New research strategies in retroperitoneal sarcoma: the case of TARPSWG, STRASS and RESAR - making progress through collaboration.

Houdt, W.J. van; Raut, C.P.; Bonvalot, S.; Swallow, C.J.; Haas, R.; Gronchi, A.

New research strategies in retroperitoneal sarcoma. The case of TARPSWG, STRASS and RESAR: making progress through collaboration

Winan J. van Houdt[a], *Chandrajit P. Raut*[b], *Sylvie Bonvalot*[c], *Carol J. Swallow*[d], *Rick Haas*[e], *and Alessandro Gronchi*[f]

Purpose of review
Retroperitoneal sarcoma (RPS) is a rare disease, and until recently, its natural history and outcome were poorly understood. Recently, collaborations between individual centers have led to an unprecedented collection of retrospective and prospective data and successful recruitment to the first randomized trial as described here.

Recent findings
A debate about the beneficial role of extended surgery in RPS triggered an initial collaboration between Europe and North America, the TransAtlantic RetroPeritoneal Sarcoma Working Group (TARPSWG). This collaboration has been instrumental in harmonizing the surgical approach among expert centers, characterizing the pattern of postresection failure of the different histological subtypes, identifying new ways to stage RPS and testing the role of preoperative radiotherapy in a randomized fashion (STRASS-1 study). The collaboration has now expanded to include centers from Asia, Australia and South America. A prospective registry has been started and a new randomized trial, STRASS-2, is in preparation to analyze the role of neoadjuvant chemotherapy for high-grade liposarcoma and leiomyosarcoma of the retroperitoneum.

Summary
Collaboration is critical to study a rare disease like RPS. Both retrospective and prospective data are useful to improve knowledge, generate hypotheses and build evidence to test, whenever possible, in clinical trials.

Keywords
leiomyosarcoma, liposarcoma, neoadjvuant chemotherapy, neoadjuvant radiotherapy, retroperitoneal sarcoma, sarcoma

INTRODUCTION

Retroperitoneal sarcomas (RPS) account for 15% of all soft tissue sarcoma [1], with an incidence of around 0.5–1 case per 100 000 [2]. Liposarcoma, either well differentiated or dedifferentiated (WDLPS or DDLPS), is the most frequent histological subtype (50-63%), followed by leiomyosarcoma (LMS) (19–23%) [3,4]. Other less frequent soft tissue sarcoma subtypes in the retroperitoneum include solitary fibrous tumor (SFT), malignant peripheral nerve sheath tumor (MPNST), synovial sarcoma and undifferentiated pleomorphic sarcoma (UPS). [3,4]. Most of the information regarding the behavior and treatment of retroperitoneal sarcoma was drawn from case series, often with a limited number of patients. This was partly because of lack of centralization of RPS care to experienced centers, and also to lack of collaboration, with only a few centers able to publish large case series. However, over the past decade, collaborations have intensified leading to a new era of extensive shared data collection as well

[a]Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands, [b]Department of Surgery, Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA, [c]Department of Surgery, Institute Curie, Paris, France, [d]Department of Surgical Oncology, Princess Margaret Cancer Centre, and Department of Surgery, Mount Sinai Hospital, University of Toronto, Toronto, Canada, [e]Department of Radiotherapy, Netherlands Cancer Institute, Amsterdam, and the LUMC, Leiden, the Netherlands and [f]Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Correspondence to Alessandro Gronchi, MD, Chair Sarcoma Service, Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian 1, 20133 Milan, Italy. Tel: +39 223903234; e-mail: alessandro.gronchi@istitutotumori.mi.it

Curr Opin Oncol 2019, 31:310–316
DOI:10.1097/CCO.0000000000000535

KEY POINTS

- The growing collaboration between major retroperitoneal sarcoma referral centers has been critical to advance the field.
- The initial approach has been ameliorated and harmonized worldwide, with a gain in local control and survival of at least 20%.
- Merging large data sets from the participating institutions has allowed to understand the variegated histologic subtypes and their different outcome.
- A first randomized study, addressing the role of neoadjuvant radiotherapy, has recently met its target accrual and results are awaited soon. A second randomized study, addressing the role of chemotherapy in selected histologic subtypes, is under preparation. This would have never been possible if the collaboration above had not been established.
- A prospective registry has also been started to collect standardized clinical data as well as radiologic and pathologic material from primary RPS patients who undergo resection at the collaborating centers. Registry-based randomized studies, in addition to conventional randomized studies, can potentially be built within the registry in order to be able to fully exploit these high-quality observational data, and put the data from conventional RCTs into broader perspective.

as initiation of prospective studies resulting in a deeper understanding of the variety and complexity of this rare malignancy.

