Atypical lipomatous tumor/well-differentiated liposarcoma and dedifferentiated liposarcoma in patients <40 years: A study of 116 patients.

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Abstract:

Background: Limited data exists on atypical lipomatous tumor (ALT)/well-differentiated liposarcoma (WDL) and dedifferentiated liposarcoma (DDLPS) in children and young adults.

Design: Cases of ALT/WDL/DDLPS arising in patients <40 years were collected from multiple institutional and consultation archives.

Results: 116 cases of ALT/WDL (75) and DDLPS (41) were identified, representing less than 5% of these tumors seen at our institutions over this time period. The patients (59M/57F) ranged from 8 to 40 years. Sites included deep central (abdomen/retroperitoneum/pelvis/groin) (n=60), extremity (n=42), trunk (n=5) head/neck (n=8), and mediastinum (n=1). Dedifferentiated patterns included: high-grade pleomorphic sarcoma, myxofibrosarcoma-like, heterologous rhabdomyoblastic differentiation, low-grade spindle cell sarcoma, and homologous lipoblastic differentiation. 41 patients experienced a local recurrence, and 11 patients with DDLPS developed metastasis. ALT arising in the extremities had lower recurrence rates than deep central WDL (5-year recurrence-free survival 88.9% vs 59.0%; p=0.002), while patients with deep central DDLPS experienced significantly more adverse events compared to WDL at this site (5-year event-free survival 11.9% vs. 59.0%) (p<0.0001). 7 (of 8) head/neck tumors had follow-up available; 5 recurred, and one patient (DDLPS) with recurrence also experienced a metastasis. The single mediastinal tumor (DDLPS) recurred and metastasized.

Conclusion: ALT/WDL and DDLPS occurring in patients < 40 years is rare but exhibits similar morphologic features to its counterparts in older adults, including potential for metastasis.
heterologous and homologous dedifferentiation in the latter. Although case numbers are limited, tumors arising in the head and neck exhibit high rates of adverse events, suggesting that classification as WDL rather than ALT is more appropriate.

Key words: liposarcoma, pediatric, MDM2

Introduction

Atypical lipomatous tumor (ALT)/well-differentiated liposarcoma (WDL) and dedifferentiated liposarcoma (DDLPS), the most common soft tissue malignancies, typically present in the 6th and 7th decades of life [1, 2]. In contrast, these neoplasms are unusual in children and young adults, with myxoid liposarcoma representing the most frequently encountered subtype of liposarcoma in this population [3-7]. Not surprisingly, limited data exists on ALT/WDL and DDLPS in patients 40 years or younger. Therefore, we sought to better understand the clinicopathologic features of these tumors in younger patients.

Materials and methods

The Institutional Review Boards of all participating institutions approved this study. The consultation and institutional anatomic pathology archives of twelve hospitals were searched for cases of ALT/WDL and DDLPS in patients 40 years of age and younger from January 1, 1960 to June 30, 2018. Cases were included if they met at least one of the following criteria: 1) classic morphology, 2) MDM2 amplification by fluorescence in situ hybridization (FISH), 3) MDM2/CDK4 expression by immunohistochemistry or 4) ring/marker
chromosomes identified by conventional cytogenetics. Classic morphology for ALT/WDL was defined as a well-differentiated lipomatous neoplasm containing atypical hyperchromatic stromal cells, while DDLPS classic morphology consisted of areas of both ALT/WDL and sarcoma (Figure 1). Superficial (dermal/subcutaneous) ALT/WDL and DDLPS without confirmatory molecular or immunohistochemical MDM2 studies were excluded. Clinicopathologic information, including patient age and sex, tumor size, and anatomic location was collected. For tumors arising in the extremity, the depth (dermal, subcutaneous, or intramuscular) of the lesion was recorded. The morphologic pattern of the dedifferentiated component was documented when material was available for review. Treatment data and clinical follow up information was acquired through the institutional electronic medical records or the submitting pathologist.

