

Adjuvant therapy for retroperitoneal sarcoma: a meta-analysis

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Research

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Abstract

Background

Adjuvant therapy is a promising treatment to improve the prognosis of cancer patients, however, the evidence base driving recommendations for adjuvant radiotherapy (ART) or chemotherapy (ACT) in retroperitoneal sarcomas (RPS) primarily hinges on observational data. The aim of this study was to evaluate the effectiveness of adjuvant therapy in the management of RPS by pooling analysis.

Methods

We searched PubMed, Web of Science, Embase, ASCO Abstracts, and Cochrane Library for comparative studies (until January 2020) comparing adjuvant therapy versus surgery alone. Data on the following endpoints were evaluated: overall survival (OS), local recurrence (LR), recurrence-free survival (RFS), and metastasis-free survival (MFS). Data were summarized as hazard ratios (HR) with 95% confidence intervals (95%CI). Risk of bias of studies was assessed with Begg's and Egger's tests.

Results

A total of 15 trials were eligible, including 9076 adjuvant therapy and 20830 surgery alone cases (20 studies for OS, 6 studies for RFS, 2 studies for LR, and 2 studies for MFS). Meta-analysis showed that ART was associated with distinct advantages as compared to surgery alone, including a longer OS (HR = 0.80, $P < 0.0001$), a longer RFS (HR = 0.61, $P = 0.0002$), and a lower LR (HR = 0.31, $P = 0.005$). However, this meta-analysis failed to demonstrate a benefit of ACT for RPS, including OS (HR = 1.11, $P = 0.19$), RFS (HR = 1.30, $P = 0.09$) and MFS (HR = 0.69, $P = 0.09$). In the sensitivity analysis, ACT was associated with a worse OS (HR = 1.19, $P = 0.0002$). No evidence of publication bias was observed.

Conclusions

Overall, the quality of the evidence was moderate for most outcomes. The evidence supports that ART achieved a generally better outcome as compared to surgery alone.

Introduction

retroperitoneal sarcomas (RPS) are the second common malignancy after soft tissue sarcoma (STS) of the extremities, accounting for 10–15% of all STS and 30% of all malignant retroperitoneal tumors [1]. R0 surgical resection is the most potential treatment to cure patients with localized disease, which means the adjacent organs that are invaded by sarcomas are often not preserved. According current studies, the rate of complete resection ranges from 41.8–76% [2]. However, local recurrence remains high even if complete

resection with negative margins is being achieved as far as possible, and is the leading cause of poor prognosis, with 5-year overall survival (OS) ranging from 39%-65% and a mortality rate of 20–75% [3–7].

To improve local control and overall survival, adjuvant therapy (AT) such as adjuvant radiotherapy (ART) has been investigated. However, there are insufficient evidences to compile treatment guidelines due to the different conclusions based on limited retrospective clinical studies (RCSs) [8–22]. For example, multiple analyses of the Surveillance, Epidemiology, and End Results (SEER) database and a retrospective analysis from French have shown that ART does not improve OS in patients with RPS [5, 9, 12, 23], but Trovik *et al* [8] and others [10, 18] who were published studies recently demonstrated a significant improvement in OS as well as recurrence-free survival (RFS) in patients undergoing ART, which is obviously confusing. In addition, although chemotherapy cannot be as a standard approach to treat RPS because of most trials were undertaken in the setting of advanced extremity sarcomas and the generalizability of these data is limited [24–25], discussing whether advanced RPS patients can benefit from adjuvant chemotherapy (ACT) is of great clinical significance.

The aim of this meta-analysis is to review the latest body of literature comparing AT with surgery alone in RPS, and to clarify the role of ART and ACT in the prognostic outcome of RPS, hoping to provide a reference for the clinicians.

Methods

Searching strategy

The meta-analysis was conducted as the guidelines of the Cochrane Handbook of meta-analysis and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. We search PubMed, Web of Science, Embase, ASCO Abstracts, and Cochrane library for eligible studies between January 2000 and January 2020 with the searching strategy: (((adjuvant radiotherapy OR postoperative radiotherapy OR postoperative chemotherapy) AND (retroperitoneal sarcomas OR retroperitoneal soft tissue sarcomas OR retroperitoneal neoplasms)) AND (surgery))). In addition, reference lists of all studies were screened to identify potentially eligible studies.

Selection criteria

Studies were included based on following criteria: 1) case-control study, retrospective cohort study or randomized clinical trial (RCT) of AT versus surgery for RPS patients; 2) PRS confirmed by pathological biopsy; 3) studies providing data of hazard ration (HR) and 95% confidence interval (CI) of local recurrence (LR), metastasis-free survival (MFS), RFS or OS for AT versus surgery for RPS. The exclusion criteria included: 1) letter, editorial or noncomparative study; 2) the cases or the groups in the study were less than 20 and 5 respectively; 3) HR and 95% CI cannot be extracted from studies; 4) non-human studies.

Data extraction and quality assessment

Two authors independently extracted data using a standard form from eligible studies. Discrepancies were resolved by consensus and invited a third investigator to interpret if the differences remained controversial after discussion. The following information was extracted from each included study: primary author, year of publication, patient source, intervention, number of patients, study type and data of OS, LR, RFS and MFS. All included studies were assessed by Newcastle-Ottawa Scale (NOS). The assessment tool focused on three aspects includes participant selection, comparability and exposure with 9 items. A study was considered of high quality if it scored 7 points or higher.

Statistical analysis

Meta-analysis was performed by Review Manager version 5.4 (Cochrane Collaboration, London, UK). HR was used as a summary statistic and calculated using either fixed-effects models or, in the presence of heterogeneity ($P < 0.10$, $I^2 > 50\%$), random-effects models. Sensitivity analysis was used to identify the possible sources of heterogeneity and detect the stability of studies by re-meta-analysis with one involved study excluded each time. Publication bias was assessed using Begg's and Egger's test with stataCorp version 15.1 (College Station, TX 77845, USA). All P-values were two-sides.

Results

Search results and characteristic of included studies

The detailed characteristics of included studies and the results of the quality assessment are summarized in Table 1. A total of 2641 references were identified form databases of PubMed, Web of Science, Embase, ASCO Abstracts and Cochrane library. After selection according to the inclusion/exclusion criteria, 15 RCSs were eligible for meta-analysis finally (Fig. 1). In these studies, 29906 patients with RPS were compared, including 9076 patients who underwent adjuvant therapy and 20830 patients who underwent surgery alone. In addition, 5 studies performed concurrent ART versus surgery and ACT versus surgery, 4 studies divide into adjuvant therapy group and surgery group with propensity score marched (PSM). The earliest study was published in 2008, and the latest in 2019. Studies were conducted in four different countries (USA, France, Norway and Italy). All studies were evaluated by NOS and the overall quality averaged 7.45 stars (range 7–8) on scale of 0–9 (Table S1).

Meta-analysis of OS

The fixed-effects meta-analysis results showed that the OS was significantly improved between patients who underwent ART when compared with patients who underwent surgery alone (HR = 0.80, 95% CI: 0.76–0.84; $P < 0.0001$) (Fig. 2A). However, there was no significant difference in ACT group versus surgery alone group (HR = 1.11, 95% CI: 0.95–1.29; $P = 0.19$) (Fig. 3A). Notable heterogeneity was seen in the latter, and the sensitivity analysis indicated that patients benefited more from surgery alone than ACT (HR = 1.19, 95% CI: 1.08–1.30; $P = 0.0002$).