DEBATING THE SURGICAL APPROACH TO PRIMARY DISEASE: THE FIRST TRANSATLANTIC COLLABORATION

The only curative treatment for primary RPS is surgery. Some 10 years ago, two major sarcoma centers reported that extended resections were associated with significantly reduced local recurrence (LR) rates and an overall survival (OS) benefit when compared with more conservative conventional approaches [5,6]. These studies were retrospective and generated a lively debate between European and North American sarcoma surgeons [7,8], triggering the first transatlantic collaboration (Trans-Atlantic RetroPeritoneal Sarcoma Working Group, TARPSWG). This culminated in the development of the first consensus guidelines about the management of primary RPS [2], based on shared experience amongst experts. The consensus stated that the best chance of resection with curative intent is at the time of primary presentation and that surgery should be aimed at achieving macroscopically complete resection with a single specimen encompassing the tumor en bloc with adherent organs/structures even if not overtly infiltrated, as a relatively liberal approach towards performing a multivisceral resection was associated with improved outcome [9–19]. Preservation of specific organs should be considered on an individualized basis and mandates a specific disease and broad technical expertise to make the appropriate decisions given the overall tumor extent/expected biology[20], anticipated morbidity and the individual patient's characteristics [21▪]. This approach was associated with 5-year LR rates for all retroperitoneal sarcomas subtypes ranging from 20 and 30%, which compares favorably with the historical 50–60% reported in all series published prior to 2009; distant metastases (DM) rates were between 21 and 33% [22–25]. This consensus was critical to harmonize the surgical approach to this disease internationally, which was particularly important given that the STRASS-1 study (see below) started to recruit soon after the development of this consensus. Given the complexity of the approach described above, an initiative to regionalize RPS care also began, in order to improve RPS patient outcomes. Recent national registry data have shown how surgery in high-volume specialized centers is associated with improved survival. [4,5,26,27,28▪].

UNDERSTANDING THE PATTERN OF FAILURE OF THE DIFFERENT HISTOLOGICAL SUBTYPES AND PREDICTING OUTCOMES FOLLOWING RESECTION

RPS is not a single disease. The first large multi-institutional collection of 1007 cases treated over a 10-year time frame in the initial TARPSWG centers was critical to our deeper understanding of the natural history of this family of diseases [4]. OS at 5 years following resection was found to be between 60 and 70% with a significant variation between histologic subtypes. For WDLPS and DDLPS, the 5-year LR rates were found to be approximately 20 versus 40% [3,4], whereas the DM rates were 1 versus 20%, and OS was 90 versus 60%, respectively. In addition, DDLPS can be further separated according to FNCLCC grade into two subgroups: G2 DDLPS are characterized by a predominantly local risk (5-year LR and DM rates 40 and <10%), whereas G3 DDLPS have a predominantly systemic risk (5-year LR and DM rates 30 and 40–50%, respectively). This is in contrast to other histological subtypes, such as LMS with a 5-year LR rate less than 10%, a DM rate of 50% and OS of around 55%. The description of the

differences in outcome has now become critical to interpret/design studies, as well as to counsel patients in the clinic [3,4].

In addition, prognostic factors for better disease-free survival (DFS) and OS have now been established to include lower grade, histological subtype (e.g. WDLPS, Grade 2 DDLPS, SFT), younger age, completeness of resection, smaller tumor size, absence of multifocal disease, avoidance of intraoperative tumor transgression and also treatment in a high-volume sarcoma center [4,5,12,29]. To better personalize prognostic information, these shared data sets were utilized to build and validate new prognostic nomograms. These nomograms are able to calculate the risk of recurrence and death after resection for primary or recurrent RPS, and are also available through an app, free to download for tablet and smartphones (www.sarculator.org) [30–34,35▪▪]. These nomograms have also been recognized by the most recent edition of the American Joint Committee on Cancer (AJCC) staging system as an alternative way to stage RPS, distinct from the more traditional TNM staging. Such nomograms have the potential to be used to stratify patients in future clinical trials.

