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Clinical Paper

The Effect of Interval From Completion of Short-Course Radiotherapy to Surgery on the Post-Operative Morbidity and Mortality of Patients with Rectal Cancer.

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ABSTRACT

Aim: Surgery is the mainstay of treatment for invasive rectal cancer. Advances in surgical technique and radiotherapy over the past few decades have resulted in improved local control and survival.[1-3] Some concern remains regarding the morbidity associated with performing surgery within a short window following radiotherapy. The current study assessed whether the interval between short-course radiotherapy and surgery influences all cause post-operative morbidity and mortality.

Methods: All patients who had undergone short-course radiotherapy for rectal cancer within the Belfast Health and Social Care Trust from 2005 to 2014 held on a prospective database were included (n=102). A retrospective review of patients' clinical records was performed and a comparison made of patients who had undergone surgery less than 4 days with those 4 or more days following completion of radiotherapy. Baseline patient and tumour characteristics, post-operative complications and readmission rates were compared. Statistical analysis was performed using SPSS ®, Version 22 (SPSS, Inc, Chicago, Illinois, USA).

Results: There was no significant difference in mortality or overall post-operative complications between groups, however, less serious complications were reduced in patients undergoing surgery less than 4 days following radiotherapy. Perineal wound complications were significantly more common in patients who had undergone surgery 4 or more days following radiotherapy.

Conclusion: Our results support the existing data that post-operative complications may be more common with increasing interval to surgery from completion of radiotherapy. Perineal wound morbidity appears significantly more common in patients who undergo surgery 4 or more days following short-course radiotherapy. A larger study to look particularly at perineal wound morbidity and interval from completion of radiotherapy is warranted.

INTRODUCTION

The two major developments in the treatment of rectal cancer have been the introduction of total mesorectal excision (TME) and the use of radiotherapy which improved local control and overall survival.[1,4] Prior to TME and radiotherapy, local recurrence was reported in 15-45% of patients with rectal cancers.[5-7] Since the widespread establishment of TME as the gold standard operative technique for rectal cancer, local recurrence rates have dropped to 5-10%.[8,9]

Even before the establishment of TME, preoperative radiotherapy has been shown to reduce local pelvic recurrence and improve survival in the Stockholm I and II trials.[10,11] Results from the Swedish Rectal Cancer Trial then demonstrated that short-course pre-operative radiotherapy reduces local recurrence by more than 50%.[12] Current standard practice for short-course pre-operative radiotherapy (SCRT) involves a standard radiation dose of 25Gy in 5Gy fractions, given over five consecutive weekdays. Surgery is then performed after 3-10 days.

The short interval between SCRT and surgery means that SCRT does not result in any significant tumour shrinkage prior to resection. The radiotherapy in general is well-tolerated although there has been reported post-operative morbidity and mortality.[13-15] Fokstuen and colleagues[16] reported that following short-course radiotherapy, an abnormal leucocyte response following surgery predisposes to an increase risk of sepsis and hence post-operative morbidity. A longer than recommended radiotherapy-surgery interval appeared to be associated with increased post-operative mortality.

The timing of surgery remains controversial. Van de Broek and co-workers[17] suggested that the postoperative mortality from non-cancer related causes is higher with longer intervals to surgery (>3days) in certain subsets of patients following completion of radiotherapy. One might hypothesise that

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post-operative morbidity increases with the interval to surgery following short fractionation radiotherapy. Different intervals from completion of radiotherapy to surgery are seen in all colorectal units due to logistics of theatre availability throughout the working week and individual consultants' job plans.

The aim of this study was to assess whether the interval between SCRT and surgery influences all cause postoperative morbidity and mortality.

METHODS

The colorectal surgery database is comprised of prospectively collated data relating to colorectal cancer resections performed within the Belfast Health and Social Care Trust. 102 patients who had undergone SCRT for rectal cancer from 2005 to 2014 were identified from the database and included in the study. Patients all underwent appropriate staging investigations and were discussed at the local Multidisciplinary Meeting (MDM) prior to commencement of short-course radiotherapy. Staging investigations were computed tomography (CT) of chest, abdomen and pelvis and pelvic MRI. Two patients could not have an MRI performed due to the presence of a cardiac pacemaker and therefore underwent endoscopic ultrasound.

Patients were all assessed by a colorectal oncologist for radiotherapy planning. A standard radiation dose of 25Gy in 5Gy fractions, given over five consecutive weekdays was used. Surgery was subsequently performed by one of 7 surgeons trained in TME after a delay of 3 to 10 days.

A retrospective review of patients' medical records was performed. A short trial of data collection was conducted to compare the data that could be gleaned from patients' notes (hard copy) compared to electronic sources. These were comparable and so the decision was made to use electronic data sources and only pull patients' charts if there were any data gaps. The main reason for this was difficulty in obtaining charts for the deceased patients.

