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CLINICAL INVESTIGATION **Rectum**

LONG-TERM RESULTS OF INTRAOPERATIVE PRESACRAL ELECTRON BOOST RADIOTHERAPY (IOERT) IN COMBINATION WITH TOTAL MESORECTAL EXCISION (TME) AND CHEMORADIATION IN PATIENTS WITH LOCALLY ADVANCED RECTAL CANCER

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Background: We analyzed the long-term results of patients with locally advanced rectal cancer using a multimodal approach consisting of total mesorectal excision (TME), intraoperative electron-beam radiation therapy (IOERT), and pre- or postoperative chemoradiation (CRT).

Patients and Methods: Between 1991 and 2003, 210 patients with locally advanced rectal cancer (65 International Union Against Cancer [UICC] Stage II, 116 UICC Stage III, and 29 UICC Stage IV cancers) were treated with TME, IOERT, and preoperative or postoperative CHT. A total of 122 patients were treated postoperatively; 88 patients preoperatively. Preoperative or postoperative fluoropyrimidine-based CRT was applied in 93% of these patients.

Results: Median age was 61 years (range, 26–81). Median follow-up was 61 months. The 5-year actuarial overall survival (OS), disease-free survival (DFS), local control rate (LC), and distant relapse free survival (DRS) of all patients was 69%, 66%, 93%, and 67%, respectively. Multivariate analysis revealed that UICC stage and resection status were the most important independent prognostic factors for OS, DFS, and DRS. The resection status was the only significant factor for local control. T-stage, tumor localization, type of resection, and type of chemotherapy had no significant impact on OS, DFS, DRS, and LC. Acute and late complications ≥Grade 3 were seen in 17% and 13% of patients, respectively.

Conclusion: Multimodality treatment with TME and IOERT boost in combination with moderate dose pre- or postoperative CRT is feasible and results in excellent long-term local control rates in patients with intermediate to high-risk locally advanced rectal cancer. © 2006 Elsevier Inc.

Locally advanced rectal cancer, Intraoperative radiotherapy, Radiotherapy, Local control, Intraoperative electron-beam radiation therapy, Multimodality treatment.

INTRODUCTION

Rectal cancer is one of the most frequent cancers in both men and women. According to the Federal Statistical Office of Germany, 12,000 inhabitants were diagnosed with colorectal cancer in 2001, accounting for 30% of all newly diagnosed gastrointestinal malignancies. Between 1990 and 1999, the mortality decreased by 15% from 9.3 to 7.9/100,000 inhabitants (www.destatis.de). This can partly be attributed to an improved surgical technique (total mesorectal excision [TME]) as well as interdisciplinary efforts, especially the routine use of combined chemoradiation in a multimodal treatment strategy (1–4). Depending on tumor stage, operation technique, and type of treatment, it is estimated that yet 5–25% of patients will develop an uncontrollable pelvic recurrence (3–6). Patterns of failure after radical surgery of rectal cancer identify the presacral-perineal space as the primary site for relapse, with 80% of all local recurrences being located in this area (7). Local dose escalation by external beam radiotherapy (EBRT) is known to be directly associated with increased tumor control, but is often limited by surrounding risk structures (small bowel, bladder) (8, 9). The most obvious rationale for integrating

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an intraoperative electron boost instead of a small volume external beam boost is that, by the intraoperative procedure, a high dose to the area of highest risk for tumor cell persistence is delivered while dose-limiting structures such as small bowel, bladder, or ureters (10–13) can be mechanically excluded. Moreover, the higher biologic effectiveness of the intraoperative single-dose radiotherapy (10 Gy intraoperative electron-beam radiation therapy [IOERT] corresponds with approximately 20–30 Gy fractionated external beam irradiation) has the potential to further improve the therapeutic ratio of local control and toxicity (14, 15). IOERT is a boosting technique that has been proven to be feasible and can easily be integrated in the multimodal treatment of locally advanced rectal cancer without increased normal tissue toxicity (16). IOERT boosts have already proven to allow dose reduction of EBRT in pediatric malignancies and sarcoma patients (17–19). The objective of this report was to analyze long-term clinical results after the treatment of locally advanced rectal cancer using a multimodal approach consisting of TME, IOERT, and moderate dose pre- or postoperative chemoradiation.

