Leading article

Radiotherapy and locally advanced rectal cancer

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Published online 10 September 2015 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.9930

Radiotherapy has been an accepted treatment for locally advanced (T3/4 N1/2) rectal cancer (LARC) since the 1990s, and preoperative chemoradiotherapy (CRT) is the standard today. Questions are emerging, however, regarding the blanket use of a multimodal approach that involves neoadjuvant CRT, total mesorectal excision (TME) and adjuvant chemotherapy in all patients without selection. In the past decade, significant advances in the management of rectal cancer have been achieved, reflecting improvements in surgical technique, MRI and histopathology reporting. The main aims have been to minimize the risk of local and distant recurrence, and preserve the sphincter with good long-term function. The introduction of systemic chemotherapeutic agents (oxaliplatin, irinotecan) and targeted biological therapies offers multiple possible modifications to the standard preoperative CRT multimodal approach.

Treatment decisions are often based on MRI in most developed healthcare systems. Although MRI-based risk stratification strategies have been incorporated into clinical practice guidelines[1] and eligibility criteria in clinical trials (NCT01558921, ISRCTN09351447)[2,3], the evidence for MRI on the basis of prospective observational studies, such as MERCURY[4], has yet to be validated in randomized phase III trials. There is variability in interpretation. Some radiologists do not define macroscopic extramural vascular invasion. Many of the clinical data on which these treatment decisions are founded predate good-quality TME, the use of MRI and modern histopathology. In this previous era, radiotherapy may well have simply compensated for poor surgery and these data may not be relevant in 2015.

High-quality TME is now performed in 70–80 per cent of patients[5], reducing local recurrence rates to approximately 2 per cent after radiotherapy or CRT, and only 6 per cent without. The rate of metastatic disease, however, remains consistently in the region of 30–35 per cent. The population at risk is also changing, as a result of screening programmes that have led to earlier diagnosis, creating further controversy between radical surgery and organ-sparing approaches for T1/2 cancers.

Difficulties in performing trials in rectal cancer reflect poor choice of primary endpoint, inadequate imaging/staging, insufficient quality assurance, variations in the quality of pathological assessment, the impact of non-operative 'watch-and-wait' strategies and the use of postoperative chemotherapy.

For many of these reasons, progress in the non-surgical aspects of treatment of LARC seems to have stalled. Various strategies have been explored in small phase II studies: integrating novel chemotherapy and/or biological agents into CRT schedules, integrating induction or consolidation chemotherapy into standard or short-course preoperative radiotherapy (SCPRT) schedules, as well as alternating chemotherapy and split-course radiotherapy. Most represent strategies to increase pathological complete response rates.

Few of these non-surgical adaptive strategies seem to have resulted in significant advances in understanding the disease or improving outcomes. Ramping up the neoadjuvant chemotherapy component, in numerous iterative attempts to add chemotherapy before CRT, seems attractive theoretically but does not appear to have resulted in tangible advantages[6,7]. In contrast, additional courses of FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin) as consolidation after CRT and before TME have the potential to increase the pathological complete response rate; theoretically this could broaden the options for patients in terms of less invasive treatment strategies[8], although long-term oncological outcomes are lacking. The European Organization for Research and Treatment of Cancer 22921 trial[9] has indicated that postoperative adjuvant chemotherapy after preoperative CRT does not improve disease-free or overall survival.

These approaches hypothesize that better results might be obtained by adding more chemotherapy to existing strategies. The question that seems to have been largely ignored is whether radiotherapy is needed at all, or whether neoadjuvant chemotherapy alone could produce the same results in the current TME era. Omitting CRT has the advantages of improved wound healing, less frequent anastomotic leaks, avoidance of long-term radiation toxicity and a smaller risk of second malignancy.

There has been little drive to replace SCPRT/CRT with neoadjuvant chemotherapy alone for resectable

cT3 cancers, although this strategy forms the basis of the ongoing PROSPECT trial (NCT01515787). Preliminary results of the Chinese FOWARC study[10] also suggest that neoadjuvant FOLFOX alone and CRT achieve similar pathological complete response rates, tumour regression grades, and downstaging and curative resection rates, but with reduced surgical morbidity for FOLFOX alone.

Future studies need defined efficacy endpoints and clear stopping rules that should be relevant to currently achieved outcomes. Local recurrence is no longer a major problem for LARC. Improvements in survival, numbers requiring a permanent stoma and quality of life should take greater precedence than the complete elimination of local recurrence.

Neoadjuvant chemotherapy has been introduced as the primary management of many cancers[11] despite a lack of evidence of superiority in terms of overall survival. The FOxTROT (Fluoropyrimidine, Oxaliplatin and Targeted Receptor pre-Operative Therapy for colon cancer) trial[12] of neoadjuvant chemotherapy in colonic cancer, which demonstrated significant downstaging, is also beginning to influence colorectal clinicians. Even if this approach does not improve survival, there may be many other potential advantages in terms of facilitating sphincter- or organ-sparing surgery, reducing surgical morbidity compared with CRT and creating opportunities for translational research in LARC.

Treatment selection for LARC now needs to take account of factors other than staging and performance status. Mucinous/signet ring tumours, representing about 20 per cent of rectal cancers, respond poorly to fluoropyrimidine or doublet chemotherapy[13,14] and may fare better with other agents. These tumours also respond poorly to conventional CRT. For this non-responsive subset, intensive neoadjuvant chemotherapy can facilitate the development of novel chemotherapy scheduling and the exploration of novel agents, and enhance the opportunity for translational research. The role of CRT in these patients needs to be clarified so that recognized adverse effects in terms of poor sexual, urinary and bowel function can be avoided.

A comparison of preoperative CRT *versus* neoadjuvant FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, oxaliplatin) followed by preoperative CRT is currently under way in a randomized phase III study in LARC (NCT01804790). Yet another trial integrating two to four courses of induction chemotherapy before CRT or SCPRT and randomized against CRT alone or SCPRT may not be the best way forward. There are potential advantages to neoadjuvant chemotherapy alone without CRT, including greater levels of treatment compliance to chemotherapy, earlier delivery of systemic therapy, and better wound healing with no long-term radiation effects. This concept is explored in the Cancer Research UK BACCHUS (Bevacizumab And Combination Chemotherapy in Rectal Cancer Until Surgery) trial (NCT01650428).

Trials randomizing chemotherapy alone against CRT might prove difficult to perform, but if chemotherapy alone is as effective as CRT they may ultimately offer major gains in terms of quality of life. Future studies that assess gene expression and mutations may identify patients who are more likely to respond to CRT and who can then avoid radical surgery. Alternatively, others may avoid radiotherapy with all its drawbacks and instead receive more aggressive chemotherapy and/or immunological or biological options.

Acknowledgements

R.G.-J. is principal investigator of the randomized phase II BACCHUS trial. The trial is funded by Cancer Research UK and Roche, who are providing the bevacizumab and funding for PET. R.G.-J. has received honoraria from Roche, Sanofi-Aventis and Merck KGaA, and research funding from Merck KGaA, Roche and Sanofi. M.H. has sat on advisory boards for Roche, Merck Sharp & Dohme, Boehringer Ingelheim, GSK and Astra Zeneca.

Disclosure: The authors declare no other conflict of interest.

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