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ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Accuracy of Preoperative Percutaneous Biopsy for the Diagnosis of Retroperitoneal Liposarcoma Subtypes

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ABSTRACT

Background. Surgery is the primary treatment for all subtypes of retroperitoneal liposarcoma, but neoadjuvant therapy may be warranted in cases of dedifferentiated liposarcoma (DDLS), which has an increased risk of recurrence and metastasis. Therefore, an accurate subtype-specific diagnosis is vital for appropriate consideration of neoadjuvant therapy. Previous studies assessing the subtype-specific accuracy of percutaneous biopsy are limited. We aimed to analyze the accuracy of preoperative percutaneous biopsy in the subtype-specific diagnosis of retroperitoneal liposarcoma and thus the reliability of percutaneous biopsy in guiding decisions about neoadjuvant treatment.

Methods. We retrospectively reviewed the medical records, including the pathologic reports, interventional radiology reports, and operative reports, of patients registered in the retroperitoneal/well-differentiated liposarcoma (WDLS/DDLS) database at The University of Texas MD Anderson Cancer Center between 1993 and 2013.

Results. We identified 120 patients who underwent 137 preoperative percutaneous biopsies followed by surgical resections. Pathologic examination following resection indicated that 74 of the patients had WDLS and 63 had DDLS. The overall diagnostic accuracy of percutaneous biopsy for identifying the subtype of liposarcoma was 62.8 % (86/137); the accuracy for identifying WDLS was significantly higher (85.1 %; 63/74) than that for identifying DDLS (36.5 %; 23/63) ($p < 0.01$).

Conclusions. Percutaneous biopsy has low accuracy in the diagnosis of retroperitoneal DDLS. This can potentially mislead physicians in the decision to implement neoadjuvant treatment. When developing treatment strategies, including clinical trials for patients with retroperitoneal liposarcoma, physicians should carefully consider the low accuracy of percutaneous biopsy in detecting DDLS.

Liposarcoma represents 24 % of soft tissue sarcomas of the extremities and 45 % of sarcomas in the retroperitoneum.[1] Liposarcomas have four histologic subtypes: well-differentiated liposarcoma (WDLS), dedifferentiated liposarcoma (DDLS), myxoid/round cell liposarcoma, and pleomorphic liposarcoma. WDLS and DDLS usually occur in the retroperitoneum and, in fact, almost all liposarcomas occurring in the retroperitoneum are WDLS or DDLS.[2] The tumor behavior varies depending on the liposarcoma subtype. WDLS is locally aggressive but does not metastasize, whereas DDLS has the potential to metastasize (20–30 % distant recurrence rate). DDLS also has a higher local recurrence rate than WDLS and six times the risk of death.[3,4]

Retroperitoneal liposarcomas can be difficult to treat. Patients with retroperitoneal liposarcomas have higher rates of local recurrence and disease-specific death than patients with liposarcomas of the extremities.[1] The primary treatment is surgical resection with a negative margin, which improves local control;[5] however, the role for resection of contiguous organs remains controversial.[4,6,7] Reports have described the efficacy of chemotherapy and/

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or radiation therapy in treating retroperitoneal sarcomas,[8,9] although recommendations regarding neoadjuvant and adjuvant therapy differ greatly even among major sarcoma treatment centers. For retroperitoneal liposarcomas, the clinical objective is to remove all macroscopic disease. Although there are some published reports that support en bloc resection of uninvolved adjacent organs to improve local control,[10,11] they are non-randomized retrospective studies that have numerous limitations related to the methodology used, confounding variables, and selection bias.[12] Moreover, none of these studies showed improved overall survival for extended resection. At this point, no randomized controlled trial supports extended resection beyond R0 resection. Therefore, unless the tumor is inseparable from adjacent organs and is likely to cause impending morbidity such as bowel obstruction, we do not advocate liberal en bloc organ resection. However, owing to the high recurrence rate and aggressive nature of retroperitoneal DDLS, neoadjuvant chemotherapy with/without radiation therapy is often considered for the treatment of retroperitoneal DDLS at the MD Anderson Cancer Center, depending on the individual patient presentation. Therefore, an accurate subtype-specific diagnosis is critical for the appropriate consideration of neoadjuvant therapy. In addition, pathological confirmation of dedifferentiation is routinely required as part of eligibility for novel therapeutic clinical trials in patients who are not appropriate candidates for surgery. The preoperative tissue diagnosis of retroperitoneal liposarcoma often employs image-guided core needle biopsy (CNB) or fine-needle aspiration (FNA). Previously, investigators have reported on the efficacy of image-guided FNA and CNB for diagnosing retroperitoneal soft tissue tumors;[13,14] however, only one study has assessed the accuracy of FNA and CNB in the subtype-specific diagnosis of liposarcoma.[15] To our knowledge, there has not been a study that has compared preoperative pathologic biopsy findings with final operative pathologic reports to assess the subtype-specific accuracy of preoperative percutaneous biopsy. We aimed to analyze the accuracy of preoperative percutaneous biopsy in the subtype-specific diagnosis of retroperitoneal liposarcoma and the reliability of percutaneous biopsy in guiding clinical decisions regarding neoadjuvant treatment.

