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Adjuvant chemotherapy in soft tissue sarcomas…Conflicts, consensus, and controversies

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Abstract

Soft tissue sarcomas (STSs) are an uncommon and diverse group of more than 50 mesenchymal malignancies. Each of these histologic subtypes represents a unique disease with distinct biologic behavior and varying sensitivity to chemotherapy. The judicious use of adjuvant/neoadjuvant chemotherapy along with surgery and radiation in the treatment of localized STS has a role in improving patient outcomes by decreasing local and distant recurrences. There is evidence that the use of adjuvant chemotherapy to a mixed cohort of chemo sensitive and insensitive sarcoma subtypes results in limited benefit. Therefore, it is of paramount importance to identify the subpopulation with high metastatic potential and to identify effective histology-specific treatment options to these patients. Present perspective, will focus on the rationale for adjuvant chemotherapy in sarcoma, with emphasis on the histology driven chemotherapy. It will outline key therapeutic opportunities and hurdles in adjuvant medical treatment of sarcoma, focusing on specific subtypes that are on the verge of new breakthroughs, as well as those in which promise has not lived up to expectations.

Key words: Adjuvant chemotherapy options, chemosensitive histologies, consensus, controversies, soft tissue sarcoma

Soft tissue sarcomas (STSs) are a challenging group of rare malignancies that make up only 1–2% of all cancers; in children, it accounts for approximately 7% of all of pediatric malignancies. They can arise from any extra skeletal connective tissue, including the peripheral nervous system and have more than 50 different histological types.[1] They can arise from any part of the body, but extremities form the most common site of which lower limb forms the majority. STSs are difficult to treat. They have over fifty different histological subtypes, yet they comprise <1% of malignancies.

The standard of care for localized disease in adults has been wide surgical resection [*en bloc* macro and microscopically complete surgical excision of the gross tumor (R0 resection)] often combined with radiotherapy (RT), but the question of using adjuvant chemotherapy to improve survival rates in high-grade STS has been a subject of controversy yet to reach a consensus.

Goals of Therapy of Soft Tissue Sarcoma

- Long-term survival
- Avoidance of a local recurrence
- Maximizing function, and
- Minimizing morbidity.

Why the question of adjuvant therapy is important to answer?

- STS constitutes a minority among malignancies.
- They are a heterogeneous group of disorders in terms of histology and molecular profile, initial sites of disease and patient characteristics, thus making the patient number of individual histologies further low, and making the conduct of well-designed clinical trials further difficult to enroll.
- The large sized, high-grade sarcomas treated with surgery alone has low cure rate.
- Metastatic STSs are rarely cured. Hence, we need to intervene in the early nonmetastatic stage to improve the prognosis.
- Surgery is the cornerstone of therapy in STS management. Systemic chemotherapy is the standard of care in pediatric sarcomas. However, its role in adult sarcomas (leiomyosarcoma, liposarcoma, and synovial sarcoma) remains controversial.
- There is therefore an urgent need to determine whether or not there are small subpopulations of patients truly benefiting from adjuvant chemotherapy (with conventional agents), and to identify prospectively these population.
- The standard treatment in adult STSs is wide surgical excision. Half of all patients with adequate local control of high-grade sarcomas develop distant metastases and despite additional treatment, ultimately die from their disease. This daunting reality has inspired the medical world to conduct relentless research effort to assess the efficacy of adjuvant therapy for adult STSs. The multitude of diverse histopathological subtypes, each with its own disease biology and clinical course, and the rarity of adult STSs as a whole greatly complicate such a research initiative. This review attempts to examine the current data that support or refute the use of adjuvant chemotherapy in the treatment of adult STSs.

Who would benefit from adjuvant therapy in soft tissue sarcoma…? What are the prerequisites to effective adjuvant therapy…?

The use of adjuvant chemotherapy as a blanket therapy to all is futile. We need to identify specific subgroups of patients most likely to die of recurrent or metastatic disease. The application of adjuvant therapy to this specific selected patient group would be a wise strategy.

- Devising histology-specific effective treatment options
- Identification of high-risk subgroups like size >5 cm, high-grade, deep to deep fascia, specific histologies based on metastatic potential and chemo sensitivity. Most patients die of distant relapse/metastatic disease. Hence timely and early incorporation of adjuvant therapy to eradicate micro metastasis is very important. The various histologies as per metastatic potential are outlined below in Table 1.

