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Adjuvant radiotherapy for the treatment of stage IV rectal cancer after curative resection

A propensity score-matched analysis and meta-analysis

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Abstract

The role of pelvic radiotherapy (RT) in stage IV rectal cancer with total mesorectal excision (TME) has not been defined. We evaluated the impact of RT on oncologic outcomes among patients with stage IV rectal cancer who underwent TME and performed a meta-analysis of published studies.

The records of stage IV rectal cancer patients who underwent TME between August 2001 and December 2011 were reviewed. Patients who received pelvic RT (RT group) and those who did not (non-RT group) were matched using a propensity score. Oncologic outcomes were compared between the groups. A systematic literature search and meta-analysis was conducted.

One hundred seventy-six patients were matched with propensity score matching, resulting in 39 patients in each group. The local recurrence-free survival (LRFS) of the RT group was significantly higher than that of the non-RT group (2-year LRFS: 100% vs 83.6%, respectively, $P=0.038$). The overall survival, disease-free survival, and systemic recurrence were not significantly different between the groups. In the meta-analysis, the RT group had a reduced risk for loco-regional recurrence than the non-RT group (RR: 0.48, 95% confidence interval: 0.29–0.79).

Pelvic RT might have benefits for loco-regional control in patients with stage IV rectal cancer who undergo TME.

Abbreviations: 5-FU = 5-fluorouracil, CI = confidence interval, CRM = circumferential resection margin, CRT = chemoradiotherapy, DFS = disease-free survival, LRFS = local recurrence-free survival, LV = leucovorin, OS = overall survival, RR = relative risk, RT = radiotherapy, TME = total mesorectal excision.

Keywords: adjuvant radiotherapy, metastatic, rectal neoplasm, surgery

1. Introduction

The incidence of colorectal cancer has increased over the past decade, and it is currently the third-most common malignancy worldwide.[1] Approximately one-third of colorectal cancer patients present with lesions in the rectum.[1] Despite popular screening tests for early detection and treatment, approximately 20% of patients have metastatic disease at the time of diagnosis, which is associated with a poor outcome (5-year survival rate of 11.9%).[2] Treatment outcomes of patients with stage IV rectal cancer have improved with recent advances in protocols and refinement of surgical techniques. Additionally, the 5-year survival rate increased by 25% to 35% when curative resection of both primary and metastatic lesions was achieved.[3–5]

As the survival of patients with stage IV resectable rectal cancer has improved, the issue of loco-regional control has gained increasing attention. Although most recurrences of colorectal cancer occur in distant organs, including the liver and lung, within the first 2 years following resection, the rate of pelvic failure has been reported to be approximately 30% to 35%.[5,6] Preoperative or postoperative radiotherapy (RT) has been reported to be effective for loco-regional control of advanced rectal cancer. It was also demonstrated that adjuvant chemo-radiotherapy (CRT) significantly reduced the rate of local recurrence compared with adjuvant chemotherapy alone. The National Comprehensive Cancer Network guidelines recommended CRT as the standard therapy for patients with

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completely resected stage II/III rectal cancer.[7] However, despite the proven benefits of RT for the treatment of stage II/III rectal cancer, there is a lack of data regarding its potential role in the treatment of stage IV rectal cancer.[8,9]

Several studies have reported the oncologic outcomes of patients who received pelvic RT for the treatment of stage IV rectal cancer; however, the results were inconsistent and the study population was both heterogeneous and subject to selection bias.[10,11] In the present study, we evaluated the potential impact of postoperative pelvic RT on the oncologic outcomes of patients with stage IV rectal cancer who underwent curative resection in 1 of 3 centers using propensity score matching analysis. A systematic review with meta-analysis was also performed, which may provide a more comprehensive overview of the impact of this treatment.

