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Surgical Timing After chemoRadiotherapy for Rectal Cancer, Analysis of Technique (STARRCAT): Results of a Feasibility Multi-Centre Randomized Controlled Trial

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ABSTRACT

Background and Objectives: The optimal time of rectal resection after long-course chemoradiotherapy (CRT) remains unclear. A feasibility study was undertaken for a multi-centre randomized controlled trial evaluating the impact of the interval after chemoradiotherapy upon technical complexity of surgery.

Methods: Patients with rectal cancer were randomised to either six-weeks or 12-weeks interval between CRT and surgery between June 2012 and May 2014 (ISRCTN registration number: 88843062). For blinded technical complexity assessment the Observational Clinical Human Reliability Analysis (OCHRA) technique was used to quantify technical errors enacted within video recordings of operations. Other measured outcomes included resection completeness, specimen quality, radiological down-staging, tumour cell density down-staging, and surgeon-reported technical complexity.

Results: Thirty-one patients were enrolled: 15 were randomized to six-weeks and 16 to 12-weeks across seven centres. Fewer eligible patients were identified than had been predicted. Of 23 patients who underwent resection, mean 12·3 errors were observed per case at six-weeks vs. 10·7 at 12-weeks (p=0·401). Other measured outcomes were similar between groups.

Conclusion: The feasibility of measurement of operative performance of rectal cancer surgery as an endpoint was confirmed in this exploratory study. Recruitment of sufficient numbers of patients represented a challenge, and a proportion of patients did not proceed to resection surgery. These results suggest that interval after CRT may not substantially impact upon surgical technical performance.

Key Words: Feasibility, Rectal Cancer, Chemoradiotherapy, Technical Performance

INTRODUCTION

Chemoradiotherapy (CRT) is used selectively in the United Kingdom for locally-advanced rectal cancer prior to surgery in order to reduce the risk of circumferential resection margin (CRM) involvement and subsequent local recurrence. Following completion of CRT, surgery is performed after an interval to allow time for tumour shrinkage; however, the optimal interval length remains unclear. The only published randomized controlled trial (RCT) investigating this question found greater down-staging with a six to eight week interval compared to an interval of less than two weeks [1]. A number of published observational studies have reported greater down-staging with intervals longer than six to eight weeks, although the results of other observational series are conflicting [2]. Recently there has been a trend amongst some teams towards operating after longer intervals of around 12 weeks, aiming to facilitate further tumour down-staging or to enable more precise surgery by allowing radiation-induced tissue inflammation and oedema to settle. A definitive large RCT is indicated to generate evidence to support clinicians' decisions about when to operate following CRT, however a feasibility study is required first to assess recruitment.

Interest has grown recently in using objective assessment methodologies to evaluate technical performance of surgery. The Objective Clinical Human Reliability Assessment (OCHRA) technique has been successfully applied to evaluate surgical technical performance at the specialist level [3,4]. This technique involves defining errors that could occur within a procedure and then observing an operation to identify errors which are enacted. This technique could provide a quantitative description of the impact of an intervention upon the technical complexity of the surgery.

STARRCAT" (Surgical Timing After chemoRadiotherapy for Rectal Cancer, Analysis of Technique) was a feasibility study with the aim of paving the way for a larger RCT by (a) testing the feasibility of trial processes, recruitment and acceptability to patients; and (b) assessing the immediate impact of the timing of surgery the interval of six vs. 12 weeks on the putative mediating variable of surgical technical complexity.

METHODS

Participants

This was a RCT with 1:1 randomization to undergo resection after an interval of either six-weeks or 12-weeks following the last fraction of CRT with intention to treat analysis. Surgery was to be scheduled within ten days of this allocated time point. These time points were chosen as they represent intervals that are both widely used today in UK centres.

The study was approved by the South West England (Exeter) Research Ethics Committee (reference 12/SW/0112) and locally at recruiting centres. Patient representatives were consulted during trial design and protocol development, and were active members of the study management group and steering committee.

