Tail-like Lesions

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Several types of soft tissue sarcomas have peripheral infiltrative growth characteristics called tail-like lesions. 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. The extent of shrinkage in tail-like lesions was related to the histopathological responses in the main part of the tumor.

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 (NCCN Clinical Practice Guidelines in Oncology, Soft Tissue Sarcoma Version 2.2021—28 April 2021, https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf), recommends neoadjuvant therapies for resectable stage II–III patients with adverse functional outcomes. These methods include radiotherapy [7], chemoradiotherapy [8], or chemotherapy [9][10]. Due to heterogeneity, the contribution of chemotherapy to the improvement of oncologic outcomes of soft tissue sarcomas was considered to be limited [11]. However, if limited to high-risk cases (high-grade malignancy, ≥5 cm in diameter, and deeply located with respect to investing fascia), the efficacy of the chemotherapy has been indicated [12][13]. Thus far, little is known about the effects of these methods on tail-like lesions.

2. Neoadjuvant Therapies on Soft Tissue Sarcomas with Tail-like Lesions

Neoadjuvant therapy was performed according to doctors' preferred methods. For radiotherapy, the clinical target volume was expected to be the gross target volume, enhanced with a gadolinium T1-weighted image, plus tail-like lesion with 1–2 cm margin. Neoadjuvant external beam radiation was 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/m^2 plus ifosfamide 10 g/m^2 (AI) or gemcitabine 1800 mg/m^2 plus docetaxel 70 mg/m^2 (GD) in 3-week intervals [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].

The tail-like sign was first introduced by Fanburg-Smith et al., in 1999 [21][22]. Tumor infiltration was pathologically proven in 83% of superficial malignant fibrous histiocytomas. The infiltrative growth pattern, connecting the tumor to the fascial plane and skeletal muscle without a discrete nodular lesion [23], is considered a primary risk factor for local recurrence [3][24].

Low-grade MFS, a myxoid variant of malignant fibrous histiocytoma [25]. Despite the low-grade characteristics of most lesions, the tumor has relentless recurrence potential [26], with a 40–60% recurrence rate [25][27]. Moreover, recurrence may transform the tumor to a higher grade [26]. This phenomenon makes it more challenging to treat recurrent tumors requiring multiple surgeries. Thus, a well-planned surgery using appropriate neoadjuvant therapy and the 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][28]. We could not prove the importance of the complete disappearance of tail-like lesions 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 is not true regression of a 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 [22]. 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 a viable tumor in seven cases and a 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 responses 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.

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 a 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.

The effect of neoadjuvant therapy on the tail-like lesion remains controversial. Several studies have concluded that preoperative radiotherapy has no effect on the tail sign [24], although others have reported positive results [29][30]. These conflicting viewpoints were due to differences in the sample sizes of the studies, or the methods used to evaluate the efficacy of neoadjuvant therapy on tail-like lesions. 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.

Despite no statistical backing, we showed favorable results for the shrinkage of tail lesions and in histopathological necrosis grades in patients treated with chemoradiotherapy. In case of resistance to radiotherapy or chemotherapy by the soft tissue sarcoma, these multimodal agents might be considered. In addition to chemoradiotherapy, some institutions perform hyperthermia to augment the efficacy of chemotherapeutic agents; 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 on comparing etoposide, ifosfamide, and doxorubicin (EIA) alone, with combined EIA and 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 detection of the tail-like lesions, because the procedure induced inflammation around the target area.

3. Conclusions

We analyzed the effect of neoadjuvant therapy on the tumor invasive front or 'tail-like lesion.' After neoadjuvant therapy, tail-like lesion 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.

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