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ORIGINAL RESEARCH

# Feasibility and Tolerability of Arterial Infusion Chemotherapy and Embolization for Recurrent/Metastatic Soft Tissue Sarcoma: A Retrospective Exploratory Study

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**Objective:** This study aimed to evaluate the feasibility and tolerability of arterial infusion chemotherapy embolization (AICE) in treating recurrent/metastatic soft tissue sarcoma (STS) and to explore relevant prognostic factors to tailor future individualized treatment.

**Methods:** A total of 113 patients with recurrent/metastatic STS treated with AICE at the Fifth Medical Center of the PLA General Hospital were included in this retrospective study. The primary outcomes were progression-free survival (PFS) and overall survival (OS). Kaplan–Meier survival curves were adopted and univariate and multivariate analyses were conducted using the Cox proportional hazards model to evaluate prognostic factors. Treatment-related adverse events (TRAEs) were graded according to the Society of Interventional Radiology (SIR) standards.

**Results:** Among the 113 patients, the median OS was 19.0 months (95% CI: 12.8–25.3) with 2-year OS rates of 45.1%. The median PFS was 11.0 months (95% CI: 8.6–13.4) with 2-year PFS rates of 25.7%. Objective response rate (ORR) was 37.2% (95% CI: 28.3%–46.8%) and disease control rate (DCR) was 76.1% (95% CI: 67.1%–83.6%). Univariate analysis revealed that tumor size, presence of distant metastasis, number of postoperative treatment regimens, pathological differentiation and neutrophil-to-lymphocyte ratio (NLR) were significantly associated with OS and PFS ($P<0.05$). Multivariate Cox analysis confirmed that tumor size, distant metastasis, number of postoperative treatment regimens, pathological differentiation and short-term efficacy were independent prognostic factors for OS ($P<0.05$). The most common TRAEs were pain (23.0%), transient bone marrow suppression (15.0%) and postoperative fever (6.2%). No severe or fatal adverse reactions and treatment-related mortalities were observed, demonstrating superior tolerability.

**Conclusion:** AICE might be a feasible and well-tolerated treatment for recurrent/metastatic STS, effectively controlling disease progression and improving survival outcomes in this retrospective cohort. Further multicenter, large-scale prospective studies were needed to validate these findings and explore the combination of AICE with immunotherapy or targeted therapy to optimize treatment strategy for STS.

**Keywords:** soft tissue sarcoma, arterial infusion chemotherapy embolization, efficacy, safety, prognosis

## Introduction

Soft tissue sarcoma (STS) represents a heterogeneous group of malignancies arising from mesenchymal tissues, comprising over 100 distinct subtypes and accounting for less than 1% of adult cancers.[1] Its low incidence and high heterogeneity make diagnosis and treatment particularly challenging.[2] According to the American Cancer Society, approximately 13,400 new STS cases and 5,140 deaths were estimated in 2023, representing about 0.8% of tumor-related deaths.[3] Although the overall incidence of STS is

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low, the diverse histological subtypes (eg, liposarcoma, leiomyosarcoma, and undifferentiated pleomorphic sarcoma) and broad biological behaviors significantly compromises patient prognosis.[4] Surgical resection with negative margins is the mainstay for localized STS and may cure considerable early-stage patients.[5] However, even with optimal surgery (often combined with radiotherapy), local recurrences occur in up to ~40–50% of cases and distant metastases develop in ~30%, contributing to worse long-term survival. Once metastases occur, 5-year survival drops below 20% in most series.[6,7]

For advanced or unresectable STS, systemic chemotherapy has been the standard first-line treatment for decades. An anthracycline-based regimen (usually doxorubicin ± ifosfamide) is the conventional therapy across most adult subtypes.[8] Unfortunately, the objective response rate (ORR) is only 20%–30%, and the median progression-free survival (PFS) is typically less than six months.[9] The historical median overall survival (OS) with first-line chemotherapy in metastatic STS is on the order of 12–18 months.[10] Nevertheless, improvements in outcomes have been modest, and no standard chemotherapy regimen has shown a clear OS advantage over doxorubicin in randomized trials. The limited efficacy of traditional chemotherapy highlights the need for novel therapeutic approaches.

In recent years, advances in targeted therapy and immunotherapy have opened new avenues for treating STS. Agents such as anti-angiogenic drugs (anlotinib) and immune checkpoint inhibitors (ICIs, pembrolizumab) have been applied to specific STS subtypes and demonstrates encouraging efficacy.[11] Single-agent pembrolizumab yields an overall 18% response rate in a pivotal Phase II trial (SARC028) that includes multiple STS subtypes. Notably, responses to ICIs varied by histology: in that study, 4 of 10 patients with undifferentiated pleomorphic sarcoma respond (40% ORR) while 0 of 10 with leiomyosarcoma respond.[12] Importantly, some subtype-specific breakthroughs have emerged. Alveolar soft part sarcoma (ASPS), a rare translocation-driven subtype, demonstrates exceptional responsiveness to ICIs. A phase II trial of the PD-L1 inhibitor atezolizumab reported a 37% ORR with prolonged disease control in advanced ASPS.[13] Despite these advances, most STS patients still fail to benefit substantially from immunotherapy or targeted agents – the overall impact on STS mortality is modest. Many common subtypes (eg, LMS, most liposarcomas) remain resistant to ICIs, and even responsive subtypes often required combination approaches for deeper and more durable responses. These findings lead to the concept of immunologically "hot" versus "cold" sarcomas and the potential for patient selection for immunotherapy. As a result, the effectiveness and long-term benefits of these emerging therapies remain limited in most cases, and more novel exploration is still needed.

