

INDIAN COUNCIL OF MEDICAL RESEARCH



CONSENSUS DOCUMENT FOR MANAGEMENT ON SOFT TISSUE SARCOMA AND OSTEOSARCOMA

*Prepared as an outcome of ICMR Subcommittee on
Soft Tissue Sarcoma and Osteosarcoma*



Indian Council of Medical Research
2016

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Indian Council of Medical Research,
Ansari Nagar, New Delhi – 110029
2016

Disclaimer

This consensus document represents the current thinking of experts on the topic based on available evidence. This has been developed by national experts in the field and does not in any way bind a clinician to follow this guideline. One can use an alternate mode of therapy based on discussions with the patient and institution, national or international guidelines. The mention of pharmaceutical drugs for therapy does not constitute endorsement or recommendation for use but will act only as a guidance for clinicians in complex decision –making.

Dr. Soumya Swaminathan
Secretary,
Department of Health Research
and Director General, ICMR

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Foreword

I am glad to write this foreword for Consensus Document for Management of Soft Tissue Sarcoma and Osteosarcoma. The ICMR had constituted sub-committees to prepare this document for management of various cancer sites. This document is the result of the hard work of various experts across the country working in the area of oncology.



This consensus document on Management of Soft Tissue Sarcoma and Osteosarcoma summarizes the modalities of treatment including the site-specific anti-cancer therapies, supportive and palliative care and molecular markers and research questions. It also interweaves clinical, biochemical and epidemiological studies.

The various subcommittees constituted under Task Force project on Review of Cancer Management Guidelines worked tirelessly in drafting cancer site-specific guidelines. Each member of the subcommittee's contribution towards drafting of these guidelines deserves appreciation and acknowledgement for their dedicated research, experience and effort for successful completion. We hope that this document would provide guidance to practicing doctors and researchers for the management of Soft Tissue Sarcoma and Osteosarcoma cancer patients and also focusing their research efforts in Indian context.

It is understood that this document represents the current thinking of national experts on this topic based on available evidence. Mention of drugs and clinical tests for therapy do not imply endorsement or recommendation for their use, these are examples to guide clinicians in complex decision making. We are confident that this first edition of Consensus Document for Management of Soft Tissue Sarcoma and Osteosarcoma would serve the desired purpose.

A handwritten signature in blue ink that reads "Soumya". The signature is fluid and cursive, with a long horizontal stroke at the end.

(Dr.Soumya Swaminathan)
Secretary, Department of Health Research
and Director-General, ICMR

Message

I take this opportunity to thank Indian Council of Medical Research and all the expert members of the subcommittees for having faith and considering me as chairperson of ICMR Task Force project on guidelines for management of some cancers.



The Task Force on management of cancers has been constituted to plan various research projects. Two sub-committees were constituted initially to review the literature on management practices. Subsequently, it was expanded to include more sub-committees to review the literature related to guidelines for management of various sites of cancer. The selected cancer sites are lung, breast, oesophagus, cervix, uterus, stomach, gallbladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukemia, acute lymphoblastic leukaemia, CLL, Non Hodgkin's Lymphoma-high grade, Non Hodgkin's Lymphoma-low grade, Hodgkin's Disease, Multiple Myeloma, Myelodysplastic Syndrome and Pediatric Lymphoma. All aspects related to management were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects. The published literature till December 2012 was reviewed while formulating consensus document and accordingly recommendations are made.

Now, that I have spent over quarter of century devoting my career to the fight against cancer, I have witnessed how this disease drastically alters the lives of patients and their families. The theme behind designing of the consensus document for management of cancers associated with various sites of body is to encourage all the eminent scientists and clinicians to actively participate in the diagnosis and treatment of cancers and provide educational information and support services to the patients and researchers. The assessment of public-health importance of the disease has been hampered by lack of common methods to investigate the overall worldwide burden. ICMR's National Cancer Registry Programme (NCRP) routinely collects data on cancer incidence, mortality and morbidity in India through its co-ordinating activities across the country since 1982 by Population Based and Hospital Based Cancer Registries and witnessed the rise in cancer cases. Based upon NCRP's three year report of PBCRs (2012-2014) and time trends on Cancer Incidence rates report, the burden of cancer in the country has increased many folds.

In summary, the Consensus Document for management of various cancer sites integrates diagnostic and prognostic criteria with supportive and palliative care that serve our three part mission of clinical service, education and research. Widespread use of the consensus documents will further help us to improve the document in future and thus overall optimizing the outcome of patients. I thank all the eminent faculty and scientists for the excellent work and urge all the practicing oncologists to use the document and give us further inputs..

Dr. G.K. Rath
Chairperson
ICMR Task Force Project

Preface

Bone and Soft Tissue Sarcoma (STS), encompasses a broad array of malignant tumors that arise in the mesenchymal tissues at any anatomical site. The practice of evidence based medicine is incomplete till the latest evidence is incorporated in day to day work yielding to practice guidelines depending on the need of a community or a country and availability of resources. It is well known that sarcomas due to its rarity can be poorly recognized, diagnosed late and treated inconsistently. It is believed that these guidelines may also help in identifying the areas that need to be strengthened and resources that are required with ultimate aim of delivery of optimum health care to one and all. ICMR consensus document is one such step towards standardization of care. The consensus document is by no means mandatory nor do they cover all clinical situations. Deviations in the actual dispensation of medical treatments as illustrated in any guideline are natural and bound to occur.

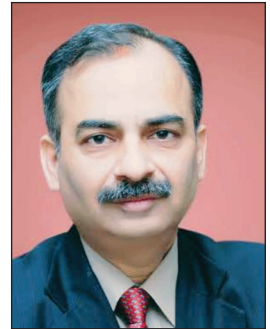
A handwritten signature in blue ink that reads "Sandeep Kumar".

Dr. Sandeep Kumar
Co-Chairperson

Subcommittee on Soft Tissue Sarcoma & Osteosarcoma

Preface

The purpose of clinical practice guidelines is to optimize patient care through recommendations based on a systematic review of evidence and an assessment of the benefits and harms of alternative care options. They represent a profession's effort to set the standards of practice based on the unbiased method of systematic review and providing the rationale for choosing the option with the largest net benefit. It therefore needs the involvement of hard-core professionals with investment of their time and effort for this labor-intensive task. The guidelines for Osteosarcoma and Ewing's sarcoma have been developed after extensive review of the contemporary literature and numerous exchanges between the experts before the preparation of the final draft. The task was mammoth especially with the fast development of technology and advances in diagnostic tools and therapeutic modalities. The guidelines though extensive and thorough are neither all-encompassing nor binding. Given the heterogeneous patient population with myriads of combinations of various confounding factors and comorbidities, the guidelines can only serve as a guide to the treating physician. As they are based on the evidence that is forever growing and often changing, the guidelines need to be reviewed and revised periodically. Like food, guidelines are best for consumption when fresh! I sincerely hope that the readers will benefit from these guidelines and this initial step will set the pace for developing guidelines for more and more diseases with major societal and healthcare impact.



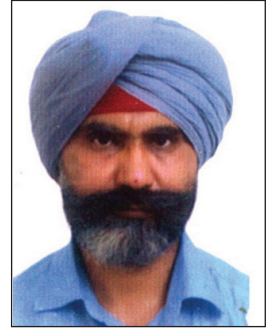
A handwritten signature in blue ink that reads "Rajesh Malhotra". The signature is written in a cursive style and is underlined with a single blue stroke.

Dr. Rajesh Malhotra
Co-Chairperson

Subcommittee on Soft Tissue Sarcoma & Osteosarcoma

Preface

Cancer is a leading cause of death worldwide. Globally Cancer of various types affects millions of population and leads to loss of lives. According to the available data through our comprehensive nationwide registries on cancer incidence, prevalence and mortality in India. Among males cancers of lung, mouth, oesophagus and stomach are leading sites of cancer and among females; cancer of breast and cervix are leading sites. Literature on management and treatment of various cancers in west is widely available but data in Indian context is sparse. Cancer of gallbladder and oesophagus followed by cancer of breast marks as leading site in North-Eastern states. Therefore, cancer research and management practices become one of the crucial tasks of importance for effective management and clinical care for patient in any country. Hence, the need to develop a nationwide consensus for clinical management and treatment for various cancers was felt.



The consensus document is based on review of available evidence about effective management and treatment of cancers in Indian setting by an expert multidisciplinary team of oncologists whose endless efforts, comments, reviews and discussions helped in shaping this document to its current form. This document also represents as first leading step towards development of guidelines for various other cancer specific sites in future. Development of these guidelines will ensure significant contribution in successful management and treatment of cancer and best care made available to patients.

I hope this document would help practicing doctors, clinicians, researchers and patients in complex decision making process in management of the disease. However, constant revision of the document forms another crucial task in future. With this, I would like to acknowledge the valuable contributions of all members of the Expert Committee in formulating, drafting and finalizing these national comprehensive guidelines which would bring uniformity in management and treatment of disease across the length and breadth of our country.



Dr R.S. Dhaliwal
Head, NCD Division

Acknowledgement

The Consensus Document on Management of Cancer is a concerted outcome of effort made by experts of varied disciplines of oncology across the nation. The Indian Council of Medical Research has constituted various sub committees to formulate the document for management of different cancer sites. The Task Force on Management of Cancers has been constituted to formulate the guidelines for management of cancer sites. The sub-committees were constituted to review the literature related to management and treatment practices being adopted nationally and internationally of different cancer sites. The selected cancer sites are that of lung, breast, oesophagus, cervix, uterus, stomach, gall bladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukaemia, ALL, CLL, NHL-high grade, NHL-low grade, HD, MM, MDS, and paediatric lymphoma. All aspects related to treatment were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects.



This document represents a joint effort of large number of individuals and it is my pleasure to acknowledge the dedication and determination of each member who worked tirelessly in completion of the document.

I would like to take this opportunity to thank Dr. GK Rath, chairperson, ICMR Task Force on Guidelines for Management of Cancer for his constant guidance and review in drafting the consensus document. The chairpersons of subcommittee Dr Sandeep Kumar and Dr Rajesh Malhotra are specially acknowledged in getting the members together, organizing the meetings and drafting the document.

I would like to express gratitude to Dr. Soumya Swaminathan, Secretary, Department of Health Research and Director General, Indian Council of Medical Research, for taking her special interest and understanding the need of formulating the guidelines which are expected to benefit the cancer patients.

I would like to acknowledge here the initiative undertaken with the able guidance of Dr. Bela Shah. I would like to thank Dr. R.S. Dhaliwal for his support and coordination in finalizing this document. I would also like to acknowledge the assistance provided by administrative staff. This document is the result of the deliberations by subcommittees constituted for this purpose. The guidelines were further ratified by circulation to extended group of researchers and practitioners drawn from all over the country. It is hoped that these guidelines will help the practicing doctors to treat cancer patients effectively and thus help them to lead a normal and healthy life.