**Immunohistochemistry**

Immunohistochemistry for MDM2 and CDK4 was performed and evaluated as previously reported[8]. Briefly, deparaffinized sections of each tumor were stained for MDM2 (clone IF2, 1:50 dilution) and CDK4 (clone DCS-31, 1:100 dilution), both from Life Technologies (Grand Island, NY) on a Leica Biosystems (Buffalo Grove, IL) Bond III automated immunostainer for 20 minutes at room temperature. A positive result required dark staining in at least 20% of tumor cells.

**Molecular studies**

MDM2 amplification was analyzed with an enumeration FISH strategy using laboratory developed chromosome specific fluorescent-labeled DNA probes. The target gene area of MDM2, 12q15 was labeled with red. A reference probe on centromere 12, D12Z3 was labeled with green. A paraffin
section from the tumor was cut 5μM thick and mounted on a silanized slide. This unstained slide was baked for 15min at 90 degrees Celsius, and then deparaffinized in xylene. Pre-treatment in 10-mM citric acid was followed by a NaCl protease treatment and dehydration. The slide and DNA probe working solution were co-denatured and hybridized. Visualization of the FISH signals was accomplished by using fluorescence microscope (CytoVision, Leica Biosystems or Abbott/Vysis). An experienced FISH technologist scanned the slide for amplification and scored a representative 30-100 tumor nuclei from the target area, dependent on individual institutional protocols.

Conventional Chromosome Analysis

Tumor cells were cultured, harvested and banded utilizing standard cytogenetic techniques according to specimen-specific protocols from each institution. When available, 20 metaphases were analyzed and results reported per 2016 International System for Human Cytogenomic Nomenclature (ISCN).

Statistical Methods

Data was summarized with frequencies and percentages or with medians and ranges, as appropriate. An adverse event was defined as a local recurrence or metastasis, and event-free survival was defined as the time from original diagnosis to the first recurrence or metastasis (whichever occurred first). Those who did not have an adverse event were censored at the time of last follow-up. Event-free survival was summarized at 5 years, along with 95% confidence intervals (CI), using the Kaplan-Meier method. Comparisons in event-free survival were assessed with likelihood ratio tests from Cox proportional hazards regression models. P-values less than 0.05 were considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC) or R [9].

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Results

A total of 116 unique cases of ALT/WDL (n=75) and DDLPS (n=41) presenting in patients <40 years were identified (Figure 2). Approximately one-third of these cases (n=34) were from a single large tertiary care hospital, and at this institution these cases represented 2% (11 of 563) of institutional and 3% (23/752) of consultation cases of ALT/WDL and DDLPS reviewed. The clinicopathologic features of the entire cohort are detailed in Table 1. The patients (59 males, 57 females) ranged in age from 8 to 40 years (median 35.6 years) at the time of diagnosis. Anatomic locations included deep central sites (abdomen/retroperitoneum/pelvis/groin)(n=60), extremity (n=42), trunk (n=5), head/neck (n=8), and mediastinum (n=1). Taking all sites together, tumor sizes ranged from 0.9 cm to 60 cm (median 15.8 cm). 42 cases had MDM2 amplification by FISH, 3 had MDM2 amplification and MDM2 expression, 15 had MDM2 expression only by immunohistochemistry, 4 cases had positive MDM2 expression and ring/marker chromosomes, and 3 had only ring/marker chromosomes. The remaining 49 patients met morphologic criteria.

