INTERSTITIAL BRACHYTHERAPY IN SOFT TISSUE SARCOMA- A SINGLE INSTITUTE EXPERIENCE

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ABSTRACT

BACKGROUND

The objective of our study is to assess the local control of the disease, locoregional failure and complications following usage of interstitial HDR Brachytherapy alone or in combination with external beam radiation therapy in truncal or extremity soft tissue sarcomas.

MATERIALS AND METHODS

From January 2014 to January 2017, a retrospective cohort analysis was conducted in our institute with 18 patients who were suffering from truncal and extremity soft tissue sarcoma. They were managed with peri-operative (n=14) or post-operative (n=4) brachytherapy (BT) to a total dose of 35- 48 Gy at 3.5 to 4 Gy per fraction twice a day through an interfraction interval of 6 hours for a period of 5-6 days in *Radical ISBT alone arm* and five days after resection at a dose of 18 to 21 Gy as upfront boost at 3 to 3.5 Gy twice a day for 3-4 days using high dose rate brachytherapy (HDR) along with an external beam radiation dose of 46- 50 Gy which was given to the tumour bed after two to three weeks of Brachytherapy in *Radical RT followed by ISBT arm*. Statistical analysis of the results of this study was done using Kaplan Meier survival analysis and log rank test (p value=0.02). Median overall survival and survival among different stage groups studied were compared by using same statistical survival analysis.

RESULTS

Patients had a median follow up period of 24 months. The median age was 42 years (9-75 years) with male to female ratio of 1.6:1. One out of 18 patients developed local recurrence and another had a recurrence in the lung. The local control rate for two years was 88% and overall survival for 1 year was 100%. The overall survival (In months) among the patients in stage wise distribution were 25.33 ± 15.04, 15 ± 12.99 and 16.16 ± 6.79 for stages I, II and III respectively. The incidence of complications was minimal in our study. We encountered 4-cases (22%) of grade II toxicity in the form of subcutaneous fibrosis and cutaneous atrophy over the treated site. There was one case (5.5%) of grade IV toxicity in the form of wound dehiscence.

CONCLUSION

Surgical resection followed by HDR BT is associated with excellent early local tumour control. Optimal multidisciplinary management could improve survival.

KEY WORDS

Soft Tissue Sarcoma, Brachytherapy, High Dose Rate, External Beam Radiotherapy.

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BACKGROUND

Soft tissue sarcoma is a group of solid tumours arising in the mesenchymal support tissue. Although surgical excision remains the main modality of treatment for extremity soft tissue sarcomas local recurrence following surgery ranges from 20-30% following amputation whereas 65% following wide local excision.[1]

Introduction of Post-operative classical external beam 3D conformal radiotherapy along with surgery to the tumour with a physical dose of 46-50 Gy in 4 to 5 weeks results in favourable 95% local control rate. Also the amputation rate falls to less than 10% in extremity soft tissue sarcomas.[2,3] Currently combination chemotherapy is being used in most soft tissue sarcoma management protocols.[4]

In Extremity soft tissue sarcomas, the Introduction of peri-operative HDR Brachytherapy with Implant doses of 1800 to 2100 cGy combined with 4500 to 5000 cGy of external beam irradiation has emerged as an innovative modality with less early and delayed RT related complications in the management of extremity soft-tissue tumours with high risk features.[5] Because of this approach not only the treatment duration is shortened but also there is relative sparing of overlying skin and surrounding normal tissues. In our study we used brachytherapy primarily as a boost to the immediate tumour or surgical bed and to use the external beam radiation to treat the tumour bed and additional normal tissue margin.

Objective

The Objective of our study is to assess the local control, locoregional failure and complications following usage of

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interstitial HDR Brachytherapy in extremity soft tissue sarcomas.

Study Design
Retrospective Cohort Study

MATERIALS AND METHODS
From Jan 2014 to Jan 2017, we retrospectively collected and analysed the data regarding the clinical, radiological (CT/MRI/PET CT), operative records, post-operative histopathological records, toxicity profile and follow up details of 18 patients of extremity soft tissue sarcomas treated with peri-operative HDR Brachytherapy from our institution.

