

## Review Article

# Indian data on bone and soft tissue sarcomas: A summary of published study results

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### Abstract

Bone sarcomas are rare tumors, approximating 0.2% of all cancers, with osteosarcoma (OGS), chondrosarcoma, and Ewing sarcoma being the most common cancers in this subset. The formation of disease management groups/clinics focused on sarcomas has resulted in better understanding and management of these uncommon tumors. Multiple large-scale retrospective data from Tata Memorial Hospital (TMH) and All India Institute of Medical Sciences have reported outcomes comparable to Western data in the field of OGS and Ewing sarcoma, with interesting prognostic factors identified for further evaluation. Soft tissue sarcomas are a rare heterogeneous group of tumors, more than 50 different tumor entities. The common subtypes identified in India include Ewing sarcoma and synovial sarcoma. Valuable work regarding brachytherapy has been done by radiation oncologists from the TMH, especially in pediatric patients.

**Key words:** Bone sarcomas, Indian data, soft tissue sarcomas

## Bone Sarcomas

### Background

Primary bone sarcomas are rare tumors, comprising approximately 0.2% of all cancers. Their true incidence is difficult to estimate because of their rarity.<sup>[1]</sup> Osteosarcoma (OGS), chondrosarcoma, and Ewing sarcoma/primitive neuroectodermal tumor (PNET) are the common bone sarcomas, as per Western data, with rare tumors such as fibrosarcomas, chordomas, and undifferentiated pleomorphic sarcoma (UPS) constituting as the remaining subtypes. Bone sarcomas constitute as the third most common cause of mortality in adolescents. Remarkable achievements with multimodality management of these tumors have led to an increase in their 5-year survival rates, from approximately 50% in the year 1970, to the range of 75–80%, presently, in the adolescent age-group.<sup>[2]</sup>

On-going studies in molecular diagnostics have also helped in differentiating this heterogeneous group of tumors. Attempts are being made to identify prognostic and predictive markers for these tumors. Over the last decade, certain centers across the country have formed groups focused toward sarcoma treatment, for example, bone and soft tissue disease management group at the Tata Memorial Hospital (TMH), Mumbai, Maharashtra, India and bone and soft tissue sarcoma (STS) joint clinic

at the All India Institute of Medical Sciences (AIIMS), New Delhi, India which has resulted in better understanding and management of these uncommon, but diagnostically, as well as therapeutically challenging tumors, eventually leading to treatment benefit for such patients. Through this summary, we have attempted to capture data from various centers across India, on various aspects of bone sarcomas, with a major focus on OGS and Ewing sarcoma.

### Demographics and distribution

Various hospital-based registries have attempted to gauge the incidence and distribution of sarcomas in the Indian population; however, there is no recent, population-based evaluation of the incidence of bone sarcomas in India. In as early as 1998, Yeole and Jussawalla published the incidence of bone malignancy in Mumbai, based on the data from the Bombay Cancer Registry. As per that registry, bone malignancies were found to represent 0.9% of all cancers with Ewing sarcoma as the most common bone malignancy.<sup>[3]</sup> As per hospital-based cancer registry, 2001, TMH, Mumbai, Maharashtra, India OGS was found to be the most common bone sarcoma, followed by Ewing sarcoma/PNET and chondrosarcoma.<sup>[4]</sup> Based on retrospectively collected data over 36 years in Karnataka, Rao *et al.* found that out of the 523 bone tumors, 39% were malignant, with

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OGS and Ewing sarcoma constituting 45.7% and 19.4% of malignant bone tumors, respectively.<sup>[5]</sup> More recent data come from the registry of JSS Medical College and Hospital, Mysore, Karnataka, India where a review of 117 cases over a period of 8 years was conducted, showed that the majority of malignant bone tumors were OGS (35.14%) with a median age of presentation being 26.87 years.<sup>[6]</sup>

### **Osteosarcoma**

The outcomes in OGS experienced a major turnaround with the addition of multiagent chemotherapy to surgery, based on the pioneering work by Rosen *et al.* in the late 70's and early 80's.<sup>[7]</sup> After the initial progress, however, over the last two decades, outcomes have stagnated with 5-year overall survival (OS) of 65–70%, with no major improvement in the subset of cases of metastatic OGS that continue to have poor outcomes. Research in this field is on-going within major cancer centers in India.

