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Surgery Versus Radiotherapy for Early Oropharyngeal Tumors: a Never-Ending Debate

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Opinion statement

Therapeutic options for early stage oropharyngeal squamous cell carcinoma (OPSCC) include both surgery and radiotherapy as single treatment modality. Retrospective data reporting on locoregional control and survival rates in early stage OPSCC have shown equivalent efficacy, although no prospective randomized trials are available to confirm these results. Given the assumed comparable oncologic results in both groups, complication rates and functional outcomes associated with each modality play a major role when making treatment decisions. Radiotherapy is used preferentially in many centers because few trials have reported higher complication rates in surgical patients. However, these adverse effects were mainly due to traditional invasive open surgical approaches used for access to the oropharynx. In order to decrease the morbidity of these techniques, transoral surgical (TOS) approaches have been developed progressively. They include transoral laser microsurgery (TLM), transoral robotic surgery (TORS), and conventional transoral techniques. Meta-analysis comparing these new approaches with radiotherapy showed equivalent efficacy in terms of oncologic results. Furthermore, studies reporting on functional outcomes in patients undergoing TOS for OPSCC did not show major long-term functional impairment following treatment. Given the abovementioned statements, it is our practice to treat early stage OPSCC as follows: whenever a single modality treatment seems feasible (T1–2 and N0–1), we advocate TOS resection of the primary tumor associated with selective neck dissection, as indicated. In our opinion, the advantage of this approach relies on the possibility to stratify the risk of disease progression based on the pathological features of the tumor. Depending on the results, adjuvant radiation treatment or

chemoradiotherapy can be chosen for high-risk patients. For tumors without adverse features, no adjuvant treatment is given. This approach also allows prevention of potential radiation-induced late complications while keeping radiotherapy as an option for any second primary lesions whenever needed. Definitive radiotherapy is generally reserved for selected patients with specific anatomical location associated with poor functional outcome following surgery, such as tumor of the soft palate, or for patients with severe comorbidities that do not allow surgical treatment.

Introduction

Oropharyngeal squamous cell carcinoma (OPSCC) arises from the epithelium of the base of tongue, tonsils, soft palate, and posterior pharyngeal wall. OPSCC is a relatively rare entity, with approximately 123,000 new cases worldwide and about 79,000 deaths each year [1]. The peak of incidence is between the sixth and seventh decade of life. The epidemiology of OPSCC has experienced a significant transition over time. Chronic exposure of tobacco and alcohol was the principal risk factors in the past. The benefit of prevention campaigns has progressively resulted in a decrease in the incidence of these tumors. In parallel, there has been a significant increase in the incidence of human papillomavirus (HPV)-associated OPSCC, particularly in younger adults [2]. HPV-associated OPSCC preferentially affects men in their 40s or 50s and is mainly confined to the palatine tonsils and to the base of tongue. The number of oral sex partners is associated with a higher risk of HPV transmission. Although HPV-associated tumors show an overall better prognosis to any treatment for a given stage, as compared with tobacco- and alcohol-related SCCs, there is not yet enough evidence accumulated allowing for a de-escalation of therapy in these patients. This aspect represents a major question in the management of OPSCC. Indeed, several clinical trials are currently underway to investigate whether such a de-escalation of therapy results in a reduction of treatment morbidity and thus could be considered in HPV-positive OPSCC patients without compromising survival. This issue is even more relevant in early stage disease where functional outcome should be the cornerstone of any treatment modality.

The prognosis of OPSCC is dependent on the tumor stage and the HPV status of the tumor [3]. For a given stage, HPV-associated OPSCC in non-smokers has the best prognosis. In the smoking population, HPV-positive tumors constitute an intermediate risk group, whereas HPV-negative OPSCC is at highest risk of cancer progression. Regardless of the HPV status, early stage OPSCC has an average 5-year survival rate of over 80 %. Most of the patients with early stage OPSCC are usually cured. They will most likely die of unrelated diseases or develop second primaries in the head and neck area, if they have a past history of heavy smoking and drinking.

