Critical impact of radiotherapy protocol compliance and quality in the treatment of retroperitoneal sarcomas: results from the EORTC 62092-22092 STRASS trial

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Original Article

Critical impact of radiotherapy protocol compliance and quality in the treatment of retroperitoneal sarcomas: Results from the EORTC 62092-22092 STRASS trial

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BACKGROUND: The European Organization for Research and Treatment of Cancer 22092-62092 STRASS trial failed to demonstrate the superiority of neoadjuvant radiotherapy (RT) over surgery alone in patients with retroperitoneal sarcoma. Therefore, an RT quality-assurance program was added to the study protocol to detect and correct RT deviations. The authors report results from the trial RT quality-assurance program and its potential effect on patient outcomes. **METHODS:** To evaluate the effect of RT compliance on survival outcomes, a composite end point was created. It combined the information related to planning target volume coverage, target delineation, total dose received, and overall treatment time into 2 groups: *non–RT-compliant* (NRC) for patients who had unacceptable deviation(s) in any of the previous categories and *RT-compliant* (RC) otherwise. Abdominal recurrence-free survival (ARFS) and overall survival were compared between the 2 groups using a Cox proportional hazard model adjusted for known prognostic factors. **RESULTS:** Thirty-six of 125 patients (28.8%) were classified as NRC, and the remaining 89 patients (71.2%) were classified as RC. The 3-year ARFS rate was 66.8% (95% confidence interval [CI], 55.8%-75.7%) and 49.8% (95% CI, 32.7%-64.8%) for the RC and NRC groups, respectively (adjusted hazard ratio, 2.32; 95% CI, 1.25-4.32; $P = .008$). Local recurrence after macroscopic complete resection occurred in 13 of 89 patients (14.6%) versus 2 of 36 patients (5.6%) in the RC and NRC groups, respectively. **CONCLUSIONS:** The current analysis suggests a significant benefit in terms of ARFS in favor of the RC group. This association did not translate into less local relapses after complete resection in the RC group. Multidisciplinary collaboration and review of cases are critical to avoid geographic misses, especially for rare tumors like retroperitoneal sarcoma. ***Cancer* 2022;128:2796-2805**. © *2022 American Cancer Society*.

KEYWORDS: protocol compliance, quality assurance, radiotherapy, retroperitoneal sarcomas, soft tissue sarcomas.

INTRODUCTION

In recent years, important scientific work has been done to further elucidate the role of radiotherapy (RT) in retroperitoneal sarcoma (RPS).[1] Recently, the results of the European Organization for Research and Treatment (EORTC) 62092-22092 STRASS trial, a phase 3 randomized study that evaluated the potential benefit of preoperative RT in terms of locoregional control, were published.[2] Overall, the trial did not meet its primary objective; therefore, preoperative RT cannot be routinely recommended for all patients with RPS.

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See editorial on pages 2701-2703, this issue.

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We thank our patients and their relatives for their willingness to participate to this study. We also thank all sites and their staff for contributing to this study. We further acknowledge the support of this study by the staff at the European Organization of Research and Treatment for Cancer (EORTC) Headquarters, Brussels, Belgium.

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.34239, **Received:** August 23, 2021; **Revised:** January 19, 2022; **Accepted:** January 28, 2022, **Published online** May 10, 2022 in Wiley Online Library (wileyonlinelibrary.com)

Because RT was delivered only to patients in that study who received preoperative RT, potential inconsistencies in the application of the RT protocol could not be balanced between treatment arms. In addition, new and innovative technological steps have been achieved since initiation of the trial and have pushed the field of radiation oncology toward increased accuracy and less dose exposure to organs at risk (OARs), rendering RT quality assurance (RTQA) even more crucial.[3] Therefore, a quality-assurance program has been included in the study protocol to detect and, by interventional review, correct potential RT protocol deviations.[4] The objective of the current work was to report the outcome of the RT protocol deviations review in the RT plus surgery arm of the EORTC 62092-22092 STRASS trial and describe the relation between these deviations and the 2 main end points of the trial: abdominal recurrence-free survival (ARFS) and overall survival (OS).

MATERIALS AND METHODS

Study Population

For this specific analysis, patients were considered eligible if: 1) they received neoadjuvant RT, 2) the individual case review of the RT planning was sent to EORTC headquarters, 3) the complete RT plan was uploaded by the institution (planning computed tomography, RT structure, and dose, at a minimum), and 4) the RT plan was reviewed by at least 1 of the radiation oncologists/expert reviewers designated before the trial started (R.H and C.L.P).

