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Review

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Management of oligometastatic disease in soft tissue sarcomas

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Abstract

Oligometastatic soft tissue sarcoma represents an intermediate state between localized and disseminated disease. Combination A combination of surgery, radiotherapy and systemic treatment significantly improves prognosis, with a 5-year overall survival as high as 50%. Due to the high prevalence of lung metastases, most of the surgical evidence is centered around lung metastasectomy. The decision to perform surgical metastasectomy remains dependent on optimal patient selection. Adequate post-surgical lung function, absence of extrapulmonary metastases, control of the primary tumor, and feasibility of achieving negative margins are major criteria for patients to undergo successful surgery. Adequate margins, longer disease-free interval, unilateral, limited number (≤ 2), metachronous and small (< 2 cm) pulmonary metastasis are some factors associated with improved survival. Radiotherapy, especially SBRT, is an effective treatment for disease control, and its use as (neo)-adjuvant therapy has shown promising results. However, studies comparing radiotherapy against surgery are missing and the efficacy of radiotherapy independent of surgery is not yet clear. Interventional radiology techniques such as percutaneous thermal ablation (PTA) or arterial embolization have also been described as potential treatment alternatives in candidates deemed not fit for surgery. Systemic treatment has traditionally consisted of an anthracycline (doxorubicin)-based regimen with the addition of ifosfamide in certain cases. Recent advances in

systemic treatment include the use of targeted therapy and immunotherapy in (oligo)-metastatic STS. However, except for certain histologies, most STS subtypes are chemoresistant, and the response to systemic treatment is poor.

Keywords: Soft tissue sarcoma, oligometastasis, surgery, treatment

INTRODUCTION

Soft tissue sarcomas (STS) are a heterogeneous group of neoplasms of mesenchymal origin composed of more than 50 different histologic subtypes[1]. STS represent 0.8% of all malignancies and result in 5,000 deaths each year in the US[2]. Most of these tumors display aggressive behavior, with high rates of metastatic disease[3]. Unlike other tumors, metastatic STS is often restricted to a single organ, with 70% of patients presenting metastasis limited to the lungs[4]. Despite the overall prevalence of lung metastasis, unusual patterns of metastatic spread characterize certain STS subtypes; extrapulmonary and brain metastasis are common in myxoid liposarcoma and alveolar soft part sarcoma, respectively[5,6]. Their prognosis depends on the presence of local recurrence and/or distant metastasis. Overall, these tumors have a 65% five-year survival rate, but this number drops to 16% in the case of metastatic sarcoma[2].

Oligometastatic disease, defined as less than five metastases in one organ or a limited number of organs, is considered an intermediate between localized and widespread metastatic disease[7]. This concept is increasingly being recognized as an opportunity to achieve long-term disease control through a combination of surgery to the metastatic site, systemic treatment, and radiation therapy (RT)[8]. Although guidelines for the management of oligometastatic disease for other malignancies are already in place, lower incidence of STS and high variability among histologic subtypes make it more difficult to implement large-scale trials and most evidence in this patient subset comes from single-institution studies, making recommendations inconsistent. The purpose of our study is to perform a comprehensive review of the literature to identify the most common approach to managing this condition that has been reported.

OVERVIEW OF TREATMENT OPTIONS

Management of oligometastatic disease in STS requires a multidisciplinary team and should consider the tumor histology and location, the number of metastases, and the interval of time preceding the development of metastasis. Treatment should aim at achieving local control, alleviation of symptoms, and improvement of prognosis[8,9].

Available treatment options include surgery to the metastatic site (metastasectomy), systemic treatment (cytotoxic, targeted therapy, and/or immunotherapy), and RT. Selection of treatment modality should always consider both the tumor characteristics (size, disease activity, treatment-resistance pattern) and the patient profile (health status, comorbidities). In most cases, a combination of surgery, systemic treatment, and/or RT is employed.

SURGERY

Surgery to the metastatic site has been described in the literature since the 1940s when Alexander *et al.* reported favorable outcomes after surgical resection of pulmonary metastases[10]. Although multiple retrospective cohort studies suggest positive outcomes for metastasectomy in oligometastatic disease, no randomized trials have ever been conducted, and the true benefit of surgery remains uncertain. In this setting, strict patient selection must be conducted to maximize the benefit of surgery.

Patient selection

Criteria for lung metastasectomy are highly variable due to different protocols among treating institutions. However, we consider an adaptation of the criteria utilized by Thomford *et al.* as a comprehensive approach to patient selection[11]. Candidates for lung metastasectomy must therefore fulfill the following criteria:

(I) Primary tumor eradicated, controlled, or amenable to control.

(II) Resection with adequate margins (R0) of the metastatic site is feasible.

(III) No evidence of extrapulmonary metastatic disease.

(IV) Patient can withstand the surgery, and post-surgery lung function is expected to be adequate.

Although most literature in oligometastatic STS refers to resection of lung metastasis, positive outcomes have also been reported with surgical management of liver metastasis[12]. We consider that these inclusion criteria can be adapted and applied to other metastatic sites, such as the liver.

Lung metastasis

Surgical approach in lung metastasectomy

The standard approach for unilateral pulmonary metastases is posterolateral thoracotomy[13]. Thoracotomy allows the surgeon to palpate the lung and locate additional nodules not found on preoperative imaging[9]. However, the main disadvantage is that exposure is limited to one hemithorax, and in the case of bilateral lung metastasis, the procedure must be performed in a staged fashion[13]. Video-Assisted Thoracic Surgery (VATS) is a minimally invasive approach that provides excellent lung visualization and decreased complication rates and length of stay compared to open surgery. The main disadvantage is, however, the loss of ability to palpate the lung and find new lesions not detected on preoperative imaging. Ultimately, the choice of surgical treatment depends on the surgeon's experience.

