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Original Article

Significance of local treatment in patients with metastatic soft tissue sarcoma

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Abstract: Metastatic soft tissue sarcomas (STS) represent enormous challenges to improve the low survival rate, which is almost the same as past 2 decades ago, although surgery, radiotherapy and radiofrequency ablation has been accepted in the treatment of metastatic STS. Moreover, STS varies between elderly and younger victims in the aspect of diagnoses, prognosis, and treatment strategies. In order to evaluate the role of local treatment in improving prognosis for patients with metastatic STS and select the proper candidates who will benefit from local therapy, a single-institution nearly 50-year experience were collected and reviewed. Finally, we found that local treatments could improve treatment response and survival, but overall survival advantage could not be seen in elderly patients. This conclusion from a single institution could serve as a basis for future prospective multi-institutional large-scale studies.

Keywords: Soft tissue sarcoma, metastasis, local treatment, prognosis

Introduction

Soft tissue sarcomas (STS), arising from almost any embryonic mesodermal tissue, account for nearly 1% of newly diagnosed malignancies annually [1]. Under multimodality treatment, patients with localized disease have estimated 5-year survival rates of about 70% [2-4]. However, metastatic STS still represents enormous challenges to improve the low survival rate [5]. Despite advances in chemotherapy, radiotherapy and surgery, the 3-year survival of patients with metastatic STS is 20-45%, which is almost the same as past 2 decades ago [6-9].

Surgery, based on existing data shown in numerous studies in prolonging survival, is one of the most common therapy option for advanced-stage STS [7, 10-14]. However, not all metastatic individuals are fit for surgical treatment. Therefore, it is necessary to select the proper candidates who will benefit from surgical procedures and carefully evaluate for possible resection. Radiotherapy, aiming to adequate local control, remains controversial in ideal treatment sequence with surgery and improvement in survival [15, 16]. Nevertheless, no data were available in comparing outcomes of surgery and radiotherapy in treatment of metastatic STS. Although most centers employed combinational regiments of neo-adjuvant or adjuvant treatment for aggressive STS, supporting evidence remains rare [15]. Based on literatures, we would expect that radiotherapy might reduce local recurrence [17]. Nowadays, radiofrequency ablation has also been accepted in the treatment of unresectable metastatic STS [18-21]. Additionally, STS varies between elderly and younger victims in the aspect of diagnoses, histologic subtypes and prognosis [22], which leads to distinct treatment strategies for these 2 group patients suffered from STS.

Our aim of this study is to determine whether local treatment (including surgery, radiotherapy and radiofrequency ablation) is critical in

Table 1. Clinicopathologic characteristics of patients with metastatic STS

Characteristic	Patients with metastatic STS (n = 142)	
Age, yrs	47.5† (range: 5-71)	
Gender (%)		
Male	60	42.3%
Female	82	57.7%
Primary tumor size (cm)	5.5† (range: 0.5-20)	
Primary tumor depth (%)		
Superficial	44	31%
Deep	98	69%
Pathological subtypes (%)		
So-called fibrohistiocytic tumors	22	15.5%
Undifferentiated sarcomas	96	67.6%
Smooth muscle tumors	22	15.5%
Fibroblastic/Myofibroblastic tumors	2	1.4%
Pathological grade (%)		
1	9	6.3%
2	13	9.2%
3	120	84.5%
Follow-up (months)		
Median	49.38	
Range	2.97-476.17	
Mean	71.05	
Local Treatment (%)		
With	79	55.6%
Without	63	44.4%

†: Median values are listed.

Table 2. Response to metastases treatment of patients with/without local treatment

Response	With local treatment (N = 79)	Without local treatment (N = 63)
CR	54 (68.4%)	27 (42.9%)
PR	13 (16.4%)	16 (25.4%)
SD	1 (1.3%)	5 (7.9%)
PD	11 (13.9%)	15 (23.8%)

†: Higher proportion of patients responded with CR and lower proportion with PR, SD and PD in with-local-treatment group than without-local-treatment group (P = 0.012).

improving prognosis for patients with metastatic STS and select the proper candidates who will benefit from local therapy.

