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# Preoperative radiotherapy combined with surgery versus surgery alone for primary retroperitoneal sarcoma: a meta-analysis

Young Rak Kim<sup>1</sup>, Chang-Hyun Lee<sup>1,2,3✉</sup>, Hangeul Park<sup>1</sup>, Jun-Hoe Kim<sup>1</sup> & Chi Heon Kim<sup>1,2,4</sup>

The efficacy of preoperative radiotherapy combined with surgery (preRT + S) for primary retroperitoneal sarcoma (RPS) remains unclear. This study aimed to compare preRT + S with surgery alone (SA) in patients with RPS. Core databases were searched for directly comparative studies depending on preRT. Thirteen studies included 2,439 patients with SA and 1,453 with preRT + S. PreRT + S in all RPS patients led to significantly low local recurrence (LR) (hazard ratios [HR], 0.575;  $p = 0.008$ ) compared to SA. Among the liposarcoma patients, PreRT + S did not clearly affect LR or abdominal recurrence-free survival (ARFS). Excluding dedifferentiated liposarcoma (DDLPS), the patients underwent preRT + S significantly improved LR (HR, 0.430;  $p = 0.002$ ) and ARFS (HR, 0.706;  $p = 0.045$ ). In another subgroup analysis of patients with well-differentiated liposarcoma and grade 1–2 DDLPS, preRT + S significantly extended ARFS (HR, 0.601;  $p = 0.014$ ) compared to SA. There was no significant difference in overall survival (OS) (HR, 0.904;  $p = 0.362$  [RPS]; HR, 0.724;  $p = 0.348$  [WDLPS + G1–2DDLPS]) between preRT + S and SA in all comparisons. PreRT + S group demonstrated higher incidence of total (odds ratio [OR], 1.580;  $p = 0.007$ ) and severe (OR, 3.680;  $p = 0.004$ ) complications than the SA group. PreRT + S prevent recurrence in patients with WDLPS and low-grade DDLPS but is associated with increased complications, resulting in similar OS compared to SA.

**Keywords** Retroperitoneal sarcoma, Neoadjuvant therapy, Radiotherapy, Liposarcoma, Surgery

Soft tissue sarcomas (STS) are a group of rare tumors of mesenchymal cell origin that account for less than 1% of all new adult solid tumors. Anatomically, STS arise in the extremities, trunk, retroperitoneal, neck, and genital regions<sup>1,2</sup>. Retroperitoneal sarcoma (RPS) accounts for 15% of all STS and has an annual prevalence rate of 0.5–5 per 100,000 people<sup>3</sup>. Although STS comprise more than 100 histopathologic subtypes, the most frequent subtypes of RPS are, in order of frequency, dedifferentiated liposarcomas (DDLPS, 32–43%), well-differentiated liposarcomas (WDLPS, 23–28%), leiomyosarcomas (18–23%), solitary fibrous tumors (5%), and malignant peripheral nerve sheath tumors (3%)<sup>4</sup>.

The primary therapy modality for RPS remains complete surgical resection, best achieved by en bloc resection of the tumor with adherent structures even if not overtly infiltrated. However, the size and extent of RPS often make margin-negative resection (R0) impossible<sup>5</sup>. Patients with primary localized RPS have shorter survival than those with STS in other sites owing to higher local recurrence (LR) rates associated with histologic types most commonly found in this location, large tumor size at diagnosis, and anatomical constraints and the thinness of the overlying peritoneum<sup>4,6</sup>. Many pathologists no longer evaluate margins for RPS, and it is commonly accepted that R0 resections are the result of insufficient sampling<sup>5</sup>. Large observational studies have reported microscopic margin-positive resection (R1) rates ranging widely from 34 to 69%<sup>5,7,8</sup>.

Owing to the limitations of surgical treatment, efforts have been made to improve the therapeutic outcomes of radiation therapy (RT). The effectiveness of perioperative RT for STS in the extremity has been established

<sup>1</sup>Department of Neurosurgery, Seoul National University Hospital, 101 Daehak-ro, Jongro-gu, 03080 Seoul, South Korea. <sup>2</sup>Department of Neurosurgery, Seoul National University College of Medicine, Seoul, South Korea. <sup>3</sup>Medical Big Data Research Center, Seoul Natl. Univ. Medical Research Center, Republic of Korea, Seoul, South Korea. <sup>4</sup>Department of Medical Device Development, Seoul National University College of Medicine, Seoul, Republic of Korea. ✉email: moyamoya@snu.ac.kr

but that for RPS remains unclear<sup>3</sup>. Different schedules of RT have been developed to improve local control; these include preoperative (preRT), intraoperative (IORT), and postoperative (postRT)<sup>9–12</sup>. The overall utilization of perioperative RT has not changed significantly over the last 20 years, but clinical guidelines regarding timing have, with the use of preRT increasing significantly, whereas that of postRT decreasing<sup>13</sup>. Despite the many studies on the efficacy of RT protocols, its role of RT in the management of RPS, including the optimal timing of treatment, remains poorly defined, as data that demonstrate improved survival are limited<sup>14</sup>. Given the high cost, time-intensive nature, and clinically meaningful complications associated with RT, it is crucial to define the role of RT in the treatment of RPS<sup>14</sup>.

