

Comparing dosimetric and cancer control outcomes after intensity-modulated radiation therapy and tomotherapy for advanced cervical cancer

DAPENG LI^{1,2*}, DANDAN WANG^{3*}, SHUAI FENG², QUANCAI CHEN⁴,
XIUGUI SHENG⁵, JUE JIA², XIAOHUI YAN², JIAN ZHU³ and YUEJU YIN^{1,2}

¹Department of Gynecological Oncology, Shandong University Cancer Center; Departments of

²Gynecological Oncology and ³Radiation Oncology Physics and Technology, Shandong Cancer Hospital and

Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, Shandong 250117;

⁴Department of Gynecology and Obstetrics, Wulian Maternal and Child Care Service Center, Rizhao, Shandong 262300;

⁵Department of Gynecological Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, Guangdong 518116, P.R. China

Received January 3, 2022; Accepted April 11, 2022

DOI: 10.3892/ol.2022.13359

Abstract. Concurrent chemoradiation therapy (CCRT) is the standard treatment for locally advanced cervical cancer. The present study aimed to compare the therapeutic responses, toxicities and dosimetric parameters between intensity-modulated radiation therapy (IMRT) and tomotherapy (TOMO) in patients with advanced cervical cancer. This retrospective study included 310 patients with stage IIB-IIIB cervical cancer who underwent CCRT, with 155 patients in each group. Intracavitary brachytherapy was performed after a course of external beam radiation therapy (EBRT), or in the last week of pelvic EBRT. The treatment planning aim at point A (defined as a reference location 2 cm above the vaginal fornix and 2 cm beside the mid axis of the uterus) was >85 Gy in an equivalent dose at 2 Gy. There was no statistical difference with regard to clinicopathological characteristics between the two groups ($P>0.05$). Improved dose conformity and dose

homogeneity ($P<0.05$) were observed in TOMO planning. TOMO provided more efficacious critical organ sparing than IMRT when assessing the percentage of normal tissue receiving at least 20 Gy (V20) for the bladder, the percentage of normal tissue receiving at least 40 Gy (V40) for the femoral head, and the V40 and V20 for the rectum ($P<0.05$). TOMO demonstrated a greater ability to protect the ovary ($P<0.05$). The acute radiation toxicity of proctitis and leukopenia were significantly lower in the TOMO group ($P<0.05$). The chronic radiation toxicity of radiation enterocolitis and cystitis was lower in the TOMO group ($P<0.05$). Thus, TOMO provided better critical organ sparing than IMRT. The radiation toxicities were acceptable. Therefore, TOMO appears to be a good option for the treatment of stage IIB-IIIB cervical cancer.

Introduction

Cervical cancer affects millions of women globally, ranking as the fourth most commonly occurring cancer among women worldwide (1). The cervical cancer incidence rate is increasing in China, with 109,700 new cases and 59,000 associated deaths recorded in 2020 (2). A combination of external beam radiation therapy (EBRT) and brachytherapy (BT) with concurrent chemotherapy is the standard treatment for locally advanced cervical cancer. Over the last 20 years, clinical outcomes have improved and toxicity has been reduced due to the development of more sophisticated planning and delivery techniques, and the introduction of computer technology and imaging (3,4).

The delivery of an adequate radiation dose to the cervical tumor area through the traditional approach is limited by the normal structures in the pelvic cavity, including the bladder and rectum, which are sensitive to radiation. Tomotherapy (TOMO) is a novel radiation therapy modality (5); it is a form of intensity-modulated radiation therapy (IMRT) that uses a helical 360-degree radiation delivery system. TOMO delivers

Correspondence to: Dr Yueju Yin, Department of Gynecological Oncology, Shandong University Cancer Center, 440 Jiyan Road, Jinan, Shandong 250117, P.R. China
E-mail: yk_688@163.com

Dr Jian Zhu, Department of Radiation Oncology Physics and Technology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, 440 Jiyan Road, Jinan, Shandong 250117, P.R. China
E-mail: zhujian.cn@163.com

*Contributed equally

Key words: cervical cancer, intensity-modulated radiation therapy, tomotherapy, therapeutic response, radiation therapy

image-guided radiation therapy by comparing daily pretreatment megavoltage computed tomography (CT) scans with CT scans performed at the time of simulation for treatment planning. The rapid opening and closing of the leaves in the collimator rotating around the patient allows TOMO to tailor the application of radiation doses to tumor regions of complex shape, while the dose to normal organs is limited (6,7). In comparison to conventional IMRT techniques, TOMO may provide sharper dose gradients around the target, leading to more efficacious sparing of surrounding normal structures and potentially fewer radiation-related side effects (8-10). However, the potential benefit of TOMO over IMRT is still unclear (11,12).

The purpose of the present study was to compare the therapeutic response, toxicities and dosimetric parameters between IMRT and TOMO in patients with advanced cervical cancer, in order to investigate an optimal treatment modality for the disease.

Patients and methods

Clinical materials. A total of 334 patients [Karnofsky Performance Status (13) ≥ 70] diagnosed with International Federation of Gynecology and Obstetrics (FIGO 2009) (14) stage IIB-IIIB cervical cancer, who underwent CCRT between August 2015 and March 2018 at the Department of Gynecological Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences (Jinan, China), were included in this study. A total of 2 patients with a history of ischemic heart disease, 3 patients with mental illness, 5 patients who were pregnant or lactating, 6 patients with a previous malignancy, 4 patients whose treatment was interrupted or prolonged for >8 weeks due to a serious complication that would affect full compliance with treatment and 4 patients who were allergic to chemotherapeutic drugs were excluded. Finally, 310 patients were selected to be retrospectively studied. The patients were randomly divided into the IMRT group ($n=155$) and the TOMO group ($n=155$) based on the type of radiotherapy technique used. The choice of radiotherapy technique was made by the patients and their doctors following a discussion on the technical differences and the differences in treatment cost. All patients completed radiotherapy within 7-8 weeks. Intracavitary BT was performed after the EBRT course was complete or in the last week of pelvic EBRT. The treatment planning aim at point A (defined as a reference location 2 cm above the vaginal fornix and 2 cm beside the mid axis of the uterus) was >85 Gy in an equivalent dose at 2 Gy (EQD2). In the IMRT group, patient ages ranged from 28 to 70 years, with a median age of 53 years. Meanwhile, in the TOMO group, patient ages ranged from 26 to 74 years, with a median age of 51 years. In this study, 17 patients with stage IIB cervical squamous cell carcinoma aged <40 years were only treated with laparoscopic ovarian suspension, without removing the cervical tumor, before radiotherapy. During the operation, the ovary was suspended on the lateral side of the paracolic sulcus, equivalent to 2-3 cm above the umbilical level, and fixed to the abdominal wall. The position of the ovary was marked with a silver clip. Before and after radiotherapy, ovarian endocrine function was evaluated according to perimenopausal

symptoms and serum hormone levels. All the procedures were performed in accordance with the Declaration of Helsinki and relevant policies in China. Ethical approval was obtained from the Ethics Committee of Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences (approval no. SDTHEC2021012058). The clinicopathological characteristics of all patients are shown in Table I.

Chemotherapy. All patients were treated with 4 cycles of concurrent chemotherapy during RT. The chemotherapy consisted of an infusion of paclitaxel (135 mg/m^2) on day 1 and cisplatin (75 mg/m^2) on day 2 every 4 weeks.

