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

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See Comment page 1257

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Summary

Background Unlike for extremity sarcomas, the efficacy of radiotherapy for retroperitoneal sarcoma is not established. The aim of this study was to evaluate the impact of preoperative radiotherapy plus surgery versus surgery alone on abdominal recurrence-free survival.

Methods EORTC-62092 is an open-label, randomised, phase 3 study done in 31 research institutions, hospitals, and cancer centres in 13 countries in Europe and North America. Adults (aged ≥18 years) with histologically documented, localised, primary retroperitoneal sarcoma that was operable and suitable for radiotherapy, who had not been previously treated and had a WHO performance status and American Society of Anesthesiologists score of 2 or lower, were centrally randomly assigned (1:1), using an interactive web response system and a minimisation algorithm, to receive either surgery alone or preoperative radiotherapy followed by surgery. Randomisation was stratified by hospital and performance status. Radiotherapy was delivered as 50·4 Gy (in 28 daily fractions of 1·8 Gy) in either 3D conformal radiotherapy or intensity modulated radiotherapy, and the objective of surgery was a macroscopically complete resection of the tumour mass with en-bloc organ resection as necessary. The primary endpoint was abdominal recurrence-free survival, as assessed by the investigator, and was analysed in the intention-to-treat population. Safety was analysed in all patients who started their allocated treatment. This trial is registered with ClinicalTrials.gov, NCT01344018.

Findings Between Jan 18, 2012 and April 10, 2017, 266 patients were enrolled, of whom 133 were randomly assigned to each group. The median follow-up was 43·1 months (IQR 28·8–59·2). 128 (96%) patients from the surgery alone group had surgery, and 119 (89%) patients in the radiotherapy and surgery group had both radiotherapy and surgery. Median abdominal recurrence-free survival was 4·5 years (95% CI 3·9 to not estimable) in the radiotherapy plus surgery group and 5·0 years (3·4 to not estimable) in the surgery only group (hazard ratio 1·01, 95% CI 0·71–1·44; log rank p=0·95). The most common grade 3–4 adverse events were lymphopenia (98 [77%] of 127 patients in the radiotherapy plus surgery group *vs* one [1%] of 128 patients in the surgery alone group), anaemia (15 [12%] *vs* ten [8%]), and hypoalbuminaemia (15 [12%] *vs* five [4%]). Serious adverse events were reported in 30 (24%) of 127 patients in the radiotherapy plus surgery group, and in 13 (10%) of 128 patients in the surgery alone group. One (1%) of 127 patients in the radiotherapy plus surgery group died due to treatment-related serious adverse events (gastropleural fistula), and no patients in the surgery alone group died due to treatment-related serious adverse events.

Interpretation Preoperative radiotherapy should not be considered as standard of care treatment for retroperitoneal sarcoma.

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Introduction

Retroperitoneal sarcomas are rare, with an annual incidence of 0·76 new cases per 100 000 people.[1] The only potentially curative treatment for primary retroperitoneal sarcoma is surgery;[2] however, rates of locoregional abdominal recurrence are high,[3,4] even at high volume centres.[5,6] The heterogeneity of retroperitoneal sarcomas with different biological behaviour, response to treatment, and oncological risks according to subtypes renders a homogeneous therapeutic approach difficult and explains the great variability in outcome that has been observed. Currently, data supporting radiotherapy in primary retroperitoneal sarcoma are limited, and justification for its use has been extrapolated from its

Research in context

Evidence before this study

Currently, data supporting the use of radiotherapy in primary retroperitoneal sarcoma are limited. Justification for its use has been extrapolated from its established role in extremity soft tissue sarcoma. To date, only one randomised trial evaluating the role of external beam radiotherapy in retroperitoneal sarcoma was attempted, 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 published up to Feb 19, 2020, reporting phase 1 and 2 trials that were not designed to establish superiority of radiotherapy. The available data for external-beam radiotherapy in retroperitoneal sarcoma come only from retrospective analyses, which have been limited by using radiotherapy preferentially for tumours that are smaller, in more favourable locations, easier to irradiate and resect, or resected in academic centres. The results and recommendations are contradictory, and consequently, the prescription of radiotherapy is highly variable and subject to dogma or bias. Expert consensus favours preoperative radiotherapy over postoperative radiotherapy to limit morbidity. We therefore aimed to evaluate the effect of preoperative radiotherapy on the abdominal recurrence-free survival rate.

Added value of this study

To our knowledge, this is the first large, international, randomised trial in primary, localised retroperitoneal sarcoma that has been successfully completed, showing that key questions in a rare cancer can be successfully addressed through multi-institutional collaborations. With 43 months of follow-up, the trial is negative, showing similar abdominal recurrence-free survival in patients receiving surgery alone and in those receiving preoperative radiotherapy plus surgery, and similar overall survival in the two groups.

Implications of all the available evidence

Preoperative radiotherapy cannot be considered as a standard of care for patients with retroperitoneal sarcoma.

established role in extremity soft tissue sarcoma.[7,8] To date, only one randomised trial evaluating external beam radiotherapy in retroperitoneal sarcoma has been attempted (ACOSOG-Z9031, NCT00091351), but that study failed to accrue and was closed after enrolling less than 20 patients. One trial[9] randomly assigned 35 patients, comparing 20 Gy intraoperative radiotherapy in combination with postoperative (35–40 Gy) external-beam radiotherapy, with postoperative external-beam radiotherapy (50–55 Gy) alone. In this trial,[9] patients who received intraoperative radiotherapy had less radiation-related enteritis but more frequent radiation-related peripheral neuropathy than control patients. Phase 1 and phase 2 trials have been reported, but they have evaluated safety, feasibility, or both, rather than the superiority of a multimodality approach.[10–12] The results of retrospective studies, including analyses of large national databases, that investigate the role of radiotherapy are contradictory.[13,14] In the absence of a high level of evidence, prescription of radiotherapy is highly variable by centre. To address a gap in knowledge, we aimed to evaluate the impact of preoperative radiotherapy on abdominal recurrence-free survival.

