CREATE Trial Proposal: Survey of current practice and potential trial participation

Approximately a quarter of newly diagnosed rectal cancer patients have features on pre-treatment pelvic MRI indicating that disease is operable but at high risk of subsequent metastatic relapse. Disease does not threaten or involve the mesorectal fascia (MRF) or levator-sphincter complex (i.e. >1mm gap between disease and MRF or levator-sphincter complex) but there are features indicating a high risk of subsequent metastatic relapse including either:

1. at least 5mm invasion of primary tumour through muscularis into the surrounding mesorectum (T3c or above)
2. or the presence of involved mesorectal lymph node(s) or extra-mural tumour deposit(s)
3. or the presence of extra-mural vascular invasion (EMVI)

With recent improvements in surgical quality and the use of preoperative radiotherapy, distant metastatic relapse is now the main cause of death in these patients with approximately one third of patients with one or more of these features relapsing systemically over the subsequent 3 years.

Both short course preoperative radiotherapy (SCPRT) delivering 25 Gy in 5 daily fractions over one week followed within a week by surgery or alternatively preoperative long-course chemoradiation (LCCRT) delivering 45-50.4 Gy in 25-28 daily fractions over 5-5.5 weeks followed by an 8-10 week gap prior to surgery, more than halve the rate of pelvic recurrence of operable rectal cancer and when SCPRT and LCCRT have been compared in randomised trials, they have proven to be equivalent in their ability to reduce local recurrence (Bujko et al 2004; Ngan et al 2012).

However, neither SCPRT nor LCCRT have any effect on distant metastatic relapse and neither improve overall survival. When SCPRT and LCCRT have been compared with one another, there is no difference in survival (Bujko et al 2004; Ngan et al 2012).

There is evidence that SCPRT or LCCRT are used variably in different treating centres both in the UK and worldwide to treat similar stages of operable rectal cancer and in some cases neither SCPRT nor LCCRT are chosen but instead patients go straight to surgery (STS).

In the survey we would firstly like to determine the variability in practice across different treating centres in three selected clinical scenarios illustrating the categories of operable rectal cancer at high risk of systemic relapse referred to above (Cases 1-3: see below).

Neoadjuvant chemotherapy (NACT) has the potential to treat microscopic distant metastases earlier in the treatment pathway than in current standard practice and thus possibly increase survival. Compliance and histological and radiological response rates are also potentially increased.

A number of phase II trials have evaluated the use of NACT in this context. The EXPERT trial used oxaliplatin/capecitabine chemotherapy prior to LCCRT and showed encouraging response rates to NACT (Chau et al 2006, Chua et al 2010) and the randomised phase II GEMCAD GCR3 study (Fernandez-Martos et al 2010)

compared NACT with postoperative chemotherapy and demonstrated reduced toxicity and increased compliance for NACT.

Internationally the concept of NACT in rectal cancer is attracting increasing interest. The phase III Dutch/Scandiavian RAPIDO trial ((NCT01558921) is currently examining the efficacy of an experimental arm of SCPRT followed by 18 weeks of oxaliplatin/capecitabine chemotherapy vs. a standard arm of LCCRT. The US phase III PROSPECT trial (NCT01515787) randomises between an experimental arm of 12 weeks of FOLFOX chemotherapy alone (using LCCRT only if imaging demonstrates less than 20% tumour regression) vs. a standard arm of LCCRT.

The currently proposed UK trial CREATE (**C**hemotherapy, **R**adiotherapy or **Ea**ch **T**hen **E**xcision for Operable Rectal Cancer at High Risk of Systemic Recurrence) is a randomised phase III trial in patients with operable rectal cancer (defined as no disease within 1mm of the CRM and therefore not overlapping with ARISTOTLE entry criteria) but who are at high risk of postoperative systemic recurrence by virtue of pre-treatment MRI demonstrating either primary tumour invasion of at least 5mm into the mesorectum (at least T3c disease) or positive mesorectal lymph nodes/tumour depostis or EMVI.

