Liddy Shriver Sarcoma Initiative

Well-differentiated and de-differentiated retroperitoneal liposarcoma: a paradigm for histology specific multimodality therapy

An ESUN Article

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Introduction

Soft tissue sarcoma represent less than 1% of all human neoplasms with approximately 7,000 new cases diagnosed in the USA per year (Ref. 1). Despite sharing a common embryologic origin from mesodermal tissue, these tumors encompass a histologically and anatomically diverse group of neoplasms. Liposarcomas are the most common histologic subtype of soft tissue sarcoma and are subdivided into five well recognized subgroups based on morphology and cytogenetic abnormalities (Ref. 2):

- Well differentiated (WD)
- Myxoid
- Round cell
- Pleomorphic
- Dedifferentiated liposarcoma (DD)

Initiated in 1962, the modern liposarcoma histological classification schema has included the category of well differentiated liposarcoma. Well differentiated and dedifferentiated liposarcoma comprise the vast majority (approximately 90%) of liposarcoma subtypes while myxoid, round cell and pleomorphic account for less than 10% of liposarcomas (Ref. 7).


Mesoderm Mesoderm comprises the middle germ cell layer and gives rise to cells that comprise cardiac and skeletal muscle, hematopoitic cells and cells producing bone, cartilage and connective tissue throughout the body. In addition this germ cell layer ultimately gives rise to the cells that make up the genitourinary system.

The term ALT for atypical lipomatous tumor was introduced in 1974 (Ref. 3). The recent World Health Organization classification of soft tissue and bone tumors grouped these lesions into one category, “atypical lipomatous tumor/well differentiated liposarcoma”. Well-differentiated liposarcomas are composed of mature adipocytes with significant variation in cell size and focal...
nuclear atypia. They typically show scattered atypical stromal cells with hyperchromatic nuclei embedded within mature adipose tissue. Fibrous septae are often present. These divide the tumor into irregular lobules infiltrated by atypical stromal cells, and are a feature especially characteristic of the Sclerosing variant of well differentiated liposarcoma (Ref. 4); see Figure 1.

![Figure 1: A.) Conventional retroperitoneal liposarcoma WD histology with mature fat and occasional enlarged atypical nuclei. B). Highly cellular nonlipogenic DD with adjacent WD. C.) Characteristic appearance of DD with markedly different size and shaped nuclei and increased spindle cell morphology](http://sarcomahelp.info/learning_center/articles/liposarcoma_retroperitoneal...)

The term **dedifferentiated liposarcoma** was advanced by Evans in 1979 to describe liposarcoma that consists of a combination of atypical lipomatous tumor (ALT) components and also cellular, non-lipogenic sarcomatous areas that have significant mitotic activity (Ref. 5). Grossly, dedifferentiated liposarcoma has the appearance of multinodular yellow masses representing ALT or WD within which discrete solid areas of dedifferentiated liposarcoma can be appreciated by their distinctive fleshy, tan-gray non-lipomatous appearance. It is unclear whether WD and DD originate from two different cellular clones or if there is a process of progressive evolution from WD to DD. However, it is unequivocally established that DD constitutes a high grade lesion with increased cellularity that is prone to disseminate and is associated with a much worse prognosis than WD which has minimal metastatic potential (Ref. 6). Many sarcoma centers do not report grade when describing liposarcoma in that WD tumors are generally considered to be low grade whereas DD tumors are typically high grade. Moreover, grade is frequently not included in multivariate liposarcoma models that include histologic subtype (Ref. 7).

Liposarcomas of the extremity and trunk enjoy significantly lower rates of local recurrence (10-16%) compared to the rate of local recurrence (43%) from liposarcomas arising within the retroperitoneum.8-10 Liposarcomas arising from within the retroperitoneum typically grow to be quite large before associated symptoms are manifest.

**Retroperitoneum:** The retroperitoneum is the anatomical space behind (retro) the abdominal cavity. It has no specific delineating anatomical structures. Organs are retroperitoneal if they only have peritoneum on their anterior side. Retroperitoneal organs: ureter, bladder kidneys, duodenum, colon, pancreas and adrenal glands.

