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RESEARCH ARTICLE

The Outcomes of Concomitant Hypofractionated Simultaneous Integrated Boost Intensity-Modulated Radiotherapy Plus Concurrent Weekly Cisplatin Monotherapy for Newly Diagnosed Locally Advanced Cancer Cervix with Positive Lymph Nodes

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ABSTRACT

Aim: Evaluate outcome of Concomitant Hypofractionated Simultaneous Integrated Boost (SIB) Intensity-Modulated Radiotherapy (IMRT) Plus Concurrent Weekly Cisplatin monotherapy for Newly Diagnosed Locally Advanced Cancer Cervix with Positive LNs in elderly patients. **Patients and Methods: T**wenty-one patients were included diagnosed with locally advanced cancer cervix ≥ 65 years old with good performance status and adequate organ functions. Eligible patients received concomitant chemotherapy in form of cisplatin monotherapy (40 mg/m^2) weekly, during radiotherapy treatment in form of External Beam Radiotherapy (EBRT) with SIB due to patients` refusal or inability to receive brachytherapy (BRT). Treatment toxicity, progression free survival (PFS) and overall survival (OS) were recorded and analyzed. **Results:** The median age reported was 70 years, (range: 65-76 years) and the median follow up period was 35 months (ranged from 18-47 months). The OS was 90.2% at 2 years and 76.8% at 3 years. The median time to progression was 27 months (ranged from11 – 46 months). The PFS was 75.6 % at 2 years and 63.5% at 3 years. **Conclusion: I**n locally advanced cervical cancer, SIB-IMRT could be considered an effective and safe treatment alternative in elderly patients or unavailable brachytherapy.

Keywords: cancer cervix, radiotherapy, SIB

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INTRODUCTION

Cervical cancer is considered one of the main causes of cancer-related deaths in females, with poor prognosis in cases with locally advanced cervical cancer (Siegel et al 2023). National Comprehensive Cancer Network (NCCN) guidelines (NCCN) guidelines 2023) recommends treatment of locally advanced cervical cancer with concurrent chemotherapy and radiation therapy (CCRT) with cisplatin-based chemotherapy plus Brachytherapy (BRT) with 5-years survival rate reaching 60–80% (Markman 2013). The presence of lymph nodes involvement has poor outcome and lower survival rates (Jürgenliemk-Schulz et al 2019).

The application of BRT after external beam radiotherapy (EBRT) is a cornerstone in treatment of patients with cancer cervix (Colombo et al 2012). However, BRT has limited availability and applicability as regard presence of contraindications for BRT treatment in some eligible patients, difficulty to receive BRT due to limited available centers for BRT treatment (long distance from patients' residence especially in patients with old age and difficulties in movement) and at last BRT technique requires long training time to acquire the desired learning curve by oncologists (Mahantshetty et al 2014).

Recently, the improvements achieved in the field of radiotherapy could offer possible treatment options for those patients. These modalities include intensity modulated radiotherapy (IMRT), followed by progression toward volumetric modulated arc therapy (VMAT) and more recently image guided radiotherapy (IGRT). Using these advanced techniques increased accuracy of radiotherapy

with possibility of targeting nodal involvement with the primary target, simultaneous integrated boosts (SIB) in patients receiving cervical EBCRT (Shumway 2017).

The alternative radiotherapy option was investigated to provide a suitable technique if BRT is not available (Barraclough et al 2008, Macchia et al 2014 and Alongi et al 2015) and the goal of the current study was to assess the safety and efficacy of Concomitant Hypofractionated Simultaneous Integrated Boost (SIB) Intensity-Modulated Radiotherapy (IMRT) with Concurrent Weekly Cisplatin monotherapy for Newly Diagnosed Locally Advanced Cancer Cervix with Positive LNs in elderly patients.

