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Clinical and Molecular Approaches to Well-differentiated and Dedifferentiated Liposarcoma

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Abstract

Purpose of Review—Liposarcoma, a rare disease, is classified into five histologic subtypes. These include well-differentiated liposarcoma (WDLS) and dedifferentiated liposarcoma (DDLs), both characterized by chromosome 12q13-15 amplification. This review will focus on the clinical management of WDLS and DDLs and examine recent molecular studies that have the potential to affect clinical management.

Recent findings—Outcome of patients with WDLS and DDLs depends on completeness of surgical resection as well as tumor location and histologic subtype. Risk of recurrence is high for patients with dedifferentiated histology or retroperitoneal location. We now understand that surgical outcomes are poor for patients with rapidly growing or incompletely resectable tumors, so these patients should be managed non-operatively. Radiation and chemotherapy have low response rates in WDLS and DDLs, but novel agents targeted at chromosome 12 gene products MDM2 and CDK4 have shown promise in pre-clinical studies and are being tested in clinical trials. Cell line, tissue microarray, and genomic analyses have identified additional targets including ZIC1, TOP2A, AURKA, and IGF-1R, which could form the basis of future therapies.

Summary—Although complete surgical resection is currently the most effective treatment for WDLS and DDLs, the majority of patients with retroperitoneal liposarcoma will eventually have recurrence and die of disease. It is hoped that a multi-modality approach, which incorporates targeted therapies and complete surgical resection, will significantly improve patient outcomes.

Keywords

liposarcoma; well-differentiated/dedifferentiated; MDM2; CDK4

Introduction

Soft tissue sarcoma is a heterogeneous disease with over 50 histological types, which have diverse biological behavior and many of which have unique genetics. The most common subtype is liposarcoma, which represents 24% of extremity and 45% of retroperitoneal soft tissue sarcoma. Even within liposarcoma, there is histologic heterogeneity. The disease is, therefore, subdivided into five histologic subtypes forming three biologic groups: (1) well-differentiated liposarcoma (WDLS) and dedifferentiated liposarcoma (DDLs), (2) myxoid/round cell liposarcoma and (3) pleomorphic liposarcoma. Histologic subtype (as well as tumor location) predicts patient outcome. Dedifferentiated, round cell and pleomorphic liposarcoma are high-grade, aggressive tumors with metastatic potential while well-differentiated and myxoid liposarcoma are low-grade tumors that follow a more indolent

clinical course [1,2]. The term atypical lipomatous tumor (ALT) is used by some pathologists as a histologically pure form of WDLS, which do not metastasize and when amenable to wide excision, particularly for extremity and truncal locations, are readily cured. Our own preference, as evidence in this review, is to use the term WDLS. In so doing, we highlight the malignant nature of a tumor which, as noted below, can progress to aggressive DDLS phenotypes, and, in the retroperitoneum and mediastinum, cause death by their local effects.

This review will focus on WDLS and DDLS, which represent the most common biologic group of liposarcoma. Ninety percent of WDLS and DDLS have amplification of chromosome 12q13-15, which contains the oncogenes *MDM2*, *HMG2*, and *CDK4*; additional genes located on this amplicon may also play a role in liposarcomagenesis [3,4]. WDLS is a locally aggressive, nonmetastasizing cancer composed of mature adipocytes. When WDLS occurs in the retroperitoneum or mediastinum, it often recurs repeatedly and may eventually result in the patient's death from uncontrolled local effects, or it may dedifferentiate and metastasize. Histologically, DDLS is represented by the abrupt transition from WDLS to a region of nonlipogenic sarcoma. Dedifferentiation occurs in ~20% of first-time retroperitoneal local recurrences and 44% of second-time local recurrences, implying the acquisition of additional aberrations within WDLS as it recurs [1]. Pure WDLS can cause local symptoms due to large tumor size. Progression of disease to DDLS, however, is associated with more aggressive local disease, the acquisition of metastatic potential, and poor patient prognosis [2].