The ICMR appreciatively acknowledges the valuable contribution of the members for extending their support in formulating these guidelines. The data inputs provided by National Cancer Registry Programme are gratefully acknowledged.



(Dr. Tanvir Kaur)
Program Officer & Coordinator

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1. Introduction

1.1 History

The first reference to the soft tissue tumors have come from Papyrus Eberus in 1500 BC. It also recommends its treatment with knife if the lesion is small¹. Others like Hippocrates (460-375 BC), Celsus (25 BC-50AD) and Galen (AD 131-200) also contributed to the initial description of the disease¹. However it was the work of Rudolf Virchow, Samuel Gross and Samuel Wilks that laid the foundation of our modern day understanding of soft tissue sarcomas (STS)²⁻⁴.

1.2 Incidence

Soft tissue sarcomas are rare tumors. They usually constitute about 1% of all malignant neoplasms. The incidence of different histologies differs in children and adults⁵ and by geographical areas. It was estimated that in the year 2008; 10390 (5720 men and 4670 women) developed soft tissue sarcomas⁶. In US, a study from the Florida cancer registry showed an annual incidence of 38 per million in 2003⁷. The analysis of large SEER database shows that the age adjusted incidence of sarcomas arising in soft tissues is 3.1/100,000 irrespective of gender⁶. These rates are a little higher in men (3.8/100,000) than women (2.6/100,000)⁶. In India, among children the incidence varies between 3.6% at Delhi to 14.8% at Barshi among males and 3.7% at Bangalore to 9.5% at Bhopal among females⁸.

1.3 Mortality

Approximately 3500 - 4000 men and women die of soft tissue sarcoma in US each year⁶. In the Surveillance, Epidemiology and End Results Program (SEER) data the reported median age of death from sarcoma was 65 years, and nearly 4.2% of this mortality occurs under the age of 20 years. The age adjusted mortality is 1.6/100,000⁶. No reliable data on mortality is available from India till date.

1.4 Epidemiology

It has been recognized in earlier studies that a number of agents (environmental and genetic) can lead to increase in incidence of soft tissue sarcomas⁵. Among the environmental agents exposure to dioxin,⁹ pesticide exposure,¹⁰ occupation as machinist, farm worker and those employed in paper and pulp industry,¹¹ after treatment of childhood cancers,¹² previous radiotherapy¹³⁻¹⁴ and among genetic factors family history,¹⁵ neurofibromatosis type 1,¹⁶ Li Fraumeni syndrome, retinoblastoma and familial polyposis coli are implicated. Werner syndrome, Rothmund-Thomson syndrome, Bloom syndrome, hereditary retinoblastoma predispose to occurrence of sarcoma. In India, among children the age adjusted incidence rates (AAR) varied from 7.2 in Kolkatta to 7.1 in Delhi in boys and 7.6 in Chennai to lowest 1.6 in Ahemadabad urban among girls.

1.5 Anatomic locations

The soft tissue tumors are found to be most commonly located in the trunk or viscera and the extremities⁷. Retroperitoneum, breast and the head and neck are the other less common sites^{7,17-20}. For osteosarcoma the site of origin is the metaphysis with rare occurrence in the diaphysis.

1.6 Pathology

The pathology of STS is diverse. The tumors are classified according to the tissue of its origin. They are classified according to the WHO classification. The tumor grade should be provided in all cases²¹. Of the various subtypes, malignant fibrous histiocytoma is the commonest followed by liposarcoma, synovial sarcoma and neurofibrosarcoma²². A detailed list of pathological types of sarcoma is given in Table 1.

2. Diagnostic work up

Diagnosis of sarcomas is based mostly on the bone/tissue biopsy and on the radiological investigations to certain extent.

2.1 Biopsy of Soft tissue

The standard approach to tissue diagnosis is multiple core needle biopsies or a large wedge biopsy for all deep seated lesions and for large superficial lesions²³⁻²⁴. Biopsies often bleed heavily during surgery but generally managed by packing. The biopsy could be in form of excision biopsy if the lesions are superficial, less than 5 cm or located in areas where the needle biopsy is either contraindicated or may prove dangerous. This biopsy should always be performed by an expert surgeon. If performing an excisional or incisional biopsy, care should be taken to place the biopsy scar properly so that it can be excised later at the time of final surgery without compromising the limb conservation. Care should also be taken that imaging of the lesion should precede biopsy. It is imperative that the site of biopsy should be properly recorded along with the depth of the lesion, as this entails a prognostic value.

A core biopsy may underestimate the grade of lesion, hence when planning a preoperative treatment, correlation with imaging findings may help in reaching a decision. The pathological diagnosis of STS is based not only on morphology but also on immunohistochemistry²¹ that helps in identifying the tissue of origin, whenever there is a doubt or in presence of high grade lesions. A definite diagnosis should always be obtained before starting any form of treatment. If required or if indicated it should always be supplemented with molecular pathology (FISH, PCR etc.)²⁵⁻²⁶. The pathological interpretation should always be done by a pathologist who is well versed with soft tissue pathology and special tests should be performed in a laboratory that is enrolled in quality control programs²¹. Biopsy related delays are common and must be avoided by anticipating the common problems and preferably a senior surgeon should obtain a reasonable tissue.

2.2 Fine needle aspiration cytology (FNAC)

Though the gold standard for diagnosis of soft tissue sarcomas is a biopsy, less invasive procedures like fine needle aspiration cytology can be used²⁷⁻²⁸. Interpretational difficulties do occur in FNAC besides the common problem of obtaining inadequate tissue. The molecular techniques can sometimes be applied to FNAC specimens in expert centers²⁹. For locally recurrent and metastatic disease, FNAC can be used to establish recurrence. Intraoperative frozen section is not usually recommended for diagnosis of soft tissue sarcomas. However, it can be important in guiding the intraoperative decisions³⁰. Intraoperative cytology along with frozen section enhances the accuracy. Its use is limited by multiplicity of the specimen³¹ and complexity involved in making a diagnosis of STS. Its use is not routinely recommended for primary diagnosis, but can be useful for guiding surgical resection margins.

2.3 Guidelines for imaging studies for soft tissue sarcoma

Imaging of soft tissue sarcoma is important and should be performed before a biopsy is taken as the hemorrhage during the biopsy can compromise the results of the imaging studies. Plain radiographs help in identifying bone involvement in extremity sarcomas³² and should always be taken if the lesions are large. Imaging is required for biopsy guidance within anatomically complex masses, staging, therapeutic response assessment and evaluation of residual mass lesions after treatment³³.

For local extent: Ultrasonography (USG), Soft Tissue X-Ray, MRI and local Computed Tomography (CT) as required

For Metastases: Chest X-Ray, CT Thorax, PET and Bone Scan as required

- **Chest X-ray**

Chest roentgenogram should be taken usually in all cases of soft tissue sarcoma to rule out pulmonary metastasis. This is not an absolute test and absence of metastasis on chest X-ray does not mean absence of metastasis. This is used as a screening test to detect large metastasis.

- **CT Thorax**

Mandatory for high grade STS and deep STS

- **Ultrasonography (USG)**

Ultrasonography³⁴ (USG) of the soft tissues is not a recommended imaging technique but its role is important when combined with doppler studies to see the relation of tumor with major vessels and chemotherapy response³⁵. Ultrasonography of the whole abdomen should be performed in all cases prior to deciding on the treatment to rule out visceral metastasis. Advance ultrasonographic techniques like 4D ultrasound are useful in select cases. Ultrasonography is also useful in detecting recurrences and guiding biopsy procedures³²⁻³⁶.

- **CT Scan**

Computerized tomography is a good imaging technique in soft tissue sarcoma. It should always be carried out with contrast enhancement. CT scan helps in staging of the disease, in delineating relations with other structures and is more useful in case of visceral and retroperitoneal sarcomas than in extremity sarcomas, where MRI is a better tool. CT scan is also a very useful modality for evaluation of response after neoadjuvant chemotherapy and for detection of lung metastasis³⁷. It is recommended that a CT scan as a minimum investigation should be done for staging and metastatic work-up before planning any treatment or biopsy. New generation 64 slice / 128 slice CT scan with non-ionic contrast and triphasic exposure where required may delineate tumor even better than MRI.

- **Magnetic Resonance Imaging (MRI)**

Magnetic resonance imaging has emerged as the preferred technique for evaluating soft tissue tumors but is limited in demonstrating the pattern of soft tissue calcification³⁸. MRI is most useful in extremity and trunk sarcoma but is limited in its utility in visceral sarcoma where a CT scan gives better results. It also differs by tumor type as for example it is difficult to diagnose liposarcoma due to absence of fat signal intensity³⁹. In-vivo magnetic resonance spectroscopy (MRS) and other newer techniques alongside MRI may give metabolomic signals to further classify a soft tissue sarcoma.

- **Positron Emission Tomography (PET)**

Positron Emission Tomography is the functional imaging which detects increased glucose uptake³³. PET has been found to be helpful in detecting the lung metastasis and response to chemotherapy and staging⁴⁰⁻⁴². PET is not universally recommended as it is not available everywhere; however, where available it provides more information than CT or MRI and may be done.

- **Scintigraphy**

Tc99m-DTPA scintigraphic studies though not routine can be performed and helps in delineating benign from malignant masses⁴³. These are also helpful in detecting bone metastases.

3. Staging and treatment of soft tissue sarcoma

3.1. STAGING

Several staging systems have been described for soft tissue sarcoma; however, the American Joint Committee on Cancer (AJCC), tumor (T), node (N), metastasis (M) classification is most acceptable. The AJCC (2010) TNM classification for sarcoma of the soft tissue is detailed in Table 2.

3.2. TREATMENT

Treatment of soft tissue sarcoma is multimodality with surgery as the mainstay of treatment⁴⁴ in non metastatic sarcoma and chemotherapy in metastatic sarcoma. The role of radiotherapy as adjuvant is fast expanding and immunotherapy is still under study trials. It is recommended that all soft tissue sarcomas should be treated with more than one modality and if possible all three modalities i.e. surgery, chemotherapy and radiotherapy be combined to achieve the best results in terms of morbidity and mortality, and hence the importance of team management cannot be understated²¹.