### **Diagnostics, prognosis, and management**

Routine diagnosis of an OGS is based on results from a well-exposed radiograph and a biopsy that unravels the histopathological subtype of OGS. Invariably neoadjuvant chemotherapy (NACT) is offered in cases of high-grade OGS, followed by surgical resection. In a study from TMH, including 100 cases of high-grade extremity-based OGS, a significant association between grade of tumor necrosis and clinical outcome was noted.<sup>[8]</sup>

Further, there has been considerable interest in the characterization of OGS cell lines and their response to various therapeutic modalities. Kumar *et al.* carried out *in vitro* cell studies in OGS cell lines MG-63 to evaluate the combined effect of anticancer drug camptothecin (CPT) and (177) Lu-EDTMP, which is a known therapeutic radionuclide. The expression of proteins such as BCL-2, PARP, and mitogen-activated protein kinase that were related to apoptotic signaling pathways was assessed by Western blotting after incubation of the cell lines (MG-63) with both (177) Lu-EDTMP and CPT. Their results indicated that cellular toxicity and apoptosis were relatively higher in MG-63 cells that were treated with CPT before treating with (177) Lu-EDTMP, in comparison with the corresponding individual controls.<sup>[9]</sup>

In terms of prognosis, vascular endothelial growth factor (VEGF) expression in cases of OGS, at the time of biopsy has been shown to have a negative influence on survival. Whether it continues to be expressed and influences outcome in tumors after NACT, has not been determined. In a study, Bajpai *et al.* evaluated VEGF expression in 31 patients and compared VEGF expression at baseline and with grade of tumor. The authors compared pre- and post-NACT VEGF expression with histological necrosis. This study confirmed the preexisting data that positive VEGF expression was concordant with high histological grade (90% concordance). The authors also revealed that postneoadjuvant VEGF expression, as well as VEGF change following NACT significantly, correlated with histological necrosis.<sup>[10]</sup> The same study group also analyzed surrogates of tumor angiogenesis through radiological imaging. In another study, they evaluated tumor angiogenesis by qualitative analysis of dynamic contrast

enhanced-magnetic resonance imaging (DCE-MRI) through the concept of time-intensity curves (TICs). TIC representing low microvascular permeability is the persistent type, while that of high permeability are plateau and washout types. The results in this 31 patients, cohort showed that TIC could correctly identify all 28 VEGF positive samples at baseline and 24/25 (96%) of VEGF positive samples and 5/6 (83%) of VEGF-negative samples after NACT correctly. While VEGF expression was found to correlate with CDE-MRI, the same was not found to correlate with diffusion-weighted-MRI and positron emission tomogram-computed tomography (PET-CT).<sup>[11]</sup>

In a recent study, using MRI and clinical findings as alternate parameters to evaluate response to NACT in patients (12 of 14 patients with OGS), Amit *et al.* observed that both dynamic MRI slope, as well clinical indicators such as change in pain, tumor girth, maximum tumor diameter, and surface temperature correlated with histological response ( $P < 0.01$ ). In another study, the same group also reported on the comparison of DCE-MRI (via slope) and volumetric assessment via static MRI as predictors of histological necrosis postchemotherapy. In that study, more than 60% reduction in slope of curve on DCE-MRI proved to be an indicator of good histological response (positive predictive value = 80%), while change in tumor volume, as measured by static MRI failed to show a significant correlation ( $P = 0.071$ ).<sup>[12,13]</sup>

Like DCE-MRI, PET-CT have also been evaluated by as a noninvasive predictor of response to chemotherapy. In a study of 31 patients, Bajpai *et al.* identified two independent variables in stepwise multivariable analysis as predictive of histological necrosis: in cases V1 (prechemotherapy volume) was  $\leq 300$  mL and SUV2:SUV1 ratio was  $\leq 0.48$ , observed good histologic response proportion was 83%, whereas in cases V1 was more than 300 mL and SUV2:SUV1 ratio exceeded 0.48, the same was 0%.<sup>[14]</sup> While metabolic burden seems to be a sensitive substitute for response evaluation, further validation is required.

