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Under the Patronage and Honoring of HRH Prince Saud bin Nayef bin Abdulaziz, Governor of the Eastern Province: Saudi Cancer Foundation Successfully Launches "AlSharqia Wardiyah 18"

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Original Article

Induction spatially fractionated GRID radiotherapy (SFGRT) radiotherapy for locally advanced extremity soft tissue sarcoma: Report of 10 years follow up.

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Abstract

Introduction: Increasing the rate of tumor necrosis by more than 90% for extremity soft tissue sarcoma (STS) with preoperative treatment has been associated with better local control and survival. Locally advanced tumors appears to be more challenging to achieve the desired necrosis rate (>90%) with preoperative chemoradiation. We aim to test a novel approach using induction spatially fractionated GRID radiotherapy (SFGRT) followed by preoperative chemoradiation in the treatment of STS looking for improved tumor necrosis rate and to report survival data after 10 years follow up.

Patients and Methods: Fourteen patients with locally advanced bulky extremity STS were included in the study. Median tumor size is 11.5 cm (8–26 cm). All patients were treated with induction 18 Gy single fraction SFGRT followed by external beam radiotherapy 50 Gy / 25 fractions / 5 weeks concurrently with chemotherapy (Iphosphamide 2 gm/m2/day x 3 days and mesna 2 gm/day x 3 days in divided doses every three weeks for total of 2 cycles). Patients were planned for surgical resection 4–6 weeks after completing neoadjuvant treatment.

Results: Twelve (86%) patients completed the planned treatment. One (7.1%) patient had treatment interruption due to grade 3 skin toxicity and 1 patient underwent an amputation of the foot mid of the neoadjuvant treatment. Thirteen (93%) patients underwent limb salvage surgical resection, one of them had positive surgical margins. Nine (65%) patients had > 90 % tumor necrosis with 2 patients having a pathological complete response. At a median follow up of 37 months, 3 patients (23%) lost their follow up with no evidence of local recurrence or distant metastasis. At 5 years follow up (median follow up 60 months), 3 (23%) patients had distant metastasis and died. At 10 years follow up (median follow up 92 months), 7 (53.8%) patients are alive with no evidence of local recurrence or distant metastasis.

Conclusion: The addition of induction spatially fractionated GRID radiotherapy SFGRT to preoperative chemoradiation showed to be an effective way to improve the rate of tumor necrosis and enhancing response to chemoradiation resulting in improvement in local control and overall survival in our small cohort over a long follow up period. Using SFGRT and neoadjuvant CCRT appeared to be safe and should be tested on a larger population with locally advanced extremity STS.

Key words: induction, radiotherapy, SGFRT, soft tissue sarcoma .

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Introduction

The treatment of advanced, bulky extremity soft tissue sarcomas remains to be a major challenge for the oncologists. Pre and/or post–operative radiation has been successfully used to lower the incidence of local recurrence for resectable tumors aiming for limb preservation surgery, the improvement in local control rates has not often translated into dramatic improvements in survival [1].

Currently the local recurrence rate after pre or post–operative radiation ranges from 10–25% dependent on the size and extent of the tumor [2]. However, the 5–year survival in high–grade tumors is only around 50% [3].

The addition of chemotherapy to preoperative radiation has yielded mixed results [4]. Combined preoperative chemotherapy and radiation theoretically has the advantage of targeting micro–metastatic disease early in the treatment course to decrease subsequent rate of distant metastasis but several studies have failed to show an improvement in disease free or overall survival[5–8]. However, the pathological response to Neoadjuvant chemo/radiation appears to be of good prognostic value[8].

Pathological response with higher percentage of necrosis in response to preoperative chemotherapy and radiotherapy has been established as a prognostic factor for osteosarcoma [9] and Ewing's sarcoma [10] and only recently has it been shown that this may also be true for soft tissue sarcoma [11, 12].

Spatially fractionated GRID radiation treatment (SFGRT) therapy is an innovative concept in radiation therapy that has utilized to overcome limitations of acute and late normal tissue tolerance. This technique was successfully utilized in the 1940's and 1950's to overcome the limitations of excessive skin dose with orthovoltage radiation in an effort to treat deep seated tumors [13–14].

