Treatment of Rectal Cancer by Chemoradiation followed by Surgery: Analysis and Early Clinical Outcome in 66 Patients

Israel L. Nudelman MD1, Vladimir Fuko MD1, Alex Geller MD2, Eyal Fenig MD2 and Shlomo Lelchuk MD1

1Department of Surgery B, and Institutes of 2Oncology and 3Gastroenterology, Rabin Medical Center (Beilinson Campus), Petah Tiqva, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

Key words: preoperative chemoradiation, downstaging, low anterior resection, rectal cancer

Abstract

Background: Abdominoperineal resection entails the need for a permanent colostomy, which significantly reduces patient self-image and quality of life.

Objective: To investigate the effectiveness of preoperative chemoradiation in increasing the resectability rates of rectal cancer and increasing the anal sphincter preservation rate.

Methods: The study group included 66 patients aged 33–84 years with T1–T3 rectal carcinoma who were treated in our institute from 1997 to 2002 with preoperative chemoradiation followed by surgery 6 weeks later. All patients underwent preoperative transrectal endoscopic ultrasound for tumor staging and localization. The duration of follow-up was 25 months.

Results: Chemoradiation led to tumor downstaging in 61 patients (92.4%), all of whom underwent low anterior resection. Only 11.4% of this group needed a temporary (6 weeks) loop colostomy/ileostomy. None of the 16 patients with post-treatment T0 tumors had evidence of malignant cells on pathologic study. Five patients (7.6%) failed to respond to chemoradiation and underwent APR. There were no major complications, such as leakage, and no deaths.

Conclusions: Neoadjuvant chemoradiation is an effective modality to downstage advanced rectal cancer, improving patient quality of life by significantly reducing the need for a terminal permanent colostomy, or even a temporary one.

APR = abdominoperineal resection

A permanent colostomy, or even a temporary one, is a serious insult to the well-being and body image of patients with rectal cancer, and it limits their quality of life. One of the main goals of surgery in rectal cancer, besides cure, is to preserve normal sphincter function. Our continuing efforts to improve local control and to maximize sphincter preservation led us to consider the use of preoperative chemoradiation in affected patients because of its many advantages, namely, increased resectability rate due to tumor downstaging, decreased small-bowel radiation toxicity, no irradiation of the anastomosis, and no need for abdominoperineal resection, or even a protective temporary colostomy/ileostomy [1].

A pilot study published in 1995 showed that patients treated with a chemoradiation protocol followed by surgery 4 to 6 weeks later had better local control and better overall survival rates compared with a group of concurrent matched controls [2]. The findings were supported by a randomized trial in the Uppsala region of Sweden, which reported that preoperative radiation was more effective and better tolerated than postoperative adjuvant therapy for downstaging and local control of advanced rectal cancers [3], improving the quality of life of these patients by reducing the number of permanent terminal colostomies.

The aim of the present study was to evaluate the early clinical outcome of 66 consecutive patients with adenocarcinoma of the rectum treated with chemoradiation followed by surgery.

Patients and Methods

Sixty-six consecutive patients (30 men, 36 women), age range 33–84 years (median 61 years), with biopsy-proven rectal adenocarcinoma were treated in our institution between May 1997 and May 2002 with a protocol of chemoradiation followed 6 weeks later by low anterior resection (61 patients) or APR (5 patients) with total mesorectal excision.

The pretreatment evaluation included rectal digital examination, rectoscopy-anoscopy biopsy with pathologic confirmation of adenocarcinoma of the rectum, full colonoscopy to exclude other synchronous cancers, abdominal and pelvic computed tomography to rule out evidence of extrapelvic spread, complete blood count, blood chemistry, transrectal endoscopic ultrasound with an endorectal probe to evaluate staging, and exact localization and measurement of the lesion [4–6].

Preoperative chemotherapy was started concomitantly with radiation therapy, according to the protocol used in our department: chemotherapy, 5-fluorouracil 180 mg/m2/day as a continuous infusion 5 days/week via a Port-a-Cath, for 5½ weeks; radiation therapy: 4,500 cGy to the whole pelvic field followed by a boost of 540 cGy to the primary tumor; radiation was delivered using a three-field technique at 180 cGy/day, 5 fractions/week for 5½ weeks.

Surgery was performed 6 weeks later. Our department policy limits the combined treatment only to patients with localized disease.

Surgical technique

Before surgery, repeated endoscopic transrectal ultrasound examination was performed to evaluate the impact of the preoperative therapy on the tumor stage (Figures 1 and 2). Tumor location (distance from the anal verge) preoperatively is shown in Figure 3.