A number of studies have been published over the last decade with regards to outcomes in OGS from India. The earliest work in this field came as early as 1993 when Pathak *et al.* published their data on 29 patients with high-grade OGS, who received sequential adriamycin and cisplatin as adjuvant therapy after definitive surgery. The relapse-free survival was 72%, and OS for the entire group was 69%, which was superior to outcomes in historical controls treated with surgery alone.<sup>[15]</sup>

A major controversy that persists in the management of OGS is the role of methotrexate in the treatment of OGS. Most of cancer centers in India offer nonmethotrexate-based chemotherapy regimens in cases of high-grade OGS. The study group from AIIMS recently published their data of 237 patients with an attempt to establish prognostic factors, as well as report outcomes in a cohort of localized OGS patients treated by a uniform protocol. They showed a 5-year event-free survival (EFS) and OS of 36.6% and 50.3% respectively, with baseline factors of symptom duration more than 4 months. They noted that good performance status predicted for better PFS, while good PS and normal serum alkaline phosphatase predicted for better OS, on multivariate analysis.<sup>[16]</sup> The group from AIIMS also evaluated whether a high tumor volume at presentation was a predictor for local recurrence (LR). They

used MRI images to calculate baseline tumor volume. However, in this retrospective analysis, the mean tumor volume in the group without LR was  $406.74 \pm 771.67$  cc, as compared to  $195.77 \pm 226.8$  cc in the group with LR, which was not found to be statistically significant.<sup>[17]</sup>

Recently, at TMH, Mumbai, the study group conducted an analysis of 239 cases of nonmetastatic OGS (unpublished, accepted for and presented at SIOP, 2015) who received an in-house chemotherapy protocol, OGS 2012.<sup>[18]</sup> Essentially, this study included dose-dense chemotherapy with doxorubicin, ifosfamide, and cisplatin in patients enrolled between November 2011 and December 2014 (4 years). The investigators found high rates of nutritional depletion at baseline in patients (Vitamin B12-48%, iron deficiency - 59%, anemia - 17%), besides low albumin levels, as predictive of poor OS. They also observed albumin and age as predictive variables for development of Grades 3 and 4 thrombocytopenia in such cases. Their estimated disease-free survival (DFS) at 2 and 3.5 years was 77% and 70%.<sup>[18]</sup>

While standard chemotherapeutic regimens are fairly well established with the drugs of importance, such as ifosfamide, doxorubicin, cisplatin, methotrexate and to some extent, etoposide, the issue of compliance to such dose dense regimens, especially in Indian patients is a major issue that requires evaluation. In a premier study at TMH, Bajpai *et al.* evaluated 124 patients of OGS, who received NACT and found that there was a significant association between histological response and compliance ( $P = 0.031$ ). However, after a median follow-up of 7.9 months, there was no difference in survival, which was likely because of the short duration of follow-up in their study.<sup>[19]</sup>

Retrospective studies have also been published on rare sites of OGS, including their treatment modalities and outcomes. These studies have been enlisted in Table 1.<sup>[20-22]</sup>

Another significant study regarding follow-up criteria, conducted by the TMH group was the trial for optimal survival of sarcomas study that evaluated differences in survival in more versus less intensive follow-up, as well as the requirement of a CT scan versus simple chest radiograph, for radiological follow-up for detecting pulmonary metastases. In a set of 500 nonmetastatic patients, the authors observed 3-year OS of 64% and 69% in 6- and 3-monthly groups, respectively and 3-year OS of 67% and 66% in chest radiography and CT scan groups, respectively, and, the authors concluded that while less frequent visits detected metastases and LR adequately, it could be conclusively revealed that 6 monthly interval of follow-up was noninferior as against 3 monthly follow-up visits.<sup>[23]</sup>

### Ewing sarcoma family of tumors

#### Diagnostics

Ewing sarcoma family of tumor (EWSFT) includes Ewing sarcoma of the bone, extrasosseous Ewing sarcoma, also referred

to as extraskeletal Ewing sarcoma (tumor growing outside of the bone), PNET, peripheral neuroepithelioma, Askin's tumor (Ewing sarcoma of the chest wall), and atypical Ewing sarcoma.

