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Original Article

Analysis of bone and soft-tissue sarcomas registered during the year 2012 at Tata Memorial Hospital, Mumbai, with clinical outcomes

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Abstract

INTRODUCTION: Primary bone and soft tissue sarcomas are rare, but diagnostically and therapeutically challenging group of tumors, requiring multidisciplinary management. There are limited documented studies from multidisciplinary teams , in the form of comprehensive analysis of these tumors, from our country. This study is an analysis of cases of osteosarcomas, Ewing sarcomas (ESs), chondrosarcomas (CSs), and soft-tissue sarcomas (STSs), registered at our institution during 2012. **METHODS:** Clinical details, including outcomes of cases of bone and STSs, during the year 2012, were retrieved from the medical records of our institution and were further analyzed. **RESULTS:** Ninety-five high-grade, extremity-based, treatment-naïve cases of osteosarcomas were treated with a novel, dose-dense, nonhigh-dose methotrexate-based OGS-12 protocol. Good histopathologic response (necrosis ≥90%) was achieved in 59% nonmetastatic and 56% metastatic patients. At a median follow-up of 48 months, the estimated 5-year event-free survival and overall survival (OS) were 67% and 78%, respectively. In the metastatic cohort at a median follow-up of 51 months, the 5-year estimated progression-free survival was 24% and OS was 26%. Among 87 (73.2%) nonmetastatic and 32 (26.8%) metastatic, analyzable cases of ES, at a median follow-up of 40 months, the disease-free survival (DFS) and OS in the nonmetastatic group were 62% and 83%; in the metastatic group, they were 37.5% and 65.6%, respectively. Among 40 cases of CSs (33 nonmetastatic and 7 metastatic), 21 had limb salvage surgery while 5 had amputation. Microscopically, 90.4% were Grade II CSs. Five-year OS and DFS were 84.6% and 71%, respectively. Among 189 high-grade, extremity-based STSs (89% nonmetastatic), synovial sarcoma was the most common subtype (31%). Eighty-five percent had limb preservation surgery; a majority were offered adjuvant radiation with or without chemotherapy. At a median follow-up of 51 (1–63) months, 3-year local control, DFS, and OS were 81%, 48%, and 64%, respectively. **CONCLUSIONS:** The novel OGS 12 and Ewing Family of Tumors 2001 protocols have shown comparable outcomes to international standards in cases of osteosarcoma and ES, respectively, and merit wider applications, especially in low- and middle-income countries (LMICs). Outcomes in STS and CSs were also comparable and underscore the importance of a multidisciplinary approach for the management of sarcomas in LMICS.

Key Words: Ewing sarcoma, management, multidisciplinary approach, osteosarcoma, soft-tissue sarcoma

Introduction

Primary bone and soft-tissue sarcomas (STSs) are rare tumors, comprising <1% of overall adult cancers.[1-3] At Tata Memorial Hospital (TMH), nearly 300–400 new cases of STSs are diagnosed, including referral cases, with an average 2.1% frequency rates in males and 1.2% in females.[4]

Despite their rarity, bone and STSs are diagnostically and therapeutically challenging tumors. Over the years, a multidisciplinary approach, including a close interaction between surgical pathologists, radiologists, surgeons, and oncologists, has brought about a significant increase in the disease-free survival (DFS) for STSs, which were previously considered as fatal.[5] This equally applies for bone sarcomas. Since 2010, the concept of disease management groups (DMGs), including the Bone and Soft-tissue DMG, initiated at TMH, has been helpful in providing a comprehensive management and care to patients afflicted with these challenging tumors.[6]

Among bone sarcomas, osteosarcoma is the most common primary malignant bone tumor of the growing skeleton. Treatment for a conventional high-grade osteosarcoma essentially consists of radical surgical excision coupled with multiagent chemotherapy.[7,8] International guidelines and Cochrane meta-analysis suggest using multiagent chemotherapy which usually includes doxorubicin, cisplatin, and a third drug: either high-dose methotrexate (HDMTX) or ifosfamide.[7-11] At TMH, Bone and Soft-tissue DMG practices a novel, institutional regimen, named 'OGS-12', for treating patients with high-grade, extremity-based OGSs. This regimen comprises eight sequential doublets of the following drugs: doxorubicin, cisplatin, and ifosfamide in four courses each, given in the neoadjuvant and adjuvant settings. This novel regimen conceptualized and developed at TMH is based on dose density principles which were established by Norton and Simon [Table 1].[12-14]

