REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY 24 (2019) 263–268

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Original research article

Adaptive radiotherapy in patients receiving neoadjuvant radiation for soft tissue sarcoma

Ramiz Abu-Hijlih, Sara Mheid, Fawzi Abuhijla, Wafa Asha, Issa Mohamad, Abdullah Alrashdan, Samer Alheet, Haitham Kana'an, Mohammad Abd Al-Raheem, Abdelatif Almousa*

Radiation Oncology Department, King Hussein Cancer Center, PO Box 1269, Amman 11941, Jordan

ARTICLE INFO

Article history:
Received 12 September 2018
Received in revised form
15 November 2018
Accepted 19 February 2019
Available online 18 March 2019

Keywords:
Radiotherapy
Soft tissue sarcoma
Neoadjuvant radiation
Adaptive radiation
Image-guided radiation

ABSTRACT

Aim: The aim of this study is to evaluate tumor volume changes during preoperative radiotherapy and to assess the role of adaptive radiation.
Background: Contemporary neoadjuvant radiotherapy utilizes image guidance for precise treatment delivery. Moreover, it may depict changes in tumor size and shape.
Materials and methods: Between 2016 and 2018, 23 patients aged ≥18 years with soft tissue sarcoma were treated with neoadjuvant radiation followed by surgical resection. The tumor volumes (cc) were measured using the Pinnacle planning system prior to starting radiotherapy and during treatment, the changes in volume and absolute differences were estimated. Moreover, patient's position on the machine was evaluated to assess setup offsets. The triggers for plan adaptation were >1 cm expansion or unacceptable setup offsets.
Results: The mean tumors volume at presentation was 810 cc (range, 55–4000). At last cone beam CT the tumor volume had changed in 14 patients (61%); it was stable in nine patients (39%). Disease regression was documented in eight patients (35%), with median shrinkage of −20.5% (range, −2 to −29%), while tumor progression was observed in six cases (26%), the median change was 12.5% (range, +10 to +25%).

Adaptive radiation was required in four patients (17%). For the remaining 19 cases (83%), the dose distribution was adequate to cover target volumes.
Conclusions: Change in soft tissue sarcoma volume during radiation is not uncommon. Image guidance should be used to reduce setup errors and to detect differences in tumor volume. Image guidance and adaptive radiation are paramount to ensure optimal radiation delivery.

* *Corresponding author.*
E-mail address: rhijlih@khcc.jo (R. Abu-Hijlih).
https://doi.org/10.1016/j.rpor.2019.02.007

1. Background

The primary therapy for soft tissue sarcomas is surgical resection. Radiotherapy is an important component of a multimodality treatment; it can be delivered before or after surgery. When given preoperatively, the irradiated volumes are smaller and the total radiation dose is lower, leading to fewer late side effects and better limb function.[1–3] Recently, radiation machines and techniques have advanced tremendously, and now radiation can be delivered more precisely toward the malignant process while sparing nearby tissues, this is achieved mainly using image guidance; such as cone beam CT (CBCT). Nowadays, CBCT is widely used during treatment delivery, it can help minimize systematic and random setup errors.[4] Moreover, CBCT allows the treating physician to visualize soft tissue structures and detect changes in tumor volume; these changes may result in under-dosage of the target area. To avoid degradation of radiation plan, new CT simulation and re-planning should be performed; defined as adaptive radiotherapy.

2. Aim

The aim of this study is to evaluate soft tissue sarcoma volume changes during preoperative radiation, and to assess the role of adaptive radiation.

3. Materials and methods

3.1. *Patient population*

Twenty-three patients aged ≥18 years were diagnosed with soft tissue sarcoma between January 2016 and July 2018. The work-up at presentation included complete physical examination and laboratory tests. All patients underwent a diagnostic biopsy; the histopathology was reviewed by an experienced musculoskeletal pathologist according to the World Health Organization (WHO) classification of soft tissue sarcoma.[5] Staging images included; bone scan and chest computed tomography (CT) to rule out distant metastasis; abdomen CT scan was added for patients with myxoid liposarcoma (MLS). Baseline magnetic resonance imaging (MRI) was performed to assess mass extension and to evaluate proximity of neurovascular bundle. The ethics committee of the Institutional Review Board (IRB) approved this study. We reviewed patients' charts, in addition to radiotherapy plan details.

