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Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC 62092: STRASS) : a multicenter, randomised, phase 3 trial

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Department of Surgical Oncology, Institut Curie, PSL University, Paris, France (S.Bonvalot, MD,PhD)

Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy (A. Gronchi, MD)

Department of Radiation Oncology, Gustave Roussy Cancer Campus, Villejuif, France (C. Le Péchoux MD)

Department of Surgical Oncology, Princess Margaret Cancer Centre, Toronto, Canada. (Pr C J Swallow ,MD)

Department of Surgical Oncology, Royal Marsden Hospital, London, England (D. Strauss MD)

Department of Surgical Oncology, Centre Léon Bérard, Lyon, France (P. Meeus MD)

Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands (F. van Coevorden MD)

Department of Surgical Oncology, Oslo University Hospital, The Norwegian Radium Hospital, Oslo, Norway (S. Stoldt MD)

Department of Surgical Oncology, Institut Bergonié, Bordeaux, France (E. Stoeckle MD)

Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland (Pr P. Rutkowski MD, PhD)

Department of Surgery, Veneto Institute of Oncology- IOV-IRCSS, Padua, Italy (M. Rastrelli MD)

Department of Surgery, Brigham and Women's Hospital; Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute; Harvard Medical School, Boston, Massachusetts, United States (C. P Raut MD, MSc)

Department of Surgical Oncology, University Hospitals Gasthuisberg, Leuven, Belgium (Pr D. Hompes, MD)

Centro di Riferimento Oncologico (CRO)-IRCCS, Aviano, Italy (A. De Paoli, MD)

Department of Radiation Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy (C. Sangalli MD)

Department of Surgical Oncology, Gustave Roussy Cancer Campus, Villejuif, France (C.Honoré MD,PhD)

Department of Radiation Oncology, Princess Margaret Cancer Centre, Toronto, Canada (P. Chung MD)

Department of Radiation Oncology, Royal Marsden Hospital, London, England (A. Miah MD)

Department of Medical Oncology, Centre Léon Bérard, Lyon, France (Pr JY. Blay MD,PhD)

Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy (M Fiore MD)

Quality Assurance in Radiotherapy, EORTC Headquarters, Brussels, Belgium. (JJ Stelmes MD)

Department of Medicine, University of Padua School of Medicine. (Pr AP Dei Tos MD)

Department of Radiation Oncology, Brigham and Women's Hospital; Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute; Harvard Medical School, Boston, Massachusetts, United States (Pr E H Baldini MD, MPH)

EORTC Headquarters, Brussels, Belgium. (S Litière PhD)

EORTC Headquarters, Brussels, Belgium (S Marreaud MD)

Department of Medical Oncology, Leiden University Medical Center, The Netherlands (Pr H. Gelderblom MD,PhD)

Corresponding author: Sylvie Bonvalot, Institut Curie, 26 rue D'Ulm, 75006 Paris, France.
Sylvie.bonvalot@curie.fr

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Abstract

Background: Unlike for extremity sarcomas, the efficacy of radiotherapy (RT) for retroperitoneal sarcoma (RPS) is not established. The aim of this study was to evaluate the impact of preoperative RT on abdominal recurrence-free survival (ARFS).

Method: The international STRASS trial (NCT01344018) randomized eligible patients (≥ 18 years of age, ASA score ≤ 2) with histologically-proven, centrally reviewed, localized primary RPS, amenable to both surgery and RT, not previously treated. Patients were randomized 1:1 to receive preoperative RT (50.4 Gy) followed by multivisceral en bloc curative-intent surgery (RT/S group) or surgery alone (S group). Randomization was stratified by hospital and performance status (0-1 vs 2). Primary endpoint was ARFS, defined by one of the following events: progressive abdominal or distant disease, patient becoming ASA 3 during RT, R2 resection, peritoneal sarcomatosis, or local relapse after surgery. All survival analyses are performed in the intent-to-treat population. The final analysis of the primary endpoint is reported herein.

Findings: Between January 2012 and April 2017, 266 patients were randomized. Median follow-up is 43.1 months (IQR 28.8-59.2). Seventeen patients were judged ineligible. ARFS at 3 years was 58.7% (95% CI 49.5-66.7) and 60.4% (95% CI 51.4-68.2) in the S and RT/S groups (HR = 1.01, log rank p = 0.95). During RT, patients experienced fatigue and GI toxicity, but grade 3 and 4 clinical toxicity were limited to 15 (11.8%) and 1 (0.8%). Lymphopenia was observed as grade 3 in 68 (54%) and grade 4 in 30 (24%) of 127 patients.

Interpretation: Preoperative RT should not be considered a standard of care treatment for RPS

Funding: EORTC and EUROSARC

Research in context

Evidence before this study Currently, data supporting the use of radiotherapy (RT) in primary retroperitoneal sarcoma (RPS) are limited. Justification for its use has been extrapolated from its established role in extremity soft tissue sarcoma. To date only one randomized trial evaluating the role of external beam RT in RPS was attempted (ACOSOG-Z9031, NCT00091351), but that study failed to accrue and was closed after enrolling fewer than 20 patients. A search of Medline using “radiotherapy” AND “retroperitoneal sarcoma” AND “clinical trial” identified 42 English-language journal articles through February 19, 2020 reporting Phase 1 and 2 trials which were not designed to establish superiority of RT. Only one trial randomized 35 patients, comparing 20-Gy intraoperative RT (IORT) in combination with postoperative (35- to 40-Gy) external-beam RT (EBRT) and postoperative EBRT (50- to 55-Gy) alone. In this trial, patients who received IORT had less radiation-related enteritis but more frequent radiation-related peripheral neuropathy than control patients. As a result, all the available data regarding EBRT in RPS come only from retrospective analyses, including large national database or multicentric studies. Such series are limited by inherent biases, including use of RT preferentially for tumors that were smaller, in more favorable locations, easier to irradiate and resect, or resected in academic centers. Furthermore, results and recommendations are contradictory, despite methodological adjustments. Consequently, in the absence of high level of evidence data, prescription of RT is highly variable by center and subject to dogma or bias. Expert consensus favors preoperative RT over postoperative RT to limit morbidity when RT is considered. STRASS was designed as an open-label, randomized phase 3 superiority trial aiming to evaluate the impact of preoperative RT on the abdominal recurrence-free survival rate (ARFS), defined by one of the following events: progressive disease or patient becoming American Society of Anesthesiologists (ASA) 3 on RT, macroscopically incomplete (R2) resection, sarcomatosis, and local relapse.

Added value of this study To our knowledge, this is the first large, international, randomized trial in primary, localized RPS successfully completed, proving that critical questions in a rare cancer such as sarcoma can be successfully addressed, through multi-institutional collaborations. With 43 months of follow up, the trial is negative with similar ARFS in both groups (RT + surgery and surgery alone) and the same OS

Implications of all the available evidence Preoperative RT cannot be considered as a standard of care for RPS patients.

