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Management of Primary Retroperitoneal Sarcoma (RPS) in the Adult: An Updated Consensus Approach from the Transatlantic Australasian RPS Working Group

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Abstract

Background.—Retroperitoneal soft tissue sarcomas comprise a heterogeneous group of rare tumors of mesenchymal origin that include several well-defined histologic subtypes. In 2015, the Transatlantic Australasian RPS Working Group (TARPSWG) published consensus recommendations for the best management of primary retroperitoneal sarcoma (RPS). Since then, through international collaboration, new evidence and knowledge have been generated, creating the need for an updated consensus document.

Methods.—The primary aim of this study was to critically evaluate the current evidence and develop an up-to-date consensus document on the approach to these difficult tumors. The resulting document applies to primary RPS that is non-visceral in origin, with exclusion criteria as previously described. The relevant literature was evaluated and an international group of experts consulted to formulate consensus statements regarding the best management of primary RPS. A level of evidence and grade of recommendation were attributed to each new/updated recommendation.

Results.—Management of primary RPS was considered from diagnosis to follow-up. This rare and complex malignancy is best managed by an experienced multidisciplinary team in a specialized referral center. The best chance of cure is at the time of primary presentation, and an individualized management plan should be made based on the 29 consensus statements included in this article, which were agreed upon by all of the authors. Whenever possible, patients should be enrolled in prospective trials and studies.

Conclusions.—Ongoing international collaboration is critical to expand upon current knowledge and further improve outcomes of patients with RPS. In addition, prospective data collection and participation in multi-institution trials are strongly encouraged.

INTRODUCTION

Retroperitoneal sarcomas (RPSs) are rare tumors, with an expected incidence of 0.5 to 1 new cases per 100,000 inhabitants per year.[1–3] RPS is not a single disease; the term encompasses a heterogeneous group of neoplasms with different biological behavior, response to treatment, and oncologic risk. There are more than 140 subtypes of soft tissue sarcoma,[4] but within the retroperitoneum, four main histological subtypes account for ≈ 90% of tumors (Table 1).

Anatomic constraints within the retroperitoneum limit the ability to achieve wide resection margins. As a consequence, local recurrence of RPS is more frequent than for extremity sarcoma and represents the leading cause of death. This is particularly true for cases of low- and intermediate-grade liposarcoma (LPS), the histopathologic subtypes of approximately one-half of sarcomas arising in the retroperitoneum. Other subtypes, such as high-grade leiomyosarcoma (LMS), pose a significant risk of developing distant metastasis, while local (i.e. abdominal non-hepatic parenchymal) recurrence after complete resection is much less common.[5–19]

Surgery remains the only curative treatment for RPS. Currently there is no definitive evidence to support the routine use of adjuvant radiation therapy (RT) or adjuvant chemotherapy.[20] The role of neoadjuvant RT has recently been prospectively evaluated in a randomized controlled trial (RCT; STRASS),[21] and a prospective randomized study is underway to investigate the role of neoadjuvant chemotherapy in RPS [EORTC1809-STRASS2].

Centralized specialist sarcoma units with expertise in the management of RPS have improved outcomes for RPS, and the associated concentrated experience has further strengthened our understanding of tumor biology and the behavior of individual histologic subtypes.[22–24] As a tangible product of the growing collaboration between referral centers in Europe and North America, the Transatlantic RPS Working Group was established in 2013.[25] The initial primary aim of the working group was to critically evaluate the current evidence and to develop a consensus document on the approach to this difficult disease, bringing together high-volume sarcoma specialist centers to generate a combined experience of the multidisciplinary management of RPS. The wider global collaboration engendered through this organization increases the ability to collate and compare prospectively collected data on this rare disease and perform prospective trials within histological subtypes, as will be the case in STRASS2.[26] The broader international collaboration instigated by the formation of this group is reflected in the 2019 name change to the Transatlantic Australasian RPS Working Group (TARPSWG).

METHODS

Terms of Reference

From an original eight institutions at its inception, TARPSWG membership has expanded across Europe, North America, Central America, South America, Australia, and Asia to now include 119 institutions. Membership in TARPSWG is granted at the institutional

level, through centralized online application, and requires that the center regularly conduct a multidisciplinary sarcoma tumor board. Drawing on the combined experience of clinicians in high-volume sarcoma specialist centers as well as evidence garnered from the published literature, consensus documents regarding the management of primary, locally recurrent, and metastatic RPS were created and published under the auspices of TARPSWG.[27–29] Members of TARPSWG convene biannually in conjunction with the annual meetings of the Connective Tissue Oncology Society and the Society of Surgical Oncology, to share data, review progress, and plan future international collaborative studies. The previous consensus statement on the management of primary RPS was conceived in 2013 as described,[27] created, discussed, edited, and approved of over the course of four sequential TARPSWG meetings held in conjunction with international conferences, and all TARPSWG members were included as authors. An update to that consensus statement was first proposed and agreed upon at a general meeting of TARPSWG held at the annual scientific meeting of the Society of Surgical Oncology in 2019, further discussed at a meeting of the TARPSWG steering committee at ASCO in 2019, and discussed in detail and approved of over the course of two further general meetings of TARPSWG held in conjunction with CTOS in Tokyo in 2019, and virtual SSO in 2020. The present document was created, edited, and revised by a writing committee, all of whom are authors, led by D. Strauss, A. Gronchi, and C. Swallow.

The following consensus statements apply to primary RPS that is non-visceral in origin, of any of the more common (well-differentiated LPS, dedifferentiated LPS, LMS, solitary fibrous tumor, malignant peripheral nerve sheath tumor, unclassified/undifferentiated pleomorphic sarcoma) or less common (e.g. synovial sarcoma, myxofibrosarcoma) histologic subtypes (see Table 1), with the following specific ancillary criteria:

- Included are sarcomas of major veins (e.g. inferior vena cava; renal veins; gonadal veins; common, external and internal iliac veins; splenic vein; portal vein; mesenteric veins), unclassified/undifferentiated pleomorphic sarcoma of the psoas, and ureteric LMS.
- Excluded are benign entities such as retroperitoneal (RP) lipoma, benign peripheral nerve sheath tumor/schwannoma, ganglioneuroma, lymphangioma, and angiomyolipoma.
- Excluded are desmoid type fibromatosis and aggressive angiomyxoma.
- Excluded are gastrointestinal stromal tumors, visceral sarcomas such as those arising from the gut or its mesentery, uterine LMS, and other gynecologic sarcomas, prostatic sarcoma, and paratesticular/spermatic cord/inguinal canal sarcoma.
- Excluded are Ewing family sarcomas, desmoplastic small round cell tumor, alveolar/embryonal rhabdomyosarcoma, sarcoma arising from teratoma, sarcomatoid carcinoma (carcinosarcoma), clear cell sarcoma, and radiation-associated sarcoma.
- Excluded are adrenal cortical carcinoma, paraganglioma, and malignant pheochromocytoma.

