Adjuvant pelvic intensity-modulated radiotherapy and concurrent docetaxel and cisplatin chemotherapy for postoperative cervical cancer with adverse risk factors: a retrospective report on toxicity and outcome in a single institution

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Abstract

Background: To retrospectively assess the toxicity of delivering postoperative intensity-modulated radiotherapy (IMRT) and concurrent cisplatin and docetaxel chemotherapy to patients with cervical cancer and adverse risk factors.

Methods: Every patient received postoperative IMRT and concurrent cisplatin and docetaxel chemotherapy. The clinical target volume (CTV) included the regional lymph node regions (obturator, common, internal, and external iliacs and presacral and para-aortic regions); the upper 2.0 cm of the vagina; and paravaginal soft tissue lateral to the vagina. Acute and late toxicities were scored using the Common Terminology Criteria for Adverse Events (CTCAE) and the Radiation Therapy Oncology Group (RTOG) late radiation morbidity scoring criteria, respectively.

Results: Seventy-six patients were treated with postoperative IMRT and concurrent cisplatin and docetaxel chemotherapy. The median follow-up was 32 months. Eight patients (10.5%) had recurrence—loco-regional recurrence in four patients (5.3%) and distant metastasis in four (5.2%). Acute grade ≥ 3 gastrointestinal and hematologic toxicity occurred in one and five patients, respectively. One patient (1.3%) suffered from late grade 3 toxicities. Seventeen patients experienced ovarian transposition, 14 (82%) of whom maintained ovarian function. Seventy-four patients (97.4%) were alive at the last follow-up.

Conclusions: Concurrent cisplatin and docetaxel chemotherapy with postoperative IMRT was safe and well tolerated, with acceptable acute and late toxicities. Moreover, the distant metastases control rates were encouraging, although loco-regional failure continued to be the primary mode of failure. Postoperative IMRT provides an opportunity to preserve endocrine function for patients with ovarian transposition.

Introduction

Radiation therapy is generally administered for cervical cancer treatment[1]. FIGO stage IB-IIA cervical carcinoma has traditionally been cured effectively by either radiotherapy or radical hysterectomy (type III) and pelvic lymph node dissection, with a 5-year overall survival (OS) rate of 80–90%[2-4]. A Japanese retrospective analysis suggested similar treatment outcomes for patients with FIGO Stage IIB lesions treated with radical hysterectomy and definitive radiotherapy, both of which showed an estimated 5-year OS rate of 69%[5]. In China, these patients are usually treated by radical hysterectomy (type III) and pelvic lymph node dissection and para-aortic lymph node sampling. Certain clinicopathologic findings have been previously identified as risk factors for recurrence in patients with cervical cancer who undergo radical surgery as their primary treatment. In general, pelvic lymph node metastasis, positive resection margin, and/or parametrial invasion are all regarded as “high-risk” factors for recurrence[6]. Moreover, large tumor size, deep stromal invasion, and lymphovascular space invasion are considered as

“intermediate-risk” factors for recurrence[7, 8]. Postoperative radiotherapy has commonly been recommended for patients with these risk factors.

The Gynecologic Oncology Group (GOG) 92 study reported that adjuvant radiotherapy significantly reduced the risk of recurrence and prolonged progression-free survival (PFS) in patients with “intermediate-risk” factors[9]. In addition, several retrospective studies have shown that postoperative pelvic radiotherapy plus concurrent chemotherapy improved prognosis in these women[10, 11]. The GOG phase III study (GOG 109/SWOG 87-97) showed that the addition of concurrent fluorouracil and cisplatin to postoperative radiotherapy significantly improved relapse-free survival (RFS) and OS, with regard to high-risk factors[12].

In light of the results of the previous clinical trial, weekly cisplatin 40 mg/m² and triweekly cisplatin 75 mg/m² remain the most popular doses for concurrent chemoradiotherapy of cervical cancer[13-16]. However, the current standard of cisplatin as a radiation sensitizer has been associated with multiple toxicities[17], and lacks control of distant occult micrometastases occurrence[12, 18]. In an effort to increase efficacy, minimize toxicity, and control distant micrometastases, further investigations are ongoing on various chemotherapeutic agents and the optimal combination for use.