Arterial Infusion Chemotherapy and Embolization (AICE) is a novel locoregional therapy that may address some limitations of systemic treatment. AICE involves the catheter-based delivery of high-dose chemotherapy directly into the arterial supply of the tumor, immediately followed by embolization of those tumor-feeding arteries. By confining cytotoxic drugs to the tumor's blood supply, AICE achieves markedly higher local drug concentrations than intravenous chemotherapy while potentially reducing systemic exposure and toxicity.[14] The embolization component induces ischemia in the tumor, causing tumor cell apoptosis and necrosis that can synergistically enhance the chemotherapeutic effect.[15] AICE has been successfully used in other malignancies – for example, hepatic arterial infusion chemotherapy with embolization is an established approach in hepatocellular carcinoma and liver metastases, known to boost tumor response when combined with systemic therapy.[16] In STS, isolated limb perfusion (a related technique delivering chemotherapy to an extremity with blood flow isolation) and intra-arterial chemo-infusion have shown high local response rates in locally advanced cases. However, research on the AICE application in STS is still in its early stages with promising results.[17] A recent systematic review indicated that intra-arterial chemotherapy with embolization might achieve high local control rates in recurrent or metastatic STS and even convert some inoperable tumors to resectable status.[18] Moreover, compared to other local treatments such as radiofrequency ablation and radiotherapy, AICE enables more precise drug delivery and profoundly impacts the tumor microenvironment, potentially synergizing with targeted drugs and immunotherapy.[19]

Despite incremental advances in systemic therapy, outcomes for advanced STS remained modest with typical median PFS of 4–6 months and limited response rates with standard regimens such as doxorubicin or targeted agents (eg, pazopanib).[20] Locoregional arterial therapies (eg, transarterial chemoembolization/embolization) had shown feasibility in small retrospective series, but contemporary data in STS—particularly regarding combined arterial infusion chemotherapy with embolization (AICE), safety, and patient selection—were scarce. We therefore conducted a retrospective exploratory study to characterize the feasibility, tolerability, and clinical outcomes of AICE in recurrent/metastatic STS in a real-world cohort. We also analyzed patient and disease factors for associations with outcomes, aiming to identify prognostic indicators that might guide patient selection and combination strategies. We hypothesized that AICE might be well tolerated and provide

meaningful disease control in advanced STS and that certain factors (like tumor burden and use of multimodal therapy) might influence survival. This study might provide insights into the role of AICE in the modern management of STS and lay the groundwork for future prospective trials combining AICE with novel systemic treatments.

# Materials and Methods

## Study Design and Inclusion Criteria

This study was designed as a single-center retrospective analysis, collecting clinical data from 113 patients with recurrent or metastatic STS who underwent AICE treatment at the Fifth Medical Center of the General Hospital of the Chinese PLA between November 2011 and April 2020. The aim of this study was to evaluate the efficacy and safety of AICE and to explore related prognostic factors. Inclusion criteria were as follows: (1) Age ≥3 years, no gender restriction; (2) histologically confirmed STS or a radiologically diagnosed unresectable tumor highly suspicious for STS in a patient with prior histopathology, with all pathological types meeting the criteria of the 2013 WHO classification of STS; (3) At least one AICE treatment in clinical practice; (4) ECOG performance status ≤3 scores; (5) Expected survival time ≥3 months; (6) Complete follow-up and clinical data. Exclusion criteria included: (1) Severe bleeding tendency, platelet count $<50\times10^9$/L, or uncorrectable coagulation dysfunction; (2) Inability to maintain the required surgical position; (3) Worse general condition (eg, extensive metastases, severe infection, high fever), cachexia, significant organ dysfunction, severe anemia, or metabolic disorders that could not be improved in the short term; (4) Extensive metastases or expected survival time <3 months. As illustrated in Figure 1, a total of 113 adult patients met these criteria and were included in the study ultimately.

This study was reviewed and approved by ethics committee of the Fifth Medical Center of PLA General Hospital. Due to the retrospective design, informed consent was waived for patients. The entire study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

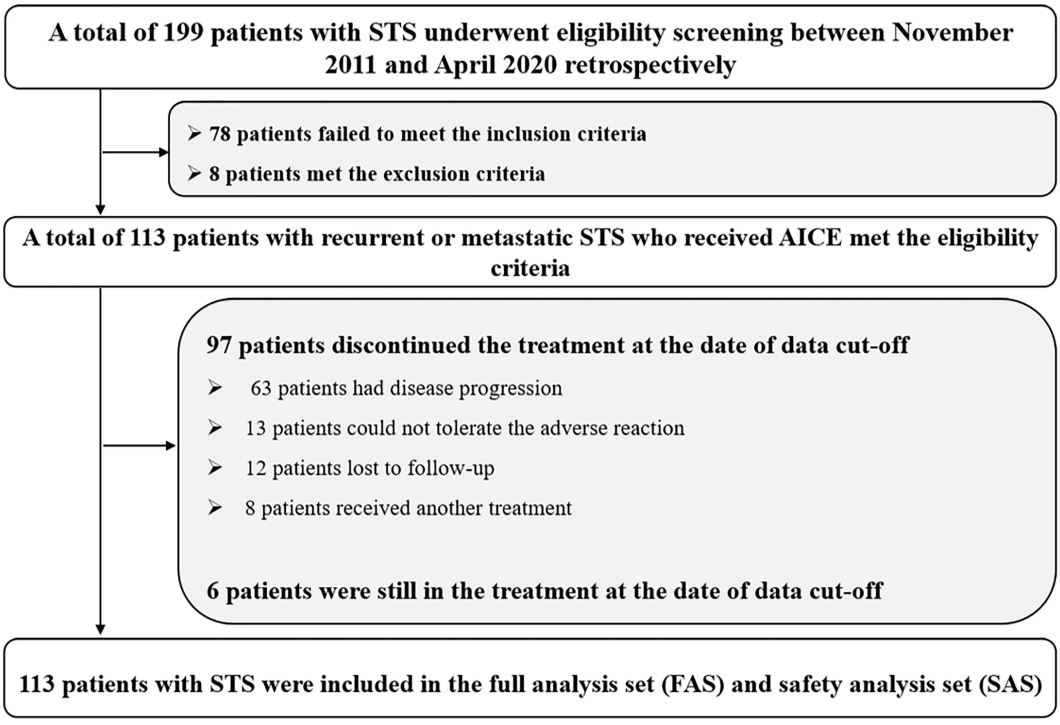


**Figure 1** Flowchart of this retrospective exploratory study regarding arterial infusion chemotherapy and embolization (AICE) for recurrent/metastatic soft tissue sarcoma.


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## AICE Treatment Procedure

Before treatment, all patients underwent imaging examinations (such as CT, MRI, or PET-CT) to confirm the size, location, and metastasis status of the tumor. Laboratory tests, including complete blood counts, liver and kidney function, and coagulation function, were performed to evaluate baseline conditions and treatment tolerance.