The excluded entities are also themselves rare tumors, and patients with these entities will also generally benefit from pretreatment pathologic diagnosis as well as multidisciplinary discussion and decision making at a center specializing in the management of soft tissue sarcomas.

In evaluating the newly identified undiagnosed RP mass, a wide spectrum of possible diagnoses must be considered. In particular, metastatic adenocarcinoma, lymphoma, metastatic germ cell tumor, and paraganglioma should be in the differential.

Rating of Consensus Statements

Principles of recommended practice from diagnosis to follow-up evaluation are summarized in 29 statements. Each statement has been categorized by level of evidence and grade of recommendation according to the scale shown in Table 2. A summary of new statements, and of significantly revised statements compared with the previous consensus document,[27] is provided in Table 3.

RESULTS: STATEMENTS OF PRINCIPLE AND RECOMMENDED PRACTICE

Systems of Care

As a rare and complex malignancy, RPS is best managed by an experienced multidisciplinary team in a specialized sarcoma referral center. Management of RPS in specialist sarcoma units is associated with improved early postoperative morbidity and a reduced risk of postoperative mortality. RPS management within a sarcoma specialist center follows significantly more clinical practice guidelines. Treatment of patients undergoing resection of primary RPS within a specialist sarcoma center is associated with a reduced risk of relapse and death from sarcoma and improved long-term overall survival (IVA).[22,24,30–33]

1a. Volume–outcome relationships in the surgical care of RPS support the regionalization of care to high-volume hospitals. The minimum annual volume of primary RPS resections that should be used to confer the status of referral or specialist center will be jurisdiction-specific. A recent quantitative analysis of data derived from the NCDB identified 13 as the minimum annual institutional volume of RPS resections that was associated with improved long-term overall survival in the USA (*IVA*).[34] Although a clear, widely applicable threshold is still lacking, members of TARPSWG who were surveyed regarding these results concurred that a minimum annual institutional surgical volume of 10–20 RPS cases was appropriate for a center to be considered one of RPS expertise (VA).[34] Institutional volume is closely associated with imperative elements such as confirmation of histologic diagnosis by an expert sarcoma pathologist, discussion of all cases at a multidisciplinary sarcoma-specific tumor board, and availability of expert multidisciplinary sarcoma care; together these are critical determinants of improved survival.

1b. The multidisciplinary team that makes management decisions should include a surgeon with specialized training in resection of RPS (*IVA*). The decision-making team should also include a radiologist, pathologist, medical oncologist, and radiation oncologist with a practice focused on caring for patients with RPS.[22,24,35,36]

1c. Given the rarity of RPS and the paucity of prospective clinical trial data, every effort should be made to include eligible patients in relevant clinical trials, particularly with international collaboration. Contribution of all RPS cases to a prospective database, whether single- or multi-institutional, is highly recommended (*VA*). An example of the latter is the comprehensive, detailed, prospective Retroperitoneal Sarcoma Registry (RESAR) database (ClinicalTrials.gov identifier NCT03838718), which has been co-created among members of TARPSWG to generate high-quality data as a basis for ongoing prospective observational studies.

Staging and Preoperative Assessment

The optimal management of RPS is facilitated by pretreatment diagnosis and staging.

Imaging

2a Thorough review of cross-sectional imaging by a sarcoma tumor board is required (IVA).[37,38]

2b The standard method for staging for the extent of primary tumor and for distant metastases is computerized tomography (CT) scan of the chest/abdomen/pelvis with intravenous (IV) contrast. Arterial phase CT imaging may be obtained to assist with operative planning, at the surgeon's discretion. Magnetic resonance imaging (MRI) is an option for patients with IV CT contrast allergy or other contraindication, Li-Fraumeni syndrome, for pelvic tumors, and for assessing the extension of tumor to specific sites (e.g. vertebral foramina, sciatic notch) that is not clear on the CT scan (*VA*).

2c Functional assessment of the contralateral kidney is typically necessary for planning treatment of the ipsilateral RPS. This may be achieved using CT with IV contrast or pharmacologic renal scan with radioisotope [differential renal scan] (*VA*).[39] A renal scan is particularly valuable in patients with IV contrast allergy or other contraindication, or if there is doubt about adequate perfusion of the contralateral kidney on CT with IV contrast.

2d Bone scan, head CT, brain MRI, and positron emission tomography (PET) scanning are usually NOT required (*VD*). Baseline PET scan may be considered prior to the treatment of high-grade RPS, but is not regarded as essential (VC).[40]

Core Needle Biopsy Image-guided percutaneous coaxial core needle biopsy (14–18 gauge) is strongly recommended (Fig. 1) as the standard of care. Biopsy may occasionally be omitted if the imaging is judged pathognomonic (e.g. heterogeneous dedifferentiated/well-differentiated LPS) by an expert radiologist within an expert multidisciplinary tumor board, and no preoperative treatment is planned (IVA).[41–44]

3a Multiple core needle cores should be obtained to allow for histologic and molecular subtyping, grading, and, ideally, biobanking (VA).

Immunohistochemistry (IHC) for non-specific mesenchymal markers such as actin and desmin, and for specific markers of histologic sarcoma subtype, should be performed at the direction of a specialized sarcoma pathologist.[4]

Staining for *MDM2* protein is a minimum standard for diagnosis of well-differentiated/dedifferentiated LPSs.[4] Additional IHC for *CDK4* protein should be performed at the discretion of the sarcoma pathologist (*IVA*). This can be supplemented with cytogenetic analysis to assess for *MDM2* gene amplification at the discretion of the pathologist (*IVA*).[45–47]

IHC for specific markers such as *STAT6*[48] should be performed at the direction of the pathologist and as required to ascertain histologic subtype; the same selective approach should be applied to testing for specific translocations to elucidate the histologic subtype (*IVA*).

Grade should be scored out of 3, according to the French Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) system.[4,49]

3b Repeat core biopsy with more extensive sampling or targeting of a different more viable area may be required (*VB*).

3c Sampling of the more solid tumor component represented by well-perfused areas on contrast-enhanced CT (Fig. 1a) or contrast-enhanced MRI is encouraged to avoid undergrading, as these areas are more likely to represent high-grade/dedifferentiated disease (*IVA*).[50] If [18F]Fluorodeoxyglucose ([18F]FDG)-PET is available, intratumoral locations with a high standard uptake value (SUV) are the preferred target areas for biopsy (*IVA*).

3d Pretreatment core needle biopsy of an RP mass can identify patients who do not require surgery, and, furthermore, enables appropriate multidisciplinary treatment planning, as well as histologic subtype- and grade-adapted surgical planning for RPS. Elective surgery for resection of an RP tumor without preoperative biopsy, without referral to a specialist center, and/or without multidisciplinary tumor board discussion is strongly discouraged (*IVE*).