Although different liposarcoma histologic subtypes can be observed in soft tissue sarcomas that arise in the retroperitoneum, histologic subtype per se is usually not incorporated into retroperitoneal disease management strategies. Complete surgical resection is a difficult challenge as these large tumors are often surrounded by a thin fibrous capsule which is frequently indistinguishable from surrounding retroperitoneal adipose tissue. Critical structures in the retroperitoneum can also pose a challenge to resectability. Accordingly, it is often difficult to obtain a margin of normal tissue around the tumor. The importance of complete macroscopic resection is well established and resection of contiguous organs in the hope of decreasing the rate...
of local failure is a common practice. However, evidence that a more extensive resection impacts survival is very limited. Among the factors that significantly influence clinical outcome, histologic subtype is recognized as an independent predictor of local recurrence (LR), distant metastasis (DM) and disease specific survival (DSS); see Ref. 7.

A Treatment Strategy According to DD and WD Histology

At the University of Texas MD Anderson Cancer Center (MDACC) we have adopted a strategy of performing less-aggressive surgery for patients based upon the specific liposarcoma histologic subtype. Tumors without a component of de-differentiation, referred to as either atypical lipomatous tumors or well-differentiated liposarcoma (WD), are associated with a less aggressive clinical course. WD tumors are characterized by repetitive local recurrence without the potential for metastasis. In contrast, de-differentiated tumors (DD) also recur at a high rate, but have the potential to metastasize and represent an aggressive clinical phenotype. Accordingly, at MDACC we recognize these tumors as distinct with differing tumor biology and clinical outcome. Utilizing this general strategy for patients with WD tumors has resulted in less aggressive surgery without the addition of chemotherapy or radiotherapy. For patients with retroperitoneal liposarcomas with evidence of de-differentiation, we adopt a more involved treatment approach that begins with neoadjuvant chemo-radiotherapy followed by aggressive surgical resection. In this review we present the rationale for this approach and discuss our clinical results vis-à-vis those centers that do not alter treatment approaches to retroperitoneal liposarcoma based on histologic subtype.

To date, the largest reported series of retroperitoneal liposarcoma resections is from Memorial Sloan-Kettering Cancer Center (MSKCC). In this experience, completeness of resection significantly impacted clinical outcome: the three year disease specific survival for patients with a margin negative resection was 87% compared with 43% for patients resected with grossly positive margins. In this series and others from the MSKCC group an aggressive surgical approach was applied based on the demonstrated prognostic significance of a complete macroscopic resection (Refs 7, 10, and 11). Moreover, retroperitoneal liposarcoma histologic subtype did not influence decisions about neoadjuvant or adjuvant chemotherapy in that none of the patients in this series received such systemic treatment. Unlike extremity liposarcoma where tumor size is known to significantly affect outcome the size of retroperitoneal liposarcomas is typically much larger; in this series the mean tumor maximum dimension was 26 cm. As an indication of aggressive surgical resection, over two-thirds of patients in this series underwent resection of contiguous organs, including nephrectomy. Interestingly, contiguous organ resection was associated with a two fold increased risk of death compared to patients not undergoing contiguous organ resection after adjusting for other prognostic factors (p=0.05); see Ref. 7. In the MSKCC series, the local recurrence rate and rate of distant metastasis was 50% and 11% respectively. On multivariate analysis of prognostic factors associated with local recurrence, distant metastasis, and disease-specific survival, only the presence of contiguous organ resection and the DD histologic subtype were significant adverse factors. It is possible that the patients receiving contiguous organ resection simply had more extensive tumor burden rather than worse biology per se. Underlying tumor biology, rather than extensive surgical resection appears to be more important determinant of clinical outcome. We hypothesize that the histologic subtype of retroperitoneal sarcomas may serve as a surrogate for tumor biology and will affect clinical outcome more than extent of initial resection if a gross total excision is performed.

