Surgery and Radiotherapy for Retroperitoneal and Abdominal Sarcoma

Both Necessary and Sufficient

Zheng Zhou, MD, PhD; Theodore P. McDade, MD; Jessica P. Simons, MD, MPH; Sing Chau Ng, MSc; Laura A. Lambert, MD; Giles F. Whalen, MD; Shimul A. Shah, MD; Jennifer F. Tseng, MD, MPH

Objective: To evaluate the effect of surgical resection and radiotherapy (RT) in retroperitoneal or abdominal sarcoma.

Design: Retrospective cohort.


Patients: Patients 18 years or older with initial diagnosis of primary retroperitoneal and nonvisceral abdominal sarcoma.

Main Outcome Measures: Survival for 2 years after diagnosis. Kaplan-Meier survival was stratified based on surgery and RT status. Cox proportional hazards model was used to assess adjusted effects of surgery and RT on survival in patients with locoregional disease.

Results: Of 1901 patients with locoregional disease, 1547 (81.8%) underwent resection; 447 (23.5%) received RT. Overall, patients who received both surgery and RT demonstrated improved survival compared with patients who underwent either therapy alone; patients undergoing mono-therapy in turn had more favorable survival compared with patients who received neither therapy (P < .001, log rank). Cox analysis demonstrated that surgical resection (hazard ratio [HR], 0.24; 95% confidence interval [CI], 0.21-0.29; P < .001) and RT (0.78; 0.63-0.95; P = .01) independently predicted improved survival in locoregional disease only. In adjusted analyses stratified for American Joint Commission on Cancer (AJCC) stage, for stage I disease (n = 694), RT provided an additional benefit (HR, 0.49; 95% CI, 0.25-0.96; P = .04) independent of that from resection (0.35; 0.21-0.58; P < .001). For stage II/III (n = 552), resection remained protective (HR, 0.24; 95% CI, 0.18-0.32; P < .001); however, RT was no longer associated with a significant benefit (0.78; 0.58-1.06; P = .11).

Conclusions: In a national cohort of retroperitoneal and abdominal sarcomas, surgical resection was associated with significant survival benefits for AJCC disease stages I to III. Radiotherapy provided additional benefit for patients with stage I disease. Resection should be offered to reasonable surgical candidates with nonmetastatic retroperitoneal/abdominal sarcomas; radiotherapy may most benefit patients with early-stage disease.
Methods

Data Source

Data were obtained from the SEER program administered by the National Cancer Institute. Seventeen tumor registries participate in the program. Combined, these sites provide a representative survey of the United States, approximating 26.0% of the population. This sampling is comparable to the general US population for a number of characteristics, including those of potentially at-risk groups. Information within the registry includes patient demographics (age, sex, and race), disease-related data (cancer site, tumor characteristics, and lymph node involvement), and first course of treatment (cancer-directed surgery and RT). Survival rate data are available through the SEER database via its linkage with the National Death Index, a centralized index of death records obtained through state vital statistics offices.

Study Cohort Inclusion and Exclusion Criteria

A retrospective cohort of patients with retroperitoneal and abdominal sarcoma was assembled based on SEER using the 1988-2005 data submission from the National Cancer Institute. Patients 18 years or older who had an initial diagnosis of primary retroperitoneal and nonvisceral abdominal sarcoma from January 1988 through December 2005 were included in the study. Disease diagnosis was established by using International Classification of Diseases for Oncology, Third Edition histology codes for primary site sarcoma coded as retroperitoneal or abdominal, including peritoneum, mesentery, or omentum (codes available on request from the corresponding author). For abdominal sarcoma, patients with nonvisceral sarcomas were included because of their similar histologic subtypes and a growth pattern of their sarcomas similar to those of retroperitoneal sarcomas. The heterogeneous groups of visceral, intestinal, or gastrointestinal stromal tumor subtypes, Kaposi sarcoma, and multiple hemorrhagic sarcomas were excluded. Subsequently, a locoregional disease cohort was generated by identifying patients coded in SEER as having local or regional disease, using the SEER_historic_stage_A variable.

