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Transoral Robotic Surgery and De-escalation of Cancer Treatment

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BACKGROUND

In this chapter, we explore transoral robotic surgery (TORS) as it relates to the de-escalation of therapy for oropharyngeal squamous cell carcinoma (OPSCC). We define treatment de-escalation as the alteration of primary and/or adjuvant therapies with the goal of reducing treatment morbidity and mortality without sacrificing oncologic outcomes. As we will discuss in this chapter, both TORS and transoral laser microsurgery (TLM) are minimally invasive surgical approaches to the tonsils and tongue base that represent an important platform for treatment de-escalation on two fronts. First, these surgical techniques have expanded candidacy for primary transoral surgical therapy, reducing the use of highly morbid open surgical approaches to tumors of the oropharynx. Second, the increasing prevalence of human papillomavirus-related (HPV(+)) tumors has changed the landscape of OPSCC and has presented a new arena in which primary surgery therapy now competes with primary chemoradiation as a viable primary treatment modality.

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Dr. Zevallos is the Chief Medical Officer and an Equity Holder in SummitDX, a start-up biotech company that seeks to develop saliva-based diagnostics for early detection of recurrence in head and neck cancer. Saliva-based diagnostics are not discussed in this manuscript.
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Historical Context:

Treatment modalities for OPSCC, both surgical and nonsurgical, have transformed significantly over the past three decades. Given that many are completing residency training in an era where transoral surgical approaches to the oropharynx is common, the historical context that produced these techniques is important to understand. Advancements in TORS, TLM, and intensity-modulated radiation therapy (IMRT) have all occurred in parallel with one other. Further, these advancements have coincided with an epidemiological shift toward the majority of OPSCC tumors being HPV(+).

Historically, treatment of OPSCC has consisted of surgery, radiation therapy (RT), and/or chemotherapy, often in combination as dictated by the stage of disease. In many instances, the choice of primary treatment modality that patients received was dictated by institutional patterns of practice. By the 1990s, the question of whether to use of surgery or radiotherapy as the primary treatment modality for OPSCC was not settled. Given the increasing use of morbidity-reducing RTs such as IMRT in the late 1990s and early 2000s[1], it was not clear that surgery to the primary site was noninferior to primary RT especially when treatment morbidity and mortality was concerned.

In 2002, a review of studies between 1970 and 2000 was performed exploring outcomes in primary surgery plus RT versus primary RT plus neck dissection. While oncologic outcomes were similar between groups, authors reported strikingly higher severe (25% vs 6%) and fatal complications (3.2% vs 0.8%) in patients treated with primary surgery.[2] As is discussed in greater detail below, it must be noted that the surgical approaches to the oropharynx during this study period often involved transcervical and/or transmandibular exposure and free flap reconstruction. Based on these findings, primary chemoradiation therapy (CRT) became an increasingly preferred primary treatment modality in many centers around this period of time.[3]

As it was became clear that the open surgical approaches described above would carry unacceptably high complication rates when compared with primary CRT, minimally invasive techniques to address tumors of the oropharynx were developed and gained popularity. TLM was initially performed in the early 1970's by Strong and Jako, who were the first to combine the CO2 laser with microlaryngoscopy.[4] Over the subsequent decades, TLM's role in treating upper aerodigestive tract malignancies expanded beyond its initial use in small laryngeal tumors.[5] By the 2000's it was clear that TLM could be used successfully to treat tumors of the tongue base and pharynx.[6]

Around the same time that TLM was becoming established as a minimally invasive modality for treatment of OPSCC, the use of the da Vinci Surgical System was expanding in other surgical fields, notably Urology and General Surgery.[7] It was quickly recognized by multiple groups as a technology whose utility could be translated for use in Head and Neck Surgery (Haus 2003, McLeod 2005, Hockstein 2005 mannequin).[8–10] Work by Hockstein, Weinstein and O'Malley brought this technology from initial simulations on mannequins and cadavers to demonstrating the safety and efficacy of TORS in human clinical trials.[11–14] TORS received US Food and Drug Administration approval in 2009 for use in pharyngeal and

laryngeal tumors.[15] TORS and TLM are now both frequently used at a number of centers for smaller primary tumors of the oropharynx.