INTRODUCTION

Retroperitoneal sarcomas (RPS) are rare, with an annual incidence of 0.76 new cases per 100,000 people (1). The only potentially curative treatment for primary RPS is surgery (2); however, rates of locoregional abdominal recurrence are high (3,4), even at high volume centers (5,6). The heterogeneity of retroperitoneal sarcomas with different biological behaviour, response to treatment and oncological risks according to subtypes render a homogenous therapeutic approach difficult and explain the great variability in outcome observed in the past. Currently, data supporting radiotherapy (RT) in primary retroperitoneal sarcoma (RPS) are limited, and justification for its use has been extrapolated from its established role in extremity soft tissue sarcoma (STS) (7, 8). To date, only one randomized trial evaluating external beam RT in RPS has been attempted (ACOSOG-Z9031, NCT00091351), but that study failed to accrue and was closed after enrolling fewer than 20 patients. Phase 1 and 2 trials have been reported, but they evaluated safety and/or feasibility rather than superiority of a multimodality approach. Results of retrospective studies, including analyses of large national databases, investigating the role of RT are contradictory (9, 10). In the absence of high-level of evidence data, prescription of RT is highly variable by center. EORTC-62092, a phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for RPS (STRASS) was designed as an open-label, randomized superiority trial aiming to evaluate the impact of preoperative RT on abdominal recurrence-free survival (ARFS), addressing a gap in knowledge. This is the first transatlantic sarcoma local treatment trial completed successfully. The final analysis of the primary endpoint is reported herein.

METHODS

Study design and participants

We enrolled patients 18 years of age or older with histologically documented and centrally reviewed, localized, primary STS of the retro or infra-peritoneal spaces of the pelvis (11,12), unifocal, non-metastatic, not previously treated, WHO performance status ≤ 2 , and with an American Society of Anesthesiologist (ASA) (13) score ≤ 2 . The tumor had to be both operable and suitable for RT based on evaluation by an institutional multidisciplinary tumor board.

Other eligibility criteria included: no extension through the sciatic notch or across the diaphragm, contrast-enhanced chest, abdomen, and pelvis computed tomography (CT) scan or magnetic resonance imaging (MRI) performed within the 28 days prior to randomization, with radiologically measurable disease (RECIST 1.1), absence of history of bowel obstruction or mesenteric ischemia or severe chronic inflammatory bowel disease, calculated creatinine clearance ≥ 50 ml/min and functional contra-lateral kidney, normal bone marrow and hepatic

function, cardiac function less or equal to NYHA II, normal 12 lead ECG, negative pregnancy test within 3 weeks prior to the first day of study treatment, and no co-existing malignancy within the last 5 years except for adequately treated basal cell carcinoma of the skin or carcinoma in situ of the cervix.

Patients were ineligible if a macroscopically incomplete (R2) surgery was anticipated on the pre-randomization CT scan or the following histological sub-types: gastrointestinal stromal tumor, rhabdomyosarcoma, primitive neuroectodermal tumor or other small round blue cell sarcoma, osteosarcoma, chondrosarcoma, aggressive fibromatosis, or sarcomatoid or metastatic carcinoma. Written informed consent protocol was obtained prior to randomization. The study protocol was approved by the institutional review boards or ethics committees of all participating institutions.

Randomization and masking

This is an open-label, randomized phase III superiority trial designed to demonstrate improved ARFS in primary RPS treated with preoperative RT plus surgery compared to surgery alone. Patients were randomly assigned 1:1 centrally by EORTC headquarters, using an interactive web response system, to receive either en bloc curative-intent surgery alone (S) or preoperative radiotherapy 50.4 Gy (28 daily fractions) followed by en bloc curative-intent surgery (RT/S). Randomization was stratified by hospital and performance status (PS) (0-1 vs 2) using a minimization algorithm. It was not balanced by histologic subtype. No masking of treatment assignments was possible because of differences in treatment. Note that only 1 patient with PS 2 was entered in the study, therefore in practice the randomization was stratified only by hospital.

Procedures

Multivisceral en bloc curative-intent surgery was performed within 4 weeks following randomization in the S group and within 4 to 8 weeks from end of RT in the RT/S group. The objective was a macroscopically complete (R0/R1) resection of the tumor mass with en bloc organ resection as necessary, based on preoperative assessment and intraoperative findings. The operative report had to indicate: whether or not sarcomatosis was discovered during laparotomy, whether or not surgery was macroscopically complete, whether or not peroperative tumor rupture occurred, and whether or not organs that were not macroscopically involved were systematically resected.

In the RT/S group, preoperative radiotherapy was delivered via a 3-dimensional conformal radiotherapy (3DCRT) or intensity modulated radiotherapy (IMRT) technique (including tomotherapy) conducted according to EORTC quality assurance in radiotherapy (QART) guidelines. A Digital Data Integrity Quality Assurance (DDIQA) procedure including a specific dummy run (DR) was mandatory for all centers for their selected irradiation technique prior to authorization. The selection of the technique was left to the discretion of each center, but it had

to then be applied for all of the center's patients included in the trial. If centers wanted to switch from 3DCRT to IMRT, they had to undergo a new DDIQA procedure. RT was started within 8 weeks after randomization in the same center as surgery. The prescribed dose was 50.4 Gy in 28 once-daily 1.8 Gy fractions, five fractions per week over 5 1/2 weeks. The gross tumor volume (GTV) included the gross disease as visualized on the planning CT scan, any co-registration and any applicable diagnostic images. The clinical target volume (CTV) had to include the GTV with a geographic expansion of 5-6 mm depending on the CT slice thickness (3-5 mm). The planning target volume (PTV) included CTV plus an additional geometrical margin of 9 mm (anteriorly and medially) and 12 mm (superiorly, inferiorly, posteriorly and laterally) to take into account patient set-up uncertainties and organ motion. According to the protocol recommendations, at least 95% of the PTV should receive 95% of the prescribed dose and no more than 10% of the PTV should receive > 107% of the prescription dose. All dose constraints regarding the contralateral kidney, the spinal cord, the liver and bowel within the peritoneal cavity had to be respected. There was a rigid program of radiotherapy quality assurance: the first 3 cases of any participating center were checked by the study QART team within the first week of radiotherapy. Details on treatments are in the full protocol accessible at: <http://www.eortc.be/services/doc/protocols/62092-22092-v3.1.pdf>.

Contrast-enhanced chest, abdomen and pelvis CT or MRI were performed within 28 days prior to randomization. Follow up scans were performed 14 weeks after randomization in the S group and 2 weeks after completing radiotherapy in the RT/S group. Thereafter, follow-up scans in both arms were planned at 24 weeks and every 12 weeks subsequently during the first year and then every 6 months until recurrence or death.

Blood counts, serum chemistry test (bilirubin, creatinine, transaminases, alkaline phosphatase, LDH, albumin) and renal function (clearance creatinine), were done within 21 days before randomization, and the 15th and 60th day after the surgical procedure. During follow up these exams were done at week 14, 24, 36, 48 and then every 12 months until recurrence or death. In the RT/S group, complete blood count and serum chemistry tests were checked every 2 weeks preoperatively during radiotherapy.

Toxicity was graded using the Common Terminology Criteria for Adverse Events CTCAE V.4.0. (14). For 60 days after the date of surgery in both arms, severity of surgical morbidity was assessed using the Clavien - Dindo scale (15).

Withdrawal criteria were disease progression, occurrence of second malignancy, unacceptable toxicity based on the investigator's judgment, patient decision and patients for whom surgery was expected to be R2 on the CT-scan performed two weeks after the end of radiotherapy in the RT/S group.