Meta-analysis of RFS

The meta-analysis in the fixed-effects model indicated that RFS was obviously improved in ART group compared with surgery group (HR = 0.61, 95% CI: 0.47–0.79; P = 0.0002), and the four sets of results showed no significant amount of heterogeneity (Fig. 2B). However, there was no significant difference in ACT versus surgery alone (HR = 1.30, 95% CI: 0.96–1.77; P = 0.09), no statistical heterogeneity was found (Fig. 3B).

Meta-analysis of LR

LR was reported in 2 PSM studies, including 101 patients in ART group and 114 patients in surgery group. The results that analyzed with random-effect model showed LR of ART group was much lower than surgery group (HR = 0.31, 95% CI: 0.13–0.71; P = 0.005) (Fig. 2C).

Meta-analysis of MFS

The MFS was reported by 2 studies in ACT versus surgery alone, 1238 participants. There was no statistical significance between the two comparisons (HR = 0.69, 95% CI: 0.45–1.06; P = 0.09), no statistical heterogeneity was found (Fig. 3C).

Publication bias

The detailed results of the meta-analysis for AT and the heterogeneity analysis are summarized in Table 2. Publication bias was determined by Begg's and Egger's tests and there was no evidence of publication bias for OS and RFS (Fig. 4 and Table S2). However, there were significant heterogeneity in two pooled analysis, sensitivity analysis showed that one of which had a different result after excluding the most heterogeneous study. We will analyze this in the later part of discussion.

Discussion

The unique biological behavior of RPS brings great challenges to clinicians in the treatment of this disease. R0 resection is the only potentially curative therapy, but the risk of LR is substantial because large size and anatomical structure of the tumor frequently preclude resection with widely clear margins. Five-year LR rates range from 28%-60% [16, 26–28]. With long-term follow-up, almost all patients, especially those with liposarcomas, are likely to recur [29]. Therefore, it is urgent to clarify the comprehensive treatment of RPS, ART, remains a controversial component of treatment. Unlike STS in extremity, there is no rigorous level I data to support ART significantly reduce LR in RPS patients, and lessons from ART trials in extremity STS are difficult to translate directly to the RPS due to the potential for significant toxicity at equivalent dose [26]. Here our pooled analysis revealed the distinct advantages of ART over surgery alone in LR of RPS patients, this is a key parameter to evaluate the prognosis of patients under different treatments. Besides, whether ART is beneficial to OS is also controversial. Several RCSs indicated consistently that ART improve local control (LC) and RFS but failed to demonstrate a statistically significant association with OS [5, 9, 12, 21]. Others obtained opposite results that ART not only improved the OS, but also has obvious curative effect in RFS and LC with a premise that the margin of surgical resection reaches R0 or R1 [3, 10, 11, 13, 16, 18]. In our meta-analysis, the results support the latter.

Anthracyclines were the first systemic chemotherapeutic agents to demonstrate activity in STS, and doxorubicin was main representative. According currently studies, using ACT in STS could not benefit patients, neither patients whose tumors remained resectable or patients who had metastasized at an advanced stage. A multicenter phase III RCT (EORTC) [30], randomized 351 patients with non-metastatic macroscopically resected II-III tumors at any site, to postoperative chemotherapy with ifosfamide and doxorubicin. The results demonstrated OS did not differ significantly between groups (HR = 0.94, 95% CI: 0.68–1.31; P = 0.72) nor did RFS (HR = 0.91, 95% CI: 0.67–1.22; P = 0.51). A retrospective study of efficiency of ACT in resected RPS [11], published in 2017, showed that utilization of ACT was associated with significantly worse long-term survival (HR = 1.30, 95% CI: 1.05–1.61; P = 0.017), but was not associated with OS in margin-positive (R1/R2) resection. However, the trend of OS improvement with ACT were found in spindle cell (HR = 0.37, 95% CI 0.10–1.38), giant cell (HR = 0.82, 95% CI: 0.32–2.13) and synovial sarcoma (HR = 0.26, 95% CI: 0.05–1.33). Here our findings show that ACT cannot benefit RPS patients from OS, RFS and MFS, and even as previously reported study, it may cause worse OS (sensitivity analysis). Although whether metastasis occurs for patients is not the main reason to cause the increase in mortality, MFS was also included in the study as a prognostic parameter for PRS. In the studies we reviewed, only two studies included MFS [16–17], and the two studies were conducted by the same author in different years.

In our study, notable heterogeneity was seen in LR of ART and OS of ACT, and only OS can perform sensitivity analysis due to lack of studies in LR. The sensitivity analysis showed that ACT was associated with worse OS, which was different from previous results of pooled analysis. In any case, the two results support that ACT cannot improve OS in patients with RPS. From another perspective, we have to admit that the result is not robust. Meanwhile, some limitations should be considered before appraising the results of this study. First, interventions in the treatment group in some studies were not limited to postoperative radiotherapy and chemotherapy, and in order to minimize the interference factors, we extracted HR form the multivariate COX regression analysis. Second, all included studies were RCSs, no RCT was found in databases we search. Finally, studies were insufficient in the sub-analysis of LR of ART and RFS of ACT duo to only two studies were included, limiting the validity of the comparisons between studies and conclusions drawn.

In this study, the quality of evidence was moderate but sufficient to establish the efficacy of ART for RPS. The relationship between ACT and the prognosis of RPS needs to be further studied, especially for patients with resectable RPS. Since there was a trend that ART is more likely to improve OS and LC of RPS patients, while ACT is for MFS, distinguishing the different efficiency between ART and ACT was also urgent. In addition, further studies could significantly change the results that ACT was associated with a wore OS, and more prognostic factors, such as pathological type, surgical resection method, dose, and related toxic complications, need to be included for analysis. Of course, all results will eventually need to be verified by multicentered RCTs.

Conclusions

Overall, our Meta-analysis showed RPS patients who underwent ART had better prognostic outcome than those who underwent surgery alone, including a longer OS, a longer RFS, and a lower LR. However, This positive therapeutic effect has not been demonstrated in ACT, either in OS, RFS or MFS.

Abbreviations

ART Adjuvant Radiotherapy

ACT Adjuvant Chemotherapy

RPS Retroperitoneal Sarcomas

OS Overall Survival

LR Local Recurrence

RFS Recurrence-free Survival

MFS Metastasis-free Survival

HR Hazard Ratios

CI Confidence Intervals

AT Adjuvant Therapy

STS Soft Tissue Sarcoma

RCS Retrospective Clinical Study

SEER Surveillance, Epidemiology, and End Results

PRISMA Preferred Reporting Items for Systematic Reviews and Meta- Analyses

RCT Randomized Clinical Trial

NOS Newcastle-Ottawa Scale (NOS)

PSM Propensity Score Matched

LC Local Control

Declarations

Ethic approval and consent to participate

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no conflict of interests.

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Authors' contributors

XL, TW, and CL contributed substantially to the conception, design and acquisition of data. XL, LM, and TW wrote the main manuscript text. XL, TW, LM, and MX prepared figures. XL, SW, MX, and TW contributed to the analysis and interpretation of the data. XL, SW, LM, and CL contributed to devising the draft of the article and all of the authors revised it critically. All authors participated in revising the manuscript and in the final approval of the version to be published.

