RESEARCH ARTICLE

Computed Tomography Manifestations of Histologic Subtypes of Retroperitoneal Liposarcoma

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Abstract

Objective: Liposarcoma (LPS) is the most common soft tissue sarcoma and accounts for approximately 20% of all mesenchymal malignancies, often occurring in deep soft tissue of retroperitoneal space. Accurate preoperative diagnosis is therefore necessary. We explored whether computed tomography (CT) could be used to differentiate between the various types of retroperitoneal liposarcoma (RPLS). Method: Forty-seven cases of RPLS, diagnosed surgically and histologically, were analyzed retrospectively. CT features were correlated with postoperative pathological appearance. Results: The study radiologist identified 29, 11, 2, 2 and 3 RPLS as atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDL), dedifferentiated liposarcoma (DDL), myxoid/round cell liposarcoma (ML/RCL), pleomorphic liposarcoma (PL) and mixed-type liposarcoma. Analysis of CT scans revealed the following typical findings of the different subtypes of RPLS: ALT/WDL was mainly visible as a well-delineated fatty hypodense tumor with uniform density and integrity margin; DDL was marked by the combination of focal nodular density and hypervascularity. ML/RCL, PL and mixed liposarcoma showed malignant biological behaviour and CT findings need further studies. Conclusions: CT scanning can reveal important details including internal components, margins and surrounding tissues. Based on CT findings, tumor type can be roughly evaluated and biopsy location and therapeutic scheme guided.

Keywords Retroperitoneal liposarcoma - histologic subtypes - computed tomography - retrospective analysis

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Introduction

Liposarcoma (LPS) is a malignant tumor composed of fat cells differentiated into a variety of cell types. Most cases originate from the deep soft tissue of the lower extremities and the retroperitoneal space. It is the most common soft tissue sarcoma in adults, accounting for 20% of sarcoma cases (Dei Tos et al., 2000). LPS is frequently encountered in the elderly (45-70 years) but not seen in the juvenile group (Bhurgri et al., 2008). Although LPS occurs mainly in males, the incidence of retroperitoneal liposarcoma (RPLS) is higher in females. Histologically, LPS is divided into five types: atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDL), dedifferentiated liposarcoma (DDL), myxoid/round cell liposarcoma (ML/RCL), pleomorphic liposarcoma (PL) and mixed-type liposarcoma (Fletcher et al., 2002). This histological diversity influences the biological behaviour and prognosis of LPS, with ALT/WDL classified as an intermediate or locally aggressive tumor while the other types are malignant (Fletcher et al., 2002); identification of the histological subtype is therefore crucial for both prognosis and effective therapy. We compared CT findings of 47 cases of RPLS with pathologic diagnoses to investigate the relationship between them and provide an initial evaluation of LPS prognosis based on CT imaging.

Materials and Methods

We carried out a retrospective analysis of 47 cases of abdominal liposarcoma, treated at our institution from January 2008 to April 2014, which were confirmed by pathology. Patients comprised 26 males and 21 females, aged 35-82 years (mean age: 54±11.5 years). All patients experienced nonspecific clinical symptoms such as abdominal mass, abdominal distension, abdominal pain, or weight loss.

Before CT scanning, all patients imbibed 1, 000 mL potable water or 1-1.5% contrast agent diluent orally to fill and engorge the gastrointestinal tract before monitoring. In each case we followed the identical procedure to scan the tumor tissue: plain and enhanced scans with 5-mm

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slice thickness and 5-mm layer spacing (16-row spiral CT, Siemens Somatom). Omnipaque at a dose of 1.5 mL/kg (total volume no more than 100 mL) was administered intravenously at a speed of 3.0-4.0 mL/s. We used intelligent monitoring, locating the monitoring point on the abdominal aorta and setting the threshold value at 120 Hu. Axial and reformatted images were reviewed on a PACS workstation. After image post-processing, a window level of 25-45 Hu and a window width of 300 Hu were chosen to observe the liposarcoma images.

