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Review

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Role of transoral robotic surgery in the salvage setting: pitfalls and challenges

Madelyn N. Stevens, Alexandra E. Kejner

Department of Otolaryngology-Head and Neck Surgery, Medical University of South Carolina, Charleston, SC 29425, USA.

Correspondence to: Dr. Alexandra E. Kejner, Department of Otolaryngology-Head and Neck Surgery, Medical University of South Carolina, 135 Rutledge Ave, MSC 550, Charleston, SC 29425, USA.

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Abstract

As rates of oropharyngeal squamous cell cancer (OPSCC) increase and patients survive longer, the number of patients with recurrence will also increase. Surgery is the primary tool for the management of locoregional recurrence when feasible, and transoral robotic surgery (TORS) techniques are a useful adjunct in effectively managing these cases. Careful patient selection, surgical planning, a thoughtful reconstructive plan, and postoperative supportive therapy are crucial for adequate oncologic and functional outcomes.

Keywords: Recurrent oropharyngeal cancer, salvage surgery, transoral robotic surgery

INTRODUCTION

Oropharyngeal cancer rates have increased substantially over the last few decades, with the majority being human papillomavirus (HPV)-related[1]. While typically associated with excellent prognosis and with recurrence rates significantly less than their HPV-negative counterparts, the rate of locoregional recurrence in HPV-positive oropharyngeal cancer has still been reported between 17%-20%, typically occurring within the first two years after treatment. Distant metastatic disease can be seen in up to 7% of these patients but is typically much later[2].

Known risk factors for locoregional recurrence include tobacco use, immunocompromised status, and primary tumor burden. Meanwhile, nodal disease and high-risk features [extranodal extension (ENE), perineural invasion (PNI), lymphovascular invasion (LVI), and nodal disease > 6 centimeters] are more associated with distant metastatic disease.

For patients with recurrent oropharyngeal carcinoma who develop locoregional failure after definitive treatment with chemoradiation, it has been found that HPV status, early detection, solitary site recurrence, and smaller volume disease burden may contribute to improved outcomes. When possible, surgical salvage for these patients, with or without adjuvant radiation, has been shown to improve survival[2,3]. Other treatment options include reirradiation protocols, cytotoxic chemotherapy regimens, immune checkpoint inhibition, and finally, clinical trials with novel immune-based therapies[4]. The focus of this review will be specifically on TORS for surgical salvage of oropharyngeal malignancies and the challenges, pitfalls, and strategies for optimization.

METHODS

A literature review was conducted using PubMed databases. The following search terms were used in various combinations: "Salvage" + "TORS" or "transoral robotic surgery" and "outcomes" "recurrence" and "survival." Studies were reviewed and those that involved salvage TORS resections of oropharyngeal malignancies were included. Only studies written in the English language were included. The level of evidence was determined using the Oxford Center for Evidence-Based Medicine Levels of Evidence[5].

RESULTS

Surgery as salvage in recurrent OPSCC

Prior to the widespread use of TORS for oropharyngeal cancer, surgical salvage was often associated with substantial morbidity, with rates of postoperative complications over 40%[6]. Surgical salvage was also considered oncologically futile due to high rates of repeat recurrence[7]. Patel *et al.* reported an 80% recurrence rate after salvage surgery (which was limited to open approaches only), with median recurrence within 6 months[6]. In their cohort, there was no significant difference in recurrence rates between HPV+ and HPV- patients, although the HPV-positive patients were more likely to fail distantly[6]. Recently, due to the overall improved prognosis of HPV-induced OPSCC and with advanced surgical techniques and earlier detection, 5-year overall survival after the development of recurrence has been seen to improve, with one meta-analysis reporting an increase from 18% to 51%. Improvements in overall survival were also seen in HPV-negative patients[3,8-10].