Sixty-one of the 66 patients underwent sphincter-sparing low anterior resection. We used a modified double-stapling technique in which the rectum was transected below the tumor perpendicular (90°) to the rectal axis with an endoscopic linear cutter (ETS-45, Ethicon Endosurgery, Cincinnati, OH, USA). This slim instrument,
taken from the laparoscopy armamentarium, can be easily introduced very deeply in the pelvis below the tumor. Its use was critical in overcoming the 1–2 cm distance that characterizes anterior resection as compared to the APR operation with end-colostomy. The colorectal anastomoses were performed transrectally with a CEEA stapler gun of 28–31 mm diameter.

Another technical problem was encountered in the 16 patients whose original tumor was downstaged to a small “ulcer” of 5 to 10 mm at its largest diameter (T_0 lesion). These tumors were very difficult to identify during surgery, and repeated concomitant rectoscopies were needed to localize them, even simultaneously with laparotomy and pelvic dissection of the rectum. They were marked by the gastroenterologist with a silk stitch according to the rectoscopy findings. Occasionally, we were able to mark them preoperatively through the rectoscope using India ink injected through a lumbar or cardiac needle. After the first few patients, to ensure identification of these remnant “ulcers” during surgery, we asked the gastroenterologist to mark them with India ink via a flexible sigmoidoscope, which has a better illumination source and displays the lesions on a video screen.

Each anterior resection anastomosis was checked for integrity and completeness of the donut tissue rings. Absence of leakage was further checked with transrectal injection of methylene blue solution through a Foley catheter. If findings were suspicious for leakage, we added silk (3-0) stitches to the anastomosis, and a protective colostomy or ileostomy was performed. Of the 61 patients who had anterior sections, 7 (11.4%) needed a protective temporary colostomy (n=5) or protective ileostomy (n=2). These were closed 6 weeks later.

**Results**

The preoperative protocol of concomitant chemotherapy and radiation was well tolerated by most of our patients. Only two patients (3%) developed grade III diarrhea. According to the endoscopic ultrasounds performed before and after chemoradiation, the distance between the anal verge and the lower edge of the tumor lengthened by approximately 20 mm, a sufficient amount to avoid APR in most cases that would otherwise not be amenable to low anterior resection. Tumor stage by endoscopic ultrasound before chemoradiation was T_3 in 51 patients (77%) and T_2 in 15 (23%). Following treatment, tumor stage was reduced to T_2 in 21 patients (32%), T_1 in 22 (33%), and T_0 in 16 (24%) [Table 1]. The T_0 tumors measured only 5–10 mm in diameter. They were very difficult to identify during surgery and there was no evidence of

<table>
<thead>
<tr>
<th>Stage of tumor</th>
<th>No. of patients</th>
<th>Stage of tumor</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>T_3</td>
<td>51 (77%)</td>
<td>T_1</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>T_2</td>
<td>15 (23%)</td>
<td>T_2</td>
<td>21 (34%)</td>
</tr>
<tr>
<td>T_1</td>
<td>22 (33%)</td>
<td>T_0</td>
<td>16 (24%)</td>
</tr>
<tr>
<td>T_0</td>
<td>16 (24%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 1. Tumor stage by transrectal endoscopic ultrasound (n=66)**
malignant cells on postoperative microscopic pathologic study (including 10–14 negative lymph nodes per specimen). The overall response rate to chemoradiation was 92.42%.

Only 5 patients (7.6%) required an APR. At presentation, all had very large $T_2$ lesions, estimated clinically to be between 4 and 6 cm or more at the largest diameter, occupying 50% or more of the rectal circumference, and located 2–4 cm from the anal verge. These patients had only a partial response to the chemoradiation protocol.

Only 11.4% of the 61 patients who had an anterior resection required a temporary colostomy/ileostomy (which was closed 6 weeks later), compared to 86% in the literature [1].

In one patient a liver metastasis was found in segment 3 at surgery and excised by non-anatomic segmentectomy. This finding was not noted on the pretreatment CT scans.

Wound infection with sepsis, treated by drainage, was observed in five patients, and a pelvic abscess, treated by CT-guided catheter drainage, occurred in two patients. There were no cases of leakage requiring repeated laparotomy. The mortality rate for the whole series was zero.

Postoperative hospital stay ranged from 8 to 10 days in 85% of the patients. During the mean follow-up of 25 months, routine carcinoembryonic antigen measurements, endoscopic ultrasonography examinations, CT scans, rectoscopies, and sigmoidoscopies revealed no signs of recurrent disease.

Late complications included a paracolostomy hernia in one patient 4 months after APR. The patient (aged 84) refused additional surgery. In six patients, a ventral hernia was diagnosed 4–6 months after surgery.