2. Methods

2.1. Patients

The medical records of 176 stage IV rectal cancer patients who underwent curative resection at the National Cancer Center, Seoul National University Hospital, or Seoul National University Bundang Hospital between August 2001 and December 2011 were retrospectively reviewed. All patients were >18 years of age, had histologically proven rectal adenocarcinoma located within 10 cm of the anal verge and synchronous metastasis, and had no history of other malignancies. Only stage IV rectal cancer patients who underwent curative resection for primary and metastatic tumors following adjuvant radiotherapy were included in the study. Primary rectal carcinomas underwent surgery according to the principle of total mesorectal excision. Patients who underwent palliative surgery had a pathological diagnosis other than adenocarcinoma, had preoperative radiotherapy, or had recurrent disease were excluded.

Although there were no definite indications for pelvic RT in stage IV rectal cancer patients, 51 patients received pelvic RT at the discretion of the physician, which was reviewed by a multidisciplinary committee. Pelvic RT was delivered to the entire pelvis at a dose of 45 Gy in 25 fractions, and was followed by a boost to the primary tumor of 5.4 Gy in 3 fractions over 5.5 weeks. All patients underwent computed tomography simulation for three-dimensional conformal RT. The superior border was placed at L5-S1 and the inferior border >3 cm caudal to the tumor level. The boost planning target volume included the gross tumor volume and mesorectum with a >2 cm margin in all directions.[12] Systemic chemotherapy was administered to 169 (96.0%) of the patients. With respect to the specific regimens, 5-fluorouracil (5-FU) plus leucovorin (LV) or capecitabine alone were mainly administered to patients in the RT group, and 5-FU/LV, capecitabine alone, 5-FU/LV/oxaliplatin, 5-FU/LV/irinotecan, capecitabine/oxaliplatin, and capecitabine/irinotecan were administered to patients in the non-RT group.

The medical history of each patient was evaluated, as well as the results of a physical examination, routine blood tests, chest radiography, and other relevant studies including colonoscopy, computed tomography of the chest, abdomen, and pelvis, magnetic resonance imaging of the rectum, positron emission tomography, and preoperative carcinoembryonic antigen levels. Tumors were staged according to the Seventh Edition of the American Joint Committee on Cancer Staging System. Recurrence was defined as the first site of recurrent disease, and local recurrence was defined as the presence of adenocarcinoma within the rectal wall or mesorectum. The study protocol was approved by the Institutional Review Board of each center.

2.2. Statistical analysis

The baseline characteristics were compared between the RT and non-RT groups using the Student t test or Wilcoxon rank-sum test for continuous variables and χ^2 or Fisher exact tests for categorical variables. To balance the differences in baseline characteristics between the 2 groups, propensity scores were generated using logistic regression modeling with all baseline variables for the likelihood of a patient receiving RT. Based on the score, each patient in the RT group was matched with 1 patient in the non-RT group. The rates of overall recurrence (including loco-regional and systemic) were compared between the matched groups using χ^2 or Fisher exact tests. To assess the effects of RT on overall survival (OS), disease-free survival (DFS), and local recurrence-free survival (LRFS), we analyzed differences in the survival functions between the groups using the Kaplan–Meier method, and compared the survival curves between the groups using log-rank tests. A P value <0.05 was considered statistically significant. All statistical analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC).

2.3. Systematic review and meta-analysis

A comprehensive search of the literature was performed in May 2015 using PubMed, Ovid, and Google Scholar to identify all publications in which oncologic outcomes among patients with stage IV rectal cancer who underwent curative resection and received adjuvant pelvic RT were evaluated. The key words were "radiotherapy" AND "rectal cancer" AND ("metastasectomy" OR "resection" OR "metastasis" OR "stage IV"). All 2-arm studies that compared outcomes between RT and non-RT groups were considered candidates. Studies regarding neo-adjuvant pelvic RT were not included due to the possibility of heterogeneity. Case reports or series that had <10 cases in each group, reviews, discussions, letters, and single-arm studies were also excluded.

