Is stapled ileal pouch anal anastomosis a safe option in ulcerative colitis patients with dysplasia or cancer?

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Accepted: 13 May 2009 © Springer-Verlag 2009

Abstract

Purpose The purpose of this study was to investigate the oncological and clinical outcome of ulcerative colitis (UC) patients with coexisting colorectal cancer/dysplasia following stapled ileal pouch-anal anastomosis (IPAA).

Materials and methods One hundred eighty-five UC patients who underwent stapled IPAA were followed prospectively in a comprehensive pouch clinic. They were divided into three groups: colorectal cancer, dysplasia, and no cancer/dysplasia. Demographic parameters, clinical data, and oncological and functional outcome of the three groups were compared.

Results Sixteen patients had cancer and 14 had dysplasia. Two of the three cancer patients who developed metastatic disease died. One patient who had rectal cancer was found to have cancer cells in the rectal cuff 10 years after IPAA. All other cancer/dysplasia patients were disease-free at 62 months (median). The 5-year survival rate was 87.5% for the cancer group and 100% for the others (p<0.0001). Chemotherapy (nine patients) did not affect pouch function. Two rectal cancer patients who received radiotherapy did not maintain a functioning pouch. Overall pouch failure rates were 19%, 7%, and 6% for cancer, dysplasia, and no-cancer/dysplasia patients, respectively (p=0.13). The mean frequency of bowel movements in 24 h was similar between the groups.

Conclusions Stapled IPAA is a reasonable option for UC patients with cancer/dysplasia. Chemotherapy is safe, but the effect of radiation on pouch outcome is worrisome. Close long-term follow-up for UC patients with cancer/dysplasia is recommended for early detection of possible recurrence.

Keywords Restorative proctocolectomy · Ulcerative colitis · Colorectal cancer · Dysplasia · Stapled anastomosis

Introduction

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is widely accepted as the procedure of choice for patients requiring surgery for ulcerative colitis (UC) [1]. The incidence of colorectal cancer (CRC) in UC patients is significantly greater than that seen in the general population [2]. One meta-analysis that reviewed 116 studies of CRC in UC from around the world found the prevalence of CRC in patients with UC to be 3.7% overall and 5.4% for those with pancolitis [3]. The incidence of cancer found in patients who come to surgery is 3.8–10% [4, 5]. When
CRC complicates UC, sometimes necessitating additional chemotherapy and/or radiation therapy, it raises the concern about the feasibility of IPAA in terms of both the functional and oncological outcome. Previous reports have shown that IPAA with mucosectomy and hand-sewn anastomosis have acceptable oncological and functional results [4, 6–8]. The role of stapled IPAA in the setting of UC complicated by CRC is controversial, and there is concern about the oncologic fate of the rectal cuff. Furthermore, the role of stapled IPAA in UC complicated by dysplasia has been infrequently addressed. In our institution, stapled IPAA has been the preferred technique for the majority of UC patients undergoing restorative proctocolectomy, including those with dysplasia or CRC. The aim of our current study was to explore the oncologic and functional outcome of UC patients with coexisting CRC or dysplasia who underwent stapled IPAA.

**Materials and methods**

The institutional ethics committee approved the study.

Our usual approach for carrying out the IPAA procedure is a stapled ileoanal anastomosis at the anorectal junction, leaving 1–2 cm of rectal mucosa. This applies to the vast majority of UC patients, regardless of the finding of dysplasia or carcinoma, and the status of the disease (except for metastatic disease). Patients are followed up prospectively in a comprehensive pouch clinic by a team consisting of a colorectal surgeon and an inflammatory bowel disease-oriented gastroenterologist. All relevant demographic and clinical information is stored on a computerized database. The clinic was established in January 2003, and previous data were collected retrospectively and entered into the database as well. The routine follow-up includes clinical examination and yearly pouch endoscopies as well as biopsies from both the pouch and the rectal cuff. Data on cancer stage, adjuvant therapy, and oncological outcome on all patients with cancer/dysplasia in the surgical specimen are collected and recorded. For the current study, the charts from the oncology clinic were also reviewed for all the patients with carcinoma.

