Systematic Review and Meta-Analysis

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Efficacy of chemoradiotherapy versus radiation alone in patients with inoperable locally advanced non–small-cell lung cancer

A meta-analysis and systematic review

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Abstract

Background: This meta-analysis compared radiotherapy (RT) versus concurrent chemoradiotherapy (RT+CT) in treating patients with inoperable stage III non–small-cell lung cancer (NSCLC).

Methods: Medline, Cochrane, EMBASE, Google Scholar databases were searched until July 28, 2015 using the following keywords non-small cell lung cancer, advanced cancer, incurable/inoperable/unresectable, chemotherapy, radiotherapy, chemoradiotherapy/chemoradiation. Randomized controlled trials (RCTs) and two-armed prospective studies that compared combined RT+CT with RT alone in patients with locally advanced (stage III) nonresectable NSCLC were eligible for inclusion. Treatment effect on overall survival, progression-free survival (PFS), and objective response rate (ORR) were evaluated.

Results: Ultimately, 13 RCT studies were included in the systematic review and meta-analysis. The 13 studies included a total of 1936 patients with incurable/inoperable stage III NSCLC, of which 975 received RT alone and 961 received RT+CT combination therapy. The average age ranged from 54 to 77 years. At 1 and 2 years after treatment, the pooled data reveal that patients receiving CT+RT combination therapy had higher overall survival (pooled hazard ratio (HR), 0.72; 95% CI, 0.62–0.84; $P < .001$; 1-yr: HR, 0.67; 95% CI, 0.54–0.84; $P < .001$; 2-year: HR, 0.57; 95% CI, 0.45–0.73; $P < .001$), higher PFS (pooled HR, 0.73, 95% CI, 0.60–0.89; $P = .002$; 1-year: HR, 0.36; 95% CI, 0.24–0.53; $P < .001$; 2-year: HR, 0.38; 95% CI, 0.23–0.63; $P < .001$).

Conclusion: Our findings show higher efficacy for concurrent CT+RT over RT alone in treating locally-advanced, unresectable stage III NSCLC.

Abbreviations: RT+CT = chemoradiotherapy, CT = chemotherapy, CI = confidence interval, HR = hazard ratio, NSCLC = non–small-cell lung cancer, ORR = objective response rate, OR = odds ratio, OS = overall survival, PFS = progression-free survival, RT = radiotherapy, RCTs = randomized controlled trials.

Keywords: chemoradiation, non–small-cell lung cancer, objective response rate, overall survival, progression-free survival, radiotherapy

1. Introduction

Non–small-cell lung cancer (NSCLC) represents greater than 80% of all lung tumors with about one-third of patients presenting with locally advanced stage III tumors that are not amenable to surgery.[1–3] For these patients post-surgical outcomes are poor.[4–8] The 5-year survival rate of surgical patients is highly variable, and surgery is associated with substantial morbidity and mortality.

Most patients who present with inoperable locally advanced NSCLC receive palliative care. The goals of treatment are to relieve pain and other symptoms and to improve or maintain the quality of life.[9] Until the 1990's radiotherapy alone was the standard treatment for patients with inoperable NSCLC, however the 5-year survival rate was poor (under 10%).[10–12] Over the last two decades, a number of studies have demonstrated that chemotherapy and radiotherapy can prolong survival and are recommended as treatment for locally advanced disease.[5,10,13–15] The combination of radiotherapy plus platinum-based chemotherapy for locally advanced NSCLC shows survival benefit compared with radiation therapy alone, and is considered the current standard of care.[4–8] The median survival time for the combined therapy ranges from 12 to 14 months while radiation alone ranges from 9 to 12 months.[4–8] The combination of radio- and chemotherapy have been recommended by guidelines for treating locally advanced disease.[16] The idea is that chemotherapy will reduce the risk of distant metastasis and radiotherapy will maintain loco-regional control.[17] The chemotherapeutic drug may also increase radio-sensitivity and increase the effectiveness of the radiation treatment.[18]

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Combined chemotherapy and radiation therapy can be given concurrently or sequentially. While concurrent therapy is associated with higher toxicity, particularly acute esophageal toxicity,[16,19] several studies and meta-analyses indicate that concurrent therapy is superior to sequential therapy in treating this disease.[15,20,21] The use of chemoradiotherapy requires the total absence of negative clinical prognostic factors, including poor performance status and weight loss.[22]

Although a number of clinical studies have compared chemoradiotherapy with radiation or chemotherapy alone,[13–15] the role of chemoradiation therapy in patients with inoperable or unresectable stage III disease and who have a poor prognosis is not uniformly agreed upon. The purpose of this study is to evaluate whether the combination of radiotherapy and chemotherapy results in longer survival than radiotherapy alone in patients with inoperable or unresectable stage III NSCLC.

