EVIDENCE BASED MANAGEMENT FOR SOFT TISSUE SARCOMA

A – Documentation of exact extent of primary tumor

Clinical examination, X-ray, MRI (MRI has become the premier imaging modality for the evaluation of musculoskeletal tumors because of its excellent soft tissue contrast, its sensitivity to bone marrow and soft tissue edema, and its multiple imaging planes).

All soft tissue masses deep to the investing fascia should be considered to be sarcoma unless proven otherwise.

B – Pathological confirmation of diagnosis by biopsy

A needle biopsy can often confirm the diagnosis. If tissue is inadequate or diagnosis uncertain an open biopsy is indicated. The closed needle biopsy technique has proven to be an extremely effective means of procuring representative tissue, is associated with low morbidity, and avoids many of the potential complications of biopsy. If limb-sparing surgery is contemplated, the biopsy should be performed by the surgeon who will do the definitive operation, since incision placement is crucial. If inconclusive, open biopsy, preferably at the centre delivering the definitive treatment. Open incisional biopsy is preferred over excision of deep tumors to minimize the difficulty of an unplanned excision with its attendant risks.

C- Staging

CT-Scan Chest – All soft tissue sarcomas except low grade T1 lesions in whom an Xray chest is done.

Additional staging investigations to rule out lymph node metastases in specific sarcomas.

USG-Abdomen and pelvis- for cases of myxoid liposarcoma, synovial sarcoma, epithelioid sarcoma, angiosarcoma and undifferentiated sarcomas.

UICC/ AJCC TNM staging system

T – Primary tumor
  T0 - No evidence of primary tumor
  T1 - Tumor 5cm or less in greatest dimension
    T1a - Superficial tumor
    T1b - Deep tumor
  T2 – Tumor more than 5cm in greatest dimension
    T2a - Superficial tumor
    T2b - Deep tumor

N – Regional Lymph Nodes
  N0 - No regional lymph node metastasis
  N1 - Regional lymph node metastasis

M – Distant metastasis
  M0 - No distant metastasis
  M1 - Distant metastasis

G – Histopathologic grade
Low grade
High grade

Stage grouping

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**D – Local control**

Limb conservation is done wherever possible. Organ and function preserving surgery with or without radiation therapy is done wherever possible. The combination of conservative surgery and post-operative radiotherapy maintains a functional limb in patients with extremity lesions and survival results are comparable to those attained with radical surgery. (Level II, Grade A)

Every effort should be made to achieve a wide (2cm is often an arbitrary choice) margin around the tumor mass, except in the immediate vicinity of functionally important neuro-vascular structures, where in the absence of frank tumor involvement, dissection is performed in the immediate perineural or perivascular tissue planes. (Level III, Grade B)

Stage IA, IB Surgery. External radiotherapy is added if margins are positive. (Level II, Grade B)

Stage II A, II B, III Surgery ± Brachytherapy + Ext. radiotherapy. If margins are grossly positive, attempt re-excision (if feasible) to get negative margins, wherever possible. (Level II, Grade A)

Stage IV N1 Mo Surgery ± Brachy + Ext. RT + Lymph Node Dissection

No M1 Surgery ± Brachy + Ext. radiotherapy

Indications for metastectomy of pulmonary metastasis.

- No extrathoracic disease
- Locoregional disease controlled or controllable
- R0 metastectomy is possible
- Good general condition

**E – Radiotherapy**

Post-operative adjuvant Radiotherapy is given to all high grade and margin positive cases in the form of Brachytherapy and/or External Radiotherapy or a combination of
the two. (Level II, Grade B)

**Pre-op vs. Post-op radiation:**
Currently we prefer post op radiotherapy. Pre-op radiotherapy is associated with a slightly increased wound complication rate with equivalent control and overall survival in patients of extremity STS. (Level II, Grade B)
All patients should have silver clips inserted during surgery to delineate tumor bed.

**Patients suitable for Intraoperative Brachytherapy:**
Brachytherapy catheters inserted uniformly to cover the entire tumor bed with 1.5 - 2.0 cm margin.

Simulation and dosimetry to be done on 4-5th postoperative day.
Dose prescription for brachytherapy - 0.5cm on either side of the implant plane.

**Brachytherapy Dose:**
- LDR - 20Gy to 25Gy @ 45 - 50cGy / hr
- HDR - 15Gy / 5# @ 3Gy / # (2# / day with 6hrs gap)

**Ext. Radiotherapy:**
Radiotherapy to be started 2-3 weeks after completion of Brachytherapy
Planning Target Volume : Gross tumor volume + 3-5cm margin

Dose:
- After LDR Brachytherapy - 50Gy / 25# / 5 weeks
- After HDR Brachytherapy - 50Gy / 25# / 5 weeks

**Patients receiving only Ext. Radiotherapy:**

Planning Target Volume (PTV) : Phase I : Gross tumor volume +
- Grade I : 3cm margin
- Grade II & III : 5cm margin
- Phase II - Gross tumor volume + 2cm margin

Essential to spare at least 1.5 - 2.0cm of limb circumference from radiotherapy portal.
Spare half circumference of uninvolved bone if possible.
Try to keep uninvolved compartment out of radiation port as far as possible.

Dose:
- Phase I - 50Gy / 25# / 5 weeks
- Phase II - R 0 : 10Gy / 5# / 1 week
  - R 1 :16Gy / 8# / 1.5 weeks
  - R 2 : 20Gy /10# / 2 weeks

In some situations, radiation therapy or chemotherapy may be used prior to surgery to convert a marginally resectable tumor to one that can be adequately resected with limb preservation; this treatment may be followed by postop radiation therapy.

