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DOSIMETRIC EVALUATION OF SPATIALLY FRACTIONATED RADIOTHERAPY (SFRT) VERSUS 3D-CONFORMAL RADIOTHERAPY FOR BULKY PELVIC CANCER

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ABSTRACT

Spatially fractionated radiotherapy (SFRT) is one of the nonconventional radiotherapy techniques utilized to treat patients with advanced bulky tumors. This study was aimed to estimate the different dosimetric parameters of the SFRT technique and compare it to the three-dimension conformal radiotherapy (3D-CRT) of bulky pelvic tumors. 3D-CRT and SFRT were designed by the Monaco treatment planning system. Twelve bulky pelvic tumor cases were selected, a single fraction with a high dose 15Gy was used. Dosimetric parameters were calculated minimum dose (Dmin), mean dose (Dmean), and maximum dose(Dmax) (Gy) for organs at risk (OARs). Also, the dosimetric parameters were calculated of tumors, Dose near maximum (D2) Gy, mean dose (D50) Gy, Dose received by 95% volume (D95) Gy, and Dose near minimum (D98) Gy. SFRT achieves fewer doses for OARs were compared to 3D-CRT. In SFRT, where OARs in close to the tumors and shielding it by multi-leaf (MLCs) with thick (1 cm) leads to more effective than other techniques. Also, SFRT was at variance with 3D-CRT techniques for different cases of D2, D50, D95, and D98 (Gy) for the tumors. There are significant differences between the two methods for all OARs for Dmin, Dmean, and Dmax (Gy), also, D2, D50, D95, and D98 (Gy) for the tumors, p –values less than 0.05. Although SFRT plans noted less coverage tumor than 3D-CRT. However, the SFRT method kills tumor cells by indirectly radiating, abscopal effect, vascular damages, and immunomodulation reactions occur by radiobiological mechanisms in this method with 15 Gy. It could be concluded that SFRT achieves more sparing and fewer complications for OARs by limiting the volume of tissues being exposed to high doses of radiation when compared with 3D-CRT.

Key Words: SFRT, 3D-CRT, Comparison, Dosimetric, OARs

INTRODUCTION

The main purpose of radiotherapy (RT) treatment is to maximize the radiation dose to the tumor while keeping normal tissues, that close with it, receive minimum dose as much as possible. Therefore, the great challenge is how to destroy tumor cells while protecting normal tissues during this treatment **(Chapman, 2003).** Radiotherapy treatment for bulky tumors is a big issue for oncologists. An increased volume of the tumors leads the normal tissues and organs at risk (OARs) to receive high doses than its tolerance dose when treated by three-dimension conventional 3D-CRT **(Billena and Khan, 2019)**. SFRT is a method that is applied to treat bulky tumors (diameter > 6cm) by irradiating the volume through isolated small openings and closing areas in the field of radiation **(Yan *et al.*, 2020).** This method is achieved via the utilization of many small beams in the field with high-dose single-fraction radiation. Specific areas of the target tissue are directly irradiated, while the surrounding areas are protected from direct high-dose radiation **(Billena and Khan, 2019)**. Many researchers suggested that bystander response, which refers to effects seen in cells that are indirectly radiated, abscopal effect, vascular damages, and immunomodulation reactions occur by radiobiological mechanisms in SFRT **(Gholami *et al.*, 2016).**

This study was aimed to estimate the difference in dosimetric parameters in SFRT and 3D-CRT techniques for bulky pelvic tumors cases (as scenarios) in radiotherapy plans and evaluate the differences between the two methods for these parameters. This study is the first practical experiment in this subject.

SUBJECTS AND METHODS

1. Computed tomography (CT) simulator: CT simulator of type (Siemens, Somatom AS, Garmany), provided with 24 multi-slices per rotation, was used to scan the cases in this study.
2. Monaco sim workstation: Three-dimensional RT treatment planning system (TPS) of type (Monaco, Elekta, Sweden) was used in this study.
2. Data collection: twelve cases were selected with bulky pelvic tumors > 6 cm, taken from TPS. They were scanned on a Siemens CT simulator, following by the export of CT images to the Monaco sim workstation, bulk tumor and organs at risk, which were close to the tumor, were delineated. When the delineation is completed, the CT images are sent to the Monaco workstation to design the treatment plans (as scenarios) of the SFRT. Each radiation field is divided into several sub-fields with an area of 1 cm^2 as shown in **Figure 1**, also 3D- CRT plan for each case was performed by TPS.