Treatment and follow-up

Treatment information was available for 96 patients, and 30 patients (WDL=8; DDLPS=22) received adjuvant chemotherapy/radiation therapy. For patients with available follow up (n=91; range 0 to 49.2 years; IQR 1.4 to 7.3 years, median=2.8 years), 41 patients had local recurrence (ALT=2; WDL=16; DDLPS=23). Three patients initially diagnosed with ALT/WDL had DDLPS in their subsequent recurrence material. Three tumors were originally diagnosed as benign lipomatous tumors (lipoma=2; spindle cell lipoma=1), and these tumors were only
correctly diagnosed at the time of recurrence. Eleven patients with DDLPS (deep central=8; extremity, head/neck and mediastinum=1 each) developed metastatic disease. Sites of metastasis included lung (n=8), liver (n=2), bone (n=1), brain (n=1), chest wall (n=1), pleura (n=1), and omentum (n=1). At last follow up, 21 patients are alive but with unknown status (15 ALT/WDL; 6 DDLPS), 43 are alive without disease (34 ALT/WDL; 9 DDLPS), 15 are alive with disease (7 ALT/WDL; 8 DDLPS), 10 died of disease (3 WDL; 7 DDLPS), 1 died of complications from chemotherapy (DDLPS), and 1 died of other causes (DDLPS; germ cell tumor). One patient, a 26 year-old male with DDLPS, was also diagnosed with lung carcinoma, hairy cell leukemia, and solitary fibrous tumor. No patients in our study were known to have a genetic syndrome.

**Extremity-based tumors**

Forty-two patients, ranging in age from 8 to 40 years (median 35.8 years), presented with tumors (ALT=36; DDLPS=6) located in the extremities with tumor sizes measuring from 3.5 cm to 60 cm (median=15 cm). Specific anatomic sites included: thigh (n=26), shoulder (n=5), arm (n=3), leg (n=5), axilla (n=2) and knee (n=1). Thirty-two were located intramuscularly, and 2 were localized to the subcutis, while the depth was unknown in the remaining 8 cases. Among those with available follow-up (median 2.2 years, range 0 to 49.2 years), 2 (of 29) patients with ALT experienced a recurrence (5-year event-free survival 88.9%, 95% CI: 68.4% to 100%), while 3 (of 5) patients with DDLPS reported a recurrence and one of these patients also developed metastatic disease (5-year event-free survival 33.3%, 95% CI: 0% to 86.7%) (p=0.19) (Table 2; Figure 3).
**Tumors arising at deep central sites**

Of those tumors (WDL=29; DDLPS=31) arising in deep central sites (abdomen/retroperitoneum/pelvis/groin), the ages of the patients ranged from 23 to 40 years (median 35.2 years). The tumors measured from 4.5 cm to 52 cm (median 20 cm). Among those with available follow-up (median 3.6 years, range 0.2 to 30.1 years), 13 of 22 patients with WDL experienced a local recurrence (5-year event-free survival 59.0%, 95% CI: 35.0% to 83.0%), while 17 (of 24) DDLPS at this site recurred and 8 metastasized (6 of these had both a recurrence and a metastasis) (5-year event-free survival 11.9%, 95% CI: 0% to 27.1%) (p<0.0001) (Table 2; Figure 3).

**Tumors arising at other sites**

Of the 8 cases (WDL=6; DDLPS=2) which occurred in the head/neck (depth: intramuscular=2, unknown=6; specific site: orbit 3, neck 2, temple 1, pharynx 1, supraglottis 1), 5 recurred (WDL=3; DDLPS=2), and one patient with DDLPS with recurrence also experienced a metastasis (7 patients with follow-up, range 0.4-15.3 years; median 5.6 years). 5 cases (4 ALT, 1 DDLPS) arose in the trunk region (intramuscular=2; subcutis =1; unknown=2), and no tumors recurred or metastasized (3 patients with follow-up, range 0.4-5.8 years; median 1.7 years). The single mediastinal tumor (DDLPS) recurred and metastasized (4 years of follow-up).
**ALT vs. WDL**

When comparing ALT arising in the extremities and WDL occurring in deep central sites, the event-free survival of ALT was statistically significantly higher (5-year event-free survival 88.9% vs 59.0%; p=0.002) (Figure 3). There were too few cases at other sites to reach statistical significance.

**Extremity-based vs. deep central DDLPS**

There was no significant difference in event-free survival between DDLPS presenting in the extremities and those arising at deep central sites (5-year event-free survival 33.3% vs. 11.9%; p=0.13) (Figure 3). There were too few cases at other sites to reach statistical significance.