Ewing sarcoma/PNET is an undifferentiated small blue round cell tumor of bone and soft tissues, predominantly seen in children and young adults characterized by recurrent balanced translocations, involving in almost all cases, *EWSR1* gene on chromosome 22 that leads to formation of fusion oncogenes such as *EWS-FLI* and *EWS-ERG* that play key role in its pathogenesis. This tumor is invariably diagnosed by histopathology with demonstration of positive immunohistochemical staining of antibody markers, such as CD99/MIC2 (diffuse, cytoplasmic membranous pattern of staining) and FLI1 in most cases, along with negative expression of Tdt in all cases. This tumor has a wide clinicopathological spectrum and in cases with equivocal immunohistochemical results and in tumors occurring at unusual locations or in older age group patients, should be ideally confirmed with molecular testing. Rekhi *et al.* from TMH, Mumbai, Maharashtra, India have published the first Indian study on molecular diagnostics of Ewing sarcoma, including validation of *EWSR1* gene rearrangement by fluorescent *in situ* hybridization (FISH) technique in Ewing sarcomas, comparing it with results from polymerase chain reaction (PCR) that is another molecular technique for identifying specific fusion genes. They observed that the FISH technique was more sensitive, as compared to PCR that detects specific chimeric transcripts. At the same time, they noted *EWSR1* rearrangement was also noted in other tumors. Therefore, they suggested that molecular results should be interpreted with clinic pathological, including immunohistochemical profile in all cases of Ewing sarcoma/PNET.<sup>[24]</sup> Furthermore, Indian researchers have contributed to some more interesting insights in the field of molecular biology and diagnostics of EWSFT. In a prospective study, Tilak *et al.* evaluated peripheral blood circulating Tregs in PNET patients (in contrast to bone marrow Tregs) at baseline and during chemotherapy and observed that peripheral blood Tregs are higher in patients than healthy controls. They observed a significant reduction in Tregs with chemotherapy treated cases and their rise at progression. However, there was no significant difference observed in this study in the EFS or OS between the high and low Treg cell groups.<sup>[25]</sup> Jully *et al.* at the Cancer Institute (WIA), Adyar, Chennai further contributed to the characterization of the junction region of this fusion protein by analyzing an *in silico* model of *EWS-FLI* fusion protein for ligand binding sites. Their analysis indicated that junction region (AA 251-343) encompasses potential ligand binding sites in the EWS-FLI1 protein and when expressed in bacteria were present as soluble form. They also observed

**Table 1: Site specific data in osteogenic sarcoma from India**

Author	Site	Number	Outcomes	Remarks
Laskar <i>et al.</i> <sup>[20]</sup>	Head and neck	50	Median OS - 45.7 months Median PFS - 13.7 months	Mandible and maxilla - favorable sites Postoperative RT improved local control with adverse prognostic factors
Puri <i>et al.</i> <sup>[21]</sup>	Pelvis	12	5 years OS - 67%	Prognostic factor - response to chemotherapy
Gulia <i>et al.</i> <sup>[22]</sup>	Periosteal OGS	18	5 years DFS - 77.8% 5 years OS - 83.3%	16 patients received chemotherapy Intramedullary involvement may suggest aggressive biology

OS=Overall survival, RT=Radiotherapy, PFS=Progression-free survival, DFS=Disease-free survival, OGS=Osteosarcoma



ectopically expressing this region in Ewing sarcoma cells inhibited tumorigenicity, and *EWS-FLII* target genes indicating a dominant negative biological effect.<sup>[26]</sup> Cathepsin L is a cysteine protease is involved in bone remodeling and expressed in activated macrophages. It is highly expressed in metastatic tumor tissue, especially with bone metastases. Biswas *et al.* evaluated the immunohistochemical expression of cathepsin L in tumor cells and tumor-associated macrophages (TAMs) in chemo-naïve EWSFT in a set of 62 archived specimens. They found that low (13%) immunohistochemical expression of cathepsin L in their patient cohort and noted that this marker did not influence the outcome. In that study, while cathepsin L expression was found to be associated with poor response to NACT, Grade 3 TAMs with cathepsin L expression was associated with improved EFS.<sup>[27]</sup>

Radiological imaging plays an important role in the diagnosis and assessment of response in EWSFT. Researchers at TMH retrospectively attempted to correlate fluorodeoxyglucose (FDG) uptake in PET scans with tumor behavior as well as evaluated whether PET-CT scan could be used as a noninvasive method to predict response to NACT. They concluded that increased FDG uptake, as measured by mean  $SUV_{max}$ , was indicative of metastatic potential of the tumor, in view of the raised SUV in metastatic versus nonmetastatic patients. They also concluded that there was significant correlation between change in metabolic activity of the primary tumor and histopathological response after NACT suggesting that FDG-PET might be an ideal noninvasive method to assess tumor behavior and response to therapy in EWS.<sup>[28]</sup>

