Does pre-operative chemoradiotherapy cause wound complications after abdominoperineal excision for rectal cancer? An observational study

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A B S T R A C T
Introduction: Neo-adjuvant chemoradiotherapy is commonly used before surgery for rectal cancer. Very low rectal cancers are still treated by abdominoperineal excision of the rectum (APER). Perineal wound complications are common after APER. There is evidence that radiotherapy increases wound complications. We wished to examine the effect of preoperative radiotherapy (SCPRT) and long course chemoradiotherapy (LCCRT) on perineal wound complications.

Methods: We undertook a review of all patients undergoing APER at one institution between 2000 and 2010. Details of SCPRT, LCCRT and both minor and major wound complications were identified by retrospective notes review.

Results: Of 74 patients suitable for analysis, 38 (51%) had recorded wound complications, with 23 (31%) having major wound complications. 43 patients (58%) underwent LCCRT and 11 (15%) SCPRT. Overall wound complications were more common in the LCCRT group than those receiving no treatment (58% vs 30%, p = 0.03), and major wound complications more common after SCPRT than LCCRT (45% vs 35%, p = 0.04) or no treatment (45% vs 10%, p = 0.04). Use of mesh led to more wound complications (71% vs 41%), but almost all of these patients received LCCRT.

Conclusions: Pre-operative LCCRT and SCPRT are both associated with increased perineal wound complications after APER.

1. Introduction

Abdominoperineal excision of the rectum (APER) was popularised in 1908 by Miles. It became the standard treatment for rectal cancer, despite the introduction of anterior resection (AR) in the 1930s. More recently, the technique of total mesorectal excision (TME), a clearer definition of safe distal margin length and better stapling devices have led to a decline in the usage of APER.

APER has two major disadvantages over AR. Firstly, the patient is left with a permanent stoma, which may decrease quality of life and has been identified by national bodies as a quality indicator in colorectal cancer care. Secondly, perineal wound complications are common after APER. These vary from minor complications such as slight gaping or over-granulation of a small portion of the wound, to major complications such as pelvic abscesses and/or full wound failure. Major wound complications often require a prolonged stay in hospital with a delayed return to daily life. They may also delay adjuvant treatment, which could lead to a poorer long-term outcome.

There is increasing evidence that preoperative radiotherapy (RT) with or without concurrent chemotherapy – is advantageous in terms of local recurrence for rectal cancer (although a survival advantage is not yet proven). There is also some evidence that preoperative RT leads to an increased rate of perineal wound complications after APER.

The aim of this study was to look at the different effects of both long-course and short-course pre-operative neo-adjuvant chemoradiotherapy on perineal wound healing after APER. We also looked at other operative factors that could influence perineal healing. Our results could help to identify future patients at high risk of wound complications, in order that the risk can then be minimised.

2. Methods

All patients undergoing APER at our institution between 1st January 2000 and 31st December 2010 were identified retrospectively using electronic theatre records and a manual search of consultant diaries. Patients who underwent APER for
inflammatory bowel disease, whose perineal wound was left open at the first operation, or who died within thirty days of operation were excluded. Patient notes were obtained and data extracted using a standard proforma, which included information on patient demographics, neoadjuvant therapy, histology, use of a drain or mesh at operation, perineal wound complications, treatment of wound complications, repeat surgery, 30 day morbidity, length of inpatient stay and subsequent mortality.

APER was performed either as a one or two surgeon procedure using a standard technique, with some procedures utilising laparoscopic mobilisation. Several different surgeons carried out the procedure, all at a single hospital site. The technique of extra-levator APER (ELAPER) and prone operation for the perineal approach were both introduced towards the end of the study period.

Perineal wound complications were identified by a detailed search of the contemporary medical and nursing notes as well as post-operative clinic letters. Any mention of perineal wound that suggested that it was not clean, healthy and dry was documented as a “mention of perineal wound” and counted as “contemporary medical and nursing notes as well as post-operative clinic letters. Any mention of perineal wound suggested that it was not clean, healthy and dry was documented as a “mention of perineal wound that suggested that it was not clean, healthy and dry was documented as a “mention of perineal wound”. Complications noted included slight opening of the skin edges, wound breakdown, wound sinus, wound collection, discharge, slough, granuloma and communication with a pelvic collection. These were then grouped into ‘minor’ complications (granulomas, discharge, slough, slight opening) and ‘major’ complications (wound opening, collections, delayed healing).