**Morphologic features of DDLPS**

The dedifferentiated component of 16 DDLPS was available for review and showed the following morphologic patterns: high-grade pleomorphic sarcoma (n=8), myxofibrosarcoma-like (n=4), heterologous rhabdomyoblastic differentiation (n=2), low-grade spindle cell sarcoma (n=1), homologous lipoblastic differentiation (n=1) (Figure 4). Metaplastic bone was observed in two cases (Figure 5). Both patients with heterologous rhabdomyoblastic differentiation experienced adverse events (one patient with recurrence and metastasis, one patient with metastasis). Follow-up was available for three of the 4 patients with myxofibrosarcoma-like areas; one patient had recurrence and metastasis while a second experienced recurrence only. Follow-up was available for only 2 patients with high-grade pleomorphic sarcoma; one of these patients experienced local recurrence. The tumor with low-grade spindle cell morphology and one with metaplastic ossification recurred, while the case with homologous lipoblastic differentiation did not recur or metastasize.
Discussion

Liposarcomas are the most commonly encountered mesenchymal malignancies in adulthood, but ALT/WDL and DDLPS are rare in patients less than 40 years of age, with myxoid liposarcoma representing the most frequent subtype of liposarcoma in this age group [3-7]. In fact, fewer than 25 bona fide cases of pediatric ALT/WDL or DDLPS have been reported in the literature, and many of the earlier cases that predated molecular genetic testing for MDM2 amplification may have instead represented myxoid liposarcoma or lipoblastoma [3, 6, 10-21]. Although young adults have been included in larger systematic studies of ALT/WDL and DDLPS, patients less than 40 years of age represent a minor subset of these cohorts and have not been analyzed separately [15, 19, 22-24]. Consequently, there is little data on the clinicopathologic features of these tumors in children and young adults.

Our results confirm that ALT/WDL and DDLPS may arise in patients 40 years or younger, but these adipocytic neoplasms are rare in this population, representing less than 5% of all ALT/WDL and DDLPS seen at a single large tertiary care institution. Given the possibility of referral bias for liposarcomas with unusual presentation, the incidence in the younger age group is likely lower than 5%. Furthermore, approximately 75% of the tumors in our series occurred in patients 30 years or older.

The clinical features and anatomic site distribution of ALT/WDL and DDLPs in younger patients seems to mirror the patterns encountered in patients older than 40 years. First, the male: female ratio is nearly 1:1, similar to older adult populations. ALT more commonly occurs at deep-seated sites in the extremities with 60% involving the thigh. Less commonly, these tumors arose in the arm, axilla, chest wall and trunk. Conversely, DDLPS most often occurred in deep central sites. Finally, as in older adults, DDLPS in young patients are capable of homologous and heterologous differentiation.
The behavior of these tumors when they present in children and young adults is also similar
to those occurring in older patients. Specifically WDL has a significantly lower 5-year
recurrence-free survival rates compared to ALT, while DDLPS in deep central sites have
significantly lower rates of 5-year event-free survival compared to WDL occurring at these
locations. While DDLPS arising in the extremity showed fewer adverse events than those
arising in the abdomen/retroperitoneum/groin/pelvis, the difference in behavior was not
statistically significant. Similarly, when examining only tumors arising in the extremity, the
difference between outcome in ALT and DDLPS did not reach statistical significance.

Given their frequency, the diagnosis of ALT/WDL is often straightforward in older adults. For
example, in this population, any deep-seated well-differentiated lipomatous tumor,
especially those at deep central sites, raises concern for ALT/WDL, and FISH for MDM2
amplification is recommended when unequivocal atypia is absent [25, 26]. However, in
children, this same pattern may lead to the consideration of a matured lipoblastoma.

Lipoblastoma, the most common pediatric lipomatous neoplasm, characterized by PLAG1
rearrangements, typically shows a lobulated low power architecture with adipocytes in
various stages of maturation within a myxoid background. Although lipoblastomas maintain
their lobular architecture as the patient ages, the adipocytes mature, and the myxoid
stroma dissipates. Consequently, the morphology of a matured lipoblastoma shows overlap
with ALT/WDL. Lipoblastoma, however, lacks atypical hyperchromatic stromal cells.