3.2. *Treatment procedure*

The management decision was discussed at the multidisciplinary meeting before starting treatment. This study included patients who received neoadjuvant radiation as a monotherapy. After obtaining consent for radiation treatment, CT-simulation was performed for all cases, the treatment position was determined by tumor location and the need for immobilization devices. Three skin markers were added to help in patients positioning on the linac. Then, MRI images (T1 – post gadolinium and T2 – weighted) were fused with the simulation scan, and registered to match bony and soft tissue anatomy. The gross target volume (GTV) was defined using CT simulation and MRI images, after that clinical target volume (CTV) and planning target volume (PTV) were created following RTOG 0630 recommendations.[6] All the radiation plans were performed using intensity modulated radiotherapy (IMRT) or volumetric modulated arc radiotherapy (VMAT); thereafter, the radiation plans were discussed at the bi-weekly quality assurance (QA) meetings for peer review. RT was delivered using a linear accelerator equipped with cone beam CT (CBCT – Elekta Synergy, Elekta Oncology Systems Ltd., UK). Radiotherapy was delivered in 2-Gy fractions over 25 sessions for a total radiation dose of 50 Gy. The treatment position offsets were corrected using image guidance. The CBCT images were uploaded to Pinnacle Version 9.6 (Koninklijke Philips N.V., Amsterdam, Netherlands), then GTV volumes were delineated again using CBCT image and volume was estimated by an automated volume calculation option in the planning software. The absolute volumes change and relative percentages were estimated.

Adaptive preoperative radiotherapy is defined as modification of the radiation plan to account for changes in tumor shape and volume during treatment. There are no consensus guidelines for adaptive radiation, a cutoff of 1 cm in the diameter has been suggested to trigger plan modification. Generally, it depends on radiation oncologist's judgment, experience and available equipment. In this study, plan adaptation was prompted by >1 cm increase, in addition to unacceptable patient setup offsets which were not amenable for correction.

The time of surgery was between 4 and 6 weeks after radiotherapy, the surgery of choice was a wide local excision with negative margins.

3.3. *Statistical analysis*

Descriptive analysis was performed in this paper; summary statistics were reported as mean and median where appropriate. The tumor volumes were estimated automatically on the Pinnacle planning system, then absolute change and percentages were calculated. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). The results were illustrated in the submitted tables.

4. Results

Neoadjuvant radiation was delivered to 23 adult patients with soft tissue sarcoma. Table 1 demonstrates patients and disease characteristics, in addition to oncologic outcomes.

The mean tumor volume at presentation was 810 cc (range, 55–4000). On last CBCT, which is obtained on the last day of radiation, the tumor volume had changed in 14 cases (61%); it was stable in nine patients (39%). Tumor growth was observed in six patients (26%), the median change was 12.5% (range, +10 to +25%). Fig. 1 shows an example for adaptive radiation in a patient with a tumor that progressed during treatment. On the contrary, disease response was documented in eight tumors (35%), median shrinkage was −20.5% (range, −2 to −29%). Fig. 2 demonstrates tumor shrinkage and related

Table 1 – Patient characteristics and disease outcome.

Gender, *n* (%)	Male – 15 (65) Female – 8 (35)
Age at diagnosis (yr)	Median 43 (19–78)
Tumor volume at presentation, cc (%)	Mean 810 (55–4000) cc
Pathology subtype, *n* (%)[a]	MLS – 6 (26) Dedifferentiated liposarcoma – 6 (26) MPNST – 4 (17) UPS – 2 (9) Others – 5 (22)
Tumor location, *n* (%)	Lower extremity – 11 (48) Retroperitoneal – 7 (30) Chest wall – 5 (22)
Depth, *n* (%)	Deep – 22 (96) Superficial – 1 (4)
Staging at presentation, *n* (%)	Non-metastatic – 22 (96) Metastatic – 1 (4)
Type of surgery, *n* (%)	Wide local excision – 15 (66) Amputation – 1 (4) Laparotomy – 7 (30)
Extent of resection, *n* (%)	R0 – 18 (79) R1 – 4 (17) R2 – 1 (4)
Status at last follow-up, *n* (%)	No evidence of disease – 18 (79) Alive with disease – 3 (13) Dead of other causes – 0 Dead of disease – 2 (8)

[a] *Abbreviations*: MLS, myxoid liposarcoma; MPNST, malignant peripheral nerve sheath tumor; UPS, undifferentiated pleomorphic sarcoma.

normal tissue irradiation, and Fig. 3 reveals the effect of tumor regression on the radiation plan.

