READ IT BEFORE YOUR PATIENTS

Oropharyngeal squamous cell carcinoma

Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial.

Nichols AC, Theurer J, Prisman E, Read N, Berthelet E, Tran E, Fung K, de Almeida JR, Bayley A, Goldstein DP, Hier M, Sultanem K, Richardson K, Mlynarek A, Krishnan S, Le H, Yoo J, MacNeil SD, Winquist E, Hammond JA, Venkatesan V, Kuruvilla S, Warner A, Mitchell S, Chen J, Corsten M, Johnson-Obaseki S, Eapen L, Odell M, Parker C, Wehrli B, Kwan K, Palma DA.
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BACKGROUND

Transoral robotic surgery (TORS) with concurrent neck dissection has supplanted radiotherapy in the USA as the most common treatment for oropharyngeal squamous cell carcinoma (OPSCC), yet no randomised trials have compared these modalities. We aimed to evaluate differences in quality of life (QOL) one year after treatment.

METHODS

The ORATOR trial was an investigator-initiated, multicentre, international, open-label, parallel-group, phase 2, randomised study. Patients were enrolled at six hospitals in Canada and Australia. We randomly assigned (1:1) patients aged 18 years or older, with Eastern Cooperative Oncology Group scores of 0-2, and with T1-T2, N0-2 (≤4 cm) OPSCC tumour types to radiotherapy (70 Gy, with chemotherapy if N1-2) or TORS plus neck dissection (with or without adjuvant chemoradiotherapy, based on pathology). Following stratification by p16 status, patients were randomly assigned using a computer-generated randomisation list with permuted blocks of four. The primary endpoint was swallowing-related QOL at one year as established using the MD Anderson Dysphagia Inventory (MDADI) score, powered to detect a 10-point improvement (a clinically meaningful change) in the TORS-plus-neck-dissection group. All analyses were done by intention to treat. This study is registered with ClinicalTrials.gov (NCT01590355) and is active, but not currently recruiting.

FINDINGS

Sixty-eight patients were randomly assigned (34 per group) between 10 August 2012 and 9 June 2017. Median follow-up was 25 months (IQR 20-33) for the radiotherapy group and 29 months (23-43) for the TORS-plus-neck-dissection group. MDADI total scores at one year were mean 86·9 (SD 11·4) in the radiotherapy group versus 80·1 (13·0) in the TORS-plus-neck-dissection group (p=0·042). There were more cases of neutropenia (six [18%] of 34 patients vs none of 34), hearing loss (13 [38%] vs five [15%]), and tinnitus (12 [35%] vs two [6%]) reported in the radiotherapy group than in the TORS-plus-neck-dissection group, and more cases of trismus in the TORS-plus-neck-dissection group (nine [26%] vs one [3%]). The most common adverse events in the radiotherapy group were dysphagia (n=6), hearing loss (n=6), and mucositis (n=4), all grade 3, and in the TORS-plus-neck-dissection group, dysphagia (n=9, all grade 3), and there was one death caused by bleeding after TORS.

INTERPRETATION

Patients treated with radiotherapy showed superior swallowing-related QOL scores one year after treatment, although the difference did not represent a clinically meaningful change. Toxicity patterns differed between the groups. Patients with OPSCC should be informed about both treatment options.

Commentary

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

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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 (e.g. 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 papilloma virus (HPV)-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 one 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 in the study. Consequently, this study compared patients who received single-modality treatments with patients who received bimodality or trimodality treatments, when post-operative 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 (e.g. 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 fibre-optic endoscopic examination of swallowing and video-fluoroscopy 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 two 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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