### Prognosis and management

EWSFT are optimally treated by multimodality management group that requires an entire dedicated team consisting of a surgical-, medical-, radiation-oncologist, and pathologist, along with rehabilitative services, orthopedicians, and counselors. While trial data sets the benchmark for treatment modalities, over time, there is a growing sense that real world hospital practice in a logistically constrained setting might put forward different management strategies. There have been several large studies from India that have been published over the last few years, and this has contributed to our understanding of EWSFT.<sup>[29-31]</sup>

In a recent large retrospective analysis conducted at AIIMS, including 224 patients with localized EWSFT, the authors evaluated potential prognostic factors and suggested that patients with combination of ESFT of spine/abdominopelvic region and baseline white blood cell (WBC) count  $>11 \times 10^9/L$  had a significantly inferior OS ( $P < 0.001$ ) and patients with combination of ESFT with symptom duration  $>4$  months, tumor diameter  $>8$  cm, and baseline WBC count  $>11 \times 10^9/L$  had significantly inferior EFS ( $P = 0.002$ ).<sup>[29]</sup> These results are at par with worldwide data which have shown inferior clinical outcomes in such cases with high volume disease ( $>200$  mL) and pelvic primaries; though baseline WBC has not been previously identified as a prognostic indicator. Another study from the same group, in cases of metastatic tumor settings, disclosed hypoalbuminemia as a unique prognostic factor associated with EFS ( $P = 0.003$ ), though age  $\leq 15$  years and radical radiotherapy as local treatment also had a trend toward inferior local control (LC) rates, although the values were statistically not significant.<sup>[30]</sup>

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The study group from AIIMS also published their data regarding prognostic factors and outcomes in extremity EWSFT. In their cohort of 158 patients, while metastases and radiotherapy (vs. surgery as primary local treatment) predicted for poorer outcomes in the entire cohort, radiotherapy was found to be noninferior to surgery in the subset of patients with localized tumors with regard to tumor diameter ( $P = 0.8$ ) or post-NACT response ( $P = 0.1$ ). The 5-year EFS, OS, and LC rates were 24.1%, 43.5%, and 55%, respectively, for the entire cohort and 36.4%, 57.6%, and 58.2% respectively, for patients without loco-regional disease.<sup>[31]</sup>

Multiple groups have published their data regarding outcomes in location specific EWSFT, which offers an understanding of the management modalities and responses in these rare tumors. These are tabulated in Table 2.<sup>[32-38]</sup> From this data, it can be seen that pelvic and spinal EWSFT seem to have poorer outcomes, compared to head and neck, extrasosseous and jaw EWSFTs.

One of the major constraints in resource-limited settings is the cost and availability of prosthesis which is essential in allowing for good functional outcomes. In this direction, there has been significant work with a technique, namely, extracorporeal radiation therapy (ECRT). Puri *et al.* published their results on 32 patients (16 OGS and 16 EWSFT) who underwent this procedure of *en bloc* resection with preservation of the adjoining joints and reconstruction with reimplantation of sterilized tumor bone after extracorporeal radiation (50 Gy). The mean resected length of bone was 19 cm with a mean time to union for all osteotomy sites being 7.3 months. There were three LR, all in soft-tissue away from irradiated graft. At the time of final follow-up, 19 patients were free-of-disease, a single patient was alive with disease, and 11 had died-of-disease. There were three LR, all away from irradiated graft.<sup>[39]</sup>

### Soft Tissue Sarcomas (STS)

Unlike bone sarcomas, STSs constitute a more heterogeneous group of tumors, with more than 50 different tumor entities that make these tumors fairly complex and diagnostically challenging. These tumors account for  $<1\%$  of all adult tumors and 15% of pediatric tumors.<sup>[40]</sup> The most common types identified have been UPS, gastrointestinal stromal tumor (GIST), liposarcoma, leiomyosarcoma, and synovial sarcoma.<sup>[41]</sup> During the past 10 years, immunohistochemistry (IHC) has been a very helpful ancillary technique for exact categorization of the various STSs, namely synovial sarcoma, malignant peripheral nerve sheath tumor (MPNST), epithelioid sarcoma, dermatofibrosarcoma protuberans, to name, but a few. Nearly one-third sarcomas are associated with a specific translocation that has helped in their further accurate diagnosis which directly influences their management. Considering certain sarcomas such as synovial sarcoma and Ewing sarcoma/PNET are relatively more chemosensitive over their mimics such as MPNSTs, their exact recognition is vital. This section will concentrate on published work in non-GIST-STSs from various centers across India.

