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CLINICAL INVESTIGATION **Cervix**

CONVENTIONAL, CONFORMAL, AND INTENSITY-MODULATED RADIATION THERAPY TREATMENT PLANNING OF EXTERNAL BEAM RADIOTHERAPY FOR CERVICAL CANCER: THE IMPACT OF TUMOR REGRESSION

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Purpose: Investigating the impact of tumor regression on the dose within cervical tumors and surrounding organs, comparing conventional, conformal, and intensity-modulated radiotherapy (IMRT) and the need for repeated treatment planning during irradiation.

Methods and Materials: Fourteen patients with cervical cancer underwent magnetic resonance (MR) imaging before treatment and once during treatment, after about 30 Gy. Target volumes and critical organs were delineated. First conventional, conformal, and IMRT plans were generated. To evaluate the impact of tumor regression, we calculated dose–volume histograms for these plans, using the delineations of the intratreatment MR images. Second conformal and IMRT plans were made based on the delineations of the intratreatment MR images. First and second plans were compared.

Results: The average volume receiving 95% of the prescribed dose (43 Gy) by the conventional, conformal, and IMRT plans was, respectively, for the bowel 626 cc, 427 cc, and 232 cc; for the rectum 101 cc, 90 cc, and 60 cc; and for the bladder 89 cc, 70 cc, and 58 cc. The volumes of critical organs at this dose level were significantly reduced using IMRT compared with conventional and conformal planning ($p < 0.02$ in all cases). After having delivered about 30 Gy external beam radiation therapy, the primary gross tumor volumes decreased on average by 46% (range, 6.1–100%). The target volumes on the intratreatment MR images remained sufficiently covered by the 95% isodose. Second IMRT plans significantly diminished the treated bowel volume, if the primary gross tumor volumes decreased >30 cc.

Conclusions: Intensity-modulated radiation therapy is superior in sparing of critical organs compared with conventional and conformal treatment, with adequate coverage of the target volumes. Intensity-modulated radiation therapy remains superior after 30 Gy external beam radiation therapy, despite tumor regression and internal organ motion. Repeated IMRT planning can improve the sparing of the bowel and rectum in patients with substantial tumor regression. © 2006 Elsevier Inc.

Cervical cancer, Intensity-modulated radiation therapy, External beam radiotherapy, Tumor regression.

INTRODUCTION

The treatment of cervical cancer has been and still is the domain of radiotherapy (1–3). In the last decade effort has been put into combining radiotherapy with other treatment modalities, mainly chemotherapy (4–9) or hyperthermia (10), resulting in better locoregional control rates and improved survival rates. However, treatment results are still not satisfactory, and radiation oncologists continue their search for strategies to optimize the radiotherapy itself. This is a challenge, because cervical tumors are large, can regress more or less rapidly and move during therapy, and are closely surrounded by critical organs.

External treatment using the four-field box technique with field borders generated according to the bony anatomy fail to encompass the target volume adequately in a number of patients (11). Therefore, visualization of the primary tumor process and its surrounding organs is one of the crucial steps in the process of improving radiotherapy. Imaging techniques such as computed tomography (CT), magnetic resonance (MR) imaging, and positron emission tomography (PET) visualize the primary cervical tumor, the pathologic lymphatic nodes, and the surrounding organs (12–15). Magnetic resonance imaging is superior to CT or examination under anesthesia in detecting the boundaries of the cervical tumor mass, with respect to parametrial invasion, infiltration into the uterus, and its invasion into the bladder and rectum (13, 16). Besides this advantage in the pretreatment setting, the regression of tumor volumes due to irradiation can be analyzed with repeated MR imaging (17–20). According to the findings of Hatano *et al.* (19), a

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substantial tumor regression can be expected after having delivered a dose of 30 Gy.

In addition to this progress in the process of defining the radiation target more precisely, radiation techniques themselves have developed rapidly in recent years. Newly developed treatment strategies and planning techniques make it possible to optimize the doses to the target volumes without increasing the dose to the critical organs. Three-dimensional conformal radiation therapy (3D-CRT) as well as intensity-modulated radiation therapy (IMRT) clearly improve dose conformity compared with conventional planning (21–25). However, during the course of radiotherapy, target volumes change position due to internal organ motion and tumor regression (26, 27). The conformal dose distributions and the steep dose gradients generated around target volumes created by 3D-CRT and IMRT planning require an accurate treatment setup and repeated monitoring to prevent a geographic miss during radiotherapy. By monitoring the treatment setup during irradiation, information will be gained concerning target volume coverage and critical organ sparing and will, if necessary, lead to an intratreatment modification of the treatment plan.