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Tables

Table I. Characteristics of Included Studies

Study (author, year)	Patient source	Type of study	Number of patients (Treat/Control)	Intervention (Treat/Control)	Outcome	HR (95%CI)	NOS score
Adjuvant radiotherapy							
Nussbaum et al 2016 ^a (19)	USA	RCS	2196/2196	Sur+RT/Sur	OS	0.78 (0.71-0.85)	8
Trovik et al 2014 ⁽⁸⁾	Norway	RCS	42/55	Sur+RT/Sur	OS	0.36 (0.18-0.72)	8
					MFS	0.42 (0.20-0.88)	
					LR	0.20 (0.09-0.45)	
Bates et al 2018 ⁽¹⁰⁾	USA	RCS	144/336	Sur+RT/Sur	OS	0.42 (0.19-0.90)	7
Tseng et al 2011 ⁽⁹⁾	USA	RCS	343/1130	Sur+RT/Sur	OS	0.92 (0.78-1.09)	7
Zhou et al 2010 ⁽¹³⁾	USA	RCS	-/-	Sur+RT/Sur	OS	0.78 (0.63-0.95)	7
Lepechoux et al 2013 ⁽¹²⁾	France	RCS	56/42	Sur+RT/Sur	OS	0.91 (0.34-1.39)	8
					RFS	0.43 (0.20-0.88)	
Chouliaras et al 2019 ^a (21)	USA	RCS	59/59	Sur+RT/Sur	OS	0.80 (0.47-1.35)	8
					RFS	0.70 (0.43-1.14)	
					LR	0.47 (0.21-1.06)	
Miura et al 2015 ^{a†} (18)	USA	RCS	938/3050	Sur+RT/Sur	OS	0.79 (0.70-0.90)	8

Gronchi et al 2012 [†] (17)	Italy	RCS	202/460	Sur+RT/Sur	OS	0.64 (0.41-1.00)	7
					RFS	0.57 (0.35-0.92)	
					MFS	2.38 (1.34-4.42)	
Gronchi et al 2009 [†] (16)	Italy	RCS	176/400	Sur+RT/Sur	OS	0.55 (0.35-0.86)	7
					RFS	0.65 (0.42-1.01)	
					MFS	1.47 (0.81-2.68)	
Stahl et al 2017 [†] (15)	USA	RCS	1132/2772	Sur+RT/Sur	OS	0.81 (0.70-0.93)	8
Klooster et al 2016 [†] (20)	USA	RCS	102/293	Sur+RT/Sur	OS	0.78 (0.58-1.05)	7
Berger et al 2018 ⁽²²⁾	USA	RCS	550/2212	Sur+RT/Sur	OS	0.80 (0.68-0.94)	7
Nathan et al 2009 ⁽⁵⁾	USA	RCS	254/1365	Sur+(RT+IORT)/Sur	OS	0.95 (0.78-1.15)	7
Adjuvant chemotherapy							
Datta et al 2017 ⁽¹¹⁾	USA	RCS	390/377	Sur+CT/Sur	OS	1.30 (1.05-1.61)	8
Miura et al 2015 ^{a‡} (18)	USA	RCS	1525/1525	Sur+CT/Sur	OS	1.17 (1.04-1.31)	8
Klooster et al 2016 [‡] (20)	USA	RCS	122/273	Sur+CT/Sur	OS	1.09 (0.83-1.45)	8
Gronchi et al 2009 [‡] (16)	Italy	RCS	182/394	Sur+CT/Sur	OS	1.30 (0.86-1.97)	7
					RFS	1.34 (0.88-	

						2.05)	
					MFS	0.72 (0.39- 1.24)	
Gronchi et al 2012 [‡] (17)	Italy	RCS	218/444	Sur+CT/Sur	OS	1.14 (0.74- 1.75)	7
					RFS	1.26 (0.80- 1.97)	
					MFS	0.66 (0.36- 1.20)	
Stahl et al 2017 [‡] (15)	USA	RCS	445/3447	Sur+CT/Sur	OS	0.82 (0.67- 0.99)	8

Notes: ^a Propensity score matched (PSM); ^{†,‡} Adjuvant radiotherapy (†) and adjuvant chemotherapy (‡) in the same study

Abbreviations: CI, confidence interval; DSS, disease-specific survival; HR, hazard ratio; LR, local recurrence; OS, overall survival; RCS, retrospective cohort study; RCT, randomized clinical trial; RFS, recurrence-free survival; RT, radiotherapy, Sur, Surgery.

Table II. Summary of Results

Categories	Studies	Patients	Model	HR (95%CI)			Heterogeneity		
				value	z	P-value	χ^2	I^2	P-value
OS									
Adjuvant radiotherapy	14	20564	Fixed	0.80 (0.76-0.84)	8.66	<0.0001	14.86	13%	0.32
Adjuvant chemotherapy	6	9342	Random	1.11 (0.95-1.29)	1.32	0.19	12.08	59%	0.03
Sensitivity analysis of adjuvant chemotherapy	5	5450	Fixed	1.19 (1.08-1.30)	3.68	0.0002	1.35	0%	0.85
RFS									
Adjuvant radiotherapy	4	1454	Fixed	0.61 (0.47-0.79)	3.78	0.0002	1.27	0%	0.74
Adjuvant chemotherapy	2	1238	Fixed	1.30 (0.96-1.77)	1.68	0.09	0.04	0%	0.85
LR									
Adjuvant radiotherapy	2	215	Random	0.31 (0.13-0.71)	2.78	0.005	2.78	54%	0.14
MFS									
Adjuvant chemotherapy	2	1238	Fixed	0.69 (0.45-1.06)	1.69	0.09	0.04	0%	0.84

Abbreviations: CI, confidence interval; HR, hazard ratio; LR, local recurrence; OS, overall survival; RFS, recurrence-free survival.