The technique has been modified for megavoltage beams to exploit the same mechanisms aiming to deliver a higher radiation dose to tumors without exceeding tolerance levels. This therapeutic gain can lead to enhanced control of these advanced neoplasms. SFGRT is given using the GRID block which is made of up to 258 separate non–confluent pencil beams [15,16]. Figure 1 represents diagrammatic design of GRID. Block.

The aim of our study is to evaluate the rate of tumor necrosis for our patients with large extremity STS treated with induction spatially fractionated GRID radiotherapy (SFGRT) followed by concurrent conventional fractionated radiation therapy and chemotherapeutic agent (Iphosphamide) (CCRT).

Secondary end points include evaluation of local control, disease free survival (DFS), overall survival (OS), acute and late toxicity of using the above–mentioned protocol.

Patients and Methods

Medical records of patients with large soft tissue sarcomas of extremity treated with above mentioned protocol in King Faisal hospital and research center (KFSHRC) Oncology Center, Riyahd, Saudi Arabia in the period between 2012–2016 were retrospectively evaluated.

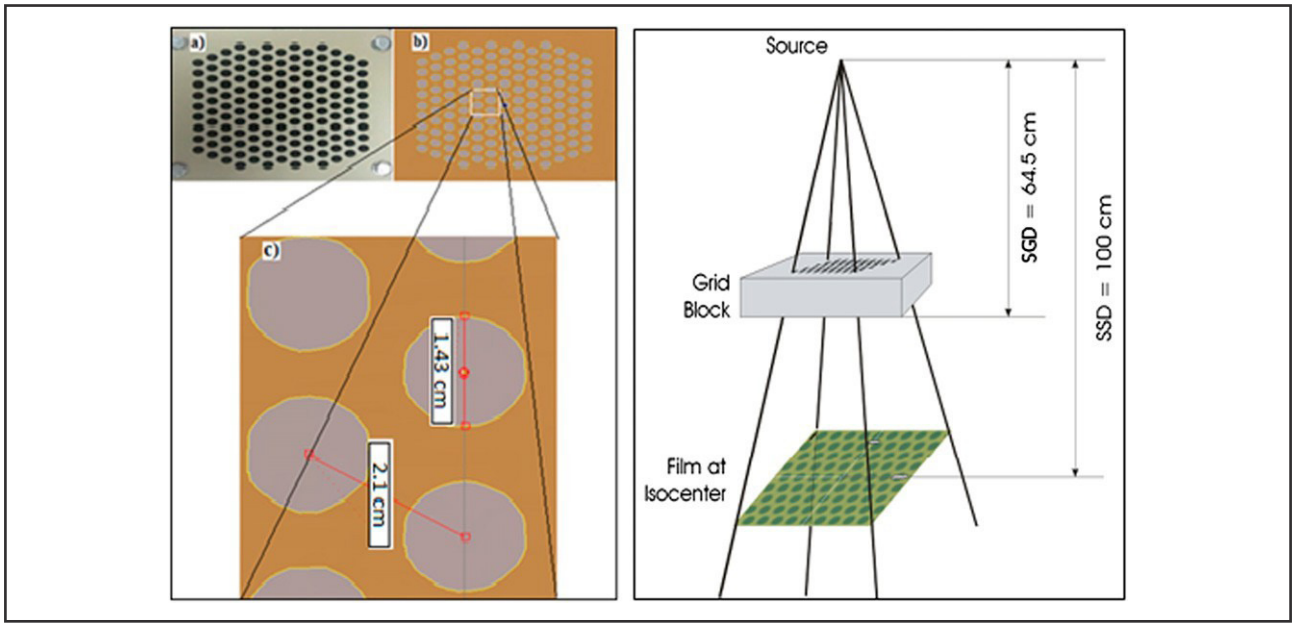


Figure_ 1 Grid block design. (a) Actual design; (b) treatment planning system design; (c) geometrical parameters; and (d) experimental set–up used to determine size and distribution of openings at the isocenter level, with a source–to–surface distance (SSD) of 100 cm and source–to–grid distance (SGD) of 64.5 cm.