Data were collected on age, gender, co-morbidities, pre-operative radiological staging (TNM), tumour height, interval to surgery, surgery performed, stoma rates, pathological staging, post-operative complications, mortality, length of stay and 6 week re-admission rates. Post-operative complications were grouped according to the Clavien-Dindo classification of surgical complications.[18] The intention was to group patients into three groups; those who had undergone surgery 0-3 days, 4-7 days and greater than seven days following completion of radiotherapy, in line with previous studies.[17] However, only two patients had undergone surgery with an interval of greater than seven days (10 days) following completion of radiotherapy and so patients were grouped into two groups; those who had undergone surgery less than 4 days and those who had undergone surgery 4 or more days following completion of radiotherapy.

Table 1

Patient and tumour characteristics for those undergoing surgery <4 days or ≥ 4 days following short-course radiotherapy

	< 4 days (n=30) n (%) or Mean±SD	**≥ 4 days** (n=65) n (%) or Mean±SD	**P Value**
Age (years)	67.1 ±8.1	63.4 ±13.0	0.184
Gender	Male 23 (76.7) Female 7 (23.3)	Male 41 (63.1) Female 24 (36.9)	0.242
ASA grade	I 9 (30.0) II 12 (40.0) III 8 (26.7) IV 1 (3.3)	I 28 (43.1) II 31 (47.7) III 6 (9.2) IV 0 (0.0)	0.048
Pre-op Dukes' stage	A 1 (3.3) B 21 (70.0) C 8 (26.7) D 0 (0.0)	A 3 (4.6) B 27 (41.5) C 33 (50.8) D 2 (3.1)	0.051
Tumour Height (cm)	5.5 ±3.1	5.8 ±2.6	0.395
Post-op Dukes' stage	A 2 (6.7) B 12 (40.0) C 14 (46.7) D 2 (6.7)	A 6 (9.2) B 19 (29.2) C 35 (56.9) D 1 (1.5) None 2 (3.1)	0.365

Table 2

Post-operative course for patients undergoing surgery <4 days or ≥ 4 days following short-course radiotherapy

	< 4 days (n=30) n (%) or Median (ICR)	**≥ 4 days** (n=65) n (%) or Median (ICR)	**P Value**
Length of stay (days)	12 (10)	14 (10)	0.535
Complications (Clavien-Dindo classification)	Overall 16 (53.3)	Overall 45 (69.2)	0.169
	I 5 (16.7)	I 7 (10.8)	0.510
	II 9 (30.0)	II 36 (55.4)	0.028
	III 7 (23.3)	III 10 (15.4)	0.394
	IV 0 (0.0)	IV 0 (0.0)	>0.999
	V 0 (0.0)	V 2 (3.1)	>0.999
Perineal wound complications	0 (0.0)	9 (26.5)	0.021
Readmission within 6 weeks	5 (16.7)	14 (21.5)	0.784

Statistical analysis of the data was performed using SPSS®Software, Version 22 (SPSS, Inc, Chicago, Illinois, USA). Categorical data were analysed using Fisher's exact test. Continuous data are represented as mean (±SD) and comparisons were made using the Mann-Whitney U-test. A P-value of less than 0.05 was considered statistically significant.

RESULTS

One hundred and two patients were identified from the colorectal database, having undergone SCRT between 2005 and 2014 within the Belfast Health and Social Care Trust. Of these, 4 patients were seen in the private sector and had all of their work-up performed privately so complete data could not be obtained. These patients were excluded. No notes were available for 2 patients and one patient never underwent surgery as a co-incidental meningioma was diagnosed during SCRT. Therefore, 95 patients were included in the analysis.

There was no significant difference in age, gender and tumour height between patients who had undergone surgery less than 4 days following completion of SCRT and those who had undergone surgery 4 or more days following completion of radiotherapy (Table 1). The ASA grade of patients who had undergone surgery less than 4 days following SCRT was higher than patients who had undergone surgery 4 or more days following completion of radiotherapy (p=0.048). The pre-operative Dukes' stage appeared to be lower in the group of patients operated on less than 4 days post radiotherapy (p=0.051). However, there was no significant difference in post-operative stage between the 2 groups.

The overall complication rate was 64.2%. There appeared to be a lower overall complication rate in those patients who had undergone surgery less than 4 days following completion of radiotherapy (53.3% vs 69.2%), however, this did not reach statistical significance (Table 2). There was a statistically significantly lower rate of grade II Clavien-Dindo complications in patients who had undergone surgery less than 4 days following SCRT (p=0.028). The rate of perineal wound complications was also significantly higher in patients who had undergone surgery 4 or more days following radiotherapy (p=0.021). There was no significant difference in mortality between the groups. Two patients who had undergone surgery 4 or more days following completion of radiotherapy died during admission. Both deaths were related to cardiorespiratory complications in patients with pre-existing cardio-respiratory dysfunction.