**F - Chemotherapy**
The role of adjuvant chemotherapy in localized STS is still unestablished. Adjuvant ifosfamide, doxorubicin/epirubicin based chemotherapy is offered to high risk patients (large, deep, high grade limb tumors or recurrent tumors). (Level II, Grade B)

**G - Recurrent STS**
Non metastatic - Re-excision ± Brachytherapy ± External RT
Metastatic - Re-excision ± Brachytherapy ± External RT
Indications for metastectomy of pulmonary metastasis.

- No extrathoracic disease
- Locoregional disease controlled or controllable
- R0 metastectomy is possible
- Good general condition

H – Follow up schedule
Patient is followed up at 3 monthly intervals for the first 2 years, 6 monthly intervals for the next 3 years and annually thereafter.
At every follow up, clinical examination of the local part & chest radiograph is done. For high grade tumors a CT scan of the chest is done at 6 monthly intervals for the first 2 years and annually for the next 3 years.
USG-Abdomen and pelvis at 6 monthly intervals for the first 2 years and annually for the next 3 years in cases of for myxoid liposarcoma, synovial sarcoma, epithelioid sarcoma, angiosarcoma and undifferentiated sarcomas.
(Currently there is inadequate evidence to suggest that intensive follow up with early detection of recurrent disease would significantly impact on survival).

I – Referred cases in which unplanned excision has been done with positive or unknown margins
Repeat excision followed by radiotherapy for high grade tumors.
(Level III, Grade B)

Soft Tissue Sarcoma - Investigations & Staging

Core needle biopsy for diagnosis of extremity soft tissue sarcoma.
Heslin MJ, Lewis JJ, Woodruff JM et al.

BACKGROUND: Classic teaching has advocated the use of open biopsy to diagnose and grade extremity soft-tissue sarcoma. Reported advantages of core needle biopsy include the minimal morbidity, cost, and time. The perceived disadvantage has been diagnostic inaccuracy. The objective of this study was to compare the diagnostic accuracy of core needle biopsy to incisional or frozen section biopsy for primary extremity masses suspicious for soft-tissue sarcoma. METHODS: Patients presenting with extremity masses were identified from our prospective soft-tissue sarcoma database (malignant) and from the clinical information center (benign) between January 1, 1990, and December 31, 1995. Biopsy and subsequent resection data were collected from the pathologic records. RESULTS: During this time, 164 primary extremity soft-tissue masses were evaluated before any biopsy. As the initial diagnostic approach, there were 60 core needle, 44 incisional, 36 frozen section, and 26 excisional biopsies. Two patients underwent two biopsy procedures. Ninety-three percent of the specimens obtained at core needle biopsy were adequate to make a diagnosis. Of the adequate core needle biopsy specimens, 95%, 88% and 75% correlated with the final resection diagnosis for malignancy, grade, and histologic subtype, respectively. Of the frozen section biopsy specimens, 94% were adequate, and accurate diagnostic results of malignancy were obtained with 88%. However, only 62% and 47% were correct for grade and histologic subtype, respectively, which was significantly different than the results obtained with incisional biopsy. The
false-negative and false-positive rates for core needle biopsy were 5% and 0% for malignancy. Two core needle biopsy specimens graded low were found to be high, and one core needle biopsy specimen graded high was subsequently found to be low on final resection. CONCLUSIONS: When read by an experienced pathologist, the results of core needle biopsy provide accurate diagnostic information for malignancy and grade. Adequate core needle biopsy obviates the need for open biopsy and can be used for rational treatment planning. In the absence of adequate tissue, open biopsy is required.

STAGING – WHICH INVESTIGATIONS ARE JUSTIFIED?

Utility of chest computed tomography for staging in patients with T1 extremity soft tissue sarcomas.
Fleming JB, Cantor SB, Varma DG et al.

BACKGROUND: National Cancer Center Network (NCCN) and Society of Surgical Oncology (SSO) practice guidelines recommend chest computed tomography (CT) as part of the staging evaluation of patients with extremity soft tissue sarcoma (STS). In the current study, the authors evaluated the use and yield of chest roentgenography (CXR) and selective chest CT to screen for pulmonary metastases in patients with T1 STS. METHODS: The utility of these staging studies was evaluated retrospectively in a cohort of 125 consecutive patients who presented to a tertiary care cancer center with T1 primary (nonrecurrent) extremity STS. Two diagnostic strategies (CXR alone vs. CXR plus chest CT) were evaluated using an incremental cost-effectiveness ratio. RESULTS: The majority of tumors (70%) were high grade. The median sarcoma size was 3.0 cm; 64 of the tumors (51%) were located deep to the investing fascia of the extremity. All patients underwent staging CXR; 1 CXR (< 1%) was suspicious for metastatic disease. Fifty-one patients (41%) also underwent chest CT; 1 chest CT, performed in the patient with a suspicious CXR, revealed metastatic disease. With a median follow-up of 76 months, 19 patients (15%) developed metachronous pulmonary metastases. The relatively low yield resulted in an incremental cost-effectiveness ratio of $59,772 per case of synchronous pulmonary metastasis detected by CXR plus chest CT. CONCLUSIONS: Less than 1% of patients with T1 primary extremity STS were found to have pulmonary metastases that were detectable using a staging algorithm that employs routine CXR with the selective use of chest CT. The findings of the current study do not support current NCCN or SSO practice guidelines for patients with high-grade T1 STS.