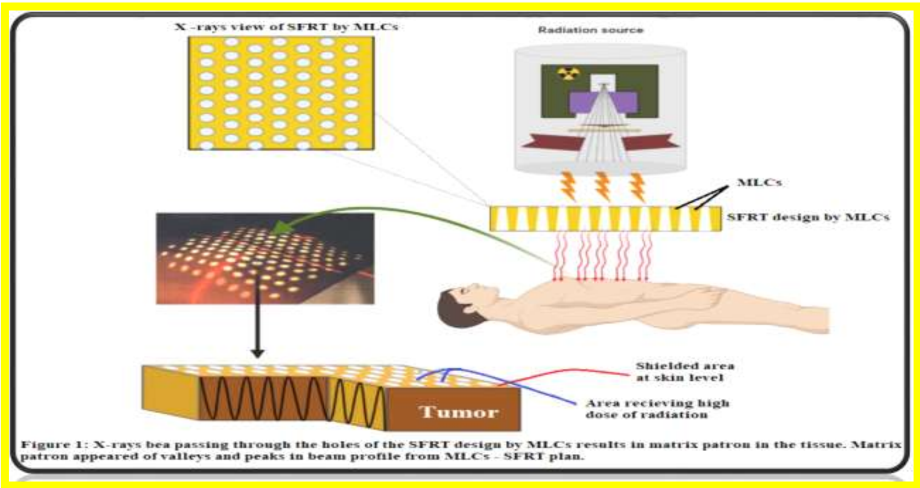

Figure 1 Scheme of the SFRT method processes

Statistical analysis was performed using Microsoft Excel 2016 (Microsoft Corp., Redmond, WA) data analysis program. Two sided paired student's t-test was used to evaluate parameters for two techniques SFRT and 3D-CRT. The quantitative data were presented in the form of mean and standard division of the mean. Significance was considered at a p-value less than 0.05.

RESULTS AND DISCUSSION

Figures 2 and 3 displays a bladder tumor case with two different treatment methods, SFRT, and 3D-CRT, respectively. To highlight the difference in the protective shields of OARs by MLCs that surrounded the tumor. Also shown the change in the shape of the shield modify by MLCs to protect the OARs in pelvic sarcoma tumors as shown in **Figures 4,5 and 6**. The SFRT plans shown the OARs being well protected from radiation doses.

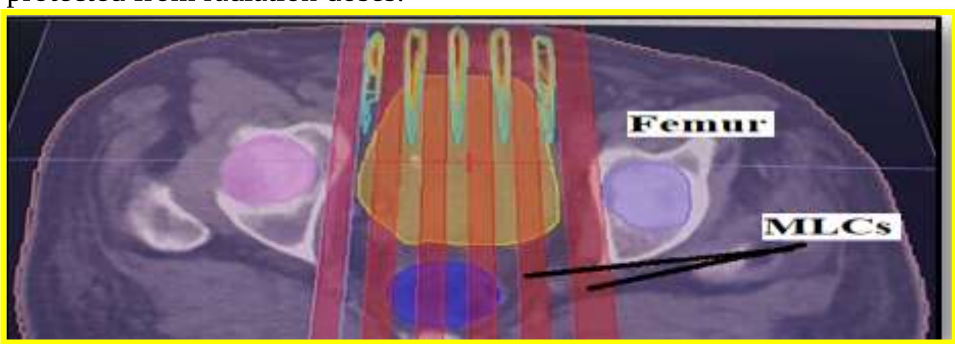

Figure 2 Screenshot of an axial view of bulky bladder tumor with SFRT plan. Radiotherapy department, Nasser institute, Cairo, Egypt.

Figure 3 Screenshot of an axial view of bulky bladder tumor with 3D-CRT. Radiotherapy department, Nasser institute, Cairo, Egypt.

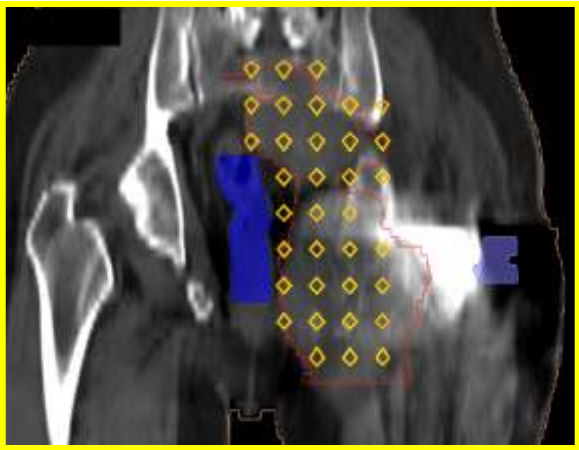

Figure 4 Screenshot of a coronal view of bulky pelvic sarcoma tumor with SFRT plan. Radiotherapy department, Nasser institute, Cairo, Egypt.

