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Comparison of Simplified Intensity-Modulated Radiotherapy versus 3-Dimensional Conformal Radiotherapy in Locally Advanced Cervical Cancer: A Dosimetric Study

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Abstract

Background: Early research describing the concept of intensity-modulated conformal radiotherapy (IMRT) was based on 7 to 9 beams to reach an adequate level of modulation. Nevertheless, its implementation demands significant resources. Our objective was to compare the compliance and homogeneity of target dose distribution between simplified IMRT and 3D-CRT in patients with cervical cancer and to assess the clinical value of simplified IMRT. **Materials and Methods**: From 2016 to 2017, 17 patients with stage IIB - IIIC cervical cancer were treated with external beam radiotherapy using simplified IMRT (12 cases) or 3DCRT (05 cases) and brachytherapy. Prior to radiotherapy, CT scans were conducted to delineate the target volume. The clinical target volume (CTV) included the uterus, primary tumor, supravaginal portion of the cervix, paracervical tissue, common iliac, internal and external iliac lymph nodes, obturator, and pre sacral lymph nodes, and the surrounding tissues. If the lower vagina was involved, the target volume included the whole vagina. The planning target volume (PTV) included the CTV with 1 cm anteriorly and 0.5 cm in all other directions. The PTV received 95% of 45 Gy (1.8 Gy/25 fraction). Dose-volume histogram, conformity index, homogeneity index, and treatment time per fraction were compared. **Results**: The 3D-CRT plan was more homogeneous than the simplified IMRT plan, while the simplified IMRT plan was more conformal. The volume of small bowels that received high-dose radiation significantly increased with simplified IMRT compared to 3D-CRT. Treatment time per fraction was 6 and 13 minutes for 3D-CRT and simplified IMRT, respectively. **Conclusion**: The simplified IMRT treatment plan is technically and dosimetrically acceptable and an alternative to the classic 3D-CRT plan for cervical cancer. It provides better dose distribution than 3D-CRT. However, the 3D-CRT treatment plan significantly reduced the overall treatment time per fraction.

Keywords

Cervical Cancer, Simplified Intensity-Modulated Radiotherapy, 3D-CRT, Dosimetry

1. Introduction

Uteri cervix cancer (UCC) is a major health problem worldwide [1]. It is the 4th most common cancer in women, with 662,301 new cases in 2022, or 7% of all female cancers [1]. The incidence of UCC varies from country to country. In China, UCC accounts for 25,000 cancer deaths [2]. In Guinea, the incidence rate is 29.1%, or nearly 27% of all cancer-related deaths [3]. Among the risk factors identified, the human papillomavirus types 16 and 18 are found in 70% of cases [4]. Radiotherapy plays a key role in the treatment, particularly when combined with chemotherapy [4] [5]. Over the years, radiotherapy has constantly developed with the introduction of intensity modulation. This is an important aspect of the treatment of pelvic cancer, helping to minimize the risk of recurrence and improve the quality of life for patients with localized or locally advanced pelvic cancer.

The first dosimetric studies of IMRT for the treatment of UCC date back to the early 2000s [6] [7]. Unlike conventional approaches, IMRT uses treatment beams of variable intensity, enabling the high-dose area to be adapted to the shape of the target volume. This approach has been documented in a number of locations, including head and neck, prostate, lung and breast cancer [8]-[10]. Besides optimizing dose distribution, tailoring the radiation field to the target volume, the IMRT planning system aims to reduce dose loss in surrounding organs at risk (OAR), especially when used for pelvic cancers treatment [11] [12]. Nevertheless, since the study by Chui *et al.* [13], it is uncertain whether IMRT for the treatment of pelvic cancer is feasible in a busy cancer center, as planning and administration take longer than the conventional 4-field box approach. In this respect, to ensure the role and quality of IMRT, too small a volume and a large number of subfields are likely to extend treatment time, cause errors and require several resources for dose verification [11]. Conversely, simplified IMRT is an intensity modulation approach that theoretically simplifies this IMRT procedure while retaining its advantages. The present study aimed to explore the feasibility of simplified IMRT for external radiotherapy of the UCC.

