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ORIGINAL ARTICLE

What is the Current Evidence Base for Management of Oropharyngeal Cancer?

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ABSTRACT

This review will provide a comprehensive overview of the current management of oropharyngeal cancer. The contemporary literature, as it relates to diagnosis and management, will be summarized and the existing limitations of our knowledge will be highlighted. Research questions which need to be addressed as a matter of urgency will be listed and ongoing clinical trials designed to fill the current gaps in our knowledge will be briefly described.

Keywords: Cancer, Chemotherapy, Clinical trials, Head and neck, Oropharynx, Radiotherapy, Transoral laser surgery, Transoral robotic surgery.

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EPIDEMIOLOGY

In a recent UK multicenter, cross-sectional study, the human papillomavirus (HPV) status of archival tumor tissue blocks, collected from 1,602 patients diagnosed with oropharyngeal squamous cell carcinoma (OPSCC) between 2002 and 2011, was determined. The overall proportion of HPV-positive OPSCC was 51.8% [95% confidence interval (CI), 49.3–54.4], and this remained unchanged throughout the decade [unadjusted risk ratio = 1.00 (95% CI, 0.99–1.02)]. In view of the doubling in incidence, it was concluded that the absolute number of both HPV-positive and HPV-negative cases in the UK was increasing.[1]

These UK data contrast with published data from other parts of the world where substantial variation has been reported in the proportion of OPSCC attributable to HPV between countries and time periods. This is likely to be a reflection of variations in multiple factors, which may include sexual behavior and rates of genital HPV infection, as well as tobacco and alcohol consumption, and highlights that trends in the etiology of OPSCC must be considered in a population-specific manner.

Patients with HPV + OPSCC are usually younger, fitter, and more affluent and who smoke less and drink less alcohol than patients presenting with HPV-OPSCC.[2,3]

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CLINICAL PRESENTATION

Tumors that originate in the tonsil represent ~60% of all OPSCC tumors. They are also the most common site of primary tumors in the context of carcinoma of unknown primary.

Base of tongue (BOT) makes up ~30% of all OPSCC tumors. As with tonsillar OPSCC, it is not unusual for BOT tumors to be asymptomatic or apparently occult, only coming to light during investigation of enlarged cervical lymph nodes.

Tumors of the oral surface of the soft palate make up the majority of the remaining 10% of OPSCC, with posterior pharyngeal wall tumors presenting relatively, rarely.

They are more likely to be HPV negative compared with OPSCC of the tonsil and BOT and, accordingly, typically behave in a more aggressive fashion with poorer outcomes.[1,4]

STAGING

Recent changes to the tumor, node, and metastasis (TNM) staging recommendations published in the American Joint Committee on Cancer (AJCC) 8th Edition Cancer Staging Manual[5] and the Union for International Cancer Control (UICC)[6] are of particular importance to the staging of OPSCC. The changes and the rationale behind them, which may have an impact on the future management of OPSCC, are reviewed in detail in Lydiatt et al.[7]

MANAGEMENT

The management of oropharyngeal carcinoma (OPC) represents an increasing clinical challenge, both because of its rising incidence, particularly in younger patients as

a result of HPV infection, and because of the significant technological advances that have occurred in radiotherapy and surgery over the last 10–20 years that have increased treatment options for patients, with little robust evidence yet of their relative merits.

This situation is further complicated by the clinical paradox that has been created following the emergence of HPV + OPSCC. The HPV status is highly prognostic in OPSCC patients treated with concurrent chemoradiotherapy (CRT). In a landmark study, Ang et al. retrospectively analyzed the outcomes of patients with stage III/IV OPSCC treated with CRT in the RTOG 0129 study by HPV status: 3-year overall survival was 82.4% in HPV-positive patients, compared with 57.1% in HPV-negative patients ($p < 0.001$). Similarly, high survival rates for HPV-positive OPSCC have been demonstrated in patients treated with primary radiotherapy (RT)/CRT and surgery.[8-13]

However, while patients with HPV+OPSCC, in general, do better in survival terms than patients with HPV-OPSCC, it must also be borne in mind that a subset of patients with HPV + OPSCC also do badly. While high T stage and number of involved lymph nodes are associated with poor outcome in this subgroup, smoking habit, which is assumed to be a surrogate of underlying tumor mutational load and/or genetic instability, appears also to be of importance.[2,3,14]

Currently, HPV-positive and HPV-negative OPSCC are managed according to the same treatment protocols, but the improved prognosis associated with HPV-positivity has raised the possibility that they could be managed differently. In particular, there is a need to continually strive for novel intensified treatments that will enhance survival in patients with HPV-OPSCC and the subgroup of patients with HPV + OPSCC, who will do badly. However, deintensified treatment strategies for patients with HPV + OPSCC, who will do well, must be potentially considered, with the aim of maintaining their current good survival outcomes, while reducing the frequency and severity of short- and long-term posttreatment adverse events.

