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Original Article

The effect of dose-painted intensity-modulated radiotherapy combined with chemotherapy for stage IIIB cervical cancer

Yunqin Liu[1*], Chunbao Zang[1*], Liting Qian[1], Ailin Wu[2], Xue Ke[1]

[1]Department of Radiation Oncology, [2]Oncology Radiotherapy Room, The First Affiliated Hospital of USTC West District, Anhui Provincial Cancer Hospital, Hefei, Anhui Province, China. [*]Equal contributors and co-first authors.

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Abstract: Objective: To investigate the effect of dose-painted intensity-modulated radiotherapy (DP-IMRT) combined with chemotherapy on stage IIIB cervical cancer. Methods: A total of 107 stage IIIB cervical cancer patients were treated with DP-IMRT combined with chemotherapy. The planning target volume (PTV) was divided into regions with different prescribed absorbed doses (so-called PTV-subvolume [PTVsv]): $PTVsv_1$ (the part of the PTV that overlaps with the organ at risk (OAR)) received 39.6-45 Gy, 1.8 Gy/fraction (fx); and $PTVsv_2$ (the part of the PTV that does not overlap with the OAR) received 44-50 Gy, 2.0 Gy/fx. The lymph nodes were simultaneously boosted; lymph nodes with a short axis dimension <1 cm received 50-55 Gy, 2.0-2.4 Gy/fx, while nodes with a short axis dimension >1 cm received 55-66 Gy, 2.2-2.6 Gy/fx. External radiotherapy was followed by intracavitary brachytherapy. Patients were followed up regularly to collect the survival information. Results: Five years after therapy, the overall survival rate and progression-free survival rate were 61.0% and 55.0%, respectively. The cumulative rates for total grade 3 or higher chronic gastrointestinal or genitourinary toxicity were 4.67% and 1.9% respectively. Conclusion: Without compromising the primary PTV, DP-IMRT achieved good outcomes for stage IIIB cervical cancer patients with a favorable gastrointestinal toxicity profile.

Keywords: Cervical cancer, chemotherapy, dose-painted IMRT, toxicity

Introduction

Globally, approximately 569,847 new cases of cervical cancer were diagnosed in 2018, along with 311,365 cancer-related deaths [1]. Cervical cancer is the second most common form of cancer and the third most common cause of death from cancer in developing country [2]. Almost 25% of patients with local advanced cervical cancer are diagnosed with stage IIIB cervical cancer, as defined by the Federation of International Gynecologists (FIGO) [3]. Typically, more advanced stages of cervical cancer (stages IIB-IVA) tend to be treated with chemoradiotherapy [4, 5]. A previous prospective randomized trial of patients with stage IIIB cervical cancer found that the 5-year overall survival (OS) was significantly higher in the chemoradiotherapy arm (54.0%) compared with the radiotherapy arm (46.0%), although there was higher rate of grade 3/4 gastrointestinal (7.9%) toxicity in the chemoradiotherapy group [4].

Intensity-modulated radiotherapy (IMRT) provides more conformal distribution of doses to the lesion and reduces the high absorption of doses in the organ at risk (OAR), thereby reducing both acute and late toxicities [6, 7]. According to consensus guidelines, in patients with stage IIIB (or higher stages) cervical cancer and those with extensive nodal involvement, it is imperative to include the entire mesorectum in the parametrial volume in the clinical target volume (CTV). Then the CTV is given a 1.5 to 2 cm margin (the nodal CTV is given a margin of 7 mm) to create the PTV [8]. Consequently, this volume of radiation is still too excessive for patients with stage IIIB cervical cancer. According to The International Commission on

Table 1. Patient characteristics (n=107)

Characteristics	
Age (years)	
Median	51
Range	30-70
Histology	
Squamous	101 (94.39%)
Adenocarcinoma	6 (5.61%)
Field	
Pelvic field	62
Extended field	45
Median tumor width at diagnosis	
Median	5
Range	3-8
Brachytherapy	
Intracavitary	95
Combine Intracavitary/interstitial	12
Chemotherapy	
Cisplatin + Paclitaxel	12
Cisplatin	57
Nadaplatin	32
Paclitaxel	6
Follow-up period (months)	
Median	38
Range	4-68
Overall treatment time (days)	
Median	53
Range	48-65

