Treatments and Outcomes in Oligometastatic Soft Tissue Soft Sarcoma – A Single Centre Retrospective Analysis

GERARD M. WALLS[1,2], SHANE H. ZAIDI[1,3], NICOS FOTIADIS[1], SIMON JORDAN[1,4],
MARCO MARUZZO[1,5], INTAN HAMID[1], OMAR AL-MUDERIS[1], KOMEL KHABRA[1],
CHARLOTTE BENSON[1,3], ROBIN L. JONES[1,3], IAN R. JUDSON[3] and AISHA B. MIAH[1,3]

[1]Royal Marsden NHS Foundation Trust, London, U.K.;
[2]Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, Belfast, U.K.;
[3]Institute for Cancer Research, London, U.K.;
[4]Royal Brompton & Harefield Trust, London, U.K.;
[5]Veneto Institute of Oncology IOV–IRCCS, Padua, Italy

Abstract. *Background/Aim: Distinguishing true oligometastatic disease from early polymetastatic disease is vital in patients with soft tissue sarcoma as contemporary treatment strategies differ significantly. Clinical factors such as tumour biology, organ involved, number of lesions, and patient fitness influence clinical decisions. Patients and Methods: A retrospective search of a prospective database identified patients with new distant relapse, treated between 2009 and 2012. Results: A total of 223 patients were included, and oligometastases were diagnosed in 81 (36%) patients, which were pulmonary in just over half of cases. These were treated with local therapy in 66 of 89 cases, and 7 patients received subsequent treatment for additional oligometastases. Metastasectomy was the most common treatment modality. A total of 16/66 patients (24%) underwent active surveillance for >6 months prior to local therapy. Conclusion: Patients with oligometastatic disease can experience durable disease control with timely multimodality treatment approaches for evolving metastatic disease, where disease biology allows.*

Soft tissue sarcomas (STS) are a rare and heterogeneous group of malignancies diagnosed in over 3,000 patients per annum in the UK (1), accounting for 1% of all cancer diagnoses (2). Factors including age, stage at presentation, tumour histological grade, size and depth can be used for prognostication. Five year survival is approximately 50% (1). Surgery is the mainstay of management for primary disease with (neo)adjuvant radiotherapy (RT) in selected cases.

Correspondence to: Dr. Gerard Walls, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, U.K. E-mail: wallsgerard@gmail.com

Key Words: Sarcomas, oligometastatic, active surveillance, multimodality, local therapy.

(Neo)adjuvant chemotherapy has not been demonstrated to offer an overall survival advantage in most STS subtypes (3), although there are data suggesting a possible survival advantage in a selected subgroup of extremity sarcomas (4).

Management of metastatic STS relies heavily on cytotoxic chemotherapy, targeted agents, palliative RT, radiofrequency ablation (RFA) and surgery. Decisions on the timing and the suitability of treatment are made based on the tempo of disease activity, tumour volume, symptom burden, previous lines of therapy and co-morbidities. For many patients with indolent STS subtypes, active surveillance is considered (5). Active symptom control with best supportive care (BSC) is recommended in all patients in parallel with the oncological treatments described above, or as the sole modality when active oncological treatments are unsuitable. Surgery in the non-curative setting for the relief of symptoms is undertaken rarely (6).

Oligometastatic disease, defined as less than five metastases in one organ or a limited number of organs (7) is increasingly recognised as an opportunity to control disease burden in the longer term (8). In recent years, managing patients with oligometastatic disease with radical, local treatments such as metastatectomy, RFA, and RT, has become a new standard of care (9).

Robust outcome data guiding clinicians and patients towards one local therapy over another are lacking (10). The Improving Outcomes Guidance for Bone and STS document published by the National Institute for Clinical Excellence in 2006 advises that patients with a diagnosis of soft tissue or bone sarcoma should have their care overseen by a dedicated sarcoma multidisciplinary team meeting (MDTM) (11). At our centre, pathways from the MDTM to each of RT, metastasectomy and RFA have been implemented for patients with oligometastatic disease.

The aim of this study was to determine patterns of care and survival outcomes for patients presenting with oligometastatic disease, in order to provide benchmark data for future studies that inform and improve guidelines.