There is an absence of randomized studies comparing primary surgical and nonsurgical approaches in the management of OPSCC, resulting in a global lack of consensus between surgeons and oncologists as to how these cancers should be managed.

Open surgery and microvascular reconstruction followed by postoperative adjuvant treatment was the historic treatment of choice for OPSCC, and is still offered by some units. However, a 2002 retrospective review of 6,400 patients with OPSCC in 51 studies showed similar rates of locoregional control, overall survival, and cause-specific survival for patients treated with open surgery and postoperative RT (PORT), compared with those treated with primary RT ± neck dissection, but a significantly higher rate of severe or fatal complications in the surgery group, together with worse functional outcomes.[15] These data raised concerns regarding the continued use of this approach and when combined with high-quality level I and meta-analysis data confirming the benefits of radiotherapy ± cisplatin-based chemotherapy[3,16] in the management of OPSCC, a major shift away from open surgery to CRT in the developed world has occurred.

This shift is reflected in UK data from successive National Head and Neck Cancer (DAHNO) audits, which confirm that by the 10th audit, CRT was given more than twice as frequently as RT alone.[17] Similarly, data from the United States have shown a linear rise (from 20 to > 60% of cases) in the use of CRT for the management of OPSCC from 1998 to 2009 with a concurrent decrease in the use of surgery and radiotherapy alone.[18]

Radiotherapy/Concurrent Chemoradiotherapy

The primary rationale for the use of RT or CRT in treating OPSCC is organ preservation and also, importantly, to preserve function while achieving high cure rates. Data from randomized trials, such as RTOG 0129,[19] comparing CRT schedules confirm that this approach can result in good oncological outcomes, particularly in HPV + OPSCC. However, it is worth reiterating that high-quality data comparing surgical and nonsurgical approaches do not exist, despite RT and CRT becoming the accepted standard of care in many centers throughout the world for early- and late-stage OPSCC respectively.

Early-stage T1 to T2 N0 to N1 OPSCC can be effectively treated with RT alone.[20] For radical treatment, RT is commonly delivered at a total dose equivalent of 70 Gy in 35 fractions, and this may be delivered as a hypofractionated schedule of 65–66 Gy in 30 fractions.

For more advanced T and/or N stage (stage III/IV, TNM 7th edition) OPSCC, CRT is the standard of care, with an RT dose equivalent of 70 Gy delivered in 35 fractions together with concurrent Cisplatin at a dose of 100 mg/m^2 given on days 1, 22, and 43 of the RT schedule. The GORTEC 94-01 study demonstrated a ≥20% 3- and 5-year survival benefit for the addition of chemotherapy to RT, albeit in the setting of low overall survival figures (3-year overall survival 51 *vs* 31%, $p = 0.02$, disease-free survival 42 *vs* 20%, $p = 0.04$ and locoregional control 66 *vs* 42%, $p = 0.03$).[21] Furthermore, meta-analysis data in 17,346 patients confirmed that, for head and neck squamous cell carcinomas (HNSCCs) as a whole, concurrent chemotherapy confers an overall survival benefit of 6.5% at 5 years ($p < 0.0001$) compared with RT alone.[16] The benefit of adding chemotherapy to

RT for the management of OPSCC specifically was confirmed in an additional systematic review.[22]

Weekly administration of low-dose cisplatin (40–50 mg/m^2) is an alternative to 3-weekly high-dose cisplatin, which has become increasingly used in clinical practice in an attempt to improve tolerance and compliance. A recent meta-analysis of 4,209 patients in 52 studies concluded that there was no difference in treatment efficacy, as measured by overall survival or response rate, between the low-dose weekly and high-dose 3-weekly cisplatin regimens.[23] The weekly regimen was associated with a higher compliance rate and significantly less toxic with regards to severe (grades III–IV) myelosuppression, nausea, and nephrotoxicity. The authors concluded that the weekly regimen needed to be prospectively compared with the standard 3-weekly regimen before being adopted into routine clinical practice. In the meantime, clinicians will continue to choose between regimens, based on institutional protocols, personal experience, and patient fitness. In patients for whom cisplatin is contraindicated, concurrent carboplatin chemotherapy [3 weekly at area under the curve (AUC) 5 or weekly at AUC 2] is an alternative that is associated with less ototoxicity and nephrotoxicity.