Cost-effectiveness of staging computed tomography of the chest in patients with T2 soft tissue sarcomas.
Porter GA, Cantor SB, Ahmad SA et al.
Cancer. 2002 Jan 1;94(1):197-204.

BACKGROUND: Published practice guidelines recommend routine chest computed tomography (CT) scanning as part of the staging evaluation for patients with T2 soft tissue sarcomas (STS), although there is no direct evidence to support this practice. The objective of this study was to determine the yield and cost-effectiveness of routine versus selective chest CT scanning for the staging of patients with T2 STS and to identify any subgroups for whom a more selective approach to chest CT scanning could be considered. METHODS: Six hundred consecutive patients with
primary, nonthoracic, T2 (> 5 cm) STS underwent both chest X-ray (CXR) and chest CT scanning to evaluate the presence of pulmonary metastatic disease (M1). The authors constructed a decision tree that modeled the outcomes of diagnostic testing for two hypothetical diagnostic strategies: 1) routine chest CT (rCT) or 2) CXR and selective chest CT (sCT). The yield and cost of each strategy were determined; the incremental cost-effectiveness ratio (ICER) was calculated as the cost per additional patient with pulmonary metastases identified by rCT versus sCT. RESULTS: The yield of rCT was higher than that of sCT (M1 disease identified in 19.2% vs. 16.0% of patients, respectively), but rCT was more costly ($1301 vs. $418 per patient, respectively). The ICER of rCT compared with sCT was $27,594 per patient identified with pulmonary metastasis. The expected yields, costs, and ICERs of the diagnostic strategies varied across patient subgroups based on grade, anatomic site, and tumor size. CONCLUSIONS: For patients with T2 STS, rCT was most cost-effective in patients with high-grade lesions or extremity lesions. The findings of this study do not support the routine use of chest CT scanning in all patients with T2 STS.

Patterns of recurrence in extremity liposarcoma: implications for staging and follow-up.
Pearlstone DB, Pisters PW, Bold RJ et al.

BACKGROUND: Liposarcoma is one of the most common histologic types of soft tissue sarcoma and presents a wide spectrum of clinical behavior. The authors examined the correlation among histologic subtypes, outcomes, and patterns of recurrence among patients with extremity liposarcomas. METHODS: A retrospective review of all patients with intermediate and high grade extremity liposarcoma referred to the University of Texas M. D. Anderson Cancer Center from January 1, 1980, to December 31, 1992, was performed. Data on clinical presentation, treatment, patterns of treatment failure, and outcome were evaluated. RESULTS: During the 13-year study period, 122 patients with intermediate or high grade extremity liposarcoma were identified: 102 patients (84%) with myxoid subtype, 18 patients (15%) with pleomorphic subtype, and 2 patients (2%) with mixed histology. There were no differences between the myxoid and pleomorphic subtype groups in tumor size (T1 vs. T2), depth in relation to the muscular fascia, or anatomic site. The median follow-up was 70 months. The 5-year overall survival rate for all intermediate and high grade extremity liposarcoma patients presenting with primary disease (n=85) was 74%; the 5-year local recurrence free survival, distant recurrence free survival, and disease free survival rates were 93%, 78%, and 73%, respectively. Among the 102 patients with myxoid tumors, 33 had distant recurrences; 31 of these were to extrapulmonary soft tissue sites (e.g., the retroperitoneum, chest wall, pleura, pericardium, pelvic sidewall, and soft tissue of the back), and 2 were to the lung only. Among the 18 patients with pleomorphic tumors, 10 had distant recurrences; 3 occurred at extrapulmonary sites, and 7 occurred in the lung only (P<0.05 for myxoid vs. pleomorphic subtypes). CONCLUSIONS: Myxoid liposarcomas often metastasized to extrapulmonary sites and did so significantly more frequently than pleomorphic tumors. Imaging of the abdomen, retroperitoneum, and extrapleural chest should be performed for accurate staging and posttreatment follow-up of patients with myxoid liposarcoma. Patients presenting with “primary” myxoid liposarcoma of the trunk should be carefully evaluated for an occult primary tumor in an extremity.
Lymph node metastasis from soft tissue sarcoma in adults. Analysis of data from a prospective database of 1772 sarcoma patients.
Fong Y, Coit DG, Woodruff JM et al.

Abstract: To examine the natural history of lymph node metastasis from sarcomas and the utility of therapeutic lymphadenectomy, clinical histories of all adult patients identified by a prospective sarcoma database for the 10-year period July 1982 to July 1991 were examined. Of the 1772 sarcoma patients, 46 (2.6%) were identified with lymph node metastasis. Median follow-up of all patients from diagnosis of lymph node metastasis was 12.9 months (range, 0 to 100 months). Median survival for nonsurvivors was 12.7 months (range, 0 to 40.7). The tumor types with the highest incidence of lymph node metastasis are angiosarcoma (5/37 total cases; 13.5%), embryonal rhabdomyosarcoma (ERMS) (12/88 total cases; 13.6%), and epithelioid sarcoma (2/12 total cases; 16.7%). Lymph node metastasis from visceral primary (p=0.004) and malignant fibrous histiocytomas (p=0.006) were associated with particularly poor prognosis. Thirty-one patients underwent radical, therapeutic lymphadenectomy with curative intent, whereas 15 patients had less than curative procedures, in most cases biopsy only. Patients not treated with radical lymphadenectomy had a median survival of 4.3 months (range, 1 to 32) whereas radical lymphadenectomy was associated with a 16.3 month median survival and the only long-term survivors (46% 5-year survival by Kaplan-Meier). The authors conclude that lymph node metastases from sarcoma are rare in adults, but vigilance is warranted, especially in angiosarcoma, ERMS, and epithelioid subtypes. Radical lymphadenectomy is appropriate treatment for isolated metastasis to regional lymph nodes and may provide long-term survival.