Neoadjuvant radiotherapy was given in two ways at our institution over this time period. Most commonly in patients undergoing an APER it was given as a long course of chemoradiation (LCCRT) using 45 Gy in 25 fractions delivered over five weeks, with concurrent fluoropyrimidine-based chemotherapy (5-fluorouracil or capecitabine-based), which was then followed by a gap of 6–8 weeks before APER. Some patients received short course pre-operative radiation therapy (SCPRT) alone, 25 Gy in 5 fractions over one week, followed by surgery usually within one week. Most patients in the current study were staged pre-operatively using pelvic MRI. LCCRT was used in patients whose disease threatened (within 2 mm) or involved the mesorectal fascia or anal sphincter/levator complex.

Statistical analysis was performed using Microsoft Excel, Softonic OpenStat software; multivariate analysis used John C. Pezzullo and Kevin M. Sullivan’s online logistic regression calculator (http://statpages.org/logistic.html). Univariate analysis between perineal wound complications and categorical variables were performed using Fisher’s exact probability test or the chi-squared test as appropriate. Continuous variables were divided into ranges for categorical analysis. Incomplete data were analysed based on what data was available and excluded only when data was missing. A p value <0.05 was considered significant.

3. Results

We identified 100 possible patients recorded as undergoing APER during the study period from theatre records. Notes for 5 patients (4 deceased) were misfiled or unobtainable. Sixteen patients were operated on for inflammatory bowel disease, 3 had wounds left open at first operation and 2 died within 30 days, leaving 74 patients suitable for further analysis (Fig. 1). Mean age of the patients was 68 years (standard deviation - 12) at the time of surgery, and 48 (65%) were male.

Perineal wound complications were recorded in 38 patients (51%). Histological stage of cancer was similar between those with wound complications and those without. Average age was significantly higher in those patients without wound complications (p = 0.026; Table 1).

Fifteen patients (39%) had minor complications (8 slight opening, 6 discharge or slough, 1 granulomas) and the remaining 23 (31% of all patients) had major complications (18 wound breakdown, 3 infection with collection, 1 persistent wound sinuses, 1 prolonged discharge with pain). Nine patients (12% of total, 27% of those with wound problems) underwent a second surgical procedure for perineal wound complications (Table 2).

### Table 2
Comparison of patients by wound complication.

<table>
<thead>
<tr>
<th>Wound complications</th>
<th>No wound complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>38</td>
</tr>
<tr>
<td>Mean age</td>
<td>65 (range 36–83)</td>
</tr>
<tr>
<td>Open APER</td>
<td>27 (71%)</td>
</tr>
<tr>
<td>Lap APER</td>
<td>7 (18%)</td>
</tr>
<tr>
<td>Lap converted to open APER</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Completion proctectomy</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>No residual cancer</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>Dukes A</td>
<td>10 (26%)</td>
</tr>
<tr>
<td>Dukes B</td>
<td>10 (26%)</td>
</tr>
<tr>
<td>Dukes C</td>
<td>10 (26%)</td>
</tr>
<tr>
<td>Dukes D</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Not recorded</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>

#### 3.1. Preoperative radiotherapy

Fifty-four patients received pre-operative radiotherapy (73%). Of these, the majority (43 patients) had LCCRT using 45 Gy in 25 daily fractions over 5 weeks (41 patients) or 34 Gy in 30 fractions over 6 weeks (2 patients). Forty-two of these 43 patients also received chemotherapy concurrent with their radiotherapy, although one of these failed to tolerate chemotherapy after the first dose (5FU). The remaining patient refused chemotherapy but accepted radiotherapy alone. All patients were analysed on an intention-to-treat basis.

The most common drug used was 5-fluorouracil (27/42), either alone (23), with irinotecan (as part of the NWCG-1 trial – 3 patients), or with folinic acid (1). The remainder received capecitabine (15/42), either alone (5) or with irinotecan (as part of the NWCG-2 trial – 10 patients).

Eleven patients underwent SCPRT using 25 Gy in 5 daily fractions over 1 week. No patients who had SCPRT had pre-operative chemotherapy.

Twenty patients (27%) did not receive neoadjuvant therapy (Table 3).

The number of patients with any wound complication after LCCRT (on an intention-to-treat basis) was 25 of 43 (58%) compared to 6 of 20 (30%) in the group who did not undergo any neoadjuvant treatment (p = 0.03 - Fisher’s exact test). There was a trend for patients undergoing SCPRT to have wound complications 7 of 11 (63%) although this did not quite reach significance when
compared with those not receiving neoadjuvant treatment \( (p = 0.07) \). There was no difference in the rate of all wound complications between LCCRT and SCPRT \( (p = 0.75; \text{Table 3}) \).

