Meta-analysis in Soft tissue sarcoma

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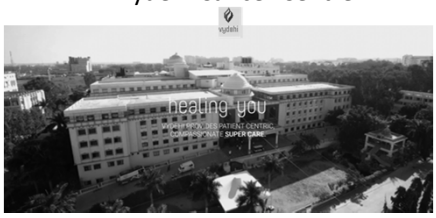
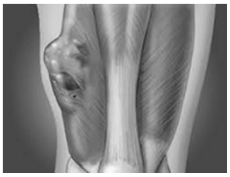


TOPICS COVERED

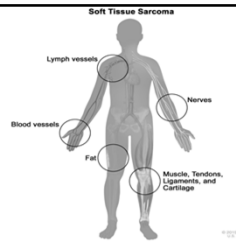
- ~~Introduction~~
- **Meta-analysis for radiation therapy in soft tissue sarcoma – in detail**
- Meta-analysis for chemotherapy in soft tissue sarcoma
- Other meta-analyses
- Summary

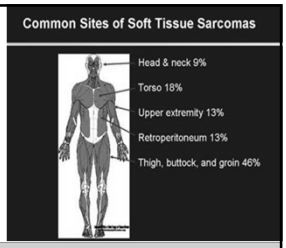
(Rhabdomyosarcoma, GIST and aggressive fibromatosis not covered)

INTRODUCTION

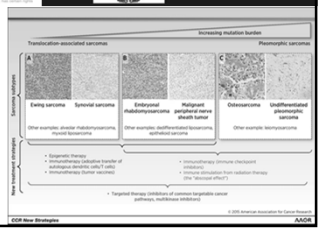


- Soft-tissue sarcomas (STSs) are a group of rare malignancies.
- Make up only 1%–2% of all cancers in adults
- Account for a higher proportion of 7-15% of all malignancies in children.



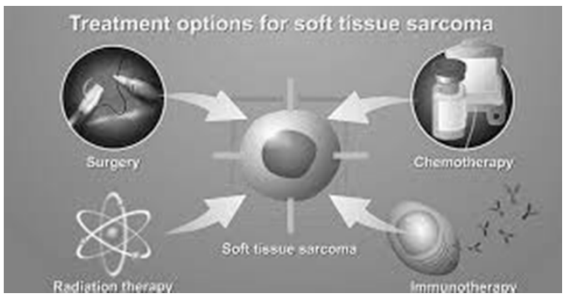


CHALLENGES



Most common Histopathological subtypes

- High-grade or undifferentiated pleomorphic sarcoma
- GIST
- Liposarcoma
- Leiomyosarcoma
- Synovial sarcoma
- Malignant peripheral nerve sheath tumor



- The standard of care for localized disease in adults with soft tissue sarcoma is wide surgical resection [en bloc macro and microscopically complete surgical excision of the gross tumor (R0 resection)
- No meta-analysis available for surgery
- **Role of radiation therapy and chemotherapy in STS will be discussed after analyzing meta-analysis**

Questions to be answered for RT

- Whether radiation improves local control?
- Whether radiation improves overall survival?
- Timing of RT- Pre op vs. post op which is better in terms of local control and overall survival

External Beam Radiation Therapy for Resectable Soft Tissue Sarcoma: A Systematic Review and Meta-Analysis (Germany, Italy, France and Norway)

Ann Surg Oncol. 2018 Mar;25(3):754-767. doi: 10.1245/s10434-017-6081-2. Epub 2017 Sep 11 Albertsmeier M, Rauch A, Roeder F

Published online: 11 September 2017

- A systematic literature search of the MEDLINE, EMBASE and PsychINFO databases was conducted to identify suitable studies.
- The search was limited to publications with available abstracts, English and German language, humans, and adults. All publications up to December 2015 were included
- Furthermore, studies on gastrointestinal stromal tumors (GISTs) and gynecological tumors (e.g. uterine leiomyosarcoma) were excluded.

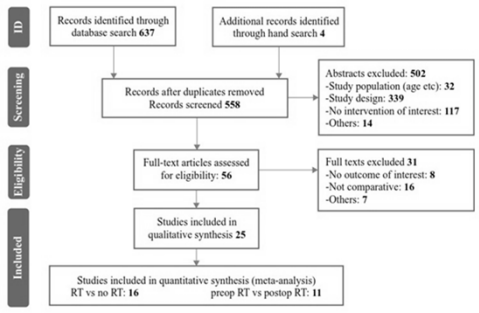


FIG. 1 Systematic literature search. *RT* radiation therapy, *ID* identification, *preop* preoperative, *postop* postoperative