Inclusion & Exclusion Criteria

Eligible patients were aged 18 years or above, had an American Society of Anaesthesiologists (ASA) grade of I, II, or III, had a histopathological-confirmed diagnosis of adenocarcinoma requiring pre-operative "long-course" CRT prior to resection with curative intent. Patients were excluded with a background of inflammatory bowel disease, metastatic disease, contraindications to MRI, or who had previous pelvic radiotherapy.

Consent, Randomization and Blinding

Decisions about indications for CRT were made at participating sites' local colorectal cancer multidisciplinary team (MDT) meetings. Written informed consent was obtained prior to randomization and commencing CRT.

The randomization schedule was prepared by the trial statistician using a computer-generated list of pseudorandom numbers and was held securely at a central research office, maintaining allocation concealment.

It was not feasible to blind the patient, surgeon or research nurse due to the nature of the intervention being investigated. However, outcome assessment of operation video recordings, resection specimen

photographs and MRI scans were performed by blinded investigators. Videos were de-identified by an administrator who allocated each case a randomly generated numeric code.

Sample Size

This feasibility study was intended to aid the power calculation for a future large study, given the limited published evidence on which to base sample size. A target recruitment of fifty patients was set for the two year recruitment period based upon participating sites' estimates of eligible patient numbers.

Study Procedures

All patients underwent baseline MRI scan of the pelvis and computer tomography (CT) scan of the chest, abdomen and pelvis prior to commencing CRT. Patients underwent a "long-course" of CRT according to local cancer network protocol, consisting of 25 fractions of 1·8Gy radiotherapy. Concurrent chemotherapy consisted of either Capecitabine or 5-Flurouracil (5-FU).

All patients had a pelvic MRI scan to evaluate response to CRT, performed approximately seven days prior to the scheduled date of their operation, and CT scan of the chest, abdomen and pelvis to evaluate for development of metastatic disease. Patients in the 12-week arm of the trial also underwent an additional "interval" MRI scan at approximately six weeks following completion of CRT.

Surgery was performed or directly supervised by consultant colorectal surgeons using either a laparoscopic or open approach. Surgeons who chose to perform laparoscopic resection had each previously performed more than fifty laparoscopic rectal cancer resection procedures and all undertake regular audit of their practice. The operation being undertaken (APE or sphincter-preserving) was also at the discretion of the operating surgeon. Post-operative care was carried out according to local unit practice. Participating sites had established Enhanced Recovery After Surgery (ERAS) programs that guided post-operative care and discharge planning.

Feasibility and Acceptability to Patients

The principal aim of this study was to assess the feasibility of conducting a future large RCT. This study therefore included all trial processes and outcome measures being considered for use in the definitive trial. Feasibility was assessed with specific focus on recruitment to time, completeness of data-capture, and acceptability of the study to patients and clinicians.

Interviews were conducted to explore patients' experience of participating in the study. These took place at around eight weeks after surgery with 14 patients, representing all recruiting sites and patients from both arms of the trial. Interviews were recorded and transcribed verbatim by an administrator for analysis by the research fellow.

Outcome Measures

Evaluation of technical errors

To evaluate the impact of timing of surgery upon technical performance, operations were video recorded and evaluated using the OCHRA technique [3,6,7]. For laparoscopic surgery, the operation was recorded directly from standard laparoscopic theatre equipment using a Medicapture 300 HD recorder (Medicapture Inc. Philadelphia, USA). For open surgery procedures were recorded using a 10mm diameter sterile 30-degree lens laparoscope, held by a research fellow wearing a sterile gown and gloves.

Rectal cancer resection procedures were divided into tasks to facilitate comparison between cases (Colon mobilization & pedicle division; Splenic flexure mobilization (if performed); Mesorectal dissection; Division of rectum & anastomosis / Perineal dissection). For laparoscopic surgery, a consensus document describing the procedural steps of the operation formed the basis of a task analysis to facilitate evaluation of surgery [8]. Interviews with experts together with previous descriptions of OCHRA were used to generate a checklist of potential errors.

Identified technical performance errors were coded and logged by a single research fellow assessor (a colorectal registrar with experience in performing these procedures). Preliminary work was undertaken to train the research fellow in assessment of rectal cancer surgery which also confirmed the reliability and validity of this technique [9]. Errors were defined as *"an action (or omission) that resulted in a negative consequence (e.g. bleeding, injury to mesorectum or hypogastric nerves) or increased the operating time of the procedure through necessitating corrective action."* Total error frequencies per case were compared between the two arms of the study.