Study Variables

For each patient, information was collected on nonidentifying demographics (age at diagnosis, sex, race, and marital status), year of diagnosis, location of tumor (abdominal vs retroperitoneal), disease status (localized, regional, or distant or metastatic), TNM classification and tumor grade, and type of treatment (surgical resection and/or RT). American Joint Committee on Cancer (AJCC) stage information in SEER is frequently missing or unknown. Therefore, for the purposes of our analyses of locoregional disease, a new variable (AJCC stage) was derived based on TNM classification and tumor grade information, as defined by the sixth edition of the AJCC Staging Manual. AJCC stage I (T1a-2b, N0, M0, grade I or II), stage II (T1a, 1b, 2a, N0, M0, grade III or IV), and stage III (T2b, N0, M0, grade III or IV).

Treatment Group Definition

Patients who were coded as receiving cancer-directed surgery with curative intent were defined as having surgical resection. Those who received only non–cancer-directed operations (eg, debulking, procedures directed at regional and/or distant sites or nodes, biopsy, exploration laparotomy, bypass, or ostomy) were considered not to have had surgical resection. For RT, patients who received preoperative, intraoperative or postoperative external beam radiation, radioisotopes, radioactive implants, or a combination of beam radiation with implants or isotopes were all classified as having had RT. SEER registries capture RT data for the first course of treatment or within 4 months of diagnosis, whichever is later. Information is not available regarding number of RT treatments.

Predictors of Treatment

A multivariate logistic regression model was used to identify independent predictors for receiving surgical resection or RT among patients with locoregional disease. Significance of individual variables, including patient information (age at diagnosis, sex, race, and marital status), tumor location (abdominal vs retroperitoneal), and tumor stage (AJCC stage I vs II/III), were examined in the model first through univariate analysis and then by a multivariate logistic regression model using backward selection. Odds ratios and 95% confidence intervals (CIs) of significant predictors for treatment type were reported from the final multivariate model.

Outcome

The primary study outcome was defined as death owing to all causes with total length of follow-up to 2 years from the initial diagnosis of sarcoma. If applicable, the date of death was ascertained. Data from patients who were alive by the end of 2 years were censored.

Survival Rate Analysis

Kaplan-Meier curves were first constructed to compare survival rates based on overall patient and disease characteristics (age category, sex, tumor location, and disease stage). Next, Kaplan-Meier survival rate analysis was performed for the subset of patients with local or regional disease, who were thus eligible for potentially curative therapy, including surgical resection and/or RT. Kaplan-Meier curves of patients who received surgical resection or RT alone, both treatments, or nei-
A total of 2504 patients with retroperitoneal and abdominal sarcomas were identified from the SEER database. Mean age was 62 years. A total of 1118 (47.4%) patients were male and 2055 (82.1%) were white. Retroperitoneal sarcomas were diagnosed in 2230 (89.1%) patients. Of the 2504 patients, 1901 (75.9%) had locoregional disease (Table 1). The remaining 603 patients had distant disease at diagnosis. Among patients with locoregional disease, 1547 (81.8%) had surgical resection, and 23.5% of these surgical patients also received RT. Sixty-four patients (3.4%) received only RT (Figure 1).

**RESULTS**

For patients with locoregional disease, an analysis of predictors of surgical resection showed that patient age, AJCC stage, and race were significant determinants. Older patients and patients with more advanced disease stage (AJCC stages II/III) were less likely to receive surgical resection, whereas white race was associated with a higher likelihood of receiving surgery.

Advanced stage (AJCC stages II/III) was a positive predictor for RT, as was retroperitoneal location. Older age, however, was associated with a lower likelihood of receiving RT. For both treatments, sex or diagnosis year appeared to be significant predictors. Neither treatment type independently predicted the other (Table 2).