Radiation Units and Measurements (ICRU) Report 83, the delineation of the primary PTV is recommended to not be compromised when the PTV encroaches or overlaps the OAR, so as to ensure an accurate absorbed dose of the PTV [9]. Alternatively, subdivision of the PTV into regions with different prescribed absorbed doses which also-called PTV sub-volume (PTV_{sv}) could be used [9].

Therefore, without compromising the primary PTV of stage IIIB cervical cancer, we used dose-painted IMRT (DP-IMRT). Previously, the PTV of IMRT for cervical cancer was reported to be a single target area, of which the total dose was 50 Gy in pelvic and 50 Gy in the rectal tissue in patients with stage IIIB cervical cancer. We innovatively divided PTV into two components, $PTVsv_1$ (the part of the PTV that overlaps with the OAR, 1.8 Gy per dose) and $PTVsv_2$ (the part of the PTV that does not overlap with the OAR, synchronously added to 2.0 Gy per dose), to receive different dose to irradiation, which can not only decrease the irradiation dose in rectum, but also ensure that the paravertebral target area receives 46-50 Gy/23-25 doses. Additionally, the lymph nodes were simultaneously boosted.

Therefore, this study aimed to investigate the toxicity and efficacy of DP-IMRT, combined with chemotherapy in patients with stage IIIB cervical cancer.

Materials and methods

This study was approved by the Ethics Committee of The First Affiliated Hospital of USTC West District, Anhui Provincial Cancer Hospital.

Patients

Retrospectively, we analyzed 107 women with cervical cancer (stage IIIB); the diagnosis was confirmed by histology pathology in all patients. We only included patients who had been administered definitive DP-IMRT combined with chemotherapy in The First Affiliated Hospital of USTC West District, Anhui Provincial Cancer Hospital between January 2013 and September 2015. We excluded any patients presenting with other forms of malignancy or distant metastases at diagnosis or refusing combined chemotherapy. In total, 62 patients received pelvic IMRT, and 45 patients received extended-field IMRT as recommended by the attending oncologists. The median age of the 107 patients was 51 years (range: 30-70 years) (**Table 1**). All 107 patients had undergone a complete medical history, gynecologic pelvic examination, physical examination, blood chemistry profile, complete blood cell count, chest computed tomography (CT), and pelvic magnetic resonance imaging (MRI)/CT. In addition, 23 patients underwent positron emission tomography (PET). Patients were staged using criteria published by FIGO (2009).

Radiotherapy techniqu

All patients received custom immobilization and CT-based planning. The CTV included the gross tumor volume (GTV), cervix, uterus, parametrium, vagina, involved nodules, and relevant draining nodal groups in accordance with