Docetaxel acts by promoting microtubule assembly but inhibits subsequent microtubule depolymerization, thus blocking cells in the G2/M phase, which is 2.5-times more sensitive to radiation than the G1/S phase[19-21]. Previous studies have confirmed the radiation sensitizing effects and radioresistant S-phase cytotoxicity of docetaxel [22, 23]. Docetaxel was tested in a phase I radiochemotherapy study of the uterine cervix, in which docetaxel at doses up to 40 mg/m²/week for 4–6 weekly cycles was well tolerated[24]. Because combined chemotherapy has a better chance to achieve control of heterogeneous tumor cell population than monotherapy, we adopted the combination of cisplatin and docetaxel by concurrent chemoradiotherapy for the treatment of “high-risk” and “intermediate-risk” cervical cancer.

A 2-field technique or 4-field technique (Box technique) is the conventional radiation therapy technique used to treat the pelvis after radical surgery for cervical cancer, and covers almost the entire tissue volume of the pelvic contents, but also increases the incidence of toxicity. As a means of reducing toxicity, intensity-modulated radiotherapy (IMRT) has been shown to decrease the incidence of acute and late toxicities. Further, IMRT includes more conformal dose distributions, confinement of the high dose portions of radiation fields, and reduction in the absorbed dose and volume of organs at risk. Chen et al. [25] demonstrated that IMRT significantly reduced gastrointestinal (GI) and genitourinary (GU) toxicities when administered as adjuvant treatment of cervical cancer.

In the current study, we retrospectively evaluated the treatment outcomes and toxicities in cervical cancer patients with “high-risk” or “intermediate-risk” who underwent radical hysterectomy (type III) with pelvic lymph node dissection and para-aortic lymph node sampling, and received postoperative pelvic IMRT with concurrent cisplatin and docetaxel chemotherapy. Our main aim was to explore the feasibility of

reducing ovarian toxicity and evaluate the variation of ovarian function in patients with ovarian transposition.

Methods

Between 2012 and 2016, women with FIGO stage IB-IIB disease who were treated at the Department of Radiation Oncology, QiLu Hospital of ShanDong University were reviewed. Seventy-six patients were identified and included in this analysis. All included patients underwent radical hysterectomy (type III) and pelvic lymph node dissection and para-aortic lymph node sampling. Postoperative pelvic IMRT and concurrent docetaxel and cisplatin chemotherapy were recommended when their pathological report displayed any one of the following “high-risk” prognostic factors: pelvic lymph node metastasis, positive parametrial involvement, a positive surgical margin, or at least two of the following “intermediate-risk” prognostic factors—deep stromal invasion (defined as an invasion into more than >half the thickness of the cervix), lymphovascular space invasion, or tumor size ≥ 4 cm. When para-aortic or common iliac lymph node metastases were identified, patients usually received extended-field radiation in our institution. Patients who had para-aortic or common iliac lymph node metastasis were excluded from the study. The initial evaluation of all patients included a history and physical exam; radiologic imaging including chest radiography, computed tomography (CT), and magnetic resonance imaging (MRI); complete blood count; and measurements of hepatic and renal function. To preserve ovarian function, 17 patients underwent ovarian transposition during the radical surgery procedure.

