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Chemotherapy Have No Role in the Management of Soft Tissue Sarcoma Review Article! Radiation Oncologist Perspective

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Abstract: ***Soft tissue sarcomas are less common cancer, merely 1% of all cancer in human body so far as site specific is concern more than 75% cases of STS occurs in adult 40% arises from lower extremities and 30% arises from trunk and retroperitoneum, 20% arises from upper extremities, 10% STS occurs in head and neck region, due never radiotherapy techniques as well as advancement in field of surgery now survival rate of soft tissue sarcoma drastically increased, chemotherapy role is yet not Clearfield in different research studies done so far, so we will be reviewing from start to end of soft tissue sarcomas management. The preliminary data from the EORTC 62931, the largest trial of adjuvant chemotherapy for STS, has failed to demonstrate any benefit from chemotherapy in local control, progression free survival or overall survival in patients treated with adjuvant chemotherapy henceforth author considered role of adjuvant chemotherapy remains unproven***

Keywords: Soft tissue sarcomas, Radiotherapy, Surgery. Chemotherapy

1. Discussion

Aetiology For the vast majority of cases, the aetiology is unknown, although there are certain genetic associations, such as the 10% lifetime risk of malignant peripheral nerve sheath tumour (MPNST) in individuals with familial neurofibromatosis, caused by mutations in the NF1 gene no other example is the increased risk of sarcomas, both bone and soft tissue, in patients who have had a familial retinoblastoma, caused by inherited mutations in the RB gene]. Similarly, there is an increased risk of sarcomas, and other cancers in families with Li-Fraumeni syndrome who have inherited mutations in the TP53 tumour suppressor gene

A large number of tumors are recognized by histological examinations are most common along Immunohistochemistry, Cytogenetics these test can be useful for advanced kind of chemotherapy selection however, for giving radiotherapy molecular test are of no significance, Tumor size and anatomical sites, which affect resectability and tumor grade are the most significant prognostic factors directly affecting the prognosis overall survival, local control for soft tissue sarcomas. Furthermore deep rather than superficial location of STS (soft tissue sarcoma), recurrences after previous surgery or radiotherapy confer the worst prognosis for sarcomas , Surgery is the most effective treatment to ensure cure of STS and the first intervention should be to remove tumor with a wide margin.

Table 1. Staging Systems for Soft Tissue Sarcoma of the Extremity or Trunk

Staging System	Description
AJCC 7th edition[a]	
T1a	Tumor ≤5 cm in greatest dimension, superficial
T1b	Tumor ≤5 cm in greatest dimension, deep
T2a	Tumor >5 cm in greatest dimension, superficial
T2b	Tumor >5 cm in greatest dimension, deep
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M0	No distant metastasis
M1	Distant metastasis
Stage groups	
Stage IA	T1a/b; N0; M0; G1
Stage IB	T2a/b; N0; M0; G1
Stage IIA	T1a/b; N0; M0; G2/3
Stage IIB	T2a/b; N0; M0; G2
Stage III	T2a/b; N0; M0; G3
	Any T; N1; M0; any G
Stage IV	Any T; Any N; M1; any G
AJCC 8th edition[b]	
T1	Tumor ≤5 cm in greatest dimension
T2	Tumor >5 cm and ≤10 cm in greatest dimension
T3	Tumor >10 cm and ≤15 cm in greatest dimension
T4	Tumor >15 cm in greatest dimension
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis
M0	No distant metastasis
M1	Distant metastasis
Stage groups	
Stage IA	T1; N0; M0; G1
Stage IB	T2, T3, T4; N0; M0; G1
Stage II	T1; N0; M0; G2/3
Stage IIIA	T2; N0; M0; G2/3
Stage IIIB	T3, T4; N0; M0; G2/3
Stage IV	Any T; N1; M0; any G
	Any T; any N; M1; any G
Vanderbilt staging system	
T1a	Tumor ≤5 cm in greatest dimension, superficial
T1b	Tumor ≤5 cm in greatest dimension, deep
T2a	Tumor >5 cm and ≤10 cm in greatest dimension, superficial
T2b	Tumor >5 cm and ≤10 cm in greatest dimension, deep
T3a	Tumor >10 cm in greatest dimension, superficial
T3b	Tumor >10 cm in greatest dimension, deep
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis
M0	No distant metastasis
M1	Distant metastasis
Stage groups	
Stage I	Any T; N0; M0; G1
	T1a; N0; M0; G2
Stage II	T1b; N0; M0; G2
	T2a/b; N0; M0; G2
	T3a/b; N0; M0; G2
	T1a/b; N0; M0; G3
	T2a; N0; M0; G3
Stage IIIA	T2b; N0; M0; G3
	T3a; N0; M0; G3
Stage IIIB	T3b; N0; M0; G3
	Any T; N1; M0; any G
	Any T; any N; M1; G1
Stage IV	Any T; any N; M1; G2/3

[a]Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.
[b]Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC, www.springer.com.