1. Patients treated with Wide resection of the primary tumour with adequate margins all around the primary tumour with surgical bed radio opaque clips placed in all 6 directions and frozen proved negative margins.
2. The entire tumour with two cms margin was added in the clinical tumour volume (CTV).
3. The planning target volume (PTV) used were 5 cms axially along tissue planes and 2 cms radially along the tissue planes which was contoured on CT images.
4. A maximum dose of 34-48 Gy delivered at 3.4-4 Gy per fraction with >6 hour inter fraction interval between the treatments. The desired dose was delivered twice a day for 5-6 days in ISBT alone arm and 18-21 Gy delivered at 3- 3.5 Gy per fraction in 6-7 days in radical RT + boost ISBT arm.
5. The same dose was prescribed to >90% of PTV.

Patients treated with following features were also included
Adjuvant radical BT (without EBRT) was delivered to small (≤ T2), superficial tumours, intermediate/high grade with complete resection. In other cases, EBRT was given. For radical ISBT, the delivered dose EQD2 was around 60 Gy and For BT boost dose EQD2 was around 18-21 Gy. The dose was given using Microselectron 18 Channel HDR Brachytherapy Machine (V3 Model of Elekta, Veenendaal, The Netherlands).

6.46 to 50 Gy of External radiotherapy delivered using a 1.25 MV Cobalt/ 6MV Linear accelerator to the planning tumour volume plus 3 cms. margin were included in our study. The results were analysed in terms of survival and failure and all the major and minor toxicities were recorded.

Treatment Planning
Before surgery and immediately after postoperative recovery period, the patients were simulated using 3-dimensional CT images obtained with 5 mm cuts from the Somatom Definition AS 20 Open model of CT simulator (Somatom, Siemens, Germany). The images then reconstructed in 3-dimensions with Oncentra TPS 4.3 version (Elekta, Veenendaal, The Netherlands). The plans were analysed using the Oncentra Treatment Planning System. The basal dose rate, high dose volume encompassing 150% isodose diameter around source, hot spot and cold spot were evaluated. Maximal skin dose was limited to less than 80% of the prescription dose. CTV D90 (defined as the minimum dose covering 90% of the CTV volumes), CTV V100%, V300% (defined as percentage volumes of CTV receiving 100% and 300% of prescription doses, respectively), and respective OAR doses were taken into account for dose evaluation. We calculated EQD2 (defined as equivalent dose in 2 Gy/fraction) for all the treated cases. For OAR, we followed the standard dose guidelines.

Follow Up
Patients were examined 3 monthly in first 1 year and 6 months thereafter. Patients then underwent clinical evaluation. CT Chest was done once in 6 months. MRI with or without contrast (or CECT) of the local site (every 6 months for 2 years, then annually) were completed for suspicious cases. The recurrences if any were documented during the follow up period.

Toxicity Assessment
Toxicities were analysed and late toxicities were measured using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical Analysis
Statistical analysis was done using Kaplan Meier survival analysis and log rank test (p value=0.02). Median overall survival and survival among different stage groups studied were compared by using Kaplan Meier survival analysis. Kaplan-Meier survival (KMS) plots were used to estimate overall survival (OS), disease-free survival (DFS). Cox regression analysis was used to estimate of influence of individual factors on survival plots.

RESULTS
With median follow up of 24 months, the median age was 43 years (9-75 years). Of total 18 studied population, 61.1% were male and 38.9% were female. 88.9% of total study population were adults. 16.6%, 38.8% and 33.3% of patients had stage 1, 2 and 3 diseases at the time of presentation respectively. Nearly 84% of patients had grade 2 and 3 diseases. Among the studied population the most prevalent site of Extremity soft tissue sarcoma was in upper limb (55.5%). 5 patients were presented with recurrent diseases. 61.1% of patients were treated with combination of EBRT and Brachytherapy and rest of the patients (39.9%) were treated with only brachytherapy. The clinical characteristics of the patients were show in table 1.

Baseline Profile	N (%)
Median Age	42 years (9-75)
Sex	
Male	11(61.1)
Female	7 (38.9)
Adults	16 (88.9)
Paediatrics	2 (11.11)
Stage	
I	3 (16.6)
II	9 (50.0)
III	6 (33.3)
Grade	
I	3 (16.6)
II	6 (33.3)
III	9 (50.0)
Site	
Lower Limb	5 (27.7)
Trunk	3 (16.6)
Upper Limb	10 (55.5)
Primary Tumour	13 (72.2)
Recurrent	5 (27.7)
Type of Radiation Therapy	
ISBT Alone	7 (38.9)
EBRT + ISBT	11 (61.1)
Neoadjuvant Chemo Therapy	
No	17 (94.4)
Yes	1 (5.6)
Adjuvant Chemo Therapy	
No	15 (83.3)
Yes	3 (16.6)

Table 1. Patients Clinical Characteristics

The histopathological reports revealed all patients were resected with Negative Margin status. The distribution of different histopathological subtypes is depicted in table 2.