2. Methods

2.1. Search strategy

This study was performed in accordance with the PRISMA guidelines. Medline, Cochrane, EMBASE, Google Scholar databases were searched until July 128, 2018 using the following search terms: non-small cell lung cancer, advanced cancer, incurable/inoperable/unresectable, chemotherapy, radiotherapy, chemoradiotherapy/chemoradiation. Ethical approval and informed consent were not necessary as the meta-analyses did not involve human subjects and does not require internal review board review and approval. Randomized controlled trials (RCTs) that compared combined chemoradiotherapy (RT+CT) with radiotherapy (RT) alone in patients with histologically confirmed, locally advanced (stage III) nonresectable NSCLC were include. Cohort study; letters, comments, editorials, case report; proceeding, and personal communications were excluded. Studies that evaluated two types of chemotherapy (e.g., etoposide plus cisplatin or irinotecan plus cisplatin, docetaxel and cisplatin vs MVP, cisplatin/etoposide vs paclitaxel/carboplatin) were excluded. Also excluded were studies designed to compare dose and sequence of RT (e.g., sequential vs concurrent), or did not report quantitatively outcomes of interest. The list of prospective studies was reviewed by 2 independent reviewers, and where there was uncertainty regarding eligibility, a third reviewer was consulted. This study was approved by the Chang Gung Medical Foundation Institutional Review Board (IRB No. 201900509B0).

2.2. Data extraction and quality assessment

The following information/data were extracted from the studies that met the inclusion/exclusion criteria: the name of the first author, year of publication, study design, number of participants in each treatment group, age and gender, cancer type, primary, secondary outcomes, and time of follow-up.

The Cochrane Risk of Bias Tool was used to assess the included studies.[23] The quality assessment was performed by 2 independent reviewers, and a third reviewer was consulted to adjudicate any uncertainties.

2.3. Outcome measures

The primary outcome for this meta-analysis was the hazard ratio (HR) for overall survival (OS). The secondary outcomes were the HR of progression-free survival (PFS) and odds ratio (OR) of objective response rate (ORR). The additional OS rate and PFS rate at 1 and 2 years after treatment were also extracted from the reports.

2.4. Statistical analysis

The study characteristics are summarized according to the number of patients, mean age, % of males, and % of disease stage for patients receiving RT alone or RT+CT treatment. The clinical outcomes, OS rate, PFS rate, and ORR are presented as (%) for the given follow-up time points. Furthermore, the HR with corresponding 95% confidence intervals (95% CI) of RT+CT treatment compared to that of RT alone in OS times and PFS times are also presented for each of the studies.

For the major effect size, the HR of the OS time and PFS time and the HR with 95% CI was calculated for each individual study and for the studies combined. For the secondary effect size odds ratio, the OR with 95% CI was calculated for dichotomous outcomes, ORR, OS rate, and PFS rate for each individual study and for the studies combined. For data reported as Kaplan–Meier curves, we extracted the survival rates at specific times to reconstruct the estimated HR and its variance, under the assumption that the rate of patients censored was constant during the study follow-up.[24] HR < 1 indicates that CT+RT treatment resulted in longer survival than did combination therapy; HR > 1 indicates that RT alone resulted in longer survival than did the other treatments; and HR $= 1$ indicated similar survival between RT alone and CT+RT combination therapy. For the other effect size, OR < 1 indicates that CT+RT combination therapy resulted in higher OS, PFS or ORR; OR > 1, indicates that radiotherapy alone resulted in higher OS, PFS or ORR; and OR $= 1$ indicated that the OS rate, PFS rate, or ORR were similar between RT alone and CT+RT combination therapy. A χ^2-based test of homogeneity was performed, and the inconsistency index (I^2) and Q statistics were determined. Fixed-effects models were used unless I^2 was $> 50\%$, in which case a random-effects model was used. The combined effects were calculated, and a 2-sided P value $< .05$ was considered significance. Sensitivity analysis was prospectively planned for the major outcomes and carried out using the leave-one-out approach to investigate the validity and robustness of the results. This approach involves performing the meta-analysis on subsets of studies in which one study is left out in turn. Publication bias was not assessed because >10 studies are required to detect funnel plot asymmetry.[25] All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ).