Diagnosis

Work-up of a patient with an extremity or abdominal/retroperitoneal mass begins with cross-sectional imaging. Unlike most histologic subtypes of soft tissue sarcoma, WDLS and DDLS can often be diagnosed by pathognomonic findings on CT and MRI. We generally recommend an MRI with and without contrast for extremity lesions and a chest/abdomen/pelvic CT for patients with an abdominal/retroperitoneal mass. The WD component resembles fat in its signal intensity, appears encapsulated, and has thick, internal septations. On imaging, DDLS will be recognized as a heterogeneous non-lipogenic mass within a region of abnormal-appearing fat [5]. Patients presenting with a primary extremity DDLS should undergo CT of the chest to rule out metastatic disease.

The majority of primary retroperitoneal WDLS and DDLS are best treated surgically without the need for core biopsy, since neoadjuvant radiation or chemotherapy has never been shown to improve outcome for these patients. Core biopsy of fat-containing retroperitoneal tumors should be reserved for those tumors that are unlikely to be completely resectable due to central vascular involvement or that have the appearance of a renal angiomyolipoma. Angiomyolipoma on CT appear as a heterogeneous mass with varying proportions of macroscopic fat, intralesional aneurysms, and hypervascular soft tissue often containing a tumor vessel extending into or through the renal parenchyma or a renal parenchymal defect.

In the extremity, sarcoma histology is more varied and tumors may require neoadjuvant chemotherapy; therefore, biopsy is frequently performed prior to surgery. On biopsy, WDLS is characterized by atypical stromal cells and lipoblasts in the context of mature fat, often with a prominent sclerotic component [6,7]. DDLS is a heterogeneous, high-grade tumor that can appear similar in morphology to malignant fibrous histiocytoma, fibrosarcoma, myxofibrosarcoma, or small blue cell neoplasms, but it is usually adjacent to a WDLS component [8,9]. In rare cases where the transition from WDLS to DDLS cannot be observed by histology, the chromosome 12q amplification, which is characteristic of WDLS/

DDLs, can be exploited to confirm diagnosis. This defect causes MDM2 and CDK4 to accumulate in DDLs cells, so immunohistochemical staining for these proteins allows definitive diagnosis of a soft tissue sarcoma as DDLs [10].

Treatment of extremity WDLs and DDLs

Extremity disease is almost always treated with a limb-sparing procedure [11]. The tumor should be resected with a 1 cm margin of adjacent normal fat or muscle tissue when possible. If this margin is not achievable because the tumor is immediately adjacent to a neurovascular bundle or bone, then the surgeon should carefully dissect and remove with the tumor an intact fascial plane or sheath from around the vessels/nerves or the adjacent periosteum. In the case of WDLs that surrounds a major neurovascular bundle, the tumor should be bivalved and carefully dissected free, taking the perineurium of the nerve or sheath surrounding the vessel. If, however, DDLs encases components of the neurovascular bundle, it may be necessary to sacrifice these structures, or, in extremely rare cases, to amputate.

Adjuvant radiation therapy is selectively utilized in patients with extremity DDLs and is not recommended in patients with WDLs. WDLs are not radiosensitive and have a less than 1% risk of distant metastasis, so any clinical benefit of radiation for this low-grade, indolent tumor is far outweighed by the long-term consequences of damage to limb function and increased risk of secondary malignancy. Adjuvant radiation should, however, be considered following a limb-sparing procedure for patients with a >5 cm DDLs that is excised with close or microscopically positive margins, particularly if a subsequent local recurrence would be likely to result in limb loss.

Adjuvant/neoadjuvant chemotherapy has little role in WDLs and DDLs. These tumors are often resistant to standard cytotoxic chemotherapies, and no data have shown a survival benefit derived from adjuvant chemotherapy. It should be noted, however, that randomized trials addressing this question have failed to accrue and data addressing the role of adjuvant chemotherapy is limited to that acquired in retrospective studies. For patients presenting with advanced, unresectable, or metastatic disease, adriamycin, docetaxel, or gemcitabine-based therapies may be utilized to palliate symptoms, but response rates are low and such treatments rarely prolong survival. For patients with a limited number of metastases (one to five), surgical resection of distal disease can be considered as a treatment option.