Treatment of early stage OPSCC can be successfully achieved with primary surgery including neck dissection, as indicated, or with definitive radiotherapy [4]. For more advanced stages, the choice is left between exclusive chemoradiotherapy and surgery, followed by adjuvant (chemo) radiation treatment. Salvage surgery is used for progressive or recurrent disease, if needed. Both options have shown similar control and survival rates in advanced stages. The choice of the best treatment for OPSCC is complex and should take into consideration many factors, including those related to the patient, to the tumor, and to the physicians in charge. First, the patient's general medical condition, age, occupation, compliance, socioeconomic status, history of previous radiotherapy, and risk factors should be carefully assessed. Second, the precise location of the tumor; its size; its proximity with bone, cranial nerves, and blood vessels; and the lymph node status of the neck and the HPV status of the tumor should be taken into account. Finally, the level of expertise of the various physicians in charge should be considered. Surgeons dealing with OPSCC should be comfortable with both open and transoral approaches, including access to state of the art transoral laser microsurgery (TLM) and/or transoral robotic surgery (TORS) technical platforms (Fig. 1). Furthermore, patients should also be offered the best reconstructive options if needed, including microvascular free flap repairs. Availability of optimal techniques for radiation administration should be available, and radiation oncologists should have a thorough knowledge of

Fig. 1. Differences between transoral laser microsurgery (TLM) and transoral robotic surgery (TORS). (**a**, left panel) Typical set-up for TLM with a microscope and a CO_2-laser connected. Of note, this is a two-hand technique. (**b**, upper right panel) Typical set-up for TORS with the surgeon on the console controlling the surgical instruments, (**c**, lower right panel) and setting up the robot to the right of the patient allowing a second surgeon at the bed-site. This is typically a four-hand technique.

treatment planning in this difficult anatomic area. Last but not the least, full access to rehabilitation services and dental medicine experts should also be a usual part of the management. Therefore, opportunities for a comprehensive treatment of OPSCC are best achieved in tertiary medical centers with a multidisciplinary approach.

Treatment

The tumor node metastasis (TNM) system from the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (IUCC) is used to stage OPSCC. The National Comprehensive Cancer Network (NCCN) clinical practice guideline has divided OPSCC in three staging categories with early stage disease comprising T1–2 and N0–1 lesions. Therapeutic options for the treatment of early OPSCC, as defined by the NCCN guidelines, will be reviewed here.

Surgery

- Early OPSCC can be successfully treated with surgery or radiotherapy as single modality. Although there is no prospective clinical trial that demonstrates the superiority of one approach over the other, many retrospective studies have shown equivalent disease-specific survival (DSS) rates [4]. The major shift in the epidemiology of OPSCC over the past decades, with increasing HPV-associated tumors, should also increase the overall prognosis of early stage tumors, regardless the modality of treatment [3]. With already excellent 5-year survival rates and because the sample size needed to show a statistical difference between the two groups would be extremely large, it is unlikely that a prospective study will ever provide strong evidence of a significant advantage of one therapeutic approach over the other. Therefore, with the advent of TOS approaches, the focus of prospective studies comparing surgery with radiotherapy should before everything else focus on functional outcomes [5].
- The main advantage of surgery over radiotherapy relies on the possibility to stratify the risk of disease progression based on unforeseen

histopathological adverse features of the tumor, namely perineural invasion, vascular embolism, the presence of microscopic N2 disease, and/or the presence of extracapsular spread (ECS) [5]. Depending on the results, adjuvant radiation treatment (perineural invasion, vascular embolism, and N2 neck) or concomitant chemoradiotherapy (ECS and positive margins) can be chosen for high-risk patients, while no adjuvant treatment is given for low-risk ones. This approach allows to prevent potential radiation-induced late complications, to keep radiotherapy as an option for any second primary neoplastic lesions whenever needed and finally to intensify treatment for patients at high risk of cancer progression. It is noteworthy that, despite the epidemiologic trend for increasing HPV-associated tumors in OPSCC, there is still a significant portion of patients with tobacco and alcohol-related SCCs who carry a 20 % risk of developing a second primary of the upper aero-digestive tract in the course of their life [6]. Offering a single modality surgical treatment with good functional outcomes to these patients might be of invaluable benefit in case a second primary tumor requires definite radiotherapy later on. Indeed, second primaries in previously irradiated field are associated with poor DSS [7]. Whether this philosophy also applies to HPV patients is a matter of debate, as it has been shown that the increased risk of a second primary SCC following an HPV-associated malignancy is not increased to the same extend [8, 9].

