

Article

Effect of Neoadjuvant Therapies on Soft Tissue Sarcomas with Tail-Like Lesions: A Multicenter Retrospective Study

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Simple Summary: It is essential to focus on the tumor invasive front (tail-like lesion)—the soft tissue sarcoma's specific peripheral infiltrative growth characteristics—to avoid leaving unexpected tumor residues during surgery. This study aimed to analyze the effect of neoadjuvant therapy for highly malignant soft tissue tumors with tail-like lesions. From 2012 to 2019, 36 patients were treated with neoadjuvant therapy, including chemotherapy, radiotherapy, or both. Consequently, we observed shrinkage and occasionally disappearance of the tail-like lesion. The lesion's regression was related to the necrosis rate of the main part of the tumor. However, regression of lesions was not directly related to the achievement of the surgery with a microscopically negative margin and improvement of oncological outcomes. Thus, a more multi-angle evaluation to elaborate the surgical strategy is necessary.

Abstract: Several types of soft tissue sarcomas have peripheral infiltrative growth characteristics called *tail-like lesions*. The efficacy of neoadjuvant therapy for tumors with tail-like lesions has not been elucidated. From 2012 to 2019, we analyzed 36 patients with soft tissue sarcoma with tail-like lesions treated with neoadjuvant therapy, including chemotherapy, radiotherapy, or both. The effect of neoadjuvant therapy on the tail sign was investigated by analyzing the change in tail-like lesions during neoadjuvant therapy and histological responses. The median length of the tail-like lesion reduced from 29.5 mm at initiation to 19.5 mm after neoadjuvant therapy. The extent of shrinkage in tail-like lesion was related to the histopathological responses in the main part. Complete disappearance of the tail-like lesion was observed in 12 patients; however, it was not related to achieving a microscopically negative margin. The oncologic outcomes did not significantly differ between cases with complete disappearance of tail-like lesions or not. This study indicated the shrinkage of tail-like lesions did not have significant effect on complete resection or improvement of clinical outcomes. A more comprehensive evaluation is needed to elaborate on the surgical strategy.

Keywords: soft tissue sarcoma; invasive front; tail-like lesion; myxofibrosarcoma; undifferentiated pleomorphic sarcoma; neoadjuvant therapy; radiotherapy; chemotherapy

1. Introduction

Soft tissue sarcomas are rare and heterogeneous entities with local or distant metastatic potential [1]. Approximately 10%–30% of patients experience local recurrences, complicating subsequent procedures and occasionally resulting in amputation [2]. Several soft tissue sarcoma types have peripheral infiltrative growth characteristics around the invasive fronts (tail-like lesions) [3,4]. The surgical intervention plan should include these reactive zones during complete resection [5,6].

Neoadjuvant therapy using radiotherapy, chemotherapy, or both is now considered, especially for locally advanced tumors, to improve resectability with appropriate margins and long-term oncologic outcomes. The National Comprehensive Cancer Network (NCCN) guideline 2021 recommends neoadjuvant therapies for resectable stage II–III patients with adverse functional outcomes. These methods include radiotherapy [7], chemoradiotherapy [8], chemotherapy [9,10], and hyperthermia (e.g., isolated limb perfusion therapy) [11]. However, little is known about the effects of these methods on tail-like lesions.

This study aimed to analyze the effect of neoadjuvant therapy on tail-like peripheral lesions based on MRI and histological evaluation of resected specimens.

2. Materials and Methods

2.1. Patients

We included patients with histologically diagnosed malignant soft tissue tumors with tail-like lesions who underwent neoadjuvant therapy for primary soft tissue tumors between January 2012 and December 2019. Certified pathologists confirmed all diagnoses at each hospital. Thirty-six patients were enrolled using independent questionnaires assigned to the 12 hospitals of the Tokai Musculoskeletal Oncology Consortium. The questionnaire included sex, age at diagnosis, histological diagnosis, histological grade according to the French Federation of Cancer Centers [12], tumor location and depth, and (neo)adjuvant therapy details. Surgical margins were classified as microscopically negative (R0), macroscopically negative but microscopically positive (R1), and macroscopically positive margins (R2) [13]. Certified pathologists determined the categorized margin status with review of the edge of the tumor and the extension of tail-like lesion. In addition, we collected information about skin reconstruction (graft or flap), prosthesis usage (e.g., total knee arthroplasty), and the necessity of manipulating major neurovascular bundles (AVN). We excluded patients with visceral location, metastasis (distant, skip lesion from the primary site, or lymph node metastasis) at diagnosis, and lack of images for proper evaluation. Also, we excluded patients who underwent amputation.