Concurrent weekly cetuximab (a monoclonal antibody targeting the epidermal growth factor receptor) may be given with RT, if there is a contraindication to platinum chemotherapy. In a randomized trial, the combination of cetuximab and RT improved median locoregional control (24.4 *vs* 14.9 months) and median duration of overall survival (49 *vs* 29.3 months) after a median follow-up of 54 months.[24] This survival difference was maintained on long-term follow-up. The addition of cetuximab to concurrent CRT did not improve outcome compared with CRT alone in a subsequent trial.[25] The results of randomized studies conducted in the United States (RTOG 1016: NCT01302834) and United Kingdom (DE-Escalate: NCT01874171) comparing the efficacy and toxicity profile of RT with concurrent cisplatin *vs* RT with concurrent cetuximab in HPV + OPSCC have recently been published and confirm that cetuximab combined with RT is inferior to cisplatin combined with RT with respect to survival and no difference in grade 3/4 toxicity was demonstrated between the regimens.

Radical RT may be given alone for patients with advanced disease, who are not fit for concurrent treatment, particularly if >70 years of age when the benefits of concurrent chemotherapy and cetuximab are reduced.

Induction (or Neoadjuvant) Chemotherapy

The use of induction chemotherapy (IC) may be beneficial in selected patients. The meta-analysis of chemotherapy in head and neck cancer[16] showed an overall survival advantage for cisplatin and 5-fluorouracil (FU) chemotherapy compared with local therapy alone for the management of HNSCC. The IC had a relatively more pronounced effect on distant metastasis rate than concurrent CRT. The benefits of using IC prior to concurrent cisplatin-based CRT have not been convincingly shown: a recent meta-analysis that included all types of HNSCC showed that IC increases toxicity and does not improve Overall survival (OS) compared with CRT alone.[26]

In the context of OPSCC, including HPV + OPSCC, the use of IC has been advocated for patients with advanced (T4, N3, N2c) disease to reduce the risk of distant metastases.[27] High-quality prospective evidence of its efficacy in these indications is currently not available.

Induction chemotherapy with the Taxotere, cisplatin, and 5-FU regimen is recommended, based on a higher response and survival rates and reduced locoregional and distant failure rates compared with PF (cisplatin and 5-FU) in a meta-analysis of five studies.[28] The regimen is associated with higher acute toxicity (neutropenic sepsis and nonhematological toxicities) and, therefore, is only suitable for patients with good performance status and minimal comorbidity.

Radiotherapy can result in significant acute (<90 days) and late (>90 days after treatment) toxicities, and late toxicities, particularly affecting salivary gland function, dentition, and swallowing, may be permanent. Concurrent chemotherapy increases the risk of late toxicity[29,30] and in the preintensity modulated radiotherapy (IMRT) era, up to 43% of HNSCC patients could develop grades III to IV late toxicities following CRT.[31] The key late toxicity affecting quality of life is swallowing dysfunction.[32] Swallowing is a primary concern for patients,[33] affecting their physical health and well-being, and is a major cause of distress and burden for family members[34] since dysphagic patients often require long-term supportive care.

Postoperative (Adjuvant) RT/CRT for OPSCC

The indications for postoperative RT and CRT for OPSCC depend on pathological risk factors for recurrence common to most head and neck squamous carcinomas. These include: primary tumor factors [close (1–5 mm) or positive (<1 mm) margins, T3 to T4 stage, perineural and/or lymphovascular invasion], and nodal factors (extracapsular spread of nodal disease and/or N2–N3 nodal stage). Randomized controlled trials conducted by the RTOG and EORTC and a meta-analysis of their results confirmed that patients with extracapsular invasion and/or microscopically involved (<1 mm) surgical resection margins around the primary tumor[35] experience significant benefit in terms of overall and disease-free survival from postoperative CRT compared with RT alone.[35] However,

postoperative CRT results in significant toxicities (including a 2% death rate) and is not generally recommended in patients >70 years of age and/or those with significant comorbidities and poor performance status.