A total of 194 UC patients were followed up in our comprehensive pouch clinic from 2003 to 2008. Thirty-two patients (16%) had dysplasia or CRC. The study cohort was divided into three groups: patients with CRC, those with dysplasia, and those with neither cancer/dysplasia. Two patients with dysplasia and seven with no cancer/dysplasia who had a hand-sewn ileoanal anastomosis were excluded, making a study cohort of 185 patients. Demographic parameters, clinical data, and oncological and functional outcome of the three groups were compared.

Pouch failure was defined either as the need to remove the pouch and establish a permanent ileostomy or the need for an ileostomy without prospect of closure.

Our indications for neoadjuvant therapy are locally advanced (T3–4 or N1) mid- and low rectal cancers (up to 11 cm from the anal verge). The regimen included high-dose radiation therapy of 45–50.4 Gy, administered 5 days per week for 5.5 weeks, usually with concomitant 5-fluorouracil (5-FU)-based chemotherapy. Surgery was planned 6–8 weeks following the completion of preoperative therapy.

The indications for adjuvant treatment are stage 2 and 3 CRCs. There were different protocols; all of them included 5-FU and leukovarin.

Continuous parameters were presented as medians and ranges or means and standard deviations. Comparisons between the three groups of patients (carcinoma, dysplasia, and controls) with regard to demographics, surgical parameters, and the various outcome variables were performed using one-way analysis of variance (ANOVA) and Kruskal–Wallis for continuous parameters. The chi-square or Fisher’s exact tests were used for categorical parameters. Whenever the ANOVA was significant, pairwise comparisons were carried out using the Gabriel and Games-Howell post hoc tests. In addition, comparisons between two groups (with and without cancer/dysplasia) regarding the clinical and demographic parameters were performed with the unpaired t test, Mann–Whitney non-parametric, chi-square, and Fisher’s exact tests, as applicable. Comparisons between the different patients’ groups with regard to overall survival and disease-free survival were performed using the log-rank test and were demonstrated by the Kaplan–Meier curves.

A p value of <0.050 was considered significant, and the SPSS for Windows software (Chicago, IL, USA), Version 14.0 was used for the analysis.

**Results**

The study cohort included 185 UC patients who underwent stapled IPAA and were followed up at the pouch clinic: 16 had carcinoma, 14 had dysplasia, and 155 had no cancer/dysplasia.

The site of malignancy among the 16 patients with cancer was colon in nine and rectum only in seven. The stage distribution of the lesions in this group is depicted in Fig. 1. Among the patients with rectal cancer, two had a total abdominal colectomy with ileorectal anastomosis due to colon cancer 8 and 10 years prior to the completion proctectomy and IPAA. Of note, seven patients (44%) had stages 0 and 1 disease. The dysplasia in the group of 14 patients was located in the colon in ten and in the rectum in
four: seven were low grade and seven were high grade. The diagnosis of cancer and dysplasia was made preoperatively in ten (63%) and 11 (79%) patients, respectively.

The patients’ characteristics are displayed in Table 1. The male/female ratio was almost 1:1 among the no-cancer/dysplasia group; there was female predominance in the carcinoma group and males predominated in the dysplasia group. The differences did not reach a level of significance. The mean age at operation was significantly higher among the patients with dysplasia and carcinoma compared to the no-cancer/no dysplasia patients (50 vs. 34 years, \( p < 0.0001 \)). The mean duration of disease before surgery was also significantly higher in patients with cancer/dysplasia than the others (22 vs. 9 years, respectively, \( p < 0.0001 \)). There was no difference in the extent of disease between the groups.

Nine cancer patients were treated by chemotherapy, one prior to proctectomy and IPAA and eight following pouch surgery but prior to ileostomy closure. Additional chemotherapy was delivered after closure of the ileostomy in one patient. Two patients received pelvic irradiation for a locally advanced mid-rectal cancer, one as neoadjuvant therapy and the other patient, without a preoperative diagnosis of cancer, in an adjuvant setting prior to ileostomy closure.