DISCUSSION

TORS as a De-escalated Surgical Therapy:

Prior to TORS and TLM, tumors that could not be approached transorally required much more invasive surgery. Historically, only select tumors of the tonsil, posterior pharyngeal wall, and soft palate were routinely removed transorally. The limited ability to properly expose base of tongue tumors as well as tonsil and posterior pharyngeal wall tumors with inferior extension prevented many modestly sized tumors from being resected transorally. In these instances, open surgical exposure was required. While open techniques did result in very good exposure of tumors, dissection and division of anatomic structures not affected by tumor is required in these approaches. Lateral and transhyoid pharyngotomies were often used to access tumors with inferior extent. Muscular attachments to the hyoid are divided in the latter approach, which may contribute to postoperative dysphagia. The pharyngotomy required in both approaches results in fistula formation in a subset of patients, and the hypoglossal and recurrent laryngeal nerves are placed at risk in this approach. Midline mandibulotomy, also known as mandibular swing, was another common means of exposing tumors of the oropharynx. This involves splitting the mandible and dividing the floor of mouth musculature. Complications associated with this technique included increased blood loss, mandibular malunion, hardware infections, fistula, inferior alveolar nerve injuries, and dysphagia.[16]

TORS and TLM may be considered treatment de-escalation because they have limited the morbidity and mortality associated with primary surgical treatment of OPSCC without sacrificing oncologic outcomes.[17–19] By improving access and exposure of tumors, these techniques have expanded the share of patients that can be successfully treated with a primary surgical approach while avoiding the risks of open approaches. Transoral approaches significantly reduce the occurrence of postoperative fistulas even when a neck dissection is performed simultaneously.[20] Because the neck and/or mandible are not disassembled during surgery and disrupted tissues are limited to an area immediately surrounding the tumor, TORS and TLM better preserves blood and nervous supply to unresected tissues of the oropharynx. This may explain the generally favorable swallowing outcomes observed with minimally invasive approaches.[17] For the same reason, defects in TORS and TLM are more amenable to healing by secondary intention, allowing many more OPSCC patients to be treated with primary surgery while avoiding the morbidity associated with locoregional flaps or free tissue transfer.[21]

Despite the advantages of transoral approaches compared to open approaches, the ability to successfully perform transoral surgery in a way that limits patient morbidity depends on individual patient factors, many of which are available preoperatively through physical examination and routine imaging. Aside from comorbidities that would limit ability to safely tolerate general anesthesia, one must consider factors related to both the patient's normal anatomy and the patient's tumor. Patients must not have significant trismus, the tongue must be able to be retracted to an extent that the field can be exposed, and other structures in the

oral cavity such as the teeth and mandibular arch must accommodate retractors. Tumors that are exophytic and mobile are generally preferred to tumors that are endophytic and fixed. Removing more than 50% of the base of tongue or 75% of the soft palate may result in significant velopharyngeal insufficiency and dysphagia, respectively.[22,23] Even in the absence of absolute contraindications to transoral surgery, there remain instances where primary CRT is preferable to surgery, especially given both approaches are sound from an oncological standpoint.

Treatment De-escalation in HPV+ disease:

While the development of less invasive surgical approaches like TORS and TLM has represented a de-escalation in primary surgical therapy for tumors of the oropharynx, these techniques also exist as part of a broader effort to de-escalate therapy specifically for patients with HPV(+) OPSCC. Although traditionally regarded as a disease caused by tobacco and alcohol use, a shift toward HPV infection representing the causative event in OPSCC has occurred since the 1980s.[24] It is estimated that 60–70% of new OPSCC diagnoses are attributable to HPV,[25] and OPSCC has surpassed cervical cancer as the most common HPV-related malignancy in the United States.[26]

Compared to HPV(−) OPSCC, HPV(+) disease has a markedly more favorable prognosis.[25–27] The observed differences in clinical outcomes are most likely explained by the fact that, despite sharing a similar macroscopic phenotype, HPV(+) and HPV(−) tumors are molecularly distinct entities.[28,29] HPV(+) tumors seem to respond well to both RT and primary surgical therapy. Sinha *et al* performed a systematic review comparing surgical versus nonsurgical treatment of HPV(+) OPSCC, which found that although there is heterogeneity between studies and a lack of randomized trials, there was no clear evidence of a difference between treatment modalities.[27]

