Oncological outcomes of abdominoperineal resection for the treatment of low rectal cancer: A retrospective review of a single UK tertiary centre experience

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ABSTRACT

Background: The use of abdominoperineal resection (APR) in the management of low rectal cancer has received criticism over high rates of incomplete resection due to tumour involvement at the circumferential resection margin. Extralevator abdominoperineal resection has been advocated as a means of improving complete resection. However, Extralevator abdominoperineal resection can result in increased cost, morbidity and reduced quality of life.

This study aims to assess the histological features and long-term outcomes of patients undergoing standard abdominoperineal resection and discusses the potential role of Extralevator abdominoperineal resection in this cohort.

Method: A retrospective review of a prospectively maintained database of rectal cancer patients at a single centre. Patients undergoing standard APR were included from 01/06/2007 to 31/05/2012 to allow a minimum 2-year follow-up. Data was collected on age, gender, co-morbidity, pre-operative stage, neo-adjuvant therapy, histology, recurrence and mortality.

Results: Seventy patients were identified (45 (64%) male, median age 67; (range 36–85)). 12 (17.1%) patients had a positive circumferential resection margin; 4 (6.1%) tumours were located anteriorly, 8 (11%) were located posteriorly or laterally and may potentially have been completely resected with extralevator abdomino-perineal resection, Number-needed to treat = 9. Positive circumferential resection margin was more common in advanced tumours (p < 0.001). Local recurrence was more common with positive circumferential resection margins (16.7% Vs 0%, p = 0.027), with no statistically significant difference in 5-year survival, although there was a tendency towards worse survival in these patients.

Conclusion: Positive circumferential resection margin following APR resulted in significantly increased local recurrence with a trend towards poorer survival outcomes. Extralevator abdomino-perineal resection may have benefited some of these patients with locally advanced tumours and postero-lateral recurrences. However, this has to be balanced against exposing patients to increased risk of adverse events. We would recommend selective use of Extralevator abdominoperineal resection for locally advanced and node-positive tumours although further studies to help refine selection criteria are required with long-term follow-up.

1. Introduction

The management of advanced low rectal cancer has seen significant changes over the last decade with the advent of extralevator abdomino-perineal excision of the rectum (ELAPE). With concerns over incomplete resection rates in abdominoperineal resection (APR) compared to anterior resection as well as high local recurrence, ELAPE has been championed by some as a means of reducing tumour involvement at circumferential resection margins (CRM) [1–3]. By ensuring a wider resection margin ELAPE should theoretically reduce the risk of tumour involvement at the circumferential resection margin and therefore reduce incomplete resection rates [4]. This improved resection rate should in turn reduce rates of local recurrence and improve disease free and cancer specific survival.
Several studies have demonstrated reduced local recurrence in selected groups of patients undergoing ELAPE, albeit with increased rates of complication and increased cost [5–17]. The larger perineal defect left following ELAPE may require additional resources to close either with mesh, be that synthetic or biological, or complex plastic surgery [18]. ELAPE has increased morbidity; with reported complication rates of up to 50% including perineal wound breakdown and revision, perineal hernia, chronic sinus and donor site complications if myocutaneous flap reconstruction is required [2,15,19]. In addition, within both the standard APR and ELAPE the anterior resection plane remains the same. Thus despite resection of a much larger volume of tissue with ELAPE, there is no wider resection achieved in the anterior plane compared to APR [16].

This study aims to assess the rate and site of CRM positivity and its impact on disease recurrence and survival in a cohort of patients undergoing standard APR. We discuss these results in the context of procedure choice between APR and ELAPE for locally advanced low rectal cancer.

2. Materials and methods

A retrospective review of a prospectively maintained database was performed (Research Registry UN: researchregistry3480). All operations were performed at a single, high-volume teaching hospital from 01/01/2007 to 31/06/2012. All patients were discussed pre-operatively at a specialist colorectal cancer multidisciplinary meeting and selected for APR with or without neo-adjuvant therapy as appropriate.

All patients undergoing abdominoperineal resection of the rectum for histologically proven rectal adenocarcinoma were included. Patients undergoing revisional or completion procedures or procedures with non-adenocarcinoma histology were excluded. Data was collected on age, gender, co-morbidity, neo-adjuvant therapy, histology (to include non-adenocarcinoma histology were excluded. Data was collected on age, gender, co-morbidity, neo-adjuvant therapy, histology (to include non-adenocarcinoma histology were excluded. Data was collected on age, gender, co-morbidity, neo-adjuvant therapy, histology (to include non-adenocarcinoma histology). Data was collected on age, gender, co-morbidity, neo-adjuvant therapy, histology (to include non-adenocarcinoma histology). Data was collected on age, gender, co-morbidity, neo-adjuvant therapy, histology (to include non-adenocarcinoma histology) were excluded.

