This is a peer-reviewed, accepted author manuscript of the following research article:
Boulouta, A.et al. "Pathologic complete response in patients with localized soft tissue sarcoma treated with neoadjuvant therapy and its correlation with clinical outcomes: a systematic review". *Cancer Treatment Reviews*. 2024. 130. https://doi.org/10.1016/j.ctrv.2024.102820

Pathologic complete response in patients with localized soft tissue sarcoma treated with neoadjuvant therapy and its correlation with clinical outcomes: a systematic review

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Abstract

Soft tissue sarcomas (STS), comprising approximately 1% of adult solid malignancies, are primarily treated with surgery, with the choice of perioperative treatment being a challenging and highly individualized decision. Clinical trials assessing neoadjuvant modalities in STS predominantly use clinical outcomes or radiologic response as endpoints, with pathologic complete response (pCR) not being employed as a designated study endpoint. Our systematic review aimed to assess the rates of pCR in clinical trials of different neoadjuvant modalities for STS and its correlation with patient clinical outcomes. 23 phase I, II and III studies were included, from which data regarding rates of pCR with each treatment, as well as correlation of pCR with clinical outcomes were retrieved. In 16 trials that assessed pCR, the percentage of patients who achieved a pCR ranged from 8 to 58%. Most of these trials did not aim to establish an association between pCR and clinical outcomes. However, among those that did investigate this correlation, a positive association was identified between pCR and both 5-year disease-specific survival (DSS) and 5-year overall survival (OS). While pCR serves as a crucial marker guiding treatment decisions in other neoplasms like triple negative breast cancer and urothelial cancer, it is not yet used in a similar setting for STS. Our findings indicate variability in patients achieving pCR across different neoadjuvant treatments for STS and a possible positive correlation with patient outcomes. Consequently, we propose considering pCR as a surrogate endpoint in future prospective trials for STS.

Keywords: soft tissue sarcoma; neoadjuvant treatment; preoperative treatment; pathologic complete response

Introduction

Soft tissue sarcomas (STS) are a heterogeneous group of malignant tumors which account for approximately 1% of adult solid malignancies, with an estimated annual incidence of 4-5/100000/year in Europe [1,2]. Surgery is the mainstay of treatment for localized STS and the choice of a proper perioperative treatment regimen remains challenging. Historically, the use of radiotherapy (RT) was preferred postoperatively for high-grade lesions, as well as for tumors with positive surgical margins [1]. In the latest years, neoadjuvant therapy has gained attention due to several advantages, particularly tumor shrinkage, improved surgical outcomes and lower rates of local relapse. There are several types of neoadjuvant therapy, namely chemotherapy, RT, targeted therapy, radiosensitizers, hyperthermia, and combinations of the above. The choice of the type of perioperative therapy is highly individualized and depends on several factors, mainly histology, tumor site, and patient age. Wide excision and RT are the standard treatment for high-grade tumors, with a shift towards the preoperative use of RT. Adjuvant or neoadjuvant chemotherapy is also proposed for patients with high-risk disease and it may be used alone or in combination with RT or hyperthermia [3].

Clinical trials for all the above neoadjuvant modalities in STS mostly use clinical outcomes or radiologic response as endpoints. While pathologic complete response (pCR) serves as a crucial marker guiding treatment decisions in other neoplasms like breast cancer and urothelial cancer, it is not yet used in a similar setting for STS. The rate of pCR, although reported in some of these trials, is not frequently correlated with patient clinical outcomes.

Methods

We performed a qualitative synthesis of published clinical trials and retrospective studies assessing different neoadjuvant modalities for localized STS.

We conducted a bibliographic search of the PubMed and Embase databases for articles published between January 1st, 1980 to January 8th, 2024. Searches were done using the following search terms: “Soft tissue sarcoma” AND (“neoadjuvant” OR “preoperative”) AND (“trial” OR “study”). Relevant articles which evaluated pCR after neoadjuvant treatment for STS were retrieved from the reference list of the studies. Inclusion criteria for our systematic review were phase I, II or III clinical trials of neoadjuvant RT, chemotherapy, TKIs or combinations of the above, as well as retrospective studies evaluating pCR after neoadjuvant treatment for STS. We excluded trials not done on humans, not written in the English language, reviews, case reports and case series.

