Cancer Control
Volume 28: 1–4

DOI: 10.1177/10732748211050770
journals.sagepub.com/home/ccx
SAGE

# Patient Selection for Surgery vs Radiotherapy for Early Stage Oropharyngeal Cancer

**Lara Hilal, MD[1], Roger Moukarbel, MD[2], Farah Ollaik, MD[1], Pei Yang, MD[3], and Bassem Youssef, MD[1]**

## Abstract

Surgery and radiation therapy are both commonly used in the treatment of early stage (AJCC stages T1-T2 N0-M0) oropharyngeal squamous cell carcinoma (OPSCC). Transoral robotic surgery (TORS) and intensity modulated radiation therapy (IMRT) have been reported to result in similar survival and disease control outcomes. However, their side effect profiles widely differ. Nevertheless, patients who experience the worst side effects and quality of life are the ones who receive the combination of TORS and adjuvant radiation or chemoradiation therapy. Thus, appropriate patient selection for surgery to minimize the need for multimodality therapy is key. We propose, in this paper, the use of sentinel lymph node biopsy in the node negative (N0) neck as a means that is worth exploring for selecting patients to either radiation therapy or surgery. Patients with a positive sentinel lymph node (SLN) would be better directed to upfront radiation. On the contrary, patients with a negative SLN biopsy would be more confidently directed towards TORS and neck dissection alone.

## Keywords

radiotherapy, chemoradiation, decision making, head and neck cancer, toxicity, prevention, sentinel lymph node biospy, oropharyngeal cancer , quality of life

Received April 26, 2021. Received revised August 31, 2021. Accepted for publication September 16, 2021.

Treatment for early stage oropharyngeal squamous cell carcinoma (OPSCC) (AJCC stages T1-T2 N0-M0) has varied over time, and both surgery and radiation therapy are currently accepted standard of care options.[1] In this article, we review some of the data on the outcomes and side effects of these 2 treatment modalities and propose sentinel lymph node (SLN) biopsy as a method that's worth investigating as a means for patient selection to either treatment option.

Radiation therapy modalities have evolved and Intensity modulated radiation therapy (IMRT) is the current standard for the majority of head and neck cancers, including the oropharynx.[2] As for surgery, transoral robotic surgery (TORS) is gaining popularity in the field with studies showing significantly lower need for adjuvant chemoradiation, lower rate of late gastrostomy and tracheostomy dependence, and lower overall treatment-related costs of care compared to non-TORS surgical procedures[3]. TORS has been reported to have comparable survival and disease control outcomes to IMRT in several retrospective series and systematic reviews with 5-year survival of 92–94% with TORS vs 84–96% with IMRT.[4-7] However, of note is the selection bias that accompanies retrospective series, where most of the TORS patients had earlier stage disease and were more fit. In addition to that, the results do not account for the fact that 26% of the TORS patients also received radiotherapy and 41% received adjuvant chemoradiotherapy.[4]

[1]Department of Radiation Oncology, American University of Beirut, Beirut, Lebanon
[2]Department of Head and Neck Surgery, American University of Beirut, Beirut, Lebanon
[3]Hunan Cancer Center, Changsha, China

**Corresponding Author:**
Bassem Youssef, Department of Radiation Oncology, American University of Beirut-Medical Center, Bliss Street, Riad El-Solh, Beirut 1107 2020, Lebanon.
Email: by04@aub.edu.lb