The recently published ORATOR trial was a phase 2 randomized controlled trial (RCT) that compared TORS plus neck dissection and indicated adjuvant therapy versus definitive CRT.[30] Patients were AJCC7 T1–2, N0–2, M0 and 88% were p16(+). There were no differences in overall survival or progression-free survival between groups. The study's primary outcome of interest was quality of life related to swallowing as measured by the MD Anderson Dysphagia Inventory (MDADI). Although patients in the CRT group had significantly higher MDADI scores compared with the TORS group, this did not amount to a clinically significant difference.[30]

Patients with HPV(+) are demographically distinct compared to patients with HPV(−) disease. Compared to HPV(−) patients, HPV(+) patients tend to be male, Caucasian, relatively younger, healthier, and are less likely to have a significant smoking history.[25] The typical demographic characteristics of the HPV(+) OPSCC population are an important consideration regarding treatment de-intensification. In HPV(−) OPSCC, the morbidity of treatment may appear justified by the comparatively low rates of survival within an aged population with relatively high rates of medical comorbidities. In contrast, the majority of HPV(+) patients respond well to treatment and because they are younger and healthier at the time of diagnosis, they may survive for decades after successful treatment. Thus, longer term

treatment morbidity that is not as frequently observed in HPV(−) patients has become a greater concern within this expanding population.

Each treatment modality brings its own unique set of risks to the OPSCC patient. Inherent risks of transoral surgery include those related to general anesthesia as well as risks associated with a short postoperative hospitalization. The most potentially severe surgical complication is postoperative bleeding from the primary surgical site. At minimum, these patients must return to the operating room for cauterization. Rarely these bleeds may lead to asphyxiation; the rate of fatal hemorrhage is estimated to be 0.17% of all TORS cases.[31] Prophylactic transcervical arterial ligation reduces the severity of postoperative bleeding events.[32] Other short term sequellae can include postoperative swelling which in some cases exacerbates obstructive sleep apnea and rarely produces a need for a temporary tracheostomy. Velopharyngeal insufficiency is a rare long-term complication of transoral surgery but may be minimized when patients are selected carefully. Dysphagia may be a short or long term complication, and is significantly more likely in patients treated with adjuvant RT or CRT.[17]

Inherent to primary or adjuvant RT are both acute and long-term treatment effects. Of the most common acute effects are mucositis and candidiasis, both of which may result in pain that limits oral intake. Dysphagia is one of the most significant complications of RT and can occur as both an early and late treatment effect. Dysphagia has been shown to be more prevalent in CRT compared to RT alone.[33] Multiple studies have established the relationship between post-treatment dysphagia and the radiation dose to the pharyngeal constrictors, glottis, and supraglottis.[34,35] A substantial proportion of patients treated with RT will experience dysphagia years after treatment.[36–38] Other long term treatment effects include xerostomia and neck fibrosis, both of which may significantly affect patient quality of life and sometimes evolve for years after treatment.[38] In addition to exacerbating dysphagia, platinum based chemotherapeutics also carry their own known treatment effects including sensorineural hearing loss and peripheral neuropathies.

The ability for primary surgical therapy to yield pathologic specimens distinguishes it from primary CRT. In theory, the tumor’s pathologic characteristics reveal potentially important information about the tumor’s biologic behavior that are not available from radiologic imaging, physical exam, or biopsy specimens. This in turn should allow for the identification of low-risk patients whose therapies can be safely de-escalated. However, in current practice primary surgical therapy only allows a minority of patients with HPV(+) disease to avoid adjuvant therapy, while a sizable portion go onto be treated with all three modalities (surgery + adjuvant CRT).[39] This is the case because in HPV(+) disease, the cervical neck metastasis is most often the first symptom that the patient experiences, thus the local metastatic extent of the disease is such that adjuvant therapy is usually indicated. While the currently used adjuvant RT and chemotherapy doses are lower relative to definitive CRT, de-escalation efforts described below aim to further reduce dose-dependent toxicity after surgical therapy.

