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Neoadjuvant treatment strategies for locally advanced rectal cancer

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Abstract

Improved surgical technique plus selective pre-operative radiotherapy, has decreased rectal cancer pelvic local recurrence (LR) from historically 25%, down to approximately 5-10%. However, this improvement has not reduced distant metastatic relapse, the main cause of death and a key issue in rectal cancer management.

The current standard is local pelvic treatment (surgery +/- pre-operative radiotherapy) followed by adjuvant chemotherapy (AC), depending on resection histology. For circumferential resection margin (CRM)-threatened cancer on baseline MRI, downstaging long-course pre-operative chemoradiation (LCPCRT) is generally used. However, for non-CRM threatened disease, varying approaches are currently adopted in the UK, including straight to surgery (STS), short-course pre-operative radiotherapy (SCPRT) and LCPCRT.

Clinical trials are investigating intensification of concurrent chemoradiation. There is also increasing interest in investigating pre-operative neoadjuvant chemotherapy (NAC) as a way of exposing micro-metastatic disease to full dose systemic chemotherapy as early as possible and potentially reducing metastatic relapse. Phase II trials suggest that this strategy is feasible, with promising histological response and low rates of tumour progression during NAC. Phase III trials are needed to determine the benefit of NAC when added to standard therapy and also to determine if it can be used instead of neoadjuvant radiotherapy based schedules. Although several measures of neoadjuvant treatment response assessment based on imaging or pathology are promising predictive biomarkers for long-term survival, none have been validated in prospective phase III studies. The phase III setting above will enable this, also providing translational opportunities to examine molecular predictors of response and survival.

Keywords

Rectal cancer, adjuvant chemotherapy; neoadjuvant chemotherapy; pre-operative radiotherapy; chemoradiation; surgery

Introduction

The current standard treatment for rectal cancer is surgery although pelvic local recurrence (LR) has historically been a major cause of morbidity and mortality. However, improvements in pre-operative assessment and surgical quality, including the widespread adoption total mesorectal excision (TME) [1].and optimal surgery for low rectal cancers [2], together with the selective use of pelvic radiotherapy, has markedly reduced pelvic LR from historically approx 25% [3], to approximately 5-10% [4,5,6,7]. However, this has not reduced the rate of distant metastatic relapse, which is now the major cause of rectal cancer death. The current review summarises neoadjuvant treatment strategies which aim to reduce such relapse, together with current thinking and directions of future research.

Both pre- and post-operative radiotherapy lower the risk of rectal cancer pelvic LR [8]. Pre-operative RT is used as either SCPRT of 25 Gy in 5 daily fractions over 1 week, followed by surgery within a week [6,7]. Alternatively LCPCRT is used, typically with 45-50.4 Gy in 1.8 Gy fractions over approximately 5 weeks with a concurrent fluoropyrimidine (either 5-Fluorouracil (FU) or capecitabine), followed by a gap of 8-10 weeks before surgery [4,5,9]. Both LCPCRT and SCPRT approximately halve the risk of pelvic LR and LCPCRT and SCPRT are equivalent in their ability to reduce LR in phase III trials of resectable rectal cancer [10.11]. Pre-operative chemoradiation (CRT) is associated with reduced LR and long-term morbidity compared to post-operative CRT [12].

Pelvic MRI scanning has been established as the investigation of choice for local staging of rectal cancer prior to surgery [13,14,15]. If disease threatens or involves the potential surgical resection margin, then the risk of LR is markedly increased

[16,17]. This is commonly defined as disease encroaching to within 1mm of mesorectal fascia (MRF) or lower rectal cancers involving the levator-sphincter complex. Shrinkage or 'downstaging' of such tumour prior to surgery, increases the chance of achieving a clear surgical margin and lowers the probability of pelvic LR. Such downstaging can be achieved by LCPCRT followed by a gap of 8-10 weeks, but is minimal with SCPRT followed by immediate surgery [18]. However, if SCPRT is followed by a gap of several weeks prior to surgery, then significant downstaging does occur [19]. Rectal cancers can be described as 'operable' if disease does not threaten or involve the surgical CRM.