2. Materials and Methods

2.1. Clinical Characteristics of Patients

The study was approved by the Institutional Review Board. Inclusion criteria were 1) adult patients (18 years of age or older) with pathologically confirmed cervical cancer and 2) written informed consent obtained from the patient between January 2016 and December 2017. Exclusion criteria were cases where the histological subtype was unknown at the time of inclusion. A total of 17 consecutive patients with locally advanced UCC admitted to the Shijiazhuang Cancer Institute were included in a 2-year prospective study. Of these, 12 received simplified IMRT and 5 3D-CRT. The median age of the patients was 54 ± 6.2 years (range: 38 - 78 years); the cancer was classified as stage IIB in 3 cases, IIIA in 4 cases, IIIB in 4 cases, IIIC in 5 cases and stage IVA in 1 case, according to FIGO 2017. Chemotherapy was concomitant in 100% of cases and was administered in a neoadjuvant setting in 47.1% of cases (**Table 1**).

Table 1. Clinical characteristics of patients.

Characteristics	Number	
	N	(%)
Median age (years)	54 ± 6.2	
Figo stage (UICC 2017)		
- IIB	03	17.6
- IIIA - IIIC	13	76.5
- IVA	01	05.9
Chemotherapy modalities		
- Concomitant	17	100
- Neoadjuvant	08	47.1
Radiotherapy		
- Simplified IMRT	12	70.6
- 3D-CRT	05	29.4
TOTAL	**17**	**100**

IMRT: Intensity-modulated radiotherapy; 3D CRT: 3-dimensional conformal radiotherapy.

2.2. Radiotherapy Procedure

2.2.1. CT Simulation

Patients were positioned under strict control of the full bladder protocol. First, they completely emptied the bladder, then 60 to 90 minutes after ingestion of the contrast agent, a CT scan injected with Optiject 300 mg and 3 mm thick slices were taken. The limits of the scan extended from the dome of the diaphragmatic cupola to 5 cm below the ischial tuberosity. They were placed in the supine position, with their hands holding each other's elbows to the forehead, their legs naturally together, and secured with a thermoformed mask.

2.2.2. Definition of Target Volumes

The target volumes and OAR were defined according to the Radiotherapy Oncology Group (RTOG) recommendations [14]. The Gross Tumor Volume (GTV) included: the uterus, primary cervical tumor, cervix, vagina, and enlarged regional lymph nodes [4]. The Clinical Target Volume (CTV) included the GTV as well as the common iliac, external iliac, internal iliac, obturator, and presacral lymph nodes and their surrounding tissues [4]. The upper limit of the CTV corresponded to the upper edge of the bifurcation of the abdominal aorta and the lower limit to the lower edge of the obturator foramen [4].

In the absence of a solid tumor or enlarged lymph nodes, the common iliac and internal and external iliac arteries were used as landmarks, with an extension of 1 cm and 0.7 cm as the anteroposterior and left-right lateral limits. Except for pelvic tissue, these limits included part of the bladder and rectum. The Planning Target Volume (PTV) corresponded to an extension of the CTV of 1 cm anteriorly and 0.5 cm in each of the other directions. The organs at risk were defined as the small intestine, sigmoid colon, rectum, bladder, femoral heads, spinal cord, and skin [4] [11]. Target volumes were delineated using Pinnacle 3 V7.0 software.

2.3. Treatment

To deliver the total prescribed dose to the isodose line covering 95% of the PTV, the simplified IMRT had 5 fields and 3D-CRT treatment plans had 4 fields, respectively.

2.4. Treatment Plan Design

2.4.1. Simplified IMRT

In clinical practice, the simplified IMRT procedure is similar to that of IMRT, including a simulation stage, delineation, design and validation of the plan and implementation, except that simplified IMRT uses the same dosimetric validation methods as 3D-CRT. In general, the average number of subfields in a single field is ≤5, the subfield area is ≥10 cm^2, the number of machine rotations is ≥10 MU, and the beam angles used in the actual treatment were 45˚, 105˚, 180˚, 255˚, and 315˚.

2.4.2. 3D-CRT

In contrast, the 3D radiotherapy treatment plan can be likened to a 4-field box. Depending on the dose distribution, it may be necessary to use steel blocks. The optimization algorithm used to design this plan corresponds to the direct optimization algorithm for machine parameters. The total dose of external radiotherapy was 45 Gy (1.8 Gy/25 fractions, 95% PTV), with an energy of 6 MV. The program priorities for delivering the treatment were the PTV, rectum, bladder, small bowel, spinal cord and femoral heads. All treatment planning was carried out on Pinnacle V7.0, and irradiated volumes, OAR, and doses were assessed using dose-volume histogram curves. Treatment was delivered using a Medscape Precise 5905 accelerator.

2.5. Program Evaluation

2.5.1. Conformity Index (CI)

$$IC = 1/VT \times VTref \times 1/Vref \times VTref$$

VTref: target volume covered by the reference isodose line, VT: target volume; Vref: total volume covered by the reference isodose line.