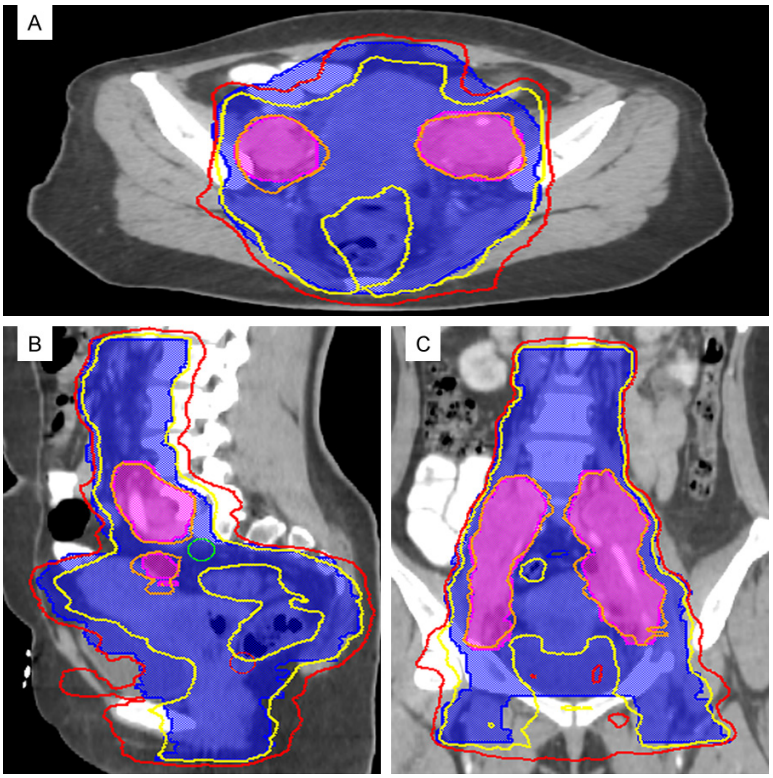

Figure 1. Illustration of an extended field of DP-IMRT. The $PTVsv_1$ (the part of the PTV that overlapped with the OAR) is displayed in blue, andcovered by 45.0 Gy (red line). $PTVsv_2$ (the part of the PTV that did not overlap with the OAR) was covered by 50 Gy and shown as a yellow line. The PTV of the enlarged lymph nodes with a short axis dimension >1 cm ($PTVnd_1$) is shown in purple and was administered 60 Gy (orange line). A. Transverse view of the isodose; B. Sagittal view of the isodose; C. Coronary view of the isodose. DP-IMRT: dose-painted intensity-modulated radiotherapy.

previously published guidelines [8]. In 45 patients, relevant draining nodal groups extended to para-aortic regional nodes. Then we added different margins to create the appropriate PTV. The cervix and the tumor were given a 10-20 mm margin; the uterus was allocated a 15-20 mm margin, and the remainder of the CTV was given a margin of 7 mm; collectively, these margins created the final PTV. Lymph nodes with a short axis dimension >1 cm were defined as $GTVnd_1$ and allocated a 5-7mm margin to create the final PTV of $GTVnd_1$ ($PTVnd_1$). Lymph nodes with a short axis dimension <1 cm were defined as $GTVnd_2$ and a margin of 5-7 mm was applied to produce a PTV of $GTVnd_2$ ($PTVnd_2$). Without compromising the primary PTV, the PTV for all patients was divided into two components: $PTVsv_1$ received 39.6-45 Gy, 1.8 Gy/fx; and $PTVsv_2$ received 44-50 Gy, 2.0 Gy/fx. $PTVnd_1$ received 55-66 Gy, 2.2-2.6 Gy/fx using an integrated boost (**Figure 1**); and $PTVnd_2$ received 50-55 Gy, 2.0-2.4 Gy/fx (**Figure 2**). The target planning constraints were set as follows: first, >99% of the PTV and >97% of the PTV received >90% >97% of the prescribed dose, respectively; second, <1% of the PTV received >115% of the prescribed dose. Dose constraints to the OAR are shown in **Table 2**. External beam radiation therapy (EBRT) was followed by high-dose-rate (HDR) intracavitary brachytherapy: five to six fractions of 5.0-6.0 Gy (prescribed to point A) once or twice a week. Twenty-one patients received vaginal brachytherapy using a vaginal tampon to boost the vaginal dose; this was usually necessary in cases where the vaginal disease invaded beyond one-thirds of the vagina. After January 2016, 12 patients also received three-dimensional (3D) CT-guided intracavitary/interstitial brachytherapy to boost the dose for eccentric large tumors (**Figure 3**).

Chemotherapy

All patients received 1-5 cycles (median 3) concurrent chemotherapy; 12 received weekly cisplatin (40 mg/m^2) plus paclitaxel (40 mg/m^2), 57 received weekly cisplatin (40 mg/m^2) alone, 32 received weekly nedaplatin (40 mg/m^2) alone, and 6 received weekly paclitaxel (40 mg/m^2) alone. The first cycle of chemotherapy was administered on day 1 of EBRT. However, we suspended the course of chemotherapy if the peripheral neutrophil count fell <1000/mm^3 or the peripheral platelet count fell <75,000/mm^3.

