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Intensity-modulated radiation therapy for advanced cervical cancer: A comparison of dosimetric and clinical outcomes with conventional radiotherapy

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ABSTRACT

Objective. The aim of this study is to evaluate the dosimetry, efficacy and toxicity of reduced field intensity-modulated radiation therapy (RF-IMRT) for patients with advanced cervical cancer.

Methods. From August 2005 to August 2010, 60 patients with stage IIB–IIIB cervical cancer underwent reduced field IMRT (RF-IMRT group) and 62 patients treated with conventional radiotherapy (c-RT group) were enrolled. The RF-IMRT plans were as follows: whole pelvic IMRT plan was performed to deliver a dose of 30 Gy firstly, then the irradiated volume was reduced to lymphatic drainage region as well as paracervix and parametrium for an additional 30 Gy boost. Intracavitary brachytherapy and concurrent chemotherapy were performed during external irradiation. The tumor coverage and normal tissue avoidance were evaluated. Treatment response, toxicities and survival were assessed.

Results. The mean dose delivered to the planning target volume was significantly higher in RF-IMRT group than in c-RT group (61.5 vs. 50.8 Gy, $P=0.046$). IMRT plans yielded better dose conformity to the target and better sparing of the rectal, bladder and small intestine. The RF-IMRT patients experienced significantly lower acute and chronic toxicities with comparable short-term effects than did those treated with conventional RT (CR: 87.7% vs. 88.3%, $P=0.496$; PR: 7.0% vs. 6.7%, $P=0.440$). No significant differences were found between treatment groups for 1 year, 3 year, and 5 year overall survival (OS) levels, although the latter approached statistical significance in favor of IMRT, while a significantly higher progression-free survival (PFS; $P=0.031$) was seen for IMRT.

Conclusions. RF-IMRT yields improved dose distributions, with lower toxicities, while providing comparable clinical outcomes. The increased PFS may be an advantage.

Introduction

Cervical cancer is one of the most frequent cancers among women worldwide [1]. Although the conditional anteroposterior and posteroanterior parallel portals or 4 fields "box" radiotherapy (4FB-RT) to boost the dose of the gross tumor was widely performed throughout the world [2], the treatment is still associated with considerable gastrointestinal, hematological, and genitourinary toxicities [3,4]. Furthermore, it is still a disappointing fact that about 30% of FIGO stages IB2 to IV cervical cancer will ultimately relapse despite the use of concurrent chemoradiotherapy (CCR)T after treatment [5,6]. Previous studies reported that 43%–53.3% of recurrence and metastasis had occurred in pelvic wall and retroperitoneal lymph nodes [7–9]. In general, these patients who don't have lymph node metastasis could get more chance to be cured after treatment. For visible lymph node metastatic lesions, the curative dose of radiotherapy (RT) was at least 60 Gy. Those patients couldn't be cured after performance of a conditional RT dose of 45–50 Gy, especially when the metastatic lesion is larger than 2 cm in diameter.

There are many factors related to pelvic relapse after RT for cervical cancer, such as individual difference, FIGO stage, histopathological features and RT doses and technique. Once recurred, the prognosis of these patients will be very poor. In principle, the use of higher radiation dose will improve the likelihood of pelvic control. However, it inevitably increases the exposure of organs at risk (OAR), which in turn restricts the application of higher dosage to target volume. In the last decade, many efforts have been made in enhancing the target coverage and reducing the dose and volume of OAR. However, the results are still unfavorable with the low long-term survival and high incidence rate of complications [10–12].

Intensity-modulated radiotherapy (IMRT) has been demonstrated to provide a relatively ideal dose distribution to the clinical target volume (CTV) while reduces the dose to OAR, consequently decreasing complications [13], with possible enhancement or no loss of curative effect. There are many dosimetric studies that show reduction of

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dose delivered to the pelvic OARs with IMRT compared with conventional RT in the treatment of cervical cancer [14–17]. In most of these studies, whole pelvic IMRT (WP-IMRT) was applied for external irradiation. However, WP-IMRT is still associated with considerable rectal and cystic toxicity. As we know, the PTV of WP-IMRT plan covered all pelvic regions except the bladder and rectum. However, "hot spots" were observed in normal tissue and sometimes high rectum and bladder volumes were unavoidable. In this study, WP-IMRT plan was performed to deliver an initial dosage of 30 Gy, then the irradiated volume was reduced to the lymphatic drainage region (common iliac, external iliac, internal iliac, obturator lymph nodes) as well as paracervix and parametrium for an additional 30 Gy boost. To the best of our knowledge, no clinical studies about this "reduced field" IMRT (RF-IMRT) for cervical cancer has been reported. Here we report our initial clinical 6 years experience for treatment of patients with advanced cervical cancer using RF-IMRT, focusing on the correlation between dosimetry, clinical outcome and toxicities.

Materials and methods

Clinical materials

In this retrospective study, 122 patients were enrolled (KPS $\geq$70) having International Federation of Gynecology and Obstetrics (FIGO) stage IIB–IIIB cervical cancer and who received CCRT from August 2005 to August 2010 at the Department of Gynecologic Oncology, Shandong Cancer Hospital. Reduced field IMRT plans were performed in 60 patients (RF-IMRT group) and conventional radiotherapy was performed in the other 62 patients (c-RT group). Intracavitary brachytherapy and concurrent chemotherapy were performed during external irradiation. In the LDR-IMRT group, ages ranged from 31 to 74 years, with a median age of 52 years. Meanwhile, in conventional RT group, ages ranged from 26 to 77 years, with a median age of 55 years. The data of clinicopathologic characteristics of all patients were shown in Table 1.

