Perineal Healing After Extralevator Abdominoperineal Resection for Low Rectal Cancer

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Abstract

Aim: The healing of the perineum was studied in patients after extralevator abdomino-perineal excision (elAPE) for low rectal cancer.

Methods: 129 patients with low rectal adenocarcinoma were operated with an elAPE in one center in a non-randomized consecutive observational study. All patients were reconstructed with a biological mesh and perineal infections were assessed against the following variables: open versus minimally invasive surgery; neoadjuvant radiotherapy versus no neoadjuvant radiotherapy; before and after the implementation of an aseptic mesh implantation regimen. All patients were observed for 2 years after surgery for possible development of a perineal hernia.

Results: The perineal wound infection rate after 3 months was 27% (10% major and 17% minor infections). The number of major perineal infections was significantly higher in patients who achieved neoadjuvant irradiation. We also found association between a high infection rate in open surgery compared to minimally invasive surgery, and in males compared to women but these findings were both shown to be multifactorial. Introduction of an aseptic regimen of pelvic floor mesh implantation had no influence on the infection rate. Two perineal hernias were identified (1.5%) during the observation period.

Conclusion: Perineal morbidity after elAPE is multifactorial but preoperative irradiation is a significant independent factor for development of postoperative infection of the healing perineum.

Keywords: Biological Mesh; Extralevator APE; Infection; Irradiation; Laparoscopy; Perineal Complications; Rectal Cancer; Robotic Surgery; Surgery, Wound Healing

Introduction

Both survival and local disease control following surgery for rectal cancer have improved during the last decade [1,2] mainly by improving the surgical technique, by precise definition of correct surgical planes relative to the tumour, and by total mesorectal excision. This has resulted in a decrease in the number of surgical specimens with positive circumferential resection margins and to a reduction in the local recurrence rate [3,4]. The cylindrical technique of Extralevator APE (elAPE) leads to wider margins and a reduction in the number of specimens with involved resection margins compared to conventional APE [5,6]. The elAPE technique includes removal of the entire pelvic floor together with the anorectum. Moreover, less of the perianal skin and ischioanal fat are removed in elAPE compared to conventional APE. These factors present a significant challenge for reconstruction, and may also lead to higher morbidity. Delayed healing of the perineal wound is a common problem and radiotherapy is shown to diminish healing [7,8]. Compromised healing has also been demonstrated to be more frequent after elAPE (32%) than after conventional APE (11%) [9,10]. We have previously shown an infection rate of 17% in 24 patients using elAPE in combination with reconstruction of the pelvic floor using a biologic mesh [11]. In the present study, we report our experience of perineal repair after elAPE for rectal cancer in 129 patients before and after the implementation of an aseptic mesh implantation regimen, and before and after the implementation of minimally invasive techniques for the abdominal part of the eAPE. We focused on perineal morbidity, including infection and hernia development.
Patients and Methods

The elAPE procedure for low rectal cancer has been performed in the colorectal surgical unit at Surgical Department, Aarhus University Hospital, Denmark, since January 2005. All tumours were primarily classified with biopsy, digital rectal examination with evaluation of whether they were mobile or fixed. The distance from the anal verge was measured on proctoscopy, and an MRI was performed in all patients [12]. Indication for elAPE was threatened margins due to involvement of the levator muscle, with no involvement of the ischioanal fat, clinically or on MRI. The study population therefore included patients with T3 and T4 tumours when the tumour was situated less than 5 cm from the anal verge. In 9 patients with recurrent disease who had a low anastomosis after previous low anterior resection and achieved chemo-radiation if no previous oncological treatment had been given. The treatment of recurrent rectal cancer in Denmark is centralized in the unit. The surgical strategy was decided for each patient in a multidisciplinary team before any preoperative chemo-radiotherapy was given, according to the Danish national guidelines [13].

