Distinguishing Between Well-Differentiated and Dedifferentiated Retroperitoneal Liposarcomas in the Preoperative Setting: A Work in Progress in the Era of Precision Medicine

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This issue of *Annals of Surgical Oncology* includes a retrospective study evaluating the predictive value of preoperative biopsy for patients affected by retroperitoneal liposarcoma.¹ This study aimed to investigate the contribution of preoperative histologic diagnosis to multimodal treatment planning.

The authors hypothesized that neoadjuvant treatment may be underused for patients affected by dedifferentiated (DD) liposarcoma due to the lack of preoperative biopsy accuracy. They accordingly reviewed 256 patients affected by well-differentiated (WD) liposarcoma and DD liposarcoma of the retroperitoneum who underwent surgery at the MD Anderson Cancer Center during a 20-year span.

Of the patients in this series, 120 (46.8 %) had undergone preoperative biopsy and were retrospectively analyzed. Compared with the final pathologic diagnosis, the preoperative biopsy was able to identify WD liposarcoma with 85 % accuracy, which was significantly higher than the accuracy for identifying DD liposarcoma (37 %). The authors claim that these different accuracy rates lead to significant undertreatment of DD liposarcoma. The report by Ikoma et al. also gives an interesting insight into the multimodal treatment strategy for retroperitoneal soft tissue sarcomas and the appropriateness of adjuvant treatment.

To date, standard treatment for primary retroperitoneal sarcoma is surgery with complete en bloc tumor resection. Whether this should be different for the two liposarcoma entities still is debated. Some authors advocate an extended systematic approach for both, whereas others, including the

authors of the current report, are in favor of a more conservative resection for WD liposarcoma. In this perspective, correct preoperative diagnosis is essential for making the proper decision because the two entities cannot be distinguished intraoperatively.

The role of neoadjuvant treatment still is debated because, to date, no randomized trials of preoperative treatment for retroperitoneal sarcoma have been concluded and reported. The National Comprehensive Cancer Network (NCCN) guidelines offer the option of preoperative radiation therapy, chemotherapy, or both based on lower-level evidence without a uniform consensus. The European Society for Medical Oncology (ESMO) guidelines, on the other hand, consider adjuvant/neoadjuvant chemotherapy as an individualized (or investigational) indication and preoperative radiation therapy as only investigational for retroperitoneal sarcomas.

One randomized trial currently is recruiting patients in Europe and North America. It explores the impact of preoperative radiation therapy in primary retroperitoneal sarcoma and includes both WD and DD liposarcomas (EORTC-62092-22092, STRASS, NCT01344018).

Outside of the investigational setting, therefore, the use of neoadjuvant therapies must be decided by a multidisciplinary sarcoma board in the context of high-risk disease or a locally advanced (and/or nearly unresectable) presentation. The main prognostic factors to be considered in decision making for local recurrence and distant metastasis of retroperitoneal sarcomas are histology subtype and tumor grade.

Dedifferentiated liposarcomas are known to exist in at least two variants: intermediate and high grade. The former has a predominant risk of local recurrence, whereas the latter carries a risk reaching 40 % for distant metastasis. For this reason, patients affected by high-grade DD retroperitoneal liposarcoma may be considered for neoadjuvant

chemotherapy.² The accuracy of preoperative biopsy for evaluating tumor grade may thus become as crucial to the indication for neoadjuvant treatments of high-risk tumors as the accuracy of discriminating between WD and DD liposarcomas.

Data on tumor grade at biopsy were unfortunately not available in the study by Ikoma et al. The relevant finding, nonetheless, is that the accuracy of biopsy for DD liposarcomas is low, and multidisciplinary sarcoma boards should be aware of this.

Computed tomography (CT) scan imaging allows clinicians to anticipate both the diagnosis of retroperitoneal liposarcoma and the possible presence of a dedifferentiated component given that heterogeneous, nonlipomatous high-density/contrast-enhanced nodules within the main tumoral mass are the usual radiologic presentation of DD liposarcoma.³ Nevertheless, no radiologic feature has a higher predictive value for DD liposarcoma than histologic diagnosis, making preoperative percutaneous biopsy the gold standard for obtaining a correct preoperative diagnosis without major risk of complications for the patient, tumor seeding, or both.⁴

To maximize the accuracy of biopsy for retroperitoneal liposarcoma, two important issues must be addressed. First, biopsy material needs to be of suitable quality and quantity. Core needle biopsy (CNB) should be recommended in all cases because the accuracy of fine-needle aspiration (FNA) may not be sufficient. A needle diameter of 16 G or larger usually is adequate for the histologic diagnosis of soft tissue sarcoma. It also is recommended that multiple cores (4–6) be obtained during the biopsy procedure to collect sufficient tissue for morphologic, immunocytochemical, and molecular diagnostic testing. Ideally, samples also should be collected for fresh-frozen tissue banking, especially if neoadjuvant treatment has been envisaged.

Second, percutaneous biopsy must be planned to provide an adequate sample of the nodular hyperdense component of the mass, which raises more suspicion of dedifferentiation. For this reason, it is best to perform an image-guided biopsy. A positron emission tomography (PET) scan may help to identify hot areas and reduce the risk of

underestimating the biologic risk. A previous study from the same institution clearly pointed to the efficacy of image-guided, “targeted” biopsy.⁵ Hence, the accuracy of a preoperative DD liposarcoma diagnosis may be optimized if percutaneous biopsy is expressly programmed as a “targeted” procedure directed to the worst-looking component of the tumor mass on the imaging findings.

This accuracy in the current study by Ikoma et al. was low, but the retrospective nature of the study and the high percentage of biopsies taken before referral (35 %) are clear limitations. Because correct diagnosis is becoming more and more critical to tailoring of the appropriate treatment to the individual patient with retroperitoneal liposarcoma, accurate preoperative biopsy should be planned to identify the areas at higher biologic risk. Contrast-enhanced CT scan and PET scan, when clinically sound, should be used to guide percutaneous biopsy.

Every effort should be made to refer retroperitoneal sarcoma patients to specialized centers from the very initial observation to maximize the accuracy of their workup. This is critical to optimizing the treatment strategy and maximizing the chance of cure.

REFERENCES

1. Ikoma N, Torres KE, Somaiah N, et al. Accuracy of preoperative percutaneous biopsy for the diagnosis of retroperitoneal liposarcoma subtypes. *Ann Surg Oncol*. doi:10.1245/s10434-014-4210-8.
2. Gronchi A, Miceli R, Allard MA, et al. Personalizing the approach to retroperitoneal soft tissue sarcoma: histology-specific patterns of failure and postrelapse outcome after primary extended resection. *Ann Surg Oncol*. doi:10.1245/s10434-014-4130-7.
3. Morosi C, Stacchiotti S, Marchianò A, et al. Correlation between radiological assessment and histopathological diagnosis in retroperitoneal tumors: analysis of 291 consecutive patients at a tertiary reference sarcoma center. *EJSO*. 2014. doi:10.1016/j.ejso.2014.10.005.
4. Wilkinson MJ, Martin JL, Khan AA, et al. Percutaneous core needle biopsy in retroperitoneal sarcomas does not influence local recurrence or overall survival. *Ann Surg Oncol*. 2014. doi:10.1245/s10434-014-4059-x.
5. Lahat G, Madewell JE, Anaya DA, et al. Computed tomography scan-driven selection of treatment for retroperitoneal liposarcoma histologic subtypes. *Cancer*. 2009;115:1081–90.