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Rectal cancer

Irradiation with protons for the individualized treatment of patients with locally advanced rectal cancer: A planning study with clinical implications

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ABSTRACT

Background and purpose: Ongoing clinical trials aim to improve local control and overall survival rates by intensification of therapy regimen for patients with locally advanced rectal cancer. It is well known that whenever treatment is intensified, risk of therapy-related toxicity rises. An irradiation with protons could possibly present an approach to solve this dilemma by lowering the exposure to the organs-at-risk (OAR) without compromising tumor response.

Material and methods: Twenty five consecutive patients were treated from 04/2009 to 5/2010. For all patients, four different treatment plans including protons, RapidArc, IMRT and 3D-conformal-technique were retrospectively calculated and analyzed according to dosimetric aspects.

Results: Detailed DVH-analyses revealed that protons clearly reduced the dose to the OAR and entire normal tissue when compared to other techniques. Furthermore, the conformity index was significantly better and target volumes were covered consistent with the ICRU guidelines.

Conclusions: Planning results suggest that treatment with protons can improve the therapeutic tolerance for the irradiation of rectal cancer, particularly for patients scheduled for an irradiation with an intensified chemotherapy regimen and identified to be at high risk for acute therapy-related toxicity. However, clinical experiences and long-term observation are needed to assess tumor response and related toxicity rates.

Rectal cancer is a very common oncological diagnosis in western civilization [1] and represents a major socioeconomic and health issue [2]. Since the German Rectal Cancer Study Group and others [3–6] showed that preoperative radiochemotherapy improves locoregional tumor control as compared to postoperative radiochemotherapy (RCT), this preoperative multimodal setting became standard in treatment of rectal cancer stage II and III Union Internationale Contre le Cancer (UICC)/American Joint Committee on Cancer (AJCC) [7].

While very good local control rates can already be achieved by this sequence, distant metastases remain a major problem with nearly unchanged incidence rates [1,3].

To encounter this problem, intensified chemotherapy regimens are tested in different prospective clinical trials, at present [6,8,9]. In this context, it is well known that, whenever treatment modalities are intensified, the risk of severe acute toxicity with subsequent treatment aborts and incidences of late side effects in long-term follow-up are increased [10–13]. On the other hand, there is evidence that especially patients with high-grade acute organ toxicity during multimodal treatment of different tumor entities seem to benefit regarding tumor response and prognosis [14–19].

To solve this dilemma, a main target of ongoing clinical research is to identify subsets of patients with a high-risk for radiochemotherapy related high-grade acute organ toxicity. For these patients, treatment modalities should be optimized in the minutest details to warrant completion of planned radiochemotherapy schedules, whenever possible. As a first step, a close meshed monitoring including complete inpatient treatment during intensified combined radiochemotherapy or at least daily physical examination during ambulant treatment is recommended. Besides these clinical approaches, alternative treatment procedures will become even more important if it will be frequently possible to select high-risk patients before planned start of combined radiochemotherapy, e.g. by basic clinical parameters or bio molecular markers [20]. For example, lowering the exposure of the organs at risk due to new or improved irradiation techniques could represent another important component to reduce treatment related toxicity without compromising tumor response. Thus, an irradiation with protons, as a new

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promising technique, could make such contributions for a subset of high-risk patients who will probably profit by this intensive therapy, in the future.

At the moment, protons are commonly used for irradiation of different tumor entities like prostate or head-and-neck cancer, but were not tested for patients with rectal cancer, yet [21–23]. Thus, as a first step, the aim of the present study was to report theoretically analyses of four different treatment plans including protons, 3D conformal technique, intensity modulated radiotherapy (IMRT), and RapidArc (RA) as a Volumetric Modulated Arc technique for the preoperative irradiation of patients with locally advanced rectal cancer. To accomplish this, 25 consecutive patients treated according to the protocol of the CAO/AIO/ARO-04-trial [6] were analyzed with respect to technical and dosimetric aspects followed by a discussion of possible future clinical implications.

