International Journal of
Radiation Oncology
biology • physics

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Retroperitoneal Sarcoma: Setting the Stage for Treatment Strategies Tailored to Histologic Subtype and Other Patient and Tumor Factors

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Received May 9, 2017. Accepted for publication May 15, 2017

The current standard of care for retroperitoneal sarcoma (RPS) is macroscopic complete resection. The appropriate extent of resection is somewhat debated (1), but most expert sarcoma surgeons favor aggressive extended resection to include adjacent organs such as colon, kidney, psoas muscle, distal pancreas, and spleen, to obtain adequate oncologic margins. Aggressive extended resection is endorsed by the Transatlantic RPS Working Group (2). The roles of radiation therapy (RT) and systemic therapy for RPS are unclear. There is a strong rationale for RT based on extrapolation from extremity and trunk soft tissue sarcoma data, but conclusive data demonstrating efficacy are lacking. Two recent large, retrospective reports demonstrated significant overall survival (OS) and local control benefits, respectively, with the addition of RT, but their validity is subject to the inherent limitations of retrospective analyses (3, 4). The European Organization for Research and Treatment of Cancer 62092 STRASS trial randomized patients with primary RPS to preoperative RT (50.4 Gy) followed by resection versus resection alone (5). The results of this well-designed trial are highly anticipated.

Several important publications in the past few years improve our understanding of the biologic behavior of RPS on the basis of specific tumor and patient factors. This new knowledge will inform treatment decision making and future trial design so we can appropriately tailor our treatment to the individual patient. The first article presents a nomogram to predict OS and disease-free survival (DFS) after resection for primary RPS (6). By incorporating many independent prognostic factors this tool improves predictive capabilities for outcome compared with the former (7th edition) American Joint Commission on Cancer staging system (7). There are currently no nomograms to predict local recurrence (LR), but the second article details patterns of local and distant recurrence (DR) based on histologic subtype (4). Better knowledge of prognosis and recurrence patterns will help guide management. For example, one could argue there will likely be a role for RT for histologic subtypes with a high propensity for LR and less of a role for subtypes with a low risk of LR.

Expert consensus groups strongly recommend that if RT is to be given, it should be given preoperatively; postoperative RT for RPS is strongly discouraged (2, 8). The conventional dose for preoperative RT is 50 Gy (8). To further improve local control, dose escalation is appealing; this is the subject of the third article, which presents the results of a phase 1 trial for RPS dose escalation using protons (9). The fourth article documents acute gastrointestinal (GI) toxicity for patients treated with conventional (50 Gy) preoperative RT and can serve as a benchmark for future studies, including those that will use dose escalation (10).

This is an exciting time for the study of RPS. Armed with better knowledge of RPS natural histories, the stage has been set for us to formulate and test new treatment strategies tailored to histologic subtype and other tumor and patient factors. In addition to disease outcomes, future studies should carefully evaluate toxicity and patient-reported quality of life outcomes. Given the rarity of RPS, this will require ongoing collaborations such as the Transatlantic RPS Working Group, which continues to grow and now comprises members from more than 50 institutions from North America, Europe, and Australia (A. Gronchi, personal communication, May 2017).

Int J Radiation Oncol Biol Phys, Vol. 99, No. 2, pp. 292–295, 2017
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2017.05.021

Gronchi et al. Outcome prediction in primary resected retroperitoneal soft tissue sarcoma: Histology-specific overall survival and disease-free survival nomograms built on major sarcoma center data sets. *J Clin Oncol* 2013. (6)

Summary: The purpose of this study was to build a nomogram to predict postoperative OS and DFS for patients with localized primary RPS. Patients who underwent resection with curative intent between 1999 and 2009 were included. The developing set included 523 patients from Istituto Nazionale dei Tumori, Milan; MD Anderson Cancer Center; and University of California, Los Angeles. Surgical resection was classified as macroscopically complete (R0/R1) or incomplete (R2). At the discretion of the treating team, chemotherapy was delivered to 40% of patients and RT to 37%. Median follow-up was 45 months. Seven-year OS was 47%, and 5-year DFS was 36%. Six significant prognostic factors were included in the nomogram for OS: age, tumor size, grade, histologic subtype, multifocality, and R0/1 versus R2 resection. Excluding patients who did not undergo complete resection, significant prognostic factors for the DFS nomogram were the same as those for OS with the exception of age, which dropped out. Grade was the most important prognostic factor, and inclusion of both grade and histologic subtype increased the nomogram predictive power. External validation was performed by applying the nomograms to a set of 135 patients who underwent resection at Institut Gustave-Roussy between 2001 and 2010. The predicted and observed outcomes were in good agreement for both nomograms, and prediction accuracy assessed by the Harrell *C* statistics (0.67, 0.68) was also very good.