**Discussion**

Our preoperative chemoradiation protocol proved to be very effective in significantly downstaging the primary advanced rectal cancer [6–8]. In about 25% of the patients, the lesion was reduced to a small ‘ulcer’ that needed to be marked before surgery for accurate identification. Complete response was noted on pathologic study, with no evidence of tumor cells in the specimen (including 10–14 negative lymph node specimens). Similar results were published in the literature in recent years [9] with complete response rates of 5–27% [1]. Furthermore, of the 92% of patients who underwent low anterior resection, only 11.4% required a temporary colostomy/ileostomy (closed 6 weeks later), with zero mortality and zero morbidity [10].

Owing to the downstaging, the distance between the anorectal ring and lower edge of the tumor was lengthened by 20 mm or more. Therefore, at least 16% of the patients (10 patients) with an initial distance of 5 cm [Figure 3] could be spared APR with terminal colostomy. Low anterior resection was performed with the double-stapling technique using an endoscopic linear cutter, which can be introduced deep into the narrow pelvis below the tumor. Overall, our procedure enabled a considerable improvement in the quality of life of these patients.

Preoperative chemoradiation has several potential advantages over adjuvant therapy, such as less acute bowel toxicity and improved sphincter preservation [11–16]. Chemoradiation followed by anterior resection with total mesorectal excision might be considered the state-of-the-art management of locally advanced rectal cancers [16–19]. In the last 3 years it has led to a significant decrease in the number of APR operations. The proportion of sphinctersaving low anterior resections has increased from 20% before the preoperative chemoradiation era to 70% today [20–22].

The routine use of a protective (temporary) colostomy/ileostomy following very low anterior resection is no longer mandatory. In our series only 11% of the low anastomoses were protected by a colostomy/ileostomy, in contrast to 86% in an earlier study [1].

This procedure, however, should be done selectively, with routine use of methylene blue test to check the anastomosis for leakage and integrity of the donut ring after application of the CEEA stapler.

Our short follow-up of 25 months is not sufficient to draw conclusions regarding long-term local recurrence and survival of patients after tumor downstaging. However, the literature reports that the postoperative pathologic appearance of the primary tumor affects neither recurrence rate nor survival, although residual tumor in lymph nodes is indicative of an increased risk of recurrence [1,4,6,15,23]. There are also recent data showing a decreased local recurrence rate with T-stage reduction [24]. Longer follow-up is also needed to determine the influence of low anterior resection with a sharp mesorectal excision on survival [11,12].

Nevertheless, our study clearly suggests that chemoradiation followed by total mesorectal excision/anterior resection with end-to-end anastomosis using the double-stapling technique and the endoscopic linear cutter may serve as a major modality in the successful treatment of rectal cancer. This combined approach can potentially avoid the need for a permanent colostomy and improve the quality of life of patients without compromising the clear surgical margins.

In future investigations, neoadjuvant trials should focus on obtaining tissue from the primary tumor to find markers that can predict resistance or improved effect. The stratification of patients on the basis of molecular markers instead of the biological tumor response may prove to be more accurate and more predictive, especially in those with large tumors that are reduced to $T_0$. It is possible that these small, 5–10 mm, lesions will require only follow-up with repeat rectoscopies and biopsies or local excision by transanal endoscopic microsurgery. This would spare patients the need for laparotomy with pelvic dissection and low anterior resection, which has all the risks and disadvantages of major abdominal surgery [25].

To date, we still do not have the definitive answer to the question of whether local incision is sufficiently safe for small, stage $T_0$, ulcer-like lesions. Only time will tell.

**References**


**Correspondence:** Dr. I.L. Nudelman, Dept. of Surgery B, Rabin Medical Center (Beilinson Campus), Petah Tiqva 49100, Israel.

Phone: (972-3) 937-6201
Fax: (972-3) 937-6251
email: slecuik@clalit.org.il

---

**Capsule**

**Loss of imprinting and cancer**

Loss of imprinting (LOI, a change in DNA methylation) of the gene encoding insulin-like growth factor-2 (IGF-2) correlates with the development of human colorectal cancer and may serve as a possible marker for cancer screening. To determine if this epigenetic change, which modestly increases IGF-2 expression, has a causal role in tumorigenesis, Sakatani and collaborators created a mouse model of LOI. The LOI mice developed twice as many intestinal tumors as did controls, and their normal intestinal epithelium was shifted toward a less differentiated state, a pathological change also detected in humans with LOI. Thus, epigenetic changes may affect cancer risk by altering the maturational state of the normal tissue from which tumors arise.

Eitan Israeli

---

**Capsule**

**Team work – the bigger the better**

What are the factors required to build a successful creative team? A network analyses to model such factors found a clear relation among team diversity, collaboration network structure, and team performance. Within a scientific discipline, greater journal impact factor correlates strongly with larger teams, a lower tendency to “over-repeat” collaborations, and significant presence of both experienced researchers and newcomers. Interestingly, in the 20th century, similar properties appear to have contributed to defining the most successful team composition for Broadway musical productions.

*Science* 2005;308:697
Eitan Israeli