Original article

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Short course preoperative radiotherapy is the single most important risk factor for perineal wound complications after abdominoperineal excision of the rectum

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Abstract

Aim To determine factors associated with perineal wound complications following abdominoperineal excision of the rectum (APER) for rectal adenocarcinoma and their effects on time to healing.

Patients and methods We studied all cases of APER performed in our unit by four consultants over 7 years. Seven out of nine factors considered important in wound healing were analysed using logistic regression and a multivariate model was built to examine interactions. Wound persistence was calculated using the Kaplan–Meier method.

Results Data were available for 94 of 96 patients [male:female, 3:2, median age 72.5 (IQR: 64–78)]. Thirty-nine (41%) patients had 25 Gray, 3-portal, fractionated 5-day short course preoperative radiotherapy (SCPRT). Dukes stages were A (34%), B (26%), C (40%). Perineal wound complications occurred in 44 (47%), 16% of these requiring return to theatre. Local recurrences occurred in 13 (15%). There was no evidence to suggest that either patient gender, age, smoking status, preoperative albumin or haemoglobin level, or T stage were associated with the development of wound complications. The odds of wound complications for a patient who had SCPRT was over 10 times that for a patient who did not have preoperative radiotherapy (odds ratio 10.15, 95% CI: 3.80–27.05, $n = 94$). Seventy-four per cent of SCPRT and 96% of non-SCPRT wounds had healed by 1 year. Estimated failed wound healing rates at 30 and 90 days were 64% (95% CI: 46–78) and 48% (95% CI: 30–64) in SCPRT patients compared with 23% (95% CI: 12–35) and 9% (95% CI: 3–20) in non-SCPRT patients (log rank test $P < 0.0001$).

Conclusion Patients who have an APER are over 10 times more likely to have a perineal wound complication if they have SCPRT than not. Two-thirds of these will not have healed by 1 month, half by 3 months and over a quarter will still remain unhealed at 1 year. This has important implications for patient management decisions. Large prospective studies are needed to evaluate the effects of a selective policy for radiotherapy administered to patients requiring APER.

Keywords Radiotherapy, rectal cancer, abdominoperineal, wound

Introduction

Perineal wound complications are common after abdominoperineal excision of the rectum (APER) for rectal adenocarcimoma. These can range from minor and short lived superficial infections or haematomas to chronic, sometimes painful and debilitating dehiscences, sinuses and cavities. These consequently utilize time and resources in terms of wound management modalities and nursing time. A variety of transposition flaps have been proposed as a means of achieving rapid perineal wound healing both as a primary and delayed procedures [1–5]. These are not without their own associated morbidities and local expertise may not always be available precluding their routine widespread use. The aims of this study were to determine factors associated with perineal wound complications and to investigate if such factors had an impact on time to healing, local recurrence and overall survival.

Patients and methods

We studied all cases of APER for rectal adenocarinoma performed in our trust over the period December

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1994–February 2002 with minimum follow up of 1 year. Transabdominal total mesorectal and transperineal anal sphincter complex excision was employed in all cases using sharp dissection and monopolar diathermy. The pelvis was drained transabdominally and the perineal wound closed primarily in two layers. All patients had prophylactic Cefuroxime (750 or 1.5 mg) and Metronidazole (500 mg) preoperatively and at least two postoperative doses of each. Data on age, sex, diabetes, immunosuppressants, smoking status, preoperative haemoglobin (Hb) and albumin levels, 5-day 3 port, fractionated, 25 Gray, short course preoperative radiotherapy (SCPRT) status, other neoadjuvant therapy, histopathological tumour (pT) stage, and wound complications were recorded as were return to theatre, length of time to healing, follow up, local recurrence and overall survival. We defined wound infection as an erythematous, tender swelling of the wound or surrounding tissue with purulent discharge yielding a positive microbiological swab culture. Local recurrence was defined as the presence of disease of the same type as the original primary within the pelvis or perineum or the end stoma after curative resection. Those perineal wounds which failed were left to heal by secondary intention with daily alginate dressing by district nurse after hospital discharge. No flap advancements were performed during the period studied.