Radiotherapy. For IMRT, a 6-MV photon beam with six to nine co-planar beams and CT-based treatment planning (Pinnacle version 9.2; Philips Healthcare) was used. The doses were delivered using a linear-accelerator equipped with multi-leaf collimators (MLCs). Inverse treatment planning was performed using the ADAC Pinnacle3 Treatment Planning System (Philips Healthcare). All plans used dynamic MLCs to shape the fields.

The TOMO plans were calculated on the Tomotherapy Planning Station Hi-Art® Version 4.2.3 workstation (Tomotherapy Inc.) with a superposition/convolution algorithm. Due to workstation limitations, CT contouring and organ at risk (OAR) images were drawn in Version 9.2 of the Pinnacle3 planning system and transferred to the TOMO planning system.

All patients underwent initial CT simulation in a supine position with their arms by their sides, using intravenous contrast agents and free breathing. A customized immobilization device was fabricated encompassing the lower abdomen, pelvis and upper thighs to make the daily setup accurate. For the scanning range, the upper boundary was at the upper edge of the first lumbar vertebral body, and the lower boundary was 5 cm below the ischium tuberosity, with a scanning layer thickness of 5 mm.

The therapy plans were delivered with doses of the planning target volume (PTV). The gross tumor volume (GTV), clinical target volume (CTV) and PTV were contoured on the individual CT slices of each patient. The PTV consisted of the CTV plus a 5-mm margin. The CTV included the whole uterus and cervix, part of the vagina depending upon the lower extent of the tumor, the paracervical, parametrial and uterosacral regions, and the common iliac, external iliac, internal iliac and obturator lymph nodes. In patients with common iliac and/or para-aortic lymph node (PALN) involvement, extended-field pelvic and para-aortic radiotherapy was recommended, up to the level of the renal vessels (or even more cephalad as directed by involved nodal distribution). The whole pelvic radiation therapy plan was performed to deliver a dose of 45-50 Gy in 1.8-Gy daily fractions, with 5 fractions per week in the center of the PTV. Parametrial boost irradiation of 5-10 Gy was performed in the patients with bulky parametrial/pelvic sidewall disease after completion of initial whole pelvic radiation at the discretion of the attending physician. For patients with common iliac lymph node or PALN metastasis, a para-aortic field radiotherapy plan was also performed at the same time. The prescribed dose was 60 Gy.

Table I. Clinicopathological characteristics of patients treated with IMRT (n=155) and TOMO (n=155).

Characteristics	IMRT group	TOMO group	P-value
Median age (range), years	53 (28-70)	51 (26-74)	0.924 ^a
FIGO stage, n			0.352
IIB	46	57	
IIIA	3	4	
IIIB	106	94	
Histological type, n			<0.999
Squamous carcinoma	146	147	
Adenocarcinoma	6	5	
Other	3	3	
Tumor size, n			0.36
≤4 cm	64	72	
>4 cm	91	83	
Tumor grade, n			0.109
G1	48	54	
G2	50	61	
G3	57	40	
Ovary conserving, n			0.212
No	149	144	
Yes	6	11	
Pathological morphology type, n			0.123
Exophytic	135	125	
Endophytic type	20	30	
Para-aortic lymph node metastasis, n			0.627
Positive	8	10	
Negative	147	145	
TNM stage, n			0.533
T2bN0	40	53	
T2bN1	6	4	
T3aN0	3	4	
T3bN0	79	71	
T3bN1	27	23	
Pelvic lymph node metastasis, n			0.388
Positive	33	27	
Negative	122	128	
Therapeutic response rate, n			
CR	147	148	0.791
PR	3	4	0.709
CR + PR	150	152	0.902

^aStudent's t-test. FIGO, International Federation of Gynecology and Obstetrics; IMRT, intensity-modulated radiation therapy; TOMO, tomotherapy; TNM, Tumor-Node-Metastasis.

OARs included the suspended ovary, intestinal pouch, rectum, bladder and bilateral femoral head, in which the ovary was considered the whole ovary marked with a silver clip at the lateral paracolic sulcus and the intestinal pouch included the intestinal canal and its surrounding mesenteric tissue as shown by contrast medium. The upper boundary of the rectum was the junction of the rectosigmoid colon, the lower boundary was the anus and the bladder included all the bladders in the filling

state. For dose limitation of OARs, the following parameters were applied: Percentage of normal tissue receiving at least 5 Gy (V5) in the ovary, <50%; percentage of normal tissue receiving at least 40 Gy (V40) in the intestinal pouch, <50%; V40 in the rectum, <40%; V40 in the bladder, <40%; and V40 in the femoral head, <5%.

To verify the setup accuracy, orthogonal electronic portal images were captured once a day in the first 3 days of

radiotherapy and then once a week during the whole course of radiotherapy. After treatment, the physicians informed the patients whether their bladder and rectum preparation were suitable, in order to help the patients to prepare their bladder and rectum on non-imaging days. On non-imaging days, patients were positioned with skin line marks. The 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 into the planning CT scan. The small bowel was contoured from the L4-5 interspace to the level of the sigmoid flexure.

Dose-volume analysis of treatment plans. Dose-volume histograms (DVHs) of the PTVs and the critical normal structures were analyzed accordingly. For PTVs, the volume, the volume covered by 95% of the prescription dose (V95), and the minimum doses delivered to 5% (D5) and 95% (D95) of the PTV were evaluated. Critical organs with functional subunits organized in a series were examined. The conformal index (CI) and homogeneity index (HI) were used to evaluate the conformity and uniformity of the plan. The volume received the mean dose for the PTV generated from the DVH. The CI [International Commission on Radiation Units and Measurements (ICRU)] for PTV was calculated using the following formula: $CI_{ICRU} = V_{TV}/V_{PTV}$, where V_{TV} was the ratio of the treated volume enclosed by the prescription isodose surface and V_{PTV} was the planning target volume (15). The HI was defined as $D5/D95$, where D5 and D95 were the minimum doses delivered to 5 and 95% of the PTV reported previously (16).

Intracavitary BT. High-dose-rate source iridium-192 was used with a vaginal ovoid applicator (Tianjin Rongli Electronics Co. Ltd.; Hanschke applicator set). Post-implantation dosimetry was performed with the RI-hzj192Ir Integrated after loading treatment planning system (Tianjin Rongli Electronics Co. Ltd.) and included calculation of the dose to Point A bilaterally, the pelvic sidewall (point B, defined as the point 3 cm from Point A and 5 cm lateral to midline) bilaterally, and the rectal point and bladder point as defined by the ICRU (17). First, a whole pelvic radiotherapy plan was created to deliver a dose of 45-50 Gy. Intracavitary BT was then administered at doses of 25-30 Gy in 4-5 fractions after the EBRT course was complete or in the last week of pelvic EBRT. The treatment planning aim at point A was >85 Gy in EQD2. During the treatment of intracavitary BT, vaginal packing with gauze pushed the bladder and rectum as far away as possible to reduce the dose. These treatments were delivered weekly.

Therapeutic effect evaluation. Therapeutic effects were assessed by clinical examination, ultrasound, CT scans or/and positron emission tomography (PET)-CT scans after 2-3 months of treatment. According to the Response Evaluation Criteria in Solid Tumors (18), therapeutic response was classified as a complete response (CR), partial response (PR), stable disease or progressive disease.

