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Timing of surgery following neoadjuvant chemoradiotherapy in locally advanced rectal cancer – A comparison of magnetic resonance imaging at two time points and histopathological responses

M.A. West [a,b,*], B.D. Dimitrov [c], H.E. Moyses [d,e], G.J. Kemp [f], L. Loughney [b,g,h], D. White [i], M.P.W. Grocott [b,g,h], S. Jack [b,g,h], G. Brown [j]

[a] *Academic Unit of Cancer Sciences, Faculty of Medicine, University of Southampton, Southampton, United Kingdom*

[b] *Integrative Physiology and Critical Illness Group, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, University Road, Southampton, United Kingdom*

[c] *Primary Care and Population Sciences, University of Southampton, Southampton, United Kingdom*

[d] *National Institute for Health Research, Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, United Kingdom*

[e] *National Institute for Health Research, Southampton Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, United Kingdom*

[f] *Department of Musculoskeletal Biology, Faculty of Health and Life Sciences, University of Liverpool, Liverpool, United Kingdom*

[g] *Critical Care Research Area, Southampton NIHR Respiratory Biomedical Research Unit, Southampton, United Kingdom*

[h] *Anaesthesia and Critical Care Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom*

[i] *Department of Radiology, Aintree University Hospital NHS Foundation Trust, Liverpool, United Kingdom*

[j] *Department of Radiology, The Royal Marsden NHS Foundation Trust, London, United Kingdom*

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Abstract

Purpose: There is wide inter-institutional variation in the interval between neoadjuvant chemoradiotherapy (NACRT) and surgery for locally advanced rectal cancer. We aimed to assess the association of magnetic resonance imaging (MRI) at 9 and 14 weeks post-NACRT; T-staging (ymrT) and post-NACRT tumour regression grading (ymrTRG) with histopathological outcomes; histopathological T-stage (ypT) and histopathological tumour regression grading (ypTRG) in order to inform decision-making about timing of surgery.

Patients and methods: We prospectively studied 35 consecutive patients (26 males) with MRI-defined resection margin threatened rectal cancer who had completed standardized NACRT. Patients underwent a MRI at Weeks 9 and 14 post-NACRT, and surgery at Week 15. Two readers independently assessed MRIs for ymrT, ymrTRG and volume change. ymrT and ymrTRG were analysed against histopathological ypT and ypTRG as predictors by logistic regression modelling and receiver operating characteristic (ROC) curve analyses.

Results: Thirty-five patients were recruited. Inter-observer agreement was good for all MR variables (Kappa > 0.61). Considering ypT as an outcome variable, a stronger association of favourable ymrTRG and volume change at Week 14 compared to Week 9 was found (ymrTRG – $p = 0.064$ vs. $p = 0.010$; Volume change – $p = 0.062$ vs. $p = 0.007$). Similarly, considering ypTRG as an outcome variable, a greater association of favourable ymrTRG and volume change at Week 14 compared to Week 9 was found (ymrTRG – $p = 0.005$ vs. $p = 0.042$; Volume change – $p = 0.004$ vs. 0.055).

* Corresponding author. Academic Unit of Cancer Sciences, Faculty of Medicine, University Surgery, University Hospital Southampton, Tremona Road, Southampton, United Kingdom. Tel.: +44 02381205308.

E-mail addresses: m.west@soton.ac.uk (M.A. West), b.dimitrov@soton.ac.uk (B.D. Dimitrov), h.e.moyses@soton.ac.uk (H.E. Moyses), g.j.kemp@liverpool.ac.uk (G.J. Kemp), l.loughney@gmail.com (L. Loughney), david.white@aintree.nhs.uk (D. White), mike.grocott@soton.ac.uk (M.P.W. Grocott), s.jack@soton.ac.uk (S. Jack), gina.brown@rmh.nhs.uk (G. Brown).

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Conclusion: Following NACRT, greater tumour down-staging and volume reduction was observed at Week 14. Timing of surgery, in relation to NACRT, merits further investigation.