### Diagnostics

Various clinicopathological studies have been published regarding different subtypes of STSs<sup>[42-49]</sup> [Table 3].

**Table 2: Site specific data in EWSFT from India**

Author	Disease site	Number of patients	Outcomes (%)	Remarks
Biswas <i>et al.</i> <sup>[32]</sup>	Pelvis	48	3 years EFS - 13.5 3 years OS - 15.4 3 years LCR - 41.3	Prognostic factor - hypoalbuminemia (both EFS, OS)
Prabu <i>et al.</i> <sup>[33]</sup>	Spine	15	EFS - 24.73	Prognostic factor - complete functional recovery
Biswas <i>et al.</i> <sup>[34]</sup>	Thoracic	84	5 years EFS - 24.4 5 years OS - 47.9 5 years LCR - 59.3	Prognostic factors for OS - metastases EFS - symptom duration >4 months, primary of skeletal origin, radical RT LCR - radical RT
Biswas <i>et al.</i> <sup>[35]</sup>	Extraosseous	60	5 years EFS - 47.1 5 years OS - 61.6 LCR - 77.9	Prognostic factors for EFS - Hb <10 g%, WBC>11×10 <sup>9</sup> /L OS - Hb <10 g%, high LDH
Qureshi <i>et al.</i> <sup>[36]</sup>	Rib	37	5 years cause specific survival - 50 5 years RFS - 44 LCR - 72	Prognostic factors RFS - poor response to chemotherapy (>5% residual tumor), resection of adjacent lung parenchyma
Qureshi <i>et al.</i> <sup>[37]</sup>	Jaw	11	5 years OS - 87.5 5 years EFS - 72.9 LCR - 90	Surgery has the advantage of identifying patients not requiring RT
Biswas <i>et al.</i> <sup>[38]</sup>	Head and neck	35	5 years EFS - 55.1 5 years OS - 68.3 LCR - 74.1	Prognostic factor EFS - positive predictor - low WBC

EFS=Event-free survival, OS=Overall survival, LCR=Louisiana cancer registry, RT=Radiotherapy, LDH=Lactate dehydrogenase, WBC=White blood cell, Hb=Hemoglobin, EWSFT=Ewing sarcoma family of tumor

**Table 3: Subsite specific pathology data in soft tissue sarcoma from India**

Author	STS subset	Remarks
Rekhi <i>et al.</i> <sup>[42]</sup>	Malignant triton tumors	Average age - 30 years 80% high-grade Mainstay of treatment - surgery Radiotherapy is effective
Rekhi <i>et al.</i> <sup>[43]</sup>	Epithelioid sarcomas (conventional and proximal type)	Common in extremities IHC markers - vimentin, EMA, CK, CD34, desmin Major treatment - surgery OS greater in conventional than proximal type Unfavorable parameters - deeper location, large size, high tumor stage
Jambhekar <i>et al.</i> <sup>[45]</sup>	Chordomas	Evaluation of brachyury expression in chordomas - 90.2% sensitivity
Rekhi <i>et al.</i> <sup>[46]</sup>	MPNST	Common in age >30 years More common in men 88.8% high-grade S-100-70.3% positivity 71.4% underwent surgery DFS - 53.1% Age <30 years, T size >5 cm, high-grade, high stage - prognostic
Rekhi <i>et al.</i> <sup>[48]</sup>	Alveolar soft part sarcoma	Median age 24 years Most common in the extremities TFE3 positive - 91%, desmin positive - 16%, SMA positive - 11% Multimodality treatment

STS=Soft tissue sarcomas, MPNST=Malignant peripheral nerve sheath tumors, IHC=Immunohistochemistry, CK=Cytokeratin, EMA=Epithelial membrane antigen, SMA=Smooth muscle actin, OS=Overall survival, DFS=Disease-free survival

At TMH, Mumbai, Maharashtra, India presently synovial sarcoma constitutes the most common adult STS, and rhabdomyosarcoma is the most common pediatric STS. As per hospital-based cancer registry, TMH, Mumbai, Maharashtra, India in the year 2001, the most common STS was spindle cell sarcoma.<sup>[50]</sup> This clearly shows the value of IHC, over these years that has been helpful in correct identification of certain

“spindle cell sarcomas,” including certain fibrosarcomas into more definite subtypes, including synovial sarcomas.