Patients and Methods

Patient characteristics. Following institutional approval, a retrospective analysis was performed of the prospectively collected Royal Marsden Hospital (RMH) database to identify patients with new distant metastasis from a localised STS treated between January 2009 - December 2012. Electronic patient records were interrogated for patient demographics, primary tumour characteristics (histological subtype, site, grade), time to recurrence, site and pattern of recurrence (oligometastatic versus disseminated). Oligometastatic disease was defined as less than five metastatic lesions in total, in one or a limited number of organs. The primary treatment modality of metastatic disease and the outcome were recorded. Dates of treatment and most recent follow-up were noted, and where systemic therapy was used, initial treatment intention, regimen of choice, number of cycles and lines of therapy were recorded. Typically, local therapy for oligometastases was undertaken after a period of several months to enable an assessment of disease tempo, especially for cases of pulmonary oligometastases. Subsequent control at the site of initial relapse following second-line treatment plus distant control of disease were noted where applicable. Modalities of treatment applied following progression of disease were recorded where possible. Specific surgical technique and dose-fractionation of RT were not recorded.

The primary endpoint of the study was to determine the incidence of patients diagnosed with STS oligometastases primarily managed with radical local therapies *i.e.*, metastasectomy, RFA or RT. Secondary endpoints were disease-free survival (DFS), local control (LC) rates for aggressively treated metastases, progression-free survival (PFS) and overall survival (OS). For those patients not managed with local therapies, the secondary end points were PFS and OS in patients receiving primary palliative chemotherapy and or primary palliative surgery for symptoms. The palliative surgery cohort was defined as those patients undergoing surgery for the relief of symptoms from locoregional or distant disease relapse. This cohort was distinct from the metastasectomy cohort where an R0 resection was deemed technically possible and disease control was maintained at other sites.

Survival outcomes. DFS was defined as the interval between primary surgery for localised disease and the date of first metastatic relapse. LC rate was defined as proportion of patients free from local progression at new metastatic disease site following local therapy for oligometastatic disease. PFS was defined as time to relapse of locally treated oligometastatic disease or recurrence at any site. Any loco-regional relapse-free patients were censored at last follow-up. OS was defined from date of relapse diagnosis to date of death with censoring of surviving patients at last follow-up.

Statistical analysis. Descriptive statistics were applied to demographics, site of original disease, grade and histological subtype. Survival analyses were calculated by Kaplan-Meier methods using GraphPad Prism (San Diego, CA, USA). Log-rank tests to determine the statistical significance of differences in survival between local therapies was not possible owing to low numbers of patients involved.

Results

Patient characteristics. A total of 223 patients with new distant relapse of STS were referred to the RMH Sarcoma MDTM between 2009 and 2012. Of these patients, 81 (36%) had oligometastases, and 142 (64%) developed polymetastatic disease. The median age at diagnosis was 59 years (range=16-93 years). The median DFS (time to development of metastatic disease) was 1.22 years (range=1.03-1.49 years) and the median follow-up was 2 years (range=0.01-5.40 years). The median DFS for the oligometastatic cohort specifically was 1.6 years. The most common histological subtypes were leiomyosarcoma (n=47, 21%), liposarcoma (n=35, 16%) and undifferentiated pleomorphic sarcoma (n=31, 14%). Table I summarises histological subtypes and grades in this patient cohort. The most common grade was grade III (n=88, 39%), followed by grade II (n=67, 30%) and grade I (n=6, 7%), with grade information not available for 51 cases (23%). The most common primary sites were extremities (n=78, 35%), retroperitoneum (n=41, 18%) and thorax (n=33, 15%), as summarised in Table II.

Frequency and time to local therapies. Of the 223 patients presenting with metastatic disease, 81 (36%) presented with oligometastatic disease. The median number of oligometastases at diagnosis was one (range=1-3) and most commonly were found in the lungs, as summarised in Figure 1. Pulmonary oligometastases were diagnosed in 44 patients (20%), and non-pulmonary oligometastases were diagnosed in 37 patients (17%) patients. Almost three-quarters of cases (n=31, 70%) with pulmonary oligometastases received local treatment. Several patients received sequential local treatment to several oligometastases; five patients on two occasions, one patient on three, equalling a total of 38 cases of treated pulmonary oligometastasis. In cases of non-pulmonary oligometastases a similar proportion of patients (n=27, 73%) received local treatment. One patient received local treatment twice, meaning 28 cases of non-pulmonary metastasis were treated. Overall, in the event of a new oligometastasis, the majority of patients (66 of 89, 74%) received a local therapy. In terms of absolute case numbers, 58 of 81 (72%) patients with oligometastases received local treatment.