R0 Resection Status

Tumour located one millimetre or less from a resection margin was considered "involved" (R1 resection) whether this was by primary spread, discontinuous spread, intravascular, perineural or intra-nodal [10].

MRI Assessment of Down-staging

MRI scans were evaluated for all patients by a single blinded radiologist. TNM stage, tumour size and height, and MRI tumour regression grade (mrTRG) were reported [11].

Histopathology Assessment

Photographs of the mesorectal surface of the whole resected specimen and serial cross-sectional slices were assessed by a blinded histopathologist using a standardized three-point scale [12]. Rates of pathological complete response, tumour regression grade, and CRM involvement were reported according to the Royal College of Pathologists guidelines for reporting colorectal cancer [13].

Tumour cell density (TCD) was assessed in both the baseline biopsy (pre-treatment) and resected specimen (post-treatment). The hematoxylin and eosin stained glass slide with the greatest amount of residual tumour was selected, and between 285 and 315 data-points analysed within each specimen. For each point, the tissue component was described: TCD was expressed as the percentage of tumour points out of all the informative points within the area of interest [14]. Within each specimen, TCD was calculated for the whole tumour area and for a $9mm^2$ area of greatest tumour density.

Surgeon-reported Complexity of Surgery

Complexity of surgery was assessed using a structured questionnaire that was completed by the surgeon following the operation using 100mm Visual Analogue Scales (VAS). .

Clinical Outcomes

Patients were prospectively followed-up for 30 days after surgery. Morbidity during the index admission and at 30-days was categorized using the Clavien-Dindo classification. [15]. Rates of the specific complications of re-operation, re-admission, anastomotic leak, and perineal wound infection/dehiscence were also collected.

Statistical Analysis

As this was a feasibility study, the analyses performed were intended to be descriptive in nature to inform a definitive study. The only outcome formally compared between groups was the number of errors identified through objective analysis of video recordings of operations. Normality of distribution for this data was tested with the Shapiro-Wilk test [16] and Q-Q plots. Two-tailed parametric testing was used for the error frequency comparison between the trial arms. To aid interpretation, a p value of less than 0.05 was considered to indicate statistical significance. Other outcome results are presented as mean or median values with standard deviation or inter-quartile range (IQR) and/or range in parentheses as appropriate, or as overall frequencies. Missing data items are presented as a proportion of total data items to allow assessment of the success of the study data capture systems. Data were analysed using Statistical Package for Social Sciences software Version 22 (IBM Inc. Armonk, USA).

RESULTS

Feasibility

Recruitment

Thirty-one patients were recruited from seven sites between 11th June 2012 and 30th May 2014. Recruitment challenges were experienced including delays in opening sites for recruitment, and

lower-than-estimated numbers of eligible patients identified for the study **[Figure 1]**. The proportion of rectal cancer presentations reported as eligible for the study varied between individual sites from 6% to 28%.

Fifteen patients were randomized to the six-week arm, and 16 were randomized to a 12-week interval **[Figure 1]**. Median age was 67 years in the six-week arm and 68 years in the 12-week arm. Baseline patient and tumour characteristics for the two groups were broadly similar **[Table 1]**.

Twenty five patients underwent surgery at their recruiting centre within the trial, although one from each trial arm had un-resectable disease at the time of surgery. Six patients did not undergo surgery due to development of metastatic disease (n=3), involved margins on the pre-operative MRI necessitating referral to a tertiary centre for exenteration (n=2), or patient choice after apparent clinical complete response to CRT (n=1). Four patients (16%; two from each arm) had their surgery scheduled more than 10 days from the allocated time period.

Acceptability

Interviewed patients from this study reported favourably on their participation and confirmed the acceptability of having their operation video recorded for analysis. Reported reasons for participating in the study were broadly divided into two main themes: helping future patients; and improving the patient's own care. Six of the interviewed patients reported a personal preference for one arm of the trial: mostly the six-week arm, citing a desire to have the cancer removed from them as soon as possible.