Emerging evidence suggests that preRT may not confer benefits for all patients with RPS<sup>15,16</sup>. A prospective randomized phase III study (EORTC-62092: STRASS) in 2020 compared the effects of surgery alone (SA) versus preRT combined with surgery (preRT + S) in patients with newly diagnosed resectable RPS. The data not only failed to show significant advantages in abdominal recurrence-free survival (ARFS) but also showed substantial serious adverse events in the preRT + S group<sup>17</sup>. Although this level 1 evidence study concluded that preRT should be avoided, a subsequent retrospective study that pooled data from STRASS and off-trial (STREXIT) argued that preRT remains useful in preventing abdominal recurrence in selected cases of WDLPS and grade 1–2 DDLPS (WDLPS + G1–2DDLPS)<sup>18</sup>. The utility of preRT for RPS remains uncertain, as advantages and disadvantages have yet to be fully integrated and evaluated.

The current study primarily aimed to collate the available evidence on the efficacy of preRT in patients with RPS. A secondary aim was to determine whether preRT was effective for tissue-specific tumors; accordingly, we designed a systematic review of the literature and a meta-analysis of clinical studies.

## Materials and methods

### Search strategy and selection criteria

This meta-analysis followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Data from clinical studies that compared preRT + S and SA for RPS were included in the analysis. PubMed, EMBASE, Web of Science, and the Cochrane Database were systematically searched on January 2, 2024, independently by two reviewers (Y.R.K. and C.-H.L.). The search terms used were “preoperative” (or “neoadjuvant”) AND “retroperitoneal sarcoma” AND “radiotherapy” (or “radiation”). There were no language restrictions in the search.

The target of the search was to obtain articles that met the following inclusion criteria: direct comparison between SA and preRT + S for RPS; assessment of LR, ARFS, overall survival (OS), and treatment-related complications; and result presentation in a form that allowed quantitative synthesis. After excluding duplicate articles, the search results were screened by title and abstract according to the following exclusion criteria: reviews, case reports, guidelines, letters, commentaries, conference abstracts, experiments, and not related to RPS.

After eliminating the excluded papers, the full text of the eligible articles was obtained and thoroughly screened again using the same exclusion criteria. We excluded articles for the following reasons: inclusion of other treatments, such as chemotherapy and hyperthermia; no comparative studies regarding the two treatment arms; recurrent tumors; regression analysis of prognostic factors; and studies regarding wound problems. The references of all included papers were also examined to identify other relevant articles. Any disagreements between the reviewers were resolved through discussion.

### Data extraction, endpoints, and variable definitions

The following data were collected from the included studies: LR, ARFS, OS, complications, total number of patients, male-to-female ratio, median age, study period, tumor size, pathological diagnosis, median dose of RT, and RT plan. The outcome of interest was the correlation between preRT and recurrence. LR was defined as recurrence in the retroperitoneal space, and excluded distant metastasis, defined as recurrence outside the retroperitoneal space (i.e., abdomen, peritoneum, chest, brain, or elsewhere)<sup>19</sup>.

ARFS was measured from the date of randomization to the date of abdominal relapse. Abdominal recurrence was defined by one of the following events: local (abdominal) or distant progressive disease during preoperative RT; inoperable tumor or patient; peritoneal metastasis found at surgery; macroscopic residual disease during surgery; or local relapse (after macroscopically complete resection)<sup>17</sup>. Death in the absence of abdominal failure and distant metastases diagnosed before abdominal failure were considered competing risks for this endpoint<sup>17</sup>.

Complications were defined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0<sup>20</sup>. Briefly, a complication was defined as any unfavorable and unintended sign, symptom, or disease occurring within 30 days of surgery, whether or not related to surgery or RT. Complications were graded in severity from 1 to 5 according to the following definitions. Grade 1 included mild symptoms that did not require intervention. Grade 2 included moderate symptoms that required non-invasive intervention. Grade 3 included severe or medically significant, but not immediately life-threatening, symptoms; prolongation of hospitalization was indicated. Grade 4 included life-threatening complications requiring urgent intervention. Grade 5 included complication-related death<sup>21</sup>.

### Quality assessment of studies

Quality assessments were conducted independently in pairs, and a consensus was reached through discussion. The quality of controlled observational cohort studies was determined using the revised Risk of Bias Assessment tool for Non-randomized Studies (RoBANS2), while that of randomized controlled trials (RCTs) was evaluated using the revised Risk of Bias (ROB2) tool<sup>22,23</sup>.

### Statistical analyses

The relative weight of each study was determined using the inverse variance method for meta-analyses. This involved computing the hazard ratio (HR) for the intervention effect and 95% confidence intervals (CIs). Pooled complication rates were analyzed by calculating the effect size based on occurrence. Heterogeneity across individual studies was assessed using the Cochran Q test and Higgins  $I^2$  statistic, with  $Q < 0.1$  or  $I^2 > 50\%$  set as the threshold for significant heterogeneity. Random- or fixed-effects models were used according to the heterogeneity of each study.

Publication bias was assessed by visual inspection of the funnel plots and calculation of the p-value (one-sided) for Egger's intercept. Trials in which specific endpoints were not reported were excluded only from the pooled analyses of the specific endpoints that were not reported. All statistical analyses were conducted using Comprehensive Meta-Analysis software ver. 3.3 (Biostat, Englewood, NJ, USA). All tests were two sided, and statistical significance was set at  $p < 0.05$ .

### Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

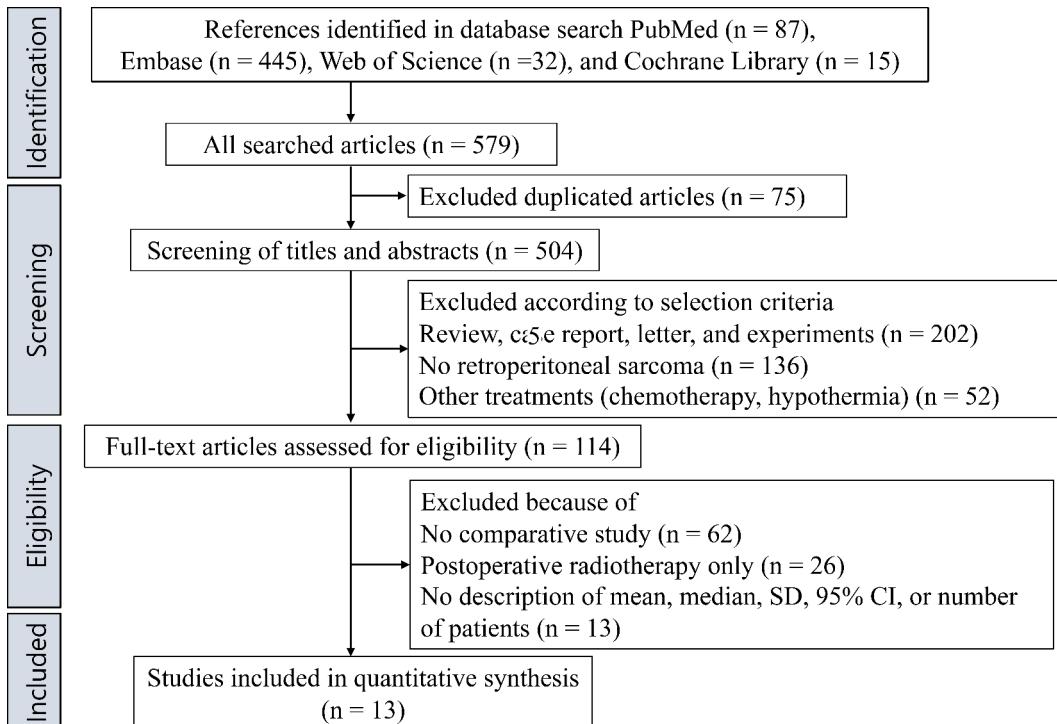
## Results

### Characteristics of the included studies

The initial literature search identified 579 studies: 87 in PubMed, 445 in Embase, 32 in the Web of Science, and 15 in the Cochrane Central Register of Controlled Trials. Of these, 75 duplicate studies and 202 case reports, review articles, letters, technical notes, and patents were excluded. After screening titles and abstracts, we further excluded 136 studies that did not report on RPS and 52 studies that included other treatments, such as chemotherapy and hypothermia. The full text of the remaining 114 studies was reviewed, and 101 studies were excluded because they lacked direct comparative analyses ( $n = 62$ ); included only postRT ( $n = 26$ ); and did not include descriptions of the mean, median, 95% CI, or number of patients ( $n = 13$ ). Finally, 13 studies were included in this meta-analysis<sup>14,17–19,21,24–31</sup>. The detailed results of the selection process are shown in Fig. 1.

### Risk of bias in the included studies

Three studies included data on IORT and postRT<sup>14,21,31</sup>. A study by Kelly et al. enrolled a patient underwent surgery and IORT were performed first, followed by postRT<sup>21</sup>. Lane et al. included 12 patients among 74 patients who underwent postRT<sup>14</sup>. The study by Stucky et al. included two (3%) patients who underwent resection and IORT without preRT for locally recurrent disease; the patients had been treated previously with surgical resection and maximum dose RT at other institutions<sup>31</sup>. One patient did not undergo preRT<sup>31</sup>. The same study also included data from 23 patients (36%) treated for locally recurrent disease<sup>31</sup>. Five studies provided propensity-score matched data<sup>17,18,28–30</sup>, which were utilized in the analysis instead of total data.



**Fig. 1.** Flow diagram of the search strategy for study selection.

## Results of syntheses

A total of 3,892 patients were included in the analyses. Of these, 2,439 patients underwent SA and 1,453 patients underwent preRT + S. Male patients accounted for 54.3% of the SA group and 56.3% of the preRT + S group. Two studies did not describe the number of men in each group<sup>24,25</sup>. The median age was 61.3 years in the SA group and 60.7 years in the preRT + S group. Four studies were excluded from the calculation of the median age due to missing values<sup>19,24,25,28</sup>. Liposarcoma was the most common histopathological subtype, occurring in 60.4% (2,349/3,892) of all patients and 57.7% of the SA and 64.5% of the preRT + S groups. Among patients with RPS, leiomyosarcoma was the second most common pathology, occurring in 21.0% in the SA and 15.9% in the preRT + S group. Detailed pathologic diagnosis of included patients was described in supplementary Table 1. One study was an RCT<sup>17</sup>, another was a prospective study<sup>27</sup>, and the others were retrospective studies. The mean RT dose was 50 Gy in nine studies and 45 Gy in two studies. One study described the range of RT dose at 45–50 Gy; the others did not describe it. The characteristics of the included studies and patients are presented in Table 1.

