Am J Transl Res 2024;16(11):7016-7035
www.ajtr.org /ISSN:1943-8141/AJTR0158820

Original Article

Efficacies of different postoperative radiotherapy techniques in patients with N2 non-small cell lung cancer: a meta-analysis

Binxi Yao[1*], Haoxiang Zhang[2*], Xi Liang[1], Tianhe Zhao[1], Jingnan Hu[1], Jianli Ge[1], Yan Han[1], Wenshu Wang[1], Wenzhong Xu[1], Jianming He[1]

[1]*Department of Radiotherapy, Hebei Province Hospital of Chinese Medicine, Hebei University of Chinese Medicine, Shijiazhuang 050011, Hebei, China;* [2]*Department of Respiratory, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China.* [*]*Equal contributors.*

Received June 27, 2024; Accepted October 30, 2024; Epub November 15, 2024; Published November 30, 2024

Abstract: Background: With clinical trials on the use of different modern precise radiotherapy techniques in the setting of postoperative radiotherapy (PORT) in N2 non-small cell lung cancer (NSCLC) accumulating, an updated meta-analysis was performed. Methods: A literature search identified studies that investigated PORT versus non-PORT in N2 NSCLC patients. Overall survival (OS) and locoregional recurrence (LR) were employed. The hazard ratio (HR) and relative risk (RR) with 95% confidence interval (CI) were analyzed. Results: Overall, 33 studies comprised 8653 patients in the PORT group and 12398 in the non-PORT group. The HR for OS was 0.95 [95% CI: 0.91-0.98, P: 0.0009]. HRs of studies employing conventional radiotherapy, 3-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) were 0.90 [95% CI: 0.78-1.04, P: 0.16], 0.82 [95% CI: 0.72-0.93, P: 0.002] and 0.77 [95% CI: 0.64-0.91, P: 0.003], respectively. All HRs favor the PORT group. The RR for LR was 0.56 [95% CI: 0.49-0.65, P<0.00001]. RRs of studies employing conventional radiotherapy, 3D-CRT and IMRT were 0.61 [95% CI: 0.50-0.75, P<0.00001], 0.58 [95% CI: 0.46-0.72, P<0.00001] and 0.58 [95% CI: 0.45-0.73, P<0.00001], respectively. Conclusion: PORT using 3D-CRT or IMRT benefits patients with N2 NSCLC in terms of LR and OS. PORT using conventional radiotherapy significantly decreases LR while it does not significantly increase OS.

Keywords: Non-small cell lung cancer, postoperative radiotherapy, 3-dimensional conformal radiotherapy, intensity-modulated radiotherapy, chemoradiotherapy

Introduction

Non-small cell lung cancer (NSCLC) accounts for >80% of all lung cancer cases and remains the leading cause of cancer-related mortality worldwide [1-3]. About two thirds of N2 NSCLC patients treated with resection combined with chemotherapy died within 5 years [4]. That partly owes to locoregional recurrence (LR) because the LR rate in patients with stage N2 is as high as 40% after complete resection and LR reduces the life expectancy sharply [4-7]. Postoperative radiotherapy (PORT) is a potential way to cure or decrease LR. Feng reported that 93% of LR sites occurred at the bronchial stump and high-risk draining lymph node stations which would have been contained within the proposed PORT clinical target volume (CTV) [8]. But its value remains controversial. Bao et al. reported that PORT significantly decreased LR and improved overall survival (OS) [9]. Debevec et al. reported that in their trial, the number of patients whose first relapse was locoregional in the PORT group (10/35, 28%) was more than that in the control group (6/39, 16%). There was no significant difference in OS between the PORT group and the control group [10]. Results of Van Houtte's study illustrated that PORT significantly decreased OS [11].

At present, modern precise radiotherapy techniques, such as 3-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT), have been widely applied. They allow delivery of high radiation doses to the gross tumor, bulky lymph nodes, and high-

https://doi.org/10.62347/JGIB9696

risk areas while sparing dose and volume of organs at risk [12, 13]. That may increase the efficacy and decrease adverse effects in patients with NSCLC [14, 15]. Moreover, clinical trials that reported the efficacy of PORT using modern radiotherapy techniques in N2 NSCLC have been accumulating [12, 16, 17]. An updated and comprehensive meta-analysis to evaluate efficacies of different radiotherapy techniques in pathologic N2 NSCLC was conducted here.

Materials and methods

Study registration

The protocol of this meta-analysis is registered in PROSPERO, under the registration number CRD42023462065 on September 20, 2023.

Search strategy

This study was designed according to the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement [18-20]. Systemic searches were conducted in PubMed, Cochrane Library and MEDLINE. Search strategies contained the following keywords variably combined by “postoperative radiotherapy”, “PORT”, “non-small cell lung cancer”, “NSCLC” and “stage N2”. Articles written in English were included.

Inclusion/exclusion criteria

Inclusion criteria: 1) Patients: Pathologically confirmed stage N2 NSCLC patients underwent complete resection followed by PORT (PORT group) or not (non-PORT group). System therapy (chemotherapy, immunotherapy, target therapy, et al.) was not taken into account. 2) Types of studies: Cohort study. 3) Language: English.

Exclusion criteria: 1) Patients were treated with radiotherapy before surgery. 2) Patients were treated with other types of local treatment, including but not limited to, radiofrequency ablation, cryoablation, high intensity focused ultrasound, and so on. 3) Duplicate published trials. 4) Studies without enough data.

Data extraction and quality assessment

Each included study was thoroughly reviewed by 2 investigators and confirmed according to review criteria. Following information was extracted: OS, LR, disease-free survival (DFS), distant metastases-free survival (DMFS). Data were independently cross-checked.

Risk bias was assessed for included Cohort trials by Cochrane Handbook 5.1.0. using RevMan (Review Manager, version 5.3 for Windows) [19, 20].

Statistical analysis

Statistical analysis was performed using RevMan. The statistical method of subgroup analysis was adopted. Statistical pooling of effect measures was based on the level of heterogeneity among studies, which was assessed with the Cochrane Q test and the I^2 statistic. No significant heterogeneity was indicated by $P>0.1$ in Cochrane Q tests and a ratio less than 50% in I^2 statistics. The hazard ratio (HR) and risk ratio (RR) were used to quantify the prognostic effect. The HR was calculated using the fixed-effects model inverse variance method. The RR was calculated using the Mantel-Haenszel method under the fixed-effects model. Publication bias was evaluated by visual inspection of funnel plots. $P\leq0.05$ was considered significant [18-20].

Results

Characteristics of included studies

As shown in **Figure 1**, a total of 5648 articles were identified initially using the above search strategy. On review of the title and abstract, 5567 articles were excluded. After further careful review of the full text, 48 studies were excluded. Finally, 33 studies, 22 retrospective studies [1, 3, 6, 17, 21-38] and 11 prospective studies [10, 11, 39-47], were eligible for meta-analysis, including 21051 patients, 8653 in the PORT group and 12398 in the non-PORT group (**Figure 1**). **Table 1** lists the identified studies and their main characteristics.

Methodology quality

Quality assessment was performed for each study in accordance with the Cochrane De-

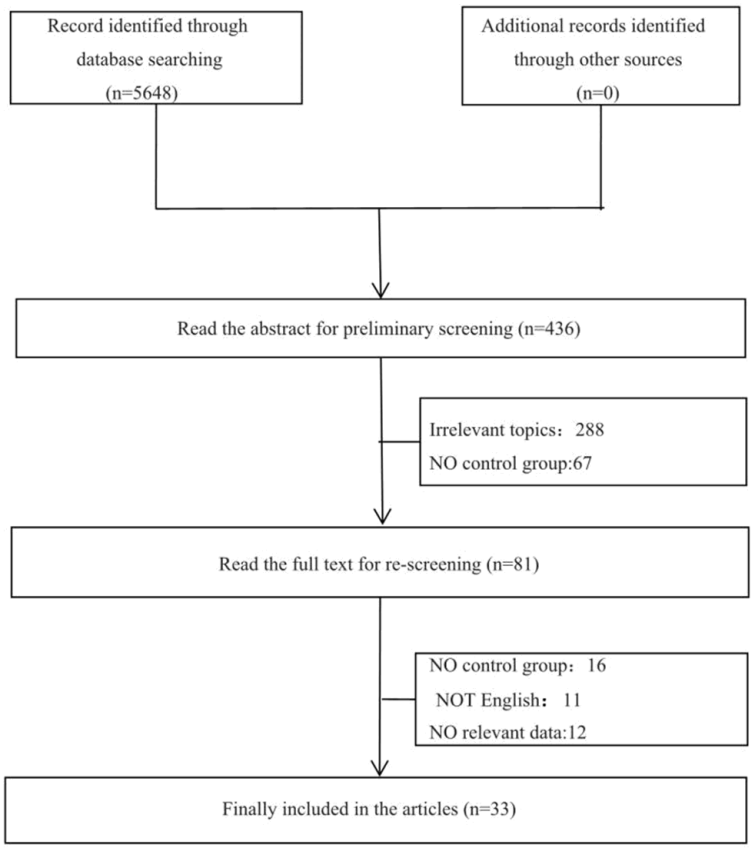


Figure 1. Flowchart of the study selection.

viation Risk Assessment tool as shown in **Figure 2**. Only 2 studies were at high risk of bias because of incomplete outcome data [23, 27].

PORT may improve OS

Twenty-nine studies provided enough data to analyze the HR for OS [1, 3, 6, 10, 17, 21-29, 31-35, 37-41, 43-47]. There were 20036 subjects, 8184 in the PORT group and 11852 in the non-PORT group. The HR of 20 retrospective studies, including 7623 patients in the PORT group and 11333 in the non-PORT group, was 0.95 [95% confidence interval (CI): 0.92-0.98, P=0.002] [1, 3, 6, 17, 21-29, 31-35, 37, 38]. This demonstrates that PORT significantly improves OS. The HR of 9 prospective studies, including 607 patients in the PORT group and 588 in the non-PORT group, was 0.91 [95% CI: 0.79-1.05, P: 0.19] [10, 39-41, 43-47]. The HR for OS favors PORT, but without significance. The pooled HR of the combination of retrospective and prospective studies was 0.95 [95% CI: 0.91-0.98, P: 0.0009] and that was concordant with the HR of the retrospective studies (**Figure 3A**). Visual inspection of the corresponding funnel plot revealed no publication bias (**Figure 3B**). If heterogeneity was not taken into account, similar results ensued. HRs of the retrospective [1, 3, 6, 17, 21-35, 37, 38], the prospective [10, 11, 39-41, 43-47], and the combination were 0.82 [95% CI: 0.75-0.90, P<0.0001], 0.98 [95% CI: 0.81-1.19, P: 0.87] and 0.86 [95% CI: 0.79-0.93, P: 0.0003], respectively (Supplementary Figure 1). Results of the retrospective and the combination indicate that PORT significantly improves OS in patients with N2 NSCLC and results of the prospective favors PORT, but without significance.

PORT significantly improves OS in patients without neoadjuvant chemotherapy, but does not improve OS in patients treated with neoadjuvant chemotherapy

Different treatment modalities were conducted. Patients were treated with neoadjuvant chemotherapy in 2 studies [21, 26]. The HR was 0.69 [95% CI: 0.40-1.19, P: 0.18]. Patients were treated without neoadjuvant chemotherapy in 11 studies [3, 22, 29, 31, 33-35, 37, 41, 43, 46]. The HR was 0.87 [95% CI: 0.81-0.94, P: 0.0003] (**Figure 4**). These findings demonstrate that PORT significantly improves OS in patients without neoadjuvant chemotherapy while it does not improve OS in patients treated with neoadjuvant chemotherapy.

PORT employing 3D-CRT or IMRT significantly improves OS and PORT employing conventional radiotherapy does not

HRs of OS in patients treated with different radiotherapy techniques were analyzed. The HR of 8 studies employing conventional radiotherapy was 0.90 [95% CI: 0.78-1.04, P: 0.16] [10, 28, 31, 39, 40, 43, 44, 46] (**Figure 5**). If heterogeneity was not taken into account, the HR was 0.92 [95% CI: 0.75-1.11, P: 0.37] [10,

Table 1. Characteristics of included studies

	Reference	Median follow-up time (months)	RT technique	Radiotherapy dose (Gy) Gy/day; Total dose (Gy)	Group	Number of patients	T Stage	Median survival time (months)	Median LRFS time (months)	Median DFS time (months)	Median DMFS time (months)
RETRO	1997; Sawyer et al. [30]	42	Linac	1.8-2.0; 45-66.4	PORT	88	T1-T4	34.7	NA	NA	NA
					Non-PORT	136	T1-T4	18.1	NA	NA	NA
RETRO	2008; Matsuguma et al. [28]	NA	Linac	2; 25.2-63.9	PORT	45	T1-T3	64.1	NA	29	NA
					Non-PORT	46	T1-T3	45.5	NA	11	NA
RETRO	2010; Scotti et al. [31]	27.6	Linac	2.0; 46-66	PORT	119	T1-T4	NA	NA	NA	NA
					Non-PORT	56	T1-T4	NA	NA	NA	NA
RETRO	2010; Zou et al. [38]	72	3D-CRT	1.8-2.0; 48-54	PORT	104	T1-T4	32	96	25	NA
					Non-PORT	79	T1-T4	24	39	16	NA
RETRO	2014; Kim et al. [6]	48	3D-CRT	1.8-2.0; 50-56	PORT	38	T1-T4	60.7	41	NA	NA
					Non-PORT	111	T1-T4	72	22	NA	NA
RETRO	2015; Feng et al. [23]	31.2	3D-CRT	1.8; 50.4	PORT	70	T1-T3	34.3	NA	22.8	23.5
					Non-PORT	287	T1-T3	31.2	NA	18.6	22
RETRO	2015; Hui et al. [25]	NA	3D/2D	2; 60	PORT	96	T1-T3	35.3	60	28	NA
					Non-PORT	125	T1-T3	17.0	14	16	NA
RETRO	2015; Robinson et al. [29]	22	NA	NA; 45-82.8	PORT	1850	NA	45.2	NA	NA	NA
					Non-PORT	2633	NA	40.7	NA	NA	NA
RETRO	2016; Zhang et al. [36]	NA	Linac	1.8; 50.4	PORT	43	T1-T3	37	24	NA	20
					Non-PORT	177	T1-T3	30	22	NA	15
RETRO	2017; Breen et al. [22]	60	3D-CRT/IMRT	1.8-2.1; 41.4-60	PORT	41	T1-T4	115.6	NA	NA	80
					Non-PORT	30	T1-T4	92.3	NA	NA	119
RETRO	2017; Herskovic et al. [24]	32.32	NA	NA; 45-117.5	PORT	516	T1-T4	53.1	NA	NA	NA
					Non-PORT	2175	T1-T4	44.5	NA	NA	NA
RETRO	2017; Zhang et al. [35]	36	Linac	1.8; 50.4	PORT	115	T1-T3	51	NA	NA	NA
					Non-PORT	219	T1-T3	32	NA	NA	NA
RETRO	2018; Brandt et al. [21]	25	3D-CRT/IMRT	NA; 50.4-54	PORT	69	T1-T4	51	NA	17	NA
					Non-PORT	30	T1-T4	30	NA	19	NA
RETRO	2018; Xu et al. [3]	38.3	3D-CRT/IMRT	1.8-2.0; 48-60	PORT	89	T1-T3	76.03	100	34	NA
					Non-PORT	157	T1-T3	49.83	70	23	NA
RETRO	2019; Su et al. [1]	68	3D-CRT/IMRT	1.8-2.0; 44-60	PORT	60	T1-T4	55	NA	NA	NA
					Non-PORT	115	T1-T4	60	NA	NA	NA
RETRO	2019; Wang et al. [32]	25	3D-CRT/IMRT	1.8-2.0; 30-66	PORT	32	NA	146	95	19	47
					Non-PORT	87	NA	32	22	13	17
RETRO	2019; Zhu et al. [37]	34.2	Linac	1.8-2.0; 48-54	PORT	46	T1-T3	32	NA	NA	NA
					Non-PORT	69	T1-T3	20	NA	NA	NA