Our search initially yielded 360 results, of which 243 were reviewed and considered irrelevant to our study. Of the remaining 117 publications, 17 case reports, 24 case series, 42 reviews and 11 written in a language other than English were excluded. Finally, we included 23 studies in our analysis. The process of finding and including articles in our systematic review is summarized in Figure 1.

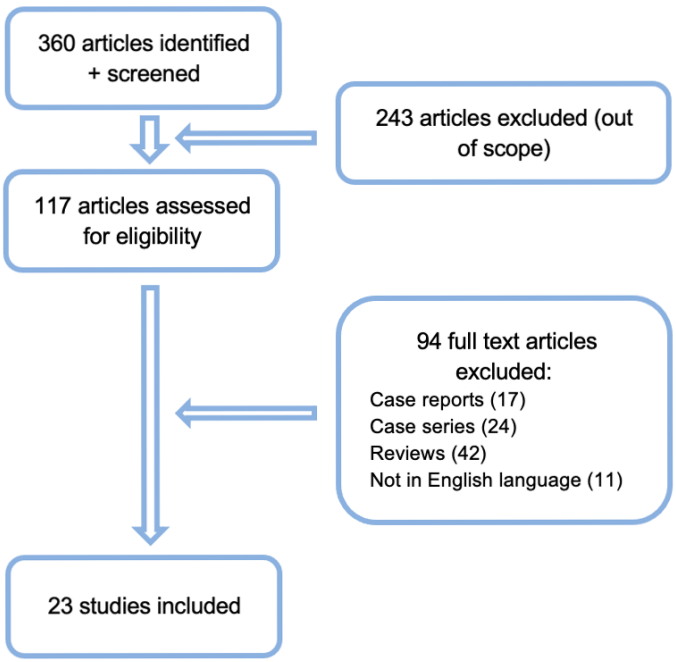

Figure 1: Flow diagram

Results

Neoadjuvant regional hyperthermia

A phase II study published in 2001 assessed the activity and safety of neoadjuvant regional hyperthermia (RHT) combined with chemotherapy in 59 patients with advanced or recurrent high-risk soft-tissue sarcoma (STS). Patients received four cycles of chemotherapy consisting of etoposide, ifosfamide and doxorubicin combined with RHT followed by surgical resection and adjuvant treatment. Pathologic complete response, defined as complete necrosis in the surgical specimen, occurred in six out of 59 patients (10.2%) and >75% necrosis, defined as favorable histological response, in 12 out of 59 patients (20.3%). The 5-yr survival rate reported in this study was 49%, but no correlation was reported between pCR and clinical outcomes [4].

In 2010, the largest randomized phase III trial of neoadjuvant chemotherapy in patients with high-risk STS (defined as size≥ 5, deep localization or tumor grade II/III) was published, which evaluated the efficacy of neoadjuvant regional hyperthermia combined with chemotherapy, namely etoposide, ifosfamide and doxorubicin, versus chemotherapy alone. The primary study results, as well as a long term-follow up, assessed clinical factors in the two groups, including response rate, local progression-free survival, 5-year and 10-year survival benefit, yet the pathologic response in the resected specimens was not assessed [5,6].

Neoadjuvant radiotherapy

In a 2010 prospective study of 25 patients receiving neoadjuvant RT alone for soft tissue sarcoma, the median percentage of pathologic necrosis on histologic examination of the resected specimens was 30% (range 5–100%). Complete or near-complete pathologic response after preoperative RT, defined as ≥95% necrosis, was shown in two tumors (8%). Complete or near-complete pathologic response was associated with favorable distant recurrence-free survival (100% 3-year event-free survival vs. 59% 3-year event-free survival) but this association was not statistically significant possibly due to the small sample size ($P = 0.50$) [7].

Neoadjuvant chemotherapy alone or in combination with radiotherapy

Preoperative chemotherapy for STS was first tested in a 1987 study by Rousse et al. This study included 34 patients with STS who received a combination of adriamycin, cyclophosphamide, cisplatin, vindesine and DTIC or a combination of cyclophosphamide, vincristine, adriamycin and DTIC as preoperative treatment [8]. At that time, only data regarding radiographic response, rather than pathologic response, were reported.

The first phase II trial of neoadjuvant chemotherapy for patients with localized STS was published in 2001 by the EORTC and the Canadian Sarcoma Group. The trial examined neoadjuvant doxorubicin and ifosfamide in adults with “high risk” STS (defined as tumors ≥8cm or grade 2/3 tumors). Patients were randomized to either surgery alone or preoperative chemotherapy with three cycles of doxorubicin plus ifosfamide followed by surgical excision. The

trial assessed patient response by radiologic criteria but did not refer to grades of pathologic necrosis [9].