Toxicity assessment. The acute and chronic toxicity from radiotherapy was evaluated using the Radiation Therapy

Oncology Group (RTOG) criteria (19) in the therapy process, after therapy and during follow-up. In patients with grade 4 hematological or non-hematological toxicity, radiation therapy was halted until toxicity resolved to at least grade 3.

Follow-up. After treatment completion, the patients were followed up at 3-month intervals for the first 2 years, at 6-month intervals for the following 3 years and annually thereafter. At each visit, a physical and pelvic examination, blood counts, clinical chemistry and chest radiography were performed. Scans of the abdomen and pelvic region were conducted using ultrasound. Imaging as appropriate (MRI, CT and PET-CT) was applied in case of a suspicion of recurrence. Suspected persistent or recurrent disease was confirmed using biopsy whenever possible. Overall survival (OS) was measured from the date of diagnosis to the time of death, or the time of last follow-up. Progression-free survival (PFS) was measured from the date of diagnosis to the time of disease recurrence, or the time of last follow-up. Overall survival (OS) and progression-free survival (PFS) were calculated from the date of diagnosis. Surviving patients were censored on the date of the last follow-up. The cause of death was confirmed by telephone, correspondence or medical record review.

Statistical analysis. The OS and PFS curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Clinical characteristics of patients, toxicities, local control, survival rates and therapeutic response rate were compared using the χ^2 test or Fisher's exact test. Age was analyzed using unpaired Student's t-test. Dosimetric parameters were analyzed using the independent-samples t-test. $P < 0.05$ was used to indicate a statistically significant difference. All analyses were performed using SPSS version 17.0 (SPSS Inc.).

Results

The clinicopathological characteristics of all patients were similar between the two groups (Table I). A total of 310 patients were included in this study. There were no statistically significant differences in terms of age, FIGO stage, histologic type, tumor size, tumor grade, pathologic morphology type, para-aortic lymph node metastasis, TNM stage, pelvic lymph node metastasis and ovary conservation between the two groups ($P=0.924$, $P=0.352$, $P>0.999$, $P=0.36$, $P=0.109$, $P=0.123$, $P=0.627$, $P=0.533$, $P=0.388$ and $P=0.212$, respectively). Lymph node metastasis is a risk factor for the recurrence and metastasis of cervical cancer (20). In the present study, lymph node metastasis was diagnosed when the minor axis of the lymph node was ≥ 10 mm, determined using contrast-enhanced CT or MRI. Pelvic lymph node metastasis (PLNM) occurred in 60 out of 310 patients; 33 patients (21.3%) were treated with IMRT and 27 (17.4%) underwent TOMO. There was no statistically significant difference between the two groups ($P=0.388$). In this study, 18 patients had para-aortic lymph node metastasis (PALNM); 8 patients underwent IMRT and 10 patients underwent TOMO (Table I). There was no statistical difference between the two groups ($P=0.627$).

DVH statistics for OARs and dosimetric parameters are described in Table II. In the comparison of TOMO and IMRT,

Table II. Dosimetric results of IMRT and TOMO for planning dosimetric parameters and organs at risk.

Parameter	TOMO group	IMRT group	P-value
PTV			
D5%	52.56±0.28	54.82±0.22	0.001
D95%	50.82±0.31	50.27±0.27	0.001
HI	1.03±0.006	1.09±0.076	0.001
CI	0.82±0.033	0.75±0.064	0.006
Bladder			
V40, %	27.31±7.16	34.13±7.97	0.029
V20, %	66.34±8.82	80.36±8.16	0.001
Dmean, Gy	29.28±3.01	33.07±3.21	0.01
Dmin, Gy	10.55±1.43	9.93±2.40	0.47
Dmax, Gy	53.34±0.88	56.35±3.22	0.007
Femoral head-L			
V40, %	0.57±0.49	1.16±0.57	0.014
V20, %	45.46±4.89	38.64±10.57	0.066
Dmean, Gy	21.46±1.07	19.84±2.40	0.054
Dmin, Gy	15.31±0.93	10.39±2.18	0.001
Dmax, Gy	42.89±2.84	42.73±5.88	0.935
Femoral head-R			
V40, %	0.50±0.55	1.43±1.01	0.014
V20, %	46.35±5.65	41.36±9.08	0.138
Dmean, Gy	21.60±0.61	20.03±2.26	0.037
Dmin, Gy	15.11±0.81	8.10±2.42	0.001
Dmax, Gy	42.67±2.27	44.28±4.94	0.337
Rectum			
V40, %	22.82±6.53	29.18±6.66	0.035
V20, %	63.41±11.94	79.36±12.01	0.005
Dmean, Gy	28.00±3.20	32.35±2.88	0.003
Dmin, Gy	12.08±1.52	12.39±2.79	0.751
Dmax, Gy	52.41±1.03	55.24±3.29	0.007
Small bowel			
V40, %	21.01±9.09	23.18±8.75	0.575
V20, %	66.25±10.00	61.55±8.63	0.251
Dmean, Gy	26.74±3.57	26.48±3.46	0.865
Dmin, Gy	1.90±0.40	1.79±0.66	0.627
Dmax, Gy	28.00±3.20	28.00±3.20	0.002
Bone marrow			
V40, %	26.81±6.08	24.82±8.33	0.53
V20, %	74.42±8.05	74.82±9.36	0.917
Dmean, Gy	29.09±2.73	32.37±3.47	0.619
Dmin, Gy	3.60±3.88	4.75±7.12	0.641
Dmax, Gy	53.71±0.98	56.89±3.04	0.004
Ovary-L			
Dmean, Gy	2.99±0.65	3.97±1.05	0.017
Dmin, Gy	2.04±0.55	2.71±0.55	0.01
Dmax, Gy	4.61±1.26	5.81±1.07	0.026
Ovary-R			
Dmean, Gy	2.98±0.59	3.84±0.73	0.007
Dmin, Gy	1.83±0.55	2.47±0.43	0.007
Dmax, Gy	4.53±0.88	5.87±1.37	0.013

Data are presented as the mean ± SD. D95, the percentage of the prescribed dose covering 95% volume of the PTV; D5, the percentage of the prescribed dose covering 5% volume of the PTV; IMRT, intensity-modulated radiation therapy; TOMO, tomotherapy; Vx, the percentage of organ receiving more or equal to x Gy; SD, standard deviation; L, left; R, right; PTV, planning target volume; CI, conformal index; HI, homogeneity index.