The MDACC Experience

Taking into account the markedly different biologic behaviors of WD compared to DD, our therapeutic approach at MDACC is tailored to reflect these differences. The treatment strategy for
a retroperitoneal liposarcoma patient presenting to the MDACC Sarcoma Center is formulated upon multidisciplinary consensus review prior to initiation of therapy. This approach is in contrast to traditional tumor board review of patients who typically undergo resection and are then considered by the multidisciplinary review panel to determine the utility of adjuvant therapy based on final review of the resected specimen pathology. Our practice is to utilize validated diagnostic imaging criteria and selective image guided biopsy of suspected foci of DD to make a preoperative diagnosis of WD versus DD in patients presenting with retroperitoneal liposarcoma. WD patients generally undergo less aggressive surgery avoiding resection of contiguous organs if possible, while patients with DD are treated with neoadjuvant chemotherapy and radiation therapy followed by aggressive surgical resection.

Using this approach, patients may realize benefits from neoadjuvant therapies that would otherwise not be demonstrable were resection performed as the initial treatment strategy. The major theoretical benefits to neoadjuvant chemotherapy are to identify patients who respond to the systemic therapy as measured by the pathologic response, and to initiate treatment of possible occult metastatic disease at the earliest possible time after diagnosis. These potential advantages are offset by several disadvantages of neoadjuvant therapy, namely that definitive resection is delayed and wound healing may be compromised. However, there is evidence to suggest that response to front line sarcoma chemotherapeutic agents may be dependent on histologic liposarcoma subtype, with DD having greater response rates than WD (Ref. 12).

We have recently reviewed our experience utilizing this approach to patients with retroperitoneal sarcoma, demonstrating that WD patients usually benefit from a less aggressive surgical approach that avoids unnecessarily extensive resection. This strategy was developed based on initial anecdotal observations of the generally indolent clinical behavior of WD tumors in contrast to the metastasis prone phenotype of DD tumors. This approach to WD tumors stands in contrast to our traditional aggressive surgical management of other retroperitoneal histologies. The treatment variables and patient outcomes of the 127 patients presenting with primary or locally recurrent resectable retroperitoneal liposarcomas are depicted in Table 1.
Table 1: Treatment characteristics and outcomes of patients presenting to MDACC with primary and recurrent retroperitoneal based on WD and DD histology

<table>
<thead>
<tr>
<th>Treatment Characteristics</th>
<th>Well-differentiated</th>
<th>De-differentiated</th>
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<tr>
<td>N=54</td>
<td>No.</td>
<td>%</td>
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<tr>
<td>Neoadjuvant chemotherapy</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Neoadjuvant radiation</td>
<td>9</td>
<td>15.5</td>
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<tr>
<td>Gross (RO) Resection</td>
<td>50</td>
<td>86.2</td>
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<tr>
<td>Positive microscopic margins</td>
<td>23</td>
<td>40.4</td>
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<tr>
<td>Multiple contiguous organ resection</td>
<td>27</td>
<td>50</td>
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<th>Patient Outcomes</th>
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<tr>
<td>Local Recurrence</td>
<td>25</td>
</tr>
<tr>
<td>Distant Metastases</td>
<td>2</td>
</tr>
<tr>
<td>Median time to recurrence (months)</td>
<td>55.5</td>
</tr>
<tr>
<td>5-year recurrence free survival (RFS)</td>
<td>41.9</td>
</tr>
<tr>
<td>5-year overall survival (OS)</td>
<td>92.1</td>
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The incidence of local recurrence was 46% for WD patients and 71% for DD patients while the incidence of distant metastases was 3.7% for WD and 45.2% for DD patients. The median overall survival at 5 years was 92.1% for WD patients and 36.5% for DD patients. On multivariate analysis, presentation status (recurrent vs. primary), multifocal disease, and pelvic location were factors significantly associated with recurrence free survival (RFS). While it is difficult to compare outcomes between published single institutional series, our outcomes are comparable to those reported by the MSKCC group in which treatment decisions are apparently not as influenced by the presence of dedifferentiation. In the MSKCC series the incidence of local recurrence was 31% for WD patients and 83% for DD patients while the incidence of distant metastasis was 1% for WD patients and 30% for DD patients at three years of follow up. The 5-year disease specific survival for tumors with WD histology was 83% compared with 20% for tumors with dedifferentiated histology (Ref. 7).