Our current paradigm for assigning patients adjuvant therapy is largely based on evidence from HPV(−) disease (Bernier 2005, Blanchard 2011).[40,41] A current source of controversy within the literature relates to whether the histopathologic predictors of adverse oncologic

outcomes in HPV(−) disease are also useful in HPV(+) disease for the assignment of adjuvant therapy. For example, multiple groups have provided evidence in the form of retrospective/cohort studies suggesting that extracapsular extension (ECE) is not a predictor of oncologic outcomes in HPV(+) OPSCC.[42–45] However, other authors have found conflicting evidence regarding ECE and advocate its inclusion in future HPV(+) OPSCC staging systems.[46–48] Ongoing prospective trials described below may provide high-quality evidence that clarifies questions regarding traditional histopathologic features and how primary surgical treatment and the use of specimens may be able to guide de-escalations in adjuvant therapy.

Multiple prospective studies are in progress or have been recently completed that investigate treatment de-escalation in HPV(+) disease treated with primary surgery. Two published studies have investigated alteration of RT, either through the exclusion of structures from the radiation field through limitation of the total radiation dose. The **AVOID** trial was a single-arm phase 2 trial that investigated the avoidance of primary tumor sites from inclusion in the radiation field if tumors were adequately resected and free of adverse histopathologic features such as perineural or lymphovascular invasion.[49] In this trial, the 2-year rate of local control was 98.3% and patients with evidence of limited toxicity.[49] **MC1273** was a phase II trial that investigated a reduced overall adjuvant RT dose of 30–36 Gy as guided by ECE status in p16(+) OPSCC patients (Ma 2019).[50] It should be noted that this was investigated in combination with simultaneous docetaxel in all patients.[50] These authors similarly demonstrated a 96.2% locoregional control rate at 2 years and favorable toxicity profile.[50] These single-arm trials provide early prospective evidence that adjuvant therapy may be safely reduced in select HPV(+) OPSCC tumors which are adequately managed with surgery.

ECOG-E3311 is a phase II RCT which has been focused primarily on assessing a reduced RT dose in patients with HPV(+) disease. While the complete results are not yet in publication, an abstract describing this trial's findings is available.[51] The total number of patients enrolled was 519, and all patients underwent transoral surgery and neck dissection for clinically T1–2 tumors which were AJCC7 stage III or IV without matting of nodes. Intermediate risk patients were those who had clear or close surgical margins, 2 to 4 positive nodes, or had ENE less than or equal to 1mm. Intermediate risk patients were randomized to either 50 or 60 Gy of RT. Low risk patients avoided RT and high-risk patients were assigned standard of care adjuvant CRT. Authors found that 2 year progression free survival was similar regardless of RT dose in the intermediate risk groups. Low risk patients who did not have adjuvant therapy had similar favorable outcomes. These authors conclude that transoral surgery may be an effective part of surgical de-escalation, with low risk patients able to avoid adjuvant therapy and selected intermediate risk patients able to benefit from lower RT doses.

Although the focus of this review is treatment de-escalation as it relates to TORS, it should be noted that substitution of cisplatin with less toxic chemotherapeutic agents has represented a major goal in HPV(+) treatment de-escalation. Recently a large RCT comparing definitive RT + cisplatin versus RT + cetuximab was completed.[52] This trial demonstrated a clear benefit of cisplatin over cetuximab for both overall and progression

free survival, suggesting that substitution of cetuximab does not represent a viable option for chemotherapeutic de-escalation in definitive CRT for HPV(+) OPSCC.[52]

Trials in Progress:

Multiple RCTs are now in progress that will add to our understanding of the effect of adjuvant treatment de-escalation after primary surgery on oncologic outcomes and treatment toxicity (Table 1). **DART-HPV** is a phase III RCT that is building on the results of MC1273 described above. The experimental group will receive 30–36 Gy + docetaxel while the experimental arm will receive standard doses of RT + cisplatin (ClinicalTrials.gov: NCT02908477). **PATHOS** is a phase III RCT which similarly compares 50 vs 60 Gy in intermediate risk patients. It also compares the removal of cisplatin with standard of care CRT in high risk patients (ClinicalTrials.gov: NCT02215265).[53] The **MINT** trial is a phase II RCT which will evaluate reduction of both RT and chemotherapy doses. Low risk patients will receive 42 Gy of IMRT alone, intermediate risk patients (those with ECE or positive margins) will receive 42 Gy + one dose of cisplatin, and high risk patients (c/pT4 or cN3) will receive standard of care adjuvant CRT (ClinicalTrials.gov: NCT03621696).