RETRO	2020; Liu et al. [26]	26	IMRT	1.8; 50.4	PORT	94	T1-T4	66	NA	NA	NA
					Non-PORT	217	T1-T4	45	NA	NA	NA
RETRO	2020; Wei et al. [33]	38	IMRT	1.8-2.0; 48-54	PORT	78	T1-T3	34	29	NA	NA
					Non-PORT	105	T1-T3	29	17	NA	NA
RETRO	2021; Mankuzhy et al. [27]	28	NA	NA	PORT	4052	NA	28	NA	NA	NA
					Non-PORT	4579	NA	27	NA	NA	NA
RETRO	2021; Wang et al. [17]	24	3D-CRT	1.8-2.0; 45-54	PORT	71	T1-T3	34.7	NA	NA	NA
					Non-PORT	71	T1-T3	31.9	NA	NA	NA
RETRO	2021; Yang et al. [34]	31.5	NA	NA	PORT	38	T1-T2	52.7	NA	38.7	NA
					Non-PORT	142	T1-T2	50.6	NA	16.7	NA
RCT	1980; Van Houtte et al. [11]	NA	Linac	2.0; 55-60	PORT	83	T1-T3	18	NA	NA	NA
					Non-PORT	92	T1-T3	30.2	NA	NA	NA
RCT	1996; Debevec et al. [10]	NA	Linac	2.5-3.0; 30	PORT	35	T1-T3	25	NA	NA	NA
					Non-PORT	39	T1-T3	18	NA	NA	NA
RCT	1996; Stephens et al. [46]	30	Linac	2.6; 40	PORT	52	T1-T2	17.5	33	NA	NA
					Non-PORT	54	T1-T2	19	22	NA	NA
RCT	1997; Mayer et al. [43]	43	Linac	2.0; 50-60	PORT	23	T1-T3	42	39	NA	NA
					Non-PORT	26	T1-T3	27	20	NA	NA
RCT	2000; Feng et al. [40]	NA	Linac	2.0-2.5; 50	PORT	61	T1-T4	44.8	NA	46	NA
					Non-PORT	44	T1-T4	27.9	NA	37.8	NA
RCT	2007; Perry et al. [44]	18.3	Linac	2.0; 50	PORT	19	NA	43	NA	NA	NA
					Non-PORT	18	NA	30	NA	NA	NA
RCT	2008; Douillard et al. [39]	43.7	Linac	2.0; 45-60	PORT	116	NA	23.8	NA	NA	NA
					Non-PORT	108	NA	47.4	NA	NA	NA
RCT	2014; Shen et al. [45]	45	3D-CRT	1.8; 50.4	PORT	66	T1-T3	40	NA	28	NA
					Non-PORT	69	T1-T3	28	NA	18	NA
RCT	2017; Sun et al. [47]	57.4	3D-CRT	2.0; 50	PORT	51	T1-T3	74.3	NA	24.7	NA
					Non-PORT	50	T1-T3	83.5	NA	21.9	NA
RCT	2021; Hui et al. [41]	46	3D-CRT/IMRT	2.0; 50	PORT	184	T1-T3	84	NA	22.1	NA
					Non-PORT	180	T1-T3	76	NA	18.6	NA
RCT	2022; LePechoux et al. [42]	57.6	3D-CRT/IMRT	2.0; 54	PORT	252	NA	NA	NA	30.5	NA
					Non-PORT	249	NA	NA	NA	22.8	NA

Note: PORT: Postoperative radiotherapy, 3D-CRT: 3-dimensional conformal radiotherapy, IMRT: Intensity-modulated radiotherapy, RT: Radiotherapy, LRFS: Locoregional recurrence free survival, DFS: Disease-free survival, DMFS: Distant metastases-free survival, RETRO: Retrospective, RCT: Randomized controlled trial.

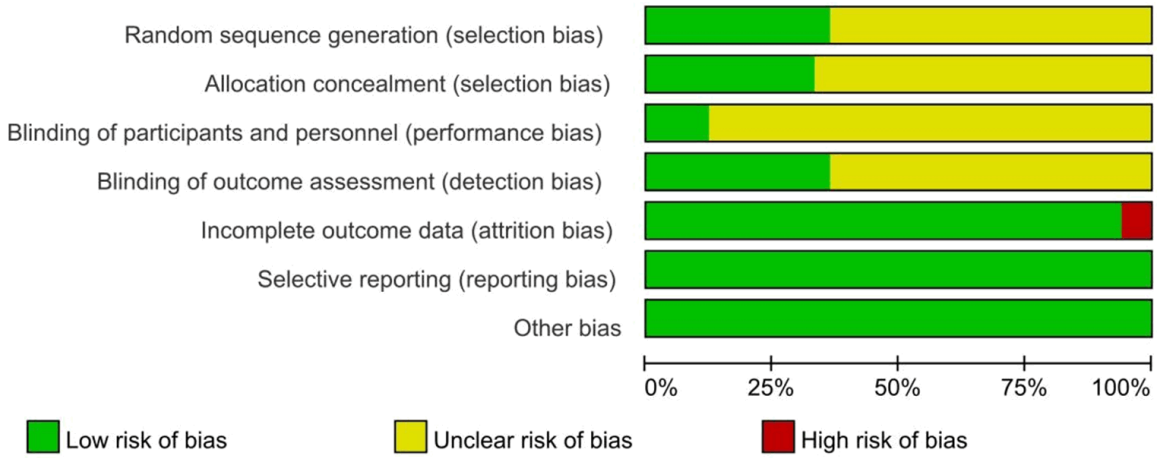
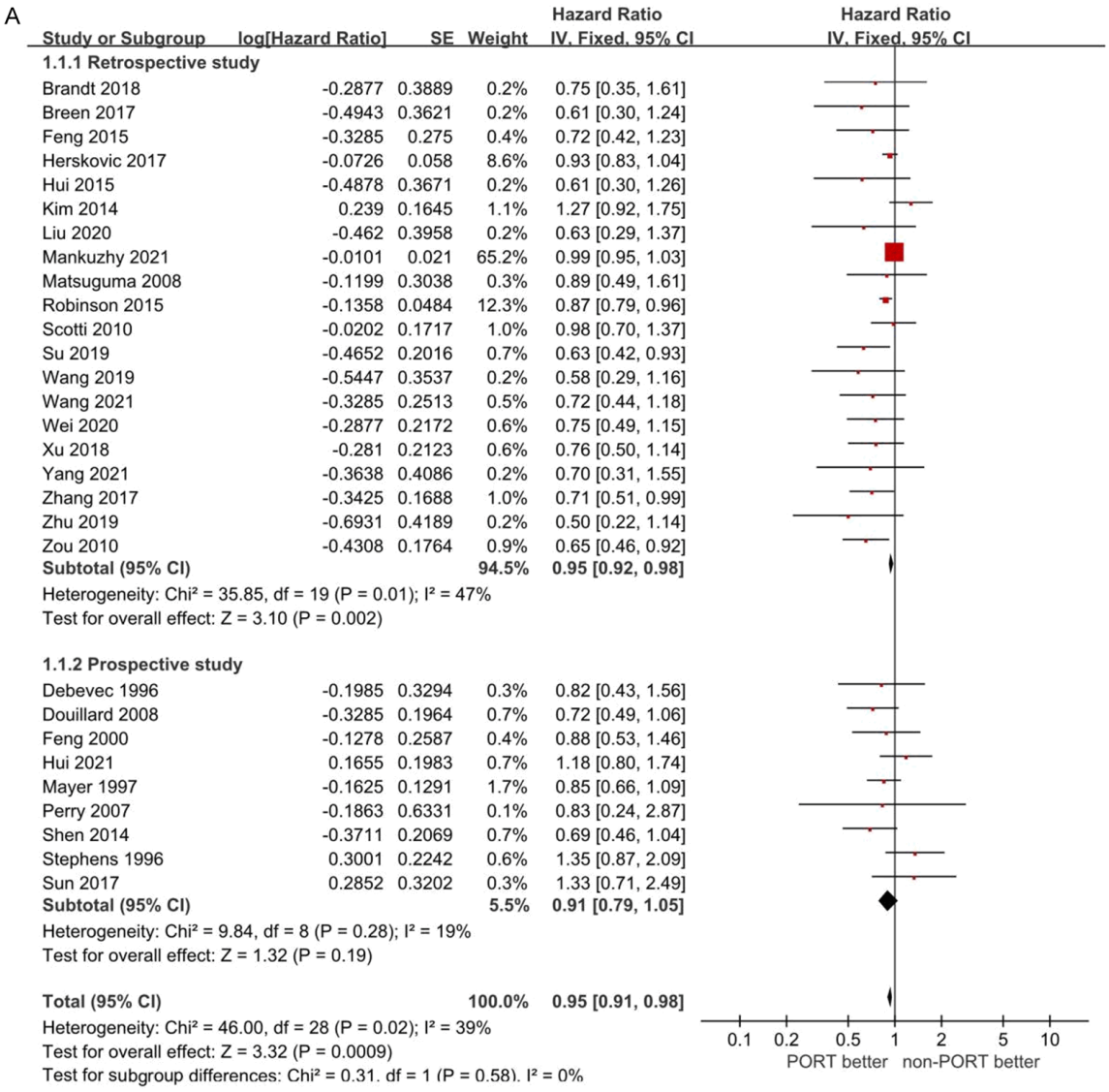


Figure 2. Risk of bias graph.



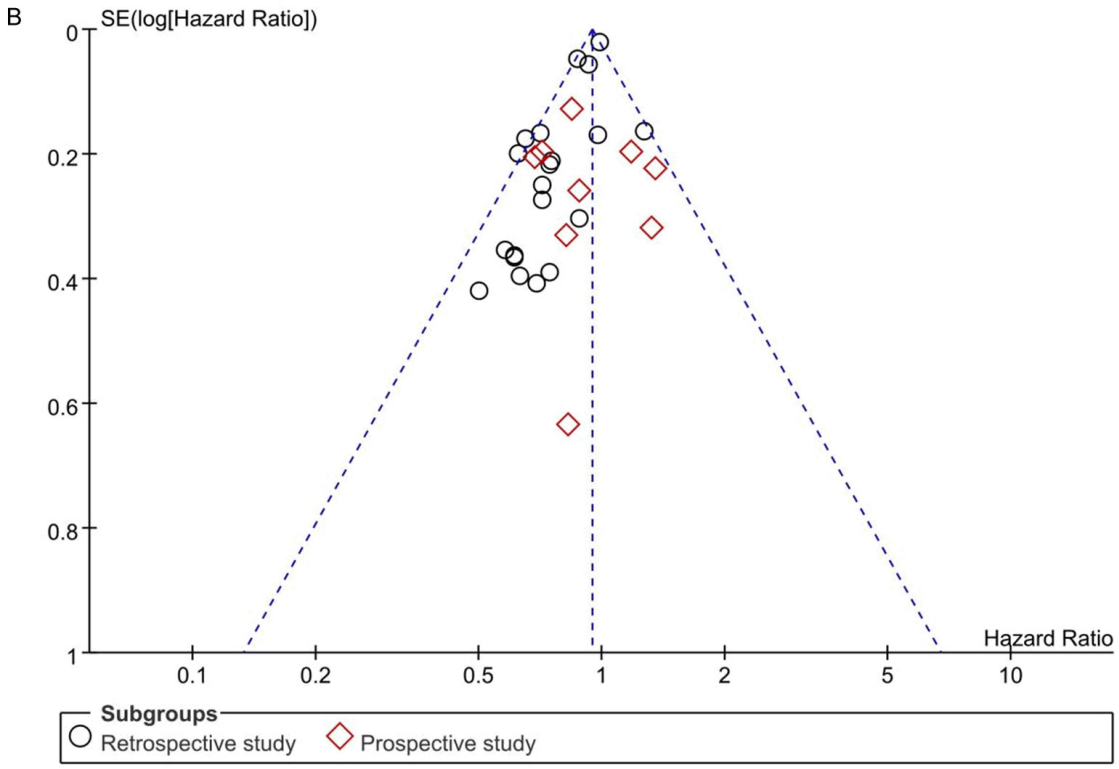


Figure 3. Pooled HRs for OS. A: Forest plot. B: Funnel plot. Note: HR: Hazard ratio, OS: Overall survival, PORT: Postoperative radiotherapy.

11, 28, 30, 31, 39, 40, 43, 44, 46] (Supplementary Figure 2). There is no significant difference in OS between the two groups. The HR of 13 studies employing 3D-CRT was 0.82 [95% CI: 0.72-0.93, P: 0.002] [1, 3, 6, 17, 21-23, 25, 32, 38, 41, 45, 47] and that of 8 studies employing IMRT was 0.77 [95% CI: 0.64-0.91, P: 0.003] [1, 3, 21, 22, 26, 32, 33, 41] (**Figure 5**). If heterogeneity was not taken into account, similar results ensued. HRs of studies employing 3D-CRT [1, 3, 6, 17, 21-23, 25, 32, 38, 41, 45, 47] and IMRT [1, 3, 21, 22, 26, 32, 33, 41] were 0.80 [95% CI: 0.67-0.95, P: 0.01] and 0.77 [95% CI: 0.64-0.91, P: 0.003], respectively (Supplementary Figure 2). All HRs favor the PORT group. These results unanimously indicate that PORT employing modern radiotherapy techniques significantly improves OS in patients with N2 NSCLC. Results of studies employing conventional radiotherapy suggest that PORT does not improve OS.

PORT as chemoradiotherapy significantly improves OS and PORT as radiotherapy does not

Impacts of different PORT regimes on OS were analyzed [1, 3, 10, 17, 25, 27, 28, 33-35, 37, 39-41, 43-47]. Patients underwent complete resection followed by concurrent chemoradiotherapy (PORT as chemoradiotherapy) in 7 trials [1, 3, 33, 35, 37, 45, 47]. The HR, including 505 patients in the PORT group and 784 in the non-PORT group, was 0.72 [95% CI: 0.61-0.85, P: 0.0001]. Patients underwent complete resection followed by radiotherapy (PORT as radiotherapy) were reported in 12 trials [10, 17, 25, 27, 28, 34, 39-41, 43, 44, 46]. The HR, including 4792 in the PORT group and 5432 in the non-PORT group, was 0.98 [95% CI: 0.94-1.02, P: 0.34] (**Figure 6**). If heterogeneity was not taken into account, the HR of 14 trials was 0.91 [95% CI: 0.79-1.05, P: 0.19] (Supplementary Figure 3). These data indicate that PORT as chemoradiotherapy significantly improves OS in patients with N2 NSCLC but PORT as radiotherapy does not.