The synthetic results of LR risk were significantly lower in patients with RPS in the preRT + S than in those in the SA group (HR, 0.575; 95% CI, 0.382–0.864; Fig 2). PreRT did not result in a significant difference in the HR of LR among patients with liposarcoma (HR, 0.581; 95% CI, 0.242–1.393). However, when patients with DDLPS<sup>26</sup> were excluded, the risk for LR in liposarcoma decreased significantly (HR, 0.430; 95% CI, 0.254–0.728) as shown in Figure 2. PreRT did not significantly affect ARFS (HR, 0.864; 95% CI, 0.674–1.108 for RPS and HR, 0.794; 95% CI, 0.588–1.072 for liposarcoma; Fig. 3). PreRT significantly delayed abdominal recurrence in the liposarcoma group when the data of patients with DDLPS were excluded<sup>26</sup> (HR, 0.706; 95% CI, 0.502–0.992; p=0.045). In the subgroup analysis of WDLPS+G1–2DDLPS, the preRT + S group was associated with a much lower risk for ARFS (HR, 0.601; 95% CI, 0.401–0.901; p=0.014) than the SA group.

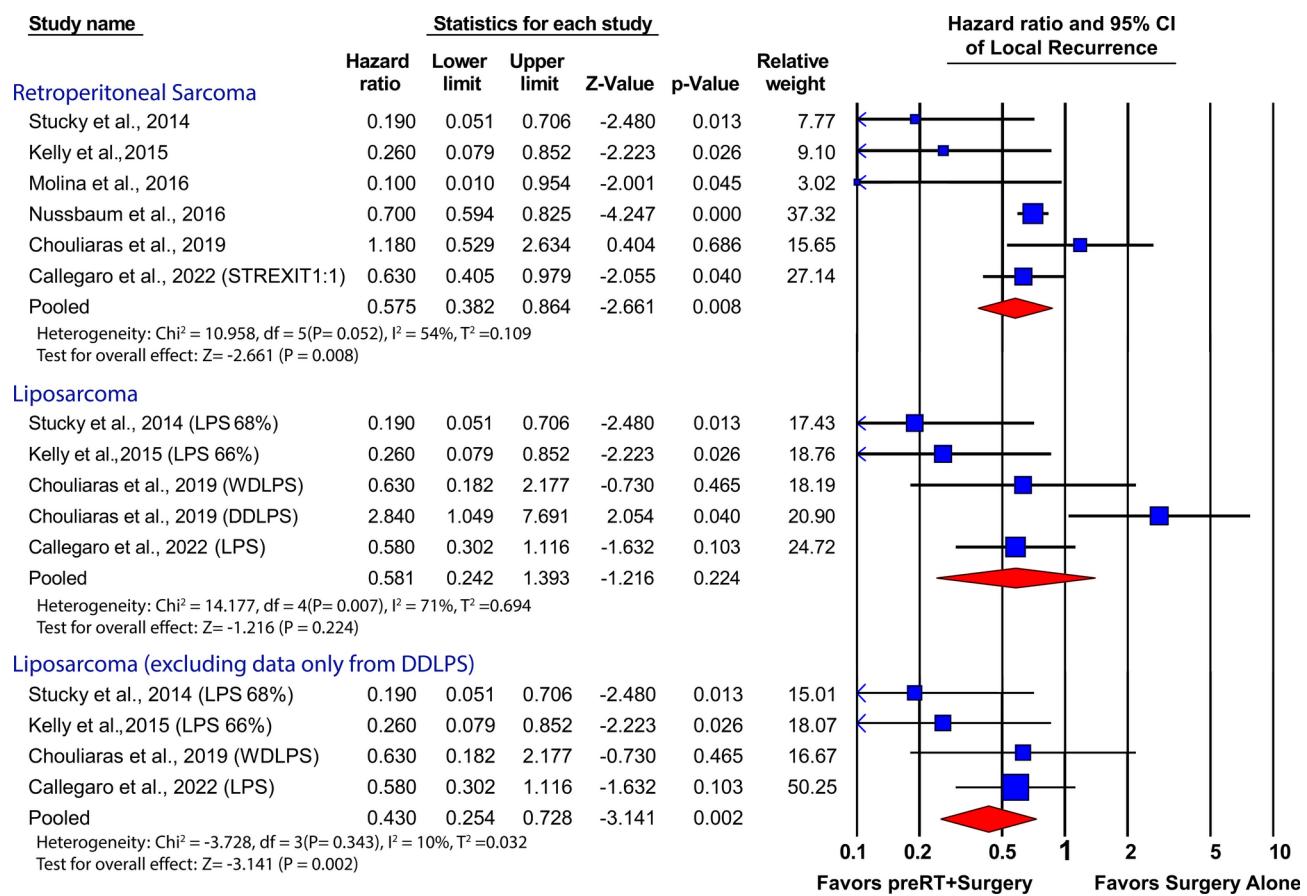
All and serious treatment-related complications were significantly more common in the preRT + S than in the SA group (Fig. 4). The OR was 1.580 (95% CI, 1.130–2.209) for all complications, 3.680 (95% CI, 1.531–8.844) for life-threatening or fatal complications (CTCAE grades 4–5), and 2.555 (95% CI, 1.559–4.186) for severe complications (CTCAE grade 3). Radiation-induced and surgery-related complications were more frequently experienced in the preRT + S group. In one RCT, one of 128 patients in the SA group and eight of 127 patients in the preRT + S group died (CTCAE grade 5)<sup>17</sup>. Among the latter, three deaths occurred during preRT<sup>17</sup>.