The RTOG 9514 phase II trial from 2006 evaluated the use of neoadjuvant chemotherapy (mesna, doxorubicin, ifosfamide, dacarbazine - modified MAID regimen) combined with preoperative RT, followed by surgery and three cycles of postoperative chemotherapy (modified MAID). In the resected specimens, a pathologic review was performed in order to assess response according to tumor necrosis percentage. Fourteen out of 51 patients (27.4%) had no viable tumor in the resected specimen and 19 out of 51 patients (37.2%) had a necrosis over 75% [10]. Even though there are data on long-term outcomes from this study reporting 5-year rates of locoregional failure and metastasis, a correlation with pCR was not investigated [11].

A 2012 phase II clinical trial assessed the rate of pCR with neoadjuvant trabectidin (1.5 mg/m^2 24h IV infusion administered every 3 weeks) in patients with locally advanced myxoid liposarcoma (ML). In the reported results three out of 23 patients (13%) achieved pCR, defined as complete disappearance of tumor tissue in the post-treatment surgical specimen (pCR rate of 13%; 95% CI, 3% to 34%) [12].

A randomized, phase II study of neoadjuvant doxorubicin and ifosfamide versus gemcitabine and docetaxel in patients with localized, high-risk STS assessed radiological response rates, hospitalization rates, 2-year and median DFS but not pathologic response [13].

Likewise, a randomized phase III trial from the Italian, Spanish, French and Polish Sarcoma Groups published in 2020, which examined the efficacy of histology-tailored (HT) neoadjuvant chemotherapy versus standard anthracycline plus ifosfamide for high-risk STS, only compared DFS and OS between the two arms and not pathologic response [14].

In a phase II trial published in 2021, 18 patients with non-metastatic extremity soft tissue sarcoma were assigned to receive doxorubicin and ifosfamide for three neoadjuvant cycles, concomitant with hypo-RT (25 Gy in 5 fractions) followed by surgery. Six patients (33%) had no residual viable tumor detected in pathologic specimens (3 of these myxoid liposarcomas), but this was not correlated with survival [15].

A more recent nonrandomized clinical trial published in 2023 evaluated the efficacy and safety of neoadjuvant trabectidin (1.5 mg/m^2 every 21 days for a total of three cycles) combined with 25 fractions of radiation for a total of 45 Gy. Five out of 39 patients (12.8%) achieved a complete pathologic response and 20 out of 39 patients (51.3%) achieved ≥90% necrosis [16]. However, these rates were not correlated with patients' clinical outcomes.

Finally, another recent study of 693 patients with primary localized resectable myxofibrosarcoma and undifferentiated pleomorphic sarcoma of the extremities and trunk wall receiving neoadjuvant chemotherapy, RT or a combination of both, sought to determine the correlation between pathologic and radiologic response and clinical outcomes. Viable tumor (VT)% was ≤5% in 13 out of 46 patients (28.2%) in the chemotherapy arm, 24 out of 99 patients (24.2%) in the RT arm and 40 out of 88 patients (45.4%) in the combination arm. In patients who received neoadjuvant chemotherapy, a VT≤5% was associated with better survival outcomes (p =

.09), whereas the same was not observed in patients who received neoadjuvant chemoradiotherapy or RT alone [17].

Combination of neoadjuvant antiangiogenic treatment and radiotherapy

In a 2011 phase II study of neoadjuvant bevacizumab alone versus bevacizumab plus RT for patients with ≥5 cm, intermediate- or high-grade resectable STS, nine out of 20 tumors (45%) had ≥80% pathologic necrosis. Of these nine tumors, two had 80–89% necrosis, four had 90–99% necrosis, and three had 100% necrosis (i.e. pCR) [18]. However, a correlation of these results with survival outcomes was not investigated.

Combination of neoadjuvant TKIs and radiotherapy

During the last decade, several trials of tyrosine kinase inhibitors (TKIs) as neoadjuvant treatment for STS, either alone or in combination with chemotherapy and/or RT, have been conducted.