THE ROLE OF RADIOTHERAPY FOR PRIMARY RETROPERITONEAL SARCOMA: THE STRASS-1 TRIAL

Due to the rarity and heterogeneity of RPS, it had been very difficult to run randomized controlled trials, leading to a lack of high-level evidence for any treatment strategy [36]. Given the high rate of LR after resection of RPS, especially in the case of liposarcoma, a study for which the rationale seemed most compelling was the evaluation of the addition of radiotherapy to surgery, with the intent of reducing LR rates. This would have been consistent with the proven role of (neo)adjuvant radiotherapy in the management of extremity sarcoma, but for RPS retrospective and single-arm prospective studies had provided conflicting results [5,37–41]. The improved collaboration between specialized sarcoma centers led to the successful recruitment of patients onto the STRASS-1 trial (EORTC 62092-22092, NCT01344018), a phase 3 multicenter randomized trial of preoperative radiation therapy followed by surgery versus surgery alone for primary RPS. This trial recruited over a period of 6 years, and closed after target accrual was met; the initial results are eagerly awaited. This is the first randomized controlled trial ever to be completed in RPS, illustrating the benefits of increased collaboration between expert centers. However, at the time of the STRASS-1 trial design, the decision was taken to include all histological subtypes and all grades, as – given the rarity of the disease – there were concerns about the feasibility of the study as a previous very similar study, ACOSOG Z9031, initiated in North America 10 years previously, failed to accrue more than a handful of patients, and was closed. Furthermore, our more sophisticated understanding of the different patterns of failure and survival and potential role of radiotherapy was gained on after STRASS-1 recruitment had begun [42▪▪]. Thus, the STRASS-1 trial will address the impact of preoperative radiotherapy on local outcome in the whole family of RPS, but it will not be able to discriminate the benefit by subtype or by grade. Hypothetically, a new study design would be required to further address the radiotherapy question for specific indications, such as tumors with a high LR rate (low-grade liposarcoma) or tumors highly sensitive to radiations (SFT) [43] Of note, in the centers that participated in STRASS-1, only 20–30% of the primary RPS patients treated at those centers were recruited onto the trial [44]. Data of patients not included in STRASS-1 were not uniformly prospectively collected, and therefore, cannot be formally used to put STRASS-1 results into perspective as far as the understanding of the role of radiotherapy in the different histological subtypes is concerned. However, these data are retrieved through the prospectively maintained databases held at most of the participating institution and this parallel analysis (the STREXIT study) will be critical for generating new hypotheses.

A PROSPECTIVE REGISTRY FOR PRIMARY RETROPERITONEAL SARCOMA: THE RESAR STUDY

The collaboration amongst sarcoma centers has now spread beyond Europe and North America to include centers in Asia, Australia and South America. The group has recently been renamed Transatlantic Australasian RetroPeritoneal Sarcoma Working Group (keeping the same acronym TARPSWG). A prospective TARPSWG registry was established as of January 2017 (RESAR, NCT03838718). This registry aims to prospectively collect standardized clinical data as well as radiologic and pathologic material from primary RPS patients who undergo resection at reference centers. Patient outcomes will be tracked in terms of OS, DFS, crude cumulative incidence (CCI) of LR and DM. In addition, analysis of the data gleaned from this prospective shared registry will allow surgeons to: estimate the efficacy and safety of surgical treatment including the extended surgical approach to primary RPS; evaluate the impact of multimodality therapy, including radiation therapy

and chemotherapy; identify clinical, radiologic and pathologic characteristics that may influence the oncologic outcome or may be used as predictors of LR/DM/OS; utilize collected pathologic material for collaborative research.

Finally, registry-based randomized studies, in addition to conventional randomized studies, can potentially be built within the registry in order to be able to fully exploit these high-quality observational data, and put the data from conventional RCTs into broader perspective.