Methods

Study design and participants

EORTC-62092 (STRASS) is an open-label, randomised, phase 3 study done at 31 research institutions, hospitals, and cancer centres in Europe (France, Italy, UK, the Netherlands, Norway, Poland, Belgium, Denmark, Sweden, Spain, and Germany, in order of the number of inclusions), Canada, and the USA (appendix p 10). Eligible patients were aged 18 years or older with histologically documented, centrally reviewed, localised, primary soft tissue sarcoma of the retroperitoneal or infraperitoneal spaces of the pelvis.[15,16] The tumour had to be unifocal; non-metastatic; not previously treated, not extending through the sciatic notch or across the diaphragm; and not originating from bone structure, abdominal, or gynecological viscera; and both operable and suitable for radiotherapy as per evaluation by an institutional multidisciplinary tumour board. A contrast-enhanced chest, abdomen, and pelvis CT scan or MRI scan was required within 28 days before randomisation, with radiologically measurable disease (as per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1). Patients were required to have a WHO performance status of 2 or lower; an American Society of Anesthesiologist (ASA)[17] score of 2 or lower; and an absence of history of bowel obstruction, mesenteric ischaemia, or severe chronic inflammatory bowel disease. In addition, patients had to have normal function (calculated creatinine clearance ≥50 mL/min and functional contralateral kidney), normal bone marrow and hepatic function (white blood cell count $\geq 2{\cdot}5 \times 10^9$ cells per L, platelet count $\geq 80 \times 10^9$ cells per L, and total bilirubin <2 times upper limit of normal); cardiac function less than or equal to New York Heart Association class II; normal 12 lead electrocardiogram; a negative pregnancy test within 3 weeks before the first day of study treatment; adequate birth control measures; no relevant previous abdominal or pelvic radiation; no co-existing malignancy within the last 5 years, except for adequately treated basal cell carcinoma of the skin or carcinoma in the cervix; and no psychological, familial, sociological, or geographical conditions that could interfere with compliance with the study protocol.

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See **Online** for appendix

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

For the **study protocol** see http://www.eortc.be/services/doc/protocols/62092-22092-v3.1.pdf

Randomisation and masking

Patients were randomly assigned (1:1) centrally, at the headquarters of the European Organisation for Research and Treatment of Cancer (EORTC), using an interactive web response system, to receive either en bloc curative-intent surgery alone or preoperative radiotherapy followed by en-bloc curative-intent surgery. Randomisation was stratified by hospital and WHO performance status (0–1 *vs* 2) using a minimisation algorithm, and was not balanced by histological subtype. No masking of treatment assignments was possible because of the differences in treatment. It should be noted that only one patient with a WHO performance status of 2 was entered into the study, and therefore in practice the randomisation was stratified only by hospital.

Procedures

Multivisceral en bloc curative-intent surgery was done within 4 weeks of randomisation in the surgery alone group and within 4–8 weeks from the end of radiotherapy in the radiotherapy plus surgery group. The objective of surgery was a macroscopically complete (R0 or R1) resection of the tumour mass with en-bloc organ resection as necessary, based on preoperative assessment and intraoperative findings. The operative report had to indicate whether sarcomatosis was discovered during laparotomy, whether surgery was macroscopically complete, whether per-operative tumour rupture occurred, and whether organs that were not macroscopically involved were systematically resected.

In the radiotherapy plus surgery group, preoperative radiotherapy was delivered via a 3D conformal radiotherapy (3DCRT) or intensity modulated radiotherapy (IMRT) technique (including tomotherapy) done according to EORTC quality assurance in radiotherapy (as detailed in the protocol). Before authorisation, a Digital Data Integrity Quality Assurance procedure, including a specific dummy run, was mandatory for all centres for their selected irradiation technique. Technique selection was left to the discretion of each centre, but it had to then apply for all trial patients at that centre. For a centre to switch from 3DCRT to IMRT or vice versa, a new Digital Data Integrity Quality Assurance procedure was required. Radiotherapy was started within 8 weeks of randomisation in the same centre as surgery. The prescribed dose was 50·4 Gy in 28 once-daily fractions of 1·8 Gy, with five fractions per week during 5·5 weeks.

The gross tumour volume included the gross disease as visualised on the planning CT scan, any co-registration, and any applicable diagnostic images. The clinical target volume had to include the gross tumour volume with a geographic expansion of 5 mm for a CT slice of 5 mm, or of 6 mm for a CT slice of 3 mm. The planning target volume included the clinical target volume plus an additional geometrical margin of 9 mm anteriorly and medially and of 12 mm superiorly, inferiorly, posteriorly, and laterally, to account for patient set-up uncertainties and organ motion. According to the protocol recommendations, at least 95% of the planning target volume should receive 95% of the prescribed dose, and no more than 10% of the planning target volume should receive more than 107% of the prescription dose. Further dose constraints were used for the contralateral kidney, spinal cord, liver, and bowel within the peritoneal cavity and are detailed in the study protocol. There was a rigid programme of radiotherapy quality assurance: the first three patients treated at any participating centre were checked by the study quality assurance in radiotherapy team within the first week of radiotherapy.

Follow-up contrast-enhanced CT or MRI scans of the chest, abdomen, and pelvis were done 14 weeks after randomisation in the surgery group and 2 weeks after completing radiotherapy in the radiotherapy plus surgery group. Thereafter, follow-up scans in both groups were planned at 24 weeks after randomisation and every 12 weeks subsequently during the first year, and then every 6 months until recurrence or death. Response assessments were done by the investigators.

Blood counts, serum chemistry tests (bilirubin, creatinine, aminotransferases, alkaline phosphatase, lactate dehydrogenase, albumin), and renal function tests (creatinine clearance) were done within 21 days before randomisation and on day 15 and day 60 after the surgical procedure. During follow-up, these tests were done at week 14, week 24, week 36, week 48, and then every 12 months until recurrence or death. In the radiotherapy plus surgery group, complete blood count and serum chemistry tests were checked every 2 weeks preoperatively during radiotherapy.

As per the protocol, adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0[18] during the preoperative period and follow-up period (as of 60 days after surgery). For 60 days after surgery, the severity of surgical morbidity was assessed using the Clavien–Dindo scale.[19]

Withdrawal criteria were disease progression, occurrence of second malignancy, unacceptable adverse events (based on the investigator's judgment), patient decision, and the expectation that surgery would be macroscopically incomplete on the basis of the CT scan done 2 weeks after the end of radiotherapy in the radiotherapy plus surgery group.

Outcomes

The primary endpoint was investigator-assessed abdominal recurrence-free survival measured from randomisation to 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), tumour 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, or local relapse (after macroscopically complete resection). Liver metastases were regarded as distant metastatic events. Patients with distant metastases were followed up until local failure was detected. Patients without one of these events were censored at the date of the last follow-up.

Secondary endpoints were tumour response to preoperative radiotherapy (as per RECIST 1.1), metastasis-free survival, abdominal recurrence-free interval, overall survival, safety, and quality of life. Metastasis-free survival was defined from the date of randomisation to the date of occurrence of distant metastases or death, whichever occurred first (alive and metastases free patients were censored at the date of the last follow-up). The abdominal recurrence-free interval was measured from the date of randomisation 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. Overall survival was defined as the time measured from the date of randomisation to the date of death, whatever the cause. Patient-reported quality of life was introduced during the course of the trial via a protocol amendment, which required administering paper QLQ-C30 questionnaires at baseline, year 1, and year 5. Compliance was low and data were too sparse to allow any meaningful estimation of treatment differences, thus, results will not be reported.