3. Results

Of the 1029 studies initially identified, 974 were removed because they were irrelevant (Fig. 1A). Fifty-five studies were fully reviewed, and 42 of these were eliminated because the study design did not meet the inclusion criteria, did not report outcomes of interest, was a one arm study or recruit patients with NSCLC stage I-II, or full text was not available. Thus, the final cohort included 13 studies.

3.1. Quality assessment

Quality assessment indicated a high risk for performance bias and detection bias and a low risk for selection bias, attrition bias, and

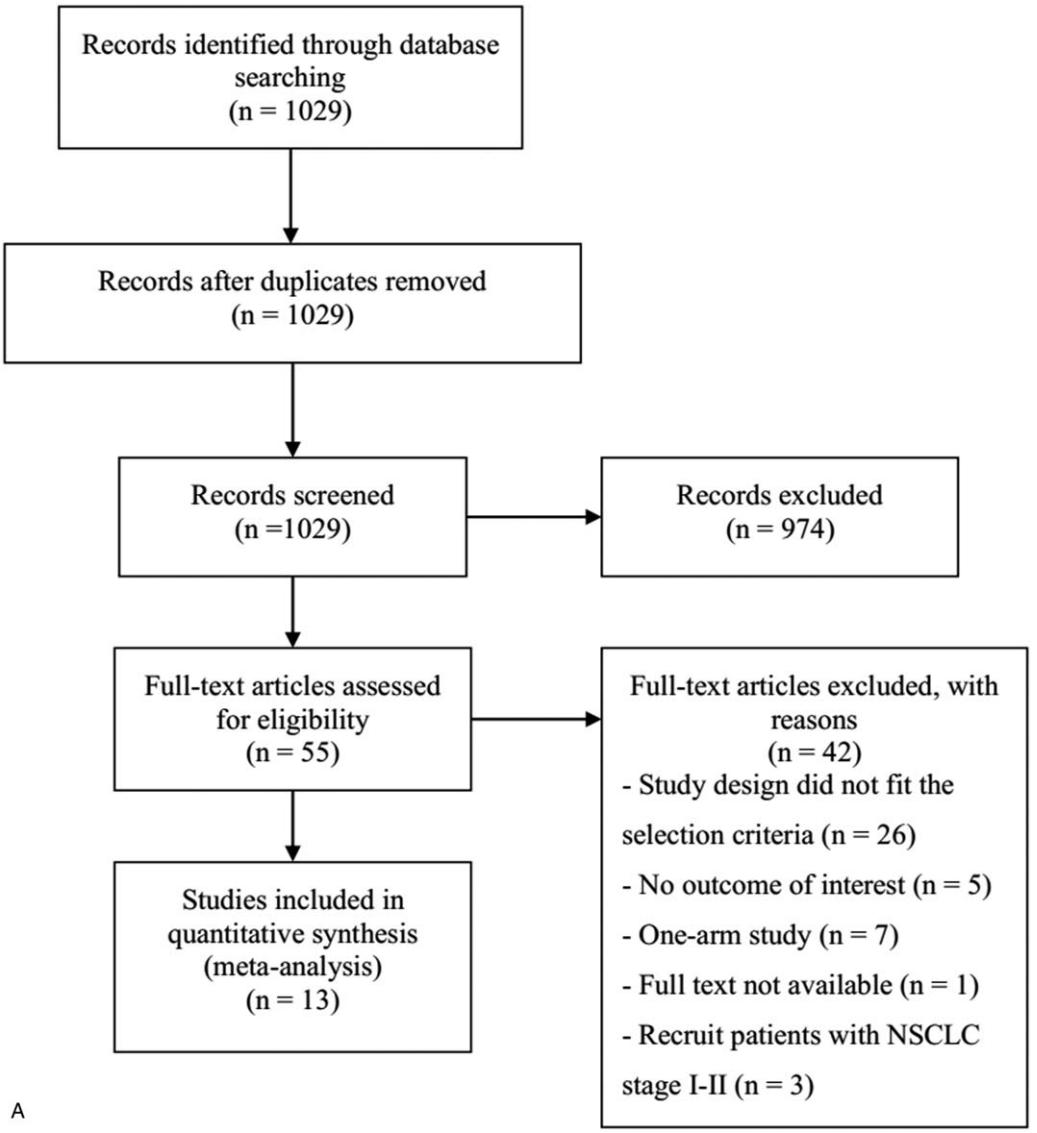


Figure 1. (A) Flow chart of study selection. Results of quality assessment using the Cochrane Risk of Bias Tool for (B) overall and (C) individual included studies.