CREATE is a pragmatic trial, designed to make the entry criteria as inclusive as possible and takes as standard treatment the treatment that the MDT decides is the correct one ('MDT choice') for the particular patient under consideration (either STS or SCPRT or LCCRT). The effectiveness of introducing 12 weeks of NACT using oxaliplatin/fluorouracil (OxMdG) or optionally oxaliplatin/capecitabine (OxCap) prior to this standard treatment will then be examined by randomising that patient to 'MDT choice' +/- NACT (Figure 1). OxMdG or OxCap have been chosen because they have proven efficacy as postoperative adjuvant treatment in colorectal cancer. The primary end point will be to determine whether 12 weeks of NACT prior to 'MDT choice' can improve 3-year disease-free survival. For inclusion patients will need to be of ECOG PS 0-1 and will be stratified at randomisation for whether the 'MDT choice' is STS vs SCPRT vs LCCRT.

Immediately following their 12 weeks of NACT patients will have a pelvic MRI in week 13 and it is anticipated that very few patients will demonstrate disease progression (Chua et al 2010). However, for those patients where 'MDT choice' had been STS or SCPRT, whose disease does progress on NACT and now threatens the CRM, the protocol will recommend LCCRT prior to surgery in order to attempt to downstage their tumour.

Patients in the standard 'MDT choice' arm will receive either 12 or 24 weeks of adjuvant postoperative chemotherapy depending on the results of the SCOT trial. Patients in the experimental arm will receive an additional 12 weeks of adjuvant postoperative chemotherapy only if SCOT demonstrates an advantage for 24 over 12 weeks of adjuvant chemotherapy.

In the survey we would secondly like to determine whether your MDT would be prepared to randomise patients in each of Cases 1-3 (below) to 'MDT choice' +/- 12 weeks of NACT in a future clinical trial and to gauge general support for such a trial.

The link to the 10 question survey is: **https://www.surveymonkey.com/s/G32KYPF**