Preoperative core needle biopsy of RPS is safe and does not adversely affect oncologic outcome. The incidence of needle tract seeding after core needle biopsy for RPS is very low but not zero. The safest method uses a coaxial technique with a sheathed needle. Physicians and patients can be reassured that the benefits of core needle biopsy in diagnosing sarcoma and determining its histologic subtype and grade far outweigh the risks (*IVA*).[43,44,51] Biopsies that are not performed under proper image guidance, or that are performed with non-sheathed needles, are strongly discouraged.[52]

4 Fine-needle aspiration (FNA)/cytology rarely yields diagnostic information, causes delay in treatment, and should be avoided (*VE*).

5 Laparotomy and open biopsy of suspected RPS should be avoided. This practice exposes the peritoneal cavity to contamination by sarcoma, distorts subsequent planes of dissection, may not provide diagnostic tissue due to the lack of three-dimensional image guidance, and may put vital neurovascular structures at risk (*VE*).

In the rare instance where percutaneous core needle biopsy is not technically feasible or is non-diagnostic despite repeated attempts at accurate image-guided targeting of lesional tissue, multidisciplinary consultation with a radiologist who possesses expertise in

assessment of RP tumors should guide subsequent management (*VA*). Indeed, some entities, such as lymphangioma and angiomyolipoma, may be recognized with near 100% accuracy by an experienced body radiologist, obviating the need for biopsy. It is recognized that uncertainty may persist, and that resection may, in rare instances, be required to yield a diagnosis. However, this should be a last resort and should only be undertaken when there is clear concern for malignancy of a type that may potentially be cured by resection. Serum analysis for tumor markers (lactate dehydrogenase [LDH] for lymphoma, α-fetoprotein [AFP] and β-human chorionic gonadotropin [B-HCG] for dysgerminomas, etc.), and interval imaging without resection may be useful tools to discern RP tumors not best managed with upfront resection.

6 Laparoscopic biopsy of suspected RPS carries the same risks as open biopsy and should be avoided (*VE*).

7 If at open or laparoscopic exploration for suspected adnexal mass no abnormalities of the uterus, fallopian tubes, or ovaries are found but an RP mass is detected, it is recommended that nothing further be done at that time. The patient should undergo subsequent dedicated imaging and referral to a sarcoma referral center. If appropriate imaging studies (CT/MRI) as well as intraoperative consultation with a member of the sarcoma surgical team are available at the time of exploration to ensure appropriate interpretation of the situation and targeting of an area that is likely to yield diagnostic tissue, intraoperative core needle biopsy can be considered but should be performed in a way that strictly minimizes the risk of peritoneal contamination as well as the risk of injury to surrounding structures. The chance that all of these conditions will co-exist is very low; if there is any doubt as to all of these conditions being met, no biopsy should be performed intraoperatively. Frozen sections should not be taken because decisions should be based only on formal pathologic evaluation of formalin-fixed tissue, often involving immunohistochemical staining and ancillary molecular testing (*VA*).

8 If at open or laparoscopic hernia repair or during any other abdominal procedure an RP mass is detected, it is recommended that nothing further be done to assess or explore the mass at that time. The patient should undergo subsequent dedicated imaging. If appropriate imaging studies (CT/MRI) as well as intraoperative consultation with a member of the sarcoma surgical team are available at the time of exploration to ensure appropriate interpretation of the situation and targeting of an area that is likely to yield diagnostic tissue, intraoperative core needle biopsy can be considered but should be performed in a way that strictly minimizes the risk of peritoneal contamination as well as the risk of injury to surrounding structures. The chance that all of these conditions will co-exist is very low; if there is any doubt as to all of these conditions being met, no biopsy should be performed intraoperatively (*VA*).

Primary Surgical Approach

9 The best chance of resection with curative intent is at the time of primary presentation. The individual management plan should be determined after discussion at a specialized multidisciplinary Sarcoma Tumor Board with presentation of both imaging and pathologic findings (IIIA).[5–15] The management team should include a surgeon with specialized

training in resection of RPS who participates in the multidisciplinary Sarcoma Tumor Board discussion (IVA). This applies equally to well-differentiated RP LPS and to the large radiographically 'benign' lipomatous mass (VA).[16]

10 Biologic behavior, response to treatment, and clinical outcome vary by histologic subtype and grade of RPS. The management plan, including the plan for resection, should thus be developed in recognition of the histologic subtype and grade (IIIA).[33,53,54]

11 Because RPS can grow to a very large size without causing symptoms, patients may present late with symptoms and signs of mass effect (e.g. malnutrition, shortness of breath, debility). Malnutrition at the time of RPS diagnosis is often present in asymptomatic patients and may escape clinical detection. Performance Status should be assessed as part of the development of an individual management plan, and nutritional support, prehabilitative physiotherapy, smoking cessation counselling and the like may be required in concert with preoperative planning (IIIB).[55,56]. Objective preoperative assessment of nutritional status, preoperative enteral nutritional supplementation for at least 2 weeks, and early postoperative institution of parenteral nutrition should be strongly considered (*IIIA*).[55,56]

12. Operative Strategy Complete en bloc gross resection is the cornerstone of management (*IIIA*).[5–16]

12a In the case of primary RPS, surgery should be aimed at achieving macroscopically complete resection, with a single specimen encompassing the tumor and involved contiguous organs (IIIA)[57] (Fig. 2). The optimal exposure for safely and effectively achieving this aim is typically a midline laparotomy, with a transverse extension on the ipsilateral side if additional exposure is required (*VE*).

The concept of adapting the operative approach to the histologic subtype has recently gained increased recognition (*VB*).[58–60]

12a.1. Intraoperative macroscopic assessment of appropriate resection margins in RP LPS can be challenging, particularly for well-differentiated LPS where tumor tissue is difficult to distinguish from normal fat. Intraoperative frozen section is not of benefit in this setting. Given the uncertainty regarding margin definition, an extended approach to systematically resect adherent viscera, irrespective of expected microscopic infiltration, should be considered for RP LPS. A policy of resecting only structures/viscera that are clearly invaded by LPS is more likely to result in residual disease being left in the operative bed (*VB*). Clearance of all ipsilateral RP fat (Fig. 2c) can achieve the goal of removing the tissue at risk of involvement by LPS. Careful review of preoperative imaging is critical to appreciation of potential extension along the inguinal/femoral canals.

Even in Grade 3 RP LPS, where eventual systemic failure is more likely, an attempt to achieve long-term local control is warranted, given the symptomatic burden of abdominal recurrence, and the same operative approach is appropriate (*VB*).