PORT decreases LR

In PORT, the CTV includes the bronchial stump and high-risk draining lymph node stations because the main purpose of PORT is to cure or decrease LR [5]. Impacts of PORT on LR were

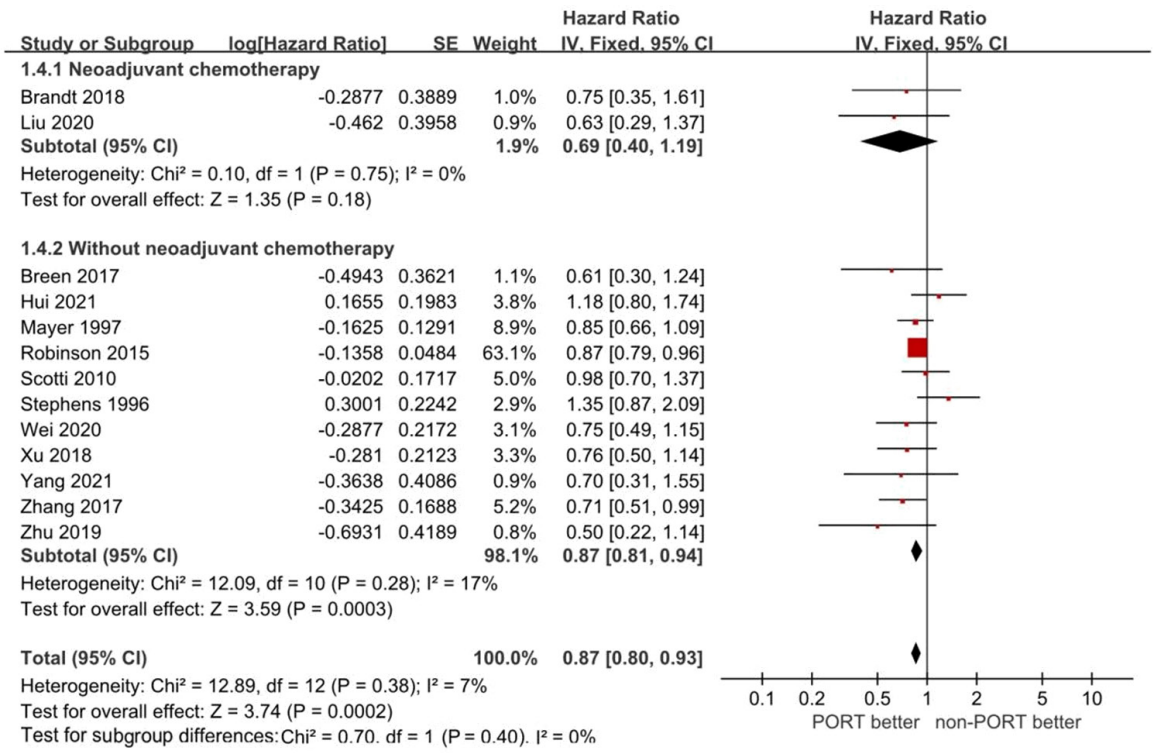


Figure 4. HR forest plot of OS in patients treated with or without neoadjuvant chemotherapy. Note: HR: Hazard ratio, OS: Overall survival, PORT: Postoperative radiotherapy.

analyzed. The RR of 10 retrospective studies, including 693 patients in the PORT group and 1190 in the non-PORT group, was 0.52 [95% CI: 0.42-0.63, P<0.00001] [1, 6, 21, 23, 26, 28, 30-33]. The RR of 9 prospective studies, including 655 patients in the PORT group and 641 in the non-PORT group, was concordant with that of the retrospective [11, 39-41, 43-47]. It was 0.62 [95% CI: 0.50-0.77, P< 0.00001]. The pooled RR of the combination of retrospective and prospective studies was 0.56 [95% CI: 0.49-0.65, P<0.00001] (**Figure 7**). If heterogeneity was not taken into account, similar results ensued. RRs of the retrospective [1, 6, 21, 23, 26, 28, 30-33], the prospective [10, 11, 39-41, 43-47] and the combination were 0.53 [95% CI: 0.43-0.66, P<0.00001], 0.58 [95% CI: 0.49-0.70, P: 0.004] and 0.61 [95% CI: 0.51-0.71, P<0.00001], respectively (Supplementary Figure 4). All RRs' values were close to 0.65. These data unanimously verify that PORT significantly decreases LR. The probability of LR in patients treated with PORT may be only about two thirds as that in patients without PORT.

PORT employing any radiotherapy techniques decreases LR

RRs of LR in patients treated with different radiotherapy techniques were analyzed. RRs of studies employing conventional radiotherapy [10, 11, 28, 30, 31, 39, 40, 43, 44, 46], 3D-CRT [1, 6, 21, 23, 32, 41, 45, 47] and IMRT [1, 21, 26, 32, 33, 41] were 0.61 [95% CI: 0.50-0.75, P<0.00001], 0.58 [95% CI: 0.56-0.72, P< 0.00001] and 0.58 [95% CI: 0.45-0.73, P< 0.00001], respectively (**Figure 8**). These data unanimously verify that PORT employing any radiotherapy techniques decreases LR.

Both PORT as chemoradiotherapy and PORT as radiotherapy significantly decrease LR

Impacts of different PORT regimes on LR were analyzed [1, 11, 25, 28, 30, 33, 39, 40, 43-47]. Patients underwent complete resection followed by concurrent chemoradiotherapy (PORT as chemoradiotherapy) in 4 trials [1, 33, 45, 47]. The RR, including 255 patients in the PORT group and 339 in the non-PORT group, was 0.51 [95% CI: 0.38-0.70, P<0.0001]. Patients

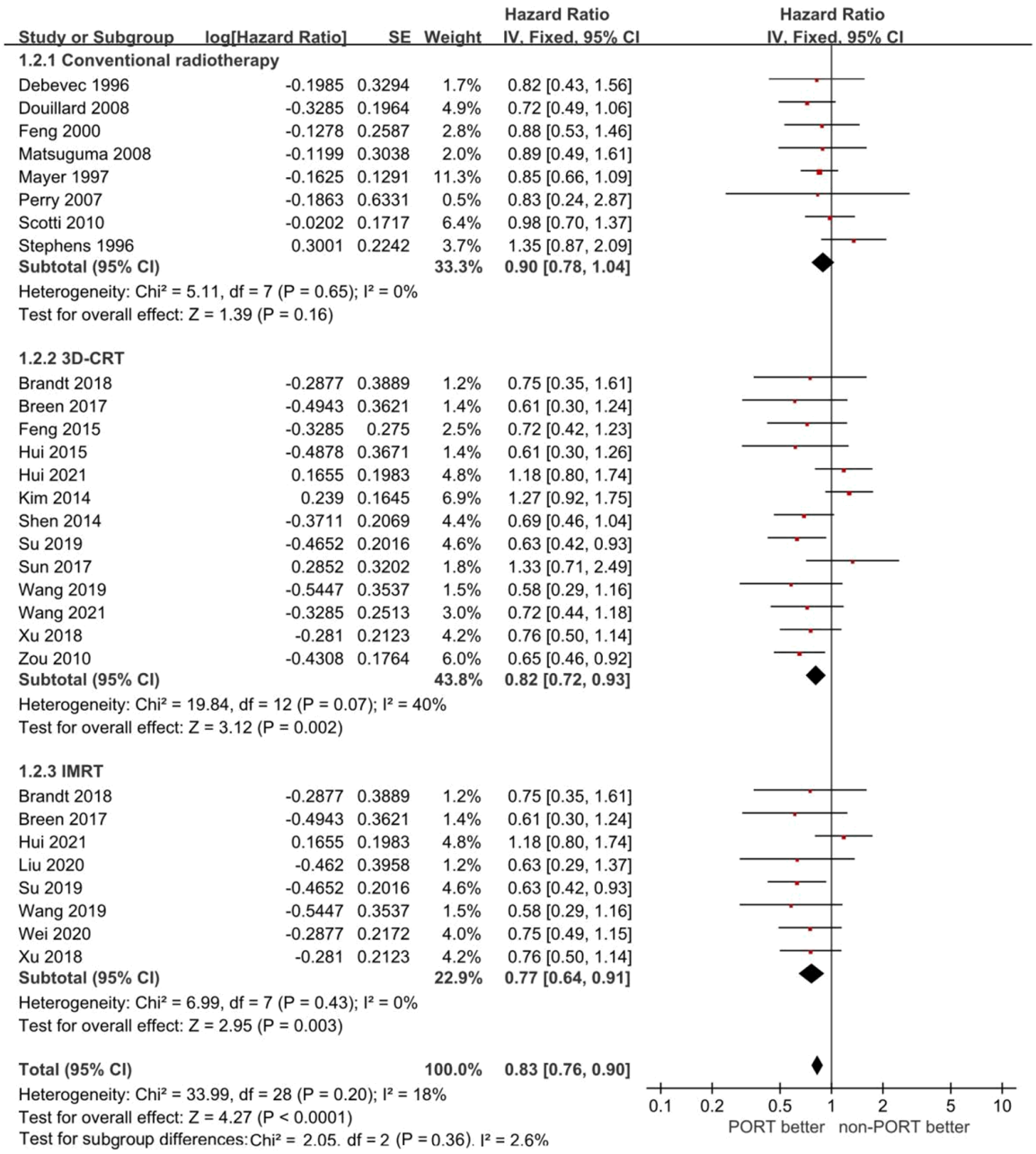


Figure 5. HR forest plot of OS in patients treated with different radiotherapy techniques. Note: HR: Hazard ratio, OS: Overall survival, 3D-CRT: 3-dimensional conformal radiotherapy, IMRT: Intensity-modulated radiotherapy, PORT: Postoperative radiotherapy.

underwent complete resection followed by radiotherapy (PORT as radiotherapy) were reported in 9 trials [11, 25, 28, 30, 39, 40, 43, 44, 46]. The RR, including 671 in the PORT group and 704 in the non-PORT group, was 0.64 [95% CI: 0.53-0.77, P<0.00001] (**Figure 9**). If heterogeneity was not taken into account, the RR of 10 trials was 0.66 [95% CI: 0.49-0.89, P: 0.007] (Supplementary Figure 5). These data unanimously verify that both PORT as chemoradiotherapy and PORT as radiotherapy significantly decrease LR.

PORT increases DFS

Impacts of PORT on DFS were analyzed. The HR of 9 retrospective studies [3, 6, 21, 23, 25, 28, 32, 34, 38], including 542 patients in the PORT

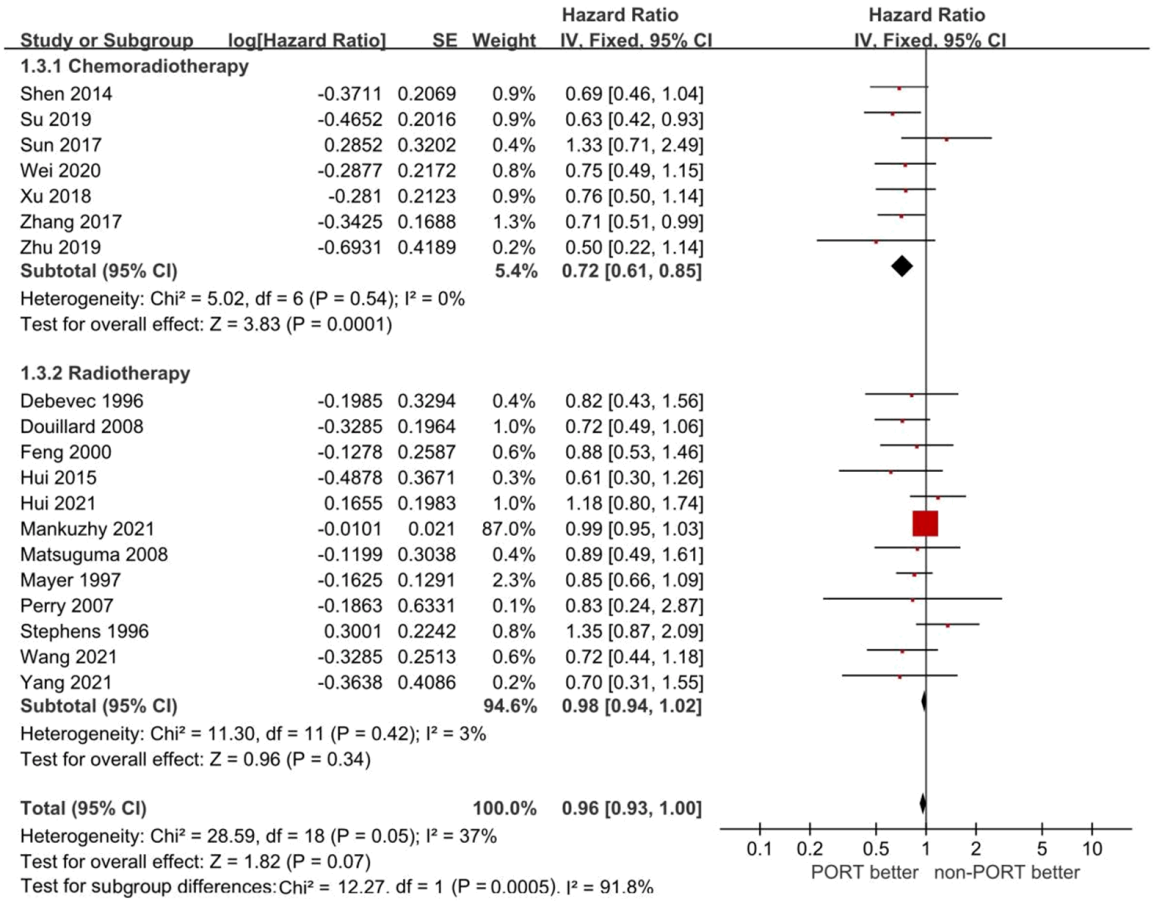


Figure 6. HR forest plot of OS in patients treated with different PORT regimes, concurrent chemoradiotherapy or radiotherapy. Note: HR: Hazard ratio, OS: Overall survival, PORT: Postoperative radiotherapy.

group and 1103 in the non-PORT group, was 0.74 [95% CI: 0.65-0.85, P<0.0001]. The HR of 5 prospective studies [40-42, 45, 47], including 614 patients in the PORT group and 592 in the non-PORT group, was 0.81 [95% CI: 0.70-0.95, P: 0.007]. The pooled HR of the combination of retrospective and prospective studies was 0.77 [95% CI: 0.70-0.85, P<0.00001] (**Figure 10**). These data unanimously verify that PORT increases DFS.

PORT employing 3D-CRT or IMRT significantly increases DFS and PORT employing conventional radiotherapy does not

HRs of DFS in patients treated with different radiotherapy techniques were analyzed. HRs of studies employing conventional radiotherapy [28, 40], 3D-CRT [3, 6, 21, 23, 25, 32, 38, 41, 42, 45, 47] and IMRT [3, 21, 32, 41] were 0.80 [95% CI: 0.54-1.18, P: 0.26], 0.80 [95% CI: 0.71-0.88, P<0.0001] and 0.78 [95% CI: 0.64-0.94, P: 0.01], respectively (**Figure 11**). These data indicate that PORT employing modern radiotherapy techniques significantly increases DFS and PORT employing conventional radiotherapy does not.

PORT does not improve DMFS

Impacts of PORT on DMFS were also analyzed. The HR of 3 retrospective studies [23, 32, 36], including 145 patients in the PORT group and 551 in the non-PORT group, was 0.84 [95% CI: 0.65-1.08, P: 0.16]. The HR of 2 prospective studies [41, 46], including 236 patients in the PORT group and 234 in the non-PORT group, was 0.90 [95% CI: 0.71-1.13, P: 0.36]. The pooled HR of the combination of retrospective and prospective studies was 0.87 [95% CI: 0.73-1.03, P: 0.11] (**Figure 12**). All HRs was lower than 1, but without significance.

