

Chemotherapy and Radiotherapy in Soft Tissue Sarcoma

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The place of Sx, RT & CT in STS Mgt.

STS are a heterogeneous group of malignant tumors of mesenchymal origin

WLE ± Adj RT has Local control rates close to 90%.

Approx 40% - 50% of patients with >5 cm, deep, High Gr STS eventually develop distant metastases - primarily in the lung.

In these cases, the 5-year survival ranges from 25% - 30% despite aggressive surgical management of metastases.

While Sx and RT have an established place in the mgt. of STS, the limited sample size, variety of chemotherapeutic regimens with discrepant results of RCTs undertaken during the past 3 decades have failed to resolve issues pertaining to the optimum role of chemotherapy in advanced/high grade STS

Role of Surgery in Primary Limb/Truncal STS

Primary aim - Complete tum excision with adequate ($\geq 1\text{cm}$) margin while maintaining optimal function

Low-grade :

- Superficial - Wide Exn**
- Deep, $\leq 5\text{cm}$ - Wide Exn**
- Deep, $> 5\text{cm}$ - Wide Exn/ Comp Res
 \pm Adj RT**

High-grade :

- Superficial - Wide Exn**
- Deep, $> 5\text{cm}$ - Wide Exn/ Comp Res +
Adj RT (Pre/Post-op)
 \pm Adj Chemo**

Limb and Trunk STS

Surgery + RT

Pisters et al. 2007 (Prospective Trial on select tumors)

T1 tumors : Extr – 60; Trunk – 26.
51(58%) – HG STS
60 (68%) - Superficial (T1a)
R0 resection → No RT = 74 (84%)
R1 resection → PORT = 14 (16%) [LR 6 pts]

Adj RT after R0 surgery

Result - Expected LRR after 10 yrs = 11%.

Inference – R0 surgery alone in selected pts. with extr & trunk leads to acceptable local control and excellent long-term survival.

Level of Evidence II

Why evidence based Rx in STS?

Rare tumours

Available data based on few RCT

Most studies : retrospective, single institution data

No universally accepted adult Rx protocols

Levels of Evidence

- Ia** Meta-analysis of RCTs
- Ib** At least one RCT
- IIa** At least one well-designed controlled study without randomization
- IIb** At least one other type of well-designed quasi experimental study
- III** Well-designed non-experimental studies
- IV** Expert committee reports, opinions of experts

Agency for Health Care Policy and Research

The U.S. Preventative Services Task Force levels of evidence

Level I : Evidence obtained from at least 1 properly designed randomized controlled trial.

Level II-1 : Evidence obtained from well-designed controlled trials without randomization.

Level II-2 : Evidence obtained from well-designed cohort or case-controlled analytic studies, preferably from more than 1 center or research group.

Level II-3 : Evidence obtained from multiple time series with or without the intervention.

Dramatic results from uncontrolled trials might also be regarded as this type of evidence.

Level III : Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

UICC/ AJCC TNM staging system

T0 - No e/o primary tumor

T1 - Tumor ≤ 5cm

T1a - Superficial tumor

T1b - Deep tumor

T2 - Tumor > 5cm

T2a - Superficial tumor

T2b - Deep tumor

N0 - No reg LN mets

N1 - Reg LN mets

M0 - No distant mets

M1 - Distant mets

G – Histopathologic grade

Low grade

High grade

Stage grouping

Stage IA	LG	T1a No Mo
	LG	T1b No Mo
Stage IB	LG	T2a No Mo
	LG	T2b No Mo
Stage IIA	HG	T1a No Mo
	HG	T1b No Mo
Stage IIB	HG	T2a No Mo
Stage III	HG	T2b No Mo
Stage IV	Any Gr Any T N1 Mo	
	Any Gr Any T Any N M1	

Clinical Presentation of STS

At primary presentation :

Stage I - 30%

Stage II - 30%

Stage III - 20%

Stage IV - 20%

Poor Prognostic Factors

Age >60 years

Greatest dimension >5 cm

Stage II – IV

Unresectable location

**High-grade histology with high mitotic activity
(hemorrhage and necrosis)**

Higher incidence local failure and mets

Limb and Trunk STS

Guidelines for Combination Rx

Primary aim - Complete tum excision with adequate (≥ 1 cm) margin while maintaining optimal function