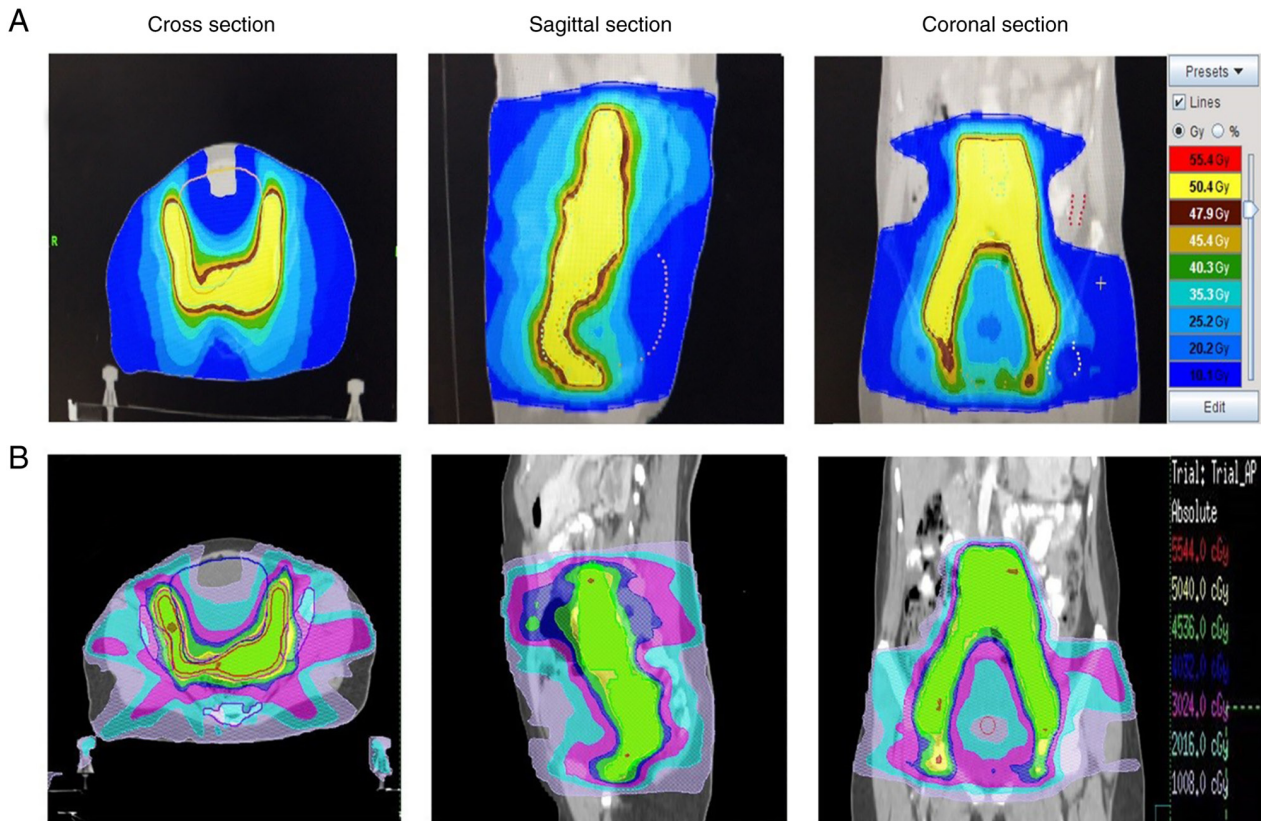


Figure 1. Isodose curves in a cross section, sagittal section and coronal section in a representative patient treated with (A) tomotherapy and (B) intensity-modulated radiation therapy.

a better CI (0.82 ± 0.0327 vs. 0.75 ± 0.064 , respectively; $P=0.006$) and HI (1.03 ± 0.006 vs. 1.09 ± 0.076 , respectively; $P<0.0001$) were observed by TOMO planning. Fig. 1A and B show the isodose curves of a cross section, sagittal section and coronary section in two representative patients treated with TOMO and IMRT, respectively; a 95% isodose curve including the PTV is indicated. TOMO provided more efficient critical organ sparing than IMRT at the mean dose, and a lower bladder V40 ($P=0.029$) and V20 ($P=0.001$), femoral head V40 ($P=0.014$), and lower rectum V40 ($P=0.035$) and V20 ($P=0.005$) were observed in the planning using TOMO compared with that using IMRT. TOMO demonstrated a superior ability to protect the left ovary (maximum dose (Dmax): 4.61 vs. 5.81 Gy, $P=0.026$; and mean dose (Dmean): 2.99 vs. 3.97 Gy, $P=0.017$, respectively) and the right ovary (Dmax: 4.53 vs. 5.87 Gy, $P=0.013$; and Dmean: 2.98 vs. 3.84 Gy, $P=0.007$, respectively). Femoral head V20 ($P=0.066$) exhibited a tendency toward more favorable values in TOMO than IMRT. There were no statistically significant differences in small bowel V20 ($P=0.251$), V40 ($P=0.575$), and bone marrow protection V20 ($P=0.917$) and V40 ($P=0.53$) between the IMRT and TOMO plans. However, TOMO yielded significantly better values for Dmax parameters for the bone marrow and small bowel, with a statistically significant level ($P=0.004$ and 0.002 , respectively). In this study, the ovarian function was preserved in 2 out of 6 patients (33.3%) in the IMRT group and in 5 patients of 11 patients (45.5%) in the TOMO group. There was no statistical difference in terms of ovarian function between the two groups ($P=0.627$).

Acute and chronic radiotherapy toxicity was assessed using the RTOG criteria. Genitourinary, gastrointestinal and hematological complications were some of the most frequent unwelcome side effects after pelvic RT. Acute major toxic effects included cystitis, proctitis, leukopenia, dermatitis and enteritis (Table III). In total, 17 patients (11.0%) in the IMRT group and 5 patients (3.2%) in the TOMO group experienced grade 3/4 acute proctitis. Grade 3/4 leukopenia occurred in 71 patients (45.8%) in the IMRT group and 60 patients (38.7%) in the TOMO group. A total of 5 patients (2.6%) in the IMRT group and 3 patients (1.9%) in the TOMO group experienced grade 3/4 acute cystitis. As shown in Table III, the acute radiation toxicity of proctitis, cystitis and leukopenia was significantly lower in the TOMO group than that in the IMRT group ($P=0.033$, $P=0.049$ and $P=0.025$, respectively). There was no statistically significant difference in the acute radiation toxicity of enteritis and dermatitis between the two groups ($P=0.055$ and 0.616 , respectively).

The chronic toxicities were mainly cystitis and enterocolitis (Table IV). Overall, 11 patients (7.1%) in the IMRT group experienced grade 3/4 late radiation cystitis. Grade 3/4 late radiation enterocolitis occurred in 10 patients (6.5%) in the IMRT group. The incidence of chronic radiation cystitis and enterocolitis in the TOMO group was 3.9% (6/155) for each. As shown in Table IV, the chronic radiation toxicity of cystitis and enterocolitis was significantly lower in the TOMO group than in the IMRT group ($P=0.041$ and 0.023 , respectively).

At the study end date in November 2019, the median follow-up time was 32 months (5-53 months) in the IMRT

Table III. Crude incidence of acute toxicity in the IMRT group (n=155) and the TOMO group (n=155) according to Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer acute radiation morbidity criteria in patients with cervical cancer.