3.2.1. Surgery

As stated above, surgery is the treatment of choice in non metastatic soft tissue sarcoma. In tumors less than 5 cm in size a wide excision with at least 2 cm margins all around (three dimensionally) should be accomplished. In larger tumors especially those on extremity every attempt should be made at limb conservation, and hence sequencing of treatment becomes important. Surgery or biopsy should always be performed by a specialist surgeon with expertise in treating soft tissue sarcomas. The final results depend heavily on the quality of primary surgery and hence there should be no compromise with it. Surgery is also the treatment of choice for sarcomas of the head and neck, viscera, retroperitoneum and breast¹⁷⁻¹⁹.

3.2.2. Amputation

With recent advances in management of soft tissue sarcoma, amputations as a treatment modality should be avoided except in select cases where it is not possible to salvage the limb with combined modality treatment or the treatment has failed. Amputation can also be done as a palliative procedure to prevent hemorrhage from the tumor or fungation in metastatic disease where life expectancy is limited, or in recurrent tumors⁴⁵⁻⁴⁷.

3.2.3. Limb conservation

Limb conservation is the treatment of choice for all soft tissue sarcomas, if possible. It is a multimodality treatment that combines surgery with adjuvant radiotherapy (external beam or brachy) or with chemotherapy (neoadjuvant, adjuvant or isolated limb perfusion)⁴⁸⁻⁵⁰. The surgery in limb conservation

should be a minimum compartmental excision or modified compartmental excision for tumors larger than 5 cm, located within a single compartment or extending to one adjacent compartment. For smaller tumors one should try to achieve at least a wide margin⁵¹ (2 cm margin) as margin positivity leads to higher failure of limb salvage⁵²⁻⁵⁴.

3.2.4. Residual disease after resection

All cases where the margin is close or positive should undergo re-excision. In R1 resections, surgery should be considered if the margin can be achieved without major morbidity or mortality and taking into account the biology of the tumor. For R2 resections surgery is mandatory. Preoperative treatment can be considered if the surgery is thought to produce major morbidity. All excised margins should be duly labelled.

3.2.5 Pathological reporting of STS after surgery

Following parameters should be minimum reported in histopathological report after resection of soft tissue sarcoma from an experienced laboratory.

- Final diagnosis and tumor type preferably using immuno-histochemistry also
- Size of tumor
- Microscopic distance from nearest resected margin
- Tumor grade
- Assessment of treatment response if a neoadjuvant treatment (chemotherapy or radiotherapy) is used

3.2.6 Radiotherapy

Role of radiotherapy in management of soft tissue sarcoma is limited to adjuvant after limb conservation or organ preserving surgeries (e.g. breast, head neck). This can be delivered to tumor bed after excision by implanting tubes for high dose rate (HDR) interstitial brachytherapy or by external beam radiation⁵¹⁻⁵⁶.

- **Adjuvant external beam radiotherapy**

Adjuvant external beam radiotherapy is recommended for all cases of limb conservation or organ preservation surgery⁵¹⁻⁵⁷. The studies have shown that the local recurrence rates are drastically lower for patients who undergo adjuvant radiotherapy compared to those who do not. The local control is achieved in over 90% patients at 5-years and in over 85% patients at 10 years⁵¹. It is recommended to deliver 50-70 Gy in divided doses (1.8-2.0 Gy fractionation) to achieve the best response^{21,57}.

- **Brachytherapy**

High dose rate interstitial brachytherapy has become essential part of limb conservation or organ preservation surgery in soft tissue sarcoma^{51,55, 58-60}. A number of institutions practice a combination of brachytherapy with external beam radiation where 20 Gy is delivered by brachy and rest by external beam.

3.2.7 Chemotherapy

Chemotherapy of the soft tissue sarcoma has now become essential component of multimodality treatment as the most important cause of treatment failure is systemic disease, with lung and bones being the most common sites of metastasis. The chemotherapy can be delivered as neoadjuvant, adjuvant or as isolated

limb or organ perfusion. It is the treatment of choice in presence of metastatic disease and when the intent of treatment is palliative. The doses and regimes of chemotherapy in STS should be read elsewhere and administered by experts.

- **Neoadjuvant**

In initial non resectable tumors or those amenable to mutilating surgery, neoadjuvant chemotherapy may have an important role to play⁶¹⁻⁶². The most important agents are ifosfamide, and anthracyclines⁶³. Most of the time these should be used in combination. Besides increase in resectability rates, neoadjuvant chemotherapy has also been reported to improve survival⁶⁴⁻⁶⁵. Gemcitabine is being used increasingly in combination with Paclitaxel or Docetaxel⁶⁶⁻⁷⁰.

- **Adjuvant chemotherapy**

Its use as a routine has remained controversial. A recent meta-analysis has confirmed the marginal efficacy of chemotherapy in localized resectable soft-tissue sarcoma with respect to local recurrence, distant recurrence, overall recurrence and overall survival. The benefit is further improved with the use of doxorubicin and ifosfamide based combinations⁷¹. With the availability of these results some centers recommend to use adjuvant chemotherapy after R0 resection for patients with soft tissue sarcoma⁷²⁻⁷³ although there is no level I evidence so far.

- **Isolated hyperthermic limb perfusion**

Isolated hyperthermic limb perfusion or regional hyperthermia using tumor necrosis factor alpha and melphalan has been tried in select cases of locally advanced disease where the disease is either not amenable to surgical resection or the resection is thought to produce significant morbidity like loss of limb^{21,74}. This is still in evolving phase and there is not enough evidence to recommend it as a procedure either alone or in combination with chemotherapy. Let these be done by those undertaking approved trials.

- **Palliative chemotherapy for advance or metastatic disease**

For metastatic advance disease chemotherapy is the treatment of choice and role of surgery is limited to prevent local complications like hemorrhage. The chemotherapy can be delivered with single agent or as combination chemotherapy depending on the performance status of the patient. The agents that may be used are ifosfamide, doxorubicin, gemcitabine and docetaxel⁷⁵⁻⁷⁶. Other newer agents include pazopanib and trabectedin. Pazopanib is generally preferred in non-adipocytic STS whereas trabectedin is used in translocation related sarcomas such as liposarcoma, leiomyosarcoma and synovial sarcoma. Immunotherapy with imatinib is recommended for rare cases of gastrointestinal stromal tumors and dermatofibrosarcoma protruberans which are not amenable to surgical resection. Such treatments are best taken up by those conducting trials on targetted therapies as these are very expensive also.

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1. Introduction

Osteosarcoma is the commonest malignant bone tumor with an incidence of 0.2 to 0.3 per 100,000/year. In adolescence it accounts for more than 10% of all solid tumors. The site of origin is the metaphysis with rare occurrence in the diaphysis. The commonest geographical area of involvement is around knee (about three-fourth of all osteosarcomas). Males are more commonly affected (M: F = 1.4:1). The commonest geographical area of involvement is around knee (about three-fourth of all osteosarcomas).

Osteosarcomas are divided into High and Low grade tumors. High grade osteosarcomas include conventional osteosarcoma, telangiectatic osteosarcoma, small cell and high grade surface osteosarcomas. Low grade osteosarcomas include low grade central and Parosteal osteosarcoma. Periosteal Chondrogenic type of osteosarcoma is an intermediate grade osteosarcoma. Osteosarcomas can be broadly classified into intramedullary, surface and extraskeletal. Conventional osteosarcoma accounts for 80%-90% of all osteosarcomas. Previous radiation therapy, Paget's disease of the bone and germ cell abnormalities such as the Li-Fraumeni syndrome (germ line mutation of the p53 gene), Werner syndrome, Rothmund-Thomson syndrome, Bloom syndrome, hereditary retinoblastoma] predispose to occurrence of osteosarcoma. Typically, the presentation is with non-mechanical pain of insidious origin that gradually becomes constant and may be present at night. Localized swelling and limitation of joint movements occur later.

The following chapters include consensus statement for Diagnosis, Staging and Treatment for osteosarcoma..

2. Staging and Diagnosis

A. Diagnosis

These include the investigations to diagnose and stage the osteosarcomas.

B. Staging

For staging osteosarcomas, radiography and biopsy are required. The consensus statements for each of these are given below:

1. Laboratory Work-up

All patients should have the following blood parameters at the pre-chemotherapy stage: Complete blood counts, serum alkaline phosphatase and serum LDH.

2. Imaging studies

2.1 For characterization of the lesion

- Plain radiograph of the affected area in two planes to describe osseous changes (location of lesion, pattern of destruction, zone of transition, margins, periosteal reaction, new bone formation,

cortical integrity, soft tissue component). The radiographs must include entire bone (joint above and below).

2.2. To define the local extent of tumor

2.2.1 Magnetic Resonance Imaging (MRI) for defining the local extent of tumor (Doing an MRI is essential in staging osteosarcomas but doing a Contrast Enhanced MRI depends on availability and surgeon's preference. It may be noted that MRI is the best imaging modality for appropriate level of oncological clearance in osteosarcomas).

- Should be performed prior to the biopsy.
- Should include the whole involved bone as well as the neighboring joints, so as to not miss skip lesions (intramedullary tumor foci without direct contact with the primary lesion).
- Should be evaluated for the intramedullary extent, soft tissue extension, relation to vessels and nerves, intraarticular extension and skip lesions.

Pre-chemotherapy MRI should be done prior to biopsy and post chemotherapy MRI should be done at least 14 days after the completion of last cycle and within 2 weeks prior to surgery.

2.2.2 Computerized Tomography (CT) Scan

- Should only be used in the case of a diagnostic dilemma, to visualize more clearly calcification, periosteal bone formation, and cortical destruction.
- Indicated as an alternative to MRI, in patients in whom MRI is contraindicated, to define the local extent of tumor.

2.3 For Systemic extent

- Chest X-ray
- NCCT scan of the thorax
- Radionuclide bone scan

2.3.1 Positron Emission Tomography (PET) scan

PET scan is not included in universal recommendations due to lack of widespread availability and cost. If PET scan facility is present at the treatment centre, it can be useful, but is not the standard of care.

- ***For pretreatment staging***
- ***For recurrence assessment***

FDG-PET is indicated to differentiate fibrosis and post therapeutic tissue changes due to healing from residual tumor tissue or local relapse.

- *For treatment response assessment: Patients should undergo fludeoxyglucose 18F positron-emission tomography (FDG-PET)/CT scanning at baseline and then 12 weeks after the start of treatment*

3. Bone Biopsy

- The surgeon who will be carrying out the definitive procedure on the patient should do the biopsy.
- Before doing a biopsy, all the laboratory and imaging work-up of the patient should have been completed.