Ewing sarcoma is the second most common bone malignancy after osteosarcoma, primarily affecting the teenage and young adolescent (TYA) population.[15] Although considered as more common in Caucasians than in Asians and African-Americans, as a result of a very high population density, a large number of Ewing sarcoma cases are seen in India.[16] At our institution, these cases are treated with a neoadjuvant chemotherapy, in the

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form of Ewing family of tumors (EFT) 2001 protocol, followed by surgical resection and/or RT. Chondrosarcoma constitutes the next common primary bone sarcoma. Surgery is the treatment mainstay for the management of chondrosarcomas, considering that these tumors are radio- and chemo-resistant. Radiotherapy (RT) is only considered for treating unresectable tumors, such as those of the axial skeleton, and to relieve pain in a palliative setting. Likewise, there is no role of chemotherapy in the treatment of a conventional chondrosarcoma. Cases of mesenchymal and dedifferentiated chondrosarcomas might get some benefit from adjuvant chemotherapy.[17]

STSs are a heterogeneous group of neoplasms, with diverse histopathologic subtypes, based on origin from various mesenchymal cells, such as fibroblasts, adipose tissue, muscles, nerves, and vessels. More than seventy different STSs have been described.[18] Extremity forms the most common site of occurrence for these tumors.[19] Most cases of STSs registered at our institute present with tumors of high grade and stage.[20] For high-grade extremity-based STSs, we offer multimodality treatment as the standard of care in our institute with the aim of limb and function preservation.

The present study is an analysis of various sarcomas registered during the year 2012, with respect to their management and clinical outcomes. Data related to individual sarcomas, including osteosarcoma, Ewing sarcoma, chondrosarcoma, and STSs, are presented and discussed herewith.

Materials and Methods

Clinical details of cases of bone and STSs, during the year 2012, were retrieved from medical records of our institution. Prior to initiating the treatment, all patients of primary bone sarcomas underwent radiographic assessment and a magnetic resonance imaging of the affected area. Staging workup includes a noncontrast computed tomogram (CT) of the thorax, along with a bone scan, as a part of the metastatic workup. Positron emission tomogram (PET)-CT scan is performed in cases of Ewing sarcoma, as a part of the metastatic workup. CT scan/bone scan or F-18 PET scans are performed in cases of chondrosarcomas.

Complete blood count, renal function test (by serum test, including creatinine levels) creatinine; DTPA scan in some patients; liver function, echocardiography, and pure serum tone audiometry are performed to assess the organ functions. Baseline demographic features (age, gender, and socioeconomic status), tumor burden markers (tumor size, lactate dehydrogenase, serum alkaline phosphatase), and nutritional parameters (body mass index, hemoglobin, albumin, transferrin-saturation, folate, and Vitamin B12) are tested and nutritional deficiencies are corrected to improve tolerance which affect compliance to treatment and may have a bearing on outcome.[13]

Postsurgery, histopathologic tumor necrosis is assessed by Huvos grading in cases of osteosarcoma and Ewing sarcoma.[14] Patients are counseled for fertility preservation options prior to initiation of the treatment.

Results

Conventional high-grade osteosarcoma

During 2012, 197 patients with osteosarcoma were registered at TMH, of which, 5% were of nonextremity sites; 18% cases received only got histopathological diagnosis, but

Table 1: 'OGS-12' chemotherapy protocol

Schedule	NACT1	NACT2	NACT3	NACT4	Surgery	ACT5	ACT6	ACT7	ACT8
Cisplatin 33 mg/m^2 (day 1-3)	√	√	XXX	XXX		√	√	√	√
Adriamycin 25 mg/m^2 (day 1-3)	√	√	√	√		XXX	XXX	XXX	XXX
Ifosfamide 1.8 g/m^2 (day 1-5)	XXX	XXX	√	√		√	√	√	√