	Surgery alone group (n=133)	Preoperative radiotherapy plus surgery group (n=133)
Age (years)	61 (53–67)	61 (52–68)
Sex		
Female	66 (50%)	62 (47%)
Male	67 (50%)	71 (53%)
WHO performance status		
0	100 (75%)	110 (83%)
1	33 (25%)	22 (17%)
2	0	1 (<1%)
Pre-operation biopsy		
Imaging-guided	123 (92%)	119 (89%)
Surgical	10 (8%)	12 (9%)
Missing	0	2 (2%)
Tumour size (mm)	167 (124–210)	160 (111–210)
Histological subtype		
All liposarcoma subtypes	100 (75%)	98 (74%)
Well-differentiated liposarcoma	42 (32%)	46 (35%)
De-differentiated liposarcoma	54 (41%)	51 (38%)
Other liposarcoma	4 (3%)	1 (<1%)
Leiomyosarcoma	22 (17%)	16 (12%)
Other	11 (8%)	18 (14%)
Data missing	0	1 (<1%)
Tumour grade at biopsy		
Low	43 (32%)	44 (33%)
Intermediate	38 (29%)	47 (35%)
High	19 (14%)	12 (9%)
Not evaluable	21 (16%)	17 (13%)
Data missing	12 (9%)	13 (10%)

Data are median (IQR) or n (%).

Table 1: **Baseline characteristics**

Statistical analysis

To assess the difference in abdominal recurrence-free survival between the two groups, the number of events and sample size were determined to provide 90% power for detecting a hazard ratio (HR) of 0·52 (which corresponds to a 20% difference in abdominal recurrence-free survival rate at 5 years, from 50% in the control group to 70% in the experimental group), at a global two-sided 5% significance level. This calculation assumed that abdominal recurrence-free survival 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 randomly assigned during 39 months, this number of events was expected to occur about 41 months after the last patient was assigned.

Two interim safety checks were required by the protocol, after 33 patients and 66 patients had been 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 tumours by 12% compared with the control group.

We calculated time-to-event endpoints using Kaplan-Meier curves in the two treatment groups.[20] We report median and associated non-parametric 95% CIs, with comparisons by Cox proportional hazards. All survival analyses were done for all participants who were randomly assigned. Safety was analysed in all patients who started their allocated treatment (ie, were operated on or received one fraction of irradiation). We calculated the abdominal recurrence-free interval using cumulative incidence curves, and we compared the treatment groups using a Fine and Gray model. Adverse events were reported using frequency tables and percentages by worst grade by study period. Tumour response was assessed in the radiotherapy and surgery group only as rates and corresponding 95% CIs.

To account for the time assessment bias that is inherent to the different follow-ups, the protocol required that the

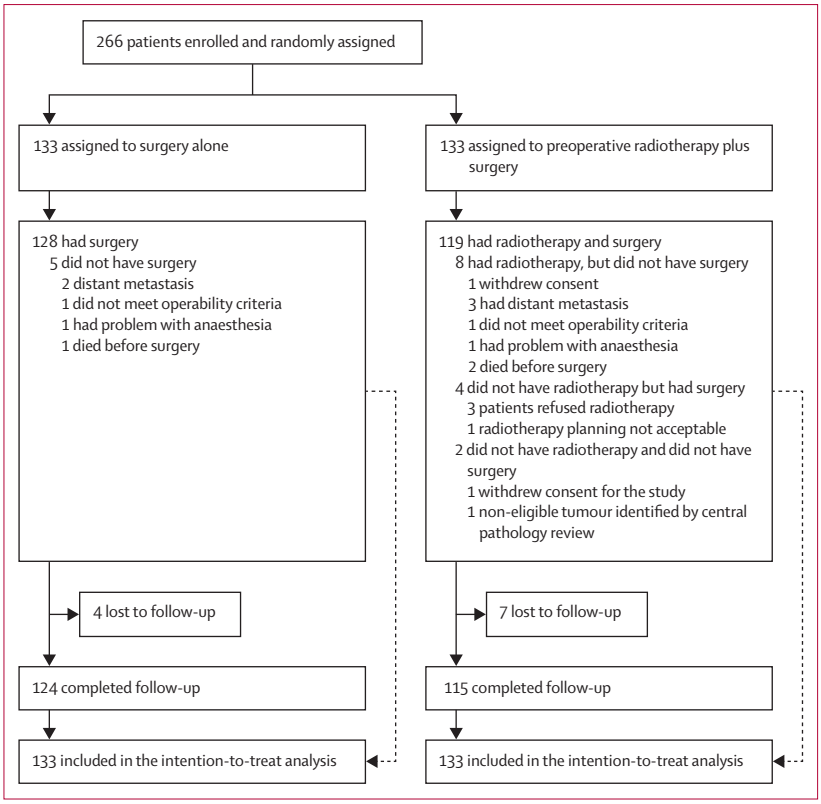

Figure 1: **Trial profile**

following corrections should be taken into account by the statistical analysis: abdominal recurrences occurring before the first assessment at 14 weeks were counted as occurring at week 14; and any progressions occurring after 14 weeks but before 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 the interim results of the study, the Independent Data Monitoring Committee recommended two unplanned sensitivity analyses for the primary endpoint. In the first sensitivity analysis, patients were considered as having no event if they subsequently had macroscopically complete resection despite local progression on radiotherapy. In the second sensitivity analysis, patients were considered as having no event if the surgery was macroscopically complete despite local progression on radiotherapy or becoming medically unfit according to the surgery operability criteria (by having an ASA score of 3).

Exploratory, post-hoc analyses were done for abdominal recurrence-free survival, metastasis-free survival, and overall survival in patients with liposarcoma, and for abdominal recurrence-free survival by sarcoma subtype and grade.

We used SAS (version 9.4) for statistical analyses. This study is registered with ClinicalTrials.gov, NCT01344018.

Role of the funding source

EORTC had a role in the study design, data collection, data analysis, data interpretation, and writing of the report. Data were collected by investigators and associated site personnel, analysed by a statistician (SL) working in EORTC headquarters, and interpreted by members of the steering committee. Raw data are available from SL. The corresponding author had the final responsibility for the decision to submit for publication and had full access to all the data.

