Incidence and Adverse Prognostic Implications of Histopathologic Organ Invasion in Primary Retroperitoneal Sarcoma

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BACKGROUND: The incidence of histopathologic organ invasion (HOI) in retroperitoneal sarcoma (RPS) is not well described. We reviewed our experience to investigate the rate and prognostic implications of HOI.

STUDY DESIGN: Patients with primary RPS who underwent surgery at our institution were reviewed. Histopathologic organ invasion was defined as microscopic organ invasion confirmed by re-review of pathology slides by an expert sarcoma pathologist. Impact of HOI on the crude cumulative incidence of locoregional recurrence, distant recurrence, and overall survival rates was analyzed.

RESULTS: Between 2002 and 2011, one hundred and eighteen patients underwent resection for primary RPS; 99 had at least 1 organ resected and, among those, HOI was present in 58% (57 of 99). Among the 77 patients with the 3 most common histologies, rates of HOI were 61% for dedifferentiated liposarcoma, 56% for leiomyosarcoma, and 40% for well-differentiated liposarcoma. In this subset, HOI was associated with no difference in 2-year crude cumulative incidence of locoregional recurrence (48% vs 47%; $p = 0.55$) or distant recurrence (46% vs 22%; $p = 0.2$). With a median follow-up of 33.6 months, HOI was an independent predictor of worse 5-year overall survival (34% vs 62%; $p = 0.04$; hazard ratio = 2.3; 95% CI 1.2 to 4.4; $p = 0.02$).

CONCLUSIONS: The likelihood of organ invasion can be predicted by histologic subtype of primary RPS. To the best of our knowledge, this is the first study to demonstrate that HOI is associated with worse overall survival. These data can help guide the minimal extent of surgical resection required for RPS. (J Am Coll Surg 2017;224:876–883. © 2017 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Sarcomas are rare soft tissue tumors that encompass more than 70 different histologic subtypes characterized by varying degrees of aggressiveness. In 2015, approximately 12,000 patients in the US will be diagnosed with a new soft tissue sarcoma, and it is estimated that nearly 5,000 patients will die of this disease.[1] Approximately 15% of sarcomas arise in the retroperitoneum.[2] The current standard of care for localized retroperitoneal sarcoma (RPS) is a macroscopically complete resection (R0/R1 resection). Five-year overall survival (OS) and local recurrence rates vary with histologic subtype as well as disease presentation (primary vs recurrent) and range from 34% to 66% and 22% to 84%, respectively.[3-7] The efficacy of neoadjuvant or adjuvant chemotherapy and radiation therapy for RPS has not been confirmed in randomized clinical trials. An ongoing phase III trial is evaluating preoperative external beam radiation therapy for RPS, and alternative modalities, such as mesh brachytherapy and radiation therapy dose escalation to high-risk regions of tumor, are being explored.[8-11] In addition, there is controversy about the appropriate extent of resection and optimal surgical approach for these typically large tumors that are often in close proximity to vital structures. A compartmental

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Abbreviations and Acronyms

DDLPS = dedifferentiated liposarcoma
DM = distant metastasis
HOI = histopathologic organ invasion
LMS = leiomyosarcoma
LRR = locoregional recurrence
OS = overall survival
RPS = retroperitoneal sarcoma
WDLPS = well-differentiated liposarcoma

resection whereby uninvolved organs are resected to obtain an oncologic margin of normal tissue has been advocated recently and has sparked debate.[3,12-15]

In addition to an R0/R1 resection, other prognostic factors include histologic subtype, grade, tumor rupture, and multifocality.[6,16-21] Although adjacent (macroscopic) organ involvement has been shown previously to be an important prognostic factor, there are limited data on histopathologic organ invasion (HOI).[6,18] Histopathologic organ invasion has only rarely been described in studies investigating organ resection for RPS, and the prognostic implications of HOI remain unclear.[6,22,23] The objective of this study was to investigate the rate of HOI by histologic subtype and to determine the prognostic implication of HOI in patients with primary retroperitoneal sarcoma.

METHODS

Patients

After IRB approval, records of all patients who underwent resection of primary RPS between January 2002 and December 2011 at Brigham and Women's Hospital were retrospectively reviewed. Patients with benign retroperitoneal masses or recurrent RPS were excluded from the study. Operative reports and surgical pathology reports were reviewed to identify the number and type of organs resected. All patients underwent a multidisciplinary evaluation at the Center for Sarcoma and Bone Oncology at the Dana-Farber/Brigham and Women's Cancer Center. In general, our institution's approach to the extent of resection is guided by preoperative imaging, intraoperative findings, and histologic subtype. Of note, this cohort of patients has been included in a multi-institutional study, but these specific data have not been reported.[24]

All major organ resections were analyzed. An organ was defined as any solid or hollow viscera, nerve, blood vessel, or muscle. Histopathologic organ invasion was defined as evidence of organ invasion not based on macroscopic evaluation or adjacent organ involvement, but rather based on microscopic evidence of invasion. Evidence of invasion was based on the microscopic description obtained from review of the surgical pathology reports and all slides were available and confirmed by re-review of pathology slides by a single expert sarcoma pathologist (VJ) (Fig. 1). Dedifferentiated liposarcoma (DDLPS) was defined as a liposarcoma with any evidence of dedifferentiation even if most of the volume was well differentiated, and well-differentiated liposarcoma (WDLPS) was defined as liposarcoma without any evidence of dedifferentiation. The iliopsoas muscle was defined as the psoas, iliacus, and/or iliopsoas muscle/tendon. Vascular structures included aorta, IVC, iliac artery or vein (common, external, and/or internal), and renal artery or vein. Involved critical nerves included femoral and sciatic nerves. Isolated ureteral involvement was recorded independently, however, when the kidney was involved in addition to the ureter, the 2 structures were combined (kidney/ureter) and not counted twice.

Tumor grade was determined using the Federation Nationale des Centres de Lutte Contre le Cancer grading system.[25] Resection margin status was defined as macroscopically complete with a negative microscopic margin (R0 $>$ 0.1 cm), macroscopically complete with a close but negative microscopic margin (R0 $<$ 0.1 cm), macroscopically complete but with a positive microscopic margin (R1), and macroscopically incomplete (R2).

Statistical analysis

Locoregional recurrence (LRR) was defined as that occurring within the pelvis, peritoneum (excluding the liver), or retroperitoneum, and distant metastasis (DM) was defined as that occurring outside these regions (ie lung, liver, and abdominal wall). Time of recurrence was defined as the date of documented pathologic or radiographic recurrence of disease. Overall survival was calculated from the date of surgery to date of death or, if not available, to the date of censoring (date of last follow-up). Overall survival was estimated using the Kaplan-Meier method.[26] The log-rank test was used to determine statistical differences for OS and crude cumulative incidence of recurrence. Univariate and multivariate regression analysis was performed using the Cox proportional hazards model. A p value <0.05 was considered statistically significant and statistical calculations and data analysis were performed using SAS software (SAS Institute). One patient who experienced cardiac arrest and expired in the operating room was excluded from outcomes analysis.

RESULTS

During the study period, 118 patients underwent resection of a primary RPS at our institution. Patient and