AICE was performed by an experienced interventional radiologist under fluoroscopic guidance. Using the modified Seldinger technique, the femoral artery was punctured, and the catheter tip was selectively placed at the proximal end of the tumor-feeding artery. Angiography was performed to confirm the catheter position and assess tumor blood supply. For the embolization decision: tumors with robust vascularity (identified via imaging or angiography) underwent arterial infusion plus embolization; those with limited blood supply received intra-arterial chemotherapy infusion alone. If the tumor had rich blood supply, interventional embolization was performed: a microcatheter was super-selected to the tumor-feeding artery, and lipiodol or microsphere embolization was injected until stasis occurred. The choice of chemotherapy regimen (cisplatin and epirubicin) was individualized based on tumor histology, prior treatments and organ function. The catheter was then left in place for arterial chemotherapy infusion (cisplatin: 70–80 mg/m², continuous arterial infusion for 4 hours; epirubicin: 50–70 mg/m², intravenously administered on days 3 and 4), every 3–4 weeks were deemed as one therapeutic cycle. Standard cisplatin dosage was 70–80 mg/m²; dose adjustments were made (eg, reduction to 50–70 mg/m²) in cases of baseline renal insufficiency (creatinine clearance <60 mL/min) or prior nephrotoxicity. If the tumor had worse blood supply, catheter infusion chemotherapy alone was performed using the same protocol directly. The intent was either cytoreduction (to facilitate subsequent surgery or radiotherapy) or palliative tumor control for metastases. The rationale for this combined approach was three-fold: First, intra-arterial administration delivered high concentrations of chemotherapeutic agents directly to tumor feeding arteries, which might enhance locoregional cytotoxic effect and potentially improve tumor shrinkage while limiting systemic exposure. Second, intravenous chemotherapy ensured systemic exposure to address micro-metastatic disease, undetectable by imaging, which arterial infusion alone could not target. Third, prior clinical studies in multiple solid tumors demonstrated enhanced response rates and improved outcomes using combined intra-arterial and intravenous chemotherapy with acceptable safety profiles,[21] supporting this dual route as a therapeutic strategy.

After the procedure, patients received vital sign monitoring and pain management. Analgesics, antibiotics and supportive care were administered as needed clinically. Postoperative imaging was performed regularly to evaluate therapeutic effects.

## Evaluation of Efficacy and Safety

Primary outcomes of this study included OS, defined as the time from the first AICE treatment to death, and PFS, defined as the time from the first AICE treatment to disease progression or death.[22] Tumor response was evaluated radiologically by cross-sectional imaging (CT or MRI) after every 1–2 cycles of AICE and at regular intervals during follow-up. Secondary outcomes included radiological response, evaluated using RECIST 1.1 criteria and categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). ORR was defined as the proportion of CR and PR among the total population. Disease control rate (DCR) was defined as the proportion of CR, PR, and SD among the total population.[23]

Treatment-related adverse events (TRAEs) were assessed at each AICE session and during follow-up, which was evaluated followed the Society of Interventional Radiology (SIR) classification system for complications, categorized into six levels: A: No treatment required, no adverse consequences; B: Simple treatment required, observation without adverse consequences; C: Necessary hospitalization, short duration (≤48 h); D: Major treatment, increased care level, prolonged hospitalization (>48 h); E: Permanent sequelae; F: Death.[24] Incidence of TRAEs per procedure and per patient was reported, including both procedure-related complications (eg, catheter-related issues and bleeding) and systemic effects of chemotherapy (hematologic or non-hematologic toxicity). Any post-AICE hospitalizations or delays in subsequent therapy due to TRAEs were also recorded.

## Follow-Up

All patients were included in a standardized follow-up protocol, with evaluations conducted every three months until death or the end of the study. Follow-up assessments included detailed imaging examinations (CT or MRI) to monitor

tumor size changes and recurrence or metastasis, laboratory tests (complete blood count, liver and kidney function, and tumor markers) to evaluate systemic condition post-treatment, and survival status recording (eg, survival time, disease progression, and adverse events). At the conclusion of the study, survival status was confirmed through telephone, outpatient visits, or inpatient records. The data cutoff date for this study was November 15, 2023, with a median follow-up duration of 23.5 months (range: 1.0–112.5 months).

## Statistical Analysis

Data analysis was performed using SPSS 25.0 software. Continuous variables were expressed as mean ± standard deviation (x±s), and comparisons between groups were conducted using *t*-tests. Categorical data were compared using the $\chi^2$-test. Survival analysis was performed using the Kaplan–Meier method to generate survival curves using Stata 14, with the Log rank test used to compare survival differences between groups, and median values with 95% confidence intervals (CI) were reported. Variables with statistical significance in univariate analysis were included in multivariate analysis using the Cox proportional hazards model. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated to assess the independent predictive value of each variable for OS and PFS. For subgroup comparisons of categorical variables, chi-square or Fisher's exact test was used, while t-tests or Mann–Whitney *U*-tests were employed for continuous variables. $P<0.05$ was considered statistically significant.

# Results

## Baseline Characteristics

This study included 113 patients with recurrent or metastatic STS and baseline characteristics were shown in Table 1, of whom 68 (60.2%) were male and 45 (39.8%) were female. The median age was 35 years (range: 3–83 years). The primary tumor locations were abdominal cavity (33.6%), limbs and hips (29.2%), pelvic cavity (20.4%), pleural cavity (9.7%), and head and neck (7.1%). The median maximum tumor diameter was 10.7cm (range: 1.5–25.3cm), with 58 patients (51.3%) having tumors ≥10 cm. At baseline, 94 patients (83.2%) had distant metastasis. Pathological grading showed that 5 patients (4.4%) were G1, 49 (43.4%) were G2, and 59 (52.2%) were G3. Clinical staging revealed that 11 patients (9.7%) were at

**Table 1** Baseline Characteristics of the 113 Patients with Recurrent/Metastatic Soft Tissue Sarcoma

| Baseline Characteristics | Total (N=113) | Percentage |
|---|---|---|
| **Age (year)** | | |
| ≤35 | 37 | 32.7% |
| >35 | 76 | 67.3% |
| **ECOG performance status score** | | |
| 0-1 | 4 | 3.7% |
| 2-3 | 109 | 96.3% |
| **Gender** | | |
| Male | 68 | 60.2% |
| Female | 45 | 39.8% |
| **Tumor location** | | |
| Head and neck | 8 | 7.1% |
| Pleural cavity | 11 | 9.7% |
| Abdominal cavity | 38 | 33.6% |
| Pelvic cavity | 23 | 20.4% |
| Limbs and hips | 33 | 29.2% |
| **Maximum diameter (cm)** | 10.7 (1.5–25.3) | |
| <10 | 55 | 48.7% |
| ≥10 | 58 | 51.3% |

(*Continued*)


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**Table 1** (Continued).

