PREOPERATIVE CHEMORADIATION FOR LOCALLY ADVANCED LOW LYING RECTAL CANCER: PRELIMINARY RESULTS

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Abstract- Optimal management of low lying locally advanced rectal cancer remains a major challenge. This study was performed to evaluate the impact of preoperative external radiation therapy combined with systemic chemotherapy on sphincter preservation and local control in locally advanced low lying (<5 cm from anal verge) rectal cancer. A total of 25 consecutive patients with biopsy proven locally advanced low lying rectal cancer were treated with preoperative 5FU (750 mg/m²/day, first and fifth week of radiation) and external beam radiation (45 GY in 25 fractions over 5 weeks) followed by radical resection. Surgery was performed 4-6 weeks after the end of chemoradiation. There was no major acute toxicity following chemoradiation and all patients completed their scheduled preoperative therapy. A complete pathologic response to preoperative chemoradiation was confirmed in 3 patients (12%). The pathologic tumor stages in the remaining patients were: T3N0 (n = 4, 18%), T3N1 (n = 3, 14%), T4N0 (n = 9, 41%), and T4N1 (n = 6, 27%). Eighteen patients (72%) had a sphincter saving surgical procedure but sphincter was finally preserved in 16 patients (64%). A perfect continence was achieved in 85% of cases. There were 2 (8%) perioperative mortality and 9 (36%) perioperative morbidity. In 3 (12%) patients a reoperation was required. At a median follow up of 27 months, local recurrence was observed in 1 patient (4.3%) and distant metastases in 5 patients (21.7%). It seems that preoperative chemoradiation for locally advanced rectal cancer may provide higher rate of sphincter preservation.

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INTRODUCTION

Optimal management of low lying locally advanced rectal cancer remains a major challenge. These tumors have been traditionally treated by abdominoperineal resection (APR) but even with total mesorectal excision (TME) and adequate radial and distal margins, radiation must be used to reduce the risk of local recurrence (1). Although postoperative adjuvant chemoradiotherapy is considered standard treatment in many centers, preoperative radiotherapy can improve local control and decrease toxicity compared with postoperative radiation (2). Also preoperative radiotherapy and specially chemoradiation can facilitate a curative resection and increase the chance of sphincter preservation. Thus with technical improvements and preoperative neoadjuvant treatment sphincter sparing procedure can be used rather than APR. The best regimen of preoperative chemoradiation is still under debate. Continuous infusion of 5-fluorocytosine (5FU) is considered standard; also, oral pyrimidine analogue (3-5) or irinotecan (6) and oxaliplatin (7, 8) have been evaluated.

We used the rapid infusion of 5FU concurrent with external pelvic radiation and our aim was to evaluate ability of this neoadjuvant treatment to preserve sphincter in locally advanced low lying rectal adenocarcinoma. Also, we evaluated tumor downstaging, surgical morbidity and patterns of failure.

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MATERIALS AND METHODS

From September 1999 to September 2001, 25 consecutive patients with primary locally advanced adenocarcinoma of the middle and lower rectum underwent proctectomy at Cancer Institute, Tehran University of Medical Science (TUMS) after preoperative chemoradiation. Locally advanced rectal cancer was defined as tumor extension through the bowel wall and/or involvement of lymph nodes, based on clinical and/or radiologic evaluations.

We included all patients with operable low lying (0.5–5 cm from anal verge) locally advanced rectal cancer (T3, 4 or N positive) limited to pelvis, younger than 85 years with Health Organization/ Eastern Cooperative Oncology Group performance status < 2 and acceptable liver and renal function. Early stages (T1, 2N0) were not included. Patients with metastatic disease, frozen pelvis (involvement of pelvic wall in computed tomography [CT]), and patient who had non radical resection with remaining residue at the end of surgery were excluded.

We got the approval of TUMS ethic committee in March 1999. Any patient who had the inclusion criteria had an initial evaluation, including complete clinical history, physical examination, blood tests (liver function tests [LFT], carcinoembryonic antigen [CEA]), chest X-ray, proctoscopy and/or colonoscopy, ultrasonography and CT scan of the abdomen and pelvis. The operating surgeon examined the patients before starting preoperative therapy and declared the distance of tumor from anal verge and the type of operation required.

Chemotherapeutic agent for all patients was 5FU with a dose of 750 mg/m/day which was administered as a rapid infusion on five consecutive days during first and last week of pelvic radiotherapy (on days 1 to 5 and 29 to 33 during radiotherapy). Acute toxicity from the 5FU was monitored closely, non hematologic toxicity was monitored by close observation and hematologic toxicity by weekly complete blood count (CBC); transfusion was considered if hemoglobin fell under 8 gm/dl. Eighteen patients received a total dose of 45 GY (25 fractions of 1.8 GY/day) during 5 weeks; 7 patients with bulky circumferential tumor were given 50.4 GY (28 fractions of 1.8 GY/day).