The study was approved by the Ethics Committee of Nagoya City University Hospital (protocol code, 60-18-0186; date of approval, February 25, 2020). The study design and procedures were conducted in accordance with the principles of the Declaration of Helsinki.

2.2. Neoadjuvant Therapy

In this study, neoadjuvant therapy was performed according to doctors' preferred methods. For radiotherapy, the clinical target volume is expected to be the gross target volume, enhanced with gadolinium T1-weighted image, plus tail-like lesion with 1–2 cm margin. Neoadjuvant external beam radiation is administered at 45–54 Gy/22–25 fr with permission for adjuvant radiation up to 60 Gy [14].

Chemotherapy was performed based on the standard chemotherapy in Japan: Adriamycin, 60 mg/m² plus ifosfamide 10 g/m² (AI) or gemcitabine 1,800 mg/m² plus docetaxel 70 mg/m² (GD) in a 3-week interval [15,16]. In some institutions, etoposide was added to the AI regimen [17].

Moreover, chemoradiotherapy with hyperthermia was performed to augment the efficacy of chemoradiotherapy [18]. In this protocol, radiotherapy was administered to the primary site for a total of 40 Gy/20 fr. For thermotherapy, an 8-MHz radiofrequency

capacitive heating system (Thermotron RF-8; Yamamoto VINITA, Osaka, Japan) was used for weekly hyperthermia with simultaneous chemotherapy [19,20].

2.3. Evaluation of Tail-Like Lesion and Response for Neoadjuvant Therapies

Tail-like lesions were evaluated using T1-weighted images with gadolinium enhancement or short TI-inversion recovery (STIR) images. A *tail-like lesion* was defined as “a curvilinear shaped tapered thick fascial enhancement extending from the primary mass, with or without irregularity of the tumor border.” The tail sign’s length was calculated from the base of the tail sign on the main mass to the top of the tail sign in the largest cross-sectional plane. The tail sign’s thickness was calculated as the length of the tail sign’s edge [21].

If a and b indicate the length (thickness) of the tail-like lesion before and after neoadjuvant therapy, the change in the tail-like lesion was evaluated using the following formula:

$$\frac{a - b}{a} \times 100 (\%)$$

The representative figures are shown in Figure A1-2.

Response evaluation criteria in solid tumors (RECIST) 1.1 was used to evaluate the main tumor’s response to neoadjuvant therapy. At each institution, a certified radiologist independently measured the greatest longitudinal dimension. The four response categories included in RECIST 1.1 are:

- Complete response (CR): disappearance of all target lesions
- Partial response (PR): target lesion’s diameter decreases by >30%
- Progressive disease (PD): target lesion’s diameter increases by >20%
- Stable disease (SD): lesion that does not meet the other criteria

The change in size was evaluated at the beginning of neoadjuvant therapy and immediately before surgery [22].

2.4. Histological Response

The four-tier histological response was defined as follows [16]:

- Grade 1: little or no effect of chemotherapy observed
- Grade 2: partial response to chemotherapy with >50% tumor necrosis
- Grade 3: >90% tumor necrosis attributable to preoperative chemotherapy, although foci of apparently viable tumors may be seen in some histologic sections
- Grade 4: no apparent viable tumor cells observed in any histological section

Certified pathologists at each hospital evaluated these histological responses.

2.5. Statistical Analysis

This study’s primary goal was to analyze the relationship between changes in tail-like lesions during neoadjuvant therapy and histological responses. The secondary goal was to analyze the effects of the pictorial changes (tail-like lesions or main part [RECIST 1.1]) and four-tier histological responses. Paired t-tests and Mann Whitney U tests were performed to compare the mean and histological responses before and after therapy. The correlations between the variables were evaluated using Pearson’s moment correlation coefficient (<0.2, no correlation; 0.2–0.4, weak correlation; 0.4–0.7, moderate correlation; and >0.7, strong correlation).

We also used the Kaplan-Meier method to estimate the overall survival (the time from diagnosis to death due to any cause), distant metastasis-free survival (the time from diagnosis to distant metastasis), and local relapse-free survival (the time from surgery to local recurrence). In the univariate analysis of oncologic outcomes, the differences between curves were analyzed using log-rank analysis. Potential risk factors for oncologic outcomes were analyzed using a stepwise Cox proportional hazards model, and hazard

ratios (HRs) were calculated. We performed this accessory analysis to show the efficacy of neoadjuvant therapy by comparing the histologically and chronologically matched patients from the administrative hospital (Nagoya City University).