12a.2. For LMS with more clearly defined borders, organs that are closely adjacent but not directly adherent to/invaded by the tumor can potentially be preserved, provided this does

not result in an avoidable positive margin. In the case of LMS arising from a major vein, specific attention should be directed to achieving microscopically negative margins on the vein of origin.

12a.3. For solitary fibrous tumors, which generally exhibit a low risk for local recurrence, a complete resection with negative margins should be the goal, but an extended approach is unlikely to be required to achieve this.

12a.4. For sarcoma of the psoas, usually an undifferentiated/unclassified pleomorphic sarcoma, the tumor may extend under the inguinal ligament into the thigh; however, these tumors are typically separated from the retroperitoneum by the psoas fascia. Surgery should aim to remove the tumor and muscle en bloc with surrounding fascia, with preservation of the nerves, vessels, and adjacent viscera if uninvolved. Dedicated analysis of high-quality preoperative imaging is required to assess the potential involvement of the inguinal ligament, which, if sacrificed, will necessitate complex reconstruction.

12a.5. For malignant peripheral nerve sheath tumor (MPNST) arising from nerves in the retroperitoneum, complete resection with negative microscopic margins should be the aim. Locally advanced MPNST of the retroperitoneum has a poor prognosis and complete resection may be very challenging. Surgical judgment must be exercised regarding sacrifice of adjacent major neurovascular structures.

12b In primary RPS, preservation of specific organs (e.g. kidney, duodenum, bladder) should be considered on an individualized basis. Appropriate decisions regarding organ sparing require specific expertise in RPS, to balance overall tumor extent/expected biology and given the individual patient's characteristics (*VA*). Judgment must be used in deciding which neurovascular structures to sacrifice, with the potential for local control weighed against the potential for perioperative morbidity and long-term dysfunction. Judgment must similarly be exercised in determining the appropriateness of *en bloc* resection of the liver and pancreas (*VA*). Data gathered by the TARPSWG collaborative on patients who underwent resection of primary RPS, the majority in referral centers, show that only 1.4% of patients underwent resection of the head of the pancreas.[61]

12c Resection of RPS requires technical expertise in multiple sites throughout the abdominal and pelvic cavity, including vascular surgery techniques for the isolation and reconstruction of large vessels. Single organ or site expertise is not sufficient (*VA*).

12d The ability to orchestrate a team of complementary surgical experts is critical to successful management of RPS patients (*VA*).

12e Surgical expertise in RPS resection requires specific anatomic knowledge of the RP space to minimize the risk of intra- and perioperative morbidity. Examples include RP autonomic and somatic nerves, the lymphatic system, paravertebral vessels, and organs of the gastrointestinal tract. The required expertise also includes experience with additional procedures such as full-thickness thoracoabdominal wall resection and reconstruction, diaphragmatic resection and reconstruction, major vascular resection and reconstruction, liver/pancreatic resection, and bone resection. These abilities, which may accrue from

the participation of multidisciplinary surgical teams, can make it possible to achieve macroscopically complete tumor resection in the majority of patients. Members of the surgical team must be familiar with the functional consequences of major neurovascular interruption, and must recognize the need to consult with reconstructive surgeons, as appropriate (*VA*).

12f If the first operation performed on a patient with primary RPS consisted only of a simple excision that left behind gross residual disease that is identified on cross-sectional imaging shortly thereafter, the timing of any subsequent surgery to attempt curative resection must be carefully considered. A period of observation is often appropriate to rule out multifocal dissemination of high-grade disease at the time of the previous procedure, in addition to allowing early postoperative adhesions to mature. If the patient does come to an attempt at curative resection, the intent should be to reproduce what would ideally have been done for the primary RPS in its original state, since the possibility of disease control may be thereby increased, despite the previous operative interference. If the gross residual disease is well-differentiated, initial surveillance may be discussed as an option, with resection reserved for significant growth or appearance of a dedifferentiated component. Surgery for recurrent RPS should be aimed simply at achieving macroscopic complete resection of the tumor tissue, including surrounding organs and structures only when overtly infiltrated (*IVA*).[28]

13 Grossly incomplete resection of RPS is of questionable benefit, may result in harm, and can be regarded only as a potentially palliative procedure for carefully selected patients. Unplanned grossly incomplete resection is to be avoided through informed imaging review, thoughtful planning, and referral to another center if appropriate (IIIA).[5–16]

14. The decision that a patient with primary RPS should not undergo surgery for the purpose of resection should only be taken after thorough consideration of technical-, biology-, and patient-related factors, by members of an experienced multidisciplinary team (*IVA*). The incidence of such ‘upfront unresectability’ reported by referral centers is in the range of 10–25%.[62,63] and would be expected to vary based on referral patterns; upfront unresectability was largely due to poor performance status and/or involvement of critical central vascular structures. The presence of synchronous distant metastatic disease generally portends a very poor prognosis and limited survival, and the majority of patients will not benefit from resection. True multifocality (discontiguous sites of intra-abdominal non-hepatic parenchymal disease distinct from the primary tumor) may be observed at the time of presentation in patients with dedifferentiated LPS; the prognosis of patients with multifocal dedifferentiated LPS is poor, and resection would be appropriate only in individuals with excellent performance status (*IVD*).[64] A recent study by members of the TARPSWG that employed quantitative and qualitative methodologies (A. Covelli, personal communication, presented at the semi annual meeting of TARPSWG, March 2021) revealed little agreement among experts regarding strict criteria for unresectability (*VC*); a Delphi process is currently underway in an attempt to guide decision making in this regard. Judicious use of non-surgical therapies in patients who are deemed upfront unresectable is contingent upon assessment of histology-specific tumor biology and patient factors.

For the purposes of being considered for enrollment into the international collaborative RCT STRASS2, which is currently open, the patient's RPS must be deemed technically resectable as judged by CT scan imaging. If R2 resection is anticipated, the patient is not eligible for trial inclusion. The criteria for technical non-resectability are defined in the trial protocol as:

- Involvement of the superior mesenteric artery, aorta, coeliac trunk, and/or portal vein;
- involvement of bone;
- growth into the spinal canal;
- invasive extension of retrohepatic inferior vena cava leimyosarcoma into the right atrium;
- infiltration of multiple major organs such as liver, pancreas, and or major vessels.

It should be emphasized that these criteria have been established for the purposes of defining the study population in a prospective trial, and that outside of this setting, each individual patient should be evaluated for technical resectability by experienced RPS surgeons, who will consider technical issues in concert with tumor- and patient-related variables.

15. Perioperative Management Complete resection of an extensive RPS may involve a long and complex operative procedure. Anesthesiologists and Operating Room nurses experienced with such procedures, including vascular resection and reconstruction, are essential to a successful operative outcome (*VA*).

15a The approach to intra- and postoperative management (including warming techniques, transfusions, anticoagulation, analgesia, nutrition, physiotherapy, etc.) should be standardized and agreed upon by relevant stakeholders (*VA*).