Advances in minimally invasive approaches and combined approaches

Transoral laser microsurgery and other transoral approaches, while technically demanding, paved the way for other transoral techniques, including TORS. The use of TORS as a salvage approach to the oropharynx has been found to not only allow for improved access to the oropharynx with improved visualization, decreased need for mandibulotomy and tracheostomy, but also has been associated with decreased hospital stay, decreased positive margins status, and decreased need for postoperative feeding tube use compared to standard open approaches[9,11]. Table 1 demonstrates outcomes for salvage TORS for oropharyngeal lesions, with a focus on recurrence and overall survival rates.

PREOPERATIVE CONSIDERATIONS

Patient selection

Patient selection and preoperative patient counseling are critical components of planning for salvage surgery. For patients requiring salvage surgery after radiation failure, the risk of radionecrosis and

Table 1. Outcomes after salvage TORS for oropharyngeal malignancies

	Level of evidence	HPV status	Number of patients	Reconstruction	Complications	Long-term gastric tube dependence	Recurrence	Overall survival (OS)	Median follow-up
Hardman *et al.*[12]	III	+ and -	259	7.2% pedicle flap, 20.1% free flap	8.1%; pneumonia, stroke, hemorrhage, free flap failure, fistulae	33.8%	29.5%	71.8%	38.5 months
Dabas *et al.*[11]	III	Not reported	30	3.3% pedicled, 0% free flap	20%: bleeding, PCF, aspiration pneumonia	3.3%	43.3% (Local: 30% Regional 3.3%, loco-regional 6.7%, distant 3.3%)	86% (median 19 months)	122 months
Asairinachan *et al.*[13]	III	+ and -	26	62% pedicle flap, 0% free flap	19% major complication	28%	23%	74% (3 years OS)	11 months
Meulemans *et al.*[14]	III	+ and -	30	0% reconstruction	43%: spondylodiscitis, hemorrhage, afunctional larynx	20%	24.2%	73.5% (2 years OS)	21.2 months
White *et al.*[9]	III	Not reported	64	0% reconstruction	20% airway edema; 10% infection; 10% hemorrhage	36%	26%	74%	12 months
D'Andrea *et al.*[15]	III	+ and -	53	22.6% pedicled flap, 67.9% free flap	32% pulmonary infection; 3.8% hemorrhage; 7.6% hematoma	23%	53.9%	59% (2 years)	22 months
Gazda *et al.*[16]	III	+ and -	17	0% reconstructed	29.4% aspiration; 29.4% pneumonia	58.8%	12.5%	72.8% (2 years)	46.7 months
Hirshoren *et al.*[17]	IV	Not reported	9	11% pedicled flap, 11% free flap	11% bleeding, 11% Pulmonary embolism	22%	Not reported	Not reported	9 months
Viros Porcuna *et al.*[18]	III	+ and -	14	57% received local or free flap	16%*	5.7%*	Not reported	Not reported	18 months
Isenberg *et al.*[19]	III	+ and -	30	Not reported	9.7% postoperative hemorrhage requiring re-operation; 22.6% infection; 25.8% infection	Not reported	Not reported	Not reported	1 month

Outcomes following salvage TORS surgery for patients with oropharyngeal tumors failing initial chemoradiation treatment with curative intent. *Data is for the entire TORS cohort, not specific to salvage surgery. TORS: transoral robotic surgery; HPV: human papillomavirus.

radiation-induced tissue injury is significant[20]. High rates of hypothyroidism, hypovascularity, hypocellularity, vessel-depleted tissues, malnutrition secondary to dysphagia, and cancer and radiation-induced cachexia are seen in post-radiation patients[21]. Advanced age, decreased performance status, and limited disease-free interval also adversely affect survival[22]. These factors affect a patient's ability to heal and recover from surgery and must be addressed in the preoperative period.

Increased rates of dysphagia and the need for long-term gastric tube have been reported for salvage surgery[11,14,16]. Speech and language pathology evaluation and counseling in the pre- and postoperative period is crucial, as well as nutritional education and optimization via a registered dietician.