All statistical analyses were performed using SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $P < 0.05$.

3. Results

3.1. Patient Characteristics

The study included 36 patients (21 males and 15 females; mean age at diagnosis, 57.9 ± 15.5 years), and the median follow-up period was 1,362 days from the first visit (interquartile range [IQR], 1001–2000) and 1,267 days after surgery (IQR, 886–1893). Histologically, the tumors were classified as undifferentiated pleomorphic sarcoma (UPS, $n = 11$), myxofibrosarcoma (MFS, $n = 13$), synovial sarcoma (SS, $n = 4$), dedifferentiated liposarcoma (DDL, $n = 4$), and others (one patient each with epithelioid sarcoma, malignant peripheral nerve sheath tumor, clear cell sarcoma, and extraskeletal Ewing sarcoma). The tumor length was 76.0 mm (IQR, 53.3–93.3), tail-like lesion's length was 29.5 mm (IQR, 23.0–37.3), and the thickness was 4.0 mm (IQR, 2.2–7.7) (Table 1).

The depth of main lesion was evaluated as superficial ($n = 13$) and deep ($n = 23$). There was difference in the median length of tumor between the tumor in deep location or superficial location (85.0 mm [IQR, 65.0–112.0] or 57.0 mm [IQR, 45.0–80.0], $p = 0.043$, Mann Whitney U tests, deep or superficial, respectively). There were no differences in the median length or thickness of tail-like lesion between the tumor in deep location or superficial location (length, 30.0 mm [IQR, 20.0–44.0] or 28.0 mm [IQR, 24.0–32.0], $p = 0.515$, thickness, 4 mm [IQR, 2.3–7.8] or 3 mm [IQR, 2.2–5.0], Mann Whitney U tests, deep or superficial, respectively).

Table 1. Characteristics of patients with a tumor with tail-like lesion.

Characteristics (N = 36)		Number
Histology	UPS	11
	MFS	13
	SS	4
	DDL	4
	Others	4
Age at diagnosis (mean, standard deviation)		57.9, 15.5
Tumor length (median, IQR)		76.0, 53.3–93.3
Tail-like lesion's length (median, IQR)		29.5, 23.0–37.3
Tail-like lesion's thickness (median, IQR)		4.0, 2.2–7.7
Location	Lower extremity	30
	Buttock	2
	Inguinal region	3
	Thigh	15
	Knee	3
	Lower leg	6
	Foot	1
	Upper extremity	3
	Upper arm	1
	Forearm	2
	Trunk	3
	Chest wall	1
	Back	2
Sex	Male	21
	Female	15
Lesion status	Primary	33
	Recurrence	3
FNCLCC grade	Grade 2	4
	Grade 3	32
Biopsy method	Needle	14
	Open	22
Depth	Superficial	13
	Deep	23

UPS, undifferentiated pleomorphic sarcoma; MFS, myxofibrosarcoma; SS, synovial sarcoma; DDL, dedifferentiated liposarcoma; IQR, interquartile range; FNCLCC, French Federation of Cancer Centers.

3.2. Effectiveness of Neoadjuvant Therapy on the Main Mass or Tail-Like Lesion

The median maximum tumor length was 76.0 mm (IQR, 53.3–93.3) at initiation and 63.0 mm (IQR, 43.3–93.8) after neoadjuvant therapy with no significant change during the treatment ($p = 0.088$). The mean rate of change in the maximum length was $-5.0\% \pm 28.4\%$ (median, -5.3% ; IQR, -24.4% to $+12.6\%$) (Figure 1a). On the RECIST 1.1, patients were categorized as SD ($n = 22$ [61.1%], not confirmed), PR ($n = 8$ [22.2%]), and PD ($n = 6$ [16.7%]). Univariate and multivariate analyses for the achievement of PR are shown in Table A1. There were no incisive biomarkers for anticipating a good response.

The median length of the tail-like lesion was 29.5 mm (IQR, 23.0–37.3), and the median thickness was 4.0 mm (IQR, 2.2–7.7) at initiation and 19.5 mm (IQR, 0–36.5; length) and 2.4 mm (IQR, 0–3.8; thickness) after neoadjuvant therapy. The mean rates of change of the tail-like lesion were -38.0% ($\pm 56.8\%$; median, -34.6% [IQR, -100 to -3.6]). In addition, the rate of change of the tail-like lesion's thickness was -41.3% ($\pm 48.7\%$; median, -26.3% [IQR, -100 to 0]) (Figures 1b and 1c). There was a partial statistical significance during this treatment (length, $p = 0.088$; thickness, $p < 0.001$). Complete disappearance of the tail lesion was observed in 12 patients. The univariate and multivariate analyses for the achievement of complete disappearance are shown in Table A2. There were no incisive biomarkers for anticipating a good response.