Application of the principles of enhanced recovery after surgery to the perioperative management of patients with RPS is feasible and beneficial (*IIIA*).[65]

15b Extended peritoneal stripping and RP space exposure, together with long operative times, can result in significant fluid shifts and requirement for fluid resuscitation, including colloids (*VA*).

15c An advanced postoperative monitoring environment is usually appropriate (*VA*).

15d Serious life-threatening complications can develop immediately, or in a delayed manner, after resection of RPS. Postoperative care should be undertaken by an experienced team of nurses and physicians (*VA*).

15e. Perioperative nutritional support may be required (*VA*). Postoperative morbidity and length of stay are better in patients who are found to be nutritionally replete upon objective preoperative assessment of nutritional status. Preoperative enteral nutritional supplementation for at least 2 weeks is feasible and well tolerated. Early postoperative institution of parenteral nutrition should be strongly considered until enteral nutrition can be resumed (*IIIA*).[55,56]

16 LPS is the most common histologic subtype of RPS (Table 1). The principal site of RP LPS recurrence is intra-abdominal/locoregional in the erstwhile retroperitoneum (*IIIA*).[5–16,33,53] Therefore, abdominal recurrence-free survival (ARFS) is an appropriate outcome to be measured in trials that include this histology. Strategies to reduce intra-abdominal recurrence should be pursued.

17 Intraoperatively, well-differentiated and low-grade dedifferentiated LPS may appear grossly similar to normal fat, and frozen section evaluation of marginal or 'suspicious' tissue is usually not helpful. The extent of resection in LPS should be guided by asymmetry shown on preoperative imaging, knowledge of functional anatomy, and experience with patterns of recurrence. Complete resection of all RP fatty tissue at risk for harboring tumor is ideal (*IIIA*).[14–16,57] Iterative surgical experience of the correlation between gross and histologic appearances facilitates strategic intraoperative decision making about the extent of resection.

18 In general, use of intraoperative frozen sections is unlikely to be helpful or to alter the extent of a well-planned and carefully executed resection. Thus, the operative plan should be crafted based on other sources of data. The approach should be imaging-based, deliberate, and not 'exploratory', avoiding dissection in marginal tumor planes unless critical structures are at risk. Frozen section analysis may be of assistance in particular circumstances, for instance to assess vessel margins in vascular LMS or neural margins in malignant peripheral nerve sheath tumors (*VA*).

Adjuvant/Neoadjuvant Therapies

19 Limited randomized trials of neoadjuvant therapy versus resection alone for RPS have been conducted to date, although several phase I and II prospective studies have been reported. Neoadjuvant therapy in the form of external beam radiation, chemotherapy, chemotherapy combined with deep-wave hyperthermia, or combined radiation and chemotherapy is safe for well-selected patients and may be considered after careful review by a multidisciplinary sarcoma tumor board (*IVC*).[66–76]

20 Intraoperative RT (IORT, with electron beam) has no proven benefit. Although it may be considered for margins considered at risk, the field is often too large and uneven for its practical application (*IVE*).[77–82] Other techniques for dose intensification at anticipated posterior margins at risk include preoperative 'dose painting', a strategy currently under prospective study.[83]

21 Postoperative/adjuvant external beam radiation after complete gross resection is of no proven benefit and is associated with significant short- and long-term toxicities. A therapeutic radiation dose can be achieved for only the minority of patients after resection, due primarily to gastrointestinal toxicity (*IVE*).[71,84,85]

22 Brachytherapy is of no proven benefit and may be associated with significant short- and long-term complications (*IVE*).[72,86,87]

23. Neoadjuvant Radiotherapy A phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with RPS (STRASS) has been performed (Fig. 3).[21] Based on recent analysis of the primary endpoint, ARFS, routine use of neoadjuvant

RT is not recommended in patients with high-grade RPS (*ID*), but may be considered in those with high risk of local (abdominal)-only recurrence, i.e. well-differentiated LPS and low-grade dedifferentiated LPS (*IB*).

23a The additional morbidity associated with preoperative RT (mostly intensity-modulated radiation therapy) was acceptable (*IC*).

23b Initial analysis at 3 years of follow-up demonstrates that when the entire study population, including all histologic subtypes, is considered, neoadjuvant radiotherapy had no apparent impact on local control or overall survival.

23c On *post hoc* subgroup analysis, ARFS was significantly better in patients with RP LPS who received neoadjuvant radiotherapy versus those who had resection alone (for the purposes of this analysis, patients who were deemed to have 'progression' on RT but nevertheless underwent resection were not *de facto* scored as having abdominal recurrence). The observed improvement in ARFS was accounted for by the well-differentiated LPS and low-grade dedifferentiated LPS subgroups (see 23d).

23d Patients with high-grade (grade 3) LPS or LMS did not seem to benefit from preoperative radiotherapy (*ID*).

23e Successful completion of the STRASS trial demonstrates the value and future potential of international collaboration within the RPS community. Results of STRASS can be used to discuss the lack of harm and potential benefit of preoperative radiation therapy for the individual patient, depending on specific histologic subtype (favors LPS) and grade (favors well-differentiated and low-grade dedifferentiated LPS). Given the predilection of RP LPS for late abdominal recurrence, more long-term data may reveal new information.

23f The STREXIT study, undertaken by high-volume RPS referral centers in parallel with STRASS, examined the baseline characteristics, treatment, and outcomes of patients who were screened for STRASS eligibility at each center. The purpose was to understand screening, eligibility, and enrollment patterns at large centers, and to analyze the potential relevance of STRASS results to the overall population of patients with potentially curable primary RPS. The STREXIT[88] study revealed significant variations in the assessment of resectability between individual referral centers, and showed that the proportional representation of various histologic subtypes/grades within STRASS was not fully reflective of the real-world experience. Patients with especially poor prognostic variables (particularly high-grade dedifferentiated LPS) were underrepresented in STRASS. These high-risk groups are the subject of enquiry in STRASS2, a randomized trial of preoperative chemotherapy versus surgery alone, which opened in November 2020.

24 Postoperative/adjuvant chemotherapy after complete gross resection is of no proven benefit (*IE*)[89,90].

25. Neoadjuvant Chemotherapy While an RCT comparing neoadjuvant chemotherapy that is histologic subtype-specific to adriamycin-ifosfamide for high-risk extremity sarcoma showed that the latter was associated with better long-term survival,[91] the results cannot

be directly extrapolated to the RPS setting, given the differences in predominant histologic subtypes, recurrence patterns, and anatomic constraints. Nevertheless, neoadjuvant chemotherapy can be discussed for use in individual patients with chemosensitive histologies such as synovial sarcoma[92] and high-grade LMS, among others (*VC*), or within prospective clinical studies.