The duration of follow-up of the 16 cancer patients was between 1 and 130 months (median, 64). In one patient, the pathology report of the surgical specimen revealed metastatic disease in the omentum. He was still diverted and receiving adjuvant chemotherapy at last follow-up. Two patients died. One patient with a T3N1 sigmoid cancer had received adjuvant chemotherapy and developed single liver metastasis 8 months following IPAA with a diverting ileostomy. She underwent combined right hepatic lobectomy and ileostomy closure and died a few hours postoperatively due to portal vein thrombosis. The other patient had a T3N0 rectal cancer that had developed 20 years after a total abdominal colectomy with ileorectal anastomosis. He died 7 months after the completion proctectomy and IPAA due to metastatic liver and lung disease. One patient was found to have cancer cells in random biopsies from the rectal cuff. She was 10 years after completion of proctectomy and IPAA due to T2N0 rectal cancer and 28 years after total abdominal colectomy with ileorectal anastomosis due to a rightsided T2N0 colon cancer. She underwent an abdominoperineal excision and is free of disease two months post surgery. The other 12 cancer patients had no evidence of disease at last follow-up.

All 14 patients with dysplasia were free of dysplasia or cancer at a median follow-up of 56 months (range, 24–175).

Pouch failure rates were higher in the cancer patients compared to the non-cancer patients, but the difference did not reach a level of significance (\( p=0.13 \)). The overall pouch failure rate in the cancer patients was 19% compared with 7% for the dysplasia patients and 6% for the no-cancer/dysplasia group. Thirteen cancer patients (81%) had a functioning pouch at last follow-up or at the time of death. One patient with metastatic colon cancer is on chemotherapy and still diverted. All other patients who had colon cancer maintained their pouch. Out of seven patients with rectal cancer two did not maintain a functioning pouch. They had locally advanced mid rectal cancer and had received radiation therapy (Table 2). The first patient had an ileoanal anastomotic stricture that required repeated dilatations. She suffered from fecal incontinence, and the pouch was eventually excised. The second patient developed a pouch-vaginal fistula: She underwent a successful gracilis muscle transposition repair but refuses ileostomy closure. Thirteen dysplasia patients (93%) had a function-

### Table 1 Demographics and clinical characteristics of the patients

<table>
<thead>
<tr>
<th></th>
<th>Carcinoma ((N=16))</th>
<th>Dysplasia ((N=14))</th>
<th>No carcinoma/dysplasia ((N=155))</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>5:11</td>
<td>9:5</td>
<td>70:85</td>
<td>0.191</td>
</tr>
<tr>
<td>Mean age at operation (years)</td>
<td>49.6±12.3</td>
<td>51.1±12.4</td>
<td>34.4±14.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean duration of disease prior to operation (years)</td>
<td>21.4±8.1</td>
<td>19.1±9.3</td>
<td>8.8±8.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Extent of colitis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left-sided</td>
<td>5 (31%)</td>
<td>3 (21%)</td>
<td>41 (28%)</td>
<td>0.702</td>
</tr>
<tr>
<td>Pancolitis</td>
<td>11 (69%)</td>
<td>11 (79%)</td>
<td>103 (72%)</td>
<td></td>
</tr>
</tbody>
</table>
ing pouch at last follow-up. One patient refuses ileostomy closure.

Of the 155 patients in the no dysplasia/cancer group, 146 (94%) maintained a functioning pouch after a median follow-up of 97 months (range, 6–334). Six patients had an indefinite ileostomy or pouch excision due to severe pouch dysfunction, and three patients refused ileostomy closure.

The mean frequency of bowel movements in 24 h was similar for the patients with cancer, dysplasia, and without cancer/dysplasia (seven, five, and eight, respectively). The incidence of pouchitis was significantly lower in the group of patients who had been operated because of dysplasia/carcinoma compared to patients who were operated mainly due to intractable disease, i.e., 18% and 60%, respectively (p=0.001).

As shown in Fig. 2, the 5-year survival rates of the patients with cancer were significantly lower than the 5-year survival rates of all other patients, i.e., 87.5% vs. 100%, respectively (p<0.0001).

### Discussion

IPAA is the elective procedure of choice for UC either as a single or a staged procedure. The risk of CRC in UC patients is real and depends on many factors, the most important ones being the age of the patient at disease onset, the extent of colitis, and the disease duration [9]. Its prevalence is estimated to be 2% at 10 years, 8% at 20 years, and 18% at 30 years of pancolitis [3]. In our study, both the age of the patient at operation and the disease duration were higher in patients with cancer, as has been previously reported by others [6, 8]. Our figures for overall incidence of cancer and dysplasia were 8% each, which correlates with the 3.8–10% reported rate of cancer in the literature [4, 5]. In contrast to data previously published by others [8, 10], we found a female predominance among patients with UC and cancer and a male predominance for patients with UC and dysplasia. This may be due to the relatively low number of patients in our dysplasia/cancer group. Nevertheless, it could be that gender differences were associated with later cancer diagnosis in women, as had been previously reported for other diseases [11].