Outcomes

The primary endpoint was ARFS measured from date of randomization to date of abdominal relapse or death, whichever occurred first. Abdominal recurrence was defined by one of the following events: local/abdominal or distant progressive disease during preoperative radiotherapy (as per RECIST 1.1), tumor or patient becoming inoperable (ASA score of 3 or involvement of superior mesenteric artery, aorta, or bone), peritoneal metastasis found at surgery, macroscopic residual disease left in at surgery (R2 resection), or local relapse (after macroscopically complete resection). Liver metastases were regarded as distant metastatic events. Patients with distant metastases were followed until local failure was detected. Patients without one of these events were censored at the date of last follow-up.

Secondary endpoints included tumor response to preoperative radiotherapy (RECIST 1.1), metastasis-free survival (MFS), abdominal recurrence-free interval (ARFI), overall survival (OS), safety and quality of life (see appendix). MFS was defined from the date of randomization to the date of occurrence of distant metastases or death, whichever occurred first (alive and metastases free patients were censored at the date of last follow-up). Abdominal Recurrence Free Interval (ARFI) was measured from the date of randomization to the date of abdominal relapse. Death in the absence of abdominal failure and distant metastases diagnosed before abdominal failure were considered competing risks for this endpoint. ARFI is described using cumulative incidence curves, and compared between the treatments arms using a Fine and Gray model. OS was defined as the time measured from the date of randomization to the date of death, whatever the cause.

Statistical analysis

The primary trial objective was to test for a difference in ARFS between the two treatment arms. The number of events and sample size were determined to provide 90% power for detecting a HR=0.52 (which corresponds to a 20% difference in ARFS rate at 5 years, from 50% in the control group to 70% in the experimental group), at a global 2-sided 5% significance level, assuming ARFS followed an exponential distribution in both groups. This test required 102 events at the time of final statistical analysis. With 256 patients planned to be randomized during 39 months, this number of events was expected to occur approximately 41 months after last patient randomized.

Two early safety checks were foreseen by the protocol, after 33 and after 66 patients were treated with each regimen; with the aim of stopping the study early if the preoperative radiotherapy increased the rate of reoperation by 20% or increased the proportion of inoperable tumors by 12% compared to the control group.

Time to event endpoints are described using Kaplan Meier curves in the two treatment arms (16). Median and associated non-parametric 95% confidence intervals (CI) are reported; comparison was by Cox proportional

hazards. All survival analyses are performed in the intent-to-treat population. Safety is analyzed in all randomized patients who have started their allocated treatment (have at least been operated or received one fraction of irradiation).

To protect against time assessment bias inherent to the different follow-up, the protocol foresaw the following corrections to be taken into account by the statistical analysis: abdominal recurrences occurring prior to the first assessment at 14 weeks were counted as occurring at week 14, and any progression occurring after 14 weeks but prior to or during week 24 were counted as occurring at week 24. This correction was not applied to patients for whom death was the first event.

In 2017, upon review of interim results of the study, the Independent Data Monitoring Committee (IDMC) recommended two (unplanned) sensitivity analyses (SA) for the primary endpoint: (1) SA1: patients were considered as having no event if they subsequently had macroscopically complete (R0/R1) resection despite local progression on RT, and (2) SA2: patients were considered as having no event if the surgery was a complete R0/R1 resection, regardless of local progression on RT or operability criteria (ASA score 3).

For exploratory purposes, outcomes of the liposarcoma (LPS) and leiomyosarcoma (LMS) subgroups were also analyzed. These post-hoc analyzes were unplanned.

We used SAS v9.4 for statistical analyses. This study is registered with ClinicalTrials.gov, number. NCT01344018
The cut-off date for this report was March 06, 2019.

Role of the funding source

The STRASS trial [62092-22092] was an international academic trial funded by EORTC and EUROSARC (FP7 Grant agreement ID: 278742). EORTC had a role in study design, data collection, data analysis, data interpretation, and writing of the report. Data were collected by investigators and associated site personnel, analyzed by statisticians (SL) working in EORTC headquarters, and interpreted by members of the steering committee. Raw data are available from SL. The corresponding author bore the final responsibility for the decision to submit for publication.

RESULTS

A total of 266 patients were registered by 31 institutions in Europe (Belgium, Denmark, France, Germany, Italy, the Netherlands, Norway, Poland, Spain, Sweden, and United Kingdom), Canada, and USA between January 18, 2012 and April 10, 2017 (appendix p 9 and 11). Clinical and pathological characteristics are shown in Table 1. Consort diagram is shown in Figure 1. Seventeen patients were deemed ineligible (5 in S group and 12 in RT/S

group). Median time to local treatment was 3 weeks (range 0.3-9.1) in the S group and 3.3 weeks (range 0 – 8) in the RT/S group. There was a delay of more than 48 h in the timing of surgery in 13 and 4 pts in S and RT/S groups, respectively (site organization, n=14; pulmonary embolism after RT, n=1; toxicity after RT, n=2). Intraoperative findings were not consistent with the pre-operative imaging in 5 (3.9%) of 128 and 7 (5.9%) of 119 patients in the S and RT/S groups. This resulted in 2 patients with a significant strategy change (1 had no resection, 1 had a multi-fragment resection).

One patient in each group did not undergo resection based on intraoperative findings. Duration of surgery was similar in both groups (287.5 and 300 minutes in S and RT/S groups). The most commonly resected organs were kidney (78.1% and 83.2%), colon (73.4% and 77.3%), and psoas or its aponeurosis (73.5% and 79%) of 128 and 119 patients in the S and RT/S groups respectively. According to operative reports, piecemeal resection was performed in 5 (3.9%) and 4 (3.4%) patients in the S and RT/S groups, respectively. Details of surgery, organs resected, and reason for resection (as part of a systematic en bloc approach or because of macroscopic invasion) are shown in Table 2.

RT technique was IMRT for 120 patients (95%) and 3DCRT for 7 patients (5%). Protocol compliance for RT was 65% (9% minor deviations, 26% major deviations). Median total dose for both IMRT and 3 DCRT were 50.4Gy (range IMRT: 7.2-66.6; range 3 DCRT: 33.0-50.4). Median dose per fraction given was 1.8 Gy (1.8-3.0). Seven patients had a deviation from the protocol on doses given (3 had RT dose reduction for GI toxicity, 3 chose to stop RT, 1 had dosimetric error (the patient who received 66.6 Gy)).

The correction against time assessment bias inherent to the different follow-up was applied to 58 patients, 23 in the S group and 35 in the RT/S group, mainly on the event times of patients with the following events.

With a median follow-up of 43.1 months (IQR 28.8-59.2), 121 events were reported in the two study arms: 61 in S group and 60 in RT/S group (appendix page 7). Corresponding ARFS at 3 years was 58.7% (95% CI 49.5-66.7) in S group and 60.4% (95% CI 51.4–68.2) in RT/S group (HR = 1.01, 95% CI 0.71-1.44, log rank p=0.95, Figure 2).

Forest plot by sarcoma subtype and grade are provided in appendix (appendix page 9).

Among 19 patients who progressed on RT and were counted as events for the primary endpoint, 3 developed distant metastases during RT and one developed hemodynamic shock during induction of anesthesia; 4 patients had no resection. However, 15 of the 19 patients did undergo macroscopically complete (R0/R1) resection (4 of whom later developed local recurrence). Three of the fifteen were qualified “non-operable” because they became ASA 3 after RT, but nevertheless underwent complete R0/R1 resection. Details on the 19 patients who progressed on RT are provided in appendix page 8. Based on the type of progression and whether surgery was

performed, they are taken into account differently in the sensitivity analysis, thereby resulting in different numbers of non-operated patients.