What to give in adjuvant chemotherapy?

Anthracyclines as a single agent or in combination:

- Adriamycin/epirubicin
- Adriamycin + Ifosphamide + MESNA (AIM)
- Adriamycin/dacarbazine
- MAID: (MESNA + ADRIA + IFOS + DACARBAZINE).

Optimal treatment regimen for adjuvant chemotherapy is still undefined. In the adjuvant setting, we have the Sarcoma

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Meta-analysis Collaboration (SMAC) update to suggest that ifosfamide is an important member of the adjuvant regimen to be used judiciously balancing the benefits with toxicity.

Evolution of Evidence for and Against Adjuvant Therapy in Adult Soft Tissue Sarcoma

Over 20 randomized trials and two meta-analyses have addressed the potential benefit of adjuvant chemotherapy for resected extremity STS in adults. Unfortunately, these have yielded conflicting data, and as a result, the benefit of adjuvant chemotherapy remains uncertain.[2]

First generation randomized trials (1970's)

The majority of early trials used doxorubicin alone or with dacarbazine, but did not employ ifosfamide, a compound reintroduced to clinical practice in mid-1980's after discovery of MESNA.

Among the first 14 published randomized trials of adjuvant doxorubicin-based therapy versus surgery alone, two reported a significant survival advantage for combination chemotherapy, three found higher survival in the observation arm, and the remainder showed no difference in outcome in the treated group [Table 2].

Sarcoma Meta-analysis Collaboration meta-analysis

Due to the growing concern that the beneficial effect was missed due to small sample size of individual studies (median patient accrual size: 76), SMAC performed an Individual patient data meta-analysis from these trials[3], which involved 1568 adults with localized resectable STS (extremities and others), and published in 1997. All evaluated studies included patients who were randomly assigned postoperatively to receive or not receive adjuvant doxorubicin-containing chemotherapy. The following benefits were noted in the chemotherapy group: It clearly demonstrated a clear biologic effect of adjuvant chemotherapy on adult STS.

Table 1: Metastatic potential of various histological subtypes of STS

Low metastatic potential	Intermediate potential	High metastatic potential
Well differentiated Liposarcoma	IMFT	Pleomorphic liposarcoma
	Haemangiopericytoma	Dedifferentiated liposarcoma
	Haemangioendothelioma	Leiomyosarcoma
	Solitary fibrous tumour	Round cell liposarcoma
		Angiosarcoma
		Synovial sarcoma
		RMS
		Ewings sarcoma
		Alveolar soft part sarcoma
		GIST

STS=Soft tissue sarcomas, IMFT=Inflammaory myofibrobalstic tumour, RMS=Rhabdomyosarcoma, GIST=GastroIntestinal stromal tumour

Table 2: First generation trials of adjuvant therapy: Adriamycin and combination[2]

Group	Period	Patient number	Regimen	DFS (%)	OS (%)
EORTC	77-88	468	ADM, CTX, DTIC, VCR	+13	+7
ECOG	78-83	168	ADM	+13	+3
SSG	81-86	181	ADM	+6	+5
GOG	73-82	156	ADM	+12	+8
UCLA	81-84	119	ADM	+4	+4
MAYO	75-81	61	ADM, ACTD, VCR, DTIC	−3	0
MDA	73-76	47	ADM, ACTD, CTX, VCR	−7	NR

EORTC=European Organisation for Research and Treatment of Cancer, ECOG=Eastern Cooperative Oncology Group, SSG=Scandinavian, GOG=Gynae Oncol, UCLA=University of Californai Los Angeles, MDA=MD Anderson, CTX=Cyclophosphamide, DTIC=Dacarbazine, ACTD=ActinomycinD, EPI=Epirubicin, IFOS=Ifosfamide, VCR=Vincristine

Recurrence free survival

- Local recurrence free survival (RFS): Significantly better. Hazard ratio (HR) for local recurrence 0.73 (95% confidence interval [CI]: 0.56–0.94)
- Distant RFS: Significantly better. HR: 0.70 (95% CI: 0.57–0.85)
- Overall RFS: Significantly better. HR for any recurrence 0.75 (95% CI: 0.64–0.87)
- Translates to an absolute 6–10% improvement in RFS at 10 years.