Metastasectomy was employed on 43 occasions (48%) (n=4 received 2 treatments), RFA on 10 occasions (11%) (n=1 received 3 treatments); RT on 15 occasions (17%); Metastasectomy was the most common treatment for pulmonary (n=26, 67%) and non-pulmonary (n=17, 61%) oligometastases and two patients received both metastasectomy and RT. In pulmonary disease, the next most commonly employed

Table I. *Histological subtypes of cohort.*

Histology	Frequency (%)
Leiyomyosarcoma	47 (21)
Liposarcoma	35 (16)
Well differentiated + Dedifferentiated elements	10
Dedifferentiated	10
Pleomorphic	7
Well differentiated	4
Myxoid/round cell	3
Not documented	1
Undifferentiated pleomorphic sarcoma	31 (14)
Myxofibrosarcoma	18 (8)
Malignant peripheral nerve sheath	13 (6)
Angiosarcoma	11 (5)
Synovial sarcoma	10 (4)
Gastrointestinal stromal tumour	10 (4)
Solitary fibrous tumour	9 (4)
Spindle cell sarcoma	7 (3)
Other	32 (14)
Total	223 (100)

Table II. *Site of primary tumour at original diagnosis for cohort.*

Tumour site	Frequency (%)
Extremity	78 (35)
Retroperitoneum	41 (18)
Thorax	33 (15)
Abdomen	30 (14)
Gynaecological	26 (12)
Head and Neck	6 (3)
Pelvis	8 (4)
Total	223 (100)

modality was RFA (n=7, 18%) followed by RT (n=5, 13%). In non-pulmonary disease, the next most commonly used modality was RT (n=10, 36%) followed by RFA (n=3, 11%). Palliative chemotherapy was administered to nine patients (11%) as part of their primary management in addition to local therapy. In 11 patients with oligometastases local therapy was deemed unsuitable by the MDTM, and all 11 patients received palliative chemotherapy alone.

In patients receiving metastasectomy, median time to surgery was 2.1 months (range=0-21 months), with eight of 43 (19%) receiving their local treatment more than 6 months after relapse, in keeping with active surveillance prior to definitive treatment. For patients receiving RFA, the median time to local treatment was 2.4 months (range=0-30 months), with three patients (33%) receiving treatment after 6 months. In the group receiving RT, the median time to treatment was

3.3 months (range=0-20 months), with five patients (38%) receiving treatment after 6 months.

Frequency of chemotherapy, surgery and BSC. A total of 102 (46%) patients in the cohort received palliative systemic therapy at any point following initial relapse. The median number of cycles received was four (range=1-32). In the 50 patients that proceeded to further lines of systemic therapy the median number of lines of therapy was one (range=1-5). Doxorubicin monotherapy was the most common treatment, given to 34 patients (33%), followed by ifosfomide in nine patients (9%) and doxorubicin/ifosfamide combination in 7 patients (7%). The remaining 52 patients received various other treatments, such as gemcitabine, imatinib and pazopinib. Palliative surgery for symptoms (n=16) was the primary treatment for 16 patients (7%) on diagnosis of distant recurrence (excludes cases of metastasectomy n=43) and three patients went on to receive chemotherapy thereafter. Two patients received palliative RT upfront. BSC was deemed to be the most appropriate primary approach in 40 patients (18%).

Control rates. i) Time to failure at oligometastatic site following local therapy. In the group with oligometastases, RFA as a first-line therapy (n=10) led to a oligometastatic site median LC of 22.2 months (95%CI=15.2-27.8), in comparison with 18.0 months (95%CI=11.6-22.8) for radiotherapy as a first-line therapy (n=13) and 13.4 months (95%CI=11.0-15.4) for metastasectomy as a first-line therapy (n=43), as shown in Figure 2.

ii) Time to progression at any site following local therapy to oligometastatic site. Median time to any site progression was longest following metastasectomy (7.9 months (95%CI=6.6-9.0)), followed by RT at 4.6 months (95%CI=3.3-5.7) and RFA at 3.3 months (95%CI=2.3-4.1). Figure 3 demonstrates the time to any site relapse for each of these three treatment modalities.

iii) PFS in palliative chemotherapy and palliative surgery groups. The median PFS for palliative chemotherapy (n=102) was PFS 4.0 months, excluding those patients with metastatic GIST treated with effective tyrosine kinase inhibitor therapy and three patients lost to follow-up. The median PFS for the small palliative surgery subset of patients (n=16) who had surgery for symptom relief was 35.0 months.