NACT=Neoadjuvant chemotherapy; ACT=Adjuvant chemotherapy; √- Offered

Table 2: Baseline characteristics

Variables	Nonmets (*n*=68)		Mets (n=27)	
	Median (%)	Abnormal values (%)	Median (%)	Abnormal values (%)
Age (years)	16 (8-56)		18 (7-44)	
ECOG				
PS 0 or 1	70		33	
PS≥2	30		67	
Tumour size (cm)	10 (1.1-20)		10 (5-20)	
Serum LDH (U/L)	230 (126-511)	79	296 (130-586)	79
SAP (IU/L)	244 (88-1216)	37	292 (64-2030)	37
Serum albumin (g/dl)	5 (3.5-5)	3	5 (3-5)	1
Serum iron (µg/dl)	55 (7-124)	59	46 (15-383)	27
Serum transferrin saturation (%)	17 (3-53)	22	13 (4.67-100)	32
hemoglobin (g/dl)	13 (10-17)	41	13 (8-16)	56
Serum Vitamin B12 (pg/ml)	223 (35-1484)	39	206 (70-1500)	41
Serum folate (ng/ml)	7 (1-182)	4	5 (2-52)	9
BMI (kg/m^2)	17 (12-27)	62	18 (8.30-26.90)	50

PS=Performance status; LDH=Lactose dehydrogenase; SAP=Serum alkaline phosphatase; BMI=Body mass index; ECOG=Eastern Cooperative Oncology Group

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did not get treatment at TMH; 15% cases were offered the best supportive care upfront (due to disseminated disease and poor performance status [PS]); and 13% cases were offered alternative protocols (partially treated outside and/or poor PS). The remaining 95 cases (48%) were treatment-naïve, high-grade, extremity-based osteosarcomas, treated with standard "in-house" OGS-12 protocol and were analyzed [Table 2 and Figure 1].

Among these 95 patients, 68 were nonmetastatic and 27 were metastatic. The baseline characteristics of these patients are shown in Table 2. Median age was 16 years (range = 8–56) for nonmetastatic and 18 years (7–44) for metastatic patients. Noticeably, a considerable number of patients had high tumor burden and were nutritionally challenged.

Out of the 68 patients, a single patient received extracorporeal RT. Among 67 analyzable patients for tumor histopathologic response, in the nonmetastatic cohort, 59% had good response (necrosis more than 90%). During the median follow-up of 48 (38–60) months, median event-free survival (EFS) and overall survival (OS) were not reached. Mean EFS was 47 (42–52) months and mean OS was 52 (48-56) months; 4-year EFS and OS were 67% and 78%, respectively [Figures 2 and 3].

There was Grade 3/4 neutropenia (including febrile neutropenia) in 19 patients (28%), Grade 3/4 thrombocytopenia in 45%, and Grade 3/4 anemia in 33% of patients. Among nonhematological toxicities, Grade 3/4 diarrhea occurred in 5% and Grade 3/4 nausea and vomiting occurred in 2% patients.

In the metastatic patient cohort, among 25 analyzable patients, 56% were good responders. At a median follow-up of 51 (42–55) months, median progression-free survival (PFS) was 15 months (11–19) and median OS was 26 months (14–37). The estimated 4-year PFS was 24% and estimated OS was 26% [Figures 4 and 5].

There was Grade 3/4 neutropenia (including febrile neutropenia) in 14 patients (52%), Grade 3/4 thrombocytopenia in 50%, and Grade 3/4 anemia in 53% patients. Among nonhematological toxicities, Grade 3/4 diarrhea occurred in 7% and Grade 3/4 nausea and vomiting occurred in 3% patients.

Ewing sarcoma

One hundred and nineteen cases of Ewing sarcoma were registered during the year 2012. Of these, 87 cases (73.2%) were nonmetastatic at diagnosis and 32 cases (26.8%) presented with metastasis. Of the 119 patients, 74 (62.2%) belonged to the TYA age group (defined as 15–29 years of age) and there was no difference in the proportion of patients presenting with metastases between TYA and non-TYA patients. All patients did not receive their complete treatment in TMH. Some were referred to other institutes of their preference for chemotherapy or surgery, as