Among all sarcomas, irrespective of adult or pediatric patients, the most frequently observed specific subtypes are Ewing sarcoma/PNET, followed by synovial sarcoma; both the entities require IHC for confirmation in all cases. Over the years, with applications of immunohistochemical stains, usage of the histopathological term “spindle cell sarcoma” has reduced, and is being replaced by rather specific histopathological subtypes. Earlier, as per 2001 cancer registry, among pediatric patients, Ewing sarcoma, followed by rhabdomyosarcoma were the most common histopathological subtypes.

Diagnosis of STS definitely requires ancillary techniques such as IHC in significant number of cases, and molecular diagnostics in certain cases, including sarcomas such as synovial sarcoma, Ewing sarcoma, and alveolar rhabdomyosarcoma that have specific underlying molecular signatures. Rekhi *et al.*, at TMH, Mumbai, Maharashtra, India evaluated the optimal diagnostic IHC panel for synovial sarcoma, including transducing like enhancer of split-1 (TLE1) a useful IHC marker for diagnosing synovial sarcoma. In a cohort of 42 tumors, they found that its sensitivity for the diagnosis of synovial sarcomas was 95.2%, while specificity was 63.7%, with tumors, such as schwannomas, neurofibromas, MPNST, and EWSFT also expressing TLE1, though to varying degrees. They concluded that TLE1, in view of its high sensitivity might be a useful marker within the optimal IHC panel comprising EMA, BCL-2, MIC2, CD34, and CK7 for substantiating a diagnosis of synovial sarcoma.<sup>[51]</sup> In another Indo-German study, Rekhi and Vogel analyzed a characteristic expression of INI1/SMARCB1 in synovial sarcomas. They concluded that a unique “weak to absent” IHC expression of INI1 is highly sensitive (88.2%) and specific (97.3%) for synovial sarcomas, irrespective of its subtypes and types of biopsies and can be used an adjunct in

diagnosis, especially in settings lacking molecular/cytogenetic analysis.<sup>[52]</sup>

### Prognosis and management

Metastatic STSs are a heterogeneous entity with limited data on treatment modalities and outcomes, especially in India. Iqbal *et al.* analyzed 119 patients with metastatic STS treated between 2003 and 2012 atavisms. They observed the most common histological type was synovial sarcoma and leiomyosarcoma. As a group with a median follow-up of 10 months, these tumors had poor outcomes with an EFS and OS of 6 and 10 months, respectively. They identified Hb <10 g%, tumor size >10 cm and single modality treatment as poor prognostic factors, in terms of OS.<sup>[53]</sup>

Another group of STSs with manifestations are retroperitoneal sarcomas (RPS). Panda *et al.* retrospectively analyzed 23 patients for treatment modalities and prognostic factors. In their study, surgery was performed in 20 (87%) patients for primary RPS and 3 (13%) for recurrent RPS at initial presentation. They observed that completeness of resection, tumor grade, and sex were prognostic factors for RPS.<sup>[54]</sup> In a study on dedifferentiated liposarcomas (DDLPS), including RPS DDLPS, Rekhi *et al.* observed surgery as the main treatment modality for these tumors.<sup>[55]</sup>

Radiotherapy is an essential component of adjuvant therapy in certain high-grade, extremity STS treated with surgery, followed by chemotherapy. Brachytherapy (BRT) alone or with external beam radiotherapy (EBRT) has been evaluated in these adjuvant settings by Indian investigators as well.

Jamema *et al.*, from TMH, Mumbai, Maharashtra, India conducted a dosimetric study quantitatively comparing electron arc (EA) versus photon intensity modulated radiotherapy (IMRT) for Askin's tumors and concluded that IMRT resulted in superior planning target volume coverage and sparing of organs at risk compared to EA plans. They added the caveat that low dose regions associated with IMRT need to be kept in mind.<sup>[56]</sup> The same group conducted a three-dimensional image-based dosimetric study to quantitatively compare geometric versus dose-point optimization in combination with graphical optimization for interstitial BRT of STS.<sup>[57]</sup> They found that optimization with dose points defined away from the implant plane and on target results in superior target coverage with optimal values of other indices.