Survival outcomes. i) Entire cohort. The median DFS for the entire cohort of 223 patients was 1.2 years (95%CI=1.0-2.0). Median OS from diagnosis of metastasis was 1.3 years (95%CI=0.9-1.6). OS at a follow-up of 2 years was 37% (95%CI=0.3-0.4), and at 5 years 12% (95%CI=0.1-0.2).

ii) Local therapies. Progression-free survival curves for the three local treatment modalities in pulmonary and non-pulmonary oligometastases are demonstrated in Figure 4 and Figure 5, respectively.
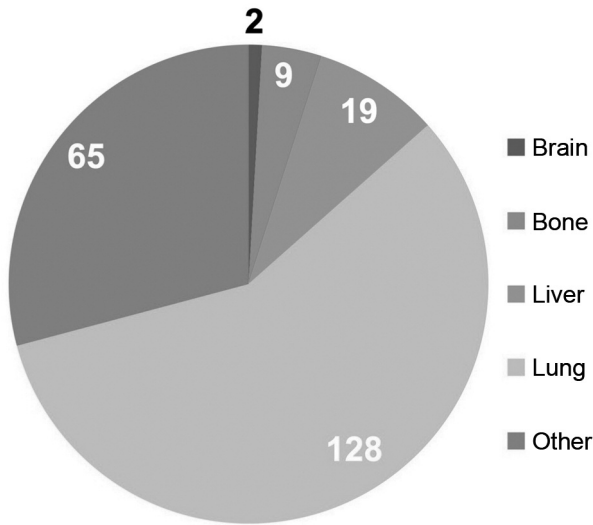
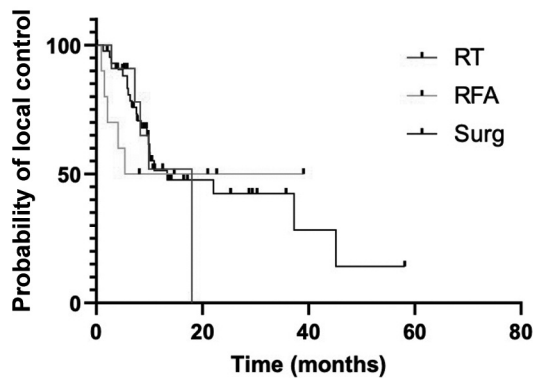Figure 1. *Site of first metastasis for cohort.*

Figure 3. *Time to progression at any site following local therapy for oligometastasis.*

Figure 2. *Time to local recurrence at site of oligometastasis treated by local therapies.*

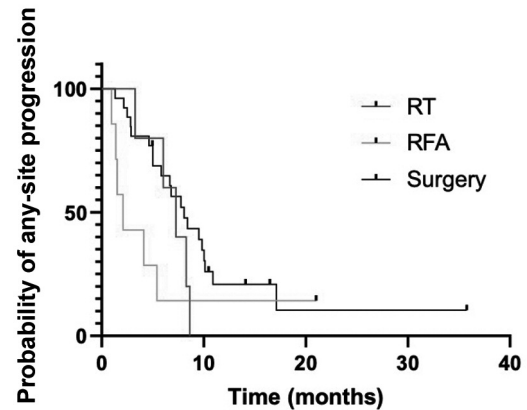Figure 4. *Progression-free survival for local therapies in pulmonary oligometastases.*

The 2-year OS for the pulmonary metastectomy group (n=26) was 62% (95%CI=0.4-0.8). Median PFS for treated pulmonary metastasectomy was 8.1 months (95%CI=6.4-9.5). PFS at 2 years was 10.4%. In patients with non-pulmonary oligometastases (n=17), the 2-year OS was 60% (95%CI=0.29-0.81), the median PFS for metastasectomy was 7.9 months (95%CI=5.9-9.6). PFS at 2 years was 15%.

In patients with pulmonary oligometastases, 2-year OS in the RFA group (n=7) was 54% (95%CI=0.1-0.8) and PFS at 2 years was 14%. For non-pulmonary oligometastases (n=3), which were all cases of liver RFA (two leiomyosarcoma, one GIST), the 2-year OS was 100% (95%CI=N/A) and PFS at 2 years was 67%.
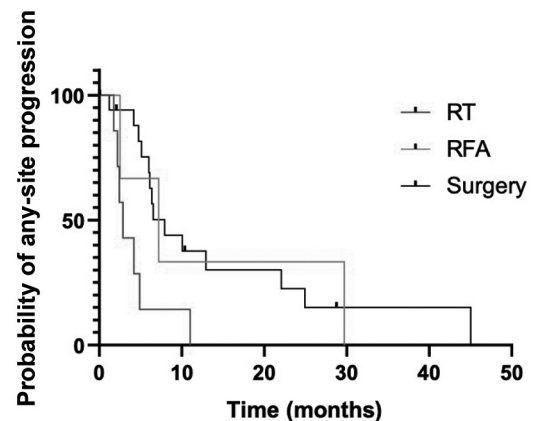

Figure 5. *Progression-free survival for locally targeted therapies in non-pulmonary oligometastases.*

In patients with pulmonary oligometastases, 2-year OS in the RT group (n=8) was 40% (95%CI=0.1-0.8). All patients progressed within 2 years. In patients with non-pulmonary oligometastases, the RT subset (n=5) had 2-year OS of 17% (95%CI=N/A). All patients progressed within 2 years.

iii) Systemic therapy and surgery. With a median follow-up of 16 months, 30 patients (87%) treated with primary surgery for symptom management were alive. Of the patients managed with best supportive care, 3% were alive at 3 years. The median OS for chemotherapy and palliative surgery groups were 16.3 and 39.3 months, respectively.