PATIENTS AND METHODS

Study Design

This was a prospective study that was conducted between May 2018 and September 2022. Twenty-six patients were included at the start of study, age ≥ 65 years with newly diagnosed, histologically confirmed locally advanced cancer cervix, according to FIGO staging 2014 International Federation of Gynecology and Obstetrics (FIGO Committee on Gynecologic Oncology 2014) with Karnofsky performance status (KPS) of ≥70 and adequate organ functions (liver, renal and hematologic)

Five patients were excluded (treatment refusal in 2 patients, severe renal impairment in 2 patients and severe liver impairment in one patient). The remaining 21 patients were eligible to receive the treatment protocol and evaluation of their response to treatment. Study enrollment within six weeks from histopathological diagnosis. Exclusion criteria was Patients with distant metastasis such as the lung and liver, as well as simultaneous malignancies at other sites. Approval was obtained from the Research ethics committee (no.35877)

Pretreatment evaluation in form of history taking, thorough physical examination, gynecologic pelvic examination, routine laboratory studies, abdomen and pelvis ultrasound, MRI and CT-scan of the chest, abdomen and pelvis. histologic proof of cervical cancer with positive lymph nodes was required in all patients before treatment.

Treatment protocol

Eligible patients were assigned to receive concurrent weekly cisplatin monotherapy (40 mg/m^2), given during radiotherapy treatment (within six weeks from diagnosis). External Beam Radiotherapy (EBRT) with Simaltineous Integrated Boost (SIB) was planned as included patients refused or were unable to receive brachytherapy (BRT). Concomitant RT was delivered once daily 2.2 Gy, 2 Gy, and 1.8 Gy/ fraction to Planned Gross Target Volume (PGTV-SIB), PGTV-N-SIB, and Planned Clinical Target Volume (PCTV), 5 d/weak, for a total of 66 Gy, 60 Gy and 54 Gy, respectively in 30 fractions over 6 weeks.

Treatment volumes were determined based on gadolinium-enhanced MRI of the pelvis and full-bladder CT- based with 3 mm slice thickness from the hilum of the kidney to 3 cm inferior to the ischial tuberosity, and from the superior pole of the left kidney in para-aortic node positive patients. The CT images were then transferred to the treatment planning system. The planning followed Radiation Therapy Oncology Group (RTOG) guidelines for contouring and delineation for CTV and the organs at risk (OARs). Treatment volume generally included the gross tumor volume (GTV) which was defined as the cervix, The clinical target volume (CTV) which was defined as GTV plus uterus, parametria, the upper part of the vagina to 3 cm inferior to the level of tumor invasion and locoregional LN (common, external, and internal iliac, obturator and presacral). The gross tumor volume node (GTVn) was identified as the contrast-enhanced lymph nodes. In case of invasion of the lower third of the vagina, we treated inguinal lymph nodes. In case of para-aortic LN involvement, the CTV was modified to start at the level of the left renal vein to include para-aortic nodes. The planning target volumes (PTVs) were outlined as follow, PTV is generated by adding 1 cm to the CTV to a dose of 54Gy and the PTV-SIB is generated by adding 0.7 cm to GTV-SIB to a total dose of 66Gy. The PTV-N-SIB is generated by adding 0.7 cm to GTV-N-SIB to a total dose of 60Gy.

The aim of planning was reaching dose coverage of at least 95% of the PTV, and no more than 10% of the PTV received more than 110% of the received dose. Adequate immobilization was required to ensure reproducibility.

The organs at risk (OARs), as kidneys, bladder, spinal cord, rectum, small bowel, femoral heads, and pelvic bone marrow. The maximum dose constraints for the rectum was V30 <60%, V50 <50%, V60<35% and for small bowel is V35<35%, V45<195cc, the maximum dose constrains for bladder is V45<35%, V50 <50%, V65<50% and the maximal dose for Femoral Heads is <50 Gy, V35 <10% and for spinal cord Dmax <45 Gy, Both Kidneys V16<25%, mean total kidney<15Gy, Bone marrow V20<75%, V40<37%, (Table 1). Prophylactic antiemetics including metoclopramide or 5 - hydroxytryptamine-3 antagonists, were routinely prescribed during concomitant hypofractionated SIB-IMRT before concurrent weekly cisplatin. IMRT treatment was delivered by inverse planning calculations using static nine fields with degrees (0, 40, 80, 120, 160, 200, 240, 280, 320) using 6 MV photon beams of (Varian Unique) LINAC, optimized by (PO-CAP137) Eclipse version13.6, Varian Unique algorithm.