Radical surgery was performed 4-6 week after completion of chemoradiation in the Trendelenburg-lithotomy position. From the abdominal incision, mobilization of the entire left colon, especially splenic flexure, and ligation of the inferior mesenteric artery and vein and sharp mobilization of the rectum and mesorectum on all sides to the level of the anorectal ring were performed. The hypogastric nerves were preserved specially in men. The perianal skin, sphincter muscle and anoderm just below the dentate line are included in deep traction sutures. The distal left colon was divided at a level to ensure adequate length to reach to anus and then the rectosigmoid was invertly pulled out from the anus and sharply incised 1 cm distal to the lowest part of tumor.

Frequently it was not possible to pull out the rectum containing bulky tumor, then we had sharply incised the anoderm just cephalad to the dentate line and the rectal muscular layer with 1-2 cm free distal margin through anal approach. All of distal margins were assessed by intraoperative frozen section and finally if a tumor free distal margin could not be obtained then an APR was performed.

The mean duration of hospitalization was 9 days. Perioperative complications and also long term morbidity were recorded. All patients received postoperative systemic chemotherapy. Follow up examinations were done at regular interval (every 2 months until 2 years and then every 4 months). At each visit an interval history, physical examination, LFT and CEA were obtained. A chest X-ray and colonoscopy were obtained yearly. CT scan was obtained when indicated by history, exam or CEA results.

In 16 patients who finally underwent sphincter preservation, sphincter function was assessed using a questionnaire based on Memorial Sloan-Kettering Cancer Center scale (Table 1).

Table 1. Memorial Sloan–Kettering Cancer Center scale

Excellent	1-2 bowel movements/day, no soilage
Good	3-4 bowel movements/day, and/or mild soilage
Fair	episodic > 4 bowel movements/day, and/or moderate soilage
Poor	incontinence

RESULTS

The mean age of the patients was 52 years (range 31–85). Other patient characteristics are shown in table 2. The median distance of the lowest edge of the tumor to the anal verge was 2.8 cm (range 0.5–5); it was lower than 3 cm in 16 patients, who were absolute candidates for APR. Tumor differentiation was not available in 6 cases (24%), was poor in 4 (16%) and good or moderate in 15 cases (60%).

All patients completed the entire course of preoperative chemoradiation. There was no grade 3 and 4 toxicity and all patients had grade 1 and 2 gastrointestinal (GI) toxicity; 2 patients had grade 2 mucosal toxicity. Sphincter preservation was done in 18 patients (72%) and APR was required in 7 (28%). Only 5 (28%) diversion (loop transverse colostomy) was done in sphincter saving group. Two patients who initially underwent coloanal anastomosis subsequently required APR due to fecal peritonitis in one and partial rupture of anastomosis and perineal abscess in another. Three (12%) patients had a complete pathologic response and in the remaining 22 patients the pathologic stages were T3N0 in 4 cases (18%), T3N1 in 3 cases (14%), T4N0 in 9 cases (41%) and T4N1 in 6 cases (27%).

Table 2. Patient and tumor characteristic (n = 25)

Character	Number (%)
Sex	
Male	18 (72%)
Female	7 (28%)
Procedure	
Sphincter saving	18 (72%)
Abdominoperineal resection	7 (28%)
T stage	
T3	7 (28%)
T4	15 (60%)
Complete pathologic response	3 (12%)
N stage	
N0	13 (52%)
N1	9 (36%)
Undetermined (complete pathologic response)	3 (12%)
Grade	
Well differentiated	5 (20%)
Moderately differentiated	10 (40%)
Poorly differentiated	4 (16%)
Undetermined	6 (24%)
Distal margin (in sphincter saving procedure)	
Negative (> 0.5 – 1 cm)	15 (60%)
Positive (microscopic in one or two points)	3 (12%)
Distance between the lower pole of the tumor and the anus	
0 – 30 mm	16 (64%)
31 – 50 mm	9 (36%)

Perioperative morbidity occurred in 4 patients (16%) including two anastomotic leak, two GI bleeding and one acute tubular necrosis and one severe wound infection (Table 3). Long term morbidity included one stricture that required rectal dilatation and one incisional hernia. There were two mortalities including one pulmonary thromboembolism on the 2nd postoperative day in an 85 years old woman with history of asthma and one acute respiratory distress syndrome on the 4th postoperative day following GI bleeding in a 65 years old man who underwent reoperation (vagotomy and pyloroplasty) because of failed endoscopic coagulation and conservative management.

