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ORIGINAL ARTICLE

Acute toxicity of postoperative intensity-modulated radiotherapy and three-dimensional conformal radiotherapy for cervical cancer: The role of concomitant chemotherapy

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Summary

Purpose: *The toxicity of postoperative radiotherapy for cervical cancer affects patients' quality of life. We evaluated acute toxicity in postoperative intensity-modulated radiotherapy (IMRT) and three-dimensional conformal radiotherapy (3DCRT) as well as the influence of dosimetric parameters and concomitant chemotherapy.*

Methods: *A total of 45 patients with early operable cervical cancer underwent postoperative IMRT with 40-45 Gy. The control group of 50 patients was treated with 3DCRT. Brachytherapy and concomitant cisplatin chemotherapy were performed in all patients according to pathologic and histologic findings. The patients were monitored for acute gastrointestinal, urological and hematological toxicity classified according to the RTOG acute radiation morbidity scoring criteria. We also analyzed the influence of dosimetric parameters on acute toxicity.*

Results: *Significant differences were found in overall acute toxicity (p=0.018), acute genitourinary toxicity (p=0.029), anemia (p=0.043) and neutropenia (p=0.027) but not in acute gastrointestinal toxicity between the IMRT and 3DCRT groups. In all patients, regarding chemotherapy administration, differences were found between the chemoradiotherapy and radiotherapy group as far as overall acute toxicity (CHRT vs RT; p=0.011) and hematological toxicity were concerned (p=0.001). Patients with ≥3 cycles of chemotherapy showed increased hematologic toxicity. In the IMRT group according to the administration of chemotherapy (chemoradiotherapy vs radiotherapy), statistically significant difference for leukopenia (p=0.009) was found and in the 3DCRT group for anemia (p=0.021) and neutropenia (p=0.029). According to chemotherapy administration (chemoradiotherapy vs radiotherapy), a statistically significant difference in leukopenia (p=0.009) was found in the IMRT group while in the 3DCRT group the differences were in anemia (p=0.021) and neutropenia (p=0.029).*

Conclusion: *IMRT is associated with lower acute toxicity and better dosimetric parameters in organs at risk (OAR) compared to 3DCRT. Higher hematological toxicity occurred when concomitant chemotherapy was performed, regardless of RT technique. Further reduction of toxicity is expected with protocol and technical improvement and research of gene-related toxicity.*

Key words: *acute toxicity, cervical cancer, concomitant chemoradiotherapy, intensity-modulated radiotherapy, three-dimensional radiotherapy*

Introduction

Cervical cancer is the fourth most frequently diagnosed cancer in the world and the fourth leading cause of cancer death in women according to the latest data from 2018 [1]. Surgery is usually performed in the early stage of disease, and postoperative pelvic radiotherapy is indicated in patients

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with intermediate and high-risk pathological factors (size of tumor, deep stromal invasion, lymphovascular invasion, parametrial invasion, positive surgical margins and pelvic lymph node metastasis) [2-4]. The early stages of disease (FIGO stage I and IIa) are associated with high overall survival rates ranging between 60% and 90% [5,6], but surgery combined with radiotherapy may be accompanied by toxicity, which can significantly reduce the patients' quality of life. The toxicity rates are even higher when chemotherapy is added to this combination treatment [7,8]. Surgical treatment can cause organ injury, postoperative adhesions and changes in the anatomical position of the organ, while concomitant chemoradiotherapy (CHRT) increases hematologic toxicity [7-9]. The morbidity of combined therapy depends on various factors: type of surgery, chemotherapy protocol, radiotherapy technique, the dose of irradiation, performance status of the patient, and other medical comorbidities.

Radiotherapy toxicity is classified by the Radiation Therapy Oncology Group (RTOG) as acute and late toxicity [10]. Acute toxicity occurs during treatment and 3 months afterwards, it affects rapidly proliferating tissues and is mostly reversible. Late toxicity is often irreversible and occurs 6 months up to several years after treatment. Gastrointestinal (GI), genitourinary (GU) and hematological toxicity (HT) are the most common after combined treatments and pelvic radiotherapy, with high incidences (urinary toxicity 40-74%, gastrointestinal toxicity 40-80%, hematological toxicity 20-74%) [11].