TABLE 1 continued

Reference (year of publication)	Study design	Rating of quality				Localization	Data for subgroup analyses		Type of intervention/ control	*N* total (intervention/ control)	Patient age, years	Reported outcome
		Study type	Quality (total max: 27)				Grading (FNCLCC)	Resection status				
			Reporting bias (max: 11)	External validity (max: 3)	Internal validity (max: 13)							
Sanfilippo et al. (2011)	RR	Low	6	1	8	E: 132, 83.5% H/N/T: 26 R: –	G1: 35, 22.2% G2/3: 123, 77.8%	R0: 130, 82.3% R1: 28, 17.7% R2: 0, 0%	Postop RT/no RT	158 (81/77)	MD (IQR): 64 (54–72)	LR, OS
Mutter et al. (2012)	RR	Low	5	1	7	E: 202, 100% H/N/T: – R: –	G1: – G2/3: 202, 100%	R0: 138, 68.3% R1: 64, 31.7% R2: –	Postop/no RT	202 (138/64)	MD (range): 63 (22–95)	LR, OS
Moreau et al. (2012)	RR	Low	6	1	7	E: 406, 97.1% H/N/T: 12, 2.9% R: –	G1: 140, 34.7% G2/3: 263, 65.3%	R0: 309, 74.5% R1: 92, 22.2% R2: 14, 3.4%	Postop RT/no RT	403 (302/ 101)	MD (range): 45 (14–88)	LR
Barsoudi et al. (2014)	RR	Low	6	1	8	E: 117, 100% H/N/T: – R: –	G1: 15, 12.8% G2/3: 102, 87.2%	R0: 58, 49.6% R1: 40, 34.2% R2: 19, 16.2%	Pre-, post, or pre- and postop RT/no RT	117 (88/29)	Mean (range): 58.6 (16–91)	LR
Cassier et al. (2014)	RR	Low	7	1	7	E: 222, 78.4% H/N/T: 21.6% R: –	G1: 283, 100% G2/3: –	R0: 105, 42.9% R1: 132, 53.9% R2: 8, 3.3%	Postop RT/no RT	283 (132/ 151)	Mean (range): 62 (25–94)	LR, OS
Trovik et al. (2014)	RR	Low	8	1	7	E: – H/N/T: – R: 97, 100%	G1: 26, 26.8% G2/3: 71, 73.2%	R0: 54, 59.3% R1 + 2: 40.7%	Pre-or postop RT/no RT	97 (42/55)	MD (range): 62 (15–83)	LR, OS

TABLE 1 continued

Reference (year of publication)	Study design	Rating of quality				Localization	Data for subgroup analyses		Type of intervention/ control	*N* total (intervention/ control)	Patient age, years	Reported outcome
		Study type	Quality (total max: 27)				Grading (FNCLCC)	Resection status				
			Reporting bias (max: 11)	External validity (max: 3)	Internal validity (max: 13)							
Toulmonde et al. (2014)	RR	Low	7	1	6	E: – H/N/T: – R: 586, 100%	G1: 152, 26.4% G2/3: 423, 73.6%	NR[a]	Periop/no RT	511 (146/365)	MD (range): 57 (18–89)	LR, OS
Kelly et al. (2015)	RR	Low	8	1	6	E: – H/N/T: R: 204, 100%	G1: 69, 33.8% G2/3: 135, 66.2%	R0: 84, 41.4% R1: 119, 58.6% R2: –	Periop/no RT	204 (32/172)	Mean (range): 61 (26–92)	LR
Baxter et al. (2015)	RR	Low	8	1	6	E: 63, 84.0% H/N/T: 12, 16.0% R: –	G1: 100, 100% G2/3: –	R0: 64, 85.3% R1/R2: 11, 14.7%	Pre- or postop RT/no RT	75 (58/17)	MD (range): 49 (16–82)	LR
Lane et al. (2015)	RR	Low	8	1	7	E: – H/N/T: – R: 74, 100%	G1: 22, 51.2% G2/3: 21, 48.8%	R0: 20, 45.4% R1: 14, 31.8% R2: 10, 22.7%	Pre-, post-, peri-, pre- and peri- or peri- and postop RT/no RT	74 (29/45)	MD (IQR): 58 (49–65)	LR, OS

E extremities, *H/N/T* head/neck, trunk wall, girdles, *R* retroperitoneum, *MD* median, *RCT* randomized controlled trial, *RR* retrospective review, *RT* radiotherapy, *preop* preoperative, *postop* postoperative, *periop* perioperative, *LR* local recurrence, *OS* overall survival, *NR* not reported, *IQR* interquartile range, *max* maximum

[a] Piecemeal resection in 80 patients (15.5%)

TABLE 1 Characteristics of the included studies for the comparison of radiotherapy versus no radiotherapy

Reference (year of publication)	Study design	Rating of quality				Localization	Data for subgroup analyses		Type of intervention/ control	*N* total (intervention/ control)	Patient age, years	Reported outcome
		Study type	Quality (total max: 27)				Grading (FNCLCC)	Resection status				
			Reporting bias (max: 11)	External validity (max: 3)	Internal validity (max: 13)							
van Doorn et al. (1994)	RR	Low	5	1	7	E: – H/N/T: – R: 34, 100%	G1: 13, 46.4% G2/3: 15, 53.6%	R0: 8, 23.5% R1: 22, 64.7% R2: 4, 11.8%	Postop RT/no RT	34 (13/21)	Mean (range): 57 (26–80)	LR
Coindre et al. (1996)	RR	Low	8	1	8	E: 331, 60.6% H/N/T: 153, 28.0% R: 62, 11.4%	G1: 79, 14.5% G2/3: 467, 85.5%	NR	Postop RT/no RT	498 (316/182)	MD (range): 52 (15–95)	LR, OS
Yang et al. (1998)	RCT	High	9	1	10	E: 216, 100% H/N/T: – R: –	G1: 50, 35.5% G2/3: 91, 64.5%	R0: 122, 87.1% R1: 18, 12.9% R2: –	Postop RT/no RT	141 (70/71)	NR	LR, OS
Choong et al. (2001)	RR	Low	8	1	8	E: 141, 100% H/N/T: – R: –	G1: 59, 44.7% G2/3: 73, 55.3%	R0: 93, 70.5% R1 + 2: 29.5%	Pre-,post-, or periop RT/no RT	132 (57/75)	MD (range): 44 (10–84)	LR
Jebsen et al. (2008)	RR	Low	6	1	7	E: 942, 86.2% H/N/T: 151, 13.8% R: –	G1: 26, 2.4% G2/3: 1062, 97.6%	R0: 609, 55.7% R1/R2: 484, 44.3%	Pre- or postop RT/no RT	1093 (462/631)	MD (range): 65 (16–95)	LR, OS
Nishida et al. (2010)	RR	Low	5	1	6	E: 40, 75.5% H/N/T: 13, 24.5% R: –	G1: 53, 100% G2/G3: –	R0: 44, 86.3% R1: 7, 13.7% R2: 0, 0%	RT (not specified)/no RT	53 (9/44)	Mean (range): 51 (17–85)	LR, OS