Grade	IMRT group, n	TOMO group, n	P-value
Leukopenia			0.025
0	15	34	
1	14	16	
2	55	45	
3	47	46	
4	24	14	
Cystitis			0.049
0	57	78	
1	66	60	
2	27	14	
3	4	3	
4	1	0	
Enteritis			0.055
0	54	62	
1	67	77	
2	30	14	
3	3	2	
4	1	0	
Proctitis			0.033
0	53	71	
1	67	64	
2	18	15	
3	16	5	
4	1	0	
Dermatitis			0.616
0	56	61	
1	72	73	
2	27	21	
3	0	0	
4	0	0	

IMRT, intensity-modulated radiation therapy; TOMO, tomotherapy.

group and 28 months (5-48 months) in the TOMO group. A total of 6 out of 155 patients (3.9%) were lost to follow-up in the IMRT group and 2 out of 155 patients (1.3%) were lost to follow-up in the TOMO group, resulting in the follow-up rates of 96.1 and 98.7% ($P=0.175$), respectively. No significant difference was observed in terms of CR, PR and total response rate (CR + PR) between the TOMO and IMRT groups (94.8 vs. 95.5%, $P=0.791$; 1.9 vs. 2.5%, $P=0.709$; and 96.8 vs. 98.1%, $P=0.902$, respectively) (Table I). A plot of the survival curves is shown in Fig. 2. There were no statistically significant differences in the 1- and 3-year OS rates between the TOMO and IMRT groups (94.7 vs. 94.8%, $P=0.544$; and 81.5 vs. 84.7%, $P=0.413$, respectively) (Fig. 2A). No significant differences were found in the 1- and 3-year PFS rates between the two

Table IV. Chronic toxicities in the IMRT group (n=155) and the TOMO group (n=155) according to Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer acute radiation morbidity criteria in patients with cervical cancer.

Grade	IMRT group, n	TOMO group, n	P-value
Cystitis			0.041
0	46	59	
1	64	72	
2	34	18	
3	9	6	
4	2	0	
Enterocolitis			0.023
0	40	55	
1	60	70	
2	45	24	
3	8	5	
4	2	1	

IMRT, intensity-modulated radiation therapy; TOMO, tomotherapy.

groups (89.5 vs. 87.0%, $P=0.904$; and 80.6 vs. 82.0%, $P=0.708$, respectively) (Fig. 2B). A plot of the survival curves for the PLNM patients is shown in Fig. 3. There were no statistical differences in the 1- and 3-year OS rates between the TOMO and IMRT groups (88.7 vs. 90.9%, $P=0.956$; and 74.3 vs. 68.9%, $P=0.882$, respectively) (Fig. 3A). In addition, no significant differences were found in the 1- and 3-year PFS rates between the two groups (81.5 vs. 78.8%, $P=0.843$; and 73.5 vs. 66.2%, $P=0.956$, respectively) (Fig. 3B). A plot of the survival curves for the patients with PALNM is shown in Fig. 4. For the patients with PALNM, there were no statistical differences in the 1- and 3-year OS rates between the TOMO and IMRT groups (90.0 vs. 75.0%, $P=0.452$; and 80.0 vs. 46.9%, $P=0.143$, respectively) (Fig. 4A). No significant differences were found in the 1- and 3-year PFS rates between the two groups with the PALNM patients (90.0 vs. 50.0%, $P=0.078$; and 70.0 vs. 25.0%, $P=0.14$, respectively) (Fig. 4B). In the IMRT group, the survival rate was lower than that in the TOMO group, but there was no statistical difference between the two groups, which may be related to the small number of cases.

Discussion

The standard treatment for patients affected by locally advanced cervical cancer is concurrent chemoradiation. Conformal radiotherapy techniques such as 3D-CRT and IMRT are being used with increasing frequency with positive results in terms of decreased toxicity due to the relative sparing of normal tissues. In the present study, when compared with traditional intensity-modulated radiotherapy, TOMO was found to can provide patients with cervical cancer with greater conformal target coverage, a more homogeneous distribution of the target dose, and more efficient bladder and rectum sparing.

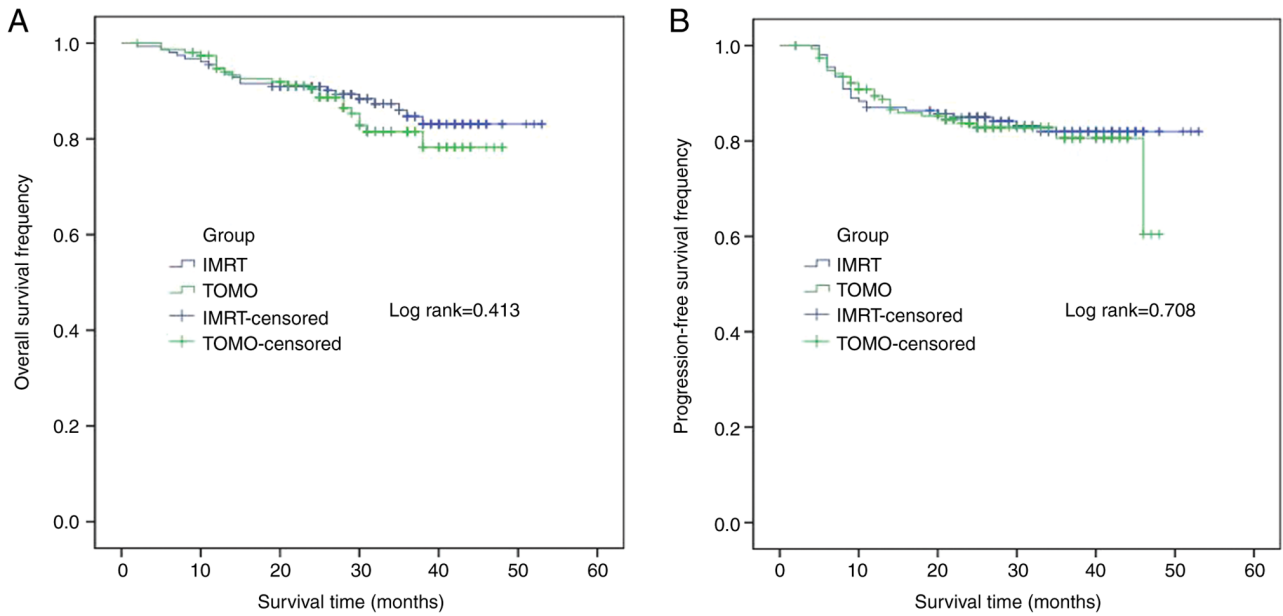


Figure 2. Survival curves (Kaplan-Meier method) showing the OS and PFS of patients with advanced cervical cancer. (A) OS and (B) PFS. OS, overall survival; PFS, progression-free survival; TOMO, tomotherapy; IMRT, intensity-modulated radiation therapy.

