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Phase II trial

Preoperative intensity-modulated and image-guided radiotherapy with a simultaneous integrated boost in locally advanced rectal cancer: Report on late toxicity and outcome

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ABSTRACT

Background and purpose: The addition of chemotherapy to preoperative radiotherapy has been established as the standard of care for patients with cT3-4 rectal cancer. As an alternative strategy, we explored intensity-modulated and image-guided radiotherapy (IMRT–IGRT) with a simultaneous integrated boost (SIB) in a prospective phase II study. Here, we report outcome and late toxicity after a median follow-up of 54 months.

Methods and materials: A total of 108 patients were treated preoperatively with IMRT–IGRT, delivering a dose of 46 Gy in fractions of 2 Gy. Patients ($n = 57$) displaying 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.

Results: The absolute incidence of grade $\geqslant 3$ late gastrointestinal and urinary toxicity was 9% and 4%, respectively, with a 13% rate of any grade $\geqslant 3$ late toxicity. The actuarial 5-year local control (LC), progression-free survival (PFS) and overall survival (OS) were 97%, 57%, and 68%. On multivariate analysis, R1 resection and pN2 disease were associated with significantly impaired OS.

Conclusions: The use of preoperative IMRT–IGRT with a SIB resulted in a high 5-year LC rate and non-negligible late toxicity.

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Current strategies in preoperative treatment of rectal cancer have been based mainly on the integration of oxaliplatin and molecular targeted drugs in the preoperative chemoradiotherapy (CRT) schedule, in an effort to improve the pathologic complete response (pCR) rate and to decrease the high incidence of distant recurrences. Based on 3 randomized trials, those agents do not seem to provide additive effects in terms of pathologic complete response (pCR) and circumferential resection margin (CRM) negative resection rates as compared to 5-fluorouracil (5-FU) based CRT, nevertheless an increased acute toxicity [1–3]. Although long-term follow-up data should be awaited, the addition of oxaliplatin to preoperative 5-FU based CRT does not seem to improve local control (LC), progression-free survival (PFS) or overall survival (OS) as compared to patients receiving 5-FU based CRT alone, according to the first follow-up data of the Prodige 2-ACCORD-12/405 trial [4]. Moreover, taking into account the lack of a significant impact on the occurrence of distant metastases or OS with the addition of 5-FU to preoperative RT and the considerable rate of grade 3 toxic effects during and after CRT [5–7], decreasing treatment related side effects remains an important endpoint in the therapeutic decision making. As an alternative strategy to the concomitant administration of chemotherapy during preoperative RT, we conducted a prospective phase II trial evaluating the efficacy and toxicity of preoperative intensity-modulated and image-guided radiotherapy (IMRT–IGRT) with a simultaneous integrated boost (SIB) by the TomoTherapy Hi-Art II System in locally advanced rectal cancer patients. We reported in previous studies on the synergism of improved dose distributions by IMRT and minimization of the setup margins by IGRT in decreasing the irradiated volume of small bowel and bladder [8,9], which resulted in a limited acute toxicity profile (1% grade $\geqslant 3$ acute toxicity) and promising 2-year LC rate of 98% in 108 cT3-4 rectal cancer patients treated preoperatively in a Phase II trial [10,11]. Here, we report on outcome and late toxicity after a median follow-up of 54 months.

Methods and materials

Inclusion criteria and study design

Patients had to present with histopathologically confirmed rectal adenocarcinoma with the inferior margin within 15 cm from

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the anal verge and evidence of T3/T4 disease on magnetic resonance imaging (MRI) or endoluminal ultrasound. Patients with unresectable metastatic disease at diagnosis were excluded. All patients signed the informed consent of the study protocol, which was reviewed and approved by the ethics committee of our institution. Based on an estimate of the potential CRM by MRI, patients with a narrow anticipated CRM ($\leqslant$2 mm) and wide CRM (>2 mm) entered the boost and no-boost group, respectively. The primary endpoint of this study was LC and the treatment was considered oncologically safe when 3 patients or less presented a local failure after 2 years, based on an accrual of 108 patients.

Radiotherapy technique

Preoperative RT was carried out with IMRT–IGRT 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 [10,11]. Briefly, we included the mesorectum and lymph nodes along the inferior mesenteric, obturator, and internal iliac vessels in the clinical target volume (CTV). The cranial border of the CTV was set at the bifurcation of the common iliac vessels into external/internal iliacs, which is corresponding with the level of L5–S1 interspace. Nonuniform planning target volume (PTV) 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 based on a previous study in our department [9]. All patients received a dose of 46 Gy in daily fractions of 2 Gy to the primary tumor, the mesorectum, and draining lymph nodes. The 57 patients of the boost group received a SIB of 0.4 Gy per day on the primary tumor, up to a total dose of 55.2 Gy (Fig 1). We tried to minimize the volume of small bowel receiving 15 Gy or greater ($V15_{SB}$ <150 ml) and mean bladder dose <21 Gy. Before each treatment session, patients underwent daily image guidance using the integrated megavoltage (MV) computed tomography (CT) modality and were repositioned after coregistration of these images with the planning kilovoltage (kV)-CT scan. Patients were advised to drink 250 ml of water 60 min prior to the planning CT and prior to every treatment session.