Discussion

Metastatic STS is an incurable entity with poor median survival (12). Palliation is complicated as systemic therapies are associated with low response rates and toxicity that can impact significantly on quality of life (QOL) (13, 14). In oligometastatic disease, a multitude of patterns of care are considered by the RMH Sarcoma MDTM in order to address the biological diversity observed, and all patients are discussed at the point of original diagnosis and first recurrence as a minimum. Multidisciplinary expertise is necessary given the complexity introduced by subtype heterogeneity, wide-ranging time to first metastasis, distribution of tumour sites, and appropriate (and available) local ablative techniques (11).

In comparison to the management of oligometastatic disease of other malignancies with established guidelines, the management of STS remains inconsistent. This is due not only to the rarity of this cancer population but also the diversity of histological subtypes. Our institutional approach is to consider patients of adequate fitness for local therapy of oligometastases depending on the histology and tempo of the disease. The modality of choice is tailored to the organs affected and clinical services available. This study has described patterns of care pertaining to the management of oligometastatic and polymetastatic STS and the results highlight the challenges in selection criteria related to recommending ablative therapies.

The cohort had a disease-free interval comparable to previous cohorts of approximately 14 months (15). Patients with pulmonary oligometastases had comparable disease control outcomes compared with extra-pulmonary sites. With our preliminary experience, surgery, RFA and RT are all suitable treatments as local ablative therapies, and our results for local treatments are comparable with the available limited published data (16-18).

Traditionally, metastasectomy has been reserved for fitter patients with oligometastatic disease (14) due to the elevated risk of adverse effects from such operative procedures. The excess risk associated with radical surgical approaches is probably coupled with superior outcomes across disease sites, although randomised studies testing this principle have failed to recruit (19). In our limited dataset, surgery provided superior PFS outcomes in both pulmonary and non-pulmonary metastases, and RT performed worst. As the paradigm of stereotactic ablative radiotherapy (SABR) for oligometastatic disease has been much refined and more widely adopted in the intervening period, future analyses may update this conclusion.

The median PFS in the oligometastases group was 6.5 months with an OS of 25.4 months. This compared to a median PFS of 4.0 months and OS of 16.3 months following primary palliative chemotherapy. Whilst oligometastatic relapse is associated with improved survival compared with polymetastatic presentation, the question remains as to whether differences relate to underlying disease biology or intervention employed.

Of note, a period of active surveillance of at least 6 months occurred for one third of patients with oligometastases in this cohort, which may be a reflection of favourable disease biology. Whilst it may be routine practice in some institutions to proceed to immediate resection (20), for pulmonary metastases for example, our data show that active surveillance is a viable alternative option, prior to committing to definitive treatment. Surveillance may not only allow for better characterisation of metastatic disease but also the patient's fitness for an operation, or alternative local intervention.

Active surveillance is a rational management approach in patients with low volume metastases and indolent biology. By gauging the tempo of disease, the most appropriate strategy for the individual patient, and indeed the selection of local therapy for oligometastatic relapse can be elicited (21). Owing to highly individualised disease courses and wide-ranging clinician preferences, the feasibility of designing and delivering a randomised study of surgery, RT and RFA is low at present (22). Furthermore, the global dogma of resecting metastases where possible and reserving RT and RFA for inoperable cases, will be difficult to challenge (23).

Doxorubicin monotherapy was the most commonly used first-line systemic treatment, followed by ifosfamide, followed by the combination of these two. Palliative surgery was offered for a very small cohort of extremely selective cases primarily pre-determined by the biological behaviour of the disease and time to development of metastatic disease. Performance status, co-morbidities, and tumour biology preclude a surgical option for most patients.

This study of a prospectively collected patient cohort provides 'real world' representation of patterns of care and current practice. Our data highlight the importance of patient selection and multi-disciplinary evaluation of oligometastatic disease. These data represent the period when many of the local therapy pathways were under development, and considerable progress in access and outcomes are likely to

be found in the cohort beyond 2013, which will potentially manifest as further advances in OS. Since this initial review, further developments in ablative therapies have reported improvements in PFS in STS and other malignancies (24, 25), providing evidence to support the integration of ablative therapies into routine clinical practice.