Whether bilateral exploration is required in the presence of unilateral lung metastasis found on preoperative imaging remains controversial, due to the high prevalence of bilateral disease in STS and the limited sensitivity of chest CT for small lung nodules[14]. Roth *et al.* compared survival rates in patients who underwent resection of metastasis by sternotomy with an exploration of both lungs or with unilateral thoracotomy[15]. They found that although median sternotomy resulted in the detection of unsuspected metastasis, overall survival was not different. Further support against bilateral exploration is provided by Younes *et al.*, who found no significant difference in overall survival in patients with recurrence in the contralateral lung and those with bilateral metastases on admission[16].

The location of the metastatic lesion is another important factor when choosing the most appropriate surgical approach to achieve sufficient surgical margins and thus diminish the risk of local recurrence. Peripheral nodules are considered accessible and adequate surgical margins can be obtained with wedge resection[17]. Central lesions are less accessible through VATS and segmentectomy is usually the recommended treatment[18].

Outcomes of lung metastasectomy

Suggestions of clinical benefit of lung metastasectomy come from observational studies. Reported five-year overall survival after lung metastasectomy ranges from 32% to 52%, which is superior to 5-year survival rates for metastatic STS as a whole[19-21]. The METASARC study, a French retrospective cohort with more than

2,000 patients with metastatic STS, reported a 44% five-year overall survival in patients receiving surgery to the metastatic site compared with 6.4% for radiotherapy alone[22]. Although the study did not perform a subgroup analysis for patients with only pulmonary metastasis, sixty-seven percent of patients included in the study had lung metastasis and 89% had only one metastatic site. Another issue with most available studies is the lack of a control group, limiting the generalizability of results. Nevala *et al.* retrospectively reported survival outcomes of 130 patients with STS and lung metastasis treated with either metastasectomy, chemotherapy, or supportive care[23]. Median overall survival after complete or incomplete metastasectomy, chemotherapy, or supportive care was 22, 18, 8 and 5 months, respectively. However, patients who did not receive surgical treatment because of exclusion criteria such as inadequate performance status or disseminated metastatic disease did not represent a proper control group.

Several prognostic factors have been reported in the literature for improved survival after lung metastasectomy [Table 1]. Here we present some of the most reported ones:

a. Adequate tumor resection (R0 margins)[23-25]

b. Disease-free interval (DFI) > 12 months[26], > 18 months[24], > 16 months[25]

c. Unilateral pulmonary metastasis[21,24]

d. Limited number (≤ 2) of pulmonary metastasis[20]

e. Small (< 2 cm) tumor size[20]

f. Metachronous metastases[26,27]

Chudgar *et al.* retrospectively reviewed 539 patients that underwent pulmonary metastasectomy for STS and found leiomyosarcoma histology, primary tumor size ≤ 10 cm, DFI > 12 months, solitary lung metastasis, and minimally invasive resection as factors associated with lower risk of death[26].

Although pulmonary metastasectomy is likely an effective treatment for improving patient prognosis, the risk of recurrence remains high even after successful R0 resection. Nevala *et al.* found an 82% rate of systemic recurrence after complete resection[23]. Other studies report similar rates of around 80%[21,26]. Although recurrence is a clear factor associated with a worse prognosis, localized lung recurrence in the absence of disseminated metastatic disease does not constitute a contraindication for secondary metastasectomy. Casson *et al.* analyzed 37 patients with secondary (recurrent) pulmonary metastasis after initial metastasectomy and reported a median survival of 28 months in patients with complete resection compared with 7 months for those with unresectable recurrent metastases[28].

Depending on the time of detection of metastases, they can be classified as *synchronous* or *metachronous*. *Synchronous* metastases are those detected at diagnosis, usually as a result of the imaging workup that follows the detection of an STS. *Metachronous* metastases, on the other side, occur after 3 months from the initial diagnosis, which typically means that the initial workup was negative for metastatic disease. Several studies have reported higher survival for patients with *metachronous* oligometastatic STS[26,27]. Chudgar *et al.* reported a median overall survival of 67 and 39 months for patients with metachronous and synchronous oligometastases, respectively[26]. They additionally performed a multivariate analysis which confirmed the worse prognosis associated with *synchronous* oligometastases (HR = 1.09, $P = 0.037$). The main limitation of