A consultant pathologist reviewed histology reports for each specimen and where CRM was reported positive, the CRM involvement and location was confirmed. CRM location was divided into anterior, lateral or posterior corresponding to anatomical relations within the pelvis. Patients were followed-up for a minimum of 2 and maximum of 5 years.

2.1. Surgical technique

All patients underwent ‘standard’ abdominoperineal resection either by laparoscopic or open approach. Abdominal dissection or the rectum for rectal cancer who underwent a completion proctectomy for local recurrence. A total of 70 patients were included in analysis. Overall, 45 (64%) patients were male with a median age of 67 years (Range 36–85 years). 56 (80%) patients received neoadjuvant therapy. 42 (60%) patients had chemo-radiotherapy (50.4 Gy in 28 fractions) combined with 5-FU over 3 months and 14 (20%) patients had radiotherapy alone (25 Gy in 5 fractions over 5 days). 42 (60%) cases were completed via a laparoscopic approach. 4 (5.7%) cases were converted from a laparoscopic to an open approach (9.5% conversion rate) and the remaining 24 (40%) cases were performed open. All tumours were within 6 cm of the anal verge.

2.2. Data analysis

Data was analysed using SPSS 21.0 (IBM SPSS Inc. Armonk, NY, USA). Comparisons between groups were made using the chi-square test or Fisher’s exact test as appropriate. Binary logistic regression was performed to assess the effect of independent variables on CRM positivity. Survival was analysed using the Kaplan-Meier technique with comparison between groups made using the Log-Rank test. The effects of co-variates on survival was analysed using Cox-regression modelling.

Variables were entered into the model in a stepwise method (variables were entered into the model if their associated significance level was < 0.05 and removed if significance level > 0.1). This study has been reported in compliance with strengthening the reporting of cohort studies in surgery (STROCSS) criteria [20].

3. Results

Seventy-four patients were identified from the database over the study period. 4 patients were excluded from the final analysis of which 3 patients were excluded due to squamous cell cancer histologically and one patient was excluded due to previous anterior resection of the rectum for rectal cancer who underwent a completion proctectomy for recurrence. A total of 70 patients were included in analysis. Overall, 45 (64%) patients were male with a median age of 67 years (Range 36–85 years). 56 (80%) patients received neoadjuvant therapy. 42 (60%) patients had chemo-radiotherapy (50.4 Gy in 28 fractions) combined with 5-FU over 3 months and 14 (20%) patients had radiotherapy alone (25 Gy in 5 fractions over 5 days). 42 (60%) cases were completed via a laparoscopic approach. 4 (5.7%) cases were converted from a laparoscopic to an open approach (9.5% conversion rate) and the remaining 24 (40%) cases were performed open. All tumours were within 6 cm of the anal verge.

Table 1 Characteristics of patients with and without circumferential resection margin involvement. Increased stage of disease is associated with an increased incidence of CRM positivity.

| Variable | CRM+ | CRM- | P value |
|----------|------|------|---------|
| Age (median (range)) | 62 (52–81) | 68 (36–85) | n/s |
| Sex (male) | 6 (50%) | 40 (69%) | n/s |
| Neo-adjuvant therapy | 8 (67%) | 48 (83%) | n/s |
| Surgical approach (laparoscopic) | 7 (58%) | 35 (60%) | n/s |
| Dukes Stage | | | |
| Complete response | 0 | 6 (10.3%) | |
| Dukes A | 0 | 18 (31%) | |
| Dukes B | 2 (16.7%) | 24 (41.4%) | |
| Dukes C | 10 (83.3%) | 10 (17.2%) | P < 0.001 |
| T stage | | | |
| T0 | 0 | 7 (12.1%) | |
| T1 | 1 (8.3%) | 9 (15.5%) | |
| T2 | 0 | 12 (20.7%) | |
| T3 | 8 (66.7%) | 27 (46.6%) | |
| T4 | 3 (25%) | 3 (5.2%) | P = 0.047 |
3.3. Survival following abdominoperineal resection for low rectal cancer

Median survival was 4 years and 4 months. No statistically significant difference was demonstrated in overall survival between those patients with an involved circumferential resection margin compared to those without (Fig. 2: Log-rank, Chi Squared 2.110, p = 0.15). Comparison was made between CRM-positive and CRM-negative patients using Cox regression analysis. Results were adjusted for age, gender, neo-adjuvant therapy and histological stage (Table 2). No significant difference was demonstrated in survival in patients with a positive circumferential margin when adjusted for gender, use of neo-adjuvant therapy or tumour stage. Advancing age was an independent risk factor for poor survival outcome (OR 1.088 [CI 1.020–1.160], p = 0.011; Table 4).