All the patients in this study has large extremity STS treated with radio–induction therapy (SFGRT) followed by concurrent conventional fractionated radiation therapy and chemotherapeutic agent (Iphosphamide), with the following inclusion criteria:

a) The patient must be 15 years of age or older.

b) The patient must have histological proven diagnosis of extremity Soft Tissue sarcoma (>5 cm in size).

c) Karnofsky Performance Status >80,

d) Adequate laboratory tests,

e) Recent MRI examination of the primary tumor site within 4 weeks of treatment initiation.

f) No evidence of distant metastasis according to staging CT scans.

All patients received radio–inductive dose of 18 Gy on the first day of treatment. Portals will encompass the total mass of tumor as determined radiologically by the CT /MRI scans. CT based treatment planning will be done for adequate localization of the tumor. The field size used will be individualized for the patient with the field applied to the edge of the gross disease without any margin. AP or PA or Oblique field may be utilized. The induction treatment dose will be 18 Gy prescribed to the 100% Iso dose (DMAX) in a single fraction using a 50:50 Grid, the detailed physical properties of the SFGRT was previously published in our previous study by Nobah et al [17]. Figure 2 represents an example of dose distribution obtained by GRID block

All the patients after the initial SGFRT received pre–operative conventional fractionated radiation therapy using Intensity modulated radiation therapy (IMRT) or 3 Dimensional conformal radiation therapy (3 DCRT) aiming at a dose of 50 Gy/25 fractions/5 weeks.

Treatment planning CT scans was done to define gross, clinical and planning target volumes. MRI scans for fusion techniques was used for better tumor volume delineation as necessary.

Radiation treatment volumes were as follow: the Gross Tumor Volume (GTV) is defined as all known gross disease determined from images and clinical information. The Clinical Target Volumes (CTV) is defined as the GTV plus areas considered to contain potential microscopic disease, with a margin 3–4 cm longitudinal and 1–1.5 cm circumferential. The Planning Target Volume (PTV) was created with 0.5–1 cm margin around CTV.

Radiation planning accepted criteria was as follow: is at least 95% of the (PTV) is covered by the prescribed dose. No more than 20% of a (PTV) receive >110% of its prescribed dose. No more than 1% of normal tissues outside the (PTV) receive >110% of the dose prescribed to the primary PTV.

All patients received Iphosphamide along with the conventional fractionation course of radiation therapy at a dose of 2 g/m2 daily for 3 consecutive days repeat every 21 days for total of two cycles along with mesna dose of 2gm/day in divided dose include 20% of mesna dose pre iphosfamide infusion, 40% two hours after iphosfamide infusion and another 40% will be by mouth 8 hr after the iphofamide infusion.

All the patients were followed once weekly during CCRT to assess for acute toxicity. Acute toxicity was

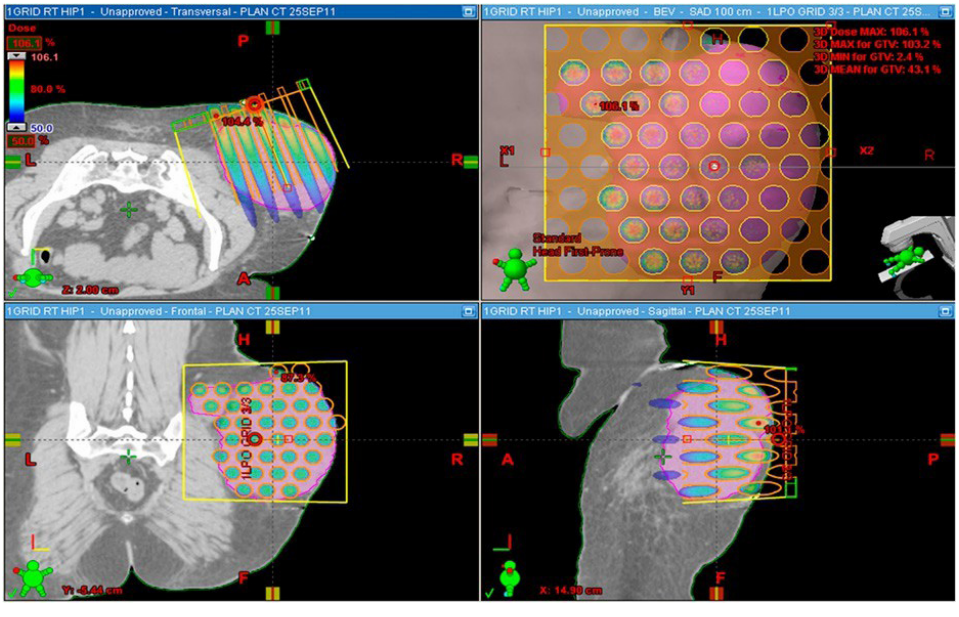


Figure_ 2: Dose distribution calculated using the Eclipse treatment planning system

evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [18]