With comparable disease outcome data, the main difference between IMRT and TORS in the treatment of early stage OPSCC is their adverse effects profile. Superior functional outcomes and better speech-, taste-, and saliva-related quality of life have been previously reported with TORS as compared to definitive radiation therapy in nonrandomized studies.[4,5] Swallowing at 1-year post treatment was also found to be better with TORS compared to chemoradiation in a small comparative study.[8] In De-Almeida et al.[6] systematic review on IMRT vs TORS for early stage OPSCC, the use of gastrostomy tube is less with TORS; however, the benefit of sparing the patients this side effect disappears when adjuvant therapy is added to the equation. However, a more recently published randomized trial, "early stage squamous cell carcinoma of the oropharynx: Radiotherapy vs Trans-oral Robotic Surgery (ORATOR) trial", showed the contrary[9]. In the ORATOR study, patients with T1-T2 N0-N2 (LN ≤4 cm) were randomized to 70 Gy of radiotherapy (with or without chemotherapy) vs TORS with neck dissection (with or without adjuvant therapy). Patients in the radiotherapy arm had superior swallowing-related QOL scores at 1 year after treatment, although the difference did not meet their set clinically meaningful change. Toxicity profiles differed between the 2 groups with more neutropenia (6 [18%] of 34 patients vs none of 34), hearing loss (13 [38%] vs 5 [15%]), and tinnitus (12 [35%] vs 2 [6%]) in the radiotherapy group vs TORS plus neck dissection, and more trismus in the TORS plus neck dissection group (9 [26%] vs 1 [3%]). Of note is that 47% of patients in the TORS group recieved adjuvant radiotherapy and 24% recieved postoperative chemoradiotherapy.[10] Another randomized trial comparing patient-reported swallowing outcomes in patients with OPSCC, supraglottic squamous cell carcinoma (SGSCC), and T1 N0 hypopharyngeal squamous cell carcinoma is still ongoing, the "European Organization for Research and Treatment of Cancer 1420 (EORTC 1420)[11]" trial.

Data suggest an additive impact of adjuvant radiation or chemoradiation on adverse functional outcomes and quality of life after TORS. While TORS is associated with some side effects, the addition of adjuvant therapy worsens those adverse effects and adds additional ones. In a prospective study by Hurtuk et al.[12] on sixty-four patients who underwent TORS, it was clearly shown that patients who undergo TORS for malignancies and receive adjuvant therapy tend to have lower Health related quality of life (HRQOL) outcomes than those who only undergo TORS alone. In one prospective cohort study, patients who underwent TORS combined with adjuvant therapy experienced poorer functional outcomes related to dysphagia and xerostomia at 1-year follow-up compared to those who only received TORS.[13] Similarly, Sethia et al.'s[14] prospective study on 111 patients highlighted that single-modality TORS maintained a better QOL (speech, eating, and social function domains) than TORS with adjuvant radiotherapy or chemoradiotherapy.

The question is how to select the TORS patients who can be spared adjuvant therapy and the side effects that result from the combination of treatment modalities. If T1-T2N0 patients undergo TORS with no adverse pathological features, then no adjuvant therapy is required.[15] However, if patients turn out to have pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism or lymphatic invasion then adjuvant radiation therapy should be considered.[15] In the presence of extranodal extension or positive margins, adjuvant concurrent chemoradiation has been shown to improve disease free survival and possibly overall survival.[16] It is worth noting, however, that the definition of an adverse feature in the context of HPV+ disease is an area of active research. For now, recommendations for HPV– and HPV+ are still similar.

In one study by Huang et al.,[17] they found that only 11%–36% of primary surgical cases were treated with TORS alone, with 15%–54% rates of postoperative radiotherapy and 11%–63% rates of postoperative chemoradiotherapy, raising concerns regarding appropriate patient selection. A good percentage of patients requiring postoperative radiotherapy are those who are found to have lymph node metastasis; thus, correctly identifying an N0 neck is of great importance. As Gregoire et al. concluded in his commentary on TORS vs IMRT for OPSCC that appropriate patient selection for TORS is critical to avoid adjuvant therapy.[18] Multiple studies have identified that occult LN metastasis in an N0 neck is around 24% and that the main levels of LN metastasis in OPSCC are II, III, and IV.[19-21] Retropharyngeal LN involvement in clinically N0 OPSCC is rare, with a pathological incidence of 1.2%.[22] Several methods have been suggested in the literature to better stage the TORS patients and select them for adjuvant therapy. In a study by Rubek et al.,[23] patients had concurrent neck dissection during the TORS procedure which identified 43% of the patients who benefited from adjuvant therapy. Spellman et al.[24] showed in their small retrospective series of 19 patients, with palatine tonsil OPSCC, that upfront selective staging neck dissection during TORS selects low-risk patients who would benefit from single modality TORS and can determine candidates for adjuvant therapy. Also, since metastasis to the retropharyngeal lymph nodes is not uncommon in OPSCC, transoral robotic retropharyngeal lymph node dissection (RPLND) during TORS is technically feasible, safe, and may provide valuable staging information to help guide selection of patients for adjuvant therapy.[25] All these reported methods require the patient to undergo surgery (TORS procedure), whether he/she was going to receive adjuvant radiation/chemoradiation or not.