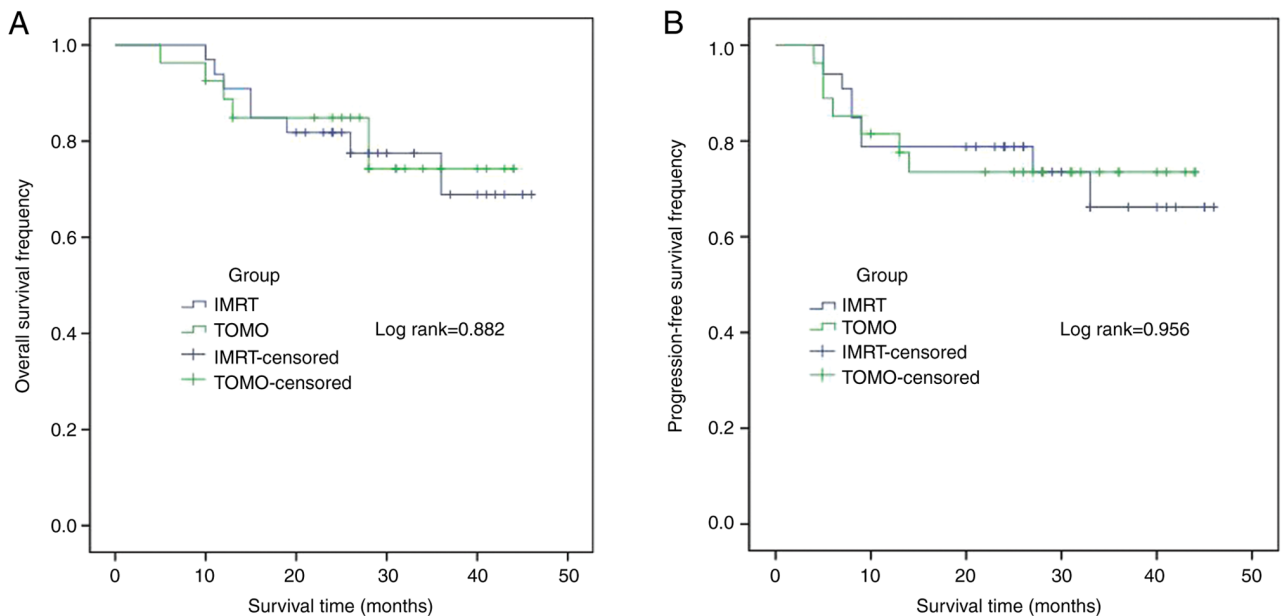


Figure 3. Survival curves (Kaplan-Meier method) showing the OS and PFS of patients with pelvic lymph node metastasis. (A) OS and (B) PFS. OS, overall survival; PFS, progression-free survival; TOMO, tomotherapy; IMRT, intensity-modulated radiation therapy.

TOMO is a 360-degree-of-freedom beam projection radiotherapy, and the number of sub-fields irradiated by a single dose is $>20,000$. The addition of further beams would result in improved conformity without the value of the objective function being affected (16). The CI value is typically 0-1, and the closer it is to 1, the better the conformability of the PTV. A larger HI represents worse PTV heterogeneity (21,22). The present study results showed that compared with intensity-modulated radiotherapy, TOMO produced a significant improvement in dose conformity (0.82 ± 0.0327 vs. 0.75 ± 0.064 , respectively; $P=0.006$) and homogeneity (1.03 ± 0.006 vs. 1.09 ± 0.076 , respectively; $P<0.001$). Several previous studies

have reported that TOMO was superior to IMRT in dose conformity (0.894 ± 0.006 vs. 0.855 ± 0.008 , respectively; $P<0.001$) and homogeneity (1.082 ± 0.006 vs. 1.106 ± 0.006 , respectively; $P=0.023$) in patients with early cervical cancer and other head and neck cancer types (23-25).

The ultimate goal of radiotherapy is to improve the dose control rate of the tumor target and reduce the dose received by normal tissue as much as possible. Since dose conformity represents the congruence between iso-dose curves and tumor contours (26), better conformity indicates potentially superior tumor target coverage and OAR protection. In the present study, TOMO provided improved critical

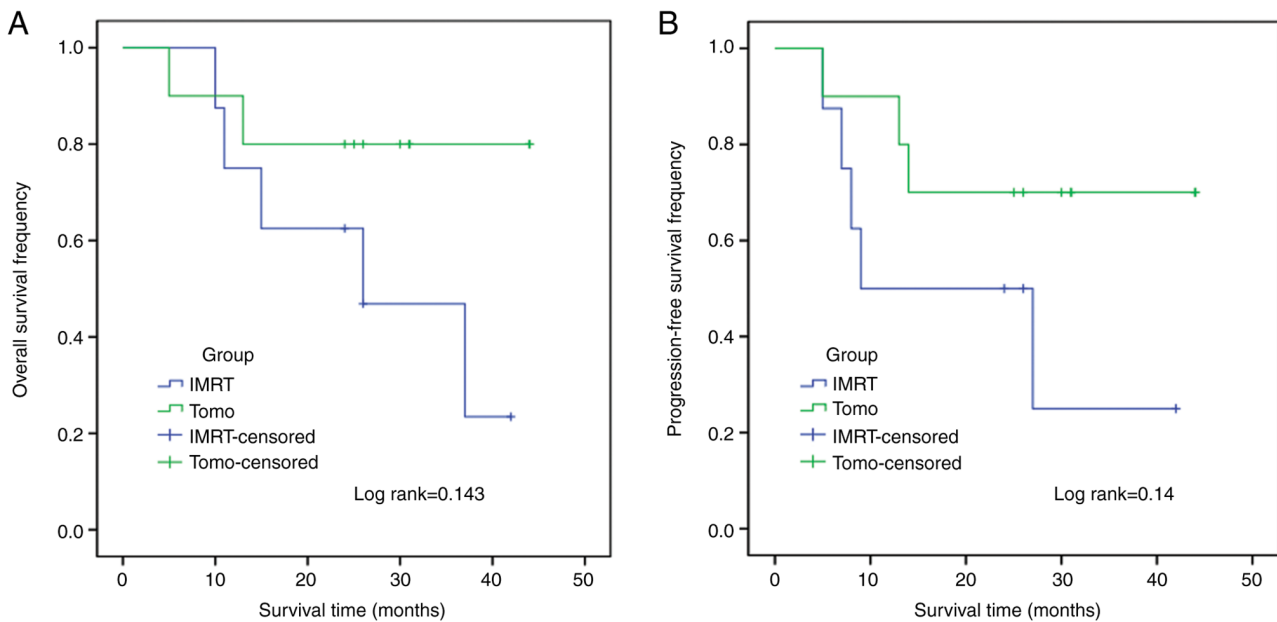


Figure 4. Survival curves (Kaplan-Meier method) showing the OS and PFS of patients with para-aortic lymph node metastasis. (A) OS and (B) PFS. OS, overall survival; PFS, progression-free survival; TOMO, tomotherapy; IMRT, intensity-modulated radiation therapy.

organ sparing compared with IMRT in terms of the average dose. Compared with IMRT, TOMO had lower bladder V40 ($P=0.029$), bladder V20 ($P=0.001$), and lower rectum V40 ($P=0.035$) and V20 ($P=0.005$) in the planning for patients with advanced cervical cancer. The femoral head V20 ($P=0.066$) showed a tendency toward more favorable values in TOMO than in IMRT, although this was not significant. Guo *et al* (23) reported that a few OARs and dosimetric parameters, including the bladder, rectum and femoral head, and ovary sparing ($P<0.001$), exhibited more favorable values in TOMO than IMRT in patients with early cervical cancer. This is consistent with several previous studies (26-30), which have indicated that TOMO outperforms IMRT in terms of dose conformity in pelvic tumors. The volume of low-dose irradiation of the intestinal, pelvic and normal tissues is decreased in patients with TOMO.