Protocol Radiotherapy

RT should have started within 8 weeks after randomization. The RT prescription dose consisted of 50.4 grays (Gy) delivered in 1.8-Gy per fraction, once daily, 5 days a week, for a total of 28 fractions. In the case of proximity to OARs, coverage of the planning target volume (PTV) by the 90% isodose (45.4 Gy) was allowed if needed to meet OAR constraints. Three-dimensional conformal RT or intensity-modulated RT techniques were allowed. The major RT volume and dose constraint definitions, as defined in the STRASS protocol, are summarized in Supporting Table 1.

Case Submission and Review

The following principles were established by the RTQA team before site activation:

- An independent review of every patient's treatment plan was mandatory for this trial. A prospective (before the start of RT) central review of the first 3 patients from each institution and, subsequently, of 1 in 10 randomly selected patients was indicated. Treatment plans for all other patients were retrospectively reviewed.
- In case of unacceptable variation, prospective cases had to be replanned by the center according to the protocol following the reviewer's advice.

Each treatment plan was registered into the EORTC's internal RT database (VODCA DB; Medical Systems Solutions, Switzerland). Additional tumor characteristics were retrospectively derived from the RT planning computed tomography. Because there is no common classification of primary tumor site for RPS, sites were classified as described by both Bonvalot et al[5] and Jacquet et al.[6] The posterior abdominal wall region was also retrospectively checked for cold spots because it is known to be a high-risk region for recurrence.[7] Finally, if the internal abdominal organs shifted from their original position because of the sarcoma mass, the tumor was considered compressive; otherwise, it was considered infiltrative.

Outcomes and Definitions

Plans were considered unacceptable in case of: 1) incorrect target volume definition or 2) incorrect dose coverage of the PTV (see Supporting Table 1). If improper OAR delineation represented the only cause for protocol deviation, the RT plan was considered compliant because no impact on tumor control was foreseen for the patient.

A composite end point—*overall RT compliance status*—was created to classify patients into 1 of 2 groups: patients who had either unacceptable RT plan compliance and/or excessive overall treatment time (>45 days) and/or received incorrect total dose received (≠50.4 Gy) were classified as *non–RT-compliant* (NRC), and the remaining patients were classified as *RT-compliant* (RC). Dose reductions to 45.4 Gy to meet OAR constraints were allowed according to the protocol, and such dose reductions were considered compliant. ARFS was measured from randomization to abdominal recurrence or death, whichever occurred first. In the study protocol, abdominal recurrence was defined by local and/or distant progression (according to Response Criteria in Solid Tumors, version 1.1) during or after RT, with tumors or patients becoming inoperable (an American Society of Anesthesiologists physical status score of 3 or involvement of superior mesenteric artery, aorta, or bone), peritoneal metastasis found at surgery, macroscopic residual disease left at surgery, or local relapse after macroscopically complete resection (mCR). Two different definitions for ARFS were proposed in 2017 by the Independent Data

Monitoring Committee as unplanned sensitivity analyses. They are referred to as the first and second sensitivity analyses (*ARFS-SA1* and *ARFS-SA2*, respectively) and are also defined in the STRASS trial main publication.[2] In the first sensitivity analysis, patients were considered as having no event if they subsequently underwent mCR despite local progression on RT. In the second sensitivity analysis, patients were considered as having no event if the surgery was macroscopically complete despite local progression on RT or as becoming medically unfit. OS was measured from randomization to death, whatever the cause.

Statistical Analysis

Patient characteristics were compared between the NCR and CR groups using the χ^2 test for categorical variables and the nonparametric Kruskal-Wallis test for continuous variables. ARFS and OS were described using Kaplan-Meier curves.[8] The median and its associated nonparametric 95% confidence interval (CI) were calculated, and comparisons between the RC and NRC groups were made using a Cox proportional hazards (PH) model adjusted for age at diagnosis, sex, World Health Organization performance status, histologic tumor type, tumor grade, and tumor size (in mm) at baseline. The cumulative sums of martingale residuals, together with the Kolmogorov-type supremum test, were used to evaluate the PH and linearity assumptions.[9] A stratified Cox model was used when the PH assumption appeared to be violated for any of the covariates. Time assessment bias inherent to the different follow-ups between the 2 treatment arms was taken into account, as described in the main publication of the STRASS trial.[2]

A 2-sided 5% significance level was considered for all analyses. No correction for multiplicity was made. SAS statistical software (version 9.4) was used for all analyses.

RESULTS

The EORTC 62092-22092 STRASS trial was activated on January 18, 2012. RT plans were collected among 31 recruiting centers. The last patient was randomized on April 12, 2017. In total, 266 patients were registered in the study, with 133 in each arm (randomization, 1:1). In total, 125 of 133 patients from the preoperative-RT arm of STRASS were eligible for the current analysis (from 10 countries and 25 institutions). Reason(s) for ineligibility are provided in Figure 1. Among these 125 patients, 8 were included although they did not undergo surgery because RT potentially could have influenced their chances of undergoing surgery or not.

