Prognostic Factors in Indian Patients Operated for Soft Tissue Sarcomas—a Retrospective Cross-sectional Analysis

Akshay Tiwari¹ · Swati Shah¹ · Ashwani Kumar Sharma¹ · Sandeep Mehta² · Ullas Batra³ · S. K. Sharma⁴ · A. K. Dewan¹

Received: 6 July 2015 / Accepted: 18 October 2016 / Published online: 2 November 2016
© Indian Association of Surgical Oncology 2016

Abstract Soft tissue sarcomas are a rare entity. While surgery is established as the mainstay of treatment, the exact role and sequencing of adjuvant therapy is not well defined. Literature on Indian patients with soft tissue sarcoma with respect to clinical profile and prognostic factors is scarce. We retrospectively analysed the data of 112 patients operated for soft tissue sarcoma of extremity or trunk (excluding retroperitoneal and mediastinal sarcomas, round cell histology) at our institute from 1 January 2009 to 31 December 2013. Around half the patients were less than 50 years of age and around a third had size more than 10 cm. Oncological outcome was correlated with various demographic, tumour-related and treatment-related factors using SPSS 22. Overall survival at 5 years was 73.2 % and event-free survival at 5 years was 42.2 %. At final follow-up (mean of 44.85 ± 4.64 months), local recurrence was seen in 31.9 % and distant metastasis was seen in 30.1 % of the patients. Using both univariate and multivariate analysis, younger age (<50 years), larger size (>10 cm, but not >5 cm) and pathologically positive lymph nodes were the only factors found significantly affecting overall survival. The clinical profile and prognosis of Indian patients with soft tissue sarcoma were found to be different from that reported in

Western literature. The impact of established prognostic indicators for soft tissue sarcoma also differed in Indian patients, which may have both prognostic and therapeutic implications.

Keywords Soft tissue sarcoma · Indian patients · Prognosis

Background

Soft tissue sarcomas (STS) are a heterogeneous group of tumours with varying histology, site and grade and constitute just 1 % of all malignancies [1], which may be the reason for a variable clinico-pathologic profile and ambiguity in the best use and sequencing of the treatment options available. With limb salvage surgery and radiation therapy as the mainstay of treatment, acceptable local recurrence rates have been achieved with an optimal functional outcome. However, distant metastasis and subsequent sarcoma-related death have not shown consistent reduction over the past two decades [2–4]. While there have been many advances in systemic chemotherapy in general, they have not been equally successful in treatment of soft tissue sarcoma.

The controversial role of adjuvant chemotherapy in soft tissue sarcoma, since its introduction [3], has motivated numerous workers to recognize select group of patients, likely to benefit the most from adjuvant chemotherapy [5, 6]. Similarly, studies on neoadjuvant therapy in STS gained momentum, but inconsistent results have led to a search for the high-risk groups [6–8]. Thus, the role of multimodality therapy and sequencing of its components remains an area of contention in the management of soft tissue sarcoma.

In the context of developing countries, revisiting the prognostic factors becomes important before recommending

✉ Akshay Tiwari
akshay_t_2000@yahoo.com

¹ Department of Surgical Oncology, Rajiv Gandhi Cancer Institute, Sector 5, Rohini, Delhi 110085, India

² Present address: Department of Reconstructive Surgery, BLK Cancer Center, Delhi, India

³ Department of Medical Oncology, Rajiv Gandhi Cancer Institute, Rohini, Delhi, India

⁴ Department of Radiation Oncology, Rajiv Gandhi Cancer Institute, Rohini, Delhi, India

treatment to our patients, as the clinical profile (and hence the impact of various prognostic factors) may be different from western population. As the availability of data on prognostic factors in Indian patients with soft tissue sarcoma is scarce [9, 10], we were prompted to perform a retrospective analysis of the clinico-pathologic profile and the prognostic factors in patients undergoing surgery for STS at a tertiary cancer centre in India.

Methods

We retrospectively analysed the data of all the patients who underwent surgical treatment for STS of extremity or trunk (excluding intra-abdominal/intra-thoracic sarcomas) at our institute from 1 January 2009 to 31 December 2013. Clinical data was collected using HIS Vista ®. A total of 133 patients were identified, out of which 12 patients with round cell histology and 9 patients having a follow-up less than 1 year were excluded from the study. The remaining 112 patients were included in the study.