Table 1. Factors associated with improved survival after lung metastasectomy

Author (year)	Patient (*n*)	Surgical approach	Metastasectomy	Outcome measure(s)	Protective factors
Nevala *et al.*, 2019[23]	74	Open thoracotomy (70%) VATS (30%)	Complete metastasectomy (55) incomplete metastasectomy (19)	5-year DFS	(1) Single nodule removed in the last complete pulmonary resection^{+} (2) median DFI before last complete pulmonary resection < 1.3^{+}
Lee *et al.*, 2016[21]	29	NA	Complete metastasectomy (100%)	5-year OS	(1) Unilateral metastasis^{+} (2) early metastatic progression^{+}
Toussi *et al.*, 2013[24]	34	Segmentectomy or wedge resection (70.6%) lobectomy (23.5%) and pneumonectomy (6%)	Complete metastasectomy (88%) incomplete metastasectomy (12%)	3-year OS	(1) Unilateral metastasis^{+} (2) complete resection
Predina *et al.*, 2011[20]	48	Open resection (73%) VATS (27%)	Complete metastasectomy (100%)	Median OS Median DFS	(1) Non-extrapulmonary metastasis^{+}
Sardenberg *et al.*, 2010[25]	77	Open thoracotomy (97%) biopsy (3%)	Complete metastasectomy (79.2%) incomplete metastasectomy (20.8%)	Postoperative complication 30-day mortality rate 90-month OS	(1) Disease free interval > 16 months^{+} (2) complete resection^{+}
Chudgar *et al.*, 2017[26]	539	Open thoracotomy (71%) minimally invasive (29%)	Complete metastasectomy (91%) incomplete metastasectomy (9%)	Median OS Median DFS	(1) Low-grade primary tumor (2) synchronous interval to first metastasis (3) ≤ 1 pulmonary metastasis^{+}
Wigge *et al.*, 2018[27]	102	Open thoracotomy (100%)	NA	Median OS	(1) Resection of primary tumor^{+} (2) progression-free interval < 12 months^{+}

DFI: Disease-free interval; DFS: disease-free survival; NA: not available; OS: overall survival; VATS: video-Assisted Thoracoscopic Surgery. $^{+}$*P*-value ≤ 0.05.

this study was that the analysis combined patients with oligometastatic and disseminated diseases; however, patients with oligometastatic STS represented 64.9% (37/57) of the overall sample.

The case displayed in Figure 1 illustrates the surgical management of oligometastatic STS by the senior author of this article. The combination of wide excision for local control and lung metastasectomy yielded excellent results, as evidenced by the 4-year disease-free survival.

Metastatic sites other than the lung

Outcomes of surgery to metastatic sites other than the lungs, especially the liver, have also been assessed in the literature[29-31]. Unlike lung metastasis, which in most cases manifests as solitary lesions, liver metastases are often present in patients with disseminated disease. Therefore, the curative role of surgery on metastatic liver lesions is under debate. Rehders *et al.* assessed the outcomes of 27 patients with STS with localized liver metastasis that underwent hepatic metastasectomy[32]. They reported a median survival of 44 months and a five-year survival of 49% after surgery[32]. In a similar study of 36 patients that underwent hepatic metastasectomy, Marudanayagam *et al.* found a median survival of 24 months and 5-year survival of 31.8%[12]. Potential limitations of these studies are the inclusion of gastrointestinal stromal tumors (GIST) and leiomyosarcoma, which in both cases represent more than 50% of all STS and are mostly localized in the abdomen and retroperitoneum. Other common STS, which most often involve the extremities, are underrepresented and robust conclusions cannot be drawn. These studies do, however, suggest a potential role for hepatic metastasectomy extending survival in a very select pool of patients with localized hepatic metastases. Although further research on this topic is needed, physicians should be aware that hepatic metastasis is usually seen as a manifestation of disseminated disease and localized hepatic metastases are an extremely infrequent event.