Assessment of patients` response to treatment

Evaluation of tumor response following the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Eisenhauera et al 2009), including stable disease, partial response, and complete response. After completion of treatment, patients' evaluation by complete medical history, clinical examination, gynecologic pelvic examination, determination of PS, hematology and clinical chemistry assessments, CT-scan of the chest, abdomenopelvic gadolinium-enhanced MRI or contrast-enhanced CT and/or positron emission tomography (PET)-CT scans, if necessary, repeated every 3 - 4 months in the first 2 years of follow up and every 6 months later.

Assessment of Toxicity

Patients were evaluated weekly during treatment. Reporting of adverse events and its grade was done following the common terminology criteria for adverse event (NCI-CTC, version 4.0), score 4 in case of life-threatening adverse event, score 3 in case of severe adverse event, score 2 in case of moderate adverse event, score 1 in case of mild adverse event. Overall survival (OS) and progression-free survival (PFS) were the primary end points. The secondary end points were tumor response and safety.

Statistical Analysis

IBM SPSS (Statistical package for the social sciences) software version 20.0. (Armonk, NY: IBM Corp) was used for data analysis. Categorical data were reported in the form of percentages and numbers. Association between the categorical variables was done using Chi-square test. Fisher's exact test was used if cell counts were less than 5. Kolmogorov- Smirnov test was used in continuous data analysis. Data were reported in form of range (minimum and maximum), mean, standard deviation (SD) and. Kaplan-Meier Survival analysis curve was used for expression of PFS and OS. Reported data was considered significant at the 5% level.

RESULTS

Twenty-one female patients ≥ 65 years old were included in this study with newly diagnosed, histologically confirmed locally advanced cancer cervix. patients' and tumor characteristics are reported in table (2). The median age reported in the study was 70 years, (range: 65-76 years). Sixteen patients (76.2%) with a Karnofsky performance status (KPS) of ≥80. All patients had LN involvement as 17 (81.0%) patients with pelvic LN affection and only 4 (19.0%) with both pelvic and para-aortic LN involvement. The mean time from the diagnosis to the start of RT plus concurrent weekly cisplatin was 3 ± 1.18 weeks, (range, 1- 5 weeks).

The median period of follow up was 35 months (ranged from 18-47 months) and in 5 patients (23.8%) omission of chemotherapy occurred. Among the 21 patients who were planned to receive concomitant hypo-fractionated SIB-IMRT plus concurrent weekly cisplatin, 16 (76.2%) finished both radiotherapy and concurrent weekly cisplatin as planned. Five patients (23.8%) prematurely discontinued cisplatin due to toxicity (in 3 patients) and for other reasons (in 2 patients).

Seventeen of our patients completed radiotherapy within the planned 6 weeks (42 ± 3 days). Unintended interruptions of radiotherapy were short in duration (median, 4 days) mainly due to administrative issues (like, equipment maintenance, technical issues, and holidays). While interruptions caused by treatment toxicity was observed in only 4 patients (19%) and the radiotherapy duration was more than 8 weeks (maximum, 66 days) because of grade 3 toxicities (Table 3).

The median time for follow up was 35 months (ranged from 18-47 months). Mortality was reported in 6 patients (28.6%) and the OS was 90.2% at 2 years and 76.8% at 3 years as shown in Figure 1. The median time to progression was 27 months (ranged from11 – 46 months). Disease progression was reported in 8 patients (38.1%) in form of distant metastasis in 3 patients (14.3%; liver in 2 cases, lung in 1 case) and local progression was observed in 5 cases (23.8%). The PFS was 75.6 % at 2 years and 63.5% at 3 years (Figure 2).

Univariate analysis showed that only FIGO staging had a statistically significant correlation with patients` survival as the advanced tumor stage had worse survival, shown in Table 4. In the current study, using SIB-IMRT technique enabled good dose distribution and coverage of both GTV and lymph nodes with sparing of organs at risk as shown in Figures 3 and 4.

