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Can Abdominal CT Imaging Help Accurately Identify a Dedifferentiated Component in a Well-Differentiated Liposarcoma?

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Abstract

Purpose—To assess the ability of CT to differentiate an atypical lipomatous tumor (ALT)/well-differentiated liposarcoma (WDLPS) from a WDLPS with a dedifferentiated component (DDLPS) within it.

Materials and Methods—Forty-nine untreated patients with abdominal atypical lipomatous tumors/well-differentiated liposarcomas who had undergone contrast-enhanced CT were identified using an institutional database. Three radiologists who were blinded to the pathology findings evaluated all the images independently to determine whether a dedifferentiated component was present within the WDLPS. The CT images were evaluated for fat content (< 25% or >25%); presence of ground-glass density, enhancing and/or necrotic nodules; presence of a capsule surrounding the mass; septations; and presence and pattern of calcifications. A multivariate logistic regression model with generalized estimating equations was used to correlate imaging features with pathology findings. Kappa statistics were calculated to assess agreement between the three radiologists.

Results—On the basis of pathological findings, 12 patients had been diagnosed with DDLPS within a WDLPS and 37 had been diagnosed with WDLPS. The presence of an enhancing or a centrally necrotic nodule within the atypical lipomatous tumor was associated with dedifferentiated liposarcoma ($p = 0.02$ and $p = 0.0003$, respectively). The three readers showed almost perfect agreement in overall diagnosis (kappa $\kappa = 0.83$; 95% confidence-interval 0.67 to 0.99).

Conclusion—An enhancing or centrally necrotic nodule may be indicative of a dedifferentiated component in well-differentiated liposarcoma. Ground-glass density nodules may not be indicative of dedifferentiation.

Introduction

In 2015 approximately 11,930 individuals in the United States will be diagnosed with and 4870 individuals will die of soft tissue sarcomas¹. Retroperitoneal sarcomas account for approximately 12% of soft tissue sarcomas². Liposarcomas, the most common retroperitoneal sarcomas are classified as atypical lipomatous tumors (ALT)/well-differentiated liposarcoma (WDLPS); dedifferentiated liposarcoma (DDLPS); myxoid or pleomorphic types^{3–5}. WDLPS and DDLPS are the most common retroperitoneal liposarcomas⁶. Variants of WDLPS include cellular atypical lipomatous tumor⁵ containing nonlipogenic fibromyxoid regions. DDLPS, a high-grade aggressive sarcoma occurs primarily in the retroperitoneum, may occur within a WDLPS, or de novo, with poor prognosis independent of tumor size^{4, 7–9}. This manuscript uses the acronym DDLPS for WDLPS with a dedifferentiated component.

Prognosis is dependent on histologic grade, tumor differentiation depends on cytologic atypia, mitoses (> 5 mitotic figures per 10 high-power field suggesting DDLPS), and necrosis⁵. Approximately 90% of WDLPSs and DDLPSs have amplification of chromosome 12q13–15, containing oncogenes *MDM2*, *HMGA2*, *CDK4* and *p16*¹⁰. Dedifferentiation has been associated with overexpression of the proto-oncogene JUN and mutation of p53 with chromosomal translocation generally occurring in the FUSCHOP fusion gene¹¹.

Prognosis of retroperitoneal liposarcomas depends on completeness of surgical resection, histologic grade, multifocal disease, invasion of adjacent structures^{12–16}. Neoadjuvant chemotherapy may benefit patients with DDLPS, albeit controversial¹⁷.

Surgical removal of tumor with en-bloc resection of involved organs may offer a chance of cure^{16, 18}. Resection of involved organs is controversial^{13, 15, 19–21}, since tumors may recur following resection. DDLPS and WDLPS differ in biological behavior²². Meric et al suggested that intermediate- to high-grade tumors treated with neoadjuvant therapy that showed radiologic response benefitted from surgical resection²³. Distinguishing between DDLPS and WDLPS may help clinicians plan treatment and identify patients who would benefit from neoadjuvant therapy and extensive surgical resection. Components within the WDLPS may have heterogeneous imaging characteristics, for example a water density nodule may be related to fibromyxoid tissue^{24, 25}. Clear imaging criteria are unavailable to distinguish DDLPS from WDLPS; studies have investigated features such as fat content and morphology of fat and non-fat components in liposarcomas by using imaging modalities, such as CT and MRI^{26–32}.

The goal of this study was to characterize CT imaging features that can be used to identify (for biopsy purposes) nodules suspected to represent a dedifferentiated component in a WDLPS.