The safety of IPAA, in terms of both oncologic and functional outcome, was previously shown in UC patients with associated CRC [4, 6–8]. Prognosis seemed to be related to cancer stage, and adjuvant chemotherapy was safely administrated to non-diverted patients. Long-term functional results for patients whose surgical specimen contained cancer were similar to those for UC patients without evidence of cancer.

The 5-year survival rate of the cancer patients in our study was 87.5%. This rate is comparable to or somewhat better than the ones reported in other studies in which mucosectomy and a hand-sewn anastomosis were performed [4, 6–8, 12]. As expected, survival among our patients was related to disease stage. Both patients who died had recurrent disease. The relatively good prognosis

<table>
<thead>
<tr>
<th>Pouch status</th>
<th>Radiation</th>
<th>Tumor staging</th>
<th>Tumor location</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional</td>
<td>No</td>
<td>T3N1</td>
<td>Upper</td>
<td>1</td>
</tr>
<tr>
<td>Functional</td>
<td>No</td>
<td>T2N0</td>
<td>Upper</td>
<td>2</td>
</tr>
<tr>
<td>Lost</td>
<td>Adjuvant</td>
<td>T3N0</td>
<td>Mid</td>
<td>3</td>
</tr>
<tr>
<td>Lost</td>
<td>Neoadjuvant</td>
<td>u*T3N0 y**T2N0</td>
<td>Mid</td>
<td>4</td>
</tr>
<tr>
<td>Functional</td>
<td>No</td>
<td>T1N0</td>
<td>Low</td>
<td>5</td>
</tr>
<tr>
<td>Functional</td>
<td>No</td>
<td>T3N0</td>
<td>Upper</td>
<td>6</td>
</tr>
<tr>
<td>Functional</td>
<td>No</td>
<td>T2N0</td>
<td>Mid</td>
<td>7</td>
</tr>
</tbody>
</table>

* u* endorectal ultrasonography staging pre-radiation, y** pathologic staging post-radiation
might be explained by the incidence of cancer diagnosed at an early stage (44% were in stage 0 and 1) in our UC patient population. This may reflect the tendency of early referral of UC patients for evaluation and specifically for surgery, especially since the introduction of restorative proctocolectomy. Indeed, a low incidence of advanced cancer among UC patients was demonstrated in other recent studies [4, 6–8] compared to earlier studies [5, 10, 13].

Chemotherapy was given as indicated to our study patients and does not seem to have influenced pouch function. In contrast, radiation therapy was associated with grave functional outcome. One patient who had post-IPAA radiation therapy eventually lost the pouch due to longstanding pouch dysfunction, and another patient who had pre-IPAA radiation therapy developed a pouch-vaginal fistula that necessitated a diverting ileostomy. While two patients are too few to draw conclusions, the ratio correlates with previously reported results of radiation therapy being associated with pouch failure. Radice et al. [7] described three pouch failures out of five cases in which postoperative radiation therapy was administered to patients with either UC or familial adenomatous polyposis. Remzi and Preen [4] described only one patient out of a group of 70 patients with UC and IPAA who was given postoperative radiotherapy. This patient had poor pouch function and cancer recurrence at the anorectal junction: He subsequently underwent abdomino-perineal resection. Gorfine et al. [6] described two patients who received radiotherapy. One received it post-pouch surgery and a pouch stricture developed, ultimately requiring excision of the pouch. The other patient received radiotherapy prior to pouch construction, and the pouch was functioning well at last follow-up. Summing up the cases in the three above-mentioned studies describing UC patients with cancer who received radiation therapy and adding the data of our study, only three out of ten patients maintained a functioning pouch. A solution to this problem might be the one suggested by Radice et al. [7] who described two patients in whom rectal cancer was identified during surgery. The dissection was stopped at the level of the levators, an ileostomy was created, postoperative radiation and chemotherapy were completed, and mucosectomy and pouch construction were performed at a later stage. The pouches survived in both these patients. Preoperative chemoradiotherapy for locally advanced mid- and low-rectal cancer has been shown in large clinical trials to achieve pathologic downstaging, with improvement of resectability and sphincter-saving surgery. Preoperative as compared with postoperative chemoradiotherapy improved local control and was associated with reduced short- and long-term toxicity [14, 15].