TABLE 2 Characteristics of the included studies for the comparison of preoperative versus postoperative radiotherapy

Reference (year of publication)	Study design	Rating of evidence				Localization	*N* (preoperative/ postoperative)	Patient age, years	Reported outcomes
		Study type	Quality						
			Reporting bias	External validity	Internal validity				
Suit et al. (1985)	RR	Low	5	1	7	E + H/N/T: 170, 100% R: –	170 (60/110)	*N* (%): <60: 114 (67) ≥60: 56 (33)	LR, OS
Frezza et al. (1992)	RR	Low	6	1	6	E: 99, 100% H/N/T: – R: –	99 (50/49)	Mean (range): 47 (13–80)	LR, WH
Cheng et al. (1996)	RR	Low	8	1	8	E: 112, 100% H/N/T: – R: –	112 (48/64)	Mean (range): 47 (18–88)	LR, OS, WH
Pollack et al. (1998)	RR	Low	8	1	9	E: 122, 63.2% H/N/T: 71, 36.8% R: –	222 (126/165)	Mean (range): Preop: 51.1 (12–79) Postop: 49.5 (6–88)	LR, WH
O'Sullivan et al. (2002)	RCT	High	10	2	9	E: 182, 100% H/N/T: – R: –	182 (88/94)	*N* (%): <50: 74 (41) 50 to < 70: 71 (39) ≥70: 37 (20)	LR, OS, WH
Zagars et al. (2003)	RR	Low	9	1	8	E: 325, 62.9% H/N/T: 192, 37.1% R: –[a]	517 (271/246)	MD (range): 49 (2–85)	LR, OS
Kirkby et al. (2005)	RR	Low	6	1	7	E: 105, 89.7% H/N/T: 12, 10.3% R: –	117 (50/58)	Mean (range): 38 (4–72)	LR, OS, WH
Schoenfeld et al. (2006)	RR	Low	5	1	7	E: 23, 100% H/N/T: – R: –	23 (7/16)	MD (range): 64 (NR)	LR
Jebsen et al. (2008)	RR	Low	6	1	7	E: 364, 82.9% H/N/T: 75, 17.1% R: –	439 (107/332)	Mean (range): 60 (16–95)	
Moore et al. (2014)	RR	Low	8	1	7	E: 220, 85.9%[b] H/N/T: 36, 14.1%[b] R: –	184 (122/62)	Median (range): 55 (9–87)[b]	WH
Toulmonde et al. (2014)	RR	Low	7	1	6	E: – H/N/T: – R: 75, 100%	75 (13/62)	MD (range): 57 (18–89)[c]	LR, OS

RCT randomized controlled trial, *RR* retrospective review, *E* extremities, *H/N/T* head/neck, trunk wall, girdles, *R* retroperitoneum, *LR* local recurrence, *OS* overall survival, *WH* wound healing, *MD* median, *preop* preoperative, *postop* postoperative, *RT* radiotherapy

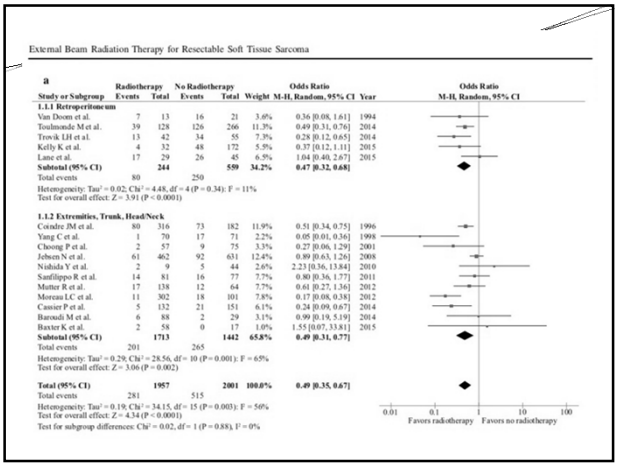
[a] Some retroperitoneal tumors are included as tumors of the trunk wall

[b] Including patients who received both preoperative and postoperative RT and patients who did not receive any RT

[c] Data for the original complete study cohort; data included in this comparison constitute a subgroup analyses

- The study chose Local Recurrence(LR) as the primary outcome
- Overall Survival(OS) was included as a secondary outcome to determine the long-term oncological effects of RT.
- For the comparison of preoperative versus postoperative RT, wound healing disorders was chosen as a secondary outcome and safety parameter.