References

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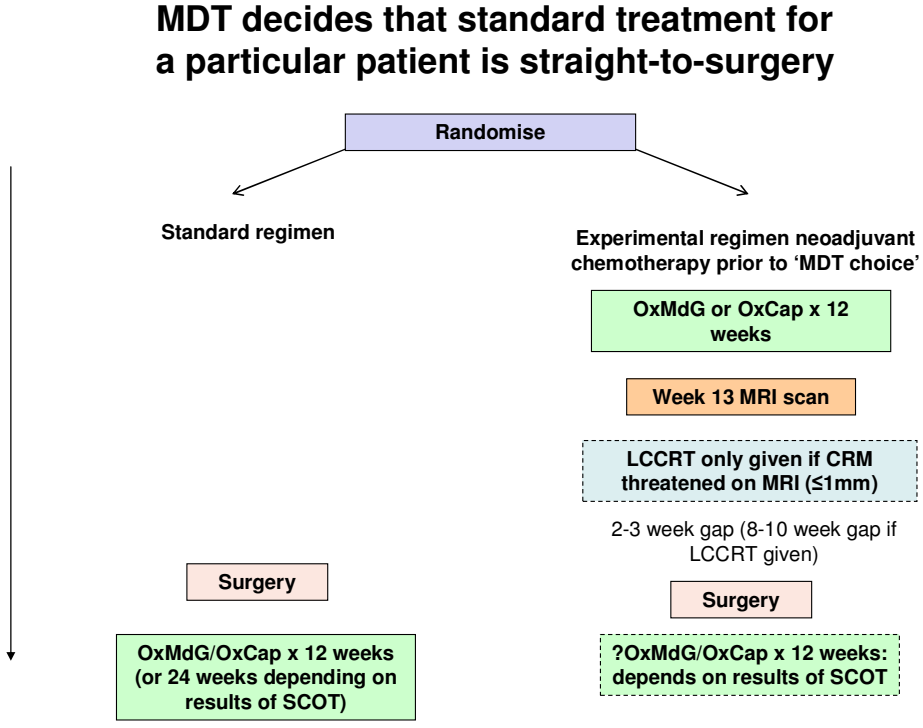
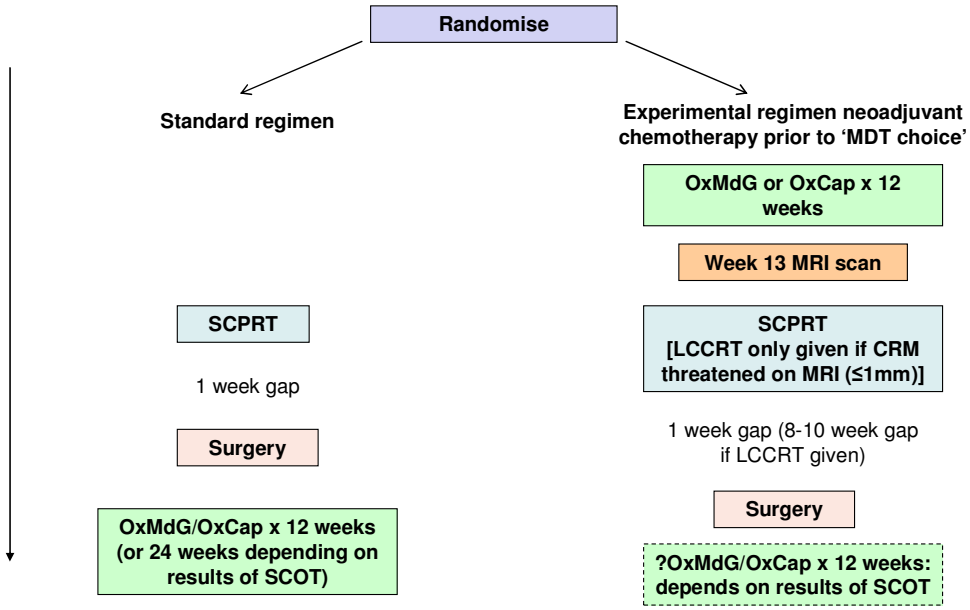
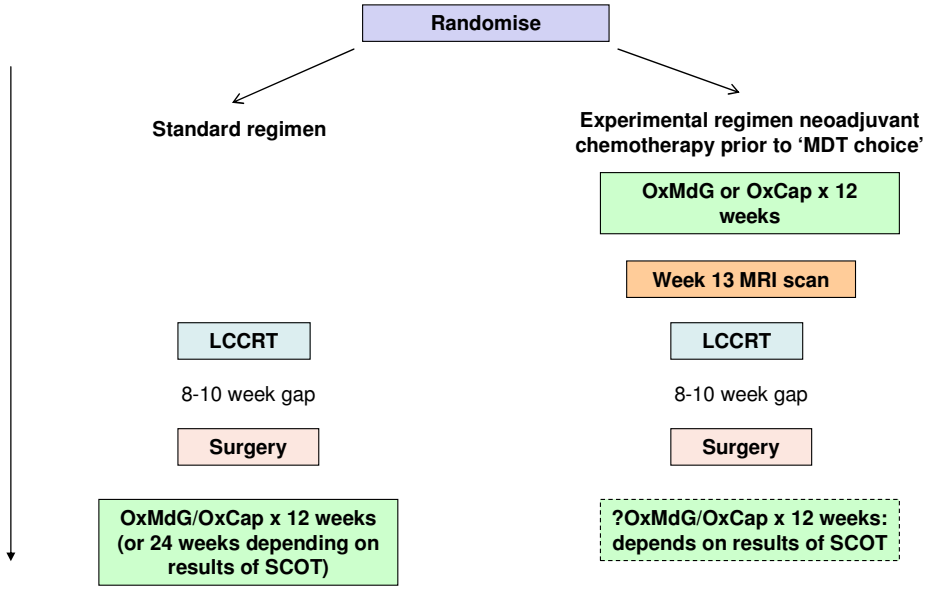
Figure 1. The CREATE trial schema illustrated for each of the three possibilities of 'MDT choice' (either STS or SCPRT or LCCRT)



