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A Clinicopathological Correlation of Pre - Operative Radiotherapy in Soft Tissue Sarcoma.

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Abstract: *The purpose of this study to evaluate the radiological and pathological response to neo-adjuvant radiotherapy in soft tissue sarcoma.Total 30 patients of soft tissue sarcoma of extremities were treated with neo-adjuvant radiotherapy followed by definitive surgery. All patients had MRI imaging pre and post radiotherapy. Radiological tumor response was assessed by volume changes on axial T1 gadolinium enhanced MRI. Pathological tumor response was assessed in terms of percentage area of necrosis in resected specimen. Radioghraphically, 73% patients demonstrated decrease in tumor volume while 24% of patient showed an increase in the tumor volume compared to the pre-radiotherapy values. The median change in tumor volume was 36%(range, -272 to 70%). The median pathologic percentage tumor necrosis was 70%(range, 0-92%). 20% of patients showed > 90% of necrosis and associated with favorable oncogenic outcome, although these association was not statistically significant. Soft-tissue sarcomas show significant pathological treatment responses in the form of hyaline fibrosis, necrosis and granulation tissue. Despite this, there is minimal early volumetric response to radiation. Although radiological partial response was predictive of pathological response, the significance of radiological progression was unclear. Myxoid and other liposarcoma tumor type were predictive of both pathological and radiological tumor response.*

Keywords: *Liposarcoma, Neoadjuvant Radiotherapy, Pathological Response, Soft tissue Sarcoma, Volumetric Response.*

I. Introduction

Soft tissue sarcomas are rare malignancies that arise from the connective tissues in any organ or at any anatomic location of the body. They represent a heterogeneous group with a wide spectrum in terms of histology and prognosis. The median age of diagnosis is 65 years. Incidence for most sarcomas increases with age from approximately 1 to 2 per 100,000 at the age of 15 years to approximately 6 per 100,000 at age of 49 years, and to as high as approximately 20 per 100,000 at age of 80 years [1]. Men are more frequently affected than women, and rates are higher among African, Americans than whites. Most sarcomas arise in a sporadic fashion, without identifiable aetiology. Associated factors can be identified in certain subsets of sarcomas, including predisposing genetic mutations, previous ionizing radiation or chemical exposures, and chronic soft tissue injury or lymphoedema.

The majority of them occur in the muscle groups of the extremities. These tumours often remain confined to the muscle comjpartment of origin. The thigh is the most common subsite of origin. 41% are located in the extremities, with 29% of all lesions occurring in the lower limb, 36% are intra-abdominal, divided between visceral (21%) and retroperitoneal (15%) lesions; 10% are truncal; and 5% are located in the head and neck region.

The WHO has defined approximately 50 tumour subtypes relevant to soft-tissue sarcomas; these are named largely according to the tissue they most closely resemble. The three most frequent histological variants are malignant fibrous histiocytoma, liposarcoma, and leiomyosarcoma[2]. Several grading scales and systems have been used for STS: a four-grade system (Broders)[3], a three grade system (low, intermediate, high) such as the National Cancer Institute (NCI)[4] grading system and that of the French Federation of Cancer Centres Sarcoma Group[5], and a binary system (high vs. low)[6]. All these grading systems have proven to correlate with overall survival and disease-free survival.

The local management of soft tissue sarcoma (STS) comprising of limb sparing surgical resection along with radiotherapy (RT) has resulted in disease control rates equivalent to amputation alone [7]. This strategy avoids radical surgery whilst maintaining good local control and without an adverse impact on overall survival (OS).There is a retrospective analysis of preoperative versus postoperative radiotherapy in Soft-Tissue Sarcoma of 821 patients published in 2010 which showed the use of pre-operative RT was associated with decreased all-cause and cancer specific mortality compared with post-operative RT. Pre-operative therapy was also associated with improved local tumor control, which may explain the association with decreased distant relapse. In addition to known prognostic factors such as stage and grade, RT sequence was identified as an independent predictor of disease outcome[8]. In a study by Roberge[9], the authors reported on radiological and pathological response to pre-operative radiotherapy for extremity and trunk soft-tissue sarcomas. They concluded that Soft-

tissue sarcomas show significant pathological treatment responses in the form of hyaline fibrosis, necrosis and granulation tissue. Despite this, there is minimal early volumetric response to radiation, especially for high-grade tumors. Although radiological partial response has been found to be predictive of pathological response, the significance of radiological progression is unclear.

In a study by Canter et al. [10] the investigators evaluated the significance of histo-pathological responses after pre-operative radiation therapy as a surrogate marker for disease outcome in STS. They reported that pathological response could be a meaningful marker for disease outcome.

The present study designed to evaluate the clinico-pathological co-relation between radiological response and histopathological response of soft tissue sarcoma after pre-operative radiotherapy.

