-ROG), which is a phase III randomised controlled trial to assess the best of radiotherapy with TORS/transoral microsurgery in patients with T1, T2, N0 disease.[66] The results, which are expected in 2021, should provide better evidence on the treatment of early-stage disease, but more work is needed to inform the management of more advanced cancers.

A patient's suitability is dictated by any coexisting conditions and their ability to cope with the treatment. Cancers of the head and neck are multifactorial diseases that behave differently within the oropharynx. Their pathophysiological behaviour also seems to vary between patients who have, and do not have, HPV.

To summarise, we are still far away from being able to recommend the best treatment, but we have raised questions as to the possibility of two distinct entities within oropharyngeal SCC. We have also identified the immediate and late complications reported during the era of conventional surgery, focused on the evidence for late toxicity after organ preservation treatment and chemoradiotherapy, and reported some encouraging results with the use of the latest technologies.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients' permission

Ethics approval not required. Patients' permission not applicable.

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