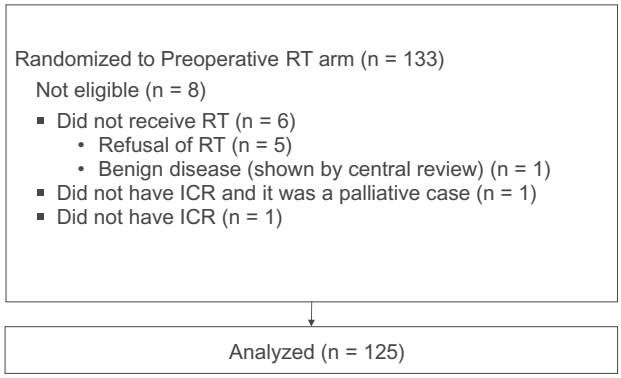


FIGURE 1. This is a Consolidated Standards for Reporting Trials (CONSORT) diagram of the current study. ICR indicates individual case review; RT, radiotherapy.

RTQA Review Process and Summary of RT Deviations

In total, 40 (32%), 20 (16%), and 65 (52%) patients had their final plan reviewed before, during, and after RT, respectively. Figure 2 summarizes the outcome of the review process and the way RT plans and patients were classified to create the RC and NRC groups. After the first review, 43 of 125 patients (34.4%) had unacceptable RT plan compliance, including 17 who were reviewed before or during RT. Eleven of these 17 plans (64.7%) could be made compliant after final review.

In total, 32 patients (25.6%) had unacceptable RT plan compliance after final review. Among the 38 deviations reported for these 32 patients, 25 deviations (65.7%) were linked to incorrect target delineation, 12 (31.6%) were linked to inadequate PTV coverage, and 1 deviation was linked because of missing information on PTV coverage. Importantly, the most common deviation made when delineating the target was a gross tumor volume geographic miss: this was observed in 16 of the 25 deviations (64%) related to target delineation.

Finally, the overall RT compliance status was NRC for 36 of 125 patients (28.8%), and the remaining 89 patients (71.2%) were classified as RC. Note that 4 patients were added to the NRC group: 2 patients because of a total dose received <50.4 Gy and 2 patients because of an overall treatment time >45 days. One patient received 45.4 Gy to meet OAR constraints, and this patient was considered compliant.