Outcome Measures

Technical Complexity Evaluation

A total of 262 individual execution errors were identified during the assessment of 88 hours of video footage. Total error frequencies were approximately normally distributed in both trial arms with mean 12·3 (sd=4·1) errors per case at six-weeks versus 10·7 (sd=4·9) errors per case at 12-weeks. The

difference between arms was 1.6 errors per case (95% confidence interval -2.3 to 5.5), with no observed statistical significance difference in the total error rate between 6 and 12 weeks arms (p=0·40).

The most common error mechanisms observed were *"dissection in wrong tissue plane,"* (n=66) *"too much blunt force applied to tissue"* (n=45) and "dissection performed *in wrong direction"* (n=34). Two hundred and thirty one errors had directly observed consequences. The most common consequences were *"bleeding"* (n=91), *"mesorectal injury into fat"* (n=57), and *"mesorectal fascia injury"* (n=49).

Where a laparoscopic technique was used, the entire procedure could be satisfactorily seen on the video and analysed using OCHRA, with the exception of the perineal dissection during APE, which was performed by an open technique in all cases. For open surgery cases, a median of 8·6% of the procedure time (range 1·9% to 15·7%) could not be evaluated due to poor views of the operating field.

R0 Resection Status

One patient in the study (4%) from the 12-week arm was found to have an involved CRM. All other patients had CRM >1mm **[Table 4]**.

MRI Assessment of Down-staging

Evaluation of down-staging between baseline and "pre-op" MRI scans are presented in **Table 2**. Six patients from the six-week arm (40%) and seven patients from the 12-week arm (50%) had down-staging of their primary tumour by at least one complete mrT stage. Lymph node down-staging was observed for 10 patients in the six-week arm (67%) and nine patients in the 12-week arm (64%). No patient had an increase in mrT stage between baseline and pre-operative scans.

Histopathology Assessment

Seven of ten patients (70%) from the 6-week arm and eight of 13 (62%) from the 12-week arm were judged to have been resected in the mesorectal fascia plane (intact mesorectum) **[Table 4]**. Median TCD for the whole tumour area in the resected specimen was 0·3% (IQR 0-0·7) for the six-week arm

and 4·3% (IQR 0·7-8·8) for the 12-week arm**[Figure 2]**. None of the five patients found to have a complete pathological response were reported as having a ymrT0 tumour on their pre-operative MRI scan.

Surgeon-reported Complexity of Surgery

Median VAS score for overall complexity of the procedure was 66mm (IQR 18-74) at six weeks versus 53mm (IQR 34-75) at 12 weeks.

Clinical Outcomes

No mortalities occurred within 30-days of surgery during the study. Five patients (22%) required admission to hospital prior to surgery due to side-effects of CRT. Operative and post-operative clinical outcomes are summarized in **Table 3**. Median length of hospital stay was 8·5 days [range 1-15 days] for the six-week arm and nine days [range 4-18 days] for the 12-week arm.

DISCUSSION

This study has shown that a definitive RCT comparing a six-week versus 12-week interval between CRT and surgery for locally-advanced rectal cancer appears safe, and feasible in terms of trial processes, data collection and analysis. The methodology of applying OCHRA into objective evaluation of the performance of rectal cancer surgery was also shown to be feasible. However recruitment challenges were encountered in this feasibility study, and a definitive study would likely require many sites or a prolonged recruitment period.

Nevertheless, the results from this feasibility study suggest that the technical complexity of surgery may not be substantially affected by the interval following CRT. No significant difference was observed between six-week or 12-week arms in the frequency of technical errors identified using the OCHRA technique, although the low recruitment meant any comparison would be under-powered. Video recording and technical performance analysis using OCHRA have previously been used in clinical practice and training environments [7,17-20]. We have shown that it is possible to expand

such a methodology and to co-ordinate the recording of operations within a multi-centre trial. Using error analysis as an outcome measure allowed the investigation of technical performance within this feasibility study using a small sample size. The substantial time required to evaluate operative video recordings may limit the application of this technique in larger studies.

Some studies have reported increased rates of tumour down-staging when a longer interval between CRT and surgery is employed [21-23]. Other studies do not, however, support these findings [2], and a data from definitive large RCTs are therefore awaited with interest [23-25].