Overall survival

- There was a trend toward improved overall survival (OS) that favored chemotherapy, but it was not statistically significant (HR for death 0.89, 95% CI: 0.76–1.03)
- There was no consistent evidence of any improvement according to age, sex, stage, site, grade, histology (although there was no central pathology review), extent of resection, tumor size, or exposure to RT
- There was a consistent evidence of a beneficial effect on survival in the subset of patients with extremity and truncal sarcomas
- Among these patients who received adjuvant doxorubicin-containing chemotherapy, there was a statistically significant benefit for chemotherapy (HR for death 0.80, $P = 0.029$)
- Translated into a 7% absolute benefit in OS at 10 years.

Criticisms of the Meta-analysis

Positive side

Individual patient data meta-analyses remedy deficiencies of individual studies such as inadequate sample size, variable exclusion of patients, and heterogeneity in reporting relevant outcomes.

Negative side

- A possible dilution of the possible beneficial effects of chemotherapy for extremity STS by the inclusion of tumors at all other locations
- A similar dilution of the effects of chemotherapy from the inclusion of patients with low-grade (5%) or unknown grade (28%) STS.

Except for one small unpublished study included in the meta-analysis, none of the other studies included ifosfamide (one of the active drugs in STS).

Questions that Remained Unanswered Despite the Promising Results of Sarcoma Meta-analysis Collaboration

- Is it possible to predecide specific subgroups of patients based on age, sex, histology, grade, location who are likely to benefit from chemotherapy?
- Should doxorubicin be used alone or in combination (and

with which drugs), and
- What is the optimum dose/schedule?

Second generation studies (EARLY 1990's)

Four additional randomized trials explored the benefit of anthracycline and ifosfamide-based combination adjuvant chemotherapy in extremity STS,[4-8] two of which suggest a possible survival benefit for adjuvant chemotherapy [Table 3].

The important aspects of the second generation trials included:
- Doxorubicin-based combinations were used in all first generation studies while ifosfamide and anthracycline combination was used in the second generation trials
- Use of granulocyte colony-stimulating factor (G-CSF) as primary prophylaxis
- More dose intense regimens
- Introduction of more restrictive selection criteria
- Due to the suggestion of survival benefit for extremity and truncal STS, future studies focused more on these sites of primary disease.

An Austrian trial[4] conducted by Brodowicz *et al*., on a small sample size of 59 patients assigned to surgery with or without adjuvant therapy did not reveal any significant difference in terms of disease free survival (DFS), local or distant recurrence rates. It is possible that the small sample size had made the study underpowered to make significant conclusions.

Italian study

In an Italian trial conducted by Frustaci *et al*.[5,6] in 2001, a total of 104 patients with high-grade, large (≥5 cm) or recurrent spindle cell sarcomas involving the extremities or girdles were randomly assigned to observation or to five cycles of adjuvant chemotherapy consisting of a dose intensive epirubicin/ifosfamide combination (epirubicin 60 mg/m^2 on days 1–2 plus ifosfamide 1.8 g/m^2 on days 1–5) with MESNA and G-CSF support. There was a premature discontinuation of accrual at 2 years, when a significant difference in the cumulative incidence of distant metastasis was found (45 vs. 28%), favoring the chemotherapy group. The OS was also significantly better in the chemotherapy arm on follow-up at 4 years (69 vs. 50%), but it lost significance at long-term follow-up over 7 years probably due to the small sample size. Interestingly, the overall relapse rates (local and distant) remained similar in two groups. This interesting finding or discrepancy is difficult to explain and is probably due to majority of patients having a local recurrence that is later managed effectively by local surgical salvage measures, individual variations in risk of relapse, dose intensity, variable drug dosing and yet unknown other factors.

Another follow-up Italian trial

This was a study conducted on 88 patients with high-risk extremity sarcoma who were randomized to undergo surgery with or without RT (n = 43) or to surgery plus chemotherapy (n = 45, 26 with epirubicin alone, and 19 to epirubicin plus ifosfamide) with or without RT[7]

The 5 year OS rate of patients treated with chemotherapy was significantly better than that of patients who did not receive chemotherapy (72 vs. 47%). However, the large number of treatment variables and the small sample size of the study make interpretation of this result cautious.