Surgical procedure

With a median time of 6 weeks after completion of preoperative IMRT–IGRT, 106 patients underwent a standardized total mesorectal excision (TME), of which 62% and 36% received a colo-anal anastomosis and abdominoperineal resection, respectively. A pCR (Dworak regression grade 4, ypT0N0) was achieved in 9 patients (8%), whereas Dworak regression grade 3 in 19 patients (18%), after evaluation of the resected specimen according to the recommendations of Quirke and Nagtegaal and van Krieken [12]. Incomplete microscopical resection (R1) was defined as a CRM of $\leqslant$1 mm from the inked non-peritonealized surface of the specimen and was reported in 8% (n = 8) of the patients. Classification according to the TNM staging of the American Joint Committee on Cancer (AJCC) revealed tumoral downstaging from cT3-4 to ypT0-2 in 40 patients (38%).

Toxicity monitoring and statistical analysis

Toxicity was scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE) version 3.0. Late toxicity was scored biyearly and updated for all patients before this article was written. Actuarial LC, PFS and OS were estimated by Kaplan–Meier analysis. Univariate (log-rank) and multivariate (Cox proportional hazards regression model) analyses were used to evaluate association between patient-related factors and treatment outcome. The association between the dose–volume constraints and late toxicity was evaluated using Fisher's Exact test and Spearman correlation analysis. A value of $p \leqslant 0.05$ indicated statistical significance.

Results

Patient characteristics

A total of 108 patients were enrolled consecutively between October 2005 and January 2010. In all, 102 patients (94%) and 93 patients (86%) had evidence of T3/T4 and N1/N2 disease, respectively, based on MRI or endoluminal ultrasound. Based on an estimate of the potential CRM by MRI, 57 patients (52%) had a T3 tumor with a narrow anticipated CRM ($\leqslant$2 mm) or a T4 tumor and entered the boost group, 51 patients (48%) had a wide CRM (>2 mm) and received no boost.

Late toxicity

We recorded a grade 3 or more late gastrointestinal (GI) toxicity in 10 patients (9%) after a median follow-up of 54 months (range, 27–79 months), of which 2 patients developed a grade 5 toxicity, 1 patient in the no-boost group with a hypogenesis of the upper müllerian structures resulting in a large volume of small bowel (1.263 ml) in the pelvis died due to grade 5 enteritis 16 months after initiation of RT, 1 patient in the boost group developed a grade 5 fistula between the small bowel and bladder and died due to septic shock 63 months after initiation of RT. Late toxicity figures are displayed in Table 1. Grade $\geqslant$2 late diarrhea was recorded in 12 patients (11%). Late symptoms of small bowel obstruction were reported by 8% of the patients, of which 2 patients and 1 patient grade 3 and 4, respectively. Of the 68 patients without a stoma, 35 patients (51%), of which 12 patients in the boost group and 23 patients in the no-boost group, experienced late fecal incontinence of whom 24, 10 and 1 patient(s), respectively grade 1, 2, and 4, the latter after intersphincteric surgery. Grade 2 and 3 stricture at the anastomotic site were observed in 10% (n = 7) and 3% (n = 2) of those patients, respectively. We did not find any difference in grade $\geqslant$2 or $\geqslant$3 late GI toxicity between the boost and no-boost groups.

Concerning late genitourinary (GU) toxicity, 4 patients (4%) experienced grade 3 or more late adverse events, of which 2 patients grade 4 urinary incontinence. One of these 2 patients received a definitive urinary diversion, the other received temporarily a suprapubic cystostomy and recovered later to a grade 2 incontinence. Twenty-nine patients (27%) reported some urinary incontinence, of whom 21 and 8 patients were grade 1 and 2, respectively. One patient developed a grade 4 ureteral stricture due to radiation fibrosis wherefore ureteronephrectomy was performed. Grade 3 urinary retention was observed in 1 patient due to neurogenic bladder wherefore daily bladder catheterization was needed. Those 4 patients all received a boost, whereas no grade $\geqslant$3 late GU toxicity occurred in the no-boost group. Of the 47 men who were sexually active before treatment, 34 patients (72%) displayed grade $\geqslant$2 erectile dysfunction. Grade 3 dyspareunia due to vaginal stenosis was reported in 1 woman, grade 2 vaginal dryness and grade 2 dyspareunia in 4 and 5 female patients, respectively. We calculated a 5-year grade $\geqslant$3 rate of any late toxicity of 13.6% (95% CI, 8–23%). Of the 14 patients (13%) experiencing any grade $\geqslant$3 late toxicity, 8 patients received a boost.

Lastly, no association was found between $V15_{SB}$ >150 ml and recorded late diarrhea (52% grade $\geqslant$1 late diarrhea compared to 46% for the patients with a $V15_{SB}$ <150 ml, p = 0.49). We found a trend to increased late small bowel obstruction for the patients with a $V15_{SB}$ >150 ml (16% grade $\geqslant$1 obstruction compared to 5% when