Comments: The above nomogram for predicting OS and DFS after resection of primary RPS was further validated with a larger independent cohort from 6 sarcoma centers (11). This validation set included 631 patients from Brigham and Women's Hospital and Dana-Farber Cancer Institute, Mount Sinai Hospital and Princess Margaret Cancer Centre, Royal Marsden Hospital, Manheim University Hospital, Maria Sklodowska-Curie Memorial Cancer Center, and Netherlands Cancer Institute. All nomogram variables were confirmed to be independently prognostic, and the Harrell *C* statistics (0.69, 0.73) suggested good calibration of the nomogram and validation cohort. This robust nomogram provides more individualized estimates of OS and DFS and has been included in the 8th edition of the American Joint Commission on Cancer staging system for RPS (12). In the future, nomograms may be developed to predict local recurrence and distant recurrence, providing further data to help guide clinical protocols and treatments adapted to specific patient risk factors.

Gronchi et al. Variability in patterns of recurrence after resection of primary retroperitoneal sarcoma (RPS): A report on 1007 patients from the multi-institutional collaborative RPS Working Group. *Ann Surg* 2016. (4)

Summary: Gronchi et al report detailed patterns of recurrence and outcomes for 1007 patients with localized primary RPS who underwent resection by high-volume sarcoma surgeons at 6 European and 2 North American institutions between 2002 and 2011. Median follow-up was 58 months. Use of RT and chemotherapy was variable (18% and 32%, respectively.) For the entire cohort, 8-year OS was 56%. Significant independent predictors for OS included age, tumor size, completeness of resection, grade, and multifocality; the association between histologic subtype and OS showed a trend ($P = .07$). Eight-year crude cumulative incidence of LR for the entire cohort was 31%, and significant predictors included age, tumor size, completeness of resection, grade, tumor rupture, multifocality, delivery of RT, and histologic subtype. Eight-year crude cumulative incidence of distant metastasis was 22%, and significant predictors included tumor size, grade, multi-focality, and histologic subtype. Patterns of recurrence varied according to histologic subtype. Well-differentiated liposarcoma demonstrated the best OS (>80% at 8 years) and minimal risk of DR. Local recurrence was seen in at least one-third of patients; this risk was constant over time, and sarcoma deaths were all related to LR. On the other hand, leiomyosarcoma was associated with an 8-year OS of only 40%. Distant recurrence was most common for this histology (approximately 50% at 8 years), and conversely, LR was quite low (approximately 10% at 8 years.) Dedifferentiated liposarcoma showed behaviors in between those of well-differentiated liposarcoma and leiomyosarcoma. At 8 years, OS was 44%, LR was >40%, and DR was approximately 20%.

Comments: In the same issue of *Annals of Surgery*, Tan et al report very similar findings based on a single-institution series from Memorial Sloan-Kettering Cancer Center (13). This report included 675 patients with primary RPS who underwent resection between 1982 and 2010. Use of RT and chemotherapy was 8% and 18%, respectively. Median follow-up was 7.5 years. Reported patterns of recurrence according to histology were strikingly similar to those of Gronchi et al. Furthermore, histologic subtype was the most important predictor of disease-specific death, LR, and DR. As the authors of both studies appropriately point out, limitations include that they are retrospective, surgical strategy and use of adjuvant therapies was variable, and quality of life outcomes were not collected. Nonetheless, the detailed analyses and robust sample sizes of these studies provide valuable information about the different biologic behaviors of RPS histologic subtypes, and the data can serve as benchmarks for future studies.