We evaluated expected CT characteristics such as tumor location, density, shape and margin. Tumors were subcategorized by the study radiologist according their fat content using a scale that ranged from 1 to 5, in which 1 represented <5% fat, 2 represented 6% to 25% fat, 3 represented 25% to 50% fat, 4 represented 50% to 75% fat, and 5 represented tumors that were >75% fat. Density of tumor was described as three situations: 'fat' presented predominant fatty mass with or without nonfatty component; 'soft tissue' presented focal fatty component within large muscle-like nonfatty mass; 'mixed' presented well-defined fatty mass and well-defined nonfatty mass. Specific radiologic tumor descriptors were defined as follows: Satellite nodular density was defined as a nodular area within the tumor with a muscle density. Cystic areas within the tumor that were less dense than water or muscle, were not fat, and did not enhance were considered necrotic areas. Calcifications were diagnosed using a noncontrast scan. Septations were considered as present when thin septa of uniform thickness were detectable within the tumor. The tumor margin radiologic appearance was characterized by the study radiologist as smooth or irregular. Enhancement of nonfatty components was evaluated as 'slight' 'moderate' or 'obvious'. A tumor was evaluated as 'infiltrating' if the study radiologist determined that a clear line of demarcation between an organ and the tumor was absent. Major vessels were considered to be involved when either encasement and/or infiltration were observed. For the purpose of this study, a board-certified radiologist with specialized interest and expertise in soft tissue tumors who was blinded to the final histopathologic diagnosis reviewed the preoperative CT scans. Sensitivity and Positive Predicted Value (PPV) were calculated for a comparison of consolidated histology with each feature.

Table 1. Correlation Between Radiologic Diagnosis and Histologic Subtype in Patients With Liposarcoma

Histologic diagnosis	Radiologic diagnosis					
	ALT/WDL	DDL	ML/RCL	PL	Mixed	Total
ALT/WDL	22	6	0	0	1	29
DDL	2	9	0	0	0	11
ML/RCL	0	0	2	0	0	2
PL	0	1	0	1	0	2
Mixed	0	1	0	1	1	3
Total	24	17	2	2	2	47

Results

Correlation between radiologic findings and histologic subtype

Forty-seven patients who had a postoperative histologic diagnosis of liposarcoma were identified as such radiologically by the study radiologist based on the presence of tumor conventional feature. We evaluated whether various CT scan features that previously were reported as distinctive of the RPLS subtype were correlated with postoperative histologic subtype determinations. Table 1 depicts the correlation between the radiologic diagnosis suggested by the study radiologist and the postoperative histologic diagnosis. We only evaluated the sensitivity and PPV of ALT/WDL and DDL on account of the small sample size without statistical significance in the other subtypes. Lahat et al. suggested an area of focal nodular/water density or a hypervascular focus may be the reliable evidence to differentiate DDL from ALT/WDL (Lahat et al., 2009). We assumed the features of ALT/WDL included predominant fatty mass or large soft tissue density mass merely with little satellite nodules, uniform density and integrity margin. In contrast, we judged DDL based on satellite nodules, hypervascular focus and infilitration. According to the above criteria, among 29 cases of ALT/WDL histologically proven six and one case was misdiagnosed as DDL and mixed lip sarcoma, respectively. So its sensitivity was 75.9%. Due to 24 cases of ALT/WDL radiologically presumed were certified as 22 cases of ALT/WDL (true) and two cases of DDL (false) by histology with the 91.7% PPV. Similarly,

Table 2. Imaging Findings Stratified by the Histologic Subtype in Patients with Liposarcoma

	ALT/WDL (lipoma-like lipsarcoma)	ALT/WDL (sclerosing lipsarcoma)	DDL	ML/RCL	PL	Mixed Liposarcoma
Density	fat	soft tissue	mixed	mixed	soft tissue	mixed
Average fat content*	4.4	1.7	3.4	3.1	2.1	3.2
Septations	strip-like	strip-like	strip-like	unclear	unclear	unclear
Margin	smooth integrity	smooth integrity	rough irregular	rough irregular	incomplete irregular	smooth integrity
Satellite nodules	visible(4/21)	visible(3/8)	common(9/11)	little(0/2)	little(0/2)	visible(1/3)
Necrotic/Cystic area	little(0/21)	little(1/8)	visible(3/11)	common (2/2)	little(0/2)	little(0/3)
Calcifications	little(0/21)	little(0/8)	little(1/11)	visible(1/2)	little(0/2)	visible(1/3)
Vascular involvement	little(0/21)	little(0/8)	little (0/11)	visible(1/2)	visible (1/2)	little(0/3)
Infiltrated organs	little(0/21)	little(0/8)	visible(3/11)	visible(1/2)	common (2/2)	visible(1/3)
Solid enhancement	slight strip-like	moderate uniform	obvious uneven	obvious uneven	obvious uneven	obvious uneven