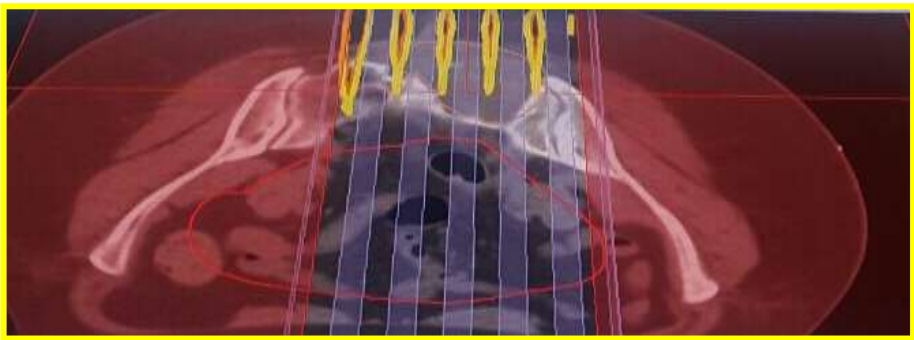

Figure 5 Screenshot of an axial view of bulky pelvic sarcoma tumor with SFRT plan showed the dose distribution and shielding OARs by MLCs. Radiotherapy department, Nasser institute, Cairo, Egypt.

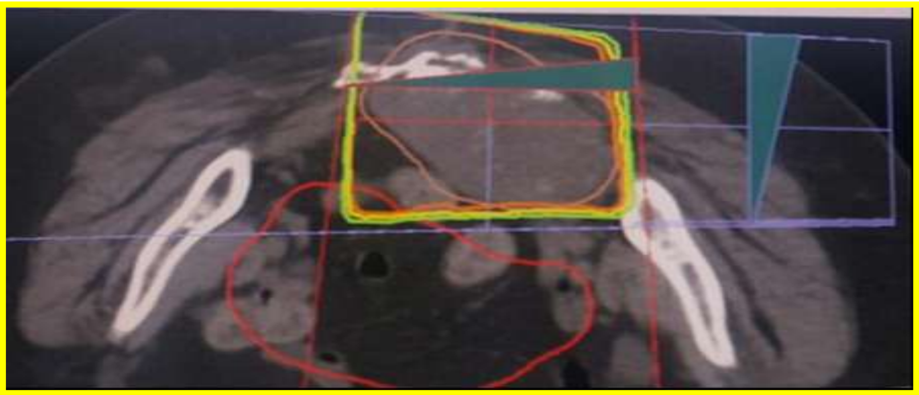

Figure 6 Screenshot of an axial view of bulky pelvic sarcoma tumor with 3D-CRT plan showed the dose distribution. Radiotherapy department, Nasser institute, Cairo, Egypt.

The dosimetric results of OARs of bulky pelvic tumors in 3D-CRT and SFRT.

Calculated and compared the mean of the Dmin, Dmean, and Dmax (Gy) for OARs for bulky pelvic tumor in 3D-CRT and SFRT by TPS as shown in **Figure 7**. The results showed for the Rt femur that SFRT technique decreased the Dmin, Dmean and Dmax received by about 1.2 Gy (92 % reduction), 5.7 Gy (95.5% reduction) and 8.3 Gy (88.9% reduction), respectively. The right (Rt) femur in our cases in this study was far from the tumors as shown in figures 4, 5 and 6 showed that the Rt femur with good shielding by MLCs in SFRT compared with the 3D-CRT. While the left (Lt) femur the results showed that SFRT technique decreased the mean of the Dmin, Dmean, and Dmax dose received by about 0.4 Gy (57% reduction), 2.8 Gy (78.4% reduction), and 9.6 Gy (79% reduction) which considered a great advantage since the femur (head and neck) are sensitive to radiation, the advanced SFRT technique were better in reducing the high dose region to femurs.