Early gastrointestinal symptoms may include diarrhea, nausea, fatigue, while late chronic toxicity mostly presents as diarrhea, malabsorption, fecal incontinence, bowel obstruction, and rectal ulceration. The acute urological symptoms include urinary frequency, dysuria, pain, and hematuria. The most severe complications such as bowel obstruction, urethral obstruction, and vesicovaginal or rectovaginal fistula are very rare, with low incidence [12-14]. Acute complications may lead to treatment breaks, prolong treatment time and reduce treatment effectiveness.

Many studies show that the development of new modern radiotherapy techniques, such as IMRT, improve target dose delivery and lead to better sparing of OAR [15], with lower grades of toxicity. IMRT also enables dose escalation to grossly enlarged metastatic lymph nodes in pelvic or paraaortic areas without increasing toxicity.

The results of our clinical data analysis showed that IMRT is a highly conformal technique. We conducted a dosimetric analysis of target volume coverage and OAR doses, and the results showed better values compared to 3DCRT. The dosimetric parameters for OAR included percentages of OAR receiving 10Gy, 20Gy, 30Gy, 40Gy, 45Gy (V10, V20, V30, V40, V45, respectively). Adequate target volume coverage was achieved with both techniques, with a reduction in irradiated OAR at a higher dose of IMRT. We expect that better dosimetric parameters would be associated with decreased toxicity. This research was conducted in order to evaluate and compare acute toxicity in patients treated with IMRT and 3DCRT, to analyze the influence of dosimetric parameters on acute toxicity and to establish the role of concomitant chemotherapy.

Methods

Between December 2015 and December 2018, 45 patients with cervical cancer underwent postoperative IMRT in our Department of Radiotherapy. Radiotherapy included external pelvic irradiation at a dose of 40-45 Gy delivered in 1.8 Gy daily fractions to the pelvic target volume. The control group consisted of 50 patients treated with 3DCRT during the same period. After external beam radiotherapy, all patients in both groups received vaginal cuff brachytherapy (3-4 weekly fractions, 6 Gy per fraction). About half of the patients in both radiotherapy groups had high-risk pathological features and were treated with concomitant cisplatin chemotherapy (CH), administered on a weekly basis at a dose of 40 mg/m^2 (one to five cycles).

Radiotherapy planning

CT simulation was performed in the supine position, from the tenth thoracic vertebral body to the bottom edge of the ischial tuberosity, with slice thickness of 0.5 cm, using a knees and feet immobilization device. Oral and intravenous contrast was administered and patients underwent adequate bladder and bowel preparation.

The consensus guidelines of the Radiation Therapy Oncology Group (RTOG) 0418 were used for contouring the target volume and OAR [16]. The clinical target volume (CTV) included central vaginal CTV (proximal vagina and paravaginal tissues) and pelvic lymph nodes CTV (common, internal and external iliacs). The planning target volume (PTV) was defined as a margin of 1 cm to the CTV. The OAR included bladder, rectum, bowel and bone marrow.

IMRT and 3DCRT plans were generated for each patient using the CMS XiO v4.8 planning system (CMS Software, The Elekta group, Stockholm, Sweden). A standard "four-field" technique was used for 3D CRT. IMRT plans were based on 6 or 7 fields in step and shoot mode. The dose volume constraints used in the IMRT plans were: for target volume- at least 99% of the PTV received 95% of the prescribed dose (PD), and no more than 2% received 107% of the PD; for OAR -bladder V45 < 80 cc, rectum V45 < 55%, bowel V45 < 195 cc, bone marrow maximum dose 50Gy, V15 < 90%, V25 < 75%. No hot spots were registered in the anterior rectal or posterior bladder wall. Dose volume histograms (DVHs)

for the IMRT and 3DCRT plans were analyzed for each patient. Patients were treated on Elekta Sinergy Platform (The Elekta group, Stockholm, Sweden) accelerators.

Acute toxicity

During radiotherapy all patients were monitored for acute complications once a week. Gastrointestinal, urological and hematological toxicity were monitored. Toxicity was graded according to the acute radiation morbidity scoring criteria of the RTOG/European Organization for Research and Treatment of Cancer/EORTC [10]: 0-no complications, 1- mild symptoms, no medication required, 2- moderate symptoms, medication required, 3/4- major symptoms that require treatment breaks, surgery or invasive procedures, 5- fatal complications.