A sequential review of the title, abstract, and full-text of each report was conducted to select articles based on the selection criteria for our study. The outcomes of interest were the rates of loco-regional and systemic recurrence. The pooled risks for loco-regional and systemic recurrence were computed and compared between the RT and non-RT groups. The relative risk (RR) and corresponding 95% confidence interval (CI) for each outcome was estimated using Mantel–Haenszel tests and RevMan 5.3 software (Cochrane, London, UK). Heterogeneity across the included studies was evaluated using Cochrane Q statistics and I^2 tests. When the value of I^2 was <30%, the included studies were considered to be homogenous, and a fixed effect model was employed. If the value was >30%, a random effect model was employed. The results were presented as forest plots. Publication bias was evaluated using funnel plots.

3. Results

A total of 176 patients were analyzed in this study. The baseline characteristics of the study populations are listed in Table 1. There were 51 patients who received RT and 125 who did not. The patients who received postoperative pelvic RT more frequently underwent abdominoperineal resection had a higher proportion of positive circumferential resection margins (CRM),

Table 1

Characteristics of the study population before and after propensity score matching.

Covariates	Before matching			After matching		
	Non-RT group (%), n = 125	RT group (%), n = 51	*P*	Non-RT group (%), n = 39	RT group (%), n = 39	*P*
Mean age at surgery, y	56.8 (SD 11.4)	56.3 (SD 11.7)	0.679	55.6 (SD 12.1)	54.4 (SD 12.5)	0.939
Sex			0.372			
Male	82 (65.6)	37 (72.5)		25 (64.1)	27 (69.2)	0.631
Female	43 (34.4)	5 (27.5)		14 (35.9)	12 (30.8)	
BMI, kg/m^2			0.528			0.808
<25	94 (75.2)	36 (70.6)		26 (66.7)	27 (69.2)	
≥25	31 (24.8)	15 (29.4)		13 (33.3)	12 (30.8)	
Tumor location from the anal verge, cm			0.397			1.000
0–5	43 (34.4)	21 (41.2)		15 (38.5)	15 (38.5)	
5–10	82 (65.6)	30 (58.8)		24 (61.5)	24 (61.5)	
Preoperative CEA, ng/mL			0.530			0.365
≤5	46 (38.0)	22 (43.1)		21 (53.9)	17 (43.6)	
>5	75 (62.0)	29 (56.9)		18 (46.1)	22 (56.4)	
Postoperative CEA, ng/mL			0.456			0.745
≤5	92 (74.2)	39 (79.6)		34 (87.2)	33 (84.6)	
>5	32 (25.8)	10 (20.4)		5 (12.8)	6 (15.4)	
T stage			0.143			0.530
T1/T2/T3	105 (84.0)	38 (74.5)		34 (87.2)	32 (82.1)	
T4	20 (16.0)	13 (25.5)		5 (12.8)	7 (17.9)	
N stage			0.276			0.820
N0/N1	43 (34.4)	22 (43.1)		18 (46.2)	17 (43.6)	
N2	82 (65.6)	29 (56.9)		21 (53.9)	22 (56.4)	
Site of metastasis			0.144			0.744
Liver	107 (85.6)	39 (76.5)		31 (79.5)	32 (82.0)	
Other	18 (14.4)	12 (23.5)		8 (20.5)	7 (18.0)	
No. of metastatic sites			0.157			1.000
1	111 (88.8)	49 (96.1)		38 (97.4)	37 (94.9)	
≥2	14 (11.2)	2 (3.9)		1 (2.6)	2 (5.1)	
Operation type			0.028			1.000
SPS	115 (92.0)	41 (80.4)		34 (87.2)	34 (87.2)	
APR	10 (8.0)	10 (19.6)		5 (12.8)	5 (12.8)	
Operative approach			0.158			1.000
Laparoscopy	29 (23.2)	7 (13.7)		7 (18.0)	7 (18.0)	
Open	96 (76.8)	44 (86.3)		32 (82.0)	32 (82.0)	
Venous invasion			0.282			0.799
No	40 (32.3)	12 (24.0)		11 (28.2)	10 (25.6)	
Yes	84 (67.7)	38 (76.0)		28 (71.8)	29 (74.4)	
Angiolymphatic invasion			0.730			1.000
No	27 (21.6)	12 (24.0)		11 (28.2)	11 (28.2)	
Yes	98 (78.4)	38 (76.0)		28 (71.8)	28 (71.8)	
Perineural invasion			0.072			0.815
No	36 (29.0)	22 (43.1)		15 (38.5)	14 (35.9)	
Yes	88 (76.8)	29 (56.9)		24 (61.5)	25 (64.1)	
Histologic grade			0.081			1.000
Low	120 (96.0)	45 (88.2)		37 (94.9)	37 (94.9)	
High	5 (4.0)	6 (11.8)		2 (5.1)	2 (5.1)	
Distal resection margin, cm			0.118			0.345
≤2	79 (63.7)	26 (51.0)		27 (69.2)	23 (59.0)	
>2	45 (36.3)	25 (49.0)		12 (30.8)	16 (41.0)	
Circumferential resection margin, mm			0.019			0.815
≤1	31 (26.3)	22 (44.9)		14 (35.9)	15 (38.5)	
>1	87 (73.7)	27 (55.1)		25 (64.1)	24 (61.5)	
Chemotherapy regimen			<0.001			0.002
Fluoropyrimidine-based	16 (12.8)	28 (54.9)		7 (18.0)	21 (53.9)	
Oxaliplatin- or irinotecan-based	103 (82.4)	22 (43.1)		31 (79.4)	18 (46.1)	
None	6 (4.8)	1 (2.0)		1 (2.6)	0 (0.0)	