The results showed for bladder that the SFRT technique decreased the Dmin, Dmean and Dmax received by about 2.6 Gy (88% reduction) and 6.5 Gy (82% reduction), and 12.2 (86% reduction) respectively. The results showed for bowel that the SFRT technique decreased the Dmin, Dmean and Dmax received by about 1.1 Gy (65.3% reduction), 5.1 Gy (77.4% reduction), and 10.5 Gy (70 % reduction), respectively. Furthermore, it was noted that the difference in the mean of Dmin, Dmean and Dmax between the SFRT and 3D-CRT for rectum was minimal about 4.2 Gy (85% reductions), 6.3 Gy (82% reduction) and 12.1 (78% reduction), respectively.

Griffin *et al.*, (2020) emphasized that SFRT manner of RT has been highly renewed. Two years ago, the Radiology workshop with three working groups (clinical, biological, and physics) was co-conducted by the National Cancer Institute and the Radiation Society to give strong testimony to the therapy and potential clinical application **(Griffin *et al.*, 2020).** The patrons of the SFRT plans in this study are directly in agreement with prior reports of **(Yan *et al.*, 2020)** when summarizing the clinical application studies of SFRT radiotherapy from 1990 to 2019 **(Yan *et al.*, 2020). Asur *et al.*, (2015)** reported successfully use in the treatment of bulky and deep-seated tumors to achieve better control of bulky tumors, it extends the treatment course minimally and a higher significance to repair normal tissues **(Asur *et al.*, 2015).** This is to large extent in agreement with our findings.

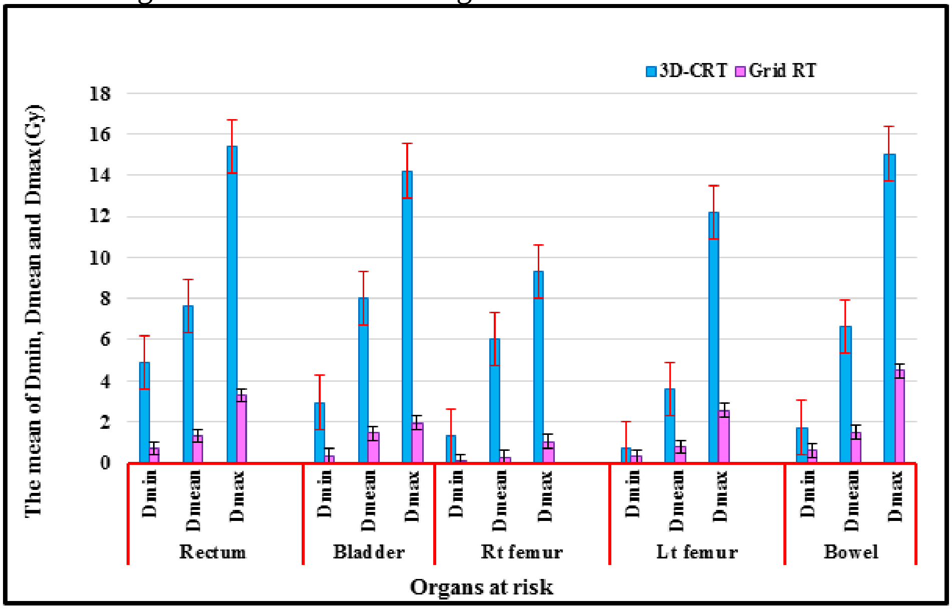

Figure 7 Comparison of the mean dose (Dmin, Dmean and Dmax) measured by TPS for the 3D-CRT and 3D-CRT techniques for OARs in bulky pelvic tumors.

Table 1 shows the mean and stander division SD of the minimum dose (Dmin) (Gy), mean dose (Dmean) (Gy) and maximum dose (Dmax) (Gy) for each OARs for bulky pelvic tumors with two techniques SFRT and 3D-CRT. The SFRT plans achieved reduction of mean doses (Dmin, Dmean, and Dmax) to all OARs compared to 3D-CRT, there is a statistical significant differences between the two techniques in all OAR as p-value < 0.05.

Table 1 Dmin, Dmean and Dmax (Gy) for organs at risk for bulky pelvic tumors with two techniques SFRT and 3D-CRT.