PATIENTS AND METHODS

Between 1991 and 2003, 243 patients were treated with TME and IOERT. Eligible were patients with intermediate- and high-risk locally advanced rectal cancer (staging before start of treatment: T3/4 tumors with perirectal invasion >5 mm or $N+$ situation) (6, 20). Twenty-nine patients with potentially resectable liver metastases met the premise of curative intention and were also included. Thirty-three patients did not receive EBRT because radiotherapy was declined by the patient or postoperative histopathologic staging revealed Stage I disease and were excluded from further analysis. The data of the resulting 210 patients were evaluable.

Initial investigation in all patients included clinical examination, complete blood cell count, serum biochemistry, carcinoembryonic antigen (CEA), endorectal ultrasound, recto- or colonoscopy with biopsy, computerized tomography of abdomen and pelvis, X-ray or computerized tomography of the chest, bone scan, and any additional test needed to evaluate specific comorbidity present at time of diagnosis. Thirty-five patients had an additional magnetic resonance imaging scan of the pelvis. Follow-up examinations were routinely performed in our institution, either in the department of surgery or radiation oncology and included clinical examination with special regard to side effects, blood count and serum chemistry, CEA, chest X-ray, and computed tomography or magnetic resonance imaging of abdomen and pelvis.

A total of 122 patients received postoperative radiation therapy. Simultaneous chemotherapy was administered in 88% of these patients, either as intravenous bolus of 350 mg/m^2 5-FU in combination with Leucovorin 20 mg/m^2 in Weeks 1 and 5 of the EBRT and sequentially every 4 weeks over 4 months after chemoradiation (69 patients) or as continuous intravenous 24 h infusion of 5-FU (1000 mg/m^2/week) during the whole course of chemoradiation (53 patients). In all 88 preoperatively treated patients, fluoropyrimidine-based chemoradiation was given either as continuous intravenous 24 h infusion of 5-FU (1000 mg/m^2/week) (70 patients) or orally as capecitabine two times daily 825 mg/m^2 (12 patients) during the whole course of chemoradiation. No adjuvant chemotherapy was given after preoperative treatment. Median age was 61 years (range, 26–82 years); 145 patients were male and 65 were female. For detailed patient characteristics see Tables 1 and 2. In preoperatively treated patients, the clinical staging was used for the further analysis, whereas in postoperatively treated patients, the further analysis was based on the histopathologic staging.

Table 1. Patients and treatment characteristics

	All patients	Preoperative CRT	Postoperative CRT
Gender			
male	145 (69%)	61 (69%)	84 (69%)
female	65 (31%)	27 (31%)	38 (31%)
Age (years)			
median	61	60	61
range	26–81	26–75	28–81
Follow-up (month)			
median	61	58	63
range	2–177	4–161	2–177
median survivors	72	62	102
range survivors	14–177	14–161	36–177
IOERT dose (Gy)			
median	10	10	10
range	8–18	8–15	10–18
IOERT energy (MeV)			
median	8	8	8
range	6–18	6–18	6–12
IOERT field size (cm)			
median	7.5	7	7.5
range	6–10	6–9.5	6–10
EBRT dose (Gy)			
median	41.4	41.4	41.4
range	16–57	28.8–55.5	16–57

Abbreviations: CRT = chemoradiation; IOERT = intraoperative electron-beam radiation therapy; EBRT = external beam radiation therapy.

Acute toxicity was assessed by applying CTC version 2.0; late toxic effects were scored according to European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group criteria. Toxicity from surgery, IOERT, and chemoradiation were pooled because of the difficulty to precisely distinguish between the contribution of each treatment.

The intraoperative radiotherapy was performed in a dedicated operation theater with an integrated Siemens Mevatron ME linear accelerator (Siemens, Concord, CA) capable of delivering 6–18 MeV electrons and thus covering a depth up to 6 cm. The IOERT dose was prescribed to the 90% isodose (dose rate of 9 Gy/min) and covered the presacral space, known as the region with the highest risk for local recurrence. In case of T4 stage, the area of fixation/infiltration was also included in the IOERT field. Median field size of the IOERT was 7.5 cm, ranging from 6 to 10 cm. The applicator diameter was chosen according to the size of the presacral space. To encompass as much presacral space as possible, all applicators employed were 22° beveled. Median IOERT dose was 10.4 Gy (10 Gy in complete resected patients [R0], 12 Gy in microscopically incomplete resection proven by instantaneous sectioning [R1], and 15 Gy in case of gross tumor residue [R2]) employing 8–12 MeV electrons (median, 8.4 MeV). Further details of our IOERT technique have been previously described (17–19). During the study period, no IOERT procedure had to be cancelled.

Electron-beam radiation therapy dose was 41.4 Gy in daily fractions of 1.8 Gy. EBRT was applied by linear accelerator (18