Treatment efficacy and patient follow-up

Responses to treatment were evaluated by a radiation oncologist and/or gynecologic oncologist after 4 weeks of treatment and then again 3 months after completion of treatment. Then

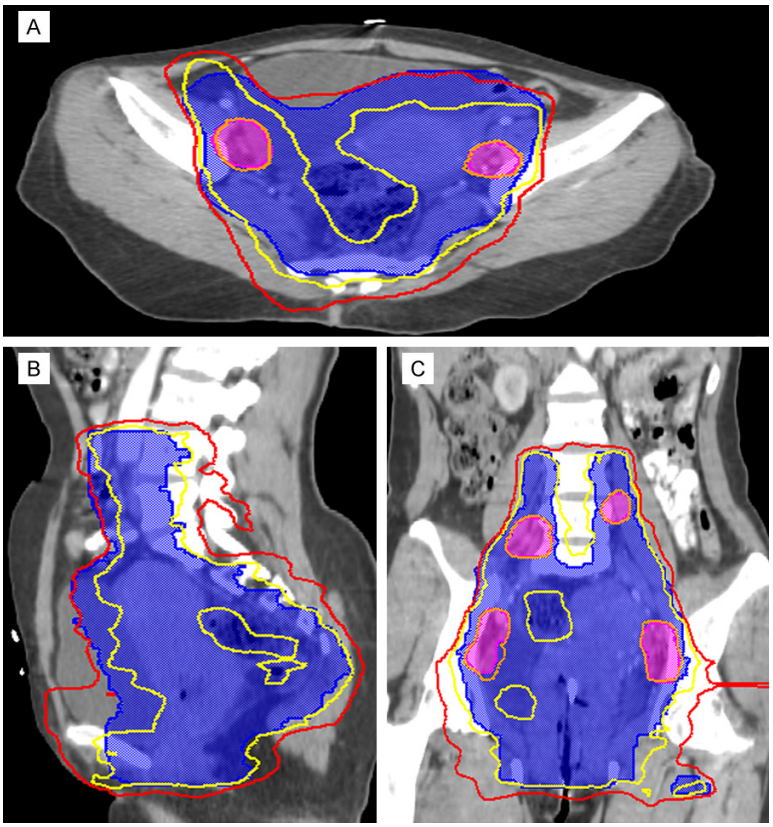

Figure 2. Illustration of a pelvic field featuring DP-IMRT. The $PTVsv_1$ (the part of the PTV that overlapped with the OAR) is displayed in blue and was treated with 41.40 Gy (red line); $PTVsv_2$ (the part of the PTV that did not overlap with the OAR) was treated with 46 Gy (yellow line); the PTV of lymph nodes with a short axis dimension <1 cm ($PTVnd_2$) is shown in purple and was treated with 55 Gy (orange line). A. Transverse view of the isodose; B. Sagittal view of the isodose; C. Coronary view of the isodose. DP-IMRT: dose-painted intensity-modulated radiotherapy.

patients were followed up every 3-4 months for 2 years and then every 6 months thereafter. Patients were followed up regularly; the last follow-up assessment was in January 2019. Six patients were lost to follow-up.

Evaluation of treatment toxicity

We analyzed acute toxicity from the start of radiotherapy to 90 days after treatment termination, and it was graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf) [10]. Late toxicity was assessed 90 days after treatment had been completed, and was graded in accordance with the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer regarding late radiation morbidity scoring criteria [11].

Statistical analysis

Data are presented as the mean ± standard deviation. For normal variables, numbers and percentages are given. PFS and OS were analyzed using Kaplan-Meier curves with Statistical Product and Service Solutions (SPSS) version 19.0.