In SA1, where local progression on RT was not regarded as a primary endpoint event for those who undergo R0/R1 resection, 113 events were reported, 61 in S group and 52 in RT/S group (appendix page 7). ARFS at 3 years was 58.7% (95% CI 49.5-66.7) in S group and 66.0% (95% CI 57.1-73.5) in RT/S group (HR = 0.84, 95% CI 0.58-1.21).

In SA2, where neither local progression nor becoming medically unfit on RT was regarded as a primary endpoint event for those who undergo R0/R1 resection, 101 events were reported, 56 in S group and 45 in RT/S group (Table 2). ARFS at 3 years was 62.2% (95% CI 53.0-70.1) in S group and 71.3% (95% CI 62.6-78.3) in RT/S group (HR = 0.78, 95% CI 0.53-1.16).

In the post-hoc exploratory analysis amongst patients with LPS histology, 81 events were observed, 44 in the S alone group and 37 in the RT/S group (appendix page 7). Corresponding ARFS at 3 years was 60.4% (95% CI 49.8-69.5) in the S group and 64.7% (95% CI 54.2-73.4) in the RT/S group (HR = 0.83, 95%CI 0.54-1.29).

In SA1, 74 events were reported, 44 in S group and 30 in RT/S group (appendix page 7). Corresponding ARFS at 3 years was 60.4% (95% CI 49.8-69.5) in S group and 71.6% (95% CI 61.3-79.6) in RT/S group (HR = 0.64, 95% CI 0.40-1.01).

In SA2, 65 events were reported, 39 in S group and 26 in RT/S group (appendix page 7). Corresponding ARFS at 3 years was 65.2% (95% CI 54.5-74.0) in S group and 75.7% (95% CI 65.6-83.2) in RT/S group (HR = 0.62, 95% CI 0.38-1.02, Figure 3).

MFS at 3 years was 68.2% (95% CI 59.0-75.8) in the S group and 68.3% (95% CI 58.8-76.0) in the RT/S group (HR = 0.89, 95% CI 0.58-1.36 log rank p= 0.59) (appendix page 2). MFS at 3 years in the LPS subgroup was 78.3 (68.3-85.5) in the S group and 76.5 (66.0 - 84.1) in the RT/S group (HR1.02, 95% CI 0.57-1.8) (appendix page 3).

ARFI at 3 years was 32.0% (24.0-40.2) in the S group and 34.3% (95% CI 26.2-42.5) in the RT/S group (HR =1.09, 95% CI 0.74-1.60 Gray K sample test p =0.658) (appendix page 5).

ARFI at 3 years in the LPS subgroup was 33.4% (24.0-43.1) in the S group and 31.1% (22.1-40.5) in the RT/S group (HR = 0.91, 95% CI 0.58 -1.42) (appendix page 6).

Overall, 47 patients died: 22 in S group and 25 in RT/S group. Corresponding OS at 3 and 5 years was 84.6% (95% CI 76.5–90.1) and 79.4% (95% CI 69.1-86.5) in S group, and 84.0% (95% CI 76.3–89.4) and 76.7% (95% CI 66.9-84) in RT/S group (HR: 1.16, 95% CI 0.65–2.05; p=0.62) (appendix page 4).

Patients could be classified as partial response in 4 (3.3%), stable in 98 (82.3%), progressive disease in 19 (15.9%) and not evaluable or early death in 11 (9.2%) of 119 patients.

After both safety analyses, in August, 2014 (33 patients per arm) and September, 2015 (66 patients per arm), there was no significant increase in the rate of inoperable tumors and no significant increase in the rate of re-operations in the RT/S group. As per study protocol, these analyses were submitted to the IDMC, which confirmed that study recruitment should continue.

RT was temporarily interrupted due to Grade 2-3 gastrointestinal (GI) toxicity in 3 (3.1%) or for administrative reasons or intercurrent causes in 25 (19.6%) of 127 patients, and was prematurely stopped at doses ranging from 7.2-39.6 Gy in four (2 on patient request, 1 due to several toxicities ranging from grade 1 to grade 3, not GI exclusive, and 1 due to general condition worsening). During RT, patients experienced fatigue and GI toxicity, but grade 3 and 4 clinical toxicity were limited to 15 (11.8%) and 1 (0.8%) of 127 patients. Biologically, lymphopenia was notably observed as grade 3 in 68 (53.5%) and grade 4 in 30 (23.6%) of 127 patients (table 3, details in appendix page 12).

Transfusion was required during surgery for 24 (18.8%) patients in the S group and for 34 (28.6%) patients in the RT/S group. There were three post-operative deaths in the S group (2.3%) and 2 in the RT/S group (1.7%). Reoperation for any complication occurred in 14 patients (11%) in each group. The most frequent complication requiring re-operation was post-operative abdominal sepsis (fistula, abscess, peritonitis, septicemia), without any difference between the 2 groups. Post-operative bleeding was the second most common reason for re-operation, accounting for less than 4% in both groups (3.9% and 1.7% in S and RT/S groups). (Details on surgical morbidity and post-operative clinical and laboratory toxicities are displayed in Tables 2 and 3 and in appendix page 12). After nephrectomy, 9 (9%) of 100 patients had grades 2 to 4 toxicity in S group and 5 (5%) of 99 patients had a grade 2 creatinine toxicity in RT/S group (table 3).

DISCUSSION

To our knowledge, this is the first large, international, randomized trial in primary, localized RPS successfully completed, demonstrating that critical questions in a rare cancer such as sarcoma can be successfully addressed through multi-institutional collaboration. This practice-changing trial is negative, with similar ARFS and OS in both

groups at 3 years of follow-up. As a consequence, preoperative RT cannot be considered as the standard of care for RPS. This replaces the prior heterogeneous approach to RT for RPS, whereby its use varied considerably based on investigator and institutional biases.

Randomization offsets selection biases inherent in retrospective series, where RT is often a proxy for tumors that are smaller (median tumor size in STRASS 16 cm), in more favorable locations, easier to irradiate, easier to resect, and resected in academic centers (17). It must be acknowledged that the trial was powered to identify a 20% difference (entire cohort). Longer follow-up is required, and another analysis with 5 years of follow-up is planned. Of note, there were twice as many LR observed in the S group as in the RT/S group (39 in S, 17 in RT/S for all patients; 30 in S, 11 in RT/S for LPS subgroup (appendix page 7)). It is possible that this difference may be directly related to the impact of RT specifically in the LPS cohort. Although it is difficult to standardize the surgical technique given the varying clinical presentations, more than 60% LPS received a compartmental resection defined by the combination of at least nephrectomy and resection of colon and psoas (or its aponeurosis) (table 2). It is also possible that the magnitude of the RT gain could be reduced by the optimization of the surgical technique.

When STRASS was designed in 2010, the risk of progressive tumor growth or worsening performance status during neoadjuvant RT and the associated potential for rendering an operable patient inoperable was unknown. Therefore we defined a composite primary endpoint that encompassed potential preoperative parameters that could jeopardize surgery, in addition to local failure following surgery. Subsequently, multicenter studies from the TransAtlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG) refined our understanding of the biology of different RPS histologic subtypes. Specifically, we demonstrated that intraabdominal local recurrence was the predominant pattern of failure for LPS, whereas distant metastasis was the principal pattern of failure for LMS (18). In addition, uncertainty about feasibility of a randomized RPS trial, coupled with the premature closure of a previous North American trial, prompted us to select a broadly defined primary endpoint. During that same period, we established a network of collaborating surgeons and radiation oncologists, TARPSWG, who agreed to a similar operative and radiotherapeutic approach (19, 20, 21, 22) and who were committed to participating and enrolling in this trial.