In 2013, a phase I trial assessed the addition of sorafenib to chemoradiotherapy in patients with high-risk extremity soft tissue sarcoma. Even though the main objective of the study was to establish the maximum tolerated dose of sorafenib, researchers did assess the rate of pCR. Out of 16 patients, seven patients (44%) had ≥95% histopathologic necrosis in the surgical specimen following preoperative chemoradiotherapy [19].

A similar study was done in the next year by Canter et al testing concomitant sorafenib with preoperative RT. Complete pathologic response, defined as ≥95% tumor necrosis was observed in three out of eight patients (37.5%) but with no data on clinical outcomes in correlation to pCR [20].

Pazopanib was first tested in a 2015 phase I study by Haas et al in which enrolled patients with high-risk deep- seated STS received pazopanib for 6 weeks combined with preoperative RT for a total of 50 Gy. Pathologic complete response, defined as ≥95% necrosis rate, was found in four out of 10 evaluated resection specimens (40%) but this was not correlated with long-term oncologic outcomes [21].

In 2016, a phase I trial of preoperative sunitinib plus RT was conducted by the German interdisciplinary sarcoma group (GISG-03). Nine patients were enrolled in the study, of which 6 patients received 25mg and 3 patients 37.5mg for 2 weeks prior to and throughout RT. Three out of nine patients (33.3%) achieved a pCR, defined as ≥95% tumor necrosis, all of which showed stable disease in the preoperative restaging. In the 23-month median follow-up, two out of three the patients who had achieved a pCR were alive with metastatic disease (AWD) and one out of three had no evidence of disease (NED) [22].

The ARST1321 trial, a multicenter, randomized, phase 2 trial of preoperative chemoradiotherapy with or without pazopanib, enrolled children and adults from 57 hospitals in the USA and Canada with unresected chemotherapy-sensitive soft tissue sarcoma of intermediate or high grade with a size ≥5cm. Patients received chemotherapy with ifosfamide and doxorubicin plus 45 Gy neoadjuvant RT, followed by surgery. They were randomly assigned to receive oral

pazopanib or placebo concurrently with chemoradiotherapy. The primary endpoint of the study was histologic response, with pathologic near complete response defined as ≥ 90% necrosis in the surgical specimen. Patients achieving a pathologic near complete response were 14 out of 24 (58.3%) in the pazopanib arm and four out of 18 (22.2%) in the control arm [23]. Interestingly, one of the exploratory endpoints of the study was to compare the response rates obtained through standard imaging and pathologic assessment, aiming to identify which correlates better with disease outcome. However, this was not determined due to the early termination of the study, as an interim boundary was crossed, so the sample size was not considered sufficient.

A 2021 phase II study by van Meekeren assessed the use of preoperative pazopanib plus RT in patients with high-risk, localized soft-tissue sarcoma. Patients received neoadjuvant RT with 50 Gy in 25 fractions or with a dose reduction to 36 Gy in 18 fractions plus concurrent pazopanib, followed by surgical resection after 4-8 weeks. The study's primary endpoint was the pCR rate, defined as ≤5% viable tumor cells. Five out of 25 patients (20%) achieved a pCR with the combination treatment [24]. The study included a median follow-up of 39 months but did not seek to correlate pCR rates with oncologic outcomes.

Neoadjuvant stereotactic ablative radiotherapy

A single-center, prospective, single-arm phase II trial from 2021 tested neoadjuvant stereotactic ablative radiotherapy (SABR) in patients with localized STS. Patients received SABR with 40 Gy in 5 fractions, followed by surgery after at least 4 weeks. In the 24 patients enrolled, the median rate of histopathologic necrosis was 65%, and five out of 25 patients (20.8%) achieved pCR, defined as ≥95% necrosis of tumor cells in the surgical specimen. The study included a median follow-up of 20.7 months and reported a 2-year estimated risk of local recurrence, distant metastasis, and cause-specific death rates but not in relation to pCR [25].

Neoadjuvant immune-checkpoint blockade

Recently, a phase II clinical trial of neoadjuvant nivolumab or nivolumab plus ipilimumab with or without radiation therapy as preoperative treatment for patients with treatment-naive primary or locally recurrent resectable undifferentiated pleomorphic sarcoma (UPS) and dedifferentiated liposarcoma (LPS) was conducted. The primary endpoint was pathologic response, indicated by hyalinization percentage, with a median of 8.8% in DDLPS and 89% in UPS. In this study, lower levels of regulatory T cells before treatment were associated with a major pathologic response, defined as hyalinization >30% [26].