Results

Treatment response

The median follow-up time was 38 months (range: 4-68 months). After 3 to 68 months of treatment, 30 (28.04%) patients experienced local (pelvic and para-aortic) and/or distant (other regions of the body) failure, and 21 patients (19.6%) died by the time of last follow-up. One patient died of leukemia, one patient died of heart disease, and the others died of local and/or distant failure. In addition, 7 (6.86%) patients had persistent disease within the field of radiotherapy, 2 (1.87%) suffered from disease relapse without distant metastasis, 9 (8.41%) experienced pelvic/regional relapse with distant metastasis, and 12 (11.21%) showed only distant metastasis. Lung was the most common distant metastatic site (**Table 3**). Overall, 18 (16.8%) patients showed persistent or local/regional recurrent disease within the field of radiotherapy, either with or without distant metastasis with a local control rate of 83.2%.

OS and PFS

The 36-month OS and PFS were 85.0% and 72.0%, respectively, whereas the 60-month OS and PFS were 61.0% and 55.0%, respectively (**Figure 4**).

Table 2. Dose constraints to the OAR

Organ	Constraints
Rectum/Bladder	Volume receiving more than 45 Gy (V45), <50% or volume receiving more than 50 Gy (V50), <50%; maximum dose <115% of the prescribed dose
Small bowel	Volume receiving more than 45 Gy (V45), less than 195 cm^3
Bone marrow	Volume receiving more than 20 Gy (V20), <75%, volume receiving more than 10 Gy (V10), <95%
Kidney	Volume receiving more than 20 Gy (V20), <20%; mean dose at the kidney (Dmean) <15 Gy
Liver	Volume receiving more than 30 Gy (V30), <40%
Spinal cord	the maximum dose <45 Gy
Femoral head	Volume receiving more than 50 Gy (V50), <5%

Note: OAR: organ at risk.

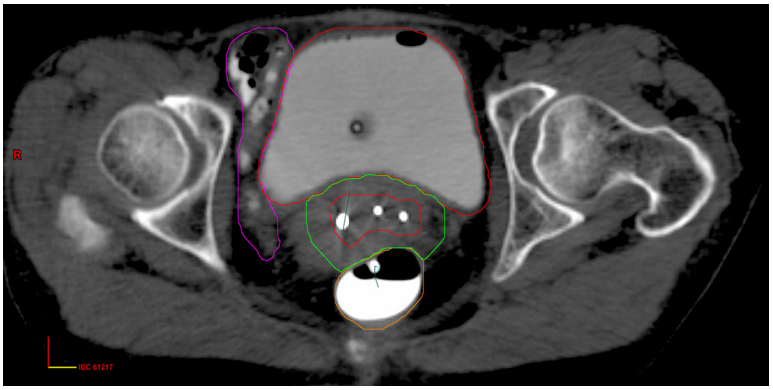

Figure 3. Illustration of the intracavitary/interstitial brachytherapy of an eccentric tumor. The left bright spot is the tandem (inserted into the uterine cavity), and the bright spots are interstitial needles (on the right). The bladder and small intestine were visualized with contrast media. The rectum was visualized with contrast media and 5 mL liquid containing atmospheric gas; a guidewire was also placed in the rectum (shown as a bright spot in a black gas area).

Table 3. Treatment responses and failures

Treatment responses and failures	Number of patients
Treatment responses	
Complete response (CR)	100 (93.5%)
Partial response (PR)	7 (6.5%)
Treatment failure	23 (21.50%)
Local/regional recurrence without metastasis	2 (1.87%)
Local/regional recurrence with metastasis	9 (8.41%)
Distant metastasis only	12 (11.76%)
Inguinal lymph nodes with bone	1
Bone only	2
Lung	4
Lung and mediastinal/supraclavicular lymph nodes	3
Lung and bone	1
Mediastinal/supraclavicular lymph nodes only	1

Treatment toxicities

Grade ≥3 acute hematological, gastrointestinal, and genitourinary toxicities occurred in 38 (35.5%), 2 (1.9%), and 1 (0.93%) patient, respectively; while 5 (4.67%) patients had grade ≥3 chronic gastrointestinal toxicity and 2 (1.9%) had grade ≥3 chronic genitourinary toxicity (**Table 4**). The median time from DP-IMRT to brachytherapy (the last day) was 53 days with a range of 48-65 days.