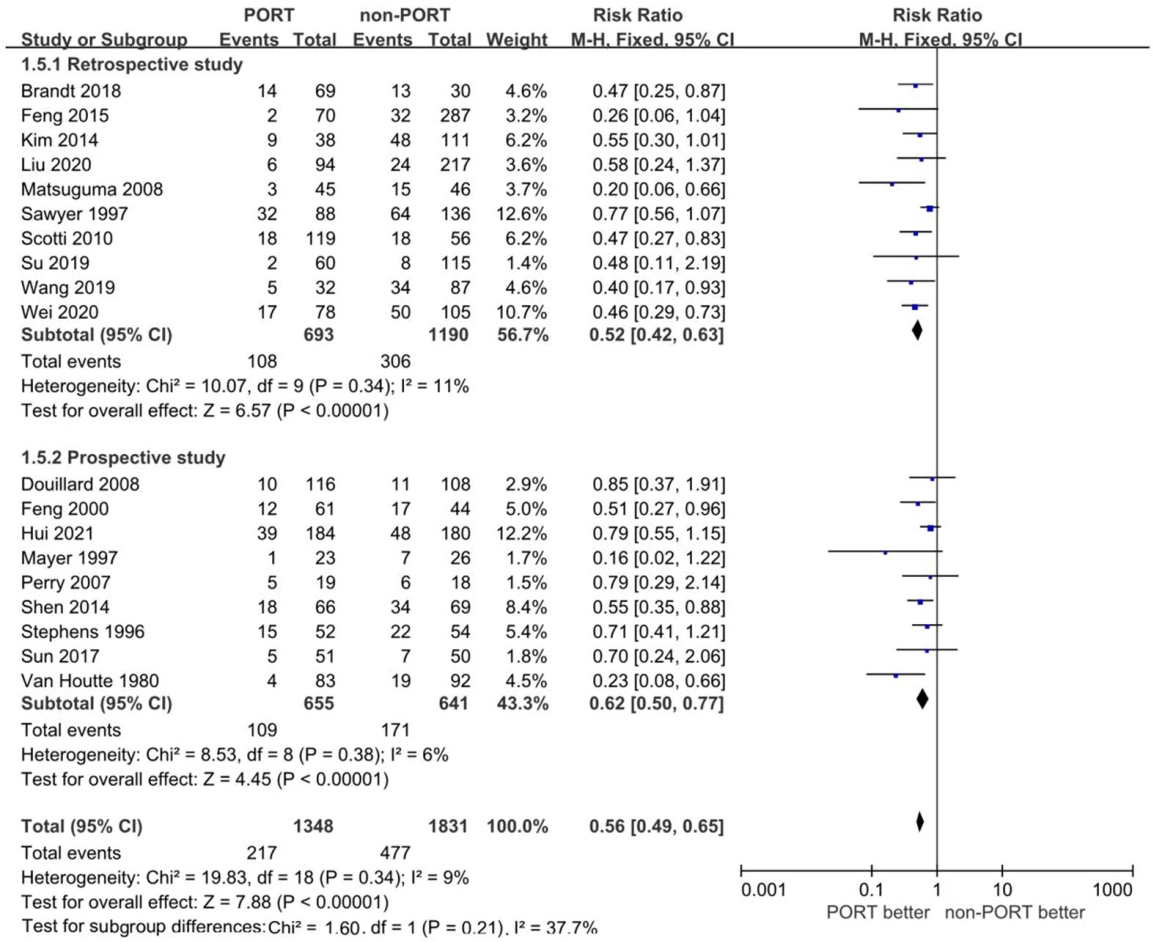


Figure 7. RR forest plot of LR. Note: RR: Relative risk, LR: Locoregional recurrence, PORT: Postoperative radiotherapy.

HRs of DMFS in patients treated with different radiotherapy techniques were analyzed. HRs of studies employing 3D-CRT [23, 32, 41] and IMRT [32, 41] were 0.90 [95% CI: 0.74-1.09, P: 0.27] and 0.88 [95% CI: 0.70-1.12, P: 0.30], respectively (**Figure 13**). All HRs were lower than 1, but without significance. These results mean that PORT does not significantly improve DMFS in patients with N2 NSCLC.

Discussion

PORT is well accepted as an essential component of multidisciplinary treatment for incompletely resected NSCLC. At present, there is no cogent evidence to support that PORT benefits N0-1 NSCLC patients after complete resection [48]. So, PORT may not be necessary and is not suggested for completely resected N0-1 NSCLC. PORT is suggested for completely resected N2-3 NSCLC. N3 patients should be at higher risk than N2 patients. It is well accepted that chemoradiotherapy or radiotherapy should be given to completely resected N3 NSCLC if the patient did not receive it before resection. There is a great debate on the role of PORT in patients with N2 NSCLC. Large number of studies reported the efficacy of PORT in N2 NSCLC and some results were contradictory.

Nowadays, with technological progress, different precise radiotherapy techniques, such as 3D-CRT and IMRT, have been applied in more and more hospitals. Modern radiotherapy techniques allow delivery of high radiation doses to the gross tumor, bulky lymph nodes, and high-risk areas [12, 13]. Dose escalation was reported to be associated with improved OS in NSCLC patients [49-51]. Moreover, modern radiotherapy techniques spare dose and volume of organs at risk and that should reduce radiation-induced toxicity [50-53]. Adverse effects of radiothera-

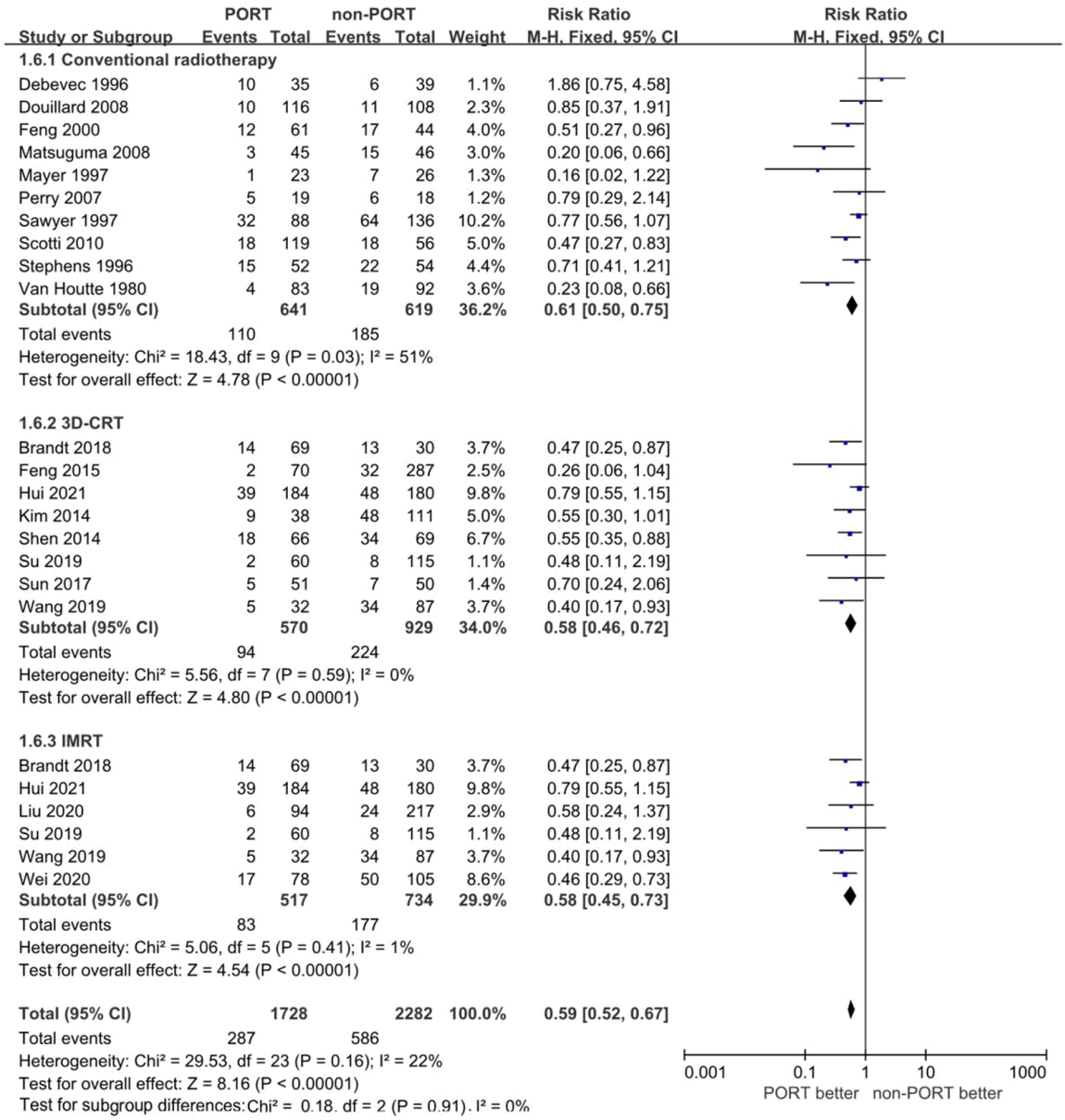


Figure 8. RR forest plot of LR in patients treated with different radiotherapy techniques. Note: RR: Relative risk, LR: Locoregional recurrence, 3D-CRT: 3-dimensional conformal radiotherapy, IMRT: Intensity-modulated radiotherapy, PORT: Postoperative radiotherapy.

py in patients with NSCLC includes pneumonitis, heart disease, esophagitis, hematologic toxicity, gastrointestinal reactions, et al. Radiation-induced toxicity might shorten survival [53-55]. For example, the incidence of symptomatic radiation-induced pneumonitis (RP) was reported to be about 20-40% in NSCLC patients [53]. RP can cause death directly and it may result in a decreased treatment intensification, such as interruption of radiotherapy or low tolerance of chemotherapy, immunotherapy and so on. Several studies demonstrated that RP was a clearly negative prognostic factor for survival [53-55]. Therefore, different radiotherapy techniques might produce different efficacies and safety in patients with NSCLC and modern radiotherapy techniques might increase the efficacy and decrease adverse effects [14, 15, 52]. Here, data of meta-analysis evaluating efficacies of different radiotherapy techniques support that hypothesis.

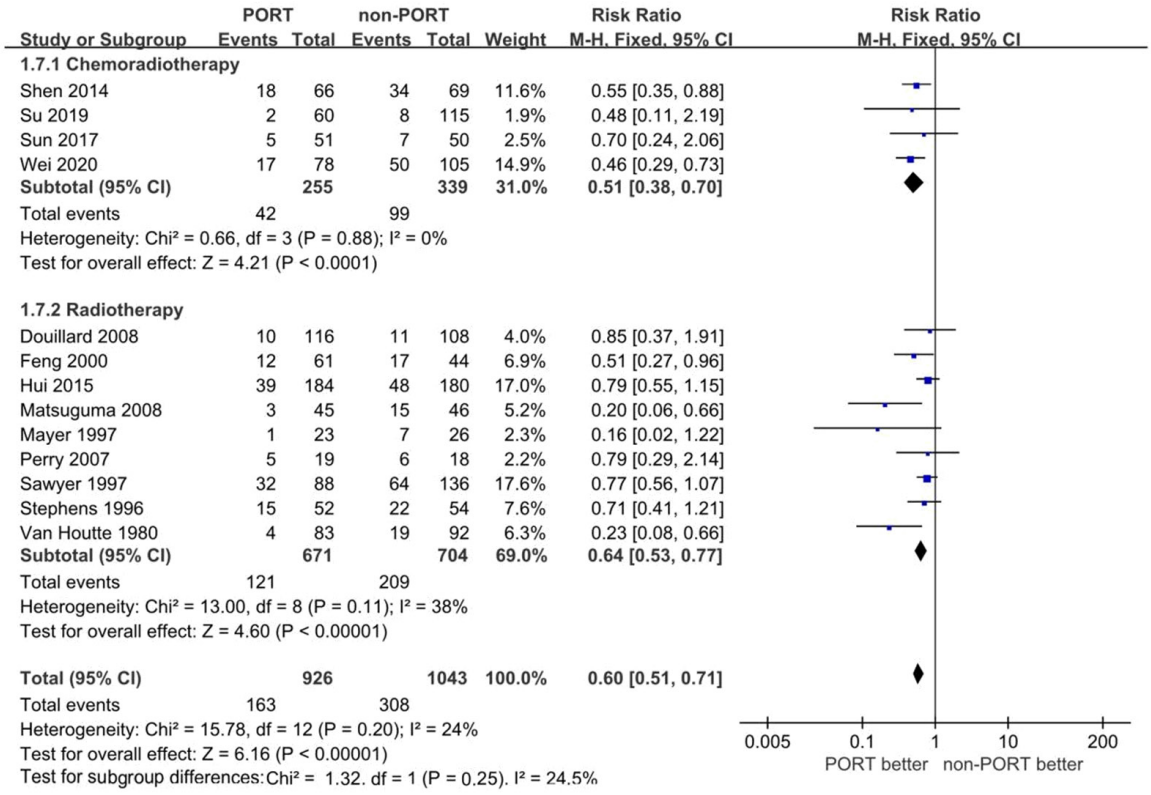


Figure 9. RR forest plot of LR in patients treated with different PORT regimes, concurrent chemoradiotherapy or radiotherapy. Note: RR: Relative risk, LR: Locoregional recurrence, PORT: Postoperative radiotherapy.

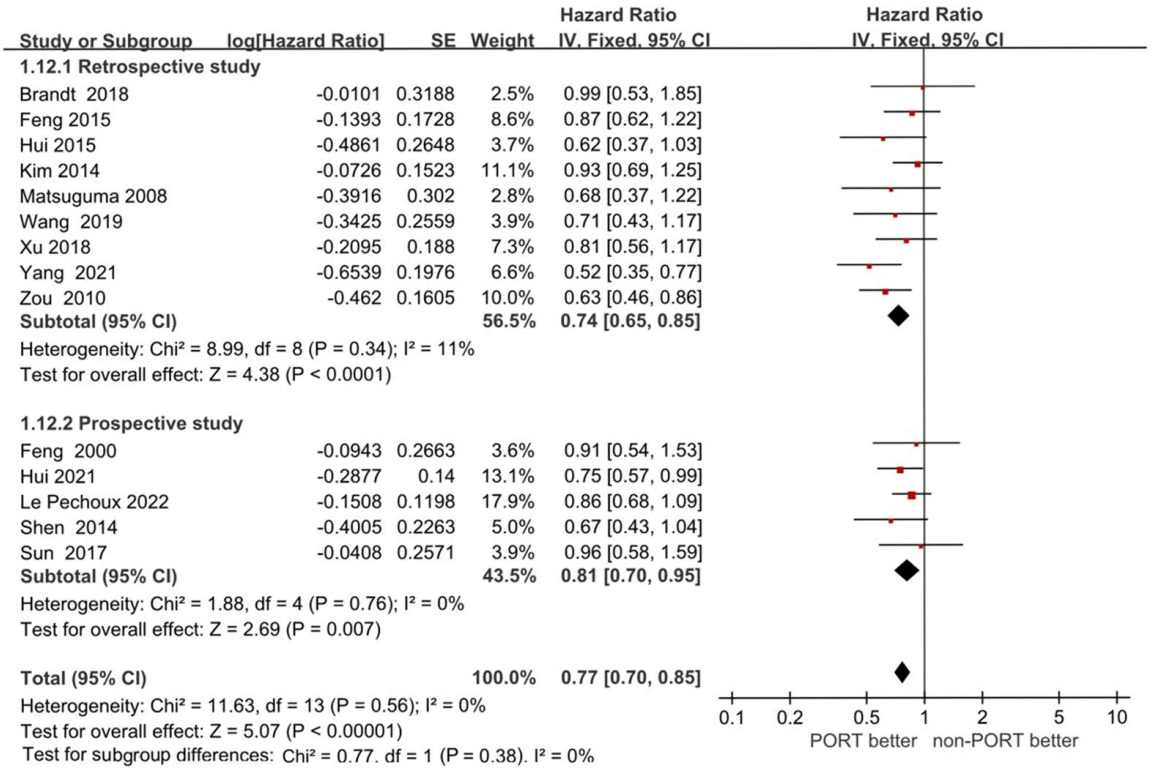


Figure 10. HR forest plot of DFS. Note: HR: Hazard ratio, DFS: Disease-free survival, PORT: Postoperative radiotherapy.