Pouch failure rates were higher in our cancer patients compared to the non-cancer patients, but the difference did not reach a level of significance (19% vs. 6%, \(p=0.10\)). Loss of the pouch in the current study patients was mainly attributable to radiation injury. One failure was related to disease progression (i.e., distant metastases). These results are comparable to previously described results with hand-sown anastomosis [7, 8]. Radice et al. [7] reported that pouch failure occurred in 16% of cancer patients compared with 7% for the non-cancer patients. Gorfine et al. [6] reported that cancer patients had a twofold rate of pouch loss as compared to non-cancer patients, although the difference did not reach a level of significance (9% vs. 4%, \(p=0.106\)). It is important to stress that our cancer group included a small number of patients, and this may have been the reason for our inability to show a significant difference between the groups. As overall, these findings imply that carcinoma patients generally have a higher risk of pouch loss.

Neoplastic changes in the columnar cuff are reported to be rare (from 0% to 0.03%) [16–19]. Furthermore, the occurrence of cancer at the anorectal mucosa is a rare outcome. Most studies have shown that the incidence of dysplasia or cancer after IPAA is strongly associated with the presence of dysplasia or cancer in the proctocolectomy specimen [8, 20]. There are 22 reported cases of adenocarcinoma in the anorectal mucosa or ileal pouch [21–24]. In the ten cases in which the cancer was located in the anorectal mucosa, six had high grade dysplasia and five had cancer in the proctocolectomy specimen [21]. The average time to cancer following IPAA was about 7 years [22]. In our cohort, one patient was found to have cancer cells in random biopsies from the retained rectal cuff mucosa 28 and 10 years after the diagnosis of colon and rectal cancer, respectively.

Several aspects of the type of the ileoanal anastomosis warrant attention. First, the risk of cancer to develop in the columnar cuff following IPAA appears to be similar whether or not mucosectomy is performed. It seems clear that mucosectomy does not rule out later development of cancer in the anorectal mucosa. In the present study, cancer developed in one out of 16 patients (6%), during a median follow-up of 5.3 years. Ziv et al. [8] reported 27 UC patients with coexisting cancer who had undergone IPAA with mucosectomy. One out of 26 patients (4%) had a local recurrence during a mean follow-up time of 4.3 years. Moreover, the majority of reported cases of adenocarcinoma after IPAA occurred in patients who underwent mucosectomy [21–24]. Second, dysplasia or early cancer that arises from the residual rectal mucosa after mucosectomy may not be easily noticeable and accessible because they develop between the pouch and the muscle layers of the cuff. Third, while mucosectomy results in more complete removal of diseased mucosa, stapled anastomosis confers a functional benefit, with improved nocturnal continence and lower incidence of pad usage, as reflected in higher
anorectal physiologic measurements [25]. Nevertheless, it is important to point out that a stapled IPAA requires accurate transaction at the anorectal junction to avoid leaving behind diseases rectal mucosa that is prone to neoplastic changes.

It should be emphasized that leaving a rectal cuff with the stapled anastomosis mandates close and long-term follow-up, which includes rectoscopy, pouch endoscopy, and random rectal and pouch biopsies, as is the policy at our comprehensive pouch clinic. Although there was only one case of new cancer/dysplasia in our cohort, we believe that such a stringent follow-up protocol is still essential since a longer follow-up might identify cases of columnar cuff dysplasia or recurrent/new cancers.

In conclusion, the stapled IPAA procedure in UC patients with cancer or dysplasia can be performed safely and has reasonable success rate. Adequate operative technique is needed to avoid cancer recurrence in the retained rectal cuff. Prognosis seems to be related to cancer stage. Chemotherapy can safely be given to these patients, but the effect of radiation therapy on pouch outcome is worrisome, especially if given following pouch surgery. We recommend a schedule of close long-term follow-up for all patients with UC and cancer or dysplasia for early detection of possible recurrence or pouch dysfunction.

Acknowledgment Esther Eshkol is thanked for editorial assistance.

References