EFFICACY OF MRI AS A DIAGNOSTIC AND STAGING MODALITY

Radiographic imaging of musculoskeletal neoplasia.
Sanders TG, Parsons TW 3rd.,
Cancer Control. 2001 May-Jun; 8(3): 221-31

BACKGROUND: Imaging is an integral part of the diagnosis, staging and evaluation of outcomes for bone and soft-tissue neoplasms. Each of the available imaging tools has a different role. METHODS: The authors reviewed the efficacy of the current imaging modalities in the diagnosis, staging, and follow-up of patients with musculoskeletal neoplasia. RESULTS: Plain-film radiography remains the gold standard in the differential diagnosis of bone lesions. Bone scintigraphy is an excellent screening modality, and computed tomography is especially useful in evaluating lesions of the axial skeleton. The superior soft-tissue resolution and multiplanar capabilities achieved with magnetic resonance imaging, however, has replaced the need for CT scans in many cases. CONCLUSIONS: The technological advances seen in recent years in all areas of imaging have improved the capabilities of these modalities to assist in the diagnosis, definition of tumor extent, and accurate staging of musculoskeletal tumors.

**Soft Tissue Sarcoma - Limb Salvage & Radiotherapy**

IS LIMB SALVAGE SAFE?
The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy.
Rosenberg SA, Tepper J, Glatstein E et al.

Abstract: Between May 1975 and April 1981, 43 adult patients with high-grade soft tissue sarcomas of the extremities were prospectively randomized to receive either amputation at or above the joint proximal to the tumor, including all involved muscle groups, or to receive a limb-sparing resection plus adjuvant radiation therapy. The limb-sparing resection group received wide local excision followed by 5000 rads to the entire anatomic area at risk for local spread and 6000 to 7000 rads to the tumor bed. Both randomization groups received postoperative chemotherapy with doxorubicin (maximum cumulative dose 550 mg/m²), cyclophosphamide, and high-dose methotrexate. Twenty-seven patients randomized to receive limb-sparing resection and radiotherapy, and 16 received amputation (randomization was 2:1). There were four local recurrences in the limb-sparing group and none in the amputation group (p1=0.06 generalized Wilcoxon test). However, there were no differences in disease-free survival rates (71% and 78% at five years; p2=0.75) or overall survival rates (83% and 88% at five years; p2=0.99) between the limb-sparing group and the amputation treatment groups. Multivariate analysis indicated that the only correlate of local recurrence was the final margin of resection. Patients with positive margins of resection had a higher likelihood of local recurrence compared with those with negative margins (p1 less than 0.0001) even when postoperative radiotherapy was used. A simultaneous prospective randomized study of postoperative chemotherapy in 65 patients with high-grade soft-tissue sarcomas of the extremities revealed a marked advantage in patients receiving chemotherapy compared with those without chemotherapy in three-year continuous disease-free (92% vs. 60%; p1=0.0008) and overall survival (95% vs. 74%; p1=0.04). Thus limb-sparing surgery, radiation therapy, and adjuvant chemotherapy appear capable of successfully treating the great majority of adult patients with soft tissue sarcomas of the extremity.

ROLE OF RADIOTHERAPY IN SOFT TISSUE SARCOMA

Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity.
Yang JC, Chang AE, Baker AR et al.

PURPOSE: This randomized, prospective study assesses the impact of postoperative external-beam radiation therapy on local recurrence (LR), overall survival (OS), and quality of life after limb-sparing resection of extremity sarcomas. PATIENTS AND METHODS: Patients with extremity tumors and a limb-sparing surgical option were randomized to receive or not receive postoperative adjuvant external-beam radiotherapy. Patients with high-grade sarcomas received postoperative adjuvant chemotherapy whereas patients with low-grade sarcomas or locally aggressive nonmalignant tumors were randomized after surgery alone. RESULTS: Ninety-one patients with high-grade lesions were randomized; 47 to receive radiotherapy (XRT) and 44 to not receive XRT. With a median follow-up of 9.6 years, a highly significant decrease (P2=.0028) in the probability of LR was seen with radiation, but no difference in OS was shown. Of 50 patients with low-grade lesions (24 randomized to
resection alone and 26 to resection and postoperative XRT), there was also a lower probability of LR (P2=.016) in patients receiving XRT, again, without a difference in OS. A concurrent quality-of-life study showed that extremity radiotherapy resulted in significantly worse limb strength, edema, and range of motion, but these deficits were often transient and had few measurable effects on activities of daily life or global quality of life. CONCLUSION: This study indicates that although postoperative external-beam radiotherapy is highly effective in preventing LRs, selected patients with extremity soft tissue sarcoma who have a low risk of LR may not require adjuvant XRT after limb-sparing surgery.

Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma.