All patients should have adequate lab results before starting any cycle of iphosphamide chemotherapy (ANC >1000 and platelets> 100,000 and normal renal function). In case of neutropenic fever or septic complications, the GCSF was used with the next course of chemotherapy or reduce the dose of iphosfamide by 20% for the subsequent cycle. In case of grade 3 or 4 neurotoxicity (somnolence > 30% of time, disorientation/ hallucination/ coma) and severe nephrotoxicity (include severe tubulopathy, renal tubular acidosis) , further use of iphosphamide was avoided. All patients were reevaluated for surgery 4–6 weeks post CCRT.

All patients were kept under regular follow up with Follow–up intervals as follows: every 3–4 months during the first 2 years, every 6 months during the 3rd–5th year, and then annually. Follow– up included history; physical examination; complete laboratory workup with CT (Chest, abdomen and pelvis) to exclude metastasis and MRI to tumor primary site to assess local recurrence.

Statistical analysis

The SPSS (Statistical Package version 28) was used to analyze the data. Median (range) will be used to describe quantitative data. Frequency and percentage were used to summarize qualitative data.

The (OS) was determined from the date of diagnosis until death or the last follow–up date, (DFS) calculated from date of surgery till the date of documented relapse, death, or last follow–up. The Kaplan–Meier technique was used to conduct the survival analysis.

Results

Total of 14 patients were included in this study, median age at diagnosis was 36.5 (17–59) years, 9 (64.2%) patients were male, detailed patients and tumor characteristics are listed in Table 1.

Twelve (86%) patients completed the planned CCRT treatment without interruption. One (7.1%) patient had treatment interruption due to Grade 3 skin toxicity and 1(7.1%) patient underwent an amputation of the foot mid of the neo adjuvant treatment due to disease progression. Eleven (78.5%) patients had clinically complete response to treatment. Thirteen (93%) patients underwent limb salvage surgical resection, one of them had positive surgical margins. Nine (64.3%) patients had > 90 % tumor necrosis with 2 (14.3%) patients have a pathological complete response, table 2.

	Total number (n=14)
Median age at diagnosis	36.5 (17–59)
Sex	
Male	9 (64.3%)
Female	5 (35.7%)
Site	
Lower Extremity	9 (64.3%)
Upper extremity	5 (35.7%)
Histopathology	
Pleomorphic sarcoma	5(35.7%)
Synovial Sarcoma	3(21.4%)
Liposarcoma	3(21.4%)
Fibrosarcoma	2(14.3%)
Clear cell sarcoma	1(7.2%)
Median tumor size in cm	
Width (w)	6.3 (5–12)
Height (h	7.6 (5.2–17)
Depth(d)	11.5 (8–26)

Table_1 patients and tumor characteristics

	Total number (n=14)
Clinical response	
Complete response (CR)	11(78.5%)
Partial response (PR)	2(14.3%)
Progressive disease (PD)	1(7.2%)
Type of surgery	
Limb salvage surgery	13(93%)
Amputation	1 (7%)
Margin status	
Negative	13(93%)
Positive	1(7%)
Pathological Tumor necrosis	
> 90 %	9(64.3%)
<90	5(35.7%)
Progression	
Yes	3(21.5%)
No	11(78.5%)
Site of progression	
Distant	3 (100%)