reporting bias (Fig. 1B and C). Less than half of the included studies performed an intent-to-treat analysis. Overall, these findings suggest the data are of medium to good quality.

3.2. Study characteristics

Thirteen RCT studies were included in the systematic review and meta-analysis (Fig. 1 and Table 1).[7,12,17,26–35] The 13 studies included a total of 1936 patients with incurable/inoperable stage III NSCLC, of which 975 received RT alone and 961 received RT +CT combination therapy. The average age ranged from 54 to 77 years. Overall, the patient characteristics were similar between the RT alone and RT+CT groups. For most of the included studies, squamous-cell NSCLC was the most common cancer type. The types of radiotherapy and chemoradiotherapy used differed across the studies and are summarized in Table 2.Clinical outcomes by interventions are summarized in Table S1, http://links.lww.com/MD/D84.

3.3. Meta-analysis

3.3.1. Overall survival. All 5 studies were included in the analysis of OS. A fixed-effect model was used, as no heterogeneity was observed among the five studies (Q, 0.917; I^2, 0%). The meta-analysis indicated that combined chemoradiotherapy reduced the risk of death in patients with stage III NSCLC compared with radiotherapy alone (pooled HR, 0.72; 95% CI, 0.62–0.84; $P < .001$) (Fig. 2A). Furthermore, the pooled data revealed that patients receiving CT+RT combination therapy had a higher OS at 1 and 2 years after treatment compared to those treated with RT alone (1-year: OR, 0.67; 95% CI, 0.54–0.84; $P < .001$; 2-year: OR, 0.57; 95% CI, 0.45–0.73; $P < .001$) (Supplementary Fig. S1A). With stratification of the pooled data for cohort location (North America, Europe, and East Asia), the difference between CT+RT and RT alone remained significant for all subgroups with respect OS and PFS except the 1- and 2-year OS of cohorts from East Asia (Table S2, http://links.lww.com/MD/D84).