Statistical analysis

Logistic regression was used to identify factors which might be associated with wound complications. Patient gender, age, smoking status, preoperative albumin and Hb, T stage and SCPRT status were analysed. The numbers of diabetic patients (3) or those on immunosuppressants (1) in each group were considered too small for meaningful analysis. A model was built in stages using Collett's [6] scheme. Factors significant at the 10% level were retained. Interactions among variables were examined and retained if significant at the 5% level. Goodness of fit was assessed using the Hosmer–Lemeshow test. Patient survival was defined as the length of time (in months) from the date of operation to the date of death. The survival times for patients who were still alive were calculated as the length of time from the date of operation to the date of last follow up and were treated as censored observations. Time to healing was defined as the length of time (in days) from the date of operation to the date of perineal wound healing as documented in the casenotes either on the ward postoperatively or at outpatient clinic. The times for patients whose wounds had yet to heal were calculated as the length of time from the date of operation to the date of last clinical assessment and were treated as censored observations. Estimates of patient survival and wound persistence were calculated using the Kaplan–Meier method. Confidence intervals for survival at a given time point were constructed using Greenwood's formula to calculate the standard errors. When comparing survivor functions, the proportional hazards assumption was assessed graphically using log–log plots. If the proportional hazards assumption was tenable, the log-rank test was used to test the equality of the survivor functions, otherwise the Wilcoxon test was used.

Results

Data were available for 94 of 96 consecutive patients [male:female, 3:2, median age 72.5 (IQR: 64–78)]. Patient population characteristics are summarized in Table 1. Perineal wound complications occurred in 44 (47%) (Table 2), 16% of these requiring return to theatre for abscess/haematoma drainage (5), haemostasis following secondary haemorrhage (1), debridement of necrotizing fasciitis (1) and re-suturing of perineal wound (1). One patient required revision of their ischaemic stoma.

Thirty-nine (41%) patients received SCPRT in the week immediately prior to surgery and this was significantly associated with wound complications (odds ratio 10.15, 95% CI: 4.13–33.07) according to the final multivariate logistic regression model. There was no evidence to suggest a lack of model fit (Hosmer–Lemeshow test, $\chi^2_4 = 1.91$, $P = 0.75$) and no evidence to suggest that patient gender, age, smoking status, preoperative albumin or preoperative Hb or pT stage were associated with the development of wound complications. There was no evidence to suggest an association between preoperative radiotherapy and the need to return to theatre (Fisher's exact test, $P = 0.31$, $n = 94$, see Table 3). No patients had long course neoadjuvant treatment. Six had adjuvant postoperative radiotherapy in the non-SCPRT group only. Only one of these had an infected wound. No long-term complications were seen in these patients.

The median (IQR) time to perineal wound healing for the SCPRT group was 70 (14–176) days compared with 14 (14–22) days for those who did not have SCPRT. Seventy-four per cent of SCPRT compared with 96% of non-SCPRT patients' wounds had healed by 1 year. Estimated failed wound healing rates at 30 and 90 days (Table 4) were 64% (95% CI: 46–78) and 48% (95%CI: 30–64) in SCPRT patients compared with 23% (95% CI: 12–35) and 9% (95% CI: 3–20) in non-SCPRT patients (log rank test $P < 0.0001$) (Fig. 1). The overall local recurrence rate was 15%, two recurring at the end stoma and two in the perineum. The original perineal wounds of

Table 1 Population characteristics.

Factor	Number (n)	Proportion	Median/mean*	IQR/SD*
Age	96		72.5	64–78
Sex				
Female	38	0.40		
Male	58	0.60		
Smoker	16 (80% male)	0.17		
Diabetes	7	0.07		
Immunosuppressants	1	0.01		
Preoperative haemoglobin	92†		13.3	12.2–14.1
Preoperative albumin	88‡		39.4*	3.9*
Tumour (T) Stage				
1/2	41	0.44		
3	38	0.40		
4	15§	0.16		
SCPRT				
Yes	39	0.41		
No	57	0.59		
Wound complication				
Yes	44	0.47		
No	50	0.53		
Return to theatre				
Yes	8	0.09		
No	86	0.91		
Local recurrence				
Yes	13	0.14		
No	81	0.86		

SCPRT, short course preoperative radiotherapy.

*One patient had no tumour in the specimen because of previous malignant polypectomy and one patient had an *in situ* carcinoma. These were treated as T stage 1/2.

†Two patients with missing data for preoperative haemoglobin were assigned the median value of 13.3.

‡Six patients with missing preoperative albumin had values imputed based on the distribution of the observed values.

§Three patients who had salvage abdominoperineal excision of the rectum after local recurrence, for the purposes of analysis were allocated the T stage 4.

Table 2 Incidence of wound complications.

Wound complication	Number of patients	Proportion	95% Confidence interval ($n = 94$)
Infection	16	0.17	0.1–0.27
Dehiscence	25	0.27	0.18–0.37
Sinus	9	0.10	0.04–0.18
All	44	0.47	0.36–0.58

Table 3 Return to theatre by preoperative radiotherapy group.

