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Clinical Investigation: Gastrointestinal Cancer

Phase II Study of Preoperative Helical Tomotherapy With a Simultaneous Integrated Boost for Rectal Cancer

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Summary

Concomitant chemotherapy with preoperative RT is standard of care for cT3-4 rectal cancer, but has considerable acute and late toxicity. An alternative to concomitant chemotherapy tested in this study was radiation alone using IMRT-IGRT with a simultaneous integrated boost by the Tomotherapy Hi-Art II system to 55.2Gy. This approach demonstrated a favorable acute toxicity profile and promising local control in patients with an anticipated narrow circumferential resection margin

Purpose: The addition of concomitant chemotherapy to preoperative radiotherapy is considered the standard of care for patients with cT3−4 rectal cancer. The combined treatment modality increases the complete response rate and local control (LC), but has no impact on survival or the incidence of distant metastases. In addition, it is associated with considerable toxicity. As an alternative strategy, we explored prospectively, preoperative helical tomotherapy with a simultaneous integrated boost (SIB).

Methods and Materials: A total of 108 patients were treated with intensity-modulated and image-guided radiotherapy using the Tomotherapy Hi-Art II system. A dose of 46 Gy, in daily fractions of 2 Gy, was delivered to the mesorectum and draining lymph nodes, without concomitant chemotherapy. Patients with an anticipated circumferential resection margin (CRM) of less than 2 mm, based on magnetic resonance imaging, received a SIB to the tumor up to a total dose of 55.2 Gy. Acute and late side effects were scored using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Results: A total of 102 patients presented with cT3−4 tumors; 57 patients entered the boost group and 51 the no-boost group. One patient in the no-boost group developed a radio-hypersensitivity reaction, resulting in a complete tumor remission, a Grade 3 acute and Grade 5 late enteritis. No other Grade ≥3 acute toxicities occurred. With a median follow-up of 32 months, Grade ≥3 late gastrointestinal and urinary toxicity were observed in 6% and 4% of the patients, respectively. The actuarial 2-year LC, progression-free survival and overall survival were 98%, 79%, and 93%.

Conclusions: Preoperative helical tomotherapy displays a favorable acute toxicity profile in patients with cT3−4 rectal cancer. A SIB can be safely administered in patients with a narrow CRM and resulted in a promising LC. © 2012 Elsevier Inc.

Keywords: Preoperative radiotherapy, Rectal cancer, Helical tomotherapy, Simultaneous integrated boost, Image-guided radiotherapy

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Introduction

Several randomized trials established the important role of preoperative radiotherapy (RT) in patients with Stage II/III rectal cancer. Of these, the Swedish Rectal Cancer Trial demonstrated, after a median follow-up time of 13 years. a decreased risk of local recurrence and an overall survival (OS) benefit of 17% (9% vs. 26%) and 8% (38% vs. 30%), respectively, with the addition of preoperative RT compared with surgery alone (1). The prognostic impact of involvement of the circumferential resection margin (CRM) in rectal cancer is well established. A national study by the Norwegian Colorectal Cancer Group reported, in the total mesorectal excision (TME)—alone arm, a 5-year local recurrence rate of 45.2% in patients with a pathologic CRM of 0 mm, compared with 8.9% in patients with a pathologic wide CRM ($\geq$3mm) (2). Moreover, short-term preoperative RT may be insufficient in high-risk patients (CRM $\leq$1 mm) according to the data from the Dutch Colorectal Cancer Group (3). By improving the pathological complete response (pCR) rate and local control (LC) rate, the concomitant addition of chemotherapy to long-course preoperative RT is considered standard of care in locally advanced rectal cancer. Two Phase III trials, European Organization for Research and Treatment of Cancer (EORTC) 22921 and Fédération Francophone de la Cancérologie Digestive (FFCD) 9203, demonstrated the advantage of preoperative 5-fluorouracil (5-FU)—based chemoradiotherapy (CRT) over RT alone with respect to LC, but not with respect to the occurrence of distant metastases or overall survival (4, 5).