Radiotherapy and Chemotherapy

All patients underwent an initial CT simulation in the supine position with their arms on their chests, using intravenous contrast agents and free breathing. Setup accuracy was ensured using a 3-point laser set with marks placed on the patient during the simulation. To identify the vaginal cuff, a cylindrical radio-opaque vaginal marker was inserted intravaginally. The clinical target volume (CTV) included regional lymph node regions (obturator, common, internal, and external iliacs, presacral region); upper half of the vagina; and paravaginal soft tissue lateral to the vagina. The external, internal, and common iliac nodal volume was based on contrast-enhanced vessels with a 0.7–1 cm circumferential margin. The superior CTV border was usually at the level of bifurcation of the common iliac artery. When required, the superior aspect of the CTV was modified anteriorly for small-bowel sparing. This procedure was performed to maintain 5-mm distance between the small bowel and the CTV when possible, because these areas are not at risk for microscopic metastasis. The presacral region was included to the level of S3 to ensure coverage of the presacral lymph nodes (Fig.1A, B, C). Accounting for patient motion and set-up uncertainty in our institution, the CTV was expanded 0.8–1 cm non-uniformly to create the planned target volume (PTV), with 0.8 cm in the left and right directions, 0.8 cm in the anterior and posterior directions, and 1 cm in the superior and inferior directions. The small bowel, rectum (defined from the sigmoid flexure to the anus), and the bladder were contoured on all patients. All patients also underwent bone marrow contouring. Seventeen patients with ovarian transposition underwent separate ovarian contouring based on clips retained by the surgeon. The pelvic field was administered 50.4 Gy in 28

fractions. There was a dose-volume limitation with no more than 50% of the ovarian volume receiving 7 Gy (Fig. 1D). The dose-volume limitation was applied to other organs at risk. Both the rectum and bladder received a dose of V45≤50%, the small intestine received a dose of V35≤45%, the bone marrow received a dose of V20≤80% and V35≤45%, the head of femur received a dose of V45≤5%, and the spinal cord received a dose of V40≤0.1 cubic centimeter (Fig. 2). The inverse treatment planning for IMRT was performed with the sliding window technique using the Philips Pinnacle³ Planning System (Andover, MA, USA). All plans used seven coplanar beams (Fig. 1E, F). All patients were treated with 6-MV photons. Cone-beam computed tomography (CBCT) imaging was performed to setup verification for the first 3 consecutive days of treatment and once per week thereafter.

Patients with a large tumor size (diameter ≥ 4 cm) before radical surgery also underwent high-dose-rate (HDR) intracavitary brachytherapy involving 20 Gy in four fractions delivered to a depth of 5 mm below the vaginal mucosa. These treatments were delivered once or twice weekly, with no pelvic IMRT treatment carried out on the day of intracavitary HDR treatment.

All patients received docetaxel 75 mg/m² followed by cisplatin 75 mg/m² on day one during the course of external beam radiotherapy (EBRT). Two courses of chemotherapy were administered at 3-week intervals during radiotherapy. Before the initiation of chemotherapy, weekly physical examinations, complete blood counts, and hepatic and renal function tests were performed. If the absolute neutrophil count was <1,000/mm³ or the platelet count was <100,000/mm³, chemoradiotherapy was delayed or interrupted until the blood counts normalized and the patient recovered.

Follow-up Evaluation and Statistical Analysis

After radiotherapy completion, all patients were evaluated by a radiation oncologist and gynecologic oncologist after one month, followed by evaluations at 3-month intervals for 2 years and every 6 months thereafter. Radiological studies and blood chemistries were ordered at the discretion of the treating oncologists. Ovarian function was evaluated by the presence or absence of postmenopausal symptoms and by the measurement of follicle-stimulating hormone (FSH) and estrogen (E2) levels. We frequently checked the FSH levels when patients returned for cancer-status follow-up during the 3-month and 6-month intervals. As transient ovarian failure may last for a long time, we defined ovarian failure as two elevated (>40 U/L) FSH levels measured at least 3–6 months apart, over 2 years of follow-up after the completion of cancer treatment. Survival was measured from the date of diagnosis to the date of death or to the date of the most recent follow-up. Time to recurrence was measured from the date of diagnosis to the date of the first failure. Acute toxicities—measured from the initiation of treatment to 90 days after completion—were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0 (CTCAE 3.0). Late toxicities—experienced more than 90 days after completion of therapy—were graded according to the Radiation Therapy Oncology Group (RTOG) late toxicity scale. Toxicities were reported as counts with percentages. The OS and disease-free survival (DFS) rates were estimated with the Kaplan–Meier method. Statistical Package for Social Sciences version 26.0 (SPSS, Chicago, IL) software was used for all statistical analysis.