| Baseline Characteristics | Total (N=113) | Percentage |
|---|---|---|
| **Distant metastasis** | | |
| No | 19 | 16.8% |
| Yes | 94 | 83.2% |
| **Pathological grade** | | |
| G1 | 5 | 4.4% |
| G2 | 49 | 43.4% |
| G3 | 59 | 52.2% |
| **Stage** | | |
| III | 11 | 9.7% |
| IV | 102 | 90.3% |
| **NLR** | | |
| ≤3 | 57 | 50.4% |
| >3 | 56 | 49.6% |
| **mGPS** | | |
| 0-1 | 78 | 69.0% |
| 2 | 35 | 31.0% |
| **Therapy[#]** | | |
| Infusion | 32 | 28.3% |
| Infusion + embolization | 81 | 71.7% |
| **Lines of previous systemic treatment** | | |
| **0** | 19 | 16.8% |
| **≥1** | 94 | 83.2% |
| **Treatment cycles** | | |
| 1 | 62 | 54.9% |
| ≥2 | 51 | 45.1% |

**Notes**: [#]Infusion=intra-arterial chemotherapy without embolization; Infusion + embolization =intra-arterial chemotherapy with arterial embolization (lipiodol or microsphere embolization).

stage III, while 102 patients (90.3%) were at stage IV. The neutrophil-to-lymphocyte ratio (NLR) was ≤3 in 57 patients (50.4%) and >3 in 56 patients (49.6%). Modified glasgow prognostic score (mGPS) was 0–1 in 78 patients (69.0%) and 2 in 35 patients (31.0%). Thirty-two patients (28.3%) received infusion therapy, while 81 patients (71.7%) underwent combined embolization. Regarding treatment cycles, 62 patients (54.9%) received 1 cycle, and 51 patients (45.1%) received ≥2 cycles.

Of the 113 patients included, 51 (45.1%) patients received the subsequent treatments, 17 (15.1%) patients failed to receive further therapy, and 45 (39.8%) patients were not available for this information. Among those who received subsequent treatment (n=51): 23 (20.4%) patients received systemic chemotherapy, 13 (11.5%) patients were treated with targeted drugs, 9 (8.0%) patients received immunotherapy, and 6 (5.3%) patients used traditional Chinese medicine.

## Pathological Subtypes

As shown in Table 2, the pathological subtype distribution showed that 17 patients (15.0%) had liposarcoma, 14 (12.4%) had leiomyosarcoma, 10 (8.9%) had malignant fibrous histiocytoma, 9 (8.0%) had fibrosarcoma, 8 (7.1%) had interstitialoma, and 8 (7.1%) had rhabdomyosarcoma. Additionally, there were 7 cases (6.2%) of synovial sarcoma, 5 (4.4%) of aggressive fibromatosis, 4 (3.5%) of myofibroblastoma, 4 (3.5%) of PNET, 4 (3.5%) of ASPS, 4 (3.5%) of undifferentiated sarcoma, and 4 (3.5%) of malignant neurinoma. Other subtypes included SFT (3 cases, 2.7%), hemangiosarcoma (3 cases, 2.7%), spindle cell sarcoma (3 cases, 2.7%), epithelioid sarcoma (2 cases, 1.8%) and others (5 cases, 4.4%).

## Survival Outcomes

As shown in Figure 2, the median PFS of the 113 patients with STS underwent AICE treatment was 11.0 months (95% CI: 8.6–13.4) with 1-year and 2-year PFS rates of 45.1% (95% CI: 35.8%–54.0%) and 25.7% (95% CI: 18.0%–34.0%), respectively.

**Table 2** Pathological Subtypes of the 113 Patients with Recurrent/Metastatic Soft Tissue Sarcoma

| Pathological Type | Number (n, %) | Pathological Type | Number (n, %) |
|---|---|---|---|
| Liposarcoma | 17 (15.0) | PNET | 4 (3.5) |
| Leiomyosarcoma | 14 (12.4) | ASPS | 4 (3.5) |
| Malignant fibrous histiocytoma | 10 (8.9) | Undifferentiated sarcoma | 4 (3.5) |
| Fibrosarcoma | 9 (8.0) | Malignant neurinoma | 4 (3.5) |
| Interstitialoma | 8 (7.1) | SFT | 3 (2.7) |
| Rhabdomyosarcoma | 8 (7.1) | Hemangiosarcoma | 3 (2.7) |
| Synovial sarcoma | 7 (6.2) | Spindle cell sarcoma | 3 (2.7) |
| Aggressive fibromatosis | 5 (4.4) | Epithelioid sarcoma | 2 (1.8) |
| Myofibroblastoma | 4 (3.5) | Others | 5 (4.4) |

Furthermore, as exhibited in Figure 3, the median OS for the entire 113-subject cohort was 19.0 months (95% CI: 12.8–25.3) with 2-year and 3-year OS rates of 45.1% (95% CI: 35.8%–54.0%) and 41.7% (95% CI: 19.6%–35.9%), respectively.

Further subgroup analysis showed that patients with tumors ≥10 cm had a median OS of 15.0 months (95% CI: 12.0–18.0), significantly shorter than 27.0 months (95% CI: 22.4–31.6) for those with tumors <10cm ($P$=0.006) (Table S1). PFS was also shorter in the ≥10cm group (9.0 months, 95% CI: 7.1–10.8) compared to the ≤10cm group (16.0 months, 95% CI: 11.9–20.1, $P$=0.011) (Table S2). Patients with distant metastasis had a median OS of 16.0 months (95% CI: 13.7–18.7), while those without metastasis had 39.0 months (95% CI: 6.3–71.7, $P$<0.001). The PFS in the metastatic group was 9.5 months (95% CI: 7.7–11.3), compared to 23.0 months (95% CI: 11.7–34.3) in the non-metastatic group ($P$=0.001). Patients who received ≥2 postoperative therapy had a median OS of 27.0 months (95% CI: 23.3–30.8), significantly longer than 13.0 months (95% CI: 10.9–15.1) in those receiving 0–1 postoperative therapy ($P$<0.001). The PFS also showed a similar trend: 11.0 months (95% CI: 13.7–20.3) for the ≥2 postoperative therapy and 7.0 months (95% CI: 6.6–7.4) for the 0–1 postoperative therapy group ($P$<0.001). Additionally, pathological grade, stage, treatment cycles and short-term efficacy were also positive characteristics associated with both OS and PFS in univariate analysis (P<0.05) (supplementary materials, Tables S1 and S2).

