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EDITORIAL

New hope from OPERA trial for surgically fit rectal cancer patients who wish to have organ preservation

The results of the long-awaited European phase 3 randomised trial OPERA (Organ Preservation for Early Rectal Adenocarcinoma) [NCT02505750] were recently presented at the world's largest oncology meeting, ASCO (American Society of Clinical Oncology) in Chicago [1]. They bring new hope for patients with early rectal cancer who wish to attempt organ preservation. The accepted traditional standard of care for rectal cancer involves radical surgery, even if this means a permanent stoma for patients who have a very small early Dukes A (cT1 or cT2/ cN0) low rectal cancer. This approach is however clearly unacceptable to some patients in the modern era [2].

National Institute of Health and Care Excellence (NICE) has previously recommended Contact X-ray Brachytherapy (CXB), also known as Papillon therapy, for patients with early rectal cancer who are not suitable for surgery [3]. However, for patients who are suitable for surgery, although NICE accepted the safety of Papillon therapy, they recommended conducting a prospective clinical trial to evaluate the efficacy of CXB compared to external beam radiotherapy. We therefore started the OPERA European randomised phase 3 trial in 2015. We randomised 148 patients, of whom 141 were evaluable, between two arms. In both arms, patients were given standard of care treatment involving external beam radiotherapy (45 Gy in 25 fractions), together with oral capecitabine chemotherapy over 5 weeks (EBCRT). In 'Arm A', this was followed by an external beam radiotherapy boost (EBRT) of an additional 9 Gy in 5 fractions to the primary rectal cancer only. In 'Arm B' (experimental arm), 90 Gy in 3 fractions using CXB boost was given to the primary tumour instead of the EBRT boost. The clinical characteristics of the patients in the two arms were well balanced. The primary end point was organ preservation at 36 months.

The results of OPERA were strongly in favour of the CXB boost, a finding which was not entirely unexpected [1]. The organ preservation rate at 36 months was significantly higher following a CXB boost in Arm B (80%) compared to Arm A (59%) ($P = 0.0027$). Moreover, for tumours <3 cm the difference between the two arms was even more apparent (97% organ preservation in Arm B compared to 63% in Arm A, $P = 0.0124$). What this means in a real-world setting is that when younger or fitter older patients with early rectal cancer seek to avoid surgery, we can more confidently offer them a choice of CXB boost after EBCRT as an alternative to surgery, as this approach is now supported by phase 3 randomised clinical trial data [1]. Historically it has been very difficult to conduct a trial, comparing radiotherapy alone (without surgery) to the current standard of care for early rectal cancer, which is surgery alone. We have also found it extremely difficult to conduct a trial of this kind as patients find it hard to accept major surgery and a stoma when equipoise is assumed. The researchers from the STAR TREC trial (NCT02945566) have experienced similar difficulties resulting in modification of the protocol, replacing randomization of surgery alone Arm as 'Standard of care' with patients' preference.

There is an increase in the elderly population throughout the developed world, and these high-risk patients are causing increasing anaesthetic and surgical challenges. The surgical mortality (5%–15%) [4] and morbidity (10%–50%) following major resectional bowel surgery is much higher in older patients. At the same time, we have also seen an increase in the number of patients being diagnosed with early-stage rectal cancers, particularly since the introduction of the National Bowel Cancer Screening Programme (NBCSP) in the UK 15 years ago. As the potential risks associated with major surgery are increasingly understood and as rectal cancer is being diagnosed at earlier stages, there is a recognition that treatment should be individualised, with extirpative surgery not necessarily being the most appropriate treatment option for all patients.

The Multidisciplinary Team (MDT) recommendations about cancer treatment are largely based on guidelines and protocols that have been produced by national bodies such as NICE [5]. However, these guidelines do not always take into consideration a patient's preferences or experiences, their religious or spiritual beliefs, or their physical and psychological ability to cope with a stoma. Some patients are willing to accept a lower chance of cancer cure in order to avoid a stoma. Some patients also find it very difficult to cope with a stoma due to disabilities such as arthritic hands or poor eyesight. Patients must live with the consequences of their treatment for the rest of their lives [6], hence we strongly advocate that they should have an opportunity to discuss all relevant treatment options with their clinical team, so that the most appropriate treatment for each individual patient can be considered carefully.

The recently published GMC guidance on 'Decision making and consent' places significant emphasis on tailoring consent to individual circumstances, placing an obligation on the clinician to explain the risks and benefits of all possible treatment modalities that may be important to a patient [7]. We therefore believe that final treatment

decisions in early rectal cancer should be made not only after MDT discussion, but after a detailed consultation with the patient during which their individual wishes and concerns are considered. We hope that with such new standards of informed consent, in combination with the promising outcomes of the OPERA trial, a greater number of patients will have an opportunity to explore organ-preserving treatment strategies for rectal cancer. This approach can potentially avoid major surgery and a stoma, and will result in many patients achieving a good long-term health-related quality of life. Moreover, if this non-surgical approach fails, the OPERA trial showed that salvage surgery can still be safely carried out later, without compromising the patient's chance of a cure [8].

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