**Overview Article**

Title:

**Trans Oral Surgery or Radiotherapy for Oropharyngeal Carcinoma – is it either or..?**

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## Abstract:

The management of oropharyngeal carcinoma represents an increasing clinical challenge, both because of its rising incidence, particularly in younger patients as a result of Human Papillomavirus (HPV) infection, and because significant technological advances have occurred in radiotherapy and surgery over the last 10 years which have increased treatment options for patients, with little robust evidence yet of their relative merits. As a result, there is a lack of clinical consensus on the optimum treatment modality, reflected in wide variation in practice between different cancer networks across the UK.

In this review, we consider the evidence base for minimally-invasive transoral surgery and for Intensity Modulated Radiotherapy (IMRT)-based primary treatment for oropharyngeal cancer, both in terms of oncological and functional outcomes. Management strategies for HPV-positive and HPV-negative disease, and for different stages of the disease, are considered. There is currently an unparalleled opportunity to shape the future management of oropharyngeal cancer, which is dependent on recruiting patients to ongoing clinical trials, in order to build an evidence base to support a clinical consensus on the optimal treatment strategies. It is likely that future, evidence-based, patient-centered decision-making will ultilize both primary radiotherapy and primary surgical treatment modalities to maximize patient benefit.

Keywords: Human Papillomavirus, oropharyngeal, radiotherapy, transoral surgery.

**Introduction:**

In parallel with many other clinical paradigms, the treatment of Head and Neck squamous cell cancer (HNSCC) has evolved over the last 20 years to utilize less invasive, more targeted therapies. For surgery, this has meant replacing open surgery, requiring lip split mandibulotomy, with transoral surgery (TOS), either using a laser (Transoral Laser Microsurgery [TLM]) or robot (Transoral Robotic Surgery [TORS]). For radiotherapy (RT), 2D-RT, utilizing large parallel opposed fields, has been replaced by Intensity Modulated RT (IMRT) or Rotational Arc Therapy/Tomotherapy. The ultimate goal with these approaches is to improve clinical outcomes, by extending survival and/or minimizing morbidity.

The management of oropharyngeal squamous cell cancer (OPSCC), affecting the tonsils, tongue base and soft palate, has generated much interest over recent years, for the following reasons:

1. There has been a substantial increase in the incidence of OPSCC across the developed world. A recently reported UK cross-sectional study reported an approximate doubling in OPSCC incidence between 2002 and 2011 (age standardised rate (ASR) 2002 = 2.1 (95% CI: 1.9, 2.2), 2011 = 4.1 (95% CI: 4.0, 4.3)). (1), as shown in Figure 1.
2. Currently, a significant proportion of OPSCCs in the UK are caused by Human Papillomavirus (HPV) infection (so-called ‘HPV-positive’ cancers), whilst the remainder are mainly caused by exposure to tobacco (‘HPV-negative’ cancers) (1). The rising incidence of HPV-positive and negative OPSCC in the UK is shown in Figure 2. It is well documented that HPV-associated OPSCCs have a better prognosis compared to HPV-negative OPSCCs (2), raising the possibility that they could be managed differently.
3. In the absence of randomized studies comparing primary surgical and non-surgical approaches to the management of OPSCC, there is a lack of consensus on how these cancers should be managed, both between surgeons and oncologists within the same Mutidisciplinary Team (MDT), and between different UK cancer networks. The 10th National Head and Neck (H&N) Cancer Audit (DAHNO 2014) provides data on recent UK trends: of 2,439 cases of OPSCC included in the audit, 1,937 were treated with curative intent and, for these, the first recorded treatment was non-surgical in 1,079 (55.7%) and surgical in 858 (44.3%) (3). However, the percentage of patients undergoing surgery as first treatment varied from 26.3% to 66.7% across different networks, reflecting the lack of clinical consensus on the optimum treatment modality. This lack of consensus is not limited to the UK and is apparent across Europe, where surgical (e.g. in Germany) and non-surgical (e.g. in Belgium) philosophies prevail in neighboring counties.

In this article, we review the evidence base for the surgical and non-surgical treatment of OPSCC, both for HPV-positive and HPV-negative disease, and consider how both treatment modalities could be used together to maximize patient benefit.