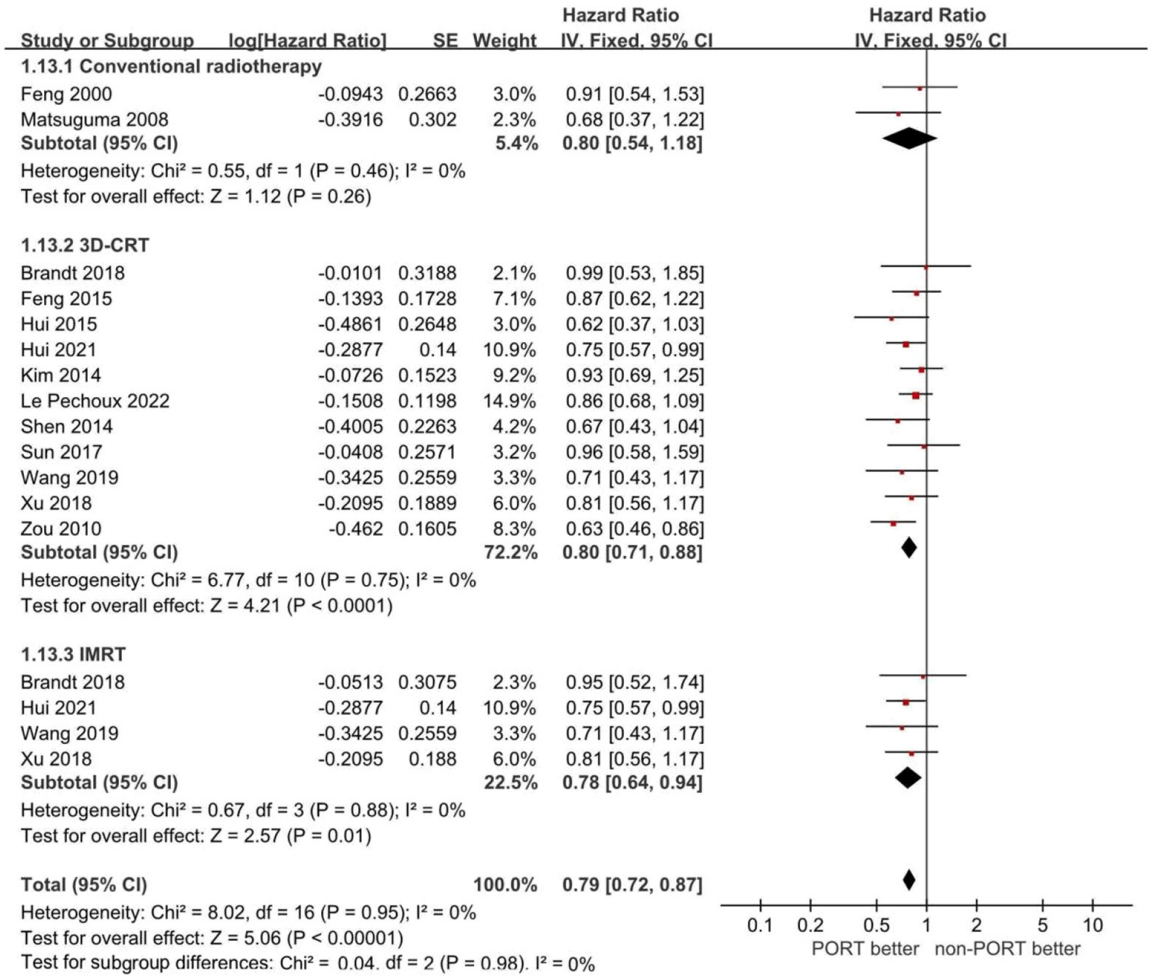


Figure 11. HR forest plot of DFS in patients treated with different radiotherapy techniques. Note: HR: Hazard ratio, DFS: Disease-free survival, 3D-CRT: 3-dimensional conformal radiotherapy, IMRT: Intensity-modulated radiotherapy, PORT: Postoperative radiotherapy.

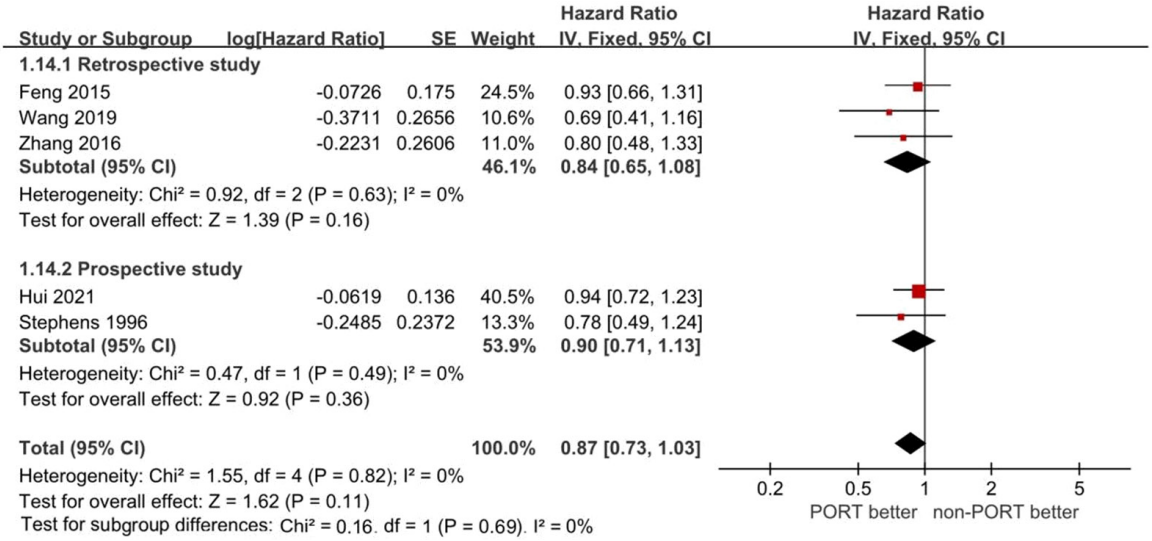


Figure 12. HR forest plot of DMFS. Note: HR: Hazard ratio, DMFS: Distant metastases-free survival, PORT: Postoperative radiotherapy.

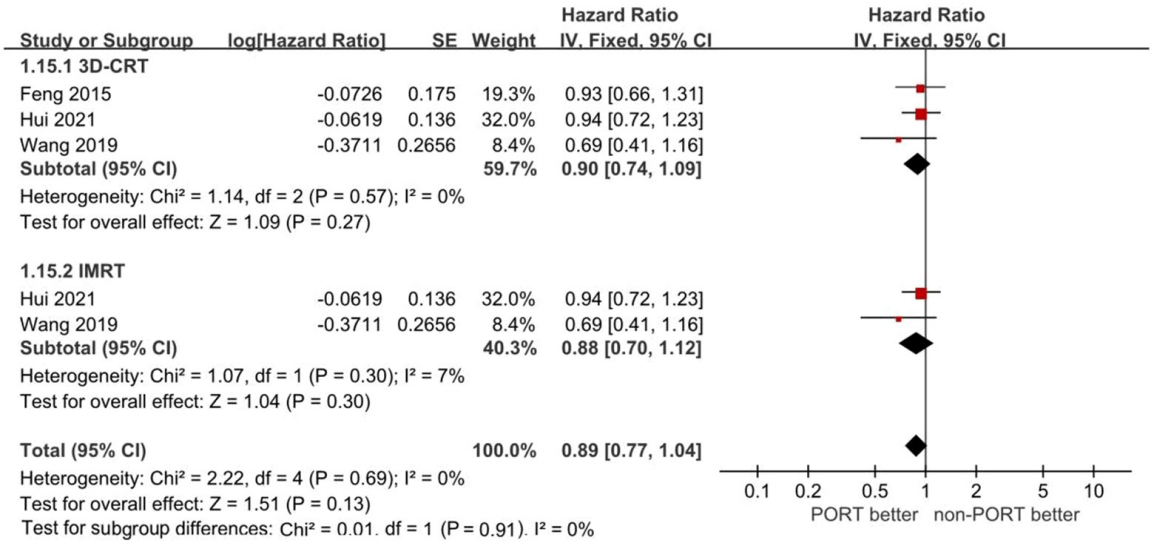


Figure 13. HR forest plot of DMFS in patients treated with different radiotherapy techniques. Note: HR: Hazard ratio, DMFS: Distant metastases-free survival, 3D-CRT: 3-dimensional conformal radiotherapy, IMRT: Intensity-modulated radiotherapy, PORT: Postoperative radiotherapy.

Our results consolidate LR decrease in patients with N2 NSCLC by PORT employing conventional radiotherapy, but we did not find solid evidence showing that PORT employing conventional radiotherapy improved OS. The HR of OS is about 0.90, but *p* value is more than 0.05. That implies that it favors the PORT group, but without significance. One possible explanation is that though PORT using conventional radiotherapy significantly decreases LR, radiation-induced toxicity might shorten survival and nullify the benefit in OS [53-55].

Our results showed that PORT using 3D-CRT or IMRT significantly decreased LR, increased DFS and improved OS in patients with N2 NSCLC. All RRs and HRs are accordant. Those unanimously indicate that PORT using modern radiotherapy techniques benefits patients. The difference in OS between conventional radiotherapy and modern radiotherapy techniques might not be due to the difference in doses delivered to CTV and planning target volume because conventional radiotherapy and modern radiotherapy techniques share similar RRs of LR. The difference in OS may be partly due to dose and volume of organs at risk spared by 3D-CRT and IMRT that may decrease radiation-induced toxicity. Radiation-induced toxicity was reported to shorten survival and nullify the benefit in OS [53-55].

The efficacy and safety of 3D-CRT or IMRT was explored in several studies. Jairam reported that the use of IMRT in the setting of PORT for local advanced NSCLC was not associated with a difference in toxicity compared to 3D-CRT [56]. Hsia's data supported that the survival outcome of patients with clinical stage III NSCLC treated with IMRT was not superior to those treated with 3D-CRT [57]. But Yu believed that use of IMRT for PORT among patients with incompletely resected NSCLC was associated with improved survival compared with 3D-CRT [15]. Here, pooled HRs of studies employing 3D-CRT and IMRT are similar. That supports that the use of IMRT for PORT in patients with N2 NSCLC may not be superior to 3D-CRT, but both IMRT and 3D-CRT may be superior to conventional radiotherapy.

In recent decades, the combination of PORT and chemotherapy, concurrent chemoradiotherapy, tends to yield better results than radiotherapy in terms of the survival outcomes, with acceptable safety profiles of both [58, 59]. Among the included studies, a few employed concurrent chemoradiotherapy (PORT as chemoradiotherapy) and most employed sequential combination of chemotherapy and radiotherapy or radiotherapy alone (PORT as radiotherapy). Data of PORT as radiotherapy showed a significant decrease in LR (P<0.00001), but no significant increase in OS (P: 0.34). PORT as

chemoradiotherapy significantly improves both LR and OS in patients with N2 NSCLC. Those findings are concordant with that chemoradiotherapy tends to yield better results than radiotherapy in terms of the survival outcomes [58, 59]. Patients with N2 NSCLC can be treated with neoadjuvant chemotherapy. Patients were treated without neoadjuvant chemotherapy in a majority of included studies. There are few data to analyze LR. Results of meta-analysis denotes that PORT significantly improves OS in patients without neoadjuvant chemotherapy (P: 0.0003), but does not improve OS in patients treated with neoadjuvant chemotherapy (P: 0.18). It is not rare that NSCLC patients were diagnosed as N1 or N0 stage before surgery while their surgical specimens proved that they were N2 or N3 stage. Those patients were usually treated without neoadjuvant chemotherapy. Our data indicate that those patients should be benefited by PORT.

Results of retrospective studies and prospective studies were not always concordant. Meta-analysis of both retrospective studies and prospective studies concordantly indicated that PORT significantly decreased LR and improved DFS. However, meta-analysis of retrospective studies indicated that PORT significantly improved OS while the HR for OS of prospective studies favored the PORT group, but without significance. Several factors might be involved. First, radiotherapy techniques. Two thirds (6/9, **Figure 3**) of prospective studies were published before 2010. At that time, conventional radiotherapy technique was popular. More than three fourths (21/27, **Figure 3**) of retrospective studies were published after 2015. Modern precise radiotherapy techniques have begun to gradually spread worldwide in the past 2 decades and are becoming the standard radiotherapy technique for the treatment of NSCLC in the past decade. Accumulating evidences and data here demonstrate that modern radiotherapy techniques are superior to the conventional radiotherapy technique in terms of the survival outcomes [14, 15, 52]. Second, PORT regimes. More than three fourths (21/27, **Figure 3**) of retrospective studies were published after 2015. Concurrent chemoradiotherapy becomes the first-line radiotherapy regime for NSCLC patients in the past decade. So, many patients may be treated with concurrent chemoradiotherapy in retrospective studies. Accumulating evidences and data here support that concurrent chemoradiotherapy may be superior to sequential combination of chemotherapy and radiotherapy or radiotherapy alone [1, 38, 47]. Third, patients' selection. The main purpose of PORT is to cure or decrease LR [5]. PORT may benefit patients at high risk of LR, but might not benefit patients at low risk or might benefit those patients a little. Lymph node status is a prognostic variable in LR and OS [60, 61]. Unfortunately, only a few studies intensively explored the role of node status in PORT [60, 61]. Wang et al. reported that PORT did not improve OS or lung cancer-specific survival in patients with metastasis in no more than 3 lymph nodes while significantly improved OS and lung cancer-specific survival in patients with metastasis in 4 or more lymph nodes [60]. Yuan et al. reported that PORT did not improve OS in patients with metastasis in no more than 4 lymph nodes but had a trend to improve OS in patients with metastasis in 5 or more lymph nodes (P=0.074) [61]. Extranodal extension, T-stages and tumor histology are prognostic variables in LR and OS, too [2, 9, 12]. Unfortunately, to our knowledge, few clinic trials intensively explored the impact of PORT in patients with or without extranodal extension, and fewer trials intensively explored in patients with different T-stages. Other factors should be involved in the difference in pooled HRs between retrospective studies and prospective studies but few clinic trials explored those factors.

Besides inherent limitations of individual trials, there are limitations to our analyses. First, treatment modalities vary considerably among different clinic trials, even in the same trial. Some patients received neoadjuvant chemotherapy, some did not. Some received chemoradiotherapy, some received radiotherapy alone. Some received immunotherapy, some received targeted therapy. Different radiotherapy techniques were used, sometimes even in one clinic trial. Different types of surgical resection were performed in one clinic trial and that happened in most of included studies. These variations make a great risk of bias in the implementation of the meta-analysis. Second, patients with different histological types of lung cancer, different T-stages, and different lymph node status were included. Different patients had different risks of LR and PORT might benefit

patients at different risks differently. Those confounders affect the efficacy of PORT more or less. Third, the sample size in each trial was small. Most of them were about 100. Consequently, confidence levels were very wide and there was a great variability. Fourth, some database, such as Web of Science, were not included in the databases searched because we do not have access.

Conclusion

PORT using 3D-CRT or IMRT benefits patients with N2 NSCLC in terms of LR, DFS and OS. PORT using conventional radiotherapy significantly decreases LR while it does not increase OS. PORT improves OS in patients without neoadjuvant chemotherapy, but does not improve OS in patients treated with neoadjuvant chemotherapy. Because a number of confounders, such as radiotherapy techniques, treatment modalities, lymph node status, T-stages, et al., affect the efficacy of PORT, studies with homogeneous samples, large sample sizes, fixed protocol are warranted to identify the efficacy of PORT in patients with NSCLC.

