Received: 26 May 2024 | Revised: 28 July 2024 | Accepted: 20 August 2024

DOI: 10.1002/ijc.35201

RESEARCH ARTICLE

Cancer Therapy and Prevention

IJC INTERNATIONAL JOURNAL of CANCER | UICC

Therapy adherence after interdisciplinary tumour board discussion is associated with improved outcome in soft tissue sarcoma: A Charité Comprehensive Cancer Centre analysis

Annika Strönisch[1] | Daniel Rau[2] | Silvan Wittenberg[2] | David Kaul[3] | Georgios Koulaxouzidis[4] | Robert Öllinger[5] | Maximilian von Laffert[6] | Armin Jarosch[7] | Frederik Schäfer[8] | Ulrich Keilholz[9] | Lars Bullinger[1,10] | Sven Märdian[2,11] | Jana Striefler[1,12] | Anne Flörcken[1,10]

[1]Department of Hematology, Oncology, and Tumor Immunology, Charité–Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Berlin, Germany

[2]Centre for Musculoskeletal Surgery, Campus Virchow-Klinikum, Charité–Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Berlin, Germany

[3]Department of Radiation Oncology, Campus Virchow-Klinikum, Charité–Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Berlin, Germany

[4]Department of Plastic, Aesthetic and Reconstructive Surgery, Congregational Hospital Linz, Sisters of Mercy, Linz, Austria

[5]Department of Surgery, Campus Virchow-Klinikum, Charité–Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Berlin, Germany

[6]Institute of Pathology, University Hospital Leipzig, Leipzig, Germany

[7]Institute of Pathology, Charité–Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Berlin, Germany

[8]Department of Radiology, Charité–Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin, Germany

[9]Charité Comprehensive Cancer Centre, Charité–Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin, Germany

[10]German Cancer Consortium (DKTK), Partner Site Berlin, German Cancer Research Centre (DKFZ), Heidelberg, Germany

[11]Clinic of Trauma, Hand and Reconstructive Surgery, University of Rostock, Rostock, Germany

[12]Department of Internal Medicine II, Oncology/Hematology/BMT/Pneumology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

Correspondence
Jana Striefler and Anne Flörcken, Department of Hematology, Oncology, and Tumor Immunology, Charité–Universitätsmedizin Berlin, Berlin, Germany.
Email: anne.floercken@charite.de and j.striefler@uke.de

Abstract

Centralising soft tissue sarcoma (STS) treatment in expert centres and implementing comprehensive therapy concepts through interdisciplinary tumour boards (ITB) has led to significant treatment progress. However, our knowledge on the implementation of the ITB recommendations and its impact on patient outcome is limited. In this retrospective analysis, we examined a cohort of 222 adult patients (pts) with primary STS who were presented to the ITB of the Charité Comprehensive Cancer Centre between 2015 and 2020. In localised disease ($n = 188$), resection was recommended in 71% ($n = 134$) of pts. The treatment modalities chemotherapy with or without regional deep hyperthermia, and radiotherapy were recommended in 37% ($n = 69$), 26% ($n = 48$) and 52% ($n = 97$), respectively. Complex multidisciplinary concepts

were established in 29% ($n = 54$) including ≥3 treatment modalities. Only partial adherence, either by choice of patient or treating physician, was associated with a higher risk of both progression (HR 4.0 95%-CI 1.6–9.7 $p < .01$) and mortality (HR 5.3 95%-CI 1.7–16.4 $p < .01$). Pts inable to follow the ITB recommendations due to complications or rapid progression showed a high-risk profile with increased mortality and progression rates (HR 18.1 95%-CI 8.5–38.2 $p < .001$; HR 21.5 95%-CI 8.5–54.7 $p < .001$). To our knowledge, this represents the first German Comprehensive Cancer Centre analysis of therapy adherence in STS. It provides further real-world evidence that full adherence to ITB recommendations and the ability to adhere to them are of prognostic value for patient outcome and underlines the importance of interdisciplinary decision-making and treatment planning for STS patients.

KEYWORDS

interdisciplinary tumour board, soft tissue sarcoma, therapy adherence

What's New?

Centralising treatment within expert centres and implementing interdisciplinary tumour boards have led to significant progress in treating soft tissue sarcoma. However, knowledge on the implementation of the board recommendations remains limited. In this retrospective analysis, about a third of the 222 cases presented to the board of the Charité Comprehensive Cancer Centre over 5 years were recommended a complex multidisciplinary treatment approach. Partial adherence was associated with a higher risk of both progression and mortality. The study provides further real-world evidence of the importance of interdisciplinary decision-making and treatment planning in soft tissue sarcoma.

1 | INTRODUCTION

Soft tissue sarcomas (STS) represent a heterogeneous disease group subdivided into about 70 further subtypes based on their histological and molecular characteristics. Representing 1% of all tumour diseases in adults, sarcomas are not only rare, but also very diverse in their clinical presentation.[1,2]

The tumour characteristics essentially determine the prognosis: The more cranial the localisation and the larger the primary tumour, the higher the associated risk of recurrence and morbidity. Additionally, the histological subtype and grading influence the prognosis particularly. High-grade sarcomas implicate a significantly higher risk of mortality and recurrence than low-grade sarcomas.[3–6] Patient characteristics, such as older age or the prevalence of concomitant diseases, are also associated with a higher mortality risk or lower tumour-specific survival.[4,5,7,8] Of particular prognostic importance is the surgical procedure and the postoperative resection status. A successful R0-resection (tumour-free resection margins) leads to a lower risk of local recurrence and better overall survival (OS).[3,5,6]

The last decades have shown that sarcoma patients benefit from treatment in specialised centres, providing close cooperation between all involved disciplines encompassing surgery, hemato-oncology, pathology, radiology and radiation oncology.[3,9] Thus, at first suspicion of a STS, it is strongly recommended to continue diagnostic work-up and treatment at a specialised sarcoma centre. Multidisciplinary discussion has been a central approach to adequate diagnostic methods, therapy planning and implementation.[3,9] Depending on the clinical context, complex treatment plans, including multiple therapeutic modalities such as surgery, standalone chemotherapy or combined with regional deep hyperthermia treatment (RHT) and radiotherapy, are indicated for optimal patient care.[3,9]

An essential tool for structured therapy coordination is the interdisciplinary tumour board (ITB). It is considered a reliable quality indicator for optimised and guideline-based sarcoma therapy,[3,9] for which patients should be presented in an ITB before initiating therapy.[3,9,10] Early investigations from the 1990s have already demonstrated an improvement in progression-free and OS through the formation of expert groups and pre-therapeutic interdisciplinary discussion.[11,12] The French network for sarcomas (NetSarc) endorsed these observations more recently. Including 12,528 patients diagnosed with STS between 2010 and 2014, NetSarc investigated the impact of ITB presentation before or after initiation of primary therapy. A pre-therapeutic ITB presentation was associated with improved guideline adherence.

Additionally, longer recurrence-free survival and tumour-free resection margins were more frequently achieved compared to post-therapeutic ITB presentation only.[13] Since the start of the NetSarc data collection in 2010, the proportion of patients presented pre-therapeutically to an ITB has significantly increased. Furthermore, a higher proportion of patients obtained guideline adherent diagnostics

and therapy programs.[14] Mainly based on this work, the ITB has become an essential part of treatment planning in STS patients.[3,9]

While the benefit of an ITB is generally recognised, little is known about the adherence to the ITB therapy recommendations and whether their implementation is linked to the patient outcome. We investigated this issue by means of a monocentric, retrospective study of patients with a primary diagnosis of sarcoma, who were presented to the sarcoma ITB of the Charité Comprehensive Cancer Centre.

2 | METHODS

This single-centre retrospective analysis included patients with a first diagnosis of STS between January 2015 and January 2020, who were presented to our sarcoma ITB at the Charité Sarcoma Centre, a part of the Charité Comprehensive Cancer Centre (CCCC) that participates in the certification program of the German Cancer Society.[10]

To identify suitable patients, a systemic database search was carried out in the internal cancer data registry by using the Gießen Tumour Documentation System (GTDS), a well-established tool for tumour documentation.[15] Patients were included according to the following criteria: Histological diagnosis of a soft tissue tumour in conformity to the specifications by the German Cancer Society[16] (excluding desmoid tumours), presentation as a primary case, at least one presentation in the in-house sarcoma ITB and no less than one therapy recommendation by an ITB.