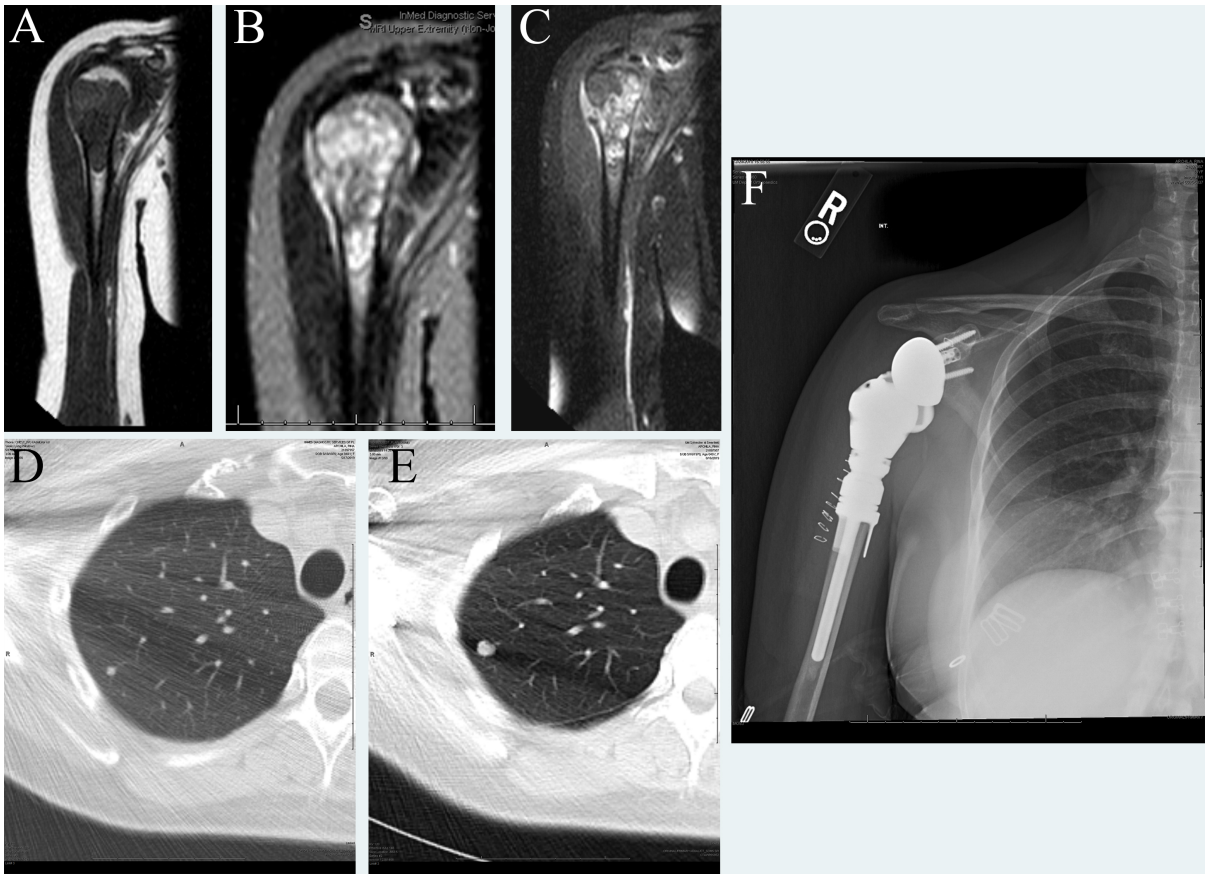

Figure 1. Fifty-six-year-old female with a diagnosis of synovial sarcoma in the right thigh underwent wide local excision 2 years prior to our consultation in an outside institution. She came to our clinic with right shoulder pain. Imaging studies showed an aggressive intramedullary lesion in the right proximal humerus with (A) T1-weighted hypointense, (B) STIR heterogeneous hyperintense, and (C) post-contrast heterogeneous enhancement. This lesion was biopsied and metastatic synovial sarcoma was diagnosed. Staging studies were done and a (D) solitary lung lesion was found suspicious for metastatic disease. The decision was made to start systemic therapy receiving two cycles, but (E) due to the growth of the lung lesion, the decision was made to proceed with (F) wide local excision of the right proximal humerus with reconstruction (reverse total shoulder replacement) and resection of the solitary lung lesion. The patient is 4 years out of surgery and is disease free.

RADIATION THERAPY

During the last two decades, the median overall survival of patients with metastatic STS has improved by 50%. This can be partially attributed to the increased use of local treatments like RT, widespread use of systemic treatment, and improvement in supportive care[33,34]. RT has historically been used as palliative treatment due to the inaccurate concept of radioresistance in STS. Newer radiation treatment strategies such as Stereotactic Body Radiation Therapy (SBRT), a highly targeted hypo-fractionated ablative RT technique, have completely changed the paradigm and expanded the use of RT outside of palliative treatment[35,36]. SBRT works through a different mechanism than conventionally fractionated RT but shares the same dose escalation principle, especially in patients with oligometastatic disease where treatment has curative intent. Although STS are not as radiosensitive as other solid malignancies, several studies have demonstrated that high rates of local control can be achieved through RT[35,37-40].

SBRT offers several advantages over surgery or radiofrequency for local control as it is non-invasive, can deliver high biological doses of radiation with minimum damage to the surrounding normal tissue, does not cause significant patient discomfort, and has a lower 30- and 90-day postoperative mortality than surgery.

Disadvantages of SBRT include self-resolving acute grade 1 toxicity and grade 2 toxicities requiring medical management in 10% of cases[35]. In addition, the number of metastases treated through RT is often limited by the radiation tolerance of surrounding tissues[9,38]. Literature on SBRT-related toxicity is conflicting, with multiple studies on STS lung metastases reporting minimal toxicity after treatment[34,35,37-39,41,42]. Loi *et al.* reported good tolerance to SBRT independent of the irradiated site in 16 patients after a median follow-up of 36 months[35]. Only 10% of patients presented with grade 2 toxicity that required medical and no chronic toxicities were observed[33]. However, additional studies on both primary lung tumors and lung metastasis treated with SBRT reported higher rates of toxicity that varied according to lesion location[43,44]. Chest wall toxicity, which includes chest wall pain and rib fractures, is a known adverse effect of SBRT on peripheric lung lesions with a reported incidence between 8%-46%[43]. For centrally-located lesions, adverse events included respiratory, gastrointestinal and cardiac events[44]. A study by Modh *et al.* reported an 8% incidence of ≥ grade 3 adverse events, including two deaths, in 125 patients with central lesions treated with 45 Gy of SBRT[44]. Another important limitation of RT treatment for lung metastases is the radiation tolerance of surrounding tissues[9,36].

Multiple retrospective studies have shown encouraging results in patients with oligometastatic disease regarding local control and survival rates[34-41,45]. SBRT can achieve successful local control over multiple tumor locations, sizes, and tumor subtypes, but is less effective for sites of tumor recurrence or near a site of prior SBRT or metastasectomy[37]. In this section, we seek to review the outcomes of RT in STS oligometastatic disease in the most common metastatic sites.

Radiation therapy in lung metastases

Metastasectomy has been the local treatment of choice for lung metastasis in the absence of disseminated extrapulmonary disease. However, it is associated with significant morbidity and mortality, and relapse occurs in around 80% of patients after metastasectomy[46,47]. In this setting, SBRT can provide an additional method of achieving effective local control of the metastatic site[41].

Retrospective studies assessing the outcomes in patients with pulmonary metastases from STS have reported 2-year local control rates between 86 and 88% and a 2-year overall survival ranging from 43% to 96% in patients receiving SBRT[37-39,41]. In all studies, mean overall survival remained below 30 months[37,39,41,48]. Similar radiation doses (50-54 Gy) and fractionation schemes (3-5 fractions) were employed by the studies, indicating consistency in treatment strategies. However, one retrospective study of 16 patients by Loi *et al.* did report a four-year overall survival of 54% and a median overall survival of 5.75 years[35]. The superior outcomes of this study reflect a possible selection bias as only patients with oligometastatic disease and controlled primary tumors were included. In comparison, most other studies included all patients with lung metastasis irrespective of control of the primary tumor or extrapulmonary metastasis. The true effect of SBRT remains unknown because most of the patients undergo surgery before RT and those that do not usually have more advanced disease or comorbidities that worsen prognosis, resulting in selection bias.