Preoperative radiotherapy?	Return to theatre?		
	Yes	No	Total
Yes	5	32	37
No	4	53	57
Total	9	85	94

Fisher's exact test, $P = 0.31$.

these latter two had healed within 2 months. Thirty-two of the 95 patients for whom survival status was known died during the period of study. Follow up for patients who were still alive ranged from 10 to 95 months with a median of 40 (IQR: 25–55, $n = 62$). A plot of the survivor function by preoperative radiotherapy status is given in Fig. 2. There was no evidence to suggest differences in survival (Wilcoxon test, $P = 0.59$, $n = 90$) or local recurrence ($\chi^2_1 = 0.14$, $P = 0.71$, $n = 94$) between SCPRT status groups (Table 5).

Table 4 Estimates of 30- and 90-day wound survival rates by preoperative radiotherapy status.

Preoperative radiotherapy?	Time since operation	
	30 days yet to heal (95% CI)	90 days yet to heal (95% CI)
Yes	64 (46–78)	48 (30–64)
No	23 (12–35)	9 (3–20)

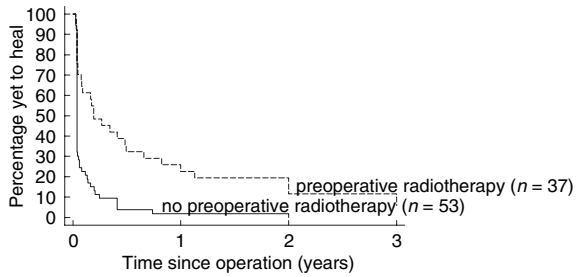

Figure 1 Perineal wound healing by preoperative radiotherapy ($n = 90$). Data on time to healing was available for 90 patients seven of whom failed to heal during the period of study. Follow up for those patients whose wounds had *not* healed ranged from 23 to 2505 days (median 58, $n = 7$). Although the maximum time to healing was 2505 days (censored observation), the next largest observation was only 1095. The survival curves presented were therefore truncated at 1095 days to avoid undue attention being given to the second half of the curve which would have been based on just one observation.

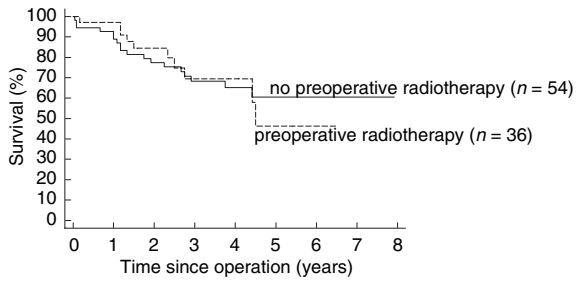

Figure 2 Patient survival curves by preoperative radiotherapy ($n = 90$) Survival times were not known for four of the patients who died and one living patient, leaving data for 90 patients available for inclusion in the analysis.

Discussion

Short course preoperative radiotherapy is advocated for use in patients with low rectal adenocarcinomas because it has been shown to decrease the risk of local recurrence after rectal resection [7–10]. Although SCPRT is better than postoperative radiotherapy at reducing local recurrence rates [11] neither have been shown conclusively to be of benefit in prolonging survival. There is also conflicting evidence to suggest that SCPRT increases perioperative mortality from causes other than rectal cancer [9–12]. Since the earlier radiotherapy trials, there has been an almost universal acceptance of the Total Mesorectal Excision technique for rectal cancers. This major surgical advance has been shown to reduce local recurrence rates and to improve survival from surgery alone [12], bringing into question the overall benefit of radiotherapy. The Dutch TME trial [13] showed that SCPRT reduces the local recurrence rate from 8.2% to 2.4% at 2 years implying that even with a properly performed TME, patients with rectal cancer benefit from preoperative radiation therapy. This was probably of benefit only to higher risk groups, i.e. close resection margins or those with nodal spread.

Table 5 Local recurrence by preoperative radiotherapy.

Preoperative radiotherapy?	Local recurrence?		
	Yes	No	Total
Yes	6	33	39
No	7	48	55
Total	13	81	94

$\chi^2_1 = 0.14$, $P = 0.71$.

For very low rectal tumours where the mesorectum becomes deficient and the boundaries between tissue planes become less distinct, the risk of local centrifugal spread into surrounding pelvic organs and sidewalls is theoretically higher than that for mid/high rectal tumours. Therefore to minimize the risk of local recurrence preoperative 'sterilization' appears attractive. But there are well-recognized complications associated with pelvic radiotherapy, both early self-limiting lethargy, nausea, diarrhoea, skin erythema or desquamation (4–48%) and wound infection (20%) as well as late serious toxicities, requiring hospitalization or surgical intervention (3–20%). Delayed radiation toxicities include radiation enteritis (4%), small-bowel obstruction (5%), rectal stricture (5%) [14] haemorrhagic proctitis (20%) osteoporotic fracture (1–5%) [9–11,15–17], thromboembolic (2–7%) [9–11,15] and fistulous (5%) [15,19] complications. The risk of cardiovascular death and morbidity is increased two- and fourfold after SCPRT [10] so patients with significant cardiovascular comorbidity may be excluded from having SCPRT.