Surgery was planned approximately 8 weeks after completion of the oncological treatment. In the early part of the series, the abdominal part of the operation was all carried out by open surgery. Since January 2012 we introduced minimally invasive techniques - either laparoscopic, or robotic assisted, laparoscopic procedures. We continued to perform the abdominal part of the operation as an open procedure in patients with advanced T4 tumours, in recurrence cases, or in patients with tumours with suspicious lymph nodes outside the mesorectal fascia described on MRI, as defined by Palmer [14]. After completion of the abdominal part of the operation, including formation of stoma, the patient was turned into the prone position, and the procedure was completed using the extra levator abdominoperineal approach [5]. Between January 2008 and October 2014, a total of 130 patients underwent an elAPE and the pelvic floor was routinely reconstructed with a biological mesh. Since January 2011 we focused on aseptic technique when implanting the mesh and introduced an implantation regimen: after the rectum and sphincter complex had been excised, we used a fresh set of sterile instruments and all scrubbed staff changed gloves. The doors were locked to the operating theater until skin sutures had been placed. The skin around the perineal wound was disinfected again before mesh implantation. Care was taken to prevent mesh-to-skin contact. A continuous intradermal suture was used to close the skin. All patients were operated approximately 8 weeks after completion of neoadjuvant therapy, or within 2 weeks of diagnosis if no preoperative neoadjuvant therapy was given. We included 4 patients who underwent palliative surgery for primary advanced rectal cancer, as they were not suitable for pelvic exenteration due to high comorbidity.

Reconstruction of the Pelvic Floor with a Biological Mesh

Since 2007 we have reconstructed the pelvic floor in all patients, using a biological mesh implant. A 10x10 cm porcine collagen mesh (Permacol, TSL/Covidien, Leeds, UK) was sutured to the pelvic sidewall with interrupted monofilament absorbable sutures (Maxon 2/0, GS-11). A suction drain was placed superficial to the mesh. The perineal wound was closed in layers and antibiotics (Ciprofloxacin and Metronidazole) were given intravenously for 3 days. Drains were removed when output was less than 25 ml/day, or not later than day 7. Patients were mobilized day 1 after surgery with no restrictions. We evaluated all patients for complications of the pelvic wound at 3 months. Perineal healing was classified as either uncomplicated healing when there were no signs of infection, or as minor healing defect: small superficial infection such as a small sinus or separation of the wound, which did not require surgical intervention, or as a major healing defect with perineal wound infection requiring any kind of surgical intervention by operative irrigation and/or debridement, radiologically guided drainage, or vacuum assisted therapy [14]. No meshes in the infected patients were removed.

Postoperative Control

All patients were seen after discharge from the hospital in the out-patient clinic after 3 months. The perineal healing was graded as either being complete (Figure 1).

Figure 1: Complete healing of the perineal wound after elAPE. as a minor complication with a small sinus but still a defect in the suture line (Figure 2).
Figure 2: Minor defect (sinus) of the perineal wound after elAPE.
or as a major complication with a wound requiring exterior follow- 
up (Figure 3).

Figure 3: Major defect of the perineal wound after elAPE.

Statistical Methods

For the univariate analysis chi-squared test and rank sum 
test were used. Small logistic regression models were constructed 
when controlling for potential influencing variables, as the amount 
of data was too small for using one large model (Tables 1a,1b).

| Surgical technique | Odds ratio | 95% CI    | p-value |
|--------------------|------------|-----------|---------|
| Open               | 1.00       |           |         |
| Laparoscopic       | 1.02       | 0.41-2.53 | 0.96    |

| Gender            | Odds ratio | 95% CI    | p-value |
|--------------------|------------|-----------|---------|
| Male               | 1.00       |           |         |
| Female             | 0.49       | 0.19-1.29 | 0.15    |

| Preoperative irradiation | Odds ratio | 95% CI    | p-value |
|--------------------------|------------|-----------|---------|
| No                       | 1.00       |           |         |
| Yes                      | 9.60       | 1.21-76.14| 0.03    |

Table 1a: Logistic regression for the odds of infection 3 months after elAPE for rectal cancer.