Regarding tumors located in the retroperitoneum, the response during treatment was comparable with other disease sites. Four cases were stable, two tumors regressed while one lesion increased in size. Table 2 shows tumor volumes (GTV) at the beginning of radiation and volume at the last acquired CBCT.

Adaptive radiation was warranted in four patients (17%), to account for intolerable setup offsets and alterations in plan target coverage. However, for the other 19 cases (83%), the radiation plan adequately covered target volumes. Noteworthy, all new plans were performed in the third week of treatment.

Data for target volumes coverage (GTV and PTV) was obtained from dose volume histogram (DVH) on Pinnacle. The target coverage endpoints followed requirements outlined in the International Commission on Radiation Units and Measurements (ICRU 83).[7]

Table 3 illustrates target volumes coverage at time of plan approval, and the DVH numbers when original plan was optimized on the new volume, and after plan adaptation.

5. Discussion

Neoadjuvant radiation has proven to be effective in the management of soft tissue sarcoma along with a favorable long-term toxicity profile. The use of this approach gives physicians an opportunity to assess treatment response using radiological and clinical parameters.[1–3]

The radiation techniques have evolved dramatically in the last few decades, introduction of IMRT revolutionized radiation delivery and improved conformality and, therefore, it was widely adopted. VMAT is a newer tool for radiation delivery using arcs; VMAT demonstrates superiority to IMRT in terms of treatment time and conformality index.[8] Based on the aforementioned advancements, RTOG sarcoma contouring consensus recommended reduced margins around the GTV whenever image guidance is used.[9] Moreover, a secondary analysis of RTOG 0630 results concluded that a CTV-to-PTV margin of 1.5 cm is required when image guidance is not employed.[10]

After introduction of CBCT, radiation oncologists become able to detect changes in tumor size during radiation treatment. Detection of such changes is crucial because it may compromise target coverage. Soft tissue sarcoma is one of the radio-responsiveness malignancies.[11,12] The decrease in tumor size during treatment may represent an early sign of disease response. On the contrary, tumor progression can exhibit disease progression and, nevertheless, it may denote reactive edema or mass liquefaction. Many studies observed tumor radiologic response in at least 50% of patients who underwent preoperative radiation.[11–14] In our series, we noticed volume differences in 61% of the patients. Tumor growth during treatment led to target volume extension beyond the irradiated area, resulting in target under-dosage. On the other hand, tumor regression resulted in the difference

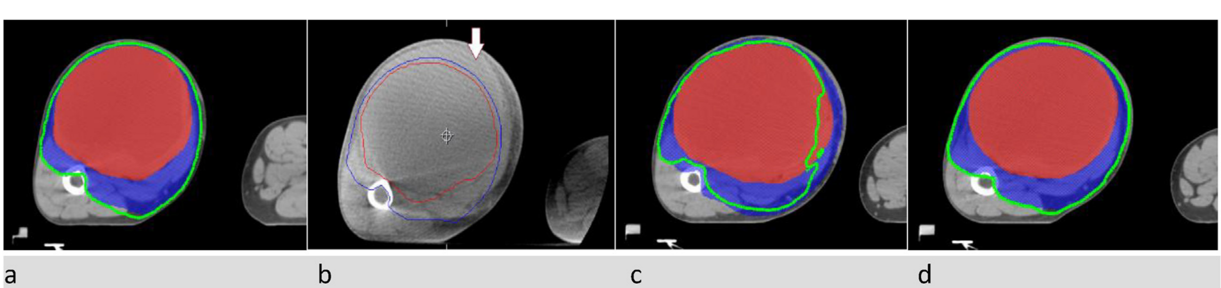

Fig. 1 – (a) VMAT plan for extremity sarcoma (GTV in red and PTV in blue). 95% isodose line (in thick green) is adequately covering the PTV. (b) CBCT after 14 fractions shows tumor growth (arrowed). (c) Original plan on the new tumor volume, there is GTV and PTV under-dosage. (d) Adaptive radiation (re-simulation and new plan), the 95% isodose line encompasses the PTV. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