Analysis of the influence of dosimetric parameters on acute toxicity

In this study, we also analyzed the influence of dosimetric parameters on acute toxicity. We analyzed bladder V10-V45 and acute urological toxicity, bowel V10-V45 and acute gastrointestinal toxicity, and bone marrow V10-V45 and acute hematological toxicity (anemia, leukopenia, neutropenia and thrombocytopenia).

Statistics

Statistical analyses were performed using SPSS software version 22.0 (SPSS, Chicago, IL). Independent samples *t* tests and Pearson's chi-square test were used. P<0.05 was considered statistically significant.

Results

There were no statistically significant differences between the IMRT and the 3DCRT groups in terms of patient age, type of surgery, pathohistological results, concomitant chemotherapy and stage characteristics.

Statistically significant differences were found in overall acute toxicity (IMRT vs 3DCRT; 60 vs 82%, p=0.018) and acute genitourinary toxicity (p=0.029) between the groups of patients treated with IMRT and 3DCRT. There were no patients with severe GU toxicity (G 3/4) in the two groups (data not shown). Hematological toxicity analysis also showed statistically significant differences in anemia (p=0.043) and neutropenia (p=0.027) as shown in Table 1. In the 3DCRT group, 24% of patients had grade 1 neutropenia compared to 4% of patients in the IMRT group, while grade 2 toxicity occurred more often in IMRT-treated patients (11 vs 4%) (data not shown). No statistical differences in overall acute gastrointestinal toxicity, leukopenia, thrombocytopenia, or treatment breaks (8 vs 9 patients) were found.

The analysis of all irradiated patients according to chemotherapy administration, revealed a statistically significant increase in overall acute toxicity (CHRT vs RT; 78.3 vs 40.9%, p=0.011) and acute hematological toxicity (65.2 vs 18.2%, p=0.001) in the chemoradiotherapy group (Table 2). According to the number of applied chemotherapy cycles (up to five cycles) an increase in hematological toxicity was found in patients with 3 or more cycles. Data are shown in Table 3.

When we compared the toxicity effect in the IMRT and 3DCRT groups according to the administration of chemotherapy (chemotherapy vs radiotherapy), a statistically significant difference in leukopenia was found (p=0.009) in the IMRT group, and in anemia (p=0.021) and neutropenia (p=0.029) in the 3DCRT group. Patients in the CH IMRT group had more frequent the following leukopenia grades: grade 1 (CH IMRT vs IMRT; 17.4 vs 9.1%), grade 2 (34.8 vs 4.5%) and grade 3 (8.7 vs 0%) compared to the IMRT group (data not shown).

Table 1. Acute toxicity in the IMRT and 3DCRT groups

Toxicity	*Radiotherapy technique*		*p value*
	IMRT n (%)	*3DCRT n (%)*	
Overall	27 (60)	41 (82)	0.018
GU	3 (6.6)	11 (22)	0.029
GI	17 (37.8)	23 (46)	0.078
Anemia	8 (17.8)	18 (36)	0.043
Leukopenia	17 (37.7)	17 (34)	0.906
Neutropenia	8 (17.7)	14 (28)	0.027
Thrombocytopenia	4 (8.9)	6 (12)	0.622

GU:genitourinary toxicity, GI:gastrointestinal toxicity

Table 2. Acute overall and hematologic toxicity in all RT patients according to the administration of chemotherapy

Toxicity	*CHRT n (%)*	*RT n (%)*	*p value*
Overall	18 (78.3)	9 (40.9)	0.011
Hematologic	15 (65.2)	4 (18.2)	0.001

GU:genitourinary toxicity, GI:gastrointestinal toxicity

Table 3. Acute hematological toxicity in all CHRT patients according to the number of chemotherapy cycles

No. of chemotherapy cycles	*No. of patients (%)*	
	Toxicity n (%)	*Non-toxicity n (%)*
1	2 (100)	0
2	0	1 (100)
3	4 (66.7)	2 (33.3)
4	5 (62.5)	3 (37.5)
5	4 (66.7)	2 (33.3)

The results represent the highest toxicity in both radiotherapy groups with concomitant chemotherapy regardless of the RT technique (Table 4).