II. Material And Methods

Suitable patients with a primary non-metastatic soft-tissue sarcoma of the extremities planned to be treated with pre-operative radiotherapy followed by surgical resection were included in study.Study entry criterias were patients with non-metastatic soft tissue sarcoma planned for pre-operative radiotherapy, histopathologically confirmed soft tissue sarcoma with subtype, no history of prior chemotherapy, no history of prior radiotherapy to the primary site.The patients with metastatic disease ,unconfirmed histopathology of STS, prior history of systemic therapy, prior history of radiotherapy to primary site were excluded.

Patients accrued into the study underwent a pre-treatment MRI scan of the primary site for documentation of the pre-treatment radiological tumour characteristics. Post-treatment MRI scans for assessment of post-treatment radiological characteristics were done 3 weeks after completion of radiotherapy. Radiological tumour response was assessed by volume changes on axial T1 gadolinium enhanced MRI. For this purpose, MRI images were transferred to a radiotherapy planning station. Contrast enhanced CT images were acquired in treatment position for radiotherapy planning. CT/ MRI image registration & fusion for accurate contouring of the tumour volume was done on the RT planning system. The tumour volume was contoured on all images and three-dimensional volumes were calculated using the treatment planning software. Proportional changes in tumour volumes were calculated by taking the absolute difference in pre-treatment and post-treatment tumour volumes divided by the pre-treatment volume.

Pre-operative external beam radiation therapy was delivered using 3 dimensional conformal radiation therapy (3DCRT)/ Intensity modulated radiation therapy (IMRT)/ or conventional techniques. The clinical target volume (CTV) included the MRI based gross tumour volume (GTV) with a margin of 2cm in the longitudinal axis & 1.5cm in the radial axis. Modifications in the CTV allowed for areas in close proximity to vital structures/ bone, at the discretion of the treating physician. The planning target volume (PTV) margin was an additional 0.7cm beyond the CTV. All patients received a dose of 50Gy/ 25 fractions/ 5 weeks @2Gy per fraction. Wide local excision was done 4–6 weeks following completion of radiotherapy. Pre-treatment core needle biopsies and post-treatment tumour specimens were reviewed by pathologists. Tumour specimens after surgical resection were processed and evaluated in a standardised manner. The tumour specimen was preserved in formalin. The surgical margins were inked and the tumours were serially sectioned. Gross estimation of percent necrosis was recorded, and multiple sections were taken from the solid areas and the surgical margins. The tumour was sampled with an average of one section per centimetre of the tumour's greatest dimension. Apart from the percentage necrosis, other standard parameters like tumour dimension& surgical margins were also documented.

Three major architectural patterns reported in the resected specimens: (a) viable tumour (b) necrotic tumour, and (c) fibrotic or hyalinised stroma. The histological changes considered to represent treatment response included absence of tumour cells in combination with one or more of the following findings: stromal fibrosis, fibrohistiocytic reaction, chronic inflammatory infiltrate in a sclero-hyalinized background, hemosiderin laden macrophages, fibromyxoidstroma and cystic change. Necrotic tumour was defined by the presence of coagulative necrosis admixed with karyorrhectic nuclear debris and surrounded by viable tumour cells. The tumour was systematically evaluated following a semiquantitative grading system of response in soft-tissue sarcoma. In each case the percent areas of viable tumour with or without necrosis with percent areas of treatment- induced fibrosis was documented such that the sum of these two components is equal to 100%. A percentage of each component was assigned to each slide so that the overall percentage provided in the report represented the integration of all slides.

III. Results And Discussion

Of the 30 patients studied in this series, 19 (63%) patients were males and 11 (37%) were females. The sites involved were thigh, knee and elbow. The patients in this study were of various histologies. Synovial sarcoma (33%), pleomorphic sarcoma (33%), liposarcoma myxoid & other (26%), leiomyosarcoma (3%) and sarcoma –not otherwise specified(3%).

After pre-operative radiation therapy 73% patients demonstrated decrease in tumor volume while 24% of patient showed an increase in the tumor volume compared to the pre-radiotherapy values. The mean decrease in tumor volumes was 729.96cm^3 (range 162 - 5915.04cm^3) while the increase in volume was 1303.06cm^3 (range 385.56 - 5000.68cm^3).

The radiological tumor response after pre-operative radiation was evaluated by comparing the pre-radiation and post-radiation tumor volumes and was expressed in the form of proportional volume change.