Asymptomatic mass with or without pain was the initial presentation in patients presenting primarily. Two-fifth patients presented after unplanned excision done outside with unknown margins or suspicion of residual disease. Thirteen patients were operated for local recurrence after primary surgery at other cancer centres (all these were patients operated by other specialised surgical oncology teams with credible histopathology and imaging reports available). One patient each with breast cancer, acute leukemia and chronic lymphoid leukemia was seen to have soft tissue sarcoma during surveillance. The clinical details were collected from case records and are outlined in Table 1.

Tumour variables were collected from histopathology reports, including histologic subtype, grade based on French Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) system, size (classified both as < or >5 cm and < or >10 cm in maximum dimension), depth, margin (microscopic involvement of cut surface considered positive/negative) and nodal status [11]. In 29 patients operated for residual disease or after neoadjuvant chemotherapy, primary size was not known, and these were labelled Tx.

Follow-up included clinical evaluation, ultrasonography/MRI of local site (if deemed necessary) and non-contrast CT chest, every 3 months for 2 years and every 6 months thereafter. Follow-up of patients was supplemented by telephonic conversation wherever required. Local or distant recurrence and survival as on December 31, 2014 or last follow-up was noted. Overall survival (OS) was calculated from the date of diagnosis to the date of last follow-up or death due to any cause. Event-free survival (EFS) and distant metastasis-free survival (DMFS) were calculated from the date of diagnosis

Table 1 Clinical details

Clinical details	No. of patients (N = 112)
Clinical presentation	
Primary	54
Secondary	
Post excision (outside)	45
Recurrence ^a	13
Tissue diagnosis	
Tru cut Bx (at our institute)	47
Review of outside slides	
Trucut Bx	11
Incisional Bx	9
Excision Bx	45
Staging workup	112
Local imaging (MRI or CT)	
CECT chest	
Surgery	
Wide local excision	112
Lymph node dissection	9
Reconstruction	38
Adjuvant radiotherapy	
EBRT	80
Interstitial brachytherapy	7
Chemotherapy	
Adjuvant	33
Neoadjuvant	5
Palliative	2

^a For patients presenting with local recurrence ($n = 13$), first surgery performed elsewhere was considered as index surgery and its date was considered as starting point for calculating survival

to the date of first event and distant metastasis respectively or to the date of last follow-up. Demographic factors, tumour factors and treatment factors were analysed for their effect on all the above-mentioned survivals.

Statistical analysis was carried out using SPSS version 22 (IBM). Survival curves and univariate analysis were obtained using Kaplan-Meier method and log rank (Mantel-Cox) test. Multivariate analysis was done for significant factors using Cox regression analysis. Significance was set at P value <0.05.

Results

The study included 112 patients with the histological distribution as described in Table 2 [11]. The details of demographic, tumour and treatment-related factors and their impact on survival are summarised in Tables 3 and 4. Wide local excision including the biopsy site or scar of previous surgery was

Table 2 Histological distribution

Histology	Number (% of total)
Liposarcoma	10 (8.9)
Epithelioid sarcoma	5 (4.5)
Synovial sarcoma	26 (23.2)
Undifferentiated pleomorphic sarcoma	25 (22.3)
Fibrosarcoma	10 (8.9)
Extraskelatal chondrosarcoma	3 (2.7)
MPNST	9 (8.0)
Leiomyosarcoma	11 (9.8)
DFSP	6 (5.4)
Angiosarcoma	3 (2.7)
Alveolar soft part sarcoma	2 (1.8)
Clear cell sarcoma	1 (0.9)

MPNST malignant peripheral nerve sheath tumour, *DFSP* dermatofibrosarcoma protuberans

performed in all patients with microscopically negative margins in all but six patients (planned positive in two patients). Synovial sarcoma and undifferentiated pleomorphic sarcoma were the most common histologic subtypes, equally prevalent in trunk and extremities. Histopathologically positive lymph nodes were seen in three patients with epithelioid sarcoma (1), DFSP with dedifferentiation into high grade STS (1) and alveolar soft part sarcoma (1).