MATERIALS AND METHODS

We retrospectively reviewed the medical records, including the pathologic reports, interventional radiology reports, and operative reports, of patients registered in the retroperitoneal WDLS/DDLS surgery database at The University of Texas MD Anderson Cancer Center between 1993 and 2013. This database includes all patients who underwent surgical resection with pathologic results of WDLS and/or DDLS—a total of 256 patients. We extracted the data of patients who underwent preoperative percutaneous biopsies (FNA and/or CNB) which were reviewed by sarcoma-specialized pathologists at the MD Anderson Cancer Center. The data extracted by chart review include date of surgery, date of biopsy, pathologic result of percutaneous biopsy, pathologic result of surgical resection, whether the biopsy was performed at the MD Anderson Cancer Center or another facility, whether chromosomal analysis of 12q15 amplification was performed, and whether and what type of neoadjuvant therapy was provided. If the biopsies were repeated on separate occasions before the surgical resection, those were counted as one set of biopsy results. As a rule, all biopsies at the MD Anderson Cancer Center were attempted in the area most suspicious for dedifferentiation on the imaging, and multiple biopsies were performed if there were multiple suspicious areas. This study was approved by the MD Anderson Cancer Center Institutional Review Board. Pathologic diagnoses from the surgical resections and preoperative percutaneous biopsies were compared, and the accuracy (number of correct results of percutaneous biopsies/all percutaneous biopsies) of percutaneous biopsy in the subtype-specific diagnosis of liposarcoma was assessed. Chi squared analysis was performed for tests of comparison (Microsoft Excel, Microsoft Corporation, Redmond, WA, USA). *P* values less than 0.05 were considered statistically significant.

TABLE 1 Accuracy of percutaneous biopsy and rate of neoadjuvant therapy

Final diagnosis	Preoperative biopsy results	*n* (%)	Neoadjuvant therapy	
			n (%)	*p* value
WDLS	WDLS (correct)	63 (85.1)	6 (9.5)	
	Other tumors (incorrect)	11(14.9)	6 (54.5)	0.0019
DDLS	DDLS (correct)	23 (36.5)	13 (56.5)	
	Other tumors (incorrect)	40 (63.5)	9 (22.5)	0.0064

The Chi square test was used for statistics

WDLS well-differentiated liposarcoma, *DDLS* dedifferentiated liposarcoma

RESULTS

All 256 patients registered in our database underwent surgical resection, with the pathologic results of WDLS and/or DDLS. Of these, 120 patients met our inclusion

TABLE 2 List of incorrect diagnosis in DDLS/WDLS cases

Final diagnosis	DDLS	*n*	WDLS	*n*
Incorrect diagnoses	WDLS	21	DDLS	3
	MFH	6	Unclassified sarcoma	4
	Rhabdomyosarcoma	1	GIST	1
	Desmoid tumor	1	Benign tumor	3
	GIST	1		
	B-cell lymphoma	1		
	Unclassified sarcoma	8		
	Benign tumor	1		

WDLS well-differentiated liposarcoma, *DDLS* dedifferentiated liposarcoma, *MFH* malignant fibrous histiocytoma, *GIST* gastrointestinal stromal tumor

criteria and underwent 137 preoperative percutaneous biopsies followed by surgical resections. Seventeen patients underwent repeat percutaneous biopsy and surgical resection on a separate occasion for recurrent disease. Final pathologic examination following surgical resection indicated that there were 74 WDLS cases and 63 DDLS cases. Eleven WDLS and 40 DDLS were initially diagnosed as other histologic tumor types based on the percutaneous biopsy specimens. Thus, the overall diagnostic accuracy of percutaneous biopsy for identifying the subtype of liposarcoma was 63 % (86/137); the accuracy for identifying WDLS was significantly higher (85 %, 63/74) than that for identifying DDLS (37 %, 23/63; $p < 0.01$) (Table 1).