Treatment of OPSCC:

**Radiotherapy (RT)/Chemoradiotherapy (CRT):**

A 2002 retrospective review of 6400 patients with OPSCC in 51 studies demonstrated similar rates of locoregional control, overall survival and cause-specific survival for patients treated with surgery and postoperative RT (PORT) compared to those treated with primary RT +/- neck dissection, but a significantly higher rate of severe or fatal complications in the surgery group, along with worse functional outcomes (4). This signaled the end for open surgical resection of OPSCC in most centres and heralded an increasing emphasis on the use of RT/CRT.

Early stage (T1-T2 N0-N1) OPSCC can be effectively treated with RT alone (5). For more advanced (stage III/IV) OPSCC, 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) (6,7). However, concurrent chemotherapy increased severe (Grade 3-4) late toxicity (82% CRT vs 47% RT alone, p=0.02), particularly affecting dentition (8). Meta-analysis data in 17,346 patients confirmed that, for HNSCCs as a whole, concurrent chemotherapy confers an overall survival benefit of 6.5% at 5 years (p<0.0001), compared to RT alone (9). In the UK, the use of CRT for OPSCC has increased in successive DAHNO reports and it is now given more than twice as frequently as RT alone (3).

Human Papillomavirus status is highly prognostic in OPSCC patients treated with CRT. In a landmark study, Ang and colleagues retrospectively analysed 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 to 57.1% in HPV-negative patients (p<0.001). Furthermore, patients with HPV-positive and HPV-negative disease could be stratified further, based on other factors, and a group of good prognosis HPV-positive patients was identified with >90% 3 year overall survival (2). Similarly high survival rates for HPV-positive OPSCC have been demonstrated in UK studies in patients treated with primary RT/CRT and surgery (10,11,12).

Toxicities of RT/CRT:

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 (8,13) and up to 43% of HNSCC patients develop grade 3-4 late toxicities following CRT (14).The key late toxicity affecting quality of life (QOL) is swallowing dysfunction (15). Swallowing is a primary concern for patients (16), affecting their physical health and well-being, and is a major cause of distress and burden for family members (17), since dysphagic patients often require long-term supportive care.

Over the past 10-15 years, Intensity Modulated RT (IMRT) has become the standard of care for RT treatment planning and delivery for OPSCC (Figure 3) – the conformal dose distributions achieved allow sparing of normal tissues and organs at risk, potentially reducing toxicities and improving QOL. The UK phase III PARSPORT study demonstrated that parotid-sparing IMRT reduces the incidence of grade 3-4 xerostomia (dry mouth) compared to conventional RT, from 83% to 29% 24 months after treatment (p=0.0001) (18). As a result of this and other data, IMRT has been widely implemented for the treatment of HNSCC in the UK: between December 2013 and February 2014, 78% of all H&N cancer radical patient episodes in England were treated with IMRT (19) and current percentages will be higher.

Late dysphagia is an issue, even in patients treated with IMRT. Feeding tube dependence, a crude measure of swallowing dysfunction, has been reported in 24% of patients at 1 year (13) and 14% at 2 years (20) following chemo-IMRT. Furthermore, patient-reported impairment in swallowing function, measured using the M.D. Anderson Dysphagia Inventory (MDADI), is seen in 80% of patients at 12 months following treatment (21). Late dysphagia correlates with mean radiation dose to the swallowing-related structures (pharyngeal constrictor muscles, glottic and supraglottic larynx, oral cavity, and cervical oesophagus), with the correlation being highest for the superior pharyngeal constrictors (22,23). The normal tissue complication probability curve for the pharyngeal musculature is sigmoidal in shape and increasing mean radiation doses between 50Gy and 60Gy are in the critical range for late dysphagia (22). The potential of dysphagia-optimized IMRT to reduce dysphagia rates, by reducing radiation doses to swallowing-related structures, is being investigated in an ongoing UK trial (DARS). Omitting chemotherapy could also potentially reduce the risk of dysphagia in selected patients, as concurrent chemotherapy increases late dysphagia rates compared to IMRT alone (13).