There was a weak or moderate relationship between the shrinkage of the maximum length of the tumor and the tail-like lesion in Pearson's moment correlation coefficient (length, $r = 0.36$, $p < 0.001$; thickness, $r = 0.42$, $p = 0.047$; Figures 1d and 1e). There was a strong relationship between the length and thickness of the tail-like lesions ($r = 0.74$, $p < 0.001$; Figure 1f).

In addition, the effectiveness of neoadjuvant therapy was depicted using waterfall-plot graphs for the maximum length of the tumor (main part) or tail sign (Figures 2a–2c).

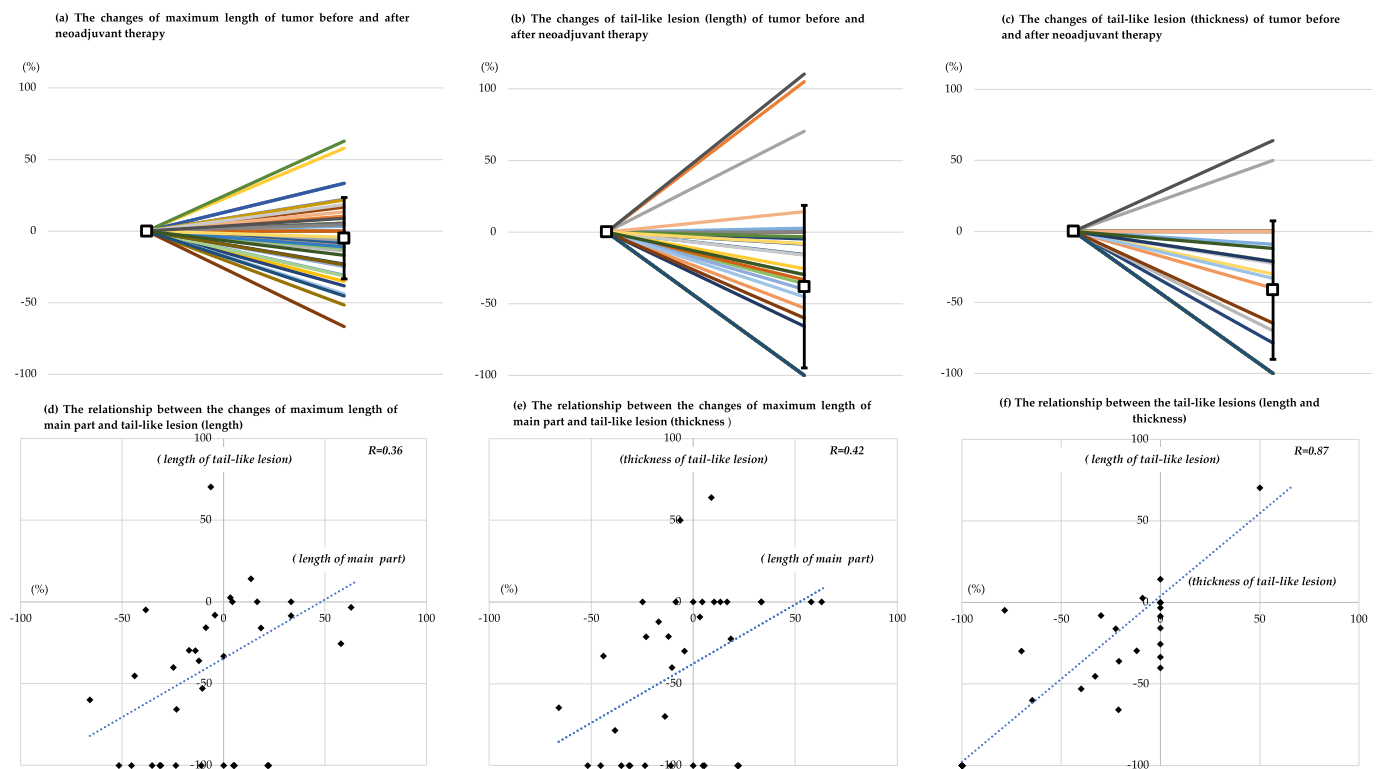
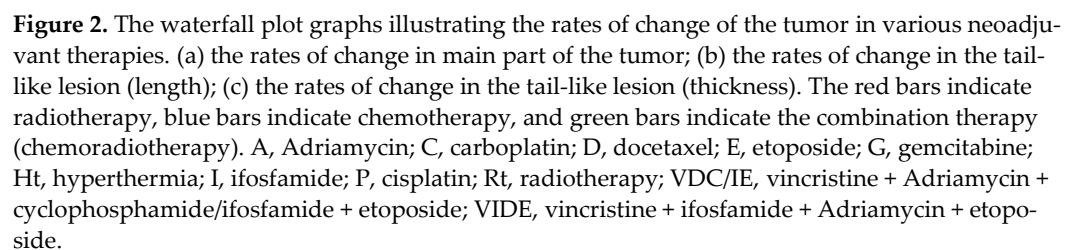