In the IMRT group, the analysis of dosimetric parameters and acute toxicity (Table 5) showed a statistically significant lower value of bladder V45 in patients with low genitourinary toxicity (4.11 vs 14.77%, p=0.006). Similarly, patients without hematological toxicity had a lower value of bone marrow V20-V45 (V10- p=0.047; V20- p=0.008; V30- p=0.022; V45- p=0.019). Bowel dosimetric parameters did not influence gastrointestinal toxicity.

Dosimetric parameters did not have a statistically significant influence on acute toxicity in the 3DCRT group.

Discussion

This study was conducted during the implementation of IMRT in our Department, in the

Table 4. Acute toxicity according to radiation technique and administration of chemotherapy in all groups

Toxicity	*IMRT n (%)*	*CH IMRT n (%)*	*p value*	*3DCRT n (%)*	*CH 3DCRT n (%)*	*p value*
GU	2 (9)	1 (4.3)	0.585	7 (28)	4 (16)	0.306
GI	8 (36.4)	9 (39.1)	0.613	15 (60)	8 (32)	0.096
Anemia	3 (13.6)	5 (21.7)	0.477	5 (20)	13 (52)	0.021
Leukopenia	3 (13.6)	14 (60.9)	0.009	5 (20)	12 (48)	0.144
Neutropenia	2 (9)	6 (26)	0.388	3 (12)	11 (44)	0.029
Thrombocytopenia	1 (4.5)	3 (4.3)	0.317	1 (4)	5 (20)	0.082

GU:genitourinary toxicity, GI:gastrointestinal toxicity, CH IMRT:concomitant chemotherapy and IMRT, CH 3DCRT:concomitant chemotherapy and 3DCRT

Table 5. Analysis of acute toxicity within groups according to radiotherapy technique and dosimetric parameters

IMRT	*V10 (%)*	*V20 (%)*	*V30 (%)*	*V40 (%)*	*V45 (%)*
Bladder					
Toxicity	100.00	99.62	98.50	73.43	14.77
Non-toxicity	100.00	99.99	98.78	68.21	4.11
p value	NS	0.433	0.911	0.788	0.006
Bowel					
Toxicity	91.09	75.76	58.41	29.41	4.27
Non-toxicity	91.34	77.29	60.28	32.02	4.49
p value	0.940	0.673	0.659	0.639	0.877
Bone marrow					
Toxicity	97.74	81.58	72.85	42.69	18.13
Non-toxicity	96.05	77.38	65.67	29.42	7.35
p value	0.047	0.008	0.022	0.080	0.019
3DCRT					
Bladder					
Toxicity	100.00	100.00	97.41	83.93	40.12
Non-toxicity	100.00	100.00	99.84	76.62	40.64
p value	NS	NS	0.257	0.322	0.969
Bowel					
Toxicity	88.29	67.25	54.58	33.91	13.03
Non-toxicity	85.59	62.37	51.76	31.31	16.04
p value	0.217	0.260	0.581	0.587	0.494
Bone marrow					
Toxicity	97.86	76.56	64.69	32.88	3.66
Non-toxicity	96.13	80.10	61.16	24.07	4.15
p value	0.503	0.056	0.108	0.222	0.733

V10, V20, V30, V40, V45: the percentage of organs at risk that received 10 Gy, 20 Gy, 30 Gy, 40 Gy, 45 Gy

learning period. A wide range of dose-volume constraints for IMRT planning can be found in the literature. Moreover, the accuracy of CTV and OAR delineation are very important in IMRT, since it has been shown that variations of only a few millimeters significantly change the dose distribution [17]. Despite the results of numerous studies, there is still no accurate value for the volume or percentage of OAR associated with a higher probability of acute toxicity.

Our clinical data, demonstrated that IMRT is a highly conformal technique with better dosimetric parameters compared to standard 3DCRT. In this study, we analyzed the occurrence and grade of acute toxicity in cervical cancer patients treated with postoperative IMRT and 3DCRT. During treatment, the patients were monitored for acute genitourinary, gastrointestinal and hematological complications. We also analyzed the influence of concomitant chemotherapy and dosimetric parameters on acute toxicity.

In our study, the patients treated with 3DCRT had more overall acute toxicity compared with the patients in the IMRT group (p=0.018). A statistically significant difference was also found for acute genitourinary toxicity (p=0.029), which was lower in the IMRT group.