Consequently, these above factors were included in the Multivariate Cox regression analysis, which identified several independent prognostic factors significantly associated with OS in patients undergoing AICE for recurrent or metastatic STS as shown in Table 3. Tumor size greater than 10 cm was associated with significantly worse OS compared to tumors

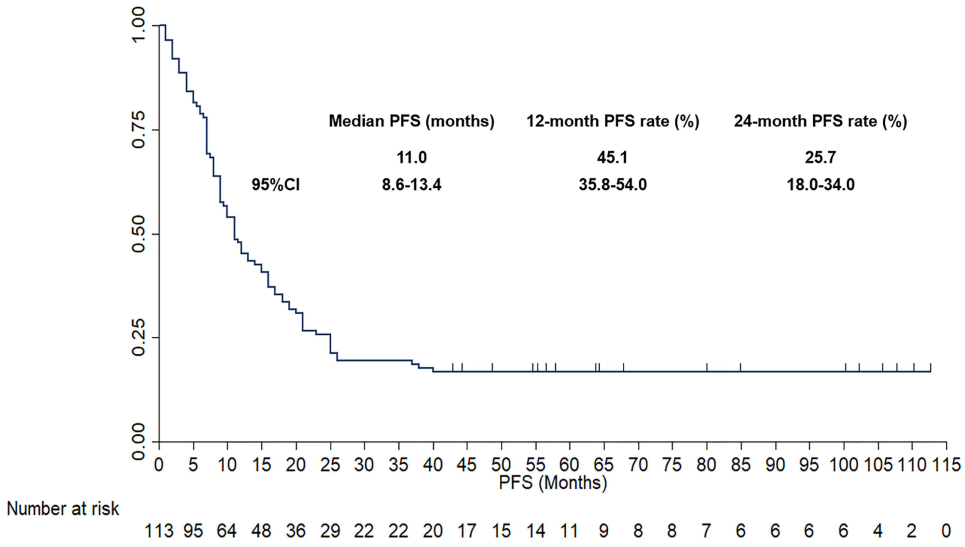


**Figure 2** Kaplan-Meier curve of progression free survival of the 113 patients with recurrent/metastatic soft tissue sarcoma.


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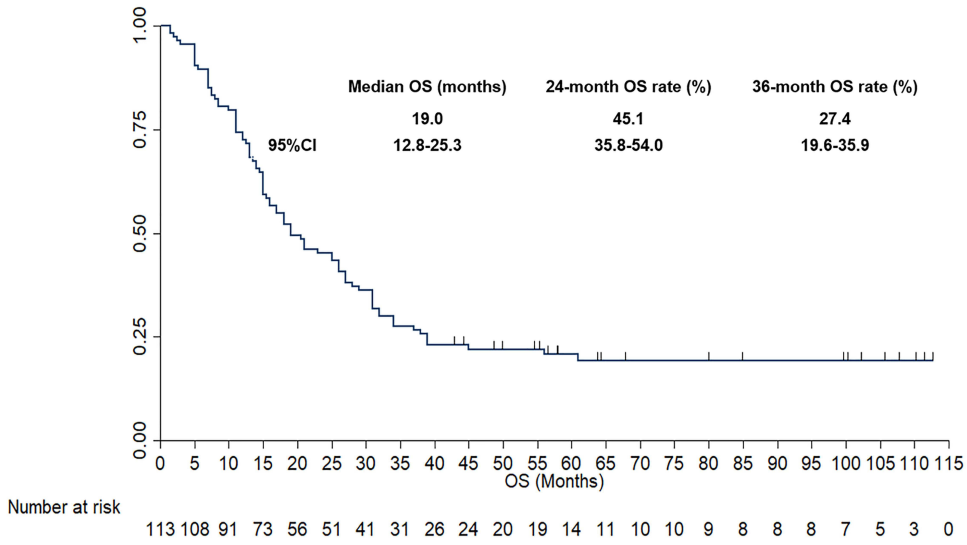


**Figure 3** Kaplan-Meier curve of overall survival of the 113 patients with recurrent/metastatic soft tissue sarcoma.

≤10 cm (HR = 1.7; 95% CI: 1.1–2.7; *P*=0.014). The presence of distant metastasis at baseline was the strongest adverse prognostic factor, conferring a 4.4-fold higher risk of death (HR=4.4; 95% CI: 2.3–8.7; *P*<0.001). Patients who received fewer treatment modalities (0–1 vs ≥2) also had significantly inferior survival (HR=2.3; 95% CI: 1.4–3.6; *P*=0.001), emphasizing the survival benefit of multimodal therapy. Higher pathological grade (G3 vs G1+G2) was independently predictive of shorter OS (HR=1.6; 95% CI: 1.0–2.6; *P*=0.043), as was advanced clinical stage (IV vs III), which was associated with a twofold increase in mortality risk (HR=2.1; 95% CI: 1.3–3.2; *P*=0.005). Additionally, short-term efficacy was an independent predictor: patients who failed to achieve PR after AICE had significantly worse survival outcomes compared to responders (HR=1.7; 95% CI: 1.0–2.8; *P*=0.049). In contrast, the number of AICE treatment cycles (1 vs ≥2) did not significantly affect OS in multivariate analysis (HR=1.3; 95% CI: 0.6–2.8; *P*=0.560).

Similarly, multivariate analysis for PFS identified several significant independent prognostic factors as shown in Table 4. A baseline NLR >3 was associated with a significantly higher risk of disease progression compared to NLR ≤3 (HR=1.6, 95% CI: 1.0–2.5, *P*=0.046). Tumor size >10cm remained an adverse factor, these patients exhibited a 1.7-fold increased risk of progression (HR=1.7, 95% CI: 1.1–2.6, *P*=0.013). Distant metastasis was still strongly predictive of worse PFS, associated with a threefold higher risk of progression (HR=3.1; 95% CI: 1.7–5.8, *P*<0.001). Similarly, limited

**Table 3** Multivariate Analysis of OS

| Characteristics | β | HR | 95% CI | *P* |
|---|---|---|---|---|
| Maximum diameter (cm)<br>>10 vs ≤10 | 0.551 | 1.7 | 1.1–2.7 | 0.014 |
| Distant metastasis<br>Yes vs no | 1.513 | 4.4 | 2.3–8.7 | <0.001 |
| Postoperative therapy<br>0–1 vs ≥2 | 0.823 | 2.3 | 1.4–3.6 | 0.001 |
| Pathological grade<br>G3 vs G1+G2 | 0.482 | 1.6 | 1.0–2.6 | 0.043 |
| Stage<br>IV vs III | 0.73 | 2.1 | 1.3–3.2 | 0.005 |
| Treatment cycles<br>1 vs ≥2 | 0.23 | 1.3 | 0.6–2.8 | 0.560 |
| Short-term efficacy<br>SD+PD vs PR | 0.51 | 1.7 | 1.0–2.8 | 0.049 |