Method

This study was approved by the institutional review board of Sun Yat-sen University Cancer Center (SYSUCC) and informed consent was obtained from each participant. Chart review was performed on 154 consecutive patients who suffered from metastatic STS with metastases between July 1965 and May 2013. Only patients with STS were included in current study, whereas those with osteosarcoma were not. Under these criteria, 142 of the 154 patients were enrolled in the final analysis, which meant 12 patients with STS were excluded from analysis because of incomplete records. Characteristics of patients and tumors at initial diagnosis of STS and development of metastases were collected and tested for relationships with progress free survival (PFS) and overall survival (OS), including the following factors: patient age, gender (male vs. female), primary tumor size, and tumor depth (superficial vs. deep) at diagnosis. In current study, WHO classification [23] was used for determination of pathological diagnosis and tumor grade. In addition, elderly, and younger patients were defined as age at diagnosis > 60 years, or < 18 years, respectively [24]. All data were reviewed and confirmed by two independent consultant pathologists and radiologists.

Local Treatment defined as underwent one or more procedure of surgery, radiotherapy or radiofrequency ablation. In detail, treatment regiments varied, including bilateral metastasis sternotomy, thoracotomy, and thorascopic surgery in surgery treatment; conventional fractionated radiotherapy and SBRT with different dose in radiotherapy; and different procedure of power and time in radiofrequency ablation. Furthermore, response to treatment was classified according to RECIST criteria (version 1.1) [25].

Statistical analysis

PFS and OS curves were estimated using the Kaplan-Meier method. PFS was calculated from the date of metastasis treatment to the

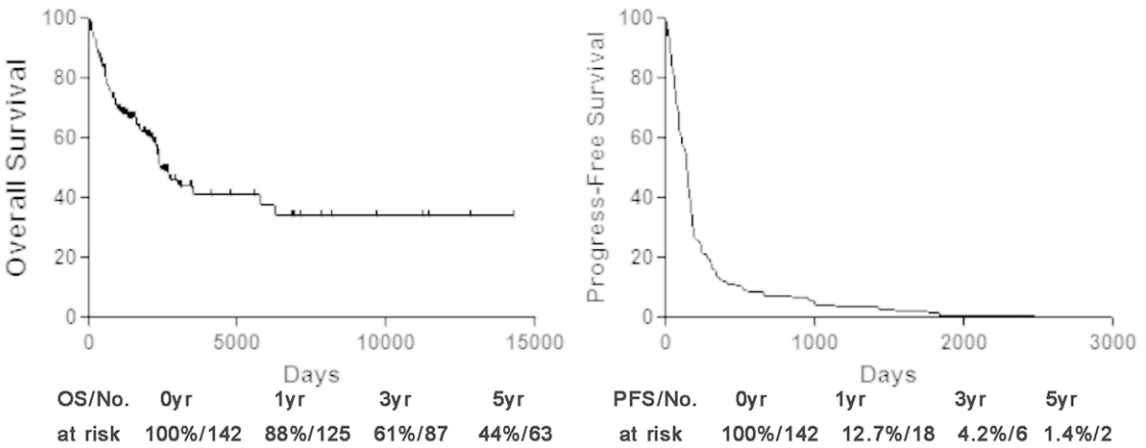

Figure 1. OS and PFS of patients with metastatic STS. PFS progress-free survival, OS overall survival.

time of metastasis progression or end of follow-up, and similarly OS from the date of initial diagnosis to the time of death reported or end of follow-up. Risk factors of PFS and OS were then assessed by univariate analysis with log rank test and multivariate analysis with Cox proportional hazards regression. Next, multivariate analysis was performed using Cox proportional hazard model. Cut-off value of PFS was established by the receiver operating characteristic (ROC) curve statistical analyses. Additionally, all models for survival analyses were adjusted for age at diagnosis. $P < 0.05$ was considered to be significant in all statistical analyses. Data analysis was performed using SPSS 18.0 (PASW Statistics 18) for Windows (SPSS Inc, Chicago, IL).