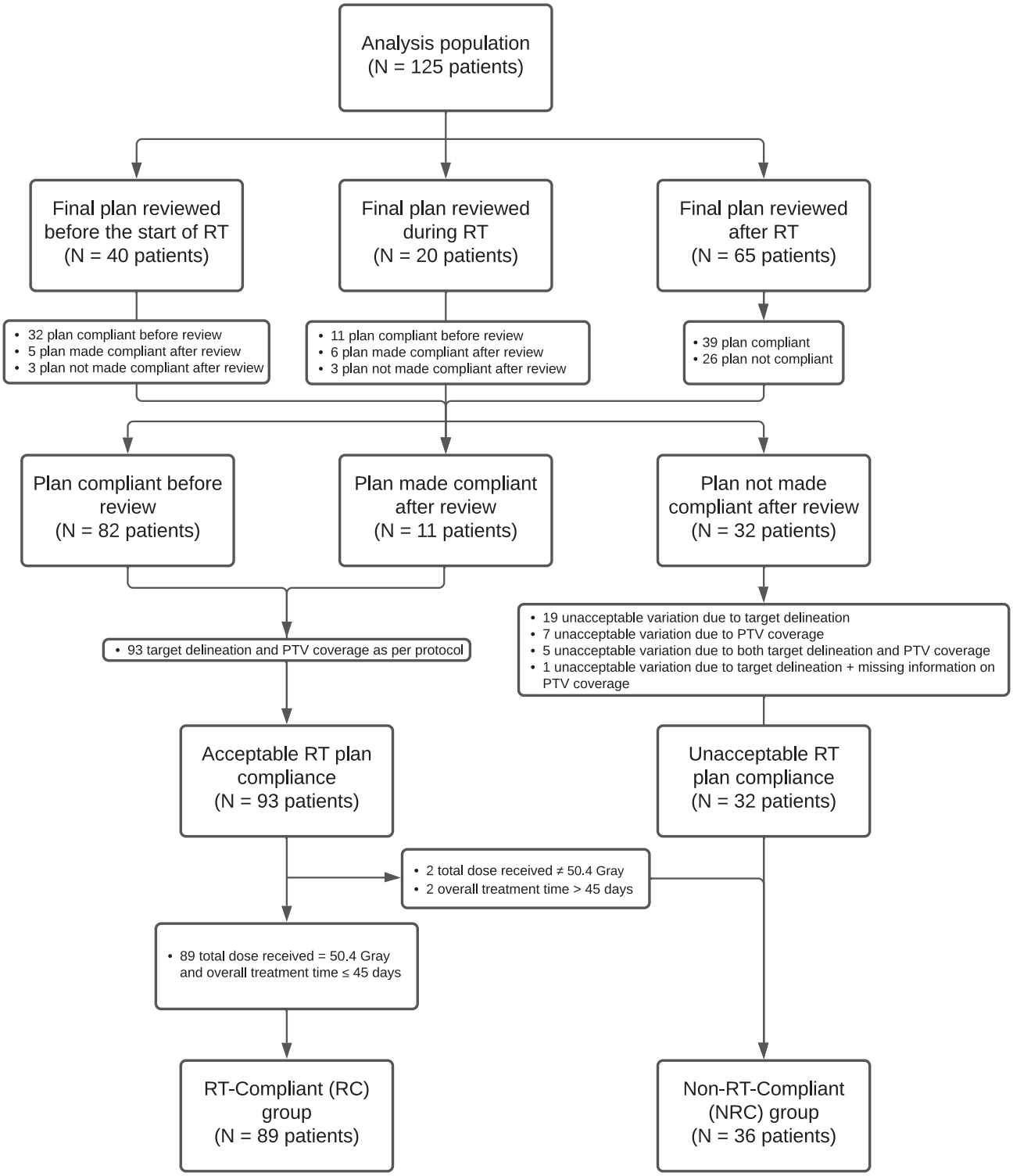


FIGURE 2. This is a flowchart of the radiotherapy (RT) quality-assurance review outcome and repartition of patients in the RT-compliant (RC) and non–RT-compliant (NRC) groups. PTV indicates planning target volume.

Factors Analyzed for Associations With Overall RT Compliance Status

Patients within the NRC group were older (NRC vs RC: 47.2% vs 31.5%, respectively, were older than 65 years). Patients who had dedifferentiated liposarcoma were more frequent in the NRC group (41.7% vs 36%), whereas those who had leiomyosarcoma were more frequent in the RC group (8.3% vs 14.6%). Histologic grade was not evaluable in 27.8% and 19.1% of patients in the NRC and RC group, respectively. Median tumor sizes were 180 and 150 mm in the NRC and RC group, respectively. In the NRC group, a higher proportion of primary tumors were located in the iliac fossa and hypochondrium (61.1% vs 32.6%). Tumors were infiltrative in 52.8% and 57.3% of patients in the NRC and RC group, respectively. In the NRC group, 66.7% of tumors were right-sided. Table 1 summarizes the patient and tumor characteristics in the RC and NRC groups.

Abdominal Recurrence-Free Survival by Overall RT Compliance Status

With a median follow-up of 30.7 months, 55 abdominal recurrences were reported, including 35 in the RC group and 20 in the NRC group (see Supporting Table 2). The corresponding 3-year ARFS rate was 49.8% (95% CI, 32.7%-64.8%) in the NRC group and 66.8% (95% CI, 55.8%-75.7%) in the RC group. The median ARFS was 2.3 years (95% CI, 0.5 years to not estimable) in the NRC group and was not reached in the RC group (Fig. 3A). The adjusted hazard ratio (HR) for the NRC group versus the RC group was 2.32 (95% CI, 1.25-4.32; $P = .008$) (see Supporting Table 3).

In the first sensitivity analysis (ARFS-SA1; local progression on RT was not regarded as an ARFS event for those who underwent mCR), 47 ARFS events were reported in 18 patients from the NRC group and in 29 patients from the RC group (see Supporting Table 2). The corresponding 3-year ARFS rate was 55.4% (95% CI, 37.9%-69.8%) and 73.1% (95% CI, 62.3%-81.3%) for the NRC and RC group, respectively. The median ARFS was 3.9 years (95% CI, 0.6 to not estimable) in the NRC group and was not reached in the RC group (Fig. 3B). The adjusted HR for the NRC group versus the RC group was 2.76 (95% CI, 1.37-5.54; $P = .004$) (see Supporting Table 4).

In the second sensitivity analysis (ARFS-SA2; neither local progression nor becoming medically unfit on RT were regarded as ARFS events for those who underwent mCR), 40 ARFS events were reported, including 13 in the NRC group and 27 in the RC group (see Supporting Table 2). The corresponding 3-year ARFS rate was 69.3% (95% CI, 51.5%-81.7%) and 75.2% (95% CI, 64.5%-83.2%) in the NRC and RC group, respectively. The median ARFS was not reached for either group (Fig. 3C). The adjusted HR for the NRC group versus the RC group was 1.67 (95% CI, 0.77-3.61; $P = .192$ (see Supporting Table 5).