Given that down-staging following CRT is mediated by cell death in response to radiation-induced DNA damage, it seems logical that a longer interval might facilitate greater down-staging. A prolonged delay could however also be associated with tumour regrowth. Although caution is needed when interpreting results from small studies such as ours, the higher TCD observed at 12-weeks might represent small areas of early tumour re-growth. Additionally, in clinical practice, accurate pre-operative identification of response to CRT can be difficult [24].

Feasibility studies are becoming increasingly recognized as an important step in the development of high-quality trials in surgery [26-28]. They can help to plan future definitive trials through assessment of recruitment and retention rates, and the success of data collection mechanisms. Patient and surgeon equipoise are major determinants of the success of recruitment into surgical RCTs [29], and preferences were observed amongst patients by the qualitative research in this study. These challenges with recruitment and pre-surgery attrition would need to be considered when estimating sample sizes, should a larger study be undertaken.

This feasibility study does have a number of limitations, and caution is needed when interpreting the data evaluating the impact of the interval upon technical complexity. Only 31 patients were recruited in the allocated time period. However, as this was a feasibility study the rate of patient eligibility and recruitment was itself an important end-point which was being tested. The reliability and validity of using the OCHRA technique for assessment of surgical technical performance may be questioned,

however the methodology was previously tested, confirming its validity for assessing rectal cancer resection and demonstrating excellent test-retest reliability [5,9].

Given the experiences and outcomes of this feasibility study, and also the large RCTs investigating the oncological impact of the interval to surgery that have been conducted during the time of our study, [23-25] it does not seem feasible to proceed to a larger RCT investigating the impact of the interval after CRT upon technical performance of surgery.

In conclusion, objective video assessment of technical performance of surgery can be used to evaluate the impact of an intervention upon the technical complexity of surgery. The results of this exploratory study suggest that the interval after CRT may not substantially impact upon surgical technical performance.

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AUTHORS' CONTRIBUTIONS

NF, GH, SF, PE, HR, BWY and EC conceived and designed the study. JF analyzed the operation videos. EC analyzed the pathology specimens and reports. HR analyzed the MRI scans. NW performed the TCD analysis. JF, PE and NK performed the data analysis. JF and NF drafted the manuscript. All authors contributed to the interpretation of the data, editing of the manuscript and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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	6 week	Missing Data	12 week	Missing Data
Total patients	15		16	
Female : Male	6 : 9	0/15	2 : 14	0/16
Age (years, median [IQR])	67 [65-73]	0/15	68 [57-73]	0/16
Body Mass Index (kg/m^2, median [IQR])	27.6 [26·2-30·7]	1/15	25.9 [22·4-28·25.8]	0/16
Smoking status: Current Previous Never	 3 7 3	2/15	 3 8 5	0/16
Performance Status: 0 1 2	 7 5 1	2/15	 14 2 0	0/16
POSSUM predicted morbidity (median [IQR])	47% [41-57%]	4/15	47% [49-55%]	0/16
POSSUM predicted mortality (median [IQR])	10% [8-13%]	4/15	10% [8-12%]	0/16
P-POSSUM predicted mortality (median [IQR])	2% [2-4%]	4/15	2% [2-3%]	0/16
Diabetes mellitus	1	2/15	1	0/16
Previous abdominal surgery	4	2/15	5	0/16
Antiplatelet therapy	3	2/15	1	0/16
Steroid therapy	0	2/15	2	0/16
Metastatic disease confirmed at baseline	0	0/15	0	0/16
Tumour height (MRI) from anal verge (mm, median [IQR])	50mm [35-60mm]	0/15	49mm [29-81mm]	0/16
Defunctioning stoma prior to CRT	1	0/15	2	0/16

Table 1 - Baseline demographic and clinical characteristics of participants.
MRI = magnetic resonance imaging, CRT = chemoradiotherapy, CRM= circumferential resection margin.