Result

142 of 154 patients with metastatic STS were eligible for the final analysis. In this group of 142 patients, the mean age was 44.35 years (range: 5-71 years, median 47.5 years); 28 patients (19.7%) belong to elderly group, 114 patients (80.3%) to younger group. 60 patients were male (42.3%) and 82 female (57.7%). Explicitly, the tumors pathological subtypes included so-called fibrohistiocytic tumors in 22 patients (15.5%), undifferentiated sarcomas in 96 (67.6%), smooth muscle tumors in 22 (15.5%), and fibroblastic/myofibroblastic tumors in 2 (1.4%). The mean follow-up for survivors as of December 2014 was 71.05 months (range: 2.97-476.17 months, median 49.38 months). Besides, the mean tumor size at diagnosis was 6.68 cm (range 0.5-20 cm, median 5.5 cm). 79 patients (55.6%) underwent local treatment, whereas 63 patients (44.4%) not (**Table 1**).

For treatment with metastatic tumor, of the 79 patients underwent local therapy in this study, 48 (60.8%) underwent surgery, 11 (13.9%) radiotherapy, 7 (8.9%) patients underwent radiofrequency ablation and 13 (16.4%) both surgery and radiotherapy.

After metastases treatment, 81 patients (57.1%) responded with CR (including radical resection), 29 (20.4%) with PR, 6 (4.2%) with SD, and 26 (18.3%) with PD. Response varies, but significant difference could be observed between patients underwent local treatment or not, although no statistical differences were seen in different sarcoma types (**Table 2**).

Univariate analysis showed that age ($P = 0.238$), gender ($P = 0.783$), size of primary tumor ($P = 0.425$), tumor depth ($P = 0.484$), pathological subtypes ($P = 0.861$) and pathological grade ($P = 0.965$) did not have any significant impact on OS. Median OS was 2411 days and 28.2% of the patients were alive without disease, 25.4% were alive with disease, 45.8% dies of disease, while 0.7% (1 patients) died from other causes (heart disease). The overall 1-, 3- and 5-year OS rates were 88%, 61% and 44% each, respectively (**Figure 1**).

Similarly, no significant impact on PFS when analyzing with age ($P = 0.801$), gender ($P = 0.309$), size of primary tumor ($P = 0.427$), tumor depth ($P = 0.404$), pathological subtypes ($P =$

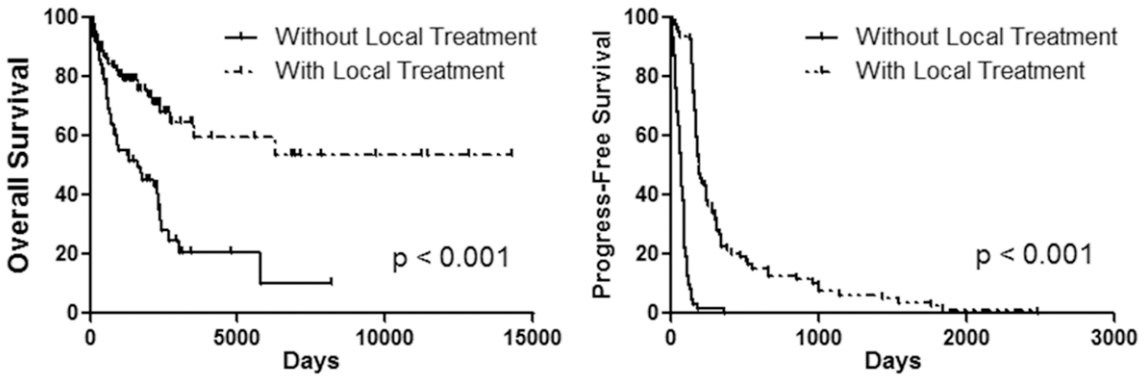

Figure 2. OS and PFS of patients with/without local treatment. PFS progress-free survival, OS overall survival.