Nineteen of 133 patients (14%) progressed on RT. Three of them developed distant metastases and thus did not undergo what would have been non-curative surgery. Fifteen of those 19 patients (11.2%) experienced local progression, but underwent macroscopically complete resection. The intermediate results led the IDMC to propose a sensitivity analysis whereby local progression on RT was no longer regarded as an event for the patients who subsequently achieved a complete resection (SA1) and regardless of operability (SA2). In addition, an exploratory analysis on patients with LPS was recommended, as this was the largest subgroup (nearly 75% of

the trial cohort) and the one with the highest risk of LR. In the subgroup analyses exploring LPS only, there was a 10% absolute ARFS benefit in favor of the RT/S group. Morbidity associated with RT was acceptable, likely because it was delivered preoperatively (21, 22, 23) and mostly via IMRT (95% of patients). Complication rates were lower in our trial than reported with postoperative radiotherapy, which ranged from 20% to 40% in previous retrospective series (24, 25, 26). RT dose of 50.4 Gy was also chosen according to the potential benefit/risks assessed by previous phase 1 and 2 studies to avoid bowel complications reported with higher doses and potential negative impact on surgery (27, 28). Rates of post-operative death (approximately 2%) and reoperation (11%) were similar in both arms and were in line with previous data from TARPSWG (29).

The trial results reported here are limited by relatively short follow up. Although total accrual seems relatively small, it is large for a rare cancer. Furthermore, there was no stratification based on histologic subtype as its differential impact on LR was only apparent in studies reported after trial initiation. Forest plot (appendix page 9) suggested preoperative RT may improve outcome in LPS and in low grade RPS, whereas there did not appear to be an RT benefit for LMS and high grade RPS. However, these results should be regarded with caution since all subgroups were individually small, a large proportion of patients was not evaluable for grade or differentiation (because of limitation based on biopsy specimen and impact of preoperative RT on those characteristics on final histology), and these subgroup analyses were not preplanned. We also cannot make any recommendation for the even rarer histologic subtypes which were grouped together in this trial. These results only apply to patients meeting all inclusion criteria, including good performance status and resectable tumors suitable for RT. Patients meeting these selection criteria achieved 5-year OS of 79.4% in the S group and 76.7% in the RT/S group, which was slightly better than in the retrospective collaborative series from TARPSWG (67% at 5 years) (18).

Considering RPS biology and the fact that our data do not support RT for LMS and high grade RPS, our next randomized study (STRASS 2,) will focus on these two groups. STRASS 2 (NCT04031677) is an international randomized trial with stratification by specific tumor histology, including only high-grade DDLPS and LMS. The primary objective will be to assess whether 3 cycles of preoperative chemotherapy improve the disease-free survival. In the experimental arm, patients will receive CT according to subtype: (Doxorubicin and Ifosfamide for high grade DDLPS and Doxorubicin and Dacarbazine for LMS). High quality observational data from RESAR study (NCT03838718), a prospective registry from the TARPSWG, could help refine which LPS subtypes may benefit from RT (30). The exact topography of LR was not registered in our trial. It is possible that increasing RT dose only to the posterior wall by means of proton beam or IMRT could increase efficacy, which is feasible up to an equivalent dose of 63 Gy (31); this is currently investigated in a phase 2 study (NCT01659203).

In conclusion, transatlantic collaboration between major RPS referral centers was critical to complete STRASS. Radiotherapy cannot be routinely recommended for all RPS patients. However, there may be some efficacy in LPS which should be further explored in a prospective clinical trial.

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Author's contribution

- SB, AG, CLP, SL, RH, SM, JYB participated in the design of the study
- All authors recruited patients, collected data, or both
- SB wrote the manuscript and all authors reviewed and approved the final version of the manuscript.

Declaration of interest

SB reports personal fees and non-financial support from Nanobiotix and PharmaMar, non-financial support from Pfizer outside the submitted work; AG reports personal fees from Novartis, Pfizer, Bayer, Lilly Oncology, SpringWorks and Nanobiotix outside the submitted work and grants and personal fees from PharmaMar outside the submitted work; CLP reports personal fees from Astra Zeneca, Amgen, Nanobiotix, Roche, Medscape, PrimeOncology, and Lilly outside the submitted work; P.R reports personal fees from Novartis, MSD, BMS, Roche, Pfizer, Blueprint Medicines, Pierre Fabre, Sanofi outside the submitted work ; PC reports personal fees from AbbVie and Astra Zeneca outside the submitted work; JYB reports grants from EUROSARC, LYRICAN, EURACAN, NETSARC+, and Intersarc during the conduct of the study; A.M. reports grants from NHS funding to the NIHR Biomedical Research Centre for Cancer at The Royal Marsden Hospital and The Institute of Cancer Research during the conduct of the study, APDT reports personal fees from Roche, PharmaMar and Bayer outside the submitted work. CJS, DS, PM, FVC, SS, ES, MR, CPR, CS, CH, MF, JJS, EHB, SL, SM, HG, DH, ADP and RLH declare no competing interests

Data sharing

The data of the study will be made available upon request. A request can be submitted via <https://www.eortc.org/data-sharing/>