It is well known that pelvic radiotherapy can cause a variety of complications, including small intestinal obstruction, radiation cystitis, urinary incontinence, fistula and pelvic fractures (31). TOMO was expected to reduce the toxicities found when treating pelvic cavity cancer in practice, in line with these dosimetric data. Retrospective studies compared the toxicity occurrence in IMRT and TOMO, and indicated positive results for TOMO (30,32). In the present study, 17 (11.0%) patients in the IMRT group and 5 (3.2%) in the TOMO group experienced grade 3/4 acute proctitis. In addition, 4 (2.6%) patients in the IMRT group and 3 patients (1.9%) in the TOMO group experienced grade 3/4 acute cystitis. The acute radiation toxicity of proctitis and cystitis was significantly lower in the TOMO group than that in the IMRT group ($P=0.033$ and $P=0.049$, respectively). These results were in concordance with the studies by Chang *et al* (32) and Yao *et al* (30), which indicated that protection of the bladder and rectum is a significant advantage of TOMO when compared with IMRT. Overall, TOMO can decrease the risk of radiation-induced toxicity in patients undergoing pelvic RT.

Ovarian transposition is mainly suitable for young patients with cervical cancer who need pelvic RT. In the present study, before pelvic RT, the arteries and veins of the ovary were dissected, ovarian blood supply was preserved, and ovaries were moved outside the irradiation field to avoid the effect of radiotherapy on ovarian function. The success of ovarian function preservation after RT is associated with a number of factors, such as the dose to the ovary during radiotherapy, the age of the patient, the location of the ovarian displacement and whether concurrent chemotherapy is administered. The dose to the ovary during radiotherapy is the most important factor that directly affects ovarian endocrine function. Therefore, postoperative radiotherapy planning is required to minimize this dose. TOMO can produce more complex radiation fields due to the changing conformation of the multi-leaf collimator. It not only ensures uniformity and conformity of dose in the target area, but also avoids OARs that need to be protected in the ray path. At the same time, its radiation contamination is smaller, so that the OARs can be accurately excluded (33). For the displaced ovaries, the target area and ovarian dose can be better considered, and the possibility of making concessions in the target range and the conformity is less. Moreover, precise image guidance can minimize the placement error, ensure the accurate implementation of the plan, achieve precise treatment and add a layer of protection for ovarian function. The ovary is a parallel organ. Damage to ovarian cells during radiotherapy is directly associated with ovarian function. In the present study, TOMO demonstrated a superior ability to protect the left ovary (Dmax: 4.61 vs. 5.81 Gy, $P=0.026$; Dmean: 2.99 vs. 3.97 Gy, $P=0.017$). Guo *et al* (23) reported that TOMO provided improved ovarian organ sparing compared with IMRT at the mean dose, and the difference was statistically significant ($P<0.001$). Therefore, TOMO radiotherapy is recommended for young patients who need pelvic radiotherapy. However, ovarian function was only preserved in 2 out of 6 patients (33.3%) in the IMRT group

and 5 out of 11 patients (45.5%) in the TOMO group. There was no statistically significant difference in ovarian function between the two groups ($P=0.627$). Although there was no significant difference between the two groups, the ratio of the TOMO group was higher than that of the IMRT group. This could be associated with the small sample size of this study. Further prospective randomized multicenter studies are needed to confirm the benefits of TOMO.

Few published studies (12,34) have explored tumor control comparing IMRT with TOMO in patients with locally advanced cervical carcinoma. The present study demonstrated a similar tumor response rate between the two groups. There was no significant difference with regard to CR, PR or total response rate (CR + PR) between the TOMO and IMRT groups (94.8 vs. 95.5%, $P=0.791$; 1.9 vs. 2.5%, $P=0.709$; and 96.8 vs. 98.1%, $P=0.902$, respectively). There was also no statistically significant difference in the 1- and 3-year OS rates between the TOMO and IMRT groups (94.7 vs. 94.8%, $P=0.544$; and 81.5 vs. 84.7%, $P=0.413$, respectively). Furthermore, no significant difference was found in 1- and 3-year PFS rates between the two groups (89.5 vs. 87.0%, $P=0.904$; and 80.6 vs. 82.0%, $P=0.708$, respectively). Wang *et al* (34) reported outcomes of patients with stage IB1-IVA cervical cancer treated with definitive IMRT. The 3-year OS and PFS rates were 83.0 and 75.0%, respectively. The study by Chang *et al* (32) included 15 patients with stage IB1-IVA cervical cancer, and all patients had received pelvic irradiation delivered by TOMO. The 3-year OS rate was 93.0% and the 3-year PFS rate was 80.0%. Together, these results indicate that TOMO is feasible for use in patients with locally advanced cervical carcinoma. The results also showed that TOMO does not significantly reduce the recurrence and mortality rates of patients. However, this is a retrospective analysis that requires further validation by prospective studies.

In conclusion, the present results showed that TOMO and IMRT were comparable in terms of mean dose, dose conformity, dose homogeneity and protection of the ovary. TOMO provided better critical organ sparing than IMRT in the lower bladder and the lower rectum, as observed in the planning. The acute and chronic toxicities were acceptable. Therefore, TOMO is a good option for treatment of FIGO stage IIB-IIIB cervical cancer, especially in young patients with ovarian transposition. Further prospective randomized multicenter studies are required to confirm the benefits of TOMO.

Acknowledgements

Not applicable.

Funding

This study was supported by the Key Technology Research and Development Program of Shandong (grant no. 2018GSF118237) and the National Natural Science Foundation for Young Scientists of China (grant no. 81602306).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

DL recorded and analyzed the experimental raw data, and was a major contributor in writing the manuscript. DW collected the clinical data, was involved in the raw data analysis, and revised the manuscript. QC and JJ contributed to recording the experimental raw data, and were involved in the raw data analysis and manuscript draft. SF and XY designed the experiment and revised the manuscript. JZ designed the experiment and analyzed the dose volume histogram data. YY designed the experiment, checked the experimental raw data and was a major contributor to the revised manuscript. XS supplied study guidance and perfected the experiment design. DL, DW, JZ and YY confirm the authenticity of all the raw data. All authors have read and approved the manuscript.

Ethics approval and consent to participate

Ethics approval was obtained from the Ethics Committee of Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences (Jinan, China; approval no. SDTHEC2021012058).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Bhatla N, Aoki D, Sharma DN and Sankaranarayanan R: Cancer of the cervix uteri. *Int J Gynecol Obstet* 143 (Suppl 2): S22-S36, 2018.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 71: 209-249, 2021.
3. Dutta S, Nguyen NP, Vock J, Kerr C, Godinez J, Bose S, Jang S, Chi A, Almeida F, Woods W, *et al*: Image-guided radiotherapy and -brachytherapy for cervical cancer. *Front Oncol* 5: 64, 2015.
4. Harkenrider MM, Alite F, Silva SR and Small W Jr: Image-based brachytherapy for the treatment of cervical cancer. *Int J Radiat Oncol Biol Phys* 92: 921-934, 2015.
5. Mackie TR, Holmes T, Swerdloff S, Reckwerdt P, Deasy JO, Yang J, Paliwal B and Kinsella T: Tomotherapy: A new concept for the delivery of dynamic conformal radiotherapy. *Med Phys* 20: 1709-1719, 1993.
6. Mackie TR, Kapatoes J, Ruchala K, Lu W, Wu C, Olivera G, Forrest L, Tome W, Welsh J, Jeraj R, *et al*: Image guidance for precision conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 56: 89-105, 2003.
7. Balog J, Mackie TR, Pearson D, Hui S, Paliwal B and Jeraj R: Benchmarking beam alignment for a clinical helical tomotherapy device. *Med Phys* 30: 1118-1127, 2003.
8. Grigorov G, Kron T, Wong E, Chen J, Sollazzo J and Rodrigues G: Optimization of helical tomotherapy treatment plans for prostate cancer. *Phys Med Biol* 48: 1933-1943, 2003.
9. van Vulpen M, Field C, Raaijmakers CP, Parliament MB, Terhaard CH, MacKenzie MA, Scrimger R, Lagendijk JJ and Fallone BG: Comparing step-and-shoot IMRT with dynamic helical tomotherapy IMRT plans for head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 62: 1535-1539, 2005.