Local Relapse After Complete Resection as a First ARFS Event by Overall RT Compliance Status

Among the subevents forming ARFS, local recurrence after mCR was of particular interest. Importantly, for each patient, only the first event that occurred was considered when computing ARFS. For the 3 definitions of ARFS (according to the protocol, SA1, and SA2), local recurrence after mCR first occurred in 13 of 89 (14.6%) versus 2 of 36 (5.6%) patients, 16 of 89 (18%) versus 3 of 36 (8.3%) patients, and 16 of 89 (18%) versus 4 of 36 (11.1%) patients in the RC and NRC group, respectively (see Supporting Table 2).

Overall Survival by Overall RT Compliance Status

Overall, 22 patients (17.6%) died, of whom 9 (8 because of progressive disease) were in the NRC group, and 13 (11 because of progressive disease) were in the RC group. The corresponding 3-year OS rates were 76.1% (95% CI, 57.9%-87.3%) and 89.7% (95% CI, 81.0%-94.5%) in the NRC and RC groups, respectively. The median OS was not reached for either group (Fig. 4). The adjusted HR for the NRC group versus the RC group was 2.42 (95% CI, 0.84-6.95; $P = .100$) (see Supporting Table 6).

DISCUSSION

This exploratory analysis indicates that having acceptable RT plan compliance, combined with a total dose received and an overall treatment time in accordance with the study protocol guidelines, is associated with better ARFS (NRC vs RC: HR, 2.32; 95% CI, 1.25-4.32; $P = .008$). Similar results were observed for ARFS-SA1, also suggesting a benefit for patients who underwent adequate surgical resection despite local progression during RT (HR, 2.76; 95% CI, 1.37-5.54; $P = .004$).

However, this association was not significant for ARFS-SA2 (HR, 1.67; 95% CI, 0.77-3.61; $P = .192$). This could be explained by the loss of statistical power because of the smaller number of events considered in ARFS-SA2 compared with other ARFS definitions. In addition, a trend toward worse OS was observed for the

TABLE 1. Patient, Tumor and Radiologic Characteristics of the Radiotherapy-Compliant and Non–Radiotherapy-Compliant Groups

Characteristic	No. of Patients (%)			*P*
	RT-Compliant, N = 89	Not RT-Compliant, N = 36	Total, N = 125	
Sex				
Men	48 (53.9)	17 (47.2)	65 (52.0)	.496[a]
Women	41 (46.1)	19 (52.8)	60 (48.0)	
Age, y				
Median	60	64	61	.046[b]
Range	24-83	34-74	24-83	
Q1-Q3	51-67	57.5-69.5	53-68	
Age: Categorized, y				
≤50	21 (23.6)	2 (5.6)	23 (18.4)	.042[a]
50-65	40 (44.9)	17 (47.2)	57 (45.6)	
>65	28 (31.5)	17 (47.2)	45 (36.0)	
WHO performance status				
0	75 (84.3)	28 (77.8)	103 (82.4)	.388[a]
≥1	14 (15.7)	8 (22.2)	22 (17.6)	
Tumor grade				
Low	32 (36.0)	11 (30.6)	43 (34.4)	.631[a]
Intermediate	31 (34.8)	13 (36.1)	44 (35.2)	
High	9 (10.1)	2 (5.6)	11 (8.8)	
Not evaluable	17 (19.1)	10 (27.8)	27 (21.6)	
Histologic tumor type				
Well differentiated liposarcoma	32 (36.0)	13 (36.1)	45 (36.0)	.798[a]
Dedifferentiated liposarcoma	32 (36.0)	15 (41.7)	47 (37.6)	
Leiomyosarcoma	13 (14.6)	3 (8.3)	16 (12.8)	
Other histologic subtypes	12 (13.5)	5 (13.9)	17 (13.6)	
Tumor size, mm				
Median	150	180	154	.137[b]
Range	37-340	37-320	37-340	
Q1-Q3	110-204	125-211.5	114-210	
Primary tumor site				
Hypochondrium	34 (38.2)	9 (25.0)	43 (34.4)	.022[a]
Iliac fossa	12 (13.5)	1 (2.8)	13 (10.4)	
Iliac fossa and hypochondrium	29 (32.6)	22 (61.1)	51 (40.8)	
Pelvis	1 (1.1)	0 (0.0)	1 (0.8)	
Psoas	12 (13.5)	2 (5.6)	14 (11.2)	
Between abdomen and lower limb	1 (1.1)	2 (5.6)	3 (2.4)	
Radiologic characteristics				
Compressive	38 (42.7)	17 (47.2)	55 (44.0)	.644[a]
Infiltrative	51 (57.3)	19 (52.8)	70 (56.0)	
Technique used				
IMRT	59 (66.3)	27 (75.0)	86 (68.8)	.253[a]
3DCRT	6 (6.7)	0 (0.0)	6 (4.8)	
VMAT	24 (27.0)	9 (25.0)	33 (26.4)	
Laterality				
Right	37 (41.6)	24 (66.7)	61 (48.8)	.039[a]
Left	44 (49.4)	10 (27.8)	54 (43.2)	
Crossing the midline	8 (9.0)	2 (5.6)	10 (8.0)	
Intraspinal extension				
No	84 (94.4)	32 (88.9)	116 (92.8)	.282[a]
Yes	5 (5.6)	4 (11.1)	9 (7.2)	
Colds spots in the zone of the posterior abdominal wall				
No cold spot	70 (78.7)	28 (77.8)	98 (78.4)	.224[a]
Posterior abdominal wall is covered by PTV, and there is a cold spot	10 (11.2)	7 (19.4)	17 (13.6)	
Posterior abdominal wall is not covered by PTV; by default, it is a cold area	9 (10.1)	1 (2.8)	10 (8.0)	