**Table 4** Multivariate Analysis of PFS

| Characteristics | β | HR | 95% CI | *P* |
|---|---|---|---|---|
| NLR<br>>3 vs ≤3 | 0.461 | 1.6 | 1.0–2.5 | 0.046 |
| Maximum diameter (cm)<br>>10 vs ≤10 | 0.541 | 1.7 | 1.1–2.6 | 0.013 |
| Distant metastasis<br>Yes vs no | 1.142 | 3.1 | 1.7–5.8 | <0.001 |
| Postoperative therapy<br>0–1 vs ≥2 | 1.172 | 3.2 | 2.0–5.1 | <0.001 |
| Pathological grade<br>G3 vs G1+G2 | 0.473 | 1.6 | 1.1–2.5 | 0.032 |
| Stage<br>IV vs III | 0.661 | 2.3 | 1.7–3.2 | 0.007 |
| Treatment cycles<br>1 vs ≥2 | 0.191 | 1.2 | 0.6–2.4 | 0.600 |
| Short-term efficacy<br>SD+PD vs PR | 0.372 | 1.4 | 0.9–2.4 | 0.150 |

treatment modality use (0–1 vs ≥2 modalities) significantly correlated with shorter PFS (HR=3.2, 95% CI: 2.0–5.1, *P*<0.001). High pathological grade (G3 vs G1+G2) was also independently associated with inferior PFS (HR=1.6; 95% CI: 1.1–2.5; P = 0.032), as was advanced clinical stage (IV vs III), which carried a 2.3-fold increased risk of progression (HR=2.3, 95% CI: 1.7–3.2, *P*=0.007). In contrast, neither the number of AICE treatment cycles (1 vs ≥2, *P*=0.600) nor short-term response status (SD+PD vs PR, *P*=0.150) was statistically significant predictors of PFS in the multivariate analysis.

## Radiological Efficacy Outcomes

According to RECIST 1.1 criteria, no patient achieved complete response (CR), 42 patients (37.2%) achieved PR, 44 patients (38.9%) had SD, and 27 patients (23.9%) had PD, yielding an ORR of 37.2% (95% CI: 28.3%–46.8%) and a DCR of 76.1% (95% CI: 67.1%–83.6%). Additionally, a 32-year-old male patient with fibrosarcoma achieved PR after two cycles of AICE treatment. The MRI scans before and after AICE treatment are shown in Figure 4. Obviously, the target lesion of fibrosarcoma was shrunk significantly, the symptom in thoracic cavity was relieved dramatically, and this patient benefited from the AICE treatment strikingly.

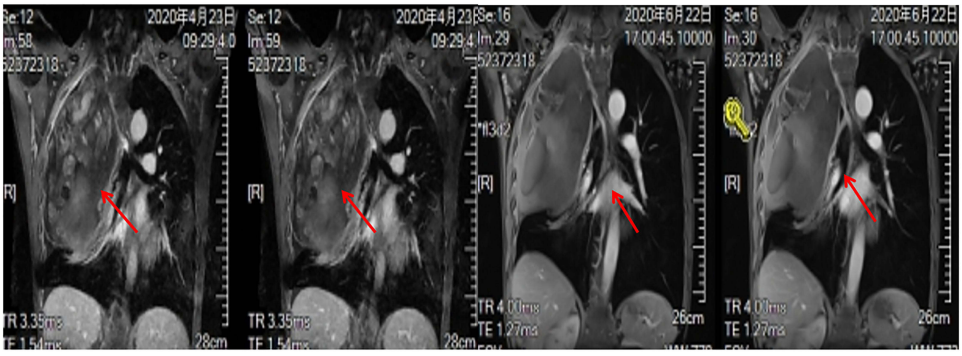


**Figure 4** MRI scan results of the changes for target lesions in the thoracic cavity of a male patient with fibrosarcoma before and after the treatment of arterial infusion chemotherapy and embolization (AICE) (Red arrows: indicated the location of the treated hepatic lesion in pre- and post-treatment MRI images).


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**Table 5** Safety Profile of the 113 Patients with Recurrent/Metastatic STS Underwent AICE Treatment

| TRAEs | A (N, %) | B (N, %) | C (N, %) | D (N, %) | Total (N, %) |
|---|---|---|---|---|---|
| Pyrexia | 5 (4.4) | 2 (1.8) | 0 | 0 | 7 (6.2) |
| Pain | 17 (15.0) | 9 (8.0) | 0 | 0 | 26 (23.0) |
| Nausea and vomit | 4 (1.9) | 0 | 0 | 0 | 4 (1.9) |
| Abnormal liver Function | 0 | 0 | 1 (0.8) | 0 | 1 (0.8) |
| Abnormal renal function | 0 | 2 (1.8) | 0 | 0 | 2 (1.8) |
| Myelosuppression | 9 (8.0) | 2 (1.8) | 4 (1.9) | 2 (1.8) | 17 (15.0) |

## Safety Profile

AICE was generally well tolerated and no treatment-related deaths (Grade F events) occurred. In total, 216 AICE procedures among the 113 subjects were analyzed for acute toxicity and procedure-related complications. As exhibited in Table 5, the most frequent TRAEs was localized pain in the treated region (23.0%). Typically, patients experienced mild-to-moderate pain (Grade A/B, eg, post-embolization syndrome) that was manageable with analgesics and resolved within days. Bone marrow suppression occurred after some AICE sessions due to high-dose regional chemotherapy (15.0%). No Grade E and F hematologic toxicity was observed, and all cytopenias were transient, managed with growth factors or supportive care as needed. Post-embolization fever (typically low-grade <38.5°C) occurred in 7 patients (6.2%). Liver enzyme elevations were noted in one patient treated for liver metastases but was mostly mild (Grade C, 0.8%), none led to liver failure. Abnormal renal function was observed in 2 patients with grade B (1.8%). According to the SIR adverse event grading: Grade A or B events (no or minor therapy needed) were recorded in the majority of AICE sessions (~85%). Grade C events (requiring additional treatment or short hospitalization) occurred in 5 patients (2.7%). Grade D events (prolonged hospitalization >48 h) occurred in only 2 patients (0.9%). No Grade E (permanent injury) events were observed. The safety profile of AICE thus appeared favorable when performed by experienced hands—most side effects were mild and self-limited, akin to or less severe than those expected with systemic chemotherapy. Importantly, systemic toxicities (such as severe myelosuppression, mucositis, or cardiotoxicity) were infrequent, presumably due to the predominantly locoregional action of the treatment. The low incidence of serious TRAEs in our cohort indicated that AICE might be delivered safely, even repeatedly, with proper supportive care.