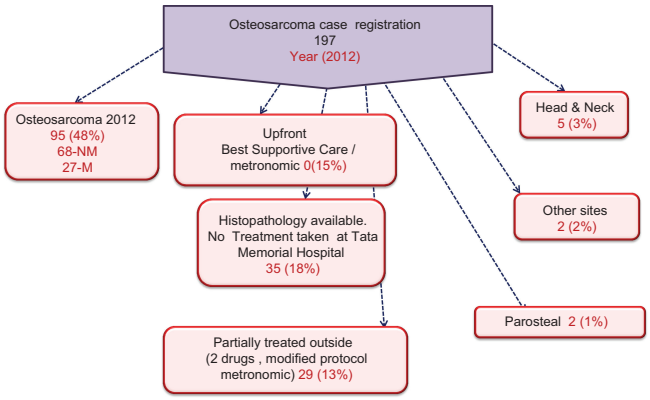

Figure 1: Patient distribution in cases of osteosarcomas

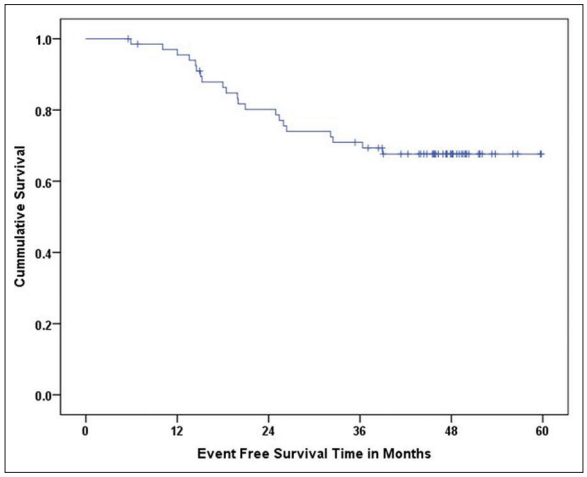

Figure 2: Event-free survival in patients with nonmetastatic osteosarcoma

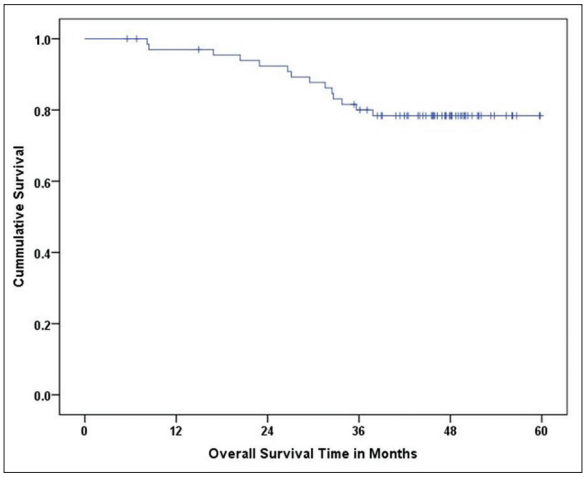

Figure 3: Overall survival in patients with nonmetastatic osteosarcoma

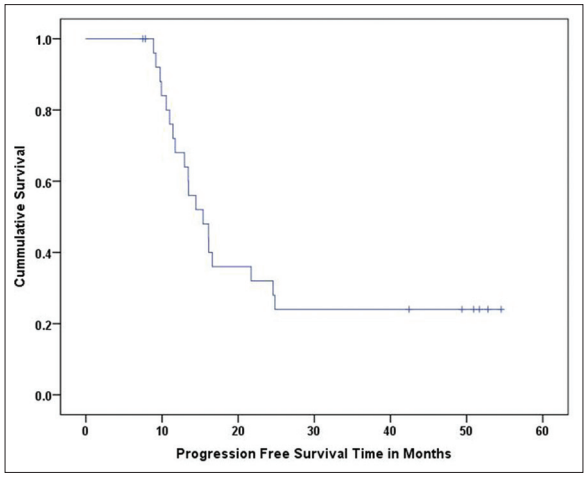

Figure 4: Event-free survival in patients with metastatic osteosarcoma

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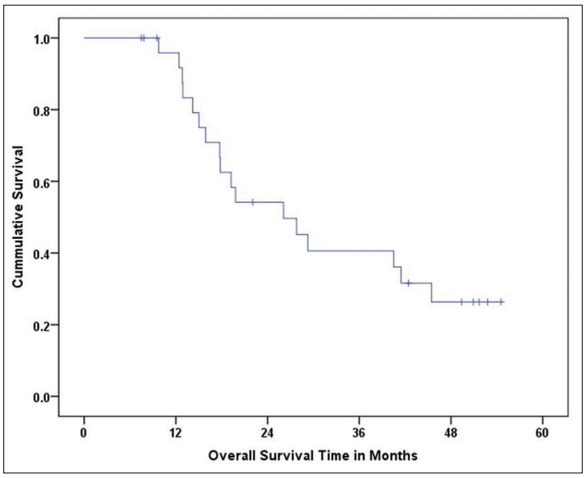

Figure 5: Overall survival in patients with metastatic osteosarcoma

prescribed. Complete treatment (defined by more than 80% of chemotherapy and local therapy) was given in TMH to 86 cases (72.26%) of Ewing sarcoma.

