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Editorial Comment to "Tertiary Lymphoid Structures Correlate With Better Prognosis in Patients With Retroperitoneal Sarcoma: A Retrospective Study"

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I read with great interest the article by Kijima et al. [1], which explores the prognostic value of intratumoral tertiary lymphoid structures (TLSs) in retroperitoneal sarcomas, particularly focusing on dedifferentiated liposarcoma (DDLPS). This study provides valuable insights into the tumor immune microenvironment of a rare and biologically heterogeneous malignancy, emphasizing the emerging role of TLSs as prognostic biomarkers.

The authors conducted a retrospective analysis of 29 patients who underwent curative-intent surgery for retroperitoneal sarcoma. TLSs were identified in 59% of cases, and their presence, particularly when ≥ 10 per $100\,mm^2$, correlated with significantly prolonged disease-specific survival. Notably, this favorable impact was observed most robustly in patients with DDLPS. Multivariate Cox analysis confirmed TLS negativity as an independent poor prognostic factor (hazard ratio 3.1, 95% confidence interval 1.4–8.1, $p = 0.02$), alongside R2 resection margins [1].

These findings are consistent with recent studies in soft tissue sarcoma suggesting that TLSs function as localized and organized immune hubs where B and T lymphocytes interact to initiate anti-tumor responses [2]. The association of high TLS density with increased infiltration of $CD8^+$ T cells, as shown in this study [1], supports the immunologically active phenotype of TLS-positive tumors. In retroperitoneal sarcomas, where response to chemotherapy is often limited [3], the presence of TLSs may reflect an intrinsic immunogenicity that could be leveraged therapeutically.

Particularly noteworthy is the study's implication that TLSs may not only reflect the underlying immune microenvironment but may also serve as a predictive biomarker for immunotherapy. The SARC028 trial demonstrated that sarcomas with high levels of tumor-infiltrating lymphocytes respond favorably to immune checkpoint inhibitors (ICIs) [4]. Moreover, the PEMBROSARC [5] trial showed that sarcomas rich in tertiary lymphoid structures (TLSs) also respond well to ICIs [5]. In the current cohort, one TLS-positive patient with high tumor mutational burden and microsatellite instability achieved a durable complete response to pembrolizumab, underscoring this potential [1].

Despite the small sample size and limitations of a single-institution retrospective design, the authors' robust immunohistochemical characterization of TLSs—including $CD21^+$ follicular dendritic cell staining—adds methodological strength. Evaluating TLS density as a stratified continuous variable further enhances its clinical utility. Future studies should aim to integrate spatial transcriptomics or multiplex imaging to better dissect TLS functional heterogeneity.

This study highlights the potential of TLSs as prognostic and possibly predictive biomarkers in retroperitoneal sarcoma,

especially DDLPS. Their presence may identify patients with a more favorable natural history and help guide immunotherapeutic strategies in otherwise treatment-resistant tumors. As the tumor immune microenvironment gains importance in soft tissue sarcoma, biomarkers like TLSs should be incorporated into future clinical trials and therapeutic strategies.

Author Contributions

Yoshiyuki Yamamoto: conceptualization, project administration, writing – original draft. **Norio Nonomura:** supervision, writing – review and editing.

Conflicts of Interest

Norio Nonomura is a member of the Editorial Board of the International Journal of Urology and the co-author of this article. To minimize bias, he was excluded from all editorial decision-making related to the acceptance of this article for publication.

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