Additionally, genetic studies, including PLAG1 and MDM2 FISH should help in this
differential diagnosis.

In young adult patients, lipoma would likely be the leading consideration in any well-
differentiated lipomatous tumor. Again, current guidelines recommend MDM2 studies for
any well-differentiated lipomatous tumor without atypia presenting at a deep central site to

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exclude WDL. However, in the extremity, work by Zhang and colleagues suggests MDM2 studies for any intramuscular well-differentiated adipocytic neoplasm without atypia if the tumor is greater than 15 cm, while subsequent modified criteria proposed by Clay et al recommend performing these studies in tumors greater than 10 cm only if the patient is older than 50 years[25, 26]. In Clay’s study, all liposarcomas in which size was the only worrisome criteria occurred in patients greater than 50 years[26]. As liposarcoma in young patients are exceedingly rare, it is likely this study had very few patients less than 40 years of age. While these criteria are practical, pathologists should be aware that ALT/WDL may occur in younger patients.

The diagnosis of DDLPS may be more problematic in the pediatric population as primitive-appearing high grade sarcomas such as rhabdomyosarcoma and the newly emerging BCOR- and CIC-rearranged sarcomas are more common. Two cases of DDLPS in our cohort harbored heterologous rhabdomyoblastic differentiation. This finding could easily be mistaken for embryonal rhabdomyosarcoma, especially on biopsy material when the well-differentiated liposarcomatous component may be missed. As BCOR and CIC-rearranged primitive sarcomas may exhibit myxoid features, DDLPS with areas resembling myxofibrosarcoma may raise the possibility of these entities. Finally, those tumors with homologous pleomorphic lipoblastic differentiation and/or myxoid stroma may mimic myxoid liposarcoma, the most common liposarcoma in children and young adults, or myxoid pleomorphic liposarcoma, a rare liposarcoma with a predilection for pediatric patients [6]. Careful examination of specimens with attention to a well-differentiated liposarcomatous component, as well as genetic studies for BCOR, CIC, FUS, DDIT3 rearrangements and MDM2 amplification will aid in appropriate classification.

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A subset of pediatric liposarcomas, including two cases of ALT/WDL reported by Debelenko et al, have been associated with Li-Fraumeni syndrome, an autosomal dominant disorder often characterized by germline TP53 mutations [17, 27]. Interestingly, both tumors detailed by Debelenko expressed p53 but lacked MDM2 staining by immunohistochemistry [17].

Only two patients in our study, 26 year old and 31 year old males with DDLPS, had other malignancies. Neither had a known genetic disorder. The MDM2 status of one was positive by immunohistochemistry while the second was unknown. Given the unusual nature of ALT/WDL/DDLPS in young patients, the majority of cases in our cohort were from consultation archives, limiting available follow-up. While it may be possible that additional patients developed second malignancies or were subsequently worked up for genetic syndromes such as Li-Fraumeni, additional studies would be necessary to more accurately determine the rate of underlying syndromes in these patients.

In conclusion, ALT/WDL and DDLPS are rare neoplasms in children and young adults. Comparable to their adult counterparts, WDL at deep seated central sites have statistically significantly lower rates of recurrence free survival compared to ALT arising in the extremities, while DDLPS arising in deep central sites have a significantly lower rate of event-free survival compared to WDL at these sites. Although case numbers are limited, tumors arising in the head/neck exhibit high rates of adverse events, likely due to difficulty in complete surgical excision similar to their retroperitoneal/mediastinal counterparts, suggesting that classification as WDL rather than ALT may be more appropriate. Finally, even though these tumors exhibit similar morphologic features as those presenting in adulthood, pathologists should be aware that these tumors may arise in patients less than 40 years of age to ensure accurate diagnosis and appropriate treatment.
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References


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**Figure legends**

Figure 1. Cases of atypical lipomatous tumor (ALT)/well-differentiated liposarcoma show a well-differentiated lipomatous neoplasm with atypical hyperchromatic stromal cells (A), whereas dedifferentiated liposarcoma (DDLPS) show areas of ALT/WDL adjacent to high grade sarcoma (B).
Figure 2: Age distribution of cases of ALT/WDL and DDLPS.