Additionally, the extent of resection and ability to achieve negative margins significantly impact disease-specific and overall survival outcomes[23,24]. Defining HPV status is also a consideration, with some studies showing HPV-positive patients having improved overall survival after salvage surgery[3,25]. When considering salvage surgery as an option, the potential need for additional adjuvant therapy should also be considered, as additional radiation may further impair swallowing function and increase the risk of osteoradionecrosis[7]. Multidisciplinary tumor board discussion and a surgical team that is well-versed in both TORS and salvage surgery are key to optimizing outcomes.

Preoperative workup

Patients being considered for salvage surgery should be evaluated with cross-sectional imaging, metastatic workup, and examination under anesthesia to assess anatomic findings[26,27] [Figure 1].

Cross-sectional imaging, including computed tomography (CT) and, in some cases, magnetic resonance imaging (MRI), can assist in assessing the feasibility of achieving negative surgical margins. CT's utility in assessing invasion into vascular and bony structures can help distinguish the extent of resection and predict the need for vascularized free tissue transfer[28]. Imaging contraindications to salvage TORS include carotid involvement, anticipated need for bilateral lingual artery sacrifice based on imaging, bone invasion, and prevertebral fascia invasion. MRI can sometimes predict the perineural spread of tumor, which may lead the surgery team to pursue an alternative treatment option[21,29]. While not a definitive contraindication, metastatic imaging should be completed in order to assess whether a solitary and treatable metastasis is present or if there is widespread metastatic disease. Decisions regarding the management of the neck should take into consideration laterality and proximity to the midline, as well as atypical lymph node involvement[4]. Positron emission tomography (PET) scan may be more sensitive for these as well as for the detection of retropharyngeal nodal disease which should be addressed at the time of surgery and often is best accessed using a TORS approach due to carotid positioning[11,30].

Examination under anesthesia in the operating room is also important. Given the substantial tissue and anatomic alterations to the upper aerodigestive tract after treatment for OPSCC, endoscopic evaluation with palpation and the consideration for mapping biopsies can be key in surgical planning. The extent of surgical resection can also be assessed to determine what type of reconstruction will be involved. Patients with isolated base of tongue disease with no communication to the pharynx may be candidates for healing by secondary intention[26,31,32]. Those with palate involvement, exposure of great vessels, pharyngotomy with communication to the neck, or bony exposure should undergo vascularized tissue reconstruction, which will be discussed further below[28,32].

Dentate patients should be evaluated for potential preoperative dental disease that may need to be addressed either prior to or at the time of surgery. In patients with severe trismus, assessment of adequate mouth opening for the introduction of robotic instruments should also be assessed. With the advent of more flexible transoral robotic systems, many of the limitations seen with the original surgical robots have been obviated[9,33].

INTRAOPERATIVE CONSIDERATIONS

Margins

Negative margins are key to disease-free survival among patients undergoing salvage surgery[25], but tumors have less predictable and more irregular margins secondary to treatment effects[21,26]. Whether due to tumors arising in remnant areas or persistent disease, these areas are often also difficult to image accurately to predict microscopic disease and thus intentionally larger margins should be considered in salvage patients[24,34]. Salvage surgery runs the risk of higher close or positive margins compared to primary surgery[35]. Patients with persistent or recurrent disease also have higher rates of lymphovascular invasion and/or perineural invasion, and this may also affect the ability to achieve negative margins[36]. Outcomes reported by White *et al.* support the use of TORS for optimizing margin control, with a 9% positive margin rate utilizing TORS compared to 29% with open approaches[9].

Management of the neck

Recurrent neck disease may be present in addition to a recurrent or new primary following treatment, with studies reporting one-third of patients requiring neck dissection to clear disease in addition to salvage TORS[11,14]. There is potential for increased morbidity, such as fistula formation, with concomitant primary salvage surgery and neck dissection[11,21]. If the extent of the disease requires free flap reconstruction, concomitant neck dissection becomes a safer option[32].