Results

In all, 76 patients were treated with postoperative pelvic IMRT and concurrent cisplatin and docetaxel chemotherapy. The clinical and pathological characteristics of these patients are shown in Table I. The median age was 45 years (range: 28–67 years). The total median treatment length of time of treatment was 43 days (range: 38–51 days). Eleven patients (85%) with stage IIB disease received neoadjuvant chemotherapy before surgery. No delay was noted in radiation therapy.

The treatments were well-tolerated. The acute and late toxicities are summarized in Table II. Diarrhea and cystitis were the most common side effects, with most patients reporting grade 1 toxicity. One patient (1%) was diagnosed with grade 3 toxicity. Leukopenia was the most common hematologic toxicity. Hematologic grade 1, 2, and 3 toxicity was present in 49%, 28%, and 7% of patients, respectively. Chemotherapy for nine patients was delayed due to a low neutrophil count. All patients received two cycles of cisplatin and docetaxel chemotherapy.

One patient (1.3%) experienced RTOG late grade 3 toxicities. This patient had a small bowel obstruction at 13 months that required partial enterectomy. Six patients had RTOG late grade 2 toxicities and underwent medical therapy. No patient experienced grade 4 toxicity, and there were no treatment-related deaths. Seventeen patients underwent ovarian transposition during radical surgical procedure. The ovaries were transposed as high or as laterally as possible, with metallic clips applied to each transposed ovary that were subsequently identified by CT simulation localization. Fourteen (82%) patients maintained ovarian function. Three patients, aged 42, 44 and 47 years, were classified as having ovarian failure.

The median follow-up time was 32 months (range: 6–71 months). Seventy-four patients (97.4%) were alive at the last follow-up, 68 patients (89.5%) had no evidence of disease, and eight patients (10.5%) had recurrence that was documented clinically or by imaging at the last follow-up (Table III). The most common sites of distant metastasis were the para-aortic lymph nodes (three patients) and supraclavicular lymph nodes (one patient). The 3-year DFS and OS rates for the entire cohort were 93.4% and 98.7%, respectively (Fig 3A, B).

Discussion

Based on the five randomized controlled trials, concurrent cisplatin-based chemoradiotherapy has become the standard treatment for locally advanced cervical cancer[12-16]. Several studies have demonstrated that the addition of concurrent chemotherapy to postoperative radiation may improve pelvic control and survival rate for patients with high- or intermediate-risk factors[10-12, 26, 27]. Although the benefit of postoperative RT combined with chemotherapy is obvious, treatment of the pelvic nodal regions carries inherent side effects. In fact, a generic GI dysfunction, urinary frequency, diarrhea, bleeding, and obstruction, have been described as major toxic consequences of surgery combined with adjuvant radiotherapy for gynecologic malignancy[28]. Based on the results of a previous clinical trial,

cisplatin or cisplatin-fluorouracil with radiotherapy failed to control distant occult micrometastases very well[12, 18]. To reduce the risk of sequelae of postoperative radiotherapy and decrease distant occult micrometastases, we explored the use of IMRT with concurrent cisplatin and docetaxel chemotherapy in our cervical cancer patients after hysterectomy (type III).

To our best knowledge, the cisplatin and docetaxel combined regimen has not been tested previously in the adjuvant setting for uterine cervical carcinoma. However, there is no standard dosing schedule of concurrent RT with cisplatin-docetaxel chemotherapy. Alvarez et al.[24] reported the results of the phase I study with RT and weekly doses of docetaxel, starting at 20 mg/m² and escalating by 10 mg/m². The maximum tolerated doses in this study were weekly 40 mg/m² docetaxel for 4–6 cycles. Rue et al.[18] showed that triweekly cisplatin 75 mg/m² chemotherapy concurrent with radiotherapy is more effective and feasible than the conventional weekly cisplatin 40 mg/m² regimen in patients with locally advanced cervical cancer.