MDT decides that standard treatment for a particular patient is SCPRT

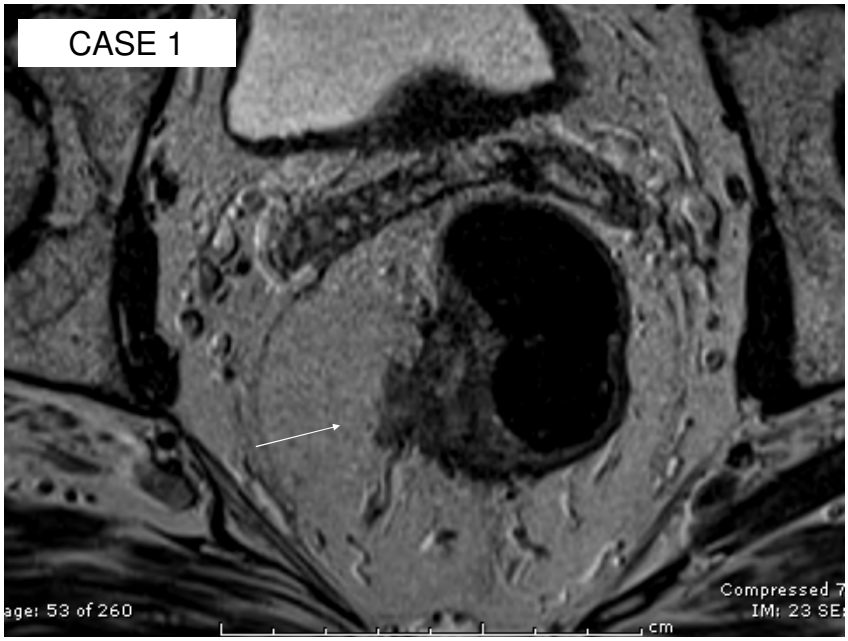


MDT decides that standard treatment for a particular patient is LCCRT

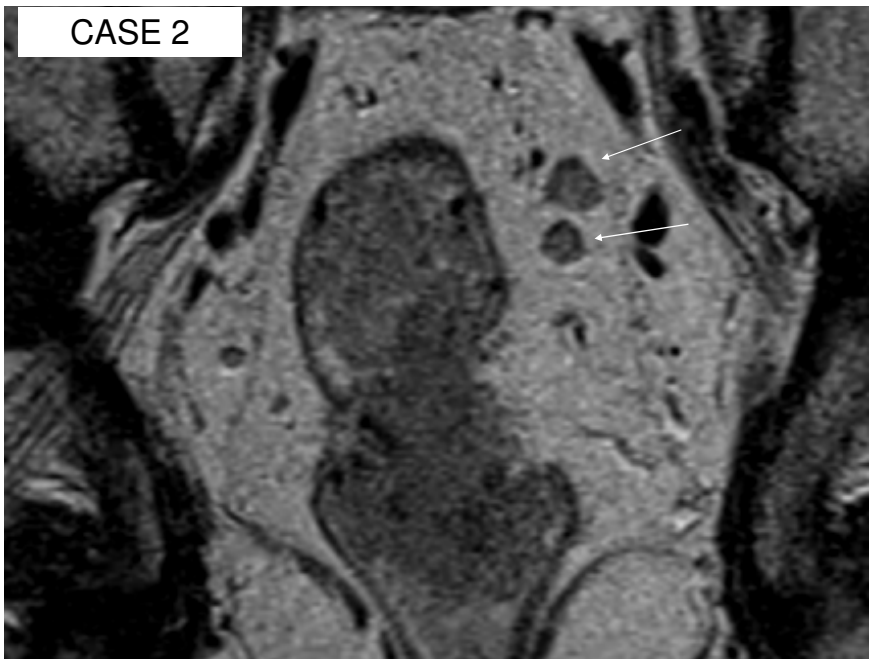


Clinical Cases for CREATE survey

Case 1: 60 year old male, WHO PS=0, histologically confirmed adenocarcinoma of the mid rectum. Pre-treatment MRI pelvis shows primary tumour is 5cm in sup-inf dimension and **T3c** with invasion of 14mm beyond muscularis into mesorectum (arrow), N0 with equivocal EMVI. Disease does not threaten CRM (i.e. all disease is >1mm away from the mesorectal fascia or levator-sphincter complex). No distant metastases on CT scan of thorax, abdomen and pelvis.



Case 2: 65 year old female, WHO PS=0, histologically confirmed adenocarcinoma of the mid and low rectum. MRI pelvis shows primary tumour is 5cm in sup-inf dimension and T3b, **N2** (two of the involved lymph nodes are indicated by arrows) and EMVI negative. Disease does not threaten CRM (i.e. all disease including lymph nodes is >1mm away from the mesorectal fascia or levator-sphincter complex). No distant metastases on CT scan of thorax, abdomen and pelvis.



Case 3: 58 year old male, WHO PS=0, histologically confirmed adenocarcinoma of the mid and upper rectum. MRI pelvis shows primary tumour is 6cm sup-inf dimension and T3b , N0 with **definite EMVI present** (arrow). Disease is located mainly posterolaterally and does not threaten CRM (i.e. all disease including EMVI is >1mm away from the mesorectal fascia or levator-sphincter complex). No distant metastases on CT scan of thorax, abdomen and pelvis.