The results of the analysis on OS are depicted in Figure 5. PreRT + S did not confer significant improvements in OS. The HR for OS was 0.904 (95% CI, 0.727–1.124) for patients with RPS, 0.809 (95% CI, 0.610–1.072) for patients with liposarcoma, and 0.724 (95% CI, 0.369–1.421) for patients with WDLPS+G1–2DDLPS. Additionally, the 5-year survival rates, another indicator of survival, did not differ significantly between the two groups, as shown in supplementary figure 1.

All funnel plots were symmetric, indicating absence of significant publication bias within the studies. The Egger test results were as follows: 2.55 (p=0.01), -1.40 (p=0.24), and -7.26 (p=0.08) for OS in RPS, liposarcoma, and WDLPS+G1–2DDLPS; -1.02 (p=0.43) and -1.62 (p=0.26) for ARFS of RPS and liposarcoma; -1.22 (p=0.08) and -1.42 (p=0.35) for LR of RPS and liposarcoma; and 1.36 (p=0.33), 0.78 (p=0.40), and -0.94 (p=0.05) for all complications, grade 4–5 complications, and grade 3 complications,

Study	Design	Study period	Major pathology, proportion	Surgery Alone		PreRT + S				
				Number	Median age	Number	Median age	RT Plan	Mean dose of RT (Gy)	
De Wever et al., 2013 <sup>27</sup>	Pro	2000–2011	Liposarcoma, 100%	30	61	29	61	3D CRT/IMRT	50	
Stucky et al., 2014 <sup>31</sup>	Retro	1996–2011	Liposarcoma, 68%	26	74	37	56	EBRT	45–50	
Kelly et al. 2015 <sup>21</sup>	Retro	2003–2011	Liposarcoma, 66%	172	61	32	57	IMRT/proton beam	50	
Lane et al., 2015 <sup>14</sup>	Retro	1990–2011	Liposarcoma, 42%	45	60	29	57	IMRT/IORT	45	
Ecker et al., 2016 <sup>28</sup>	Retro	2004–2013	Liposarcoma, 100%	173	63*	174	63*	EBRT	50	
Molina et al., 2016 <sup>19</sup>	Retro	1991–2013	Liposarcoma, 100%	14	ND	27	ND	IMRT	50·4	
Nussbaum et al., 2016 <sup>30‡</sup>	Retro	2003–2011	Liposarcoma, 40%	1126	59.5†	563	59.2†	ND	50	
Chouliaras et al., 2019 <sup>26</sup>	Retro	2000–2016	Liposarcoma, 39%	294	60	56	59.3	IMRT/missing data	50	
Bachmann et al., 2020 <sup>24</sup>	Retro	2003–2018	DDLPS, 100%	4	57*	6	57*	IMRT	45	
Bonvalot et al., 2020 <sup>17</sup>	RCT	2012–2017	Liposarcoma, 74%	133	61	133	61	3D CRT/IMRT	50·4	
Bredbeck et al., 2022 <sup>25</sup>	Retro	1998–2015	Liposarcoma, 63%	72	59*	17	59*	ND	50·4	
Callegaro et al., 2022 <sup>18§</sup>	Retro	2012–2017	Liposarcoma, 67%	101	65	101	63	ND	50·4	
Erstad et al., 2023 <sup>29</sup>	Retro	2004–2017	WDLPS, 100%	104	63	104	62	ND	ND	
Erstad et al., 2023 <sup>29</sup>	Retro	2004–2017	DDLPS, 100%	145	70	145	67	ND	ND	

**Table 1.** Baseline characteristics of included studies. PreRT + S, preoperative radiotherapy combined with surgery; RT, radiotherapy; Pro, prospective study; Retro, retrospective study; 3D CRT, three-dimensional conventional radiotherapy; IMRT, intensity-modulated radiotherapy; EBRT, external beam radiation therapy; ND, not described; DDLPS, dedifferentiated liposarcoma; RCT, randomized controlled trial; WDLPS, well-differentiated liposarcoma. \*Median age of total patients. † Mean age. ‡ Matched (2:1) dataset. § Matched (1:1) dataset.



**Fig. 2.** Forest plots comparing risk of local recurrence between preoperative radiotherapy combined with surgery (preRT + S) and surgery alone. PreRT + S was associated with a significantly lower hazard ratio (HR) in retroperitoneal sarcoma but not in liposarcoma. When the patients with dedifferentiated liposarcoma (DDLPS) in the study by Chouliaras et al.<sup>26</sup> were excluded from the liposarcoma group, the preRT + S group had a significantly low HR for local recurrence.