The median duration for treatment completion (starting from neoadjuvant chemotherapy followed by local therapy and adjuvant chemotherapy) was 50 weeks (range = 35–72 weeks).

At a median follow-up of 40 months (range= 3–53 months), the DFS and OS of the nonmetastatic group of patients with Ewing sarcoma were 62% and 83%, respectively, and that of the metastatic group of patients with Ewing sarcoma were 37.5% and 65.6%, respectively.

On evaluation, the DFS of the TYA patients with Ewing sarcoma was significantly lower than that of the non-TYA patients, but the OS was not found to be statistically different. Patients belonging to the TYAs were less regular during their follow-up visits.

Chondrosarcoma

Forty cases of chondrosarcoma were registered in the Bone and Soft-tissue DMG during 2012. Pelvis was the most common site of occurrence (14 cases), followed by proximal femur (9), distal femur (4), scapula (4), sacrum (3), proximal humerus (3), and 1 case each in the dorsal spine, tibia, fibula, and in the hand.

Thirty-three cases were nonmetastatic; 6 had pulmonary metastasis and a single patient had both pulmonary and skeletal metastases. Eleven patients were either referred outside or preferred to take treatment at another institution. Patients with multiple bony and pulmonary metastases were treated with the best supportive care. Two patients with thoracic cage involvement were referred to the thoracic DMG, for further care. Thus, a total of 26 patients were operated in bone and soft-tissue service.

We were able to achieve limb salvage in 21 cases and the remaining 5 cases underwent amputation. On evaluation of the excised surgical specimens, all except one patient had free resection margins. Microscopic evaluation revealed Grade II chondrosarcoma in 19 patients, Grade III in 3 patients, Grade I in a single patient, dedifferentiated chondrosarcoma in 2 patients, and mesenchymal chondrosarcoma in a single patient. One patient died in the immediate postoperative period due to intraoperative complications. Five out of 26 patients developed pulmonary metastasis and 1 patient developed local recurrence with pulmonary metastasis. During the last follow-up, 21 patients were disease free, 3 patients died of disease recurrence, and 1 patient was alive with disease. Finally, we observed a 5-year OS of 84.6% with a DFS of 71%.

Soft-tissue sarcomas

One hundred and eighty-nine cases of high-grade extremity-based STSs were registered during 2012. Most patients were males (63%). Median age was 41 years (range = 6–80 years). The most common histopathologic subtype was synovial sarcoma (31%), followed by spindle cell sarcoma not otherwise specified (29%), pleomorphic sarcoma (11%), and liposarcoma (6%).

Of these patients, 104 (55%) were treated in our institute with curative intent. Most patients were nonmetastatic (89%) at presentation. Lower-extremity lesions were more common than those of upper extremity (72 vs. 32). A significant proportion (34%) of our patients (n = 64) underwent some form of surgery outside before presenting to us with residual/recurrent lesions. Most of the patients presented with large tumors (<5 cm = 14 [13%], 5–10 cm = 43 [41%], and >10 cm = 47 [45%]). Most patients underwent surgery (wide local excision), followed by adjuvant radiation with or without chemotherapy, depending on the histopathologic findings. Of the 104 patients, 88 (85%) underwent limb preservation surgery. Upfront amputation was done for 16 cases (15%).

Adjuvant RT was recommended for majority (77/88 = 88%) of the patients undergoing limb-preserving surgery. RT was offered in the form of postoperative adjuvant external RT in 60 (46/77), preoperative external RT in 27% (21/77), and interstitial brachytherapy in 13% (10/77). Preoperative external RT was offered to patients with borderline resectable tumors (n = 21). All patients receiving preoperative RT subsequently underwent limb salvage surgery. For patients with metastatic disease at presentation, upfront pulmonary metastasectomy along with the surgery for the primary tumor was performed in 7/11 (64%) patients. One-third of our patients required plastic and/or vascular reconstruction (n = 34). Adjuvant chemotherapy details were available in 29 patients.