PURPOSE: This trial was performed to evaluate the impact of adjuvant brachytherapy on local and systemic recurrence rates in patients with soft tissue sarcoma. PATIENTS AND METHODS: In a single-institution prospective randomized trial, 164 patients were randomized intraoperatively to receive either adjuvant brachytherapy (BRT) or no further therapy (no BRT) after complete resection of soft tissue sarcomas of the extremity or superficial trunk. The adjuvant radiation was administered by iridium-192 implant, which delivered 42 to 45 Gy over 4 to 6 days. The two study groups had comparable distributions of patient and tumor factors, including age, sex, tumor site, tumor size, and histologic type and grade. RESULTS: With a median follow-up time of 76 months, the 5-year actuarial local control rates were 82% and 69% in the BRT and no BRT groups (P=.04), respectively. Patients with high-grade lesions had local control rates of 89% (BRT) and 66% (no BRT) (P=.0025). BRT had no impact on local control in patients with low-grade lesions (P=.49). The 5-year freedom-from-distant-recurrence rates were 83% and 76% in the BRT and no BRT groups (P=.60), respectively. Analysis by histologic grade did not demonstrate an impact of BRT on the development of distant metastasis, despite the improvement in local control noted in patients with high-grade lesions. The 5-year disease-specific survival rates for the BRT and no BRT groups were 84% and 81% (P=.65), respectively, with no impact of BRT regardless of tumor grade. CONCLUSION: Adjuvant brachytherapy improves local control after complete resection of soft tissue sarcomas. This improvement in local control is limited to patients with high-grade histopathology. The reduction in local recurrence in patients with high-grade lesions is not associated with a significant reduction in distant metastasis or improvement in disease-specific survival.

Role of radiotherapy in soft tissue sarcoma, Review article
Calais G; Cancer Radiother 1997.
Radiation therapy is generally used as a surgical adjuvant in the treatment of soft tissue sarcomas. Postoperative external beam irradiation is the most commonly applied treatment. The majority of retrospective studies have suggested that radiation therapy could reduce the incidence of local recurrence. Radiation is recommended in case of deep tumor location, inadequate surgical margins and grade 3 tumor. A total dose of 55 to 65 Gy using large volume with initial field margin of 5 cm are recommended. Radiation therapy can also be delivered in preoperative fashion, but the majority of the studies have reported a higher wound complication
rate. The value of brachytherapy for reducing the risk of local recurrence has been demonstrated in a randomized trial, especially for patients with high grade tumors. The combination of external radiation (40 to 45 Gy) and brachytherapy (15 to 20 Gy) seems to be the optimal adjuvant local strategy.

**TIMING OF RADIOTHERAPY**

**Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial.**
O'Sullivan B, Davis AM, Turcotte R et al.

BACKGROUND : External-beam radiotherapy (delivered either preoperatively or postoperatively) is frequently used in local management of sarcomas in the soft tissue of limbs, but the two approaches differ substantially in their potential toxic effects. We aimed to determine whether the timing of external-beam radiotherapy affected the number of wound healing complications in soft-tissue sarcoma in the limbs of adults. METHODS : After stratification by tumour size (< or = 10 cm or >10 cm), we randomly allocated 94 patients to preoperative radiotherapy (50 Gy in 25 fractions) and 96 to postoperative radiotherapy (66 Gy in 33 fractions). The primary endpoint was rate of wound complications within 120 days of surgery. Analyses were per protocol for primary outcomes and by intention to treat for secondary outcomes. FINDINGS : Median follow-up was 3.3 years (range 0.27-5.6). Four patients, all in the preoperative group, did not undergo protocol surgery and were not evaluable for the primary outcome. Of those patients who were eligible and evaluable, wound complications were recorded in 31 (35%) of 88 in the preoperative group and 16 (17%) of 94 in the postoperative group (difference 18% [95% CI 5-30], p=0.01). Tumour size and anatomical site were also significant risk factors in multivariate analysis. Overall survival was slightly better in patients who had preoperative radiotherapy than in those who had postoperative treatment (p=0.0481). INTERPRETATION : Because preoperative radiotherapy is associated with a greater risk of wound complications than postoperative radiotherapy, the choice of regimen for patients with soft-tissue sarcoma should take into account the timing of surgery and radiotherapy, and the size and anatomical site of the tumour.

**Preoperative vs. postoperative radiotherapy in the treatment of soft tissue sarcomas: a matter of presentation**
Pollack A, Zagars GK, Goswitz MS et al.

PURPOSE : Radiotherapy for soft tissue sarcoma is typically preoperative or postoperative, with advocates of each. In this study, the relationship of the sequencing of radiotherapy and surgery to local control was examined. METHODS AND MATERIALS : The cohort consisted of 453 patients with Grade 2-3 malignant fibrous histiocytoma, synovial sarcoma, or liposarcoma treated from 1965-1992. Retroperitoneal sarcomas were excluded. Median follow-up was 97 months. There were 3 groups of patients that were classified by the treatment administered at our institution: preoperative radiotherapy to a median dose of 50 Gy given before excision at MDACC (Preop; n=128); postoperative radiotherapy to a median dose of 64 Gy given after excision at MDACC (Postop; n=165); and radiotherapy to a median dose of 65 Gy without excision at MDACC (RT Alone; n=160). Those in the RT Alone Group had gross total excision at an outside center prior to referral. RESULTS :
Histological classification, whether locally recurrent at referral, and final MDACC margins were independent determinants of local control in Cox proportional hazards multivariate analysis using the entire cohort. The type of treatment was not significant; however, tumor status at presentation (gross disease vs. excised) affected these findings greatly. Gross disease treated with Preop was controlled locally in 88% at 10 years, as compared to 67% with Postop (p=0.01). This association was independently significant for patients treated primarily (not for recurrence). In contrast, for those presenting after excision elsewhere, 10-year local control was better with Postop (88% vs. 73%, p=0.07), particularly for patients treated primarily (91% vs. 72%, p=0.02 in univariate analysis; p=0.06 in multivariate analysis). Re-excision at MDACC (Postop) resulted in enhanced 10-year local control over that with RT Alone (88% vs. 75%, p=0.06), and was confirmed to be an independent predictor in multivariate analysis (p=0.02). CONCLUSION: Local control was highest with Preop in patients presenting primarily with gross disease, and with Postop in patients presenting primarily following gross total excision. The data suggest that 50 Gy is inadequate after gross total excision, possibly due to hypoxia in the surgical bed.

