Ann Surg Oncol (2016) 23:3440–3443
DOI 10.1245/s10434-016-5344-7

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – BONE AND SOFT TISSUE SARCOMAS

Guidelines for the Treatment of Recurrent Retroperitoneal Sarcoma: Are we Trying to Fit a Square Peg into a Round Hole?

Barry Feig, MD[1] and Robert Benjamin, MD[2]

[1]Department of Surgical Oncology, M.D. Anderson Cancer Center, Houston, TX; [2]Department of Medical Oncology, M.D. Anderson Cancer Center, Houston, TX

Soft tissue sarcoma is a rare disease that occurs in approximately 12,000 patients per year in the United States. Of that small population, only about 30 % of those tumors originate in the retroperitoneum.[1] This group is further subdivided by the unique finding of there being close to 100 separate histologic diagnoses that make up this group of patients.[2] The distinctiveness of behavior of each histologic subtype has only fairly recently become universally accepted.[3] These numbers serve to exemplify the rarity and uniqueness of treating soft tissue sarcoma, particularly those of the retroperitoneum.

This issue of *Annals of Surgical Oncology* includes an article that provides guidelines for the treatment of recurrent retroperitoneal sarcomas.[4] The current trend in clinical management is the creation of treatment guidelines for specific disease processes. The underlying hypothesis that guidelines derived from a subset of patients with the more common histologic subtypes can be generalized to all individuals within a disease group needs to be carefully scrutinized. In disease processes that are consistently definable and reproducible, guidelines provide an algorithmic, consistent approach to the practice of medicine. However, the use of guidelines can be potentially misleading, even harmful, particularly if applied to patients, tumors, or disease processes that do not quite fit the criteria for inclusion in the guidelines, leaving the potential for interpretative license in choosing which of the steps of the algorithm to apply and which to ignore. This is a realistic concern with retroperitoneal sarcoma. Unfortunately, with a rare disease such as sarcoma, it is extremely difficult to create guidelines that are able to be consistently reproduced for all of the variety of diagnoses that exist within the constellation of histologic subtypes that fall under the umbrella categorization of sarcoma. This is exemplified in the current series of published guidelines on the treatment of recurrent retroperitoneal sarcomas. In this article, these guidelines cover only five of the approximately 100 histologic diagnoses of sarcoma that exist. In general, the most useful guidelines are those based on the most robust clinical evidence. Unfortunately, the rarity of retroperitoneal sarcomas results in a paucity of data based on a high level of evidence. Of the 42 statements included in the current article, 52 % are based on level 5 evidence (studies without control groups, case reports, expert opinions) and 45 % are based on level 4 evidence (retrospective cohort studies or case–control studies). Only one statement is based on level 3 data (prospective cohort studies). This glaring lack of high-quality clinical data makes the generation of guidelines extremely subjective and therefore open to criticism and individual interpretation.

Although the guidelines in the current article cover the most common histologic diagnoses seen in this anatomic location (retroperitoneum), there are multiple other histologic diagnosis that can, and do, occur in the retroperitoneum. Even within each histologic grouping, the clinical behavior of these tumors can be extremely variable. For example, some have "pushing" margins, and there is a clear plane of dissection allowing the tumor to be separated from surrounding tissues and organs; others extensively infiltrate surrounding structures. Some present primary problems of local management; others can present with metastatic disease that would mitigate the influence that the extent of local resection has on outcome. What happens to the patient who comes to a "sarcoma center of excellence" that does not see a significant number of