Fifteen of 43 patients in the LCCRT group had major wound complications \( (35\%) \), compared with 2 of 20 who did not receive neoadjuvant therapy \( (10\%) \) – there was no significant difference \( (p = 0.99) \). Five of 11 patients in the SCPRT group had major wound complications \( (45\%) \), which was significantly higher than the LCCRT group \( (p = 0.04) \) and the group without neoadjuvant therapy \( (p = 0.04; \text{Table 3}) \).

Of the 42 patients receiving pre-operative chemotherapy, 13 patients received a doublet regimen containing irinotecan plus a fluoropyrimidine \( (5\text{FU} \text{or capecitabine}) \). Five patients in this group \( (38\%) \) had wound complications, compared with 20 of 29 \( (69\%) \) receiving chemoradiotherapy regimens containing a single agent fluoropyrimidine. This difference did not quite reach statistical significance \( (p = 0.06, \text{Fisher’s exact test}) \). Three of 13 patients receiving irinotecan had major wound complications \( (23\%) \) compared to 12 of 29 receiving a single agent \( (41\%) \) which was not a significant difference \( (p = 0.94) \).

### 3.2. Stage of disease

Information on pre-operative staging was unfortunately unobtainable in some patients (mostly in patients early in the study period) and hence has not been used for analysis.

In terms of post-operative staging, a histology report was unobtainable for one patient. For the remainder, 21 patients were node positive, or had metastases at the time of operation \( (\text{Dukes C}) \). Only one patient’s tumour was of unknown stage aka stage not available \( (\text{Dukes C}) \). For the remainder, 21 patients were node positive, or had metastases at the time of operation \( (\text{Dukes C}) \).

### 3.3. Use of mesh

Twenty-one patients had a mesh placed as part of the APER operation. Of these, 15 were porcine dermal collagen \( (14 \text{ Permacol}^\text{TM}, \text{Covidien}; 1 \text{ CollaMend}^\text{TM}, \text{Bard}) \), 3 porcine small intestinal submucosa \( (\text{SurgiSIS}^\text{TM}, \text{Cook}) \), and 3 polyglyclan 910 \( (\text{Vicryl}^\text{TM}, \text{Ethicon}) \). There was no record of why mesh had been chosen in these patients, and equally no record of why it was omitted in other patients.

Fifteen of 21 patients in whom mesh was used had wound problems \( (71\%) \) compared with 23 of 53 \( (43\%) \) in the group that did not receive mesh \( (p = 0.02) \). Of note however is that the majority of the patients in whom mesh was used received either SCPRT \( (2) \) or CRT \( (18) \).

When comparing patients who received standard pre-operative CRT and mesh with those who received CRT alone, there was no significant difference in wound complications \( (12 \text{ of } 18 \ (67\%) \text{ vs. } 13 \text{ of } 25 \ (52\%), p = 0.8) \), suggesting that pre-operative CRT was the most important factor.

### 3.4. Use of drains

Perineal wound drains were recorded either in the operative note, contemporary medical record or nursing notes as being placed, present and/or removed in 60 patients. In patients without drains, wound complications occurred in 8 of 14 \( (57\%) \), and in 30 of 60 where drains were placed \( (50\%, p = 0.42) \).

### 3.5. Multivariate analysis

A multivariate analysis was performed, looking at neoadjuvant therapy, age, sex, use of drains and use of mesh as possible factors. When all perineal wound complications were considered, age \( (p = 0.047, \text{OR} 0.63) \), mesh \( (p = 0.027, \text{OR} 3.26) \) and neoadjuvant therapy \( (p = 0.029, \text{OR} 3.39) \) were identified as predictors. In this analysis the combination of younger age and mesh was a strong independent predictor of complications \( (p = 0.0156) \).

When major wound complications were considered, only neoadjuvant therapy as a significant factor \( (p = 0.01, \text{OR} 5.73) \).

Excluding short course radiotherapy patients from the analysis showed similar results, with only LCCRT as a significant predictor of all wound complications \( (p = 0.018, \text{OR} 5.33) \). For major wounds, again LCCRT was the only significant factor \( (p = 0.018) \), although adding use of a drain improved the prediction of wound complications very slightly \( (p = 0.017) \). Numbers in the SCPRT group were too small to examine independently via logistic regression, although it should be noted that all three patients who received mesh had a wound infection.