In patients undergoing RT, it is important to identify factors associated with poor treatment response and worse prognosis. Loi *et al.* found that a disease-free interval < 24 months from initial diagnosis to first metastasis was the only predictor of reduced local control, disease-free survival, and overall survival[35]. This might be explained by an inverse relationship between time from initial diagnosis and the duration of the scattering phase of malignant cells from the primary tumor[45,49]. No additional data on prognostic factors for success or failure of SBRT in oligometastatic STS is available, if not resulting from surgical studies.

Radiation therapy in spine metastases

Spine metastases in STS are rare, and published studies about therapeutic approaches towards spinal cord or root involvement are limited to case reports or small case series[40,45,50,51]. Surgical management offers the best option for local control, but its feasibility is limited mainly because of the anatomical location of the lesion and limited marginal or wide resections[40,50]. RT also presents limitations given the radiosensitivity of the spine. Oncologic emergencies like spinal cord compression are difficult to manage because patients are usually not good surgical candidates, and chemotherapy is usually not useful because of chemoresistance or previous exposure. RT can only be used with low doses that are far below the required doses for eradication and are usually indicated only as palliative management[50].

SBRT, however, allows larger effective doses of radiation to be delivered to spinal tumors without radiation injury. Thames *et al.* described that sarcomas may have a lower alpha/beta ratio, making hypofractionated RT probably a more effective option[52]. Chang *et al.* report a series with a median survival of 21 months and a local progression-free survival of 20 months[40]. Less favorable results were reported by Merismky *et al.*, with improvement in pain and performance in 14 out of 23 cases and a lower median survival of 5 months[50]. Based on these results, hypofractionation radiation delivery obtains better local control and survival in metastatic spinal sarcomas than conventional RT[40].

Radiation therapy in brain metastases

Brain metastases in STS are uncommon, frequently preceded by lung metastasis, and their incidence is not precisely known[6,53]. There is no consensus regarding the management of brain metastases and a multidisciplinary approach is required. Gonzalez *et al.* conducted a SEER population-based cohort study and reported that surgical resection with or without adjuvant RT represented the most frequent treatment with no statistically significant difference in the overall use of RT[6]. Patients with all known lesions surgically removed tend to live longer[54].

SBRT is usually applied in cases of sarcoma brain metastasis alone or in combination with whole-brain RT. Increasing the amount of radiation in a single fraction appears to increase efficacy[53]. When SBRT is combined with whole-brain radiation (WBRT), the local control is improved because of the cumulative dosage delivered. The 1-year survival rate was not significant, with 38.5% in the WBRT + SBRT and 28.4% ($P = 0.42$). The 12-month brain tumor recurrence rate was significant, with 46.8% in WBRT + SBRT and 76.4% in SBRT alone ($P < 0.001$). Salvage brain treatment was also significantly more frequently required in the WBRT + SBRT versus SRS group ($P < 0.001$). Whole brain radiation is commonly added to SBRT when there are a greater number of lesions and when they are over 2 cm in size[55].

INTERVENTIONAL RADIOLOGY

Image-guided interventional therapies are increasingly becoming more popular in metastatic STS. Procedures like percutaneous thermal ablation (PTA) or arterial embolization may be used as alternatives or complements to surgery or RT in patients with oligometastatic disease[9]. Ablation aims to achieve the same goal as surgical resection, but instead of removing the tumor, it destroys the tumor cells *in situ*. Despite destroying most of the tumor, remnants of antigens remain. This feature of ablation can stimulate a systemic antitumor immune response that surgical resection cannot. While ablation therapies alone can elicit immune responses, they are often not potent enough to induce a strong antitumor response. Combining immunomodulators with traditional ablative techniques can augment the induced immune response, leading to systemic antitumor activity. Promising evidence suggests that this synergistic enhancement of the immune response can be effective[56].

PTA can be categorized as burning (radiofrequency, microwave, highly-intensity focused ultrasound) or freezing (cryoablation). PTA is a minimally invasive procedure that can be performed in an outpatient setting, has minimal complications, decreased morbidity, and reduced recovery time compared to surgery. This treatment strategy is usually reserved for patients who are not surgical candidates, refuse elective surgery or have failed other treatments.

While percutaneous image-guided cryoablation has limited evidence for managing STS, studies suggest it could benefit patients with recurrent or unresectable lesions for both curative and palliative treatment. The technique offers advantages such as intraprocedural monitoring for accuracy and the ability to target irregularly shaped lesions with multiple probes. However, it is important to maintain an adequate distance from the skin and neurovascular structures to avoid necrosis[57].

A case treated with cryoablation by one of the authors is displayed in Figure 2.

Radiofrequency ablation (RFA) is the most common ablation technique in metastatic STS, with reported one- and three-year overall survival of 92.2% and 65.2%[58]. A French multicenter trial in 213 patients with oligometastatic STS reported that local treatment, which included RFA in 16% of cases, resulted in a median overall survival of 45.3 months compared to 18.6 months in those without local treatment[59]. Although the study suggested improved outcomes with RFA, significant overlap with surgery for local control was present and did not allow for individually assessing the efficacy of RFA.