The EORTC

This study by Woll *et al*.,[8] randomly assigned a total of 351 patients with completely resected STS to observation versus five cycles of adjuvant chemotherapy (doxorubicin 75 mg/m^2 and ifosfamide 5 g/m^2 per cycle). There was no statistically significant difference in terms of DFS or OS. We need to be cautious in interpreting the results of the study as it included a heterogeneous group of high and low risk patients (67% extremity tumors, 60% high-grade, 40% ≥10 cm) and suboptimal dosage of ifosfamide.

Sarcoma Meta-analysis Collaboration meta-analysis update 2008

In 2008, a meta-analysis update[9] was conducted with the inclusion of total of 18 randomized trials of 1953 patients with localized and resectable STS between 1973 and 2002, including the Austrian and both Italian trials mentioned above, but not including the most recent large negative EORTC trial. Five of these 18 trials used doxorubicin plus ifosfamide, while the others used doxorubicin alone or in combination with other agents.

The interesting results from this update that favored the chemotherapy arm included:

Recurrence free survival

- Local recurrence odds ratio (OR): 0.73 (95% CI: 0.56–0.94)
- Distant recurrence OR: 0.67 (95% CI: 0.56–0.82)
- Overall recurrence OR: 0.67 (95% CI: 0.56–0.82).

Overall survival benefit

- Ifosfamide + doxorubicin:
  Odds ratio for death 0.56, (95% CI: 0.36–0.85)

Table 3: Second generation trials

Author	Year	Num.	HPR	Regimen	Outcome measure	Outcome (%)	Significance
BRODOWICZ[4] (Austrian)	2000	59	Lipo, MFH, SS	ADM, IFOS, DTIC	DFS	77/57	NS
					LR	6/21	NS
					DR	19/36	NS
FRUSTACI (Italian)[5,6]	2001	104	MFH, SS, Lipo	EPI + IFOS	DFS (2 year)	72/45	S
					DFS (4 year)	50/37	NS
					OS (2 year)	85/72	NS
					OS (4 year)	69/50	S
					OD (7 year)		NS
PETRIOLI (Italian f/u)[7]	2002	88	MFH, Lipo, eio	EPI + IFOS	DFS	69/44	S
					OS	72/47	S
WOLL (EORTC)[8]	2007	351	Leio, Lipo, SS, MFH	ADRIA + IFOS	DFS	52/52	NS
					OS	64/69	NS

Lipo=Liposarcoma, MFH=Malignent Fiberous Hystiocytoma, SS=Soft Tissue Sarcoma, Leio=Leiomyosarcoma, ADM=Adriamycin, EPI=Epirubicin, IFOS=Ifosfamide, DTIC=Dacarbazine

- Doxorubicin alone:
  Odds ratio for death 0.84 (95% CI: 0.68–1.03).

The risk reduction for death with doxorubicin and ifosfamide combination was 11% (30/41%), underscoring the vital role of ifosfamide in the adjuvant treatment of sarcomas.

Pooled analysis of the EORTC trials

Another pooled analysis of individual patient data from two large adjuvant trials by EORTC,[10] on the total of 819 patients, treated with doxorubicin and ifosfamide-based chemotherapy was negative. The addition of adjuvant chemotherapy did not have any survival advantage over surgery alone except in the group that underwent incompletely (R1) resections. There were no factors (size, histology, grade) found significant as predictors of improved survival on multivariate analysis.

Why has adjuvant chemotherapy failed so far possible hypothesis adding fuel to the fire of controversies?

- Every study of adult STS has been on a heterogenous group of patients with varies histologies and molecular subtypes. This introduces too high levels of heterogeneity making identification of chemo effective subtypes difficult[11]
  The quality of the definitive local therapy (surgical R0 resection) has definitely improved over the decades, thus nullifying the added benefit of adjuvant therapy[11]
- The criteria used to select patients for adjuvant therapy is mostly hypothesis generating as of today and not yet truly predictive of survival.