### 4. Discussion

Wound complications after APER for low rectal cancer result in a high morbidity for patients and are both common and potentially serious. Previous studies have shown an increased likelihood of wound complications after long-course neoadjuvant radiotherapy, with or without chemotherapy, although this finding is not universal.

The current study confirms that a 5-week course of external beam LCRT combined with either concurrent 5-fluorouracil or capecitabine chemotherapy significantly increases the likelihood of overall perineal wound complication compared to patients not receiving CRT. Irinotecan did not appear to increase the risk of any wound complications. However the numbers are small in each of these subgroups and a larger \( (\text{or pooled}) \) analysis would be needed to confirm these results. If this finding is confirmed with larger numbers of patients however, then this is relevant to the UK phase III ARISTOTLE trial which aims to accrue a total of 920 patients and started recruitment in early 2012. This trial randomises patients with MRI-defined locally advanced rectal cancer to receive LCRT using concurrent capecitabine with or without additional irinotecan.

In the Dutch TME randomised trial it was shown that SCPRT causes a statistically significantly increased rate of perineal wound complications following APER \( (26\%) \) compared to those who did not receive any pre-operative radiotherapy \( (18\%).\) This observation was repeated in the UK CR07 trial \( (35\% \text{vs. } 22\%).\) Our study has shown a significant increase in major wound complications after SCPRT, both compared to LCRT and no neo-adjuvant treatment. There was also a trend for an increase in all wound complications. However the numbers are small and further data would be needed to corroborate this.

Use of mesh or drains, which were placed according to the surgeon’s judgement, did not appear to influence wound healing beyond the preoperative LCRT or SCPRT given in these groups. In particular, 90% of patients in whom mesh was placed received LCRT – this may be because these tumours were more advanced. Certainly
we have noticed more patients having mesh placed after ELAPER was adopted. Histological nodal status and (radiological) metastases did not influence wound complications. Mean (and maximum) age was greater in the group without wound complications, suggesting that this equally had no effect. Multivariate analysis has suggested that age, mesh and drain may all have a small effect in some cases. Because the numbers in each subgroup were small they should be interpreted with caution and further studies with larger numbers would be required to confirm the results.

Our study has a number of limitations. The numbers are small and any findings must be interpreted in this context. In particular, the number of patients undergoing SCPRT was very small. Despite this we found a significant increase in major perineal wound complications and a trend towards an increase in all perineal wound complications.

This is a retrospective, non-randomised study. However, because pre-operative CRT is established as a standard of care in the treatment of low rectal cancer it is unlikely that randomised data will become available in the future comparing CRT with no treatment of low rectal cancer it is unlikely that randomised data would be required to confirm the results.

The rate of wound complications (51%) was high compared to previous studies. Previously reported rates vary between 14% and 47%. Our high percentage may be due to the low threshold for reporting complications (any mention of wound problems in the medical or nursing record). However, more than a third of these (14 of 38, 37%) required no treatment other than topical dressings, with a further 3 (8%) receiving antibiotics or silver nitrate and no other intervention. It is possible that these patients would not be recorded in a prospective trial as having a wound complication as their problems (‘slight’ wound opening, discharge) are subjective. However even if these groups are discounted that still leaves 21 of 74 patients (28%) with more significant wound complications, which is still relatively high. One possible explanation is the high percent of the APER patients who received pre-operative LCCRT or SCPRT (55 of 74, 74%).

5. Conclusions

Pre-operative LCCRT is significantly associated with an increase in perineal wound breakdown, irrespective of use of mesh, drains and stage of disease. Pre-operative SCPRT also increases the likelihood of a major perineal wound complication. Further studies and meta-analysis are needed to confirm this data and also to consider the effect that wound complications have on overall and disease-free survival.

Patients undergoing neoadjuvant therapy should be warned of the increased risk of perineal wound problems. Unconventional techniques such as primary vacuum therapy or skin flaps may need to be considered in patients undergoing pre-operative LCCRT and SCPRT who will then undergo abdominoperineal excision of the rectum.

Ethical approval

Local approval by research department of the hospital.

Funding

None.

Authors contribution

D Hoare – Data collection, statistical analysis, writing of paper, review.
A Maw – Study design, review.
S Collins – Writing, review.

Conflict of interest

None.

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