Histological Sub Types	(N) (%)
Malignant Fibrous Histiocytoma	(3) (16.6%)
Pleomorphic Spindle Cell Sarcoma	(1) (5.5%)
Undifferentiated Sarcoma	(1) (5.5%)
Recurrent Malignant Fibrosis Histiocytoma	(1) (5.5%)
Pleomorphic Leiomyosarcoma	(1) (5.5%)
Aggressive Fibromatosis	(4) (22.2%)
Synovial Sarcoma	(1) (5.5%)
Recurrent Fibromatosis	(2) (11.1%)
Myxoid Fibrosarcoma	(3) (16.6%)
Round Cell Liposarcoma	(1) (5.5%)

Table 2. Histological Sub Types

The type of dosimetric analysis used in the study were depicted in table 3.

ISBT/ Dosimetry Type	Parameters	Median (Range)	Mean ± Standard Deviation	EQD2** α/β = 10 ± EBRT, Median (GY)
CTV Dosimetry#				
Radical ISBT*	D90##	4Gy (3.5-4)	4.1 ± 0.5 Gy	60.7 (33.4-67.4)
	V100^	92.7% (90.50-94.88)	92.70 ± 2.33%	-
	V300^	6.3% (4.11 – 7.73)	6.11 ± 1.49%	
Boost ISBT	D90	3.57Gy (3.5-4.0)	3.68 ± 0.15 Gy	73.6 (68.6-78.6)
	V100	90.9% (85-96.8)	89.8±2.4%	-
	V300	6.39% (4.45-8.33)	5.7 ± 1.84%	-
Skin Dosimetry	D10cc+	2.8 Gy (1-8.4)	5.9 ± 1.5 Gy	-
	V100	17.8% (0-74.4)	22.9 ± 10.5%	-

Table 3. Dosimetric Analysis

*ISBT – interstitial brachytherapy; **EQD2 α/β =10 – equivalent dose in 2Gy/fraction; #CTV – clinical target volume; ##D90 – defined as the minimum dose covering 90% of the CTV volumes; ^ V100%, V300% - defined as percentage volumes of CTV receiving 100% and 300% of prescription doses, respectively; + D10cc dose – defined as maximum dose received by minimum 10cc volumes of skin.

Of 18 patients analysed, excellent local control was seen in almost all patients. The overall local control rate was 88%. Of 18 patients analysed, only one patient had local recurrence (5.6%) in the left upper limb which was a case of malignant fibrous histiocytoma and it was treated by second brachytherapy. Another patient had distant failure as metastases in the lung (5.6%) which was managed with chemotherapy. We came across four cases (22%) of grade II toxicity in the form of subcutaneous fibrosis and skin atrophy over brachytherapy site. There was one case (5.5%) of grade IV toxicity which was in the form of wound dehiscence. In our study we found the 2-year overall survival rate was 100 %.

Median Follow up	24 months (6-42)
Progression	1 (5.5%)
Local recurrence	1 (5.5%)
Lung Metastasis	1 (5.5%)
Liver Metastasis	nil
Over all RR (2 yr)	100% (BT boost: 85.7%/ radical BT: 100%)
Local control (2 yr)	88% (BT boost: 90.5%/ radical BT: 83.2%)
Survival (months) Stage I Stage II Stage III	Mean ± SE (95% Cl) 25.33 ± 15.04 15 ± 12.99 16.16 ± 6.79

Table 4. Outcome (survival) Analysis

The overall survival (in months) among the patients in stage wise distribution were 25.33 ± 15.04, 15 ± 12.99 and 16.16 ± 6.79 for stages I, II and III respectively which was shown in Fig.1 and disease-free survival in Fig. 2