Results

Between Jan 18, 2012, and April 10, 2017, 266 patients were enrolled in the trial (table 1; appendix p 9). 19 (7%) patients did not have the study treatment as allocated, including five (4%) of 133 patients in the surgery alone group and 14 (10%) of 133 patients in radiotherapy plus surgery group. Therefore, 128 patients from the surgery alone group had surgery, and 119 patients in the radiotherapy plus surgery group had both radiotherapy and surgery (figure 1). The cut-off date for this report was March 6, 2019. The median time to local treatment was 3·0 weeks (IQR 1·9–3·9) in the surgery group and 3·3 weeks (IQR 2·3–4·4) in the radiotherapy plus surgery group. There was a delay of more than 48 h in the timing of surgery in 13 (10%) of 128 patients in the surgery group (due to site organisation) and four (3%) of 119 patients in the radiotherapy plus surgery group (due to site organisation [n=1], pulmonary embolism after radiotherapy [n=1], or toxicity after radiotherapy [n=2]). Intraoperative findings were not consistent with the preoperative imaging in five (4%) of 128 patients in the surgery group and seven (6%) of 119 patients in the radiotherapy plus surgery group, which resulted in a substantial strategy change for two patients (one patient from the surgery group had no resection, and one from the radiotherapy plus surgery group had a multifragment resection).

The duration of surgery was similar in both groups (median 288 min [IQR 205–376] in the surgery group and median 300 min [IQR 235–380] in the radiotherapy plus surgery group). The most commonly resected organs were the kidney (100 [78%] surgery patients and 99 [83%] radiotherapy plus surgery patients), the psoas muscles or its aponeurosis (94 [73%] surgery patients and 94 [79%] radiotherapy plus surgery patients), and the colon (94 [73%] of surgery patients and 92 [77%] of radiotherapy plus surgery patients; table 2). According to the operative reports, piecemeal resection was done in five (4%) of 128 patients in the surgery group and four (3%) of 119 patients in the radiotherapy plus surgery group (table 2).

The radiotherapy technique was IMRT for 120 (95%) of 127 patients who received radiotherapy and 3DCRT for seven (5%) patients. Protocol compliance for radiotherapy was 65% (12 [9%] patients had minor deviations and 33 [26%] had major deviations). The median total

dose for both IMRT and 3DCRT was 50·4 Gy (IQR 50·4–50·4 in both cases). The median dose per fraction given was 1·8 Gy (IQR 1·8–1·8 in both cases). Seven (6%) patients had a deviation from the protocol on doses given: three (2%) had radiotherapy dose reduction for gastrointestinal toxicity, three (2%) chose to stop radiotherapy, and one (<1%) had a 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 surgery group and 35 in the radiotherapy plus surgery group). With a median follow-up of 43·1 months (IQR 28·8–59·2), 121 abdominal recurrence-free survival events were reported in the two study groups: 61 in the surgery group and 60 in the radiotherapy plus surgery group (appendix p 6). Corresponding abdominal recurrence-free survival at 3 years was 58·7% (95% CI 49·5–66·7) in the surgery group and 60·4% (51·4–68·2) in the radiotherapy plus surgery group. Median abdominal recurrence-free survival was 4·5 years (95% CI 3·9 to not estimable) in the radiotherapy plus surgery group and 5·0 years (3·4 to not estimable) in the surgery only group (HR 1·01, 0·71–1·44, log rank p=0·95; figure 2). Post-hoc analyses of abdominal recurrence-free survival by sarcoma subtype and grade are provided in the appendix (p 8).

Among 19 patients who progressed on radiotherapy, three (16%) developed distant metastases during radiotherapy and one (5%) developed haemodynamic shock during induction of anaesthesia (appendix p 7). Four (21%) had no resection, but 15 (79%) did have macroscopically complete resection (four [27%] of whom later developed local recurrence). Three (20%) of this group of 15 patients were qualified as non-operable because they reached an ASA score of 3 after radiotherapy, but they nevertheless had macroscopically complete resection. On the basis of the type of progression and whether surgery was done, the 19 patients who progressed on radiotherapy were analysed differently in the sensitivity analysis, thereby resulting in different numbers of non-operated patients. Of note, twice as many local relapses were observed in the surgery group than in the radiotherapy plus surgery group (appendix p 6).

In the first sensitivity analysis, in which local progression on radiotherapy was not regarded as a primary endpoint event for those who had macroscopically complete resection, 113 events were reported: 61 (54%) in the surgery group and 52 (46%) in the radiotherapy plus surgery group (appendix p 6). Abdominal recurrence-free survival at 3 years was 58·7% (95% CI 49·5–66·7) in the surgery group and 66·0% (57·1–73·5) in the radiotherapy plus surgery group (HR 0·84, 95% CI 0·58–1·21).

In the second sensitivity analysis, in which neither local progression nor becoming medically unfit on radiotherapy were regarded as primary endpoint events for those who had macroscopically complete resection, 101 events were reported: 56 (55%) in the surgery group and 45 (45%) in the radiotherapy plus surgery group

	Surgery alone group (n=128)	Preoperative radiotherapy plus surgery group (n=119)
Intraoperative findings in alignment with the preoperative imaging procedures		
Yes	123 (96%)	111 (93%)
No	5 (4%)	7 (6%)
Data missing	0	1 (<1%)
Resection of the sarcoma		
Yes, macroscopically complete in one block	122 (95%)	114 (96%)
Yes, piecemeal	5 (4%)	4 (3%)
No	1 (<1%)	1 (<1%)
Sarcomatosis discovered during surgery	7 (5%)	7 (6%)
Organ resection		
Kidney (with or without adrenal gland)		
Yes	100 (78%)	99 (83%)
Macroscopically involved	43 (34%)	53 (45%)
Systematically resected	57 (45%)	46 (39%)
Psoas muscles or aponevrosis		
Yes	94 (73%)	94 (79%)
Macroscopically involved	28 (22%)	25 (21%)
Systematically resected	66 (52%)	69 (58%)
Colon or mesocolon		
Yes	94 (73%)	92 (77%)
Macroscopically involved	42 (33%)	38 (32%)
Systematically resected	52 (41%)	54 (45%)
Diaphragm		
Yes	31 (24%)	39 (33%)
Macroscopically involved	19 (15%)	25 (21%)
Systematically resected	12 (9%)	14 (12%)
Spleen		
Yes	25 (20%)	21 (18%)
Macroscopically involved	7 (5%)	4 (3%)
Systematically resected	18 (14%)	17 (14%)
Pancreas tail		
Yes	20 (16%)	19 (16%)
Macroscopically involved	10 (8%)	7 (6%)
Systematically resected	10 (8%)	12 (10%)
Small intestine		
Yes	12 (9%)	17 (14%)
Macroscopically involved	7 (5%)	6 (5%)
Systematically resected	5 (4%)	11 (9%)
Inferior vena cava		
Yes	8 (6%)	8 (7%)
Macroscopically involved	8 (6%)	7 (6%)
Systematically resected	0	1 (<1%)
Iliac vessels		
Yes	8 (6%)	12 (10%)
Macroscopically involved	5 (4%)	8 (7%)
Systematically resected	3 (2%)	4 (3%)
Pancreas head		
Yes	3 (2%)	2 (2%)
Macroscopically involved	1 (<1%)	1 (<1%)
Systematically resected	2 (2%)	1 (<1%)