Materials and Methods

Patients

Three hundred and sixty patients with WDLPS or DDLPS were identified using an institutional database from 2005 through 2014. The study was approved by the institutional review board. All patients to be included in the study were required to have had CT scans acquired prior to therapy (surgery, pre-operative chemotherapy, or radiation therapy). CT scans were acquired following administration of 125 cc of intravenous 350 mg iodine/ml (Optiray 350, Mallinckrodt Pharmaceuticals) at 3 cc per second with a scan delay of 60 seconds on a General Electric, Waukesha, WI scanner in the portal venous phase of contrast enhancement. Only patients who had a non contrast study were included. Images were acquired at 2.5-mm thickness, table speed of 18.75 mm/sec, and a pitch of 0.938 at 120 kVp; auto mA (current) was used based on the size of the patients (range 300–500 mA). All images were then reconstructed at 2.5-mm axial sections. The non-contrast scan had the same imaging parameters and was performed prior to injection of intravenous contrast. Two-percent barium sulfate was used as an oral contrast agent. 311 patients were excluded from the study, 190 patients did not have preoperative CT scans, 31 patients received radiation and/or chemotherapy prior to resection and 90 patients did not have images reconstructed at 2.5mm slice thickness. Forty-nine patients met all the above inclusion criteria and all patients had surgical resection of the tumor with a negative margin. Direct correlation of the surgical pathological specimen was made with the imaging findings.

Image Interpretation

Three faculty radiologists M.P, T.S and C.J with imaging experience 11, 8, and 4 years respectively, who were blinded to the pathology findings evaluated all the CT scans independently on a Philips PACS reading station. The radiologists documented their imaging findings for the pre- and post-contrast CT scans on an Excel spreadsheet.

Qualitative Analysis

Tumors were evaluated for the following internal characteristics: percentage of visible fat (or >25%) (Fig. 1) within the mass, calcifications, presence of a capsule, septations, and presence or absence of soft tissue nodules. Nodules within the ALT were characterized as (i) ground-glass density (attenuation lower than that of the adjacent psoas muscle and a hazy internal architecture; (Fig. 2 and 3), (ii) enhancing (higher attenuation than muscle on visual assessment (Fig. 4), or (iii) necrotic (solid enhancing mass with central area of low attenuation; Fig. 6). A final diagnosis of WDLPS or DDLPS was then documented by the radiologist based on the visual enhancement of the tumor greater than the muscle or HU values of an enhancing nodule >20 compared to that of the psoas muscle and/or presence of a necrotic nodule.

Quantitative Analysis

An ROI of 20 mm² was drawn within the psoas muscle at the level of the L4 vertebral body on the contralateral side of the tumor, and the Hounsfield unit (HU) value was recorded for the precontrast and the contrast-enhanced images. An ROI of 20 mm² was also drawn on

any intensely enhancing nodule within the ALT on the contrast-enhanced image, and HU values were recorded for the contrast-enhanced image and the corresponding non-contrast image. The HU ratio of the nodule to the psoas muscle was calculated for the contrast-enhanced and the non contrast images. The percent enhancement of the nodule was calculated. The largest size of the ALT was recorded. A tumor was considered to be a WLDPS if it had no nodules, ground glass nodules only or had nodules which did not enhance > that of the contralateral psoas muscle by 20HU. A tumor was considered to be a WDLPS with a dedifferentiated component if it has any enhancing nodule which enhanced > the contralateral psoas muscle >20HU.

For survival analysis the date of surgery, pathology classification (DDLPS or WDLPS), indicator of recurrence, date of recurrence, and date of last follow-up were included as variables. Post-surgery pathology classifications (DDLPS and WDLPS) were used for comparison.

Statistical Analysis

Summary statistics of patient characteristics and reader assessments were calculated as frequencies and percentages. Patients' ages, lesion sizes, and HU of the enhancing nodules were summarized as means with standard deviations and ranges. For overall diagnosis, pathology results were considered the gold standard.

A multivariate logistic regression model with generalized estimating equations (GEE) was used to correlate imaging features with pathology findings^{33, 34}. The GEE method took into account the correlation between ratings for the same patient. A backward elimination procedure was used to identify the final model, with only significant features remaining. Kappa statistics were calculated to assess agreement between the three radiologists in assessing the five features (calcifications, presence of a capsule, septations, and presence of absence of soft tissue nodules).

The HU values of all the enhancing nodules documented by the three radiologists were used to extrapolate a cutoff value for differentiating WDLPS from DDLPS, and a cutoff value of 90 HU was chosen to increase the specificity after carefully evaluating the HU values of the enhancing nodules within the WDLPS. With this cutoff value, we generated a second multivariate logistic regression model with the GEE method to predict the probability of a lesion being de-differentiated, on the basis of the presence of a ground-glass density nodule or /and centrally necrotic nodule in the ALT.