Retroperitoneal WDLs and DDLs

Retroperitoneal liposarcomas are difficult to treat. Patients with retroperitoneal WDLs and DDLs have higher rates of local recurrence and disease-specific death compared to their counterparts with extremity tumors, and have higher rates of local recurrence than patients with retroperitoneal leiomyosarcoma and malignant peripheral nerve sheath tumors. Again, complete surgical resection is the mainstay of therapy. Rarely, in a patient with multiple comorbidities or advanced age, an incidentally identified lesion, and no symptoms, a tumor without solid components can be observed with reimaging as an undefined subset of WDLs may not progress.

Because the boundary between WDLs and normal fat is often difficult to discern, tumors should be resected with a margin of normal retroperitoneal fat when possible, so as to minimize the chance of leaving residual disease. The utility of resecting adjacent viscera is debated amongst experienced sarcoma surgeons. In a study of 177 patients with retroperitoneal liposarcoma, the resection of contiguous organs (other than kidney) was associated with increased rates of local and distant recurrence [1], suggesting that liposarcomas that require resection of adjacent organs are more biologically aggressive.

Because of this result and because WDLS and DDLS invade adjacent organs infrequently, our practice has been to remove adjacent organs only if direct tumor extension is observed or a plane of dissection cannot be safely developed between the tumor and adjacent organ. In these cases (most commonly representing recurrent disease), colon, spleen, and distal pancreas are resected en bloc. Encasement of the kidney by tumor can be managed by resecting the renal capsule with the tumor and preserving the parenchyma in cases where the hilum is not involved. In recurrent disease, patients will potentially require nephrotoxic agents (e.g., ifosfamide) and trial enrollment often requires normal kidney function; anticipation of such eventualities provides additional incentive to perform nephron-sparing.

Recently, surgeons from the Istituto Nazionale Tumori and the Institut Gustave Roussy presented retrospective data on 249 consecutive patients with retroperitoneal sarcoma (all types) treated by a frontline aggressive approach that entails routine resection of adjacent viscera in an attempt to provide a margin of normal tissue around the tumor [12]. The rate of local recurrence at 5 years (22%) was lower than in historical controls (41%) [13]; however, surgical morbidity was increased. While these data are intriguing, we note that local recurrence can often be salvaged by additional surgery and that an aggressive frontline approach does not improve margins at the site of essential structures such as the porta hepatitis or the visceral vessels. Recurrence in these regions is often the reason that salvage surgery cannot be performed.

The treatment of locally recurrent retroperitoneal WDLS and DDLS remains a challenge. Patients with asymptomatic local recurrence of WDLS may often be followed off therapy with serial scans, monitoring carefully for disease progression and development of other sites of retroperitoneal disease. Surgery is often best delayed as additional disease sites may arise, and a period of observations will mean that all developing sites of disease can be completely resected during a single operation. Among patients whose recurrent WDLS is symptomatic or progressive, those with disease that cannot be completely resected due to involvement of central vascular structures may be treated with novel targeted agents. Occasionally patients with symptomatic local recurrence of WDLS may benefit from surgical debulking procedures but these patients should be carefully selected since most studies have shown no improvement in survival following incomplete resections of WDLS and DDLS. Following an R2 resection of locally recurrent WDLS and DDLS, three-year disease-specific survival is similar to survival of patients who do not undergo surgical exploration.

The average growth rate of a locally recurrent liposarcoma, defined as the maximal linear tumor size of the local recurrence divided by the time interval to local recurrence, may help select patients likely to benefit from repeat surgical resection. In a retrospective study of 105 patients with local recurrence following complete gross resection of a retroperitoneal liposarcoma, 19 had tumors that grew at a rate greater than 0.9 cm per month. Disease-specific survival in these patients was significantly lower than that for patients with more indolent disease, even in the context of complete gross resection of the recurrence (median 21 versus 100 months). In fact, disease-specific survival in patients with these high-growth-rate tumors was not significantly different from that of matched patients who did not undergo resection [14]. Therefore, we now employ a treatment algorithm in which patients who present with locally recurrent WDLS and DDLS growing at a rate greater than 1 cm per month are routinely referred for chemotherapy or treatment on clinical trials with targeted agents. We do not recommend initial surgical management in patients with this type of aggressive disease and usually perform surgery only on those patients whose tumors respond well to systemic therapy and can subsequently be completely resected.