The following data were extracted from the patient files for analysis: age, gender, histological subtype and grading, tumour stage at initial diagnosis, Eastern Cooperative Oncology Group Performance Status (ECOG),[17] presentation to the ITB and its therapy recommendations, data on the performed therapy, resection status and course of disease. The Charlson Comorbidity Index (CCI) was calculated based on the documented concomitant diseases.[18] The study's primary endpoints were disease-specific overall survival (DOS) and progression-free survival (PFS). If the patients did not continue their treatment or follow-up at the Charité, primary care doctors were contacted to complete data on follow-up and outcome.

Therapy recommendations comprised the treatment modalities (TM) of tumour resection, chemotherapy with or without RHT, radiotherapy and follow-up care. Therapy adherence to the ITB recommendations was divided into the categories 'complete implementation of the therapy recommendation', 'partial implementation of one TM' and 'omission of at least one TM'. A TM was considered 'partially implemented' if, for example, the planned radiation dose was not achieved or the intended chemotherapy regimen was not completed. Tumour resection could only be classified as 'complete' or 'omitted'. If the recommended TM could not be carried out (for instance, due to rapid disease progression), the patient was assigned to the category 'inability of therapy adherence', as in this case a potential impact of the ITB cannot be assessed.

Statistical data analysis was performed using IBM SPSS Statistics 27 (IBM Corp., Armonk, N.Y., USA) and R (RStudio 2021.09.2). After descriptive analysis, *t*-tests and Mann–Whitney-U-tests were applied for metric variables, and chi-square (χ^2) or Fisher's exact test was applied for categorical variables if appropriate. DOS and PFS were calculated for survival time analyses. As the therapeutic approach differs substantially for localised and metastatic tumour stages, these groups were analysed separately. The log-rank test was used for univariate survival time analysis and Cox regression to calculate the Hazard ratio (HR). A Cox regression with a time-dependent covariate was performed for multivariate survival time analysis on patients with localised disease. Therapy adherence was considered a time-dependent variable. Due to a low event count, a limited number of variables were selected for the multivariate survival time analysis based on data completeness and clinical value. A statistically significant result was assumed at a significance level of $\alpha = 0.05$.

For better readability, the percentages in the text are stated in integers.

3 | RESULTS

3.1 | Patient characteristics

A cohort of 222 patients with initial diagnosis between January 2015 and January 2020 was identified. Of these, 47% ($n = 104$) were female and 53% ($n = 118$) male. The median age at first diagnosis was 59.6 years (range 20.7–95.9 years). The majority of patients (85%, $n = 188$) had a localised tumour, 15% ($n = 33$) already showed metastases at first diagnosis. While 21% ($n = 47$) of patients presented with low-grade, 69% ($n = 152$) had high-grade sarcoma (note in 10%, $n = 23$, tumour grade was unknown). The primary lesion was mainly localised ($n = 116$) on the extremities (52%), in 38% ($n = 85$) on the trunk, and 10% ($n = 21$) on the head and neck region. The largest histological subgroup was represented by liposarcomas (29%, $n = 64$), followed by undifferentiated pleomorphic sarcomas (17%, $n = 37$) and myxofibrosarcomas (16%, $n = 35$) (cf. Table 1). The performance status was generally considered good: 57% ($n = 126$) presented with an ECOG of 0 and 9% ($n = 20$) with an ECOG of 1. Furthermore, no relevant comorbidities were documented for 61% ($n = 136$) of the patients, resulting in a CCI of 2. A proportion of 38% ($n = 85$) of patients presented relevant other comorbidities resulting in a CCI >2 (cf. Table 1).

3.2 | Interdisciplinary tumour board

37% ($n = 82$) of patients were presented once during first-line therapy, whereas 36% ($n = 80$) were discussed twice, and 27% ($n = 60$) ≥ three times in the ITB to re-evaluate the treatment plan (e.g., postoperative presentation in the ITB). Prior to ITB discussion, 100% ($n = 222$) of patients had received imaging and 69% ($n = 153$) had histological confirmation by biopsy. 79% ($n = 175$) received a treatment recommendation from the ITB within 30 days of histological diagnosis. In 21% ($n = 47$), 30 days were exceeded.

TABLE 1 Patient characteristics.

Variable	$n = 222$	Sorted by gender	
		Female, $n = 104$	Male, $n = 118$
Sex			
Female	104 (46.8%)		
Male	118 (53.2%)		
Age at diagnosis (years)			
Median	59.6	53.8	60.8
Range	20.7–95.9	20.6–95.9	23.2–88.7
Standard deviation	16.7	17.1	16.4
Stage at diagnosis			
Localised	188 (84.7%)	92 (88.5%)	96 (81.4%)
Metastasised	33 (14.9%)	12 (11.5%)	21 (17.8%)
Unknown	1 (0.5%)	–	1 (0.8%)
ECOG			
0	126 (56.8%)	69 (66.3%)	57 (48.3%)
1	20 (9.0%)	7 (6.7%)	13 (11.0%)
2	7 (3.2%)	2 (1.9%)	5 (4.2%)
3	2 (0.9%)	1 (1.0%)	1 (0.8%)
Unknown	67 (30.2%)	25 (24.0%)	42 (35.6%)
Mean	0.3	0.2	0.3
Range	0–3	0–3	0–3
Standard deviation	0.6	0.5	0.7
Charlson Comorbidity Index			
2	136 (61.3%)	74 (71.2%)	62 (52.5%)
>2	85 (38.2%)	30 (28.8%)	55 (46.6%)
Unknown	1 (0.5%)	–	1 (0.8%)
Mean	3.5	3.1	3.8
Range	2–11	2–10	2–11
Standard deviation	2.4	2.1	2.6
Localisation			
Extremities	116 (52.3%)	49 (47.1%)	67 (56.8%)
Trunk	85 (38.3%)	47 (45.2%)	38 (32.2%)
Head/neck	21 (9.5%)	8 (7.7%)	13 (11.0%)
Histologic grading			
Low grade	47 (21.2%)	17 (16.3%)	30 (25.4%)
High grade	152 (68.5%)	78 (75.0%)	74 (62.7%)
Unknown	23 (10.4%)	9 (8.7%)	14 (11.9%)
Histologic subtypes		–	–
Liposarcoma	64 (28.8%)		
Undifferentiated pleomorphic sarcoma	37 (16.7%)		
Myxofibrosarcoma	35 (15.8%)		
Leiomyosarcoma	21 (9.5%)		
Angiosarcoma	12 (5.4%)		
Undifferentiated spindle-cell sarcoma	8 (3.6%)		
Synovial sarcoma	7 (3.2%)		
Alveolar soft part sarcoma	2 (0.9%)		
Epithelioid sarcoma	5 (2.3%)		

(Continues)

TABLE 1 (Continued)

Variable	$n = 222$	Sorted by gender	
		Female, $n = 104$	Male, $n = 118$
Clear cell sarcoma	2 (0.9%)		
Undifferentiated/unclassified sarcoma	6 (2.7%)		
Undifferentiated round cell sarcoma	1 (0.5%)		
Rhabdomyosarcoma	1 (0.5%)		
Malignant tenosynovial giant cell tumour	1 (0.5%)		
Malignant peripheral nerve sheath tumour	2 (0.9%)		
Dermatofibrosarcoma protuberans	5 (2.3%)		
Myxoinflammatory fibroblastic sarcoma	3 (1.4%)		
Solitary fibrous tumour	2 (0.9%)		
Fibrosarcoma	2 (0.9%)		
Hemangioendothelioma	3 (1.4%)		
Endometrial stromal sarcoma	1 (0.5%)		
Uterine leiomyosarcoma	2 (0.9%)		

Treatment had already been started in 44% ($n = 97$) of patients before a recommendation was given. 37% ($n = 83$) of patients had already undergone resection, and 6% ($n = 14$) had started chemotherapy. The indication for resection was based in 46% ($n = 38$) of the 83 cases on a suspected benign or low-grade neoplasia, in 15% ($n = 12$) on the suspicion of a malignancy other than a sarcoma and in 16% ($n = 13$) on an emergency situation. In 21% ($n = 17$) the reason is unknown.

In 43% ($n = 6$) of the 14 patients who had already started chemotherapy, therapy had been initiated by an external oncologist. In 57% ($n = 8$) the reason was not documented.