	RT VS. NO RT	PREOP VS POSTOP RT
No. of studies	16	9
RCT	1	1
RR	15	8
Extremity	6	9
Retroperitoneum	5	1
Head and Neck		3
Trunk wall		4
Mixed	4	
Median follow up	47 months to 9.6 yrs.	12 months to 7.1 yrs.
Sample size	34 to 1093	23 to 517



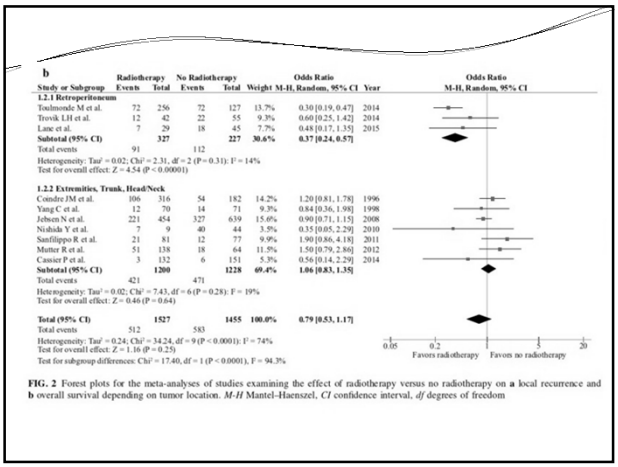
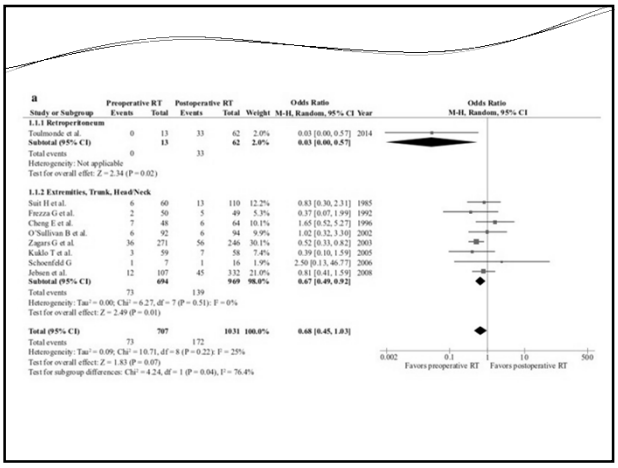
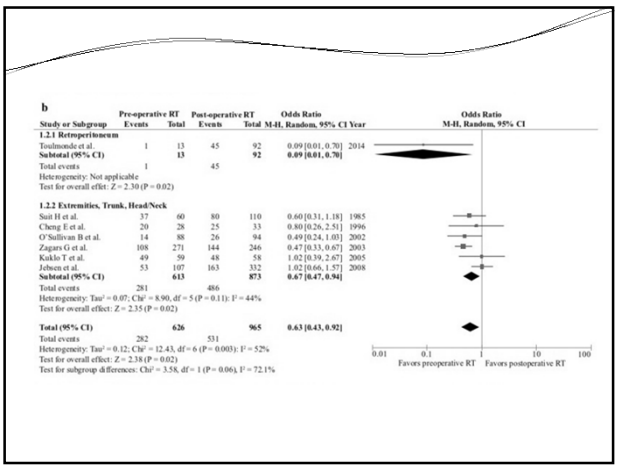


FIG. 2 Forest plots for the meta-analyses of studies examining the effect of radiotherapy versus no radiotherapy on **a** local recurrence and **b** overall survival depending on tumor location. *M-H* Mantel–Haenszel, *CI* confidence interval, *df* degrees of freedom





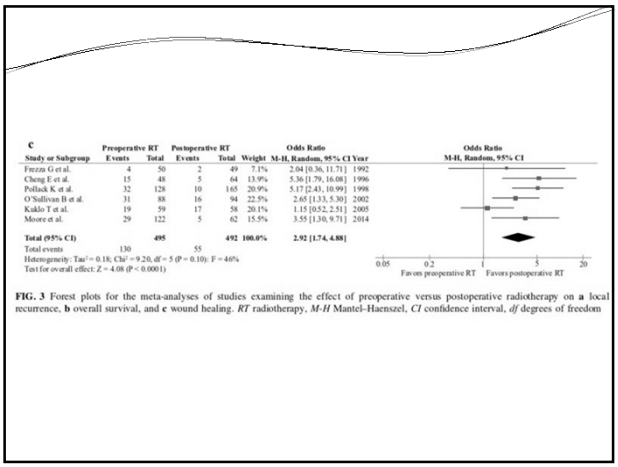


FIG. 3 Forest plots for the meta-analyses of studies examining the effect of preoperative versus postoperative radiotherapy on **a** local recurrence, **b** overall survival, and **c** wound healing. *RT* radiotherapy, *M-H* Mantel–Haenszel, *CI* confidence interval, *df* degrees of freedom

	RT VS. NO RT	PREOP VS. POSTOP RT
No. of patients	3958	Retroperitoneal tumors = 75 Extremity, head/neck, or trunk wall tumors=1663
Local control	• RT significantly reduced the risk of LR, with a combined OR of 0.49 (95% CI0.35–0.67, p = 0.003). • Five studies including 803 patients investigated retroperitoneal tumors. All studies except one showed a positive effect of RT, resulting in a combined OR of 0.47 (95% CI 0.32–0.68, p \0.0001). • The majority of 11 studies including 3155patients with extremity, head/neck, or trunk wall tumors also showed a positive effect of RT, resulting in a combined OR of 0.49 (95% 0.31–0.77, p = 0.002) for these locations.	• The study on retroperitoneal STSs found a significant advantage for preoperative RT (OR 0.03, 95% CI 0.00–0.57, p = 0.02). • For other tumor locations, results differed across smaller studies but the two largest series found a positive effect of preoperative RT, resulting in a reduced combined OR favoring preoperative radiation (OR 0.67, 95% CI 0.49–0.92, p = 0.01).