Mundt et al [18] analyzed a group of 40 patients with cervical and endometrial carcinoma treated with IMRT compared to patients treated with traditional conventional radiotherapy. A statistically significant difference in the reduction of acute grade 2 GI toxicity was found in the IMRT group (IMRT vs 3DCRT; 60 vs 91%, p=0.002). None of the patients had severe grade 3 gastrointestinal toxicity. A difference was also found in the percentage of patients treated with antidiarrheal drugs (34 vs 75%, p=0.001) and in the reduction of acute grade 2 GU toxicity (10 vs 20%). The results for acute GU toxicity are similar with our study where only one patient had acute grade 2 GU toxicity in both groups and no patients had grade 3 toxicity. We did not find a statistically significant difference in gastrointestinal toxicity. A phase II multi-institutional French trial [19] also showed the benefits of IMRT in postoperative endometrial cancer, with a reduction of acute GI toxicity (≥grade 2) below 30%. The incidence of GU grade 2 toxicity was also lower than 20%.

Mundt et al [20] also showed a reduction in chronic gastrointestinal toxicity. Patients treated with IMRT had a lower rate of GI toxicity (11.1 vs 50%). The reduction was found for grade 1, 2 and 3 toxicity (30 vs 8.3%; 16.7 vs 2.8%, 3.3 vs 0%). Cordoba et al [21] concluded that endometrial cancer patients treated postoperatively with IMRT had late toxicity grade 1-2 below 5%. Chen et al [22] showed that the IMRT group of patients had a significant reduction in acute gastrointestinal and genitourinary toxicity compared to the 3DCRT group (GI 36 vs 80%, p=0.00012; GU 30 vs 60%, p=0.022). Their results also demonstrated lower rates of chronic GI and GU toxicity (GI 6 vs 34%, p=0.002; GU 9 vs 23%, p=0.0231).

In our study, more patients treated with 3DCRT had hematological toxicity compared to the IMRT group. Statistical significance was found for anemia (p=0.043) and neutropenia (p=0.027). In the 3DCRT group, 24% of patients had grade 1 neutropenia compared to 4% of patients in the IMRT group, while grade 2 toxicity occurred more often in the IMRT-treated patients (11 vs 4%). Significance was not found for leukopenia and thrombocytopenia. The analysis of patient data according to chemotherapy administration revealed that patients who underwent CH had statistically significant more overall toxicity (p=0.011) and hematological toxicity (p=0.001) regardless of radiotherapy modality. Patients who had 3 or more cycles of CH showed near doubled hematologic toxicity.

Peters et al [23] obtained results similar to ours. In their study about 74% of patients treated with CHRT in postoperative setting developed grade ≥2 leukopenia compared to patients treated only with radiotherapy. Dueñas-Gonzalez et al [24] compared the administration of combination chemotherapy (cisplatin and gemcitabine) versus monotherapy in cervical cancer and found better disease control in the case of combination chemotherapy but a significantly higher incidence of grade 3/4 leukopenia (60 vs 17.5%) and neutropenia (25 vs 17.5%).

IMRT with pelvic bone marrow sparing resulted in a clinically significant reduction of hematologic toxicity. In our study, dividing the patients in two subgroups according to cisplatin administration (chemoradiotherapy vs radiotherapy) did not lead to a statistically significant difference in acute genitourinary and gastrointestinal toxicity in the IMRT group. A statistically significant difference in leukopenia was found between the subgroups (CH IMRT vs IMRT p=0.009). Patients in the CH IMRT group developed leukopenia more frequently. In the analysis of two subgroups in 3DCRT group (CH-3DCRT vs 3DCRT) according to cisplatin administration, statistically significant differences were found in hematological toxicity (anemia;p=0.021 and neutropenia;p=0.029) with higher toxicity in the chemoradiotherapy group.