DISCUSSION

EBRT to the pelvis plus Brachytherapy in locally advanced cancer cervix allows target volume to reach high dose and spares organs at risk to decrease risk of toxicity to normal tissues and improve target coverage (Barillot et al 1997, Perez et al 1998) Replacement of this scenario with other one to receive the whole dose treatment as EBRT without brachytherapy was investigated but with poor results.(Ulmer et al 1983) the continuous evolution in the field of IMRT raises the concern that it could replace brachytherapy in treatment of cervical cancer (Alongi et al 2012, Alongi et al 2013)

Up till now, guidelines support the importance of brachytherapy due its advantage as regard organ immobilization, better conformity in dose distribution and higher dose delivery to tumor tissue with minimal dose reaching normal tissue (Viswanathan et al 2012) however, some data assume that increase in fraction size affect tumor cell killing in this category of patients receiving concurrent chemoradiotherapy (Kavanagh et al 2002). According to the mentioned evidence, the current study aimed to evaluate the outcome of Concomitant Hypofractionated Simultaneous Integrated Boost IMRT Plus Concurrent Weekly Cisplatin monotherapy in locally advanced carcinoma of the cervix with positive LNs in patients refusing or unable to receive brachytherapy.

In univariate analysis, FIGO staging was a statistically significant factor in relation to DFS ($p = 0.012$) as worse survival was observed in more advanced stage which agrees with data reported by Mazzola et al in 2017 as clinical outcomes was better for stage II in comparison to stage III (3year local control rate 91% vs 67%, respectively). In the present study, the median time to progression was 27 months (ranged from11 – 46 months) and the PFS was 75.6 % at 2 years and 63.5% at 3 years. While Mazzola et al in 2017 reported higher local control rates (80% at 3 years) but with shorter time to progression (median 24, with range of :6-30 months) than our study. Some authors stated that homogenous and conformal dose delivery is better in IMRT-SIB than with sequential IMRT in different organs. That aroused concerns about replacing brachytherapy boost with SIB technique (Guerrero et al 2005).

In the current study, dosimetric parameters for each volume were illustrated in Table 1 with adequate target coverage and dose delivery with significant reduction in hot spots with subsequent decreased radiotherapy toxicity. Feng et al in 2016 conducted a comparative study between SIB-IMRT and sequential techniques in cancer cervix and reported similar data as regard coverage of pelvic target volume (V90% and V95%) in both groups, with hot spots reduction (V110% and V115%) on using the SIB option. With similarity in both studied groups as regard the coverage of boost target volumes, with minimal heterogeneity of the dose. Our reported data as regard target coverage and dose to organs at risk are similar to the data reported by Feng et al in the SIB group (Table 1).

Table 1. Doses to organs at risk (OAR) and target volumes.

Organs at risk and Target volumes	SIB-IMRT
PTV 54	
V95%	98.5%
V110%	1.12%
PTV 60	
V95%	99.96%
V110%	0%
PTV 66	
V95%	99.2%
V110%	0%
Rectum	
Mean	41.32 Gy
0.1cc	51.2 Gy
1cc	49.6 Gy
2cc	48.3 Gy
V30	77.7 %
V45	19.4 %
Bladder	
Mean	46.8%
0.1cc	51.2%
1cc	49.5%
2cc	49.6%
V30	97%
V45	50.9%
Small bowel	
Mean	22.08 Gy
250cc	35.98 Gy
1cc	54 Gy
2cc	52.17 Gy
V30	29.9%
V45	10.46%
Femoral head (right)	
Mean	21.26 Gy
0.1cc	39.01 Gy
V30	13.65%
Femoral head (left)	
Mean	18.2 Gy
0.1cc	38.35 Gy
V30	10.17%

SIB:simultaneous integrated boosts, IMRT: Intensity-Modulated Radiotherapy, PTV: planned target volume, Gy: gray

As regard avoidance of organs at risk, it was accomplished in our study with the SIB plan as shown in Table 1 which confirms previously published data by Feng et al 2016 supporting SIB plan to spare organs at risk with improvements in physical dose supporting that SIB matched or exceeded sequential IMRT plan.

The toxicity encountered in our study were mostly grade I and II as listed in table (3) as interruptions caused by radiotherapy toxicity happened in only 4 patient (19%). This tolerable toxicity confirms other published data showing that SIB to positive lymph nodes resulted in similar acute toxicity rates to available data involving sequential IMRT with special concern

Table 2. Distribution of different parameters among studied cases, (n = 21)