Emerging evidence suggests there may be a role for sentinel lymph node biopsy (SLNBx) in head and neck cancer[37,38]. Kulcsar *et al.* describe utilizing SLNBx for early-stage OPSCC with clinically N0 neck disease as a minimally invasive option[39]. Particularly in salvage surgery, SLNBx provides an opportunity to obtain locoregional control while minimizing morbidity and postoperative complications[40]. Current data is limited, and additional studies are needed.

Reconstruction

While a full review of reconstructive options is outside the scope of this review, reconstruction in salvage TORS is crucial for coverage of bony exposure, reconstruction of soft palate defects to aid speech and swallowing by avoiding velopharyngeal insufficiency (VPI), protection of exposed vessels, and repair of communication into the neck[41]. Reconstruction can improve functional outcomes and decrease postoperative morbidity, which is particularly crucial in the salvage setting[4,8,42] [Figure 1].

For defects where reconstruction is needed, Gehanno *et al.* described the technique of velopharyngoplasty by maximizing the use of the native mucosal surfaces to imbricate the pharynx to the palate using the superior constrictors, base of tongue mounding, and primary hypopharyngeal closure[43]. The Gehanno technique addresses multiple issues but can be limited with regard to salvage defects where local tissue may be limited. In primary TORS, local reconstruction with nearby muscular mucosal tissue can be utilized[32]; however, in previously radiated patients, this tissue integrity may be compromised and less amenable to rotation (decreased microvascular circulation). Asairinachan *et al.* describe the use of facial artery musculomucosal flaps in 13 patients following salvage TORS, resulting in adequate wound healing in small lateral pharyngeal wall defects[44]. Other pedicled reconstructive options for obtaining tissue from outside the radiation field include the submental artery island flap[45] and the nasoseptal flap[46]. However, these local options may not be available due to patient characteristics or post-radiation effects. Because of this, the Gehanno technique was further refined by Chepeha *et al.* to include free tissue transfer as part of a template-based approach in patients who need more tissue volume for great vessel coverage as well[47]. Additionally, the defect size in salvage TORS may preclude the ability to perform a Gehanno style reconstruction, and thus, patients may be more likely to need a free flap for additional tissue coverage[32]. The impact of chemoradiation on microvascular free flaps is difficult to assess as the data is heterogenous, but it has been associated with an increase in free flap failure and complications[8]. Nevertheless, microvascular free flaps for reconstruction of large defects (more than two subunits) may lead to decreased postoperative complications like great vessel exposure and salivary fistula.

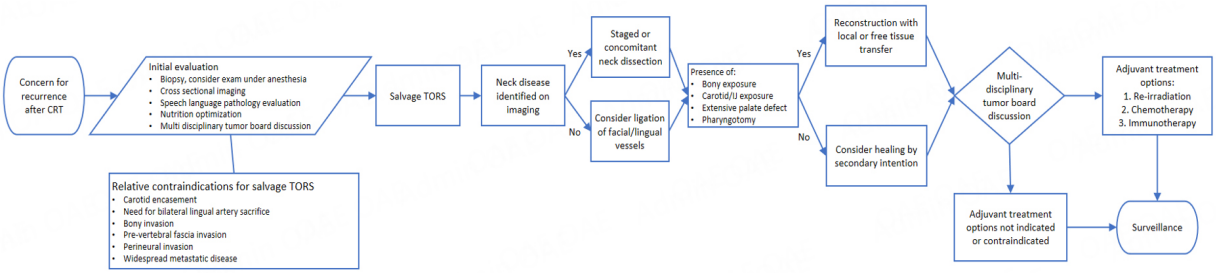

Figure 1. Algorithm for preoperative workup, intra-operative considerations, and postoperative care for patients undergoing salvage TORS for recurrence after chemoradiation. CRT: chemoradiation; TORS: transoral robotic surgery; IJ: internal jugular.