OARs	Dmin(Gy)		Dmean (Gy)		Dmax(Gy)	
	Mean ± SD		Mean ± SD		Mean ± SD	
	3D-CRT	SFRT	3D-CRT	SFRT	3D-CRT	SFRT
Rectum	4.92±1.17	0.7±0.37	7.6±2.39	1.3±0.49	15.42±0.46	3.31±1.67
P-value	0.00001		0.001		0.0002	
Bowel	1.73±0.5	0.6±0.36	6.66±2.72	1.5±0.5	15.06±0.55	4.48±2.04
P-value	0.03		0.001		0.001	
Bladder	2.95±0.07	0.35±0.07	7.98±0.11	1.43±0.14	10.65±6.93	2±0.42
P-value	0.00001		0.0009		0.001	
Rt femur	0.7	0.3	6.02	0.27	9.33	1.03
Lt femur	2.62±0.65	0.31±0.21	3.62±0.36	0.78±0.41	12.22±2.84	2.56±1.71
P-value	0.0003		0.0007		0.008	

Table 2 shows the dosimetric parameters of SFRT at variance with 3D-CRT techniques for different cases of bulky tumors, Dose near maximum (D2) Gy, mean dose (D50) Gy, Dose received by 95% volume (D95) Gy, and Dose near minimum (D98) Gy for the tumors, that calculated by TPS according to the report of ICRU 83 **(Menzel, 2010)**. Comparison of 3D-CRT with SFRT showed that the decrease in the D98 (Gy) to pelvic sarcoma by more than 10 Gy (70.5% reduction). For the bladder tumor the dose reduction was more than 10.3 Gy (72% reduction). A decrease in the D95 (Gy) of the pelvic sarcoma and bladder tumors more than 9.9 Gy (67.8% reduction) and 9.7 Gy (66.9% reduction), respectively for SFRT. Meanwhile, a decrease in the D50 (Gy) to the pelvic sarcoma and bladder tumors by more than 6 Gy (40% reduction) and 6 Gy (39% reduction) for SFRT. While, a decrease in the D50 to the the pelvic sarcoma and bladder, were more than 1 Gy (7.6% reductions) and 0.8 Gy (5% reduction) respectively for SFRT. There are statistically significant differences between techniques in all bulky tumors in this study for D98, D95, D50, and D2 Gy as p-value <0.05.

Table 2 The comparison between D2(Gy), D50(Gy), D95 (Gy), and D98(Gy) in SFRT with 3D-RT for the different pelvic tumors by TPS, Mean, and SD.

tumors		D 98(Gy)		D95 (Gy)		D50 (Gy)		D2 (Gy)	
		3D-CRT	SFRT	3D-CRT	SFRT	3D-CRT	SFRT	3D-CRT	SFRT
Pelvic Sarcoma	Mean	14.37	4.18	14.68	4.72	15.38	9.08	16.55	15.28
	± SD	0.255	0.735	0.311	0.43	0.26	0.36	0.32	1.13
	P-value	0.00001		0.00004		0.00003		0.03	
Bladder	Mean	14.4	4.02	14.55	4.81	14.55	9.11	16.44	15.61
	± SD	0.10	0.40	0.15	0.64	0.157	1.26	0.77	1.19
	P-value	0.0002		0.0009		0.003		0.04	

From **Table 2** calculated coverage index which is defined as ratio of minimum dose within target volume to prescribed dose (PD) and ideal value of its 0.9 to 1 **(Krishna *et al.*, 2016).**

Coverage= D98 dose (Gy) / Prescribed dose PD (Gy)----- 1

Calculated and comparison the coverage tumors by **Eqe. 1** for pelvic sarcoma and bladder tumors in 3D-CRT (0.958 and 0.96), respectively and (0.27 and 0.26), respectively in SFRT.

The advance technique SFRT greatly reduced the radiation dose to OARs as shielding it in SFRT is extremely easy by MLCs. Although SFRT plans that noted less coverage tumor than 3D-CRT, SFRT method causes kill tumor cells by biological processes. **(Fukunaga *et al.*, 2021)** investigated that SFRT method kill cell tumors by both direct (DNA) damages and bystander effect occur with therapy, so non-irradiated cells respond to signals produced by gap junction neighboring irradiated cells. Also, experimentally and in clinical studies, observations have provided strong evidence indicating that molecular events leading to various biological effects, including genetic damage, from irradiated to non-irradiated cells and abscopal effect, induced by radiation effects as a possible referee of response to radiotherapy **(McMahon *et al.*, 2013), (Jin *et al.*, 2014)** described a simple clinical useful 3D- conformal MLCs-based on the SFRT-therapy technique that resulted in enhanced target coverage for the deep seated bulky tumors with reduced skin toxicity and other internal critical structures.