However, we propose exploring another method using Sentinel lymph node biopsy upfront to better stage the patients with minimal morbidity and select them to undergo the surgery route using TORS and neck dissection upfront or to alternatively receive definitive radiation therapy upfront. This approach might be able to spare some of the patients the risk of

experiencing the side effects of a combined modality approach.

Sentinel lymph node biopsy is a reliable technique that has been mainly used in breast (with reliability reaching 98%) and Gynecologic malignancies to save patients the morbidity of lymphadenectomy.[26,27] It is also an option for oral carcinoma and has made it to the NCCN guidelines.[15] The accuracy of sentinel node biopsy for nodal staging of early stage oral carcinoma has been tested extensively in multiple studies including single-center as well as multiinstitutional trials against the standard of upfront neck dissection with a pooled sensitivity of .93 and negative predictive values ranging from .88 to 1.[28-31] Stoeckli et al assessed the feasibility of sentinel node biopsy in oral and OPSCC. It was initially done in the context of an elective neck dissection in order to assess the validity and feasibility of the sentinel lymph node (SLN). SLN detection rate was 93% by lymphoscintigraphy and reached 100% by gamma probe. In their follow-up observational study, they only performed elective neck dissection in the case of a positive SLN. Only 2 patients out of 31 (6%) who had negative SLN biopsy experienced a neck recurrence after a mean follow-up of 19 months, which results in a SLN negative predictive value of 94%.[32] Another study by Hoft et al. that included 50 patients with oral, OPSCC (tonsil, palate, base of tongue, and oropharyngeal wall) or laryngeal carcinoma also showed that sentinel lymph nodes localization had high diagnostic accuracy in their cohort using a gamma probe.[33]

In conclusion, the majority of studies on early stage OPSCC demonstrate equivalence of disease outcomes between TORS and definitive radiation therapy using IMRT. However, the 2 modalities of treatment have been reported to have different side effects profiles, with one randomized trial showing more dysphagia with TORS compared to IMRT. However, the worst side effects and QOL outcomes are observed in cases that require the combination of TORS with adjuvant radiation or chemoradiation. Thus, appropriate patient selection for TORS is critical to avoid the incremental toxicity of the addition of adjuvant radiotherapy. Future randomized trials are needed to compare treatment toxicity between the current standard of care and our proposed method of using SLN biopsy for treatment modality selection (definitive IMRT vs TORS and neck dissection) for patients with early stage OPSCC. One proposed study would be as follows: Patients with T1/T2-N0 M0 OPSCC would be enrolled and randomized to one of 2 arms. Patients in arm one would be treated with TORS and neck dissection, with or without adjuvant therapy (standard of care). Patients in arm 2 would undergo upfront sentinel lymph node biopsy; those with a positive SLN biopsy would be treated with definitive IMRT while those with a negative SLN biopsy would undergo TORS and neck dissection (experimental arm). Primary endpoint would be treatment-related toxicity. Our hypothesis is that the use of SLN biopsy (experimental arm approach) will potentially significantly decrease the need for multimodal therapy for patients with early stage T1/T2 N0 OPSCC and thus decrease treatment-related toxicity.

## Authors' Note

Our study did not require an ethical board approval because it did not contain human or animal trials.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## ORCID iD