Table_2 clinical, pathological response and type of surgical management

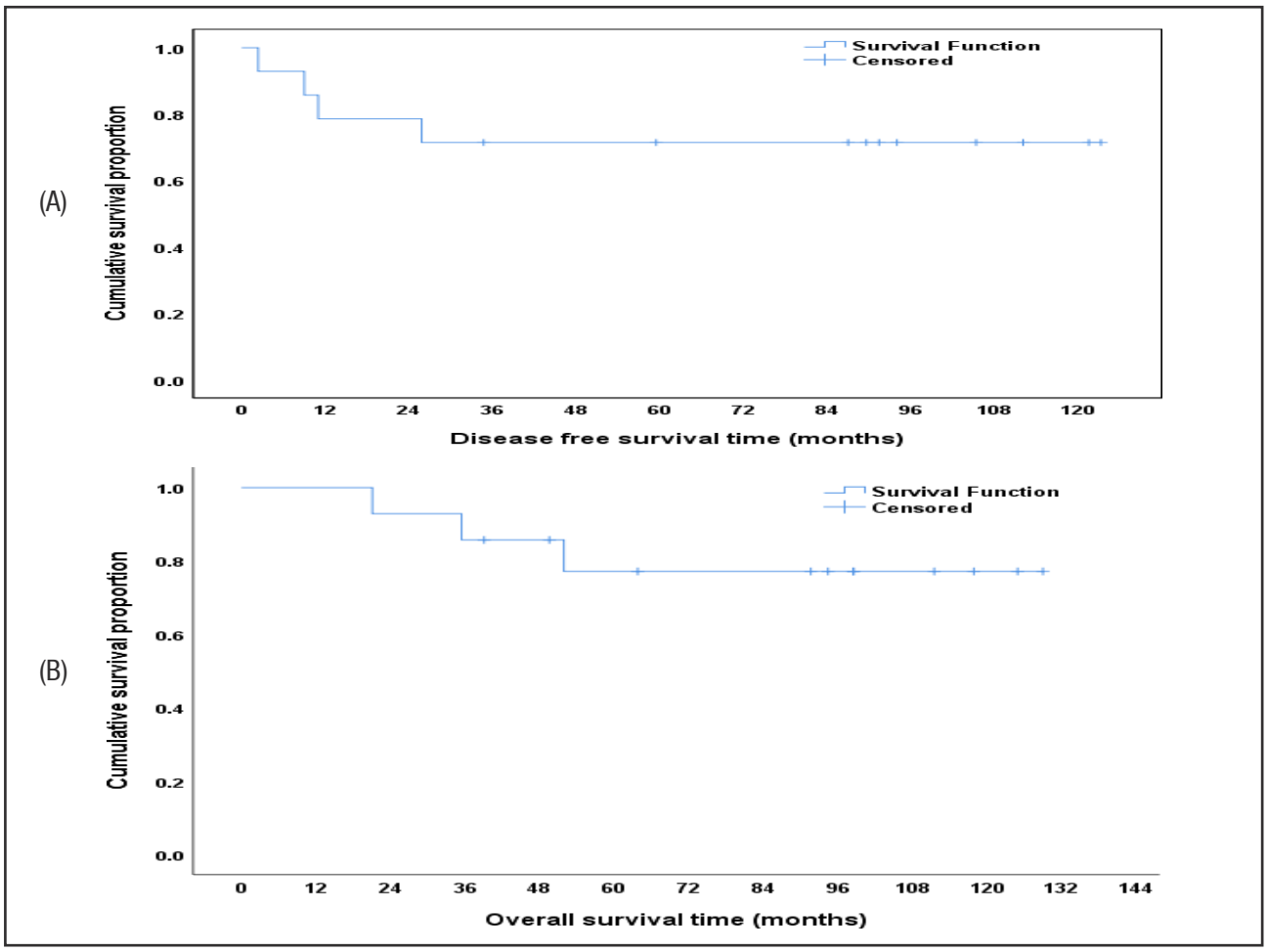


Figure_ 3: (A) DFS curve for whole study group, (B) OS for the whole study group

Thirteen patients (93%) were subjected to analysis, at a median follow up of 37 months, 3 patients (23%) lost their follow up with no evidence of local recurrence or distant metastasis at last follow up visit. At a 5 years follow up (median follow up 60 months), 3 (23%) patients had distant metastasis and died. At 10 years follow up (median follow up 92 months). 7 (53.8%) patients are alive with no evidence of local recurrence or distant metastasis. The DFS at 2, 5 and 10 years were 78.6%, 71.4% and 71.4% respectively, The OS at 2, 5 and 10 years were 93.3%, 77.1% and 77.1% respectively, figure 3.