Figure 1. The rates of change of the tumor and the relationship between the main part and tail-like lesion. (a) The rates of change of the maximum length of the tumor. (b) The rates of change of the tail-like lesion (length). (c) The rates of change of the tail-like lesion (thickness). (d) The relationship between the changes of maximum length of the main part of the tail-like lesion (length). Squares indicate the means, and the error bars indicate the standard deviations. (e) The relationship between the rate of change of maximum length of the main part and the tail-like lesion (thickness). (f) The relationship between the tail-like lesions' length and thickness.



Histopathological efficacy was evaluated using a four-tier grading system. The responses were as follows: G1, 15 patients (42%); G2, 13 patients (36%); G3, seven patients (19%); and G4, one patient (3%) (Table 2). The median change in the maximum tumor length was +8.9% (IQR, -4.27 to 33.3) in G1 response, -12.1% (IQR, -27.8 to 7.9) in G2, and -33.3% (IQR, -43.5 to -2.2) in G3+4 patients. There were significant differences between G1 and G2 ($p = 0.006$), G1, and G3+4 ($p = 0.001$, Figure 3a). In addition, the median change in the length of the tail-like lesion was -8.5% (IQR, -100.0 to 0.0) in G1 response, -45.2% (IQR, -100.0 to -14.9) in G2 response, and -80.0% (IQR, -100.0 to -20.1) in G3+4 patients (Figure 3b). There were significant differences between G1 and G3+4 groups ($p = 0.05$). Moreover, the median change in the thickness of the tail-like lesion was -9.1% (IQR, -100.0 to 0.0) in G1 response, -40.0% (IQR, -100.0 to 0.0) in G2 response, and -89.3% (IQR, -100.0 to -16.2) in G3+4 patients (Figure 3c). There were significant differences between G1 and G3+4 groups ($p = 0.03$).

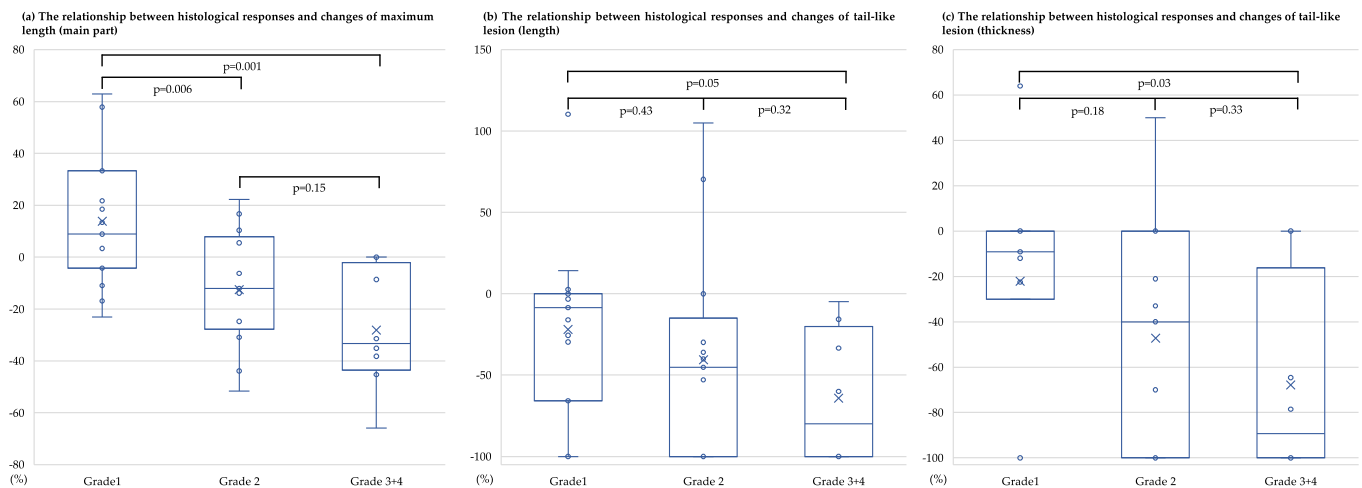


Figure 3. The box-whisker plot graphs about the relationship between the histopathological evaluations and the shrinkage of tumor. (a) The relationships between the histopathological response and the changes of maximum length of the main part; (b) the relationships between the histopathological response and changes of tail-like lesion (length); (c) the relationships between the histopathological response and changes of tail-like lesion (thickness).