Biopsy Results and Frequency of Neoadjuvant Therapy

Among the 63 DDLS patients, 40 (64 %) were incorrectly diagnosed with other types of tumors (Table 2). Among these 40 patients with incorrect diagnosis, 53 % (21/40) were diagnosed as WDLS, while 48 % (19/40) were diagnosed as malignancies other than WDLS (Table 2). Significantly more patients who were correctly diagnosed with DDLS underwent neoadjuvant therapy than those who were incorrectly diagnosed with other types of tumors: 57 % (13/23) versus 23 % (9/40) ($p < 0.01$; Table 1).

Moreover, among the 74 WDLS patients, 11(15 %) were incorrectly diagnosed with other types of tumors (Table 2). Of the 63 patients who were correctly diagnosed with WDLS on the basis of percutaneous biopsy, 6 (10 %) received neoadjuvant treatment because of their large tumor size, whereas of the 11 patients who were incorrectly diagnosed with other types of tumors, 6 (55 %) underwent neoadjuvant therapy ($p < 0.01$) (Table 1).

TABLE 3 Image guidance and accuracy of percutaneous biopsy

Image guidance	Biopsy diagnosis		Total	Accuracy (%)
	Correct	Incorrect		
CT	46	18	64	71.9
MRI	1	4	5	20.0
US	11	6	17	64.7
Fluoroscopy	1	2	3	33.3
Total	59	30	89	66.3

CT computed tomography, *MRI* magnetic resonance imaging, *US* ultrasonographic

Subset Analysis of Factors Affecting Biopsy Accuracies

Among the 137 biopsies, 89 were performed at our facility and 48 were performed at other facilities. Of 89 biopsies performed at our facility, four patients underwent repeat biopsies on separate occasions—three in the WDLPS group and one in the DDLPS group. The reason for repeating the biopsy was 'non-diagnostic' for two patients and 'initial biopsy was performed at OSH' for two patients. Since this patient group was small, no statistic evaluation was performed. If the biopsy was performed at another facility, specimens were re-examined by sarcoma-specialized pathologists at the MD Anderson Cancer Center. The diagnostic accuracy of the biopsies performed at our facility did not differ significantly from that of biopsies performed at other facilities (66 vs. 56 %, respectively; $p = 0.25$).

Although 26 biopsies were performed for recurrent retroperitoneal liposarcoma, and although the pathologists had access to the pathologic reports from the previous surgical resections, a previous history of surgical resection and a finding of retroperitoneal tumor on the previous pathologic report did not improve the subtype-specific diagnostic accuracy. The other 111 biopsies were first-time biopsies in patients without a history of previous operative intervention. No significant difference in diagnostic accuracy was noted between the biopsies performed in the patients with a previous pathologic report and the first-time biopsies (62 vs. 65 %, respectively; $p = 0.82$).

We conducted a subset analysis of the 89 biopsies that were performed at our facility to assess the impact of the image guidance method employed. Sixty-four biopsies were performed with computed tomography (CT) guidance, five were performed with magnetic resonance imaging (MRI) guidance, 17 were performed with ultrasonographic (US) guidance, and three were performed with fluoroscopic guidance; the accuracies of the subtype-specific diagnosis for each image guidance method were 72, 20, 65, and 33 %, respectively (Table 3). No significant difference in accuracy was noted between CT and US

guidance ($p = 0.56$), but MRI guidance was less accurate than CT guidance ($p = 0.017$).

All 89 biopsies included CNB; FNA was performed in 70 biopsies in addition to CNB. Due to the retrospective nature of the study, it was impossible to determine why 19 patients only had a CNB. The information from both biopsies was used to determine a final pathologic diagnosis. Again, due to the retrospective nature of the study, it was impossible to separate out the contribution of the type of biopsy to the final diagnosis. The needle size used for CNB was in the range of 12–22 gauge; a large size (12–17 gauge) was used in 43 biopsies, a small size (18–22 gauge) was used in 45 biopsies, and the needle size was not known in one biopsy. Using a larger needle size did not improve the diagnostic accuracy of CNB (72.1 % in the large-needle group and 62.2 % in the small-needle group; $p = 0.32$).

The diagnostic accuracy of biopsy did not improve over the study period. Among 89 biopsies performed at our facility, 43 were performed in 1993–2005 (early group) and 46 were performed in 2006–2013 (late group). There was no statistically significant difference in accuracy between the groups (74.4 % in the early group and 58.7 % in the late group; $p = 0.12$).

Chromosomal analysis of 12q15 amplification, which yields positive results in 90 % of cases of WDLS/DDLS,[17,18] was performed on eight percutaneous biopsy specimens as part of the pathologic examination. Seven had positive results for 12q15 amplification (sensitivity for WDLS/DDLS detection, 87.5 %); all eight specimens, including the case with negative results for 12q15 amplification, were diagnosed as either WDLS or DDLS (the patient with negative results for 12q15 had a history of recurrent WDLS). Thus, chromosomal analysis helped rule out other types of sarcoma but was not helpful in distinguishing WDLS from DDLS. Overall, the subtype-specific diagnostic accuracy of percutaneous biopsy with 12q15 amplification analysis was 63 % (5/8).