For these models we used the number of overall infections after 
three months as outcome and influencing variables were: gender, 
surgical technique, and preoperative irradiation. P-values less than 
5 % were considered as statistically significant. Stata IC12 was 
used for statistical analysis (StataCorp, college Station, TX, USA).

Results

In 121 with a primary rectal cancer the preoperative MRI 
showed T3 or T4 tumour in 78% and 9 patients had a local recurrent 
disease from a previous rectal cancer. The male–female ratio was 
86/44. Patient characteristics are shown in (Table 2).

| Age, years | Median | IQR |
|------------|--------|-----|
|            | 70     | (62-77) |

| Sex | Male | Female |
|-----|------|--------|
|     | 86   | 43     |

| Tumour stage | Stage I + II | Stage III | Stage IV |
|--------------|--------------|-----------|---------|
|              | 18           | 75        | 27      |

| Recurrence | 9 |
|------------|---|

| R-stage | R0 | R1+R2 |
|---------|----|-------|
|         | 112| 17    |

| Preoperative irradiation | Odds ratio | 95% CI    | p-value |
|--------------------------|------------|-----------|---------|
| No                       | 24         |           |         |
| Yes                      | 105        |           |         |

| Infection after 3 months | Odds ratio | 95% CI    | p-value |
|--------------------------|------------|-----------|---------|
| No                       | 94         |           |         |
| Minor                    | 22         |           |         |
| Major                    | 13         |           |         |

| Implantation regimen | Odds ratio | 95% CI    | p-value |
|----------------------|------------|-----------|---------|
| No                   | 53         |           |         |
| Yes                  | 76         |           |         |

Table 2: Patient characteristics in 129 patients undergoing elAPE for rectal cancer.
Eighty-eight patients were operated as an open procedure and 41 patients as a minimally invasive procedure (12 laparoscopic and 29 robot-assisted laparoscopic operations). We included 4 patients with primary advanced rectal cancer who underwent palliative surgery, since they were not suitable for pelvic exenteration due to high comorbidity. The total risk of having a perineal infection at 3 months after eLAPE was 27% (10% major infection and 17% minor infection), as shown in (Table 3).

|                  | No | Minor | Major | p   |
|------------------|----|-------|-------|-----|
| Age, years       |    |       |       |     |
| Median           | 70 | 68    | 68    |     |
| Sex              |    |       |       |     |
| Male             | 58 (67) | 20 (23) | 8 (9) | 0.03 |
| Female           | 36 (84) | 2 (5)  | 5 (12)|     |
| Tumour stage     |    |       |       |     |
| Stage I + II     | 18 (100) | 0     | 0     |     |
| Stage III        | 53 (71) | 15 (20)| 7 (9) | 0.11 |
| Stage IV         | 16 (59) | 6 (22) | 5 (19)|     |
| Recurrence       | 7 (78) | 1 (11) | 1 (11)|     |
| Pre-operative irradiation |    |       |       |     |
| No               | 71 (68) | 21 (20) | 13 (12)| 0.02 |
| Yes              | 105  |       |       |     |
| Operative technique |    |       |       |     |
| Open             | 63 (72) | 12 (14)| 13 (15)| 0.02 |
| Laparoscopic      | 31 (76) | 10 (24)| 0     |     |
| Implantation regimen |    |       |       |     |
| No               | 57 (75) | 12 (16) | 7 (9) | 0.80 |
| Yes              | 37 (70) | 10 (19)| 6 (11)|     |

Table 3: Number of minor and major infection (percentage in parenthesis) of the perineum in 129 patients 3 month after undergoing eLAPE for rectal cancer.