We believe this study is the first to report that triweekly cisplatin 75 mg/m² and docetaxel 75 mg/m² chemotherapy concurrent with radiotherapy is feasible and has better survival outcome than reported in previous studies [10, 12, 36]. In the present study, we found that the 3-year OS rate was 98.7%. Postoperative pelvic IMRT with concurrent cisplatin and docetaxel chemotherapy was effective in preventing local recurrence. Although distant sites are the most common sites of failure, the distant relapse control rate was good. Only four patients (5.3%) developed local recurrence, and four patients (5.2%) had distant recurrence. This result is better than those of previous studies[25, 29, 32]. A possible explanation of our results is that the high peak concentration of cisplatin and docetaxel may be more effective not only in enhancing the synergy of chemoradiation but also in eliminating micrometastases, with resulting decrease of local failure and distant metastasis and eventual improvement in survival.

A retrospective planning study conducted a dosimetric comparison of pelvic IMRT and conventional pelvic radiotherapy plans for gynecologic cancer and demonstrated that IMRT can improve target coverage and reduce the dose to critical structures in gynecologic patients[25]. Hsselle et al.[30] showed that IMRT shows a reduced incidence of acute toxicities in patients with cervical cancer. Kim et al.[29] have reported grade 3 to 4 acute GI toxicity and GU toxicity in 3% and 11% of patients, respectively. In comparison, our study showed acute grade 3 GI toxicity in 1% of the patients, and there was no grade 3 GU toxicity. These results are very similar to those reported in previous studies that used pelvic IMRT and concurrent cisplatin chemotherapy[25, 36]. The use of IMRT greatly assisted in the conformality of dose distribution, confined the high-dose portions of radiation fields, and reduced the absorbed dose and volume of critical organs, resulting in reduced overall toxicity. Grade 1-2 GI and GU toxicities occurred more frequently in our study than in the one by Chen[25]. However, these were easily managed and did not cause delay in therapy.

To reduce myelotoxicity, we used the bone marrow-sparing IMRT approach. This technique has been shown to dosimetrically reduce the volume of bone marrow irradiated[31]. In our study, the volume of marrow receiving 20 Gy was reduced to <80%, and the volume receiving 35 Gy was reduced to <45%.

Acute grade 3 hematologic toxicity was seen in 7% of our patients. This finding is similar to the hematologic toxicity reported by Chen (6%)[25] and is superior to the results reported by Kim et al. (30%)[29] and Shih et al.(32.3%)[36]. This difference may be related to the use of triweekly cisplatin and docetaxel chemotherapy. In addition, other risk factors may account for these differences in toxicity, including low body mass index, smoking, and other causes of microvascular disease.

Mundt et al.[32] suggested that definitive pelvic IMRT is associated with less chronic GI toxicity than conventional pelvic RT (11% vs. 50%). Shih et al.[36] reported that no patients who underwent postoperative pelvic IMRT and concurrent chemotherapy experienced grade 3 or higher late toxicities. However, as there has been no randomized controlled clinical study yet, it is not clear whether concurrent chemotherapy increases the incidence of late toxicity in the setting of adjuvant therapy. Our result showed 1.3% of patients had grade 3 late toxicity, which is similar to a previous study's results with a grade 3 late toxicity rate of 1.8%[25], despite our follow-up being relatively limited. In this study, the addition of concurrent triweekly cisplatin and docetaxel chemotherapy to pelvic IMRT did not increase late GI and GU toxicities.

We further evaluated the feasibility of IMRT to retain ovarian function. The degree and persistence of ovarian damage and suppression of ovarian function is related to the patient's age and the dose of radiation delivered to the ovaries[33]. The importance of the radiation dose is clear because a low dose can save many follicles and repair the damage induced in some of them. For over three decades, ovarian function has been maintained by transposing the ovaries out of the field of irradiation, which reduces ovarian exposure. Bidzinski et al[34]. confirmed that ovarian function was preserved when the ovaries were transposed at least 3 cm from the upper border of the field. In our study, 17 patients underwent ovarian transposition to a position as high or as lateral as possible during radical surgery procedure before radiotherapy. Fourteen (82%) patients retained ovarian function; 11 of these patients had ovarian transposition at 3–3.5 cm from the upper border of the pelvic field (above the iliac crest), while the remaining three patients had ovarian transposition to 1.5 cm from the radiation field edge. We used a dose-volume limitation with <50% of the ovarian volume receiving 7 Gy for IMRT. The median ovarian dose was 3 (2.5–3.4) Gy. Three (18%) patients experienced ovarian failure; one of them was 42 years old with ovarian transposition at 1.5 cm from the radiation field edge and the other two were 44 and 47 years old with ovarian transposition at 3–3.5 cm from the upper border of the field. As previously described in the literature, ovarian transposition is of limited value in patients who are older than 40 years, because they have an intrinsically reduced fertilization potential as well as a much higher risk of ovarian failure despite transposition than younger women[35].