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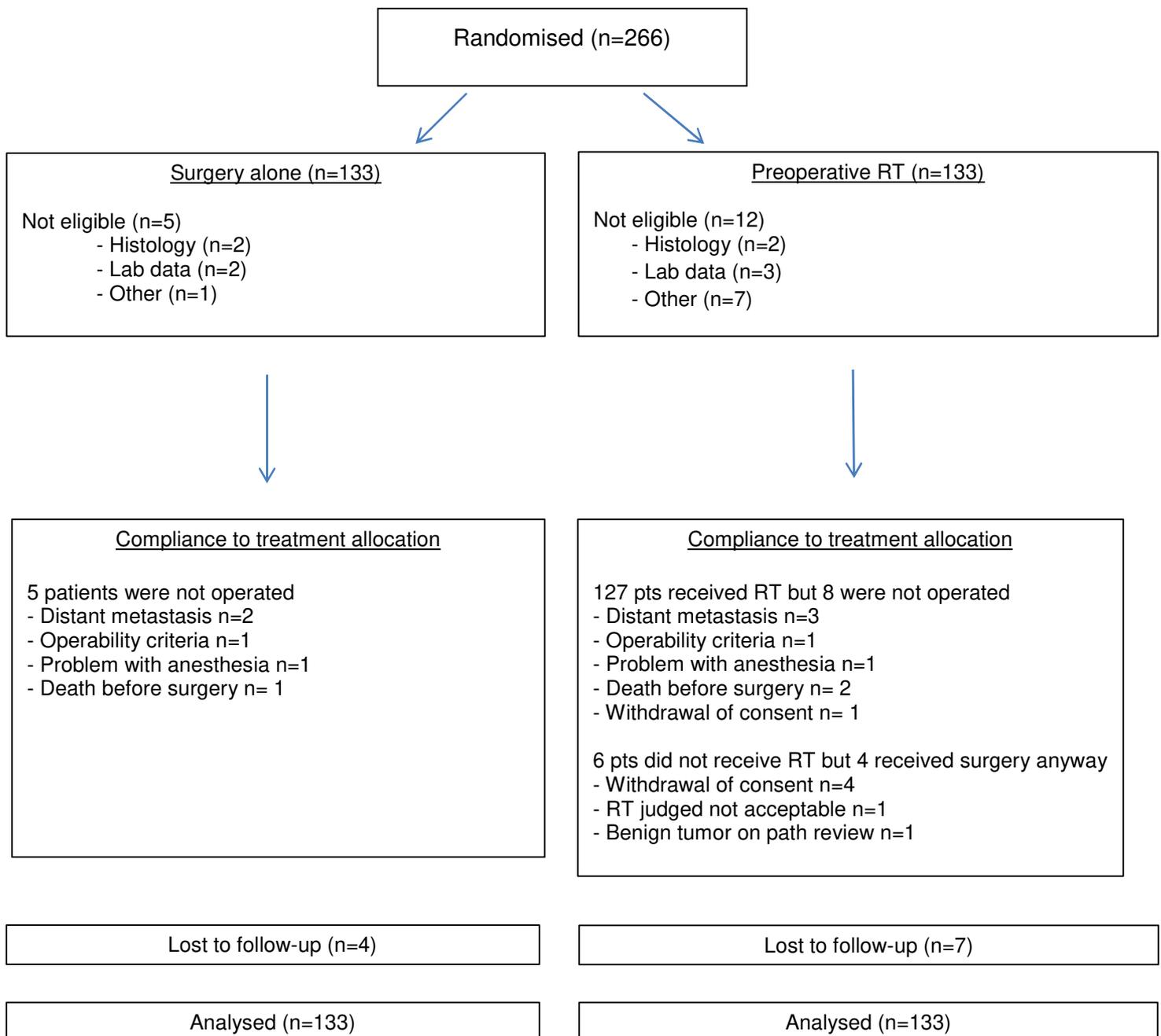
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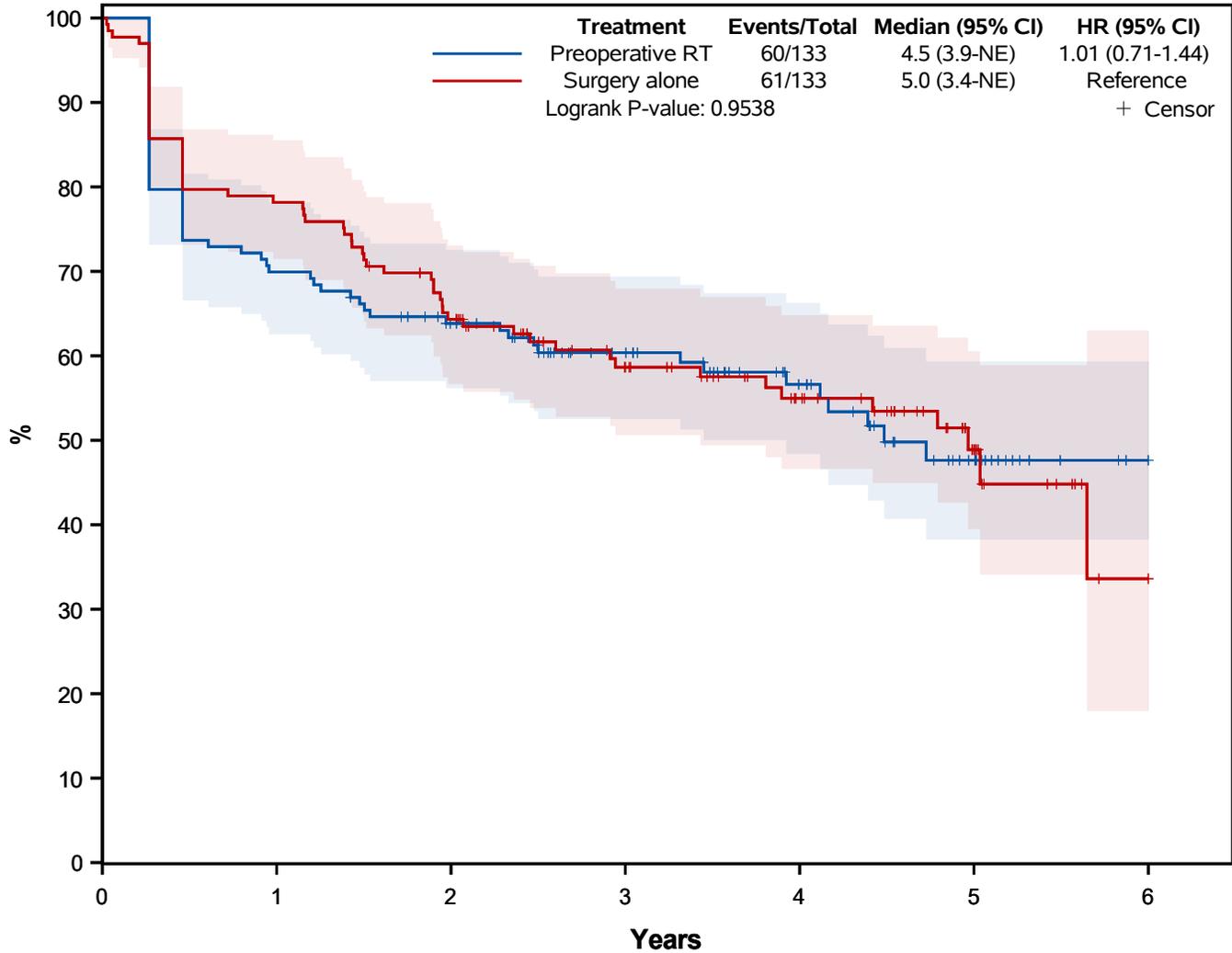
Figure 1: Randomization and Follow-up among Patients in STRASS Trial