Our results suggest that the risk of perineal wound complication is considerably higher in patients who undergo SCPRT, being over 10 times that for a patient who does not have SCPRT. Despite wide confidence intervals this odds ratio indicates a strong association

between SCPRT and wound complication in keeping with other studies and should not be overlooked.

The vascular and extracellular matrix effects of SCPRT (decreased expression of angiogenic bFGF and VEGF and increased expression of collagenases MMP-2 and MMP-9) are known to continue long after the initial course [19] and it is not surprising that delayed healing is seen in this group of patients. It may be suggested that local recurrence was responsible for delayed healing, however only two of 13 patients who had local recurrence had perineal wounds which never healed. In our series two-thirds, one-half and one-quarter of SCPRT patients' perineal wounds still had not healed by 1 and 3 months and 1 year postoperatively respectively. This suggests that whilst delayed perineal wound healing is a major concern in SCPRT patients after APER, continued healing occurs up to and beyond 1 year postoperatively. A variety of transposition flaps have been proposed as a means of achieving rapid perineal wound healing both as a primary and delayed procedures [1–5]. These are not without their own complications and timing of the procedure must be considered carefully to avoid early local recurrence and allow for spontaneous healing, therefore the routine use of primary myocutaneous flaps cannot be recommended and a selective policy of delayed flap closure may be better applied.

Patients with extreme age and/or significant cardiovascular co-morbidity were selected out by the oncologists and one might have expected this, and T stage, to be confounders (in that a small mobile tumour may be expected not to have had SCPRT thereby introducing selection bias). This has not been borne out by our study since neither younger age nor earlier T stage was associated with reduced incidence of wound complication. During the earlier years of our study group the rationale for patient referral for SCPRT was based on individual consultants' preferences with some referring all cases requiring APER for preoperative radiotherapy and others being more selective [20]. With the advent of subspecialization and the involvement of the multidisciplinary teams in the planning of the patients' cancer journeys SCPRT is considered for all patients with rectal carcinoma, in line with the 2001 guidelines of the Association of Coloproctology of Great Britain and Ireland [21], on an individual basis. Accordingly it can be seen that in the years studied there has been a recent increase in the proportion of patients receiving SCPRT. In light of our findings a more selective policy regarding SCPRT may be more beneficial. Colorectal surgeons and oncologists are now favouring long course chemoradiotherapy as neoadjuvant treatment for locally advanced rectal cancer and no neoadjuvant treatment for low-risk tumours. None of the patients in our study underwent long course treatment. Our findings cannot be directly applied to this group of patients but they suggest that further studies are needed to investigate the effects of long course chemoradiotherapy on perineal wound healing, specifically in patients undergoing APER. With improved techniques of preoperative magnetic resonance staging of low rectal tumours and prediction of likelihood of successful R0 resection it may be possible to be more selective about those patients we irradiate in the future, reducing the numbers of perineal wound complications without increasing the risk of local recurrence.

The symptoms of recurrence are invariably miserable for patients but so are those of a persistent perineal wound. Detailed analysis of local recurrence risk was not the remit of this study and conclusions cannot be drawn from our findings in this regard because of the small study numbers. However our limited data seem to support the Dutch TME Trial subgroup analysis that the addition of SCPRT is of little benefit for low rectal cancers, i.e. those requiring APER (Fig. 2). At present we have to advise patients that with SCPRT they have a limited chance of reduction of local recurrence risk with virtually no survival advantage. However in light of our results patients who undergo SCPRT will have a greatly increased risk of a perineal wound complication. The associated pain, discomfort, distress, social alienation and demands on community district and practice nursing are considerable disadvantages of perineal wound complications. Against these, the benefits of radiotherapy have to be weighed on an individual basis.

Conclusion

Our findings suggest that SCPRT is the most significant and controllable risk factor for perineal wound complication after APER. Individual patient age, comorbidity, clinical tumour stage and the likely effects on quality of life should such a complication occur, must be considered against any local recurrence risk reduction from SCPRT. Large prospective studies are needed to evaluate the effects of a selective policy for radiotherapy administered in patients specifically requiring APER.

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