**Primary surgery:**

Transoral Laser Microsurgery (TLM) and Transoral Robotic Surgery (TORS) are minimally invasive surgical techniques for OPSCC, which have the potential to excise T1-T2 (and some T3) tumours with considerably less long-term functional deficit than open surgery. Transoral surgery (TOS) of the primary tumour is usually performed in conjunction with a neck dissection, either carried out at the same time, or as a staged procedure. Although early stage (T1-T2 N0-N1) OPSCC can be effectively treated with surgery alone (24), adjuvant treatment is required in most patients, usually due to advanced nodal disease.

A retrospective US study of 204 patients with stage III-IV OPC treated with primary 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 (25). A retrospective series from Liverpool, UK of 153 patients with T1-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 (TMJ, manuscript submitted). Similarly good outcomes have been reported following TORS: a cohort study of 410 patients from 11 centres 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 (26).

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 TOS in early stage OPSCC (27). Furthermore, a systematic review comparing the effectiveness of IMRT and TORS for T1-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 were reported for IMRT and TORS, which for IMRT included gastrostomy tubes (43%), oesophageal stenosis (4.8%) and osteoradionecrosis (2.6%) and for TORS as described below.

Adjuvant treatment following transoral surgery for OPSCC:

Transoral surgery for early stage OPSCC is generally well tolerated, with a median length of hospital stay after surgery of approximately 4.4 days (25). Acute complications include haemorrhage (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 (28). Temporary nasogastic tubes are required in up to 47% of patients post-operatively but most patients can manage an oral diet without a tube by 4 weeks following surgery (29,30). Long-term functional outcomes after TOS appear favourable in small studies: in a study of 30 patients with early (mainly T1-2 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 (24).

However, in most reported series of TOS, the majority of patients also undergo adjuvant therapy, either with post-operative RT (PORT, 21-58% of cases) or post-operative CRT (POCRT, 16-62% of cases (25,30,31,32). The decision to recommend adjuvant treatment may be based on primary tumour factors (close (1-5mm) or positive (<1mm) margins, T3-4 stage, perineural and/or lymphovascular invasion) or, more commonly, nodal factors (extracapsular spread of nodal disease and/or N2-N3 nodal stage). These factors are variably interpreted (33), explaining the different proportion of patients undergoing PORT and POCRT in reported studies.

It is clear that adjuvant treatment increases acute and late toxicity associated with transoral surgery. In the largest TLM series (25), 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 (30), 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 more than 2 years after treatment. In 81 patients treated with TORS (34), all patients were discharged post-operatively 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 (HRQOL) scores were also significantly worse in patients who underwent adjuvant treatment compared to 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 (PSS-H&N) scores at 6 and 12 months following treatment were significantly better following TORS alone compared to TORS followed by PORT which were, in turn, better than after TORS and POCRT (35). 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 to POCRT (36).

Optimizing the treatment paradigm for OPSCC:

Early stage OPSCC, T1-T2 N0-N1, can be managed by primary transoral surgery or primary IMRT, with similar oncological outcomes in non-randomised comparisons (28). Transoral surgery may offer benefits in terms of reduced treatment duration, avoidance of acute radiation toxicities and enhanced late function, but only if adjuvant treatment is avoided. An EORTC phase III randomised study (‘Best-Of’) comparing late function (MDADI at 12 months following treatment) after TOS and IMRT in patients with (HPV-positive and negative) T1-T2 N0 M0 OPSCC is due to open in 2016 and could inform future practice for early stage disease.

Patients with T3-4 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 being studied in ongoing UK clinical trials (DARS and De-ESCALaTE-HPV respectively), as means of reducing toxicities in these patients. Poor prognosis OPSCC, including HPV-positive current smokers (37) with advanced disease and patients with HPV-negative disease, may benefit from treatment intensification and an ongoing UK study (COMPARE) is exploring this possibility.

Transoral surgery alone cannot replace radiation-based treatment for T1-T2 OPSCC associated with more advanced (N2-N3) nodal disease, as most patients also require adjuvant therapy. One could therefore reasonably argue that these patients should also be treated with primary CRT, in order to avoid the need for TOS+PORT or even ‘triple modality’ (TOS+POCRT) therapy. However, there are a number of reasons that TOS combined with adjuvant therapy, is a treatment paradigm that warrants further investigation in these patients:

