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ORIGINAL ARTICLE

Implementation of intensity-modulated radiotherapy and comparison with three-dimensional conformal radiotherapy in the postoperative treatment of cervical cancer

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Summary

Purpose: *Within implementation of intensity-modulated radiotherapy (IMRT) in the postoperative irradiation of cervical cancer we evaluated and compared IMRT and three-dimensional conformal radiotherapy (3DCRT) dosimetric parameters for target volumes and organs at risk (OAR).*

Methods: *We randomized 95 patients with cervical cancer, UICC stage I-III, in groups depending of the type of external beam postoperative radiotherapy. Forty-five patients were treated with IMRT and 50 with 3DCRT. All patients underwent brachytherapy, and according to risk factors some of the patients had concomitant cisplatin chemotherapy. The study was done in a period of three years from December 2015. Analysis of dosimetric parameters for target volume coverage and OARs was performed.*

Results: *IMRT plans showed better conformity compared to 3DCRT plans, represented with homogenity index and conformity index, with higher maximum dose (PTV_{105} and D_2). Both plans achieved adequate planning target volume coverage described with PTV_{95}. Statistically significant difference between groups was found for bladder, rectum and bowel high dose regions: bladder V45 (p=0.000), rectum V40 (p=0.043) and V45 (p=0.000), bowel V45 (p=0.000), and bone marrow dosimetric parameters V20-V45; all were better in IMRT plans. Significant difference was found for volume of patient body normal tissue receiving dose of 20Gy, which was higher in IMRT.*

Conclusion: *IMRT is a highly conformal technique. Satisfactory target volume coverage was achieved with both techniques, with better sparing of OARs in the IMRT group. With this technique improvement, we expect better quality of life in cervical cancer patients with good prognosis.*

Key words: *cervical cancer, dosimetric parameters, intensity-modulated radiotherapy, three-dimensional radiotherapy*

Introduction

Although the use of well organized screening and prophylactic vaccination have reduced the incidence and mortality in developed countries, cervical cancer is still a significant health problem in Serbia. According to data from 2018 Serbia is amongst the top five countries in Europe with this problem [1].

The primary therapeutic option for early-stage cervical cancer is radical hysterectomy with pelvic lymphadenectomy. In the group of patients with increased risk for disease relapse (intermediate and high-risk pathological factors) postoperative pelvic radiotherapy (with or without platinum-based chemotherapy) is indicated [2]. Compared to

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patients treated only with surgery, postoperative radiotherapy reduces risk for local recurrence to 47% [3]. For most patients a combination of external beam radiotherapy (EBRT) and brachytherapy is used. Technological progress and implementation of imaging techniques, such as computed tomography (CT), magnetic resonance (MRI), positron-emission tomography (PET) and also improvement of treatment planning systems led to the development of modern complex radiotherapy techniques like intensity-modulated radiotherapy (IMRT). IMRT represents a highly conformal technique based on purposely altered intensity of each radiation beam, with a goal to improve dose delivery to target volumes and OARs by reducing their dose [4]. Advantages of IMRT compared to conventional and three-dimensional conformal radiotherapy (3DCRT) led to increased usage of this technique in the treatment of different malignancies [5].

Postoperative radiotherapy in patients with cervical cancer is closely related to development of OARs toxicity. The occurrence of complications is particularly pronounced when several modalities of treatment are combined [6]. Toxicity can significantly reduce the quality of life in this group of patients with good prognosis and overall survival. The most common postirradiation toxicities are gastrointestinal, genitourinary as well as haematological [7,8].

In many developing countries, there was lack of adequate radiotherapy equipment, so the use of modern radiotherapy techniques was limited [9]. The goal of this study was to present our initial clinical experience in the implementation of IMRT in cervical cancer patients, during the learning period. We compared dosimetric parameters between the groups patients treated with postoperative IMRT and 3DCRT.