(Table 2 continues on next page)

	Surgery alone group (n=128)	Preoperative radiotherapy plus surgery group (n=119)
(Continued from previous page)		
Liver		
Yes	4 (3%)	9 (8%)
Macroscopically involved	3 (2%)	7 (6%)
Systematically resected	1 (<1%)	2 (2%)
Bladder		
Yes	2 (2%)	2 (2%)
Macroscopically involved	1 (<1%)	1 (<1%)
Systematically resected	1 (<1%)	1 (<1%)
Rectum		
Yes	3 (2%)	4 (3%)
Macroscopically involved	1 (<1%)	3 (3%)
Systematically resected	2 (2%)	1 (<1%)
Resection including at least colon, kidney, and psoas muscles or aponevrosis (all patients)	69 (54%)	69 (58%)
Resection including at least colon, kidney, and psoas muscles or aponevrosis (patients with liposarcoma)	58/96 (60%)	60/89 (67%)
Resection including at least colon, kidney, and psoas muscles or aponevrosis (patients with leiomyosarcoma)	9/22 (41%)	3/16 (19%)
Any per-operative complication		
Yes	35 (27%)	44 (37%)
No	92 (72%)	75 (63%)
Data missing	1 (<1%)	0
Transfusion during surgical procedure		
Yes	24 (19%)	34 (29%)
No	65 (51%)	50 (42%)
Data missing	39 (30%)	35 (29%)
Other details		
Procedure requiring digestive stomy	2 (2%)	2 (2%)
Procedure requiring urinary stomy	1 (<1%)	1 (0<1%)
Postoperative femoral palsy	2 (2%)	2 (2%)
Duration of surgery (min)	288 (205–376)	300 (235–380)
Duration of hospitalisation (days)	12 (8–18)	14 (10–20)
Postoperative death	3 (2%)	2 (2%)
Re-operated	14 (11%)	14 (12%)

Data are n (%) or median (IQR).

Table 2: **Details of surgery, resection, and complications**

(appendix p 6). Abdominal recurrence-free survival at 3 years was 62·2% (95% CI 53·0–70·1) in the surgery group and 71·3% (62·6–78·3) in the radiotherapy plus surgery group (HR 0·78, 95% CI 0·53–1·16).

In the post-hoc, exploratory analysis of patients with liposarcoma histology, 81 events were observed: 44 (54%) in the surgery group and 37 (46%) in the radiotherapy plus surgery group (appendix p 6). The corresponding abdominal recurrence-free survival at 3 years was 60·4% (95% CI 49·8–69·5) in the surgery group and 64·7% (54·2–73·4) in the radiotherapy plus surgery group (HR 0·83, 95% CI 0·54–1·29). In the post-hoc, first sensitivity analysis of patients with liposarcoma, 74 events were reported: 44 (59%) in the surgery group and 30 (41%) in the radiotherapy plus surgery group (appendix p 6). The corresponding abdominal recurrence-free survival at 3 years was 60·4% (95% CI 49·8–69·5) in the surgery group and 71·6% (61·3–79·6) in radiotherapy plus surgery group (HR 0·64, 95% CI 0·40–1·01). In the post-hoc, second sensitivity analysis of patients with liposarcoma, 65 events were reported: 39 (60%) in the surgery group and 26 (40%) in the radiotherapy plus surgery group (appendix p 6). The corresponding abdominal recurrence-free survival at 3 years was 65·2% (95% CI 54·5–74·0) in the surgery group and 75·7% (65·6–83·2) in the radiotherapy plus surgery group (HR 0·62, 95% CI 0·38–1·02; figure 3).

Metastasis-free survival at 3 years was 68·2% (95% CI 59·0–75·8) in the surgery group and 68·3% (58·8–76·0) in the radiotherapy plus surgery group (HR 0·89, 0·58–1·36; log rank p=0·59; appendix p 1). In the liposarcoma subgroup (post-hoc analysis), metastasis-free survival at 3 years was 78·3% (68·3–85·5) in the surgery group and 76·5% (66·0–84·1) in the radiotherapy plus surgery group (HR 1·02, 0·57–1·80; appendix p 2).

The abdominal recurrence-free interval at 3 years was 32·0% (95% CI 24·0–40·2) in the surgery group and 34·3% (26·2–42·5) in the radiotherapy plus surgery group (HR 1·09, 95% CI 0·74–1·60; Gray K-sample test p=0·66; appendix p 4). In the liposarcoma subgroup (post-hoc analysis), the abdominal recurrence-free interval at 3 years was 33·4% (95% CI 24·0–43·1) in the surgery group and 31·1% (22·1–40·5) in the radiotherapy plus surgery group (HR 0·91, 95% CI 0·58–1·42; appendix p 5).

Overall, 47 (18%) of 266 patients died, of whom 22 (47%) were in the surgery group and 25 (53%) were in the radiotherapy plus surgery group. In the surgery group, the corresponding overall survival at 3 years was 84·6% (95% CI 76·5–90·1) and at 5 years was 79·4% (69·1–86·5), and in the radiotherapy plus surgery group overall survival was 84·0% (76·3–89·4) at 3 years and 76·7% (66·9–84·0) at 5 years. Median overall survival was not reached in either group (95% CI not reached to not reached in both groups; HR 1·16, 95% CI 0·65–2·05; p=0·62; appendix p 3).

According to RECIST version 1.1, four (3%) of 119 patients who had radiotherapy plus surgery were classified as having partial response, 98 (82%) as having stable disease, 19 (16%) as having progressive disease on CT scan, and 11 (9%) as not evaluable or early death.

After both interim safety analyses, in August, 2014 (33 patients per group) and September, 2015 (66 patients per group), there was no significant increase in the rate of inoperable tumours or the rate of re-operations in the radiotherapy plus surgery group (data not shown). As per study protocol, these analyses were submitted to the Independent Data Monitoring Committee, which confirmed that study recruitment should continue.