APR = abdominoperineal resection, BMI = body mass index, CEA = carcinoembryonic antigen, RT = radiotherapy, SD = standard deviation, SPS = Sphincter-preserving surgery.

and more frequently received fluoropyrimidine-based chemotherapy than those who did not. Synchronous metastasectomy was performed in 49 (96.1%) patients of the RT group and in 118 (94.4%) patients of the non-RT group. Propensity score matching was conducted based on the 6 variables that were determined to be the most important for the final matching. These variables included T stage, CRM, number of metastases, operation type, angiolymphatic invasion, and histologic grade. As a result, 39 patients who received adjuvant RT were successfully matched with the same number of patients who did not.

The mean follow-up period was 42.8 months (range, 1.7–143.3). The 2-year OS rate and median OS time were 81.8% and 45.2 months for the non-RT group, and 77.8% and 56.8 months for the RT group, respectively. No significant difference in OS was observed between the 2 groups ($P=0.388$) (Fig. 1A). The 2-year DFS rates of the non-RT and RT groups were 22.6% and 35.8%, respectively ($P=0.709$) (Fig. 1B). The median DFS times of the non-RT and RT groups were 14.0 and 13.3 months, respectively. During the follow-up period, pelvic local recurrence was observed in 8 (10.3%) of 78 patients, 7 (17.9%) of the patients who did not receive pelvic RT, and 1 (2.6%) patient who received pelvic RT. The 2-year LRFS rates of the non-RT and RT groups were 83.6% and 100%, respectively ($P=0.038$) (Fig. 1C). The median LRFS was not reached in either group. The rate of systemic recurrence was 72.2%, and there was no significant difference between the RT and non-RT groups (69.2% vs 79.5%, respectively, $P=0.3$).

3.1. Systematic review and meta-analysis

A total of 97 studies were identified in our initial search. After completing the selection process using the predefined inclusion and exclusion criteria, 4 studies were considered eligible for the meta-analysis (supplementary Figure 1, http://links.lww.com/MD/B381).[10,11,13,14] There were no randomized controlled studies, and all studies were retrospective. Three hundred seventy-seven patients (129 who received adjuvant RT and 248 who did not) with stage IV rectal cancer who received postoperative RT after curative resection were included in the study. The median OS varied across the 4 studies, ranging from 27 to 61.8 months. The median DFS ranged from 11 to 18.2 months. None of the studies revealed significant differences in OS and DFS between the RT and non-RT groups.