Methods

Selection of patients and CT simulation

This study included 95 patients with pathologically confirmed cervical cancer treated from December 2015 to December 2018, in our Department of radiotherapy. After diagnostic procedures and appropriate FIGO staging all patients underwent surgery. The oncology board indicated adjuvant radiotherapy (with or without chemotherapy) according to the protocol, in case of pathologic risk factors present. The patients were divided into two groups: 45 patients were treated with IMRTand 50 with 3DCRT. All patients were irradiated with combination of EBRT and brachytherapy. EBRT of the pelvis was performed with a dose of 40-45 Gy in 22/25 fractions, 1.8 Gy per day, 5 days per week delivered to the planning target volume. HDR brachytherapy (Ir 192) of the vaginal cuff was performed in 3-4 applications, with 6 Gy per application (calculated at 0.5 cm from the applicator surface), once a week. The patients were randomized so that half in both groups had a concomitant cisplatin chemotherapy in dose of 40 mg/m^2, once weekly.

Imaging for radiotherapy planning for all patients was prepared by CT simulation of whole abdomen and pelvis by Light Speed RT4 scanner (General Electric Healthcare, Boston, US). Scans of 5 mm slice thickness were performed in supine position, using oral and intravenous contrast administration. In order to maintain a constant bladder volume, patients were instructed to empty the bladder and then drink 500 ml of water, one hour before CT simulation and at every EBRT fraction. Patients also had adequate preparation for the rectum and bowel. A vaginal marker was inserted to indicate the position of the vaginal apex. Then, CT images were transferred to treatment planning system (TPS) linked Focal stations for delineation and further planning on XiO treatment planning system (XiO TPS v4.8, CMS Software, the Elekta group, Stockholm, Sweden).

Contour of target volumes and organs at risk

For target volumes and OARs delineation, we used consensus guidelines of the Radiation Therapy Oncology Group (RTOG) 0418 [10]. The clinical target volume (CTV) included the vaginal cuff, upper vagina and paravaginal tissues and the regions of draining lymphatics. The planning target volume (PTV) was defined by a margin of 1 cm to the CTV. OARs included bladder, rectum, bowel and bone marrow, and were contoured according to International Commision on Radiation Units and Measurements (ICRU) report 62 and 83 [11]. The target volumes and OAR are contoured on every axial CT slice. External contour of bones were defined as bone marrow, according to Mell et al [12].

Treatment planning and plan evaluation

To generate all treatment plans, 3DCRT and IMRT, CMS XiO planning system was used (Figure 1). Patients was treated on Elekta Synergy Platform linacs (The Elekta group, Stockholm, Sweden), multileaf colimator (MLC) of 1cm thickness.

3DCRT was conducted using "four-field box" technique (anterior, posterior, right and left lateral) with 6

Table 1. Dose-volume constraints used for IMRT planning

Target and organs at risk	*Constraints*
PTV	At least 99% of the PTV received 95% of PD No more than 2% received 107% of PD
Bladder	V45 < 80 cc
Rectum	V45 < 55%
Bowel	V45 < 195 cc
Bone marrow	maximal dose 50 Gy V15 < 90% V25 < 75%

PD: prescribed dose, Vx: volume receiving xGy

and 15 MV photon energies. The beams were conformed to the PTV so that the 95% of the prescibred dose covered the entire volume (at least 99% of PTV), with the maximum protection of OARs.

IMRT plans were based on 6 to 7 fields with 6 MV photon energy. Beam dose modeling was achieved through step-and-shot linac technology to obtain appropriate fluence map for every beam. Dose-volume constrains used for IMRT inverse planning are shown in Table 1. For plan optimisation and segmentation, used were the Segment weight optimisation (SWO) algorithm on 3mm grid size model.

Each of IMRT and the 3DCRT plan were quantitatively and qualitatively analyzed by a radiation oncologist and medical physicist, with dosimetric quality check before the start of the treatment. For the verification of patient treatment position, megavoltage portal I-view GT system was used.

Dosimetric parameters

The dosimetric parameters for target volumes and OARs were compared between IMRT and 3DCRT plans. Target volumes coverage data included: percentage of PTV receiving 95%, 100%, 105% and 110% of the prescribed dose (PTV_{95}, PTV_{100}, PTV_{105}, PTV_{110}, respectively), the maximum and minimum doses represented by the doses received by 2% (D_2) and 98% (D_{98}) of the target volume, homogeneity and conformity index. Homogeneity index (HI) and conformity index (CI) were calculated according to formulas [13]:

HI=D5/D95 (minimum dose that covers 5% of the PTV volume and minimum dose that covers 95% of the PTV volume). It means that HI is always >1 (ideal plan is HI=1). CI=CF (Cover factor) x SF(Spill factor); CF-percentage of the PTV volume receiving at least the prescribed dose, SF-volume of the PTV receiving at least the prescription dose relative to the total prescription dose volume. CI value closer to 1 indicated better dose conformity of the plan. The volumes of patient body normal tissues receiving 10 Gy and 20 Gy were also calculated. We characterized them by Tot10 and Tot20.