	6 week	Missing Data	12 week	Missing Data
Baseline MRI T stage				
T1	0	0/15	0	0/16
T2	0		0	
T3	13		15	
T4	2		1	
Baseline N stage				
N0	5	0/15	2	0/16
N1	6		11	
N2	4		3	
Baseline CRM status				
>1mm	5	0/15	8	0/16
<1mm	10		8	
mrTRG				
mrTRG1	0	0/15	1	0/16
mrTRG2	6		6	
mrTRG3	4		5	
mrTRG4	5		3	
mrTRG5	0		1	
Pre-op T stage				
T0	0	0/15	1	2/16
T1	0		0	
T2	5		6	
T3	9		6	
T4	1		1	
T down-staged	6	0/15	7	2/16
T up-staged	0	0/15	0	2/16
Pre-op N stage				
N0	10	0/15	11	2/16
N1	5		1	
N2	0		2	
N down-staged	10	0/15	9	2/16
N up-staged	2	0/15	0	2/16
Pre-op CRM status				
>1mm	8	0/15	9	2/16
<1mm	7		5	

Table 2 – Radiological staging and down-staging of tumours on MRI scans at baseline and on *"pre-op"* scan in week prior to planned surgery date.

CRM= circumferential resection margin, mrTRG = MRI tumour regression grade, up/down-staged = *increase/decrease in T/N stage between "baseline" and "pre-op" scans*

	6 week	Missing Data	12 week	Missing Data
Operation performed APE Ant Resection+anastomosis Sphincter-pres+end stoma	 4 5 1	0/10	 7 4 2	0/13
Approach Laparoscopic Open Lap converted to open	 5 4 1	0/10	 5 5 2	0/13
ASA Grade I II III	 1 5 4	0/10	 1 12 0	0/13
Total Operating Time (minutes, median [IQR])	305min [269-333min]	0/10	350 min [300-425min]	0/13
Blood Loss: <100ml 100-500ml 501-1000ml >1000ml	 3 2 2 3	0/10	 2 6 4 1	0/13
Length of stay (days, median [IQR])	8.5 days [5·5-8·5 days]	0/10	9 days [6-12 days]	0/13
Re-admission	3	0/10	2	0/13
Re-operation	0	0/10	1	0/13
Anastomotic dehiscence	1 (of 5 Ant. resection)	0/5	0 (of 4 Ant. resection)	0/4
Perineal dehiscence/infection	3 (of 4 APE)	0/4	3 (of 7 APE)	0/7
Highest Clavien-Dindo grade of complications at discharge 0 I II III IV V	 5 0 4 1 0 0	0/10	 5 0 7 1 0 0	0/13
Highest Clavien-Dindo grade of complications at 30-days 0 I II III IV V	 2 1 5 2 0 0	0/10	 4 1 7 1 0 0	0/13

Table 3 – Operative and post-operative outcomes for patients who underwent tumour resection.
APE= Abdominoperineal excision.

	6 week	Missing Data	12 week	Missing Data
Resection margin status R0 R1 R2	 10 0 0	0/10	 12 1 0	0/13
CRM distance >1mm/CR <1mm / Involved	 10 0	0/10	 12 1	0/13
Overall mesorectal quality muscularis propria mesorectal fat mesorectal fascia	 1 1 7	1/10	 2 2 8	1/13
Tumour Regression 0 (No marked regression) 1 (Minimal residual tumour) 2 (No residual tumour/ mucus lakes only)	 1 6 3	0/10	 6 3 3	1/13
Pathological complete response (ypT0 and ypN0)	3	0/10	2	0/13
ypT stage ypT4 ypT3 ypT2 ypT1 ypT0	 1 1 4 1 3	0/10	 1 6 3 1 2	0/13
ypN stage ypN2 ypN1 ypN0	 1 2 7	0/10	 2 2 9	0/13
EMVI identified	1	1/10	1	1/13

Table 4 – Pathology outcomes for patients who underwent tumour resection.
CRM = circumferential resection margin; CR = complete response; EMVI = extramural venous invasion

FIGURE LEGENDS

Figure 1 - CONSORT 2010 Flow Diagram for the STARRCAT feasibility RCT

Figure 2 – Percentage Tumour Cell Density identified on slides from the baseline biopsy and resection specimen (for resection specimen, the percentage TCD for both the whole tumour area and a $9mm^2$ area of apparent greatest tumour density are reported)