All patients underwent a wide excision except eight patients who underwent amputation for extremity sarcomas (two above knee amputation, two below knee amputation, one ray amputation, one hip disarticulation, one knee disarticulation and one shoulder disarticulation). Five out of these underwent amputation for local recurrence and the other three as a primary procedure. Out of the 36 local recurrences, 5 patients underwent amputation, 20 patients underwent a wide excision and the remaining were treated with best supportive care. Reconstruction was done in 38 patients using skin graft/bone graft/local fasciocutaneous flaps/randomised or pedicled myocutaneous flap or free flap. Wound-related morbidity was seen in 21.2 % of the patients, which was higher in patients requiring reconstruction (28.9 vs 17.3 %, $P = \text{ns}$) and was not increased in patients undergoing secondary surgery after neo-adjuvant therapy or previous unplanned excision. Most of the wound complications were minor and were managed with dressings, while five patients required secondary flaps and one required amputation subsequently.

Out of 88 patients (77.8 %) receiving radiotherapy, more than half received 40–60 Gy, while almost equal numbers of the remaining received less than or more than the mentioned range. Ifosfamide + adriamycin was the primary chemotherapy regimen in neoadjuvant or adjuvant setting and gemcitabine + docetaxel followed by pazopanib was given

to 2 patients with progressive disease. At final follow-up (mean of 44.85 ± 4.64 months, 95 % confidence interval = 35.66–54.04), OS was 82.1 % and EFS was 49.1 %. During the same time period, distant metastasis was seen in 30.1 % of the patients. On further analysis, the actuarial 5-year DMFS, EFS and OS were projected to be 59.9, 42.1 and 73.1 % respectively.

Overall Survival

Of the various patient and tumour factors evaluated for their relation with survival using univariate analysis, younger age (<50 years), larger size (>10 cm) (Fig. 1) and histopathologically positive lymph nodes were the only factors found significant. All these factors remained significant on multivariate analysis also. At final follow-up, 82.1 % patients were alive. Though overall survival was poor in some rare histologies like angiosarcoma and alveolar soft part sarcoma, histology did not significantly alter overall survival.

Distant Metastasis-Free Survival

Synovial sarcoma, epithelioid sarcoma and rare histologies like angiosarcoma and alveolar soft part sarcoma were the most common histologies seen in patients having distant metastasis. Pulmonary metastasis was the most common site of distant metastasis and was managed with palliative chemotherapy and best supportive care. Nine patients had metastasis in extra-pulmonary sites, identified in bone, brain, jejunum, liver and pancreas. The histologic subtypes seen in these patients were undifferentiated pleomorphic sarcoma ($n = 4$), synovial sarcoma ($n = 3$), MPNST ($n = 1$) and fibrosarcoma ($n = 1$). Jejunal and pancreatic metastasis were resected, patient with brain metastasis received radiotherapy and others received palliative chemotherapy. On univariate analysis, tumours which were grade 3, deep, or more than 10 cm were found to have significantly shorter distant metastasis-free survival. Positive margins and pathologically positive lymph nodes also showed higher number of distant metastasis ($P < 0.5$). Size >10 cm (Fig. 1) and pathologically positive lymph nodes were the only factors found significant on multivariate analysis.

Event-Free Survival

Statistically more events were seen in tumours, which were deep, >10 cm, grade 2 or 3, had positive margins, or had pathologically positive lymph nodes. While other factors got nullified, depth and pathologically positive lymph nodes remained significant on multivariate analysis.