Arterial embolization is another interventional radiology treatment aimed at suppressing blood supply to the metastatic site, resulting in ischemia and tumor necrosis. Image-guided arterial embolization is primarily indicated for patients with unresectable sarcoma and isolated hepatic metastases or minimal extrahepatic disease. Rajan *et al.* reported a 40% three-year overall survival and a median survival of 13 months in patients with sarcomas metastatic to the liver after chemoembolization with cisplatin, doxorubicin, mitomycin-C, Ethiodol, and polyvinyl alcohol particles[60].

Magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) has shown promise in improving bone pain and quality of life in patients with disseminated disease and focal metastatic bone pain that is unresponsive to palliative radiotherapy[61,62]. While data regarding the management of bone metastasis in STS is limited, several studies suggest that MR-HIFU could be a valuable tool for the palliative management of STS oligometastatic disease[61-63].

SYSTEMIC TREATMENT AND TARGETED THERAPY

The efficacy of chemotherapy in oligometastatic STS remains controversial due to conflicting evidence. The high heterogeneity between STS subtypes and the low prevalence of this malignancy has limited the development of effective systemic therapies, and no major breakthroughs have occurred in the last 20 years. Furthermore, most treatment guidelines are biased in favor of the most common STS such as liposarcoma, leiomyosarcoma, and undifferentiated pleomorphic sarcoma[64].

In the 1970s, the treatment of sarcomas was based on the use of vincristine, actinomycin-D, and cyclophosphamide (VAC)[65]. Although the VAC regimen showed clinical responses as high as 23.5%, most studies that evaluated this clinical response were conducted in pediatric rhabdomyosarcoma. Still, in other types of STS, the clinical response was even lower[65]. Doxorubicin, an antitumor antibiotic, was introduced at the same time, with studies showing a response rate of 10%-25% among all STS types[66]. However, the response rate can be altered depending on the dose: 0% at 25 mg/m^2, 11% at 50 mg/m^2, 20% at 60 mg/m^2,