Kaplan-Meier survival curves were generated to confirm the prognosis of these tumors as documented in the literature and to determine whether survival of patients who have WDLPS was similar to survival of DDLPS patients. Log-rank test was used to compare overall survival of WDLPS and DDLPS patients. Survival estimates and confidence intervals were obtained using the SAS Proc Life-test tool. All tests were two-sided, and *p*-values of 0.05 or less were considered statistically significant.

Results

Study Population

There were 20 female and 29 males patients (Table 1a). Of the 49 patients, 12 had been diagnosed with DDLPS and 37 had been diagnosed with WDLPS by pathology. There were 29 (59%) males and 20 (41%) females. Mean tumor size was 17.10 cm (standard deviation ± 7.5 cm, range (4 cm-to 35 cm). The average time to recurrence was 741.1 days (standard deviation ± 442.3 days). Twenty patients (41%) experienced recurrence after surgery, and 29 (59%) did not have a recurrence. Only one patient who had a WDLPS recurred as a DDLPS.

Qualitative Analysis

The accuracy, specificity, sensitivity, and negative and positive predictive values for diagnosis of WDLPS with a dedifferentiated component are shown in Table 1b. All readers correctly identified 11 out of 12 DDLPS (sensitivity = 91.67%). However, readers 1 through 3 only identified 26, 28, and 25 out of 37 WDLPS (specificities = 70.27%, 75.68%, and 67.57%), respectively (Table 2). The three radiologists had almost perfect agreement amongst their overall diagnosis: kappa $\kappa = 0.83$, 95% confidence interval 0.63 to 0.99 (Table 3). The three radiologists had substantial agreement in characterizing the percentage of fat, enhancing nodules, and central necrosis. Moderate agreement was observed for ground-glass density nodules.

Quantitative Analysis

The multivariate logistic regression model showed that the presence of an enhancing nodule and the presence of a centrally necrotic nodule in the ALT were associated with DDLPS ($p = 0.02$ and $p = 0.0003$, respectively). The odds ratio for the use of an enhancing-nodule threshold of >90 HU (absolute HU and not comparing it to the psoas muscle) to identify a dedifferentiated component in an ALT was 8.38 (Table 4). The area under the curve of 0.84 confirmed that nodule enhancement was highly predictive of dedifferentiation (Fig. 7). Tumor size, the presence of a capsule, and septation were not necessarily associated with dedifferentiation.

Survival

Based on our data, we estimated by Kaplan-Meier analysis a 3-year post surgery survival probability of about 79% for patients with pathologically proven DDLPS, with a 95% confidence interval of 51% to 100%. For patients with pathologically proven WDLPS, we estimated a 3-year survival probability of about 93%, with a 95% confidence interval of 84% to 100%; the probability remained the same for 5-year survival. The survival rates of WDLPS and the DDLPS patients (with diagnoses based on pathology findings after resection) differed significantly (log-rank $p < 0.001$) (Fig. 8). It was not possible to estimate a 5-year survival rate for DDLPS patients because most patients were either lost to follow-up or died in less than 5 years after surgery.

Discussion

Our findings suggest that (i) presence of an enhancing nodule higher than that of the psoas muscle, (ii) presence of central necrosis in a nodule, and (iii) visible fat content 25% within the mass may suggest DDLPS, absence of these findings may exclude DDLPS.

All three radiologists correctly identified 92% (11 of 12) of DDLPS. Eight patients (one DDLPS and seven WDLPS) were misdiagnosed by all three radiologists. A threshold of >90 HU for nodule enhancement, decreased the false-positive DDLPS diagnoses from 13 to 3 (applying to the reads by all three readers). High concordance of pathologically and radiologically diagnosed DDLPS suggests that our proposed imaging criteria may be reliable indicators of DDLPS. Given the high NPV (96%), DDLPS are unlikely to be missed by our method.

Calcification has been reported as a sign of dedifferentiation³⁵; we did not find it to be a diagnostic factor, and is in agreement with the findings of Hong et al.³¹.

Lahat and colleagues and others have suggested that presence of a water density nodule (ground-glass density) is indicative of DDLPS^{28, 32}; however we did not find this to be the case. Our findings agree with Kim and colleagues, who concluded based on pathology in 4 of 10 patients that ground-glass nodules may be related to myxoid components²⁴. It is known that a combination of water density and high-density areas, similar to that in the adjacent muscle, may be related to a fibromyxoid/myxoid component^{29, 36} and not necessarily dedifferentiation and this correlated with our results.