	RT vs. No RT	Preop vs. postop RT
Overall survival	• 10 studies • All tumor locations did not show a significant benefit of RT • However, the analysis of data from three studies including 554 patients with retroperitoneal tumors found a significantly positive effect of RT, with a combined OR of 0.37 (95% CI 0.24–0.57, p \0.00001). • The results of seven studies including 2428 patients with extremity, head/neck, or trunk wall tumors were not consistent and the combined OR was not statistically significant.	• In total, six studies compared the effect of preoperative versus postoperative RT on OS (n = 1534), while one study included 105 patients with retroperitoneal STSs. In this study, a significant advantage for preoperative RT (OR 0.09, 95% CI 0.01–0.70,p = 0.02) was found. • For the other tumor locations(n = 1486), the combined OR showed a trend favoring preoperative RT compared with postoperative RT, but failed to reach statistical significance (OR 0.71, 95% CI0.49–1.01, p = 0.06).

Wound Healing

- Among those studies comparing preoperative versus postoperative RT, six studies including 987 patients reported wound complications . Most patients had tumors of the extremities and none had retro-peritoneal sarcoma.
- Meta-analysis of results from the included studies showed a significantly increased risk of wound complications for preoperative RT (OR 2.92, 95% CI 1.74–4.88, p \0.0001).

Heterogeneity in the Studies

- Substantial heterogeneity was found for studies on LR comparing RT versus no RT for those with tumors located in the extremities, trunk wall, and head and neck (I2= 65%),

CONCLUSIONS

- The available evidence suggests that RT is effective in reducing LR in STSs.
- For retroperitoneal STSs, a positive effect on OS was demonstrated in a small number of nonrandomized studies, while there was no OS benefit in other tumor locations.
- The preferred sequence of RT remains unclear; the only randomized controlled trial found no difference between preoperative and postoperative RT in STS of the limbs with respect to LR and OS.

A Systematic Review and Meta-Analysis of Oncologic Outcomes of Pre- Versus Postoperative Radiation in Localized Resectable Soft-Tissue Sarcoma (Canada)

Emad Al-Absi, , Forough Farrokhyar, Rajrish Sharma,
Ann Surg Oncol (2010) 17:1367–1374
DOI 10.1245/s10434-009-0885-7

The objective of this study was to perform a systematic review of the available literature and meta-analysis to determine the oncologic outcomes (local recurrence and overall survival) in localized resectable STS after pre versus postoperative radiotherapy.

- A systematic search through the following databases was performed: MEDLINE, EMBASE, Cancer Lit, and the Cochrane of Systemic Reviews.
- Studies that compared outcomes between preoperative and postoperative radiotherapy cohorts in localized resectable STS were included.

- To be included, the studies also had to report oncologic outcomes (local recurrence and overall survival) in both groups.
- The outcome measures targeted for analysis were local recurrence and overall survival.
- Five studies met the inclusion criteria and were identified as appropriate for this meta-analysis

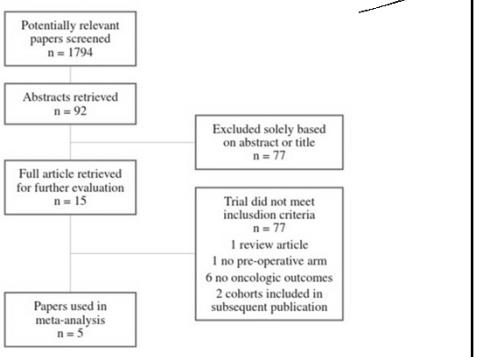


FIG. 1 Literature review flow diagram showing literature search and article exclusion process; 5 articles were eventually found appropriate for use in the meta-analysis

- All five studies (one RCT and four retrospective cohort studies) included patients with STS treated with surgical resection and pre- or postoperative radiation.
- The study publication dates ranged from 1985 to 2005.
- The studies included a total of 1,098 patients, 526 of whom had received preoperative radiotherapy and 572 of whom had received postoperative radiotherapy.

TABLE 1 Patient demographics and treatment characteristics

Characteristic	Kuklo et al.[27]	Zagars et al.[28]	Suit et al.[29]	Cheng et al.[14]	O'Sullivan et al.[12]
Mean patient age (years)					
Preoperative	–	–	–	47	23% >70
Postoperative	–	–	–	54	18% >70
Combined	37.7	49	–	–	
Length of follow-up (years)					
Preoperative	6.1	6.4	–	–	–
Postoperative	8.4	9.1	–	–	–
Combined	–	8.7	–	5.3	3.3
Tumor size >10 cm (%)					
Preoperative	35.5	42	43	–	35
Postoperative	26	21	18	–	33
Tumor location (% extremity)					
Preoperative	–	73	–	–	100
Postoperative	–	51	–	–	100
Radiation dose (mean Gy)					
Preoperative	51	50	50–52	48	50
Postoperative	63	60	64–66	62	66
Chemotherapy (% received)					
Preoperative	23.7	53	–	–	–
Postoperative	20.7	42	–	–	–
Resection margin (% positive)					
Preoperative	–	24	–	40	17
Postoperative	–	12	–	42	15

TABLE 2 Summary of oncologic outcomes

Study	Total no. of patients	Patients provided with preoperative radiation	Patients provided with postoperative radiation	Mets before surgery	Mets after surgery	Local recurrence with preoperative radiation	Local recurrence with postoperative radiation	Survival rate with preoperative radiation (%)	Survival rate with postoperative radiation (%)
Kuklo et al.[27]	117	59	58	–	–	3	4	83.1	82.8
Zagars et al.[28]	517	271	246	105	97	36	56	62	41
Suit et al.[20]	170	60	110	21	23	6	13	73	62
Cheng et al.[14]	112	48	64	–	–	7	6	75	79
O'Sullivan et al.[12]	182	88	94	–	–	–	–	88	72
Total	1,098	526	572					Avg. 76	Avg. 67