3.3 | Therapy recommendation by the ITB

3.3.1 | Localised tumour stage

Curative treatment was intended in the majority (96%, $n = 181$) of the 188 patients with localised disease. A palliative concept was pursued in 4% ($n = 7$). In 71% ($n = 134$) of patients, the ITB recommended a tumour resection: 38% ($n = 72$) of them as primary resection and 33% ($n = 62$) after neoadjuvant therapy. No surgery was recommended in 29% ($n = 54$), because in 91% ($n = 49$) of these patients, surgery had already taken place before ITB evaluation and a re-resection was not indicated. Therefore, in only 9% ($n = 5$) of these 54 cases, surgical removal was not initially recommended in favour of a palliative approach.

Chemotherapy was proposed for 37% ($n = 69$) of patients ($n = 188$). In 28% ($n = 53$) of the cases, chemotherapy was advised as neoadjuvant, in 5% ($n = 9$) as adjuvant, and rarely (2%, $n = 3$) as a combination of both neoadjuvant and adjuvant chemotherapy. Palliative intended chemotherapy was indicated in 2% ($n = 4$).

Of these 188 patients, 26% ($n = 48$) were eligible for regional deep hyperthermia (RHT). According to the recommendation, RHT was advised neoadjuvantly in 24% ($n = 45$) and adjuvantly in 2% ($n = 3$) of patients.

The ITB indicated radiotherapy in 52% ($n = 97$) of patients, of whom 50% ($n = 94$) received it adjuvantly, 1% ($n = 2$) neoadjuvantly, and one patient as a palliative procedure. In 48% ($n = 91$) of patients, additional radiation was not considered necessary. Within the radiation group, 88% ($n = 85$) had a high-grade sarcoma. A low-grade sarcoma was present in the non-radiation group in 48% ($n = 44$).

A multimodal approach combining at least three available TMs mentioned above was recommended in 29% ($n = 54$) of patients. In 31% ($n = 59$), only one TM was recommended.

In 14% ($n = 27$) of patients only a recommendation for follow-up was made, as 26 patients had already received a resection without prior ITB recommendation. With 77% ($n = 20$), the majority had a low-grade sarcoma and in 69% ($n = 18$) an R0-status had been achieved by the initial resection. One patient was not eligible for therapy due to severe comorbidities and therefore received the recommendation follow-up meaning best supportive care (cf. Figure 1A–D).

3.3.2 | Metastasised tumour stage

In individuals with metastatic disease ($n = 33$), a potentially curative therapy concept was pursued in 30% ($n = 10$). The remaining patients (70%, $n = 23$) were treated with palliative intent. Systemic chemotherapy was the predominant TM and indicated in 91% ($n = 30$) of patients. 67% ($n = 22$) received a recommendation for chemotherapy in a palliative, 24% ($n = 8$) in a curative intent. In the case of curative intent, the ITB recommended systemic chemotherapy to be administered neoadjuvantly in 12% ($n = 4$), adjuvantly in 9% ($n = 3$) and both neoadjuvantly and adjuvantly in 3% ($n = 1$). Additional 12% ($n = 4$) of

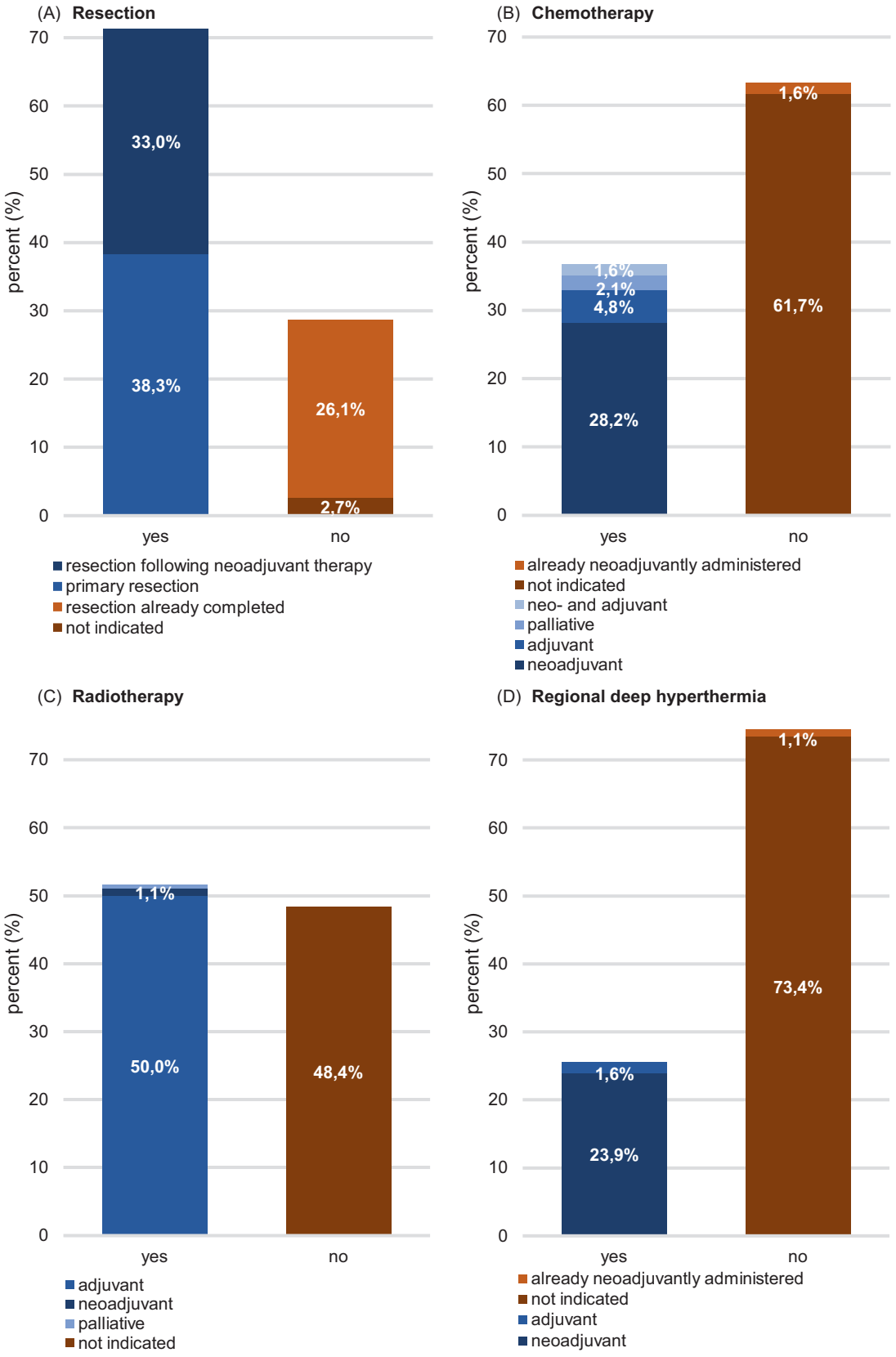

FIGURE 1 Therapy modalities recommended by the ITB for localised tumour stage ($n = 188$). (A) Resection; (B) Chemotherapy; (C) Radiotherapy; (D) Regional deep hyperthermia.

patients were suitable for RHT. Of these, 9% ($n = 3$) received RHT as part of a neoadjuvant and 3% ($n = 1$) as part of a palliative concept.

Surgery was proposed in 39% ($n = 13$) of patients. Of these, 6% ($n = 2$) as primary resection, 18% ($n = 6$) after neoadjuvant therapy and 15% ($n = 5$) due to a high risk of complications or as debulking surgery. 27% ($n = 9$) of the patients had already undergone surgery without ITB recommendation, and 33% ($n = 11$) of patients were not considered suitable for surgery.

Radiotherapy was indicated in 15% ($n = 5$) of cases, 6% ($n = 2$) were advised to receive adjuvant radiotherapy, and in 9% ($n = 3$) palliative radiotherapy was recommended. The majority (85%, $n = 28$) was not considered eligible for radiotherapy.

3.4 | Adherence to ITB therapy recommendations

3.4.1 | Localised tumour stage

In 8% ($n = 15$) of 188 patients with localised disease, adherence to the ITB recommendations could not be verified due to lacking data in the patients´ files. In 69% ($n = 119$) of the remaining 173 patients the ITB recommendations were fully implemented. Of these 173 patients, 8% ($n = 13$) implemented one TM only partially, and 9% ($n = 15$) did not implement one or more recommended TM. Thus, in a total of 16% ($n = 28$), although regarded feasible, the recommendations were partially not realised. The main reasons in these 28 cases without complete adherence were patient refusal in 57% ($n = 16$), decision by the treating physician in 14% ($n = 4$), and delay in continuing treatment in 14% ($n = 4$) of the cases. The exact reason was not documented in 14% (n = 4).