Pathologic complete response in STS

A pathologic complete response in the context of neoadjuvant treatment for solid malignancies refers to the absence of viable cancer cells in the surgical specimen obtained after

the completion of neoadjuvant therapy [27]. While pCR after neoadjuvant treatment is of high prognostic value in several malignancies, including bone sarcomas in which it has been established as an indicator of prognosis, its significance has been unclear for STS and thus is not commonly used as a surrogate marker in STS trials [28,29].

Despite the several trials of neoadjuvant therapy for STS mentioned above, only some of them report the rate of pCR in the tumor specimens and even fewer associate it with clinical response and survival. However, there are studies reporting a correlation between pCR and clinical outcomes. Schmidt et al. studied clinical and pathologic features of patients receiving chemotherapy for STS. They concluded that the amount of viable tumor after chemotherapy is an indicator of short-term effect of therapy [30]. In 2001, Eilber et al., studied the association between treatment-induced pathologic necrosis and patient outcomes in high-risk extremity STS and found a positive correlation between pathologic necrosis and local recurrence and overall survival. Specifically, the 5- and 10-year local recurrence rates were 6% and 11%, respectively, for patients with pCR versus 17% and 23%, respectively ($p=0.002$), for patients with <95% pathologic necrosis [31]. Donahue et al., evaluating neoadjuvant chemotherapy with or without radiation in 55 patients with high-grade retroperitoneal sarcomas concluded that histopathologic response is associated with an improved disease-specific survival (DSS). Fourteen out of 55 patients (25.4%) achieved ≥95% histopathologic necrosis and were defined as responders. The 5-year DSS for responders was 83%, significantly higher than the 34% for non-responders ($p=0.002$) [32].

Pathologic complete response and its correlation with patient outcomes has gained more interest in recent years. In 2018, a systematic review and meta-analysis of 1663 patients from 21 studies of neoadjuvant therapy in STS aimed to evaluate the clinical significance of pCR in STS and concluded that <90% necrosis in the tumor specimen post-neoadjuvant treatment is associated with increased risk of recurrence (hazard ratio [HR] 1.47; 95% CI: 1.06–2.04; $p=0.02$) and death (HR 1.86; 95% CI: 1.41-2.46; $p < 0.001$) [33]. In the long-term update of RTOG 9514 and RTOG 0630, two NRG Oncology phase II trials for patients with localized, high-grade STS receiving neoadjuvant chemoradiotherapy or RT alone, respectively, Wang et al., sought to determine the prognostic significance of pCR in STS. With a median follow-up of over 5 years, overall survival was 100% for patients who had pCR versus 76.5% (RTOG 9514, 95% CI 62.3-90.8) and 56.4% (RTOG 0630, 95% CI 43.3-69.5) for patients who did not achieve a pCR [34]. These two studies proved that pCR is associated with improved survival outcomes and indicate that it should be used as a surrogate marker for STS clinical trials.

Table 1 summarizes the trials assessed in this study, the evaluation of pCR in each of them, as well as clinical correlations.

Pathologic complete response in patients with localized soft tissue sarcoma treated with neoadjuvant therapy and its correlation with clinical outcomes