Additionally, there are multiple ongoing RCTs which compare various forms of primary surgical therapy against primary nonsurgical therapy (Table 2). Some of these trials also include de-escalated treatment protocols. **ORATOR II** is a RCT which will compare two modes of de-escalated primary treatment. One group will be randomized to a de-escalated definitive RT regimen (60 Gy +/− chemotherapy) and the other to transoral surgery and neck dissection +/− adjuvant RT (50–60 Gy)(ClinicalTrials.gov: NCT03210103). The **QoLATI** study will compare TORS plus neck dissection against IMRT +/− chemotherapy (ClinicalTrials.gov: NCT04124198). A trial by the **European Organization for Research and Treatment of Cancer** of patients with early stage OPSCC is being conducted that will compare IMRT + selective neck dissection against transoral surgery, selective neck dissection, and adjuvant therapy as indicated by risk factors(ClinicalTrails.gov: NCT02984410). A trial by **Universitätsklinikum Hamburg-Eppendorf** will compare transoral surgery and neck dissection and adjuvant therapy as indicated by risk factors against standard primary CRT (ClinicalTrials.gov: NCT03691441).

SUMMARY

TORS and TLM allow for improved access and exposure to oropharyngeal tumors and have expanded the share of patients that can have adequate surgical resection while avoiding invasive open surgical approaches. Compared to HPV(−) disease, HPV(+) OPSCC is molecularly and clinically distinct. HPV(+) OPSCC patients respond well to therapy and are younger and healthier at the time of diagnosis. Because they can survive for decades after treatment, long-term treatment sequelae are an increasingly important consideration within the growing population of HPV(+) OPSCC survivors. Initial evidence indicates that transoral surgery may have an important role in future HPV(+) treatment de-intensification by providing pathologic staging data which may justify the avoidance or de-escalation of adjuvant therapeutic regimens. Numerous trials are in progress that investigate strategies for de-escalating adjuvant therapies after surgery or compare outcomes of primary surgery

against primary CRT. We expect the evidence that will emerge in the coming decade will better define the roles of TORS, radiation, and chemotherapy in the treatment of HPV(+) OPSCC.

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Clinics Care Points:

- By improving access and exposure of tumors, transoral robotic surgery (TORS) and transoral laser microsurgery (TLM) have expanded the number of patients that can be successfully treated with primary surgery transorally, thus avoiding the high morbidity associated with historical open surgical approaches to tumors of the oropharynx.
- Compared to human papillomavirus negative (HPV(−)) oropharynx squamous cell carcinoma (OPSCC), HPV(+) disease is molecularly and clinically distinct, responding more favorably to treatment and affecting a younger and healthier population of patients. Because HPV(+) OPSCC patients may survive for decades after diagnosis, an important goal is to establish appropriate treatment regimens that reduce treatment morbidity without affecting oncologic success.
- Recent trials indicate that transoral surgery may have an important role in future HPV(+) treatment de-intensification by providing pathologic staging data which may justify the use of de-escalated adjuvant therapeutic regimens.
- Ongoing prospective trials addressing HPV(+) OPSCC treatment de-escalation and choice of primary treatment modality are more numerous than those that have been completed to date. Over the coming decade, these trials will greatly expand our understanding of the roles of TORS, radiation, and chemotherapy in the primary treatment of HPV(+) OPSCC.