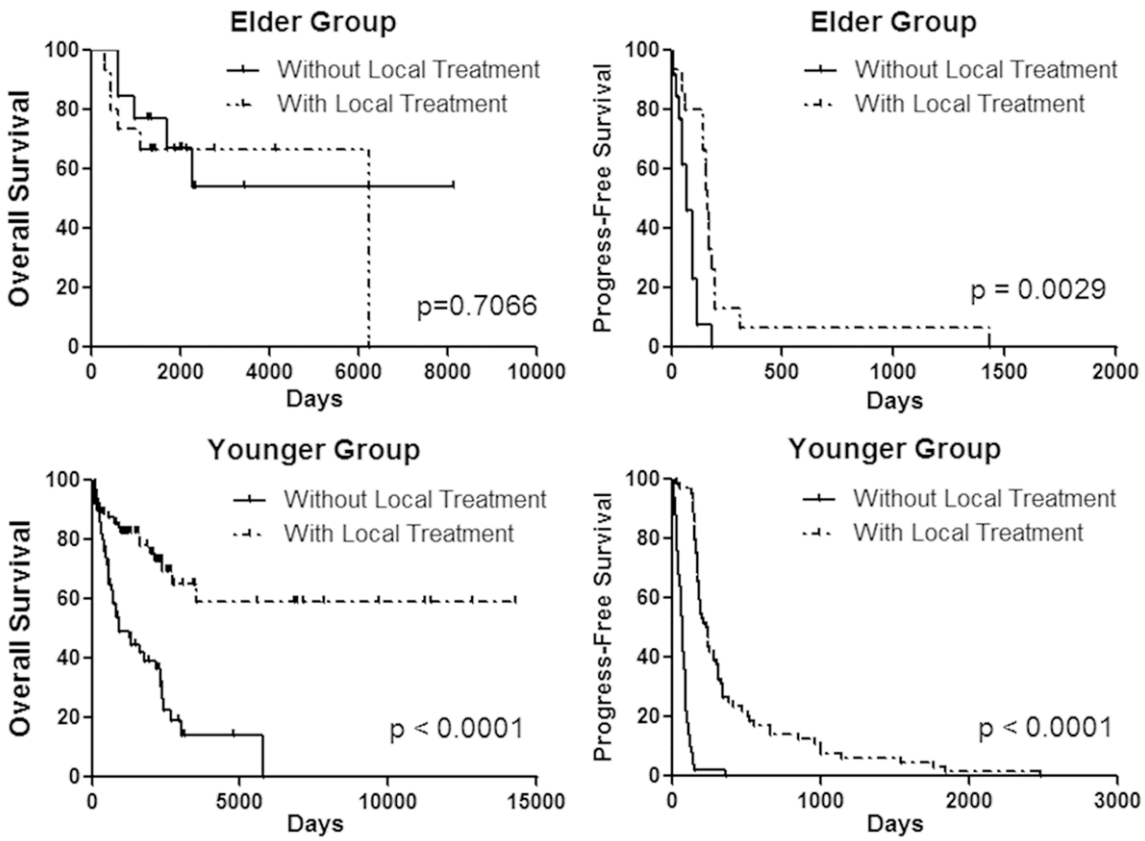

Figure 3. OS and PFS of patients with/without local treatment in different age group. PFS progress-free survival, OS overall survival.

0.796) or pathological grade (P = 0.900). Median PFS was 147 days and the overall 1-, 3- and 5-year PFS rates were 12.7%, 4.2% and 1.4% each, respectively (**Figure 1**).

OS was significantly worse in the without local treatment group (median OS 1638 days) than the local treatment group (median OS 6262 days) (P < 0.001). Likewise, patients without local treatment had a significantly worse PFS (median PFS 74 days) than those with local treatment (median PFS 195 days) (P < 0.001). The OS and PFS curves for the two groups are shown in **Figure 2**.

Importantly, although the benefit for PFS of local treatment could be observed in both elder and younger group, the benefit for OS of local treatment was not present in elder patients group (P = 0.7066, **Figure 3**).