1. Reported complication rates after TOS are lower than after open surgery.
2. Functional outcomes following TOS +/- PORT/POCRT and primary CRT have not been compared in a randomized study. Small studies suggest a possible functional advantage to upfront TOS, although further data is needed. In a matched case-control study of 37 patients with stage III-IV OPSCC, MDADI scores were significantly better at 6- and 12-months in patients after TORS + PORT/POCRT compared to after primary CRT (38). A UK study also reported improved early swallowing outcomes (including MDADI score) 3 months after treatment in 23 patients with stage III-IVA OPSCC treated with TLM +/- PORT/POCRT compared to a historical CRT cohort (39).
3. Up-front surgery can allow adjuvant treatment stratification, based on pathological risk factors for recurrence. This may allow concurrent chemotherapy to be withheld in the absence of ‘high risk’ pathological risk factors (positive margins and/or ECS). The corollary is that for patients who exhibit high-risk pathological features, ‘triple-modality’ treatment is likely to be mandated.
4. TOS +/- de-intensified adjuvant therapy may be explored as a potential means of improving long-term function, whilst maintaining good oncological outcomes, in patients with HPV-positive OPSCC. This is being investigated in the UK phase II/III PATHOS study described below (ClinicalTrials.gov NCT02215265) (40), as well as in 2 ongoing US studies (ECOG 3311 [NCT01898494] and ADEPT [NCT01687413]).
5. TOS +/- intensified adjuvant therapy could be explored as a potential means of improving oncological outcomes in poor prognosis HPV-positive OPSCC and HPV-negative OPSCC. This is being explored, along with other strategies, in the COMPARE study.

PATHOS: Post-operative adjuvant treatment for HPV-positive tumours

Adjuvant treatment decisions are based on pathological risk factors for recurrence established >20 years ago in studies that included a heterogenous group of HNSCC, none of which were tested for HPV (41); their relevance to the selection of adjuvant therapy regimens and doses in the context of HPV-positive disease have been questioned (42). HPV-positive cell lines have higher radiosensitivity compared to HPV-negative lines *in vitro* (43,44) and preliminary results from a phase II study (ECOG 1308) have shown high local control and survival rates after reduced dose RT (54Gy in 27 fractions) in 90 patients with stage III-IV OPSCC, following a complete response to induction chemotherapy (45). POCRT for HNSCC is recommended for ‘high risk’ pathological features (positive margins and/or ECS) based on combined analysis of the EORTC 22931 and RTOG 9501 studies (46). However, ECS does not appear to be prognostic in HPV-positive OPSCC, at least in the absence of soft tissue deposits (47,48, TMJ unpublished data). In retrospective studies, POCRT did not improve overall survival compared to PORT in patients with ‘high risk’ features following TLM (49) and had no effect on disease-free survival in ECS-positive patients (47).

Patients recruited into PATHOS will undergo TOS and neck dissection prior to pathological risk stratification as shown in Figure 4. Patients with transorally resectable T1-T2 (and selected T3) tumours, with N0-N2b nodal disease are eligible, whereas T4 and N2c-N3 disease are excluded because of their higher risk of distant metastatic disease (50). The aim of PATHOS is to determine whether reducing the intensity of adjuvant treatment after TOS in HPV-positive OPSCC, either by lowering RT dose in patients with ‘intermediate-risk’ pathological risk factors (close margins, N2 disease, perineural invasion, vascular invasion), or omitting chemotherapy in patients with ‘high-risk’ pathological risk factors (positive margins and/or ECS), will result in better swallowing function, whilst maintaining excellent clinical outcomes. The primary outcome of the PATHOS phase II study will be long-term patient reported swallowing function measured using the MDADI score at 12 months post-treatment. Secondary outcomes will include local control rates and survival, as well as a panel of objective and self-reported swallowing assessments. If the phase II study is successful, PATHOS will continue to a pan-European phase III study with overall survival as the primary endpoint.

**Discussion:**

There is an unparalleled opportunity in the UK at the present time to shape the future management of OPSCC for patient benefit. Most oncology centres offer IMRT as a standard of care for HNSCC and, in parallel, many surgical units now offer transoral laser or robotic surgery to minimize the impact of surgery on the patient. There are currently 4 UK randomized controlled trials available for patients with OPSCC and, whenever possible, patients should be offered access to these studies in order to build an evidence base to inform future management. It appears likely that future evidence-based, patient-centered decision-making will ultilize both primary RT and primary surgical treatment modalities to effectively manage OPSCC.

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