There was no significant difference in length of hospital stay (12 days vs 14 days) or readmission rates within 6 weeks (16.7% vs 21.5%) between the two groups. Of note, there were 4 readmissions due to perineal wound complications, each of whom had undergone surgery 4 or more days following completion of radiotherapy.

DISCUSSION

Pre-operative short-course radiotherapy is widely used in the UK and Northern Europe to reduce local recurrence rates in patients with rectal cancer, treated with TME. In this study, we investigated the effect of interval from completion of SCRT to surgery on overall post-operative morbidity and mortality.

There is a high morbidity associated with rectal surgery following SCRT. The overall morbidity was 62.1% which included any variation from the normal post-operative course. The in-hospital mortality rate was 2.1% (n=2), with both patients being operated on 4 or more days following last fraction of radiotherapy (p=0.99) and not from surgical causes. These figures are comparable with several published clinical trials. Early results from the Dutch TME trial showed a 3% in-hospital mortality. They also reported a 51% post-operative complication rate.[19] Peterson et al. analysed 657 patients from the Stockholm III Trial and found a

post-operative complication rate of 52.5% in patients who underwent short-course radiotherapy and immediate surgery (n=270).[20] In the current study we included any deviation from the normal post-operative course as a complication, for example, prolonged ileus and chest infections. It is not clear if these were included in the studies mentioned above, which may account for our slightly higher post-operative complication rate.

There was no significant difference in overall complications between patients who had undergone surgery less than 4 days following completion of SCRT and those operated on with an interval of 4 or more days (p=0.17). However, on comparing different grades of complications according to the Clavien-Dindo classification, there appeared to be fewer low grade complications in patients who had undergone surgery less than 4 days following completion of SCRT. This reached statistical significance for Clavien-Dindo grade II complications (p=0.027).

When we looked specifically at perineal complications in patients who underwent abdomino-perineal resections, we found that there was a statistically significant difference between the groups. There were no perineal complications in the 17 patients who were operated on less than 4 days following SCRT, however, 26.5% (9/34) of patients who were operated on 4 or more days following radiotherapy developed perineal complications (p=0.021). However, this study was not designed to detect differences in individual post-operative complications and the sample size is relatively small in comparison with other published studies. Therefore, this result should be interpreted with caution. A recent meta-analysis of 32 studies by Musters et al. investigating perineal wound healing after abdomino-perineal resection for rectal cancer, showed a perineal wound complication rate of 15.3% in patients who did not undergo neo-adjuvant radiotherapy.[21] In the patients who underwent neo-adjuvant radiotherapy the perineal wound complication rate rose to 30.2% after conventional surgery.

Perineal wound complications are a significant source of morbidity for patients and are often very slow to heal in the post-radiotherapy setting. Chadwick et al showed that one-half of patients' perineal wounds had not healed by three months post-operatively and one-quarter by one year.[22] In our study, 4 patients were readmitted within 6 weeks post-operatively with perineal wound complications and required negative pressure dressings.

Several theories have been proposed to account for the increased post-operative morbidity following radiotherapy for rectal cancer. The Dutch Colorectal Cancer Group suggest that there is a radiation induced increase in systemic cytokines.[23] Another theory is that bone marrow depression may result in suppression of pre-operative leucocyte counts or the leucocytosis usually seen following abdominal surgery.[20,23,24] However, this does not necessarily explain why patients who undergo surgery within 3 days of completion of SCRT have fewer complications. It may be that the radiotherapy has not reached its maximum potential to cause complication at 0-3 days post completion.

This study looked at different intervals from radiotherapy completion to surgery which were related to consultants' job plans. This inherently meant that different surgeons were being compared as well as the interval to surgery. Only 2 surgeons routinely operated on patients within 3 days of completion of radiotherapy. However, the study was conducted within a colorectal unit in which there is no significant difference between individual surgeon outcomes. The study included both laparoscopic and open surgery and we did not specifically compare this. Laparoscopic resections were however performed in both interval groups. In the data analysis, no specific complications which were attributable to a laparoscopic approach were observed.

CONCLUSION

Pre-operative radiotherapy in combination with TME has significantly reduced local recurrence rates from rectal cancer. However, its effect on long-term survival has been less impressive. Our study correlates with results from previous studies in terms of complications following SCRT. They also support the suggestion that post-operative complications are more common with increasing interval to surgery from completion of radiotherapy. This needs to be considered when scheduling patients for surgery.

In our results, there was a significant difference in the rates of perineal wound complications in patients who had undergone surgery 4 or more days following completion of radiotherapy. A larger study population in a study specifically designed to look at the differences in perineal wound complications with interval from radiotherapy is warranted.

We have no conflicts of interest to declare.

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