Only one (7.1%) patient developed Grade 3 acute skin toxicity requiring treatment interruptions, the other seen adverse effects were only grade 1 and 2, the details of the adverse events were detailed in table 3.

Discussion

One of the advantages of using SFGRT in treatment of extremity STS is that the dose distribution from it mimics that obtained with interstitial brachytherapy, especially with modern high dose rate (HDR) units [19].

Clinical experience with open field radiation indicates that such doses (> 1500 cGy) would not only produce significant acute morbidity but also substantial late toxicity, however, the SFGRT doses of > 1500 cGy have been utilized in conjunction with definitive doses of conventionally fractionated radiation and chemotherapy without adding to the morbidity or detracting from tolerance of the normal tissues [20].

The potential radiobiological advantage of the SFGRT goes beyond the protection of normal tissue damage and lie in its ability to significantly eradicate a large volume of tumor cells prior to initiation of conventionally fractionated radiation therapy. At a single does fraction of 1800 cGy through the open field core regions of the grid, several logs of tumor cells both oxygenated and hypoxic are likely to be killed [20].

Mohiuddin et al [21] had earlier published the results of 61 patients who received a total of 72 treatments delivered with megavoltage SFGRT radiotherapy. Twenty–four cases in the pelvis, 22 cases in the abdomen, 13 cases in the extremities, 9 cases in the thorax, and 4 cases in the head and neck were treated. The SFGRT doses ranged from 10 to 25 Gy in a single fraction combined with conventional

Toxicity	Number of patients (n=14)
Acute	
1) Nausea/vomiting	7(50%)
Grade 1	5(71.4%)
Grade 2	2(28.6 %)
2) Diarrhea	1(7.2%)
Grade 1	1(100%)
3) Skin toxicity	12(85.7%)
Grade 1	5(41.7%)
Grade 2	6(50%)
Grade 3	1(8.3%)
4) Cystitis	1(7.2%)
Grade 1	1(100%)
5) Pain at site of tumor	9(64.3%)
Grade 1	4 (44.4%)
Grade 2	5 (55.6%)
6) Edema at site of tumor	3(21.4%)
Grade 1	2(66.6%)
Grade 2	1(33.4%)
Late	
1) Joint stiffness	1(7.2%)
Grade 1	1(100%)
2) Lymphedema	2(14.3%)
Grade 1	1(50%)
Grade 2	1(50%)
3) Wound healing impairment	4(28.6%)
Grade 1	3(75%)
Grade 2	1(25%)

Table_3 detailed acute and late toxicity with grades.

fractionated external beam radiotherapy of dose of 8 to 78 Gy. Dramatic relief was obtained in 91% of patients with 27 patients showed complete relief of symptoms. This included 31 patients treated primarily for symptoms due to massive bulk (>10 cm) of the tumors. Six of 31 (19%) achieved a complete response and 22 of 31 (71%) obtained a partial response. Overall palliative response was achieved in 100%, (6 of 6) patients given a dose 15 Gy or greater.

Overall response appeared independent of whether a SFGRT treatment was utilized exclusively or if it was combined with external beam radiotherapy (82% vs. 92%). However the complete response was greater for patients treated in combination with an external beam radiation dose of 40 Gy or greater (36% vs. 20%).A surprising feature of the responses was that the complete response was higher in tumors thought to be radio resistant. Eight of 18 patients with soft tissue sarcomas showed a complete response (44%) and 3 of 6 melanomas (50%) showed a complete response rate as compared to 4 of 13 squamous cell carcinomas (30.8%) and 2 of 35 adenocarcinomas (5.7%).

One of the important prognostic factors in STS management is the tumor necrosis percentage post neo adjuvant treatment, a meta–analysis done by salah et al [22] which concluded that tumor necrosis <90% following neo adjuvant therapy is associated with increased recurrence risk and inferior OS in patients with STS.