Abbreviations: 3DCRT, 3-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; PTV, planning target volume; Q, quartile; RT, radiotherapy; VMAT, volumetric modulated arc therapy; WHO, World Health Organization;
[a]This *P* value was determined using the $\chi 2$ test.
[b]This *P* value was determined using the Kruskal Wallis test.

NRC group compared with the RC group (HR, 2.42; 95% CI, 0.84-6.95; $P = .100$).

Importantly, despite having observed better ARFS (according to the protocol and SA1) and a trend toward better OS in favor of the RC group, higher frequencies of local relapse after mCR were observed in the RC group for all ARFS definitions. These differences could not be fully explained by an imbalance in the frequency of other subevents, especially for ARFS-SA2 (17.9% vs 11.1%) (see Supporting Table 2). Because the main aim of RT is to increase local control,[10] we offer possible reasons that could explain this surprising finding:

- Preoperative RT might not have a clinically relevant impact on local control after mCR in patients with RPS (and, as such, neither does compliance to RT). This is very unlikely and is in direct contradiction to the main studies, which reported twice as many local relapses after mCR in the surgery group compared with the preoperative-RT group (47 vs 23 relapses).
- Compliance to RT might have a long-term impact on local control, and this could only be assessed by following these patients longer. Indeed, long-term recurrences are common in this setting.[11-13]
- Leaving out a part of the tumor (eg, mostly well differentiated part) might not affect local control, especially for cases in which the nondelineated part could be resected during surgery. This would have a major impact on the analysis because incorrect target delineation was the most common reason for unacceptable overall RT compliance, of which 64% was caused by gross tumor volume miss.

Overall, RT deviations were present in a substantial number of patients (28.8%). However, in the years after the STRASS protocol, international consensus guidelines for RPS have been published.[14] Therefore, if similar trials were done today, less interobserver variability, such as inadequate RT target volume delineations, would be expected compared with what was observed in STRASS.[15] Furthermore, the reason for not reviewing all patients before starting RT was to optimize resources at the time of trial initiation. Therefore, 1 lesson of this trial should be that, if RT represents the investigated treatment, a prospective review of all patients should be mandatory.

Interestingly, there were twice as many tumors expanding from the hypochondrium to the iliac fossa in the NRC group compared with the RC group, suggesting an association between position/volume of the tumor and a higher risk of noncompliant overall RT status (61.1% vs 32.6%). In addition, a higher rate of tumors situated on the right side in the NRC group (66.7%) was observed. We can hypothesize that RPS sarcoma situated on the right site are often in contact or even infiltrating the liver hilus, and thus the upper limit of the tumor is difficult to identify, especially in case of significant organ motion.