Mets metastases

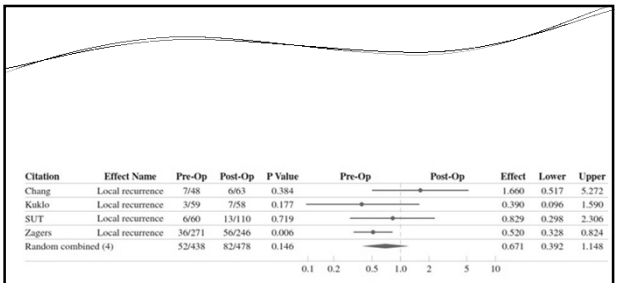


FIG. 2 Forest plot for local recurrence showing random-effects methods of combined results

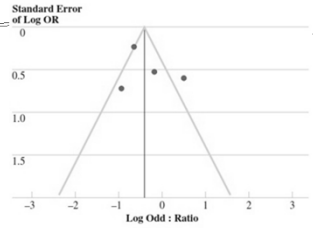


FIG. 3 Funnel plot for the 4 studies reporting local recurrence

The funnel plot for all studies is asymmetrical , indicating one study with larger confidence intervals than expected, but studies fell evenly within the top of the inverted funnel. This funnel plot pattern indicates the presence of a small amount of publication bias. The P value for heterogeneity was 0.259 and the variability (I2=25%)

Local Recurrence

- Four studies were included in the analysis for local recurrence.
- These studies included a total of 916 patients, 134 of whom experienced local recurrences.
- Of these 134 patients, 52 had received preoperative radiation and 82 had received postoperative radiation.

- The risk for local recurrence was calculated by both fixed- and random-effect methods.
- The risk for local recurrence was lower in the group that had received preoperative radiotherapy (OR 0.61, 95% CI 0.42–0.89) when the fixed-effects method was used, but this was not statistically significant (OR 0.67, 95% CI 0.39–1.15) when the random-effects method was used

Survival Analysis

- Data from all five studies eligible studies were used to analyze the survival rate of the 1098 patients who received radiotherapy for STS. Raw data for the number of deaths were only provided in two studies. However, time-dependent survival was provided in all studies.
- The average survival rate was 76% (range 62–88%) for patients in the preoperative radiotherapy group and 67% (range 41–83%) for the postoperative group).

Limb- sparing surgery plus radiotherapy results in superior survival: an analysis of patients with high- grade, extremity soft-tissue sarcoma from the NCDB and SEER

Stephen J. Ramey, Raphael Yechieli, Wei Zhao
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Cancer Medicine. 2018;1–12.

- The National Cancer Database (NCDB) and the Surveillance, Epidemiology, and End Results (SEER) Program were analyzed separately to identify patients with stage II- III, high- grade E- STS diagnosed between 2004 and 2013 and treated with (1) amputation alone, (2) limb- sparing surgery (LSS) alone, (3) preoperative radiation therapy (RT) and LSS, or (4) LSS and postoperative RT.

- Multivariable analyses (MVAs) and 1:1 matched pair analyses (MPAs) examined treatment impacts on overall survival(OS) (both databases) and sarcoma mortality (SM)(SEER only).
- From the NCDB and SEER, 7828 and 2937 patients were included.
- On MVAs, amputation was associated with inferior OS and SM.

- Relative to LSS alone, both preoperative RT and LSS (HR, 0.70; 95% CI: 0.62- 0.78) and LSS and postoperative RT (HR, 0.69; 95% CI: 0.63- 0.75) improved OS in NCDB analyses with confirmation by SEER.
- Estimated median survivals from MPA utilizing NCDB data were 7.2 years with LSS alone (95% CI: 6.5- 8.9 years) vs 9.8 years (95% CI: 9.0- 11.2 years) with LSS and postoperative RT.

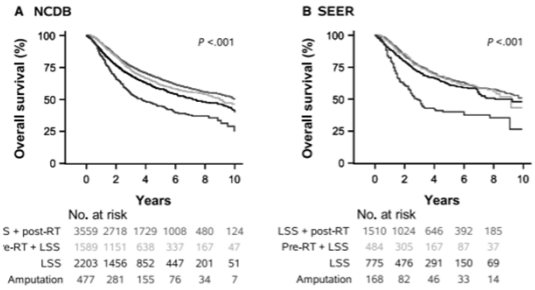
- A MPA comparing preoperative RT and LSS to LSS alone found median survivals of 8.9 years (95% CI: 7.9- not estimable) and 6.6 years (95% CI: 5.4- 7.8 years).
- Optimal high grade E- STS management includes LSS with preoperative or postoperative RT as evidenced by superior OS and SM

TABLE 3 Median survival and 3-, 5-, and 7-y overall survival (OS) rates (%) using after propensity score matched data

