Management of Ulcerative Colitis in Patients with Rectal Cancer

30

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Introduction

While medical therapy is the first line of treatment for ulcerative colitis (UC), proctocolectomy can provide a curative option. Approximately 20% of patients with ulcerative colitis will require surgery in their lifetime [1]. Indications for surgery are medically refractory disease, complicated disease, extraintestinal manifestations, toxic colitis, failure to thrive, dysplasia and cancer. In most cases, a restorative proctocolectomy with an ileal pouch-anal anastomosis (IPAA) is the preferred method to provide concurrent cure of ulcerative colitis and reconstruction of the gastrointestinal tract. The risk of developing colorectal cancer with ulcerative colitis over a lifetime is estimated between 5% and 13.5% [2]. In cases of ulcerative colitis complicated by rectal cancer, the choice of operative procedure becomes more challenging. An alternative to IPAA would be a total proctocolectomy with end ileostomy (TPC). In UC patients with rectal cancer, the need for neoadjuvant chemoradiation and adjuvant chemotherapy, in addition to other patient and disease dependent variables, may impact long term outcomes including overall survival and quality of life (Table 30.1).

Table 30.1 PICO table

Patients	Intervention	Comparator	Outcome
Ulcerative colitis with rectal cancer	Total Proctocolectomy with Ileal Pouch Anal Anastomosis	Total Proctocolectomy with end ileostomy	Cancer specific disease free survival and Health Related Quality of Life

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Search Strategy

A relevant PICO (Patients, Intervention, Comparator and Outcome) table was generated. A comprehensive literature search of MEDLINE, PubMed and Cochrane database of Collected Research between 1980 and 2018 was performed to identify articles on rectal cancer and ulcerative colitis, colectomy, IPAA, disease free survival, cancer specific survival and quality of life. Key search terms included the following: ulcerative colitis, colectomy, proctocolectomy, IPAA, rectal cancer, survival, quality of life, ileostomy. Studies that included rectal cancer patients with Crohn's disease or familial adenomatous polyposis were excluded from the analysis. Given the paucity of the literature, some articles that did not compare directly IPAA with total proctocolectomy and end ileostomy were also included.

Results

Very few studies report survival outcomes after surgery for rectal cancer in patients with ulcerative colitis, and no studies report quality of life measures in these patients. In addition, all studies are plagued with very low number of subjects and retrospective design.

The largest study to date measuring the oncologic outcomes of patients with ulcerative colitis and rectal cancer has been reported by Merchea [3]. In this retrospective review of 41 patients, the majority had proctocolectomy with end ileostomy. IPAA was done in 11 patients, abdominoperineal resection with end colostomy in 2 patients and subtotal colectomy with end ileostomy in 1. There was a clear preference for patients with early stage (I and II) rectal cancer to undergo an IPAA while patients with more advanced stage (III and IV) underwent non-restorative operations. Consequently, very few of the IPAA patients received either neoadjuvant (n = 1) or adjuvant treatment (n = 3) (radiation and/or chemotherapy). Half of the IPAA patients received a stapled anastomosis and the rest a handsewn anastomosis. Postoperative morbidity was not related to the type of surgery. Five-year disease free and overall cancer specific survival was 62% and was not found to be related to the type of procedure. As expected, the recurrences and deaths occurred in patients with advanced rectal cancer (stage III and IV). The authors concluded that rectal cancer in ulcerative colitis is rare, usually presents in early stage and that IPAA is feasible and safe for early stage disease.

In an older study from Ziv [4], a mixed group of ulcerative colitis patients with colon (n = 20) and rectal cancer (n = 7) underwent IPAA; local recurrence occurred in 2 patients (7.7%) and 3 died, but none from rectal cancer. The authors noted that most of their patients had early stage cancers, which may have accounted for the high rate of IPAA and the excellent overall outcomes. They concluded that IPAA can be used for curative intent as long as adequate margins are achieved.