OARs dosimetric comparison between IMRT and 3DCRT plans was presented by percentage of organ volume that received different dose levels -10 Gy, 20 Gy, 30 Gy, 40 Gy, 45 Gy (V10, V20 ,V30, V40, V45, respectively).

Statistics

Statistical analysis was performed using SPSS software version 22.0 (SPSS, Chicago, IL). We used independent *t*-tests samples and Pearson's chi-square test for comparison of the groups. $P<0.05$ was considered statistically significant.

Results

Clinicopathologic characteristics of patients

Clinicopathologic characteristics of patients are shown in Table 2. There was no statistically significant difference for age, histology, type of surgery

Table 2. Patient clinicopathologic characteristics

Characteristics	*IMRT*	*3DCRT*	*p value*
No. of patients	45	50	
Age (years)			0.094
Range	25-74	23-75	
Mean	51	55	
Histology, n(%)			0.985
Squamous cell	35 (77.8)	39 (78)	
Adenocarcinoma	5 (11.1)	5 (10)	
Adenosquamous	3 (6.7)	3 (6)	
Other	2 (4.4)	3 (6)	
Surgery, n(%)			0.974
Radical hysterectomy	38 (84.4)	46 (86)	
TAH-BSO	7 (15.6)	7 (14)	
UICC stage, n			0.084
Ib1	9	19	
Ib2	6	6	
IIa	7	6	
IIb	16	14	
IIIb	7	5	
Chemotherapy	23	25	0.899
Brachytherapy maximum dose (Gy)			
Bladder	3.95	3.75	0.499
Rectum	4.53	4.07	0.081

TAH-BSO: total abdominal hysterectomy with bilateral salpingo-oophorectomy

and UICC stage between IMRT and 3DCRT groups. The mean age of patients in the IMRT group was 51 years compared to 55 years in the 3DCRT group. In both groups the most frequent tumor type was squamous cell carcinoma (77.8% in the IMRT group vs 78% in the 3DCRT group), and most patients had UICC stage Ib1 and IIb. Wertheim-Meigs radical hysterectomy was the initial treatment for most patients (IMRT vs 3DCRT 84.4% vs 86%). No statistically significant difference was found for brachytherapy bladder maximum dose (3.95 Gy vs 3.75 Gy) and brachytherapy rectum maximum dose (4.53 Gy vs 4.07 Gy) between the groups.

Dosimetric comparison of PTV coverage

Results of PTV coverage for IMRT and 3DCRT plan are shown in Table 3. Although it was shown adequate dose coverage for target volume in both groups, statistically significant difference was found between PTV_{95} (IMRT vs 3DCRT; 99.27% vs 99.90%; p=0.000), PTV_{105} (2.63 vs 0.04; p=0.000), and D_2 (4.55 vs 4.44; p=0.029). Statistically significant difference with better values for IMRT were also established for homogeneity index (1.06 vs 1.04, p=0.000), conformity index (0.64 vs 0.58; p=0.000) and volume of body normal tissue that received 20 Gy (p=0.014) (Figure 1).

Table 3. Summary of PTV coverage data for IMRT and 3DCRT plans

	PTV_{95} (%)	PTV_{100} (%)	PTV_{105} (%)	PTV_{110} (%)	D_2 (Gy)	D_{98} (Gy)	HI 5/95	CI	Tot10 (cm^3)	Tot20 (cm^3)
IMRT	99.27	65.60	2.63	0.0	45.57	42.03	1.06	0.64	11060	7194
3DCRT	99.90	72.39	0.04	0.0	44.43	42.01	1.04	0.58	10880	6579
p value	0.000	0.058	0.000	NS	0.029	0.963	0.000	0.000	0.661	0.014

PTV_{95}, PTV_{100}, PTV_{105}, PTV_{110}: percentage of PTV receiving 95%, 100%, 105%, 110% of prescription dose; HI: homogeneity index; CI: conformity index; Tot 10, Tot 20: volume of patient body normal tissue receiving 10 Gy and 20 Gy