# Discussion

In this retrospective study, we evaluated the clinical outcomes and safety of AICE in a large series of patients with recurrent or metastatic STS. Our results demonstrated that AICE was feasible and active in this setting, achieving a notable ORR of 37.2% and DCR of 76.1% of the 113 patients with SIS with a median PFS of 11.0 months and median OS of 19.0 months. These outcomes compared favorably to historical outcomes of advanced STS treated with systemic chemotherapy alone.

For instance, first-line doxorubicin-based chemotherapy typically yielded an ORR around 18–25% and median PFS ~4–6 months in metastatic STS.[25] In our cohort, AICE led to a substantially higher response rate and prolonged disease control, suggesting that the locoregional intensification provided by intra-arterial therapy might enhance tumor shrinkage and delay progression. The median OS of 18.0 months observed with AICE also exceeded the 12 months median OS reported for doxorubicin in advanced STS (in trials where many patients cross over to second-line therapy).[26] While cross-trial comparisons should be made cautiously, this signaled a potential survival benefit. Some patients in our series achieved prolonged survival beyond 2–3 years, particularly those who responded well to AICE and were able to undergo subsequent surgical resection or receive additional therapies. It was notable that outcomes were especially improved in patients who received multimodal treatment (AICE combined with other systemic or local therapies), reflecting the importance of an integrated approach in managing advanced sarcoma.

The enhanced efficacy of AICE might be attributed to its mechanism of action. By delivering chemotherapy directly into the tumor's arterial supply and immediately blocking outflow, AICE resulted in extremely high local drug concentrations and prolonged drug-tumor contact time,[27] enhancing drug exposure in the tumor microenvironment while reducing systemic

toxicity.[28] This likely resulted in more effective tumor cell killing than systemic administration, which was limited by dose and systemic toxicity. Additionally, the embolization-induced ischemia potentiated chemotherapy effects by causing tumor hypoxia and nutrient deprivation, which might lead to tumor cell apoptosis and necrosis synergistically.[29] Our finding that the ORR and DCR with AICE exceeded typical chemotherapy alone supported this synergistic effect. Similar approaches, such as transarterial chemoembolization in hepatocellular carcinoma, had shown superior local tumor control compared to chemotherapy alone, due to combined cytotoxic and ischemic injury.[16] This highlighted the role of AICE as an effective treatment option, particularly for patients with localized disease burden or chemo-resistant tumors.[30] Moreover, AICE's localized delivery likely spared patients from the full systemic toxicity of high-dose chemotherapy. Indeed, we observed a favorable safety profile with most AEs being mild (Grade 1–2) and no treatment-related deaths. The absence of severe bone marrow suppression or other life-threatening toxicities in most patients highlighted that AICE might be repeated and combined with other therapies without rendering patients too fragile – a critical consideration in sarcoma where maintaining quality of life was important.[31] In our study, no patient had to discontinue AICE due to toxicity, and many went on to further treatments, underscoring its tolerability. Additionally, it was difficult to isolate the specific contribution of the arterial infusion vs the intravenous chemotherapy in our regimen. We did not observe clear evidence of an abscopal effect (tumor regression at sites not treated by AICE) beyond what might be expected from systemic chemotherapy. The improved outcomes in our series were therefore interpreted as the result of the integrated AICE approach, rather than an immune-mediated abscopal phenomenon.

Interestingly, we identified several prognostic factors that influenced outcomes after AICE, many of which mirrored known prognosticators in advanced STS. Tumor size emerged as a significant factor: patients with bulky tumors (≥10 cm) had significantly worse PFS and OS. Large tumors might be less penetrable by infused chemotherapy and might have regions of poor blood supply, limiting drug delivery even with arterial infusion. These findings aligned with previous study, where larger tumors were associated with poor outcomes due to limited drug penetration, higher tumor burden, and increased vascular complexity.[32] The restricted diffusion of chemotherapeutic agents within larger tumors might undermine AICE efficacy. Our data suggested that even with AICE, very large sarcomas remained difficult to control, and adjunctive strategies (like more extensive embolization or repeated cycles) might be needed. Distant metastasis at the time of AICE was, not surprisingly, an adverse factor for survival (HR ~3 for OS). Metastatic patients had a median OS of only 12 months despite AICE, compared to 36 months in those with isolated local recurrence. This underscored that AICE, being a locoregional therapy, primarily benefited the control of targeted lesions and could not by itself address widespread disease. However, it should be noted that statistical significance ($P$<0.05) alone did not imply meaningful impact on patient outcomes. Effect size and its CI must be considered to gauge clinical usefulness. Narrow ranges supported more definitive conclusions, whereas wide CIs illustrated uncertainty despite statistical significance.[33] In several subgroup analyses, 95% CIs for HRs were broad (eg, HR 0.55 [95% CI, 0.28–1.05]), crossing the null value—indicating no statistical significance and high uncertainty. No firm conclusion about benefit could be made in such cases.

Another important consideration was that our patient cohort spanned nearly a decade (2011–2020), during which there had been significant advances in systemic therapy for STS. In particular, the approval and adoption of new targeted agents, and in some subtypes, immunotherapy, had expanded post-chemotherapy treatment options. For instance, recent reviews described improved median PFS and OS in patients receiving targeted therapies in addition to traditional chemotherapy.[34] Patients treated later in our cohort might have access to newer systemic agents or immunotherapy, resulting in longer survival independent of AICE. This temporal heterogeneity might confound our survival analyses. As such, comparisons of outcomes across treatment years should be interpreted with caution. Future work should include stratification by treatment era and detailed documentation of subsequent therapies to better isolate the effect of AICE. Patients with metastatic STS likely required combination of AICE with effective systemic therapy to improve their prognosis.[35] Indeed, in our series, some metastatic patients who had durable survival were those who also received systemic treatments (eg, targeted therapy or second-line chemo) in parallel with AICE, reflecting a multimodal approach.[36] For metastatic STS patients, AICE alone might not be sufficient to achieve durable disease control. A multidisciplinary approach incorporating AICE with systemic therapies, such as immunotherapy or targeted therapy, was likely required.[37] Recent advancements in immunotherapy, such as PD-1/PD-L1 checkpoint inhibitors, demonstrated promising efficacy in certain sarcoma subtypes.[38] Integrating AICE to achieve local tumor control with systemic immunotherapy might enhance survival outcomes by addressing both local and distant disease progression. The combination of AICE with targeted therapies, such as tyrosine kinase inhibitors (eg, pazopanib), might also improve disease control, particularly in chemo-resistant

or poorly vascularized tumors. Additionally, immunotherapy combined with AICE provided enhanced immune activation through tumor antigen release and the promotion of an inflammatory microenvironment for metastatic SIS.[39]