In 2003, Remzi [5] reported the outcomes of 70 patients undergoing IPAA for colorectal cancer. Twenty six patients had rectal cancer and more than half of them underwent mucosectomy with a handsewn anastomosis. Most of them were early

Table 30.2 Studies of IPAA and Rectal Cancer

Study	Patients with rectal cancer	5 Year-recurrence	5 Year—survival	Quality of evidence
Merchea [3]	28 TPC vs 11 IPAA	38%	62%	Low
Ziv [4]	7 IPAA	0%	100%	Low
Remzi [5]	26 IPAA	3.8%	96%	Low
Hotta [7]	9 IPAA	0%	100%	Low
Gorfine [8]	14 IPAA	N/A	79%	Low

stage cancer (Stage I and II) and only 7 were stage III. The advanced stage patients received adjuvant chemotherapy without radiation therapy. One rectal cancer patient received adjuvant radiation therapy that was associated with pouch failure and development of cancer recurrence. Only one of the rectal cancer patients died during the average 6.1 years of follow up. This group concluded that IPAA should be considered in patients with coexisting colorectal cancer and UC. Surgery along with chemotherapy, when needed, can provide good prognosis with very good functional outcomes.

Finally, in a study that we did not include in our PICO analysis, McLeod [6] compared IPAA to TPC, but included patients with Crohn's disease and familial adenomatous polyposis. A total of 27 patients had rectal cancer; as in the previous studies, patients with advanced T4 tumors with poor differentiation did not receive an IPAA. Use of radiation was much more common in the TPC group. Overall disease free survival was comparable between the 2 groups and median time to recurrence or death was 14 months for both groups. The authors recommended IPAA as a safe alternative to TPC with end ileostomy, but not in those with T_3 or T_4 lesions, or those with threatened radial margins (Table 30.2).

Although there are several studies comparing the IPAA versus TPC for UC for health related quality of life measures, there are no studies on patients that also have rectal cancer. Although most studies without rectal cancer patients demonstrate comparable quality of life for both groups, in patients with rectal cancer there are two distinct differences in management which can affect overall pouch function: the increased use of handsewn anastomosis (especially for distal rectal tumors) and the need for neoadjuvant chemoradiation or adjuvant chemotherapy.

IPAA with mucosectomy and handsewn anastomosis is a more demanding procedure that consists of stripping the anal transitional zone and suturing the anastomosis. Alternatively, the stapled anastomosis retains the distal rectal mucosa (possibly increasing the risk for local recurrence), but is superior in terms of postoperative defecatory function. It has been shown extensively that the stapled technique has a superior functional outcome and better quality of life than hand-sewn anastomosis with mucosectomy [9]. The oncologic advantage of the hand-sewn technique is challenged in several articles that support the use of a stapled approach. In 2009, Zmora [10] and Cohen [11] demonstrated that for most colorectal cancer patients with ulcerative colitis, the stapled IPAA is a reasonable and safe option.

The use of radiation therapy before or after IPAA has not been analyzed extensively. This is because in all the published studies, it is clearly stated that the

Table 30.3 Studies of the consequence of radiation therapy and IPAA

Study	Rectal cancer	Postoperative radiation	IPAA failure	Quality of evidence
Radice [13]	21	5	3	Low
Remzi [5]	26	1	1	Low
Gorfine [8]	14	2	1	Low
Inoue [14]	1	1	0	Low

majority of the IPAAs were performed for early stage cancers and that most of the patients with advanced rectal cancers declined radiation therapy. Wu [12] reported the largest cohort of patients with rectal cancer with preoperative radiation therapy that received an IPAA (n = 9), and compared their outcomes with patients undergoing IPAA without pelvic radiation. Chronic pouchitis was significantly more common in patients with neoadjuvant chemoradiation. Furthermore, almost half of the rectal cancer radiated patients (43%) lost their pouch during the follow up period, while only 17% of the non-radiated pouches were excised over the same time period. The average time for a radiated pouch to fail was 60 months. The study concluded that pelvic radiation administered prior to IPAA creation appears to be associated with worse pouch outcomes.