**KAPLAN-MEIER SURVIVAL RATE ANALYSIS**

Kaplan-Meier survival rate analysis based on overall patient and disease characteristics showed significantly worse survival outcome in patients older than 80 years (P < .001, log-rank test) and with nonretroperitoneal disease (P = .002, log-rank test) (data not shown). Among the 1901 patients with locoregional disease, 589 deaths (31.0%) occurred during the 2-year follow-up period. Crude analysis based on Kaplan-Meier curves showed distinct differences in survival outcomes for patients who received both surgical treatment and RT vs surgery or RT alone vs neither, where the RT alone and neither treatment groups frequently represented patients with stage II and III disease and had the worst outcome. An overall significant difference was found in terms of median survival (P < .001, log-rank test) (Figure 2).

**LOCOREGIONAL DISEASE COHORT: COX REGRESSION ANALYSIS**

Univariate analysis based on Cox proportional hazards modeling showed significant survival benefit associated with either surgical resection (HR, 0.24; 95% CI, 0.21-0.29) or RT (0.78; 0.63-0.95) in patients with locoregional diseases. Older age, male sex, and advanced AJCC stage (II/III) were individually associated with higher risk of mortality (Table 3).

Multivariate analysis, adjusting for patient characteristics and year of diagnosis and stratified by AJCC stage (I vs II/III), showed survival benefit provided by surgical resection in the stage I and II/III groups, providing 65.0% to 76.0% risk reduction for mortality in locoregional disease (stage I: HR, 0.35; 95% CI, 0.21-0.58; stage II to III: 0.24; 0.18-0.32). The benefit of RT in addition to surgical resection was most pronounced in patients with AJCC stage I disease who had an additional 50.8% risk reduction (HR, 0.49; 95% CI, 0.25-0.96). No statistically significant independent benefit of RT in patients with stage II to III disease was found (HR, 0.78; 95% CI, 0.58-1.06; P = .11). Patient age but not tumor location was a significant risk factor for mortality in both the stage I and stage II to III groups. Furthermore, male sex and earlier year of diagnosis (1988-1993) appeared to be risk factors for poor outcomes in patients with stage II to III disease (Table 3).

**COMMENT**

Results from this large national cohort of patients with retroperitoneal and abdominal sarcomas showed that surgical resection was associated with a significant survival advantage in locoregional disease and that the benefit persisted.

![Diagram](image-url)
across both AJCC stage I and II/III disease groups. Radiotherapy provided a significant additional benefit for patients with AJCC stage I disease more than 2 years after diagnosis.

There is a paucity of literature evaluating the survival benefit provided by surgical resection and/or RT in treating retroperitoneal and abdominal sarcoma. Among patients with locoregional disease, surgical resection provides the only means of a potentially curative treatment. Given the high late recurrence rate of the disease, however, there has been a long controversy regarding the benefit of perioperative RT to treat residual disease after surgery. The results shown by different studies were varied. A previous study performed by Porter et al showed an overall relatively low use of adjuvant RT (25.9%) after retroperitoneal sarcoma surgery. A recent phase 3 randomized controlled trial to compare preoperative RT plus surgery vs surgery alone, conducted by the American College of Surgeons Oncology Group (ACOSOG Z9031), was prompted by a similar question, and the study is currently under way.

By using the national SEER database, which contains relatively comprehensive information regarding patient and tumor characteristics and survival rate data, we studied 2504 patients with retroperitoneal and abdominal sarcoma. Survival benefit of surgical resection and RT was evaluated among 1901 patients with locoregional disease who were thus eligible for potentially curative therapy to reduce confounding by disease severity. Of note, RT was primarily used in addition to surgical resection rather than as single-modality treatment. A 65.0% to 76.0% risk reduction in mortality was found to be associated with surgical resection in locoregional sarcoma, and a further 50.8% reduction was offered by the addition of RT to patients with AJCC stage I disease. Reduced benefit by RT (22.1% risk reduction) was found with AJCC stage II to III diseases and was no longer significant after adjusting for age, sex, race, and temporal trends. Although RT has been routinely recommended for patients with more advanced-stage disease to preoperatively or postoperatively address the issues of margin status and residual disease, our results suggest that RT may most benefit those patients with operable earlier-stage sarcoma.