Figure 1: AJCC Staging in soft tissue sarcoma.

Good prognostic factors soft tissue sarcomas are:
1) Size less than 5cm.
2) Site superficial in origin.
3) Grade low grade

Bad prognostic factors are
1) Size more than 5cm
2) Site deeper in origin.
3) Grade High grade.

Grading of Soft tissue Sarcomas:
Tumor well differentiated/ Moderately differentiated /Poorly differentiated, Depending upon factors
1) Number of mitosis per high power field.
2) Nuclear cytoplasmic ratios.
3) Amount of necrosis present in tumor tissue.

Test done with help of DNA flow cytomertry that tell us DNA poloidy status like Anuepoloid tumors are high grade and Diploid tumors are of low grade.

In general various prognostic factors in STC are identified:
1) **Grade** its most important predictor of both overall survival and disease free survival in patients in soft tissue sarcoma, like five year recurrence free survival found to be like Grade-1 is 68%., Grade 2 is 50% and grade -3 only 25% having recurrence free survival .

2) **Size** 5cm is cut off if less than this good prognosis and more than 5cm having bad prognosis.
3) **Site ex**tremities tumor do better in compare to trunk or retro peritoneum site tumors because of easy accessibility of tumor for radiotherapy and surgery as well.
4) **Disease status** primary tumor does better in compare to recurrent tumors.
5) 5-Skin involvement ulcerations of over line skin makes the survival worst**.**
6) **Lymph node status** Presence of regional lymph node decreases disease free survival (DFS) as well as overall survival.
7) **DNA Poloidy Status of tumor:** Aneupoloid tumors are high grade thus decreases survival in compare of Diploid tumors having low grade and good survival rate.
8) **Surgical margin status** margin positive tumors having increases risk of loco regional recurrences hence decreases the survival rate.
9) **Age:** Younger the age better the survival rate of STS.

Soft Tissue Sarcomas & Lymphnode Metastasis:
Overall lymphnode metastasis in STS found to be only in 4% cases, however there are few STS those having high propensity towards lymphnode metastasis example are, Synovial sarcoma, Epitheloid sarcoma, Rhabdomayosarcomas above verities of STS having as high as 14 to 20% of lymphnode metastasis

Rhabdomayosarcoma: It accounts 15% of all sarcomas they arise from striated muscles (skeletal muscle), which are highly differentiated and rarely undergo mitosis, three kind of Rhabdomayosarcoma are described, Alveolar type, Embryonal type these verity found commonly in childhood but Pleomorphic type found in adult .

Synovial Sarcomas: Arises from tenosynovial tissues are two types Monophasic or Biphasic type, this variety of STS commonly involves joint tenosinovial tissues.

Epetheloid Sarcomas: Usually involves extremities and involving commonly aponeurotic structure and having high propensity of lymphnode involvements.

Malignant Fibrous Histocytoma : They arises from histocytes cells more commonly found in adult in more than 40% cases usual age of presentations is 6^{th} to 7^{th} decades of life

Management of soft tissue sarcomas:

Imaging: Any patient with a suspected STS should be referred to a diagnostic centre for triple assessment with clinical history, imaging and biopsy. Whilst the preferred method of imaging is MRI, other options including computerized tomography (CT) or ultrasound may be appropriate depending on local expertise. Patients with a confirmed STS should be staged with a high resolution CT chest to exclude pulmonary metastases prior to definitive treatment, although plain chest X-ray may be acceptable in a minority of cases (e.g., the very elderly and those with small low grade lesions) . CT abdomen and isotope bone scan are not recommended as routine staging investigations, however depending on the histological type and other clinical features, further staging assessments may be recommended (e.g., regional lymph node assessment for synovial sarcoma, clear cell sarcoma or epithelioid sarcoma; abdominal and pelvic CT scan for Myxoidliposarcoma). Positron emission tomography (PET) scanning may be helpful in specific circumstances (e.g., prior to radical amputation following recurrent disease), but cannot at the present time be recommended as a routine staging investigation in patients with STS.