In our series, the tumor burden as measured by tumor size was comparable between WD and DD tumors with the median size of the tumors measuring 20 cm and 17 cm respectively. Over 65% of the WD tumors measured >15 cm compared to 55% of the DD tumors which is similar to the median tumor burden reported in the MSKCC series. Despite the comparable sizes of the WD and DD tumors, our apparently less aggressive surgical approach to WD patients resulted in only 46.6% of the WD patients undergoing resection of contiguous organs whereas over 70% of DD patients in our series underwent contiguous organ resection. Interestingly, we achieved equivalent rates of complete tumor resection while using this organ sparing strategy (WD: 86.2%; DD: 85.7%); see Ref. 16. In the MSKCC series, the incidence of contiguous organ resection was not stratified by histologic subtype, rendering further inter-series comparisons problematic.

Preoperative Diagnosis of WD and DD Retroperitoneal Liposarcoma

The success of this less-aggressive treatment approach requires accurate preoperative...
determination of WD versus DD retroperitoneal liposarcoma histology. At MDACC we utilize radiographic correlates of dedifferentiation to enhance the likelihood of obtaining informative tissue for diagnosis at the time of the CT scan guided biopsy of suspected DD regions. Since retroperitoneal liposarcomas are frequently large and heterogeneous, a random biopsy specimen retrieved from a limited area within the tumor may be very inaccurate; therefore, other diagnostic tools are also needed as adjuncts to unequivocally establish the DD diagnosis. CT scanning has been particularly useful in helping to identify areas of WD and DD within a given retroperitoneal liposarcoma in that retroperitoneal liposarcomas characteristically have an overall fatty appearance with areas of “streakiness” due to the presence of cellular stromal elements within the tumor (Ref. 14). As a general paradigm, the more well-differentiated the tumor, the more its imaging appearance will resemble that of adipose tissue, whereas foci of DD have a CT appearance more consistent with that of high grade tumor.

**Computed tomography** (CT) is a medical imaging method employing tomography. Digital geometry processing is used to generate a three-dimensional image of the inside of an object from a large series of two-dimensional X-ray images taken around a single axis of rotation. The word "tomography" is derived from the Greek tomos (slice) and graphein (to write).

To establish radiographic markers of DD we examined a series of 78 patients (45 with DD and 33 with WD). Features previously reported as possible discriminators between low and high grade tumors were evaluated. One feature, the presence of focal nodular/water density, was identified as a radiographic surrogate marker for discriminating between the two differing histologies. Focal nodular/water density describes an area of nodularity within the tumor that has a density similar to muscle is depicted in Figure 2.

![Figure 2: A CT-scan with representative focal nodular/water density representing DD liposarcoma with adjacent WD tumor.](Image)

Forty-four out of 45 patients (97.8%) with postoperative pathologic diagnosis of DD were radiologically identified as DD by the study radiologist based on the presence of focal nodular/water density; however 16 patients with WD were diagnosed as DD based on this imaging criterion. In contrast, all 17 tumors that lacked areas of focal nodular/water density were confirmed to by WD on pathologic analysis of the resected specimen. The positive predictive value (PPV) of focal nodular/water density to predict DD histology therefore was 73.3% while the negative predictive value (NPV) was 100%. Taken together, these data suggest that preoperative CT imaging is very sensitive to detect DD histology based the presence of focal nodular/water density; however, its specificity is relative low. Moreover, as the negative predictive value (NPV)
of this marker was 100% it appears that the diagnosis of WD can be based on CT scanning alone.

**Predictive Values:** The positive predictive value (PPV), or precision rate, is the proportion of patients with positive test results who are correctly diagnosed. It is the most important measure of a diagnostic method as it reflects the probability that a positive test reflects the underlying condition being tested for. Its value does however depend on the prevalence of the disease, which may vary. The negative predictive value (NPV) is the proportion of patients with negative test results who are correctly diagnosed.