4. Discussion

In this study we investigated CRM positivity, risk of tumour recurrence and its impact on survival in patients undergoing abdominoperineal resection for low rectal cancer. We have demonstrated similar rates of CRM positivity as reported elsewhere in the literature although a wide variation exists for this figure. Klein et al. reported a CRM positive rate of 7% in their cohort compared to 20% in the Asplund et al. series whereas Kennelly and colleagues report a rate of 13.9% perhaps reflecting different patient selection criteria and thresholds for considering a more extensive resection [11,15,27]. Furthermore, through logistic regression analysis we have shown that both advanced stage of disease as well operative conversion from laparoscopic to open abdominoperineal resection increases the risk of CRM positivity. Increased risk of CRM positivity with conversion to the open approach may reflect difficult pelvic dissection due to difficult tumour anatomy making a clean and complete dissection very difficult. This will not be helped by an open procedure with a more limited view compared to laparoscopic guidance. Consequently, positive CRM in our cohort translated to an increased incidence of local tumour recurrence. Moreover, the majority of these patients had locally advanced tumours, with Dukes C or T3-4 according to the TNM staging criteria. This finding is consistent with data from a large multicentre study by Kennelly et al. demonstrating that CRM positivity was dictated by tumour stage rather than surgical technique, with advanced tumour stage having a higher risk of CRM positivity [27]. Thus, the implication that obtaining clear resection margins may be more difficult in more advanced cancers with
abdominoperineal resection.

Local recurrence is a potential consequence of positive CRMs with our study showing a greater proportion of patients with positive CRMs developing recurrent disease. Neoadjuvant therapy in APR reduces risk of local recurrence as demonstrated by Ramsay et al. with 3 year follow-up results for 43 patients undergoing standard APR for rectal cancer following neo-adjuvant chemoradiotherapy [33]. In our study, 80% of patients received neo-adjuvant therapy, which did not significantly affect CRM positivity or overall survival. This is likely due to earlier stage tumours in those not selected to receive neoadjuvant therapy. However, 10.3% of patients showed a complete pathological response to neoadjuvant chemo-radiotherapy and there is an argument for such responders to have surgery delayed and be observed for disease progression [35]. This remains an area of controversy and further research is needed.

Following the resection, CRM positivity, survival or local recurrence between ELAPE and standard APR though patients undergoing ELAPE had longer length of stay and more perineal wound complications [15]. The use of myocutaneous flaps to close the perineal defect after ELAPE adds additional complexity, time, cost and risk of complication both at the perineum and the donor site [18,28]. Closure with mesh be it synthetic or biological also ads cost although may reduce the risk of perineal hernia – a morbidity complication requiring complex surgery to repair [29–31]. A recent systematic review demonstrated significant increase in wound complications in their secondary analyses although Musters et al. recent published a meta-analysis specifically examining wound healing and demonstrated no significant difference between standard APR and ELAPE [32]. Increased risk exists whenever additional procedures are performed and this should form part of the decision-making and informed consent process when considering any additional benefit ELAPE will give to the patient. This recent evidence suggests an improvement in patient selection for the use of this technique is warranted. To resolve this discrepancy in outcomes high-quality randomised controlled trials are needed; the most recent systematic review of ELAPE including only one such study. The Dutch BIOPEX-study is the only recruiting trial registered with clinicaltrials.gov ([https://clinicaltrials.gov]) assessing the role of ELAPE in the management of low rectal cancer [26].

The most up to date data from the UK, recently presented from the Pelican cancer group LORC database, has revealed around 65% of APRs performed in the UK are Extralevator [34]. We have demonstrated that potentially 8 (11%) of our cohort of unselected low rectal cancer patients could have benefited from this procedure. Furthermore, universal ELAPE resection applied our whole cohort of patients whilst potentially avoiding 8 additional CRM + resections, would have required an additional 62 ELAPE resections. This use of ELAPE would give a number needed to treat of 9 to prevent one CRM + resection.

Cox regression analysis of co-variants affecting survival. Advancing age was associated with poor survival outcomes. No other factors were associated with a significant difference in survival.

| B     | S.E. | Wald | df | Sig. | Exp(B) | 95% C.I.for EXP(B) |
|-------|------|------|----|------|--------|-------------------|
| Sex (Female) | -.338 | .564 | .359 | 1     | .549   | .713 .236 2.156 |
| Age   | .084 | .033 | 6.483 | 1     | .011   | 1.088 1.020 1.160 |
| Neo-adjuvant | .913 | .566 | .117 | 1     | .733   | 1.213 .400 3.679 |
| Histology | .222 | 5.222 | .746 | 1     | .356   | .766 .701 .067 7.279 |
| - Dukes A | .447 | 1.098 | .166 | 1     | .684   | 1.564 .182 13.454 |
| - Dukes B | 1.299 | 1.122 | 1.341 | 1     | .247   | 3.667 .407 33.076 |