TARGET VOLUME IN RADIOTHERAPY

Conservative surgery and adjuvant radiation therapy in the management of adult soft tissue sarcoma of the extremities: clinical and radiobiological results.
Mundt AJ, Awan A, Sibley GS et al.

PURPOSE: The outcome of adult patients with soft tissue sarcoma of the extremities treated with conservative surgery and adjuvant irradiation was evaluated to (a) determine the appropriate treatment volume and radiation dosage in the postoperative setting, and (b) correlate in vitro radiobiological parameters obtained prior to therapy with clinical outcome. METHODS AND MATERIALS: Sixty-four consecutive adult patients with soft tissue sarcoma of the extremities (40 lower, 24 upper) who underwent conservative surgery and adjuvant irradiation 7 preoperative, 50 postoperative, 7 perioperative) between 1978 and 1991 were reviewed. The initial radiation field margin surrounding the tumor bed/scar was retrospectively analyzed in all postoperative patients. Initial field margins were < 5 cm in 12 patients, 5-9.9 cm in 32 and > or = 10 cm in 6. Patients with negative pathological margins were initially treated with traditional postoperative doses (64-66 Gy); however, in later years the postoperative dose was reduced to 60 Gy. Thirteen cell lines were established prior to definite therapy, and radiobiological parameters (multitarget and linear-quadratic) were obtained and correlated with outcome. RESULTS: Postoperative patients treated with an initial field margin of < 5 cm had a 5-year local control of 30.4% vs. 93.2% in patients treated with an initial margin of > or = 5 cm (p=0.0003). Five-year local control rates were similar in patients treated with initial field margins of 5-9.9 cm (91.6%) compared with those treated with > or = 10 cm margins (100%) (p=0.49). While postoperative patients receiving < 60 Gy had a worse local control than those receiving > or = 60 Gy (p=0.08), no difference was seen in local control between patients receiving less than traditional postoperative doses (60-63.9 Gy) (74.4% vs. those receiving 64-66 Gy (87.0%) (p=0.5). The local control of patients treated in the later years of the study, with strict attention to surgical and radiotherapeutic technique, was 87.6%. Severe late sequelae were more frequent in patients treated with doses > or = 63 Gy compared to patients
treated with lower doses (23.1% vs. 0%) (p<0.05). Mean values for Do, alpha, beta, D, n and SF2 obtained from the 13 cell lines were 115.7, 0.66, 0.029, 2.15, 0.262, respectively. Four of the 13 cell lines established prior to therapy ultimately failed locally. The radiobiological parameters of these cell lines were similar to the other nine cell lines in terms of radiosensitivity. CONCLUSIONS: Our data confirm the importance of maintaining an initial field margin of at least 5 cm around the tumor bed/scar in the postoperative setting. No benefit was seen with the use of margins > or = 10 cm. In addition, patients undergoing wide local excision with negative margins can be treated with lower than traditional postoperative doses (60 Gy) without compromising local control and with fewer chronic sequelae. Finally, it does not appear that inherent tumor cell sensitivity is a major determinant of local failure following radiation therapy and conservative surgery in soft tissue sarcoma.

**RADIOTherapy DOSE**

*Management of extremity soft tissue sarcomas with limb-sparing surgery and postoperative irradiation: do total dose, overall treatment time, and the surgery-radiotherapy interval impact on local control?*

Fein DA, Lee WR, Lanciano RM et al.

PURPOSE: To evaluate potential prognostic factors in the treatment of extremity soft tissue sarcomas that may influence local control, distant metastases, and overall survival. METHODS AND MATERIALS: Sixty-seven patients with extremity soft tissue sarcomas were treated with curative intent by limb-sparing surgery and postoperative radiation therapy at the Fox Chase Cancer Center or the Hospital of the University of Pennsylvania, between October 1970 and March 1991. Follow-up ranged from 4-218 months. The median external beam dose was 60.4 Gy. In 13 patients, interstitial brachytherapy was used as a component of treatment. RESULTS: The 5-year local control rate for all patients was 87%. The 5-year local control rate for patients who received < or = 62.5 Gy was 78% compared to 95% for patients who received > 62.5 Gy had larger tumors (p=0.008) and a higher percentage of Grade 3 tumors and positive margins than patients who received < or = 62.5 Gy. The 5-year local control rate for patients with negative or close margins was 100% vs. 56% in patients with positive margins (p=0.002). Cox proportional hazards regression analysis was performed using the following variables as covariates: tumor dose, overall treatment time, interval from surgery to initiation of radiation therapy, margin status, grade, and tumor size. Total dose (p=0.04) and margin status (p=0.02) were found to significantly influence local control. Only tumor size significantly influenced distant metastasis (p=0.01) or survival (p=0.03).