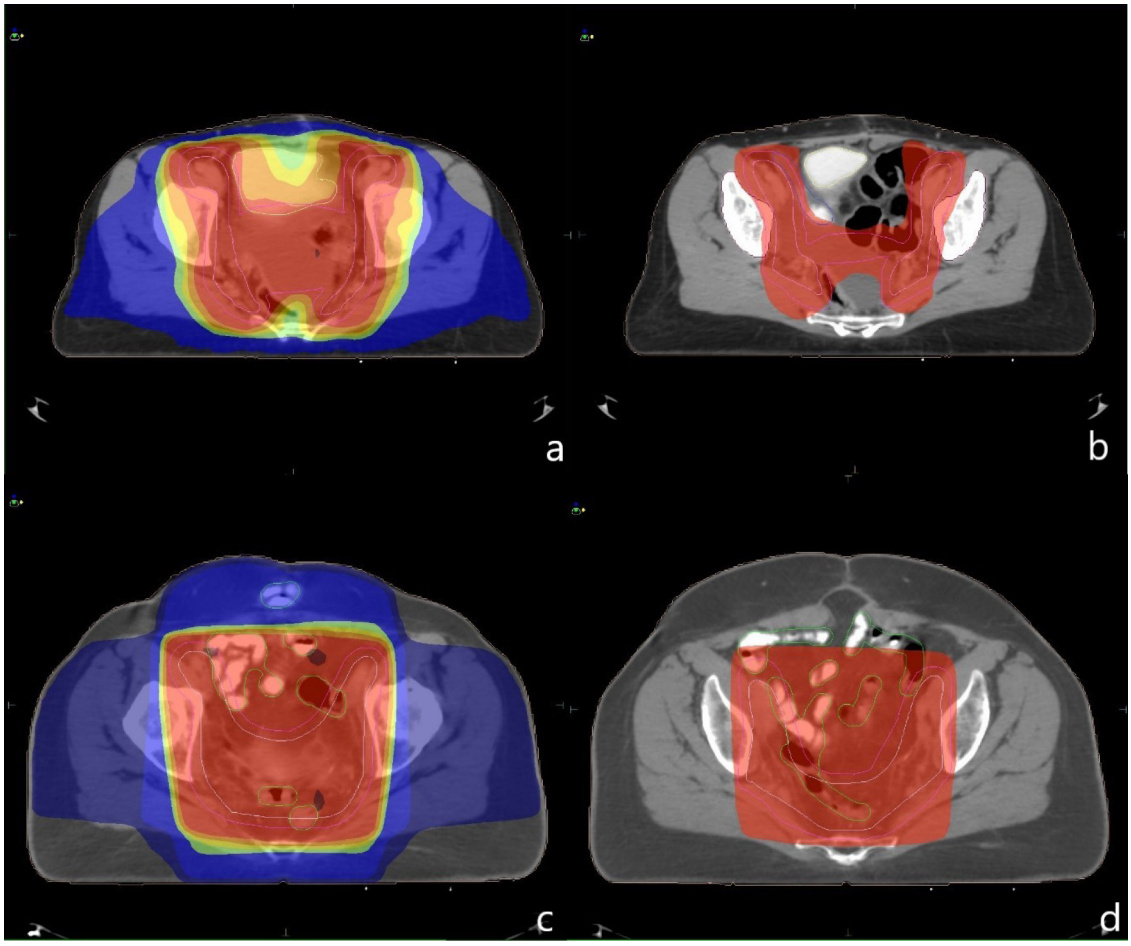

Figure 1. Dose distribution of IMRT **(a,b)** and 3DCRT **(c,d)** treatment plan. The red volume represents the high-dose regions, while the blue volume shows the body normal tissue that received lower-doses.