One-hundred-and-five patients (81%) achieved preoperative irradiation (Table 2). Irradiation was significantly associated with perineal healing problems, since 12% had a major infection and 20% a minor infection after 3 months compared to 0% in the non-irradiated group (p=0.02), (Table 3). The total risk of having a perineal infection after 3 months was significant higher in the irradiated patients (33%, 34 of 105 patients; p< 0.04) compared to 4% (1 of 24 patients) in the non-irradiated patients and. Patients operated by open approach had a 28% risk of having an infection after 3 months (15% major and 13% minor), and when operated laparoscopically they had a risk of 24% (0% major and 24% minor); (Table 4).

|                  | No | Yes | p   |
|------------------|----|-----|-----|
| Healed           | 23 | 71  |     |
| Infection        | 1  | 34(p=0.04) |     |

Table 4: The effect of neoadjuvant irradiation on the healing of the perineum 3 months after surgery in 129 patients undergoing extralevator abdomino-perineal excision for low rectal cancer and reconstruction of the pelvic floor with a biologic mesh.

Also, the risk of having perineal infection was significant higher in men compared to females (p=0.03; Table 2). Also, the surgical approach seemed to interfere with the postoperative morbidity, since open surgery lead to a higher infection rate than laparoscopic and robotic surgery (p=0.02; Table 2). No meshes in the infected patients were removed. Fifty-three patients underwent surgery before the introduction of the implantation regimen and 76 patients after. The total infection rate throughout the period was unchanged. Also, we found that the infection rate before and after implantation regimen was unchanged in the patients operated by open laparotomy (p=0.65).

When comparing the groups we found significant higher T-staging in the patients operated by open laparotomy (p=0.005; (Table 5) and this was explained by the selection of the patients for open laparotomy in more advanced cases in order to achieve clear resection margins.

|                  | Open | Laparoscopic/robotic | p-value |
|------------------|------|----------------------|---------|
| Number of patients| 88   | 41                   |         |
| Age, years       |      |                      | 0.4     |
|                   | median | 69                   |         |
| Sex              |      |                      | 0.78    |
| Male             | 58    | 28                   |         |
| Female           | 30    | 13                   |         |
| Tumour stage     |      |                      |         |
| Stage I + II     | 10    | 8                    |         |
| Stage III        | 45    | 30                   | 0.005   |
| Stage IV         | 25    | 2                    |         |
| Recurrence       | 8     | 1                    |         |
| R-stage          |      |                      | 0.18    |
| R0               | 74    | 38                   |         |
| R1+R2            | 14    | 3                    |         |
| Preoperative irradiation |      |                      |         |
| No               | 11    | 13                   |         |
Infection after 3 months

| Infection after 3 months | Yes | No | Minor | Major | Implantation regimen | 0.009 |
|--------------------------|-----|----|-------|-------|-----------------------|-------|
|                          | 77  | 63 | 12    | 13    | 53                    | 0.009 |
|                          | 28  | 31 | 10    | 0     | 41                    | 0.0001|

Table 5: Open versus laparoscopic/robotic surgery in 129 patients undergoing eAPE for rectal cancer. P-values mono-variance analysis.

There was no difference in the radically operated patients evaluated by the R-staging between the open and the laparoscopically operated patients. To investigate whether the significant results in mono-variance analysis could be caused by potential influencing variables between the groups, we performed multivariable logistic regression analysis. This analysis showed irradiation as the only independent factor indicating effect on the healing process (p = 0.03); (Tables 1a,1b), whereas sex and the surgical approach were dependent on other factors since the difference on these two factors disappeared when doing multivariable analysis. Furthermore, no difference between the parameters was shown comparing patients who underwent robot assisted laparoscopic surgery with those patients who underwent laparoscopic surgery.

Two hernias (1.5%) were diagnosed in the cohort: one perineal hernia occurred early after surgery as described and one perineal hernia was found at the one-year control in a 75-year-old woman without clinical symptoms.

A total number of 130 patients underwent an eAPE for rectal cancer. One patient was excluded from the healing study after a failure of the mesh fixation at the pelvic sidewall and was readmitted just after discharge from the hospital with a defect in the wound containing small bowel. She had a secondary reconstruction performed with a VRAM-flap. Two patients were re-operated for bowel obstruction in the study period, and both cases were caused by intraperitoneal adhesions without involvement of the mesh. Four patients presented with pelvic sepsis above the mesh and all were drained trans-cutaneous through the mesh.