The median follow-up of the surviving patients was 51 months (range = 1–63 months). During the last follow-up, 55 patients were alive and disease free. The 3-year local control, DFS, and OS were 81%, 48%, and 64%, respectively [Table 3]. Distant metastases, predominantly in the lungs, was the most common site of relapse in our patients (n = 50; 48%). Isolated local relapse was seen in only seven patients [Table 4]. Of the seven

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Table 3: Clinical outcomes in 104 cases of soft -tissue sarcoma

Event	3 years (%)	5 years (%)
LC	81	75.7
DFS	48	38.6
OS	64	57.6

LS=Local control; DFS=Disease -free survival; OS=Overall survival

Table 4: Patterns of failure in cases of soft -tissue sarcoma

Event	Number of cases
Local recurrence	7
Distant metastases	38
Both	12

patients who underwent upfront pulmonary metastasectomy, two were alive and disease free.

Fourteen patients had postoperative and post-RT adverse sequelae. Three patients experienced wound dehiscence with or without development of a nonhealing wound that required major intervention in the form of debridement, secondary suturing, and hyperbaric oxygen therapy.

Discussion

The present study describes the institutional practice of managing bone and STSs at TMH, including the analysis of cases registered in the Bone and Soft-tissue DMG during the year 2012.

Intensive protocols aimed at cure must be based on the evidence of efficacy and safety of the regimen as well as ability to administer the regimen optimally in a given setting.

HDMTX is an important drug in the treatment of a high-grade osteosarcomas and is widely practised in the Western world. However, there is no randomized evidence of its superiority over nonHDMTX-based regimens, till date.[21,22] Further, stringent pharmacokinetic monitoring with inpatient treatment requirements, unpredictable serious toxicities, and cost makes it challenging, especially in low- and middle-income countries.[23,24]

Although HDMTX is considered fertility sparing, this is negated by the use of cisplatin, the other alkylator used in the HDMTX-based regimens. Hence, both ifosfamide- and HDMTX-based regimens demand fertility specialist review and prior sperm preservation in males. In females, gonadal toxicity is age dependent (rather than dose), and majority of the prepubertal and pubertal females regain menstrual functions after alkylator-based therapy.[25-27]

The outcome of the non-HDMTX-based, dose-dense, OGS-12 protocol, with respect to histopathologic response (59% in nonmetastatic patients), is comparable to that of HDMTX-based regimens, such as those practiced at the Memorial Sloan Kettering Cancer Centre (65%), COSS (43%), and INT0133 (48%),[28-30] as well to some of the previously practiced the non-HDMTX-based regimens, such as OS 99 (61%) and OS 91 (51%).[7,31] Two Indian studies have shown good histopathologic response rates of 33% and 42%, respectively.[32,33]

It is noteworthy that the 4-year EFS of 67% and OS of 78% of a 100% outpatient treatment regimen, OGS-12, for the patients treated in the year 2012, are comparable to international standards,[28-36] especially in a nutritionally challenged and high tumor burden population, such as ours.

The described novel, dose-dense, non-HDMTX-based "OGS-12" regimen was developed in the medical oncology department of Tata Memorial Cancer Centre, and the performance of the protocol was tested in a clean cohort of patients with high-grade, extremity-based osteosarcomas, who were treatment naive and whose Eastern Cooperative Oncology Group (ECOG) PS allowed to administer the "OGS-12" protocol, comprising a neoadjuvant phase, followed by surgery and then an adjuvant phase. Prior inadvertent treatment is a known confounder of prognosis (besides nonextremity sites and grade) and the community doctors being the first referral point, this is a significant problem in low- and middle-income countries (LMICs).[35] The results of this protocol from a larger cohort are recently published and the results achieved are comparable to international standards (with or without HDMTX-based therapy).[36]

Previously, we experienced significant toxicity, dose reductions, and delays in treated cases of osteosarcomas, when we were using a 4 drug, dose-intense protocol, which was not in synchronization with dose density principles.

During our initial measures, we tried to enhance chemotherapy compliance using universal growth factor prophylaxis, patient education, and reducing dose modifications and delays. An earlier study from our group has shown that compliance has a direct bearing on clinical outcomes.[13] Taken one step ahead, we conceptualized a dose-dense "OGS-12" protocol which comprises essentially of a neoadjuvant phase, followed by surgery and adjuvant phase. As prior inadvertent treatment is a known confounder for prognosis and so as grade and nonextremity sites, to ensure uniformity, only treatment-naive, high-grade, extremity-based cases of osteosarcomas, who were planned and took (either completely or partly) chemotherapy at Tata Memorial Cancer Center, were taken. The remaining patients were offered protocols other than "OGS-12" (including 2 drug protocol or "OGS-12-like" regimen with modifications based on their prior treatment, concomitant medical conditions, and ECOG PS).