Bassem Youssef https://orcid.org/0000-0002-7382-9624

## References

1. NCCN Guidelines Panel. Head and neck cancers. *Head Neck Cancers*. doi:10.1007/978-3-030-30766-0_4.
2. Ghosh-Laskar S, Yathiraj PH, Dutta D, et al. Prospective randomized controlled trial to compare 3-dimensional conformal radiotherapy to intensity-modulated radiotherapy in head and neck squamous cell carcinoma: long-term results. *Head Neck*. 2015;38(S1):E1481-E1487. doi:10.1002/hed.24263.
3. Motz K, Chang H-Y, Quon H, Richmon J, Eisele DW, Gourin CG. Association of transoral robotic surgery with short-term and long-term outcomes and costs of care in oropharyngeal cancer surgery. *JAMA Otolaryngol Head Neck Surg*. 2017;143(6):580-588. doi:10.1001/jamaoto.2016.4634.
4. Yeh DH, Tam S, Fung K, et al. Transoral robotic surgery vs. radiotherapy for management of oropharyngeal squamous cell carcinoma - a systematic review of the literature. *Eur J Surg Oncol*. 2015;41(12):1603-1614. doi:10.1016/j.ejso.2015.09.007.
5. Ling DC, Chapman BV, Kim J, et al. Oncologic outcomes and patient-reported quality of life in patients with oropharyngeal squamous cell carcinoma treated with definitive transoral robotic surgery versus definitive chemoradiation. *Oral Oncol*. 2016;61:41-46. doi:10.1016/j.oraloncology.2016.08.004.
6. de Almeida JR, Byrd JK, Wu R, et al. A systematic review of transoral robotic surgery and radiotherapy for early oropharynx cancer: a systematic review. *Laryngoscope*. 2014;124(9):2096-2102. doi:10.1002/lary.24712.
7. Morisod B, Simon C. Meta-analysis on survival of patients treated with transoral surgery versus radiotherapy for early-stage squamous cell carcinoma of the oropharynx. *Head Neck*. 2016;38(suppl 1):E2143-E2150. doi:10.1002/hed.23995.
8. Chen AM, Daly ME, Luu Q, Donald PJ, Farwell DG. Comparison of functional outcomes and quality of life between transoral surgery and definitive chemoradiotherapy for oropharyngeal cancer. *Head Neck*. 2015;37(3):381-385. doi:10.1002/hed.23610.