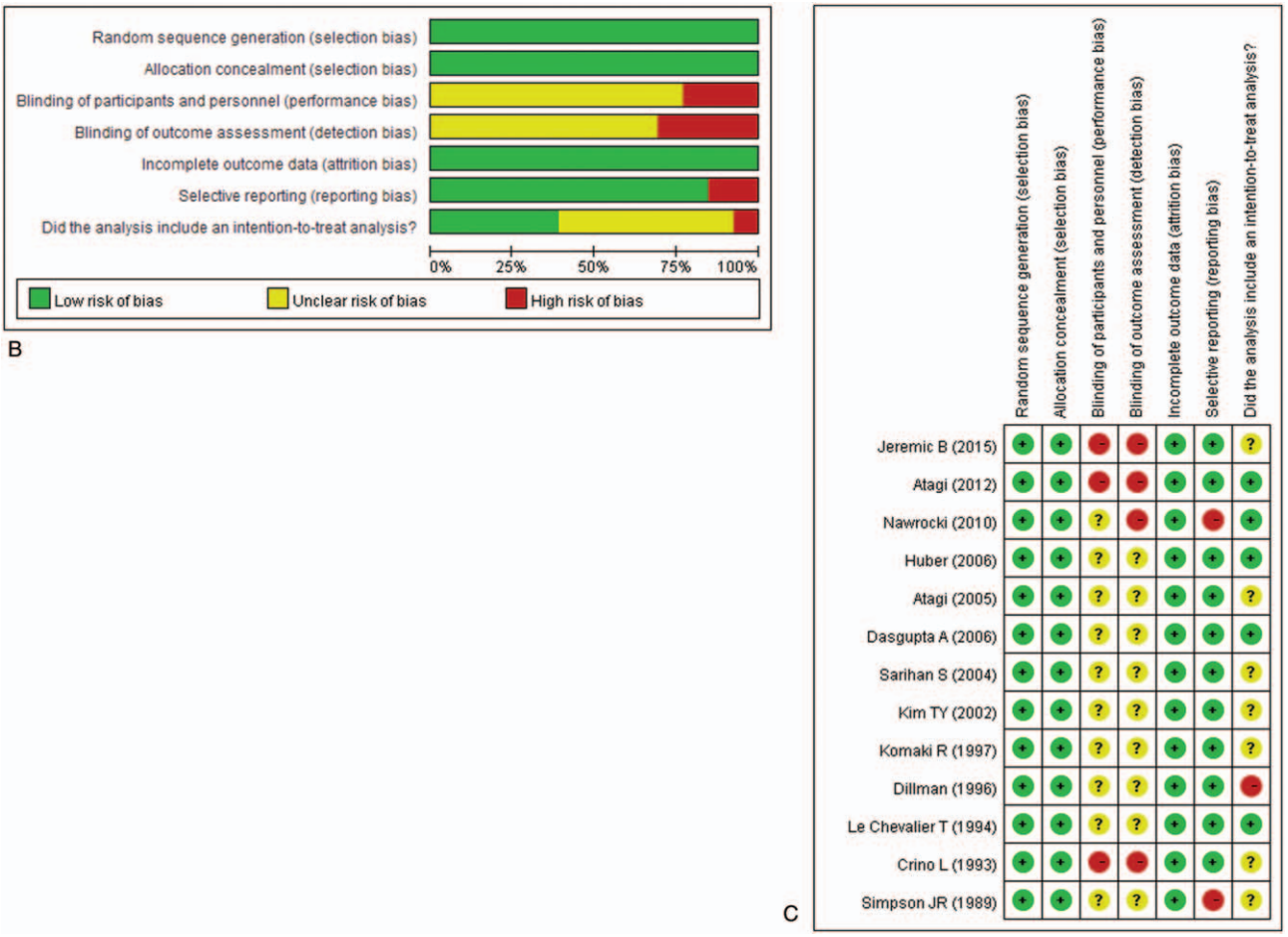


Figure 1. Continued

3.3.2. Progression-free survival. For PFS, 5 studies provided sufficient information for estimating the HRs. A significant heterogeneity was observed among the five studies (Q statistic = 9.597, I^2 = 58.32%) (Fig. 2B); therefore, a random-effects model was used. The overall analysis revealed combined chemo-radiotherapy provided a significant PFS benefit over radiotherapy alone (pooled HR, 0.73; 95% CI, 0.60–0.89; $P = .002$) (Fig. 2B). Furthermore, there were 4 studies with 1-year and three studies with 2-year PFS available. The pooled data also revealed that patients treated with CT+RT combination therapy had a higher PFS at 1 and 2 years after treatment compared to those treated with RT alone (1-year: HR, 0.36; 95% CI, 0.24–0.53; $P < .001$; 2-year: HR, 0.38; 95% CI, 0.23–0.63; $P < .001$) (Supplementary Fig. S1B, http://links.lww.com/MD/D84).

3.3.3. Objective response rate. Eleven studies provided an ORR (complete response plus partial response) and were included in the meta-analysis. A fixed-effect model was used, as no heterogeneity was observed among the studies (Q statistic, 18.09; I^2, 44.73%). The meta-analysis showed that patients treated with combined chemoradiotherapy had a higher ORR than did those treated with radiotherapy alone. However, this difference was not statistically significant (pooled OR, 0.88; 95% CI, 0.72–1.08; $P = .222$) (Fig. 2C).

3.4. Sensitivity analysis

Sensitivity analysis was performed using the leave-one-out approach, in which the analysis was performed repeatedly with each study removed once (Table 3). The direction and magnitude of combined estimates for OS and PFS did not vary markedly with the removal of any one study, indicating that these findings were robust and the data were not overly influenced by any given study. For ORR, removal of Simpson et al[30] resulted in the difference between treatments becoming significant (P, .041); however removal of all other studies resulted in no change in magnitude or direction of the ORR. Overall, the sensitivity analysis indicates that no one study overly influenced the pooled estimates, demonstrating that the findings are robust.

3.5. Overall quality of the meta-analysis findings

According to the GRADE approach, the quality of evidence for this meta-analysis was moderate (GRADE score, 3 points).