**Discussion and Conclusions**

This study reports perineal morbidity in a large single centre series of eAPE cases. We have been able to compare the perineal morbidity after eAPE and pelvic floor reconstruction using a biologic mesh, following both open surgery and minimally invasive surgery. During the study period we initiated a specific aseptic mesh implantation regimen to assess whether this could influence the infection rate of the perineal wound. Finally, we observed all patients for a minimum of 2 years to see whether they developed a perineal hernia. By univariate analysis we found a significantly higher infection rate in patients undergoing open surgery for more advanced disease compared to patients who underwent minimally invasive techniques. The difference however disappears after multivariate analysis indicating that this difference is multifactorial. Both techniques were equal concerning primary oncological outcome, since no difference was seen in the R-staging between the groups. Moreover, we showed a significant association between preoperative irradiation and healing problems of the perineum after surgery; that difference was also seen after multivariate analysis. Infection of the perineal wound often results in prolonged problems, leading to impaired quality of life and is well recognized after standard APE, with a frequency of up to 66% [15]. Also, after reconstruction with various musculocutaneous flaps, such as VRAM or gluteal flap, the infection rates have been reported to vary form less than 10%, up to 50% [16]. An overall infection rate of 9% after eAPE in one study [17] and 7.5% major and 7.5% minor infections [18] in another study are in accordance with our previous findings showing that reconstruction of the pelvic floor with a biological after eAPE with a biological mesh has an overall risk of 17% of perineal wound complications [11]. The present study demonstrates an overall 27% infection risk with 10% risk of major perineal infection and 17% minor infection 3 months after an eAPE. Open surgery tended to have a higher risk of infection compared to laparoscopic cases. Further analysis revealed that the more advanced cases were carried out using open surgery, which might explain that association.

Contamination during the procedures in the operating theater could be a causative factor in the number of infections. However, we found no effect on the infection rate after implementing an aseptic implantation regime. Previously, a lower incidence of surgical site infections is described after laparoscopic colectomy compared with open colectomy in more than 37000 patients [19]. The same reduction in infection rate was demonstrated when comparing laparoscopic and open surgery for rectal cancer [20]. The reduction in infection rate could be explained by reduced surgical stress on the patient after minimal invasive surgery, which could affect the tissue healing, and the benefits of mobilization of the patient early after surgery [21]. The effects of laparotomy on the intestinal permeability, systemic endotoxemia, and bacterial translocation were investigated in open versus laparoscopic surgery for colon cancer in 72 patients, but no difference was found in these parameters [22]. Comparison of infection rates is very dependent upon how infection is defined. In this study we distinguished between no infection, minor infection, and major infection after 3 months. Major infection is the most important factor from the point of view of influence on quality of life, whereas minor infection only has few consequences for the patient. Recently, a
meta-analysis showed an infection rate after eAPE of 14.8% after 30 days in non-irradiated patients and of 37.5% in the same patient group after having undergone preoperative irradiation. The overall infection rate in patients reconstructed with a biological mesh was shown to be 7.3% [23].