Transoral Surgery (TOS)

- Transoral approaches to the oropharynx involve resection of tumors through an open mouth without external incision [5]. It includes TLM, TORS, and conventional techniques using monopolar cautery or laser techniques. Resection through this approach is fast and should result in minimal cosmetic and functional morbidity.
- Transoral surgery (TOS) techniques are ideally suited, but not restricted, for early (T1–2) primary tumors. Resection in pieces with pre-operative margin mapping of the tumor-host interface using frozen section analysis has proven to be oncologically sound with TLM techniques [10•]. In contrast, "en bloc" resection is usually favored by transoral robotic surgeons. Comparative analysis on the positive margin rates between the two techniques has shown similar results [11–14, 15•]. To date, no study has looked into the local recurrence rate as well as the oncologic and functional outcomes between TLM and TORS.
- The major restriction of TOS is the limitation of exposure. Good visualization of the entire tumor as well as additional 1–2 cm mucosal and deep margins should always be ensured before considering such approach. This aspect is best assessed during pre-therapeutic endoscopic work up of the patient. Specific conditions, such as trismus, height of the mandible, and the presence of teeth can make adequate resection of the tumor impossible regardless the technique used.

- TLM and TORS have revolutionized TOS by improving general tumor exposure and providing easy access to difficult anatomic sites, such as the base of tongue and the vallecula. A recent retrospective national cancer database review showed that TORS, together with high volumes centers, was both associated with significant lower rates of positive surgical margins as compared with non-robotic approaches [16]. Obtaining negative surgical margins is of crucial importance in the treatment of early stage OPSCC, since their positivity call for adjuvant chemoradiotherapy, resulting in unnecessary adverse functional outcomes.
- The potential difficulty of exposure together with the potential necessity to remove tumors in peaces has called into question the oncologic safety of TOS approaches. Several papers, based on retrospective studies, have independently shown comparable oncologic outcomes as compared with external beam radiation [17, 18, 19••]. However, these studies rely on historical data which are vulnerable to selection bias, even in matched cohort analysis. Nevertheless, DSS seem to be invariably comparable between the two treatment modalities. The most recent meta-analysis on early stage OPSCC reported a 5 years DSS of 90.4 % (95 % confidence interval (CI)=85.6–95.2 %) in the radiotherapy group and 89.6 % (95 % CI=81.8–97.3 %) in the TOS group (evidence level class IV) [19••]. The qualities of studies were similar in both groups. Equivalent prognostic rates were reported in other studies [17, 18, 19••].
- Incidence of complication rates following TOS is low [17]. The major adverse events include postoperative hemorrhages with a reported rate of 2.4 % and a fistula formation risk of 2.5 %, which can be avoided in the vast majority of cases by performing neck dissection in a delayed manner or by not removing level I during the selective neck dissection. Finally, the reported rate of tracheotomy tube placement at the time of surgery is 12 % with a vast majority of patients being de-cannulated prior to discharge [20••].
- Although not restricted to early stage OPSCC, several studies have investigated the functional outcomes of TORS and TLM [13, 21••, 22–26]. It should be noted that in the majority of the patients included in these studies, adjuvant radiotherapy, and occasionally chemoradiotherapy, were used. Nevertheless, all studies reported excellent functional outcomes at 1 year following treatment (Table 1). The vast majority of patients recovered baseline function as assessed by different validated scores, such as the Functional Oral Intake Score (FOIS), the Functional Outcome Swallowing Scale (FOSS), the M.D. Anderson Dysphagia Inventory (MDADI), the Performance Status Scale for Head and Neck Cancer (PSS-HN), and the University of Washington Quality of Life (UW-QOL). A systematic review was recently conducted assessing the functional outcome after TORS for OPSCC [27••]. Again, among the 12 papers comprising 441 patients, a significant portion was advanced stages and underwent adjuvant treatment. Functional outcomes included feeding tube dependence, speech ratings,