NEOADJUVANT CHEMOTHERAPY FOR HIGH-RISK RETROPERITONEAL SARCOMA: STRASS 2

While waiting for the results of STRASS-1, we decided to address the question of the possible role of neoadjuvant chemotherapy in the subgroups of RPS with a high metastatic potential: high-grade DDLPS and LMS. An attempt to formally study the possible benefit of chemotherapy in these high-risk histologic subtypes has not previously been performed. A second randomized study is, therefore, in preparation: the EORTC-1809-STBSG – STRASS 2 study, intended to be an international randomized multicenter, open-label phase 3 trial, with stratification by specific tumor histology and including only high-grade DDLPS and LMS. The aim is to evaluate whether neoadjuvant chemotherapy reduces the development of DM in these well defined histologic entities. It will be the first time that a randomized controlled neoadjuvant trial will include only high-grade RPS and only two specific histological subtypes. This means that a biopsy before surgery, which has been shown to be safe [45,46▪,47], is mandatory prior to trial enrolment. Thanks to the collaboration between EORTC STBSG and TARPSWG the success of STRASS-1, encourages the collaborative network to believe that such a focused trial is in fact feasible.

In addition, another novelty of STRASS-2 is to select two slightly different chemotherapy regimens for the two histological subtypes included in the study. Anthracycline-based chemotherapy is still the cornerstone of first-line treatment in localized soft tissue sarcoma [48]. For patients with good performance status, it is usually combined with ifosfamide, and the combination is standard of care when neoadjuvant treatment is given in most sarcoma types. Therefore, this regimen is chosen as the chemotherapy arm for high-grade LPS. However, in LMS, there is growing retrospective evidence that ifosfamide should be substituted with dacarbazine, consistent with the results of a recent large retrospective comparison among different anthracycline-based regimens in the first-line management of advanced leiomyosarcoma [49,50]. The neoadjuvant setting is preferred over the adjuvant setting for RPS, as patients will have to undergo a major abdominal procedure with a high chance to lose one kidney. Moreover, preliminary evidence of efficacy of neoadjuvant anthracycline–ifosfamide chemotherapy in extremity high-risk soft tissue sarcoma has been published. Also, the neoadjuvant setting provides insight into response with the tumor *in situ*, with potential for greater insight into clinical consequences, prognostic information and research opportunities.

Two interim analyses for futility are foreseen in the study design, in order to be able to detect histotype-specific effects, which will allow for extending the trial for one of the histotypes if necessary. The interim analyses will be after approximately 40 and 67% of events have occurred (around 4 and 5 years after the first patient is enrolled, respectively). These time points were strategically chosen to facilitate the collection of sufficient evidence, but also allow for adaptation while the study is still recruiting patients in the event that the effect of preoperative chemotherapy is limited to one histotype.

In addition to understanding the impact of neoadjuvant chemotherapy on DFS and OS, this study will also be used for various imaging, translational research and quality-of-life projects. Also, the RESAR registry for all primary RPS will be formally linked to STRASS-2. This will allow the comparison of real-life data to randomized data, to provide an overview of all possible data and maximize the information gained and to optimize our ability to generate new hypotheses.

TREATMENT OF RECURRENT DISEASE

Treatment of locally recurrent or residual RPS is difficult [51▪], and so is proper research for this groups of patients. Recently, a consensus paper has been published by the TARPSWG group discussing the treatment options for these patients [52]. Again, although this is a very valuable article, many of the recommendations were based on opinions amongst experts, rather than on high level evidence. However, this effort was followed by the collection of a large retrospective series of patients treated at several institutions in the TARPSWG collaborative [53]. The analysis of this large multi-institutional series has aided the understanding of the role of surgery at first recurrence and the outcome of the different histological subtypes after a second resection. A novel specific nomogram for outcome following resection of recurrent

RPS has been developed and is available from the 'Sarculator' app [35▪▪]. In addition, data on perioperative morbidity as well as outcome after second recurrence will be provided. These data will be the historical benchmark against which to test any possible new multimodal treatment regimen, and will help to generate new hypotheses to test prospectively, ideally in a randomized fashion.