Only anthracycline based regimens have been used till date in randomized studies irrespective of histologies, when we know that it would be futile to treat Gastrointestinal stromal tumours with anthracyclines instead of imatinib which works wonders in them[11]

What impact does histology have on outcomes?

Adjuvant chemotherapy is the standard of care in pediatric sarcomas like rhabdomyosarcomas, which have been addressed in large randomized studies of single histological subtype.

But, unfortunately, this is not feasible with adult sarcomas due to the rarity of the diagnosis, heterogeneity in histology/molecular profile. It is well known from studies in the metastatic setting that that myxoid/round cell liposarcomas and synovial sarcomas are relatively chemosensitive subtypes of STS.

It has been hypothesized and postulated that adjuvant chemotherapy benefits the group of patients selected on the basis of histology, grade and tumor size but it has not been answered or validated in prospective randomized studies. Hence, the conflict and controversy continues.

The conclusions have been drawn from retrospective reports[12-16] on chemo sensitive subgroups of patients and results have always been conflicting. However, these retrospective analysis need to be analyzed and interpreted with caution due to the many biases that possibly operate in them. Selection bias: Chemotherapy was likely recommended for those patients whose tumors were thought to have the highest risk of recurrence, while those thought to have more favorable outcomes were not offered chemotherapy.

- In an Italian study[13] on 271 patients with Localized Synovial sarcoma adjuvant chemotherapy was received by 61 patients and it resulted in a significant improvement in 5 years DFS (60/48%).The benefit was greater in the subgroup of patients older than 17 years, with tumors larger than 5 cm
- In another retrospective analysis of 674 adult patients with high-grade large >5 cm extremity STS treated at MSKCC and MD Anderson,[14] 50% of patients received adjuvant doxorubicin-based chemotherapy. There was no statistically significant difference between the outcomes of chemotherapy and local therapy alone patients with respect to size, site, subtype, or resection margin status. But, need to be noted that in this study, 50% of the patients who did not receive chemotherapy had 5–10 cm primary tumors, while only 42% of those receiving chemotherapy had this relatively favorable tumor size. In addition the histology was liposarcoma (chemo sensitive histology) in 21% of the control patients compared to 14% in the treatment group.

Summary

The role of adjuvant chemotherapy for patients with a resected STS remains a controversy. STS is, in fact, STSs…A heterogenous group of diverse histological and molecular subtypes.

In 2015, it was the emergent need of the hour to determine if there is a small selected subgroup of STS patients truly benefiting from adjuvant chemotherapy. This needs to be tested ideally in prospective studies with control arm. It might be wise to conduct such studies initially in specific subgroups histological or molecular subtypes associated with high-risk of relapse and those, which are chemosensitive subtypes.

We are still far from achieving a standard of care in adult STS. We need to have a risk stratified approach similar to breast cancer for adjuvant therapy. Patients with small <5 cm, low-grade sarcoma may be exempted from adjuvant chemotherapy outside of a clinical trial setting. Adjuvant chemotherapy is never a substitute for poor surgery with resection margins positive.

In well selected, high-risk group of patients adjuvant chemotherapy with agents known to be active for that specific subtype could be a wise option likely to have significant clinical benefit. Since STSs constitute a heterogenous bag of rare tumors (STSs rather), they should be managed by an experienced multidisciplinary team of specialists comprising minimum of oncosurgeon, pathologist, radiologist, radiation and medical oncologist so that optimal care is ensured at every step from diagnosis, prognostication and treatment, and most informed decisions are taken by the team with the patient and for the patient.

When to give and what to give as adjuvant therapy[16,17] needs to be discussed on an individual case by case basis, taking into consideration PS of the patient, comorbidities, age, site of disease (extremity/retroperitoneal/trunk), size, grade and histological subtypes. We need to discuss benefits balanced with the risks of short term and long term toxicity including sterility, cardiomyopathy, renal dysfunction, second malignancy, QOL impairment.

Advances in molecular characterization of these tumors would fuel in more research on molecular targeted therapy so that in the future we have individualized and personalized therapy not just for individual histological subtypes but also for individual patients. We need to develop potential future prognostic/predictive biomarkers to identify whom to treat and what to treat with adjuvant therapy…

The conflicts and controversies continue amidst efforts at consensus…

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