Furthermore, in 15% ($n = 26$) of the 173 patients under investigation, it was impossible to implement the ITB recommendation: Of these 26 patients, 54% ($n = 14$) suffered rapid disease progression and 27% ($n = 7$) encountered complications or side effects of the therapy. In two cases (8%), the recommendation could not be implemented for technical reasons; two patients (8%) died, and one patient's (4%) general condition did not allow further therapy.

3.4.2 | Metastasised tumour stage

In the group with metastasised disease ($n = 33$), 30% ($n = 10$) were fully adherent to the ITB recommendations. In one case (3%), adherence data was missing. In 9% ($n = 3$) of patients, one TM was partially realised, and in 12% ($n = 4$), one or more TM were not performed. Of the seven cases with only partial adherence, 29% ($n = 2$) refused to follow the recommended modality. In 57% ($n = 4$), the treating physician had declined it; in one case, the reason was unknown.

The proportion of patients incapable of adherence was considerably higher in those with metastasised disease (46%, $n = 15$). The main reasons were rapid disease progression (60%, $n = 9$) and therapy complications (27%, $n = 4$). In one patient, the TM was technically not feasible (7%), and another patient was too frail (7%).

Further details on TMs eventually applied in localised and metastasised disease and patient outcomes at the end of primary therapy are shown in the Supplementary Material (Table S1).

3.5 | Survival analysis

3.5.1 | Localised tumour stage

The median follow-up time was 2.3 years (range 0–5.8 years) for patients with localised disease. Of the 188 patients, 31% ($n = 58$) developed local recurrence or metastatic disease during the observation period, 23% ($n = 43$) died. In 74% ($n = 32$), the cause of death was related to STS, in 12% ($n = 5$) to other causes, and in 14% ($n = 6$) the cause remains unknown.

The mean OS amounted to 4.5 years (95%-confidence interval CI 4.2–4.8 years), whereas the mean DOS was 4.8 years (95%-CI, 4.5–5.1 years) and the mean PFS was 4.0 years (95%-CI 3.6–4.4 years). The median survival could not be calculated because, at the end of the observation period, more than 50% of the patients were still alive, or no progression had occurred.

Univariate analysis showed a significant correlation between therapy adherence and survival ($p < .001$). Patients with complete adherence to ITB recommendations (69%, $n = 119$) showed the longest DOS (5.4 years) and PFS (4.7 years). Patients without compliance to ITB recommendations due to inability to implement these (15%, $n = 26$) had the worst prognosis: the mean DOS was 1.4 years and the PFS 0.9 years. However, patients who had partially failed to comply with therapy or had omitted one or more TM (16%, $n = 28$) also revealed a shorter mean DOS (4.8 years; 2.2 years) and PFS (3.0 years; 1.5 years) (cf. Figure 2A,C).

An ECOG >0 and a CCI >2 were significantly associated with shorter DOS (4.7 vs. 3.0 years, $p < .01$; and 5.1 vs. 3.7 years, $p < .01$, respectively). The PFS was also significantly shorter, with a CCI of 2 (4.2 vs. 3.0 years; $p = .04$). Age >60 years showed a trend towards shorter DOS (5.0 vs. 4.5 years, $p = .06$), whereas no difference was found for PFS. For sarcomas localised on the trunk and head and neck region, respectively, a significantly shorter DOS (4.0 years; 3.2 years) and PFS (3.1 years; 2.7 years) was observed. In comparison, the DOS was 5.3 years and the PFS 4.5 years for sarcomas of the extremities. Low-grade sarcomas had a longer PFS than high-grade sarcomas (4.6 vs. 3.6 years; $p = .02$). Concerning DOS, there was only a trend to shorter DOS in patients with high-grade sarcoma (5.1 vs. 4.5 years, $p = .05$). A tumour-free resection margin (R0) was associated with longer DOS and PFS (5.3 vs. 4.3 years, $p < .01$; 4.5 vs. 3.0 years, $p < .001$). Regarding gender, we did not find any correlations (cf. Table 2).

In the multivariate survival time analysis, a significant association with prognosis was observed for therapy adherence. Patients with an inability to adhere to therapy had the highest risk of death (HR 21.5, 95%-CI 8.5–54.7) or progression (HR 18.1, 95%-CI 8.5–38.2) compared to patients who completely adhered to the recommended therapy. Also, the omission of one or more TM, despite their potential

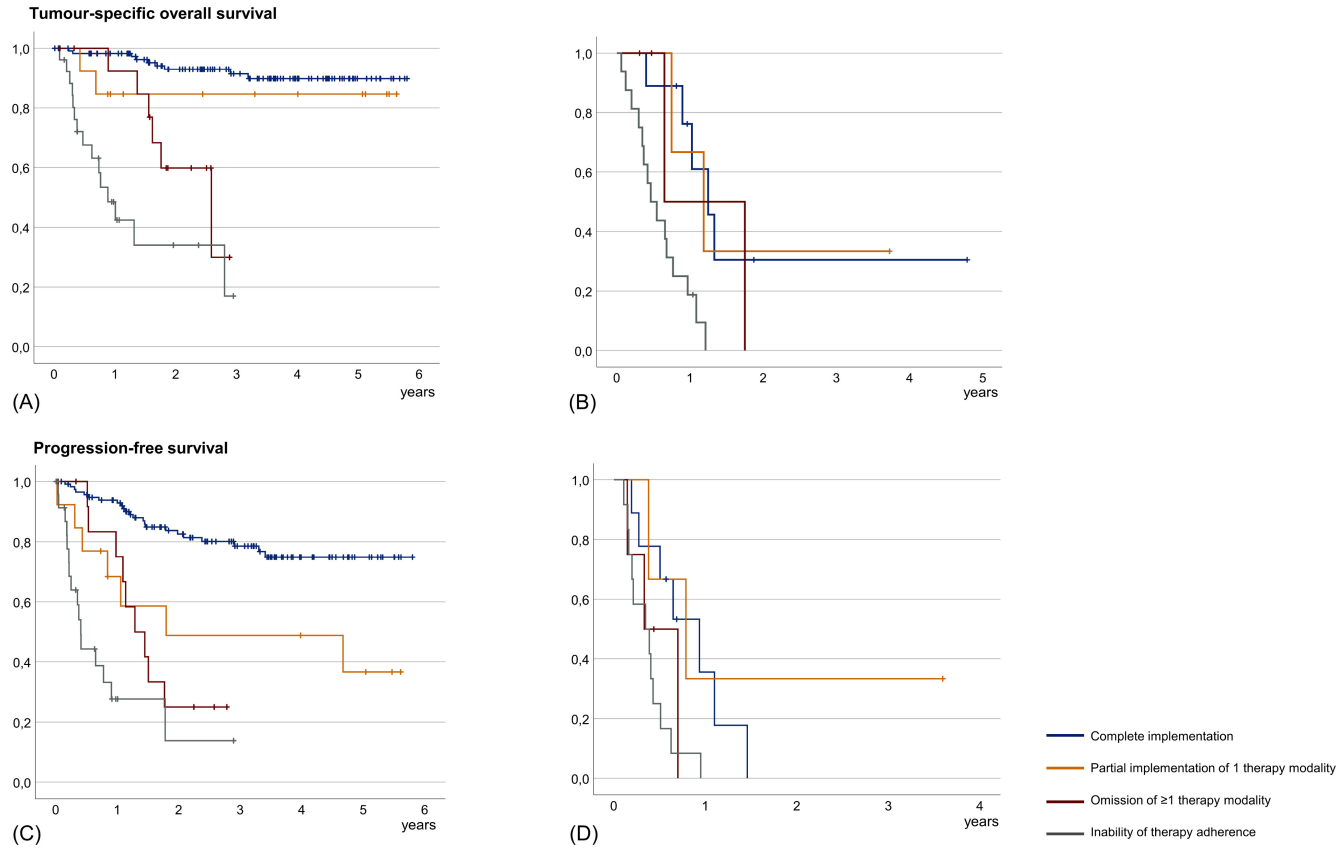

FIGURE 2 Survival time–adherence to therapy recommendations. (A) Tumour-specific overall survival localised disease. (B) Tumour-specific overall survival metastasised disease. (C) Progression-free survival localised disease. (D) Progression-free survival metastasised disease.

feasibility, was associated with a higher risk of both death and progression (HR 5.3, 95%-CI 1.7–16.4; HR 4.0, 95%-CI 1.6–9.7). If a TM was only partially implemented, this did not influence the risk of death but was significantly associated with an increased risk of progression (HR 3.7, 95%-CI 1.4–10.2). The localisation of the sarcoma on the trunk was also linked to an increased risk of death (HR 2.7, 95%-CI 1.2–6.1). For age, gender, CCI, and histological grading, no effect on prognosis was observed for either DOS or PFS (cf. Table 3).