Table 4. Summary of OAR dose distribution for IMRT and 3DCRT plans

OAR		*Dmean (Gy)*	*V10 (%)*	*V20 (%)*	*V30 (%)*	*V40 (%)*	*V45 (%)*
	IMRT	41.18	100.00	99.96	98.76	68.56	14.06
Bladder	3DCRT	50.73	100.00	100.00	99.30	78.23	40.53
	p value	0.264	NS	0.202	0.478	0.122	0.000
	IMRT	41.97	99.55	99.13	98.62	76.78	20.30
Rectum	3DCRT	43.22	99.81	99.43	98.51	87.39	51.14
	p value	0.027	0.202	0.429	0.852	0.043	0.000
	IMRT	30.58	91.25	76.71	59.57	31.04	4.41
Bowel	3DCRT	28.43	85.21	64.62	53.06	32.51	14.66
	p value	0.058	0.036	0.000	0.049	0.680	0.000
	IMRT	31.89	95.44	79.68	62.64	29.11	5.04
Bone marrow	3DCRT	32.88	96.35	78.05	67.28	33.53	9.93
	p value	0.050	0.059	0.042	0.003	0.202	0.006

D: mean dose; V10, V20, V30, V40, V45: percentage of organs at risk receiving 10 Gy, 20 Gy, 30 Gy, 40 Gy, 45 Gy

Dosimetric comparison for OARs

Dosimetric data for OARS: mean dose and volume percentage of organs receiving 10 Gy, 20 Gy, 30 Gy, 40 Gy, 45 Gy (V10, V20, V30, V40, V45) are shown in Table 4. Statistically significant difference between groups was found for bladder and rectum high dose regions; bladder V45 (p=0.000) and rectum V40 (p=0.043),V45 (p=0.000) and mean dose to rectum (p=0.028).

Bone marrow dosimetric data showed that IMRT plan were better for almost every volumetric and mean dose (p=0.059); V20 (p=0.042), V30 (p=0.003), V45 (p=0.007). Statistically significant difference was also found for all the bowels volumetric doses V10 (p=0.036), V20 (p=0.000) , V30 (p=0.049), V45 (p=0.000).

Discussion

Cervical cancer is one of the most common malignancies in women in Serbia. Early stages of disease are associated with good prognosis, and quality of life of these patients is important in the evaluation of treatment effect. Modern EBRT technique like IMRT is related to better conformity, reduced treatment toxicity and its application depends on the availability of technical equipment. During the implementation of modern techniques in postoperative cervical cancer radiotherapy and learning period, we analysed our first treatment results of IMRT technique and compared to standard 3D conformal radiotherapy.

Comparison of clinical and pathological parameters between the two groups showed no statistically significant difference. It is known that brachytherapy has an important role in developing post-irradiation toxicity [14], but in our study there were no statistically significant differences in brachytherapy maximum bladder and rectum doses between groups.

Our dosimetric analysis for IMRT and 3DCRT included dosimetric evaluation of parameters for PTV coverage and OARs delivered doses. The results showed that adequate target coverage was achieved by both techniques (IMRT vs 3DCRT; 99.90% vs 99.27%). The maximum dose, represented by D_2 (p=0.029) and PTV_{105} (p=0.000) parameters was statistically significant higher for IMRT. Statistically significant difference was also found for the values of homogeneity index and conformity index. Both indexes were better in the IMRT group, showing better conformity of IMRT technique.

Results of all of the mentioned dosimetric parameters in our study are similar to the results reported in other studies. Yang et al [15] studied the dosimetric comparison of three radiotherapy techniques: 3DCRT, IMRT and helical tomotherapy (HT) in patients with endometrial cancer. In their results it was shown excellent coverage of PTV for all techniques. Statistically significant difference was found for PTV_{105} (p=0.08) and PTV_{110} (p=0.01). Higher values of PTV_{110} were found in IMRT, while PTV_{105} was higher in 3DCRT. The values of HI and CI were statistically significant better in IMRT (0.87 vs 0.61; 1.10 vs 1.08). HT dosimetric parameters were similar to IMRT. Our study results showed higher PTV_{105} in the IMRT group, with no statistical difference for PTV_{110}, while conformity and homogeneity index were better in the IMRT.

Naik et al [16] performed a dosimetric analysis in patients with locally advanced cervical cancer treated with 3DCRT and IMRT. Their analysis, showed excellent target volume coverage in both

techniques; IMRT plans were statistically better (IMRT vs 3DCRT; 99.86% vs 98.8%, p=0.004). Similar to results in our study, Naik et al found higher values of maximum doses in IMRT (106.73% vs 105.28%). In their study, IMRT plans had 7 to 9 fields, while we used IMRT plan based on 6 or 7 fields. Many studies analysed the influence of number of fields on target volume coverage, but no significant improvement was achieved with more than 9 fields, like it was shown in the study of Yang et al. [15].