SYSTEMIC TREATMENT FOR METASTASTIC OR LOCALLY ADVANCE DISEASE

The mainstay of management of metastatic RPS remains palliative chemotherapy, and no new strategy has been developed specifically for RPS. Currently, anthracycline-based therapy remains standard first-line treatment [54–56]. Median overall survival for patients with inoperable soft tissue sarcomas treated with chemotherapy is limited to 15–19 months. Recently, a number of agents have emerged as second–line treatment, including gemcitabine/docetaxel, high-dose ifosfamide monotherapy, trabectedin, pazopanib and eribulin [57–59,60▪▪,61,62]. For leiomyosarcoma, doxorubin combined with dacarbazine seems a relatively valid strategy, although it has never been properly evaluated in a randomized controlled trial [49]. The CDK4 and MDM2 amplifications in well and dedifferentiated liposarcomas have been targeted in single-arm trials evaluating their respective inhibitors, showing some activity in terms of disease stabilization [63] Currently, the European EORTC-1202-STBSG is evaluating cabazitaxel in metastatic or recurrent dedifferentiated liposarcoma. This single arm phase 2 study has met its accrual and we are currently awaiting the results. Finally, a large United States-based pharma-sponsored trial is currently accruing patients for unresectable dedifferentiated liposarcoma, testing the KCP-330-020 compound (Selinexor, XPO1 inhibitor) in a phase 3 randomized controlled trial (NCT02606461)

CONCLUSION

An international collaborative between reference centers dedicated to optimizing the treatment of RPS was started 10 years ago and has resulted in a better understanding of this rare disease. A new study of neoadjuvant chemotherapy (STRASS-2) is presently planned. This will be linked to a parallel observational study based on prospectively collected registry data (RESAR) of patients not in the trial. Both the trial and the registry will be used as a platform to initiate many auxiliary studies including examination of imaging, radiomics, tumor biology and new quality-of-life tools for RPS. A close collaboration between academic networks and partners from the pharmaceutical industry, as well as patient advocates, will be essential to study new compounds in a similar histotype-specific fashion in recurrent or metastatic RPS.

Acknowledgements

None.

Financial support and sponsorship

The STRASS-1 study was partially funded through a European Union grant (Eurosarc FP7 278472).

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Brennan MF, Antonescu CR, Moraco N, Singer S. Lessons learned from the study of 10,000 patients with soft tissue sarcoma. Ann Surg 2014; 260:416–421.
2. Trans-Atlantic RPSWG. Management of primary retroperitoneal sarcoma (RPS) in the adult: a consensus approach from the Trans-Atlantic RPS Working Group. Ann Surg Oncol 2015; 22:256–263.
3. Tan MC, Brennan MF, Kuk D, *et al.* Histology-based classification predicts pattern of recurrence and improves risk stratification in primary retroperitoneal sarcoma. Ann Surg 2016; 263:593–600.
4. Gronchi A, Strauss DC, Miceli R, *et al.* Variability in patterns of recurrence after resection of primary retroperitoneal sarcoma (RPS): a report on 1007 patients from the Multiinstitutional Collaborative RPS Working Group. Ann Surg 2016; 263:1002–1009.
5. Bonvalot S, Rivoire M, Castaing M, *et al.* Primary retroperitoneal sarcomas: a multivariate analysis of surgical factors associated with local control. J Clin Oncol 2009; 27:31–37.
6. Gronchi A, Lo Vullo S, Fiore M, *et al.* Aggressive surgical policies in a retrospectively reviewed single-institution case series of retroperitoneal soft tissue sarcoma patients. J Clin Oncol 2009; 27:24–30.
7. Pollock RE. Extended surgery for retroperitoneal sarcoma: too much surgery for some and not enough for others? Con. Oncology (Williston Park) 2013; 27:641–642.
8. Gronchi A. Extended surgery for retroperitoneal sarcoma: the key to maximizing the potential for cure and survival. Pro Oncology (Williston Park) 2013; 27:640; 642.
9. Gronchi A, Miceli R, Allard MA, *et al.* Personalizing the Approach to Retroperitoneal Soft Tissue Sarcoma: Histology-specific Patterns of Failure and Postrelapse Outcome after Primary Extended Resection. Ann Surg Oncol 2014; 1447–1454.
10. Gronchi A, Miceli R, Allard MA, *et al.* Personalizing the approach to retroperitoneal soft tissue sarcoma: histology-specific patterns of failure and postrelapse outcome after primary extended resection. Annal Surg Oncol 2015; 22:1447–1454.
11. Stoeckle E, Coindre JM, Bonvalot S, *et al.,* French Federation of Cancer Centers Sarcoma Group. Prognostic factors in retroperitoneal sarcoma: a multivariate analysis of a series of 165 patients of the French Cancer Center Federation Sarcoma Group. Cancer 2001; 92:359–368.
12. Strauss DC, Hayes AJ, Thway K, *et al.* Surgical management of primary retroperitoneal sarcoma. Br J Surg 2010; 97:698–706.
13. Bonvalot S, Raut CP, Pollock RE, *et al.* Technical considerations in surgery for retroperitoneal sarcomas: position paper from E-Surge, a master class in sarcoma surgery, and EORTC-STBSG. Ann Surg Oncol 2012; 19:2981–2991.
14. Gladdy RA, Gupta A, Catton CN. Retroperitoneal sarcoma: fact, opinion, and controversy. Surg Oncol Clin N Ame 2016; 25:697–711.