Table 3 Impact of demographic, tumour and treatment-related factors on survival

	Number (% of total)	Distant metastasis (<i>P</i> value for DMFS)	Event-free survival (<i>P</i> value for EFS)	Overall survival (<i>P</i> value for OS)
Total	112	34 30.4 %	55 49.1 %	92 82.1 %
Age				
<50 years	55 (49.1 %)	32.1 %	46.4 %	75.0 %
>50 years	57 (50.9 %)	29.1 % (0.585)	50.9 % (0.438)	89.5 % (0.024)
Sex				
Male	73 (65.2 %)	30.1 %	53.4 %	82.2 %
Female	39 (34.8 %)	30.2 % (0.422)	41.0 % (0.926)	82.1 % (0.584)
Grade				
I	15 (13.3 %)	6.7 %	86.7 %	93.3 %
II	25 (22.3 %)	24 %	44.0 %	88.0 %
III	60 (53.5 %)	59 % (0.271)a (0.031)b (0.172)c	44.3 % (0.017)a (0.012)b (0.904)c	75.4 % (0.552)a (0.132)b (0.263)c
Size				
< 5 cm	24 (21.4 %)	20.8 %	66.7 %	91.7 %
> 5 cm	59 (52.6 %)	33.9 % (0.226)	44.1 % (0.054)	78.0 % (0.095)
Size				
< 10 cm	56 (50.0 %)	17.9 %	58.9 %	91.1 %
> 10 cm	27 (24.1 %)	55.6 % (0.001)	33.3 % (0.017)	63.0 % (0.001)
Depth				
Superficial	13 (11.7 %)	0 %	76.9 %	100 %
Deep	99 (88.3 %)	33.3 % (0.010)	45.5 % (0.004)	79.8 % (0.066)
Site				
Trunk	29 (25.8 %)	27.6 %	58.6 %	86.2 %
Extremity	73 (64.2 %)	31.3 % (0.704)	45.8 % (0.303)	80.7 % (0.528)
Margins				
Negative	106(94.6 %)	28.3 %	50.9 %	83.0 %
Positive	6 (5.4 %)	66.6 % (0.008)	16.7 % (0.032)	66.7 % (0.191)
LN				
Negative	109 (97.3 %)	28.4 %	50.5 %	84.0 %
positive	3 (2.7 %)	100 % (0.000)	0.0 % (0.001)	0.0 % (0.000)
Residual				
Present	31 (27.4 %)	33.3 %	53.3 %	80.0 %
Absent	14 (12.4 %)	21.4 % (0.606)	42.9 % (0.374)	85.7 % (0.681)
RT				
No	25 (22.4 %)	16 %	68.0 %	96.0 %
Yes	87 (77.6 %)	34.4 % (0.284)	43.6 % (0.162)	78.2 % (0.062)
Chemo				
No	72 (64.2 %)	19.2 %	46.6 %	84.9 %
Yes	40 (35.8 %)	47.5 % (0.057)	53.8 % (0.452)	76.9 % (0.301)

Values in bold are significant

DMFS distant metastasis-free survival, EFS event-free survival, OS overall survival, a grade I vs II, b I vs III, c II vs III, RT radiotherapy

Discussion

The treatment of soft tissue sarcoma in Indian patients in our study showed an actuarial 5-year DMFS, EFS and OS of 59.9, 42.1 and 73.1 % respectively, an inferior survival outcome as compared to western literature [12–14]. Besides, an analysis of clinical profile in the present study shows that only 13, 21 and 11.5 % of tumours were low grade, <5 cm and superficial respectively. On multivariate analysis, size >10 cm and histopathologically proven lymphadenopathy had the most profound impact on DMFS and OS. The clinical profile and prognosis of soft tissue sarcoma have been shown to have ethnic variation [15], and it is imperative that we analyse the outcome of treatment including the impact of the established prognostic indicators in Indian patients.

On comparing the clinical profile in our study with that of other studies in developing countries and the western world, we realised that most of the patients with localised STS in our population will be placed in a higher stage as per the AJCC 2010 staging system (more than half of the patients were grade 3 and more than 5 cm and around 90 % were deep) [9, 16]. This has two implications. Firstly, it may explain the survival outcomes of our study, which appear to be poorer than that in western studies but are not inferior to those when the stage is matched [6, 8]. Secondly, a large part of our population will be in a high risk group which lacks consensus regarding the role of adjuvant chemotherapy [2, 5, 6, 8]. As adjuvant chemotherapy shows variable results even when used selectively in high grade or stage III patients, a clarity on the indications of adjuvant chemotherapy is all the more important for our patients.