Figure 3. Kaplan-Meier plot comparing event-free survival of extremity-based ALT/DDLPS and deep central WDL/DDLPS.

Figure 4. The dedifferentiated component was variable including cases resembling undifferentiated pleomorphic sarcoma (A) and myxofibrosarcoma (B). A single case had homologous lipoblastic differentiation (C). In one case, the dedifferentiated component contained spindle cells with relatively little atypia (D).

Figure 5. Metaplastic bone formation was also identified in two cases of DDLPS.
Table 1: Clinical features of entire cohort

<table>
<thead>
<tr>
<th></th>
<th>ALT/WDL (N=75)</th>
<th>DDLPS (N=41)</th>
<th>Total (N=116)</th>
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<td>Sex, N (%)</td>
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<tr>
<td>Male</td>
<td>36 (48.0%)</td>
<td>23 (56.1%)</td>
<td>59 (51%)</td>
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<tr>
<td>Female</td>
<td>39 (52.0%)</td>
<td>18 (43.9%)</td>
<td>57 (49%)</td>
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<tr>
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<tr>
<td>N</td>
<td>73</td>
<td>41</td>
<td>114</td>
</tr>
<tr>
<td>Median</td>
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<tr>
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<td>Median</td>
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<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Range</td>
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<tr>
<td>Site, N (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Deep central</td>
<td>29 (38.7%)</td>
<td>31 (75.6%)</td>
<td>60 (52%)</td>
</tr>
<tr>
<td>Extremity</td>
<td>36 (48.0%)</td>
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<td>Trunk</td>
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<td>1 (2.4%)</td>
<td>5 (4%)</td>
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<td>Mediastinum</td>
<td>0 (0.0%)</td>
<td>1 (2.4%)</td>
<td>1 (1%)</td>
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<td>Size, cm</td>
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<td>N</td>
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<tr>
<td>Median</td>
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<td>Adjuvant chemotherapy/radiation, N (%)</td>
<td>8/62 (12.9%)</td>
<td>22/34 (64.7%)</td>
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<tr>
<td>Available follow-up</td>
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<tr>
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<td>Adverse events, N</td>
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Table 2. Comparison of adverse events since diagnosis by anatomic site

<table>
<thead>
<tr>
<th>Site (range, median follow-up)</th>
<th>N=</th>
<th>N with follow-up</th>
<th>Adverse event</th>
<th>Recurrence</th>
<th>Metastasis</th>
<th>5-year event free survival (95% CI)</th>
<th>P value</th>
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<td></td>
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<tr>
<td>ALT</td>
<td>36</td>
<td>29</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>88.9% (68.4%, 100%)</td>
<td>0.19</td>
</tr>
<tr>
<td>DDLPS</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>33.3% (0%, 86.7%)</td>
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</tr>
<tr>
<td>Deep central (0.2-30.1y; median 3.6 y)</td>
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<td></td>
<td></td>
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<tr>
<td>ALT</td>
<td>29</td>
<td>22</td>
<td>13</td>
<td>13</td>
<td>0</td>
<td>59.0% (35.0%, 83.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DDLPS</td>
<td>31</td>
<td>24</td>
<td>19</td>
<td>17</td>
<td>8</td>
<td>11.9% (0%, 27.1%)</td>
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<tr>
<td>Head and neck (0.4-15.3 y; median 5.6 y)</td>
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<tr>
<td>ALT</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td>3</td>
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</tr>
<tr>
<td>DDLPS</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Trunk (0.4-5.8 y; median 1.7 y)</td>
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</tbody>
</table>

y, years; Deep central, abdomen/retroperitoneum/pelvis/groin
<table>
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<th>ALT</th>
<th>4</th>
<th>3</th>
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<tr>
<td>Mediastinum</td>
<td>(4 y)</td>
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</tr>
<tr>
<td>DDLPS</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

y, years; NA, not available