Table 2. The relationship between the histological response and the change of the main lesion (based on RECIST 1.1).

RECIST, Response Evaluation Criteria in Solid Tumors; PD, progressive disease; SD, stable disease; PR, partial response.

3.4. Impact of Neoadjuvant Therapy on the Margin Status

Overall, 27 patients underwent R0 resection. The relationship between the margin status and patient characteristics, surgical procedure, and response to neoadjuvant therapy is summarized in Table A3. The patients with superficial lesion underwent more frequently the plastic surgery than deep lesion (the number of plastic surgery = 4/23, 10/13, deep or superficial, respectively, $p < 0.001$, chi-square analysis). Univariate analysis re-

		RECIST 1.1			Total
		PD	SD	PR	
Histologi- cal re- sponse	G1	5	10	0	15
	G2	1	9	3	13
	G3	0	3	4	7
	G4	0	0	1	1
Total		6	22	8	36

vealed that patients other than UPS or MFS chemotherapy more frequently achieved R0 resection (the number of R0 resection = 15/24, 12/12, UPS+MFS, SS+DLS+others, respectively, $p=0.016$, chi-square analysis). Although there was no statistical difference in the patients with good response to neoadjuvant therapy according to RECIST 1.1, there was no R1 resection in good responders (the number of R0 resection = 19/28, 8/8, SD or PD, PR, respectively, $p=0.06$, chi-square analysis). The disappearance of the tail-like lesion was not related to R0 resection (the number of R0 resection = 9/12, 18/24, the patients with disappearance of the tail-like lesion or not, respectively, $p=1.0$, chi-square analysis). Moreover, there were no apparent differences in patients who underwent a difficult surgery, including skin reconstruction, manipulation of AVN, or insertion of a prosthesis.

3.5. Oncologic Outcomes of Neoadjuvant Therapy

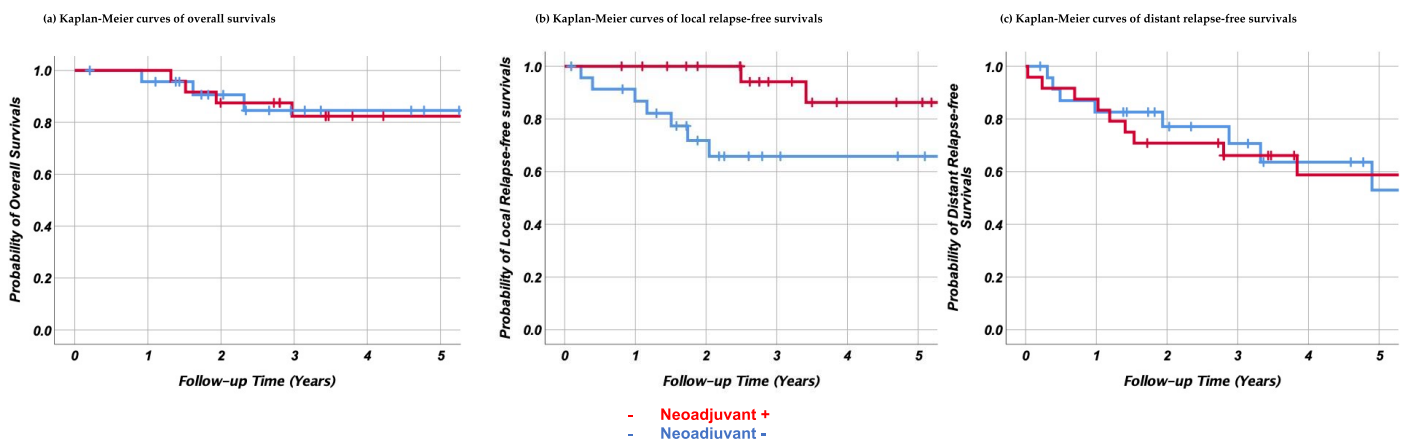
We evaluated oncologic outcomes as accessory endpoints. Overall, the oncologic outcome at the end of follow-up, seven patients died of disease, one died of another disease, four were alive with disease, 24 had no evidence of disease. The overall survival was $85.1\% \pm 6.2\%$, distant relapse-free survival (D-RFS) was $65.5\% \pm 8.1\%$, and local relapse-free survival (L-RFS) was $92.6\% \pm 5.0\%$ at five years. Univariate analysis results of these outcomes are summarized in Table A4.