We have previously demonstrated that reconstruction with a VRAM flap is a safe method with low infection rate, but we only use this method in patients with wide ischioanal and wide perianal skin resections, and for vaginal reconstruction since it has a high donor-site morbidity [24]. But the use of musculocutaneous flaps after eAPE seems to be over-treatment, except for exenterative procedures and ultralow situated adenocarcinomas. Since the perineal wound by definition is contaminated after removal of the specimen, a biologic mesh is preferred over the less expensive synthetic meshes, since it seems to be more resistant to infection. Furthermore, a biologic mesh is associated with lower costs per patient compared to a VRAM flap [25]. The incidence of symptomatic perineal hernia following conventional APE is estimated to be from 0.2 to 0.62 percent and 6 percent after more aggressive surgery. Factors such as smoking, and chemo-radiation are both shown to increase the risk of perineal hernia development [15,26]. Eighty-one percentage of the patients in this study received preoperative radiotherapy and the relatively high risk of healing problems is explained by this factor. The overall 5-year survival after rectal cancer in Denmark increased from 37% in 1994 to 51% in 2006 [2] as a result of a variety of improvements, including the implementation of total mesorectal excision, and centralisation and specialisation of the surgical treatment of rectal cancer. More recently, the focus has been on improving the surgical treatment of low rectal cancer, which has accelerated the implementation of eAPE. Our previous results show that extensive resection with removal of the pelvic floor justifies the need for reconstructive procedures to prevent later development of hernia [11].

Based on our initial MRI we have used eAPE in low rectal tumours, when they were classified as a T3 or T4 tumour and that it was unsuitable for sphincter sparing surgery. The number of pathological T1 and T2 tumours may be due to either a misclassification by MRI or more likely a downsizing of the tumour by the chemo-radiation. The high rate of perineal wound healing problems is a significant problem after primary closure of the pelvic floor and perineum after standard APE and wound healing complications are increased after the implementation of preoperative radiotherapy [10] for reducing the number of involved resection margins. A 26% wound complication rate after standard APR without radiotherapy and of 71% in patients given preoperative radiotherapy [17] indicates a compromised healing capability caused by the radiotherapy. Since 1997 we have used the vertical rectus abdominis musculocutaneous flap as a safe method for reconstruction after ischioanal APE for anal cancers, and for salvage anal cancer, and we have shown a low rate of perineal complications using this method [27]. Preferred to use the gluteal muscle flap for pelvic floor reconstruction after eAPE [5]. We found a high frequency of hernia using this reconstruction method and changed to use a biologic implant [11]. In a systematic review no difference was demonstrated in the rate of complications when comparing mesh and flap reconstruction after eAPE [28]. Several improvements were observed using a biological mesh compared to reconstructive plastic surgical techniques: the implantation is easy to learn and can be performed without plastic surgical assistance. Moreover, the operating time is reduced, and the postoperative regimens are less restrictive. The properties of these biologics allow easy implantation when reconstructing the perineum after eAPE. The risk of infection is significant, but the consequences of infection are not found to be serious when biologic implants are used. No meshes were removed as a result of infection during the study period. Also, it is possible to close the wound with minimal tension on the skin sutures since eAPE leaves more intact perianal skin compared to conventional APE, and it thereby facilitate closure beyond a pelvic mesh, which may benefit wound healing. The low incidence of perineal hernia reported in this study may have been be higher if the patients had been evaluated after 2 years by CT, in combination with Vasalva’s maneuver, however the most important outcome is of clinically significant hernia.

The use of minimally invasive surgery is accepted to be equal to open surgery as regards the oncological results in non-advanced cases [29]. The advantages of the eAPE procedure are lower rates of tumour perforation, and less waist of the specimen leading to a lower number of positive Circumferential Resection Margins (CRM) compared to traditional APE. The eAPE technique also results in a minimal waist of perineal fat as the technique requires dissection in the extraspincteric plane [5]. The present study indicates that the oncological results comparing open and laparoscopic approaches of the abdominal part of the eAPE procedure is safe but is dependent on accurate preoperative staging by MRI. We, however, still recommend open access for more advances cases e.g. positive lymph nodes outside the mesorectal fascia. In conclusion, in patients having an eAPE and pelvic floor reconstruction with a biological mesh, the infection rate is lower when the abdominal part is performed by minimal invasive techniques compared to open surgery, but this finding is shown to be multifactorial and could be a result of more advanced tumours being operated on using open surgery. Preoperative irradiation, however, increased the risk of infection of the perineal wound after eAPE and this finding was demonstrated to be an independent factor. A specific aseptic implantation regimen during the mesh implantation has no effect on the morbidity.

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