This study has several limitations including its retrospective nature, limited cohort size and limited follow-up duration. Cohort size is likely to have had an effect on these data for the non-pulmonary oligometastases in particular. The heterogeneity of the histology, primary site, previous treatment, site of metastases, and systemic regimens also complicates the interpretation of the findings, making it difficult to draw firm conclusions about particular subtypes. Unfortunately, data on tumour size were not available for this analysis. As a guiding principle, thoracic metastectomy was considered where a segmentectomy or lobectomy were deemed to be adequate, and RFA or RT, dependent on the location, when lesions were generally <5 cm.

Other limitations of this study are the absence of patient-reported and clinician-assessed QOL indices (26), cost-effectiveness analyses (27, 28) and complication recording (29, 30) of the local interventions. With regard to side effects in particular, whilst the toxicity profile of RT has been established (31), the acute and late side effects of metastasectomy (32) and RFA (33, 34) are reported with considerable variation, and real-world data pertaining to STS patients in particular would be informative. Bronchopleural fistula, pneumothorax and chest wall pain can occur following RFA and metastasectomy (depending on organ involvement) and the rates of such complications will be as important to determine as the cancer-specific outcomes in prospective studies.

Despite these limitations, this analysis provides important data for informed design of future observational registry studies, and eventually, interventional studies. Factors that appropriately stratify patients to local and palliative treatments described should be investigated, particularly as minimally invasive ablative techniques are now increasingly available. It is likely that histology-specific sub-studies will be required to fully address some research questions. Lastly, linked translational research is warranted to determine predictive biomarkers for the response of oligometastatic disease to invasive local therapy in this highly diverse patient cohort.

Conclusion

There are a number of modalities available to treat oligometastatic STS. A period of active surveillance can be considered prior to local therapy to gauge the tempo of metastatic disease. Depending on the clinical context, our retrospective data show that metastasectomy, radiotherapy and radiofrequency ablation lead to similar outcomes, with a trend to best local control with metastasectomy. This study contributes data for the design of future oligometastatic STS studies, which are desperately needed to provide an evidence base in this challenging clinical scenario.

Conflicts of Interest

Authors' Contributions

Conception: GW, RL, AM; Data Collection: GW, IH; Statistics: GW, KK, OA; Interpretation: all Authors; Early Manuscript Drafts: GW, RL, AM; Final Drafting: all Authors.

Acknowledgements

References

1 Cancer Research UK. Risks and causes of soft tissue sarcomas 2015. Available at: https://www.cancerresearchuk.org/about-cancer/soft-tissue-sarcoma/risks-causes [Last accessed on April 13, 2021]

2 Rydholm A: Improving the management of soft tissue sarcoma. Diagnosis and treatment should be given in specialist centres. BMJ 317(7151): 93-94, 1998. PMID: 9657781. DOI: 10.1136/bmj.317.7151.93

3 Woll PJ, Reichardt P, Le Cesne A, Bonvalot S, Azzarelli A, Hoekstra HJ, Leahy M, Van Coevorden F, Verweij J, Hogendoorn PC, Ouali M, Marreaud S, Bramwell VH, Hohenberger P and EORTC Soft Tissue and Bone Sarcoma Group and the NCIC Clinical Trials Group Sarcoma Disease Site Committee: Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial. Lancet Oncol 13(10): 1045-1054, 2012. PMID: 22954508. DOI: 10.1016/S1470-2045(12)70346-7

4 Gronchi A, Palmerini E, Quagliuolo V, Martin Broto J, Lopez Pousa A, Grignani G, Brunello A, Blay JY, Tendero O, Diaz Beveridge R, Ferraresi V, Lugowska I, Merlo DF, Fontana V, Marchesi E, Braglia L, Donati DM, Palassini E, Bianchi G, Marrari A, Morosi C, Stacchiotti S, Bagué S, Coindre JM, Dei Tos AP, Picci P, Bruzzi P and Casali PG: Neoadjuvant chemotherapy in high-risk soft tissue sarcomas: Final results of a randomized trial from Italian (ISG), Spanish (GEIS), French (FSG), and Polish (PSG) sarcoma groups. J Clin Oncol 38(19): 2178-2186, 2020. PMID: 32421444. DOI: 10.1200/JCO.19.03289

5 Greenberg DD and Crawford B: Surveillance strategies for sarcoma: Results of a survey of members of the Musculoskeletal Tumor Society. Sarcoma *2016*: 8289509, 2016. PMID: 27478404. DOI: 10.1155/2016/8289509