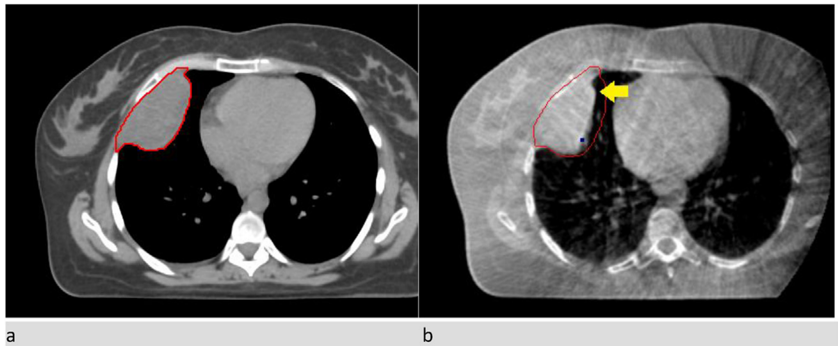

Fig. 2 – (a) Chest wall synovial sarcoma, delineated (GTV in red) on CT simulation image. (b) CBCT after 12 fractions shows tumor shrinkage (yellow arrow), resulting in normal lung irradiation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

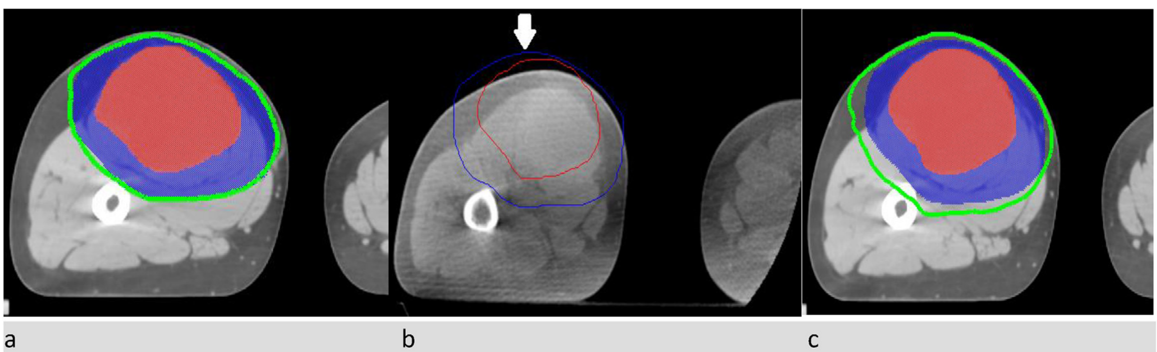

Fig. 3 – (a) VMAT plan for extremity MLS (GTV in red and PTV in blue). 95% isodose line (in thick green) encompasses the PTV on CT simulation image. (b) CBCT after 15 fractions shows significant tumor shrinkage (white arrow); original GTV and PTV contours are outside body anatomy. (c) Tumor response resulted in changes in target shape and volume, consequently 95% isodose line encroaches to normal nearby tissues, thus requiring adaptive radiation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in target's shape and volume, producing unacceptable offsets in patient setup. When we explored the effect of such scenarios on radiation dose distribution, the isodose lines were expanding into normal surrounding tissues. This conclusion necessitates the utilization of image guidance during neoadjuvant radiation.

Deckie et al. reported the results of 22 patients, enrolled in a prospective extremity IMRT trial, who received adaptive radiation. They observed disease progression in 14 tumors and eight regressed during treatment. The trigger for adaptive radiation was ≥1 cm, and the mean time for second simulation was 13 fractions.[15,16] Another study by Betgen et al. looked at sarcoma volumes change during preoperative radiation. They observed volume change in 52% of patients with tumor shrinkage noticed only in MLS patients.[13] Recently, Haas et al. investigated tumor volume changes in 93 sarcoma patients; they reported a considerable size difference in 44% of cases and adaptive radiation was needed in 8% of the plans.[17] Our results came in concordance with these reports, change in tumor volume is expected in about half of patients receiving neoadjuvant radiation and the rate of required adaptive radiation was between 8% and 30% of patients.[18–21] In addition, we did not find a correlation between tumor response and specific site or histologic subtype, with the exception of MLS, which had a predilection for regression in our cohort: additionally, none of these tumors showed disease progression.