The Proportional Volume Change (PVC) of each patient was calculated using the following formula:

$$PVC = \frac{\text{(Pre-radiation tumor volume)} - \text{(Post-radiation tumor volume)}}{\text{(Pre-radiation tumor volume)}}$$

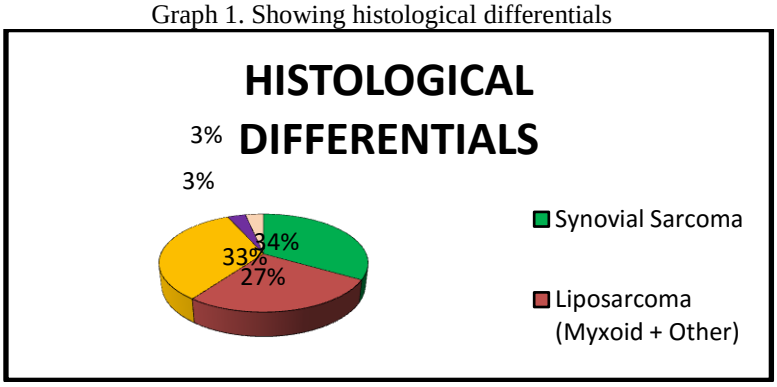
The partial tumour volume response ($\geq$ 50% reduction in tumour volume) was seen in 43% of study cases and <50%reduction was seen in 30% of cases. While total 27% cases showed increase in tumour volume. When we evaluated these patients with various histologies with reference to proportional volume change, we found that out of 33% of synovial sarcoma, 60% cases showed the decrease in tumour volume after pre-operative radiation while 40% showed increase in size. Of the patients with pleomorphic sarcoma, 30% cases showed increased in tumour volume and 70% cases showed decrease in volume. Amongst patients with liposarcoma all patients showed a decrease in tumour volume after radiotherapy. The statistical evaluation between histology and proportional tumour volume change by paired T test showed that the relationship between proportional tumour volume change and type of tumour histology was significantly associated ($p = 0.000$).

The pathological tumour response was assessed and compared based on three major architectural patterns in the resected specimens: (a) viable tumour (b) necrotic tumour, and (c) fibrotic or hyalinised stroma. . The relationship between histological subtypes and percent necrosis was documented. 90% patients showed the some pathological response in the form of necrosis. When compared within various histological subtypes, the mean value of necrosis documented was 68.3% for liposarcomas, 33% for synovial sarcoma and 81.6% for pleomorphic sarcoma. The statistical evaluation between histology and percent necrosis by paired T test showed that the relationship between percent necrosis and type of tumour histology was significantly associated ($p = 0.000$). The comparative analysis of necrosis between the various histopathological subtypes revealed that pleomorphic sarcoma showed the maximum necrotic change (81.6%) while synovial sarcoma showed the least (33%) ($p=0.000$).

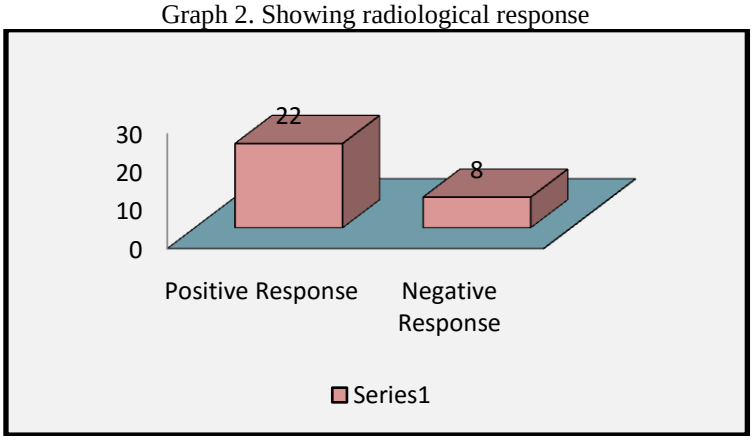
The radiological changes following preoperative radiotherapy (proportional volume change) was compared with the histological parameters (percent area of necrosis) in order to evaluate the clinic-pathological correlation of the radiological & pathological parameters. The statistical evaluation between radiological and pathological response was done by Mann-Whitney U test. For patient with positive radiological response a mean value of percent area of necrosis was 65 (0-91%), while for patient who had negative response a mean value of percent area of necrosis was 70 (50-92%). Suggesting that radiological regression in tumor volume was not a true indicator of tumor necrosis. The changes in tumor volume did not correlate with percentage tumor necrosis ($p=0.32$). Statistical co-relation between radiological (proportional volume change) and pathological response (percent area of necrosis) was evaluated using the Pearson Correlation. It found that the pathological and radiological tumor responses were not correlated as ($p= 0.238$). Suggesting that radiological regression in tumor volume was not a true indicator of tumor necrosis.

IV. Graphs

Graph 1. Showing histological differentials



Graph 2. Showing radiological response



V. Conclusions

In this prospective non randomised study showing radiological and pathological co-relation after giving pre-operative radiation, we came at the following conclusions.

Volumetric response after pre-operative radiation is significantly correlated with histology of tumour. Pathological response in the form of necrosis is also significantly associated with histology of tumour. There is discordance between pathological and radiological response in pre-operative radiation. The volumetric response is not seen in all patients treated with pre-operative radiation. The surrogate marker for outcome in form of overall survival, disease free interval needs to be evaluated by long term follow up.

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