Acknowledgements

This work was supported by the Fund of Hebei Administration of Traditional Chinese Medicine (2023020).

Disclosure of conflict of interest

None.

Abbreviations

NSCLC, Non-small cell lung cancer; PORT, Postoperative radiotherapy; CTV, Clinical target volume; OS, Overall survival; LR, Locoregional recurrence; 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, Intensity-modulated radiotherapy; DFS, Disease-free survival; DMFS, Distant metastases-free survival; HR, Hazard ratio; RR, Relative risk; CI, Confidence interval; RP, Radiation-induced pneumonitis; RCT, Randomized controlled trial.

Address correspondence to: Jianming He and Wenzhong Xu, Department of Radiotherapy, Hebei Province Hospital of Chinese Medicine, Hebei University of Chinese Medicine, Shijiazhuang 050011, Hebei, China. Tel: +86-311-69095542; E-mail: hejianming@hebcm.edu.cn (JMH); xuwenzhong@hebcm.edu.cn (WZX)

References

[1] Su L, Chen M, Su H, Dai Y, Chen S and Li J. Postoperative chemoradiotherapy is superior to postoperative chemotherapy alone in squamous cell lung cancer patients with limited N2 lymph node metastasis. BMC Cancer 2019; 19: 1023.

[2] Yang R, Gong J, Liao Z, Yu J, Zhang J and Xie C. Value of postoperative radiotherapy for stage IIIa-N2 non-small cell lung cancer: an analysis based on SEER database. Transl Cancer Res 2022; 11: 2194-2204.

[3] Xu Y, Li J, Wang J, Hu X, Ma H, Li P, Zheng X and Chen M. Association between clinicopathological factors and postoperative radiotherapy in patients with completely resected pathological N2 non-small cell lung cancer. Oncol Lett 2018; 15: 2641-2650.

[4] Billiet C, De Ruysscher D, Peeters S, Decaluwé H, Vansteenkiste J, Dooms C, Deroose CM, De Leyn P, Hendrikx M, Bulens P, Le Péchoux C and Mebis J. Patterns of locoregional relapses in patients with contemporarily staged stage III-N2 NSCLC treated with induction chemotherapy and resection: implications for postoperative radiotherapy target volumes. J Thorac Oncol 2016; 11: 1538-1549.

[5] Kelsey CR, Light KL and Marks LB. Patterns of failure after resection of non-small-cell lung cancer: implications for postoperative radiation therapy volumes. Int J Radiat Oncol Biol Phys 2006; 65: 1097-1105.

[6] Kim BH, Kim HJ, Wu HG, Kang CH, Kim YT, Lee SH and Kim DW. Role of postoperative radiotherapy after curative resection and adjuvant chemotherapy for patients with pathological stage N2 non-small-cell lung cancer: a propensity score matching analysis. Clin Lung Cancer 2014; 15: 356-364.

[7] Xu L, Xie HN, Chen XK, Bi N, Qin JJ and Li Y. Patient prognostic scores and association with survival improvement offered by postoperative radiotherapy for resected IIIA/N2 non-small cell lung cancer: a population-based study. Thorac Cancer 2021; 12: 760-767.

[8] Feng W, Fu XL, Cai XW, Yang HJ, Wu KL, Fan M, Xiang JQ, Zhang YW and Chen HQ. Patterns of local-regional failure in completely resected stage IIIA(N2) non-small cell lung cancer cases: implications for postoperative radiation therapy clinical target volume design. Int J Radiat Oncol Biol Phys 2014; 88: 1100-1107.

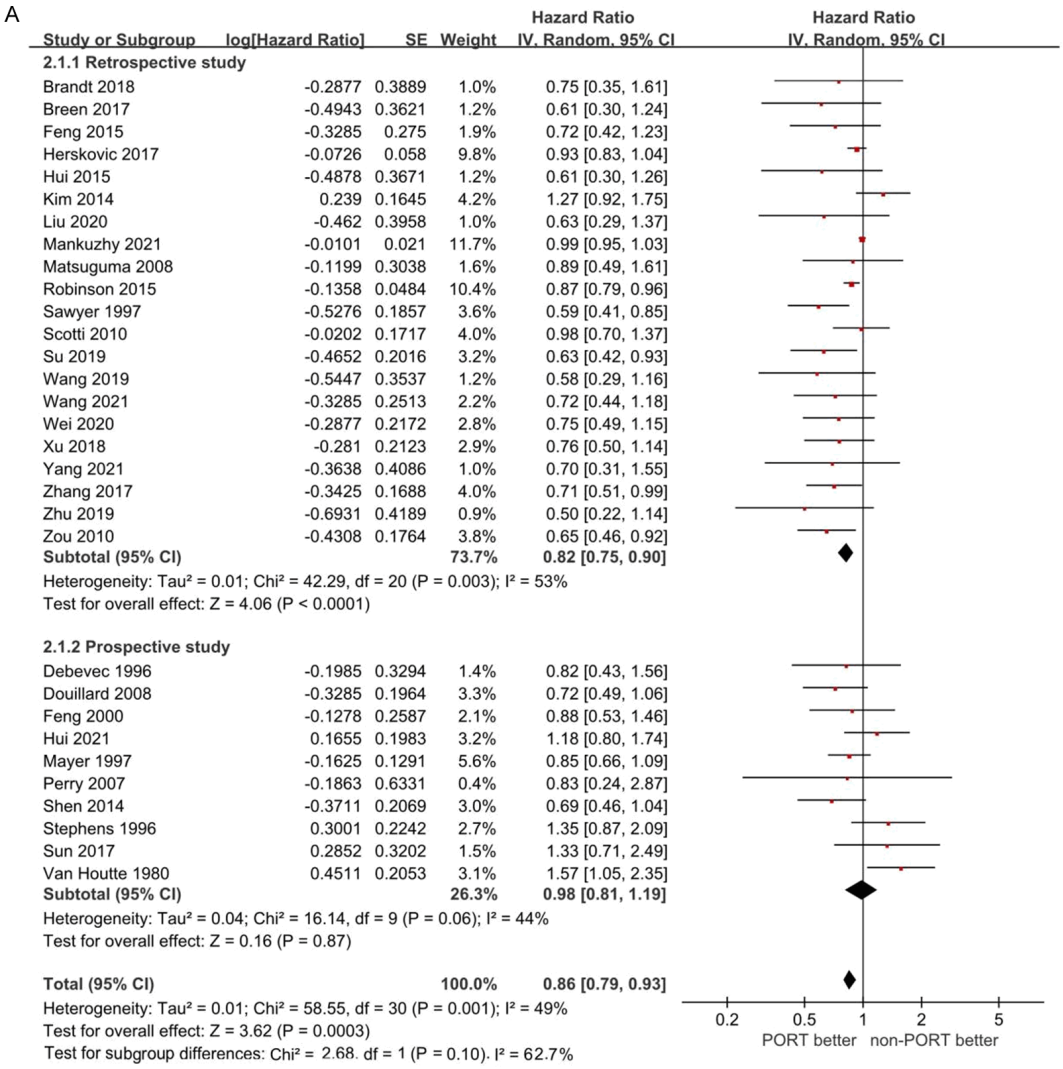
[9] Bao Y, Yang X, Men Y, Kang J, Sun X, Zhao M, Sun S, Yuan M, Ma Z and Hui Z. Postoperative radiotherapy improves survival of patients with ypN2 non-small cell lung cancer after neoadjuvant chemotherapy followed by surgery - a propensity score matching study of the surveil-

lance, epidemiology, and end results database. Thorac Cancer 2022; 13: 404-411.
[10] Debevec M, Bitenc M, Vidmar S, Rott T, Orel J, Strojan P and Kovac V. Postoperative radiotherapy for radically resected N2 non-small-cell lung cancer (NSCLC): randomised clinical study 1988-1992. Lung Cancer 1996; 14: 99-107.
[11] Van Houtte P, Rocmans P, Smets P, Goffin JC, Lustman-Maréchal J, Vanderhoeft P and Henry J. Postoperative radiation therapy in lung caner: a controlled trial after resection of curative design. Int J Radiat Oncol Biol Phys 1980; 6: 983-986.
[12] Predina J, Suliman R, Potter AL, Panda N, Diao K, Lanuti M, Muniappan A and Jeffrey Yang CF. Postoperative radiotherapy with modern techniques does not improve survival for operable stage IIIA-N2 non-small cell lung cancer. J Thorac Cardiovasc Surg 2023; 165: 1696-1709, e1694.
[13] Wang X, Han Y, Zhi Z, Xu W, Ge J, Liang X, Li D and He J. Delineation of the "oropharyngeal mucosa" and limiting its dose in head and neck cancer patients spares the oropharynx without compromising target coverage. Cancer Control 2024; 31: 10732748241283621.
[14] Sibley GS, Mundt AJ, Shapiro C, Jacobs R, Chen G, Weichselbaum R and Vijayakumar S. The treatment of stage III nonsmall cell lung cancer using high dose conformal radiotherapy. Int J Radiat Oncol Biol Phys 1995; 33: 1001-1007.
[15] Yu B, Jun Ma S, Waldman O, Dunne-Jaffe C, Chatterjee U, Turecki L, Gill J, Yendamuri K, Iovoli A, Farrugia M and Singh AK. Trends in postoperative intensity-modulated radiation therapy use and its association with survival among patients with incompletely resected non-small cell lung cancer. JAMA Netw Open 2022; 5: e2230704.
[16] Zhang CC, Hou RP, Xia WY, Zeng WQ, Liu J, Wang JM, Lv CX, Luo QQ, Zhao H, Yu W, Zhang Q, Zhu ZF, Cai XW, Feng W and Fu XL. Prognostic index for estimating the survival benefit of postoperative radiotherapy in pathologic N2 non-small cell lung cancer: a real-world validation study. Lung Cancer 2021; 156: 100-108.
[17] Wang T, Jiang T, Han Y, Zhu A, Xin S, Xue M, Xin X and Lu Q. Effects of postoperative adjuvant radiotherapy on stage IIIA-N2 non-small cell lung cancer and prognostic analysis. J BUON 2021; 26: 328-335.
[18] Huang J, Li H, Wang X, Liang X, Zhao T, Hu J, Bai H, Ge J, Sun S and He J. Impacts of ezetimibe on risks of various types of cancers: a meta-analysis and systematic review. Eur J Cancer Prev 2023; 32: 89-97.
[19] Liang X, Zhao T, Liu J, Hu Z and He J. Paraneoplastic dermatomyositis accompanying nasopharyngeal carcinoma: a systematic review and meta-analysis. Hong Kong J Dermatol 2020; 28: 149-158.
[20] Wang X, Li Q, Sun S, Liang X, Li H, Huang J, Zhao T, Hu J, Liu J, Hu Z, Duan Y and He J. Network meta-analysis and cost-effectiveness analysis of infliximab, cyclosporine and tacrolimus for ulcerative colitis. Medicine (Baltimore) 2022; 101: e31850.
[21] Brandt WS, Yan W, Leeman JE, Tan KS, Park BJ, Adusumilli PS, Bott MJ, Molena D, Isbell J, Chaft J, Rimner A and Jones DR. Postoperative radiotherapy for surgically resected ypN2 non-small cell lung cancer. Ann Thorac Surg 2018; 106: 848-855.
[22] Breen WG, Merrell KW, Mansfield AS, Wigle DA, Garces YI, Park SS, Olivier KR and Hallemeier CL. Predictors of relapse and evaluation of the role of postoperative radiation therapy in a modern series of patients with surgically resected stage III (N2) non-small cell lung cancer. Adv Radiat Oncol 2016; 2: 12-18.
[23] Feng W, Zhang Q, Fu XL, Cai XW, Zhu ZF, Yang HJ, Xiang JQ, Zhang YW and Chen HQ. The emerging outcome of postoperative radiotherapy for stage IIIA(N2) non-small cell lung cancer patients: based on the three-dimensional conformal radiotherapy technique and institutional standard clinical target volume. BMC Cancer 2015; 15: 348.
[24] Herskovic A, Mauer E, Christos P and Nagar H. Role of postoperative radiotherapy in pathologic stage IIIA (N2) non-small cell lung cancer in a prospective nationwide oncology outcomes database. J Thorac Oncol 2017; 12: 302-313.
[25] Hui Z, Dai H, Liang J, Lv J, Zhou Z, Feng Q, Xiao Z, Chen D, Zhang H, Yin W and Wang L. Selection of proper candidates with resected pathological stage IIIA-N2 non-small cell lung cancer for postoperative radiotherapy. Thorac Cancer 2015; 6: 346-353.
[26] Liu L, Zheng Z, Li J, Li Y and Ni J. Supraclavicular recurrence in completely resected (y)pN2 non-small cell lung cancer: implications for postoperative radiotherapy. Front Oncol 2020; 10: 1414.
[27] Mankuzhy NP, Almahariq MF, Siddiqui ZA, Thompson AB, Grills IS, Guerrero TM, Lee KC, Stevens CW and Quinn TJ. The role of postoperative radiation therapy for pN2 non-small-cell lung cancer. Clin Lung Cancer 2021; 22: e5-e17.
[28] Matsuguma H, Nakahara R, Ishikawa Y, Suzuki H, Inoue K, Katano S and Yokoi K. Postoperative radiotherapy for patients with completely resected pathological stage IIIA-N2 non-small cell lung cancer: focusing on an effect of the number of mediastinal lymph node stations