Synopsis:

This chapter outlines the ways that transoral robotic surgery and transoral laser microsurgery relate to treatment de-escalation in the treatment of head and neck cancer. Treatment de-escalation has particular importance in the context of HPV-related oropharynx squamous cell carcinoma, which generally responds well to therapy but leaves many survivors with decades of treatment related sequelae. We compare these less invasive transoral approaches to previously used open approaches to the oropharynx. We discuss the topic of treatment de-escalation in HPV-related disease and outline completed and ongoing clinical trials investigating the choice of primary treatment modality and de-escalation of adjuvant therapy.

Table 1:

Adjuvant Therapy De-escalation Trials in Progress

Name	Title	Phase	Interventions	Enrollment	Estimated Completion	Primary Outcome Measure(s)	NCT #	Study Sponsor
DART-HPV	DART-HPV: A Phase III Evaluation of De-escalated Adjuvant Radiation Therapy for HPV-Associated Oropharynx Cancer	3	Reduced RT (30 – 36 Gy, depending on risk group) + docetaxel is compared with 60 Gy +/− cisplatin	214	2024	Adverse Events Rate	NCT02908477	Mayo Clinic
PATHOS	A Phase III Trial of Risk stratified, Reduced Intensity Adjuvant Treatment in Patients Undergoing Transoral Surgery for Human Papillomavirus(HPV)-Positive Oropharyngeal Cancer	3	Intermediate risk group: reduced RT (50 Gy) is compared with 60 Gy; High risk group: adjuvant CRT is compared with adjuvant RT alone	1100	2026	MDADI/ Overall survival co-primary endpoint	NCT02215265	Lisette Nixon
MINT	Phase II Trial of Surgery Followed by Risk-Directed Post-Operative Adjuvant Therapy for HPV Related Oropharynx Squamous Cell Carcinoma: “The Minimalist Trial(MINT)”	2	Low risk group: reduced RT (42 Gy) alone, intermediate risk group: reduced RT (42 Gy) one cisplatin dose, high risk group: standard of care (60 Gy + 3 doses cisplatin)	43	2022	Percent weight loss in patients during modified adjuvant CRT	NCT03621696	Washington University School of Medicine

Data from clinicaltrials.gov; Abbreviations- RT: radiation therapy, CRT: chemoradiation therapy, Gy: Gray, PFS: progression-free survival, MDADI:MD Anderson Dysphagia Inventory

Table 2:

Trials in Progress Comparing Primary Treatment Modalities

Title	Phase	Interventions	Enrollment	Estimated Completion	Primary Outcome Measure(s)	NCT#	Study Sponsor
A Randomized Trial of Treatment De-Escalation for HPV-Associated Oropharyngeal Squamous Cell Carcinoma Radiotherapy vs. Trans-Oral Surgery (ORATORIO II)	2	De-escalated primary CRT (60 Gy +/− cisplatin) is compared with transoral surgery, neck dissection and adjuvant RT (50–60 Gy, depending on risk)	140	2028	Overall Survival	NCT03210103	Lawson Health Research Institute
Quality of Life After Primary Transoral Robotic Surgery vs Intensity-modulated Radiotherapy for Patients With Early-stage Oropharyngeal Squamous Cell Carcinoma: A Randomized National Trial (QoLATI)	2	TORS, neck dissection +/− CRT is compared with primary CRT.	138	2029	Swallowing related quality of life (MDADI)	NCT04124198	Christian von Buchwald
Phase III Study Assessing The “Best of” Radiotherapy Compared to the “Best of” Surgery (Trans-oral Surgery (TOS)) in Patients With T1-T2, N0 Oropharyngeal Carcinoma	3	Transoral surgery and neck dissection is compared with RT and neck dissection	170	2026	Change in MDADI scores	NCT02984410	European Organization for Research and Treatment of Cancer (EORTC)
Comparative Effectiveness Trial of Transoral Head and Neck Surgery Followed by Adjuvant Radio(Chemo)Therapy Versus Primary Radiochemotherapy for Oropharyngeal Cancer	4	Transoral surgery, neck dissection +/− CRT is compared with primary CRT	280	2023	Time to local or locoregional failure or death from any cause	NCT03691441	Universitätsklinikum Hamburg-Eppendorf

Data from clinicaltrials.gov; Abbreviations- RT: radiation therapy, CRT: chemoradiation therapy, Gy: Gray, MDADI:MD Anderson Dysphagia Inventory