Laskar *et al.* performed a retrospective analysis of fifty pediatric patients with STSs, who received BRT as part of loco-regional treatment. Most patients had synovial sarcomas (32%). After a median follow-up of 51 months, the LC, DFS, and OS were 82%, 68%, and 71%, respectively. LC was superior in patients with tumor size <5 cm, symptom duration <2 months, and lower histopathological tumor grade. There were no differences in LC rates between HDR and LDR BRT.<sup>[58]</sup> Earlier, in 1998, the same group from TMH also published their experience with BRT in the adult STS patients. In a cohort of 151 patients, spindle cell sarcoma was found to be the most common STS (30%), with the extremities involved in 75% patients. In patients receiving BRT only, 25 out of 33 (75%) were locally controlled after a median follow-up of 30 months. After successful salvage of local failures, the overall LC improved to 82%. Treatment-related complications

were <1%. They concluded that the sequential combination of limited surgery and tumor bed BRT with or without EBRT provided an effective alternative to more morbid procedures.<sup>[59]</sup>

In a recent study, Sharma *et al.* evaluated the role of perioperative high-dose-rate interstitial brachytherapy (PHDRIBT) in combination with EBRT in patients with localized STS. In their study, PHDRIBT was started on the 3<sup>rd</sup> postoperative day to an HDR dose of 16 Gy over 4 fractions in 2 days, and then 4 weeks later, followed by EBRT. They observed a 5-year OS and DFS of 67% and 63%, respectively, with no LR. Major toxicity observed in this study was delayed wound healing in 5.7% of patients with common late toxicity being chronic skin/subcutaneous fibrosis in 9.6% patients.<sup>[60]</sup>

### Conclusions

- As per hospital registry data, OGS is the most common bone sarcoma, followed by Ewing sarcoma and chondrosarcoma
- Percentage of post-NACT tumor necrosis is significantly associated with survival in conventional high-grade OGS
- VEGF expression has been shown to correlate with histological necrosis, pre- and post-chemotherapy in OGS. DCE-MRI might serve as a surrogate for tumor angiogenesis in cases of OGS
- Nonmethotrexate-based multiagent chemotherapy regimens seem to be economic and as efficacious as methotrexate-based chemotherapy in OGS with less complex pharmacokinetic monitoring, and acceptable toxicity as per studies from TMH and AIIMS
- Compliance is an important component of treatment in OGS. Early data from TMH have shown that compliance correlates with histological necrosis
- *EWSR1* gene rearrangement detected by FISH testing is useful in diagnosis of Ewing sarcomas, especially in cases with tumors occurring at unusual sites, in uncommon age-groups, and in cases with equivocal immunohistochemical features. *EWSR1* testing was found to be more sensitive than PCR testing, the latter tests for specific fusion transcripts. Molecular results should be correlated with clinicopathological and immunohistochemical results in all cases
- Increased FDG uptake on FDG-PET-CT, as measured by mean  $SUV_{max}$ , was indicative of metastatic potential of the tumor in Ewing sarcoma. FDG-PET-CT might also correlate with response after chemotherapy
- Multiple prognostic factors in Ewing sarcomas include WBC, albumin levels, symptom duration >4 months, tumor diameter >8 cm; these require further validation as prognostic markers
- ECRT seems like a viable alternate option to artificial prosthesis
- STSs are a heterogeneous group of tumors with IHC and molecular diagnostics being increasingly used to differentiate the different subtypes, especially the ones that are chemosensitive, such as Ewing sarcoma/PNET and syovial sarcoma. Several clinicopathological studies have been published on various STSs. Synovial sarcoma and Ewing sarcoma/PNET are the most common types of STSs as per Hospital registry



- Optimal diagnostic panel for synovial sarcoma includes EMA, BCL-2, MIC2, and CD34, with the addition of TLE1, a new sensitive marker for diagnosis of synovial sarcoma, as per study from TMH. A unique “weak to absent” expression of INI1/SMARCB1, is fairly specific for diagnosis of synovial sarcoma and can be useful especially in settings lacking molecular diagnostics
- BRT alone or with EBRT has been evaluated in adjuvant settings in the treatment of STSs by Indian investigators with heartening results
- On the evaluation of outcomes when BRT has been used for adjuvant treatment in pediatric STSs, LC has been found to be superior in patients with tumor size <5 cm, symptom duration <2 months, and lower histopathological tumor grade.

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### Conflicts of interest

There are no conflicts of interest.

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