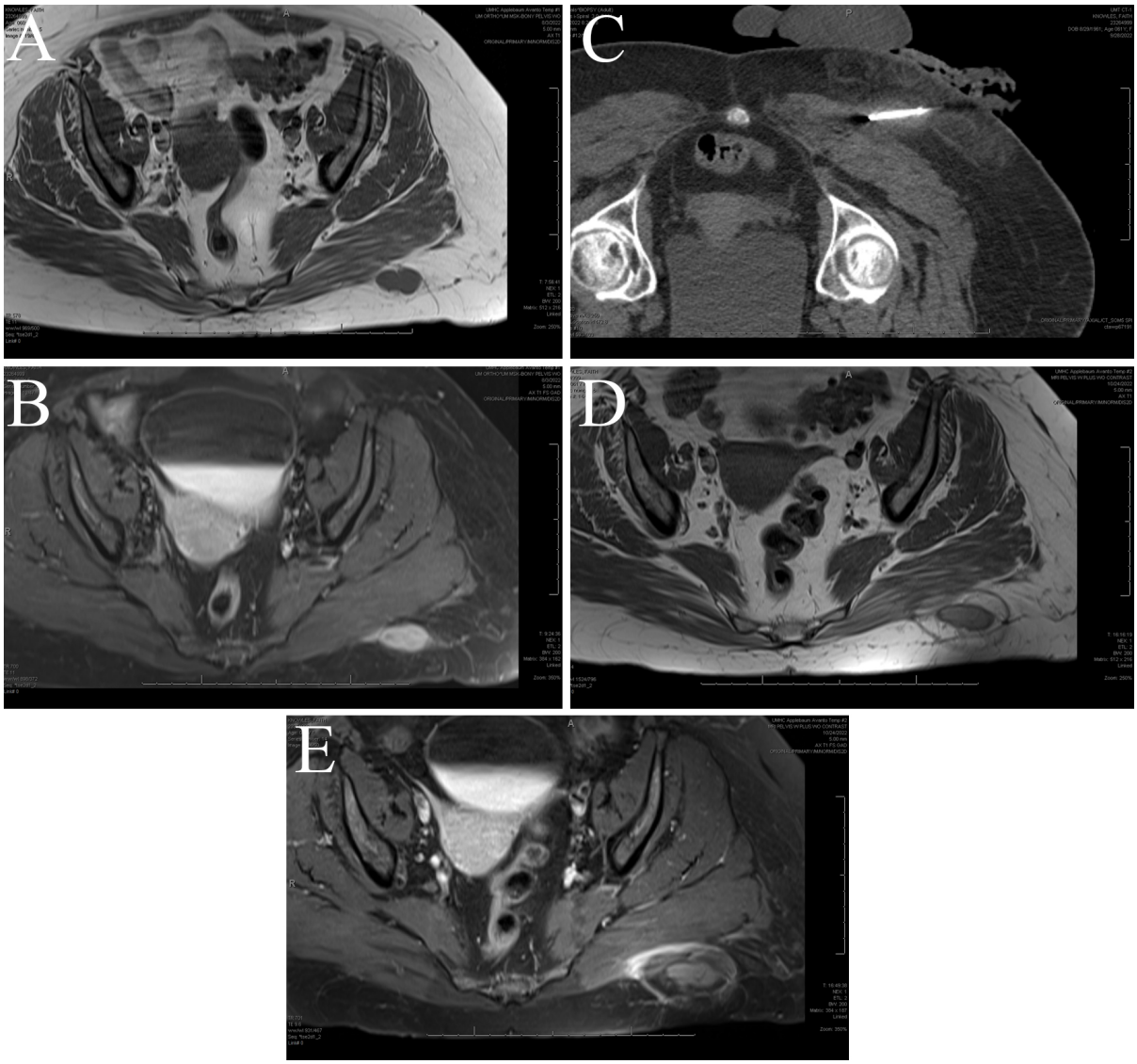

Figure 2. Seventy-year-old patient with a diagnosis of extraskeletal osteosarcoma of the right thigh. She underwent preoperative radiation and wide local excision. One year later, she developed a soft tissue mass within the subcutaneous gluteal area. This was a biopsy-proven metastatic lesion. Staging studies did not show additional metastatic disease. The decision was made to perform local control with cryoablation. The mass can be seen on (A) T1 and (B) post-contrast imaging prior to cryoablation. Cryoablation was successful (C), and the post-cryoablation results can be seen on (D) T1 and (E) post-contrast imaging. At six months post-procedure, the patient is disease free.

and 37% at 75 mg/m^2[67]. Modern studies target 75 mg/m^2 of doxorubicin as an adequate dose[68], with higher doses being barely used due to the risk of toxicity and marginal benefits. Currently, doxorubicin is considered the most effective agent and is consistently used in the treatment of STS.

A study made by the European Cooperative Oncology Group (ECOG) compared doxorubicin to doxorubicin plus ifosfamide[69]. The combination regimen showed a response rate of 34%, compared to 20% in the group receiving doxorubicin (P = 0.03). However, the use of combination chemotherapy had considerably more myelosuppression and no improvement in overall survival[69]. It is important to note that this study was done prior to the availability of hematopoietic growth factors. Both treatments were again compared in a phase 3 randomized controlled trial (RCT). Combination therapy, doxorubicin (75 mg/m^2)

plus ifosfamide (10 g/m^2), was compared with single-agent doxorubicin (75 mg/m^2); both groups received growth factor support[70]. The trial reported no significant difference (P = 0.075) in overall median survival between the combination group (14.4 months) and the doxorubicin group (12.8 months). However, statistically superior median progression-free survival and overall response were found in the combination group[70]. Due to the lack of a clear survival benefit, the authors concluded that the addition of ifosfamide should be kept for patients in whom tumor shrinkage is specifically desired[71].

Systemic treatment by histology

In addition to providing an overview of systemic treatment in oligometastatic disease, we consider it important to review some of the histopathologic STS with clearly defined chemotherapy regimens.

(a) Liposarcoma

Anthracycline-based chemotherapy is used as a first-line treatment for advanced-stage or metastatic liposarcoma. Subgroup analysis of a phase 3 RCT in advanced STS showed that liposarcoma had a stronger tumor response to chemotherapy than other subtypes[72]. Additional studies have reinforced the efficacy of doxorubicin-based therapy, especially in patients with myxoid liposarcoma and round cell liposarcoma[71].

(b) Leiomyosarcoma

Doxorubicin is the drug of choice in non-uterine leiomyosarcoma. The use of ifosfamide is usually held as a second-line treatment because of its worse toxic profile. Other second-line regimens include gemcitabine + docetaxel, and trabectedin.

In uterine cases, gemcitabine plus docetaxel has shown to be the most helpful treatment and should be used as the first line. Second-line options include doxorubicin, trabectedin, or temozolomide[73].

(c) Synovial sarcoma

Synovial sarcoma is acknowledged as one of the most chemo-sensitive subtypes of STS and is particularly sensitive to alkylating agents. Combination of doxorubicin plus ifosfamide is highly recommended for these cases. Furthermore, some patients with synovial sarcoma appear to benefit from trabectedin[74].

(d) Epithelioid sarcoma

Although rare, this type of cancer is highly aggressive. A recent international phase 2 study demonstrated the potential of Tazemetostat in treating individuals with advanced epithelioid sarcoma that had a deletion of INI1/SMARCB1[75]. Moreover, Tazemostat showed a good safety profile, with the most common side effects being fatigue, nausea, and decreased appetite.

Targeted therapy

Targeted therapies have revolutionized the current treatment of specific STS histologies, offering great treatment response with a much better adverse events profile than standard chemotherapy. Since the 2000s, multitarget tyrosine kinase inhibitors have become available and serve as a powerful complement to cytotoxic therapy. Pazopanib, a VEGF receptor inhibitor, has been approved for the treatment of non-adipocytic STS[71]. In a phase 3 RCT, pazopanib showed significant improvement in progression-free survival in non-adipocytic STS; however, overall survival was not different between treatments[76]. Other