Figures

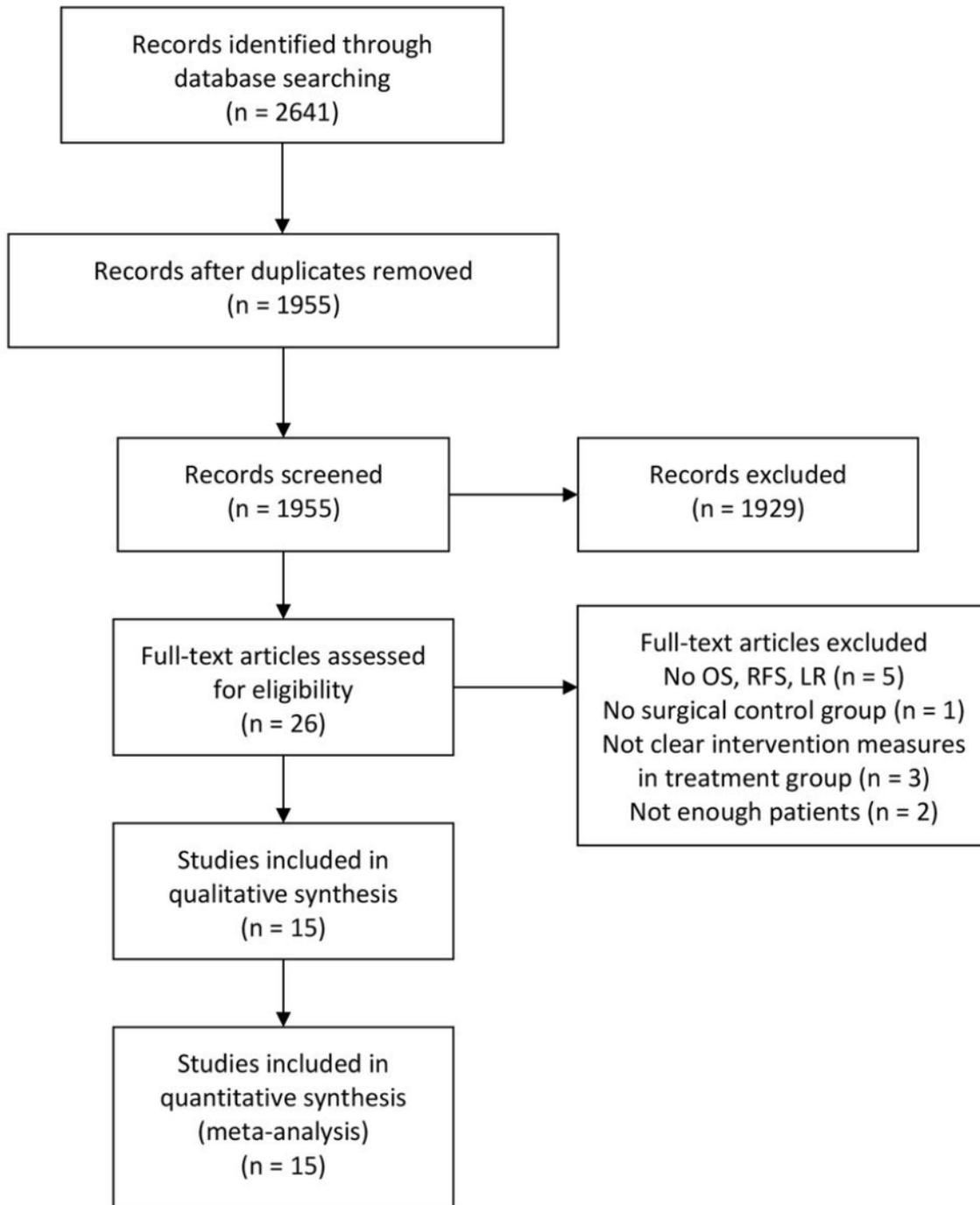


Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Flowchart of studies included in the review with reasons for exclusion.

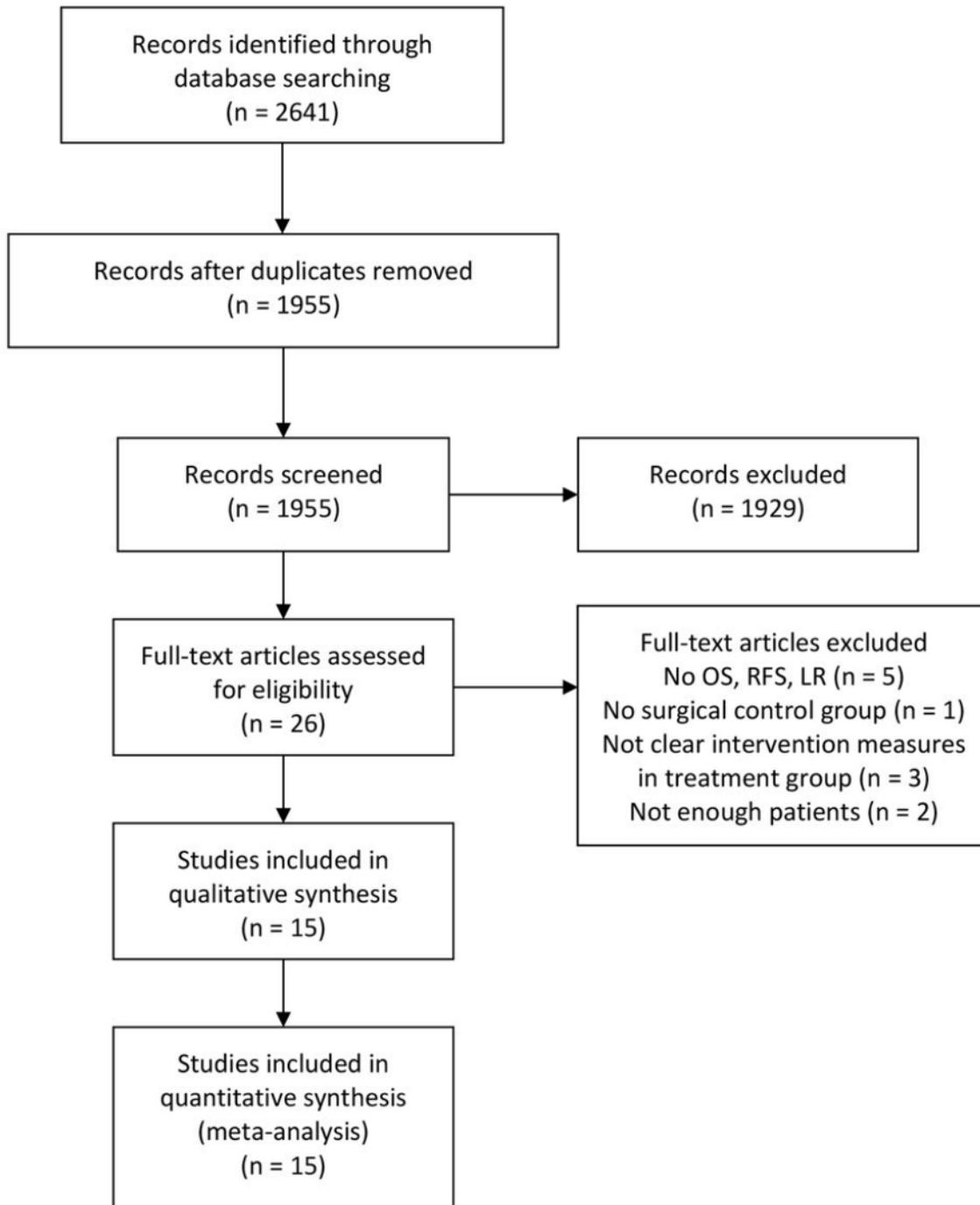


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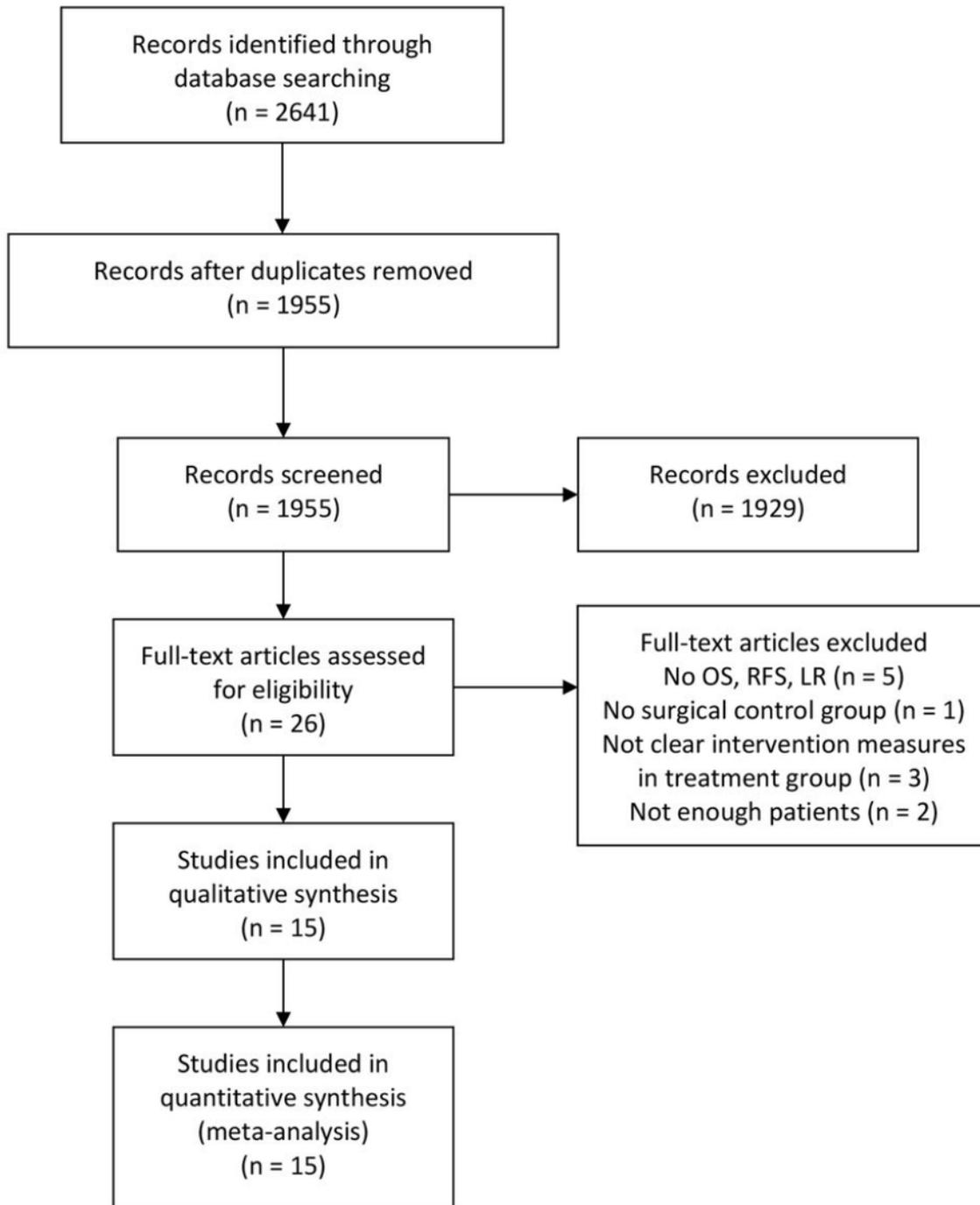


