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CLINICAL INVESTIGATION **Rectum**

PHASE II STUDY OF PREOPERATIVE HELICAL TOMOTHERAPY FOR RECTAL CANCER

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Purpose: To explore the efficacy and toxicity profile of helical tomotherapy in the preoperative treatment of patients with rectal cancer.

Patients and Methods: Twenty-four patients with T3/T4 rectal cancer were included in this nonrandomized noncontrolled study. A dose of 46 Gy in daily fractions of 2 Gy was delivered to the presacral space and perineum if an abdominoperineal resection was deemed necessary. This dose was increased by a simultaneous integrated boost to 55.2 Gy when the circumferential resection margin was less than 2 mm on magnetic resonance imaging. Acute toxicity was evaluated weekly. Metabolic response was determined in the fifth week after the end of radiotherapy by means of fluorodeoxyglucose-positron emission tomography scan. A metabolic response was defined as a decrease in maximal standardized uptake value of more than 36%.

Results: The mean volume of small bowel receiving more than 15 Gy and mean bladder dose were 227 ml and 20.8 Gy in the no-boost group and 141 ml and 21.5 Gy in the boost group. Only 1 patient developed Grade 3 enteritis. No other Grade 3 or 4 toxicities were observed. Two patients developed an anastomotic leak within 30 days after surgery. The metabolic response rate was 45% in the no-boost group compared with 77% in the boost group. All except 1 patient underwent an R0 resection.

Conclusions: Helical tomotherapy may decrease gastrointestinal toxicity in the preoperative radiotherapy of patients with rectal cancer. A simultaneous integrated radiation boost seems to result in a high metabolic response rate without excessive toxicity. © 2008 Elsevier Inc.

Rectal cancer, Preoperative radiotherapy, Intensity-modulated radiotherapy, Helical tomotherapy, Simultaneous integrated boost.

INTRODUCTION

Short-term preoperative radiotherapy (RT) decreased the risk of local recurrence in patients with rectal cancer who underwent total mesorectal excision (TME) (1). In the TME-alone arm, the circumferential resection margin (CRM) appeared to be a strong prognostic factor for local recurrence. A CRM of 2 mm or less (narrow CRM) was associated with a 16% risk of local recurrence compared with 5.8% in patients with more mesorectal tissue surrounding the tumor (wide CRM) (2). Preoperative RT significantly decreased the rate of local recurrence at 2 years in patients with a wide CRM to 0.9%, whereas it was inefficient in patients with a narrow CRM (3). In an attempt to improve the outcome of patients with locally advanced rectal cancer, the German Rectal Cancer Study Group compared preoperative 5-fluorouracil (5-FU)–based chemoradiotherapy (CRT) with standard postoperative 5-FU–based CRT (4). Preoperative CRT was superior in terms of local control and toxicity (5). However, it was still associated with acute and late Grade 3 or 4 toxic effects in 27% and 14% of patients, respectively. Two recent Phase III trials, European Organization for Research and Treatment of Cancer 22921 and Fédération Francophone de Cancérologie Digestive (FFCD) 92933, showed an advantage of preoperative 5-FU–based CRT over RT alone with respect to local control, but not with respect to the occurrence of distant metastasis or survival (6, 7).

Current strategies in rectal cancer are based mainly on the integration of oxaliplatin, irinotecan, capecitabine, cetuximab,

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and/or other molecular-targeted drugs in the preoperative CRT schedule (8–12). However, considering the excellent local control rates in patients with a wide CRM and the lack of a significant overall survival impact of preoperative RT or CRT, decreasing the toxicity seems a priority.

One way to achieve this is to decrease the volume of normal tissue that is irradiated. Considering the horseshoe-shape form of the planning target volume (PTV), with the small bowel and bladder lying in the middle, intensity-modulated RT (IMRT) seems to be the treatment of choice. The concave and sharp dose gradients created by IMRT of course are less forgiving than conventional RT plans in terms of treatment uncertainties and require daily accurate positioning, which can be obtained with the recent evolution in image-guided RT (IGRT). The TomoTherapy Hi·Art II System (TomoTherapy Inc., Madison, WI) offers an elegant way to implement this concept in daily practice because it fully integrates IGRT by means of megavolt (MV) computed tomography (CT) scanning and IMRT by means of dynamic rotational therapy (helical tomotherapy) (13). Another potential advantage of this technique is the possibility to deliver a simultaneous integrated radiation boost on the gross tumor volume. This may represent an alternative strategy to the concomitant administration of chemotherapy to high-risk patients.

Based on these considerations, we decided to evaluate the use of helical tomotherapy in preoperative RT for patients with rectal cancer. We treated 24 patients with T3–T4 tumors by using 23 fractions of 2 Gy. Patients with a narrow CRM received a simultaneous integrated boost to a cumulative dose of 55.2 Gy. The aims of this Phase II study are to explore the toxicity profile and efficacy of this approach and optimize IMRT of patients with rectal cancer.