Figure 2: Abdominal Recurrence-Free Survival (ARFS) in all population

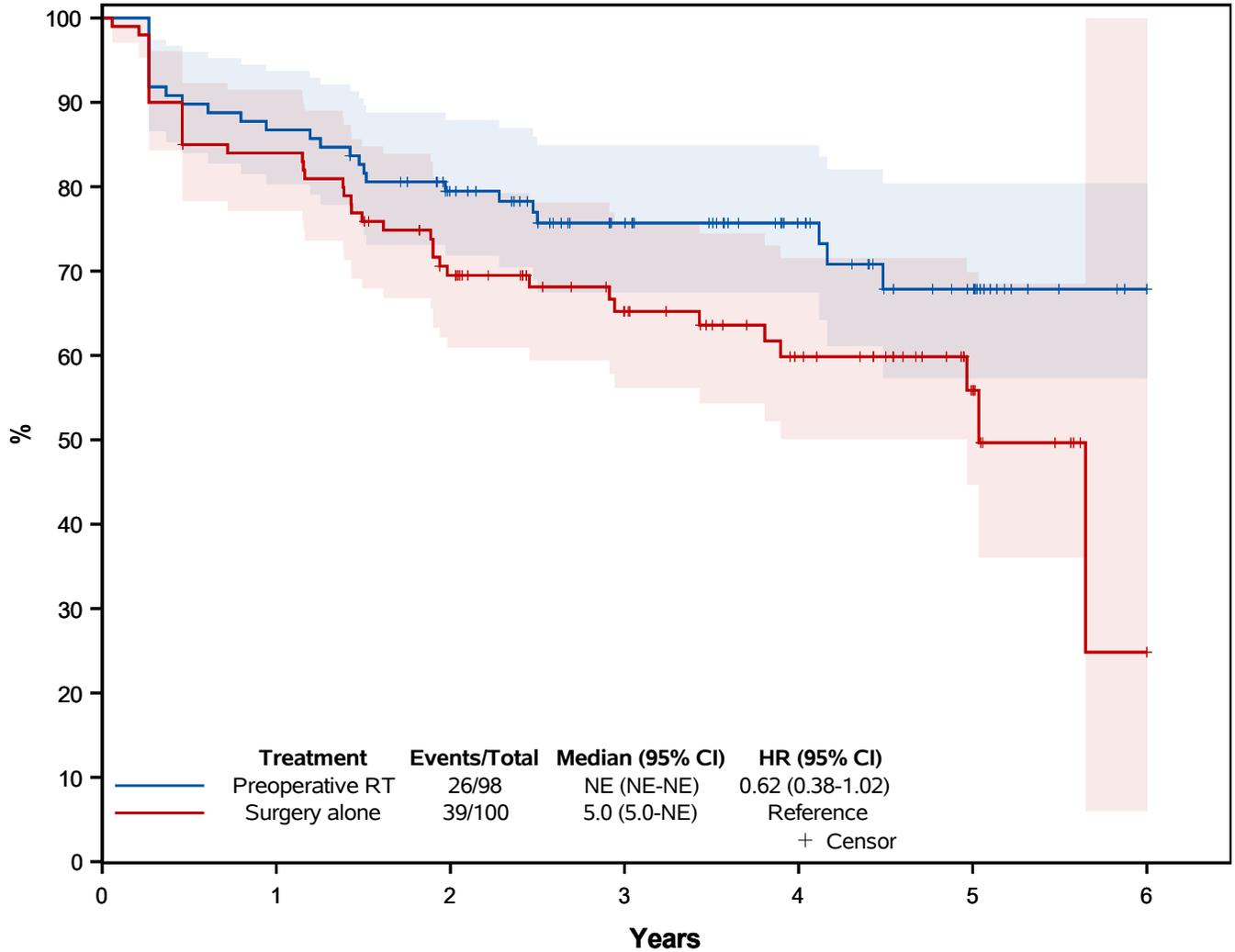
Figure 3: SA2: Abdominal Recurrence-Free Survival (ARFS) in liposarcoma (LPS) population

Figure 1: Randomization and Follow-up among Patients in STRASS Trial





	Number at risk (Number censored)						
	0	1	2	3	4	5	6
Preoperative RT	133 (0)	93 (0)	78 (7)	57 (24)	38 (40)	17 (56)	3 (70)
Surgery alone	133 (0)	103 (1)	82 (4)	57 (23)	40 (37)	17 (57)	2 (70)



	Number at risk (Number censored)						
	0	1	2	3	4	5	6
Preoperative RT	98 (0)	85 (0)	69 (9)	50 (25)	34 (41)	18 (54)	4 (68)
Surgery alone	100 (0)	83 (1)	64 (6)	44 (23)	30 (34)	13 (50)	1 (60)

Table 1 : Baseline characteristics

	Surgery alone (N=133) N (%)	Pre-operative RT (N=133) N (%)	Total (N=266) N (%)
Age: Median /Range	61 (26 – 81)	61 (24 – 83)	61 (24 – 83)
Male/Female	67 (50.4)/ 66 (49.6)	71 (53.4)/ 62 (46.6)	138 (51.9)/128 (48.1)
WHO performance status			
0/1	100 (75.2)/33 (24.8)	110 (82.7)/ 22 (16.5)	210 (78.9)/ 55 (20.7)
2	0 (0.0)	1 (0.8)	1 (0.4)
Pre-op Biopsy			
Imaging-guided /Surgical	123 (92.5)/10 (7.5)	119 (89.5)/ 12 (9.0)	242 (91.0)/ 22 (8.3)
Missing	0 (0.0)	2 (1.5)	2 (0.8)
Median Tumor size (mm) /Range	167/46 - 480	160/37 - 340	160/37 - 480
Histological subtype			
Well-differentiated liposarcoma	42 (31.6)	46 (34.6)	88 (33.1)
Dedifferentiated liposarcoma	54 (40.6)	51 (38.3)	105 (39.5)
Other liposarcoma	4 (3.0)	1 (0.8)	5 (1.9)
<i>All sub-types liposarcoma</i>	<i>100 (75.2)</i>	<i>98 (73.7)</i>	<i>198 (74.5)</i>
Leiomyosarcoma	22 (16.5)	16 (12.0)	38 (14.3)
Other	11 (8.3)	18 (13.5)	29 (10.9)
Missing	0 (0.0)	1 (0.8)	1 (0.4)
Grade of the tumor (biopsy)			
Low	43 (32.3)	44 (33.1)	87 (32.7)
Intermediate	38 (28.6)	47 (35.3)	85 (32.0)
High	19 (14.3)	12 (9.0)	31 (11.7)
Not evaluable	21 (15.8)	17 (12.8)	38 (14.3)
Missing	12 (9.0)	13 (9.8)	25 (9.4)

Table 2: Surgery and per/post-operative complications

	Surgery alone	Preoperative RT
	(N=128)	(N=119)
	N (%)	N (%)
Intraoperative findings in alignment with the preoperative imaging procedures (No/Yes/ Missing)	5 (3.9)/ 123 (96.1)/ 0 (0.0)	7 (5.9)/ 111 (93.3)/ 1 (0.8)
Resection of the sarcoma (No/Yes, macroscopically complete in one bloc/Yes, in several pieces)	1 (0.8)/ 122 (95.3)/ 5(3.9)	1 (0.8)/ 114 (95.8)/ 4(3.4)
Sarcomatosis discovered during surgery	7(5.5)	7(5.9)
Organ resection (Yes/macroscopically involved/systematically resected)		
Kidney +/- adrenal gland	100(78.1)/ 43 (33.6)/ 57(44.5)	99(83.2)/ 53 (44.5)/46 (38.7)
Psoas muscles or aponevrosis	94(73.5)/ 28 (21.9)/ 66 (51.6)	94(79)/ 25 (21.0)/ 69 (58.0)
Colon/meso	94(73.4)/42 (32.8)/ 52 (40.6)	92(77.3)/38 (31.9)/ 54 (45.4)
Diaphragm	31(24.2)/19 (14.8) /12 (9.4)	39(32.8)/ 25 (21.0) / 14 (11.8)
Spleen	25(19.6)/ 7 (5.5) /18 (14.1)	21(17.7)/ 4 (3.4) / 17 (14.3)
Pancreas tail	20(15.6)/10 (7.8) /10 (7.8)	19(16)/ 7 (5.9) / 12 (10.1)
Small intestine	12(9.4)/ 7 (5.5)/ 5 (3.9)	17(14.2)/ 6 (5.0) /11 (9.2)
Inferior vena cava	8(6.3)/ 8 (6.3) /0 (0.0)	8(6.7)/ 7 (5.9) / 1 (0.8)
Iliac vessels	8(6.2)/ 5 (3.9) /3 (2.3)	12(10.1)/ 8 (6.7)/ 4 (3.4)
Pancreas head	3(2.4)/ 1 (0.8) / 2 (1.6)	2(1.6)/1 (0.8) / 1 (0.8)
Liver	4(3.1)/ 3 (2.3)/ 1 (0.8)	9(7.6)/7(5.9) / 2 (1.7)
Bladder	2(1.6)/1 (0.8) / 1 (0.8)	2(1.6)/1 (0.8) / 1 (0.8)
Rectum	3(2.4)/ 1 (0.8)/ 2 (1.6)	4(3.3)/ 3 (2.5)/ 1 (0.8)
Resection including (at least) colon /Kidney/ Psoas muscles or aponevrosis (All patients)	69 (54%)	69 (58%)
Resection including (at least) colon /Kidney/ Psoas muscles or aponevrosis (LPS patients)	58(60%)	60 (67%)
Resection including (at least) colon /Kidney/ Psoas muscles or aponevrosis (LMS patients)	9(41%)	3(19%)
Any per operative complication (Yes/ No/missing)	35(27.3)/ 92(71.9)/1(0.8)	44(37)/ 75 (63.0) / 0(0.0f)
Transfusion during surgical procedure (Yes/No/missing)	24(18.8)/ 65(50.8)/ 39(30.5)	34(28.6)/ 50 (42.0)/35 (29.4)
Procedure requiring digestive/urinary stomy	2 (1.6)/ 1 (0.8)	4 (3.4)/ 1 (0.8)
Post-operative femoral palsy	1(0.8)	2(1.6)
Duration of surgery Median (min) (Range)	287.5 (97 - 829)	300 (102 - 888)