4. Discussion

Patients with locally advanced stage III NSCLC tumors are not amenable to surgery, and the best treatment and optimal management of these patients is not clear.[1,2] This meta-analysis

Table 1

Summary of characteristics of selected studies.

				RT alone				RT+CT			
First author (year)	Country	Subtypes of NSCLC (Adenocarcinoma/ Squamous-cell/ Large-cell/ Adenosquamous carcinoma/Others)	Study design	No. of patients	Mean Age (y)	Male (%)	Stage of disease (IIIA/IIIB) (%)	No. of patients	Mean Age (y)	Male (%)	Stage of disease (IIIA/IIIB) (%)
Jeremic B (2015)	Canada	44.6%/43.1%/4.6%/0%/7.7%	RCT	31	59.6	84%	64%/35%	34	60.2	85%	52%/58%
Atagi (2012)	Japan	44.5%/48.7%/1%/1%/5%	RCT	100	77	84%	54%/46%	100	77	80%	51%/49%
Nawrocki (2010)	Poland	14.1%/73.7%/0%/0%/9.1%	RCT	48	66	94%	23%/77%	51	66	90%	31%/69%
Huber (2006)	Germany	19.5%/56.4%/9.2%/0%/3.3%	RCT	113	61	83%	10%/90%	99	62	87%	10%/90%
Atagi (2005)	Japan	37.0%/58.7%/4.3%/0%/0%	RCT	23	77	83%	48%/52%	23	77	70%	52%/48%
Dasgupta A (2006)	India	32.8%/59.7/6%/0%/1.5%	RCT	32	58*	N/A	75%/25%	35	58*	N/A	69%/31%
Sarihan S (2004)	Turkey	17.1%/82.9%/0%/0%/0%	RCT	20	63*	100%	25%/55%	21	55*	95%	19%/57%
Kim TY (2002)	Korea	18%/74.2%/0%/0%/7.9%	RCT	46	59*	91%	35%/65%	43	54*	81%	33%/67%
Komaki R (1997)	USA	38.2%/44.1%/9.9%/0%/10.9%	RCT	152	61	69%	44%/50%	152	60.7	72%	45%/49%
Dillman (1996)	USA	32%/39%/28%/0%/%	RCT	77	60*	75%	100%	78	60*	76%	100%
Le Chevalier T (1994)	France	0%/48.4%/8.2%/NA/NA	RCT	177	59	95%	N/A	176	58	99%	N/A
Crino L (1993)	Italy	25.8%/62.1%/4.5%/0%/7.6%	RCT	33	63*	85%	N/A	33	61*	93%	N/A
Simpson JR (1989)	USA	32.6%/47.3%/20.1%/0%/0%	RCT	123	<60y: 52 60-70y: 64 71-80y: 7	75.6%	N/A	116	<60y: 55 60-70y: 54 71-80y: 7	66.4%	N/A

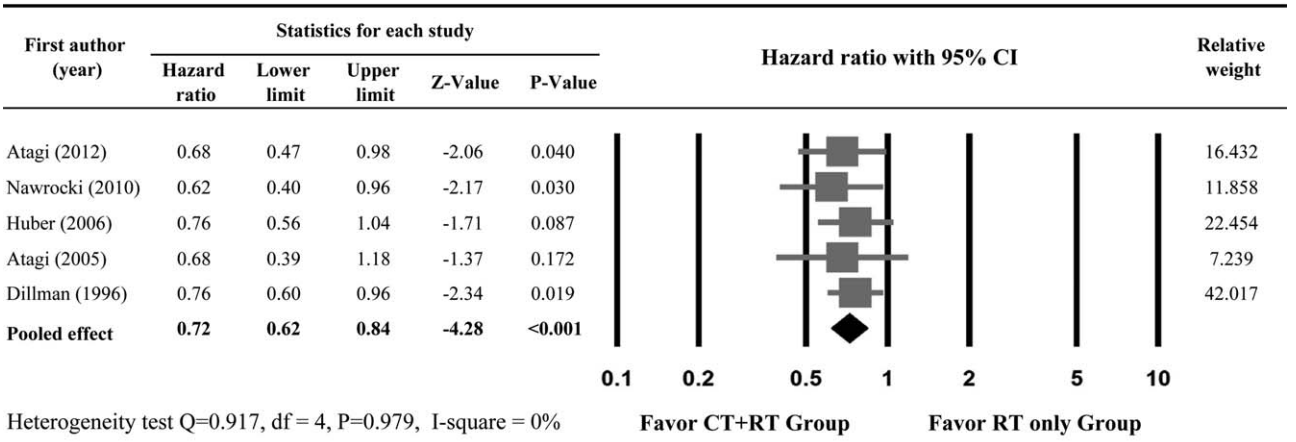
NSCLC = non-small cell lung cancer; RCT = randomized controlled trials; NRCT = non-RCT prospective studies = RT = radiotherapy; CT = chemotherapy.
* Median

Table 2

The protocol of radiotherapy and chemoradiotherapy.