*Average fat content was scored as follows: 1, <5% fat; 2, 6%-25% fat; 3, 25%-50% fat; 4, 50%-75% fat; and 5, >75% fat

we calculated the sensitivity and PPV for the prediction of DDL histology were 81.8% and 52.9%, respectively. Taken together, it seems that the diagnosis of ALT/WDL can be based on CT scanning alone because of the high sensitivity and PPV. Moreover, these data suggest that CT scan guided biopsy is necessary for suspicious DDL due to the low PPV, although the sensitivity of a focal nodular density area as a marker of DDL is high.

CT criteria for the different pathological subtypes of liposarcoma

The maximum diameter of the liposarcomas studied ranged from 8 to 43 cm, with 53% being smaller than 20 cm, 22% between 20-30 cm and 25% larger than 30cm. Six giant tumors (the maximum diameter >40cm) spreaded throughout most of the abdomen were confirmed by surgery that they were retroperitoneal liposarcomas with cross-peritoneal growth.

Among the 47 cases of liposarcoma, twenty-nine, eleven, two, two and three case were diagnosed as ALT/WDL, DDL, ML/RCL, PL and mixed liposarcoma, respectively. ALT/WDL in our study includes two subtypes, lipoma-like liposarcoma and sclerosing liposarcoma. All features that we used in this evaluation are presented in Table 2. Twenty-one cases of lipoma-like liposarcoma which were pathologically diagnosed comprised tumors of mainly fat-like density with a CT value of -110-76 Hu and an average fat content of 4.4. Imaging revealed strip-like septation with soft tissue density. The tumors were completely encapsulated. Four of the 21 cases (19.0%) exhibited multiple solid satellite nodules of different sizes surrounding the large mass (Figure 1a). The remaining eight cases were diagnosed as sclerosing liposarcoma and displayed non-uniform soft tissue density (CT scale 24-40 Hu) with stripes or patches of hyperdensity and a clear margin, together with little or no fat content. Three of them (37.5%) had focal nodular masses (Figure 1d). The eleven cases of DDL could be seen as cystic and solid masses with mixed fat density, with septations evident in the cysts. The focal nodular density area was commonly seen (81.8%). Three cases of DDL (27.3%) underwent cyst degeneration and necrosis (Figure 2). Both of the two ML/RCL cases appeared mixed density with fluid components (CT scale 10-20 Hu) within a hyperdense pattern of irregular stripes and an integral capsule. The one case exhibited obvious large-scale calcification (Figure 3a). The two cases were certified as PL with a mass taking on the appearance of soft tissue density (CT value 85 Hu). Nodular local peritoneal invasion and fibrous ecphymas around part of the edge were observed (Figure 3b). The three case of mixed liposarcoma showed unrepresentative images of varying density, involving solid, fatty density and calcification (Figure 3c).

CT enhancement pattern of liposarcoma

All cases were analyzed by plain and enhanced CT scans. In the cases of lipoma-like liposarcoma only the envelope, reticular connective tissue and soft tissue nodules were slightly and unevenly enhanced (Figure 1a, b). Sclerosing liposarcoma showed slight or moderate enhancement. The density of enhanced mass was relatively uniform (Figure 1d, e). The other cases (including DDL, ML/RCL and PL) presented a similar enhancement pattern in which hypervascular solid components were visible as obvious, heterogeneous and nodular or flake-like enhancement in the arterial phase, then delayed enhancement in the portal venous and delayed phase (Figure 2a, b, c). In addition, we discovered two cases of DDL and one case of ML/RCL which showed strip enhancement of the intratumoral vasculature.