Both SCPRT and LCPCRT cause acute but more importantly late morbidity. Currently considerably more is known concerning late morbidity related to SCPRT than LCPCRT because of longer follow-up periods in relevant studies [20]. Late adverse events associated with radiotherapy included bowel obstruction, bowel dysfunction presenting as faecal incontinence to gas, loose or solid stool, evacuation problems or urgency and sexual dysfunction [21,22]. A recent report did not find any increase in second malignancy in clinical trials of pelvic radiotherapy [23]. Fewer late adverse events were reported in recent studies which generally used smaller radiotherapy volumes and improved multi-field techniques.

Reduction of rectal cancer LR has not had any significant impact on distant metastatic relapse and this is now the major cause of death [6,7]. .Features on histological examination of resected specimens predict increased risk of post-operative systemic recurrence including more than 5mm invasion of disease through the muscularis into the mesorectum (≥T3c) [24,25], extra-mural vascular invasion (EMVI) [26] and lymph node involvement (LN+) [27]. For patients with such features, with optimum surgery and selective use of pre-operative radiotherapy, DM relapse is

approximately 6-fold greater than LR (approximately 30% vs. 5%) [6,7,28] and is now the main cause of death. MRI scanning is the pre-treatment investigation which can most reliably identify such features [13,14,15].

The significance of pathological response to radiation

One measure of the effectiveness of neoadjuvant treatment is the pathological complete response (pCR) rate. The proportion of patients achieving a pCR using a concurrent fluoropyrimidine is usually approximately 12-15% although there is no internationally agreed definition of pCR [29].

It is tempting to use pCR as a measure of the effectiveness of neoadjuvant treatment because it is a readily obtainable short-term end point. It has been demonstrated that individuals who achieve a pCR following LCPCRT have better survival than those who do not [30]. However, the evidence above [30] is mainly retrospective and comes from a pooled analysis of individual patient data generated in selected non-randomised phase II trials or retrospective cohorts [31]. A variety of pathological parameters were examined in the large randomised FFCD 9203 trial [32], including T downstaging to ypT0 and tumour regression grade (TRG). None fulfilled all the Prentice criteria as surrogate endpoints for long-term clinical outcomes. Thus pCR may be useful as a signal of activity of a novel schedule but it is generally regarded as an unsuitable primary end point for phase III trials

Strategies to Intensify Neoadjuvant Therapy

The different research strategies to improve neoadjuvant therapy include the intensification of concurrent CRT by the addition of an additional chemotherapy drug or targeted therapy, the addition of NAC before or after pre-operative (C)RT, or

investigation of whether NAC can be used instead of standard preoperative radiotherapy based treatment.

Increasing the efficacy of pre-operative chemoradiation

A review of phase II and III studies identified an overall pCR rate of 13.5 per cent using single agent fluoropyrimidine radiosensitisation [33]. It was suggested that the pCR rate may be increased with increased doses of radiotherapy and the addition of a second cytotoxic drug.

After a series of single arm phase II studies, five randomised phase III trials have been performed adding oxaliplatin to either 5FU or capecitabine during CRT, with mixed results. Only two have published long term outcomes as full-length reports, the French ACCORD12 [34] and German AIO-04 [28] trials. In 598 patients the ACCORD 12 trial compared 45Gy capecitabine CRT with 50Gy oxaliplatin and capecitabine and reported no difference in the rate of pCR (the primary endpoint) or 3-year DFS or OS [34].

The German CAO/ARO/AIO-04 trial randomised 1265 patients to 5FU-containing LCPCRT and 16 weeks of 5FU-based postoperative chemotherapy with or without oxaliplatin. The DFS was increased from 71.2% to 75.9% (HR 0.79, p=0.03) [28]. However the benefit of intensified CRT is not know due to the addition of oxaliplatin to both the concurrent and adjuvant chemotherapy components and the use of different 5FU dose intensity between treatment arms.

The NSABP R-04 [35] and PETTAC 6 trials [36], reported in abstract form, do not describe any improvement in cancer outcomes for their primary end point (LR and DFS respectively) and data is awaited from the STAR 01 study [37].

Several promising phase II trials incorporating irinotecan have been reported [38] but as yet no phase III trials. The ongoing UK phase III ARISTOTLE trial (ISRCTN09351447) is examining the addition of irinotecan to capecitabine in MRI-defined rectal cancer threatening or involving the CRM.

