Moving forward with organ preservation in rectal cancer

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The concept of radical cancer surgery is about 150 years old and was developed at a time when patients presented with large tumours and surgery was the only treatment option available. The belief that the more extensive the operation, the greater the chance for cure peaked at the end of the first half of the 20th century. Gradually, however, surgeons tried to maintain the same oncological outcomes with less mutilating resections, often combining surgery and radiotherapy, and sometimes even with radiotherapy as the primary approach and surgery as the backup plan. This approach has improved the quality of life of many patients with, for instance, breast cancer, head and neck cancer, limb sarcoma, and anal cancer. Management of rectal cancer has been late to adopt less radical approaches to preserve quality of life, with the main research focus of the past 40 years being on improving oncological results with different combinations of surgery, radiotherapy, and chemotherapy, rather than on quality of life. But that is changing, much to the delight of patients, who highly value a good functional outcome as an important treatment goal, often more than clinicians are aware of.[1] Against this background, the report in *The Lancet Gastroenterology & Hepatology* by Simon Bach and colleagues[2] on the TREC study, a small randomised, open-label trial on organ preservation in rectal cancer, deserves attention.

A number of studies have shown that once a patient achieves a clinical complete response after chemoradiotherapy, a watch-and-wait policy is a good alternative to major rectal resection.[3,4] Other reports have shown the feasibility of a local excision strategy after chemoradiotherapy.[5,6] However, none of these studies addressed the most relevant clinical question for patients with a small or intermediate tumour—what is better, moving straight to a major rectal resection, or starting treatment with radiotherapy with the explicit goal of organ preservation? The TREC study is the first to address this question. TREC was a small randomised trial that aimed to determine the feasibility of recruiting patients to a larger subsequent randomised trial. For clinical decision making, a large trial should provide reliable data on the quality of life and the oncological outcomes with the two approaches. Remarkably, despite its small size and exploratory nature, TREC already shows convincing evidence of better quality of life in the organ preservation group. This is both a blessing and a curse: a blessing because it shows that organ preservation lives up to its promise of benefit for the patient, but also a curse because it makes a large-scale randomised trial to provide solid evidence on oncological outcomes much harder to run. All organ preservation studies suggest that the potential oncological risk is small, requiring a large number of patients to adequately power such a trial. Given the high interest of patients in quality of life, many patients will have a clear preference for organ preservation when presented with the current data, and will object to randomisation. Trial methodology should, therefore, be adapted so that it aligns with the interest of patients while also providing data to estimate oncological outcomes. The ongoing STAR-TREC trial (NCT02945566), building on both the results of the TREC study and the similar CARTS[6] study, is a good example where the study design was changed into a partially randomised patient preference study with the primary endpoint of successful organ preservation to accommodate the preferences of patients.

The use of a short course of radiotherapy (5×5 Gy) in organ preservation also deserves attention. There is a widespread misconception that short-course radiotherapy is less effective and associated with more toxicity than a standard fluorouracil-based long course of chemoradiotherapy. The evidence so far suggests that a short course of radiotherapy is actually associated with less toxicity and that its efficacy is similar to that of a long course of radiotherapy.[7] In addition to the obvious advantages in cost and efficiency, a short course of radiotherapy can be combined more easily with systemic therapy.[8] The high proportion of patients who successfully achieved organ preservation in the TREC study warrants further exploration of short-course radiotherapy in this setting.

Current colorectal cancer screening programmes are detecting many rectal tumours when they are small, and it is now time to move beyond the time-honoured concept of radical cancer surgery. We must determine the means by which to identify those small tumours that require a local excision only, which radiotherapy-based regimens provide the best response in which tumours, and which patients are better off going straight to surgery. Nothing will be black or white, and ultimately the patient and

the doctor will have to weigh the pros and cons of the different options. This is where science meets art.

I declare no competing interests.

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Chronic hepatitis B: identifying who needs to be treated and improving linkage to care

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Hepatitis B is a global health problem. Despite access to hepatitis B vaccines since 1981, and effective affordable antivirals (WHO-prequalified generic tenofovir costs US$32 per annum),[1] in 2015, WHO estimated that 257 million people were living with chronic hepatitis B virus (HBV) infection worldwide.[2] Mortality due to complications of cirrhosis and hepatocellular carcinoma is increasing globally, with 900 000 deaths reported annually in 2015.[2]

Despite the burden of disease associated with chronic HBV, in 2016, only an estimated 27 million (10·5%) of the WHO-estimated 257 million people infected with HBV had been diagnosed, and 4·5 million (17%) of the 27 million diagnosed were receiving treatment.[1] Many individuals with HBV monoinfection in sub-Saharan Africa still struggle to access tenofovir monotherapy.[1] Addressing the morbidity and mortality associated with chronic HBV requires identification, linkage to care, and simplified treatment algorithms that are region-appropriate. Nucleos(t)ide analogue therapy is not curative, and is usually lifelong with associated adherence issues; thus, it is important to have clear criteria for initiation of therapy, as well as for national departments of health and policy makers to have a clear indication of the numbers needed to treat to have adequately funded viral hepatitis elimination programmes.

There is a lack of information about the proportion of people infected with HBV who are eligible for treatment, which limits the interpretation of global treatment coverage and hinders the ability to move to universal access to HBV screening and antiviral therapy, particularly in the setting of a silent chronic infection that is usually acquired in childhood and which only presents clinically in adulthood when complications of cirrhosis or hepatocellular carcinoma arise.[3] Accurate information about the proportion of people infected with HBV requiring treatment is limited by several factors, including insufficiency of affordable point-of-care diagnostics, clear referral pathways for access to treatment, and data suggesting differences in the numbers of people requiring treatment when applying WHO 2015 criteria as compared with European Association for the Study of the Liver (EASL) criteria.[4–6]

The decision to treat hepatitis B is dependent on three criteria; namely, degree of necroinflammation (alanine aminotransferase [ALT] levels), HBV replication (HBV DNA concentration), and the stage of the disease. The major guidelines (WHO, American Association for the Study of Liver Diseases, EASL, and Asian-Pacific