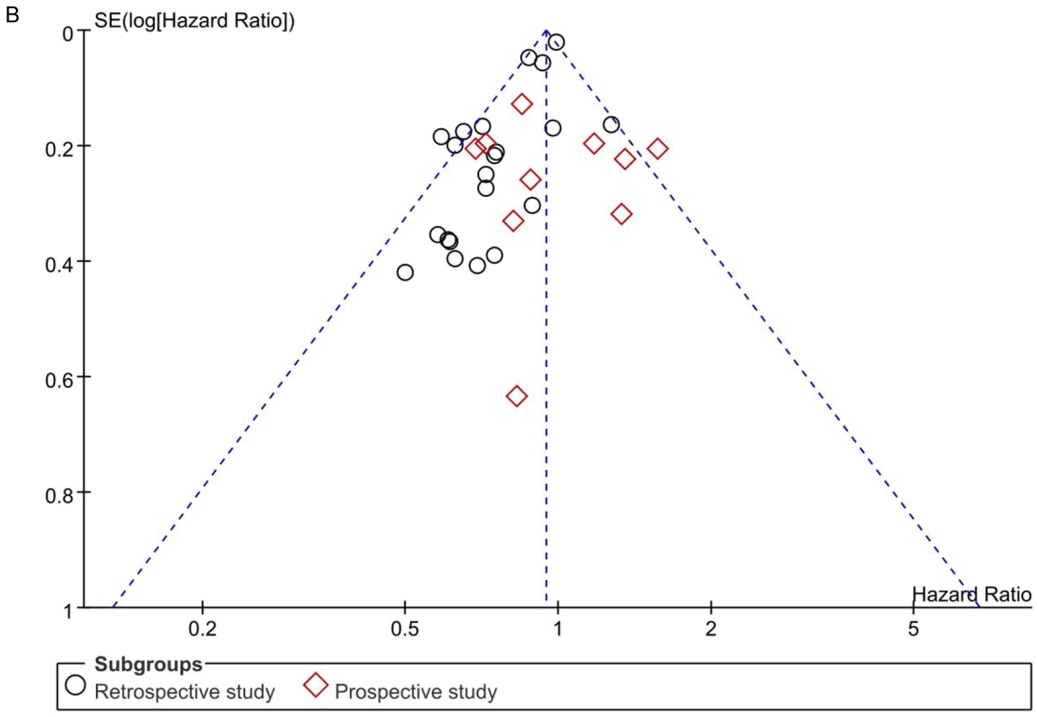
involved. Interact Cardiovasc Thorac Surg 2008; 7: 573-577.
[29] Robinson CG, Patel AP, Bradley JD, DeWees T, Waqar SN, Morgensztern D, Baggstrom MQ, Govindan R, Bell JM, Guthrie TJ, Colditz GA, Crabtree TD, Kreisel D, Krupnick AS, Patterson GA, Meyers BF and Puri V. Postoperative radiotherapy for pathologic N2 non-small-cell lung cancer treated with adjuvant chemotherapy: a review of the national cancer data base. J Clin Oncol 2015; 33: 870-876.
[30] Sawyer TE, Bonner JA, Gould PM, Foote RL, Deschamps C, Trastek VF, Pairolero PC, Allen MS, Shaw EG, Marks RS, Frytak S, Lange CM and Li H. The impact of surgical adjuvant thoracic radiation therapy for patients with nonsmall cell lung carcinoma with ipsilateral mediastinal lymph node involvement. Cancer 1997; 80: 1399-1408.
[31] Scotti V, Meattini I, Saieva C, Agresti B, de Luca Cardillo C, Bastiani P, Livi L, Mangoni M, Di Cataldo V, Marrazzo L, Rampini A, Cipressi S, Bruni A, Santini P and Biti G. Post-operative radiotherapy in N2 non-small cell lung cancer: a retrospective analysis of 175 patients. Radiother Oncol 2010; 96: 84-88.
[32] Wang W, Men Y, Wang J, Zhou Z, Chen D, Xiao Z, Feng Q, Lv J, Liang J, Bi N, Gao S, Wang L and Hui Z. Postoperative radiotherapy is effective in improving survival of patients with stage pIII-N2 non-small-cell lung cancer after pneumonectomy. BMC Cancer 2019; 19: 478.
[33] Wei W, Zhou J, Zhang Q, Liao DH, Liu QD, Zhong BL, Liang ZB, Zhang YC, Jiang R, Liu GY, Xu CY, Li Zhou H, Zhu SY, Yang N, Jiang W and Liu ZG. Postoperative intensity-modulated radiation therapy reduces local recurrence and improves overall survival in III-N2 non-small-cell lung cancer: a single-center, retrospective study. Cancer Med 2020; 9: 2820-2832.
[34] Yang H, Wang K, Li S, Li Y and Yuan L. The prognostic role of PORT and EGFR mutation status in completely resected stage IIIA/N2 non-small cell lung cancer patients with postoperative chemotherapy. Pathol Oncol Res 2021; 27: 1609898.
[35] Zhang B, Yuan Z, Zhao L, Pang Q and Wang P. Nomograms for predicting progression and efficacy of post-operation radiotherapy in IIIA-pN2 non-small cell lung cancer patients. Oncotarget 2017; 8: 37208-37216.
[36] Zhang B, Zhao L, Yuan Z, Pang Q and Wang P. The influence of the metastasis pattern of mediastinal lymph nodes on the postoperative radiotherapy's efficacy for the IIIA-pN2 non-small-cell lung cancer: a retrospective analysis of 220 patients. Onco Targets Ther 2016; 9: 6161-6169.
[37] Zhu Y, Fu L, Jing W, Kong L and Yu J. Radiotherapy for patients with completely resected pathologic IIIA(N2) non-small-cell lung cancer: a retrospective analysis. Cancer Manag Res 2019; 11: 10901-10908.
[38] Zou B, Xu Y, Li T, Li W, Tang B, Zhou L, Li L, Liu Y, Zhu J, Huang M, Wang J, Ren L, Gong Y, Che G, Liu L, Hou M and Lu Y. A multicenter retrospective analysis of survival outcome following postoperative chemoradiotherapy in non-small-cell lung cancer patients with N2 nodal disease. Int J Radiat Oncol Biol Phys 2010; 77: 321-328.
[39] Douillard JY, Rosell R, De Lena M, Riggi M, Hurteloup P and Mahe MA; Adjuvant Navelbine International Trialist Association. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant navelbine international trialist association (ANITA) randomized trial. Int J Radiat Oncol Biol Phys 2008; 72: 695-701.
[40] Feng QF, Wang M, Wang LJ, Yang ZY, Zhang YG, Zhang DW and Yin WB. A study of postoperative radiotherapy in patients with non-small-cell lung cancer: a randomized trial. Int J Radiat Oncol Biol Phys 2000; 47: 925-929.
[41] Hui Z, Men Y, Hu C, Kang J, Sun X, Bi N, Zhou Z, Liang J, Lv J, Feng Q, Xiao Z, Chen D, Wang Y, Li J, Wang J, Gao S, Wang L and He J. Effect of postoperative radiotherapy for patients with pIIIA-N2 non-small cell lung cancer after complete resection and adjuvant chemotherapy: the phase 3 PORT-C randomized clinical trial. JAMA Oncol 2021; 7: 1178-1185.
[42] Le Pechoux C, Pourel N, Barlesi F, Lerouge D, Antoni D, Lamezec B, Nestle U, Boisselier P, Dansin E, Paumier A, Peignaux K, Thillays F, Zalcman G, Madelaine J, Pichon E, Larrouy A, Lavole A, Argo-Leignel D, Derollez M, Faivre-Finn C, Hatton MQ, Riesterer O, Bouvier-Morel E, Dunant A, Edwards JG, Thomas PA, Mercier O and Bardet A. Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (Lung ART): an open-label, randomised, phase 3 trial. Lancet Oncol 2022; 23: 104-114.
[43] Mayer R, Smolle-Juettner FM, Szolar D, Stuecklschweiger GF, Quehenberger F, Friehs G and Hackl A. Postoperative radiotherapy in radically resected non-small cell lung cancer. Chest 1997; 112: 954-959.
[44] Perry MC, Kohman LJ, Bonner JA, Gu L, Wang X, Vokes EE and Green MR. A phase III study of surgical resection and paclitaxel/carboplatin chemotherapy with or without adjuvant radia-

tion therapy for resected stage III non-small-cell lung cancer: cancer and leukemia group B 9734. Clin Lung Cancer 2007; 8: 268-272.
[45] Shen WY, Ji J, Zuo YS, Pu J, Xu YM, Zong CD, Tao GZ, Chen XF, Ji FZ, Zhou XL, Han JH, Wang CS, Yi JG, Su XL and Zhu WG. Comparison of efficacy for postoperative chemotherapy and concurrent radiochemotherapy in patients with IIIA-pN2 non-small cell lung cancer: an early closed randomized controlled trial. Radiother Oncol 2014; 110: 120-125.
[46] Stephens RJ, Girling DJ, Bleehen NM, Moghissi K, Yosef HM and Machin D. The role of postoperative radiotherapy in non-small-cell lung cancer: a multicentre randomised trial in patients with pathologically staged T1-2, N1-2, M0 disease. Medical Research Council Lung Cancer Working Party. Br J Cancer 1996; 74: 632-639.
[47] Sun JM, Noh JM, Oh D, Kim HK, Lee SH, Choi YS, Pyo H, Ahn JS, Jung SH, Ahn YC, Kim J, Ahn MJ, Zo JI, Shim YM and Park K. Randomized phase II trial comparing chemoradiotherapy with chemotherapy for completely resected unsuspected N2-positive non-small cell lung cancer. J Thorac Oncol 2017; 12: 1806-1813.
[48] Wang EH, Corso CD, Park HS, Chen AB, Wilson LD, Kim AW, Decker RH and Yu JB. Association between radiation dose and outcomes with postoperative radiotherapy for N0-N1 non-small cell lung cancer. Am J Clin Oncol 2018; 41: 152-158.
[49] Brower JV, Amini A, Chen S, Hullett CR, Kimple RJ, Wojcieszynski AP, Bassetti M, Witek ME, Yu M, Harari PM and Baschnagel AM. Improved survival with dose-escalated radiotherapy in stage III non-small-cell lung cancer: analysis of the National Cancer Database. Ann Oncol 2016; 27: 1887-1894.
[50] Fenwick JD, Landau DB, Baker AT, Bates AT, Eswar C, Garcia-Alonso A, Harden SV, Illsley MC, Laurence V, Malik Z, Mayles WPM, Miles E, Mohammed N, Spicer J, Wells P, Vivekanandan S, Mullin AM, Hughes L, Farrelly L, Ngai Y and Counsell N. Long-term results from the IDEAL-CRT phase 1/2 trial of isotoxically dose-escalated radiation therapy and concurrent chemotherapy for stage II/III non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2020; 106: 733-742.
[51] Yang E, Shin YS, Joo JH, Choi W, Kim SS, Choi EK, Lee J and Song SY. Outcome of dose-escalated intensity-modulated radiotherapy for limited disease small cell lung cancer. Radiat Oncol J 2023; 41: 199-208.
[52] Wang D, Bi N, Zhang T, Zhou Z, Xiao Z, Liang J, Chen D, Hui Z, Lv J, Wang X, Wang X, Deng L, Wang W, Wang J, Wang C, Lu X, Xu K, Wu L, Xue W, Feng Q and Wang L. Comparison of efficacy and safety between simultaneous integrated boost intensity-modulated radiotherapy and conventional intensity-modulated radiotherapy in locally advanced non-small-cell lung cancer: a retrospective study. Radiat Oncol 2019; 14: 106.
[53] Inoue A, Kunitoh H, Sekine I, Sumi M, Tokuuye K and Saijo N. Radiation pneumonitis in lung cancer patients: a retrospective study of risk factors and the long-term prognosis. Int J Radiat Oncol Biol Phys 2001; 49: 649-655.
[54] Wang JY, Chen KY, Wang JT, Chen JH, Lin JW, Wang HC, Lee LN and Yang PC. Outcome and prognostic factors for patients with non-small-cell lung cancer and severe radiation pneumonitis. Int J Radiat Oncol Biol Phys 2002; 54: 735-741.
[55] Jairam V, Pasha S, Soulos PR, Gross CP, Yu JB, Park HS and Decker RH. Post-operative radiation therapy for non-small cell lung cancer: a comparison of radiation therapy techniques. Lung Cancer 2021; 161: 171-179.
[56] Hsia TC, Tu CY, Chen HJ, Chen SC, Liang JA, Chen CY, Wang YC and Chien CR. A population-based study of primary chemoradiotherapy in clinical stage III non-small cell lung cancer: intensity-modulated radiotherapy versus 3D conformal radiotherapy. Anticancer Res 2014; 34: 5175-5180.
[57] Nakamichi S, Horinouchi H, Asao T, Goto Y, Kanda S, Fujiwara Y, Nokihara H, Yamamoto N, Ito Y, Watanabe SI and Ohe Y. Comparison of radiotherapy and chemoradiotherapy for locoregional recurrence of non-small-cell lung cancer developing after surgery. Clin Lung Cancer 2017; 18: e441-e448.
[58] Lee HC, Kim YS, Oh SJ, Lee YH, Lee DS, Song JH, Kang JH and Park JK. The single institutional outcome of postoperative radiotherapy and concurrent chemoradiotherapy in resected non-small cell lung cancer. Radiat Oncol J 2014; 32: 147-155.
[59] Shih BC, Jeon JH, Chung JH, Kwon HJ, Lee JH, Jung W, Hwang Y, Cho S, Kim K and Jheon S. Prognostic significance of the extranodal extension of regional lymph nodes in stage III-N2 non-small-cell lung cancer after curative resection. J Clin Med 2021; 10: 3324.
[60] Wang S, Ma Z, Yang X, Wang Y, Xu Y, Xia W, Chen R, Qiu M, Jiang F, Yin R, Xu L and Xu K. Choice of postoperative radiation for stage IIIA pathologic N2 non-small cell lung cancer: impact of metastatic lymph node number. Radiat Oncol 2017; 12: 207.
[61] Yuan C, Tao X, Zheng D, Pan Y, Ye T, Hu H, Xiang J, Zhang Y, Chen H and Sun Y. The lymph node status and histologic subtypes influenced the effect of postoperative radiotherapy on patients with N2 positive IIIA non-small cell lung cancer. J Surg Oncol 2019; 119: 379-387.