Low-grade : **Superficial - Wide Exn**
 Deep, ≤ 5 cm - Wide Exn
 Deep, > 5 cm - Wide Exn/ Comp Res
 \pm Adj RT

High-grade : **Superficial - Wide Exn**
 Deep, > 5 cm - Wide Exn/ Comp Res +
 Adj RT (Pre/Post-op)
 \pm Adj Chemo

Level of Evidence II

Surgery-RT Partnership

Rosenberg et al 1982

43 patients with HG extremity STS

Randomzn – Amputation Vs. WLE + Ext. RT 50 Gy

Dox + CTX + MTX to both arms

Inference – RT improves func. outcome

No diff. in DFS or OS

4 LR in RT group

RT did not compensate for R1 status

Level of Evidence II

RT – Pre or Post op?

Preop RT : Well-oxygenated tissue

Lower RT dose

Limited field size

Davis et al 2005 : RCT with 190 patients with Extr STS

Pr. Endpoint : Complcn rate (Fibrosis, joint, stiffness, edema)

	<u>Preop RT</u>	<u>Postop RT</u>
Dose	50 Gy/25 fr	66Gy/33 fr
OS (Med FU 3.3 yrs) -	85%	72% (p=0.05)
Wound complications*	35%	17% (p=0.01)

Acute commoner in peri-op pd. but chronic higher in post-op due to larger fields and higher dose

Guidelines - Adjuvant RT

Multiple studies since 1980s for conservative Sx + Adj RT show LC 78% to 91% with no improvement in OS

Recommended dose and technique :

Pre-Op – 50 Gy

Post-Op – ≥ 60 Gy (≥ 5 cm margin)

IMRT

Helical Tomotherapy

Post-RT Toxicity depends upon :

Size and location of the tumor

Doses > 68 Gy - 70 Gy

Cormier JN et al. 2004

Level of Evidence III

Limb and Trunk STS

Brachytherapy for STS

Pisters et al 1997 (PRT)

Aim : Minimize extent of normal tissue radiated

Allow local dose escalation to areas at highest risk.

164 pts subjected to resection and randomized intra-op. to :

Adj Brachy (42–45 Gy over 4–6 days.)

Vs.

No further Rx

Result (Med FU of 76 months) :

5-year local control rates - 82% with Brachy

vs. 69% for no further Rx

Benefit limited to patients with high grade lesions.

Overall local control was 91% (same as for Ext RT)

Level of Evidence II

Final Word : Pre or Post op?

Preference for Pre-op vs. Post-op radiation remains institution-dependent

Tumor location may help in decision making :

Higher incidence of wound complications in lower extr tumors

Chemoradiation for STS

Rationale –

Downstaging of the tumor to facilitate R0 Resection

The risk of distant mets with lesions :

5.1-10 cm	= 34%
10.1-15 cm	= 43%
15.1-20 cm	= 58%

(Spiro et al, 1997)

Optimum cases – High Grade STS

Chemo-responsive entities

Adjuvant CT in STS

In 2007, EORTC performed the largest adjuvant trial of CT with Dox & Iphos and reported it at the ASCO Annual Meeting

The trial failed to demonstrate any significant difference in the RFS or OS rate. The probable reason for the discrepancy in results is due to clubbing of different histologic subgroups and different sub sites.

A full report of the EORTC 62391 is eagerly awaited.

Adjuvant chemotherapy cannot be recommended as standard for all patients of STS

It may be considered in a select population of high grade extremity sarcoma, more than 5 cm or recurrent high grade tumors.

Level of evidence: II

Adjuvant ChemoRx in STS

Cochrane Review 2011

Sarcoma Meta-analysis Collaboration (SMAC)

Premise : Individual RCTs have shown no efficacy of Adj CT

Objective : To study if Adj CT reduces LR after Sx ± RT

Search included : Cochrane Trials Register, UKCCCR Register of Cancer Trials, PDQ, EMBASE, MED- LINE and CancerLit –

14 trials of Dox-based CT involving 1568 pts. Med FU 9.4 years.