In the radiotherapy plus surgery group, radiotherapy was temporarily interrupted because of grade 2–3

gastrointestinal adverse events in three (2%) of 127 patients and for administrative reasons or intercurrent causes in 25 (20%) patients, and it was prematurely stopped at doses ranging from 7·2 Gy to 39·6 Gy in four (3%) patients (two [2%] on patient request, one [<1%] because of several grade 1–3 adverse events that were not only gastrointestinal, and one [<1%] because of the patient's general condition worsening).

The most common grade 3–4 adverse events were lymphopenia (98 [77%] of 127 patients in the radiotherapy plus surgery group *vs* one [1%] of 128 patients in the surgery alone group), anaemia (15 [12%] *vs* ten [8%]), and hypoalbuminaemia (15 [12%] *vs* five [4%]; table 3, appendix pp 11–15). In the surgery alone group, the most common (grade 3–4) adverse events were anaemia (10 [8%]) and hypoalbuminaemia (5 [4%]). Serious adverse events were reported in 30 (24%) of 127 patients in the radiotherapy plus surgery group, and in 13 (10%) of 128 patients in the surgery alone group. One (1%) of 127 patients in the radiotherapy plus surgery group died due to treatment-related serious adverse events (gastropleural fistula), and no patients in the surgery alone group died due to treatment-related serious adverse events.

Transfusion was required during surgery for 24 (19%) of 128 patients in the surgery group and 34 (29%) of 119 patients in the radiotherapy plus surgery group who started their allocated treatment (ie, were operated on or received one fraction of irradiation). There were three (2%) postoperative deaths in the surgery group and two (2%) in the radiotherapy plus surgery group. Reoperation for any complication occurred in 14 (11%) patients in each group. The most frequent complication requiring reoperation was postoperative abdominal sepsis (fistula, abscess, peritonitis, or septicaemia), which affected nine (7%) of 128 patients in the surgery group and eight (7%) of 119 patients in the radiotherapy plus surgery group. Postoperative bleeding was the second most common reason for reoperation, accounting for 5 (4%) in the surgery group and 2 (2%) in the radiotherapy plus surgery group. Details on surgical morbidity and postoperative clinical and laboratory adverse events are given in the appendix (p 11). After nephrectomy, two (2%) of 100 patients had grade 3 and one (1%) patient had grade 4 creatinine adverse events in the surgery group, and none of 99 patients had a grade 3 or 4 creatinine adverse event in the radiotherapy plus surgery group (table 3).

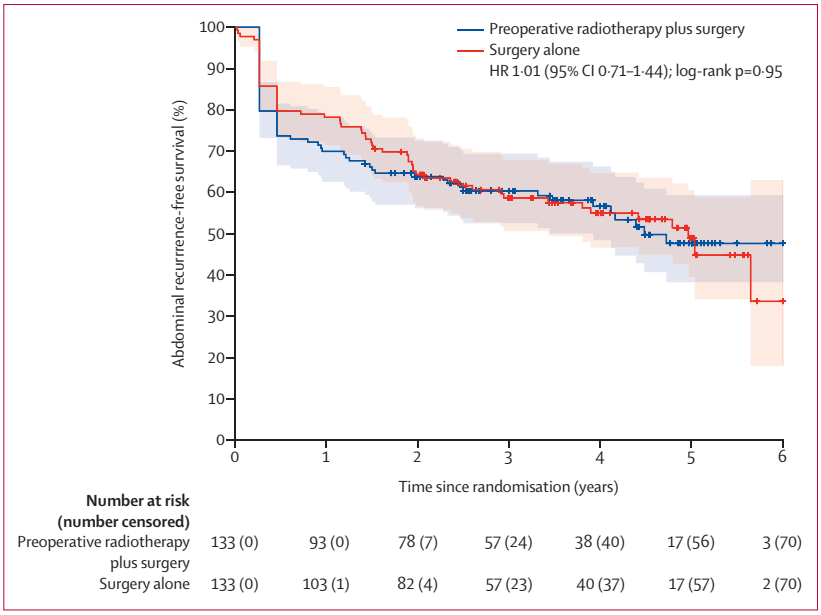

Figure 2: **Abdominal recurrence-free survival in all patients**
Shaded areas around the lines represent the 95% CI. HR=hazard ratio.

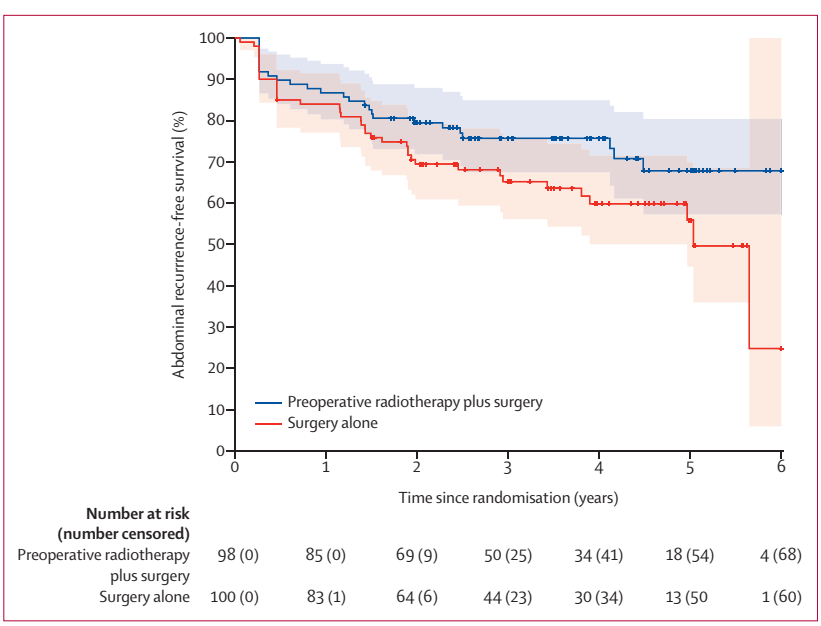

Figure 3: **Second sensitivity analysis of abdominal recurrence-free survival in the liposarcoma subgroup**
Shaded areas around the lines represent the 95% CI.

Discussion

To our knowledge, this is the first large, international, randomised trial in primary, localised retroperitoneal sarcoma that has been successfully completed, and shows that key questions in a rare cancer can be addressed through multi-institutional collaboration. This trial is negative, with similar abdominal recurrence-free survival and overall survival in both groups at 3 years of follow-up. As a consequence, preoperative radiotherapy cannot be considered as the standard of care for retroperitoneal sarcoma. This conclusion replaces the heterogeneous approach to radiotherapy for retroperitoneal sarcoma, whereby its use varied considerably based on investigator and institutional biases.