Study	Sarcoma location	Treatment	Number of patients treated	pCR definition (% necrosis)	pCR rate (%)	Clinical correlation
Issels et al, 2001 [4]	Any	RHT + ChT	59	100	10.2	N/A
Canter et al, 2010 [7]	Any	RT	25	≥95	8	Increased DRFS - not statistically significant (p=0.50)
Leite et al, 2021 [25]	Extremity	SABR	25	≥95	20.8	N/A
Rouesse et al, 1987 [8]	Any	ChT	34	N/A	N/A	N/A
EORTC + Canadian Sarcoma group, 2001 [9]	Any	ChT (AI)	67	N/A	N/A	N/A
RTOG 9514, 2006 [10,34]	Extremity, body wall	ChT (MAID) + RT	66	100	27.4	Superior 5-yr OS (100% vs 76.5%)
EORTC 62961-ESHO 95, 2010 [4,5]	Any	ChT (AI + E) + RHT	50	N/A	N/A	N/A
Gronchi et al, 2012 [12]	Any	ChT (trabectidin)	23	100	13	N/A
Donahue et al, 2010 [32]	Retroperitoneal	ChT +/- RT	55	≥95	25	Superior 5-yr DSS (83% vs 34%, p = 0.002)
RTOG 0630 [33]	Extremity	ChT vs ChT+RT	98	100	N/A	Superior 5-yr OS (100% vs 56.4%)
Davis et al, 2015 [13]	Any	ChT (AI vs GT)	80	N/A	N/A	N/A
Gronchi et al, 2020 [14]	Extremity, trunk wall	ChT	287	N/A	N/A	N/A
Gobo Silva et al, 2021 [15]	Extremity	ChT (AI) + hypoRT	18	100	33	N/A
Sanfilippo et al, 2023 [16]	Extremity, trunk wall	ChT (trabectidin) + RT	41	100	12.8	N/A
Danieli et al, 2023 [17]	Extremity, trunk wall	ChT	46	>95	28.2	Superior survival (p 0.09)
		RT	99	>95	24.2	No positive association
		ChT+RT	88	>95	45.4	No positive association
Yoon et al, 2011 [18]	Any	Bv +/- RT	20	100	33.3	N/A
Meyer et al, 2013 [19]	Extremity	Sorafenib + ChT + RT	16	≥95	44	N/A
Canter et al, 2014 [20]	Extremity	Sorafenib + RT	8	≥95	37.5	N/A
Haas et al, 2015 [21]	Extremity	Pazopanib + RT	10	≥95	40	N/A
GISG-03, 2016 [22]	Any	Sunitinib + RT	9	≥95	33.3	N/A
ARST1321, 2020 [23]	Any	Pazopanib + ChT (AI) + RT	24	>90	58.3	N/A
		ChT + RT (control arm)	18	>90	22.2	N/A
Van Meekeren et al, 2021 [24]	Any	Pazopanib + RT	25	>95	20	N/A

Table 1

Discussion

In the present study we sought to analyze the correlation between pCR to neoadjuvant treatments in STS and survival outcomes. Our analysis of pCR following neoadjuvant modalities for STS showed variability among different treatments. Specifically, there was a range of 10.2-33% when pCR was defined as no viable tumor in the resected specimen, 8-45.4% when pCR was defined as ≥95% necrosis and 22.2-58.3% when pCR was defined as >90% necrosis. Most of the clinical trials published to date assessed the rate of pCR. However, limitations to our retrospective study were that pCR was not defined in the same manner in all of the trials, as well as that the correlation between pCR and clinical outcomes were only investigated in a few of them. Among the studies that did investigate this correlation, a positive link was found between pCR and inferior rates of local relapse, as well as superior 5-yr DSS and OS [10,17,32,34].

Soft tissue sarcomas comprise a group of different entities managed with multimodality treatments. Surgery is the standard treatment for locoregional disease, and historically, radiation therapy or chemotherapy was used postoperatively in select cases [3]. However, lately, there is a growing inclination towards neoadjuvant treatment. The decision for using neoadjuvant or adjuvant treatments is based upon "high-risk" features of the tumor, namely histologic type and grade, size, and R0/R1 resection, but there are no specific guidelines or standard use of specific regimens, even in referral centers, as decisions are made on a case-to-case basis [35,36]. The relatively low pCR rates with different neoadjuvant modalities for STS reported above indicate the need for trials on new treatments, such as targeted therapies and immune checkpoint inhibitors alone or combined with chemotherapy or TKIs, in order to achieve higher rates of pCR.

pCR serves as a crucial marker in predicting clinical outcomes and guiding treatment decisions in other neoplasms like breast cancer, urothelial cancer, and bone sarcomas [37,38,39,40,41]. In the early stages of these tumors, pCR is a marker that should always be included in the pathology report, as it may indicate prognostic outcomes and guide the choice of postoperative treatment. In the case of STS, pCR is not yet used in a similar setting, as it is rarely reported and not considered for treatment decisions. As our findings indicate a possible positive correlation between pCR and patient outcomes, we propose coming to an exact definition of pCR for STS and considering it as a surrogate endpoint in future prospective trials for STS in order to improve clinical outcomes and select an optimal therapeutic approach tailored to each patient.

Conclusions

Our findings indicate variability in pCR definition and pCR rates across different neoadjuvant modalities for STS, with a range of 8-58.3%. Among the clinical trials that tried to assess a correlation between pCR and clinical outcomes, a positive association was found between pCR achievement and inferior rates of local relapse, as well as superior 5-year DSS and OS. We propose to develop an expert consensus on pCR definition which will aid in future clinical trial design.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

None

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