To ensure compliance in "OGS-12" protocol, nutritional deficiencies were tested *a priori* and were periodically and appropriately addressed; with the help of universal growth factor prophylaxis, the maintenance of dose density and intensity was ensured. As per our recent study, the outcomes of this "OGS-12" protocol were found to be comparable to international standards, with or without HDMTX.[36]

Notably, in another study from our institute, wherein comparisons of outcomes were drawn from all osteosarcoma patients, with tumors at extremity and pelvic sites, who

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were either treated during the period 2006–2011 or 2012–2013 (with or without "OGS-12" protocol), including a comparatively smaller sample in the latter group, there was 6% absolute difference in OS, in favor of post 2012 treatment. However, this difference did not show a statistical significance.[37] Nonetheless, in a way, this reinforces the importance of uniform chemotherapy protocols in a homogeneous population with adequate chemotherapy compliance.[13] Further, this also clearly signifies the need to educate peripheral doctors regarding principles of sarcoma care so as to ensure early referral of the patients without inadvertent treatment to centers with multidisciplinary sarcoma expertise, including in LMICs.[35,36]

The toxicities with OGS-12 are of the same pattern, compared to other international trials; with a trend toward lesser hematological toxicity, which is partially explained by the use of cisplatin instead of carboplatin, primary G-CSF prophylaxis, as well as correction of nutritional deficiencies before the initiation of therapy.[7,28,30,31,34] In metastatic patients also, the response rates, survival figures, and toxicity rates were found to be comparable to that of other international studies.[38-40] Besides optimal treatment, compliance of patients to treatment has an impact on clinical outcomes. In an earlier study, we observed a statistically significant association between good histopathologic response and compliance ($P = 0.031$).[13] Data from that study brought to the fore the correlation of survival and compliance using "good necrosis" as a surrogate indicator of "good survival." Therefore, there should be every attempt to improve compliance to the prescribed therapy.

With the improvement in the chemotherapy armamentarium over the last 3–4 decades and collaborative multidisciplinary approaches, the survival in patients with Ewing sarcoma has improved from 10% to nearly 70% in nonmetastatic disease. However, metastatic presentations still portend poor long-term cure rates, of 20%–40%.[40] The currently used standard of care protocols for Ewing sarcoma, including EFT 2001 protocol, are based on the principles of combination chemotherapy, using doxorubicin, ifosfamide, vincristine, cyclophosphamide, and dactinomycin in a preferably, dose-intense manner with the help of filgrastim.[41] Patients in our series received similar multiagent chemotherapy, but the dose intensity was 3 weekly, as opposed to the 2 weekly in the Children Oncology Group series. The DFS of 62% and OS of 83% in our series were comparable to the published literature with the used chemotherapy regimen.[42]

Most cases of chondrosarcomas in our study were treated with surgical resection. During metastatic workup, we noticed metastatic deposits to lungs in six patients (14%) which was much higher than that of other studies. In a study by Yang *et al*.,[43] out of 37 cases of chondrosarcoma, only 4 patients had pulmonary metastasis and there was no skeletal metastasis. This difference might be attributable to the fact that our study cohort included cases of dedifferentiated and mesenchymal chondrosarcomas, which are associated with higher rates of metastasis. In addition, most of our patients presented at a clinically advanced stage with large volume disease. Some of those cases were either treated with alternative medicine or mismanaged at general orthopedic centers, with limited experience in treating oncology cases.

In this study, we managed to achieve limb salvage in 21 cases and 5 cases underwent amputation for varied reasons, and our local recurrence rates were low which may be attributed to the wide excision with adequate margins concept described by Enneking. Most studies claim that a failure to achieve complete resection with clear margins (R0) at the local site is a reason for local recurrence and distant recurrence [Table 5].[43-45] The final histopathology in our series showed a single patient with Grade III chondrosarcoma who died of disease and 2 cases of dedifferentiated chondrosarcoma, including one, who died and another of a mesenchymal chondrosarcoma, with unresectable disease. These patients did worse than patients with Grade II chondrosarcoma. These results are similar to the published studies.[17,43-47] Three patients died of disease; a single patient had a history of a prior curettage done outside with a chondrosarcoma Grade III; another patient had a dedifferentiated chondrosarcoma with a pathological fracture and one patient with chondrosarcoma Grade II, who underwent internal hemipelvectomy, had a margin-positive pelvic resection. He developed an unresectable local recurrence and distant recurrence. Fiorenza *et al*.[46] made an interesting observation that the development of a local recurrence was only relevant to survival if the patient had synchronous metastasis, when the diagnosis of local recurrence was made. In patients without metastases at the time of detection of local recurrence, further wide excision provided a good chance for cure. The OS for chondrosarcomas in our study was 84.6% and DFS was 71%, comparable to the published studies.[43-45]