Randomisation offsets selection biases inherent in retrospective series, where radiotherapy is often a proxy for tumours that are smaller (the median tumour size in

	Surgery alone group (n=128)				Preoperative radiotherapy plus surgery group (n=127)							
					During radiotherapy				During study including follow-up			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Clinical disorder												
Patient's worse grade	74 (58%)	26 (20%)	3 (2%)	0	106 (83%)	15 (12%)	1 (1%)	1 (1%)	75 (59%)	39 (31%)	8 (6%)	2 (2%)
Blood and lymphatic system	0	0	0	0	2 (2%)	0	0	0	4 (3%)	0	0	0
Cardiac	3 (2%)	0	0	0	1 (1%)	0	0	1 (1%)	2 (2%)	0	1 (1%)	2 (2%)
Ear and labyrinth	0	0	0	0	1 (1%)	0	0	0	3 (2%)	0	0	0
Endocrine	1 (1%)	0	0	0	0	0	0	0	3 (2%)	0	0	0
Eye	2 (2%)	0	0	0	2 (2%)	0	0	0	2 (2%)	0	0	0
Gastrointestinal	42 (33%)	11 (9%)	1 (1%)	0	109 (85%)	4 (3%)	0	1 (1%)*	98 (77%)	15 (12%)	2 (2%)	1 (1%)
General (oedema limbs, fatigue, fever, pain)	41 (32%)	0	0	0	84 (66%)	5 (4%)	0	0	88 (69%)	8 (6%)	0	0
Immune system	0	0	0	0	0	0	0	0	1 (1%)	0	0	0
Infection	8 (6%)	1 (1%)	0	0	3 (2%)	1 (1%)	0	0	10 (8%)	8 (6%)	1 (1%)	0
Injury and procedural complications (burn, dermatitis radiation, spinal fracture, wound complication)	7 (5%)	4 (3%)	0	0	30 (24%)	0	0	0	41 (32%)	4 (3%)	0	0
Investigation (weight loss)	24 (19%)	3 (2%)	0	0	50 (39%)	1 (1%)	0	0	59 (46%)	7 (6%)	0	0
Metabolism and nutrition	11 (9%)	5 (4%)	1 (1%)	0	48 (38%)	6 (5%)	1 (1%)	0	53 (42%)	12 (9%)	1 (1%)	0
Musculoskeletal	25 (20%)	1 (1%)	0	0	25 (20%)	1 (1%)	0	0	33 (26%)	4 (3%)	0	0
Neoplasms (benign, malignant, and unspecified)	2 (2%)	0	0	0	4 (3%)	1 (1%)	0	0	4 (3%)	1 (1%)	0	0
Nervous system	31 (24%)	2 (2%)	1 (1%)	0	24 (19%)	..	0	0	45 (35%)	3 (2%)	0	0
Psychiatric	3 (2%)	0	0	0	7 (6%)	1 (1%)	0	0	11 (9%)	2 (2%)	0	0
Renal and urinary	10 (8%)	4 (3%)	0	0	7 (6%)	0	0	0	15 (12%)	3 (2%)	1 (1%)	0
Reproductive and breast	9 (7%)	0	0	0	0	0	0	0	5 (4%)	1 (1%)	0	0
Respiratory	9 (7%)	2 (2%)	0	0	13 (10%)	1 (1%)	0	0	18 (14%)	3 (2%)	1 (1%)	0
Skin and subcutaneous	7 (5%)	0	0	0	14 (11%)	1 (1%)	0	0	15 (12%)	1 (1%)	0	0
Vascular	12 (9%)	6 (5%)	0	0	8 (6%)	3 (2%)	1 (1%)	0	13 (10%)	7 (6%)	2 (2%)	0
Biological event												
Anaemia	29 (23%)	10 (8%)	†	0	17 (13%)	7 (6%)	†	0	46 (36%)	15 (12%)	†	0
Leukopenia‡	2 (2%)	0	0	0	22 (17%)	0	0	0	28 (22%)	0	0	0
Lymphopenia‡	14 (11%)	1 (1%)	0	0	15 (12%)	68 (54%)	30 (24%)	0	18 (14%)	67 (53%)	31 (24%)	0
Thrombocytopenia‡	1 (1%)	0	1 (1%)	0	1 (1%)	0	0	0	2 (2%)	0	1 (1%)	0
Hyperbilirubinaemia	18 (14%)	0	0	0	9 (7%)	0	0	0	20 (16%)	1 (1%)	0	0
Hypoalbuminaemia‡	34 (27%)	5 (4%)	0	0	14 (11%)	7 (6%)	0	0	42 (33%)	15 (12%)	0	0
Alkaline phosphatase	43 (34%)	1 (1%)	0	0	29 (23%)	0	0	0	80 (63%)	2 (2%)	0	0
Alanine aminotransferase	47 (37%)	3 (2%)	0	0	24 (19%)	0	0	0	54 (43%)	2 (2%)	0	0
Aspartate aminotransferase	30 (23%)	1 (1%)	0	0	25 (20%)	0	0	0	50 (39%)	1 (1%)	0	0
Serum creatinine	75 (59%)	2 (2%)	1 (1%)	1 (1%)	6 (5%)	0	0	0	80 (63%)	0	0	0
Serum creatinine after nephrectomy	48/100 (48%)	2/100 (2%)	1/100 (1%)	0	0	0	0	0	31/99 (31%)	0	0	0

Data are n (%). Safety was analysed in all patients who started their allocated treatment (ie, were operated on or received one fraction of irradiation). Chapter headings of the Common Terminology Criteria for Adverse Events version 4.0 are presented here; full details of adverse events are in the appendix (pp 1–15). *Patient completed radiotherapy, but within one month afterwards (before surgery) died of cardiac arrest, haematemesis, and upper gastrointestinal haemorrhage. †Grade 4 anaemia cannot be determined based on haemoglobin values. ‡Because the lower and upper limits of normal were not reported, it is not possible to distinguish between grade 0 and 1, so only grade 2 events are reported for these events.

Table 3: **Clinical and biological adverse events in the preoperative period and follow-up**

STRASS was 16 cm), in more favourable locations, easier to resect, and resected in academic centres.[21] It must be acknowledged that this trial was powered to identify a 20% difference within the entire cohort. Longer follow-up is required, and another analysis with 5 years of follow-up is planned. Twice as many local relapses were observed in the surgery group than in the radiotherapy plus surgery group, possibly related to the impact of radiotherapy, specifically in the liposarcoma cohort. Although it is difficult to standardise the surgical technique, given the varying clinical presentations, more than 60% of patients with liposarcoma received a

compartmental resection, as defined by the combination of at least nephrectomy and the resection of the colon and psoas (or its aponeurosis). It is also possible that the magnitude of the radiotherapy gain could be reduced by optimising the surgical technique.