2.5.2. Homogeneity Index (HI)

$$HI: D5\%/D95\%$$

D5% and D95% are the radiation doses at 5% and 95% of the PTV volume, respectively; Maximum dose (Dmax) to organs at risk and percentage of total volume irradiated with 20 Gy and 40 Gy (V20 and V40).

2.6. Statistical Analysis

The results of the two (2) treatment plans were analyzed by the ANOVA test and compared by the LSD method using SPSS 22.0 software.

3. Results

3.1. PTV Dose Distribution Characteristics

The uniformity of the dose distribution in the PTV with the 3D-CRT treatment plan was better than that with simplified IMRT; while the conformity of the dose distribution with simplified IMRT appeared to be superior to that in 3D-CRT (Table 2).

Table 2. Comparison of dose distribution in PTV, conformity index, homogeneity, and number of machine rotations after simplified IMRT and 3D-CRT.

Parameters	Radiotherapy		P
	Simplified IMRT	3D-CRT	
CI	0.75 ± 0.05	0.56 ± 0.03	0.000
HI	1.15 ± 0.02	1.09 ± 0.02	0.000
Machine rotation	751.20 ± 101.61	277.10 ± 8.08	<0.001
Dmax (Gy)	54.99 ± 2.23	49.90 ± 0.94	<0.001
Dmin (Gy)	31.80 ± 7.30	40.94 ± 0.69	0.001
Dmean (Gy)	48.74 ± 0.67	47.01 ± 1.76	0.003

Dmax: Maximum dose; Dmin: Minimum dose; Dmean: mean dose; CI: Conformity index; HI: Homogeneity index; IMRT: Intensity modulated radiotherapy; 3D-CRT: 3-dimensional conformal radiotherapy.

3.2. Treatment Lead Time

The number of machine rotations for both treatment plans is summarised in

Table 2. The actual machine occupancy time was 6 minutes for 3D-CRT and 13 minutes for simplified IMRT, including the time taken to change the angle of the machine and the time taken to set up the blocks manually.

3.3. Doses Received and Volume of OAR

Dmax to the bladder (48.77 ± 0.97 vs 51.99 ± 3.02; p = 0.012), rectum (49.56 ± 1.03 vs 51.99 56 ± 3.02; p = 0.001) and small intestine (48.04 ± 1.29 vs 52.36 ± 1.48; p = 0.001) appeared lower with the 3D-CRT treatment plan than that with the simplified IMRT treatment plan (Table 3). However, the simplified IMRT treatment plan was significantly better than the 3D-CRT treatment plan for protecting the bladder, small intestine, and rectum (Table 3).

Table 3. Comparison of dose and volume percentage of OARs after simplified IMRT and 3D-CRT.

OARs	Parameters	Radiotherapy		P
		Simplified IMRT	3D-CRT	
Rectum	Dmax (Gy)	51.99 ± 3.02	49.56 ± 1.03	0.012
	V40 (%)	71.10 ± 13.45	87.80 ± 8.25	0.004
	V30 (%)	92.90 ± 8.54	95.20 ± 6.11	0.495
	V20 (%)	97.80 ± 4.26	98.10 ± 4.01	>0.05
Intestine	Dmax (Gy)	52.36 ± 1.48	48.04 ± 1.29	<0.001
	V40 (%)	14.20 ± 5.73	23.00 ± 9.35	0.007
	V30 (%)	28.00 ± 8.56	29.70 ± 9.97	>0.05
	V20 (%)	55.58 ± 5.88	66.00 ± 5.21	<0.001
Bladder	Dmax (Gy)	51.99 ± 3.02	48.77 ± 0.97	0.001
	V40 (%)	72.30 ± 11.58	87.80 ± 8.25	<0.001
	V30 (%)	54.30 ± 6.63	86.80 ± 9.95	<0.001
	V20 (%)	79.80 ± 10.89	100 ± 0.47	<0.001

OARs: Organs at risk; Dmax: Maximum dose; IMRT: Intensity modulated radiotherapy; 3D CRT: 3-dimensional conformal radiotherapy.