With the addition of the results from our study, the pooled risks for loco-regional and systemic recurrence were estimated and compared between the 2 groups. Overall, 455 patients (168 in the RT group and 287 in the non-RT group) were analyzed. The RT group had a significantly reduced risk for loco-regional recurrence compared with the non-RT group (RR; 0.48, 95% CI; 0.29–0.79, $P=0.004$) (Fig. 2). There was no significant difference in the risk of systemic recurrence between the 2 groups (RR; 1.10, 95% CI; 0.96–1.25, $P=0.17$) (Fig. 3). Relatively symmetric-shaped funnel plots were generated in both analyses (Fig. 4), indicating a low possibility of publication bias.

4. Discussion

The role of adjuvant RT in the treatment of stage IV rectal cancer is not yet clear. Four studies have investigated the potential impact of adjuvant RT on oncologic outcomes among stage IV rectal cancer patients who underwent curative resection; however, the results were inconsistent. Kim et al[11] demonstrated that adjuvant pelvic RT significantly reduced the rate of local recurrence in patients with stage IV rectal cancer and synchronous hepatic metastasis. In contrast, An et al and Chang et al reported that the addition of pelvic RT to stage IV rectal cancer treatment after curative resection of the primary and metastatic lesions did not result in statistically significant beneficial effects in terms of the LRFS, DFS, and OS.[10,13] Lee et al[14] also concluded that pelvic RT did not improve loco-regional control and OS. Interestingly, pelvic RT did have oncologic benefits with respect

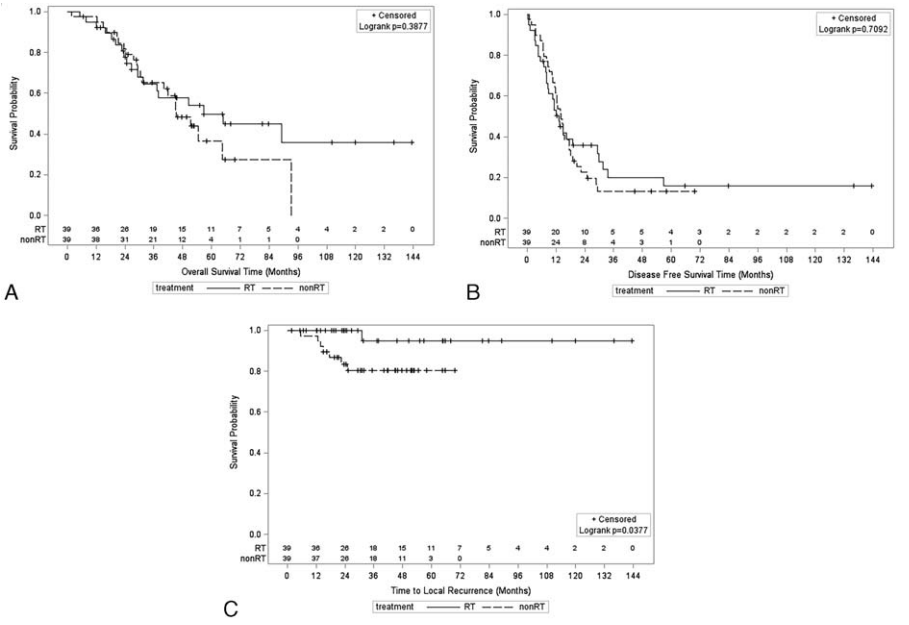

Figure 1. Kaplan–Meier curves after propensity score matching for overall survival (A), disease-free survival (B), and local recurrence-free survival (C). RT = radiotherapy.