Table 4 Multivariate Cox analysis for prognostic factors in DMFS, EFS and OS

Factors	DMFS		EFS		OS	
	HR (95 % CI)	P value	HR (95 % CI)	P value	HR (95 % CI)	P value
Age					0.313 (0.118–0.831)	0.020*
Depth	0.450 (0.314–0.541)	0.973	5.660 (1.361–23.543)	0.017*		
Size (10 cm)	1.876 (1.002–3.513)	0.049*	1.026 (0.696–1.514)	0.897	2.021 (1.073–3.806)	0.029*
Grade	1.269 (0.695–2.316)	0.438	0.965 (0.729–1.278)	0.803		
Margins	1.442 (0.308–6.750)	0.642	2.358 (0.883–6.300)	0.087		
LN	9.464 (2.409–37.17)	0.001*	5.583 (1.643–18.975)	0.006*	13.480 (3.607–50.38)	0.000*

DMFS distant metastasis-free survival, EFS event-free survival, OS overall survival, LN pathologically positive lymph nodes, Size (10 cm) size more than or less 10 cm

* $P < 0.05$ (significant)

We did not find any significant difference in the oncological outcome among the more common histopathological varieties. Other Indian series show synovial sarcoma and MFH/UPS as the commonest histopathological variety, as was seen in our patients [9]. Grade is another widely accepted prognostic factor for soft tissue sarcomas [17]. We found low-grade tumours to have lower recurrence rate, but with no impact on distant metastasis and overall survivals. At the same time, deep tumours were also found to have a profound oncological impact, a fact reiterated by most other studies [18–20].

Margins have been considered a very important prognostic indicator in a patient with a soft tissue sarcoma [21]. While we had a significantly better DMFS and EFS in patients with a microscopically negative margin, margins had no effect on oncological outcome on multivariate analysis. This may be explained by the fact that even the patients having a positive margin were those with larger size, recurrence, or other poor prognostic factors and were not many. However, other workers [22, 23] have shown that at a specialised centre, a

“planned positive margin” in order to preserve the function or form or to reduce the morbidity does not result in a poorer survival.

Ours is a tertiary care cancer centre, and a large majority of patients presented to us secondarily after having undergone a “whoops” procedure (46 patients), at a non-specialised centre. A history of a prior intervention in a soft tissue sarcoma is a common entity seen in both the developed and developing countries, however with a higher frequency in the latter [9, 13, 24, 25]. It is significant that the OS, EFS and DMFS remained the same for patients undergoing primary surgery and surgery after whoops procedures. This finding endorses the outcome of many other studies [13], barring a few [24] and reiterates the general consensus that the outcome of a whoops procedure is no worse provided the patient is referred in time to a specialised centre.

Histopathologically proven lymphadenopathy, a rare observation in soft tissue sarcomas (3.7 %) [26], was shifted from stage IV to stage III in AJCC seventh edition as survival

Fig. 1 Impact of size >10 cm on OS and DMFS. For patients operated for local recurrence ($n = 13$), first surgery was considered as index surgery and its date was considered as starting point for calculating survival

was better than systemic metastasis. However, all three (2.7 %) of our patients having positive nodes developed distant metastasis and succumbed to the disease. On the other hand, adjuvant radiotherapy and chemotherapy showed no statistically significant difference in EFS or OS in our series. This is explained by the fact that decision on adjuvant treatment was made by a multidisciplinary board, based on the established indications, and was offered only to select high risk group patients.

The soft tissue sarcomas which are high grade, deep and more than 5 cm in size have been reported to have poor prognosis consistently and thus form the basis of the present staging system [18–20]. A third of our patients had a tumour size more than 10 cm, reflecting a delay in referral and healthcare seeking behaviour of our patients as compared to western population [11, 27]. It was interesting to note that in our study, a cutoff of 10 cm tumour size showed a significant difference in oncological outcome (on both univariate and multivariate analysis) while that of 5 cm did not do so. Furthermore, it was seen that patients in the subgroup with tumour size more than 10 cm had a tendency for a lesser chance of distant metastasis if they received adjuvant chemotherapy ($P = 0.052$).