Table 1. Functional outcomes of transoral surgical (TOS) approaches for oropharyngeal squamous cell carcinoma (OPSCC)

Study	Method	TNM	Adjuvant treatment	Functional outcomes at 1 year
Chen 2015[21••]	TORS/TLM	T1-3/N1-2c	RT 100 %	UW-QOL for swallowing at 91.5/100
Leonhardt 2012[24]	TORS	T1-4/N0-2b	CRT 19 %/RT 60 %	PSS-HN back to baseline for eating, reduced for speech
More 2012[25]	TORS	T1-3/N0-2c	CRT 60 %/RT 20 %	MDADI back to baseline
Sinclair 2011[26]	TORS	T1-2/N0-2c	CRT 31 %/RT 45 %	MDADI from pre-tx 82 to post-tx 74
Genden 2011[22]	TORS	T1-2/N0-2c	CRT 60 %/RT 20 %	PSS-HN and FOIS back to baseline
Haughey 2011[13]	TLM	T1-4/N0-3	CRT 16 %/RT 58 %	FOSS back to 0–2 in 87 %
Grant 2006[23]	TLM	T1-4/N0-3	CRT 0 %/RT 47 %	FOSS back to baseline

TLM transoral laser microsurgery, *TORS* transoral robotic surgery, *RT* radiotherapy, *CRT* chemoradiotherapy, *FOIS* functional oral intake score, *FOSS* functional outcome swallowing scale, *MDADI* M.D. Anderson Dysphagia Inventory, *PSS-HN* performance status scale for head and neck cancer, *UW-QOL* University of Washington Quality of Life

velopharyngeal insufficiency, pneumonia, and oral intake measures. Chronic gastrostomy tube dependence ranged from 0 to 7 %, regardless of the disease stage. MDADI scores ranged from 65.2 to 78. Incidence of posttreatment pneumonia was 0–7 %. Rates of transient hyper nasality were 4–9 %. Predictors of poor swallowing outcomes included baseline function, TNM stage, and primary tumor location in the base of tongue as well as adjuvant chemoradiation therapy. Altogether, these data suggest good functional outcomes in patients treated with TOS approaches (evidence level class IV). Another systematic review confirmed these results [18]. Given the fact that none of the available studies have specifically addressed the question of functional outcomes in patients with early stage OPSCC, it is tempting to speculate that the functional expectations could be even higher in patients undergoing TOS without the need of adjuvant treatment. Indeed, retrospective sub-group analysis showed that TOS patients treated with single modality do functionally better compared with those requiring adjuvant therapies [12, 13]. This important hypothesis should be validated in carefully planned prospective studies with functional outcomes evaluating the dynamics of recovery as primary endpoints. Such studies are currently being designed in Canada (ORATOR-trial) and Europe (EORTC-GORTEC-SAKK 1420; "Best-of"-trial) and should give definite answer to which of surgery or radiotherapy do best in term of functional outcomes for early stage OPSCC [28, personal communication EORTC]. To date, only two studies have directly compared TOS approaches with definitive radiotherapy +/− chemotherapy [21••, 29]. Although not restricted to early stage disease, these two retrospective analyses have both reported significantly better swallowing outcomes in the TOS groups.

- The cost-effectiveness of TOS plus risk-stratified adjuvant therapy as compared with up-front chemoradiation for advanced stage OPSCC has also been evaluated [30, 31]. The results show that a TOS plus risk-stratified approach is more cost-effective than up-front exclusive chemoradiation therapy, both in the USA and in Europe.