Mundt et al [18] also showed a reduction in hematological toxicity in the IMRT-treated group of patients compared to the 3DCRT group (31 vs 60% grade ≥2 leukopenia). Brixey et al [25] found that

patients treated with CH 3DCRT had more grade ≥ 2 leukopenia (60 vs 31.2%, p=0.08) compared to the CH IMRT subgroup. INTER-TECC-2 study is a multicenter clinical trial designed to evaluate bone marrow-sparing in IMRT with concomitant cisplatin in cervical cancer patients. The results showed reduced rates of hematological toxicity, particularly grade 3/4 neutropenia after adjuvant chemoradiation (22.2%) [26]. Lewis et al [27] used strict bowel constraints for both low dose (V15 <200 cc) and high dose (V40 <100 cc) regions in the study of postoperative bowel sparing image-guided IMRT with concurrent cisplatin. Their results showed reduced gastrointestinal and hematological toxicity, as well as simultaneous sparing of bowel and bone marrow. In the majority of most trials the whole bone is contoured as a surrogate for bone marrow [28]. With advanced imaging like fluoro-thymidine positron emission tomography (FLT-PET) and MRI, active bone marrow can be defined, which leads to more precise IMRT planning and reduction of hematological toxicity [29].

In our study, analysis of the influence of dosimetric parameters on acute toxicity showed a statistically significant lower value of bladder V45 and lower genitourinary toxicity in the IMRT group (p=0.006), but there was no influence of bowel dosimetric parameters on gastrointestinal toxicity. Isohashi et al [30] concluded that patients with grade 2 and more chronic gastrointestinal toxicity had also higher value of small bowel V15-V45. A prospective randomized study conducted by Naik et al [31] compared dosimetric parameters and acute toxicity in patients with inoperable cervical cancer who underwent CHRT. The dosimetric parameters for their IMRT plans showed statistically significant differences in small bowel V45 and bone marrow V20 compared to the 3DCRT plans. Better dosimetric parameters in patients treated with the IMRT technique were also followed by a decrease in acute grade 2 urinary toxicity (IMRT vs 3DCRT; 20 vs 45%) and grade 3 (5 vs 15%), as well as gastrointestinal toxicity grade 2 (20 vs 45%) and grade 3 (5 vs 20%). We found similar results for acute genitourinary toxicity, but no difference in gastrointestinal toxicity.

Our results showed that IMRT patients without hematologic toxicity had a lower value of bone marrow V20-V45. Hui et al [32] also showed that IMRT plans had better bone marrow V30, V40 and V50 with a significant reduction in grade 2 leukopenia and neutropenia (80 vs 90%; 40 vs 80%). Heron et al [33] found in their comparative dosimetric study of dose-volume histograms between IMRT and 3DCRT that the volume of all OAR receiving doses over 30Gy was reduced in IMRT-treated patients; for volume as follows: 52% for the small bowel, 66% for the rectum and 36% for the bladder. Simpson et al [34] showed that a decrease in the V45 of the small bowel by 100cc reduced grade 2 toxicity by 50%.

Radiobiology has shown that despite the use of modern radiotherapy techniques, the patient's genetic sensitivity has a very important impact on the occurrence of toxicity. Some authors suggest that the influence of the genetic component could be up to 80% [35]. Radiosensitivity as a polygenic trait, which depends on the interaction of many genes and genetic products, was the subject of genome-wide association studies (GWAS) [36]. Over 300 human GWAS studies have examined over 1800 diseases and traits of some malignancies in order to identify malignancies such as prostate and breast cancer [37,38]. The investigation in further advancement of radiotherapy technique and analysis of genetic components in radiosensitivity is needed, with the goal to improve treatment result and decreases related toxicity. Further research is required in order to improve radiotherapy techniques and analyze the genetic components involved in radiosensitivity in order to achieve better treatment outcomes and decrease treatment-related toxicity.

Conclusion

The analysis of the first results of IMRT implementation in our Department demonstrated satisfactory dosimetric values of IMRT plans compared to 3DCRT. Regarding acute toxicity, reductions were found in overall, genitourinary and hematological toxicity that were observed when the IMRT technique was used compared to 3DCRT. The influence of some dosimetric parameters on acute toxicity was also demonstrated. Concomitant chemotherapy was related to higher rates of hematological toxicity regardless of radiotherapy technique, but with lower toxicity in IMRT-treated patients versus the 3DCRT group. We did not find significance for gastrointestinal toxicity according to radiotherapy technique. Further improvement are needed: detailed protocol for the contouring of OAR (especially the bowel and bone marrow), with more precise dose/volume constraints and good quality assurance, which will improve the dosimetric parameters and reduce toxicity.

Conflict of interests

The authors declare no conflict of interests.

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