Material and methods

From 04/2009 to 5/2010, 25 consecutive patients with locally advanced rectal cancer (UICC stage II or III) were treated with preoperative radiochemotherapy at the department of Radiooncology at the University Medical Center Göttingen. All patients received pelvic irradiation with 50.4 Gy (1.8 Gy per fraction) and concomitant 5-FU-based chemotherapy. By default, the irradiation was carried out using RapidArc with two arcs (full gantry rotation around the patient) and photon energy of 6 $MV_{photons}$. Median age was 62.5 years (range 44–73); further patient characteristics are summarized in table 1. All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

Definition of target volumes and dose constraints

For all patients, four different treatment plans were calculated and analyzed. During the planning CT-scan all patients were placed prone using a belly board to reduce doses to small bowel mechanically as best as possible. Target volume definition and organs at risk (OARs) were outlined once on the same CT scan for all planning procedures by the same physician. The Clinical-Target-Volume (CTV) was defined according to the protocol of the CAO/AIO/ARO-04-trial [6] and included the presacral nodes, the complete mesorectal fascia and the common and internal iliac lymph nodes. The Planning-Target-Volume (PTV) was defined by adding a 3D anisotropic margin of 10 mm to the CTV. All treatment plans were generated according to current ICRU recommendations [24]. The dose distribution for all photon plans was calculated with the anisotropic analytical algorithm (AAA version 8.9, Varian Medical System, Helsinki, Finland) with a grid size of $0.2 \times 0.2 \times 0.2$ cm [25,26] and for the proton plans with the algorithm PCS (version 8.9, Varian Medical System, Helsinki, Finland) with a grid size of $0.25 \times 0.25 \times 0.25$ cm The critical structures including bladder, small bowel, anal sphincter, body and testes were contoured on each CT slice for the following dose-volume-histogram (DVH) analyses. The dose to the OARs was aimed to be as low as possible and must at least comply with the following constraints: bladder $\geqslant$65 Gy in $\leqslant$25% volume and $\geqslant$40 Gy in $\leqslant$50% volume; small bowel $\geqslant$50 Gy in $\leqslant$10 cm^3 volume and $\geqslant$40 Gy in $\leqslant$100 cm^3 volume; testes: as low as possible depending on the individual PTV.

Characteristics of planning procedure according to treatment technique

3D conformal

For 3D conformal (3D) plans, a three-field technique was customized for all individual PTV's using the treatment planning system (TPS) Eclipse (version 8.9, Varian Medical Systems, Helsinki, Finland). Beam angels were set to 0°, 90°, and 270° (Varian scale IEC 601) and irradiation was planned with photon energies of 6 $MV_{photons}$ for beam direction 0° and 20 $MV_{photons}$ for beam directions 90° and 270° and individual adopted weighting with a reference to a basic approach of 1.4:0.8:0.8. The Millennium 120 multi leaf collimator (MLC) (Varian Medical Systems, Palo Alto, CA, USA) was used to shape the treatment fields. The collimator angle was set to 0° and the dose rate to 300 monitor units per minutes (MU/min). For manual planning optimization, wedges (45° or 60°) were individually adopted for every patient.

Table 1
Pre-treatment characteristics of patients entered in study.

Characteristic	No. patients (%)
Gender	
Male	15 (60)
Female	10 (40)
UICC-stage	
II	6 (24)
III	19 (76)
T-status	
2	2(8)
3	16(64)
4	7(28)
N-status	
0	6 (24)
1	17 (68)
2	2 (8)

IMRT

The IMRT plans were calculated according to the dynamic sliding window method [21,27] with seven fixed gantry angles (0°, 51°, 103°, 154°, 206°, 257°, and 309°) and collimator angle 0°. The IMRT treatment fields were optimized using the dose volume optimizer (DVO, version 8.9.08, Varian Medical System, Helsinki, Finland). For gantry angels 0°, 51°, and 309° photon energy of 6 $MV_{photons}$ and for the angels 103°, 154°, 206°, and 257° 20 $MV_{photons}$ were prescribed. The dose rate was set to 500 MU/min.

RapidArc

RapidArc was introduced into clinical practice in several institutes after an intensive validation at planning level where it was compared to IMRT or other approaches [28–36]. All RapidArc plans were designed using a progressive resolution algorithm (PRO, version 8.9.08, Varian, Medical Systems, Helsinki, Finland). The single arc treatment field was split in 177 control points. The modulation was achieved by delivering 177 control points. For each control point, the beam aperture, as defined by the MLC, changed with the gantry angle. To deliver the intensity modulated dose to the patient, the dose rate varied between 0 MU/min to a maximum of 600 MU/min and the gantry rotation between 0.0°/sec and a maximum of about 4.8°/sec. To minimize the contribution of tongue and groove effect during the treatment the collimator was rotated between 15° and 45°.

Protons

All intensity modulated proton plans were generated by a generic proton beam through a spot scanning optimization technique implemented in Eclipse (version 8.9, Varian Medical Systems, Helsinki, Finland). Optimization of the weight values for the spots was performed starting from a dose deposition coefficient matrix which was calculated as the dose that would be deposited in each of the cloud points when irradiating each single spot of the initial list with unit intensity as was described in detail before [37]. The maximum energy available was 250 MeV with energy modulation in