4. Discussion

Advances in computer science applied to medicine and medical imaging have enabled conventional radiotherapy to enter the era of precision. IMRT is a form of precision radiotherapy that simultaneously satisfies two conditions: 1) Firstly, during real-time irradiation, the shape of the irradiation field automatically conforms to the shape of the tumor (target volume); 2) Secondly, to ensure that the dose is uniform across all target volumes, the output dose rate at any point in each field systematically adapts to the shape of the target volume [15]. The aim is to increase radiation dose to the tumor and to minimize the volume and dose loss to the surrounding organs, without compromise. Many authors have reported the advantages of IMRT over the 3D-CRT, in terms of OAR protection and better dose conformity in the PTV for pelvis cancers [16]-[18]. However, the fact remains that, its implementation requires significant resources, and is time-consuming for the dose prescription validation. Given these constraints, simplified IMRT has been developed to reduce the work intensity, save resources, and maximize the benefits of IMRT. To this end, we compared 17 cases of UCC radiotherapy using simplified IMRT techniques and 3D-CRT and analysed the characteristics of dose distribution in the PTV. Our results demonstrated that the homogeneity of the dose distribution was better with the 3D-CRT treatment plan than simplified IMRT; while the conformity of the dose distribution in the PTV was better with simplified IMRT than 3D-CRT. Although the difference is non-significant, our findings differ from those of Wen G *et al.* [19] who reported better results with simplified IMRT than 3D-CRT in terms of conformity and homogeneity in the PTV with higher Dmax and Dmean in the target volumes. Additionally, in the second set of our analyses, we investigated whether simplified IMRT could improve Dmax and protect OAR. Our results suggest that the protection of OAR such as the bladder and small intestine was significantly better with simplified IMRT, with a higher Dmax in PTV (54.99 ± 2.23 vs 49.9 ± 0.94; <0.001), V40bladder (72.30 ± 11.58 vs 87.80 ± 8.25; <0.001), V30bladder (54.30 ± 6.63 vs 86.80 ± 9.95; <0.001), V20bladder (79.80 ± 10.89 vs 100 ± 0.47; <0.001) and V40intestinal (14.20 ± 5. 73 vs 23.00 ± 9.35; <0.007), V30intestinal (28.00 ± 8.56 vs 29.70 ± 9.97; >0.05), V20intestinal (55.58 ± 5.88 vs 66.00 ± 5.21; <0.001), respectively. Gunnlaugsson A. *et al.* [20] reported a strong correlation between the occurrence of grade ≥ 2 diarrhea and the volume of irradiated intestine in 28 patients treated with chemoradiotherapy for rectal cancer. They reported an incidence of 11% of diarrhea for an irradiated intestine volume ≤ 150 cm^3 at a dose level > 15 Gy and 52% when the volume was >150 cm^3. Moreover, among intraperitoneal OARs, the small intestine is considered as the most important organ in pelvic radiotherapy. [20] [21]. Exposure of the small intestine to a dose higher than the dose constraints applied to the intestine can lead to acute and late toxicities such as diarrhea, dyspepsia, intestinal obstruction, or intestinal perforation [17]. In contrast, for some authors the tolerance dose of the bladder is higher than other intra-pelvic OAR. The total dose of 2/3 and the total irradiated volume of the bladder are estimated at 80 Gy and 65 Gy, respectively. The incidence of grade 3 or 4 post-radiation cystitis is much lower, at between 1% and 2%. Therefore, in the future, the cost-effectiveness of IMRT will be discussed in relation to its actual clinical efficacy.

In the present study, the actual machine occupancy time was 6 minutes for 3D-CRT and 13 minutes for simplified IMRT. Bakiu E *et al.* [22] and Lee SW *et al.* [23] observed similar results in previous studies. It can be deduced that 3D-CRT offers the advantage of better dose homogeneity in the PTV and a 2-fold reduction in treatment time compared with simplified IMRT. However, OAR protection remains a dosimetric limitation of 3D-CRT.

5. Strengths and Study Limitations

This is one of the first studies carried out in our institution and was performed with a predefined methodology and protocol. Apart from the synthesis of results for the comparison between simplified IMRT and 3D-CRT in the treatment of CCU, our group analysis showed that the machine occupation time and the protection of organs at risk are variable from one technique to another. This deserves to be taken into account for a better selection of patients. However, in addition to the fact that this is a series with few women, our study shows a lack of data on the local control, survival, and cumulative acute dose-limiting toxicities of external beam radiotherapy and brachytherapy.

6. Conclusion

Compared with 3D-CRT, IMRT is a fundamental option for the treatment of cervical cancer, especially for those with stages IIB to IIIC. It is gaining importance with the improvement of simplified techniques that contribute significantly to reducing toxicities and improving patient comfort.

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Compliance with Ethical Standards

The research involved human participants only and institutional ethical clearance was obtained. Informed consent was obtained from every participant of the study in the presence of a neutral witness.

Conflicts of Interest

The authors declare no conflicts of interest.

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