However, Grade 3 toxic effects are commonly observed during and after chemoradiation, and are limiting radiation-dose escalation in a volume-dependent way. The German Rectal Cancer Study Group and Braendengen *et al.* reported any Grade $\geq$3 acute toxicity in 27% and 28% and any Grade $\geq$3 late toxicity in 14% and 17% of the patients undergoing CRT, respectively (6, 7). This justifies the implementation of more targeted radiation techniques such as intensity-modulated RT (IMRT), as its creation of steep dose gradients results in sparing of the surrounding healthy tissues, while allowing dose escalation to the tumor (8, 9). Because the resulting sharp dose gradients are less forgiving than conventional RT plans in terms of treatment uncertainties, daily positioning by image guidance is advisable (10—13). The TomoTherapy Hi-Art II System is a linac that fully integrates image—guided radiation therapy (IGRT) by means of megavolt (MV) computed tomography (CT) scanning and IMRT by means of dynamic rotational therapy (helical tomotherapy). Besides a decrease of the normal tissue complication probability (NTCP) and a minimization of the setup margin, another advantage of this technique is the possibility of delivering a simultaneous integrated radiation boost (SIB) on the gross tumor volume (14—16). As an alternative strategy to the concomitant administration of chemotherapy, we explored prospectively the feasibility and toxicity of helical tomotherapy with a SIB in locally advanced rectal cancer patients in a Phase II trial. In a previous report, we confirmed the activity and safety of helical tomotherapy in 24 patients (14). In the present article, we report on the early and late outcome of 108 patients with cT3—4 rectal cancer treated preoperatively with helical tomotherapy in a Phase II trial. The primary endpoint was LC, and the secondary endpoints were acute and late toxicity, the number of complete resections (R0), progression-free survival (PFS), and OS.

Methods and Materials

Patient population

Patients eligible for this study presented with histopathologically confirmed rectal adenocarcinoma with the inferior margin within 15 cm from the anal verge. In addition, the tumor had to have evidence of T3/T4 or N1/N2 disease on magnetic resonance imaging (MRI) or endoluminal ultrasound. Patients were required to have a European Cooperative Oncology Group (ECOG) performance status of 0 to 2, to be >18 years of age, and to be considered medically fit to undergo surgery. Patients with unresectable metastatic disease at diagnosis were excluded. Informed consent was obtained for the study protocol. The protocol was reviewed and approved by the ethics committee of our institution.

Pretreatment evaluation

Pretreatment evaluation included a digital rectal examination, laboratory test, colonoscopy, biopsy, endoluminal ultrasound,MRI of the pelvis, and fluorodeoxyglucose (FDG)—positron emission tomography (PET) and CT using a dedicated PET-CT camera (Gemini TF, Philips Medical Systems, Cleveland, OH). The CRM was evaluated on MRI as described by the MERCURY study group (17). This group showed that MRI enabled measurement of the depth of extramural tumor spread within 0.5 mm of histopathological assessment. Based on an estimate of the potential CRM by MRI, considering the mesorectal fascia to be the presumed circumferential extent of the surgical resection, patients with a narrow anticipated CRM ($\leq$2 mm), *i.e.,* a tumor to be found to extend within 2 mm of the mesorectal fascia on MRI, and wide CRM (>2 mm) were classified in the boost and no-boost groups, respectively.

Radiotherapy technique

Radiotherapy was carried out using the TomoTherapy Hi-Art II System (TomoTherapy Inc., Madison, WI). Irradiation technique, contouring details, treatment planning and positioning have been described extensively in previous studies (14—16). Essentially, the primary tumor, its mesorectum, and the lymph nodes along the internal iliac and inferior mesenteric vessels were included in the CTV. The primary tumor was delineated after fusion of CT, MRI (T2 weighted turbo spin echo) and FDG-PET images. The entire bladder and individual loops of small bowel and their mesentery were contoured from mid L4 to the lowest extent in the pelvis. In a previous study by Tournel *et al.*, an appropriate CTV-to-PTV margin was calculated by combining the internal organ movement by measuring the deformation of the mesorectum, and the intrafraction movement based on bony anatomy by use of MV-CT imaging (16). Based on this study, nonuniform margins of 8 mm in both lateral directions, 11 mm in the anterior, 7 mm in the posterior, and 10 mm in the craniocaudal directions were applied for the IMRT-IGRT plans. Patients were positioned in prone position with the patient's head placed in a prone pillow to avoid induced rotation in the transverse plane by torque of the neck and shoulders. Pitch and yaw rotations were avoided as much as possible by using laser marks on the patient's skin. Before each treatment session, patients underwent scanning using the integrated