Discussion

Here we presented series of patients representing a single-institution nearly 50-year experience in the management of metastatic STS. As an important subgroup of STS [26, 27], metastatic STS still have an unsatisfying prognosis, despite of continuous treatment development [28-30]. Previous studies reported little prognosis improvement of metastatic STS in last decades [28, 30]. This is why we set to determine whether local treatment (including surgery, radiotherapy and radiofrequency ablation) is useful in improving prognosis for patients with metastatic STS, and select the proper candidates who will benefit from local therapy.

Although it is generally considered to be incurable of metastatic diseases, patients underwent surgical resection with pulmonary metastatic STS has been reported a relatively remarkable proportion of long-term survivors, which leads surgical approaches becoming a cornerstone of management of pulmonary metastatic STS [31]. Previous studies in lung metastases of sarcoma indicated the utility and a statistically better OS in those underwent aggressive surgical approaches [7, 14, 32]. Several studies [10, 12] even showed a curable subset of patients if a complete response of metastatic disease could be achieved by surgery. Although phase III studies comparing surgical procedures to other options in metastatic sarcoma are still lacking, an advantage survival for aggressive resection in these patients was supported by substantial retrospective data.

However, both physiologically and medically preoperative assessments are key to identifying patients might benefit most from surgery of metastatic STS. RFA or radiotherapy would also provide acceptable local control, thus representing reasonable alternative to surgery for oncological inoperable patients.

Radiotherapy has been proved to serve a consistent role in reducing local recurrence rate and a trend in survival advantage, thus providing an additional option in effective local disease control [33]. Although conformal treatment techniques have been in use for many decades with affordable toxicities, continuous technologic advances, including intensity-modulated radiotherapy and proton beam radiotherapy, could minimize normal tissue exposure and decrease late effects [34]. Additionally, due to the reason that most patients could not be suitable for repeating thoracotomies, it would be reasonable to choose radiotherapy as a more safe and effective method for achieving a similar benefit, especially for patients with restricted cardiopulmonary reserve or unsatisfying performance status when disease recurred again [35-37].

RF ablation, another relatively safe and effective therapeutic options, has also been accepted in patients with unresectable primary and metastatic diseases, even in selected elderly patients and advantaging trends in survival have been observed in some literatures [18-21, 38, 39].

Both systemic and local treatment have important contribution to survival improvement [29, 40]. The efficacy would be better when local treatment of metastatic STS companied with effective systemic treatment. Moreover, multidisciplinary treatment combining local and systemic treatment should be highly recommended [41]. Nonetheless, local treatment remains a remarkable and challenging therapeutic issue in metastatic STS [26, 42].

Although evidence of local treatment proved the efficacy in metastases therapy, the role of aggressive local treatment remains controversial in elderly patients [43, 44]. Only few literatures concerning the management of metastatic STS in elderly patients, but reports indicated different therapy strategy should be adopted because of widely differences in the aspect of life expectancy and tolerance for aggressive therapeutic regimens [45, 46].

Several limitations remain in this study. First, all the data were retrospectively collected, thus clinical and survival comparisons might be influenced by selection bias due to its retrospective nature. Second, a relatively small number of elder group were examined in this study, due to the reason that metastatic STS are extremely rare. It is substantial that the result of local treatment not improving OS in

elder group might be caused by a Type II error, although it has been showed to be sufficient number in elder group to identify the significance of PFS improvement. Third, local treatment regimens varied among the retrospectively reviewed patients, which weakens the strength of our conclusions.

In current study, local treatments were found to be effective and significant procedures in achieving better treatment response and improving both OS and PFS for patients with metastatic STS. Remarkably, elder metastatic STS patients should be carefully assessed before local treatment. Although PFS was extended under local treatment, the improvement of OS could not be observed. This conclusion from a single institution could serve as a basis for future prospective multi-institutional large-scale studies.

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Disclosure of conflict of interest

The authors declare no competing interests.

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