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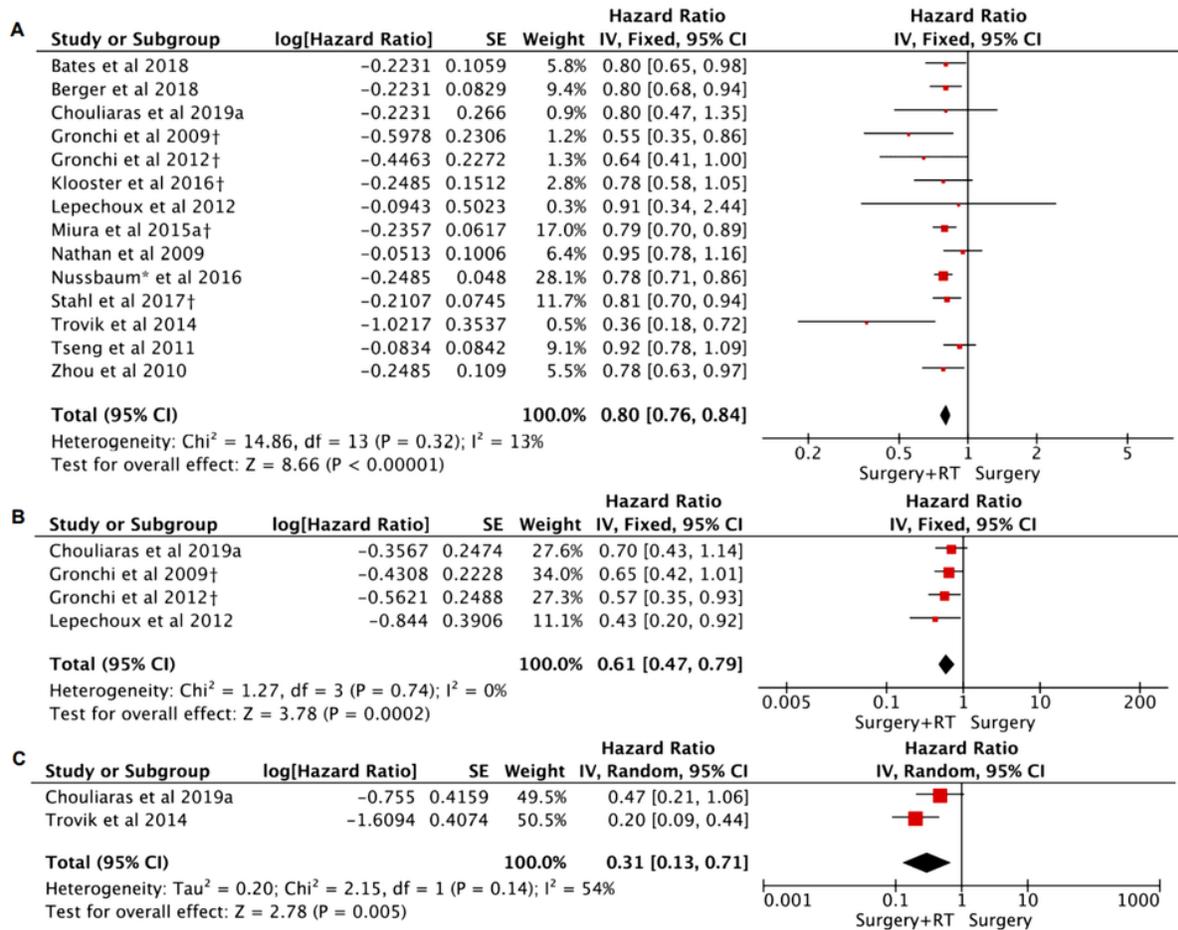


Figure 2

Forest plot and pooled analysis of hazard ratio for overall survival (OS) (A), recurrence-free survival (RFS) (B), and local recurrence (LR) (C) in RPS patients with adjuvant radiotherapy.