Evaluation of dosimetric parameters for all OARs (bladder, rectum, bowel and bone marrow) was performed in our study. Benefit of IMRT technique was demonstrated at the high level doses data. Statistically significant difference was found for bladder V45 and the rectum V40, V45 and the mean dose. These findings are in correlation with the study of Lv et al [17] who established statistically significant difference for V20 et V30 bladder and V30, V40 and V45 for rectum. In their study, IMRT showed superiority to conformal treatment with better conformity index (0.89 vs 0.54), but also with a higher maximum dose (57.40 Gy vs 52.86 Gy), as shown in our study.

Isohashi et al [18] compared IMRT and 3DCRT in patients with cervical cancer after radical hysterectomy, with concurrent Nedaplatin-based chemotherapy. Their results showed statistically significant difference for bowel V30, V40 and V45 with lower doses in the IMRT group (p=0.018; 0.001; 0.001). Lv et al [17] found that IMRT plans had higher bowel V10 compared to 3DCRT, but lower values for dose above 30 Gy. In our study, bowel data showed advantage of IMRT technique compared to 3DCRT for V45, while the values of V10, V20 and V30 were statistically significantly higher in the IMRT. The higher values of some bowel and bladder dosimetric parametres in our study can be explained by the fact that in the beginning of IMRT implementation in our department less demanding constraints for planning were applied.

Many studies have shown that patients treated with IMRT had significantly less acute and chronic gastrointestinal toxicity. Isohashi et al [18] concluded that patients with chronic gastrointestinal toxicity grade 2 and more had also higher value of small bowel V15-V45. Chopra et al [19] found that V15 of small and large bowel loops are independent predictors for high grade late toxicity.

Hematologic toxicity is of particular importance in the radiotherapy of the pelvic region, especially in patients treated with concomitant chemoradiotherapy. Therefore, it is important to reduce the dose that bone marrow receives. Bone marrow dosimetric data in our study showed that IMRT had lower values for mean dose (p=0.059) and for all doses above 20 Gy. This is similar with the results of Hui et al [20] who compared hematologic toxicities in patients treated with IMRT and 3DCRT and showed that IMRT had better V30 (62.93% vs 76.91%), V40 (31.36% vs 39.60%) and V50 (9.79% vs 15.44%). No statistically significant difference was found for V10 and V20. In their study a significant reduction of leucopenia and grade 2 neutropenia was shown (80% vs 90%; 40% vs 80%). Klopp et al [21] determined that hematologic toxicity is related to bone marrow mean dose and value of V40, while the results of Mell et al [22] and Albuquerque et al [23] demonstrated that bone marrow V10 and V20 doses more accurately predicted hematologic complications compared to V30 and V40 doses.

It was found, that with larger number of irradiation fields in IMRT, greater volume of body normal tissue are exposed to low doses. Our results found statistically significant difference for volume of patient body normal tissues receiving 20 Gy (IMRT vs 3DCRT; p=0.014), and no statistically significant difference for dose of 10 Gy. In the study of Yang et al [15], the results showed that IMRT and HT plans had a greater volumes of patients body normal tissue, that received below 10 Gy, compared to 3DCRT. This parameter is very important since a larger volume of normal tissue that receives low dose might be associated with a higher risk for secondary cancers in that region. Hall and Wuu [24] showed that IMRT almost doubled the incidence of second malignancies compared with conventional radiotherapy (from about 1% to 1.75%) for patients surviving 10 years, especially for younger patients.

Conclusion

The results in this study confirm that IMRT is a highly conformal technique. Most of dosimetric parameters showed better values compared to 3DCRT. Recommended target volume coverage was achieved with both techniques, with higher maximum dose in the IMRT group. A reduction of OARs volume irradiated with a higher dose was shown in the IMRT group and acute and late toxicity should be investigated further. Our results showed that the importance of quality and adequate use of the technique in the learning period with further IMRT protocol improvement. We expect that this technique advantages will lead to better treatment results and quality of life in cervical cancer patients with good prognosis.

Conflict of interests

The authors declare no conflict of interests.

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