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ScienceDirect

EJSO 41 (2015) 899–904

EJSO the Journal of Cancer Surgery

www.ejso.com

Metastasis in dedifferentiated liposarcoma: Predictors and outcome in 148 patients

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Accepted 13 January 2015
Available online 24 January 2015

Abstract

Objective: To describe the pattern of dedifferentiated liposarcoma (DDLPS) metastases and to analyze their predictors and outcome.
Materials and methods: In this retrospective study, we reviewed the imaging and clinical records of all consenting patients with histopathology-confirmed DDLPS seen from 2000 through 2012. The predictive value of clinical and histopathologic parameters for metastasis later in the disease course was analyzed using univariate and multivariate analyses. Survival of patients with and without metastasis was compared using Log-rank test.
Results: Records of 148 patients (57 women, 91 men; mean age 59 years, range 30–87 years) were reviewed. Distant metastases were observed in 44/148 patients (29.7%), 9/44 (20.5%) at presentation and 35/44 (79.5%) developing them later at a median interval of 8 months (IQR = 0.80–26 months). Median duration of follow-up was 38 months (IQR = 18–74 months) with 77/148 patients (31 with metastases) deceased at the time of analysis. Median survival was 28 months (IQR = 10–56 months) for patients with metastases and 38 months (IQR, 17–65 months) for patients without metastases (p = 0.0123, Log-Rank test; Hazard ratio 1.79 [95% confidence interval 1.11–2.84]). Lung was the most common site of metastases (33 patients, 22.3%). On univariate analysis, grade and local recurrence were associated with subsequent risk of metastasis where as age, tumor size, site, *de novo* dedifferentiation, number of previous surgical resections, margin positivity and chemoradiation were not. On multivariate analysis, high tumor grade (p-value = 0.0005, OR 5.05; 95% CI 2.01–13.48) and local recurrence (p-value = 0.0025, OR 4.46; 95% CI 1.67–13.40) predicted metastasis.
Conclusion: Lung was most frequent site of DDLPS metastases. Risk of developing metastatic disease was statistically associated with tumor grade and local recurrence. Metastatic disease was associated with decreased survival.

Keywords: Dedifferentiated liposarcoma; Metastasis; Predictors; Survival

Introduction

Liposarcomas (LPS) are a heterogeneous group of mesenchymal tumors that have variable biologic behavior ranging from indolent disease to extremely aggressive tumors that can be rapidly fatal. The most recent histologic

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http://dx.doi.org/10.1016/j.ejso.2015.01.012
0748-7983/

taxonomy of LPS recognizes three major categories: (a) atypical lipomatous tumor, well-differentiated (WDLPS) and dedifferentiated LPS (DDLPS); (b) myxoid and round cell LPS; and (c) pleomorphic LPS.[1] DDLPS is a tumor of the sixth and seventh decades and most commonly occurs in the retroperitoneum.[1] Initially defined by Evans in 1979 as WD LPS with high-grade non-lipogenic components, the spectrum of DDLPS was expanded to include WDLPS with low-grade dedifferentiation.[2] Most DDLPS arise *de novo* (90%) with very few (10%) arising as secondary tumors from previously diagnosed WD LPS.[2] Of all the LPS subtypes, distant metastases are more frequently encountered with myxoid/round cell LPS and pleomorphic LPS than with WD/DDLPS. The reported incidence of distant metastases in DDLPS varies between 1 and 18%[3] and most patients with DDLPS die of locally aggressive tumors rather than distant metastases.[2,4]

There is scant literature on metastases in DDLPS. Though rare, it is known that metastasis in DDLPS often results in a rapidly fatal course.[3] However, there are no reported clinical or molecular biomarkers that can reliably predict the metastatic risk of DDLPS. A recent study performed evaluated the predictors of outcome in patients with primary, localized, retroperitoneal DDLPS after surgery.[5] Herein we report the pattern of metastases and analyze predictors of metastases as well as the influence of metastases on outcome in patients with DDLPS arising in all anatomic locations.

Materials and methods

Patients were prospectively consented to an Institutional Review Board-approved protocol permitting the research use of medical records, and patients with WD/DDLPS seen at our institution between January 2000 and December 2012 were identified from the pathology database. The histopathology of all cases was confirmed as part of routine oncologic care. The electronic medical records and imaging of patients was initially screened by one radiologist to identify patients who either had distant metastatic disease at presentation or developed later.

All available imaging in patients who developed metastatic disease was systematically reviewed in consensus by two cancer imaging fellowship-trained radiologists with 8 and 15 years of experience. One of these radiologists also performed the initial screen to identify patients with metastases. In each patient, the site, number (single or multiple), and the date of detection of metastasis were recorded. Distant metastatic disease was confirmed in all patients either by histopathology or by the presence of unequivocal progression or response to treatment on serial imaging studies. Intra-abdominal metastases other than liver and nodal metastases were excluded due to difficulty in distinguishing these from local recurrence of retroperitoneal liposarcomas. Deposits in the abdominal wall (subcutaneous and intramuscular) distant from the site of surgery were considered as metastases whereas those occurring near the surgical scar were considered as local recurrences. Nodal metastases were confirmed either by histopathology or were presumed based on a typical anatomic location on imaging.

Demographic data, date of initial diagnosis of LPS, type of management (surgery, chemotherapy, radiotherapy), date of surgical resection, number of resections if multiple, duration of follow-up, and outcome were noted in all patients. In the patients who developed metastatic disease, the time from diagnosis of primary to development of metastatic disease, from diagnosis of primary to death or last follow-up, and the time from diagnosis of metastasis to death or last follow-up were calculated. Similarly, the time from diagnosis to death or last follow-up was calculated in patients who did not develop metastasis. From the histopathologic data, tumor characteristics including site, size and grade of the primary tumor, presence of heterologous differentiation (rhabdomyoblastic, leiomyosarcomatous, or osseous), and surgical margins, when available were noted. The presence of an associated WD component and whether the DD component was *de novo* or secondary were also noted.

For statistical analysis of the predictors of metastases, patients who presented with metastasis were excluded and only patients who developed metastasis later in the disease course were included. The influence of age (continuous variable), site of the primary tumor, size of the primary tumor (continuous variable), number of surgical resections, type of dedifferentiation, histopathological grade, positivity of surgical margins, local recurrence and presence of concurrent chemoradiation on development of metastasis later in the disease course was analyzed with univariate analysis. For multivariate analysis, due to small number of patients with metastasis, only four variables were analyzed using regression analysis: site of the primary tumor, histopathologic grade, local recurrence and concurrent chemoradiation. Given that positivity of surgical margins increases the risk of local recurrence, only local recurrence was included in the multivariate analysis. Due to small number of patients with primary tumor arising in the inguinoscrotal region, extremities and other sites, tumors arising in the abdomen/pelvis, chest and head and neck were grouped together in one group and tumors arising in the inguinoscrotal region and extremities in another group. A two-tailed p-value of 0.05 was considered to be statistically significant for this analysis. Survival between each pair was compared using the Log-rank test. All the statistical analyses were performed using JMP® Pro 10.0.0 (SAS Institute Inc, Cary, NC).

Results

In total, 234 patients diagnosed with WD/DD LPS or atypical lipomatous tumor were identified. Of these, 86 patients with only WD LPS or atypical lipomatous tumor during their disease course were excluded. The remaining