Adaptive radiation is a time consuming procedure which demands extra effort from the radiation team; for instance, it requires close interpretation of CBCT, in addition to second simulation and re-planning, which is problematic mainly in busy facilities. Furthermore, Kv-CBCT suffers from a low image quality creating obstacles in tumor definition and volume calculation. This, combined with inter-observer delineation variability, makes this approach more challenging.

Online adaptive radiotherapy is a newer approach, using better image guidance tools, such as MR-linac, to perform deformable image registration and automatic contouring and re-planning. However, these steps require a mean of 90 min, making this technique more convenient for other forms of radiation, such as stereotactic radiation.[22] The future may carry new evolving techniques to provide more efficient adaptive platforms.

The limitations of this study are the retrospective nature and associated selection bias. Additionally, GTV volumes were delineated on low image quality (CBCT). Nevertheless, only few reports in the literature studied this evolving technique

Table 2 – Gross target volume (GTV) at presentation and last CBCT with percent of change.

Pathology subtype	Volume at presentation	Volume at last CBCT	Absolute change (cc)	Percentage (%)	Volume
MLS	840	600	−240	−29	Decrease
Synovial	120	90	−30	−25	Decrease
MLS	530	400	−130	−24	Decrease
MPNST	980	750	−230	−23	Decrease
MLS	768	630	−138	−18	Decrease
MPNST	150	130	−20	−13	Decrease
Leiomyosarcoma	90	80	−10	−11	Decrease
MLS	360	350	−10	−2	Decrease
Dedifferentiated liposarcoma	1125	1125	0	0	Same
Synovial	410	410	0	0	Same
Dedifferentiated liposarcoma	430	430	0	0	Same
Dedifferentiated liposarcoma	1600	1600	0	0	Same
MLS	1120	1120	0	0	Same
MPNST	55	55	0	0	Same
Dedifferentiated liposarcoma	1320	1320	0	0	Same
MLS	800	800	0	0	Same
Leiomyosarcoma	290	290	0	0	Same
UPS	210	230	20	10	Increase
Spindle cell	4000	4400	400	10	Increase
UPS	135	150	15	11	Increase
MPNST	710	810	100	14	Increase
Dedifferentiated liposarcoma	750	900	150	20	Increase
Dedifferentiated liposarcoma	1875	2350	475	25	Increase

MLS, myxoid liposarcoma; MPNST, malignant peripheral nerve sheath tumor; UPS, undifferentiated pleomorphic sarcoma.

Table 3 – GTV and PTV 95% isodose line coverage.[a]

Patient number. Change in volume	GTV coverage on original plan	PTV coverage on original plan	GTV coverage with target volume change (before plan adaptation)	PTV coverage with target volume change (before plan adaptation)	GTV coverage with target volume change (after plan adaptation)	PTV coverage with target volume change (after plan adaptation)	Treatment position offsets before plan adaptation[b]
1. Increase	99.86%	96.16%	91.7%	86.84%	99.78%	97.12%	Not acceptable
2. Increase	100%	95.16%	93.2%	89.8%	100%	98%	Acceptable
3. Decrease	99.76%	96.34%	100%	100%	99.41%	96.28%	Not acceptable
4. Increase	99.62%	97.6%	92.9%	88.6%	99.86%	97.32%	Acceptable

[a] Target volumes coverage requirements followed ICRU 83 recommendations.
[b] Changes in patient anatomy may result in positioning errors; sometimes setup offsets are tolerable, but in some cases cannot be corrected.

in soft tissue sarcomas, our conclusion was similar to other reports; optimal neoadjuvant radiation for sarcoma patients requires image guidance to detect if changes occur during treatment, and to evaluate difference that my entail plan adaptation.[13,16]

6. Conclusions

Soft tissue sarcoma volumes frequently change during neoadjuvant radiotherapy, so image guided radiotherapy is crucial to detect these changes. We observed volume difference in more than half of the patients, indicating heightened awareness of potential setup error and possible alterations in radiation dose distribution.

Adaptive radiation is mandated in many patients; the timing of a second simulation is usually the third week. The suggested triggers for plan adaptation are >1 cm expansion and unacceptable setup offsets.

In the era of precise radiation delivery, image guidance and adaptive radiotherapy should be considered the standard of care for patients receiving neo-adjuvant radiation for soft tissue sarcoma.

Conflict of interest

None declared.

Financial disclosure

None declared.

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