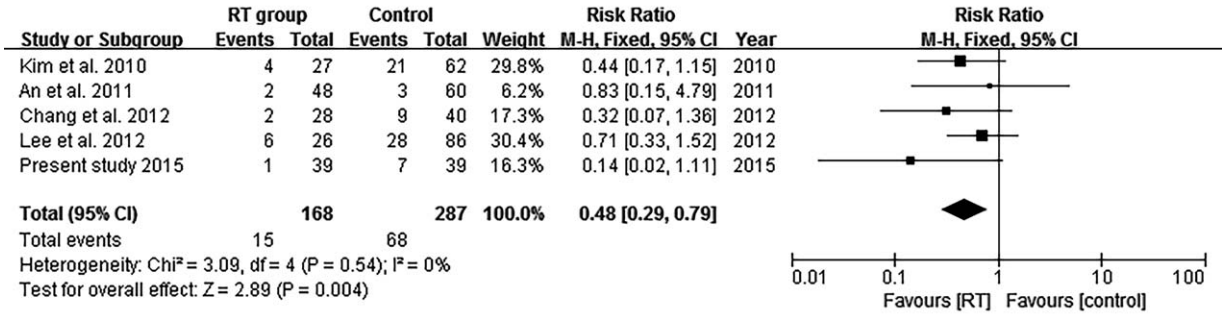

Figure 2. Meta-analysis of the effect of postoperative radiotherapy on local recurrence in stage IV rectal cancer. CI = confidence interval, DF = degrees of freedom, RT = radiotherapy.

to the LRFS in patients with pT4 disease. Considering the lack of strict criteria for adjuvant RT and the nonrandomized case assignments in all 4 studies, the inconsistent results might be attributable to heterogeneity in the characteristics of patients in the RT and non-RT groups, which could have resulted in selection bias.

The present study employed propensity score matching analysis to match patients in the RT group with those in the non-RT group. This allowed us to control for the probability of a patient receiving 1 treatment over another, and reduced the risk of selection bias associated with nonrandomized case assignments. Another common weakness of previous studies was small sample size. Although a trend toward decreasing incidence of loco-regional recurrence in the RT group was observed compared to the control in all previous studies, the difference between the groups was not statistically significant, possibly due to an insufficient sample size. Indeed, Chang et al[13] suggested that at least 60 cases could be required in each group to determine whether there were statistically significant differences in the oncologic outcomes between the 2 groups; however, none of the studies included a sufficient number of cases. We analyzed a total of 455 patients (168 who received RT and 287 who did not) using meta-analytic methods to overcome the limitations of previous single-center studies involving small sample sizes.

In the present study, adjuvant RT reduced the rate of loco-regional recurrence, and the RT group had a significantly higher LRFS than did the non-RT group, after adjusting for the impact of other factors. The oncologic benefits were further supported by the results of the meta-analysis, which demonstrated that the RT group had a significantly reduced risk of local recurrence compared with the non-RT group. It is likely that adjuvant RT can have a protective effect against loco-regional recurrence after surgical resection in stage IV rectal cancer patients as well as in completely resected stage II/III patients.

Although statistically significant, the actual difference in LRFS was not very large between the 2 groups in our study, compared with the difference observed with the meta-analysis. The hazard ratio of LRFS in the meta-analysis was 0.48, which means that the non-RT group had about a 2-fold higher chance of local recurrence than did the RT group. However, the hazard ratio is a relative measure of treatment effect, not the absolute risk. The total number of local recurrences in our study was only 8 (10.3%), and the actual difference of LRFS was not that large between the 2 groups.

Loco-regional control of rectal cancer is clearly one of the most important issues for improving treatment outcomes and patient quality of life. Several studies have demonstrated that pelvic failure significantly affects patient quality of life in terms of fatigue, nausea/vomiting, and pain.[15–17] According to a study by Wong et al[17], >80% of patients with locally recurrent rectal cancer experienced severe pain, and approximately 25% of them experienced bleeding, discharge, and urinary problems, which could significantly impact quality of life. Our results indicated that adjuvant RT did not increase OS or DFS times of patients with stage IV rectal cancer; however, it did have potential oncologic benefits in terms of reducing the risk of local recurrence, which could be important for improving patient quality of life. However, because RT itself can increase the number of morbidities, including bowel dysfunction,[18,19] additional studies are required to validate these conclusions.