Discussion

Treating cervical cancer with stage IIIB poses specific problems for radiation oncologists, because the tumor volume is usually large and there is also a high chance of local relapse [12-14]. Previous studies have described 5-year overall survival rates of only 30-50% when these patients are treated with radiotherapy alone [12-16]. A recent meta-analysis of the application of chemoradiotherapy for cervical cancer reported that the absolute benefit was only 3% for stage III-IVA tumors after 5 years, and the concomitant use of chemotherapy resulted in an increased incidence of hematological and gastrointestinal side effects [17]. Other studies have reported that the grade 3-4 late toxicity rate in patients with locally advanced cervical cancer is 11% with chemoradiotherapy [18]. IMRT is known to reduce toxicity and improve overall survival of cervical cancer patients in stage I-IV who received primary treatment [19, 20].

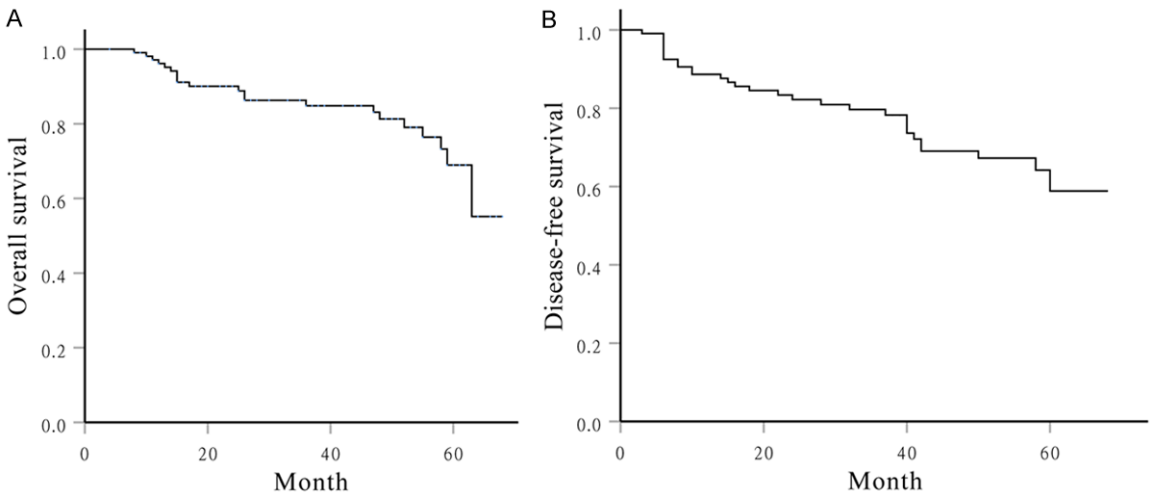

Figure 4. Kaplan-Meier curve analysis of (A) OS and (B) PFS of 107 patients treated with DP-IMRT. OS: overall survival; DP-IMRT: dose-painted intensity-modulated radiotherapy.

Table 4. Treatment toxicity

Toxicity	Case (%)				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Acute					
Gastrointestinal	23 (31.5)	61 (57.0)	21 (19.6)	2 (1.9)	0 (0)
Genitourinary Hematological	61 (57)	43 (40.2)	2 (1.9)	1 (0.9)	0 (0)
Anemia	29 (27.1)	47 (43.9)	24 (22.4)	7 (6.5)	0 (0)
Leukopenia	2 (1.9)	19 (17.8)	62 (57.9)	20 (18.7)	4 (3.7)
Neutropenia	2 (1.9)	20 (18.7)	58 (54.2)	22 (20.6)	5 (4.7)
Thrombcytopenia	49 (45.8%)	31 (29.0)	21 (19.6%)	4 (3.7)	2 (1.9)
Late					
Gastrointestinal	56 (53.3)	25 (23.4)	21 (19.6)	5 (4.7)	0 (0)
Genitourinary	86 (80.4)	12 (11.2)	7 (6.5)	2 (1.9)	0 (0)