Given the large size of WDLPS and DDLPS at presentation, precise sampling of the tumor to get the correct pathologic diagnosis can be difficult. Ikoma et al³⁷ concluded that percutaneous biopsy had low accuracy in diagnosing retroperitoneal DDLPS, this may have been due to incorrect nodule selection for biopsy. The variable morphology of DDLPS may cause pathologists to suspect different sarcoma subtypes. The dedifferentiated component of liposarcoma can mimic other tumors^{7, 37, 38}, such as malignant fibrous histiocytoma (currently termed undifferentiated pleomorphic sarcoma). Imaging can help identify appropriate areas for biopsy³⁹. In addition, our findings (and the findings of others) indicate that if a ground-glass density area is biopsied with a negative pathology result for dedifferentiation, the biopsy may still be accurate as this nodule may represent a fibromyxoid component of ALT^{29, 36}.

To prevent sampling error, we suggest biopsy of a nodule that has an HU value of >90 or enhancement at least 20HU > than that of the psoas muscle or a centrally necrotic nodule in the WDLPS.

The presence of an incomplete (R2) resection margin in DDLPS can shorten progression and disease-free survival, and aggressive resection to achieve a negative margin is recommended in such cases⁴⁰. In contrast, WDLPSs are indolent, with significantly better prognosis and higher 5-year overall patient survival (95% vs. 40%)¹⁵ and correlated with our findings that the survival of WDLPS was better than those who had DDLPS. WDLPSs are four times less likely to recur locally than DDLPS¹³, and distant metastases are 10–40% less likely¹⁶,

depending on tumor grade. Literature suggests that recurrence does not affect overall survival of patients with WDLPS²², and aggressive multi-organ resection may not be necessary²². The 10-year disease-specific survival rate of WDLPS patients has been reported to be 63%, compared to 33% for DDLPS patients⁴¹. DDLPSs have a tendency toward systemic metastases¹⁶. The 3 year survival for DDLPS was 79% and for WDLPS was 93% in our study.

Neoadjuvant chemotherapy and radiation therapy⁴² is at times used in DDLPS due to the aggressive nature of this disease,³⁷ albeit controversial^{18, 43}. In contrast WDLPS are unlikely to metastasize and have a slower rate of local progression, and may benefit more from active surveillance⁴⁴. Since prognoses and treatment for WDLPS and DDLPS are quite different²², accurate diagnosis is crucial for the selection of appropriate treatment⁴⁵.

Our study had several limitations. The study was retrospective, performed at a single institution and only patients whose CT imaging data matched certain parameters were included. Only patients with WDLPS and DDLPS were included and hence the sensitivity and specificity in differentiating these may be high, however this study was not designed to differentiate between the different non-fat containing retroperitoneal sarcomas. To reevaluate the cases misdiagnosed by radiology, we applied a cutoff value of 90 HU, and a repeated multivariate analysis helped us to correctly diagnose the WDLPS cases; this cutoff value was not prospectively determined. All nodules seen within the ALT on imaging were not directly correlated with the pathology findings prospectively; however the final pathology results of the entire surgically resected tumor were correlated with the imaging findings.

In conclusion, CT is an effective imaging modality for diagnosing a DDLPS within a WDLPS in the retroperitoneum. If a fat containing tumor contains no nodules it is unlikely to be dedifferentiated or if it only contains ground-glass density nodules, it may not be an indicator of dedifferentiation. On the other hand, if a tumor contains soft tissue nodules that have central necrosis or enhancement attenuation > 90 HU, or are enhancing higher than the psoas muscle these nodules should be biopsied to exclude DDLPS. In future, a prospective study may be able to confirm our findings.

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Fig. 1.
73-year-old woman with an atypical lipomatous tumor /well-differentiated liposarcoma.
Axial non-contrast CT image shows a fat attenuation mass (arrow) without any interspersed nodules or septation, consistent with well-differentiated liposarcoma.

Fig. 2.

47-year-old man with a well-differentiated liposarcoma of the retroperitoneum containing a fibromyxoid component.

Axial contrast-enhanced CT image shows a mass in the retroperitoneum. The mass has fat intermixed with nodules. The nodule indicated (arrow) had relatively low attenuation (<90 HU).

Fig. 3.

34-year-old man with a well-differentiated liposarcoma with a myxoid component.

A, Axial contrast-enhanced CT image shows a mass in the retroperitoneum. The mass has fat intermixed with nodules. The nodule indicated (arrow) had relatively low attenuation (<90 HU).

B, Axial contrast-enhanced CT image reveals incidental calcification.

Fig. 4.

63-year-old man with a dedifferentiated liposarcoma within an atypical lipomatous tumor/ well differentiated liposarcoma.