Recommendations regarding adjuvant and neoadjuvant therapy differ greatly even among major sarcoma centers. As noted above, adjuvant chemotherapy has never been shown to provide a clinical benefit and is not routinely employed [15]. With adjuvant radiation, however, several small retrospective studies have suggested improved rates of local control, and the modality is recommended by many clinicians [16]. Nevertheless, no improvement in overall survival has been observed, and randomized trials addressing the benefit of neoadjuvant radiation in retroperitoneal sarcoma have failed to accrue. In this context, and given the significant risk of radiation enteritis, we employ radiation sparingly in our own practice, reserving it for the neoadjuvant setting in the rare patients with disease that appears marginally resectable on preoperative imaging.

Molecular approaches to WDLS and DDLS

Because WDLS and DDLS respond poorly to systemic chemotherapy, it is essential that novel molecular targets be identified to provide new possibilities for therapies. WDLS and DDLS have been known for some time to be characterized by amplification of genes on chromosome 12q. Neochromosomes carry supernumerary copies of the recognized oncogenes *HDM2*, *HMGA2*, and *CDK4*, all of which have been implicated in liposarcomagenesis. shRNAs directed against MDM2 and CDK4 inhibit proliferation of liposarcoma cell lines *in vitro* [17], and targeting of MDM2 and CDK4 is an active area of clinical research [18].

MDM2 is essential for ubiquitination and degradation of the tumor suppressor p53. *MDM2* amplification is, therefore, thought to result in reduced levels of p53 and thus to induce transformation of the progenitor cell [19,20]. To modulate p53, MDM2 requires the function of a RING domain, which binds to p53 [21]. Competitive inhibitors (e.g., nutlin) of the MDM2-p53 interaction have been developed [22]. In DDLS cell lines, nutlin treatment increases both p53 levels and apoptotic rates [23]. Given these data, MDM2 inhibitors are now in clinical trials for WDLS and DDLS; results are eagerly awaited.

Drugs that inhibit CDK4 are also being developed. This protein kinase modulates the G1/M cell cycle transition. *In vitro*, inhibition of CDK4 protein leads to proliferation arrest [17]. In clinical trials, CDK4 inhibitors have good safety profiles; however, efficacy has not yet been reported. CDK4 overexpression appears to correlate with a chromosome 12q amplicon distinct from that associated with gain of MDM2 and HMGA2, and a small set of WDLS with good prognosis do not have increased levels of CDK4 protein [24]. Thus, CDK4 may be essential for progression, but not initiation, of liposarcoma, and inhibiting CDK4 may not be sufficient to induce tumor cell death. Instead, CDK4 inhibitors may slow tumor growth, be effective in only a subset of patients, or prove to be ineffective as single agents.

To continue the search for molecular targets in WDLS and DDLS, several groups are seeking to identify aberrantly regulated genes that are essential to liposarcomagenesis and whose protein products are potentially targetable by small-molecule inhibitors. To facilitate these studies, primary cell lines and tumor xenografts have been developed from WDLS and DDLS tumors. The receptor tyrosine kinases MET, AXL, KIT, and IGF-1R are upregulated in these cell lines as compared to adipocytes, and could be studied as potential drug targets [25].