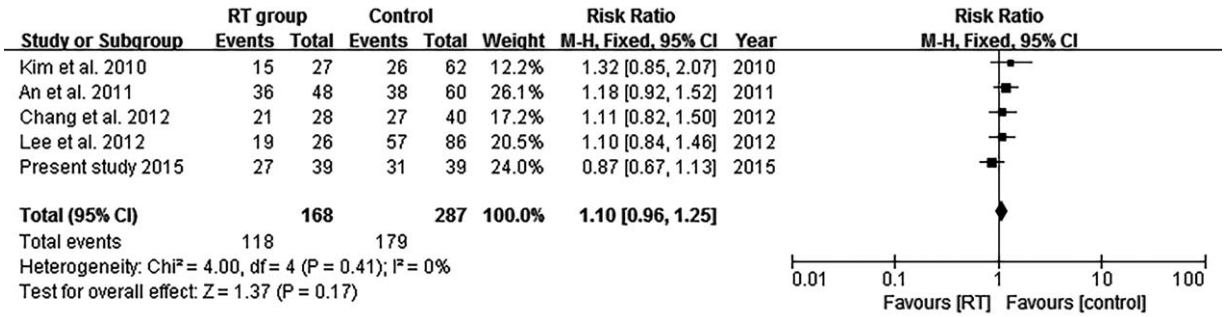

Figure 3. Meta-analysis of the effect of postoperative radiotherapy on distant metastasis in stage IV rectal cancer. CI = confidence interval, DF = degrees of freedom, RT = radiotherapy.