First Received: 23 May 2016;
Published Online: 22 June 2016

B. Feig, MD
e-mail: bwfeig@mdanderson.org

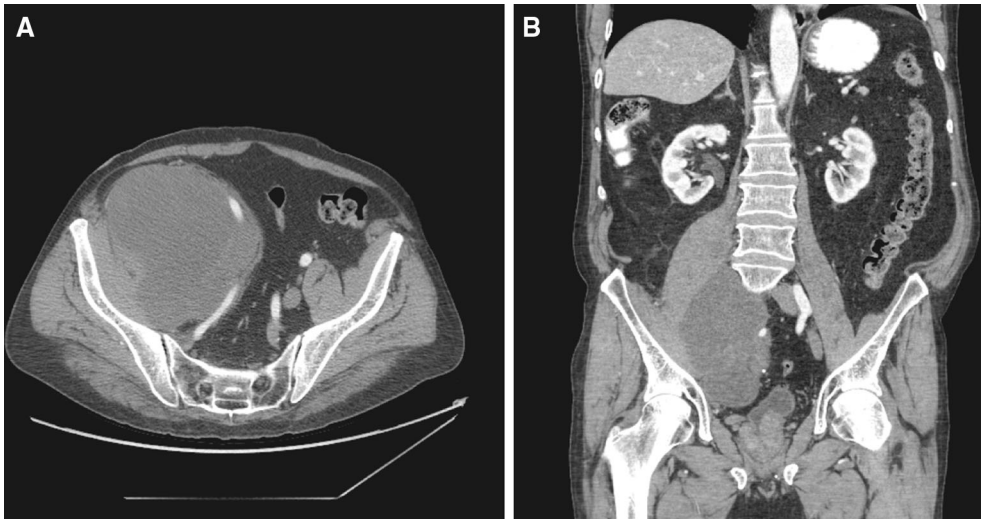

FIG. 1 Contrast-enhanced abdominal computed tomography depicting high-grade unclassified pleomorphic sarcoma. From (**a**) axial and (**b**) coronal images, this tumor could be arising from psoas muscle, iliacus muscle, or even iliac vasculature

retroperitoneal sarcomas on a regular basis, but the patient has one of the diagnoses that are not included within these guidelines? There exists the potential to try and fit one of these orphan diagnoses into the framework of the existing guidelines. This is clearly not an ideal clinical scenario and leaves the possibility of patients being led down an erroneous pathway. For example, a recurrence after the resection of a primary well-differentiated liposarcoma may be well-differentiated, dedifferentiated, or a mixture of both liposarcoma histologies. Often this histologic determination can be difficult, even for an experienced sarcoma pathologist, to make via a core needle biopsy. Frequently histologic definition is made from a combination of the pathologic and radiographic findings, with a heavy dose of clinical gestalt. This distinction can be clinically relevant as the patient with a well-differentiated recurrent liposarcoma might be observed or have surgery, while a dedifferentiated recurrent liposarcoma might be entered into a systemic therapy trial before surgery.

Although the concept of having a collaborative international effort to organize the thought processes and direction for the treatment of this rare disease has significant merit, the availability of generalized guidelines for public use is fraught with several additional potentially significant concerns. The Transatlantic Retroperitoneal Sarcoma Working Group (TARPWG) was established in 2013 by inviting representatives from 11 "high volume sarcoma centers" to participate.[5] It is not possible to determine how a high-volume center was defined by the group. Although nine centers agreed to participate (six from Europe and three from North America), it is notable that the two largest sarcoma centers in North America (MD Anderson Cancer Center and Memorial Sloan Kettering Cancer Center) have chosen not to participate in the generation of these guidelines. One potential concern is the inherent difficulty in being able to generalize the care of these patients—again, the result of the multiple histologic diagnoses and the rarity of the disease. These factors also necessitate a large volume of patients and a dedicated multidisciplinary team effort in order to truly have a sarcoma center of excellence. Because each one of the histologic diagnosis of sarcoma has its own unique behavior, a dedicated sarcoma pathologist is a necessity as part of this multidisciplinary sarcoma team. Even with that luxury, it is often extremely difficult to obtain a definitive pathologic diagnosis for many of these soft tissue tumors. This makes it problematic when trying to fit these individual patients, who have tumors that are difficult to categorize histologically, into the framework of general guidelines. The ability to have all of the components necessary to have a true sarcoma center of excellence is a rarity even at most large cancer centers.

This problem is highlighted in a recent publication from the TARPWG that looked at the variability in the patterns of recurrence of retroperitoneal sarcomas.[6] A specific subset analysis in this article evaluated outcomes stratified by the institution where the treatment was provided. This analysis was intended to illuminate whether different institutional strategic approaches to these tumors could potentially affect the outcome. Although eight institutions contributed data for this analysis, three of the centers had to be grouped together as a result of "limited numbers." Therefore, if three of the centers did not do enough sarcoma surgery at their own institutions to be individually evaluated, how we can be sure that these centers are experienced enough to truly be considered sarcoma centers

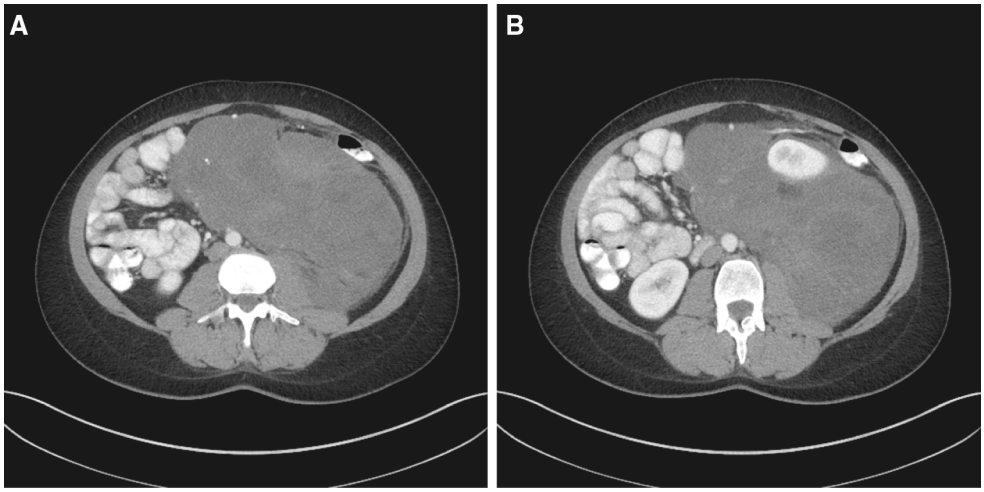

FIG. 2 Contrast-enhanced abdominal computed tomography depicting high-grade sarcoma. Based on imaging, tumor could be originating from colon, colonic mesentery, kidney, or psoas muscle