9. Nichols AC, Yoo J, Hammond JA, et al. Early-stage squamous cell carcinoma of the oropharynx: radiotherapy vs. trans-oral robotic surgery (ORATOR) - study protocol for a randomized phase II trial. *BMC Canc*. 2013;13(1):133. doi:10.1186/1471-2407-13-133.
10. Nichols AC, Theurer J, Prisman E, et al. Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial. *Lancet Oncol*. 2019;20(10):1349-1359. doi:10.1016/S1470-2045(19)30410-3.
11. EORTC. *Study Assessing the " Best of " Radiotherapy vs the " Best of " Surgery in Patients with Oropharyngeal Carcinoma (Best of)*. Brussels, Belgium: European Organisation for Research and Treatment of Cancer; 2016. https://clinicaltrials.gov/ct2/show/NCT02984410.
12. Hurtuk AM, Marcinow A, Agrawal A, Old M, Teknos TN, Ozer E. Quality-of-life outcomes in transoral robotic surgery. *Otolaryngol Head Neck Surg*. 2012;146(1):68-73. doi:10.1177/0194599811421298.
13. Achim V, Bolognone RK, Palmer AD, et al. Long-term functional and quality-of-life outcomes after transoral robotic surgery in patients with oropharyngeal cancer. *JAMA otolaryngol Head Neck Surg*. 2018;144(1):18-27.
14. Sethia R, Yumusakhuylu AC, Ozbay I, et al. Quality of life outcomes of transoral robotic surgery with or without adjuvant therapy for oropharyngeal cancer. *Laryngoscope*. 2018;128(2):403-411. doi:10.1002/lary.26796.
15. NCCN. *Head and Neck Cancers*. Plymouth Meeting, PA: National Comprehensive Cancer Network; 2018. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf.
16. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck*. 2005;27(10):843-850. doi:10.1002/hed.20279.
17. Huang SH, Hansen A, Rathod S, O'Sullivan B. Primary surgery versus (chemo)radiotherapy in oropharyngeal cancer. *Curr Opin Otolaryngol Head Neck Surg*. 2015;23(2):139-147. doi:10.1097/MOO.0000000000000141.
18. Grégoire V, Nicolai P. Choosing surgery or radiotherapy for oropharyngeal squamous cell carcinoma: is the issue definitely settled? *Lancet Oncol*. 2019;20(10):1328-1329. doi:10.1016/S1470-2045(19)30495-4.
19. Lim YC, Koo BS, Lee JS, Lim J-Y, Choi EC. Distributions of cervical lymph node metastases in oropharyngeal carcinoma: therapeutic implications for the N0 neck. *Laryngoscope*. 2006;116(7):1148-1152. doi:10.1097/01.mlg.0000217543.40027.1d.
20. Li XM, Wei WI, Guo XF, Yuen PW, Lam LK. Cervical lymph node metastatic patterns of squamous carcinomas in the upper aerodigestive tract. *J Laryngol Otol*. 1996;110(10):937-941.
21. Candela FC, Kothari K, Shah JP, Patterns of cervical node metastases from squamous carcinoma of the oropharynx and hypopharynx. *Head Neck*. 2006;12(3):197-203. doi:10.1002/hed.2880120302.
22. Panda S, Thakar A, Kakkar A, et al. Is the retropharyngeal lymph node the first echelon node for carcinoma tonsil? Prospective evaluation and literature review. *Eur Arch Oto-Rhino-Laryngol*. 2021;278(10):3995-4004. doi:10.1007/s00405-020-06585-5.
23. Rubek N, Channir HI, Charabi BW, et al. Primary transoral robotic surgery with concurrent neck dissection for early stage oropharyngeal squamous cell carcinoma implemented at a Danish head and neck cancer center: a phase II trial on feasibility and tumour margin status. *Eur Arch Oto-Rhino-Laryngol*. 2017;274(5):2229-2237. doi:10.1007/s00405-016-4433-3.
24. Spellman J, Sload R, Kim P, Martin P, Calzada G. Staging neck dissection and transoral robotic surgery treatment algorithm in palatine tonsil cancer. *Otolaryngol Head Neck Surg*. 2018;158(3):479-483. doi:10.1177/0194599817742615.
25. Troob S, Givi B, Hodgson M, et al. Transoral robotic retropharyngeal node dissection in oropharyngeal squamous cell carcinoma: patterns of metastasis and functional outcomes. *Head Neck*. 2017;39(10):1969-1975. doi:10.1002/hed.24786.
26. Borgstein PJ, Pijpers R, Comans EF, van Diest PJ, Boom RP, Meijer S. Sentinel lymph node biopsy in breast cancer: guidelines and pitfalls of lymphoscintigraphy and gamma probe detection. *J Am Coll Surg*. 1998;186(3):275-283.
27. Collarino A, Vidal-Sicart S, Perotti G, Valdés Olmos RA. The sentinel node approach in gynaecological malignancies. *Clin Trans Imag*. 2016;4(5):411-420. doi:10.1007/s40336-016-0187-6.
28. Alkureishi LWT, Ross GL, Shoaib T, et al. Sentinel node biopsy in head and neck squamous cell cancer: 5-year follow-up of a European multicenter trial. *Ann Surg Oncol*. 2010;17(9):2459-2464. doi:10.1245/s10434-010-1111-3.
29. Govers TM, Hannink G, Merkx MAW, Takes RP, Rovers MM. Sentinel node biopsy for squamous cell carcinoma of the oral cavity and oropharynx: a diagnostic meta-analysis. *Oral Oncol*. 2013;49(8):726-732. doi:10.1016/j.oraloncology.2013.04.006.
30. Pezier T, Nixon IJ, Gurney B, et al. Sentinel lymph node biopsy for T1/T2 oral cavity squamous cell carcinoma-a prospective case series. *Ann Surg Oncol*. 2012;19(11):3528-3533. doi:10.1245/s10434-011-2207-0.
31. Liu M, Wang SJ, Yang X, Peng H. Diagnostic efficacy of sentinel lymph node biopsy in early oral squamous cell carcinoma: a meta-analysis of 66 studies. *PloS One*. 2017;12(1):e0170322. doi:10.1371/journal.pone.0170322.
32. Stoeckli SJ. Sentinel node biopsy for oral and oropharyngeal squamous cell carcinoma of the head and neck. *Laryngoscope*. 2007;117(9):1539-1551. doi:10.1097/MLG.0b013e318093ee67.
33. Höft S, Maune S, Muhle C, et al. Sentinel lymph-node biopsy in head and neck cancer. *Br J Canc*. 2004;91(1):124-128. doi:10.1038/sj.bjc.6601877.