6 Smolle MA, Schaffler A, Leithner A, Van Praag VM, Bergovec M, Szkandera J, Liegl-Atzwanger B, Niethard M, Tunn PU, Van De Sande M and Andreou D: Incidence, treatment and outcome of abdominal metastases in extremity soft tissue sarcoma: Results from a multi-centre study. J Surg Oncol *121(4)*: 605-611, 2020. PMID: 32003475. DOI: 10.1002/jso.25856

7 Hellman S and Weichselbaum RR: Oligometastases. J Clin Oncol *13(1)*: 8-10, 1995. PMID: 7799047. DOI: 10.1200/JCO.1995.13.1.8

8 Hohenberger P, Kasper B and Ahrar K: Surgical management and minimally invasive approaches for the treatment of metastatic sarcoma. Am Soc Clin Oncol Educ Book: 457-464, 2013. PMID: 23714570. DOI: 10.14694/EdBook_AM.2013.33.457

9 Reyes DK and Pienta KJ: The biology and treatment of oligometastatic cancer. Oncotarget *6(11)*: 8491-8524, 2015. PMID: 25940699. DOI: 10.18632/oncotarget.3455

10 ESMO/European Sarcoma Network Working Group: Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol *25(Suppl 3)*: iii102-iii112, 2014. PMID: 25210080. DOI: 10.1093/annonc/mdu254

11 National Institute for Health and Clinical Excellence. Improving Outcomes for People with Sarcoma, 2006. Available at: www.nice.org.uk/guidance/csg9 [Last accessed on September 5, 2021]

12 Karavasilis V, Seddon BM, Ashley S, Al-Muderis O, Fisher C and Judson I: Significant clinical benefit of first-line palliative chemotherapy in advanced soft-tissue sarcoma: retrospective analysis and identification of prognostic factors in 488 patients. Cancer *112(7)*: 1585-1591, 2008. PMID: 18278813. DOI: 10.1002/cncr.23332

13 Gough N, Koffman J, Ross JR, Riley J and Judson I: Does palliative chemotherapy really palliate and are we measuring it correctly? A mixed methods longitudinal study of health related quality of life in advanced soft tissue sarcoma. PLoS One *14(9)*: e0210731, 2019. PMID: 31557183. DOI: 10.1371/journal.pone.0210731

14 Treasure T, Milošević M, Fiorentino F and Macbeth F: Pulmonary metastasectomy: what is the practice and where is the evidence for effectiveness? Thorax *69(10)*: 946-949, 2014. PMID: 24415715. DOI: 10.1136/thoraxjnl-2013-204528

15 McMillan RR, Sima CS, Moraco NH, Rusch VW and Huang J: Recurrence patterns after resection of soft tissue sarcomas of the chest wall. Ann Thorac Surg *96(4)*: 1223-1228, 2013. PMID: 23891404. DOI: 10.1016/j.athoracsur.2013.05.015

16 Treasure T, Fiorentino F, Scarci M, Møller H and Utley M: Pulmonary metastasectomy for sarcoma: a systematic review of reported outcomes in the context of Thames Cancer Registry data. BMJ Open *2(5)*: e001736, 2012. PMID: 23048062. DOI: 10.1136/bmjopen-2012-001736

17 Nakamura T, Matsumine A, Yamakado K, Matsubara T, Takaki H, Nakatsuka A, Takeda K, Abo D, Shimizu T and Uchida A: Lung radiofrequency ablation in patients with pulmonary metastases from musculoskeletal sarcomas [corrected]. Cancer *115(16)*: 3774-3781, 2009. PMID: 19514086. DOI: 10.1002/cncr.24420

18 Dhakal S, Corbin KS, Milano MT, Philip A, Sahasrabudhe D, Jones C and Constine LS: Stereotactic body radiotherapy for pulmonary metastases from soft-tissue sarcomas: excellent local lesion control and improved patient survival. Int J Radiat Oncol

Biol Phys *82(2)*: 940-945, 2012. PMID: 21277105. DOI: 10.1016/j.ijrobp.2010.11.052

19 Chang JY, Senan S, Paul MA, Mehran RJ, Louie AV, Balter P, Groen HJ, McRae SE, Widder J, Feng L, van den Borne BE, Munsell MF, Hurkmans C, Berry DA, van Werkhoven E, Kresl JJ, Dingemans AM, Dawood O, Haasbeek CJ, Carpenter LS, De Jaeger K, Komaki R, Slotman BJ, Smit EF and Roth JA: Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol *16(6)*: 630-637, 2015. PMID: 25981812. DOI: 10.1016/S1470-2045(15)70168-3