When STRASS was designed in 2010, the risk of progressive tumour growth or worsening performance status during neoadjuvant radiotherapy, 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 jeopardise surgery, in addition to local failure following surgery. Subsequently, multicentre studies from the TransAtlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG) refined our understanding of the biology of different retroperitoneal sarcoma histological subtypes. Specifically, we showed that intra-abdominal local recurrence was the predominant pattern of failure for liposarcoma, whereas distant metastasis was the principal pattern of failure for leiomyosarcoma.[22] In addition, uncertainty about feasibility of a randomised retroperitoneal sarcoma 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[23–25] and were committed to participating and enrolling patients in this trial.

19 (14%) of 133 patients progressed on radiotherapy. Three (16%) of them developed distant metastases and thus did not undergo what would have been non-curative surgery. 15 (79%) of those 19 patients had local progression but had macroscopically complete resection. The intermediate results led the Independent Data Monitoring Committee to propose a sensitivity analysis whereby local progression on radiotherapy was no longer regarded as an event for the patients who subsequently achieved a complete resection (first sensitivity analysis) and regardless of operability (second sensitivity analysis). In addition, an exploratory analysis on patients with liposarcoma was recommended, because this was the largest subgroup (nearly 75% of the trial cohort) and had the highest risk of local recurrence. In the subgroup analyses exploring patients with liposarcoma only, there was a 10% absolute abdominal recurrence-free survival benefit in favour of the radiotherapy plus surgery group. The morbidity associated with radiotherapy was acceptable (ie, during radiotherapy, 15 patients had a worst grade adverse event of grade 3 and one had the worst as grade 4), probably because it was delivered preoperatively[25–27] and mostly via IMRT (95% of patients). Complication rates were lower in our trial than have been reported with postoperative radiotherapy, ranging from 20% to 40% in retrospective series.[28–30] A radiotherapy dose of 50·4 Gy was chosen according to the potential benefits and risks assessed by previous phase 1 and 2 studies, to avoid bowel complications reported with higher doses and the potential negative impact on surgery.[10,11] Rates of postoperative death (about 2%) and reoperation (11%) were similar in both groups and were in line with previous data from TARPSWG.[31]

The trial results reported here are limited by the short follow-up. Although total accrual seems relatively small, it is large for a rare cancer. Furthermore, there was no stratification based on histological subtype, because its differential impact on local recurrence was only apparent in studies that were published after the trial's initiation. Subgroup analyses of abdominal recurrence-free survival by sarcoma subtype and grade suggest that preoperative radiotherapy might improve the outcome in liposarcoma and in low-grade retroperitoneal sarcoma, whereas there did not appear to be a radiotherapy benefit for leiomyosarcoma and high-grade retroperitoneal sarcoma.[22] However, these results should be regarded with caution because all subgroups were individually small, many patients were not evaluable for grade or differentiation (because of limitations based on biopsy specimen and the impact of preoperative radiotherapy on those characteristics on final histology), and these subgroup analyses were not preplanned. We also cannot make any recommendation for the even rarer histological subtypes that were grouped together in this trial. These results only apply to patients meeting all inclusion criteria, including a good performance status (ie, WHO performance status of 1 or 2) and resectable tumours that are suitable for radiotherapy. Patients meeting these selection criteria achieved 5-year overall survival of 79·4% (95% CI 69·1–86·5) in the surgery group and 76·7% (66·9–84·0) in the radiotherapy plus surgery group, which was slightly better than in the retrospective collaborative series from TARPSWG (67% at 5 years).[22]

Considering retroperitoneal sarcoma biology and the fact that our data do not support radiotherapy for leiomyosarcoma and high-grade retroperitoneal sarcoma, our next randomised study (STRASS 2; NCT04031677) will focus on these two groups. STRASS 2 is an international randomised trial with stratification by specific tumour histology, including only high-grade de-differentiated liposarcoma and leiomyosarcoma. The primary objective will be to assess whether three cycles of preoperative chemotherapy improve disease-free survival compared to surgery alone. In the experimental group, patients will receive chemotherapy according to subtype: doxorubicin and ifosfamide for high grade dedifferentiated liposarcoma, and doxorubicin and dacarbazine for leiomyosarcoma. High-quality observational data from the RESAR study[30] (NCT03838718), a prospective registry from the TARPSWG, could help refine which liposarcoma subtypes might benefit from radiotherapy. The exact topography of local recurrence was not assessed in our trial. It is possible that increasing radiotherapy 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;[32] this approach is currently being investigated in a phase 2 study (NCT01659203).

In conclusion, transatlantic collaboration between major retroperitoneal sarcoma referral centres was crucial to completing STRASS. Radiotherapy cannot be routinely recommended for all retroperitoneal sarcoma patients. The role of radiotherapy in liposarcoma should be further explored in a prospective clinical trial.

Contributors

SB, AG, CLP, JYB, SL, SM, and RLH contributed to the design of the study. All authors contributed to recruiting patients, collecting data, or both. SB wrote the manuscript and all authors reviewed and approved the final version of the manuscript.

Declaration of interests

SB reports personal fees and non-financial support from Nanobiotix and PharmaMar, and non-financial support from Pfizer, outside the submitted work. AG reports personal fees from Novartis, Pfizer, Bayer, Lilly Oncology, SpringWorks, and Nanobiotix, and grants and personal fees from PharmaMar, all outside the submitted work. CLP reports personal fees from AstraZeneca, Amgen, Nanobiotix, Roche, Medscape, PrimeOncology, and Lilly, outside the submitted work. PR reports personal fees from Novartis, Merck Sharp & Dohme, Bristol-Myers Squibb, Roche, Pfizer, Blueprint Medicines, Pierre Fabre, and Sanofi, outside the submitted work. PC reports personal fees from AbbVie and AstraZeneca, outside the submitted work. AM reports grants from National Health Service (NHS) funding to the National Institute for Health Research Biomedical Research Centre for Cancer at The Royal Marsden Hospital and The Institute of Cancer Research, during the conduct of the study. JYB reports grants from European Clinical Trials in Rare Sarcomas (EUROSARC), Lyon Integrative Cancer Research Program (LYRICAN), the European Network for Rare Adult Solid Cancers (EURACAN), NetSarc+, and Intersarc, during the conduct of the study. APDT reports personal fees from Roche, PharmaMar, and Bayer, outside the submitted work. All other authors 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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