10. Chen YJ, Liu A, Han C, Tsai PT, Schultheiss TE, Pezner RD, Vora N, Lim D, Shibata S, Kernstine KH and Wong JY: Helical Tomotherapy for radiotherapy in esophageal cancer: A preferred plan with better conformal target coverage and more homogeneous dose distribution. *Med Dosim* 32: 166-171, 2007.
11. Lian J, Mackenzie M, Joseph K, Pervez N, Dundas G, Urtasun R and Pearcey R: Assessment of extended-field radiotherapy for stage IIIC endometrial cancer using three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, and helical tomotherapy. *Int J Radiat Oncol Biol Phys* 70: 935-943, 2008.
12. Hsieh CH, Wei MC, Lee HY, Hsiao SM, Chen CA, Wang LY, Hsieh YP, Tsai TH, Chen YJ and Shueng PW: Whole pelvic helical tomotherapy for locally advanced cervical cancer: Technical implementation of IMRT with helical tomotherapy. *Radiat Oncol* 4: 62, 2009.
13. Karnofsky DA and Burchenal JH: The clinical evaluation of chemotherapeutic agents in cancer. In: *Evaluation of Chemotherapeutic Agents*. Macleod CM (Ed.). Columbia University Press, New York, NY, p196, 1949.
14. Pecorelli S: Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet* 105: 103-104, 2009.
15. International Commission on Radiation Units and Measurements (ICRU): Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU Report 50). ICRU Report, 62. ICRU, Bethesda, MD, 1999.
16. Wang X, Zhang X, Dong L, Liu H, Gillin M, Ahamad A, Ang K and Mohan R: Effectiveness of noncoplanar IMRT planning using a parallelized multiresolution beam angle optimization method for paranasal sinus carcinoma. *Int J Radiat Oncol Biol Phys* 63: 594-601, 2005.
17. International Commission on Radiation Units and Measurements (ICRU). Dose and volume specification for reporting intracavitary therapy in gynecology. ICRU Report, 38. ICRU, Bethesda, MD: ICRU1985.
18. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancy J, Arbuck S, Gwyther S, Mooney M, *et al*: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 45: 228-247, 2009.
19. Bruner DW: Outcomes research in cancer symptom management trials: The radiation therapy oncology group (RTOG) conceptual model. *J Natl Cancer Inst Monogr* 37: 12-15, 2007.
20. Peters WA III, Liu PY, Barrett RJ II, Stock RJ, Monk BJ, Berek JS, Souhami L, Grigsby P, Gordon W Jr and Alberts DS: Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol* 18: 1606-1613, 2000.
21. Zhou GX, Xu SP, Dai XK, Ju ZJ, Gong HS, Xie CB, Yin LM and Yang J: Clinical dosimetric study of three radiotherapy techniques for postoperative breast cancer: Helical Tomotherapy, IMRT, and 3D-CRT. *Technol Cancer Res Treat* 10: 15-23, 2011.
22. Chitapanarux I, Nobnop W, Tippanya D, Sripan P, Chakrabandhu S, Klunklin P, Onchan W, Jia-Mahasap B and Tharavichitkul E: Clinical outcomes and dosimetric study of hypofractionated Helical Tomotherapy in breast cancer patients. *PLoS One* 14: e0211578, 2019.
23. Guo MF, Liu XF, Liu L and Wang D; Department of Gynecologic Oncology, Chongqing University Cancer Hospital& Chongqing Cancer Institute&Chongqing Cancer Hospital: (A dosimetric study of helical tomotherapy in radiotherapy after ovarian-conserving radical surgery for young patients with early-stage cervical cancer). *J Chongqing Med Univ* 044: 39-42, 2019.
24. Wiezorek T, Brachwitz T, Georg D, Blank E, Fotina I, Habl G, Kretschmer M, Lutters G, Salz H, Schubert K, *et al*: Rotational IMRT techniques compared to fixed gantry IMRT and tomotherapy: Multi-institutional planning study for head-and-neck cases. *Radiat Oncol* 6: 20, 2011.
25. Clemente S, Wu B, Sanguineti G, Fusco V, Ricchetti F, Wong J and McNutt T: SmartArc-based volumetric modulated arc therapy for oropharyngeal cancer: A dosimetric comparison with both intensity-modulated radiation therapy and helical tomotherapy. *Int J Radiat Oncol Biol Phys* 80: 1248-1255, 2011.
26. Yang R, Xu S, Jiang W, Wang J and Xie C: Dosimetric comparison of postoperative whole pelvic radiotherapy for endometrial cancer using three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, and helical tomotherapy. *Acta Oncol* 49: 230-236, 2010.
27. Engels B, De Ridder M, Tournel K, Sermeus A, De Coninck P, Verellen D and Storme GA: Preoperative helical tomotherapy and megavoltage computed tomography for rectal cancer: Impact on the irradiated volume of small bowel. *Int J Radiat Oncol Biol Phys* 74: 1476-1480, 2009.
28. Tournel K, De Ridder M, Engels B, Bijdekerke P, Fierens Y, Duchateau M, Linthout N, Reynders T, Verellen D and Storme G: Assessment of intrafractional movement and internal motion in radiotherapy of rectal cancer using megavoltage computed tomography. *Int J Radiat Oncol Biol Phys* 71: 934-939, 2008.
29. Gattaneo GM, Dell'oca I, Broggi S, Fiorino C, Perna L, Pasetti M, Sangalli G, di Muzio N, Fazio F and Calandrino R: Treatment planning comparison between conformal radiotherapy and helical tomotherapy in the case of locally advanced-stage NSCLC. *Radiat Oncol* 88: 310-318, 2008.
30. Yao B, Wang SH, Wang YD, Liu Q and Lu N: Acute and late toxicities and efficacy of helical tomotherapy and concurrent chemotherapy in the treatment of locally advanced cervical cancer. *Oncol Prog* 14: 544-547, 2016.
31. Rose BS, Aydogan B, Liang Y, Yeginer M, Hasselle MD, Dandekar V, Bafana R, Yashar CM, Mundt AJ, Roeske JC and Mell LK: Normal tissue complication probability modeling of acute hematologic toxicity in cervical cancer patients treated with chemoradiotherapy. *Int J Radiat Oncol Biol Phys* 79: 800-807, 2011.
32. Chang AJ, Richardson S, Grigsby PW and Schwarz JK: Split-field helical tomotherapy with or without chemotherapy for definitive treatment of cervical cancer. *Int J Radiat Oncol Biol Phys* 82: 263-269, 2012.
33. Lin MA: Clinical Application of Tomotherapy System. *China Medical Devices* 29: 12-14, 2014 (In Chinese).
34. Wang W, Zhang F, Hu K and Hou X: Image-guided, intensity-modulated radiation therapy in definitive radiotherapy for 1433 patients with cervical cancer. *Gynecol Oncol* 151: 444-448, 2018.



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.