The clinical response to radiation therapy alone as neo adjuvant management in extremity high grade and bulky STS is poor as evident by data from McGill University [23] where 50 patients with STS were evaluated with pre and post radiation MRI (23.5 days following 50 Gy in 5 weeks preoperative radiation). The median regression of high–grade STS was 0.5% and 13.5% in low grade STS when myxoid liposarcoma is excluded indicating the radio–resistant nature of bulky high–grade tumors.

The clinical response was also correlated with the degree of tumor necrosis in the resected specimen. High grade tumors showed a median tumor necrosis of 50% in comparison to 67.5% in low grade tumors, however this dropped to 10% when myxoid liposarcoma was excluded. 25% of patients had positive surgical margin, in comparison to our study results, where 11 (78.5%) patients had clinically complete response to treatment and 13 (93%) patients underwent limb salvage surgical resection, one of them (7.7%) had positive surgical margins. The median tumor necrosis is 90% even after exclusion of myxoid liposarcoma cases with nine (65%) patients had > 90 % tumor necrosis which was dropped to (57.1%) after exclusion of myxoid liposarcoma cases.

The good Tumor necrosis >90% rate (65%) with PCR rate of 14.8% in our study may explain the good local control in our patients cohort with no patients developed local recurrence, with a local control rate of 100% at 10 years which is higher than reported in other trials using conventional neo adjuvant CCRT in management of STS. In a phase II study conducted by Kraybill et al [24] where they include 66 patients with high–grade soft tissue sarcoma > or = 8 cm in diameter of the extremities and body wall, patients received three cycles of neo adjuvant chemotherapy (CT; modified mesna, doxorubicin, ifosfamide, and dacarbazine [MAID]), interdigitated

preoperative radiation therapy (RT; 44 Gy administered in split courses) , and three cycles of postoperative CT (modified MAID), the 3–year rate for local– regional failure is 17.6%. Another study conducted by Wang et al [25], 64 patients with STS received neo adjuvant CCRT Five–year local failure rate was 0% in patients with PCR only while it was 11.7% (95% CI, 3.6%–25.1%) for patients with less than PCR. The third study was conducted by Chawdhari et al [26] where adults with large (≥5 cm; median, 12.9 cm), grade 3 extremity STS who were treated with neo adjuvant chemo radiotherapy consisted of 3 cycles of mesna, doxorubicin, and ifosfamide (MAI) and 44 Gy (22 Gy in 11 fractions between cycles of MAI) after which patients underwent surgical resection and received 3 additional cycles of MAI, the 3 years local relapse rate is 5%. The improved local control rate in our patient cohort in comparison to these studies might be attributed to use of SFGRT, this improvement happened in spite of using single agent iphosphamide concurrent with radiation therapy in our current study in comparison to use of full course of chemotherapy in the previous mentioned studies.

Regarding toxicity profile, we found our used protocol is tolerable, all the included patients completed their treatment course safely apart from only 1 (7.1%) patient who developed Grade 3 acute toxicity requiring treatment interruption with no other recorded G3 or G4 acute or late toxicity in comparison to the study conducted by Kraybill et al [24] where, three patients (5%) experienced fatal grade 5 toxicities (myelodysplasias, two patients; infection, one patient). Another 53 patients (83%) experienced grade 4 toxicities; 78% experienced grade 4 hematologic toxicity and 19% experienced grade 4 non–hematologic toxicity. In another study conducted by Chawdhari et al [26], the non–hematologic grade 4 toxicity rate was 7.7%.

The limitations of our study include the small number of patients included and the retrospective nature of the study along with all known disadvantages.

Conclusion

The addition of induction spatially fractionated GRID radiotherapy SFGRT to preoperative chemoradiation therapy in management of bulky advanced extremity STS showed to be an effective way to improve the rate of tumor necrosis and response to chemo radiation therapy resulting in improvement in local control and survival in our STS patients over a long follow up period. Using SFGRT and neoadjuvant CCRT appeared to be safe and should be tested on a larger population with locally advanced extremity STS.

Funding and Conflict of interest

The authors declare no conflict of interest.

No research support or grant had been received.

Ethical approval

This study was reviewed and accepted by Research Ethics Committee (REC) in King Faisal specialized hospital, Riyadh, Saudi Arabia, with related project RAC No 2121088.

Informed consent of patients is taken and CRF for all patient details are kept with the corresponding author.

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