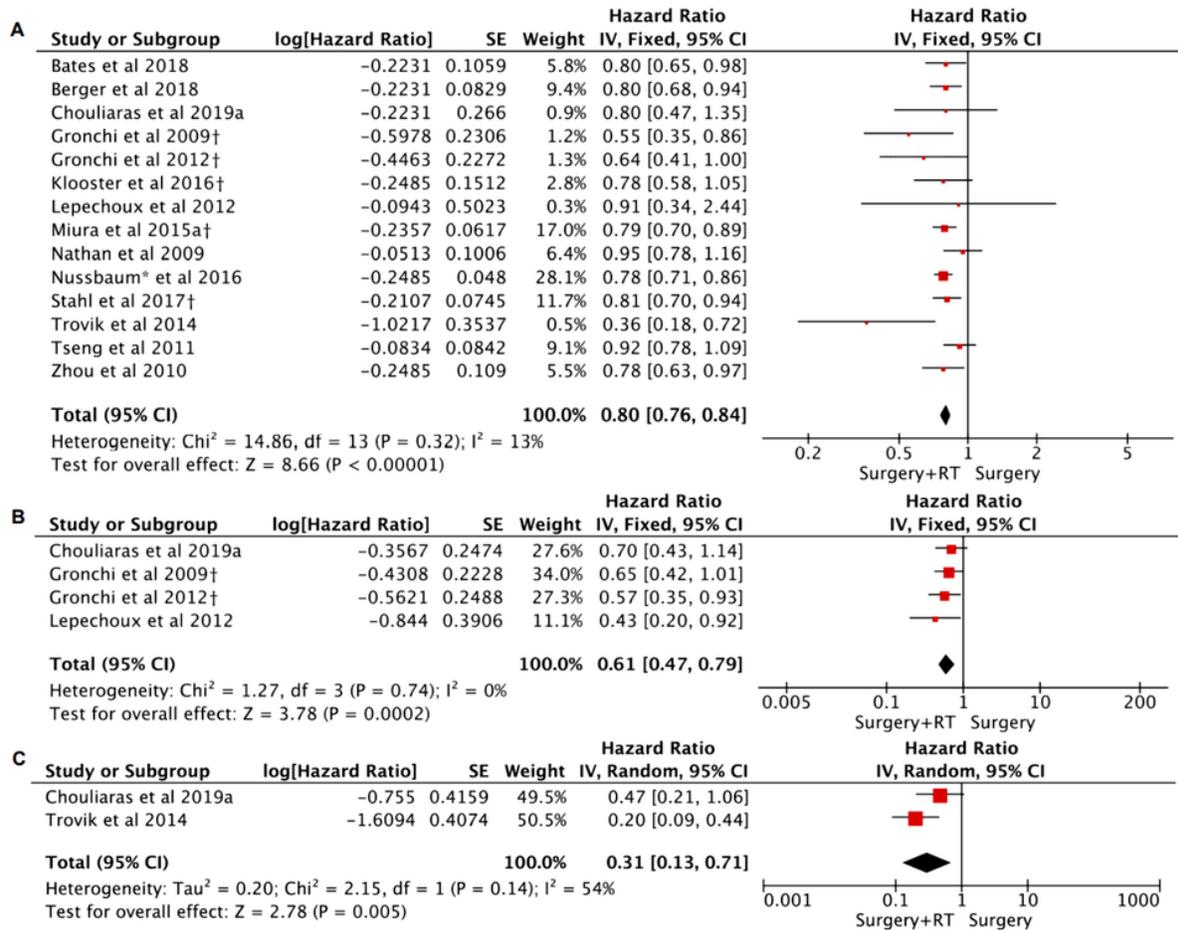


Figure 2

Forest plot and pooled analysis of hazard ratio for overall survival (OS) (A), recurrence-free survival (RFS) (B), and local recurrence (LR) (C) in RPS patients with adjuvant radiotherapy.

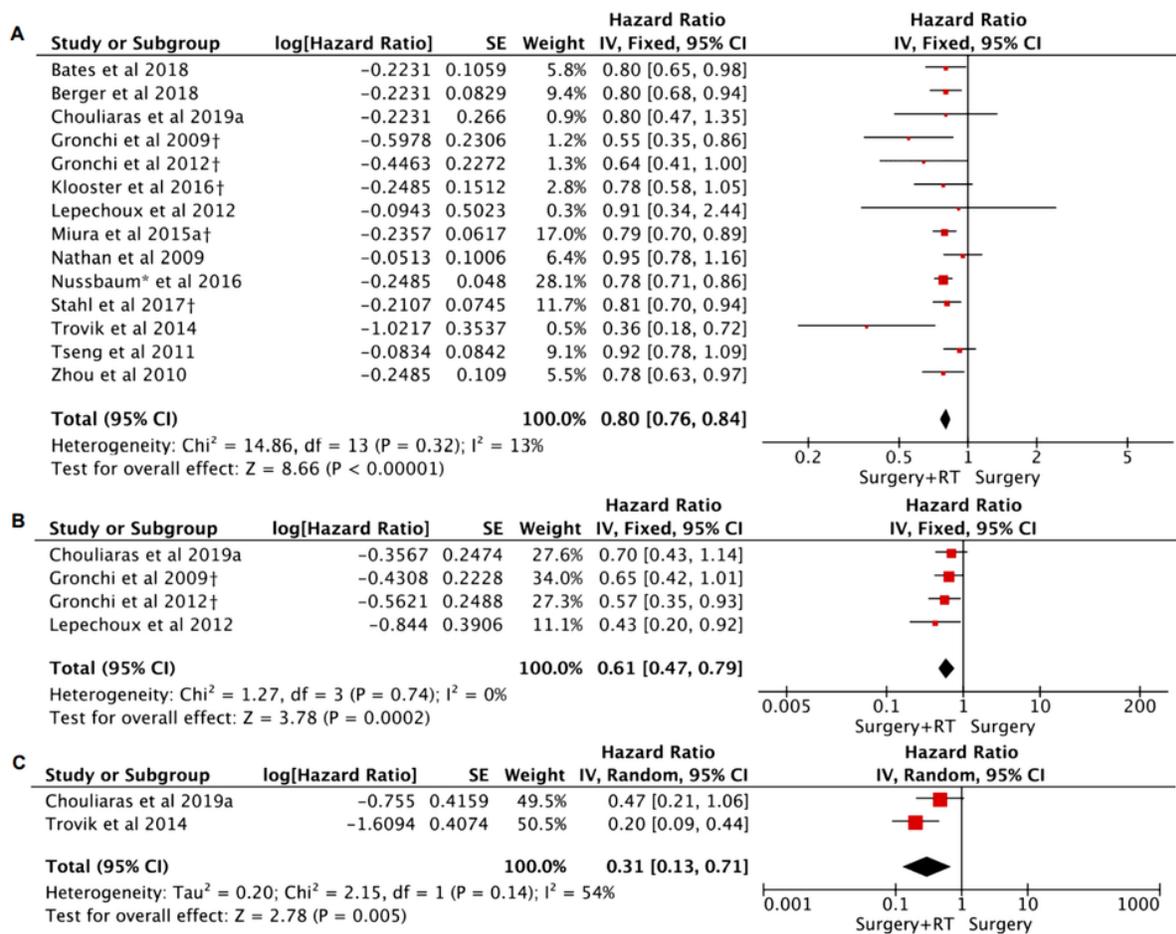


Figure 2

Forest plot and pooled analysis of hazard ratio for overall survival (OS) (A), recurrence-free survival (RFS) (B), and local recurrence (LR) (C) in RPS patients with adjuvant radiotherapy.

