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Organ-preserving approaches in oesophageal cancer

Rebecca C Fitzgerald

MRC Cancer Unit, Hutchison-MRC Research Centre, University of Cambridge, Cambridge CB2 0XZ, UK

Oesophagectomy is part of the mainstay of treatment for oesophageal cancer. Because most affected patients are elderly and have associated comorbidities, surgery is challenging. Furthermore, recovery from surgery can take up to a year and, in view of the poor survival associated with this cancer type, many patients will not regain their preoperative quality of life.¹

A meta-analysis² suggested that neoadjuvant therapy improves overall survival for patients with operable oesophageal cancer. Furthermore, neoadjuvant chemoradiotherapy can achieve complete pathological responses in around a third of treated patients. In the CROSS trial,³ neoadjuvant chemoradiotherapy followed by oesophagectomy was associated with an absolute overall survival benefit of 13% (95% CI 5.0–18.4) at 5 years compared with surgery alone. Furthermore, no viable tumour cells remained after combined treatment in 18 (49%) of 37 patients with squamous cell carcinoma and 28 (23%) of 121 patients with adenocarcinoma.³ These findings beg the question as to whether all patients with localised oesophageal cancer should have definitive chemoradiotherapy, with surgery reserved as a salvage option. However, in view of the disease's poor prognosis, any decision to forego surgery needs to be weighed carefully and depends upon an accurate assessment of treatment response.

Endoscopy-based surveillance relies on the presence of macroscopically visible abnormalities to trigger suspicion of local recurrence. In a study of endoscopic surveillance about a third of patients with local recurrence could be salvaged through surgery.⁴ This low proportion of patients benefiting from surgery could be because of selection bias, favouring recruitment of patients for definitive chemoradiotherapy who were unfit for surgery, or because endoscopy was not done frequently enough to detect early lesions. ¹⁸F-fluorodeoxyglucose (FDG) PET–CT is another surveillance approach, in which early metabolic changes are used to assess response. A systematic review⁵ identified eight studies in which PET was predictive of pathological response and five in which no correlation was noted. These conflicting results could be because of differences in patients' characteristics, including histological subtypes, variability in clinical timeline for acquisition of PET data between studies, and difficulties in interpretation of the PET images because of radiotherapy-induced inflammation.⁵

rcf29@mrc-cu.cam.ac.uk.

I am a named inventor on patents pertaining to the Cytosponge. The Cytosponge TFF3 technology has been licensed to Covidien GI solutions (now owned by Medtronic) by the Medical Research Council. Covidien Solutions and Medtronic have not been privy to this manuscript or the data therein.

In *The Lancet Oncology*, Bo Jan Noordman and colleagues⁶ used a multimodal approach in the preSANO trial to prospectively predict response to neoadjuvant therapy in patients with oesophageal cancer, involving endoscopic biopsy and endoscopic ultrasonography of oesophageal tissue, fine needle aspiration of suspicious lymph nodes to detect locoregional disease, and ¹⁸F-FDG PET for detection of distant metastasis. The rigorous biopsy protocol required sampling at two or three timepoints during surveillance, when biopsies were taken in a targeted and random manner, with a bite-on-bite method. This involved repeatedly taking a biopsy from the same spot to achieve deeper sampling and maximise the chance of finding tumour cells, which could be residing in the submucosal layer. One of the limitations of the study was that not all patients underwent all diagnostic modalities. Nevertheless, the proportion of false-negative cases decreased from 31% (95% CI 13–49) with standard biopsies to 11% (1–21) with bite-on-bite biopsies coupled with endoscopic ultrasonography and fine needle aspiration. The authors argue that, because the endoscopy and biopsy could be repeated regularly, oncological outcomes might improve because of early disease detection, when patients are still eligible for surgery.

The preSANO trial results are encouraging, but there is still a way to go to achieve the accuracy required for clinical decision making. The wide-area transepithelial sampling brush is an alternative endoscopic sampling method that is comparatively abrasive and obtains a spatially wide and deep sample, including the muscularis mucosae layer. Although application of this technique has focused on Barrett's oesophagus, it could also have utility in the diagnosis of patients with oesophageal cancer.⁷ Alternatively, the Cytosponge is a non-endoscopic cell-sampling device that can be used in an office setting regularly. The entire oesophagus is sampled by this sponge on a string, which is retrieved, and thus the sampling bias inherent in endoscopic biopsies is reduced. Furthermore, the Cytosponge is not operator dependent. This technology has been used for the detection of Barrett's oesophagus, squamous atypia, and mutational abnormalities.^{8,9} The detection of new onset atypia, or mutations such as p53 within an oesophagus previously cleared of these abnormalities through definitive chemotherapy could be used for early identification of disease recurrence in patients with oesophageal cancer. A feasibility study is now underway to test the diagnostic validity of this approach (CYTOFLOC trial, IRAS 227234).

A blood sample would provide the ultimate, non-invasive marker for persistent or recurrent disease, and rapid progress in cell-free tumour DNA assays combined with proteomic markers,¹⁰ could enable regular monitoring to be done after chemoradiotherapy. The sensitivity of this approach could be increased by personalising the cell-free tumour DNA assay. Further research in this area is needed.

Overall, the preSANO trial is a welcome step towards minimisation of the morbidity associated with the standard of care for patients with oesophageal cancer, an important research area.

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