Tumour size more than 10 cm is not included in the current AJCC staging system. However, literature supports further tumour size based stratification. Ramanathan et al. observed a progressive decline in survival with increase in tumour size, within each histological grade. As the AJCC system did not correlate with prognosis, they formulated modified staging system with multiple size stratification (T1, T2, T3, T4 = <5, 5–10, 10–15, >15 cm) which correlated well with the survivals [28]. Another study depicted increase in distant metastasis with tumour size, i.e. 34, 43 and 58 % for <5 cm, 5–10, 10–15 cm [29]. Few recent studies show size >10 cm to be an independent adverse prognostic factor, especially when the survivals were improved with limb salvage surgery and radiotherapy [30, 31]. Another study, which failed to show survival benefit of adjuvant chemotherapy to persist beyond 1 year in stage III patients (high grade, deep, size >5 cm), did show poor prognosis in patients with size >15 cm [5]. Similarly, recent studies showing feasibility and survival benefit of neoadjuvant chemotherapy (size >10 cm) [32] and neoadjuvant chemoradiation (size >8 cm), [4, 33–35] use large tumour size to define high risk groups. All this leads us to believe that that tumour size subgrouping beyond 5 cm is important to define high risk groups and support our results seen with tumour size more than 10 cm.

The recommendation of chemotherapy for larger tumours is based on the premise that larger tumours will be biologically more aggressive and hence more likely to benefit from chemotherapy. However, tumour size is function of another factor besides biological aggressiveness- that is delay in presentation. We hypothesise that a patient with a given aggressiveness of tumour in a developing country is more likely to

have a larger tumour size as compared to developed world, because of a delayed presentation. This may be a reason for the 10 cm cutoff affecting survival in our patients (meaning that the more aggressive varieties will present with a size of not 5 but 10 cm), and we recommend this cutoff for patients in a developing/resource poor setting for prognostication and, more importantly, for deciding on indication and sequencing for chemotherapy.

With the availability of only a few studies on Indian patients [9, 10], our study assumes significance by being one of the larger studies from a tertiary cancer centre in India, focussing on the impact of prognostic factors with modern treatment. The differences thus seen may be subtle but need a mention as they may have a potential to aid in management. However, we have to admit that our study has certain limitations. It was a retrospective analysis and included only patients who were operated upon (and hence, had an inherently better prognosis than patients who might have been treated non-operatively/with palliative intent). Moreover, these were patients presenting to a tertiary cancer centre in a large metropolitan city, which may not be catering to the real cross section of the society. We need longer follow-up and larger multicentric trials in Indian patients to analyse outcome specific to our population and to validate the outcome of this study.

Conclusions

Soft tissue sarcomas in Indian patients have a different clinical profile and outcome compared to those in western literature. It may be worthwhile revisiting the established prognostic indicators before using them in our patients, which may have a different impact on our patients as compared to those reported in world literature.

Acknowledgments We acknowledge the contribution of Miss Kahkasha in collection and analysis of data.

Authors' Contributions AT conceptualised the study, contributed to data acquisition and interpretation, was involved in drafting and reviewing the manuscript and gave final approval for the manuscript. SS contributed to data acquisition, was involved in drafting and reviewing the manuscript and gave final approval for the manuscript. AKS contributed to data acquisition, was involved in reviewing the manuscript and gave final approval for the manuscript. SM contributed to data analysis and interpretation, was involved in reviewing the manuscript and gave final approval for the manuscript. UB was involved in data analysis and interpretation, critically revised the manuscript and gave final approval for the manuscript. SKS contributed to data analysis and interpretation, was involved in drafting the manuscript and gave final approval for the manuscript. AKD contributed to data analysis and interpretation, was involved in reviewing the manuscript and gave final approval for the manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent Consent was obtained from all the patients for use of their medical information for research purposes, without revealing any specific information of the patient.