With a median follow up of 27 months pelvic or local recurrence was documented in one patient who underwent coloanal anastomosis. He was a 73 years old man with a moderately differentiated node positive adenocarcinoma 3 cm from anal verge. He had a good response to preoperative treatment and his stoma was closed 3 weeks after proctectomy and he had completed postoperative chemotherapy. In his routine follow up colonoscopy one year after surgery, local recurrence in anal canal was found, CEA, chest X-ray and abdominal CT scan were normal but there were several pulmonary metastases in thoracic CT scan, thus there was no isolated pelvic recurrence in the absence of metastatic disease. 5 patients developed distant metastases. The primary site of metastases were the liver (n=2), the lung (n=1 with simultaneous local recurrence), the brain (n=1) and the peritoneum (n=1).

One of the patients with hepatic metastases underwent three metastasectomy and now she is candidate for a right hepatic lobectomy, but refuses the operation; she is one of the three complete pathologic responders and she has not local recurrence despite multiple liver metastases. The second complete pathologic responder developed peritoneal seeding and ascites and the third one is alive without disease. At the time of this preparing this paper, 3 patients have died, 2 alive with disease and the remaining 18 are alive and disease free.

Table 3. Complications of the operation after chemoradiation*

Complication	APR (n=7)	Sphincter Saving (n=18)
Leak	-	2 (11%)
Wound infection	1 (14%)	0
Pulmonary emboli	0	1 (5.5%)
Upper GI bleeding	2 (28%)	0
ATN	1 (14%)	0
Stenosis	-	1 (5.5%)
Incisional hernia	0	1 (5.5%)
Total	4 (57%)	5 (28%)

Abbreviations: APR, abdominoperineal resection; ATN, acute tubular necrosis; GI, gastrointestinal.
* Data are given as number (percent).

DISCUSSION

The Swedish rectal cancer trial has demonstrated that preoperative high dose radiotherapy reduces failure rate and improves survival (9). The addition of chemotherapy during the course of radiation is advocated based on the high risk for disseminated disease and use of chemotherapeutic agent as a radiosensitizer (10-18).

Sphincter preservation is the primary goal of preoperative chemoradiation for rectal cancer. Preoperative chemoradiation has been shown to reduce both the size and the proliferative activity of rectal tumor (13). Also comparing with postoperative chemoradiation, it has many advantages including tumor bed sterilization, lower total dose of radiation, easier displacement of the small bowel and lower rate of radiation enteritis (2, 19-25).

In a review of all randomized trials of preoperative and postoperative radiation for locally advanced rectal cancer, it has been considered that preoperative radiation is more dose efficient than postoperative radiation (26). Although it has been shown that patients treated with combined preoperative chemoradiation have done better than patients treated by postoperative adjuvant therapy (14, 27-36), few studies have achieved sufficient patient numbers and long term follow up to establish difference in outcomes among the treated group.

The rate of sphincter saving procedures ranges from 17% (30) to 84.3% (34), local recurrence rates were 0 to 11%, disease free survival and overall survival range from 60 to 80% and 72 to 100%, respectively, with a median follow up time ranging from 22 to 38 months.

The median follow up time of our study is 27 months and it is not sufficient for predicting our control rate, because it has been shown (37) that 5 years is required to detect 80% of all failures in patients who have undergone preoperative adjuvant therapy for rectal cancer, also the small number of patients (25 cases) in our study make every conclusion unreliable.

We think that we must improve other weak points of this study including preoperative staging, rapid infusion of chemotherapeutic agent and selective diversion. We can not evaluate exactly tumor downstaging in this study because our preoperative staging was done by digital rectal exam, sigmoidoscopy and CT scan; only two patients have had endorectal ultrasonography and magnetic resonance imaging (MRI). We were obligated to use rapid infusion and unfortunately sometimes bolos dose of 5FU because of administrative problems, but we knew that protracted infusional administration of 5FU concomitant to radiation showed better survival than bolus administration and we could have lower toxicity and better tolerance with continuous infusion of 5FU. Fortunately, toxicity was never severe enough to require suspension of treatment, most of them were grade I and II and easily manageable.

We have not done diversion routinely in every coloanal anastomosis. It is difficult to recognize suitable candidates for a single-stage procedure and a high mortality rate has been reported after uncovered anastomotic dehiscence. Diverting stoma reduces severity of anastomotic leakage and it might eliminate the need for permanent colostomy and perineal resection in our two cases of anastomotic leakage.

In view of small size of the study group and short follow up time our data should be interpreted with caution, and it seems that with the aid of preoperative chemoradiation sphincter saving can be feasible and survival rate can improve. The present study demonstrates that sphincter preservation is feasible in approximately 64% of patients after preoperative chemoradiation for low lying locally advanced rectal cancers that otherwise would required APR, but further studies and longer follow up is required to confirm these preliminary results.

Conflicts of Interests

We have no conflicts of interest.

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