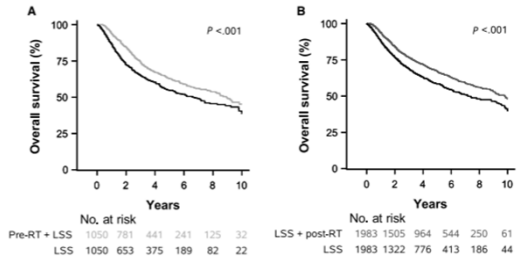
			OS rates (95% CI)		
Dataset	**Treatment**	**Median survival (y)**	**3 y**	**5 y**	**7 y**
NCDB	LSS alone	6.6 (5.4, 7.8)	65.0 (61.9, 68.0)	55.0 (51.4, 58.3)	49.1 (45.1, 53.0)
	Pre-RT + LSS	8.9 (7.9, NE)	73.9 (71.0, 76.6)	62.2 (58.8, 65.5)	56.1 (52.3, 59.8)
NCDB	LSS alone	7.2 (6.5, 8.9)	68.9 (66.6, 71.0)	58.6 (56.0, 61.0)	51.0 (48.1, 53.8)
	LSS + post-RT	9.8 (9.0, 11.2)	76.6 (74.6, 78.5)	67.2 (64.8, 69.4)	59.2 (56.4, 61.8)
SEER	LSS alone	6.9 (4.7, NE)	64.3 (58.2, 69.9)	53.3 (46.2, 59.9)	48.2 (40.0, 55.8)
	Pre-RT + LSS	9.2 (8.2, NE)	74.6 (69.0, 79.4)	65.4 (58.9, 71.1)	61.0 (53.8, 67.4)
SEER	LSS alone	8.1 (7.0, NE)	70.9 (67.0, 74.3)	60.9 (56.5, 65.0)	54.1 (48.9, 59.0)
	LSS + post-RT	9.7 (8.8, NE)	79.4 (76.0, 82.4)	69.2 (65.1, 73.0)	62.1 (57.3, 66.5)
			Cumulative incidence rates of sarcoma mortality (95% CI)		
Dataset	**Treatment**		**3 y**	**5 y**	**7 y**
SEER	LSS alone		27.4 (22.1, 32.9)	35.2 (28.7, 41.6)	36.2 (29.6, 42.9)
	Pre-RT + LSS		21.8 (17.1, 26.9)	28.7 (23.1, 34.5)	29.8 (23.9, 35.8)
SEER	LSS alone		19.6 (16.5, 22.8)	26.7 (23.0, 30.6)	29.9 (25.7, 34.3)
	LSS + post-RT		16.2 (13.4, 19.3)	24.6 (21.0, 28.4)	26.3 (22.5, 30.3)

NE, not estimable; CI, confidence interval; LSS, limb-sparing surgery; RT, radiation therapy; pre-RT, preoperative RT; post-RT, postoperative RT.

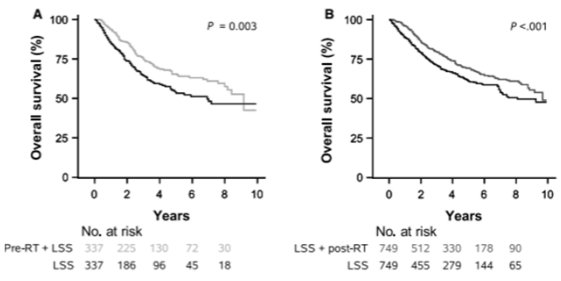
Overall Survival by treatment

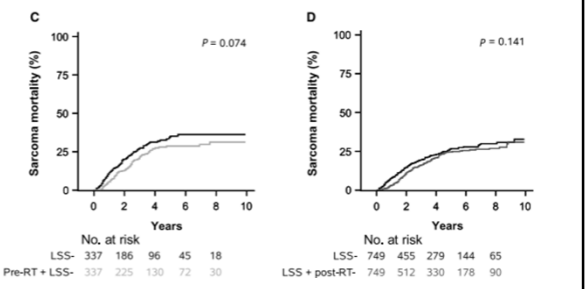


A. Preoperative Radiotherapy (pre-RT) + Limb-Sparing Surgery (LSS) vs. LSS alone.
B. LSS + Postoperative Radiotherapy (post-RT) vs. LSS alone



A. Overall Survival Comparison of Preoperative Radiotherapy (pre-RT) + Limb-Sparing Surgery (LSS) vs LSS alone.
B. Overall Survival Comparison of LSS + Postoperative Radiotherapy (postRT) vs.LSS alone.
C. Sarcoma Mortality Comparison of pre-RT + LSS vs.LSS alone.
D. Sarcoma Mortality Comparison of LSS + post-RT vs.LSS alone





- The study found that adding RT (either preoperative or postoperatively) to LSS was associated with increased OS and reduced SM in patients with high- grade E- STS.
- Amputation was associated with worse survival outcomes in all analyses.
- There were no significant differences in survival based on the timing of radiotherapy (i.e., preoperative or postoperative).
- In conclusion, LSS combined with RT is the optimal treatment option for most patients with high- grade E- STS.

Adjuvant chemotherapy in advanced STS of adults

- While there is a clear role for adjuvant and neoadjuvant chemotherapy in paediatric and young adult patients with rhabdomyosarcomas (RMSs), Ewing's sarcomas (ESs) and osteosarcomas (OSs), the role of adjuvant chemotherapy in adult sarcomas (leiomyosarcoma, liposarcoma, and synovial sarcoma) remains controversial.

- 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

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

Adjuvant chemotherapy for soft-tissue sarcoma: review and meta-analysis of the published results of randomised clinical trials.

J. F. Tierney, V. Mosseri, L. A. Stewart
Br J Cancer. 1995 Aug; 72(2): 469–475.

- Fifteen published randomised trials comparing adjuvant chemotherapy with no chemotherapy in soft-tissue sarcoma (STS) were identified (1546 patients).

- The meta-analysis of the published data suggests an improvement in survival at 2 years (OR = 0.73, 95% CI = 0.53-0.99, P = 0.044) and at 5 years (OR = 0.59, 95% CI = 0.45-0.78, P = 0.0002) in favour of chemotherapy.
- The only reliable means of assessing the current evidence on whether adjuvant chemotherapy has a role in the treatment of patients with STS, is to collect, check and reanalyze individual patients data (IPD) from each trial centrally, and formally combine the results in a stratified time-to-event analysis.