Biopsy: The standard approach to diagnosis of a suspicious mass is core needle biopsy—several cores should be taken to maximise diagnostic yield. However, an Incisional biopsy may be necessary on occasion and excisional biopsy may be the most practical option for superficial lesions <5 cm diameter. The biopsy should be planned in such a way that the biopsy tract can be safely removed at the time of definitive surgery to reduce the risk of seeding and should be performed either at a diagnostic clinic or by a sarcoma surgeon or radiologist following discussion with the surgeon. Fine needle aspiration (FNA) is not recommended as a primary diagnostic modality, although it may be useful in confirming disease recurrence**.**

Histology-Diagnosis: Histological diagnosis should be made according to the WHO Classification to determine the grade and stage of the tumour]. The grade should be provided in all cases where possible based on a recognised system. Because of tumour heterogeneity, a core biopsy may not provide accurate information about grade. In addition, certain translocation-driven sarcomas have a relatively uniform cellular morphology and, as such, can be misleadingly scored as intermediate, rather than high grade. This is especially true for myxoid/round cell liposarcoma, for which a different grading system based on the percentage of round cells is often used. Additional information may be provided by radiological imaging but histology may be modified following assessment of the complete surgical resection specimen. Pathologic diagnosis relies on morphology and immunohistochemistry. It should be complemented, for those diagnoses characterized by a chromosomal translocation, using molecular pathology, for example, fluorescent in-situ hybridisation (FISH) or reverse transcription polymerase chain reaction (RT-PCR), in particular when the clinical pathologic presentation is unusual, or the histological diagnosis is doubtful.

Classification of Margins: Four categories of surgical margin have been described histologically: intralesional, marginal, wide and radical. Intralesional Margin runs through tumour and therefore tumour remains. Marginal Surgical plane runs through Pseudocapsule (reactive zone). The local recurrence rate is high because of tumour satellites in the reactive tissue. Wide Surgical plane is in normal tissue but in the same compartment as the tumour. The recurrence rate is low and is related only to skip lesions in the affected compartment.

Radical the tumour is removed including affected compartments and there is a minimal risk of local recurrence. If feasible, it is recommended that tumour

samples should be collected and frozen both for future research and because new molecular pathological assessment techniques may become available later that could yield new information of direct value to the individual patient.

Surgery for Localised Disease: Surgery is the standard treatment for all patients with adult-type, localised soft tissue sarcomas, and it should be performed by an appropriately trained surgeon. Evaluation of the resectability of a tumour is determined by the surgeon in consultation with the MDT, and depends on the tumour stage and the patient's co-morbidity. The primary aim of surgery is to completely excise the tumour with a margin of normal tissue. What constitutes an acceptable margin of normal tissue is not universally agreed but is commonly accepted as 1 cm soft tissue or equivalent (e.g., a layer of fascia). However, on occasion, anatomical constraints mean that a true wide resection is not possible without the sacrifice of critical anatomical structures (such as major nerves, or blood vessels) and in this situation, it may be acceptable to leave a planned microscopic positive surgical margin, having considered the risks of recurrence and morbidity of more radical surgery and having discussed these fully with the patient.

For patients who have undergone surgery and have an unplanned positive margin, re-excision should be undertaken if adequate margins can be achieved. Macroscopic residual disease imparts a poor prognosis and local control is unlikely to be achieved even with addition of post operative radiotherapy.

Patients with tumours that, because of size or position, are considered borderline resectable should be considered for down staging treatment (neo-adjuvant) with either chemotherapy or radiotherapy depending on histology of the tumour and the performance status of the patient.

Adjuvant Radiotherapy: Postoperative radiotherapy is considered to be the standard approach for nearly all intermediate or high-grade soft tissue sarcomas. This allows preservation of function with similar local control rates and survival to radical resection (i.e., compartmental excision/amputation). The majority of patients with low grade tumours will not require radiotherapy, however it should be considered for those with large, deep tumours that are incompletely resected, especially if adjacent to vital structures that could limit further surgery in the future. Patients who have undergone a compartmental resection or amputation do not require adjuvant irradiation assuming that the margins are clear.

Figure 2: Preoperative radiotherapy indications

The recommended postoperative radiation dose is 60–66 Gy in 1.8–2 Gy fractions. A two-phase technique using a shrinking field is commonly employed; 50 Gy to the initial larger volume followed by 10–16 Gy to a smaller volume. This dose may need to be reduced if the field includes critical structures (for example the brachial plexus).