James, *et al.*, (2020) mentioned as SFRT provides another approach for dose escalation while sparing skin and soft tissues between beamless, which may lead to less perioperative and wound problems due to a greater possibility for healing into dose-escalated areas from neighboring spared parts **(Snider *et al.*, 2020)**. This is to large extent in agreement with our findings.

Various trials have been conducted a deeper insight into the radiation effect on tumor cells with doses 12 Gy, and endothelial apoptosis activation has been shown on the tumor models. Also, they noticed cytokine releases, bystander reactions, and abscopal doses required by conventional radiation to impact at least 10 Gy doses **(Li *et al.*, 2018), (Tubin and Raunik 2017).** This is to large extent in agreement with our findings.

CONCLUSION

A high dose of radiation is delivered by SFRT without exceeding the tolerance dose of OARs when minimizing the volume of OARs that are being exposed to high doses.

The future work: SFRT method will need to study the measurement of dosimetric parameters by different ionization chambers in tumor or normal tissues radiated.

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تقيم الجرعات الاشعاعية بالعلاج الاشعاعي المجزء مقابل العلاج الاشعاعي المطابق ثلاثي الابعاد لسرطانات الحوض الضخمة

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العلاج الاشعاعي المجزء هو احدى تقنيات العلاج الإشعاعي غير التقليدية المستخدمة لعلاج مرضى اورام(سرطان) الحوض الضخمة المتطورة.

تهدف هذه الدراسة الى تقدير متغيرات الجرعات الاشعاعية لتقنية العلاج الاشعاعي المجزء ومقارنتها مع العلاج المطابق ثلاثي الابعاد لاورام الحوض الضخمة.

تم تصميم خطط العلاج الاشعاعي المطابق ثلاثي الابعاد مع العلاج المجزء (SFRT) بواسطة نظام تخطيط العلاجي موناكو. تم اختيار اثنتي عشرة حالة أورام حوضية

ضخمة ، و استخدام جرعة اشعاعية عالية 15 كري بجلسة واحدة .تم حساب معدل الجرعات (الصغرى) والجرعة المتوسطة والجرعة القصوى بوحدة (الكري) للأعضاء المعرضة للخطر (الانسجة السليمة) (OARs) .كما تم حساب معدلات قياس الجرعات للأورام كالجرعة القريبة من الحد الأقصى (D2) بالكري ومتوسط الجرعة Gy (D50) والجرعة المستلمة بنسبة 95٪ من حجم الورم Gy (D95) والجرعة القريبة من الحد الأدنى Gy (D98) **النتائج** حقق SFRT جرعات أقل للانسجة السليمة عند مقارنتها بـ العلاج الاشعاعي المطابق ثلاثي الابعاد. في SFRT، حيث OARs تكون قريبة جدا من الورم وحمايتها بواسطة الصفائح المتعددة لتسديد الاشعاع (MLCs)بسمك (1 سم) يؤدي إلى حماية من الاشعاع أكثر من التقنيات الأخرى. أيضًا ، يختلف SFRT عن تقنية العلاج الاشعاعي المطابق ثلاثي الابعاد لحالات مختلفة من الاورام D2 و D50 و D95 و D98 (Gy) . توجد فروق ذات دلالة إحصائية بين الطريقتين (OARs) لكل من Dmin و Dmean و Dmax (Gy) ، وكذلك D2 و D50 و D95 و D98 (Gy) للأورام ، وقيم p أقل من 0.05. على الرغم من أن خطط SFRT لاحظت وجود تغطية أقل للورم من العلاج الاشعاعي المطابق الثلاثي . ومع ذلك ، فإن طريقة SFRT تقتل الخلايا السرطانية عن طريق الإشعاع غير المباشر ، والتأثير المطلق ، وتلف الأوعية الدموية ، وتفاعلات التحوير المناعي التي تحدث بواسطة الآليات الإشعاعية الحيوية في هذه الطريقة مع جرعة مفردة وعالية 15 كري. الاستنتاجات: يحقق SFRT مزيدًا من التجنيب ومضاعفات أقل لـ OAR وذلك عن طريق الحد من حجم الأنسجة التي تتعرض لجرعات عالية من الإشعاع عند مقارنتها بالعلاج المطابق ثلاثي الابعاد.