15. Miah AB, Hannay J, Benson C, *et al.* Optimal management of primary retroperitoneal sarcoma: an update. Exp Rev Anticancer Ther 2014; 14:565–579.

16. Swallow CJ, Catton CN. Improving outcomes for retroperitoneal sarcomas: a work in progress. Surg Oncol Clin N Am 2012; 21:317–331.

17. Singer S, Antonescu CR, Riedel E, Brennan MF. Histologic subtype and margin of resection predict pattern of recurrence and survival for retroperitoneal liposarcoma. Ann Surg 2003; 238:358–370.

18. van Houdt WJ, Zaidi S, Messiou C, *et al.* Treatment of retroperitoneal sarcoma: current standards and new developments. Curr Opin Oncol 2017; 29:260–267.

19. Messiou C, Moskovic E, Vanel D, *et al.* Primary retroperitoneal soft tissue sarcoma: imaging appearances, pitfalls and diagnostic algorithm. Eur J Surg Oncol 2016; 43:1191–1198.

20. Fairweather M, Wang J, Jo VY, *et al.* Incidence and Adverse prognostic implications of histopathologic organ invasion in primary retroperitoneal sarcoma. J Am Coll Surg 2017; 224:876–883.

21. MacNeill AJ, Gronchi A, Miceli R, *et al.* Postoperative morbidity after radical
■ resection of primary retroperitoneal sarcoma: a report from the Transatlantic RPS Working Group. Ann Surg 2018; 267:959–964.

This article describes factors correlated with higher morbidity after surgery for retroperitoneal sarcoma.

22. Lehnert T, Cardona S, Hinz U, *et al.* Primary and locally recurrent retroperitoneal soft-tissue sarcoma: local control and survival. Eur J Surg Oncol 2009; 35:986–993.

23. Bonvalot S, Miceli R, Berselli M, *et al.* Aggressive surgery in retroperitoneal soft tissue sarcoma carried out at high-volume centers is safe and is associated with improved local control. Ann Surg Oncol 2010; 17:1507–1514.

24. Lewis JJ, Leung D, Woodruff JM, Brennan MF. Retroperitoneal soft-tissue sarcoma: analysis of 500 patients treated and followed at a single institution. Ann Surg 1998; 228:355–365.

25. Hassan I, Park SZ, Donohue JH, *et al.* Operative management of primary retroperitoneal sarcomas: a reappraisal of an institutional experience. Ann Surg 2004; 239:244–250.

26. Gutierrez JC, Perez EA, Moffat FL, *et al.* Should soft tissue sarcomas be treated at high-volume centers? An analysis of 4205 patients. Ann Surg 2007; 245:952–958.

27. van Dalen T, Hennipman A, Van Coevorden F, *et al.* Evaluation of a clinically applicable postsurgical classification system for primary retroperitoneal soft-tissue sarcoma. Ann Surg Oncol 2004; 11:483–490.

28. Keung EZ, Chiang YJ, Cormier JN, *et al.* Treatment at low-volume hospitals is
■ associated with reduced short-term and long-term outcomes for patients with retroperitoneal sarcoma. Cancer 2018; 124:4495–4503.

This article illustrates the potential oncological benefit of centralizing care for retroperitoneal sarcoma to experienced center.

29. Gronchi A, Lo Vullo S, Colombo C, *et al.* Extremity soft tissue sarcoma in a series of patients treated at a single institution: local control directly impacts survival. Ann Surg 2010; 251:506–511.

30. Pasquali S, Gronchi A. Neoadjuvant chemotherapy in soft tissue sarcomas: latest evidence and clinical implications. Ther Adv Med Oncol 2017; 9:415–429.