In addition, to determine the importance of neoadjuvant therapy, we compared patients who had no adjuvant therapy only in the UPS+MFS population. A total of 24 patients were compared to those who underwent neoadjuvant therapy ($n = 24$). Kaplan-Meier curves for with and without neoadjuvant therapy groups revealed that the overall survival was $82.4\% \pm 8.1\%$ and $84.6\% \pm 8.3\%$, D-RFS was $58.8\% \pm 11.1\%$ and $53.1\% \pm 13.6\%$, and L-RFS was $86.3\% \pm 9.2\%$ and $65.8\% \pm 10.7\%$, respectively (Figure 4). Univariate analysis revealed that L-RFS was significantly higher in patients who received neoadjuvant therapy ($p = 0.031$; hazard ratio, $HR = 0.21$). There were no differences in overall survival ($p = 0.64$, $HR = 1.34$) and D-RFS ($p = 0.93$, $HR = 1.04$) (Figure 4). The differences in the basic characteristics are summarized in Table A5. Neoadjuvant therapy was performed exclusively for younger patients, higher-grade tumors, lower extremities, and longer tail-like lesions.

Figure 4. The Kaplan-Meier curves comparing patients who underwent neoadjuvant therapy with those who did not, among UPS + MFS subtypes. (a) overall survival, (b) local relapse-free survival, and (c) distant relapse-free survival. The red and blue lines indicate patients with and without neoadjuvant therapy, respectively.

4. Discussion

The tail-like sign was first introduced by Fanburg-Smith et al. in 1999 [23,24]. Tumor infiltration was pathologically proven in 83% of superficial malignant fibrous histiocytoma.



mas. The infiltrative growth pattern, connecting the tumor to the fascial plane and skeletal muscle without a discrete nodular lesion [25], is considered a primary risk factor for local recurrence [3,26].

This study partially focused on low-grade MFS, a myxoid variant of malignant fibrous histiocytoma [27]. Despite the low-grade characteristics of most lesions, the tumor has relentless recurrence potential [28] with a 40%–60% recurrence rate [27,29]. Moreover, recurrence may transform the tumor to a higher grade [28]. This phenomenon makes it more challenging to treat recurrent requiring multiple surgeries. Thus, a well-planned surgery using appropriate neoadjuvant therapy and complete removal of possible extensions of the tumor is important in the primary setting.

The characteristics of tail-like lesions have been extensively discussed. In some cases, the lesion mainly consisted of reactive edema with no viable or invading tumor

[5,30]. In this study, we could not prove the importance of tail-like lesion's complete disappearance after neoadjuvant therapy, and the disappearance was not related to achieving R0 resection or improvement of oncological outcomes. This is partially because the complete disappearance of tail-like lesions consisting of edema and inflammation was not true regression of the tumor. An accurate image diagnosis to distinguish between actual and false tail-like lesions is necessary for a tumor's ideal resection with adequate surgical margins to minimize damage to the adjacent important structures and maximize resectability without any residual tumor.

Histopathologically, the tail-like lesion comprised the viable tumor and infiltrated into the fascia or subcutaneous fat layer accompanied by fibrous tissue [24]. These viable tumors changed into necrotic tissue after effective neoadjuvant therapy. However, the tail-like lesion's traces remained as empty fibrous tissue budding around the tumor. Therefore, it is difficult to distinguish whether the skin contains neoplastic cells. Histopathological analysis of 18 patients by Imanishi et al. reported that after preoperative radiotherapy, the tail sign contained viable tumor in seven cases and non-viable tumor in five cases. Likewise, we evaluated the actual effect of neoadjuvant therapy in tail-like lesions and proved the relationship between histological response in the main tumor lesion and regression of the tail-like lesion. These findings indicate that neoadjuvant therapy's efficacy in the main part can be a useful surrogate marker of efficacy in tail-like lesions.

We also showed that the achievement of R0 resection was related to the tumor subtype with high residue rates in UPS or MFS. Although not statistically significant, the patients who responded to the neoadjuvant therapy tended to achieve R0 resection, suggesting that effective neoadjuvant therapy and reactivity to therapy are essential for a tumor's complete resection. However, we should take into consideration that even for a certified pathologist, it is difficult to evaluate the true extension of the tumor along with tail-like lesion after neoadjuvant therapy, which comprise fibrous tissue, fibroblast cells, or degenerated tumor. This implies that some cases of pathological evaluations of margin status might not be precise.