In this series 72% of patients had pre-referral CT-guided biopsies and in only 22 cases (28%) a CT guided biopsy was performed at MDACC. All the 17 tumors identified as WD based on preoperative CT imaging criteria and confirmed on postoperative pathologic assessment to be WD were also diagnosed as WD on preoperative biopsy. In such patients a preoperative biopsy may therefore not be needed as the diagnosis of WD can be made by CT imaging criteria alone. Out of the 60 tumors that were radiographically identified as DD based on the presence of focal nodular/water density, preoperative biopsy showed DD in 34 (56.7%) cases and WD in 26 (43.4%). In Thirteen patients out of the 26 cases (50%) diagnosed as WD based on preoperative biopsy were found to be DD on postoperative pathologic assessment. The majority of biopsies performed in this series were obtained prior to evaluation at MDACC. It is unlikely that such pre-referral biopsies were taken from areas within the tumor suspicious for DD. Accordingly, we analyzed the 22 CT guided biopsies performed at MDACC. Twelve were taken from suspicious areas from within the tumor identified by the presence of focal/nodular water density by preoperative CT imaging. Of these, all six biopsies confirmed on final pathology as DD were also identified as DD on preoperative CT-guided biopsy. Conversely, 9 CT-guided biopsies taken from non-suspicious areas (fatty or ground glass opacities) were interpreted as WD and 5, nearly 50%, were diagnosed as DD on final postoperative pathologic assessment.

Taken together, these data suggest that a preoperative CT scan-guided biopsy is highly sensitive and specific for DD when taken from suspicious areas of focal/nodular water density. Our approach to a patient who presents with a retroperitoneal liposarcoma is as follows: CT scan to identify and localize areas of a focal nodular/water density as ascertained by the radiologist; if no focal/nodular water density areas are found the tumor is considered to be WD and a biopsy is unnecessary. If areas of a focal nodular/water density are detected then a CT-guided biopsy of these suspicious areas is needed to differentiate between DD and WD. Patients diagnosed as DD by CT-guided biopsy may therefore be considered for neoadjuvant systemic chemotherapy while WD patients generally undergo less aggressive surgery up-front with an aim to avoid resection of contiguous organs if possible.

**Future Studies**

Recently, the ability of fluorodeoxyglucose (FDG) PET imaging to assess clinically relevant liposarcoma parameters was evaluated in 54 patients prior to therapy. Sarcomas with the most metabolically active areas may have more aggressive tumor biology. In this study significant differences were found for the maximum standardized uptake value (SUVmax) between histologic subtype; tumor SUVmax was found to be a significant correlate of disease-free survival and time to relapse. The mean tumor SUV max was 2.3 for WD, 4.8 for DD and 5.6 for the pleomorphic histologic subtype. Patients with SUVmax >3.6 had a significantly shorter disease-free survival of 21 months compared with 44 months in patients with a SUVmax <3.6.15 In the future, PET-CT may provide even more accurate assessment of retroperitoneal liposarcoma histological subtype, and this possibility merits prospective evaluation.
Positron emission tomography (PET) is a nuclear medicine imaging technique that produces a three-dimensional image of functional processes in the body. The system detects pairs of gamma-rays emitted indirectly by a positron-emitting radioisotope (tracer), which is introduced into the body on a biologically active molecule. If the biologically active molecule chosen for PET is FDG (a derivative of glucose), the concentrations of tracer imaged then give tissue metabolic activity, in terms of glucose uptake.

In our series, DD patients had a five-year overall survival rate of 36.5% despite an aggressive surgical approach combined with high dose systemic chemotherapy. Clearly novel systemic therapies are needed to treat this and other histologic subtypes that are resistant to current multimodality approaches. The ability to identify and therapeutically exploit a unifying molecular abnormality that is associated with a specific histologic subtype is best exemplified by the dramatic success of imatinib mesylate (Gleevec or STI-571) for gastrointestinal stromal tumors (GISTs). Differential gene, RNA, and protein expression patterns identified by high throughput techniques such as cDNA and miRNA arrays as well as tissue microarray and/or proteomic profiling may offer insight into previously unappreciated sarcomagenesis pathways.