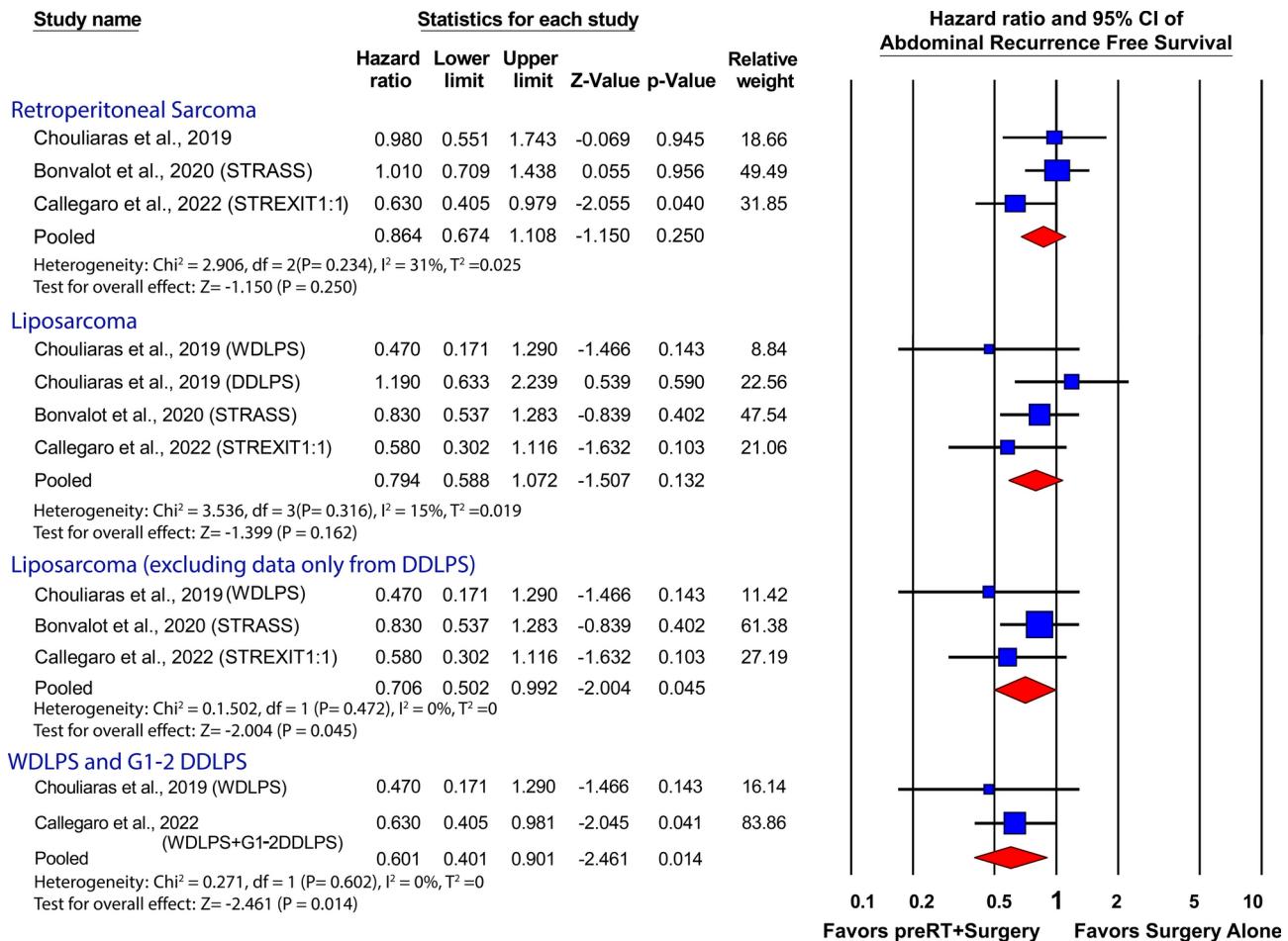
respectively. In the sensitivity analysis with regard to OS in RPS, single-study elimination affected the overall results of the meta-analysis.

## Discussion

This study found that preRT + S did not significantly improve OS compared to SA for RPS and liposarcoma. Patients with RPS in the preRT + S group had a significantly lower risk for LR. PreRT had no efficacy in reducing the risk of LR and abdominal recurrence in patients with liposarcoma. In contrast, upon excluding data from a study that focused solely on DDLPS, patients with liposarcoma exhibited significantly lower LR and ARFS rates. Subgroup analysis of patients with WDLPS + G1–2 DDLPS showed a significant reduction in ARFS with preRT. The preRT + S group was also associated with a significantly higher incidence of all and serious complications.

The preRT + S group demonstrated a tendency toward favorable outcomes regarding LR and abdominal recurrence. The conflicting findings regarding the use of preRT across studies may be attributed to the heterogeneity of the target diseases. We performed a tissue-specific subgroup analysis that included liposarcoma and WDLPS + G1–2 DDLPS. PreRT led to a significantly low risk for LR in RPS but not in liposarcoma. While four of the five datasets supported the efficacy of preRT + S for reducing LR, one dataset that included only DDLPS favored SA. After excluding the DDLPS data, preRT in the liposarcoma group resulted in a significantly lower LR. Regarding abdominal recurrence, preRT was not beneficial in all RPS or DDLPS. However, preRT was associated with significantly reduced abdominal recurrence in WDLPS and low-grade DDLPS. Collectively, these findings support that preRT may have some efficacy in reducing the risk of LR and abdominal recurrence in WDLPS and low-grade DDLPS but likely not in high-grade DDLPS.

Although LR and ARFS tended to be favorable in the preRT + S group of RPS, liposarcoma, and WDLPS + G1–2 DDLPS, a similar tendency was not discerned regarding OS. The difference in the outcomes between recurrence and OS may be related to the presence of complications. The incidence of all and severe (CTCAE-4 and 5) complications was significantly higher in the preRT + S than in the SA group. Additionally, higher rates of both radiation-induced and surgical complications were observed in the preRT + S group. Complications may have thus negatively affected survival in the preRT + S group.