DISCUSSION

In this study, we aimed to assess the accuracy of preoperative image-guided percutaneous biopsy in the subtype-specific diagnosis of retroperitoneal liposarcoma. We noted an unexpectedly low subtype-specific diagnostic accuracy, particularly in cases of DDLS. Moreover, we observed that an incorrect diagnosis on the basis of preoperative percutaneous biopsy misled physicians in the decision to implement neoadjuvant treatment in a substantial proportion of patients.

The low accuracy of percutaneous biopsy in the diagnosis of DDLS may have two causes: technical sampling error and the variable morphology of DDLS. First, technical sampling error is the most significant problem affecting the diagnosis of DDLS. DDLS is a heterogeneous high-grade tumor which is defined by the presence of regions of non-lipogenic sarcomatous tissue (dedifferentiated component) within a WDLS.[16] The interface between well-differentiated and dedifferentiated areas is abrupt in most DDLS cases; occasionally, these tumors exhibit a mosaic pattern.[17] If a sample is obtained only from the well-differentiated component of the tumor, then the pathologic finding will be WDLS. In the present study, 53 % (21/40) of false-negative DDLS cases were diagnosed as WDLS; these appear to be most likely due to technical sampling error. Second, the variable morphology of DDLS may mislead pathologists to suspect other types of sarcoma. The dedifferentiated component of DDLS is required to have a mitotic rate of at least 5 mitotic figures per 10 high-power fields by definition, but interpretative difficulties arise when WDLS contains areas with increased cellularity but with a mitotic rate lower than in the typical DDLS.[18] Moreover, the dedifferentiation component can resemble or be identical to numerous other tumors.[19–21] In the present study, an incorrect diagnosis of malignancies other than WDLS was made in 48 % (19/40) of false-negative DDLS cases; the incorrect diagnoses included malignant fibrous histiocytoma, rhabdomyosarcoma, desmoid tumor, gastrointestinal stromal tumor, low grade B cell lymphoma, and unclassified sarcoma. This indicates the variability of DDLS morphology and the difficulty in its pathologic interpretation.

A retrospective study by Nikolaidis et al. on the accuracy of image-guided percutaneous biopsy for the subtype-specific diagnosis of retroperitoneal liposarcoma reported a slightly lower accuracy for WDLS (67 %) and a higher accuracy for DDLS (78 %)[15] than we found in our study (85.1 and 36.5 %, respectively). However, their study was limited by its design: all the biopsies were performed for research purposes, after obtaining surgical biopsies and final diagnosis. The pathologists were aware of the pathologic results of the prior surgical biopsies at the time of the pathologic evaluation of the needle biopsies. Therefore, the accuracy of the percutaneous biopsy was likely overestimated in their study, especially for DDLS.

To prevent sampling error, images, including CT and/or MRI, need to be thoroughly reviewed at the time of biopsy. If a dominant area of increased density is observed on images (indicating a potential area of dedifferentiation), then that area should be targeted for biopsy via image guidance. In this study, there was no difference in the accuracy between CT and US guidance. This result supports the statement that physicians can use either CT or US guidance if the area of possible dedifferentiation can be approached with the selected guidance. When the radiographic suspicion of DDLS is high and the pathologist is

unable to confirm the presence of DDLS, it may be reasonable to perform a repeat biopsy of the area or treat the tumor as DDLS if neoadjuvant treatment is indicated. To prevent misinterpretation of the dedifferentiated portion of the DDLS (in cases in which the dedifferentiated portion of the tumor is biopsied), it is important to also obtain a sample from the WDLS portion of the tumor. In addition, when the pathologic interpretation is difficult, identifying 12q15 amplification is extremely helpful to distinguish WDLS from benign adipocytic neoplasms and DDLS from other sarcomas.

The limitations of this study were its retrospective nature and the fact that the pathologists were not blinded to the previous radiology reports and operative reports in cases in which this information was available. However, the main strength of the study is the inclusion of a relatively large number of retroperitoneal liposarcoma biopsies, despite the rarity of the disease.

CONCLUSIONS

Percutaneous biopsy has low accuracy in the diagnosis of DDLS. This can mislead physicians in the decision about whether to implement neoadjuvant treatment. In cases in which other clinical and radiographic findings are suggestive of dedifferentiation in patients with extensive retroperitoneal tumors, the lack of pathologic confirmation of DDLS by percutaneous biopsy should not rule out the potential use of neoadjuvant therapy.

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