Chemotherapy

All patients were treated with concurrent chemotherapy during RT. The concurrent chemotherapy consisted of continuous infusion of 5-fluorouracil (5-FU) (500 mg/m2) on d1 to 2 and cisplatin (40 mg/m^2) weekly (n = 43); carboplatin area under the curve (AUC) 2 and paclitaxel (45–50 mg/m^2) weekly (n = 79).

Table 1
Clinicopathologic characteristics of RF-IMRT and c-RT patients.

Factor	RF-IMRT group (n = 57)	c-RT group (n = 60)	*P* value
Age (years, median [range])	52 (31–74)	55 (26–77)	0.385
FIGO stage (no.)			
IIB	29 (50.9%)	33 (55.0%)	0.161
IIIA	10 (17.5%)	8 (13.3%)	
IIIB	18 (31.6%)	19 (31.7%)	
Histopathologic grade*			0.292
Good or moderate	39 (68.4%)	43 (71.7%)	
Poor	18 (31.6%)	17 (28.3%)	
Histological type (no.)			0.327
Squamous cell carcinoma	44 (77.2%)	46 (76.7%)	
Adencarcinoma	13 (22.8%)	14 (23.3%)	
Regimens of chemotherapy			0.083
5-FU + cisplatin	17 (29.8 %)	23 (38.3%)	
Paclitaxel + carboplatin	40 (70.2%)	37 (61.7%)	
Weekly cycles of chemotherapy			0.103
5 weeks	36 (63.2%)	41 (68.3%)	
4 weeks	19 (33.3%)	15 (25.0%)	
3 weeks	2 (3.5%)	4 (6.7%)	
Delivered RT dose (Gy, mean [range])	61.5 (58–63)	50.8 (45–55)	
Dose delivered to Point A (Gy, mean [range])	94.4 (87.4–101.2)	90.7 (80.8–99.2)	0.390
Dose delivered to Point B (Gy, mean [range])	72.5 (68.5–77.4)	66.4 (52.0–71.6)	0.347

Abbreviations: RF-IMRT = reduced field IMRT; c-RT = conventional radiotherapy. FIGO = the International Federation of Gynecology and Obstetrics.

Radiotherapy

Conventional RT was planned using an ADAC Treatment Planning System and delivered with 15MV X-ray from a Varian 21EX (Palo Alto, CA). Pelvic radiation was delivered by anteroposterior and posteroanterior parallel portals with the dose of 45 Gy to 55 Gy (median: 51 Gy) with a 4 cm in wide midline block after 30 Gy to reduce the exposure of the bladder and rectum. The 4-fields box plan was adopted in obese patients with a separation of more than 20 cm (anteroposterior, posteroanterior, right lateral and left lateral conformal fields). Minimum margins were the upper margin of L4–5(superiorly), the lower margin of the obturator foramen or the lowest extension of the disease (inferiorly), and 1.5–2.0 cm beyond lateral margins of true bony pelvis. For the lateral fields, the anterior margin was the anterior edge of symphysis pubis. The posterior margins at the S2–S3 interspaces were used. For patients with positive paraaortic lymph nodes (PALNs) metastasis, anteroposterior and posteroanterior-field box para-aortic field RT plan was performed. After the initial dose of 30 Gy was given, the RT plan was changed into 2 anterior and posterior fields to achieve the intended prescription dose of 45–55 Gy. The designed prescription dose was delivered at 1.8–2.0 Gy daily fraction, 5 fractions per week.

For IMRT, all patients underwent CT simulation in a supine position with their arms by their sides. A customized immobilization device was fabricated encompassing the lower abdomen, pelvis, and upper thighs to minimize variability in the daily setup.

First, whole pelvic IMRT plan was performed to deliver a dosage of 30 Gy. The irradiated volume included the whole uterus, cervix and part of the vagina depending upon the lower extent of tumor, the paracervical, parametrium, uterosacral regions as well as common iliac, external iliac, internal iliac and obturator lymph nodes. Then the irradiated volume was reduced to the lymphatic drainage region (common iliac, external iliac, internal iliac, obturator lymph nodes) as well as the paracervical, and parametrium. The planning target volume (PTV) was defined as the CTV plus a 5-mm margin. The PTV was adjusted so that the 50% isodose curve could get through Point A (a reference point 2 cm lateral and 2 cm superior to the cervical os). For patients with positive PALNs metastasis, para-aortic field IMRT plan was also performed at the same time.

To verify the setup accuracy, we took orthogonal electronic portal images weekly. The gross tumor volume (GTV), CTV and PTV were contoured on the individual axial CT slices of each patient. Normal structures, including the small bowel, rectum, bladder, kidney and pelvic bone marrow were also entered on to the planning CT scan. The rectum was defined from the level of sigmoid flexure to the anus. The small bowel was contoured from the L4–5 interspace to its lowest extent in the pelvis.

A 5- to 9-field equally spaced coplanar IMRT plan was generated for each patient using an identical starting set of dose-volume constraints, all patients were treated with 15-MV X-ray. The designed prescribed dose was 60 Gy in 2.0 Gy per fraction, 5 fractions per week in the center of the PTV. Our planning goals were to provide a homogenous PTV dose while minimizing the dose delivered to the small bowel, bladder and rectum. The PTV dose volume histogram (DVH) was calculated to ensure that <1% of the PTV received 110% of the prescribed dose.

Conventional treatment planning for comparison

For comparison, we also delineated the CTV, PTV, and normal tissue for c-RT plan. c-RT plans were generated using Pinnacle3 treatment planning system (Philips Healthcare, Madison, Wisconsin,