		Surgery alone	Preoperative RT
		(N=128)	(N=119)
		N (%)	N (%)
Duration hospitalization (days)	Median (Range)	12 (2-59)	14 (4-89)
Post-operative death		3 (2.3)	2 (1.7)
Re operated		14 (10.9)	14 (11.8)

Table 3 Clinical and biological toxicity in the pre-operative period and follow up

Grade (CTCAE V.4.0.)	During RT (N=127) N (%)				On Study								
	1+2	3	4	5	RT/S group (N=127) N (%)				S group (N = 128) N (%)				
					1+2	3	4	5	1+2	3	4	5	
Clinical disorder													
Patient's worse grade	106 (83.4)	15 (11.8)	1 (0.8)	1 (0.8)	75 (59.1)	39 (30.7)	8 (6.3)	2 (1.6)	74 (57.8)	26 (20.3)	3 (2.3)		
Blood and lymphatic system	2 (1.6)				4 (3.1)								
Cardiac	1 (0.8)			1 (0.8)	2 (1.6)		1 (0.8)	2 (1.6)	3(2.4)				
Ear and labyrinth	1 (0.8)				3 (2.4)								
Endocrin					3 (2.4)				1 (0.8)				
Eye	2 (1.6)				2 (1.6)				2 (1.6)				
Gastro intestinal	109 (85.2)	4 (3.1)		1 *** (0.8)	98 (77.2)	15 (11.8)	2 (1.6)	1 (0.8)	42 (32.8)	11 (8.6)	1 (0.8)		
General (edema limbs, fatigue, fever, pain)	84 (65.6)	5 (3.9)			88 (69.3)	8 (6.3)			41 (32.0)				
Immune system					1 (0.8)								
Infection	3 (2.4)	1 (0.8)			10 (7.9)	8 (6.3)	1 (0.8)		8 (6.2)	1 (0.8)			
Injury and procedural complications (Burn, dermatitis radiation, spinal fracture, wound Complication)	30 (23.6)				41 (32.3)	4 (3.1)			7 (5.4)	4 (3.1)			

Investigation (weight loss)	50 (29.4)	1 (0.8)			59 (46.5)	7 (5.5)			24 (18.7)	3 (2.3)		
Metabolism and nutrition	48 (37.8)	6 (4.7)	1 (0.8)		53 (41.7)	12 (9.4)	1 (0.8)		11 (8.6)	5 (3.9)	1 (0.8)	
Musculo skeletal	25 (19.6)	1 (0.8)			33 (25.9)	4 (3.1)			25 (18.7)	1 (0.8)		
Neoplasms benign, malignant and unspecified	4 (3.1)	1 (0.8)			4 (3.1)	1 (0.8)			2 (1.6)			
Nervous system	24 (18.9)				45 (35.4)	3 (2.4)			31 (24.2)	2 (1.6)	1 (0.8)	
Psychiatric	7 (5.5)	1 (0.8)			11 (8.7)	2 (1.6)			3 (2.3)			
Renal and urinary	7 (5.5)				15 (11.8)	3 (2.4)	1 (0.8)		10 (7.8)	4 (3.1)		
Reproductive and breast					5 (3.9)	1 (0.8)			9 (7.0)			
Respiratory	13 (10.3)	1 (0.8)			18 (14.1)	3 (2.4)	1 (0.8)		9 (7.0)	2 (1.6)		
Skin and subcutaneous	14 (11.0)	1 (0.8)			15 (11.8)	1 (0.8)			7 (5.5)			
Vascular	8 (6.3)	3 (2.4)	1 (0.8)		13 (10.2)	7 (5.5)	2 (1.6)		12 (9.4)	6 (4.7)		
Biological events												
Anemia	17 (13.4)	7 (5.5)	**	0	46 (36.2)	15 (11.8)	**	0	29 (22.7)	10 (7.8)	**	
Leukopenia*	22 (17.3)	0	0	0	28 (22.0)	0	0	0	2 (1.6)	0	0	0
Lymphopenia*	15 (11.8)	68 (53.5)	30 (23.6)	0	18 (14.2)	67 (52.8)	31 (24.4)	0	14 (10.9)	1 (0.8)	0	0
Thrombocytopenia*	1(0.8)	0	0	0	2 (1.6)	0	1(0.8)	0	1(0.8)	0	1(0.8)	0
Hyperbilirubinemia	9 (7.1)	0	0	0	20 (15.7)	1 (0.8)	0	0	18 (15.0)	0	0	
Hypoalbuminemia*	14 (11.0)	7 (5.5)	0	0	42 (33.1)	15 (11.8)	0	0	34 (26.6)	5 (3.9)	0	0

Alkaline phosphatase	29 (22.8)	0	0	0	80 (63.0)	2 (1.6)	0	0	43 (33.6)	1 (0.8)	0	0
SGPT	24 (18.9)	0	0	0	54 (42.5)	2 (1.6)	0	0	47 (36.7)	3 (2.3)	0	0
SGOT	25 (19.7)	0	0	0	50 (39.4)	1 (0.8)	0	0	30 (23.5)	1(0.8)	0	0
Serum creatinine	6 (4.7)	0	0	0	80 (63.0)	0	0	0	75 (58.6)	2 (1.6)	1 (0.8)	1(0.8)
Serum creatinine after nephrectomy					31/99 (31.3)	0	0	0	48/100 (48.0)	2 /100 (2.0)	1/100 (1.0)	0

* Due to ULN/LLN not being reported, it is not possible to distinguish between grade 0 and 1 as per CTCAE guidelines, so only grade 2 events are reported for these events.

** Grade 4 anemia according to CTCAE 4.0 cannot be determined based on hemoglobin values (described as “Life-threatening consequences; urgent intervention indicated”)

*** Patient completed RT, but within one month after RT (before surgery) had grade 5 cardiac arrest, hematemesis and upper gastrointestinal haemorrhage