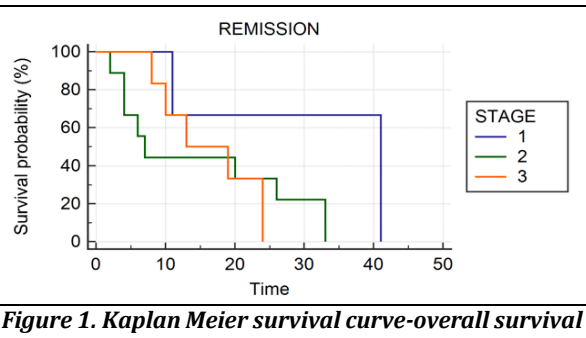

Figure 1. Kaplan Meier survival curve-overall survival with respect to the stage

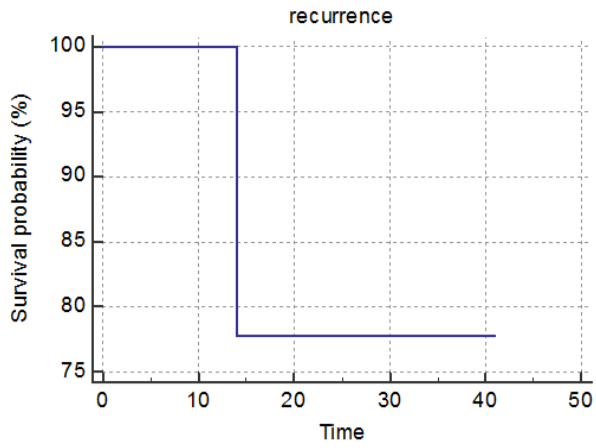

Figure 2: Kaplan meier survival curve-disease free survival

Survival time	month
Endpoint	recurrence

Cases Summary

Number of events [a]		Number censored [b]		
N	%	N	%	Total Sample Size
2	11.11	16	88.89	18
[a]recurrence = 1 [b]recurrence = 0				

Mean and Median Survival

Mean	SE	95% CI for the Mean	Median	95% CI for the Median
35.000	3.742	27.666 to 42.334	-	-

On Cox regression analysis, stage of the disease and Total EQD2 dose were significant factors for Disease free survival.

DISCUSSION

The role of radiation in the management of soft tissue sarcomas has been already documented in many studies. Yang et al.[6] randomly compared the soft tissue sarcoma patients managed with limb salvage surgery without radiotherapy to with adjuvant EBRT. The study reported that addition of adjuvant EBRT has improved the local control rate with only one local recurrence among 710 studied patients during median follow up period of 9.6 years. But addition of adjuvant EBRT did not significantly improved the overall survival rate. From this study we can realise the importance of addition of post-operative EBRT in management of extremity soft tissue sarcomas.

A small subset of patients treated with adjuvant HDR brachytherapy resulted in similar conclusions to our study.[7-10] A prospective study of adjuvant HDR brachytherapy alone in children reported high local control.[11]

A study similar to our study was conducted by Chun et al.[12] and it reported that the patients with STS had a median follow up period of 31 months. In this study, out of 17 patients with extremity soft tissue sarcomas by using HDR ISBRT no patient had local failure. One patient had wound dehiscence, and another had delayed wound healing. Pister et al[13] randomized 164 patients with STS who had postoperative brachytherapy versus no brachytherapy. The median follow-up was 76 months with 5-year actuarial survival and local control rate of 82% versus 69%. In our study we came across only one local recurrence following radiotherapy. This was treated with second brachytherapy. The another had distant metastasis in the lung which was treated by chemotherapy.

In viani's series of paediatric patients, they observed 4-cases of wound dehiscence, erythema, telangiectasia and fibrosis.[14] Similar to our study results, Grade 3 or greater wound complications can probably be decreased using meticulous treatment planning to decrease the tissue volume encompassed by the 150% isodose line.[15]

Unlike a study reported by Cynthia L. Emory MD et al.[16] Our study reports showed that least number of complications following HDR brachytherapy in post-operative setting. ISBT using 192Ir sources (± EBRT) as adjunct to radical surgery improves Local control in STS. ISBT catheters can be directly placed over respected tumor bed during surgery for delivering high-dose to subclinical microscopic disease. The

low statistical significance in our study is because of small sample size and lack of homogeneity of radical/boost ISBT approach.

CONCLUSION

Perioperative brachytherapy is a way of delivering conformal radiation to high risk tumour bed. No treatment related loss of life or limb was observed in our study. Four patients had moderately severe fibrosis. Excellent local control and DFS have been observed in ISBT ± EBRT. Stage of the disease and total dose in terms of EQD2 are the two major factors influencing outcome.

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