	No. (%)
Age (years)	
Mean ± SD.	70.33 ± 3.29
Median (Min. – Max.)	70 (65 – 76)
FIGO Tumor stage	
IIB	7 (33.3%)
IIIA	3 (14.3%)
IIIB	8 (38.1%)
IVA	3 (14.3%)
Lymph nodes	
Pelvic	17 (81%)
Para aortic	4 (19%)
Grade	
II	5 (23.8%)
III	16 (76.2%)
Lymph vascular (LV invasion)	
NA	2 (9.5%)
No	7 (33.3%)
Yes	12 (57.1%)
Karnofsky Performance status	
<80	5 (23.8%)
≥80	16 (76.2%)
Chemotherapy	
Completion	16 (76.2%)
Omission	5 (23.8%)

SD: Standard deviation

of acute bowel injury if dose exceeded 50 Gy (Cihoric et al 2014). Moreover, Vargo et al 2014 retrospectively stated that a median dose of 55 Gy in 25 fractions is well tolerated and provided adequate nodal control.

According to Poorvu et al 2013 no association between GIT and duodenal toxicities and radiotherapy dose with nodal boosts reaching 65 Gy. With small intestine doses to 2 cc and 0.1 cc were lower in the SIB plans for majority of patients, including those with para-aortic LN boost volumes.

Mazzola et al 2017 reported that combination of weekly cisplatin with VMAT-SIB for treatment of advanced cervical carcinoma could be a valuable treatment option especially in the elderly population, the 3-year OS and local control were 93% and 80%, respectively. In the elderly setting, stage II patients had more advantages from this technique. While the clinical outcomes in stage III patients depends largely on higher-dose effect.

Table 3. Distribution of treatment toxicity, (n = 21)

Toxicity	Acute				Late			
	G1	G2	G3	G4	G1	G2	G3	G4
GIT	6	7	2	0	6	0	0	0
Vaginal	8	7	1	0	3	0	0	0
Rectal	5	5	0	0	2	1	0	0
Urinary	7	6	1	0	2	0	0	0
Hematological	4	1	0	0	2	0	0	0

G: grade

Table 4. Univariate analysis for the studied parameters affecting OS, (n = 21)

	P	Univariate analysis HR (95% C.I)
Age (years)	0.888	1.021 (0.763 – 1.367)
FIGO staging	0.012*	15.450 (1.830 – 130.452)
Pelvic Lymph nodes	0.530	26.596(0.001 –743287.6)
Grade III	0.831	1.271 (0.141 – 11.465)
Presence of lymph vascular (LV invasion)	0.221	4.015 (0.434 – 37.119)
Performance status ≥80	0.514	2.097 (0.227 – 19.382)
Time before radiotherapy (week)	0.311	0.634 (0.263 – 1.529)
Omission chemotherapy	0.593	1.633 (0.271 – 9.842)

*OS: overall survival, C.I: Confidence interval, HR: Hazard ratio, LL: Lower limit, UL: Upper Limit, *: significant at p ≤ 0.05.*