- There should be no contamination of normal tissues
- Biopsy incision should be in line with the planned incision for definitive treatment. Avoid transverse incision.
- The surgeon should such plan the biopsy scar that it should fall in line with the incision of the definitive surgery when it is done at a later date (so that it could be excised).
- Core needle biopsy is the preferred method of biopsy in bone tumors. Image guided biopsy should be done in deep-seated lesions.
- Adequate homeostasis should be maintained at all times.
- Deep dissection in case of open biopsies should be sharp with avoidance of major neurovascular planes. No exsanguination of the limb is done in case a tourniquet is being used. Drain exit site should allow excision at the time of definitive surgery.
- Samples should be taken for microbiological culture as well as histology.
- All samples should be adequately stored and labeled (with patient's informed consent for the same). All details should be made available to the pathologist on a biopsy requisition form.
- Samples should be interpreted by an experienced pathologist. There should be appropriate communication between surgeon, radiologist and pathologist. All biopsy material should go to a single pathologist.
- Image guided biopsies (using an image intensifier, CT scan or navigation) should be used for deeper lesions like those in the pelvis. Imaging studies can also indicate the most representative part of the lesion.
- Fresh tissue is needed for molecular studies and should be taken before formalin fixation.
- Tumor banking should be considered wherever the facilities and the informed consent are available for later analysis as well as diagnosis and translational research into molecular pathology of cancer.

Prognostic factors for osteosarcoma of the extremities and trunk

Worse prognosis with

- Older age
- Location of tumor at proximal extremity or axial skeleton
- Large tumor volume
- Elevated serum alkaline phosphatase or lactate dehydrogenase (LDH)
- Metastases at the time of presentation
- Poor histological response to preoperative chemotherapy

The WHO classification of bone tumors is detailed in Table 3. The UICC/TNM staging is detailed in Table 4.

3. Management practices for treatment

Therapeutic guidelines

This includes management practices for chemotherapy, surgery and radiotherapy in osteosarcomas given below

3.1 Consensus Statement for Chemotherapy in Osteosarcomas

Multiagent chemotherapy is the standard of care in osteosarcomas. Doxorubicin, cisplatin, high-dose methotrexate, etoposide and ifosfamide have demonstrated antitumor activity in osteosarcoma. Most current protocols incorporate these agents in 3 or 4 drug combinations. Most current protocols are based on four to six drug combinations. Minimum of 3 cycles are recommended prior to local control. The above chemotherapy combinations should be administered with adequate supportive care including growth factors. Immune modulator muramyl tripeptide added to postoperative chemotherapy may improve overall survival and is approved in Europe for patients younger than 30 years of age with completely resected localized osteosarcomas. Chemotherapeutic drugs may result in renal, cardiac, and auditory dysfunction in addition to common side effects like myelo suppression, infection and neuropathy. Patients must therefore have baseline renal function testing and assessment of cardiac function as well as an audiogram (in case of treatment with cisplatin). Sperm banking is recommended for male patients of reproductive age while female patients would benefit with counseling by a fertility physician.

A variety of pre-and post operative combinations are used in common practice though ideal combination and optimal treatment duration is not yet defined. The addition of adjuvant and neoadjuvant chemotherapy regimens has improved outcome in patients with localized osteosarcoma.

- **Neoadjuvant Chemotherapy**

Neoadjuvant chemotherapy is recommended for all patients with high grade osteosarcoma. It is associated with an improved prognosis in patients with high-grade localized osteosarcoma with 2 year. Event Free Survival (EFS) and Overall Survival (OS) reported as 75% and 94% respectively. Good histo-pathological response (greater than 90% necrosis) to neoadjuvant chemotherapy has been shown to be predictive of survival regardless of the type of chemotherapy administered after surgery. The 5-year DFS and OS in good and poor responders have been reported as 67.9% vs 51.3% ($p < 0.0001$) and 78.4% versus 63.7% ($p < 0.0001$) respectively².

The results of neoadjuvant chemotherapy in patients with metastatic disease at presentation remain poor and the 2-year EFS and OS have been reported as 21% and 55% respectively.

Chemotherapy should be considered prior to wide excision in patients with periosteal osteosarcoma and high-grade osteosarcoma. Postoperative chemotherapy is recommended for patients with low grade (intramedullary or surface) or periosteal sarcoma with pathologic findings of high-grade disease and all cases of high-grade osteosarcoma.

- **Adjuvant Chemotherapy**

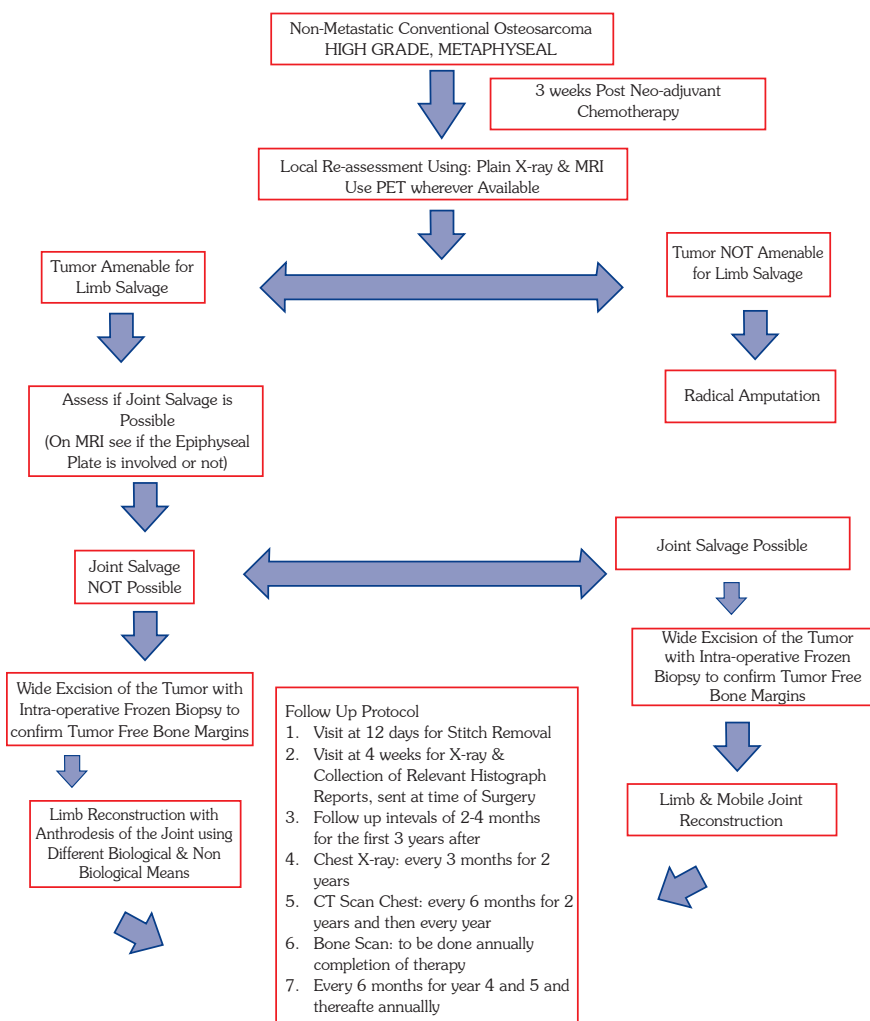
Preoperative chemotherapy is recommended in patients with high-grade osteosarcoma prior to wide excision, following which patients should receive several more cycles of combination chemotherapy. Combination of etoposide with ifosfamide has been evaluated and found to be beneficial in poor responders in retrospective analysis. Samarium 153 ethylene diamine tetramethylene phosphonate (153 Sm-EDTMP) has also been shown to be effective for pain palliation in patients with osteosarcoma local recurrences or osteoblastic bone metastases.

3.2. Consensus Statement for Surgery of Osteosarcomas

The goal of surgery is safe removal of the tumor with maximum preservation of function. Limb salvage should be considered in most patients if reasonable function can be expected. Surgery of the primary tumor should be performed only after adequate preoperative staging and planning has been done. The goal is to achieve adequate oncologic clearance. Conventionally, quantitative parameters are used to define resection margins. A marrow margin of 3 cm as evaluated on the T1 weighted MRI image is usually considered adequate clearance in osteosarcomas. It is important to achieve a tumor free margin in the operating room itself and this can be confirmed by a frozen biopsy sent from the margins of the parent bone after tumor resection. Due to anatomical constraints, it is not always possible to achieve these absolute distances. The margin can be quantitatively less in the case of resistant anatomic barriers, such as muscular fasciae, periosteum, joint capsule, tendon, tendon sheath, epineurium, vascular sheath and cartilage.

Decisions about the optimal surgical procedure (i.e. limb salvage or amputation) should be made on an individual case to case basis depending on various factors (patient's age, tumor site, size, extent and response to neoadjuvant therapy). The type of surgical reconstruction will depend on patient and surgeon choice, experience and facilities available following discussion of the risks and benefits of different options. An amputation is indicated in all cases where limb salvage is not possible. Wide excision is the primary treatment for patients with low-grade (intramedullary and surface) osteosarcoma.

Management practices for osteosarcomas



3.3 Consensus Statement for Radiotherapy in Osteosarcoma

Osteosarcoma (OS) has a reputation of being radioresistant and therefore radiotherapy (RT) is not usually practiced in the management of OS. However, RT may be useful in select group of patients.

- **Indications for Radiotherapy in Osteosarcomas**

Postoperative RT: Indicated in patients with positive or close surgical margins especially for the sites like pelvis, thorax, head and neck etc.

Dose: 50-60 Gy in 25-30 fractions over 5-6 weeks.

Palliative RT: Indicated in incurable or metastatic patients for alleviation of local symptoms like pain, bleeding, fungation or metastatic symptoms like dyspnea, spinal cord compression, brain metastases etc.

Dose: 8-20 Gy in 1-5 fractions.

Extracorporeal and Intra-operative RT: The extracorporeal technique includes en bloc resection of the tumor and surrounding soft tissues, irradiation of the specimen, and re-implantation, often with the aid of prostheses. With definitive Intra Operative RT, the operative field is exposed and radiotherapy is administered. No resection of the tumor is performed. Extracorporeal irradiation is associated with rates of local recurrence similar to those seen in other limb salvage procedures (<5%). The reported local control rate for definitive Intra Operative RT is 20% to 25%.

Doses: Extracorporeal RT: 50 Gy in a single fraction.

Intra-operative RT: 45-80 Gy in a single fraction

Radionuclide Therapy

Indicated in the treatment of bony metastatic osteosarcoma using various bone seeking radio-isotopes like rhenium, strontium and samarium. The major toxicity is decrease in the platelet and white blood cell counts. It provides good pain relief.

Techniques of Irradiation

An immobilization device is generally needed. The field should be contoured specifically to the anatomic site for the individual patient. In most cases, multiple fields are used. To maintain a functional limb after irradiation, a strip of skin should be spared, and one should avoid high-dose irradiation to the full width of the joint. Treatment on Linear Accelerator is preferred over cobalt unit. Use of modern RT techniques like Intensity-Modulated Radiation Therapy (IMRT) or conformal RT is encouraged.