Notably, considerable patients (45.1%) in our study received additional systemic treatments (such as targeted drugs or immunotherapy) following AICE administration. Patients who achieved longer survival were often those who benefitted from such multimodal therapy. This suggested that part of the observed survival outcomes might reflect the combined effect of AICE with other therapies. Additionally, we also found that receiving ≥3 treatment modalities overall was independently associated with better OS and PFS. This finding suggested that a multidisciplinary approach – incorporating surgery, radiotherapy, systemic therapy, and AICE when appropriate – yielded synergistic benefits. This finding highlighted the importance of multimodal therapy in improving survival outcomes in STS. Combined therapies that integrated AICE with radiotherapy, targeted therapies, or immunotherapy might achieve synergistic effects.[40] For example, a patient might receive AICE to shrink the tumor, then surgery to resect it, then postoperative radiotherapy to sterilize margins, and perhaps systemic therapy to control micro-metastatic disease. Such an aggressive approach, when feasible, might extend survival in sarcoma. Our data supported the concept that multimodal therapy was crucial for optimizing outcomes, especially in a disease as complex as STS. The lack of an objective response (PR/CR) to AICE was a predictor of worse survival (those who only had SD or PD fared poorer), indicating that tumor chemosensitivity still played a large role. Patients whose tumors responded to AICE had significantly longer OS, likely because AICE effectively debulked disease and slowed progression, enabling them to transition to other therapies or simply maintain better performance status. This finding was in line with general oncology wisdom that depth of response correlates with survival in metastatic disease,[41] although it could also reflect underlying tumor biology (responsive tumors were less aggressive).

AICE was generally well tolerated in our study, with the majority of TRAEs being mild or moderate. The most common TRAEs included mild-to-moderate pain (23.0%), bone marrow suppression (15.0%) and pyrexia (6.2%). According to the SIR grading system, most TRAEs were classified as Grade A or B, requiring minimal or no treatment.[42] This safety profile compared favorably to systemic chemotherapy, which often resulted in more severe hematological and gastrointestinal toxicities.[43] Catheter-related complications were rare and managed effectively with appropriate intervention. This emphasized the importance of standardized catheter placement techniques and postoperative monitoring to further reduce complications.[44] Noteworthily, while only two cases (1.8%) of kidney injury were noted, the lack of definitive attribution to cisplatin underscored the need for improved nephrotoxicity surveillance. Literature demonstrated dose ≥100 mg/m² cisplatin, reduced eGFR, age and concomitant nephrotoxic medications were risk factors for acute kidney injury.[45] Future protocols should include routine pre- and post-cycle renal function tests, hydration protocols, and formal dose adjustment criteria. These measures might help preserve renal function while maintaining therapeutic efficacy.

Magnetic Resonance Imaging (MRI) configuration and biomarkers were shown to hold promise in predicting tumor behavior and recurrence in STS. For instance, Sedaghat et al (2022) demonstrated that primary STS morphology—whether polycyclic/multilobulated or ovoid/nodular—might help predict the configuration of recurrent tumors on MRI. Recurrences of polycyclic/multilobulated primaries were most often ovoid/nodular or polycyclic/multilobulated, while primary tumors with a streaky configuration recurred more variably.[46] This suggested that MRI shape/configuration might serve as a prognostic imaging feature. Other study similarly identified MRI features that correlated with tumor grade or treatment outcome. For example, Schmitz et al (2024) found that features such as tumor heterogeneity, peritumoral edema, and contrast enhancement on MRI were significantly associated with high STS grade, and radiomics models achieved strong performance (AUC ~0.97) in distinguishing high-versus low-grade tumors.[47] In our cohort, while imaging was not uniformly analyzed for configuration or advanced MRI biomarkers across all patients, Figure 4 illustrated clear MRI evidence of lesion reduction after AICE. Incorporating standardized MRI morphologic or functional biomarker assessments into future protocols—for example, assessing tumor shape, volumetric changes, heterogeneity and diffusion metrics—might likely enhance prediction of which patients benefited most from AICE, earlier detection of response and better stratification for locoregional therapy.

Limitations existed in this study inevitably. Firstly, its retrospective, single-center design might introduce selection bias, as patients receiving AICE might constitute a selected subgroup, which affected the external validity of our findings. Secondly, the absence of a control group restricted the ability to make causal inferences. Therefore, our results were hypothesis-generating and should be validated in prospective, randomized, multicenter trials. Thirdly, our heterogeneous patient cohort, comprising different STS subtypes and treatment histories, might confound outcomes and limit the

precision of subgroup comparisons. Fourthly, these limitations collectively constrained the generalizability of our findings across diverse clinical settings. Future research should seek to address these issues by employing multicenter designs with stratified or controlled comparisons. Additionally, the treatments given alongside or after AICE were not uniform-some patients received subsequent systemic therapy, which might confound survival outcomes. Finally, nearly all participants in this cohort had ECOG performance status of 2–3 (96.3%), and only a small minority were in the 0–1 category (3.7%). Therefore, our findings regarding tolerability and efficacy were most applicable to patients with performance status of 2–3. The small size of the ECOG 0–1 subgroup (n=4) did not allow meaningful statistical comparison with performance status of 2–3 subgroup. Future studies should aim to enroll sufficient numbers of patients in both strata, or prospectively stratify by ECOG, to clarify whether better performance status was associated with improved outcomes or reduced toxicity under the AICE regimen. However, we attempted to account for this by analyzing multimodal therapy as a variable, and it did emerge as beneficial.

## Conclusion

In conclusion, AICE demonstrated significant feasibility in improving disease control and survival in recurrent or metastatic STS patients with an acceptable safety profile. Tumor size, metastatic status and combined treatment regimens were identified as key prognostic factors influencing outcomes. By integrating AICE into multimodal treatment strategies and exploring novel combinations, the prognosis of STS patients could be further improved. Future studies should aim to optimize treatment protocols and validate these findings in larger, multi-center prospective cohorts. With further validation, AICE might become an important component of sarcoma care, augmenting systemic therapies and helping to optimize treatment design and therapy sequencing in the era of personalized sarcoma management.

## Consent Statement

Despite the informed consent was waived by the Ethics Committee of the Fifth Medical Center of PLA General Hospital, we confirmed that the data of the patients included in this study was anonymized or maintained with confidentiality.

## Disclosure

The authors declare that there are no conflicts of interest in this work.

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