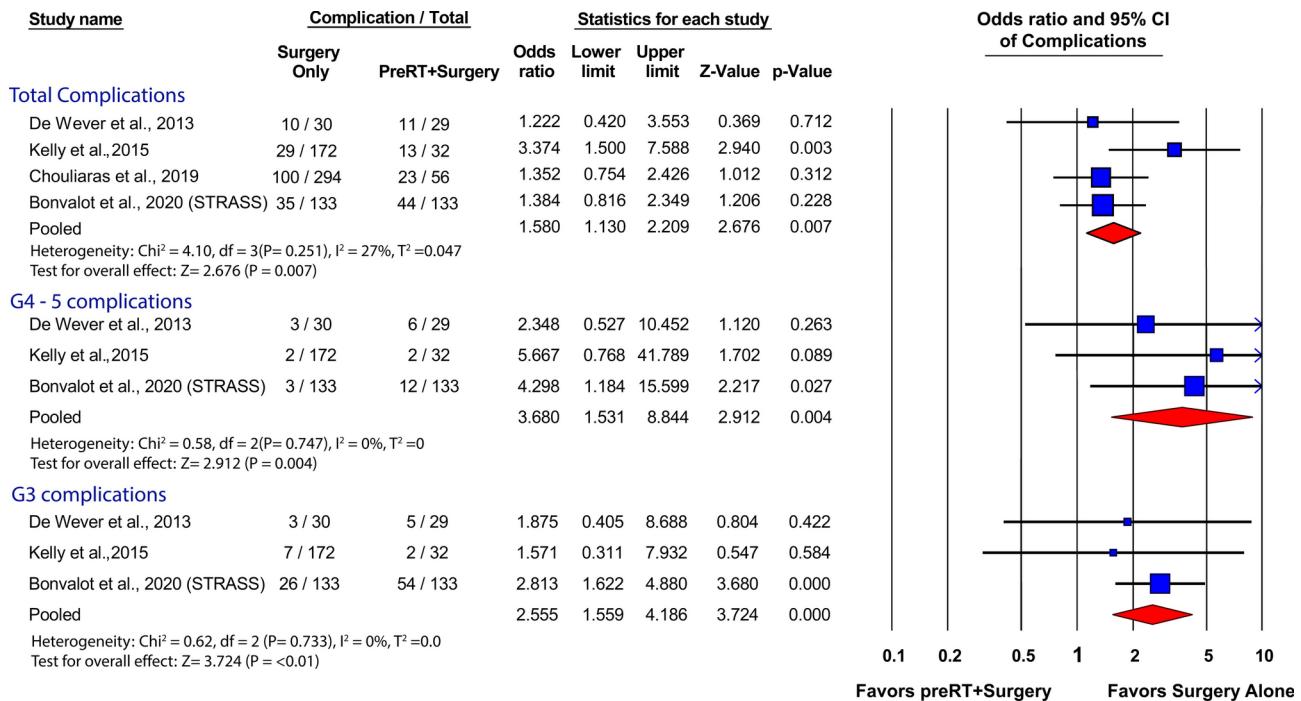


**Fig. 3.** Forest plots of risk of abdominal recurrence-free survival (ARFS). The hazard ratio (HR) of ARFS was comparable between all patients with retroperitoneal sarcoma and the liposarcoma subgroup who received preoperative radiotherapy. The HR of ARFS decreased significantly in the subgroup of patients with dedifferentiated liposarcoma (DDLPS) in the study by Chouliaras et al.<sup>26</sup> and patients with well-differentiated liposarcoma and grade 1–2 dedifferentiated liposarcoma (WDLPS and G1–2DDLPS).

The HR for LR increased from 0.2 to 1.2 from 2014 through 2022, indicating that the advantages of RT decreased and surgical outcomes improved with time. Recent studies have demonstrated that SA is not inferior to preRT + S for LR<sup>18,26</sup>. Although RT techniques have evolved from conventional RT to intensity-modulated RT/radiosurgery to minimize adverse effects, RT at a dose of 50 Gy is associated with significant unavoidable complications<sup>32</sup>. Substantial evidence supports the efficacy of preRT in preventing LR and abdominal recurrence, especially in patients with WDLPS + G1–2DDLPS. If complications related to the use of RT decrease substantially, preRT may prove beneficial in patients with RPS.

Although the utility of preRT in STS has been described in several meta-analyses<sup>33–36</sup>, to the best of our knowledge, this is the first study to incorporate two milestone studies<sup>17,18</sup> and clearly define preRT and RPS, with scientific significance. The first RCT (STRASS) comparing preRT + S and SA for primary RPS was published in 2020<sup>17</sup>. A subsequent retrospective study, which included data from STRASS and off-label (STREXIT) results, was published in 2022<sup>18</sup>. Our study included updated, well-designed studies and performed subgroup analysis by histological type. Cury et al. performed a meta-analysis of only extremity STS<sup>34</sup>.