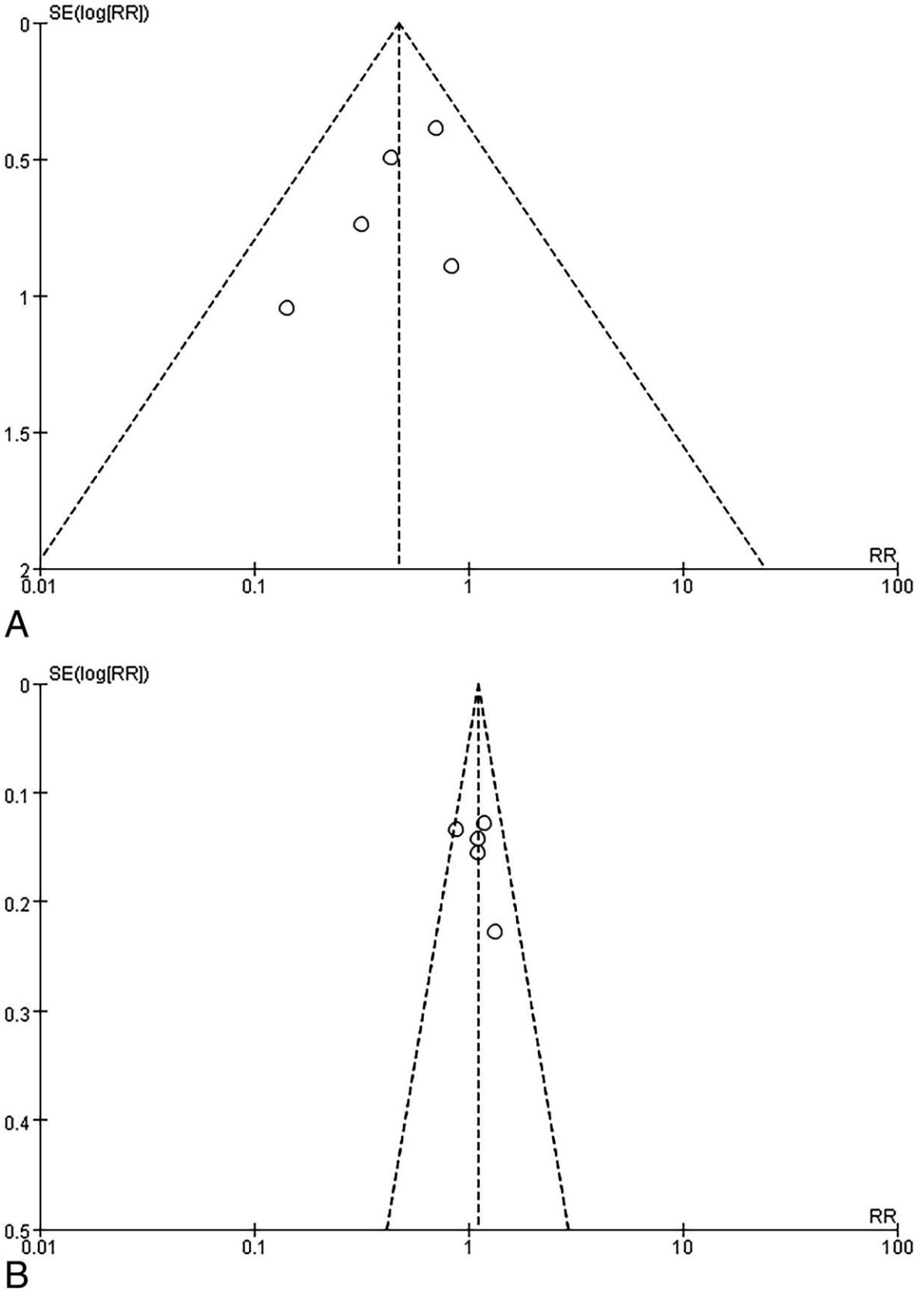

Figure 4. Funnel plot. A, The risk of local recurrence with or without preoperative radiotherapy in patients with stage IV rectal cancer. B, The risk of distant metastasis with or without preoperative radiotherapy in patients with stage IV rectal cancer. RR = relative risk, SE = standard error.

The rate of systemic recurrence of the RT group was comparable with that of the non-RT group in the present study. The meta-analysis demonstrated that the RT group had a 10% higher risk of systemic recurrence compared with the non-RT group, although the difference was not significant ($P = 0.17$). The higher rate of systemic recurrence in the RT group might have led to similar or slightly lower OS and DFS times in this group compared with the non-RT group, despite the potential benefits of RT for loco-regional control. This could be explained by differences in the chemotherapy regimens between the 2 groups. Studies have shown that irinotecan- or oxaliplatin-based regimens resulted in superior outcomes to the conventional regimen of 5-FU plus leucovorin.[20,21] However, many clinicians tend to choose 5-FU-based regimens during RT because of the possibility of high toxicity with the other regimens. Consistent trends were observed across all studies, in that patients in the RT group were more frequently treated with 5-FU-based regimens, while patients in the non-RT group were more frequently treated with irinotecan- or oxaliplatin-based regimens. The heterogeneous chemotherapy regimens could have affected oncologic outcomes, including systemic control in the RT group.

Several limitations of the present study should be taken into consideration when interpreting our results. First, the study had a retrospective design and was therefore subject to inherent biases, although we tried to minimize bias by using propensity score matching analysis. Second, although the meta-analysis was performed based on 5 studies and there were relatively consistent trends among the studies, all of the included studies were retrospective and there was no randomized controlled study. Therefore, the results were insufficient for drawing solid conclusions. Finally, our study was limited in that there was a lack of specific data on patient quality-of-life and the adverse effects of RT.

Our results suggest that RT could have oncologic benefits for loco-regional control in patients with stage IV rectal cancer who undergo curative resection, which is consistent with the findings of the meta-analysis. Pelvic RT could be considered in these patients to reduce the rate of loco-regional recurrence. Additional large-scale, well-controlled studies are required to confirm these conclusions.

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