20 Krüger M, Schmitto JD, Wiegmann B, Rajab TK and Haverich A: Optimal timing of pulmonary metastasectomy – is a delayed operation beneficial or counterproductive? Eur J Surg Oncol *40(9)*: 1049-1055, 2014. PMID: 24746934. DOI: 10.1016/j.ejso.2014.03.017

21 Grilley-Olson JE, Webber NP, Demos DS, Christensen JD and Kirsch DG: Multidisciplinary management of oligometastatic soft tissue sarcoma. Am Soc Clin Oncol Educ Book *38*: 939-948, 2018. PMID: 30231386. DOI: 10.1200/EDBK_200573

22 Treasure T and Macbeth F: Doubt about effectiveness of lung metastasectomy for sarcoma. J Thorac Cardiovasc Surg *149(1)*: 93-94, 2015. PMID: 25439472. DOI: 10.1016/j.jtcvs.2014.09.073

23 Tetta C, Londero F, Micali LR, Parise G, Algargoush AT, Algargoosh M, Albisinni U, Maessen JG and Gelsomino S: Stereotactic body radiotherapy versus metastasectomy in patients with pulmonary metastases from soft tissue sarcoma. Clin Oncol (R Coll Radiol) *32(5)*: 303-315, 2020. PMID: 32024603. DOI: 10.1016/j.clon.2020.01.005

24 Chalkidou A, Macmillan T, Grzeda MT, Peacock J, Summers J, Eddy S, Coker B, Patrick H, Powell H, Berry L, Webster G, Ostler P, Dickinson PD, Hatton MQ, Henry A, Keevil S, Hawkins MA, Slevin N and van As N: Stereotactic ablative body radiotherapy in patients with oligometastatic cancers: a prospective, registry-based, single-arm, observational, evaluation study. Lancet Oncol *22(1)*: 98-106, 2021. PMID: 33387498. DOI: 10.1016/S1470-2045(20)30537-4

25 Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, Mulroy L, Lock M, Rodrigues GB, Yaremko BP, Schellenberg D, Ahmad B, Griffioen G, Senthi S, Swaminath A, Kopek N, Liu M, Moore K, Currie S, Bauman GS, Warner A and Senan S: Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet *393(10185)*: 2051-2058, 2019. PMID: 30982687. DOI: 10.1016/S0140-6736(18)32487-5

26 Younger E, Wilson R, van der Graaf WTA and Husson O: Health-related quality of life in patients with sarcoma: Enhancing personalized medicine. J Clin Oncol *36(16)*: 1642-1643, 2018. PMID: 29668370. DOI: 10.1200/JCO.2018.77.9819

27 Lachance C and Campbell K: Stereotactic body radiotherapy for oligometastatic cancer: a review of clinical effectiveness and cost-effectiveness [Internet]. Ottawa (ON), Canadian Agency for Drugs and Technologies in Health, 2019. PMID: 31433609.

28 Jones DR: Determining the value of pulmonary metastasectomy. Eur J Cardiothorac Surg *50(5)*: 800, 2016. PMID: 27369119. DOI: 10.1093/ejcts/ezw181

29 Rehders A, Hosch SB, Scheunemann P, Stoecklein NH, Knoefel WT and Peiper M: Benefit of surgical treatment of lung metastasis

in soft tissue sarcoma. Arch Surg *142(1)*: 70-5; discission 76, 2007. PMID: 17224503. DOI: 10.1001/archsurg.142.1.70

30 Kim M, Son SH, Won YK and Kay CS: Stereotactic ablative radiotherapy for oligometastatic disease in liver. Biomed Res Int *2014*: 340478, 2014. PMID: 24868526. DOI: 10.1155/2014/340478

31 Li Y, Tao S, Li M and Li D: The role of radiation therapy in the modern management of oligometastatic disease. J BUON *22(4)*: 831-837, 2017. PMID: 29155507.

32 Marulli G, Mammana M, Comacchio G and Rea F: Survival and prognostic factors following pulmonary metastasectomy for sarcoma. J Thorac Dis *9(Suppl 12)*: S1305-S1315, 2017. PMID: 29119019. DOI: 10.21037/jtd.2017.03.177

33 Hiraki T and Kanazawa S: Lung radiofrequency ablation: potential as a therapy to oligometastasis and oligorecurrence. Pulm Med *2012*: 196173, 2012. PMID: 23125926. DOI: 10.1155/2012/196173

34 Jones RL, McCall J, Adam A, O'Donnell D, Ashley S, Al-Muderis O, Thway K, Fisher C and Judson IR: Radiofrequency ablation is a feasible therapeutic option in the multi modality management of sarcoma. Eur J Surg Oncol *36(5)*: 477-482, 2010. PMID: 20060679. DOI: 10.1016/j.ejso.2009.12.005