Transcervical Approaches

- Open surgical approaches to the oropharynx are rarely indicated for early stage OPSCC. They include transpharyngeal and transmandibular approaches. Both techniques come with a significant degree of morbidity. The overall complication rate with open surgical procedures ranges from 45 to 60 % [32, 33]. The lateral pharyngotomy approach carries the risk of lesion to the hypoglossal and superior laryngeal nerves whereas the mandibular swing approach involves a mandibular osteotomy, a full-thickness split of the lip and of the floor of mouth as well as the potential division of the lingual nerve. A transitory tracheotomy is needed in 98 to 100 % of cases [20••, 34]. The time of recovery from those surgical procedures is obviously much longer as compared to TOS, and the functional and esthetic outcomes are invariably less favorable, including lip and chin scars, malocclusion, compromised swallowing, chronic aspiration, and altered speech articulation. Long-term gastrostomy tube dependence in transcervical approaches is between 6 and 39 % [34, 35]. TOS approaches come with better swallowing function, lower tracheotomy rate as well as shorter times to decannulation and hospitalization [20••, 36••].
- Although TOS or radiotherapy should always be preferred over open surgery for early stage OPSCC, transmandibular or transpharyngeal approaches still may be the only therapeutic option available in specific situations. These include patients presenting with severe trismus and a previous history of radiotherapy of the head and neck area that both contraindicate first-line treatment modalities. Functional outcomes in these cases are invariably poor [7].

Management of the Neck

- The oropharynx is extremely rich in lymphatic vessels. The rate of patients presenting with clinically positive or occult lymph node metastasis is between 15 and 75 % depending on the subsite involved and the T stage [37, 38]. This implicates that the vast majority of patients with early stage OPSCC require treatment of the neck.
- Retropharyngeal node involvement, as well as contra lateral prophylactic neck treatment whenever there is clinical neck disease on one side, or the primary tumor is central, or crosses the midline, should always be considered when discussing treatment plan [38].
- The use of elective neck dissection has the advantage of providing pathological staging of the neck as compared to radiotherapy.

However, the value of neck dissection may not be as reliable as in other head and neck area. This is due to the less predictable lymphatic drainage pathways in OPSCC as well as the difficulty to address the retropharyngeal nodes surgically [37]. This argument is often brought up by the radiotherapists' community when discussing treatment options for early stage OPSCC. However, this argument has never proved to result in better oncologic outcomes in early stage OPSCC, as suggested by equivalent DSS rates between surgery and radiotherapy in most retrospective analyses [17, 18, 19••].

- Most of the patients undergoing selective neck dissection show some degree of spinal accessory nerve dysfunction resulting in the recognized shoulder syndrome of pain, weakness, and deformity [39, 40]. Although this appears to be reversible in the majority of cases, it should be taken into account when discussing treatment options for early stage OPSCC.

Reconstruction

- The objectives of reconstructive surgery following surgical treatment of OPSCC are to restore the integrity and the functions of the oropharynx, namely deglutition, respiration, and speech [41]. Successful reconstruction requires thorough knowledge of the physiological functions of the different oropharyngeal sub-units as well as the various reconstructive techniques available to restore them.
- Free microvascular flaps have revolutionized the field of oropharyngeal reconstruction [34]. They overcome most of the limitations of local and regional flaps. Free flap reconstructive techniques are currently limited to the restoration of the anatomical shape and possibly the sensation of the resected portion of the oropharynx. Motor functions of the organ can however not be duplicated.
- Early stage OPSCC treated with TOS approaches usually does not require reconstruction. Defects of the lateral pharyngeal walls of less than 4 cm in greatest dimension and tongue base resection of less than 1/2 of the initial volume with preservation of at least one lingual artery and one hypoglossal nerve can be left to heal by secondary intention with excellent functional outcomes. Defects of greater dimension usually require reconstruction to avoid retraction of the tongue or pharyngeal stenosis. Free fasciocutaneous flaps achieve the best results to these purposes [34].
- Early stage soft palate SCC deserves special consideration since surgical treatment of this area carries the risk of secondary velopharyngeal insufficiency, even in early stage disease. Very superficial lesions can be removed efficiently with partial thickness resection and left to granulate with excellent functional results. However, full-thickness defects involving more than half of the soft palate must be reconstructed to avoid poor functional outcomes. This is best achieved with free fasciocutaneous flap

reconstruction [42]. Therefore, the benefit of such an invasive approach for early stage lesions should be carefully balanced with the advantage of a more conservative option, such as radiotherapy, which carries both excellent functional and oncological outcomes.