25a Consideration of preoperative chemotherapy or chemoradiation with cytoreductive intent is particularly relevant in the case of technically unresectable or borderline resectable RPS that could potentially be rendered more amenable to safe, grossly complete resection through tumor downsizing.[76] Targeted therapy can also be considered as a preoperative cytoreductive strategy for locally advanced tumors of a specific rare histology, for instance use of a mammalian target of rapamycin (mTOR) inhibitor in a perivascular epithelioid cell tumor (PEComa), or use of an anaplastic lymphoma kinase (ALK) inhibitor in an inflammatory myofibroblastic tumor. Along the same lines, the potential sensitivity of solitary fibrous tumor to radiation therapy should also be considered (*IVB*).[93]

25b The EORTC-62961 RCT examined the addition of deep-wave hyperthermia to perioperative CT for patients with high-risk sarcoma of the abdomen, trunk, or extremity, the majority of whom were also treated with postoperative RT.[76] Receipt of hyperthermia was associated with improved local progression-free survival, particularly in subgroup analysis of patients with abdominal sarcoma who underwent R0/R1 resection,[75] however, this modality is not widely available or employed.

26 Patients with high-grade dedifferentiated LPS or high-grade LMS should be considered for entry into the STRASS2 trial of preoperative chemotherapy versus resection alone for potentially curable primary RPS (Fig. 4).

Follow-Up Evaluation

27. Monitoring for Recurrence Risk of recurrence after grossly complete resection of RPS does not plateau, even after 15–20 years. Patients should be followed indefinitely (*IIIA*).[5–19]

27a Recurrence that is apparent on imaging may predate symptomatic recurrence by months to years. Follow-up assessment should include clinical evaluation and cross-sectional imaging (*VA*). CT chest may not be required, particularly in low-grade histologies (*IVB*).[94]

27b The median time to recurrence of high-grade RPS is <5 years after definitive treatment (*IIIA*).[5–19] The interval between follow-up evaluations is not evidence-based but should likely be shorter initially (e.g. 3–6 months). After 5 years, annual follow-up evaluation is appropriate (*VB*).[95]

28 Evaluations of long-term function and quality of life after therapy for RPS are lacking. Ideally, quality of life should be assessed both pre- and postoperatively (*VA*).[96,97]

29. Long-term outcomes after resection of RPS vary significantly. The probability of recurrence locally or at distant site(s) varies according to tumor factors such as histologic subtype, grade, size, and multifocality; patient characteristics such as age and comorbidities; and treatment variables, including completeness of resection, tumor rupture and center

expertise. The relative contribution of each prognostic variable to the oncologic outcome of RPS patients can be weighted by combining them in prognostic tools such as nomograms, which can be used to provide individualized prognostic information and assist decision making and discussion around the possible benefit from neoadjuvant or adjuvant strategies in high-risk patients. One of these nomograms, which has also been endorsed by the AJCC 8th edition, can be accessed through the free-to-download app Sarculator (www.sarculator.org).[18,53,98–101]

CONCLUSION

Given the rarity of RPS, international collaboration is critical for expanding upon current knowledge. RPS is not a single disease, and the contributions of histologic subtype and grade to tumor biology must be considered in deciding on optimal management. Patients with RPS should be cared for in high-volume sarcoma treatment centers with special expertise in its management. Prospective randomized trials on a rare disease are feasible thanks to collaboration among referral centers. Institutional membership in the TARPSWG across the globe has grown enormously since its inception and continues to increase, with the inclusion of surgical, medical, and radiation oncologists, radiologists, and pathologists to recapitulate the multidisciplinary team involved in patient management.

DISCLOSURE

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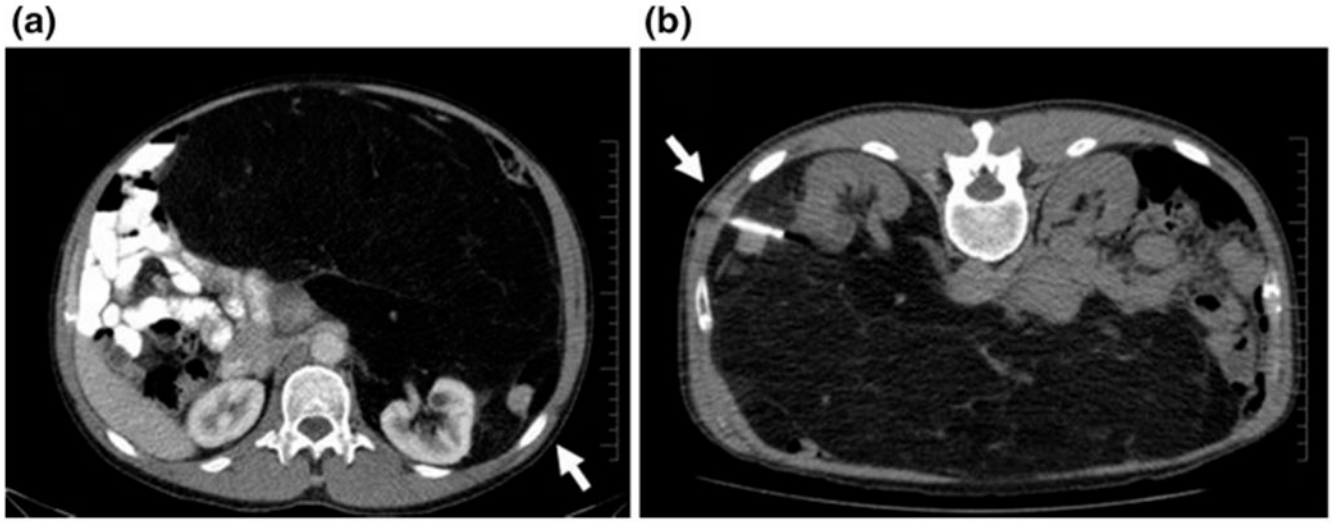

FIG. 1.