Volume of Irradiation

The treatment volume is determined by plain radiographs, bone scan, CT, and MRI. It is customary to define the tumor volume based on the largest volume of these studies (the “worst-case volume”). A margin of 2-5 cm is then allowed.

3.4 Follow Up

Examination during surveillance should include a complete physical examination, chest imaging and imaging of the primary site. Bone scan and/or PET scan may also be considered if clinically indicated.

Once treatment is completed, surveillance is recommended.

*Every 3 months for the first 2 years

*Every 4 months for the 3rd year

*Every 6 months for 4th and 5th year

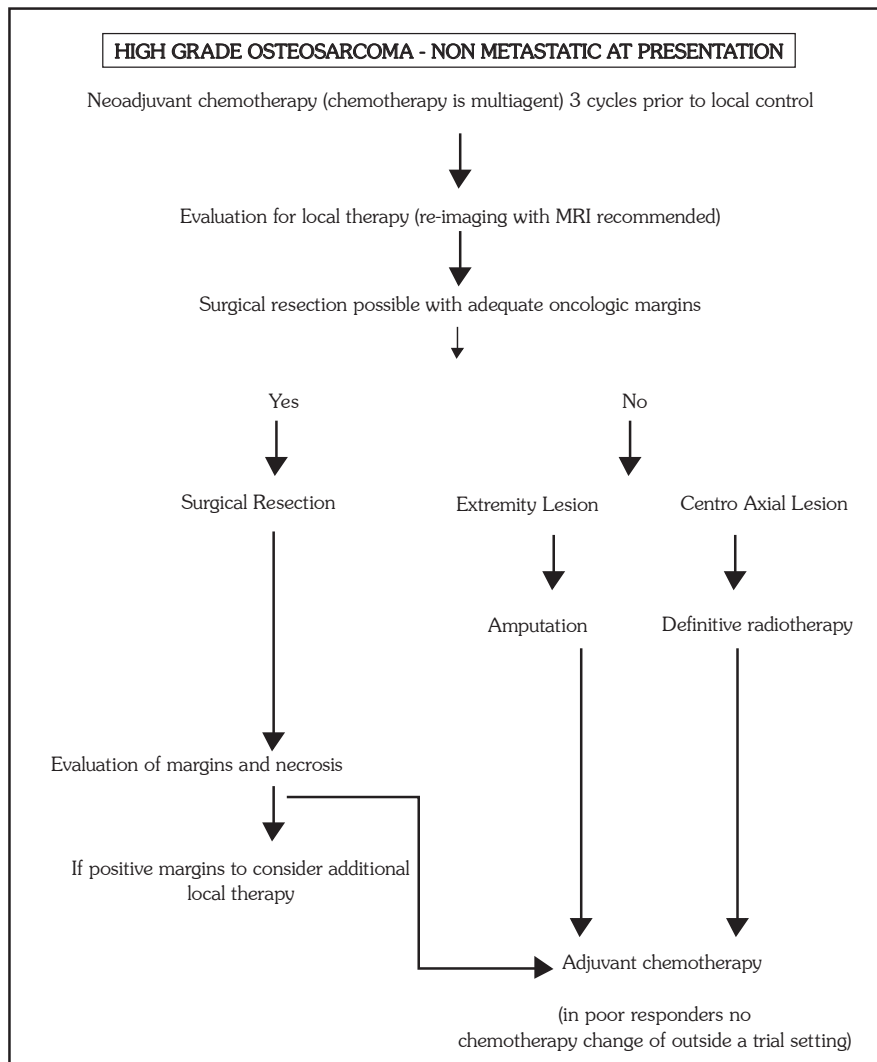
*Yearly thereafter

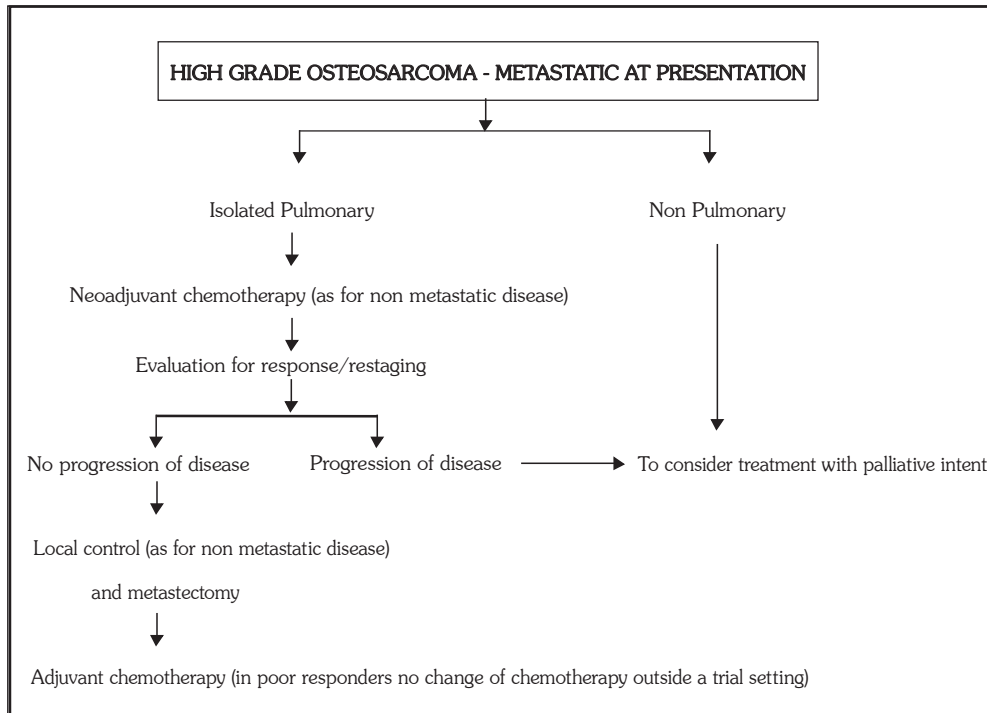
The relapse is treated with chemotherapy and/or resection if possible. Responders are followed up with surveillance while further relapse is considered for resection, Samarium or palliative RT.

3.5 Osteosarcoma with metastatic disease at presentation

Metastatic disease at presentation has worse outcomes. The presence of solitary pulmonary metastasis amenable to resection has the same overall survival as non metastatic disease.

Primary metastatic osteosarcoma patients should be treated with curative intent along with principles of non-metastatic osteosarcoma. Surgical removal of all known metastatic deposits is mandatory if cure is to be aimed. Approximately 30% of all patients with primary metastatic osteosarcoma and more than 40% of those who achieve a complete surgical remission become long term survivors.





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1. Introduction

Ewing sarcoma (including primitive neuroectodermal tumor of bone) is the second most common primary malignant bone tumor in children and adolescents. The median age at diagnosis is around 15 years. It is more common among males (M: F=1.5:1). The incidence of Ewing sarcoma is around 0.3/100,000/year. The most frequent sites of involvement are the long bones, pelvis, ribs, and the vertebral column. Histologically it is a high-grade tumor.

The management practices for Ewing Sarcoma need both Staging and Treatment practices. These are as follows:

A. Diagnosis: These include the investigations to diagnose and stage the Ewing Sarcomas. Almost one fourth patients are diagnosed with metastatic disease (lung 10%, bone/bone marrow 10%, combination or other 5%). Staging strategies must be tailored to detect lung, bone and bone marrow metastases.

B. Staging: For staging Ewing sarcomas; laboratory work up, radiography and biopsies are required. The consensus statements for each of these are given below:

1. Laboratory Work-up

All patients should have the following blood parameters at the pre-chemotherapy stage: Haemoglobin, total leucocyte counts, differential counts and serum LDH. All patients must have a bone marrow biopsy and bone marrow aspiration before starting treatment.

2. Radiography: Radiography is to be used for the following purposes

2.1 For characterization of the Lesion

- Plain radiographs of the affected area in two planes to describe osseous changes (location of lesion, pattern of destruction, zone of transition, margins, periosteal reaction, cortical integrity, soft tissue component)

2.2 To define the local extent of tumor

2.2.1 MRI for defining the local extent of tumor (doing an MRI is essential in staging Ewings sarcomas but doing a contrast enhanced MRI depends on availability and surgeon's preference. It may be noted that MRI is the best imaging modality for appropriate level of oncological clearance in Ewings sarcomas)

- Should be performed prior to the biopsy.
- Should include the whole involved bone as well as the neighboring joints, so as to not miss skip lesions (intramedullary tumor foci without direct contact with the primary lesion).

- Should be evaluated for the intramedullary extent, soft tissue extension, relation to vessels and nerves, intraarticular extension, skip lesions.
- Pre-chemotherapy MRI should be done prior to biopsy.
- Post chemotherapy MRI should be done at least 14 days after the completion of last cycle and within 2 weeks prior to surgery. Change in the size of the soft tissue mass confirms tumor response.

2.2.2 Computerized Tomography (CT) scan

- Should only be used in the case of a diagnostic problem or doubt, to visualize more clearly calcification, periosteal bone formation, and cortical destruction.
- Indicated as an alternative to MRI, in patients in whom MRI is contraindicated, to define the local extent of tumor

2.3 For Systemic extent

1. Chest X-ray
2. NCCT scan of the thorax
3. Radionuclide bone scan
4. Bone Marrow Biopsy

2.3.1 PET scan is not included in universal recommendations due to lack of widespread availability and cost. However, If PET scan facility is present at the treatment centre, it can be useful.

For recurrence assessment: FDG-PET is indicated to differentiate fibrosis and post therapeutic tissue changes due to healing from residual tumor tissue or local relapse.

For treatment response assessment: Patients should undergo fludeoxyglucose 18F positron-emission tomography (FDG-PET)/CT scanning at baseline and then 12 weeks after the start of treatment.

3. Bone Biopsy

- The surgeon who will be carrying out the definitive procedure on the patient should do the biopsy.
- Before doing a biopsy, all the laboratory and imaging work-up of the patient should have been completed.
- There should be no contamination of normal tissues
- In the appendicular skeleton, the biopsy incision should be in the long axis of the bone. Avoid transverse incision.
- The surgeon should such plan the biopsy scar that it should fall in line with the scar of the definitive surgery when it is done at a later date (so that it could be excised).
- Core needle biopsy is the preferred method of biopsy in bone tumors but open biopsy should be considered in patients with deep lying lesions or where a previous core biopsy has failed to give a definitive tissue.
- Adequate homeostasis should be maintained at all times.
- Deep dissection in case of open biopsies should be sharp with avoidance of major neurovascular planes. In case a tourniquet is used, no exsanguination of the limb should be done. Drain exit site should allow excision at the time of definitive surgery.
- Samples should be taken for microbiological culture as well as histology.