Results : Overall RFS – Absolute Benefit of 6 to 10% at 10 yrs.

OS – Absolute Benefit of 4% at 10 yrs.

No consistent e/o a difference in effect with age/sex/ stage/site/ grade/histology/resection extent/ tumour size or effect of RT

Strongest evidence in f/o improved survival for extremity STS

Inference : *Dox based Adj CT significantly improves time to local and distant rec. & Overall RFS with, some evidence of a trend towards improved OS.*

Level of Evidence I

Rationale for NACT in STS

For locally advanced or High Gr STS

Reduction in radiation volumes

**Selection of potential subjects for
additional Adj Rx**

? Improvement in LRFS, DMFS & OS

Studies in NACT

Pisters et al 1997 (MDAH) - Stage IIIB Extr STS

3 cycles of pre-op Dox + DTIC, CTX + ADIC.

**Results - DFS and OS similar to historical studies
where pts were randomized to post-op CT**

**Even the subset of 'responders' did not
gain in LRFS, DMFS or OS.**

Studies in NACT

Kraybill 2006 (Phase II RTOG trial)

66 pts of HG STS > 8 cm

3 cycles of NACT with MAID alternating with RT → 3 postop MAID

Estimated 3 yr DFS - 56.6%, , distant DFS - 64.5% & OS 75.1%

Toxicity significant : 84% experiencing a grade 4 toxicity

2/5 amputations were considered Rx-related

***Conclusions : Such an aggressive NACT regimen to be performed
in a clinical trial setting.***

NACT + Combined CT/RT

DeLaney et al 2003 (Mass Gren Hosp)

Study - 19 Pts with HG STS of extremity > 8 cm were treated with :
3 cycles Pre-op CT - Mesna, Adriamycin, Ifosfamide & Dacarbazine
(MAID) alternating with RT (44 Gy) → Surgery → Postop CT ± RT*

*R1 cases -16 Gy post- op.

Results – 5 yr local control, freedom from distant metastases, DFS
& OS[#] all improved cf. historical controls.

OS increased from 58% to 87%

Conclusions - Overall benefit and general applicability of such
regimens is not clear in the absence of multi-center,
randomized trials.

RT + Concomitant Dox

Samuel Aguiar et al 2009 – Retrospec Analysis

49 pts with advanced extremity STS with \geq R1 Resection

Rx Schedule : Preop RT (30 Gy/12 Fr) + Concom Dox (60 mg/m²) D_{1,8,15}

Main endpoints : Local rec-free survival,
Mets-free survival and
Overall survival.

Median FU : 32.1 months.

Results : 5 yr LRFS - 81.5%, , Mets -free survival - 46.7%. OS - 58.3%.

High Gr STS - 5 yr LRFS - 36.3% , Mets -free survival - 41.2%

Severe wound complications in 41.8%

These precluded Adj CT in 73.7% of eligible pts.

Conclusions : Good local control rate but poor distant RFS & OS.

High wound complication rate affected planned adj Rx

Future Directions

New approaches are needed to advance treatment options and to provide alternatives to current neoadjuvant chemotherapy regimens with their associated significant toxicity.

Refinement of Pre-op RT is one current area of investigation. RTOG 0630 is a phase II study of preop IGRT for primary extremity STS aimed at reducing late radiation morbidity.⁴²

This study consists of 2 cohorts :

Cohort A – NACT ± Adj CT + 50Gy/25 Fr *Or*
Conc./ Interdigitated CT + 44Gy/22 Fr

Cohort B – Only 50 Gy/25 Fr and no CT

All subjects will then receive Sx → Post-op RT Boost in R1 cases

Cohort A closed in January 2010 and results are pending.

A randomized trial of the EORTC of pre-op CT (Dox & Ifosfamide) Vs. local treatment alone has been completed and final results are pending

Other approaches under investigation are – NAHT & Isolated Limb Perfusion