CT-guided percutaneous core needle biopsy of a large lipomatous tumor arising from the left retroperitoneum. CT guidance facilitated targeted sampling of the more solid area within the mass (**a** white arrow shows the location of this area on diagnostic CT; **b**, core needle is indicated by the white arrow), yielding a diagnosis of low grade dedifferentiated liposarcoma. The optimal treatment strategy was then discussed at Multidisciplinary Sarcoma Tumor Board. *CT* computed tomography

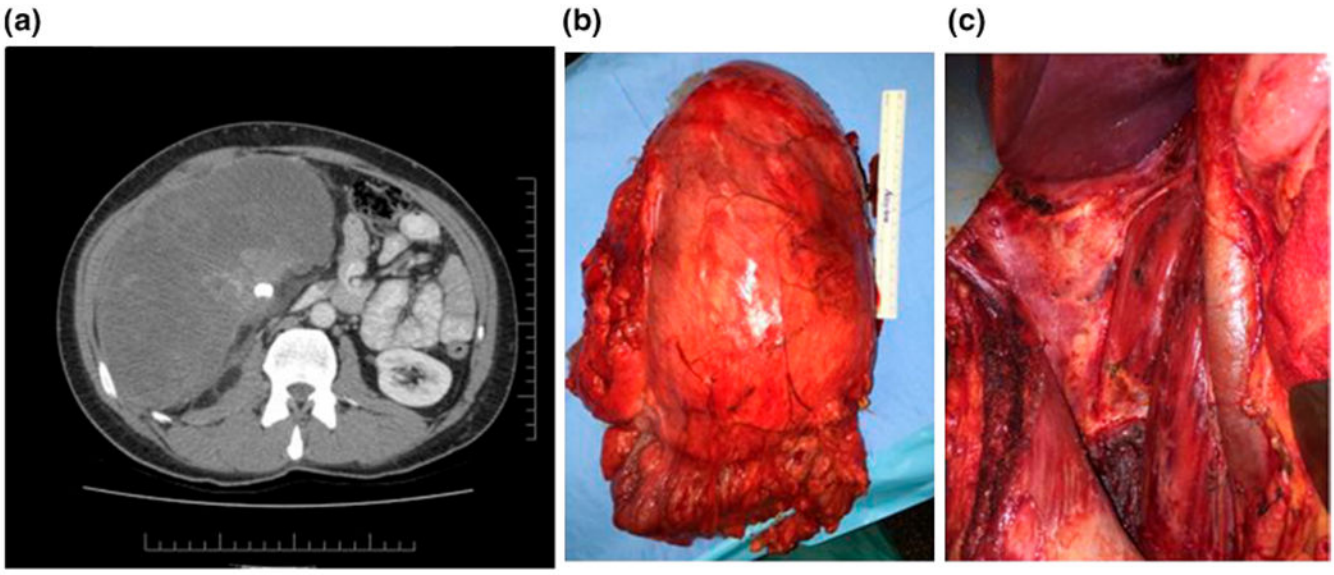

FIG. 2.

Dedifferentiated liposarcoma in a 76-year-old man. (**a**) Contrast-enhanced computed tomography scan of a right retroperitoneal mass. (**b**) Surgical specimen. The tumor was removed en bloc with the right kidney and right colon. (**c**) Surgical field after tumor removal.

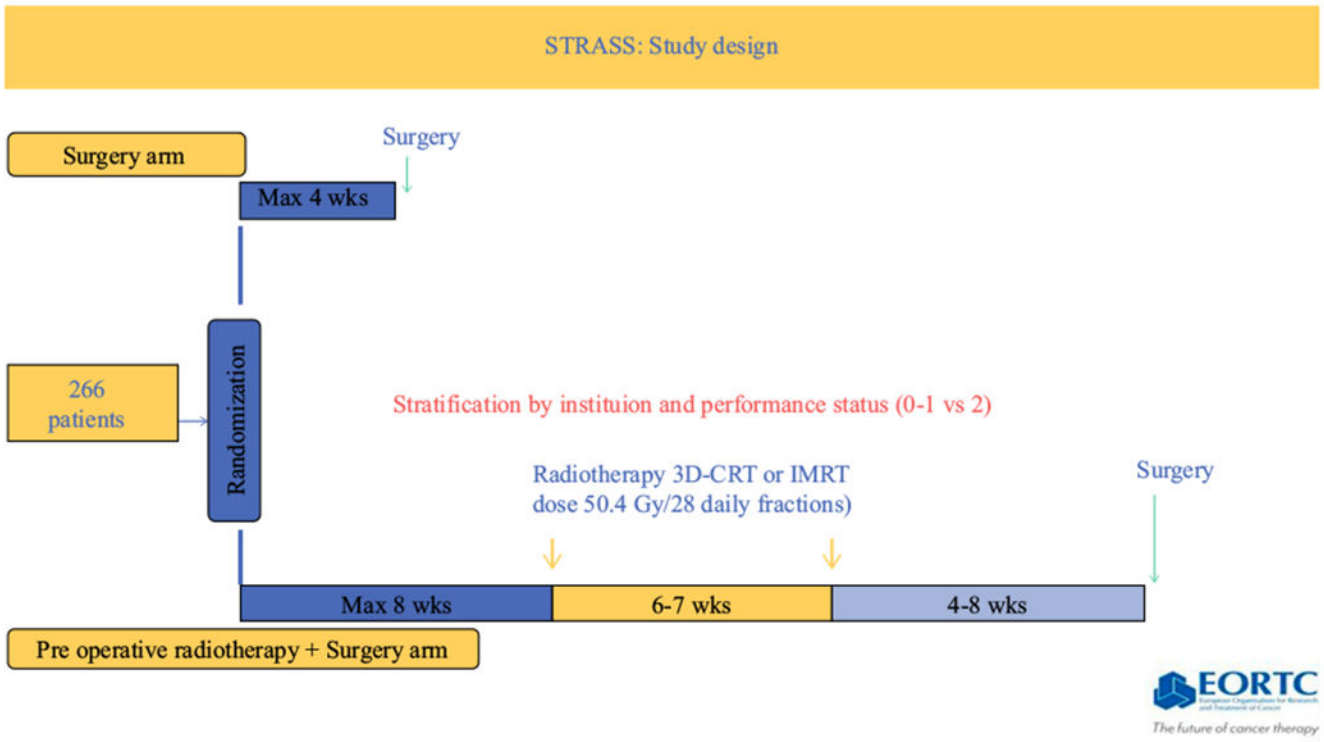

FIG. 3.

EORTC62092 RCT – STRASS. Preoperative radiotherapy versus resection alone, study design. *RCT* randomized controlled trial, *CRT* conformal radiotherapy, *IMRT* intensity-modulated radiation therapy, *max* maximum