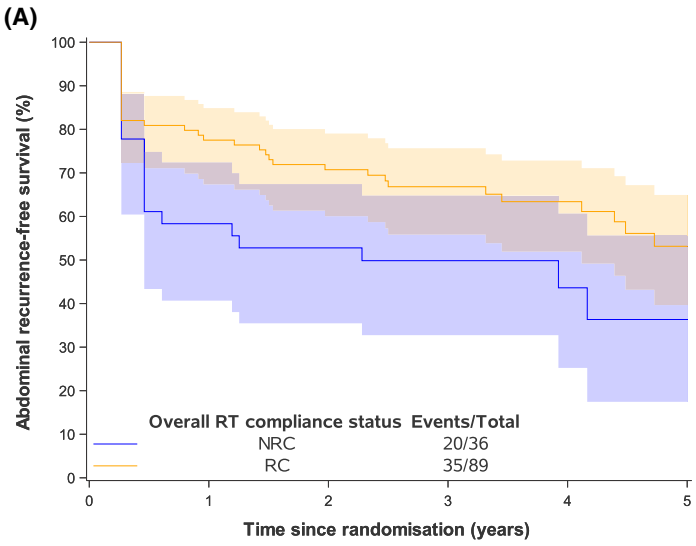
The results of this analysis are on par with other RTQA trial evaluations[16,17] reporting the association between RTQA results and survival outcome data in other settings. Other treatment characteristics have been demonstrated to have a significant impact on clinical outcome, such as the execution of first surgery in a sarcoma reference center (HR, 0.843; 95% CI, 0.799-0.889; $P < .001$)[18,19] and the type of surgery (compartmental resection vs simple complete resection: 3.29-fold lower rate of abdominal recurrence).[5]

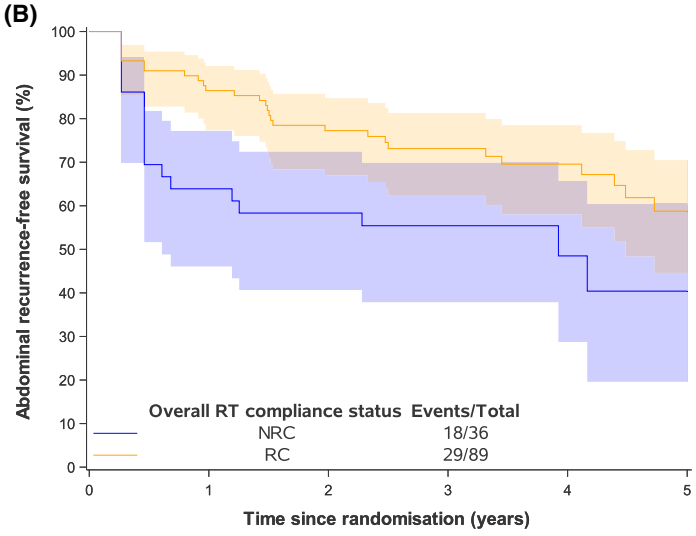
Unfortunately, the number of patients enrolled is not a good proxy for patient volume in this study because the patients were fragmented over 31 sites, resulting in very few sites with >5 patients enrolled, which makes it difficult to correlate noncompliant RT plans with center volume/experience.

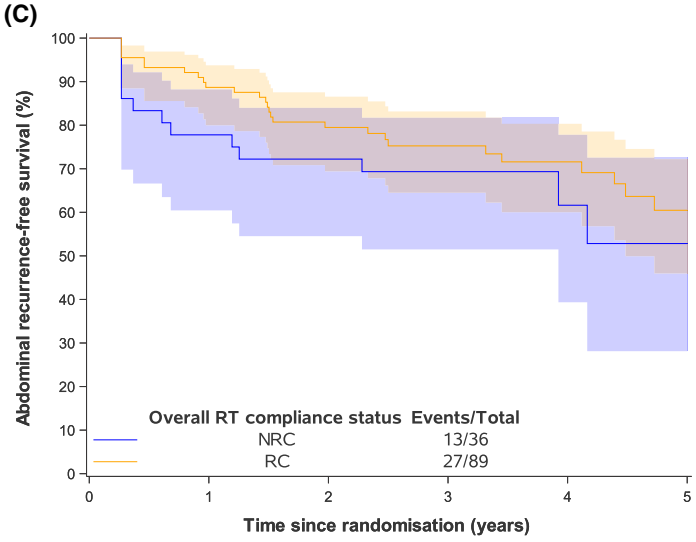
Several limitations should be mentioned when interpreting our results. These analyses are based on a limited number of events in both the NRC and RC groups. Moreover, although there was a significant association between overall RT compliance status and ARFS after adjusting for confounding factors, this does not prove causality.

The current analysis was the first instance of an EORTC trial with fully digital, remote RT planning data collection and review, and several lessons can be learned from it: first, RTQA remains essential in state-of-the-art trial development, and adequate resources should be made available to allow for a larger proportion of plans to be prospectively reviewed. Second, although being RT-compliant was associated with better ARFS, this association did not translate into a reduction in the frequency of local relapse after mCR in favor of the RC group. These results underline the importance of redefining adequate

FIGURE 3. Abdominal recurrence-free survival (ARFS) is illustrated between the radiotherapy (RT)-compliant (RC) and non–RT-compliant (NRC) groups, with ARFS defined (A) according to the protocol and according to (B) the first sensitivity analysis and (C) the second sensitivity analysis. Shaded areas around the lines represent 95% confidence intervals.