Remarkably, the subgroup of non-adherent patients ($n = 28$) differed from the remaining study cohort in only few characteristics. The subgroup of non-adherent patients included a higher proportion of women (75.0% vs. 43.4%, χ^2-test[df 1] = 9.3, $p < .01$, Phi = 0.2, $p < .01$) and high-grade sarcomas (92.0% vs. 69.6%, χ^2-test[df 1] = 5.4, $p = .02$, Phi = 0.2, $p = .2$). Age, performance status, localisation, the proportion of resections before ITB recommendation as well as the postoperative resection status did not differ significantly from the remaining study cohort (data not shown). In contrast, the subgroup of patients ($n = 26$) who were unable to adhere to treatment had a higher mean age of 65.7 versus 57.1 years (t[171] = −2.4 standard deviation 3.5, $p = .01$) compared to the rest of the study cohorts and had a reduced performance status with an ECOG ≥1 (36.4% vs. 13.7%, Fisher's exact test $p = .03$, Cramer V = 0.2, $p = .01$) CCI >2 (57.7% vs. 23.8%, χ^2-test[df 1] = 12.3, $p < .001$, Phi = 0.3, $p < .001$). Additionally, fewer sarcomas were localized on the extremities (38.5% vs. 61.2%, Fisher's exact test $p = .04$, Cramer V = 0.2, $p < .05$) and there was a higher proportion of high-grade sarcomas (96.0% vs. 68.9%, χ^2-test[df 1] = 7.9, $p < .01$, Phi = 0.2, $p < .01$). Regarding the resection status, R0-status was achieved in fewer cases (42.9% vs. 87.0%, Fisher's exact test $p = .001$, Cramer V = 0.3, $p < .001$). A resection prior to the ITB recommendation was only performed in a small proportion of cases (11.5% vs. 38.1%, χ^2-test[df 1] = 6.9, $p < .01$, Phi 0.2, $p < .01$). There were no differences in gender. In summary, this subgroup had an unfavourable risk profile.

3.5.2 | Metastasised tumour stage

The median follow-up time was 0.7 years (range 0.1–4.8 years) for patients with metastases at first diagnosis ($n = 33$). Of these patients, 79% ($n = 26$) were diagnosed with progression during follow-up. A total of 82% ($n = 27$) died during this period. Here, the cause of death was predominantly due to progressive disease (89%, $n = 24$) and in only one case (7%) due to another cause. The median and the mean OS was 0.8 (95%-CI 0.4–1.1 years) and 1.2 years (0.7–1.7 years), the median and the mean DOS was 0.9 years (95%-CI 0.5–1.3 years) and 1.3 years (95%-CI 0.8–1.9 years), respectively. Disease progression was diagnosed after a median of 0.4 years (95%-CI 0.3–0.6 years) and a mean of 0.7 years (95%-CI 0.4–1.0 years).

TABLE 2 Univariate survival analysis localised tumour stage.

Tumour-specific overall survival								
	Log rank-test				Cox regression			
Variable	Number of cases, *n*	Events	Mean in years (95%-CI)	*p*-value	Beta	HR	95%-CI	*p*-value
Sex	188	32						
Female	92		4.6 (4.2–5.1)		Ref.			
Male	96		4.8 (4.5–5.3)	$p = .39$	−0.31	0.7	0.4–1.5	$p = .39$
Age	188	32						
<60 years	98		5.0 (4.6–5.3)		Ref.			
>60 years	90		4.5 (4.0–5.0)	$p = .06$	0.67	2.0	1.0–4.0	$p = .48$
Localisation	188	32						
Extremities	107		5.3 (5.0–5.6)		Ref.			
Trunk	64		4.0 (3.4–4.6)		1.32	3.8	1.7–8.2	**$p < .01$**
Head/neck	17		3.2 (2.4–3.9)	**$p < .01$**	1.23	3.4	1.2–10.0	**$p = .03$**
Histologic grading	172	31						
Low-grade	47		5.1 (4.6–5.5)		Ref.			
High-grade	125		4.5 (4.1–5.0)	**$p = .05$**	1.01	2.7	1.0–7.8	$p = .06$
Charlson Comorbidity Index	188	32						
=2	135		5.1 (4.7–5.4)		Ref.			
>2	53		3.7 (3.0–4.3)	**$p < .01$**	1.01	2.7	1.4–5.5	**$p < .01$**
ECOG	131	28						
=0	109		4.7 (4.3–5.1)		Ref.			
≥1	22		3.0 (1.8–4.2)	**$p < .01$**	1.1	3.1	1.4–6.9	**$p < .01$**
R-status[a]	165	17						
R0	136		5.3 (5.0–5.5)		Ref.			
R1/R2/RX	29		4.3 (3.4–5.2)	**$p < .01$**	1.48	4.4	1.7–11.4	**$p < .01$**
Adherence to therapy recommendations	173	32						
Complete implementation	119		5.4 (5.1–5.6)		Ref.			
Partial implementation of 1 therapy modality	13		4.8 (3.8–5.8)		0.96	2.6	0.6–12.2	$p = .22$
Omission of ≥1 therapy modality	15		2.2 (1.8–2.6)		2.11	8.3	2.8–24.1	**$p < .001$**
Inability of therapy adherence	26		1.4 (0.9–1.9)	**$p < .001$**	3.30	27.1	11.3–64.9	**$p < .001$**
Progression-free survival								
	Log rank-test				Cox regression			
Variable	Number of cases, *n*	Events	Mean in years (95%-CI)	*p*-value	Beta	HR	95%-CI	*p*-value
Sex	180	56						
Female	87		3.6 (3.0–4.1)		Ref.			
Male	93		4.3 (3.8–8.8)	$p = .12$	−0.42	0.7	0.4–1.1	$p = .12$
Age	180	56						
<60 years	95		4.0 (3.5–4.5)		Ref.			
>60 years	85		3.9 (3.3–4.4)	$p = .57$	0.15	1.2	0.7–2.0	$p = .57$
Localisation	180	56						
Extremities	105		4.5 (4.0–4.9)		Ref.			
Trunk	59		3.1 (2.4–3.8)		0.89	2.4	1.4–4.3	**$p < .01$**
Head/neck	16		2.7 (1.8–3.5)	**$p < .01$**	0.71	2.0	0.9–4.7	$p = .10$
Histologic grading	167	53						
Low-grade	47		4.6 (4.0–5.2)		Ref.			

TABLE 2 (Continued)

Progression-free survival								
	Log rank-test				Cox regression			
Variable	Number of cases, *n*	Events	Mean in years (95%-CI)	*p*-value	Beta	HR	95%-CI	*p*-value
High-grade	120		3.6 (3.2–4.1)	**$p = .02$**	0.88	2.4	1.1–5.1	**$p = .02$**
Charlson Comorbidity Index	189	56						
=2	129		4.2 (3.8–4.6)		Ref.			
>2	51		3.0 (2.3–3.6)	**$p = .04$**	0.57	1.8	1.0–3.1	**$p = .04$**
ECOG	126	45						
=0	105		3.7 (3.2–4.2)		Ref.			
≥1	21		2.9 (1.7–4.1)	$p = .21$	0.46	1.6	0.8–3.3	$p = .22$
R-status[a]	160	42						
R0	132		4.5 (4.1–4.8)		Ref.			
R1/R2/RX	28		3.0 (2.1–3.9)	**$p < .001$**	1.08	3.0	1.6–5.6	**$p < .01$**
Adherence to therapy recommendations	170	55						
Complete implementation	118		4.7 (4.4–5.1)		Ref.			
Partial implementation of 1 therapy modality	13		3.0 (1.7–4.4)		1.27	3.6	1.4–8.9	**$p < .01$**
Omission of ≥1 therapy modality	14		1.5 (1.1–2.0)		1.71	5.6	2.5–12.2	**$p < .001$**
Inability of therapy adherence	25		0.9 (0.5–1.4)	**$p < .001$**	3.06	21.4	10.9–41.8	**$p < .001$**

Note: Significant *P*-values are shown in bold to emphasise them.
Abbreviation: CI, confidence interval.
[a]Patients, who received a resection.