Table 2. Predictors for Surgical Resection and Radiotherapy in Patients With Locoregional Disease From a Multivariate Logistic Regression Model (n=1246)*

<table>
<thead>
<tr>
<th>Predictor</th>
<th>(+) Treatment</th>
<th>(+) Treatment (Reference Category)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical resection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y (mean [SD])</td>
<td>61.0 (14.4)</td>
<td>66.5 (14.3)</td>
<td>0.97 (0.96-0.99)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AJCC stage II/III disease</td>
<td>468 (84.8)</td>
<td>635 (91.5)</td>
<td>0.54 (0.37-0.77)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Retroperitoneal location</td>
<td>1021 (80.3)</td>
<td>82 (91.1)</td>
<td>0.71 (0.33-1.51)</td>
<td>.37</td>
</tr>
<tr>
<td>Male sex</td>
<td>493 (87.1)</td>
<td>610 (89.7)</td>
<td>0.83 (0.58-1.18)</td>
<td>.29</td>
</tr>
<tr>
<td>White race</td>
<td>922 (89.5)</td>
<td>181 (83.8)</td>
<td>1.87 (1.22-2.87)</td>
<td>.004</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>279 (89.7)</td>
<td>824 (88.1)</td>
<td>1.21 (0.78-1.86)</td>
<td>.39</td>
</tr>
<tr>
<td>Diagnosis year, 1994-1999</td>
<td>318 (89.6)</td>
<td>785 (88.1)</td>
<td>0.80 (0.43-1.47)</td>
<td>.47</td>
</tr>
<tr>
<td>Diagnosis year, 2000-2005</td>
<td>596 (87.0)</td>
<td>507 (90.4)</td>
<td>0.69 (0.40-1.20)</td>
<td>.19</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age per year, mean (SD)</td>
<td>58.6 (13.3)</td>
<td>62.6 (14.7)</td>
<td>0.98 (0.97-0.99)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AJCC stage II/III disease</td>
<td>166 (30.1)</td>
<td>145 (20.9)</td>
<td>1.73 (1.33-2.26)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Retroperitoneal location</td>
<td>296 (25.6)</td>
<td>15 (16.7)</td>
<td>1.81 (1.01-3.25)</td>
<td>.04</td>
</tr>
<tr>
<td>Male sex</td>
<td>149 (26.3)</td>
<td>162 (23.8)</td>
<td>1.21 (0.93-1.57)</td>
<td>.16</td>
</tr>
<tr>
<td>White race</td>
<td>247 (24.0)</td>
<td>64 (29.6)</td>
<td>0.78 (0.56-1.08)</td>
<td>.14</td>
</tr>
<tr>
<td>Surgical resection</td>
<td>279 (25.3)</td>
<td>32 (22.4)</td>
<td>1.21 (0.79-1.87)</td>
<td>.38</td>
</tr>
<tr>
<td>Diagnosis year, 1994-1999</td>
<td>88 (24.8)</td>
<td>223 (25.0)</td>
<td>0.97 (0.64-1.46)</td>
<td>.88</td>
</tr>
<tr>
<td>Diagnosis year, 2000-2005</td>
<td>173 (25.3)</td>
<td>138 (24.6)</td>
<td>0.96 (0.66-1.39)</td>
<td>.82</td>
</tr>
</tbody>
</table>

Abbreviations: AJCC, American Joint Commission on Cancer; CI, confidence interval; OR, odds ratio.

*Data are given as number (percentage) of patients unless otherwise indicated. Excludes patients with missing data.