- All samples should be adequately stored and labeled (with patient's informed consent for the same). All details should be made available to the pathologist on a biopsy requisition form.
- Samples should be interpreted by an experienced pathologist. There should be appropriate communication between surgeon, radiologist and pathologist. All samples should go to a single pathologist.
- Image guided biopsies (using an image intensifier, CT scan or navigation) should be used for deeper lesions like those in the pelvis. Imaging studies can also indicate the most representative part of the lesion.
- Fresh tissue is needed for molecular studies and should be taken before formalin fixation.
- Tumor banking should be considered wherever the facilities and the informed consent are available for later analysis as well as diagnosis and translational research into molecular pathology of cancer.

Histology of Ewing Sarcoma

The tumor cells are positive for PAS and CD 99 (MIC2). Sufficient material should be provided for conventional histology, immunohistochemistry, molecular pathology and biobanking (fresh, unfixed material). Molecular biology studies have shown that all these tumors share a common gene rearrangement involving the EWS gene on chromosome 22, most commonly reciprocal translocation t (11; 22) (q24;q12) but others may occur. Most Ewing Sarcomas can be recognized with classical haematoxylin-eosin (H&E) and immunohistochemistry including CD99 along with other immunohistochemical stains to adequately rule out other round blue cell tumors, such as rhabdomyosarcoma, lymphoma; additionally immunohistochemistry is needed to rule out other CD 99 positive sarcomas such as synovial sarcoma. However, EWS translocation detection is mandatory when clinical-pathological presentation is unusual, or histological diagnosis is doubtful. A reference laboratory for ES diagnosis should have both FISH (good choice when only formalin-fixed paraffin embedded tissue or touch tissues (imprints) available) and RT-PCR (when frozen tissue is available). Light microscopic analysis of bone marrow aspirates and biopsies from metastases are mandatory for staging. Cytogenetic analysis by chromosome banding techniques applying Multicolor FISH/Spectral FISH can be helpful to detect multi chromosomal rearrangements in cases in which more conventional molecular techniques (FISH, RT-PCR) cannot help.

Prognostic Factors

Worse prognosis with

1. Bone metastases: Bone metastases are associated with a poorer outcome than lung/pleura metastases (<20% survival compared with 20%-40% at 5 years).
2. Tumor size or volume
3. Serum LDH levels
4. Axial localization
5. Older age (>15 years)
6. Poor histological response to preoperative chemotherapy.
7. Incomplete or no surgery for local therapy.

2. Management practices for treatment

2.1. Therapeutic guidelines

ES is a radiation sensitive tumor. Radiotherapy, in combination with chemotherapy can achieve local control but definitive surgery when feasible has to be regarded as the first choice of local therapy. Incomplete surgery even when followed by postoperative radiotherapy is not superior to RT alone and should be avoided. However incomplete surgery should be followed by post operative radiotherapy.

Therapeutic practices include practices for radiotherapy, chemotherapy and surgery in Ewing sarcomas and are as follows:

2.1.1 Consensus statement for Radiotherapy in Ewing's Sarcomas

Ewing Sarcoma is considered a radiosensitive tumor and therefore radiotherapy (RT) plays an important role in the management. Definitive Radiotherapy is an alternative to surgery in selected group of patients. It can be practiced in following settings:

Definitive RT: Radiotherapy alone should be applied if complete surgery is not feasible. Mainly indicated in patients with inoperable lesions in sites like spine, skull, pelvis, head and neck, thorax etc.

Postoperative RT: indicated in patients with gross residual disease or positive surgical margins or poor histological response in the surgical specimen (i.e.>10% viable tumor cells), although this has to be discussed with the multidiscipline team before a final decision is made.

Palliative RT: indicated in incurable or metastatic patients for alleviation of local symptoms like pain, bleeding, fungation or metastatic symptoms like dyspnea, spinal cord compression, brain metastases etc.

Whole Lung Irradiation: indicated for patients with lung metastases especially when they are multiple and non-resectable.

Hemithorax Irradiation: indicated for a rib primary with pleural effusion, RT is given to the corresponding hemithorax.

Doses of RT

Definitive RT: 55-60 Gy in 28-30 fractions over 5-7 weeks. Initial dose 45 Gy to wide field (pre-chemotherapy volume) plus boost of 10-15 Gy to the reduced field.

Post-operative RT: For margin positive disease, 45-50.4 Gy in 25-28 fractions over 5-6 weeks. Initial dose 45 Gy to wide field plus boost of 5.4 Gy to the reduced field. For gross residual disease, total dose of 55.8 Gy should be delivered (45 Gy to wide field plus 10 Gy boost to reduced field).

Palliative RT: 8-20 Gy in 1-5 fractions.

Whole Lung Irradiation: 15 Gy in 10 fractions over 2 weeks.

Hemithorax Irradiation: 15 Gy in 10 fractions over 2 weeks.

Techniques of Irradiation

An immobilization device is generally needed. The field should be contoured specifically to the anatomic site for the individual patient. In most cases, multiple fields are used. To maintain a functional limb after irradiation, a strip of skin should be spared, and one should avoid high-dose irradiation to the full width

of the joint. Treatment on Linear Accelerator is preferred over cobalt unit. Use of modern RT techniques like Intensity-modulated radiation therapy (IMRT) or conformal RT is encouraged.

Volume of Irradiation

The treatment volume is determined by plain radiographs, CT and MRI. It is customary to define the tumor volume based on the largest volume of these studies. MRI is preferred at the time of planning if available. The radiation fields are tailored depending on the primary site. The initial field should include the prechemotherapy tumor volume with a 2 to 4 cm margin. The boost should be to the residual tumor volume at the time of radiotherapy plus a 1.5- to 2.0-cm margin. For extremity lesions, spare a 1–2 cm strip of skin to prevent lymphedema.

For whole lung irradiation, both lungs are irradiated (lung bath). For hemithorax irradiation, the entire hemithorax including chest wall is treated. Dose to the heart is minimized by shielding.

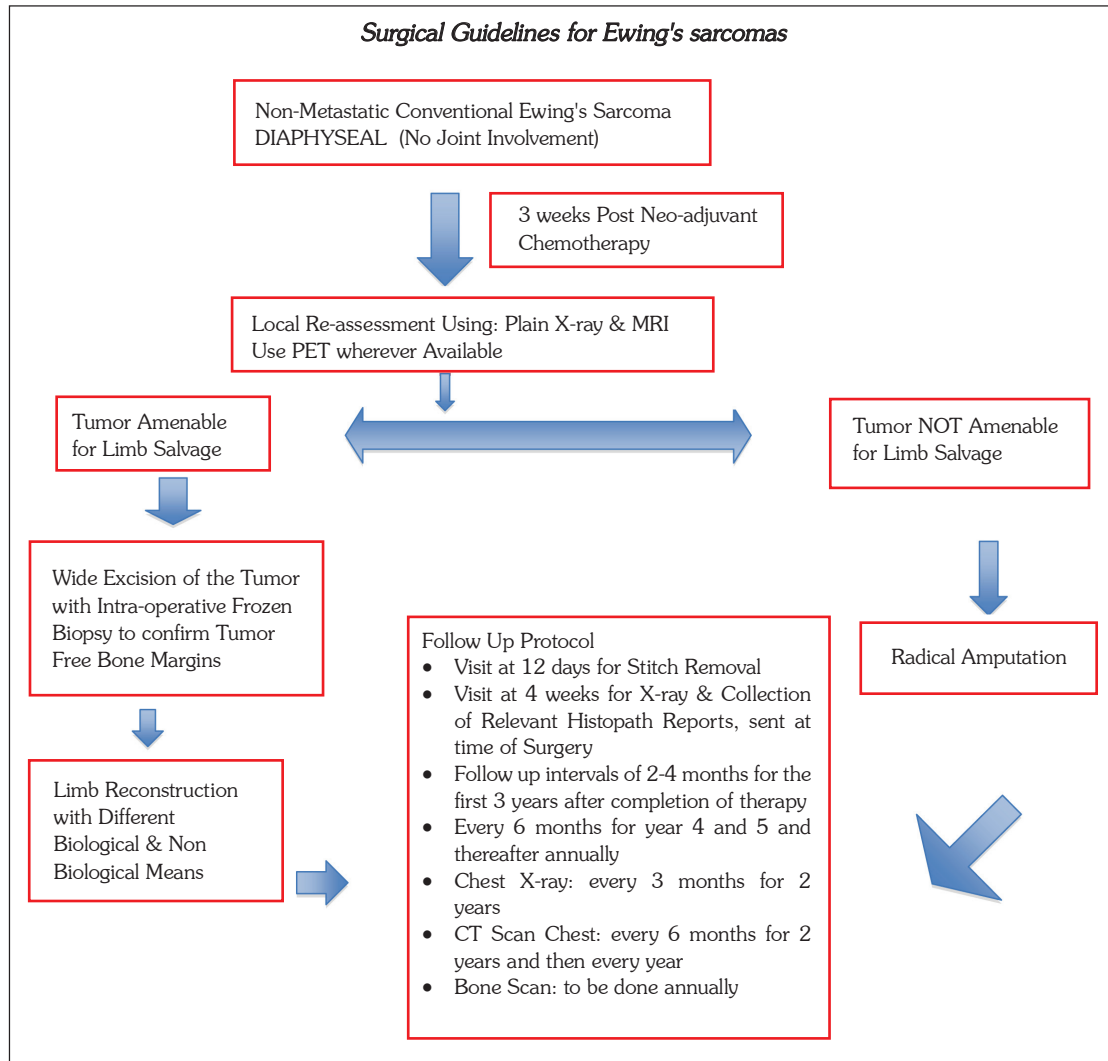
2.1.2. Consensus statement for Chemotherapy in Ewing's Sarcomas

In localized disease, with surgery or radiotherapy alone, 5-year survival is <10%. Current multi modality treatments including chemotherapy have shown 60-70% survival in localized and about 20-40% in metastatic disease. All current trials employ 3-6 cycles of initial chemotherapy after biopsy followed by local therapy and another 6-10 cycles of chemotherapy usually applied at 3 week intervals. Treatment duration is about 48 weeks. Multiagent chemotherapy is the standard of care in Ewing sarcomas. Agents considered most active in Ewing sarcoma include doxorubicin, cyclophosphamide, ifosfamide, vincristine, dactinomycin, and etoposide. Most current protocols incorporate these agents in 4 to 6 drug combinations. The above chemotherapy combinations should be administered with adequate supportive care. Chemotherapeutic drugs may result in renal, cardiac, and auditory dysfunction in addition to common side effects like myelosuppression, infection and neuropathy. Patients must therefore have baseline renal function testing and assessment of cardiac function. Sperm banking is recommended for male patients of reproductive age while female patients would benefit with counseling by a fertility physician.