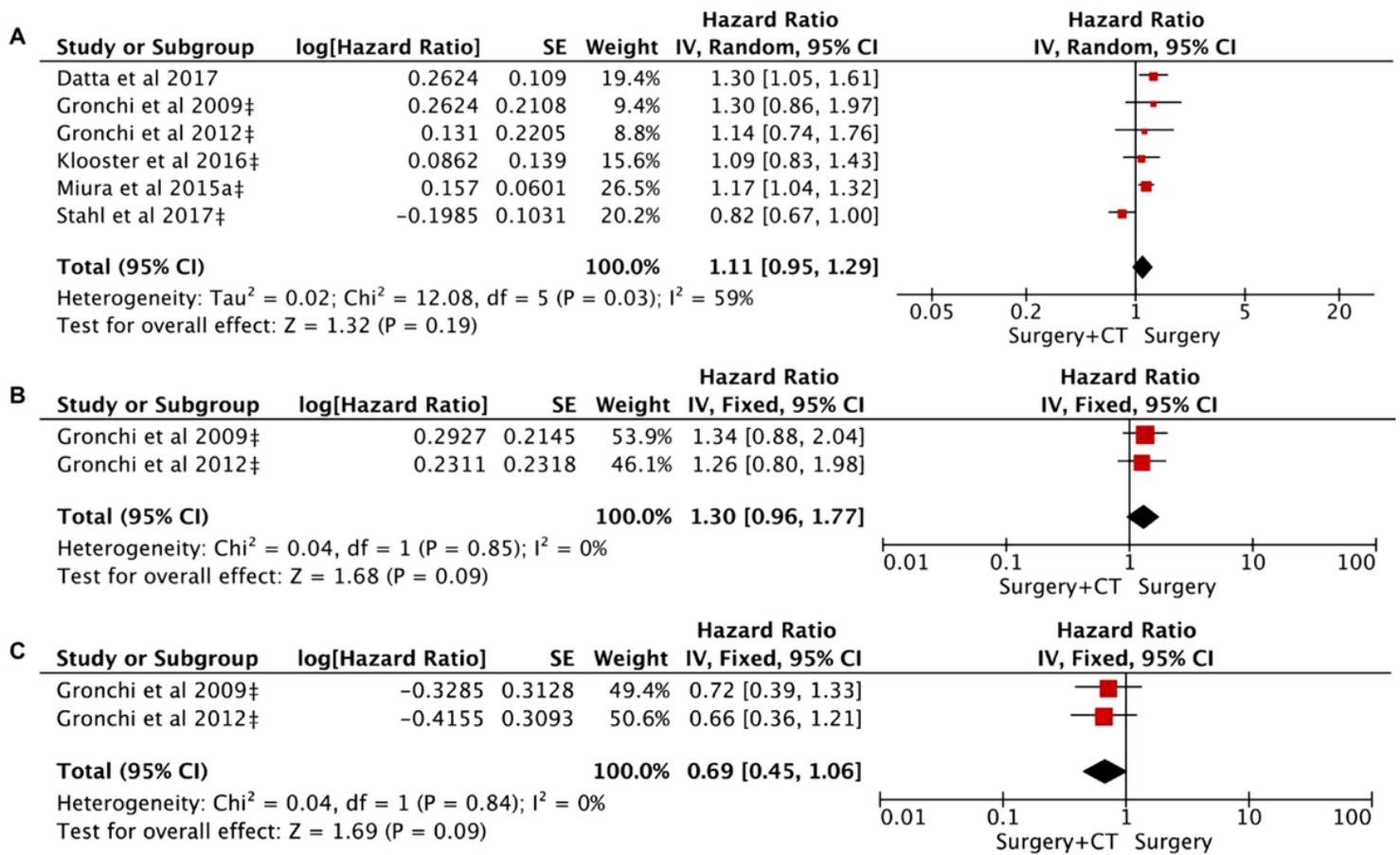


Figure 3

Forest plot and pooled analysis of hazard ratio for overall survival (OS) (A), recurrence-free survival (RFS) (B), and metastasis-free survival (MFS) (C) in RPS patients with adjuvant chemotherapy.

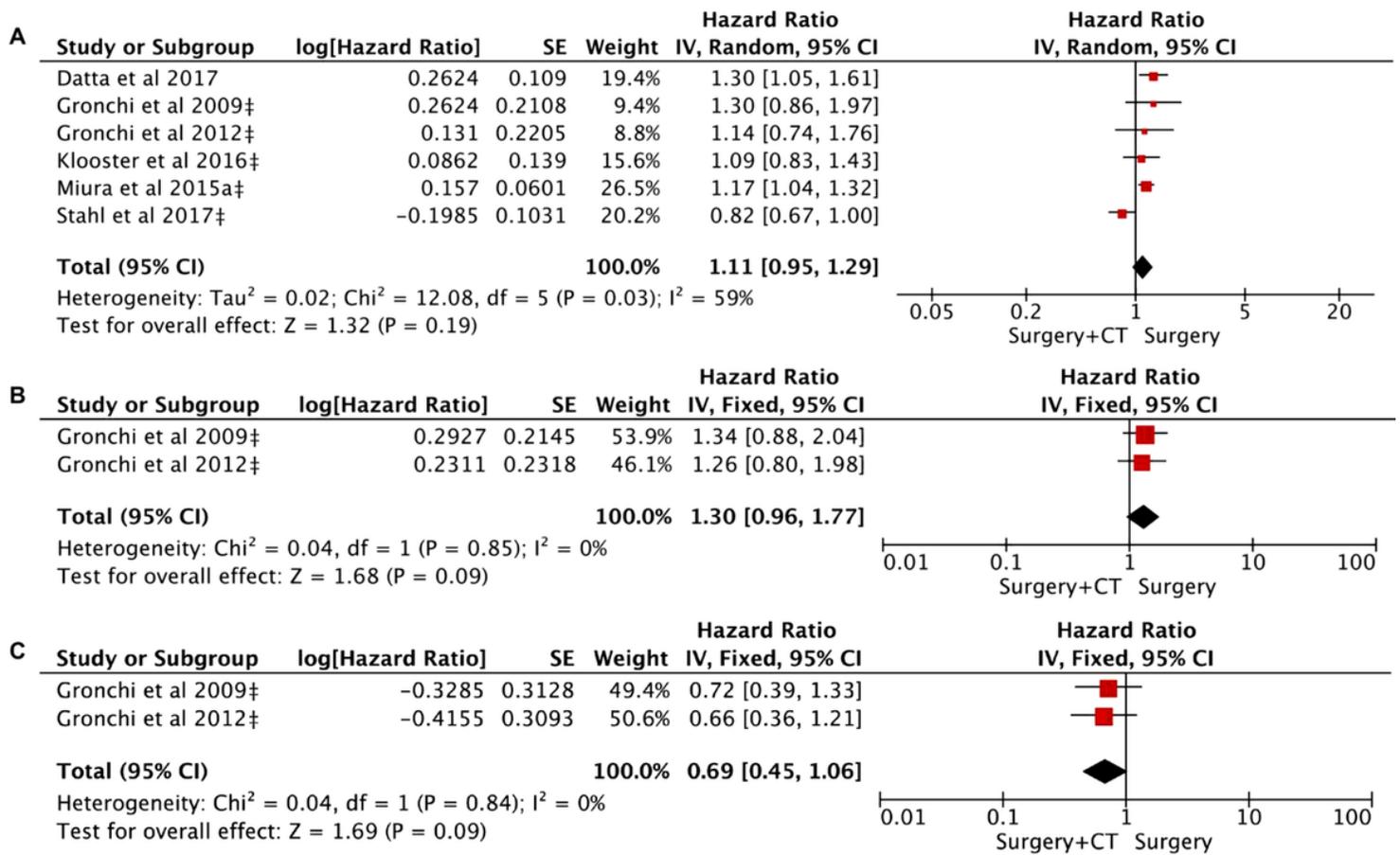


Figure 3

Forest plot and pooled analysis of hazard ratio for overall survival (OS) (A), recurrence-free survival (RFS) (B), and metastasis-free survival (MFS) (C) in RPS patients with adjuvant chemotherapy.

