Choosing surgery or radiotherapy for oropharyngeal squamous cell carcinoma: is the issue definitely settled?

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Published Online
August 12, 2019
http://dx.doi.org/10.1016/S1470-2045(19)30495-4

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With the development in the mid-2000s of minimally invasive surgery such as transoral laser microsurgery and transoral robotic surgery (TORS), more and more institutions started to favour the use of surgery for early oropharyngeal squamous cell carcinoma (OPSCC), arguing an alleged faster recovery, a lower incidence of late morbidity (eg, swallowing dysfunction and xerostomia), and a better quality of life in comparison with intensity modulated radiation therapy (IMRT).[1] This trend was further increased with the rising prevalence of human papillomavirus-driven OPSCC.[2] However, no randomised controlled study had ever been done to compare the functional outcome and morbidity of radiotherapy and minimally invasive surgery.

In *The Lancet Oncology*, Nichols and colleagues[3] report the first-ever randomised controlled trial comparing functional outcome of radiotherapy (with or without concomitant chemotherapy) versus TORS and neck dissection (with or without adjuvant concomitant chemoradiotherapy) for the treatment of T1 or T2, N0-2 OPSCC. With a median follow-up of 27 months (IQR 20–48), this study concluded that the MD Anderson Dysphagia Index (MDADI) total score at 1 year was in favour of radiotherapy (86·9, SD 11·4 in the radiotherapy group versus 80·1, SD 13·0 in the TORS plus neck dissection group; p=0·042), and remains so with time. Other endpoints, such as the percentage of patients receiving total oral diet with no restriction, also favoured radiotherapy. The incidence of treatment-related toxicity grade 2 or higher was similar between the two treatment strategies, as were the overall survival and progression-free survival.

Nichols and colleagues need to be congratulated for doing this trial, which shed light on a controversial issue regarding the optimal treatment modality for early-stage OPSCC. However, their study raises several issues.

First, although only patients with T1–T2 tumours were eligible, patients with disease stage up to N2 were also included into the study. Consequently, this study compared patients who received single-modality treatments with patients who received bimodality or trimodality treatments, when postoperative radiotherapy or chemoradiotherapy was used. Whether a better selection of patients could favour surgery is however not a straightforward question; indeed, even for patients who only received surgery, subgroup analyses showed that the MDADI score was in favour of radiotherapy or concomitant chemoradiotherapy, but the difference between groups tended to be even less clinically significant.

Second, in this trial, a 1 cm margin around the primary tumour was required, whereas in OPSCC, with special reference to HPV-driven tumours, smaller margins (eg, 2 mm) are considered as negative, thus not requiring any adjuvant treatment.[4,5] The authors did not provide any detailed information about the margin status, the margin control, or the need for local reconstruction, which are important information to evaluate the appropriateness of surgical resection, and to appreciate whether a more minimally invasive but still adequate surgery would have resulted in less impaired swallowing function.

Third, 80% of patients included in the trial had p16-positive tumours, raising questions about treatment de-escalation, such as requirement of adjuvant treatment after surgery, radiation dose, and the necessity of concomitant chemotherapy. Trials such as the PATHOS (NCT02215265) and ECOG3311 (NCT01898494) trials are being carried out, randomly assigning patients to treatment with no adjuvant or decreased-intensity treatments after TORS for OPSCC. In the meantime, it should be re-emphasised that there is no data to support treatment de-escalation for HPV-driven OPSCC, as shown for radiotherapy.[6,7]

Fourth, the optimal assessment of swallowing has not yet been established, and MDADI is a subjective evaluation whose scores are strongly influenced by anxiety and depression.[8] In the setting of a prospective study, adding objective tests such as fiberoptic endoscopic examination of swallowing and videofluoroscopy would be advisable.

Fifth, MDADI evaluation is reported up to 3·5 years after treatment, which might be a little short to fully establish the late toxicity of radiotherapy. Swallowing impairment after radiotherapy is typically observed in the first 2 years after treatment, but in about

10–20% of patients, dysphagia continues to worsen leading to a progressive decline in quality of life.[9,10]

Sixth, because the ORATOR study was of modest sample size, confirmatory trials would be welcome. The ORATOR-2 trial (NCT03210103) has been launched in patients with HPV-driven early tumours to compare deintensified post-operative radiotherapy to deintensified IMRT. The European Organisation for Research and Treatment of Cancer started a trial in early-stage pharyngeal squamous cell carcinoma to compare TORS to IMRT. In these two studies, the endpoint is the patient-reported swallowing function over the first year using the MDADI score.

In conclusion, the trial of Nichols and colleagues showed that radiotherapy (with or without concomitant chemotherapy) is functionally better than TORS (with or without adjuvant concomitant chemoradiotherapy) for the treatment of OPSCC. This finding suggests the utmost importance of appropriate patient selection for minimally invasive surgery to avoid the use of adjuvant treatment modality.

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We declare no competing interests.

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CDK4/6 inhibitors: taking the place of chemotherapy?

The treatment landscape for advanced breast cancer has shifted dramatically over the past decade with the successive approvals of a multitude of targeted therapies. Specifically, CDK4/6 inhibitors have introduced a new treatment framework in the management of postmenopausal patients with hormone-receptor-positive, HER2-negative disease, who comprise the majority of patients with breast cancer. Clinical practice patterns have begun to veer away from a single-agent chemotherapy approach in the metastatic setting and towards upfront combination therapies with targeted agents in addition to endocrine therapy. Clearly delineating evidence, however, is needed to guide selection of one regimen over another in many cases.

In *The Lancet Oncology*, Mario Giuliano and colleagues[1] report the results of a comprehensive assessment of phase 2 and 3 randomised controlled trials comparing outcomes of postmenopausal patients with hormone-receptor-positive, HER2-negative metastatic breast cancer across a range of regimens based on endocrine therapy versus chemotherapy with and without incorporation of targeted therapies.

Comparing the findings across 140 randomised controlled trials pooled for the network meta-analysis, which includes data from a respectable 50 029 patients, chemotherapy-inclusive regimens were consistently found to be better than hormone monotherapy, albeit with significantly more toxicity. The more relevant finding supported by this study, however, was the inability to establish the effectiveness of chemotherapy-based regimens over the common comparator of palbociclib plus letrozole. In turn, the combination of a CDK4/6 inhibitor and endocrine therapy was


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Published **Online**
September 4, 2019
http://dx.doi.org/10.1016/S1470-2045(19)30507-8

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