A variety of targeted agents have been added to chemoradiation regimes including the anti-EGFR monoclonal antibody cetuximab. However several phase 2 trials have mostly suggested reduced pCR rates and shorter DFS with no consistent relationship to KRAS status. Bevacizumab has also been added to CRT but with pCR rates reported no better than 5FU-based CRT alone and with some increases in operative morbidity (reviewed in Glynne-Jones et al) [39]. A variety of other agents have also been used concurrent with CRT in early phase trials, including gefitinib, panitumumab and erlotinib with variable results.

At present no reliable predictive biomarkers of response to LCPCRT have been identified, which have subsequently been verified as useable in routine clinical practice [38,39] although this is currently a very active area of research. Fluoropyrimidine CRT therefore remains the current standard of care and intensification the focus of clinical trials.

Rationale for neoadjuvant chemotherapy in rectal cancer

Systemic chemotherapy has the potential to treat micrometastases, decrease distant relapse and improve survival. Current UK rectal cancer practice is to give local pelvic treatment first (surgery+/-radiotherapy), then consider systemic AC. However, the benefit of AC is modest. A meta-analysis of 20 studies in 9,785 subjects predating widespread implementation of TME and preoperative radiotherapy found that AC

with FU improved disease-free survival (DFS) (HR=0.75, CI: 0.68-0.83) and OS (HR 0.83, CI 0.76-0.91) [40]. However, a more recent meta-analysis of four trials which included preoperative radiotherapy, questions the benefit of postoperative AC (HR for DFS 0·91, CI 0·77–1·07; p=0·230), although only 75 of 1196 patients included in the report had oxaliplatin in addition to a fluoropyrimidine. [41] Many individuals exhibit poor tolerance of this package of treatment due to morbidity from radiotherapy and pelvic surgery resulting in failure to start AC or dose reductions [42]. Of 506 rectal cancer patients due to receive AC post LCPCRT in one study, only 43% tolerated the full course and 27% never started treatment [4,42].

Giving systemic chemotherapy before local treatment has the potential to improve treatment delivery, and treats micrometastases with full dose chemotherapy months earlier than with AC. Using NAC potentially rapidly improves symptoms from responding pelvic tumour [43] and also allows earlier reversal of a defunctioning stoma, with potential quality of life (QoL) and health economic benefits. However, there are also theoretical potential disadvantages to using NAC. The delay in surgery could possibly allow disease progression in the interim. Also selection of radiotherapy-resistant clones by NAC might reduce the efficacy of subsequent radiotherapy.

Overall survival benefit from NAC has been demonstrated in oesophageal [44] and gastric cancer [45], and the approach is under evaluation for colon cancer in the CRUK FOxTROT trial, in which analysis of the first 150 accrued patients has shown no increase in surgical morbidity after NAC [46].

Phase II studies of NAC in rectal cancer show that it is well tolerated and produces tumour downstaging, and there is minimal risk of progression during NAC. EXPERT/EXPERT-C used 12 weeks oxaliplatin/capecitabine (OxCap) NAC before

chemoradiotherapy (CRT) and surgery in a total of 186 subjects. In 169 patients assessed with MRI post NAC only 1% (2 patients) progressed and the overall response rate by intention to treat was 63% [43,47,48]. GCR3 was a randomised phase II study of pre-operative OxCap followed by CRT then surgery vs. CRT then surgery then post-operative OxCap in 108 patients. Less toxicity ($p=0.0004$) and better compliance ($p<0.0001$) for the same regimen used as NAC compared with AC was demonstrated [49].

Addition of NAC to preoperative treatment

A Dutch ph II study evaluated the use of SCPRT followed by systemic chemotherapy {50}. This led to the RAPIDO trial, a phase III trial comparing SCPRT followed by 12 weeks of CAPOX chemotherapy prior to surgery, with standard LCPCRT (NCT01558921) in patients with locally advanced tumours (T4a-b or N2 or EMVI positive or MRF threatened or involved pelvic side wall nodes) and M0 disease. The current target accrual is 885 patients with a primary end point 3-year DFS. Recruitment should complete in 2016.

The UK COPERNICUS multicentre phase II study, funded by Cancer Research UK, recruited 60 patients and showed that delivery of 8 weeks of OxFU prior to SCPRT then immediate surgery is feasible and does not jeopardise successful surgery, with evidence of histological downstaging [51]. 2011 NICE guidance [52] identified NAC as a key research question in rectal cancer with the opportunity to impact upon survival.