Table 4

From 8 studies demonstrated no significant difference in CRM positivity rate [24,25]. Indeed, a recent report from the Swedish Colorectal cancer registry including 1397 patients actually demonstrated an increase in CRM positivity following ELAPE and local recurrence at 3 years follow-up [6]. This increase in CRM positivity following ELAPE has also been demonstrated by another database review from the Danish Colorectal Cancer Group [11]. In addition, some studies have encouraged caution in the use of ELAPE owing to increased morbidity from the procedure [8]. Asplund et al. demonstrated no difference in CRM positivity, survival or local recurrence between ELAPE and standard APR though patients undergoing ELAPE had longer length of stay and more perineal wound complications [15]. The use of myocutaneous flaps to close the perineal defect after ELAPE adds additional complexity, time, cost and risk of complication both at the perineum and the donor site [18,28]. Closure with mesh be it synthetic or biological also ads cost although may reduce the risk of perineal hernia – a morbidity complication requiring complex surgery to repair [29–31]. A recent systematic review demonstrated significant increase in wound complications in their secondary analyses although Musters et al. recent published a meta-analysis specifically examining wound healing and demonstrated no significant difference between standard APR and ELAPE [32]. Increased risk exists whenever additional procedures are performed and this should form part of the decision-making and informed consent process when considering any additional benefit ELAPE will give to the patient. This recent evidence suggests an improvement in patient selection for the use of this technique is warranted. To resolve this discrepancy in outcomes high-quality randomised controlled trials are needed; the most recent systematic review of ELAPE including only one such study. The Dutch BIOPEX-study is the only recruiting trial registered with clinicaltrials.gov ([https://clinicaltrials.gov]) assessing the role of ELAPE in the management of low rectal cancer [26].

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This proportion of tumours approximately corresponds to the reduction locally advanced (T4 or N1-2) tumours, many sited anteriorly. In our cohort of patients, most CRM positive results were in the pelvic floor. The use of ELAPE in the management of low rectal cancer is growing [21]. This increase is in response to reported poor surgical outcomes following standard APR when compared to anterior resection [1]. Responsibility for these poor outcomes has been in part attributed to surgical waisting around the sphincter complex resulting in incomplete resection and increasing risk of local recurrence [22]. Since Holm et al. published their report of a cylindrical APR in 2007 other studies have reported favourable results from this wider resection [1]. However, as demonstrated by Bökkerink et al., there has been a significant improvement in the care of all patients undergoing APR over the last decade regardless of surgical approach [23]. Moreover, ELAPE does not address anterior CRM involvement, nor involvement at the circumferential margin above the pelvic floor. In our cohort of patients just over a third of those with a positive CRM had involved anterior margins. With the exception of the one patient with intra-operative tumour perforation, surgery in these patients would not deliver disease free resection margins without recourse to multi-organ resection. In addition, larger cohort studies and subsequent systematic reviews have recently challenged earlier smaller studies reporting reduced CRM positive rates in ELAPE compared to APR. In a review of published data by Krishna et al., in 2013, the authors failed to demonstrate significantly lower rates of CRM positivity following ELAPE compared to standard APR and Zhou et al. in an updated systematic review of 2672 patients
at a colorectal cancer MDT should allow more effective use of ELAPE for the benefit of patients.

5. Conclusion

In low rectal cancer surgery, positive CRM following APR results in significantly increased local recurrence and potentially poorer long-term survival outcomes. ELAPE has been shown to dramatically reduce the rate of CRM positivity, however this improvement is not without potential increased cost, additional surgery, increased morbidity and poor patient quality of life. In our cohort, we identified a select group of patients with advanced low rectal cancer with positive posterolateral positive CRM who may have benefited from ELAPE. We would recommend the default use of ELAPE in advanced low rectal cancer after downsizing with neo-adjuvant therapy although further studies to refine selection criteria for this procedure are required.

6. Limitations

The major limitations of the current study are that it is a retrospective study of a single high volume tertiary centre in the United Kingdom. Although the general approach of each of the surgeons was similar with regards to workup and technique, individual techniques cannot be entirely homogenous and this is difficult to factor for in our study. Our results will also be applicable to a similarly resourced centre dealing with a similar volume of patients. Additionally we do not currently have long-term follow-up data, which will help determine the overall survival of abdominoperineal resection patients with positive circumferential resection margins.

Ethical approval

Information board review committee has given NOC for this study, that will be uploaded.

Source of funding

Nil.

Author contribution

AH→ Design, data collection, writing.
AT→ Design, Data Analysis, writing.
HC→ Data collection.
CH→ Pathology input.
RD→ Design, Supervision.

Conflicts of interest

Nil.

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Guarantor

Anwar Hussain.

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