Transoral Surgery

A retrospective US study of 204 patients with stages III to IV OPC, treated with primary transoral laser microsurgery (TLM) and neck dissection, reported 3-year rates of local control, overall survival, and disease-free survival of 97, 86, and 82% respectively, which were higher in HPV-positive patients.[11] A retrospective series from Liverpool, UK of 153 patients with T1 to T3 OPSCC (66% were HPV-positive) treated with TLM and neck dissection, reported 3-year rates of disease-specific survival, overall survival, and disease-free survival of 91.7, 84.5, and 78.2%, respectively, again better in patients with HPV-positive disease.[12]

Similarly, good outcomes have been reported following transoral robotic surgery (TORS): a cohort study of 410 patients from 11 centers treated with TORS ± adjuvant RT/CRT reported 2-year rates of locoregional control, disease-specific survival, and overall survival of 91.8% (95% CI, 87.6–94.7%), 94.5% (95% CI, 90.6–96.8%), and 91% (95% CI, 86.5–94.0%), respectively.[36]

No randomized studies have yet compared outcomes following transoral surgery and RT/CRT for OPSCC. Nevertheless, a recent meta-analysis on early-stage OPSCC reported comparable 5-year disease-specific survival rates of 90.4% (95% CI, 85.6–95.2%) for RT and 89.6% (95% CI, 81.8–97.3%) for transoral surgery (TOS) in early-stage OPSCC.[27] Furthermore, a systematic review comparing the effectiveness of IMRT and TORS for T1 to T2 OPSCC[28] reported similar survival outcomes in 1,287 IMRT patients (2-year overall survival 84–96%) and 702 TORS patients (2-year overall survival 82–94%). A different profile of adverse events was reported for IMRT and TORS, which for IMRT included gastrostomy tubes (43%), esophageal stenosis (4.8%), and osteoradionecrosis (2.6%) and for TORS as described.

Transoral surgery for early and intermediate-stage OPSCC is generally well-tolerated, with a median length of hospital stay after surgery of approximately 4.4 days.[11] Acute complications include hemorrhage (2.4%) and fistula (2.5%). Temporary tracheostomy tubes are needed in 12% of patients at the time of surgery but most are decannulated prior to discharge.[37] Temporary nasogastic tubes are required in up to 47% of patients postoperatively, but most patients can manage an oral diet without a tube by 4 weeks following surgery.[38,39] Long-term functional outcomes after TOS appear favorable in small studies: in a study of 30 patients with early (mainly T1–T2 N0–N1) OPSCC treated with TORS and neck dissection (without adjuvant treatment), all patients were taking a full oral diet without a feeding tube after a median follow-up of 2.7 years.[13]

However, in most reported series of TOS, the majority of patients also undergo adjuvant therapy, either with PORT (21–58% of cases) or postoperative CRT (POCRT, 16–62% of cases).[11,12,39-41] It is clear that adjuvant treatment increases acute and late toxicity associated with transoral surgery. In the largest TLM series,[11] adjuvant treatment doubled gastrostomy tube use from 17 to 33%, and 19% of patients remained gastrostomy tube-dependent 12 months after treatment. In 66 OPSCC patients treated with TORS,[39] 97% were tube-free and managing an oral diet 4 weeks after surgery, but 27% (18/66) required a gastrostomy tube during their adjuvant therapy and 3 (4.5%) remained gastrostomy tube-dependent for more than 2 years after treatment. In 81 patients treated with TORS,[42] all patients were discharged postoperatively on full oral diet, but 13 (16%) required gastrostomy tube placement during adjuvant treatment; of these, 5 remained in place for over a year. Eating domain health related quality of life scores were also significantly worse in patients who underwent adjuvant treatment compared with those who did not. Increasing age (>55 years) and extent of TORS resection predicted the need for a gastrostomy tube, and high T stage (pT3/pT4) predicted the need for permanent tube feeding. Not surprisingly, functional outcomes following POCRT appear to be worse than after PORT. In 38 OPSCC patients, speech, diet, and eating (performance status scale for head and neck cancer patients) scores at 6 and 12 months following treatment were significantly better following TORS alone compared with TORS followed by PORT which were, in turn, better than after TORS and POCRT.[43] Furthermore, a systematic review of TORS for OPSCC showed clear demarcation in swallowing outcomes across a variety of outcome measures in patients who received PORT compared with POCRT.[44]

Management of the Neck

The role of the neck dissection in the treatment of OPC is well standardized and outlined in detail in the UK Head and Neck Cancer Multidisciplinary Management Guidelines 2016.[45]

FUTURE

Optimizing Treatment for OPSCC: Ongoing Clinical Trials

An EORTC phase III randomized study (EORTC 1420, "Best-Of" NCT02984410) comparing late function (MDADI at 12 months following treatment) after TOS and IMRT in patients with (HPV-positive and negative) T1 to T2 N0 M0 OPSCC is due to open imminently and could inform future practice for early-stage disease by

providing much-needed level I evidence following a head-to-head comparison of surgical *vs* nonsurgical treatment.