PATIENTS AND METHODS

This study was approved by the ethics committee of the UZ Brussel (2005/121). Each patient gave written informed consent before being accrued.

Eligibility criteria

Eligibility criteria included histopathologically confirmed rectal adenocarcinoma with an inferior border within 15 cm of the anal verge. The tumor had to have evidence of T3 or T4 disease on magnetic resonance imaging (MRI). Patients with unresectable metastatic disease with Eastern Cooperative Oncology Group performance status greater than 3 and patients not deemed fit for surgery were excluded. Pregnant or lactating patients, women with childbearing potential who lacked effective contraception, and patients younger than 18 years also were excluded. No upper age limit was defined.

Pretreatment evaluation

Pretreatment evaluation included a complete history and physical examination, digital rectal examination, colonoscopy, biopsy, MRI of the pelvis, fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan, chest radiograph, and electrocardiogram. Endoluminal ultrasound was used for defining tumor extension within the mucosa and submucosa, when indicated. Complete laboratory tests included a full blood count, blood electrolytes, creatinine, urea, liver transaminases, γ-glutamyltransferase, alkaline phosphatase, total bilirubin, and carcinoembryonic antigen.

The CRM was evaluated on MRI as described by the Magnetic Resonance Imaging and Rectal Cancer European Equivalence (MERCURY) study group (14). This group showed that MRI enabled measurement of the depth of extramural tumor spread within 0.5 mm of histopathologic assessment. Based on MRI, patients were divided into a group with a wide CRM (>2 mm) and a group with a narrow CRM (≤2 mm).

Preoperative RT

Preoperative RT was performed using helical tomotherapy (TomoTherapy Hi·Art II System). Patients with a wide CRM received 23 fractions of 2 Gy within 5 weeks. The primary tumor, its mesentery, and lymph nodes along the internal iliac and inferior mesenteric vessels were included in the clinical target volume (CTV_46 Gy). The perineum was included if an abdominoperineal resection was deemed necessary by the surgeon. Patients with a narrow CRM received a simultaneous integrated boost to 55.2 Gy on their primary tumor (CTV_55.2 Gy), which was delineated after fusion of CT, MRI (T2 weighted turbo spin echo), and FDG-PET images on a Pinnacle 7.4 contouring system (Philips Medical Systems, Milpitas, CA). The MRI (axial T2 weighted turbo spin echo; 3-mm slice thickness) was used as reference radiologic image to delineate the primary tumor and its mesentery. Lymph nodes along the internal iliac and inferior mesenteric vessels were delineated on CT scan (window, 500; level, 750). The FDG-PET was performed essentially for response evaluation and integrated in the contouring system as experimental imaging. Metabolic volume (MV) was measured by means of summation of the pixels with a standardized uptake value (SUV) of 2.5 or greater. The CTV_46 Gy was expanded with 1 cm toward the PTV_46 Gy, according to the national Project on Cancer of the Recturn (PROCARE) guidelines (15). A less conservative CTV-PTV margin of 0.5 cm was applied for the CTV_55.2 Gy, considering the experimental character of the simultaneous integrated boost and that daily positioning with MV-CT imaging should minimize the setup margin.

The small bowel and bladder were delineated as organs at risk. Treatment planning was performed using the integrated planning system, based on collapsed cone superposition. The goals were to give at least 95% of the prescribed dose to at least 95% of the PTVs while keeping irradiated volumes of the organs at risk as low as possible. Based on data from Baglan *et al.* (16), we tried to minimize the volume of small bowel receiving 15 Gy or greater (V_{15}) considering its strong relationship with Grade 3+ acute small-bowel toxicity.

A fan beam thickness (FBT) of 2.5 cm was used for treatment planning. This choice was made because the larger available FBT of 5 cm resulted in a too-large penumbra in the craniocaudal direction, thus irradiating more healthy tissue. Using the smaller available FBT of 1 cm resulted in an average overall treatment time of more than 1 hour compared with 25 minutes with the FBT of 2.5 cm. Pitch ranged from 0.287 to 0.31 (17). No research in pitch optimization was performed. Modulation factor varied from 2 to 3, depending on homogeneity and conformity index. The reported dose–volume histograms (DVHs) are the mean of the entire group of patients, with the SD plotted by a dashed line. Target dose homogeneity was evaluated by using an inhomogeneity factor: $U = (D_{99} - D_1)/Dmed$, where D_{99} is the dose below which 99% of the volume was treated (surrogate for maximum dose), D_1 is the dose below which 1% of the PTV was treated (surrogate for minimum dose), and Dmed is median PTV dose. The gradient toward the boost region was evaluated by means of the conformity index (total volume