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 , which involved 1568 adults with localized resectable STS (extremities and others), and published in 1997.

Adjuvant chemotherapy for localized resectable soft-tissue sarcoma of adults: meta-analysis of individual data

The Lancet,Volume 350, Issue 9092, 6 December 1997, Pages 1647-1654

- 1568 patients from 14 trials of doxorubicin-based adjuvant chemotherapy were included (median follow-up 9·4 years).

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.

Interpretation

- The meta-analysis provides evidence that adjuvant doxorubicin-based chemotherapy significantly improves the time to local and distant recurrence and overall recurrence-free survival. There is a trend towards improved overall survival.

- Proponents applauded the individual patient data approach of this meta-analysis, which would remove any deficiencies of individual studies that had an inadequate sample size, heterogeneity of reported outcomes and variable exclusion of patients

Criticisms of the Meta analysis

- 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.
- More importantly, only one of the trials in the meta-analysis used ifosfamide, which was becoming an apparent important player in systemic therapies for advanced /metastatic STS, in combination with doxorubicin.

Sarcoma Meta analysis Collaboration meta analysis update 2008

Cancer :Volume113, Issue3, 1 August 2008, Pages 573-581

- In 2008, a meta analysis update 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, 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.

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)
- 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.

Conclusions

- Compared with the original SMAC analysis, adjuvant chemotherapy continued to demonstrate a similar trend in RFS improvement.
- In terms of overall survival benefit, however, there was now evidence of significant improvement in overall survival in patients treated with ifosfamide and doxorubicin combination (OR for death 0.56; 95% CI 0.36 to 0.85), in contrary to patients treated with doxorubicin alone, which did not meet statistical significance (OR for death 0.84 (95% CI 0.68 to 1.03)).

What are the available evidence for neoadjuvant chemotherapy in STS?

- While there appears to be a list of compelling theoretical and practical advantages of neoadjuvant chemotherapy in STS, as opposed to in the postoperative setting, there is a surprising lack of evidence specifically addressing the role of chemotherapy when used in a neoadjuvant manner.

RTOG-9514 study

- 66 patients with large tumor size more than 8cm, high grade primary or locally extremity
- Preop chemoradiation followed by resection and post op chemo with doxorubicin based regimen improves local control and OS,DFS rates in patients with high grade STS of extremity and body wall
- However pre-op arm had significant short term toxicities

In contrast, the results of a randomized study that compared surgery alone vs. preop chemo follwed by surgery in 134 patients with high risk tumors did not show a major survival benefit.

Meta-analysis of ifosfamide-based combination chemotherapy in advanced soft tissue sarcoma

Verma S, Younus J, Stys-Norman D, Haynes AE,
Cancer Treatment Reviews, Volume 34, Issue 4, June 2008, Pages 339-34

- In patients with metastatic soft tissue sarcoma, the routine addition of ifosfamide to standard first line doxorubicin-containing regimens is not recommended over single agent doxorubicin. However, it may be reasonable to employ such combinations in patients with symptomatic, locally-advanced, or inoperable soft tissue sarcoma where response might render such tumours resectable.

Doxorubicin-Based Chemotherapy for the Palliative Treatment of Adult Patients with Locally Advanced or Metastatic Soft-Tissue Sarcoma: A Meta-Analysis and Clinical Practice Guideline

Vivien H. C. Bramwell, Dale Anderson, and Manya L. Charette
Sarcoma Volume 4, Issue 3, Pages 103-112
http://dx.doi.org/10.1080/13577140020008066

- Eight randomized trials comparing doxorubicin-based combination versus doxorubicin single-agent chemotherapy were reviewed
- Single-agent doxorubicin is an appropriate first-line chemotherapy option for advanced or metastatic soft-tissue sarcoma.
- Some doxorubicin-based combination chemotherapy regimens, given in conventional doses, produce only marginal increases in response rates, at the expense of increased adverse effects, and with no improvements in overall survival.

SUMMARY

- STS constitutes a minority among Malignancies.
- They are a heterogeneous group of disorders in terms of histology and molecular profile
- Surgical resection with appropriate negative margin is the standard primary treatment for most patients with STS.
- In all tumor locations, RT significantly reduced the risk of Local recurrence.

- When compared with preop vs. post op, retroperitoneal STSs found a significant advantage for preoperative RT in terms of local control. For other tumor locations, results were conflicting on meta-analysis.
- In terms of overall survival, a positive effect on OS was demonstrated for retroperitoneal STSs in a small number of nonrandomized studies, while there was no OS benefit in other tumor locations on meta-analysis. (Though NCDB/SEER analysis was associated with increased OS and reduced sarcoma mortality in patients with high grade Extremity STS).

- A significantly increased risk of wound complications for preoperative RT is seen
- A non significant trend towards reduced late toxicities (fibrosis, edema & joint stiffness) is observed with preop compared to postop radiation.
- The use of preoperative RT has been on the rise for all the sites and may be recommended for all the sites except the tumors which are low grade, less than 5 cms and when resected margin more than 1 cm .

- For patients elect to proceed with adjuvant chemotherapy, the use of both ifosfamide and an anthracycline, in combination with MESNA, is recommended.
- Without clear evidence to support the widespread use of neoadjuvant chemotherapy in patients with STS, presently, neoadjuvant chemotherapy can be considered in selected patients on a case-by-case basis.
- Single-agent doxorubicin is an appropriate first-line chemotherapy option for advanced or metastatic soft-tissue sarcoma

THANK YOU