Treatment and prognosis of liposarcoma

All patients underwent tumor radical resection at the first visit. In an effort to complement surgery, the administration of radiation therapy has been tried in only five cases with a giant or high-risk tumor. Three patients died during follow-up: two cases of RPLS died of tumor recurrence and three died of other diseases. Ten of the forty-seven patients (21.7%) appeared recurrence, including five cases of ALT/WDL (17.2%), four cases of DDL (36.4%) and one case of PL (50%). Multiple

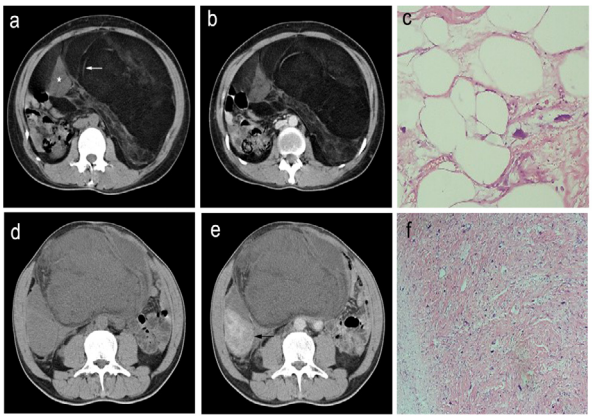

Figure 1. Lipoma-Like Liposarcoma. A) Plain Scan Shows Masses of Uneven fat Density with an Integral Envelope, Reticular Separation (white arrow) and Soft Tissue Nodules (white star). **B)** Solid ingredients exhibit mild enhancement. **C)** Under the microscope, tumors can be seen to be composed of fat cells with scattered fatty blast cells, and separated into asymmetrical lobules by fibrous tissue. Sclerosing type. **D)** Plain scan shows well-circumscribed soft tissue masses. **E)** The central larger mass exhibits no enhancement, while the right nodular soft tissue is unevenly enhanced (black arrow). **F)** Under the microscope, tumors appear to consist of areas of dense collagen fibrosis associated with atypical spindle cells and vesicular fat mother cells

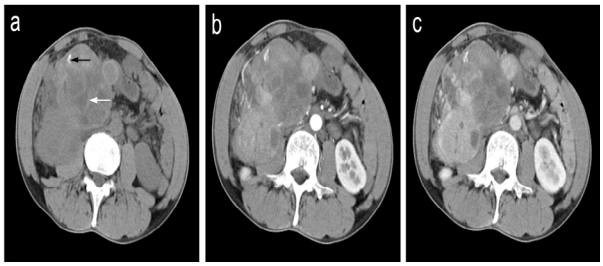

Figure 2. Dedifferentiated Liposarcoma. A) Plain Scan Shows Multiple Uneven Irregular Masses of Nodular Soft Tissue with Segregation, Cystic Degeneration (white arrow) and Calcification (black arrow). **B), C)** Solid composition presents nodular enhancement in the arterial phase and further enhancement in the venous phase

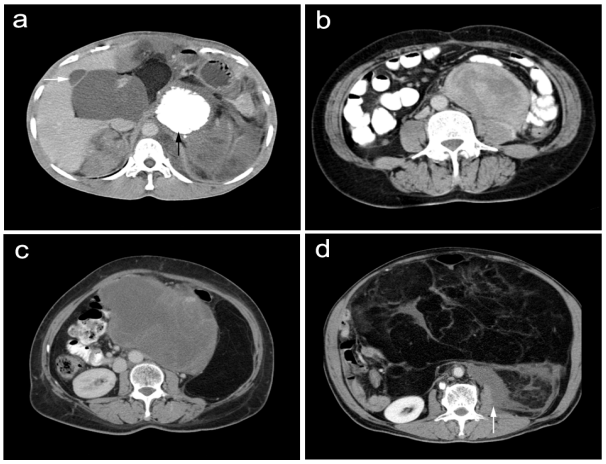

Figure 3 A) Myxoid/round Cell Liposarcoma. The Tumor Mainly Consists of Areas of Mixed Cystic and Solid Density with Large Areas of Calcification (black arrow) and an Irregular Envelope (white arrow). **B)** Mixed-type liposarcoma: Areas of both solid and fat density are evident, without any characteristic manifestations. **C)** Pleomorphic liposarcoma: The masses with muscular density indicate nodular fibrous ecphymas around the edge, with local necrosis and little fat composition. **D)** Enhanced scan of lipoma-like liposarcoma in the venous phase reveals that the boundary (white arrow) between solid tumor components and the left psoas muscle has become blurred. This suggests involvement of the psoas muscle