Two studies compared dose delivery by sequential IMRT and simultaneous integrated boost IMRT. Data showed that simultaneous integrated boost IMRT significantly reduced the dose of radiation experienced by the OAR [21, 22]. According to ICRU Report 83, without compromising the primary PTV, we separated the pelvic or extended-field PTV into two components: $PTVsv_1$ received 39.6-45 Gy, 1.8 Gy/fx; and $PTVsv_2$ received 44-50 Gy, 2.0 Gy/fx; enlarged lymph nodes were boosted Simultaneously. DP-IMRT assured an adequate irradiation dose and volume of the parametrium, while reducing the percentage volume of the rectum and bladder receiving >45 Gy and/or >50 Gy [9]. One previous study reported that the 60-month OS rate for 111 stage IIIB cervical cancer patients (81 patients received IMRT and planned intracavitary brachytherapy) was over 50% [6]. In 2017, the INTERTECC-2 study reported that bone marrow-sparing IMRT resulted in acute grade ≥3 hematological and gastrointestinal toxicities in 19.3% and 12.0% of patients, respectively. Data also showed that chronic grade ≥3 toxicities occurred in 7.6% of patients, and that the 2-year OS and DFS were 90.8% and 78.6% for IB-IVA cervical cancer, respectively [23]. Previous studies have described 5-year OS of only 28.9-54% when patients with stage IIIB cervical cancer are treated with concurrent chemoradiation [4, 24, 25]. Compared to these previous studies and despite the fact that our patients had relatively advanced stages of cervical cancer (stage IIIB), after a relatively long follow-up period, definitive DPIMRT was shown to be very effective (36- and

60-month OS were 72% and 61.0%) and relatively safe. However, we observed acute grade ≥3 hematological toxicity in 35.5% of patients. It is necessary to restrict the dose of radiation to the bone marrow using PET-guided bone marrow-sparing IMRT [23, 26]. In the current study, five (4.67%) patients experienced chronic grade ≥3 gastrointestinal toxicity; three of whom developed an obstruction in the small intestine. There is published evidence suggesting the presence of a strong dose-volume relationship with regards to the development of small bowel toxicity when treating pelvic tumors [27]. Therefore, we suggest that radiation oncologists should reduce the dose of radiation to the small bowel as much as possible.

In recent years, image-guided brachythrapy has resulted in a major change in clinical practice. The EMBRACE study reported that the actuarial local control rate at 3/5 years for stage IIIB cervical cancer was 79%/75% [26]. Overall, the study suggested that image-guided brachytherapy improved pelvic control by approximately 10% compared to conventional 2D brachytherapy, and OS and cancer-specific survival improved by 10% and 14%, respectively [28]. In our study, we used traditional brachytherapy on orthogonal X-rays to plan treatments; only 12 patients received additional 3D CT-guided intracavitary/interstitial brachytherapy. Our study showed that the local control rate was 83.2%. Further improvements in survival rates may be achieved by using image-guided brachytherapy (including interstitial techniques), which could lead to further reductions in local and pelvic recurrence in advanced stages of disease [29-32].

Conclusion

Without compromising the primary PTV, we used DP-IMRT to ensure the adequate radiation to the parametrial volume, while reducing the percentage volume of the rectum and bladder receiving >45 Gy and/or >50 Gy. Our study achieved good outcomes with favorable acute and chronic gastrointestinal toxicity profiles. Further improvements in survival can be achieved with the use of image-guided brachytherapy (including interstitial techniques) and/or intensified chemotherapy. However, our study was a retrospective analysis that compared historical cohorts rather than a randomized controlled trial. Thus, it is necessary to further perform a study with a large sample size to verify the safety and efficacy of this treatment regime in cervical cancer patients.

Acknowledgements

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Disclosure of conflict of interest

None.

Address correspondence to: Liting Qian, Department of Radiation Oncology, The First Affiliated Hospital of USTC West District, Anhui Provincial Cancer Hospital, No.107 Huanhu East Road, Hefei 231000, Anhui Province, China. Tel: +86-13966716-720; E-mail: qianliting720@163.com

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