For therapy adherence, an influence on median DOS and PFS was also observed ($p = .01$; $p < .05$). Patients with the inability of therapy adherence had the shortest median DOS and PFS compared to patients who could fully adhere to the ITB recommendations (0.6 vs. 1.2 years; 0.4 vs. 0.9 years, cf. Figure 2B,D). A CCI >8 and an ECOG >0 were associated with significantly shorter median DOS (1.6 vs. 0.6 years, $p = .03$; 1.3 vs. 0.5 years, $p = .03$). Likewise, median PFS was significantly lower in patients with a CCI higher than 8 (0.6 vs. 0.3 years, $p < .01$), whereas no difference was found for ECOG. Localisation, gender and age did not significantly influence DOS or PFS (cf. Table 4). Regarding patient characteristics, metastasised patients with inability to follow the ITB recommendations ($n = 15$) did not differ in age, sex, performance status and resection status in comparison to the remaining study cohort (data not shown).

4 | DISCUSSION

This work demonstrates that adherence and the ability to adhere to multimodal treatment plans by an ITB are associated with improved outcomes for STS patients. These factors add to the well-established risk factors, such as elevated CCI, localisation and R-status, that were also of prognostic relevance concerning DOS and PFS in our cohort. High-grade histology was significantly associated with shorter PFS.

The benefit of complete adherence to the ITB recommendations was demonstrated in a prolonged DOS and PFS, which was mainly seen for localised and less prominent for metastasised disease. The omission of a recommended TM was associated with a poorer prognosis. Disregarding histological grading, the group of non-adherent patients did not differ significantly from the remaining study cohort in terms of potential risk factors. The highest risk of mortality and progression was found in the subgroup that did not have the opportunity to follow the ITB recommendations. This may be at least partly explained by the finding that these patients showed more risk factors for an aggressive disease course. Naturally, this group must be considered separately, and no clear conclusions about the effectiveness of the ITB may be drawn. In metastasised disease, it was noticeable that almost half of the patients suffered from rapid progression or complications and were not able to follow the ITB recommendations. A difference in the risk profile was not observed here. The proportion of patients who received an ITB recommendation after >30 days did not differ within the various adherence groups. Therefore, a delay in ITB presentation is unlikely to cause the inability to implement the ITB recommendations.

Consequently, the statistical analysis revealed an association with a shorter DOS and PFS for non-adherent patients as well as for patients inable to follow the ITB's recommendations. Although the number of patients with localised disease was considerably smaller, they also demonstrated shorter survival. Sarcoma patients benefit from interdisciplinary therapeutic concepts and specialised care in certified centres, which has been demonstrated in several studies and has thus created the scientific basis for these fundamental therapeutic principles.[19] Interdisciplinary treatment at expert centres is associated with improved diagnostics, better

TABLE 3 Multivariate survival analysis localised tumour stage.

Tumour specific overall survival (number of cases $n = 173$, events $=32$)				
	Cox regression			
Variable	**Beta**	**HR**	**95%-CI**	***p*-value[a]**
Localisation				
Extremities	Ref.			
Trunk	0.98	2.7	1.2–6.1	$p = .02$
Head/neck	0.22	1.3	0.4–4.1	$p = .71$
Charlson Comorbidity Index				
=2	Ref.			
>2	0.55	1.7	0.8–3.8	$p = .16$
Adherence to therapy recommendations				
Complete implementation	Ref.			
Partial implementation of 1 therapy modality	0.56	1.8	0.4–8.6	$p = .47$
Omission of ≥1 therapy modality	1.67	5.3	1.7–16.4	$p < .01$
Inability of therapy adherence	3.07	21.5	8.5–54.7	$p < .001$
Progression-free survival (number of cases $n = 172$, events $= 51$)				
	Cox regression			
Variable	**Beta**	**HR**	**95%-CI**	***p*-value[a]**
Sex				
Female	Ref.			
Male	−0.35	0.7	0.4–1.3	$p = .25$
Localisation				
Extremities	Ref.			
Trunk	0.51	1.7	0.9–3.1	$p = .12$
Head/neck	0.03	1.0	0.4–2.8	$p = .95$
Histologic grading				
Low-grade	Ref.			
High-grade	0.17	1.2	0.5–2.9	$p = .71$
Charlson Comorbidity Index				
=2	Ref.			
>2	0.31	1.4	0.7–2.6	$p = .35$
Adherence to therapy recommendations				
Complete implementation	Ref.			
Partial implementation of 1 therapy modality	1.31	3.7	1.4–10.2	$p = .01$
Omission of ≥1 therapy modality	1.38	4.0	1.6–9.7	$p < .01$
Inability of therapy adherence	2.90	18.1	8.5–38.2	$p < .001$

Note: Significant *P*-values are shown in bold to emphasise them.
Abbreviations: CI, confidence interval for the hazard ratio; HR, hazard ratio; Ref. reference group.
[a]*p*-value of each individual variable.

surgical outcomes, lower recurrence rates and prolonged survival.[19] In addition, Blay et al. observed that patients treated at expert centres or presented in an ITB more frequently exhibited unfavourable characteristics and yet benefited from a better outcome than patients treated outside centres.[13,20] However, our project reveals a particularly vulnerable patient group with a high-risk profile who suffers from impaired outcomes and an aggressive disease course, which, despite optimised interdisciplinary therapy management, appears to be currently unalterable. As we refuse to accept this as an irrevocable circumstance, we hereby emphasize the need to deepen our understanding of sarcomas' clinical course to personalise therapeutic approaches.

The ITB ensures a structured exchange between all involved disciplines. However, regarding the benefit of an ITB, the literature shows partly contradictory results: Blay et al. published a study on >12,000 STS patients, demonstrating that a pre-therapeutic ITB

TABLE 4 Univariate survival analysis metastasised tumour stage.

Tumour-specific overall survival									
	Log rank-test					Cox regression			
Variable	Number of cases *n*	Events	Mean in years (95%-CI)	Median in years (95%-CI)	*p*-value	Beta	HR	95%-CI	*p*-value
Sex	33	24							
Female	12		1.4 (0.5–2.2)	1.0 (0.5–1.4)		Ref.			
Male	21		1.1 (0.6–1.6)	0.7 (0.0–1.3)	$p = .47$	0.32	1.4	0.6–3.2	$p = .46$
Age	33	24							
<60 years	16		1.3 (0.4–2.2)	0.7 (0.5–0.8)		Ref.			
>60 years	17		1.2 (0.7–1.7)	1.0 (0.6–1.3)	$p = .79$	−0.11	0.9	0.4–2.0	$p = .8$
Localisation	33	24							
Extremities	8		1.1 (0.6–1.6)	0.8 (0.5–1.0)		Ref.			
Trunk	21		1.2 (0.6–1.8)	0.9 (0.5–1.3)		0.12	1.1	0.4–3.1	$p = .82$
Head/neck	4		1.0 (0.2–1.9)	0.2 (–)	$p = .86$	−0.28	0.8	0.1–3.9	$p = .74$
Charlson Comorbidity Index	33	24							
=8	24		1.6 (0.9–2.3)	1.0 (0.5–1.6)		Ref.			
>8	9		0.6 (0.3–0.8)	0.4 (0.4–0.5)	**$p = .03$**	1.00	2.7	1.1–6.8	**$p = .03$**
ECOG	24	18							
=0	17		1.3 (0.6–2.0)	1.0 (0.6–1.3)		Ref.			
≥1	7		0.5 (0.1–0.8)	0.4 (0.0–0.7)	**$p = .03$**	1.11	3.0	1.1–8.5	**$p = .04$**
Adherence to therapy recommendations	32	24							
Complete implementation	9		2.2 (0.9–3.5)	1.2 (0.9–1.6)		Ref.			
Partial implementation of 1 therapy modality	3		1.9 (0.4–3.4)	1.2 (0.5–1.9)		0.35	1.4	0.3–7.5	$p = .68$
Omission of ≥1 therapy modality	4		1.2 (0.1–2.3)	0.6 (–)		0.73	2.1	0.4–10.7	$p = .38$
Inability of therapy adherence	16		0.6 (0.4–0.8)	0.5 (0.2–0.7)	**$p = .01$**	1.7	5.5	2.0–15.0	**$p < .001$**
Progression-free survival									
	Log rank-test					Cox regression			
Variable	Number of cases *n*	Events	Mean in years (95%-CI)	Median in years (95%-CI)	*p*-value	Beta	HR	95%-CI	*p*-value
Sex	28	24							
Female	12		0.6 (0.4–0.7)	0.5 (0.3–0.7)		Ref.			
Male	16		0.7 (0.3–1.1)	0.3 (0.2–0.5)	$p = .95$	0.03	1.0	0.4–2.5	$p = .95$
Age	28	24							
<60 years	13		0.5 (0.4–0.7)	0.4 (0.2–0.6)		Ref.			
>60 years	15		0.8 (0.3–1.2)	0.5 (0.2–0.8)	$p = .53$	−0.28	0.8	0.3–1.8	$p = .53$
Localisation	28	24							
Extremities	7		0.5 (0.3–0.6)	0.4 (0.4–0.5)		Ref.			
Trunk	20		0.7 (0.3–1.1)	0.4 (0.1–0.6)		−0.21	0.8	0.3–2.2	$p = .68$
Head/neck	1		1.5 (–)	1.5 (–)	$p = .48$	−1.34	0.3	0.0–2.5	$p = .24$
Charlson Comorbidity Index	28	24							
=8	21		0.8 (0.4–1.2)	0.6 (0.4–0.9)		Ref.			
>8	7		0.3 (0.2–0.4)	0.3 (0–0.26)	**$p < .01$**	1.5	4.5	1.6–12.3	**$p < .01$**
ECOG	19	17							
=0	15		0.5 (0.3–0.6)	0.5 (0.4–0.7)		Ref.			
≥1	4		0.4 (0.0–0.9)	0.2 (0.0–0.4)	$p = .89$	−0.10	0.9	0.3–3.3	$p = .89$