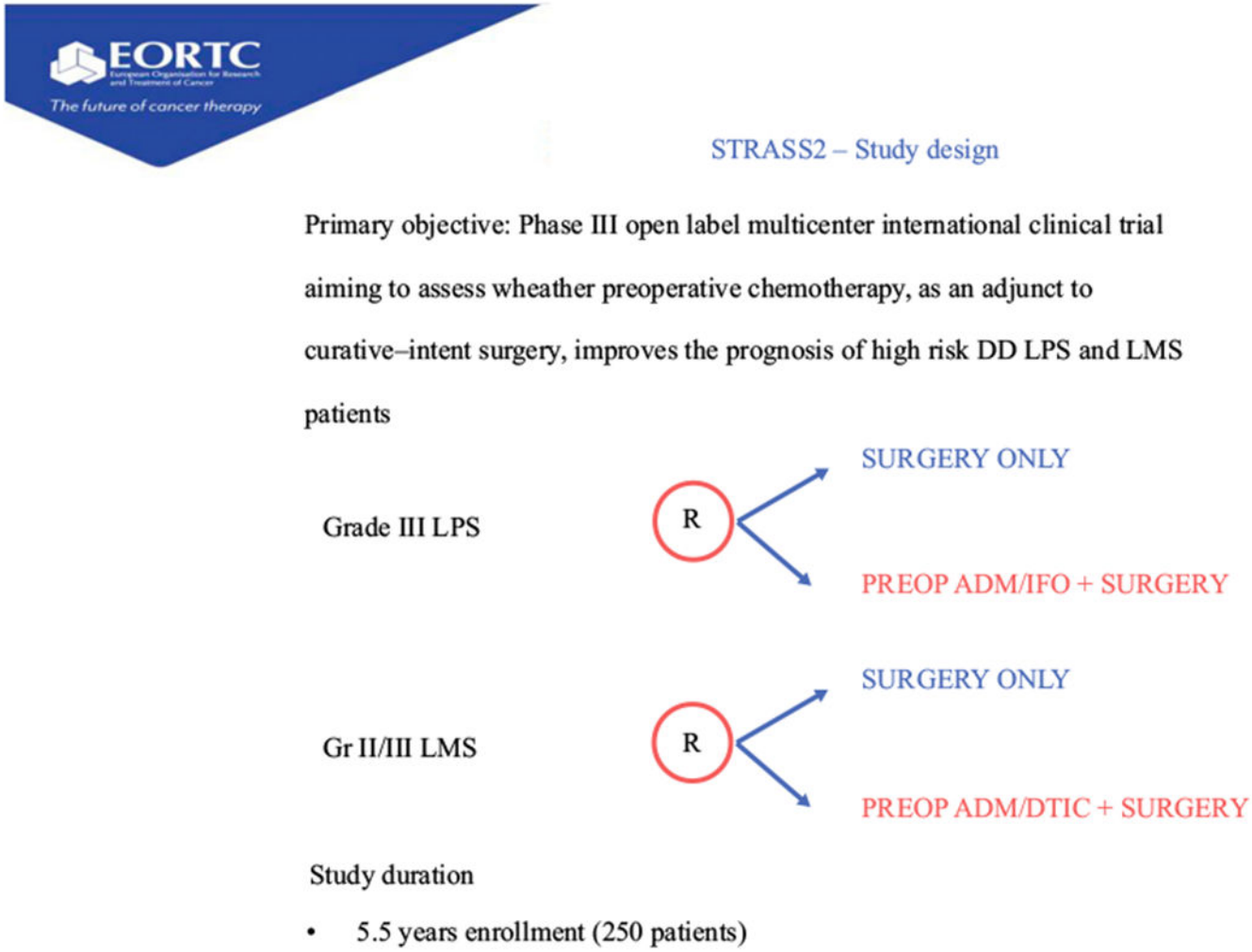

FIG. 4.

EORTC1809 RCT – STRASS2. Preoperative chemotherapy versus resection alone, study design. *RCT* randomized controlled trial, *DD LPS* dedifferentiated liposarcoma, *LMS* leiomyosarcoma, *Preop* preoperative

TABLE 1

Histologic subtypes of primary retroperitoneal sarcoma

Histologic subtype	MSKCC, 2016 [*n* = 675]	TARPSWG, 2020 [*n* = 1942]	Total [*n* = 2617]
Well-differentiated liposarcoma	186 (28%)	446 (23%)	632 (24%)
Dedifferentiated liposarcoma	213 (32%)	829 (43%)	1042 (40%)
Leiomyosarcoma	140 (23%)	352 (18%)	492 (20%)
Solitary fibrous tumor	33 (5%)	105 (5%)	138 (5%)
Malignant peripheral nerve sheath tumor	23 (3%)	54 (3%)	77 (3%)
Other	69 (9%)	156 (8%)	164 (8%)
Unclassified/undifferentiated pleomorphic sarcoma (UPS)	–	61 (3%)	
Sarcoma NOS	35 (5%)	21 (1%)	
Translocation associated and other	34 (5%)	74 (4%)	

Data are expressed as *n* (%)

MSKCCC Memorial Sloan-Kettering Cancer Center,[101] *TARPSWG* Transatlantic Australasian Retroperitoneal Sarcoma Working Group,[102] *NOS* not otherwise specified

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TABLE 2

Level of evidence (I–V) and grade of recommendation (A–E)

I	Evidence from at least one large randomized controlled trial of good methodologic quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small or large randomized trials with a suspicion of bias (lower methodologic quality) or meta-analyses of such trials or those with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without a control group, case reports, experts' opinions
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or disadvantages (e.g. adverse events, costs), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Adapted from the Infectious Diseases Society of American-United States Public Health Service Grading System[103]

TABLE 3

New and significantly revised consensus statements

Management phase/ context	New statement	Significantly revised statement
Systems of care	1a. Minimum annual institutional volume of RPS resections for best outcomes 1c. Importance of prospective data collection	1. Expanded rationale for management in specialist sarcoma unit/referral center including specialized pathology review and imaging review, plus MDT discussion
Staging and preoperative assessment	RPS classification by histologic subtype (Table 1) Targeting of more solid, vascular components of RP mass during core biopsy (Fig. 1)	3a. Addition of fundamentals of pathologic evaluation, determination of histologic subtype 3d. Expanded rationale for pretreatment biopsy and evidence of safety 7,8. Role for intraoperative consultation with members of the sarcoma team during gynecologic and hernia repair procedures at which an RP mass is discovered
Primary surgical approach	12a,15. Histologic subtype-specific resection strategies 14. Definition of unresectability (real-world vs. for trials)	12f. Tailored management of gross residual tumor after initial inadequate resection, including consideration of histologic subtype (Fig. 2) 15a. Feasibility of implementing principles of ERAS in RPS 16. Rationale for use of abdominal recurrence-free survival as a study endpoint 17. Emphasis on surgeon experience to guide the extent of resection
Adjuvant/neoadjuvant treatment	23a–f. Detailed discussion of the results of the STRASS RCT of neoadjuvant RT (Fig. 3), and implications for current clinical practice 25. Rationale to consider neoadjuvant chemotherapy 25b. Results of the EORTC-62961 RCT of neoadjuvant chemotherapy with RHT showing benefit with RHT 26. Description of STRASS2 (Fig. 4) and the importance of optimizing international site participation	20. Safety of dose intensification using dose painting
Follow-up evaluation	29. Rationale for nomogram use in clinical decision making	27a. Omission of CT chest scan after resection of low-grade tumor

RPS retroperitoneal sarcoma, *MDT* Multidisciplinary Tumor Board, *RP* retroperitoneal, *ERAS* enhanced recovery after surgery, *RCT* randomized controlled trial, *RT* radiation therapy, *RHT* regional hyperthermia, *CT* computed tomography