Trial Registration Number: NCT01325909

Keywords: Magnetic resonance imaging; Surgery; Rectal cancer; Tumour regression; Time for surgery; Neoadjuvant chemoradiotherapy

Introduction

In the UK colorectal cancer is the third commonest cause of cancer death[1,2] and ~5000 patients underwent surgery for rectal cancer (71% aged > 65 years) during 2014. In 25% of these patients, major resection was preceded by neoadjuvant chemoradiotherapy (NACRT),[3] with the aim of controlling local disease and achieving tumour downsizing and negative resection margins, with marginal gains in overall survival.[4–8]

Although there is not universal agreement, NACRT is now generally considered for T3c+, and tumours that appear to invade or are in close proximity to the mesorectal fascia on preoperative imaging because of the decreased likelihood of achieving a tumour-free circumferential resection margin with upfront surgery alone. The selection of appropriate patients for neoadjuvant chemoradiotherapy rather than surgery is heavily dependent on accurate preoperative locoregional staging of the depth of transmural penetration, extramural venous invasion, the presence or absence of suspicious perirectal nodes outside of the mesorectal package, and the likely status of the circumferential resection margin. Locoregional tumour staging is mainly accomplished through physical examination, endoscopy, computed tomography (CT) scans, magnetic resonance imaging (MRI), and transrectal ultrasound (TRUS). High-resolution pelvic magnetic resonance imaging (MRI) is now the gold-standard in preoperative rectal cancer staging in many UK institutions [9]. In our institution, the decision to administer NACRT is based on identifying MRI-defined circumferential resection margin (CRM) threatened cancers.

Histopathologists grade tumour response in three ways: firstly assessment of the status of the CRM, secondly the depth of tumour spread and nodal status (ypT and ypN stage), and thirdly by evaluating tumour regression grade (ypTRG).[9,10] A number of studies have shown that both ypT and ypN stage are independent predictors of outcome, and several retrospective studies report a link between outcome and histopathology assessment of final stage or tumour regression after NACRT.[11,12] Accurate preoperative assessment of response to therapy may permit the clinical teams to modify definitive treatment.[13] A number of different methods have been proposed for assessing response of rectal cancer to NACRT on MRI. These include post-treatment T staging (ymrT), volume reduction between baseline and post-treatment,[14] modified Response Evaluation Criteria in Solid Tumors (RECIST) measurement[15,16] and the use of multi-parametric MRI sequences (diffusion-weighted and dynamic contrast imaging).[17,18] In addition to these assessment criteria, the MERCURY study group has developed an MRI-based tumour regression grading (ymrTRG) system by applying the principles of histopathology ypTRG[19,20] and showed that MRI assessment of ypTRG following preoperative therapy predicted survival.[19] It has been suggested that there may be benefits in prolonging the interval between end of NACRT and surgery beyond the common 6–8 weeks,[21–23] but evidence is limited.

The aim of this study was to assess MRI-defined *favourable* versus *unfavourable* responders (ymrT, ymrTRG and change in volume) at two time-points post-NACRT and to compare these evaluations with histopathological ypT and ypTRG, in an attempt to inform decisions about optimal timing of surgery with respect to NACRT. We also explored the level of interobserver agreements between central and local MR reviewers for ymrT, mrTRG and volume change at both time points.

Patients and methods

Patients and study design

This prospective pilot trial was performed as a nested sub-study within a larger trial[24] approved by the North West – Liverpool East Research and Ethics Committee (11/H1002/12) and registered with ClinicalTrials.gov (NCT01325909). Written informed consent was obtained from all patients. We recruited consecutive patients between August 2012 and August 2014 referred to the colorectal multi-disciplinary team (MDT), age ≥18 years, with locally advanced (circumferential resection margin threatened – defined as tumour within 2 mm of the mesorectal fascia or if any T3/4 tumour was arising at <5 cm from the anal verge) resectable rectal cancer, scheduled for standardized NACRT on the basis of tumour, node, metastasis (TNM) classification >T2/N+ with no distant metastasis[25] and WHO Performance Status < 2.[26] Exclusion criteria were: inability to give informed consent, non-resectable disease, and patients who declined surgery or NACRT, or who received non-standard NACRT.

All patients underwent TNM staging involving flexible sigmoidoscopy to obtain tissue for histological diagnosis, completion colonoscopy, chest, abdomen and pelvis