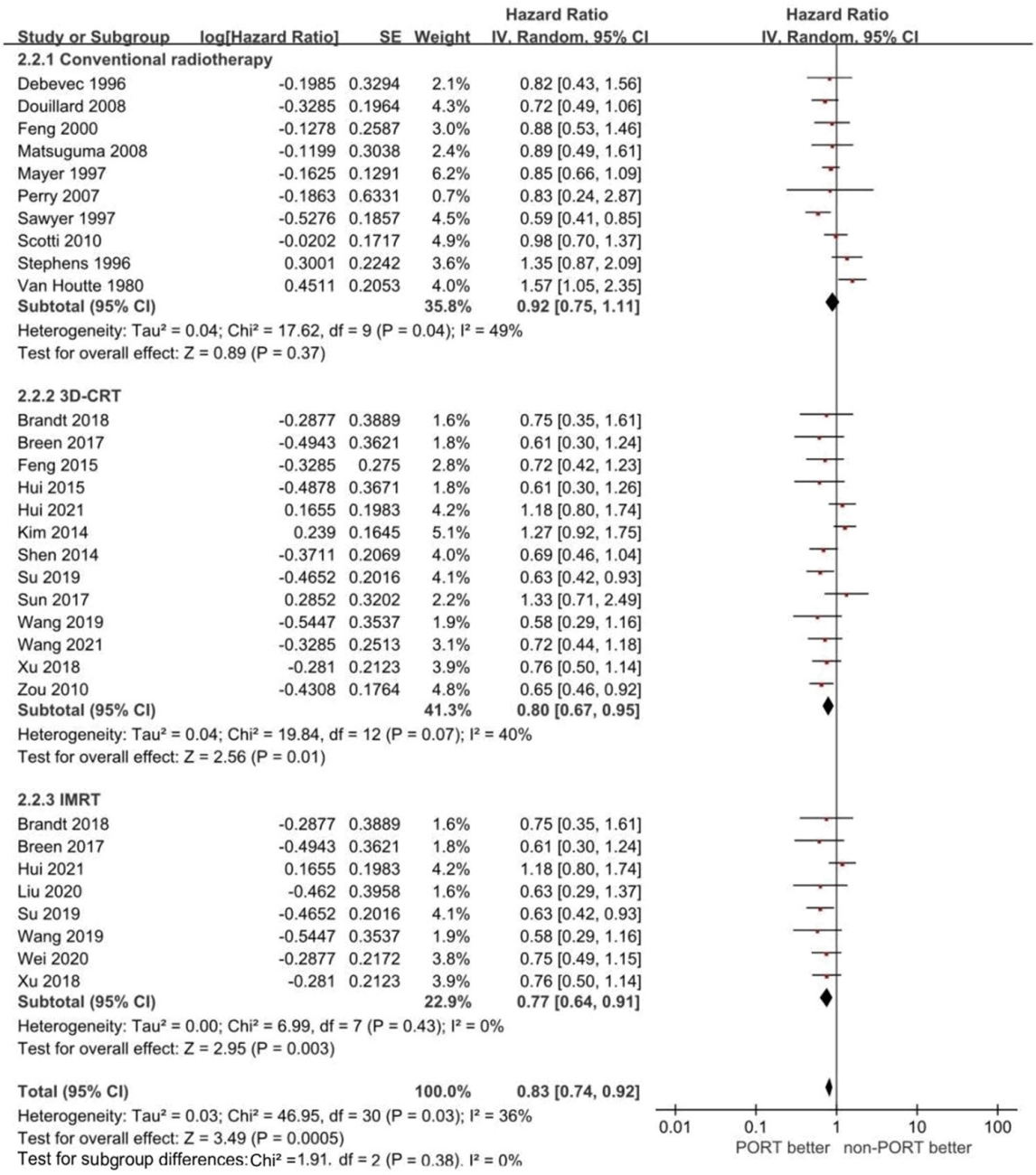
A


Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio IV, Random, 95% CI
2.1.1 Retrospective study
Brandt 2018 -0.2877 0.3889 1.0% 0.75 [0.35, 1.61]
Breen 2017 -0.4943 0.3621 1.2% 0.61 [0.30, 1.24]
Feng 2015 -0.3285 0.275 1.9% 0.72 [0.42, 1.23]
Herskovic 2017 -0.0726 0.058 9.8% 0.93 [0.83, 1.04]
Hui 2015 -0.4878 0.3671 1.2% 0.61 [0.30, 1.26]
Kim 2014 0.239 0.1645 4.2% 1.27 [0.92, 1.75]
Liu 2020 -0.462 0.3958 1.0% 0.63 [0.29, 1.37]
Mankuzhy 2021 -0.0101 0.021 11.7% 0.99 [0.95, 1.03]
Matsuguma 2008 -0.1199 0.3038 1.6% 0.89 [0.49, 1.61]
Robinson 2015 -0.1358 0.0484 10.4% 0.87 [0.79, 0.96]
Sawyer 1997 -0.5276 0.1857 3.6% 0.59 [0.41, 0.85]
Scotti 2010 -0.0202 0.1717 4.0% 0.98 [0.70, 1.37]
Su 2019 -0.4652 0.2016 3.2% 0.63 [0.42, 0.93]
Wang 2019 -0.5447 0.3537 1.2% 0.58 [0.29, 1.16]
Wang 2021 -0.3285 0.2513 2.2% 0.72 [0.44, 1.18]
Wei 2020 -0.2877 0.2172 2.8% 0.75 [0.49, 1.15]
Xu 2018 -0.281 0.2123 2.9% 0.76 [0.50, 1.14]
Yang 2021 -0.3638 0.4086 1.0% 0.70 [0.31, 1.55]
Zhang 2017 -0.3425 0.1688 4.0% 0.71 [0.51, 0.99]
Zhu 2019 -0.6931 0.4189 0.9% 0.50 [0.22, 1.14]
Zou 2010 -0.4308 0.1764 3.8% 0.65 [0.46, 0.92]
Subtotal (95% CI) 73.7% 0.82 [0.75, 0.90]
Heterogeneity: Tau² = 0.01; Chi² = 42.29, df = 20 (P = 0.003); I² = 53%
Test for overall effect: Z = 4.06 (P < 0.0001)
2.1.2 Prospective study
Debevec 1996 -0.1985 0.3294 1.4% 0.82 [0.43, 1.56]
Douillard 2008 -0.3285 0.1964 3.3% 0.72 [0.49, 1.06]
Feng 2000 -0.1278 0.2587 2.1% 0.88 [0.53, 1.46]
Hui 2021 0.1655 0.1983 3.2% 1.18 [0.80, 1.74]
Mayer 1997 -0.1625 0.1291 5.6% 0.85 [0.66, 1.09]
Perry 2007 -0.1863 0.6331 0.4% 0.83 [0.24, 2.87]
Shen 2014 -0.3711 0.2069 3.0% 0.69 [0.46, 1.04]
Stephens 1996 0.3001 0.2242 2.7% 1.35 [0.87, 2.09]
Sun 2017 0.2852 0.3202 1.5% 1.33 [0.71, 2.49]
Van Houtte 1980 0.4511 0.2053 3.1% 1.57 [1.05, 2.35]
Subtotal (95% CI) 26.3% 0.98 [0.81, 1.19]
Heterogeneity: Tau² = 0.04; Chi² = 16.14, df = 9 (P = 0.06); I² = 44%
Test for overall effect: Z = 0.16 (P = 0.87)
Total (95% CI) 100.0% 0.86 [0.79, 0.93]
Heterogeneity: Tau² = 0.01; Chi² = 58.55, df = 30 (P = 0.001); I² = 49%
Test for overall effect: Z = 3.62 (P = 0.0003)
Test for subgroup differences: Chi² = 2.68, df = 1 (P = 0.10), I² = 62.7%
Hazard Ratio IV, Random, 95% CI
0.2 0.5 1 2 5
PORT better non-PORT better

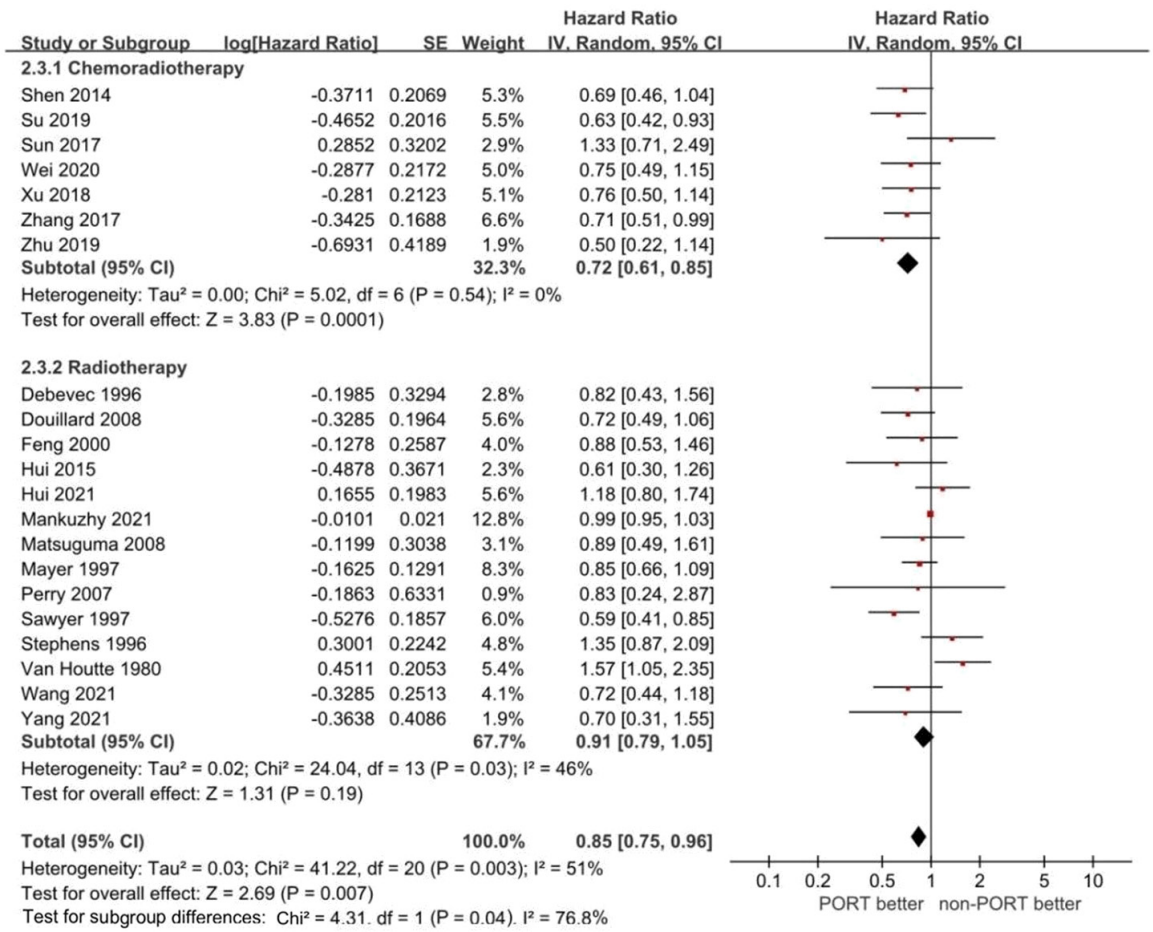
B


SE(log[Hazard Ratio])
0
0.2
0.4
0.6
0.8
1
0.2 0.5 1 2 5
Hazard Ratio
Subgroups
Retrospective study
Prospective study

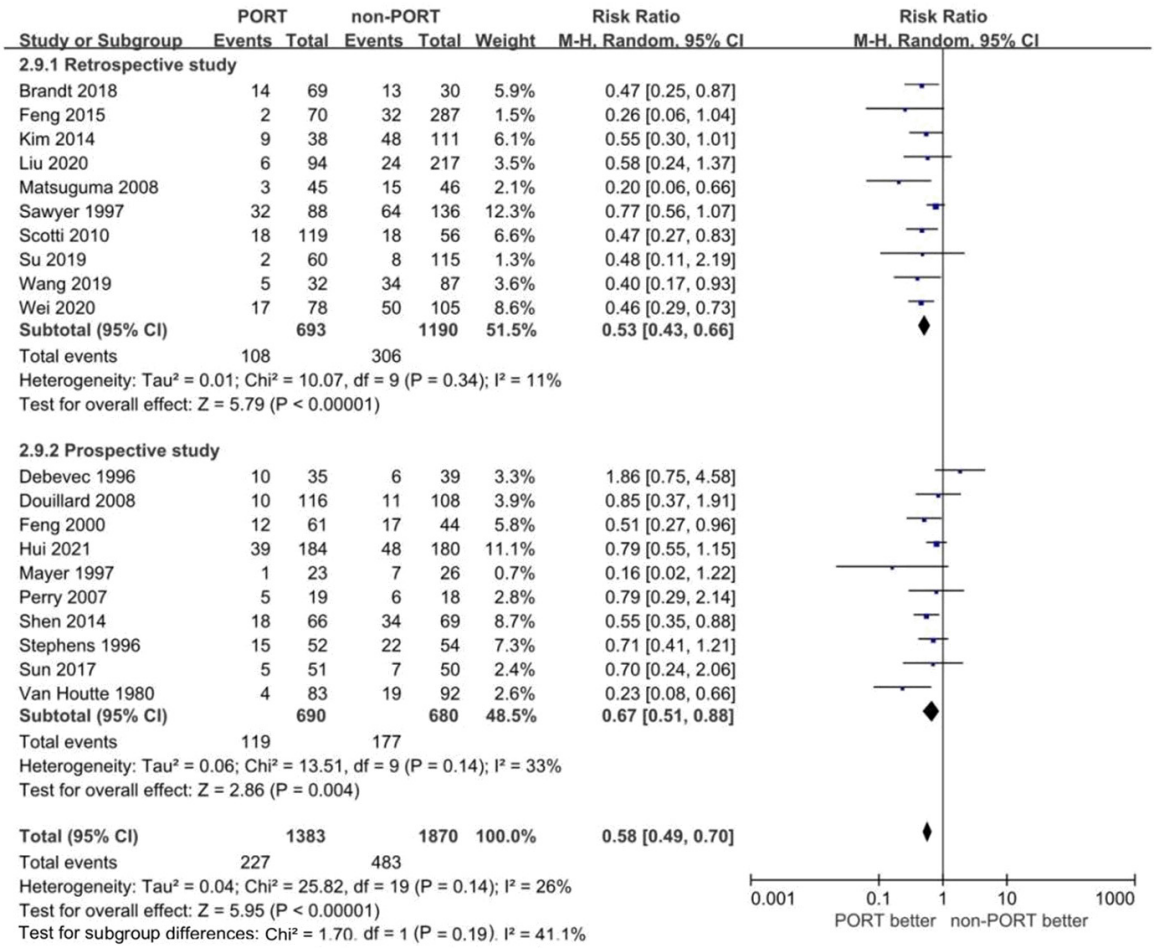
Supplementary Figure 1. Pooled HRs for OS, regardless of heterogeneity. A: Forest plot. B: Funnel plot. Note: HR: Hazard ratio, OS: Overall survival, PORT: Postoperative radiotherapy.



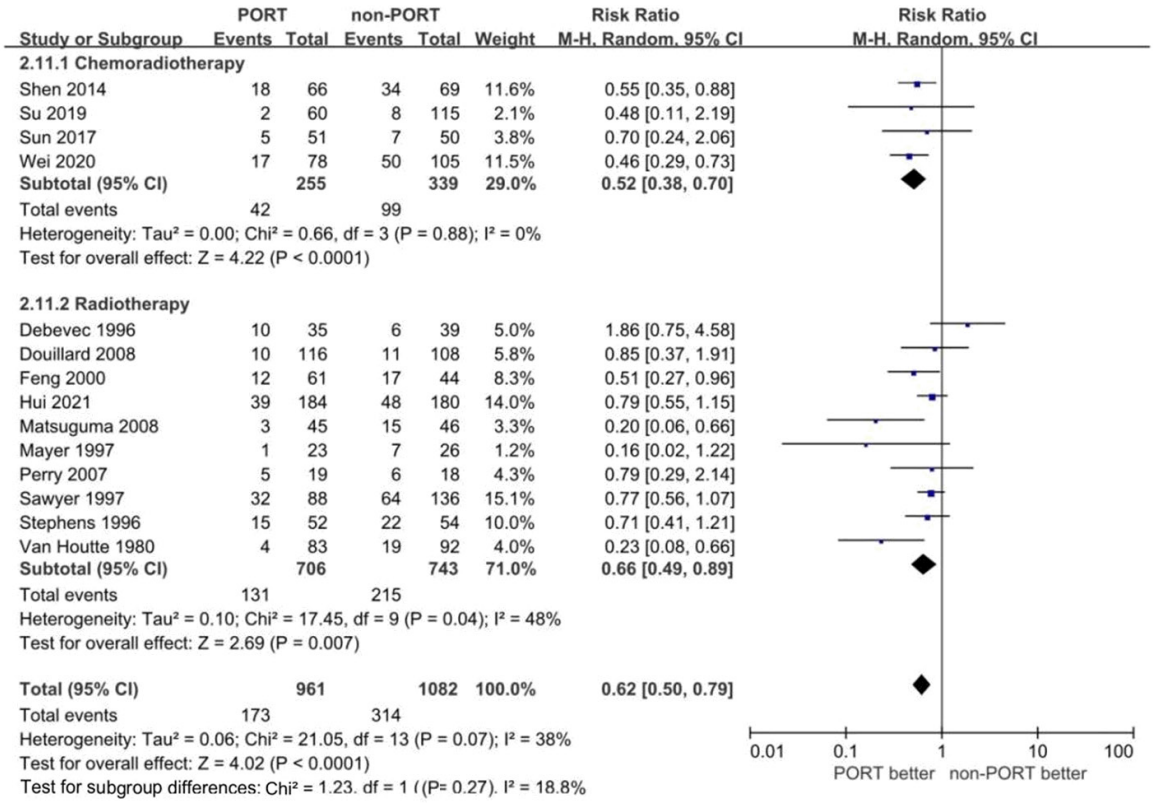
Supplementary Figure 2. HR forest plot of OS in patients treated with different radiotherapy techniques, regardless of heterogeneity. Note: HR: Hazard ratio, OS: Overall survival, 3D-CRT: 3-dimensional conformal radiotherapy, IMRT: Intensity-modulated radiotherapy, PORT: Postoperative radiotherapy.



Supplementary Figure 3. HR forest plot of OS in patients treated with concurrent chemoradiotherapy or radiotherapy, regardless of heterogeneity. Note: HR: Hazard ratio, OS: Overall survival, PORT: Postoperative radiotherapy.



Supplementary Figure 4. RR forest plot of LR, regardless of heterogeneity. Note: RR: Relative risk, LR: Locoregional recurrence, PORT: Postoperative radiotherapy.



Supplementary Figure 5. RR forest plot of LR in patients treated with concurrent chemoradiotherapy or radiotherapy, regardless of heterogeneity. Note: RR: Relative risk, LR: Locoregional recurrence, PORT: Postoperative radiotherapy.