Regarding STSs, the current analysis included patients with intermediate- and high-grade sarcomas only. Among immunohistochemistry and molecular tests, the latter in select cases had a crucial role in ascertaining the exact histopathologic subtype. All cases were reviewed by expert sarcoma pathologists. Synovial sarcoma was found to be the most common histopathologic subtype in our cohort, as similarly observed in a few earlier published series.[20, 48-49] Keeping in conformity with our Bone and Soft-tissue DMG guidelines, all patients are evaluated and considered for limb and function preservation with a multidisciplinary approach comprising application of surgery, radiation, and chemotherapy.

Table 5: Comparison between overall and disease-free survival across various studies in chondrosarcomas

Study group	OS (%)	DFS (%)
Yang *et al*.[43]	83	70
Andreou *et al*.[44]	72	57
Kamal *et al*.[45]	43	70
Present study	84.6	71

DFS=Disease -free survival; OS=Overall survival

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Invariably, more than half of the patients affiliated with STSTs undergo some surgical intervention before presenting to an orthopedic oncologist. Suboptimal excision and inappropriate biopsy technique complicate further management and compromise outcomes.[50] In the present study cohort, recurrent tumors comprised 62% of the cases. According to most documented studies, limb salvage rates in STSs account for 80%–90%.[51] These rates were similar to 85% observed in this study. Previously, two large series from the Indian subcontinent have revealed a modest limb salvage rate of around 70% in STSs.[49,52] Reconstruction ability improves the salvage rates in extremity sarcomas.[53] One-third of our patients underwent plastic and/or vascular reconstruction and possibly this led to an improvement in the salvage rates.

The role of adjuvant RT is well established and almost all patients receive either external beam RT or brachytherapy as a part of the limb salvage protocol.[54] The tolerance to radiation has been acceptable and none of our patients had major short- or long-term toxicities. We routinely perform around 10–20 brachytherapy procedures annually for patients presenting with high-grade extremity-based STTs. Results of brachytherapy procedure have been published earlier from our institute.[55] In this study, preoperative RT was offered to borderline resectable tumors, and limb salvage surgery could be performed in all those patients. Two of those patients also received adjuvant RT, in view of positive resection margins.

Role of adjuvant chemotherapy in STSs is evolving and we offer it to select patients with large-sized (exceeding 5 cm), high-grade extremity tumors and with specific chemosensitive histopathologic subtypes, such as synovial sarcomas, myxoid liposarcomas, and leiomyosarcomas.[56] This underscores the value of exact subtyping of these sarcomas. In our cohort, data were available for 29 patients who received adriamycin-based chemotherapy. Most of those patients tolerated the chemotherapy reasonably.

Less than 10% patients with STS presented with metastases at the time of diagnosis and had a poor prognosis. Metastasectomy might offer a chance for better survival in such cases.[57,58] Two out of seven patients in this cohort, who underwent upfront metastasectomies, have been long-term survivors. Thus, in a select group of patients with resectable metastases, curative treatment can be offered.

Conclusions

- We suggest using novel, cost-effective, outpatient-based "OGS-12" protocol, a dose-dense, non-HDMTX-based sequential doublet regimen, especially in LMICs with economic and infrastructural challenges. Attempts for enhancing compliance among patients to chemotherapy can have a significant improvement in clinical outcomes
- With the existing chemotherapy protocol for Ewing sarcoma, DFS and OS were comparable to other international studies. Patients with metastatic disease at presentation had relatively poorer clinical outcomes
- Conventional chondrosarcomas are optimally treated with surgical resection, including clear margins, which influences relatively better clinical outcomes
- We recommend that STSs should be treated in a specialized center with a multidisciplinary setup for an optimum treatment outcome.

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Conflicts of interest

There are no conflicts of interest.

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