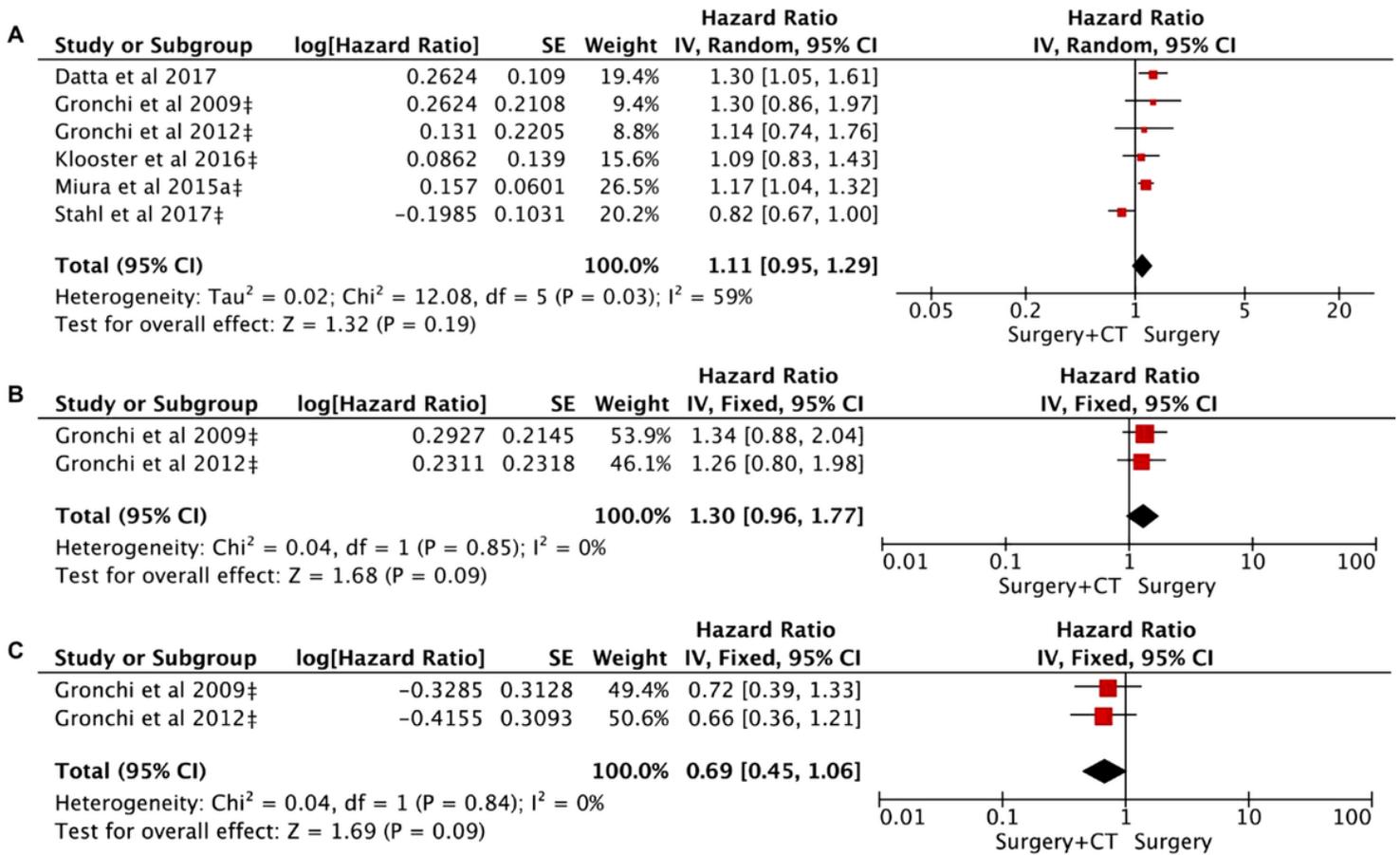


Figure 3

Forest plot and pooled analysis of hazard ratio for overall survival (OS) (A), recurrence-free survival (RFS) (B), and metastasis-free survival (MFS) (C) in RPS patients with adjuvant chemotherapy.

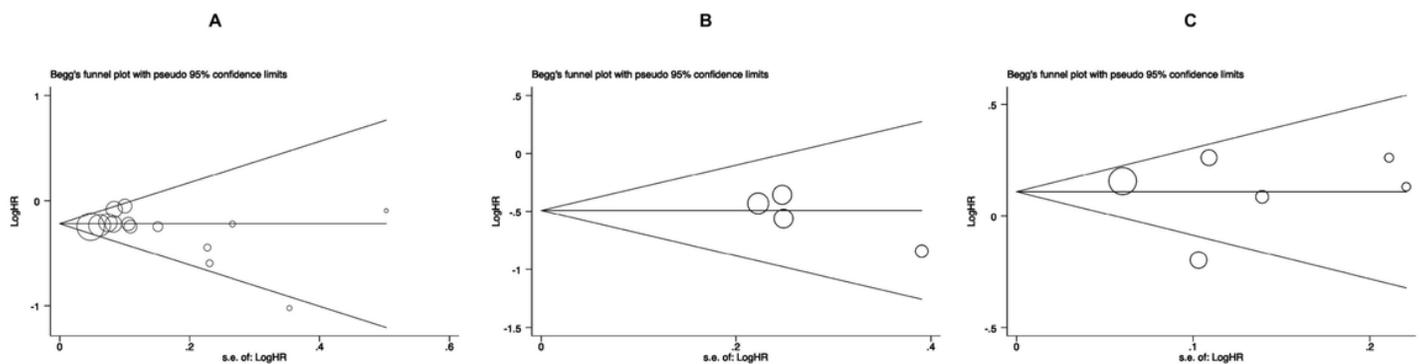


Figure 4

Begg's test for overall survival (OS) and recurrence-free survival (RFS) in RPS patients with adjuvant radiotherapy (AB), and overall survival (OS) in RPS patients with adjuvant chemotherapy (C).

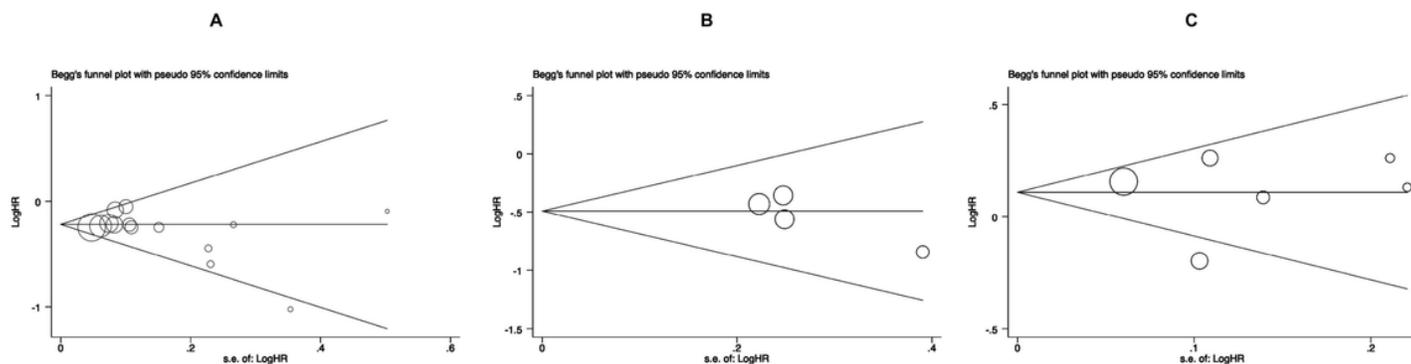


Figure 4

Begg's test for overall survival (OS) and recurrence-free survival (RFS) in RPS patients with adjuvant radiotherapy (AB), and overall survival (OS) in RPS patients with adjuvant chemotherapy (C).

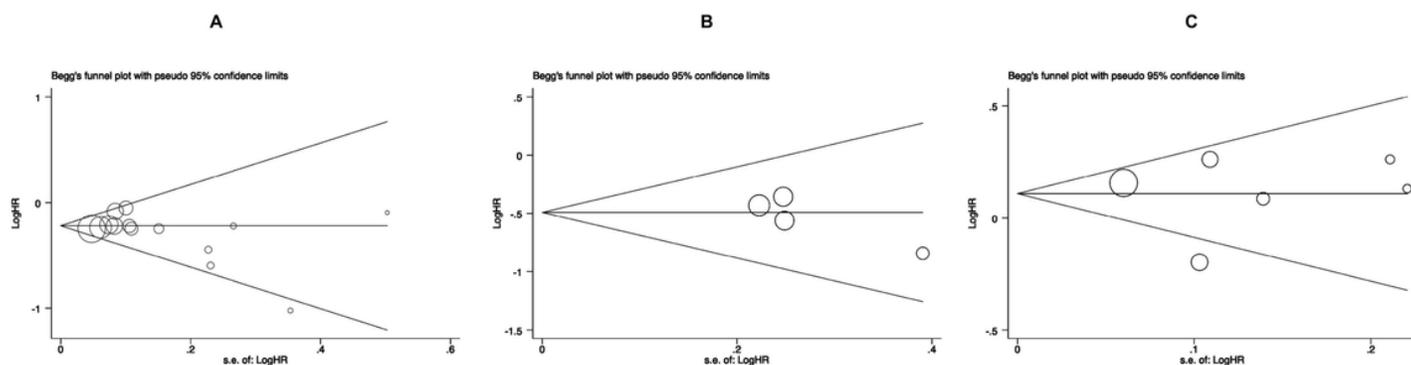


Figure 4

Begg's test for overall survival (OS) and recurrence-free survival (RFS) in RPS patients with adjuvant radiotherapy (AB), and overall survival (OS) in RPS patients with adjuvant chemotherapy (C).

Supplementary Files

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