CONCLUSION: Postoperative radiation therapy doses > 62.5 Gy were noted to significantly improve local control in patients with extremity soft tissue sarcomas. This is the first analysis in the literature to demonstrate the independent influence of total dose on local control of extremity soft tissue sarcomas treated with adjuvant postoperative irradiation.

| Soft Tissue Sarcoma - Chemotherapy |

Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial.
Frustaci S, Gherlinzoni F, De Paoli A et al.
PURPOSE: Adjuvant chemotherapy for soft tissue sarcoma is controversial because previous trials reported conflicting results. The present study was designed with restricted selection criteria and high dose-intensities of the two most active chemotherapeutic agents. PATIENTS AND METHODS: Patients between 18 and 65 years of age with grade 3 to 4 spindle-cell sarcomas (primary diameter \( \geq 5 \) cm or any size recurrent tumor) in extremities or girdles were eligible. Stratification was by primary versus recurrent tumors and by tumor diameter greater than or equal to 10 cm versus less than 10 cm. One hundred four patients were randomized, 51 to the control group and 53 to the treatment group (five cycles of 4'-epidoxorubicin 60 mg/m\(^2\) days 1 and 2 and ifosfamide 1.8 g/m\(^2\) days 1 through 5, with hydration, mesna, and granulocyte colony-stimulating factor). RESULTS: After a median follow-up of 59 months, 60 patients had relapsed and 48 died (28 and 20 in the treatment arm and 32 and 28 in the control arm, respectively). The median disease-free survival (DFS) was 48 months in the treatment group and 16 months in the control group (\( P = .04 \)); and the median overall survival (OS) was 75 months for treated and 46 months for untreated patients (\( P = .03 \)). For OS, the absolute benefit deriving from chemotherapy was 13% at 2 years and increased to 19% at 4 years (\( P = .04 \)). CONCLUSION: Intensified adjuvant chemotherapy had a positive impact on the DFS and OS of patients with high-risk extremity soft tissue sarcomas at a median follow-up of 59 months. Therefore, our data favor an intensified treatment in similar cases. Although cure is still difficult to achieve, a significant delay in death is worthwhile, also considering the short duration of treatment and the absence of toxic deaths.

**Soft Tissue Sarcoma - Surgery**

**SURGICAL MARGINS; IMPORTANCE IN LOCAL RECURRENCE AND IMPACT ON SURVIVAL**

Analysis of the prognostic significance of microscopic margins in 2,084 localized primary adult soft tissue sarcomas.

Stojadinovic A, Leung DH, Hoos A et al.


OBJECTIVE: To define the significance of positive microscopic resection margins in a large cohort treated for soft tissue sarcoma. METHODS: The authors analyzed 2,084 patients with localized primary soft tissue sarcoma (all anatomic sites) treated from 1982 to 2000. Clinicopathologic variables studied included tumor site, size, depth, histologic type, grade, and resection margin status. Treatment other than resection was not analyzed. Study endpoints included local and distant recurrence-free and disease-specific survival rates, estimated by the Kaplan-Meier method. Univariate and multivariate analyses were performed using the log-rank test and the Cox proportional hazards model. RESULTS: Median follow-up was 50 months. After primary resection, 1,624 (78%) patients had negative and 460 (22%) had positive resection margins. Having positive margins nearly doubled the risk of local recurrence and increased the risk of distant recurrence and disease-related death. Seventy-two percent of patients with positive margins had no recurrence. Resection margin did not predict local control for retroperitoneal sarcomas or fibrosarcomas. Resection margin remained significantly associated with distant recurrence-free survival and disease-specific survival across all subsets after adjusting for other prognostic variables. The overall 5-year disease-specific survival rates for negative
and positive margins were 83% and 75%. CONCLUSIONS: Positive microscopic resection margins significantly decrease the local recurrence-free survival rate for other-than-primary fibrosarcoma and retroperitoneal sarcomas, and independently predict distant recurrence-free survival rates and disease-specific survival rates for all patient subsets. Adjuvant therapy should be considered in the management of soft tissue sarcoma to increase local control. Because 72% of positive margins did not equate with inevitable local recurrence, considerable clinical judgment is required in considering additional treatment. Microscopic resection margins should be considered for inclusion in staging systems and treatment algorithms that address local recurrence.

**Association of local recurrence with subsequent survival in extremity soft tissue sarcoma.**

PURPOSE: The aim of this study was to analyze local recurrence in a large cohort of prospectively followed patients with primary extremity soft tissue sarcoma. In particular, we analyzed the correlation of local recurrence with subsequent metastasis and disease-specific survival. PATIENTS AND METHODS: Patients who underwent treatment for primary extremity soft tissue sarcoma from July 1982 through July 1995 at Memorial Sloan-Kettering Cancer Center were the subject of this study. Local recurrence, distant metastasis, and disease-specific survival were used as end points of the study. The influence of local recurrence on subsequent distant metastasis and disease-specific survival were examined using the Cox proportional hazards model. RESULTS: We treated 911 patients, of whom 297 (33%) developed recurrent disease. Local recurrence occurred in 116 patients (13%), metastasis in 167 (18%), and synchronous local recurrence and metastasis in 13 (2%). Of 116 patients who developed local recurrence, 38 subsequently developed metastasis and 34 died of disease. Metastasis after local recurrence was predicted in patients with initial high-grade (P=.005; risk = 3.5) or deep (P=.02; risk = 2.9) tumors. Tumor mortality after local recurrence was predicted in patients with initial high-grade (P=.007; risk = 3.7) or large (> 5 cm; P=.01; risk = 3.2) primary tumors. DISCUSSION: These findings suggest that there is a strong association of local recurrence with the development of subsequent metastasis and tumor mortality, and that local recurrence is a poor prognostic factor. It would seem prudent to consider patients who develop local recurrence and have high-grade tumors as being at high risk for systemic disease and therefore eligible for investigational adjuvant systemic therapy.