2.1.3. Surgical practices for Ewing's sarcomas

Complete surgery, where feasible is regarded as the best modality of local control. Intralesional surgery should be avoided as it offers no advantage over radiotherapy alone. Surgery of the primary tumor should be performed only after adequate preoperative staging and planning has been done. The goal is to achieve adequate oncologic clearance. Conventionally, quantitative parameters are used to define resection margins. A marrow margin of 3 cm as evaluated on the T1 weighted MRI image is usually considered adequate clearance in Ewing's sarcomas. It is important to achieve a tumor free margin in the operating room itself and this can be confirmed by a frozen section sent from the margins of the host bone after tumor resection. Due to anatomical constraints it is not always possible to achieve these absolute distances. The margin can be quantitatively less in the case of resistant anatomic barriers, such as muscular fasciae, periosteum, joint capsule, tendon, tendon sheath, epineurium, vascular sheath and cartilage.

Decisions about the optimal surgical procedure (i.e. limb salvage or amputation) should be made on an individual case to case basis depending on various factors (patient's age, tumor site, size, extent and response to neoadjuvant therapy). The type of surgical reconstruction will depend on patient and surgeon choice, experience and facilities available following discussion of the risks and benefits of different options. A radical amputation is indicated in cases where limb salvage is not possible. It involves the removal of the whole compartment bearing the tumor. RT is also an option in this group of patients.



For adult patients with ES and extraskeletal ES, same treatment principles are applicable/followed/relevant/practiced.

Metastatic and Recurrent Disease

Patients presenting with lung only metastatic disease are treated with chemotherapy as for patients with localized disease; however, they have worse prognosis. Those with metastasis to bone and/ or bone marrow are generally treated with palliative intent although a small proportion of them with good response to chemotherapy have a potential to achieve long term complete remission. The principles of local site control remain same as for those with localized disease provided these patients achieve response at metastatic sites of disease.

High dose chemotherapy followed by autologous stem cell rescue is promising but convincing evidence of benefit is pending.

Whole lung irradiation may confer an advantage in patients with lung metastases. Role of surgical resection of residual metastases is less well defined.

Patients with bone or bone marrow metastases and patients with recurrent disease have 5 year survival rates of only 20%.

The only prognostic factor in relapse is the time to relapse with patients relapsing later than 2 years from initial diagnosis having better outcomes.

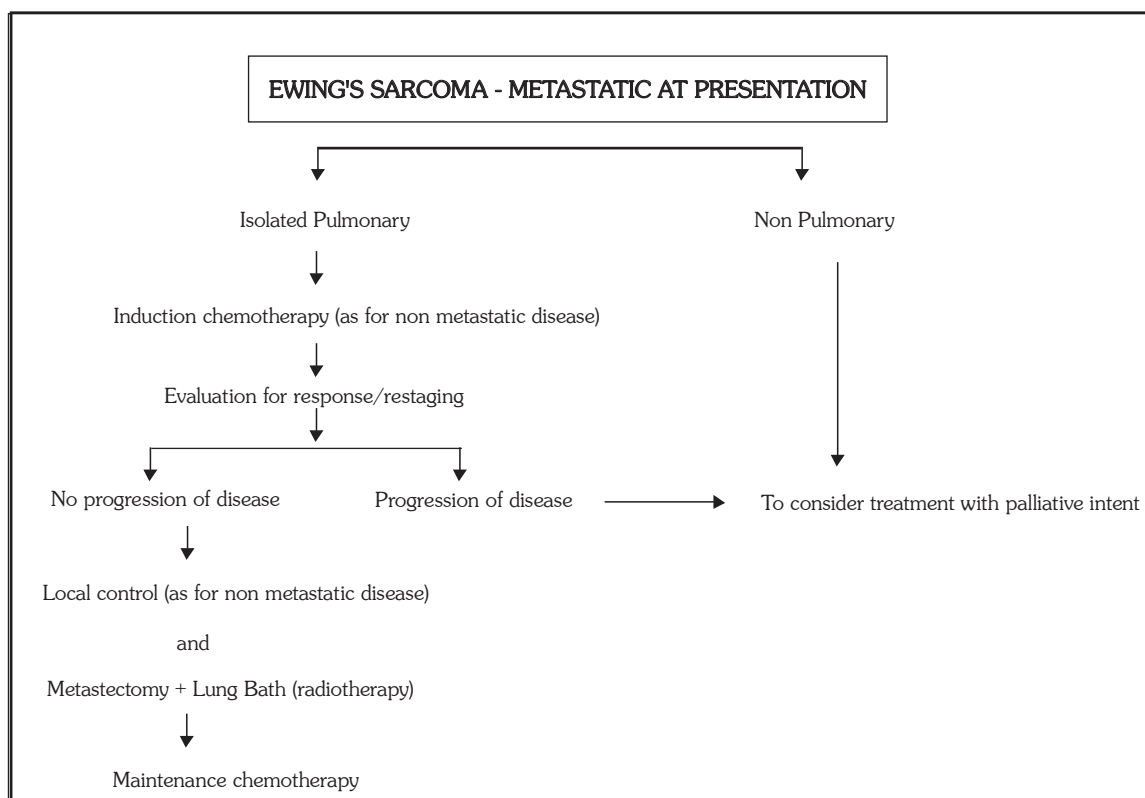
Chemotherapy regimens for relapsed disease are not standardized and are usually based on alkylating agents (cyclophosphamide, high dose ifosfamide) in combination with topoisomerase inhibitors (etoposide, topotecan) or irinotecan with temozolomide.

Follow up

Follow up intends to detect either local recurrence or metastatic disease early when treatment may be effective. Follow up should include physical examination, local examination, local imaging and chest x-rays/CT scan, bone scan, assessment of function and, any complications of reconstruction. It is also important to evaluate long term toxicity effects of chemotherapy and radiotherapy.

Recommended intervals for follow up after completion of chemotherapy are

- Every 3 months for the first two years
- Every 4 months for years 3rd & 4th
- Every 6 months for year 5
- And then annually



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4 ABBREVIATIONS

STS - Soft Tissue Sarcoma

SEER - Surveillance, Epidemiology and End Results program

WHO - World Health Organization

FISH - Fluorescent in Situ Hybridization

PCR - Polymerase Chain Reaction

FNAC - Fine Needle Aspiration Cytology

USG - Ultrasonography

CT - Computerized Tomography

MRI- Magnetic Resonance Imaging

PET - Positron Emission Tomography

DTPA - Diethylene-Triamine-Pentaacetate

AJCC - American Joint Committee on Cancer

HDR - High Dose Rate

DTIC - Dimethyltriazeno imidazole carboxamide (dacarbazine)

LDH - Lactate Dehydrogenase

NCCT - Negative Contrast Computed Tomography

EFS - Event Free Survival

OS - Overall Survival

RT - Radiotherapy

IORT - Intra-operative RT

IMRT - Intensity Modulated Radiation Therapy

FDG-PET - Fludeoxyglucose 18 F Positron-Emission Tomography

RT-PCR - Reverse Transcriptase PCR

H & E - Haematoxylin and Eosin

***Desirable/Ideal:** Tests and treatment that may not be available at all centres but the centres should aspire to have them in near future.

Essential: Minimum that should be offered to all the patients by all centres treating patients with cancer.

Table 1: WHO classification of SOFT TISSUE TUMORS

▶ **ADIPOCYTIC TUMOURS**

Benign

Lipoma 8850/0*
Lipomatosis 8850/0
Lipomatosis of nerve 8850/0
Lipoblastoma / Lipoblastomatosis 8881/0
Angiolipoma 8861/0
Myolipoma 8890/0
Chondroid lipoma 8862/0
Extrarenal angiomyolipoma 8860/0
Extra-adrenal myelolipoma 8870/0
Spindle cell/ 8857/0
Pleomorphic lipoma 8854/0
Hibernoma 8880/0

Intermediate (locally aggressive)

Atypical lipomatous tumour/
Well differentiated liposarcoma 8851/3

Malignant

Dedifferentiated liposarcoma 8858/3
Myxoid liposarcoma 8852/3
Round cell liposarcoma 8853/3
Pleomorphic liposarcoma 8854/3
Mixed-type liposarcoma 8855/3
Liposarcoma, not otherwise specified 8850/3

▶ **FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS**

Benign

Nodular fasciitis
Proliferative fasciitis
Proliferative myositis
Myositis ossificans
Fibro-osseous pseudotumour of digits
Ischaemic fasciitis
Elastofibroma 8820/0
Fibrous hamartoma of infancy
Myofibroma / Myofibromatosis 8824/0
Fibromatosis colli
Juvenile hyaline fibromatosis
Inclusion body fibromatosis
Fibroma of tendon sheath 8810/0
Desmoplastic fibroblastoma 8810/0
Myofibroblastoma 8825/0

Calcifying aponeurotic fibroma 8810/0

Angiomyofibroblastoma 8826/0

Cellular angiofibroma 9160/0

Nuchal-type fibroma 8810/0

Gardner fibroma 8810/0

Calcifying fibrous tumour

Giant cell angiofibroma 9160/0

Intermediate (locally aggressive)

Superficial fibromatoses (palmar / plantar)

Desmoid-type fibromatoses 8821/1

Lipofibromatosis

Intermediate (rarely metastasizing)

Solitary fibrous tumour 8815/1

and haemangiopericytoma 9150/1

(incl. lipomatous haemangiopericytoma)

Inflammatory myofibroblastic tumour 8825/1

Low grade myofibroblastic sarcoma 8825/3

Myxoinflammatory

fibroblastic sarcoma 8811/3

Infantile fibrosarcoma 8814/3

Malignant

Adult fibrosarcoma 8810/3

Myxofibrosarcoma 8811/3

Low grade fibromyxoid sarcoma 8811/3

hyalinizing spindle cell tumour

Sclerosing epithelioid fibrosarcoma 8810/3

► SO-CALLED FIBROHISTIOCYTIC TUMOURS

Benign

Giant cell tumour of tendon sheath 9252/0

Diffuse-type giant cell tumour 9251/0

Deep benign fibrous histiocytoma 8830/0

Intermediate (rarely metastasizing)