(Continues)

TABLE 4 (Continued)

Progression-free survival									
	Log rank-test					Cox regression			
Variable	Number of cases *n*	Events	Mean in years (95%-CI)	Median in years (95%-CI)	*p*-value	Beta	HR	95%-CI	*p*-value
Adherence to therapy recommendations	28	24							
Complete implementation	9		0.8 (0.5–1.1)	0.9 (0.4–1.4)		Ref.			
Partial implementation of 1 therapy modality	3		1.6 (0.0–3.2)	0.8 (0.1–1.4)		0.08	1.1	0.2–5.7	$p = .93$
Omission of ≥1 therapy modality	4		0.5 (0.2–0.8)	0.3 (0.0–0.7)		1.67	5.2	1.3–21.7	**$p = .02$**
Inability of therapy adherence	12		0.4 (0.2–0.5)	0.4 (0.0–0.6)	**$p < .05$**	1.77	5.9	2.2–15.7	**$p < .001$**

Note: Significant *P*-values are shown in bold to emphasise them.
Abbreviation: CI, confidence interval.

was associated with a better surgical outcome and a lower local recurrence rate.[13] In an early French study by Ray-Coquard et al., fewer local recurrences were observed if a pre-therapeutic ITB had taken place.[12] In contrast, Marec-Bérard et al. could not identify ITB presentation as prognostically relevant.[21] Further data analyses by Netsarc observed a lower recurrence risk with pre-therapeutic ITB presentation but a higher mortality risk. The authors discussed that an adverse prognostic factor may not have been considered or that the presented patients were particularly complex cases.[20]

Our study focused mainly on adherence to the ITB recommendations. This subject has been addressed in only few comparable studies: A retrospective study of Ewing-sarcoma patients by Kreyer et al. found 77% adherence to the ITB recommendations. In patients with metastatic disease, compliance with the ITB recommendations was associated with improved OS. In contrast, no correlation was observed between survival and surgical outcome in localised disease.[22] Another study by Hollunder et al. investigated adherence to the ITB recommendations in 320 sarcoma cases. In this analysis, 59% of the ITB recommendations were implemented entirely, and 15% partially. Exceptions occurred in 9% of the cases because of physicians' decisions, due to side effects or comorbidities, and patient wishes. However, 18% of the patients died before therapy started.[23]

Further studies on the role of the ITB focussing on other tumour entities resulted in similar observations: The University of Leipzig, Germany, studied a cohort of 1246 patients with gastrointestinal tract carcinomas. In 64% of cases, the ITB recommendations were fully implemented. The main reasons for non-adherence were comorbidities and patient refusal. In patients with palliative intended therapy, deviations from the ITB recommendations were more frequently observed.[24] Ranganashyam et al. described a cohort of 221 patients with head and neck tumours. Adherence to therapy was documented in 78%. Remarkably, the reasons for non-adherence in 22% were patient refusal in the majority of cases (74%), and disease-specific factors in 22%. Non-adherent patients also showed a shorter OS, although it should be noted that this group more often displayed an advanced disease.[25]

Hence, a therapy adherence of 69% in patients with localised disease in our cohort is comparable with the range in the exemplary studies mentioned above. However, in metastasised disease, our data on therapy adherence in only 30% significantly deviates from the existing data, possibly due to the low number of cases.

Additional potential pitfalls in interpreting the role of the ITB in STS treatment in our study are that other known risk factors should have been taken into account within the scope of a retrospective data collection. Unfortunately, not all specific risk factors could be entirely collected: The ECOG was missing in 30% of cases. However, due to data incompleteness, we opted against its inclusion in the multivariate survival analysis to ensure a better cohort representation. Consequently, the results should be interpreted with caution due to the unaccounted performance status. Additionally, tumour size, a prognosis-determining variable, was not considered. The observation periods were very short in some cases due to loss of contact. Thus, the outcome and the therapy adherence of these respective patients could not be included in the analysis. The partial quantitative measurement of therapy adherence should also be viewed cautiously, as the TM could only be compared to a limited extent. Furthermore, a potential confounding factor might have been the heterogeneity of the study cohort. Differences in patients´ characteristics and in particular in the histological subtype as well as the grading inevitably lead to different therapy concepts, making the recommendations of the ITB only partially comparable. Our study cohort included histologic subtypes (e.g., hemangioendothelioma or solitary fibrous tumour) that frequently show a less aggressive disease course. We intentionally included these patients, recognizing that these individuals are discussed in real-life ITB and are included in the specifications by the German Cancer Society.[16] Furthermore, they may also demonstrate a malignant disease course, which was also observed in our study. According to prevailing guidelines, interdisciplinary treatment is deemed essential in those cases.[9] Desmoid tumours were not considered due to their merely locally aggressive properties without metastatic potential.[1]

In addition, introduction to the ITB was not performed pre-therapeutically for all cases. For example, if a sarcoma resection had

already been performed and a re-resection was not indicated, this TM was not considered in the ITB recommendations and, thus not in the evaluation of adherence. Taking this heterogeneity into account, we performed a subgroup analysis including patients with localised disease without prior therapeutic intervention and recommendation of at least two TMs. In accordance with our previously presented results, the univariate analysis showed a shorter DOS when one or more TM could not be implemented (Supplementary Material Table S2). The reasons for the considerable proportion of interventions prior to ITB presentation are presumably due to the comparatively old data from a system that is subject to a continuous learning process. Since the start of treatment of the first patient in this cohort, multiple efforts have been made at our sarcoma centre to consistently implement quality features of sarcoma treatment such as pre-therapeutic ITB presentation. Additionally, due to their diverse clinical presentation, sarcomas are initially seen by a variety of disciplines and here too, awareness and sensitivity to the possibility of a sarcoma diagnosis is a long learning process.

Furthermore, this study primarily focuses on the ITB for therapy management. The complex diagnostic procedures for suspected sarcoma cases, or the entire treatment, requiring, for example, a close collaboration among surgeons, pathologists, and radiologists for a successful resection,[3] are marginally portrayed. Therefore, this work provides just a partial perspective on the significance of interdisciplinarity in STS treatment, emphasizing the need for a more comprehensive representation of the entire process.

Summarising our analysis, non-adherence was associated with a higher risk of recurrence and mortality, underscoring the importance of following the ITB recommendations. In addition, we observed a subgroup with a high-risk profile that could not be appropriately treated because of rapid progression or treatment complications. It is essential that specific patient characteristics not considered in the analysis might have been present and should be investigated in future studies. It remains evident that known risk factors such as the histologic subtype, histological grading, tumour size, localisation and general condition of the patient are still predominant determinants for the development of a therapeutic concept as well as for the prognostic assessment of the sarcoma disease.