In this planning study of patients with cervical cancer, we used MR imaging before and during radiotherapy to compare conventional, conformal, and IMRT plans with respect to target volume coverage and critical organ sparing. Internal organ motion and tumor regression were taken into account by generating the treatment margins, i.e., the clinical target volume (CTV) and planning target volume (PTV) expansions. By repeated MR imaging we were able to compare the plans before the onset of treatment and after having delivered a dose of about 30 Gy. Finally we investigated, whether creating second conformal and IMRT plans (based on the delineations of the intratreatment MR images) would improve the target coverage and critical organ sparing.

METHODS AND MATERIALS

Patients

Fourteen patients with cervical cancer treated at our department between March 2003 and April 2004 were enrolled in the planning study. Thirteen patients had squamous cell carcinoma, 1 patient had adenocarcinoma. For staging purposes, a radiation oncologist and a gynecologic oncologist together performed an examination under anesthesia. Further evaluation included complete blood count, chemistry profile, chest X-ray, and abdominal ultrasonography. Staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO) classification (28). Four patients had Stage IB, 3 had Stage IIA, 2 had Stage IIB, 1 had Stage IIIA, 3 had Stage IIIB, and 1 had Stage IVA cervical cancer.

In accordance with our standard treatment protocol the patients were treated with EBRT, 45 Gy in 25 fractions of 1.8 Gy. Pulsed dose rate (PDR) brachytherapy was administered twice using a Fletcher-Suit-Delclos applicator. Depending on the doses to rectum and bladder, a maximum of 17.40 Gy to point A was delivered with each insertion. The first brachytherapy insertion was performed after 17 fractions of 1.8 Gy and the second, immediately after 25 fractions of 1.8 Gy. In case of parametrial involvement or pathologic lymph nodes, additional external fields were given after the second brachytherapy insertion to deliver an additional 10 Gy in 5 fractions. Seven patients received concomitant weekly chemotherapy (40 mg/m^2 cisplatin i.v.). One patient was treated with one course of neoadjuvant chemotherapy (70 mg/m^2 cisplatin on Days 1, 8, and 15, with etoposide 50 mg for 14 days). Six patients were treated with radiotherapy alone.

Imaging

Each patient underwent a CT scan (CT Aura; Philips Medical Systems, Best, The Netherlands) with oral and i.v. contrast. Contiguous 3-mm slices were made from the iliac crest to the ischial tuberosities. To accurately delineate the regions of interest, MR images were made using a 1.5-T MRI scanner (Gyroscan NT Intera; Philips Medical Systems, Best, The Netherlands). All 14 patients underwent MR imaging before treatment and during treatment, after about 30 Gy. Neither rectal nor bladder contrast was used. Intratreatment MR images were made to measure tumor response during irradiation. Images were acquired according to the following protocol: axial T2-weighted 6.6-mm-thick images of the whole abdomen and pelvis, axial and sagittal T2-weighted 4.5-mm-thick images using a Synbody coil from the body of L5 to the ischial tuberosities, axial T1-weighted spectral fat saturation inversion recovery (SPIR) 4.5-mm-thick images, and T1-weighted SPIR images with gadolinium contrast from the pelvis.

For treatment planning, the MRI datasets were registered to the CT scan using a mutual information–matching algorithm (VTK CISG Registration Toolkit; Kitware, York). While the original MRI datasets were used, we extracted a dataset containing only the bony anatomy obtained from the CT using a threshold algorithm. This dataset was used so that the bony anatomy of the CT and the two MRI datasets could be matched, whereas changes due to internal organ motion and tumor regression did not influence the match. This procedure is consistent with our clinical practice of portal imaging position verification during external beam radio-

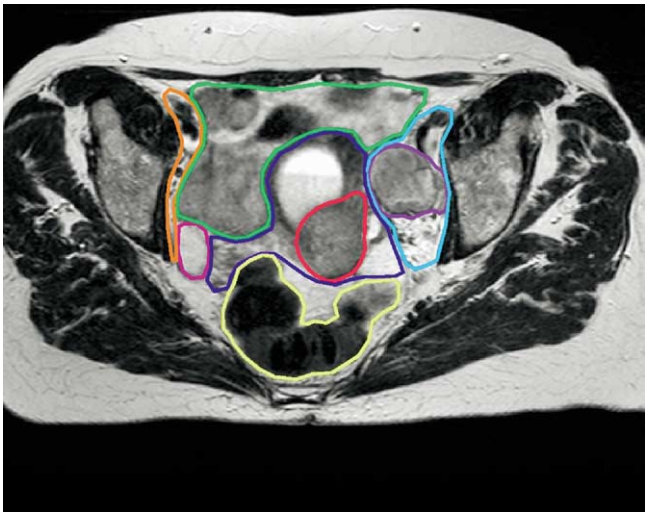

Fig. 1. Delineation of the regions of interest on a T2-weighted magnetic resonance image: Bladder, pink; bowel, green; rectum, yellow; primary gross tumor volume, red; primary clinical target volume, blue; left nodal gross tumor volume, purple; left nodal clinical target volume, light blue; right nodal clinical target volume, orange.