Several studies have demonstrated that postoperative radiation is linked to a high chance for pouch failure (see Table 30.3).

Recommendations Based on Data

Patients with ulcerative colitis and early (T_1 or T_2, N_0) rectal cancer can undergo IPAA instead of TPC with end ileostomy and expect comparable oncologic outcomes (Weak Recommendation based on Low Quality Evidence).

Patients with ulcerative colitis requiring neoadjuvant or adjuvant chemoradiation for locally advanced rectal cancer should not be offered IPAA, but rather undergo a TPC with end ileostomy (Strong Recommendation based on Moderate Quality Evidence).

Personal View

Patients with rectal cancer in the setting of ulcerative colitis need to undergo a sound oncologic operation and at the same time, attempt to have a curative resection for their ulcerative colitis. The sequence from dysplasia to cancer in the background of inflammation from ulcerative colitis patients is less predictable, and may occur at a rate faster than what is seen with the traditional adenoma to carcinoma sequence [15]. Thus, patients with ulcerative colitis and colorectal cancer are at higher risk of developing another cancer in the remaining inflamed colon or rectum. This can occur in the remaining rectum when total abdominal colectomy is performed for

either initial colon cancer treatment or severe colitis, and there is a subsequent delay in removing the retained rectum. In those patients undergoing TAC for dysplasia or cancer, close surveillance of the rectum is necessary to avoid the development of a second rectal malignancy, prior to either completion proctectomy or IPAA reconstruction.

Thus, UC patients with a rectal cancer have two options; either an IPAA or a TPC with end ileostomy. The current data is insufficient to support a firm recommendation. While all available data suggests that oncologic outcomes for both procedures are equivalent, it is clear that in all the studies, there was a very strict pre-selection of patients. IPAA can be safely performed as a primary or secondary procedure in conjunction with radical resection of the tumor bearing rectum in most early (T_1, T_2, N_0) rectal cancer patients. As in patients who do not have ulcerative colitis, if the tumor is invading sphincter muscles or reaches the level of the dentate line, radical resection without reconstruction is recommended. In a similar fashion, for symptomatic patients (i.e. bleeding or obstructing tumor) or with metastatic disease, a TPC with an end ileostomy would be the lowest risk procedure to get the patient to chemotherapy as soon as possible.

A significant challenge remains for patients with more advanced rectal cancer who require neoadjuvant chemoradiation or adjuvant chemoradiation. Patients with locally advanced rectal malignancies who undergo IPAA are at greater risk of pouch excision, diversion and death. Preoperative combined chemoradiation for Stage II or III rectal lesions followed by IPAA is theoretically possible; however with the small amount of data presently available, these patients are at significantly increased risk for pouch failure and subsequent pouch excision. In addition, a significant number of colorectal cancers may be found only after the surgical excision is done ostensibly for dysplasia and adjuvant chemoradiation therapy may then be required. Patients with rectal lesions who already received an IPAA and now require postoperative chemoradiation are probably best treated by deferring the radiation and utilizing just chemotherapy. Postoperative adjuvant chemotherapy is compatible with this approach, and does not appear to increase the risk for pouch failure or any other complications. The use of preoperative chemotherapy has recently emerged as an option in the care of patients with locally advanced rectal cancers but has not been studied in IPAA patients.

In conclusion, early stage (T_1, T_2, N_0) upper and mid rectal tumors in the setting of ulcerative colitis can be safely treated with restorative proctocolectomy (IPAA) with acceptable oncologic and functional outcomes when compared to TPC with end ileostomy. Adjuvant chemotherapy if needed is safe. Distal rectal tumors in patients should be considered for TPC with end ileostomy.

Neoadjuvant or adjuvant chemoradiation is associated with high incidence of pouch failure and complications. Thus, IPAA is not recommended in patients with locally advanced tumors that need neoadjuvant radiation therapy. No data exists on the role of neoadjuvant chemotherapy for locally advanced rectal tumors in the setting of ulcerative colitis with subsequent IPAA.

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