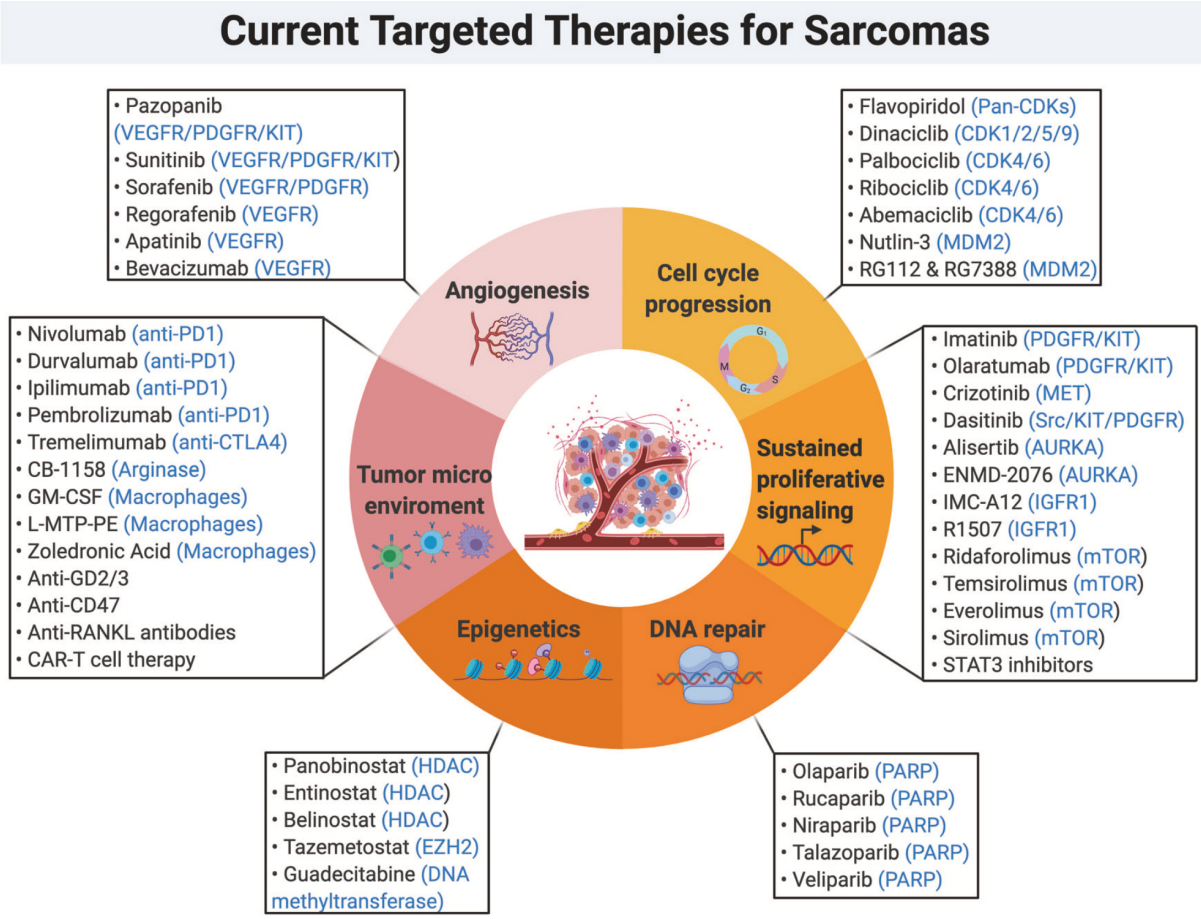

Figure 3. Current targeted therapies for soft tissue sarcomas and their associated pathways. Displayed with permission from Damerell *et al.*[85].

target therapies are useful in certain STS histologic subtypes. In patients with dermatofibrosarcoma protuberans (t17;22), imatinib has shown clinical benefit[77]. Other potential effective targeted therapies include crizotinib in inflammatory myofibroblastic tumors[78] and cediranib and sunitinib in alveolar soft part sarcoma[79]. One of the greatest success stories of targeted therapy in STS is GIST, where imatinib and sunitinib have shown high rates of treatment response and disease remission[80]. In the setting of metastatic disease by GIST, approximately one-third of patients can achieve disease control for 5 years after treatment with tyrosine-kinase inhibitors[81]. Another promising targeted therapy is larotrectinib, which inhibits TrkA, TrkB, and TrkC. Recent phase 1 and 2 clinical trials investigating the efficacy of larotrectinib in fusion-positive cancers found that 55% of patients responded to treatment, and those who received treatment remained free of progression after one year with no significant adverse events reported[82]. Additionally, a recent case report reported the successful use of larotrectinib in treating an NTRK fusion cervical sarcoma, resulting in no evidence of disease at imaging after 15 months of treatment[83] Larotrectinib has also shown effectiveness in treating NTRK-rearranged spindle cell neoplasms[84]. Although an in-depth review of currently available targeted therapy drugs goes beyond the scope of this article, we consider that a summary of available drugs and the molecular pathways involved might be helpful to the reader [Figure 3].

CONCLUSIONS

Oligometastatic STS is an increasingly recognized tumor presentation with an opportunity to achieve long-term tumor control. A multidisciplinary approach combining surgery, radiation therapy, and systemic treatment is usually employed. Lung metastasectomy through either thoracotomy or Video-Assisted Thoracic Surgery (VATS) yields excellent results in patients with oligometastatic disease. Successful results in sites other than the lungs, such as the liver, have also been described. Radiation therapy is an effective (neo)-adjuvant treatment and has a role in both local control and palliation. However, its efficacy in the absence of surgery has not yet been proven. Systemic treatment, widely employed as adjuvant therapy in metastatic STS, has limited efficacy due to high tumor heterogeneity.

In the setting of a rare family of tumors such as STS, future studies should focus on improving the diagnostic and treatment guidelines for oligometastatic STS. Oligometastatic disease in STS still lacks clear boundaries, and treatment is extremely heterogeneous. Therefore, studies should now focus on approaching oligometastatic STS with a standard treatment that can later be implemented on a wider scale. Although the development of new drugs for STS remains elusive, recent successes such as the Alliance A091401 have shown that trials can be completed in a time-efficient manner. Open-label trials such as the Alliance study can therefore streamline the assessment of the efficacy of newer drugs in a rare disease such as STS.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study and was involved in manuscript writing: Gonzalez MR, Inchaustegui ML, Ruiz-Arellanos K, de Souza FF, Subhawong TK, Pretell-Mazzini J

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All authors declared that there are no conflicts of interest.

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Not applicable.

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