Conclusion

Concurrent cisplatin and docetaxel chemotherapy with postoperative pelvic IMRT in cervical cancer patients with “high-risk” or “intermediate-risk” is safe and well-tolerated, with acceptable acute and late toxicities. The distant control rates are promising and superior to those reported in previous studies, although distant metastases continue to be the predominant reason for treatment failure. The

locoregional control rates were also good. IMRT provides an opportunity to preserve endocrine function for patients with ovarian transposition.

Abbreviations

OS: overall survival; RFS: relapse-free survival; IMRT: intensity-modulated radio-therapy; GI: gastrointestinal; GU: genitourinary; CT: computed tomography; MRI magnetic resonance imaging; CTV: clinical target volume; PTV: planned target volume; CBCT: Cone-beam computed tomography; HDR: high-dose-rate; EBRT: external beam radiotherapy; FSH: follicle-stimulating hormone; E2:estrogen; radiotherapy: RT; RTOG: Radiation Therapy Oncology Group; CTCAE 3.0:Common Toxicity Criteria for Adverse Events, version 3.0; RTOG: Radiation Therapy Oncology Group ; DFS: disease-free survival

Declarations

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None

Authors' contributions

All authors read and approved the final version of the manuscript. Idea and conception: Guangyu Zhang, Cong Wang, Chunli Fu. Data collection: Guangyu Zhang, Fangfang He, Youzhong Zhang, Haijian Wu, Qingwei Wang, Chunli Fu. Data interpretation: Guangyu Zhang, Fangfang He, Haijian Wu, Cong Wang. Manuscript writing: Guangyu Zhang, Fangfang He, Youzhong Zhang, Haijian Wu, Qingwei Wang, Cong Wang, Chunli Fu

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Availability of data and materials

Not applicable, entire data is shown within the manuscript / tables

Ethics approval and consent to participate

The protocol of this retrospective study was approved by the local ethics committee of the QiLu Hospital of Shandong University.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests

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Tables

Table 1. Patient characteristics

Patients	
Intermediate-risk	44
High-risk	32
KPS	
1. 74	
70-80	2
Age (years)	45(28-67)
BSA(m ²)	1.7(1.5-1.9)
FIGO Stage	
I B	40
II A	23
II B	13
Pathology	
Squamous	45(59%)
Adenocarcinoma	18(24%)
Adenosquamous	13(17%)
Tumor diameter>4 cm	12
LVSI	27
DSI	35
PLN	23
PPI	9
Ovarian transposition	17

KPS, Karnofsky; BSA, Body surface area; FIGO, International Federation of Gynecology and Obstetrics;

LVSI, lymphovascular space invasion; DSI, deep stromal invasion; PLN, positive lymph nodes; PPI, positive parametrial involvement.

Data are presented as number, percentage, or median (range).

Table 2. Treatment-related toxicities

No. (%)	Grade 1	Grade 2	Grade 3	Grade 4
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Acute toxicities

Hematologic	35(49%)	20(28%)	5(7%)	0
Gastrointestinal	40(56%)	11(15%)	1(1%)	0
Genitourinary	23(32%)	13(18%)	0	0

Late toxicities

Gastrointestinal fistula	0	0	0	0
Genitourinary fistula	0	0	0	0
Diarrhea	2(3%)	4(5%)	0	0
Obstruction	0	2(3%)	1(1.3%)	0

Table 3. Result at last follow-up

Result at last follow-up	No.(%)
Failure	8(10.5%)
LRF	4(5.3%)
DM	3(3.9%)
LRF+DM	1(1.3%)
No recurrence	68(89.5%)
Death due to disease	2(2.6%)

LRF: loco-regional failure, DM: distant metastasis

Supplementary Files

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