31. Pasquali S, Pizzamiglio S, Touati N, *et al.,* EORTC – Soft Tissue and Bone Sarcoma Group. The impact of chemotherapy on survival of patients with extremity and trunk wall soft tissue sarcoma: revisiting the results of the EORTC-STBSG 62931 randomised trial. Eur J Cancer 2019; 109:51–60.

32. Tattersall HL, Callegaro D, Ford SJ, Gronchi A. Staging, nomograms and other predictive tools in retroperitoneal soft tissue sarcoma. Chin Clin Oncol 2018; 7:36.

33. Callegaro D, Miceli R, Mariani L, *et al.* Soft tissue sarcoma nomograms and their incorporation into practice. Cancer 2017; 123:2802–2820.

34. Callegaro D, Miceli R, Gronchi A. Sarcoma nomograms: a light over the darkness. Oncoscience 2017; 4:15–16.

35. Raut CP, Callegaro D, Miceli R, *et al.* Predicting survival in patients under-
■■ going resection for locally recurrent retroperitoneal sarcoma: a study and novel nomogram from TARPSWG. Clin Cancer Res 2019; doi: 10.1158/1078-0432.CCR-18-2700. [Epub ahead of print]

This article describes the role of a nomogram to predict outcome after resection of locally recurrent retroperitoneal sarcomen, which can be of added value in the clinical decision-making process regarding treatment of these patients.

36. ACOSOG Protocol Z9031: a phase III randomized study of preoperative radiation plus surgery versus surgery alone for patients with retroperitoneal sarcomas (RPS); 2014. Available at: http://clinicaltrials.gov/show/NCT00091351.

37. Jones JJ, Catton CN, O'Sullivan B, *et al.* Initial results of a trial of preoperative external-beam radiation therapy and postoperative brachytherapy for retroperitoneal sarcoma. Ann Surg Oncol 2002; 9:346–354.

38. Van De Voorde L, Delrue L, van Eijkeren M, De Meerleer G. Radiotherapy and surgery-an indispensable duo in the treatment of retroperitoneal sarcoma. Cancer 2011; 117:4355–4364.

39. Tseng WH, Martinez SR, Do L, *et al.* Lack of survival benefit following adjuvant radiation in patients with retroperitoneal sarcoma: a SEER analysis. J Surg Res 2011; 168:e173–e180.

40. Nussbaum DP, Rushing CN, Lane WO, *et al.* Preoperative or postoperative radiotherapy versus surgery alone for retroperitoneal sarcoma: a case-control, propensity score-matched analysis of a nationwide clinical oncology database. Lancet Oncol 2016; 17:966–975.

41. Pisters PW, Ballo MT, Fenstermacher MJ, *et al.* Phase I trial of preoperative concurrent doxorubicin and radiation therapy, surgical resection, and intraoperative electron-beam radiation therapy for patients with localized retroperitoneal sarcoma. J Clin Oncol 2003; 21:3092–3097.

42. Haas RLM, Bonvalot S, Miceli R, *et al.* Radiotherapy for retroperitoneal
■■ liposarcoma: a report from the Transatlantic Retroperitoneal Sarcoma Working Group. Cancer 2019; doi: 10.1002/cncr.31927. [Epub ahead of print]

This article describes the role of radiotherapy in the treatment of retroperitoneal sarcoma with data from a large retrospective database for the TARPSWG collaboration. Although in univariate analysis, radiotherapy seems beneficial, this effect disappears after multivariate analysis.

43. Haas RL, Walraven I, Lecointe-Artzner E, *et al.* Radiation therapy as sole management for solitary fibrous tumors (SFT): a retrospective study from the Global SFT Initiative in collaboration with the sarcoma patients EuroNet. Int J Radiat Oncol Biol Phys 2018; 101:1226–1233.

44. Raut C, Strauss D, Haas R, *et al.* Why primary retroperitoneal sarcoma (PRPS) patients (PTS) undergoing treatment at STRASS institutions did not enroll in STRASS: the STREXIT STUDY from EORTC STBSG AND TARPSWG. In: CTOS Annual Meeting, 2018, p. 135.

45. Van Houdt WJ, Schrijver AM, Cohen-Hallaleh RB, *et al.* Needle tract seeding following core biopsies in retroperitoneal sarcoma. Eur J Surg Oncol 2017; 43:1740–1745.