Taking the above evidence into account, the UK Colorectal Clinical Studies Group are developing a randomised phase III trial in MRI-defined patients at high risk of post-operative metastatic relapse (baseline MRI shows either ≥T3c or N+ or EMVI+).

One trial design being considered is comparing standard local pelvic treatment followed by AC to an experimental arm of NAC followed by standard local pelvic treatment. The treating MDT would choose the appropriate standard local pelvic treatment for the individual patient being considered (STS or SCPRT or LCPCRT) and stratification for this choice would be carried out at randomisation. In the UK there is marked variation in multi-disciplinary team (MDT) policies for use of preoperative radiotherapy. In a survey conducted between July and September 2014 in 91 MDTs serving 58 of the 59 UK radiotherapy centres, in patients with the high-risk features on pre-treatment MRI of either ≥T3c or N+ or EMVI+, overall 40% of MDTs would go straight to surgery (STS), 35% treat with SCPRT and 25% with LCPCRT (NCRI Anorectal Subgroup, unpublished).

In addition to a primary survival outcome, secondary outcomes including treatment compliance, time with defunctioning stoma, QoL and health economic measures, would also be important. A NAC phase III trial also provides excellent opportunities for linked translational research aimed at identifying biomarkers predictive of long-term outcome. Such biomarkers could be derived from imaging such as tumour regression grade (TRG) or response of EMVI [53,54]. Alternatively they could be pathological, such as changes in TRG or in tumour cell density (TCD) [55,56], or molecular, such as stratifiers of response to chemotherapy and radiotherapy.

In the USA consideration is being given to adopting NAC as standard in rectal cancer treatment, without phase III trial data showing a benefit compared to standard AC [57]. However, many would consider this move premature and believe that phase III trial evidence is required.

A non-randomised trial examining 4 sequential study groups in the USA and Canada, recruited between 2004 and 2012 [58]. Group 1 had LCPCRT followed by

TME 6-8 weeks later. Groups 2, 3 and 4 had two, four and six, 2-weekly cycles of mFOLFOX delivered between LCPCRT and TME. The pCR rate increased, being 18%, 25%, 30%, 38% for groups 1-4 respectively. Whether this represents increased downstaging because of a greater gap between LCPCRT and surgery (6, 8, 12 and 16 weeks for groups 1-4 respectively) is unclear. In addition, whether the promising phase II results with NAC will translate into improved survival must await definitive phase III trial evidence.

NAC instead of standard preoperative radiotherapy regimens

A small phase II study of 32 patients reported a pCR rate of 25% using 12 weeks of OxFU (plus bevacizumab for the first 8 weeks), without radiotherapy [59]. The US PROSPECT trial NCT01515787 is currently enrolling less advanced patients with operable T2-3N0-1 disease 5-12cm from the anal verge, not requiring an abdomino-perineal resection and not threatening CRM (>3mm from CRM). Preoperatively patients are randomised between LCPCRT using concurrent fluoropyrimidine vs. chemotherapy alone using 12 weeks of FOLFOX. Patients in the latter group will receive LCCRT only if they demonstrate 'less than 20% tumour regression'. Recruitment commenced in early 2012 with a target of 1060 patients and the primary end point of an initial phase II element is R0 resection rate and phase III DFS.

Conclusions

For many years the focus of rectal cancer treatment has been local pelvic control. Now that improved pre-operative assessment and surgical quality, together with selective use of pre-operative radiotherapy has reduced pelvic recurrence to less than 5-10% in many institutions, distant metastatic relapse is the main cause of

death. There is considerable interest in the intensification of neoadjuvant treatment, including systemic therapy as a means of addressing micro-metastatic disease as early as possible in the treatment paradigm.

It is essential that well designed phase III trials are performed and their results scrutinised in detail to determine the benefit of such approaches. This includes determining whether intensification of chemotherapy during radiotherapy results in improved cancer related outcomes. Even if this approach produces limited overall benefits it is important to determine whether subsets of patients might benefit using the clinical trial evidence. It is also essential that trials are successfully completed or initiated that test the addition of NAC to standard treatment and whether NAC can replace pre-operative radiotherapy regimens. All of these trials will also provide excellent translational research opportunities with the aim of identifying further predictive molecular biomarkers for tumour response and long-term survival.

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