Plexiform fibrohistiocytic tumour 8835/1

Giant cell tumour of soft tissues 9251/1

Malignant

Pleomorphic 'MFH' / Undifferentiated

Pleomorphic sarcoma 8830/3

Giant cell 'MFH' / Undifferentiated

Pleomorphic sarcoma with giant cells 8830/3

Inflammatory 'MFH' / Undifferentiated

Pleomorphic sarcoma with prominent inflammation 8830/3

► **SMOOTH MUSCLE TUMOURS**

Angioleiomyoma 8894/0
Deep leiomyoma 8890/0
Genital leiomyoma 8890/0
Leiomyosarcoma (excluding skin) 8890/3

► **PERICYTIC (PERIVASCULAR) TUMOURS**

Glomus tumour (and variants) 8711/0
Malignant glomus tumour 8711/3
Myopericytoma 8713/1

► **SKELETAL MUSCLE TUMOURS**

Benign

Rhabdomyoma 8900/0
Adult type 8904/0; fetal type 8903/0; genital type 8905/0

Malignant

Embryonal rhabdomyosarcoma 8910/3
(incl. spindle cell, 8912/3
botryoid, anaplastic) 8910/3
Alveolar rhabdomyosarcoma
(incl. solid, anaplastic) 8920/3
Pleomorphic rhabdomyosarcoma 8901/3

► **VASCULAR TUMOURS**

Benign

Haemangiomas of subcut/deep soft tissue: 9120/0
capillary 9131/0
cavernous 9121/0
arteriovenous 9123/0
venous 9122/0
intramuscular 9132/0
synovial 9120/0
Epithelioid haemangioma 9125/0
Angiomatosis
Lymphangioma 9170/0

Intermediate (locally aggressive)

Kaposiform haemangioendothelioma 9130/1

Intermediate (rarely metastasizing)

Retiform haemangioendothelioma 9135/1
Papillary intralymphatic angioendothelioma 9135/1
Composite haemangioendothelioma 9130/1
Kaposi sarcoma 9140/3

Malignant

EEpithelioid haemangioendothelioma 9133/3
Angiosarcoma of soft tissue 9120/3

► CHONDRO-OSSEOUS TUMOURS

Soft tissue chondroma 9220/0

Mesenchymal chondrosarcoma 9240/3

Extraskeletal osteosarcoma 9180/3

► TUMOURS OF UNCERTAIN DIFFERENTIATION

Benign

Intramuscular myxoma 8840/0

(incl. cellular variant)

Juxta-articular myxoma 8840/0

Deep ('aggressive') angiomyxoma 8841/0

Pleomorphic hyalinizing

angiectatic tumour

Ectopic hamartomatous thymoma 8587/0

Intermediate (rarely metastasizing)

Angiomatoid fibrous histiocyoma 8836/1

Ossifying fibromyxoid tumour 8842/0

(incl. atypical / malignant)

Mixed tumour/ 8940/1

Myoepithelioma/ 8982/1

Parachordoma 9373/1

Malignant

Synovial sarcoma 9040/3

Epithelioid sarcoma 8804/3

Alveolar soft part sarcoma 9581/3

Clear cell sarcoma of soft tissue 9044/3

Extraskeletal myxoid chondrosarcoma 9231/3

("chordoid" type)

PNET / Extraskeletal Ewing tumour

pPNET 9364/3

extraskeletal Ewing tumour 9260/3

Desmoplastic small round cell tumour 8806/3

Extra-renal rhabdoid tumour 8963/3

Malignant mesenchymoma 8990/3

Neoplasms with perivascular epithelioid

cell differentiation (PEComa)

clear cell myomelanocytic tumour

Intimal sarcoma 8800/3

*Morphology code of the International Classification of Diseases for Oncology (ICD-O) and the Systematize Nomenclature of Medicine (<http://snomed.org>).

Table 2: UICC – AJCC TNM classification of SOFT TISSUE SARCOMA

Soft Tissue Sarcomas ICD-O C38.1-3, C47-49

Rules for Classification

There should be histological confirmation of the disease and division of cases by histological type and grade.

Anatomical Sites

1. Connective, subcutaneous, and other soft tissues (C49), peripheral nerves (C47)
2. Retroperitoneum (C48.0)
3. Mediastinum: anterior (38.1); posterior (C38.2); mediastinum, NOS (C38.3)

Histological Types of Tumors The following histological types are included, with ICD-O morphology codes:

Alveolar soft part sarcoma	9581/3
Epithelioid sarcoma	8804/3
Extraskeletal chondrosarcoma	9220/3
Extraskeletal osteosarcoma	9180/3
Extraskeletal Ewing sarcoma	9260/3
Primitive neuroectodermal tumour (PNET)	9473/3
Fibrosarcoma	8810/3
Leiomyosarcoma	8890/3
Liposarcoma	8850/3
Malignant fibrous histiocyoma	8830/3
Malignant haemangiopericytoma	9150/3
Malignant mesenchymoma	8990/3
Malignant peripheral nerve sheath tumour	9540/3
Rhabdomyosarcoma	8900/3
Synovial sarcoma	9040/3
Sarcoma, not otherwise specified (NOS)	8800/3

The following histological types are not included:

Kaposi Sarcoma

Dermatofibrosarcoma (protuberans)

Fibromatosis (desmoid tumour)

Sarcoma arising from the dura mater, brain, hollow viscera, or parenchymatous organs (with the exception of breast sarcomas).

Angiosarcoma, an aggressive sarcoma, is excluded because its natural history is not consistent with the classification.

Gastrointestinal stromal tumours are separately classified in the Digestive System Tumours section..

Regional Lymph Nodes

The regional lymph nodes are those appropriate to the site of the primary tumour. Regional node involvement is rare and cases in which nodal status is not assessed either clinically or pathologically could be considered N0 instead of NX or pNX.

TNM CLINICAL CLASSIFICATION

T- Primary Tumour: TX- Primary tumour cannot be assessed, T0- No evidence of primary tumour, T1- Tumour 5cm or less in greatest dimension, T1a- Superficial tumour*, T1b Deep Tumour*, T2- Tumour more than 5cm in greatest dimension, T2a- Superficial tumour*, T2b Deep tumour*

N- Regional Lymph Nodes:

NX - Regional lymph nodes cannot be assessed, N0 - No regional lymph node metastasis, N1 Regional lymph node metastasis

M- Distant Metastasis: M0- No distant metastasis, M1-Distant metastasis,

G- Histopathological Grading

Translation table for three-and four-grade system to a two-grade (low grade vs high grade) system

TNM Two-grade System	Three-grade System	Four-grade System
Low grade	Grade 1	Grade 1
	Grade 2	Grade 2
High grade	Grade 2	Grade 3
	Grade 3	Grade 4

Stage Grouping

Stage IA	T1a	N0	M0	Low grade
	T1b	N0	M0	Low grade
Stage IB	T2a	N0	M0	Low grade
	T2b	N0	M0	Low grade
Stage IIA	T1a	N0	M0	High grade
	T1b	N0	M0	High grade
Stage IIB	T2a	N0	M0	High grade
Stage III	T2b	N0	M0	High grade
	Any T	N1	M0	Any grade
Stage IV	Any T	Any N	M1	Any grade

Summary - Soft Tissue Sarcoma

T1	< 5cm
T1a	Superficial
T1b	Deep
T2	> 5cm
T2a	Superficial
T2b	Deep
N1	Regional lymph nodes
	Low grade
	High grade

Physical examination, diagnostic radiology and biopsy provide the AJCC criteria input data needed to stage STS. *The AJCC system uses 4 histologic grades whilst the recommended UK system (FNCLCC) uses 3. The matching grades are G1 = low grade, G2 = intermediate grade and G3 and G4 = high grade. Reproduced from Sobin L, Gospodarowicz M, Wittekind C (Eds.). *TNM classification of malignant tumors (seventh edition)*. Wiley-Blackwell, Delhi press, Delhi 2009; 157-61.

Table 3: WHO classification of PRIMARY MALIGNANT BONE TUMORS

- 1) Osteosarcoma
 - i) Intramedullary high-grade
 - a. Osteoblastic
 - b. chondroblastic
 - c. fibroblastic
 - d. mixed
 - e. small cell
 - f. Other (telangectic, epithelioid, chondromixoid fibroma-like, chondroblastoma-like, osteoblatoma like, giant cell rich)
 - ii) Intramedullary low-grade
 - iii) Juxtacortical high grade (high grade surface osteosarcoma)
 - iv) Juxta cortical intermediate grade chondroblastic (periosteal osteosarcoma)
 - v) Juxta cortical low grade (parosteal osteosarcoma)
- 2) Chondrosarcoma
 - a) Intramedullary
 - i) Conventional (Hyline/myxoid)
 - ii) Clear cell
 - iii) dedifferentiated
 - iv) mesenchymal
 - b) Juxtacortical
- 3) Primittive neuroectodermal tumors/Ewings' sarcoma
- 4) Angiosarcoma
 - a) Conventional
 - b) Epithelioid angiosarcoma
- 5) Fibrosarcoma / Malignant fibrous histiocytoma
- 6) Chordoma
 - a) Conventional
 - b) dedifferentiated
- 7) Adamentinoma
 - a) Conventional
 - b) Well differentiated - osteofibrous dysplasia like
- 8) Other
 - a) Liposarcoma
 - b) leiomyosarcoma
 - c) malignant peripheral nerve sheath tumor
 - d) rhabdomyosarcoma
 - e) malignant mesenchymoma
 - f) malignant hemangiopericytoma

Table 4: UICC/AJCC TNM classification for BONE TUMORS (7th Edition - 2010)

Primary tumor (T)

- Tx- Primary tumor can not be assessed
- T0- No primary tumor
- T1- Tumor 8 cm or less in greatest dimension
- T2- Tumor more than 8 cm in greatest dimension
- T3 - Discontinues tumor in primary bone site

Regional lymph nodes

- Nx- Nodes cannot be assessed
- N0- No regional node metastasis
- N1- Regional node metastasis

Distant metastasis

- M0- No distant metastasis
- M1- Distant metastasis
- M1a- Lung
- M1b- Other distant sites

Anatomic stage / Prognostic grouping

Stage IA	T1	N0	M0	G1,2 low grade Gx
Stage IB	T2, 3	N0	M0	G1,2 low grade Gx
Stage IIA	T1	N0	M0	G3,4 high grade
Stage IIB	T2	N0	M0	G3,4 high grade
Stage III	T3	N0	M0	G3,4 high grade
Stage IVA	Any T	N0	M1a	Any G
Stage IVB	Any T	N1	Any M	Any G
	Any T	Any N	M1b	Any G

Histological grade

- Gx- Grade cannot be assessed
- G1- Well differentiated low grade
- G2- Moderately differentiated low grade
- G3- Poorly differentiated
- G4- Undifferentiated



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