A unique characteristic (and the basis for the definition of dedifferentiated liposarcoma) is the presence of dedifferentiated areas within a sarcoma that consists of predominantly well-differentiated histology. This phenomenon begs the question of whether the dedifferentiated component represents an area of WD that has regressed to resemble an earlier stage of developmental cellular maturation as reflected by a dedifferentiated phenotype. Alternatively, areas of dedifferentiation may represent differing stages of maturity in the original sarcoma progenitor cells, also referred to as mesenchymal stem cells. The latter hypothesis is reminiscent of the accepted progression of leukemogenesis in which a lymphoid stem cell type arrests at differing stages of normal lymphoid stem cell maturation, then acquires potential for the transformed phenotype of a cell type specific leukemia or lymphoma (Ref. 16).

Recently, Matushansky et al. proposed a developmental model of sarcomagenesis to define the differentiation-based classification of liposarcomas (Ref. 17). Using RNA isolated from human mesenchymal stem cells (hMSC) growing in adipocyte conditioned media, gene expression profiling was performed at predetermined days of hMSC-adipocytic differentiation to identify groups of adipocyte differentiation-specific genes. In parallel, to identify genes specific to the sarcomagenesis process that are not involved in the maturation process, a list of genes differentially expressed between normal fat tissue and each liposarcoma histologic subtype were generated from tumor tissue. Genes corresponding to the stage of normal differentiation were analyzed by comparing the two groups of gene sets.

Mesenchymal Stem Cell (MSC): Mesenchyme is embryonic connective tissue that is derived from the mesoderm and that differentiates into hematopoietic and connective tissue, whereas MSCs do not differentiate into hematopoietic cells. Mesenchymal stem cells are multipotent stem cells that differentiate into a variety of cell types such as: osteoblasts, chondrocytes, myocytes, adipocytes and beta-pancreatic islet cells.

Hierarchical clustering analysis of the adipocyte maturation gene set revealed that dedifferentiated and pleomorphic liposarcomas were associated with early maturation time points, whereas myxoid/round cell and well-differentiated were associated with late time points in a maturation process that more closely resembled that of normal fat. Each tumor subtype was compared to its
corresponding normal cell stage of differentiation. Using differential gene expression analysis, two distinct gene sets were identified: genes overexpressed in liposarcomas that mark the stage of differentiation arrest, and a distinct set of genes overexpressed in liposarcomas that are not found in the corresponding stage of differentiation which could be enriched for genes critical to sarcomagenesis (Ref. 17). In the future it is likely that sarcomas will be classified by their molecular pathologic characteristics that both defines the histologic subtype and are also prognostic of the metastatic phenotype.

Conclusions

In conclusion, the biologic behaviors of well differentiated and dedifferentiated liposarcomas are significantly different. Using two distinct surgical and multidisciplinary approaches we propose that these tumors may be optimally managed as separate disease entities. We have established radiographic criteria that correlate with the presence of the dedifferentiated retroperitoneal liposarcoma components useful in maximizing the accuracy of pre-therapy image-directed diagnostic biopsy. In the future, the characterization of molecular pathways critical to liposarcomagenesis will hopefully facilitate development of individualized treatment strategies based on specific tumor biology, thereby enhancing multidisciplinary therapy for this challenging group of diseases.

Abbreviations and Glossary

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ALT</td>
<td>Atypical lipomatous tumor</td>
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<tr>
<td>Clone</td>
<td>A group of identical cells that share a common ancestry, meaning are derived from the same mother cell</td>
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<tr>
<td>DD</td>
<td>Dedifferentiated</td>
</tr>
<tr>
<td>DM</td>
<td>Distant metastasis</td>
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<tr>
<td>DSS</td>
<td>Disease specific survival</td>
</tr>
<tr>
<td>Fibrous septae</td>
<td>Partitions within tissue.</td>
</tr>
<tr>
<td>LR</td>
<td>Local recurrence</td>
</tr>
<tr>
<td>Mitotic activity</td>
<td>Describes cells that are actively dividing and progressing through the cell cycle.</td>
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<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>Prospective evaluation</td>
<td>Evaluation of a patient prior to initiating therapy.</td>
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<td>RFS</td>
<td>Recurrence free survival</td>
</tr>
<tr>
<td>RPLS</td>
<td>Retroperitoneal liposarcoma</td>
</tr>
<tr>
<td>WD</td>
<td>Well Differentiated</td>
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