When choosing donor sites, it is essential to consider their impact on breathing, speech, and swallowing. While the thinness and pliability of the radial forearm free flap make it a good option for oropharyngeal reconstruction, a thin superficial anterolateral thigh flap has also been described and may be an option in patients who do not have a forearm as an option[27,48].

POSTOPERATIVE CONSIDERATIONS

Complications

Complications following TORS surgery have been well-described, including hemorrhage, airway compromise, chronic dysphagia, and spondylitis[49]. Reported rates among patients receiving salvage TORS surgery vary[9,11-16]. Despite a relatively high complication rate reported by Gazda *et al.* at 58%, there was no difference in complication rates between the salvage and primary TORS groups[16]. Potentially, due to the cumulative effects of chemoradiation and salvage surgery, increased late complications (including spondylodiscitis, prolonged weight loss/dysphagia, and necrosis leading to carotid blowout) are possible[14]. Nevertheless, these complication rates are improved from the high morbidity rates reported for traditional open approaches to salvage oropharyngectomy[6,9]. Hemorrhage following salvage TORS is a potentially life-threatening complication and may be mitigated by selective arterial embolization or ligation[50].

Surveillance and Adjuvant treatment

There are no clear guidelines for surveillance and adjuvant treatment following salvage TORS. Gazda *et al.* suggest a surveillance timeline of every 3 months for the first 3 years, followed by every 6 months for two years, then annually[16]. Again, multidisciplinary tumor board discussion well-versed in salvage therapy should be utilized for adjuvant treatment planning, as well as careful patient selection. Reirradiation, palliative chemotherapy, and immunotherapy may be feasible for high-risk pathologic features based on prior radiation dosages, and patient performance status, although this is not frequently described in the literature[2,11,15,51,52] [Figure 1].

FUTURE DIRECTIONS

Optical imaging techniques

Intraoperative molecular imaging to optimize solid tumor and lymph node visualization is ongoing for head and neck cancers[53,54]. Improve visualization techniques, in combination with TORS approaches, allow for better identification of tumors. While indocyanine green fluorescence has been shown to improve margin status in head and neck cancers[55], this has proven difficult to utilize during TORS surgery. A novel technique utilizing indocyanine green in combination with the existing da Vinci robotic near-infrared system has shown promising results[56].

Neoadjuvant vaccination/immunotherapy prior to surgery

Immunotherapy via anti-PD1 and PDL1 inhibitors has provided new options for recurrent malignancies of the head and neck[4]. For HPV-positive OPSCC specifically, ongoing clinical trials of therapeutic HPV vaccines in combination with immunotherapy demonstrate tumor response rates in 33% of patients[57]. There has been increasing interest in combining HPV-targeted and immunotherapy techniques with other traditional modalities, including surgical salvage[58,59].

LIMITATIONS

The data presented here is limited by the potential risk of bias or heterogeneity in the studies included. The studies often have small sample sizes or case series, limiting their applicability. Further, the institutions implementing technically difficult techniques associated with salvage TORS may be at the higher end of the learning curve and experience, making their outcomes difficult to replicate.

CONCLUSION

Here, we review current literature and best practices for salvage TORS, with a potential schema for treatment outlined in [Figure 1]. Given the lack of large, multi-institutional cohort studies, best practices are difficult to ascertain. For recurrent or persistent oropharyngeal cancer after definitive treatment, salvage transoral robotic surgery with or without reconstruction offers a potential treatment option for patients who are candidates. Importantly, patient selection and counseling are paramount to optimize outcomes, as well as multidisciplinary tumor board discussion.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception, design, manuscript preparation, critical revisions, figure/table creation, and final approval: Stevens MN, Kejner AE

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All authors declared that there are no conflicts of interest.

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Not applicable.

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