Axial contrast-enhanced CT image shows a mass in the retroperitoneum. The mass has fat intermixed with an enhancing nodule (arrow). The nodule had high enhancement (112 HU) and was consistent with a dedifferentiated component on biopsy.

Fig. 5.

62-year-old man with a dedifferentiated liposarcoma interspersed with myxoid tissue was misdiagnosed as a well differentiated liposarcoma (pitfall).

A, Axial contrast-enhanced CT image shows a mass (arrow) with a HU of 67 in the retroperitoneum with incidental calcifications (arrowhead).

B, Needle biopsy. The initial diagnosis was well-differentiated liposarcoma. Following resection, the pathology changed to well-differentiated liposarcoma with a dedifferentiated component, based on a rate of >5 mitotic figures per 10 high-power fields. No obvious fat component was visible within the mass.

C, Coronal reconstructed post contrast CT image shows the soft tissue component of the tumor (black arrow) and the fatty component (white arrow). Note that the soft tissue component is almost similar in attenuation to the adjacent muscles.

Fig. 6.
64-year-old man with a dedifferentiated component in a well differentiated liposarcoma.
Axial contrast-enhanced CT image shows a large retroperitoneal mass with central necrosis (arrow).

Fig. 7. ROC curve for correlation of HU values with tumor differentiation status. The area under the curve (AUC) 0.84 indicates that HU values are highly predictive of differentiation status.

Fig. 8. Probability of a patient with retroperitoneal liposarcoma remaining alive over time. The log-rank p -value of <0.001 indicates that patients with well-differentiated liposarcomas (dashed line) were likely to have longer overall survival than patients with dedifferentiated liposarcomas (solid line).

Table 1a

shows patient characteristics

Gender	Number	%
F	20	40.8
M	29	59.1
Status		
Alive	40	81.6
Deceased	9	18.4
Recurrence		
No	29	59.1
Yes	20	40.8
Pathology		
De-differentiated	12	24.5
Well-differentiated	37	75.5

Table 1b

Concordance of Radiological Diagnoses with Pathology Diagnoses of Retroperitoneal Liposarcomas

Variable	% Concordance for Radiologist:		
	1	2	3
Accuracy	75.5	79.6	73.4
Sensitivity	91.7	91.7	91.7
Specificity	70.3	75.7	67.6
PPV	50.0	55.0	47.8
NPV	96.3	96.6	96.2

PPV and NPV, positive and negative predictive values, respectively.

Concordance of Radiological Diagnoses with Pathology Diagnoses of Retroperitoneal Liposarcomas by three readers

Table 2

Reader	Diagnosis	Pathology					
		de-differentiated			well-differentiated		
		N	Col%	Row%	N	Col%	Row%
1	de-differentiated	11.0	91.7	50.0	11.0	29.7	50.0
	well-differentiated	1.0	8.3	3.7	26.0	70.3	96.3
2	de-differentiated	11.0	91.7	55.0	9.0	24.3	45.0
	well-differentiated	1.0	8.3	3.5	28.0	75.7	96.6
3	de-differentiated	11.0	91.7	47.8	12.0	32.4	52.2
	well-differentiated	1.0	8.3	3.9	25.0	67.6	96.2

Table 3

Agreement between Three Radiologists in Assessing CT Image Characteristics of Atypical Lipomatous Tumors

Variable	Kappa (95% CI)
% Fat	0.77 (0.61–0.93)
Enhancing nodule	0.75 (0.59–0.91)
Ground-glass nodule	0.54 (0.37–0.70)
Central necrosis	0.66 (0.50–0.82)
Capsule	–0.09 (–0.25–0.07)
Overall diagnosis	0.83 (0.67–0.99)

* Kappa Statistic interpretation –<0=poor agreement, 0.01–0.20 =slight agreement, 0.21–0.40 =fair agreement, 0.41–0.60= Moderate agreement, 0.61–0.80 =substantial agreement, 0.81–1.00= Almost perfect agreement.

CI, confidence interval.

Table 4

Odds Ratios Obtained with a Multivariate Logistic Regression Model for the Probability of a Tumor Being Dedifferentiated

Variable	Odds Ratio	<i>p-value</i>
Nodule (Enhancing Vs Ground glass)	5.88 (1.51–22.83)	0.01
Central necrosis (yes vs. no)	25.82 (6.13–108.79)	<0.0001
HU (< 90 vs. >90)	8.38 (1.42–49.35)	0.02

HU, Hounsfield units.

Note—the method of generalized estimating equations was used, with accounting for correlation between the ratings by the three radiologists for the same nodule within an atypical lipomatous tumor.