Neoadjuvant therapy for infiltrative tumors remains controversial. Several studies concluded that preoperative radiotherapy had no effect on the tail sign [26], while others have reported contradictory results [31,32]. Our provisional data suggested that neoadjuvant therapy improved the local control rate by comparing the histologically and chronologically matched patient cohorts. However, selection bias may have affected the results; therefore, a validation study is needed to confirm our findings by analyzing the prospective or data-matched cohorts.

This study has several limitations. First, our MRI evaluation permitted the presence or disappearance of the tail sign in both contrast T1-weighted and STIR images. Theoretically, the former indicated tumor viability and the latter an edematous tissue [33]; therefore, detection bias should be considered. Second, several definitions of the tail-like sign have been proposed. Fanbeug-Smith defined a tail-like sign as "a pathological tumor extension along normal tissue planes for >2 mm from the edge of the main mass [3]." The pictorial definition by Ferenbro et al. modified the perspective as "an irregular surface with spicula-like extensions into the surrounding tissue of >25% of the circumference on an MR T2-weighted image." Subsequent definitions described it as "a crawling change beyond the fascia [26,30]," "a well-defined, sharp or tapering, pointed curvilinear projection at least 1.0 cm in length on T1-weighted image with contrast [34]," and "a tapered fascial enhancement extending from the tumor margin with >2 mm thickness." We used Yoo et al.'s definition [21]; a different definition might affect the reproducibility of this study. Third, our multicenter study permitted various procedures as "neoadjuvant therapy" because the study's primary objective was to analyze the changes in tail-like lesions during neoadjuvant therapy, but not the oncological outcomes. Thus, the chemotherapy's intensity or the area of radiotherapy should be normalized while focusing on the oncological outcomes. In addition to chemoradiotherapy, some institutions perform hyperthermia because a recent phase-III randomized study (EORTC 62961) showed that regional hyperthermia increases the benefit of preoperative chemotherapy in patients with localized

high-risk STS when compared to etoposide, ifosfamide, and doxorubicin alone, or combined EIA with hyperthermia [18]. However, according to the NCCN 2021 guidelines, hyperthermia with preoperative chemotherapy is not recommended, and the results need to be confirmed in large cohort studies. The addition of hyperthermia influenced the tail-like lesion's detection since the procedure induced inflammation around the target area.

Anyway, this study is the first to analyze the effect of neoadjuvant therapy on soft tissue tumors with tail-like lesions. Further researches are expected to validate the data in a more sophisticated manner.

5. Conclusions

Our multicenter study analyzed the effect of neoadjuvant therapy on the tumor invasive front or 'tail-like lesion.' After neoadjuvant therapy, tail-like lesion's shrinkage was observed in many patients and was related to the effect on the main part of the tumor; however, we could not confirm the relationship between shrinkage of tail-like lesion and resectability or oncologic outcomes.

Supplementary Materials: Tables A1–A5 and Figure A1-2 are available online at www.mdpi.com/xxx/s1.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent was obtained from the patients to publish this paper.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1. Univariate and multivariate analyses for good response to neoadjuvant therapy.

Table A2. Univariate and multivariate analyses for the disappearance of tail-like lesions.

Table A3. Univariate and multivariate analyses for achievement of R0 resection.

Table A4. Univariate and multivariate analyses for oncologic outcomes.

Table A5. Basic characteristics of patients with or without neoadjuvant therapy.

Figure A1. The representative cases and the way to calculate the tail-like lesion (deep located lesion, 65-year-old, male, myxofibrosarcoma, sartorius muscle). A1a indicated T1-weighted image; A1b indicated T2-weighted image; A1c indicated T1 weighted image with gadolinium enhancement + fat suppression [raw image]; A1d indicated the way to calculate. Purple dots indicated the length of main lesion. Red dots indicated the length or thickness of tail-like lesion. White dots indicated the tails around the tumor.

Figure A2. The representative cases and the way to calculate the tail-like lesion (superficial located lesion, 59-year-old, male, undifferentiated pleomorphic sarcoma, buttocks). The patients underwent 2 cycles of EIA treatment. A2a indicated T1 weighted image with gadolinium enhancement + fat suppression [raw image, before chemotherapy]; A2b indicated T1 weighted image with gadolinium enhancement + fat suppression [raw image, after chemotherapy]; A2c-d indicated the ways to calculate. Purple dots indicated the length of

main lesion. Red dots indicated the length or thickness of tail-like lesion. White dots indicated the tails around the tumor.

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