recurrences arose at gradually decreasing intervals after resections. Pathological results confirmed that cells in two of five recurrent ALT/WDL cases presented more differentiation during relapse.

Discussion

Soft tissue sarcoma (STS) is a rare disease that constitutes less than 1% of all human cancers (Clark et al., 2005). Dugandzija T reported that STS average age standardized incidence rate of 1.90/100, 000 fits into the range of STS values in the world and the investigated period showed a slight increase in the incidence rate (Dugandzija et al., 2014). Of all adult STS histologic subtypes, LPS is the most common, accounting for approximately 15% (Dei Tos et al., 2000); RPLS is the most frequent histologic subtype of sarcoma in this anatomic locus (40%) (Linehan et al., 2000). Considering the evident effect of early operation, it is critical to accurately diagnose relying on histological findings from biopsy (Storm et al., 1991). However, the large retroperitoneal space, patients with retroperitoneal liposarcoma have no obvious symptoms in the early stages until the mass develops enough to press or invade the circumferent architecture. Accordingly, imaging methods, especially CT and MRI examination, play an important role in early detection, localization and preliminary typing. The objective of our current study was to evaluate this diagnostic approach and to validate the accuracy of CT scanning in differentiating RPLS subtypes. We also sought to propose an algorithm for the diagnosis and treatment of RPLS.

In the five histologic subtypes, ALT/WDL, a locally aggressive tumor is regarded as the most common type of liposarcoma. According to its cellular components, liposarcoma is divided into four subtypes: lipoma-like, sclerosing, spindle-cell and inflammatory type, but in this study we observed only the two former subtypes. Re-evaluating of potential CT scan markers for ALT/WDL, we deem the following feature suggest well differentiation of RPLS: a predominant fatty or large -area soft tissue density mass with uniform density and integrity margin. Meanwhile, using hypovascularity or slight enhacement as an additional criterion is possible to increase the specificity (Kransdorf et al., 2002). Notably, ALT/WDL as an intermediate tumor has a high recurrence rate. The other four subtypes of liposarcoma had biologic behaviours of malignant tumors. Among of them, DDL appears the high incidence of disease. The combination of focal nodular density and hypervascularity as markers of DDL show quite reliable sensitivity but relatively low PPV because of the appearance in certain ALT/WDL cases with main nonfatty components (Hong et al., 2010). ML/RCL or PL is infrequent but high malignant. Cysts suggestive necrosis is more sensitive for ML/RCL and mucus liposarcomas show amorphous linear or mottling enhancement (Coli et al., 2000; Barlie et al., 2002). PL show commonly severe infiltration and the CT and MRI image appearance resembled those of nonfatty soft tissue masses with foci of necrosis (Xiao et al., 2005). Mixed-type liposarcoma is relatively rare and is composed of various liposarcoma cells. CT findings show different appearances but no unique characteristic. The latter three subtypes need further study due to inadequate cases without statistical signification.

Our retrospective analysis confirms CT scanning as a meaningful adjuvant diagnosis of lipsarcoma has an overwhelming advantage on initial impression of prognosis, preoperative localization of gigantic tumor and so on. Puncture site of biopsy in RPLS should depend on evaluation of suspicious areas performed by CT scan when diagnosis is uncertain. In our study, margin irregularity, infiltration into adjacent organs, calcification, necrosis and hypervascularity all are radiologic imaging markers of malignant behaviour (Murphey et al., 2005). To be specific, integrity or irregular tumor boundary might be valuable in determining the absence or presence of extracapsular invasion and identifying whether or not excision might be possible. For example, CT revealed that one case of ALT/WDL developed a blurred boundary between the tumor and surrounding tissue, and surgery confirmed infiltration of the left musculus psoas major (Figure 3d). What's more, Enhanced CT scans are thus useful in displaying differentiation stage. The arterial phase is suitable for revealing tumor blood vessels and heterogeneous enhancement as a malignant feature. Remarkably, the ratio between solid and fat components has not been associated with the typing and malignant grade of liposarcoma.