**AJCC stage I was the reference category.

Abdominal sarcoma was the reference category.

Diagnosis year, 1988-1993, was the reference category.

Figure 2. Kaplan-Meier curve of overall survival rate in patients with locoregional disease with or without surgery and/or radiotherapy.
Moreover, we do not anticipate the extent of surgery to regional diseases that are potentially surgically resectable. A relatively homogeneous patient population with locoregional reports. Our primary analysis was based on a retrospective and/or intraoperative), as 1 combined group of treatments, our results still suggested that initial surgery plus RT produced a better overall survival rate compared with surgery alone during a 2-year follow-up in stage I disease. We considered different radiotherapies, including time sequence of perioperative RT (eg, preoperative, postoperative and/or intraoperative), as 1 combined group of treatment in addition to surgery compared with surgery alone, and the current study did not try to discern treatment effect among different RT methods.

Second, there is a concern of lack of detailed operative reports. Our primary analysis was based on a relatively homogeneous patient population with locoregional diseases that are potentially surgically resectable. Moreover, we do not anticipate the extent of surgery to differ substantially between our comparison groups of surgery vs surgery plus RT in the initial treatment of locoregional disease, minimizing the concern of confounding in this case. As to the lack of knowledge on margin status in surgery, one could reasonably assume that patients with positive margins likely underwent more extensive surgical resection and were more likely to receive RT in addition to surgery. Although there might be an increased risk of recurrence and mortality associated with patients with positive margins in the surgery plus RT group, we were still able to show that combined treatment was superior to surgery alone in terms of overall survival rate during the study period (Figure 2). Therefore, the lack of knowledge of margin status is unlikely to change our conclusion. However, missing margin status limits our ability to assess disease-free survival rate as an outcome, if positive margin is associated with higher risk of recurrence, in which case margin status if available needs to be adjusted in the comparison to reduce potential bias. A similar argument pertains to the missing information about tumor histologic type. Despite the fact that different tumor histologic types may influence the choice of RT, and, hence, potentially heterogeneous RT responsiveness and outcomes in the surgery plus RT group, we were able to show that this group performed better than surgery alone in stage I disease.

Third, the SEER database does not contain information regarding chemotherapy that patients may have received. However, there is no obvious reason to suspect that chemotherapy would be broadly indicated outside a clinical trial among patients with locoregional disease, and their use, if any, would be substantially different across our 2 comparison groups.

Finally, we have shown the treatment effects on overall survival rate rather than progression-free survival rate during 2-year follow-up because of the lack of information regarding disease recurrence. Two-year follow-up was chosen a priori as a reasonable cutoff point because of concerns of greater loss to follow-up and compromised data quality associated with longer study duration.

Our results suggest that resection should be offered to all reasonable surgical candidates given the magnitude of survival benefit and that RT may most benefit those patients with operable stage I sarcoma. This finding suggests a need for improved tailoring of treatments for stage I retroperitoneal and abdominal sarcomas. Careful analyses of the results of currently ongoing and future randomized controlled trials are warranted to confirm and expand these findings.

Accepted for Publication: October 27, 2009. Correspondence: Jennifer F. Tseng, MD, MPH, Surgical Outcomes Analysis and Research (SOAR), University of Massachusetts Medical School, Worcester, MA 01655 (jennifer.tseng@umassmemorial.org). Author Contributions: Study concept and design: Zhou, McDade, Lambert, Shah, and Tseng. Acquisition of data: Zhou, Simons, Ng, Shah, and Tseng. Analysis and interpretation of data: Zhou, McDade, Ng, Lambert, Whalen, Shah, and Tseng. Drafting of the manuscript: Zhou. Critical revision of the manuscript for important intellectual content: Zhou, McDade, Simons, Ng, Lambert, Whalen, Shah, and Tseng. Statistical analysis: Zhou, Ng, and Tseng. Ob-

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REFERENCES