Gene expression profiling has been performed on primary tumor tissue to address the mechanisms of liposarcomagenesis [23]. Sixty-nine liposarcomas and nine normal fat samples were profiled using Affymetrix U133A microarrays. This analysis identified 998 genes that had ≥ 2 -fold difference in expression between WDLS and DDLS and normal fat. Through Ingenuity pathway analysis, these genes were found to affect numerous cellular pathways. One of the most significant of these was, not surprisingly, the cell cycle/

checkpoint pathway including CDK4, MDM2, CDC2, CDC7, and cyclins B1, B2, and E2. It is possible that, in addition to CDK4 and MDM2, other components of this pathway could be targeted for liposarcoma therapies. Three of the most strongly overexpressed genes in DDLS and WDLS were *TOP2A*, *RRM2*, and *ZIC1*. *TOP2A* (topoisomerase 2) and *RRM2* (ribonucleotide reductase M2 polypeptide) can be targeted by currently available drug combinations. *ZIC1*, which encodes a transcription factor normally expressed only in the adult cerebellum, was shown in subsequent experiments to be essential for liposarcomagenesis, suggesting that drugs directed against *ZIC1* may likewise have therapeutic benefit.

A more extensive analysis of DDLS was recently performed as part of the Sarcoma Genome Project in collaboration between Memorial Sloan-Kettering Cancer Center and the Broad Institute at MIT [17]. Fifty DDLS samples were examined to identify not only aberrantly expressed genes, but also copy number alterations and somatic mutations that could contribute to liposarcoma initiation and progression. Point mutations were identified in *CTNNB1* (beta-catenin), *CDH1* (E-cadherin), *EPHA1* (ephrin A1), and *FBXW7* (a component of the ubiquitin protein ligase complex), each of which has potential oncogenic effects on the liposarcoma cell. Amplification on chromosome 12q was confirmed as a common feature in DDLS, but amplification was also observed to affect chromosomes 1q, 5p, and 20q. To identify previously unrecognized oncogenes essential for liposarcomagenesis, 385 genes from amplified regions were subjected to an shRNA screen in three DDLS cell lines. For 27 genes, including *CDK4*, shRNA knockdown inhibited proliferation of cell lines, identifying these genes as potential oncogenes (Table 1). A function for MDM2 was not observed in the screen even though it is known to be essential for liposarcoma cell growth, demonstrating that even an extensive screen of this nature may underestimate the complexity of the genomic alterations that induce tumor formation.

Conclusion

While surgical cure of WDLS and DDLS is possible, outcomes in patients with recurrent, unresectable, and metastatic disease remain poor. Over 50% of patients with WDLS or DDLS will eventually die of disease. Therefore, it is essential that we continue to examine the molecular mechanisms underlying liposarcomagenesis and work toward the development of novel therapeutic strategies for liposarcoma patients. Recent large-scale genomic analyses have confirmed that liposarcomagenesis is a complex process, but have also provided us with significant insight into the molecular mechanisms involved. Targeted therapies based on these findings are already in clinical trials. It is likely that, as these studies mature, we will observe improved clinical outcomes for our patients with WDLS and DDLS.

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Key points

- WDLS and DDLS of the extremity should be treated with surgical resection; adjuvant therapy in the form of radiation is used only for patients with >5 cm DDLS that was resected with close or microscopically positive margins, and chemotherapy is reserved for patients with unresectable systemic disease.
- Most WDLS and DDLS in the retroperitoneum should also be treated with surgical resection, but systemic therapy with chemotherapy or targeted agents should be considered if surgery would likely to leave gross disease behind or if the average tumor growth rate of the local recurrence is greater than one centimeter per month.
- Targeted therapies aimed at protein products encoded by the 12q amplicon, including MDM2 and CDK4, are currently in clinical trials.
- A rapidly expanding knowledge base in the field of liposarcoma biology has the potential to improve outcomes in WDLS and DDLS patients.

Table 1

Selected genes amplified in WDLS and DDLS and necessary for cell proliferation

Symbol	Gene Name	Function
CDK4	Cyclin-dependent kinase 4	Modulation of the G1/M cell cycle transition
YEATS4	Yeats domain containing 4 (Gas41)	Repression of p53 tumor suppressor pathway
CTDSP2	CTD small phosphatase 2	Inhibition of bone morphogenic protein signaling
GLI1	GLI family zinc finger 1	Mediation of hedgehog signaling
AURKA	Aurora kinase A	Regulation of chromosome segregation