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Editorial

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Myxoid liposarcoma: a well-defined clinical target variant in radiotherapy for soft tissue sarcoma

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Soft tissue sarcomas (STS) are a heterogeneous group of malignancies originating from mesenchymal tissues that show even more diverse characteristics than those originating from epithelial tissues [1]. Despite the diverse histological types of STS, these are generally managed and researched as uniform diseases due to their rarity, except for several unique histologic subtypes [2,3]. Nevertheless, the distinct characteristics, variety of treatment responses, and differences in oncologic outcomes between the subtypes of STS, strongly suggest the need for patient- and/or subtype-specific customized treatment approaches [1].

The efficacy of radiotherapy (RT) in resectable STS on reducing local recurrence has been quite clearly confirmed in meta-analysis [4]. Additionally, preoperative RT was significantly more advantageous than postoperative RT in terms of local control rate either in retroperitoneal sarcomas or sarcomas of other sites. This beneficial effect on the local control of preoperative RT in STS is highlighted even more in view of its' lower radiation dose, small target volume, and reducing long-term toxicities, including fibrosis, edema, and joint stiffness. Furthermore, preoperative RT may prevent tumor seeding during surgical management, and thicken and eliminate or minimize viable tumor cells in the pseudocapsule, which can be used as a reference for resection to achieve wider surgical margins [5].

Despite the proven advantages of preoperative RT in STS, the objective response rate is quite limited, at approximately 25% (range, 0% to 50%) in actual clinical practice, except for myxoid liposarcoma (MLS) [6]. Considering that definite surgical resection is planned and unnecessary resection of the surrounding normal organs should be minimized, it is clear that the change in tumor volume itself is also one of the crucial outcomes that cannot be ignored in the management of STS [7]. The importance of tumor volume response could be particularly emphasized for locally advanced unresectable sarcomas [8].

MLS is one of the five types of liposarcomas according to the 2020 World Health Organization classification [1]. MLS is clearly distinguished from the other subtypes of liposarcoma by the presence of the pathognomonic fusion gene *FUS-DDIT3* (also known as *TLS-CHOP*) or less often, as much as 10%, ESWR1-DDIT3 [9], although the variability of the fusion gene transcript is not associated with clinical outcome [10]. MLS also shows unique clinical features, like occur more younger age, and mostly in the thigh rather than the retroperitoneum, and metastasize to sites other than the lungs, including soft tissue or bone [11]. The most notable difference is that, unlike other subtypes of sarcoma, including other types of liposarcomas, which are generally considered resistant to radiotherapy, MLS is much more sensitive to RT. One explanation for the higher RT responsiveness of MLS

is that the mutant fusion proteins containing DDIT3 fail to allow growth arrest in response to radiation [12].

According to the results of the study by Boxberg et al. [6], when preoperative RT was performed in STS, the volume of residual viable tumor was 15% (range, 3% to 60%) in MLS, which was numerically lower than that of other sarcoma subtypes. Pitson et al. [13] reported that there was almost no decrease in tumor volume in malignant fibrous histiocytoma, whereas a statistically significant decrease in MLS was observed after 50 Gy in 25 fractions of preoperative RT. This higher RT sensitivity of MLS is also directly correlated with an excellent local control rate compared to other subtypes after RT and complete surgical resection. Chung et al. [12] reported 97.7% for MLS compared with 89.6% for other subtypes of STS ($p = 0.008$) in terms of 5-year local recurrence-free survival after surgical resection with preoperative or postoperative RT. As mentioned earlier, this high RT responsiveness of MLS is a very important feature that can further elevate the role of preoperative RT, especially in patients with very large tumor size.

Recently, Lee et al. [14] reported an interesting article in the *Radiation Oncology Journal* on volume reduction and short-term surgical outcomes in large-sized MLS after 50 Gy over 25 fractions of preoperative RT, in which 24 patients were analyzed by dividing them into two groups based on the pretreatment tumor size of 10 cm. There was no significant difference between the two groups in terms of volume reduction, with a mean percentage of 56.3% (range, 22.4% to 90.9%) in the large compared with 64.5% (range, -18.4% to 91.7%) in the small tumor group. Interestingly, these figures of proportional reduction rate of MLS are similar to the 59% of the previous study results of Pitson et al. [13], which increases the reliability of the MLS showing a high objective response regardless of tumor size after RT. In addition, there was a tendency for a higher rate of major wound complications in the pre-RT large tumor group, which is thought to have a larger radiation-irradiated volume of normal tissue, but operative duration was found to have a greater correlation with the post-RT tumor size than the pre-RT tumor size. In fact, the higher incidence of postoperative wound complications that were found to be significantly higher in preoperative RT over postoperative RT is the main reason for avoiding the addition of preoperative RT in real-world clinical practice [4]. Although a significant decrease in wound complications was not observed in the study by Lee et al. [14], the reduction in resected tissue could reduce the risk of wound complications. This point may be more important, especially in radiosensitive MLS, in that the local control rate is sufficiently satisfactory even after limited resection following preoperative RT [15].

Recently, the Dose Reduction of Preoperative Radiotherapy in Myxoid Liposarcoma (DOREMY) trial, a prospective single arm phase II study, showed favorable clinical outcomes of 100% local control after median follow-up time of 25 months after 36 Gy over 18 fractions of preoperative intensity-modulated RT [16]. Based on the dose de-intensification in MLS compared to conventional preoperative RT using mainly 50 Gy, relatively low 17% of wound complication requiring intervention were also reported in this study. Furthermore, this reduced, moderate dose of preoperative RT showed favorable outcomes in terms of resectability improvement and tumor volume reduction as median value of 60% (interquartile range, 74 to 41) in a subgroup study of some patients enrolled in the DOREMY trial [17]. Additional large-scale studies focusing on the optimal radiation dose, and time interval between the completion of RT and surgical resection, considering postoperative wound complications as well as tumor response, will be needed in MLS.

The study by Lee et al. [14] had several important limitations, including a small sample size and retrospective design as the authors admitted. However, it provides valuable clinical information to compare the RT response and postoperative wound complications of large MLS with small MLS, which remains a concern for experts in this field through consistent treatment of relatively rare tumors. In MLS, which shows a markedly different, well-defined RT response from other subtypes of STS, and satisfactory local control through preoperative RT and surgical resection, continuous researches should be necessary focus on the reduction of postoperative wound complications through the modification of radiation dose, duration of RT and surgery interval, and extent of surgical resection in the future.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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