CT manifestations and intraoperative findings confirmed six giant tumors almost throughout the whole abdomen were confirmed by surgery that they were retroperitoneal liposarcomas with cross-peritoneal growth. The results suggest that retroperitoneal masses be seen to compress organs in the retroperitoneum, such as the pancreas, kidney, adrenal gland, colon and stomach.

Retroperitoneal macrovessels and their branches could move forward or laterally, and may be partly encapsuled (Pohnán et al., 2008; Selmani et al., 2011; Fernandez-Pello et al., 2012). In contrast, abdominal and pelvic liposarcomas mainly exhibit a tiny amount of blurred fat in the interspace or even the absence of fat between the tumor and the adjacent abdominal or pelvic wall. Sometimes, considering the inherent cross-sectional scanning pattern, a narrow fat space is not conducive to accurately locating large tumors, in particular with the atrophy of adjacent organs (Jeanmonod et al., 2011; Leao et al., 2012). In such cases multi-slice spiral CT scanning with multiplanar reconstruction can reveal the retroperitoneal structure and tumor location more clearly. In addition, MRI scanning could be available for initial diagnosis considering the different signal intensity between fatty and parenchymal tissue on T1- and T2-weighted images (Song et al., 2007).

Surgery for RPLS is the mainstay of therapy and primarily consists of resection of the tumour along with a cuff of surrounding healthy tissues that necessarily implies resection of adjacent viscera (ESMO, 2012). Some retrospective analysis shows nearly all patients are treated with surgery, and more studies use adjuvant radiotherapy than chemotherapy (Ngan et al., 2013; Yetisyigit et al., 2013). In an effort to complement surgery, with inherent limitations of resection and high recurrence and the canceration rate of LPS, the administration of other treatment modalities, such as radiation therapy and chemotherapy, has been tried (Cui et al., 2012; Gronchi et al., 2014). Radiotherapy proved to benefit local control and CT showed a potential impact on the outcome of high-risk extremity LPS. The combination of CT to RT was attempted with the aim to improve the sensitivity of these tumours to RT and provide a systemic coverage as well (Tierney et al., 1997; Pervaiz et al., 2008; Woll et al., 2012; El-Bared et al., 2014). To compare the safety and efficacy of chemotherapy in patients with STS, Cao et al. demonstrates that epirubicin-based chemotherapy is effective and well tolerated and Kaya et al. suggests that the combination of gemcitabine plus docetaxel is an active and tolerable regimen as a second line therapy (Kaya et al., 2012; Cao et al., 2013). Endostar combined with chemotherapy resulted in a higher disease control rate and longer progression-free survival (Zhang et al., 2013). In the study of Asia-Pacific region, specialists suggest RPLS be multi-disciplinarily managed with a team involving pathologists, radiologists, surgeons, radiation therapists and medical oncologists because of the different histotypes, sites, and disease stages assessed (Duman et al., 2012).

In conclusion, liposarcoma is often misdiagnosed due to its insidious onset and slow growth with no typical symptoms. Consequently, a tumor might be extremely large when diagnosed. Surgical excision is the first choice for liposarcoma as this can prevent tumor recurrence and metastasis. Before surgery, imaging examination is the standard method of diagnosis. Detailed analysis of plain and enhanced CT images has the advantage of allowing a qualitative diagnosis as well as a preliminary prognostic evaluation. It could help surgeons to determine the optimal extent of excision. In addition, it could guide comprehensive therapeutic scheme such as preoperative intensity modulated radiation therapy (IMRT) for highly malignant types of lipsarcoma. Further research should be undertaken for the sensitivity and specificity of CT manifestations of RPLS histologic subtypes.

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