References

- Lachenmayer A, Yang Q, Eisenberger CF, Boelke E, Poremba C, Heinecke A et al (2009) Superficial soft tissue sarcomas of the extremities and trunk. *World J Surg* 33(8):1641–1649
- Woll PJ, Van Glabbeke M, Hohenberger P, Le Cesne A, Gronchi A, Hoekstra HJ et al. editors (2007) Adjuvant chemotherapy (CT) with doxorubicin and ifosfamide in resected soft tissue sarcoma (STS): interim analysis of a randomised phase III trial. ASCO Annual Meeting Proceedings
- Tierney JF, Mosseri V, Stewart LA, Souhami RL, Parmar MK (1995) Adjuvant chemotherapy for soft-tissue sarcoma: review and meta-analysis of the published results of randomised clinical trials. *Br J Cancer* 72(2):469
- Mullen JT, Kobayashi W, Wang JJ, Harmon DC, Choy E, Hornicek FJ et al (2012) Long-term follow-up of patients treated with neoadjuvant chemotherapy and radiotherapy for large, extremity soft tissue sarcomas. *Cancer* 118(15):3758–3765
- Cormier JN, Huang X, Xing Y, Thall PF, Wang X, Benjamin RS et al (2004) Cohort analysis of patients with localized, high-risk, extremity soft tissue sarcoma treated at two cancer centers: chemotherapy-associated outcomes. *J Clin Oncol* 22(22):4567–4574
- Italiano A, Delva F, Mathoulin-Pelissier S, Le Cesne A, Bonvalot S, Terrier P et al (2010) Effect of adjuvant chemotherapy on survival in FNCLCC grade 3 soft tissue sarcomas: a multivariate analysis of the French Sarcoma Group database. *Ann Oncol* 21(12):2436–2441
- Eilber FC, Brennan MF, Eilber FR, Eckardt JJ, Grobmyer SR, Riedel E et al (2007) Chemotherapy is associated with improved survival in adult patients with primary extremity synovial sarcoma. *Ann Surg* 246(1):105
- Pisters PW, Patel SR, Varma DG, Cheng S-C, Chen NP, Nguyen HT et al (1997) Preoperative chemotherapy for stage IIIB extremity soft tissue sarcoma: long-term results from a single institution. *J Clin Oncol* 15(12):3481–3487
- Shukla NK, Deo SV (2011) Soft tissue sarcoma-review of experience at a tertiary care cancer centre. *Indian Journal of Surgical Oncology* 2(4):309–312
- Chaudhary AJ, Laskar S, Badhwar R et al (1998) Interstitial brachytherapy in soft tissue sarcomas. The Tata Memorial Hospital experience. *Strahlentherapie und Onkologie: Organ der Deutschen Röntgengesellschaft* 174(10):522–528
- Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A editors (2010) *Soft Tissue Sarcoma. AJCC cancer staging manual*. 7th ed. New York: Springer, 291–298
- Cai L, Mirimanoff R-O, Mouhsine E, Guillou L, Leyvraz P-F, Leyvraz S, et al. Prognostic factors in adult soft tissue sarcoma treated with surgery combined with radiotherapy: a retrospective single-center study on 164 patients. *Rare Tumors* 2013;5(4)
- Rutkowski P, Trepka S, Ptaszynski K, Kołodziejczyk M (2013) Surgery quality and tumor status impact on survival and local control of resectable liposarcomas of extremities or the trunk wall. *Clin Orthop Relat Res* 471(3):860–870
- Tsukushi S, Nishida Y, Urakawa H, Kozawa E, Ishiguro N (2014) Prognostic significance of histological invasion in high grade soft tissue sarcomas. *Springer Plus* 3(1):544
- Martinez SR, Robbins AS, Meyers FJ, Bold RJ, Khatri VP, Goodnight JE (2008) Racial and ethnic differences in treatment and survival among adults with primary extremity soft-tissue sarcoma. *Cancer* 112(5):1162–1168
- Qadir I, Umer M, Umer HM, Uddin N, Karsan F, Rabbani MS (2012) Managing soft tissue sarcomas in a developing country: are prognostic factors similar to those of developed world? *Margin* 8:10
- Guillou L, Coindre J-M, Bonichon F, Nguyen BB, Terrier P, Collin F et al (1997) Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. *J Clin Oncol* 15(1):350–362
