Bringing organ preservation closer for selected patients with rectal cancer

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Not all patients with rectal cancer require surgery after neoadjuvant treatment. Instead, for those with a clinical complete response (cCR) after neoadjuvant therapy, a watch and wait approach can be started. In up to 25% of patients managed in this way, the tumour recurs or persists, but a salvage total mesorectal excision can be performed without substantially jeopardising oncological outcomes for many of these patients.[1,2] The problem is that complete response after neoadjuvant treatment cannot be predicted in advance. As a general rule, smaller tumours or more intensive treatment increase the chance of cCR.[3] Organ preservation implies that surgical morbidity and mortality, especially in older and frail patients, can be avoided, as well as poor functional outcome due to surgical nerve damage (eg, impotence, micturition and defecation disorders, and the need for a permanent stoma), which can have a negative impact on quality of life. The downside is that preoperative radiotherapy might also result in substantial short-term and long-term morbidity, especially in patients who do not need preoperative treatment for their oncological treatment and could go straight for local excision or rectal resection. Overtreatment of these patients will lead to a higher frequency of surgical complications and poorer functional outcome.

In *The Lancet Gastroenterology & Hepatology*, Jean-Pierre Gérard and colleagues report findings from the phase 3 OPERA trial comparing neoadjuvant chemoradiotherapy with radiation dose escalation with contact x-ray brachytherapy boost or external beam radiotherapy boost in early cT2–cT3ab (N0–1) rectal adenocarcinoma.[4] Patients who had a complete response to neoadjuvant chemoradiotherapy were followed up under a watch and wait policy, and those with a small downsized remaining tumour underwent local excision. The primary outcome of the study was organ preservation at 3 years. The study was designed with two experimental groups: one for small tumours up to 3 cm fitting in the contact x-ray brachytherapy endoscope and a second for larger tumours, which were first downsized by chemoradiotherapy and subsequently treated with contact x-ray brachytherapy. A significant benefit in organ preservation with contact x-ray brachytherapy boost was found during the first interim analysis and the independent data monitoring committee advised early closure of recruitment. However, full assessment of the role of addition of contact x-ray brachytherapy became more difficult due to the smaller numbers in both groups.

The Kaplan-Meier estimate of organ preservation at 3 years was 97% among patients with small tumours who were treated with a contact x-ray brachytherapy boost, and an unprecedented number had cCR or near cCR (30 [94%] of 32). 27 (19%) of the 141 patients in the intention-to-treat population underwent local excision. Of note, at restaging, MRI overstaged half of the patients with suspicious tumour remnants. The inherent overstaging of MRI could have led to the inclusion of some primary T1 tumours.[5] However, such inclusion would have occurred in all groups, and interference with the final outcome is unlikely.

Several studies have tried to increase the organ preservation rate by intensifying neoadjuvant treatment.[6] The OPERA study is the first to provide high-level evidence that, in small rectal cancers, organ preservation can be realised with upfront contact x-ray brachytherapy, chemoradiotherapy, and, if necessary, local excision. For the first time, organ preservation becomes a treatment goal for selected patients, rather than a lottery. The contribution of contact x-ray brachytherapy is apparent and should lead to a change in practice. The ongoing STAR-TREC study (NCT02945566)[7] will shed more light on the role of chemoradiotherapy alone and response in patients with early rectal cancer. The results for the experimental group with larger tumours who received contact x-ray brachytherapy after chemoradiotherapy is less conclusive. Pooling results from both groups does not seem logical, because both tumour stage and treatment method differ. The OPAXX study is a randomised phase 2 study comparing contact x-ray brachytherapy and local excision for tumour remnants after chemoradiotherapy and could provide complimentary data, which might help to differentiate the role of local excision and contact x-ray brachytherapy.

For the **OPAXX study** see https://dccg.nl/trial/opaxx

The OPERA study has brought organ preservation within reach for most patients with small rectal cancers who are willing to accept the morbidity of radiotherapy, but more research is still needed, because questions remain to be answered. A centralised, multidisciplinary approach within a research framework in collaborating expert centres could be a way to proceed.

We declare no competing interests.

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