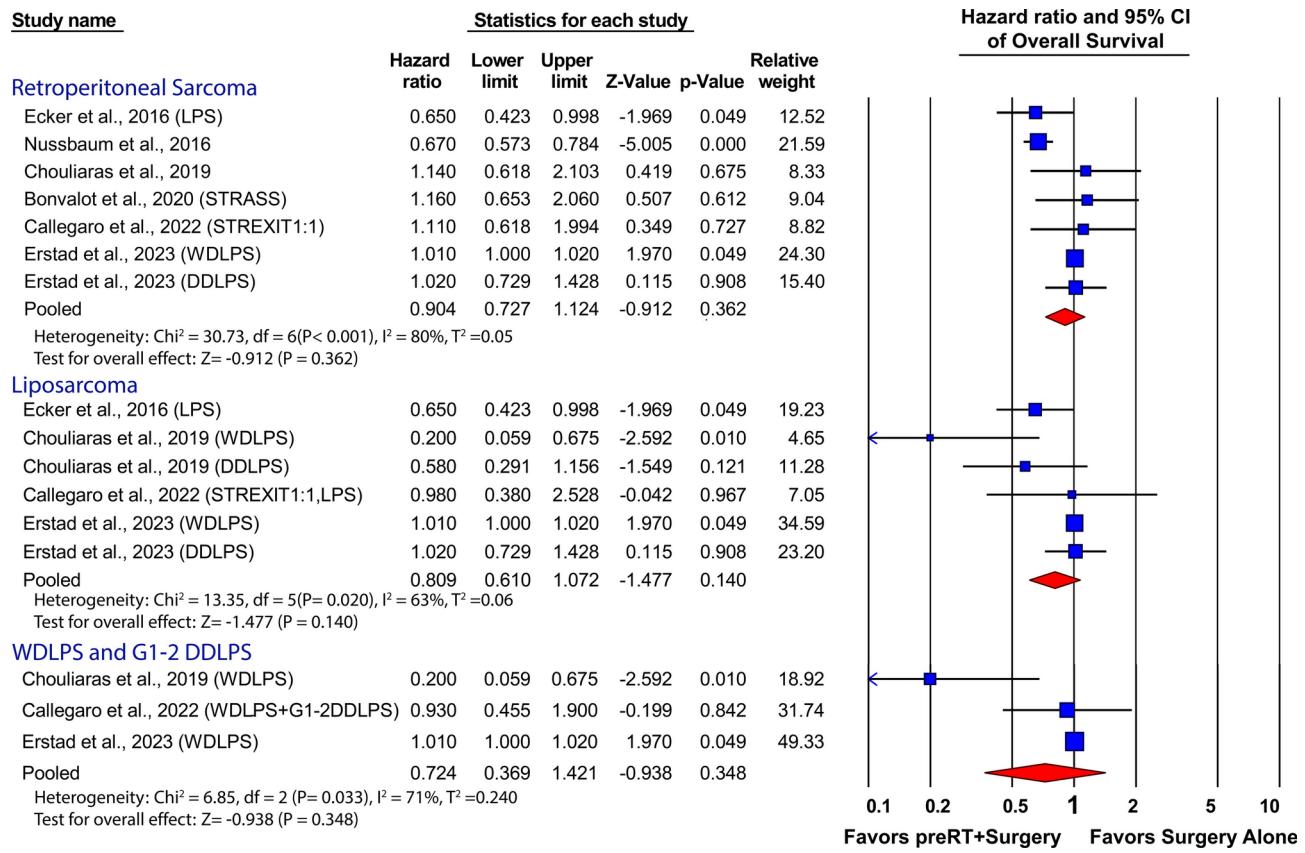
Despite these strengths, some limitations of this study must be acknowledged. First, the heterogeneous nature of these tumors should be considered. RPS includes several pathologies associated with STS. Given that liposarcoma accounted for 60.4% of the cases, subgroup analysis was performed in patients with liposarcoma. Among the liposarcoma group, outcomes may vary broadly depending on tumor size and grade. Unfortunately, the tumor sample sizes were insufficient for subgroup analyses according to histology, grade, and size. Consequently, the findings of this study are limited to the interpretation of surgically resectable primary RPS, which includes approximately 60% of liposarcomas with diameters ranging from 15 to 20 cm. However, this study clearly shows that preRT may prolong recurrence-free survival for low-grade liposarcomas such as WDLPS and G1–2 DDLPS, although the strategy is associated with an increased rate of complications. Second, it is unclear whether the two groups were identical, except for the treatment plan. We utilized propensity-matched data from each included study<sup>18,29,30</sup> to minimize the differences between the two groups. Although this approach led to adjustments in the number of patients included in those studies, the comparisons should be more accurate.



**Fig. 4.** Forest plots comparing the incidence of complications. In comparison with the surgery alone (SA) group, the group that received preoperative radiotherapy combined with surgery (preRT + S) had a significantly higher odds ratio for all, grade 4–5 (life-threatening or death), and grade 3 (severe) complications.

## Conclusion

PreRT + S had some efficacy in reducing the risk of LR and abdominal recurrence in patients with WDLPS and low grade DDLPS but the benefits may not extend to all RPS patients. Considering the significant increases in the incidence of all and serious complications, RT does not affect OS in patient subgroups. Collectively, current evidence on the efficacy and complications of preRT indicates that clinicians need to plan treatments aimed at minimizing complications for specific tumors for which preRT is effective.



**Fig. 5.** Forest plots for overall survival outcomes reveal no significant difference after preoperative radiotherapy (preRT) in retroperitoneal sarcoma, liposarcoma, and well-differentiated liposarcoma and grade 1–2 dedifferentiated liposarcoma (WDLPS and G1–2DDLPS).

## Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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## Author contributions

Y.R.K. and C.H.L wrote the first draft of the manuscript. C.H.L designed this study. H.P and J.H.K prepared figures, C.H.K. reviewed the results and edited the manuscript. All authors reviewed the manuscript.

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## Declarations

### Competing interests

The authors declare no competing interests.

### Additional information

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**Correspondence** and requests for materials should be addressed to C.-H.L.

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