Interventional Procedures

Radiotherapy

- Treatment of OPSCC with radiotherapy is achieved by external beam radiation therapy using high-energy photons generated by a linear accelerator. Precise determination of the tumor location, using both traditional (CT-scan and/or MRI) and metabolic (PET-scan) imaging modalities, is mandatory to achieve efficient targeting of the tumor and minimize complications by avoiding unnecessary radiation exposure to normal surrounding structures. Intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) have become the standard of care for head and neck cancer. Further development of these techniques has led to creation of image-guided adaptive radiotherapy (IGART) which may further improve sparing of normal tissue thereby minimizing toxicity [43].
- The use of heavy charged particles, such as protons or carbon ions, remains investigational. Proton therapy (PT) provides better sparing of normal anatomical structures when treating relatively small lesions [44]. Whether this theoretical advantage translates into improved functional outcomes remains unknown. A randomized clinical trial addressing this question is currently underway, comparing IMRT with IMPT for OPSCC and oral cavity SCC (NCT01893307).
- As previously mentioned, early stage OPSCC can be effectively treated using either radiotherapy or surgery alone. Therefore, the main focus when discussing treatment options should be the functional outcomes as well as the prevention of late complications and the risk of second primary tumor development in a previously irradiated area. While radiotherapy techniques have tremendously improved over the past decades and already demonstrated significant reduction of late toxicity effects, these issues are still relevant and deserve special consideration.
- The most common long-term complication of radiotherapy is xerostomia caused by radiation damage to the salivary glands [45, 46]. This effect is more important when concurrent chemotherapy is added. However, this side effect has become less pronounced with IMRT techniques, as demonstrated in several prospective trials [47–49].
- Osteoradionecrosis (ORN) of the mandible is a complication of radiotherapy that might have significant impact on the quality of

life [50]. It is defined as the exposure of irradiated bone in the absence of tumor recurrence. Symptoms of ORN range from asymptomatic bone exposure to significant necrosis of the mandible leading to potential serious complications that include fistula formation, infection, and pathologic fracture. Radiation treatment of OPSCC put patients at risk of ORN. The time of onset of ORN is quite variable and may appear several years after completion of the radiation therapy [51]. In a recent systematic review of the literature including 31 studies and over 4200 patients, the incidence of ORN was reported to range from 5 to 7 % [52]. Most importantly, the incidence rate did not appear to be influenced by the technique of radiation treatment, making this complication still relevant in the area of IMRT.

- Trismus is another underestimated complication of radiotherapy. It is defined as a limitation of mouth opening resulting from a combination of contraction and fibrosis of the masticator muscles. Treatment of OPSCC puts patients at risk of trismus [53]. The inability to fully open the jaw has impact on nutrition, speech, and oral hygiene. Some degree of trismus is seen in almost every patient treated for OPSCC, regardless the treatment modality. However, the incidence is higher in patients receiving radiotherapy [53]. The incidence has been reported to be as high as 25 % with old techniques of radiotherapy [54]. This rate has dropped to 5 % with the emergence of IMRT [55].
- Ischemic stroke can be a late side effect of radiotherapy in head and neck cancer patients [56]. This is particularly true for patients with long life time expectancy. A retrospective cohort study was performed in 367 patients under the age of 60 years who received between 50 and 60 Gy neck irradiations for head and neck tumors [57]. The relative risk of stroke was 5.6 % (expected, 2.5; 95 % CI=3.1–9.4 %) and the cumulative risk at 15 years was 12 % (95 % CI=6.5–21.4 %) as compared to age and sex-adjusted population-based rates. This is of particular concern in early stage OPSCC where overall survival rates are particularly high and patients tend to be rather young.
- Considering the abovementioned risks of radiation-induced late toxicity effects, it is the authors' opinion that, whenever early stage OPSCC can be treated with TOS approach and neck dissection as indicated, patients should be preferentially offered this option of treatment or entered into a trial that is comparing TOS against IMRT. This philosophy is supported by many others [5]. However, this strategy should ideally come with anticipated good functional outcomes and with high likelihood of unnecessary adjuvant treatment. Whenever pretreatment factors are predictive of poor functional outcomes and/or adverse oncologic features following surgery (e.g., significant soft palate involvement or presence of a clinically positive retropharyngeal node) radiotherapy should then be considered.

Compliance with Ethics Guidelines

Conflict of Interest

Yan Monnier and Christian Simon declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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