Adjuvant Chemotherapy: The role of adjuvant chemotherapy remains unproven. Although currently not regarded as standard treatment, and it may be considered for individual patients with potentially chemosensitive subtypes on the basis that benefit cannot be excluded, even though it has not been proven. It may be also considered in situations where local relapse would be untreatable or where adequate radiotherapy could not be administered owing to the sensitivity of adjacent structures, for example, spinal cord. A meta-analysis published in 1997 reported an improvement in local control and progression free survival, however although there was a trend towards an overall survival benefit this was not statistically significant. These data have been supported by two more recent over views. The latter did not use original trial data and included a large Italian trial which, when published in 2001, reported a significant survival benefit for adjuvant. Chemotherapy, however this has not been maintained with long-term follow up . The preliminary data from the EORTC 62931, the largest trial of adjuvant chemotherapy for STS, has failed to demonstrate any benefit from chemotherapy in local control, progression free survival or overall survival in patients treated with adjuvant chemotherapy. Interestingly however it did demonstrate improved survival in both groups compared with previous studies. This was thought to be due to improved surgical techniques and increased use of adjuvant radiotherapy. The results of the final analyses are awaited with interest, together with an up-dated meta-analysis.

Radiotherapy Recommendations:

1) Postoperative radiotherapy is recommended following surgical resection of the primary tumour for the majority of patients with high-grade tumours, and for selected patients with large or marginally excised, low-grade tumours.
2) The recommended dose for postoperative radiotherapy is 60–66 Gy; in 2 Gy per fraction

3) Pre-operative radiotherapy is advantageous in terms of long-term functional outcome with equivalent rates of disease control when compared with postoperative radiotherapy. There is however an increased risk of postoperative wound complications.

Role of Brachytherapy in soft tissue sarcoma:: Flexible weir implant commonly used, we can use horizontal implant or vertical implant but horizontal implant having advantage as we need less number of implants for same tumor volume, precaution is to be taken that between two catheters distance must not be less than 1cm and should not be more than 1.5 cm. ***In Low grade sarcoma,*** Brach therapy to be used if size of tumor is more than 5cm or in case of recurrences in low grade soft tissue sarcoma, dose used in such cases is 36Gy in 9 fractions. During implant care must be given to protect neurovascular bundle near tumor bed so we use Jelfoam or spacers to maintain adequate gap between catheter and neurovascular bundle.

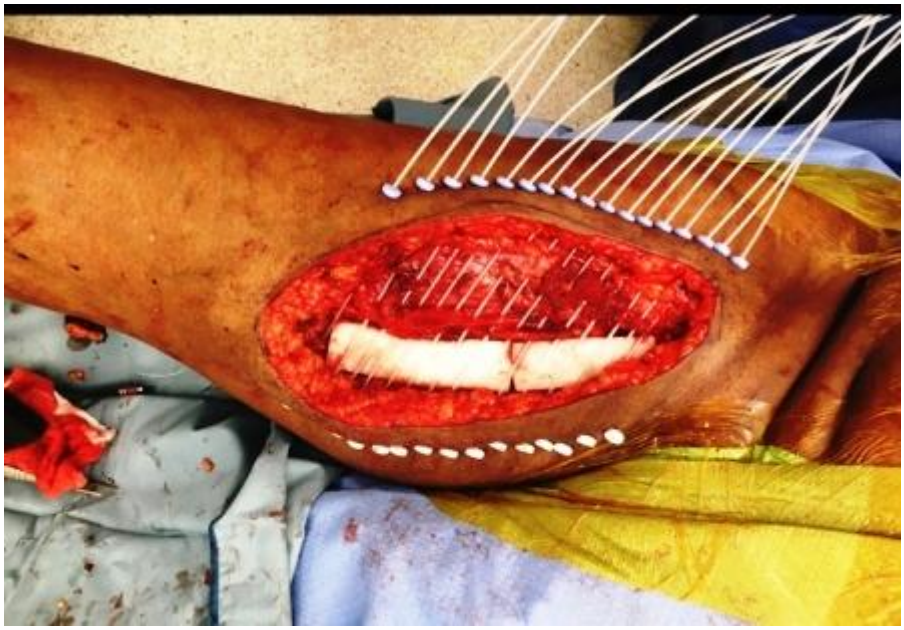

Figure 3: HDR Brachytherapy catheters in situ

Do and donts in Brachytherapy:

1) Brachytherapy planning requires military discipline.
2) Radiation oncologist must be fully aware of each and every applicators about its dimensions, length etc.
3) Tip of Applicators and first dwell point distance must be fully aware of, distance travel by source from catheter tip to first dwell point is known as ***INDEXER LENGTH***.
4) After implantation is being done covering tumor volume as required with margin we get an CECT done is ideal to acquires images and with help of scan images we target delineation.

Conflict of Interest: None

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