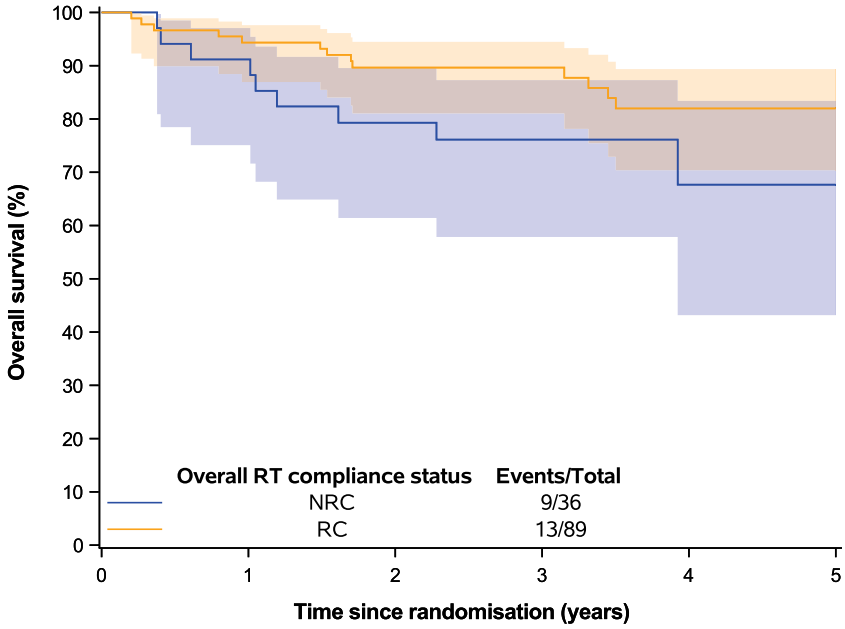


FIGURE 4. Overall survival is illustrated between the radiotherapy (RT)-compliant (RC) and non–RT-compliant (NRC) groups. Shaded areas around the lines represent 95% confidence intervals.

RT volume delineations in patients with RPS, in strong collaboration with the operating surgeon and radiologist,[18] to avoid geographic misses. These findings are of an exploratory nature and must be validated in an independent study before reaching a firm conclusion.

FUNDING SUPPORT

Work by Facundo Zaffaroni and Nicolas Sauvé as Fellows at European Organization of Research and Treatment for Cancer (EORTC) headquarters was supported by a grant from the EORTC Cancer Research Fund (ECRF), and work by Najlaa's Alyamani was supported by a grant from Kom op tegen Kanker (Stand up to Cancer), the Flemish Cancer Society of Belgium.

ACKNOWLEDGEMENT

Kom op tegen kanker funds for Emmanuel van der Schueren fellowship in radiotherapy quality assurance of clinical trials.

CONFLICT OF INTEREST DISCLOSURES

Bernd Kasper is Chair of the EORTC Soft Tissue and Bone Sarcoma Group and is a Board Member of the Sarcoma Patients EuroNet. The remaining authors made no disclosures.

AUTHOR CONTRIBUTIONS

Rick Haas: Performed the analysis and supervised the article. **Jean-Jacques Stelmes:** Conceived and designed the analysis and wrote the article. **Facundo Zaffaroni:** Conducted statistical analyses and wrote and reviewed the article. **Nicolas Sauvé:** Conducted statistical analyses and wrote and reviewed the article. **Enrico Clementel:** Collected the data and reviewed the article. **Raquel Bar-Deroma:** Collected the data and reviewed the article. **Cecile Le Péchoux:** Collected the data and reviewed the article. **Saskia Litière:** Conducted statistical analyses and reviewed the article. **Sandrine Marreaud:** Reviewed the article. **Najlaa Alyamani:** Provided data and reviewed the article. **Nicolaus H. J. Andratschke:** Reviewed the article. **Claudia Sangalli:** Provided data and reviewed the article. **Peter W. Chung:** Provided data and reviewed the article. **Aisha Miah:** Provided data and reviewed the article. **Coen Hurkmans:** Reviewed the article. **Alessandro Gronchi:** Provided data and reviewed the article. **Judith V. M. G. Bovée:** Reviewed the article. **Hans Gelderblom:** Reviewed the article. **Bernd Kasper:** Reviewed the article. **Damien Charles Weber:** Supervised, wrote, and reviewed the article. **Sylvie Bonvalot:** Supervised, wrote, and reviewed the article.

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