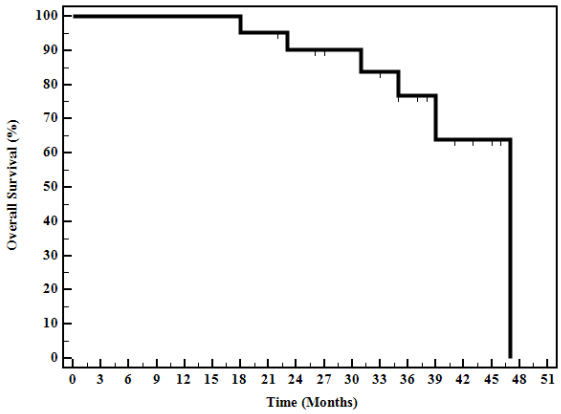

Figure 1. Kaplan-Meier survival curve for overall survival

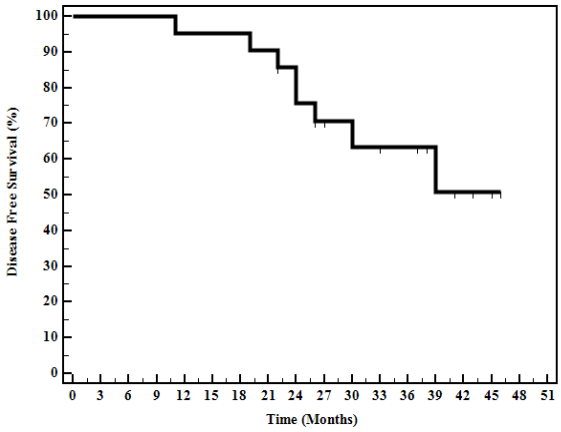

Figure 2. Kaplan-Meier survival curve for progression free survival

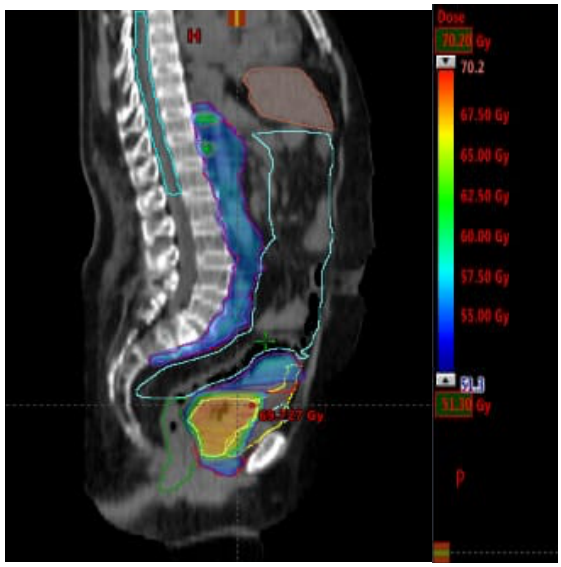

Figure 3. Dose distribution in both axial and sagittal views in SIB-IMRT plans. Good target and paraaortic lymph node coverage.

According to NCCN guidelines, EBRT with dose of 45 Gy in conventional fraction regimen (1.8-2 Gy) followed by boost of brachytherapy reaching ≥ 80Gy and dose of 10 -15 Gy to boost LNs as additional sequential boost is effective but with increases treatment period and additional dosimetric drawbacks as regard organs at risk (Koh et al 2010, Song et al 2013 and Vargo et al 2014).

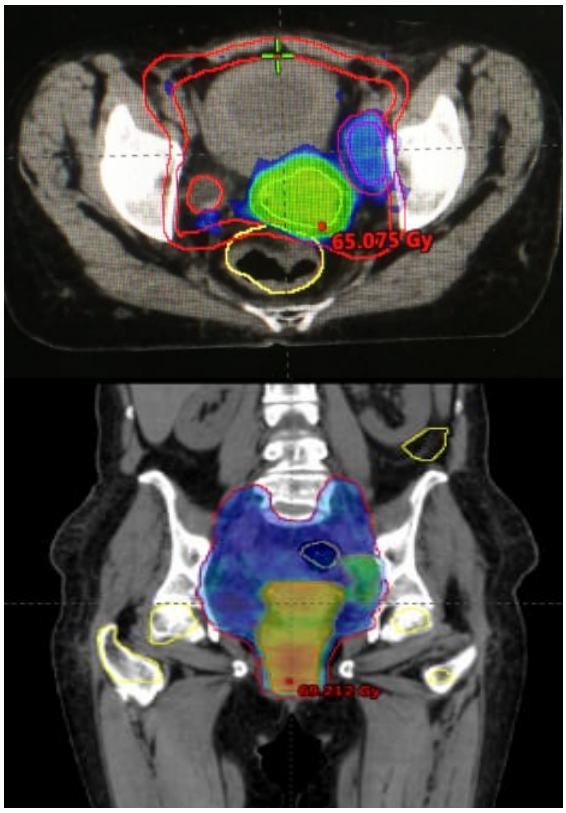

Figure 4. Dose distribution in both axial and coronal views in SIB-IMRT plans. Good target and pelvic lymph node coverage.

In our research we considered IMRT with SIB that gives boost dose plus initial dose at the same time with less fractions number and shorter overall treatment time. This practice is also supported by some studies revealing that increasing radiotherapy treatment time will be associated with poor pelvic disease control (Shaverdian et al 2013).

CONCLUSION

In locally advanced cervical cancer, hypofractionated SIB-IMRT Plus concurrent cisplatin can be used as an alternative treatment option in elderly patients or when brachytherapy is not available. It showed high efficacy in dose delivery to target organ with dose reduction to OAR reducing radiotherapy toxicity with comparable efficacy.

CONFLICTS OF INTEREST

Authors have no conflicts of interest.

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