of excellence? This analysis also highlights the fact that there is still significant controversy as to the correct approach to the treatment of these tumors. The authors performed this institutional based analysis for only two histologic subtypes: well-differentiated liposarcoma and leiomyosarcoma. Even with only these two subtypes being evaluated, the treatment patterns (as pointed out by the authors) were not consistent across the institutions with respect to the administration of radiotherapy as well as in terms of the aggressiveness of surgery (reflected by the number of organs that were resected at the time of surgery). Although the authors might argue that these disparities may reflect the need for consistency within the treatment regimen of these tumors, an alternative argument could certainly be made that this is a reflection of the diversity and variability of this heterogeneous group of tumors both histologically and anatomically, which again makes it extremely difficult to have a regimented treatment algorithm for this disease.

In addition, in the current article, the authors include what they term "usual recurrent retroperitoneal sarcomas." By their definition, this includes "liposarcoma, leiomyosarcoma, solitary fibrous tumor, peripheral nerve sheath tumors, synovial sarcoma, etc." Inclusion of the term "etc." in this listing is concerning and serves to exemplify the variability of pathologic diagnosis and the inconsistency of these classifications. Additionally, the authors specifically include undifferentiated pleomorphic sarcomas (UPS) of the psoas muscle as a specific category. Does this imply that UPS tumors only originate from the psoas muscle or that these guidelines only apply to the UPS tumors that originate from the psoas muscle? As demonstrated in Fig. 1, it can be extremely difficult to tell where these tumors originate. Similar concerns are raised by the exclusion of "visceral sarcomas… arising from the gut or its mesentery" and "uterine LMS [leiomyosarcoma]," as the site of origin in these cases can often be difficult to differentiate as well. These tumors are frequently large and occupy a significant portion of the abdominal cavity with proximity to a number of organs within the region, making it extremely difficult to distinguish which is the primary tissue of origin and which organs are only secondarily abutted or invaded. Figure 2 is an example of a sarcoma that intraoperatively appeared to be arising from the mesentery of the left colon, but its tissue of origin could easily have been attributed to the kidney or colon. Additionally, at least 13 histologic subtypes are specifically excluded from these guidelines. With more histologic subtypes excluded than included, does this not demonstrate another example of the difficulty of trying to produce a concise treatment algorithm for retroperitoneal sarcomas due to the multiple histologies, the unique clinical behavior of each of these individual histologies, and the unique behavior based on the location of these tumors?

In the end, we must remember that guidelines are just that—guidelines. Not all disease processes are amenable to treatment by set guidelines; the variability of behavior, histologic subtype, and rarity of the tumor makes sarcoma less adaptable to this type of algorithmic approach. There is clearly a benefit to having extensive clinical experience, particularly with a rare, diverse group of tumors. Although guidelines can be beneficial in tumors that are well defined and have a consistent pattern of behavior, one would hope that the art of medical care is not being lost just because a suitable pathway is not available, or even worse, if good clinical judgment is being superseded by a pathway.

Therefore, when it is appropriate (as may be the case with sarcoma), we must resist the temptation to try and force a square peg to fit into a round hole.

DISCLOSURE The authors declare no conflict of interest.

REFERENCES

1. Siegel R, Miller K, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin.* 2016;66:7–30.
2. Crago A, Brennan M. Principles in management of soft tissue sarcoma. *Adv Surg.* 2015;49:107–22.
3. Anaya DA, Lahat G, Wang X, et al. Establishing prognosis in retroperitoneal sarcoma: a new histology-based paradigm. *Ann Surg Oncol.* 2009;16:667–75.
4. Trans-Atlantic RPS Working Group. Management of recurrent retroperitoneal sarcoma (RPS) in the adult: a consensus approach from the Trans-Atlantic RPS Working Group (TARPWG). *Ann Surg Oncol.* 2016. doi:10.1245/s10434-016-5336-7.
5. Management of primary retroperitoneal sarcoma (RPS) in the adult. A consensus approach from the Transatlantic RPS Working Group. *Ann Surg Oncol.* 2015;22:256–63.
6. Gronchi A, Strauss D, Miceli R. 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;263:1002–9.