**METASTECTOMY IMPROVES SURVIVAL**

**Pulmonary metastases from soft tissue sarcoma: analysis of patterns of diseases and postmetastasis survival.**

OBJECTIVE: To report the patterns of disease and postmetastasis survival for patients with pulmonary metastases from soft tissue sarcoma in a large group of patients treated at a single institution. Clinical factors that influence postmetastasis survival are analyzed. SUMMARY BACKGROUND DATA: For patients with soft tissue sarcoma, the lungs are the most common site of metastatic disease. Although
pulmonary metastases most commonly arise from primary tumors in the extremities, they may arise from almost any primary site or histology. To date, resection of disease has been the only effective therapy for metastatic sarcoma. METHODS: From July 1982 to February 1997, 3149 adult patients with soft tissue sarcoma were admitted and treated at Memorial Sloan-Kettering Cancer Center. During this interval, 719 patients either developed or presented with lung metastases. Patients were treated with resection of metastatic disease whenever possible. Disease-specific survival was the endpoint of the study. Time to death was modeled using the method of Kaplan and Meier. The association of factors to time-to-event endpoints was analyzed using the log-rank test for univariate analysis and the Cox proportional hazards model for multivariate analysis. RESULTS: The overall median survival from diagnosis of pulmonary metastasis for all patients was 15 months. The 3-year actuarial survival rate was 25%. The ability to resect all metastatic disease completely was the most important prognostic factor for survival. Patients treated with complete resection had a median survival of 33 months and a 3-year actuarial survival rate of 46%. For patients treated with nonoperative therapy, the median survival was 11 months. A disease-free interval of more than 12 months before the development of metastases was also a favorable prognostic factor. Unfavorable factors included the histologic variants of liposarcoma and malignant peripheral nerve tumors and patient age older than 50 years at the time of treatment of metastasis. CONCLUSIONS: Resection of metastatic disease is the single most important factor that determines outcome in these patients. Long-term survival is possible in selected patients, particularly when recurrent pulmonary disease is resected. Surgical excision should remain the treatment of choice for metastases of soft tissue sarcoma to the lung.

IS REEXCISION NECESSARY AFTER UNPLANNED EXCISION WITH POSITIVE OR UNKNOWN MARGINS?

Residual disease following unplanned excision of soft-tissue sarcoma of an extremity.
Noria S, Davis A, Kandel R et al.

Abstract: Sixty-five patients who had been referred to our unit for additional management after an unplanned excision of a soft-tissue sarcoma of an extremity at another institution were studied retrospectively to determine the prevalence of residual tumor and to identify factors that predict which patients will have a tumor following such an excision. Unplanned excision was defined as excisional biopsy or unplanned resection of the lesion without benefit of preoperative imaging and without regard for the necessity to resect the lesion with a margin of normal tissue. In each patient, histological evaluation of the specimen removed at the unplanned excision had demonstrated positive resection margins, but postoperative physical examination on our unit revealed no gross evidence of residual tumor and no tumor was identified on cross-sectional imaging of the local site. Patients who had evidence of residual disease on physical examination or on imaging were thought to have definite evidence of sarcoma at the site of the operative wound and were therefore excluded from the study. After multidisciplinary consultation, all patients had a repeat resection at our cancer center. Extensive pathological sampling of the specimen from this second procedure was carried out, with sections obtained at mean intervals of 1.2 +/- 0.7 centimeters. Nodules initially thought to indicate disease were identified grossly in twenty-seven (42 percent) of the sixty-five
patients, but histological evaluation confirmed the presence of tumor in only sixteen (59 percent). Histological evidence of sarcoma was identified in seven additional patients in whom gross nodules were not apparent in the specimen. Thus, sarcoma was identified in a total of twenty-three (35 percent) of the sixty-five patients. The mean duration of follow-up was forty-six months (range, twenty-four to eighty months; median, thirty-nine months). The margins of the second resection were positive in nine (39 percent) of the twenty-three patients who had residual sarcoma. Five (22 percent) of the twenty-three had a local recurrence. Four of the five patients who had a local recurrence had positive margins on repeat resection. This rate of local recurrence (five of twenty-three patients) was significantly higher than that in the remainder of our patients who had a soft-tissue sarcoma of an extremity (sixteen [7 percent] of 227) (p=0.03). There was no association between the detection of sarcoma at the second procedure and the initial size or grade of the tumor, the use of irradiation preoperatively, or the interval between the initial, unplanned excision and referral to our cancer center. These data indicate that it is not possible to predict which patients will have residual tumor at the site of the operative wound. Therefore, it is prudent to advise repeat excision for all patients who have had an unplanned excision of a soft-tissue sarcoma of an extremity. Unplanned excision complicates decision-making in the treatment of this disease and should be avoided.