- Coindre J-M, Terrier P, Bui NB, Bonichon F, Collin F, Le Doussal V et al (1996) Prognostic factors in adult patients with locally controlled soft tissue sarcoma. A study of 546 patients from the French Federation of Cancer Centers Sarcoma Group. *J Clin Oncol* 14(3):869–877
- Pisters PW, Leung DH, Woodruff J, Shi W, Brennan MF (1996) Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. *J Clin Oncol* 14(5):1679–1689
- Zagars GK, Ballo MT, Pisters PWT, Pollock RE, Patel SR, Benjamin RS et al (2003) Prognostic factors for patients with localized soft-tissue sarcoma treated with conservation surgery and radiation therapy. *Cancer* 97(10):2530–2543
- Alamanda VK, Crosby SN, Archer KR, Song Y, Schwartz HS, Holt GE (2013) Predictors and clinical significance of local recurrence in extremity soft tissue sarcoma. *Acta Oncol* 52(4):793–802
- Gerrand CH, Wunder JS, Kandel RA, O'Sullivan B, Catton CN, Bell RS et al (2001) Classification of positive margins after resection of soft-tissue sarcoma of the limb predicts the risk of local recurrence. *Journal of Bone & Joint Surgery, British Volume* 83(8):1149–1155
- O'Donnell PW, Griffin AM, Eward WC, Sternheim A, Catton CN, Chung PW et al (2014) The effect of the setting of a positive surgical margin in soft tissue sarcoma. *Cancer* 120(18):2866–2875
- Umer HM, Umer M, Qadir I, Abbasi N, Masood N (2013) Impact of unplanned excision on prognosis of patients with extremity soft tissue sarcoma. *Sarcoma* 2013
- Morii T, Aoyagi T, Tajima T, Yoshiyama A, Ichimura S, Mochizuki K (2015) Unplanned resection of a soft tissue sarcoma: clinical characteristics and impact on oncological and functional outcomes. *J Orthop Sci* 20(2):373–379
- Riad S, Griffin AM, Liberman B, Blackstein ME, Catton CN, Kandel RA et al (2004) Lymph node metastasis in soft tissue sarcoma in an extremity. *Clin Orthop Relat Res* 426:129–134
- Pervaiz N, Colterjohn N, Farrokhhyar F, Tozer R, Figueredo A, Ghert M (2008) A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. *Cancer* 113(3):573–581
- Ramanathan RC, A'Hern R, Fisher C, Thomas JM (1999) Modified staging system for extremity soft tissue sarcomas. *Ann Surg Oncol* 6(1):57–69
- Delaney TF, Rosenberg D, Harmon DC et al (2002) Soft tissue sarcomas. In: Price P, Sikora K (eds) *Treatment of cancer*. 4. Arnold, London, pp. 867–907
- Atean I, Pointreau Y, Rosset P, Garaud P, De-Pinieux G, Calais G (2012) Prognostic factors of extremity soft tissue sarcoma in adults. A single institutional analysis. *Cancer radiotherapie: journal de la Societefrancaise de radiotherapieoncologique*. 16(8):661–666
- Potter BK, Hwang PF, Forsberg JA, Hampton CB, Graybill JC, Peoples GE et al (2013) Impact of margin status and local

- recurrence on soft-tissue sarcoma outcomes. *The Journal of Bone & Joint Surgery* 95(20):e151
32. Grobmyer SR, Maki RG, Demetri GD, Mazumdar M, Riedel E, Brennan MF et al (2004) Neo-adjuvant chemotherapy for primary high-grade extremity soft tissue sarcoma. *Ann Oncol* 15(11):1667–1672
 33. Kraybill WG, Harris J, Spiro IJ, Ettinger DS, DeLaney TF, Blum RH et al (2010) Long-term results of a phase 2 study of neoadjuvant chemotherapy and radiotherapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall. *Cancer* 116(19):4613–4621
 34. Hong NJL, Hornicek FJ, Harmon DC, Choy E, Chen Y-L, Yoon SS et al (2013) Neoadjuvant chemoradiotherapy for patients with high-risk extremity and truncal sarcomas: a 10-year single institution retrospective study. *Eur J Cancer* 49(4):875–883
 35. Kraybill WG, Harris J, Spiro IJ, Ettinger DS, DeLaney TF, Blum RH et al (2006) Phase II study of neoadjuvant chemotherapy and radiation therapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. *J Clin Oncol* 24(4):619–625