5 | CONCLUSION

This study presents the first comprehensive analysis of therapy adherence in STS patients at a large Comprehensive Cancer Centre in Germany. The results demonstrate the importance of interdisciplinary treatment in the framework of an ITB and confirm its independent clinical and prognostic value. This project also outlines the potential constraints and ongoing challenges inherent in the progressively optimized landscape of interdisciplinary sarcoma therapy. While larger cohorts are warranted for validation, we further emphasise focusing STS treatment at certified sarcoma centres and enhancing commitment to pursuing therapy adherence following the mandatory discussion of cases within certified ITBs.

AUTHOR CONTRIBUTIONS

Annika Strönisch: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; visualization; writing – original draft; writing – review and editing. **Daniel Rau:** Writing – original draft; writing – review and editing. **Silvan Wittenberg:** Resources; writing – review and editing. **David Kaul:** Resources; writing – review and editing. **Georgios Koulaxouzidis:** Writing – original draft; writing – review and editing. **Robert Öllinger:** Resources; writing – review and editing. **Maximilian von Laffert:** Resources; writing – review and editing. **Armin Jarosch:** Resources; writing – review and editing. **Frederik Schäfer:** Resources; writing – review and editing. **Ulrich Keilholz:** Resources; writing – review and editing. **Lars Bullinger:** Resources; writing – original draft; writing – review and editing. **Sven Märdian:** Writing – original draft; writing – review and editing. **Jana Striefler:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; supervision; validation; visualization; writing – original draft; writing – review and editing. **Anne Flörcken:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; supervision; validation; visualization; writing – original draft; writing – review and editing.

ACKNOWLEDGEMENTS

The continuous support of the Charité Comprehensive Cancer Centre enabled the project. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets supporting the findings of this study can be retrieved from the corresponding author based on reasonable request.

ETHICS STATEMENT

Our study has been performed with institutional ethical review board approval of the Ethics Committee of Charité Universitätsmedizin Berlin (Approval Number EA2/240/20) and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients in accordance with institutional guidelines.

ORCID

Annika Strönisch https://orcid.org/0000-0002-0961-4602

REFERENCES

1. WHO Classification of Tumours Editorial Board. *WHO Classification of Tumours. Soft Tissue and Bone Tumours*. Vol 3. 5th ed. International Agency for Research on Cancer (WHO); 2020.
2. Stiller CA, Trama A, Serraino D, et al. Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. *Eur J Cancer*. 2013;49(3):684-695. doi:10.1016/j.ejca.2012.09.011
3. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). A. S3-Leitlinie Adulte Weichgewebesarkome, Langversion 1.1, AWMF-Registernummer: 032/044OL. 2022. https://www.leitlinienprogrammonkologie.de/leitlinien/adulte-weichgewebesarkome/.

4. Lahat G, Tuvin D, Wei C, et al. New perspectives for staging and prognosis in soft tissue sarcoma. *Ann Surg Oncol*. 2008;15(10):2739-2748. doi:10.1245/s10434-008-9970-6
5. Pisters PW, Leung DH, Woodruff J, Shi W, Brennan MF. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. *J Clin Oncol*. 1996;14(5):1679-1689. doi:10.1200/JCO.1996.14.5.1679
6. Trovik CS, Bauer HC, Alvegård TA, et al. Surgical margins, local recurrence and metastasis in soft tissue sarcomas: 559 surgically-treated patients from the Scandinavian sarcoma group register. *Eur J Cancer*. 2000;36(6):710-716. doi:10.1016/s0959-8049(99)00287-7
7. Maretty-Nielsen K, Aggerholm-Pedersen N, Safwat A, Baerentzen S, Pedersen AB, Keller J. Prevalence and prognostic impact of comorbidity in soft tissue sarcoma: a population-based cohort study. *Acta Oncol*. 2014;53(9):1188-1196. doi:10.3109/0284186X.2014.888494
8. Maretty-Nielsen K, Aggerholm-Pedersen N, Safwat A, et al. Prognostic factors for local recurrence and mortality in adult soft tissue sarcoma of the extremities and trunk wall: a cohort study of 922 consecutive patients. *Acta Orthop*. 2014;85(3):323-332. doi:10.3109/17453674.2014.908341
9. Gronchi A, Miah AB, Tos APD, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol*. 2021;32(11):1348-1365. doi:10.1016/j.annonc.2021.07.006
10. Erhebungsbogen Sarkomzentren–Zertifizierung der Deutschen Krebsgesellschaft. Dokumente, DKG (Accessed August 23, 2021). https://www.krebsgesellschaft.de/zertdokumente.html.
11. Wiklund T, Huuhtanen R, Blomqvist C, et al. The importance of a multidisciplinary group in the treatment of soft tissue sarcomas. *Eur J Cancer*. 1996;32(2):269-273. doi:10.1016/0959-8049(95)00520-X
12. Ray-Coquard I, Thiesse P, Ranchère-Vince D, et al. Conformity to clinical practice guidelines, multidisciplinary management and outcome of treatment for soft tissue sarcomas. *Ann Oncol*. 2004;15(2):307-315. doi:10.1093/annonc/mdh058
13. Blay JY, Soibinet P, Penel N, et al. Improved survival using specialized multidisciplinary board in sarcoma patients. *Ann Oncol*. 2017;28(11):2852-2859. doi:10.1093/annonc/mdx484
14. Blay JY, Italiano A, Penel N, et al. 1316O improved nationwide survival of sarcoma patients 10 years after establishment of the NETSARC+ reference center network. *Ann Oncol*. 2022;33:S1145-S1146. doi:10.1016/j.annonc.2022.07.1449
15. GTDS. Gießen Tumour Documentation System (Accessed December 31, 2022). http://imigtds.med.uni-giessen.de/gtds/gtdsengl.htm.
16. Kennzahlenbogen Sarkomzentren – Zertifizierung der Deutschen Krebsgesellschaft. Dokumente | DKG (Accessed February 29, 2024). https://www.krebsgesellschaft.de/zertdokumente.html.
17. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the eastern cooperative oncology group. *Am J Clin Oncol*. 1982;5(6):649-655.
18. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383. doi:10.1016/0021-9681(87)90171-8
19. Strönisch A, Märdian S, Flörcken A. Centralized and interdisciplinary therapy Management in the Treatment of sarcomas. *Life*. 2023;13(4):979. doi:10.3390/life13040979
20. Blay JY, Honoré C, Stoeckle E, et al. Surgery in reference centers improves survival of sarcoma patients: a nationwide study. *Ann Oncol*. 2019;30(7):1143-1153. doi:10.1093/annonc/mdz124
21. Marec-Bérard P, Aho S, Berger C, et al. Clinical management of adolescents and young adults suffering from sarcoma in the French Rhône-Alpes region: a prospective exhaustive cohort with 10 years follow up. *Eur J Surg Oncol*. 2020;46(7):1301-1309. doi:10.1016/j.ejso.2020.03.218
22. Kreyer J, Ranft A, Timmermann B, et al. Impact of the interdisciplinary tumor Board of the Cooperative Ewing Sarcoma Study Group on local therapy and overall survival of Ewing sarcoma patients after induction therapy. *Pediatr Blood Cancer*. 2018;65(12):e27384. doi:10.1002/pbc.27384
23. Hollunder S, Herrlinger U, Zipfel M, et al. Cross-sectional increase of adherence to multidisciplinary tumor board decisions. *BMC Cancer*. 2018;18:936. doi:10.1186/s12885-018-4841-4
24. Krause A, Stocker G, Gockel I, et al. Guideline adherence and implementation of tumor board therapy recommendations for patients with gastrointestinal cancer. *J Cancer Res Clin Oncol*. 2023;149(3):1231-1240. doi:10.1007/s00432-022-03991-6
25. Rangabashyam MS, Lee SY, Tan SY, et al. Adherence of head and neck squamous cell carcinoma patients to tumor board recommendations. *Cancer Med*. 2020;9(14):5124-5133. doi:10.1002/cam4.3097

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Strönisch A, Rau D, Wittenberg S, et al. Therapy adherence after interdisciplinary tumour board discussion is associated with improved outcome in soft tissue sarcoma: A Charité Comprehensive Cancer Centre analysis. *Int J Cancer*. 2025;156(4):802-816. doi:10.1002/ijc.35201