46. Almond LM, Tirotta F, Tattersall H, *et al.* Diagnostic accuracy of percutaneous
■ biopsy in retroperitoneal sarcoma. Br J Surg 2019; 106:395–403.

This article describes the discrepancy between the diagnosed grade on biopsy and the final grade as determined after resection frequently leading to undergrading of the tumor on biopsy.

47. Berger-Richardson D, Swallow CJ. Needle tract seeding after percutaneous biopsy of sarcoma: risk/benefit considerations. Cancer 2017; 123:560–567.

48. Frustaci S, Gherlinzoni F, De Paoli A, *et al.* Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. J Clin Oncol 2001; 19:1238–1247.

49. D'Ambrosio L, Touati N, Blay J-Y, *et al.* Doxorubicin plus dacarbazine (DoDa), doxorubicin plus ifosfamide (DI) or doxorubicin alone (Do) as first line treatment for advanced leiomyosarcoma (LMS). A retrospective study from the EORTC Soft Tissue and Bone Sarcoma Group (STBSG). J Clin Oncol 2018; 36(15_suppl):11574–11574.

50. Sleijfer S, Ouali M, van Glabbeke M, *et al.* Prognostic and predictive factors for outcome to first-line ifosfamide-containing chemotherapy for adult patients with advanced soft tissue sarcomas: an exploratory, retrospective analysis on large series from the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG). Eur J Cancer 2010; 46:72–83.

51. Swallow CJ. Strategic delay: histology- and biology-driven decision-making in
■ recurrent retroperitoneal sarcoma. Ann Surg Oncol 2018; 25:2117–2119.

This article illustrates the difficult decision-making process for treatment of recurrent retroperitoneal sarcoma.

52. Trans-Atlantic RPSWG. Management of Recurrent Retroperitoneal Sarcoma (RPS) in the adult: a consensus approach from the Trans-Atlantic RPS Working Group. Ann Surg Oncol 2016; 23:3531–3540.

53. MacNeill AJ, Miceli R, Strauss DC, *et al.* Postrelapse outcomes after primary extended resection of retroperitoneal sarcoma: a report from the Trans-Atlantic RPS Working Group. Cancer 2017; 123:1971–1978.

54. Ryan CW, Merimsky O, Agulnik M, *et al.* PICASSO III: a phase III, placebo-controlled study of doxorubicin with or without palifosfamide in patients with metastatic soft tissue sarcoma. J Clin Oncol 2016; 34:3898–3905.

55. Maki RG, Wathen JK, Patel SR, *et al.* Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. J Clin Oncol 2007; 25: 2755–2763.

56. Judson I, Verweij J, Gelderblom H, *et al.* Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol 2014; 15:415–423.

57. van der Graaf WT, Blay JY, Chawla SP, *et al.,* EORTC Soft Tissue and Bone Sarcoma Group; PALETTE study group. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012; 379:1879–1886.

58. Schoffski P, Chawla S, Maki RG, *et al.* Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. Lancet 2016; 387: 1629–1637.

59. Demetri GD, von Mehren M, Jones RL, *et al.* Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. J Clin Oncol 2016; 34:786–793.

60. ■■ Trans-Atlantic Retroperitoneal Sarcoma Working Group. Management of metastatic retroperitoneal sarcoma: a consensus approach from the Trans-Atlantic Retroperitoneal Sarcoma Working Group (TARPSWG). Ann oncol 2018; 29:857–871.

This article summarizes the current evidence and expert opinions regarding the management of metastatic retroperitoneal sarcoma, within the TARPSWG collaboration.

61. Sanfilippo R, Bertulli R, Marrari A, *et al.* High-dose continuous-infusion ifosfamide in advanced well differentiated/dedifferentiated liposarcoma. Clin Sarcoma Res 2014; 4:16.

62. Martin-Liberal J, Alam S, Constantinidou A, *et al.* Clinical activity and tolerability of a 14-day infusional Ifosfamide schedule in soft-tissue sarcoma. Sarcoma 2013; 2013:868973.

63. Dickson MA, Schwartz GK, Keohan ML, *et al.* Progression-free survival among patients with well differentiated or dedifferentiated liposarcoma treated with CDK4 inhibitor palbociclib: a phase 2 clinical trial. JAMA Oncol 2016; 2:937–940.