Similarly, the currently recruiting Canadian ORATOR phase II clinical trial (NCT01590355) will attempt to address the same problem.

Patients with T3 to T4 OPSCCs, which are not transorally resectable, should undergo primary CRT as the standard of care. Dysphagia-optimized IMRT, aiming to minimize radiation dose delivery to swallowing-related structures, and/or the use of cetuximab instead of cisplatin with RT, are Dysphagia-optimized IMRT, aiming to minimize radiation dose delivery to swallowing-related structures is currently being investigated in an ongoing UK clinical trial (DARS, ISRCTN: 25458988) as means of reducing toxicities in these patients.

In addition, The Quarterback Trial (NCT01706939): A Randomized Phase III Clinical Trial Comparing Reduced and Standard Radiation Therapy Doses for Locally Advanced HPV Positive Oropharynx Cancer has completed recruitment and is in follow-up.

As an alternative approach, the UK phase II/III PATHOS study (ClinicalTrials.gov NCT02215265)[40] and the US study (ECOG 3311 [NCT01898494]) are currently exploring transoral surgery (TLM or TORS) ± deintensified adjuvant as a potential means of improving long-term function, while maintaining good oncological outcomes, in patients with HPV-positive OPSCC.

The PATHOS[46] is currently recruiting patients with HPV+OPSCC, who will undergo transoral surgery and a neck dissection. Postsurgical pathology will allow stratification into three distinct risk groups. While a low-risk group I will receive no adjuvant treatment, an intermediate-risk group II will be randomized between standard and reduced dose adjuvant IMRT, and a high-risk group III will be randomized between adjuvant CRT and standard dose IMRT alone. A European phase III extension to the ongoing UK phase II is planned to investigate whether deintensified adjuvant treatment schedules for patients with intermediate-stage HPV + OPSCC, undergoing transoral surgery, results in noninferior survival outcomes and improved swallowing function.

In contrast, poor prognosis OPSCC, including HPV-positive current smokers[47] with advanced disease and patients with HPV-negative disease may benefit from treatment intensification, and an ongoing multiarm, multistage (MAMS) UK study (COMPARE, UKCRN Study No: 18621) is exploring this possibility.

Translational Research

What is clear is that many questions relating to the epidemiology and natural history of oral HPV infection and its relationship to the development of HPV + OPSCC remain.

Some of the more pressing questions that are currently the basis of ongoing research include:

- Why do a small percentage of infected individuals fail to clear the initial HPV infection and why do a proportion of these then go on to develop HPV + OPSCC?
- Is the mechanism of infection and virally mediated transformation the same for OPSCC as for cervix cancer and why is HPV16 the predominant genotype involved in OPSCC, while HPV18, together with HPV16, has a more significant role in the development of cervix cancer?
- Why is OPSCC more responsive to treatment than cervix cancer despite presenting with clinicopathological features traditionally associated with poor outcome?
- Does an as-yet undetected HPV+OPSCC premalignant lesion exist?
- Why is there a significant male:female gender bias?
- Why has this new discrete disease entity only emerged in that last 3–4 decades?

Moreover, there is an urgent need to identify robust predictive risk-stratifying biomarkers, which will identify the subgroup of patients with HPV+ disease. The identification of such biomarkers is planned as a translational program of research allied to several of the clinical trials highlighted above, e.g., RTOG 1420, PATHOS, De-Escalate, and COMPARE.

Following on from this, there is also an urgent need to identify novel treatments that will reduce rates of treatment failure and/or enhance life-expectancy in patients who relapse.

Of particular note in this context is the recent publication of the CheckMate 141 clinical trial.[48] This randomized, open-label, phase III clinical trial randomized 361 patients with recurrent SCCHN, in a 2:1 ratio to receive nivolumab or standard single-agent systemic therapy. Overall survival was significantly longer in the group that received Nivolumab compared with the group treated with standard systemic therapy [7.5 *vs* 5.1 months: hazard ratio (HR) for death = 0.70; 97.7% CI 0.51–0.96]. A *post hoc* exploratory analysis of 178 patients with OPSCC for whom p16 status was known confirmed that among the patients with p16+ tumors, OS was 9.1 months in the nivolumab group *vs* 4.4 months in the standard therapy group (HR for death = 0.56; 95% CI 0.32–0.99), suggesting that PD-1 blockade may have a discriminatory advantage in patients with HPV + OPSCC in the recurrent/metastatic setting.

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