Significance of Microscopic Margin Status in Completely Resected Retroperitoneal Sarcoma

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Purpose: We determined whether microscopic margin status is an independent prognosticator in patients who underwent complete resection of retroperitoneal sarcoma.

Materials and Methods: A total of 99 patients with a median age of 55.4 years (range 26.0 to 81.9) underwent complete surgical resection for primary (79) or recurrent (20) retroperitoneal sarcoma between September 1990 and January 2010. Median followup was 36.0 months (range 1.0 to 221.1).

Results: Microscopic involvement of the margins was detected in 24 patients and local recurrence developed in 69 (69.7%). Univariate analysis showed that pain, recurrent disease and higher Fédération Nationale des Centres de Lutte Contre le Cancer grade were associated with an increased risk of local recurrence. On multivariate Cox analysis presenting symptoms and grade were significantly associated with local recurrence-free survival, including pain vs other symptoms (HR 1.7, p = 0.035) and grade 3 vs 1 (HR 2.4, p = 0.028). A total of 25 patients (25.3%) died of retroperitoneal sarcoma. Histological subtype, grade and tumor margin status were prognostic for disease specific survival. Cox regression analysis revealed that certain factors were significantly associated with disease specific survival, including other sarcomas vs liposarcoma (HR 2.8, p = 0.030) and positive vs negative margins (HR 3.4, p = 0.005).

Conclusions: Although complete surgical resection is possible in patients with retroperitoneal sarcoma, the procedure is associated with a high recurrence rate even in patients with negative margins. Microscopically clear margins reliably predict disease specific survival but not local control.

Key Words: soft tissue neoplasms, sarcoma, liposarcoma, Korea, prognosis

Abbreviations and Acronyms

BMI = body mass index

DSS = disease specific survival

FNCLCC = Fédération Nationale des Centres de Lutte Contre le Cancer

LR = local recurrence

RS = retroperitoneal sarcoma

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Study received Seoul National University Hospital institutional review board approval.

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Soft tissue sarcoma represents less than 1% of all malignancies[1] and RS accounts for approximately 10% of all soft tissue sarcomas. Aggressive surgical management, including multivisceral resection, is often required. However, achieving surgical resection with adequate margins is often problematic due to the anatomical site and invasiveness of these tumors. Although gross total excision is a practical, realistic goal that is associated with lower local and distant recurrence rates, and improved overall survival,[2] there is no consensus on the significance of microscopic margin status in RS.

Several groups have identified independent predictors of recurrence and survival for patients with RS, including the nature of the presentation (primary vs recurrent), histological subtype, tumor grade and resection completeness.[3–5] However, these studies typically included patients with unre-

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sectable or metastatic disease. Furthermore, the clinical characteristics of RS have mainly been reported from high volume centers in the United States and Europe, and these findings may not be generalizable to a broader population. To date only 2 published RS studies have been from Asia.[6,7]

We retrospectively analyzed data on a group of adult Korean patients with RS to determine 1) the outcome of complete surgical resection and 2) whether microscopic margin status is an independent prognosticator.

MATERIALS AND METHODS

Patients

The study was approved by the Seoul National University Hospital institutional review board. Between September 1990 and January 2010 demographic data on all patients treated for soft tissue sarcoma at our institution were entered into a database. Clinical and followup data were obtained by reviewing the respective medical charts. Patients with desmoid or gastrointestinal stromal tumors, pediatric sarcoma and other histological diagnoses not typically classified as adult soft tissue sarcomas were excluded from analysis.

Using clinical and histological evaluation we identified 112 patients with confirmed RS who underwent surgical resection. In all cases the aim of resection was macroscopically complete removal of tumor, including adjacent organs when indicated. A total of 13 patients were excluded from analysis due to metastatic disease at diagnosis, neoadjuvant chemotherapy, neoadjuvant radiotherapy or surgical treatment for palliative purposes only. Thus, 99 patients with completely resected, nonmetastatic disease were included in analysis.

These patients were evaluated according to baseline history and physical examination, and the results of laboratory tests, computerized tomography and/or magnetic resonance imaging of the abdomen and pelvis, chest radiography or chest computerized tomography and bone scan.

Pathological Findings

The pathology slides of all 99 patients were re-reviewed for current study purposes. Histological review and reclassification were performed by 1 of us (KCM). Tumor burden was determined according to the sum of the maximum diameter of the primary tumor, as reported at the initial surgical resection. Specimen margins were inspected for evidence of microscopic disease. Histology was classified according to the WHO classification scheme for soft tissue sarcoma histological subtypes.[8] Histological grade was determined according to the FNCLCC grading system, as previously described.[9,10]

Followup

For all patients physical examination, computerized tomography of the abdomen and pelvis, and chest radiography were done at least once every 6 months for 5 years and annually thereafter. These procedures had been performed earlier when indicated by the emergence of new symptoms. Median followup was 36.0 months (mean 50.5, range 1.0 to 221.1).

Statistical Analysis

All data are shown as the percent of patients or the median and range. The primary end points of analysis were DSS, defined as time from date of surgery to date of death secondary to the disease or a complication of the disease, and time to LR, defined as the time from date of surgery to date of LR.

The Kaplan-Meier method was used to calculate survival estimates for LR and absolute survival. The log rank test was used to determine associations between variables and primary end points. Univariate survival analysis was performed for certain variables, including sex; age (less than 55 vs 55 years or greater), BMI (less than 23 vs 23 kg/m^2 or greater), American Society of Anesthesiologists score, presenting symptoms (pain vs other symptoms), presentation nature (primary vs recurrent), tumor site (retroperitoneum vs pelvis), tumor size (14 or less vs greater than 14 cm), histology (liposarcoma vs other sarcomas), FNCLCC grade, margin status and adjuvant therapy. Age, BMI and tumor size were stratified into 2 groups using the median as the cutoff. Although adjuvant therapies were neither prospectively randomized nor uniformly administered, these treatment related factors are reported and were included in the statistical analysis of outcome.

All variables significant at the 0.05 level on univariate analysis were entered into a Cox proportional hazard model to identify independent predictors of DSS and time to LR. HRs and corresponding 95% CIs are reported. All analysis was done using SPSS®, version 13.0. Statistical significance was considered at 2-tailed $p < 0.05$.

RESULTS

Patient Characteristics

Of the 99 patients 55 (55.6%) were male and 44 (44.4%) were female. Median age at diagnosis was 55.4 years (range 26.0 to 81.9). A total of 79 patients (79.8%) had a primary tumor and 20 (20.2%) presented with LR. Median diameter of resected tumors was 14.0 cm (range 2.0 to 45.0) and 7.1% of tumors had a diameter of less than 5 cm. A total of 82.8% of tumors were liposarcoma or leiomyosarcoma. Of resected tumors 80.8% were moderate or high grade sarcoma. Data on microscopic margin involvement were available on 24.2% of the patients.

Survival

LR-free rate. For the total patient sample the actuarial probability of freedom from LR was 36.8% at 3 years and 23.7% at 5 years (fig. 1, *A*). LR developed in 69 patients (69.7%) at a median of 15.9 months (95% CI 1.0–87.7). Of these 69 patients 44 underwent a total of 82 further operative procedures (mean 1.8 per patient). Kaplan-Meier survival rate analysis showed that patients with pain, recurrent disease or higher FNCLCC grade had a significantly