Study name First author (yr)	CT dosage/ intervals	RT dosage/ intervals	Median of follow-up time (months)
Jeremic B (2015)	up to 3 cycles of **platinum**-based CHT	low dose palliative RT (10 Gy in a single fraction or 16 Gy in 2 fractions given with one week split	4.15 yr
Atagi (2012)	30 mg/m^2 (30 min iv) of **carboplatin** 1 h before every RT, for the first 20 fractions	60 Gy in 30 fractions over 6 weeks	19.4
Nawrocki (2010)	2 cycles (**cisplatin** 80 mg/m^2 on day 1, **Navelbine** 25 mg/m^2 on days 1 and 8)	30 Gy/10 fractions	41
Huber (2006)	60 mg/m^2 of **paclitaxel** weekly over 6 weeks, up to 6 hours before RT, starting on day 1 of RT	60 Gy	13.6
Atagi (2005)	30 mg/m^2 (30 min iv) of **carboplatin** 1 h before every RT, for the first 20 fractions	60 Gy in 30 fractions over 6 weeks	NA
Dasgupta A (2006)	**Cisplatin** 80 mg/m^2 on day 1 and **Etoposide** 100 mg/m^2 day 1–3 intravenously q3 weeks for 3 cycles followed by radiotherapy (6000 cGy/30 fractions) and 3 more cycles of Chemotherapy, with the same regimen.	6500 cGy/30 fraction	NA
Sarihan S (2004)	**Paclitaxel** 30 mg/m^2 per week: n=12; 60 mg/m^2 per week: n=9	59.4 Gy (54 – 59.4 Gy)	NA
Kim TY (2002)	Induction of **cisplatin, etoposide, and vinblastine** (PEV) chemotherapy with cisplatin 20 mg/m^2 on days 1 to 5, etoposide 100 mg/m^2 on days 2 to 4, and vinblastine 6 mg/m^2 on day 1, which was repeated every 3 weeks for 3 courses, after which time the patients underwent radiotherapy.	1.8 Gy to 2.0 Gy standard fractions daily 5 times weekly for a total dose of 60Gy to 65 Gy.	NA
Komaki R (1997)	**Cisplatin** 100 mg/m^2 days1 and 29 with **vinblastine** 5mg/m^2 weekly for 5 weeks	60 Gy at 2.0 Gy per day	6 years
Dillman (1996)	**Vinblastine**5 mg/m^2 for 5 week iv on days1,8,15,22,29 and**cisplatin** 100mg/m^2 given monthly iv over a 30-to 60-min period on days1 and 29	60 Gy in 20 fractions over a 4-week period to the original tumor volume/10 fractions over a 2 week period to the boost volume.	84
Le Chevalier T (1994)	3 monthly cycles of VCPC (**vindesine**, 1.5 mg/m^2 on days 1 and 2; **lomustine**50 mg/m^2 on day 2,25 mg/m^2 on day 3; **cisplatin** 100 mg/m^2 on day 2; **cyclophosphamide** 200 mg/m^2 on days 2-4).	65 Gy	61
Crino_ L (1993)	**Cisplatin** 100 mg/m^2 given intravenously over 30 min on day 1 and **etoposide**120 mg/m^{2}given intravenously over 45 min on day 1-2-3.	The daily fractionation was 2000 cGy for a total dose of 5600 to 6000 cGy within 6 weeks	6 years
Simpson JR (1989)	**Misonidazole** 400 mg/m^2 2–4 h prior to RT daily for 5–6 weeks to a maximum dose of 12 g/m^2 or until tumor progression).	50 Gy large field and 10 Gy boost	minimum of 4.0 years or untildeath.

CT = chemotherapy; RT = radiotherapy; iv = intravenous injection; Gy = gray.



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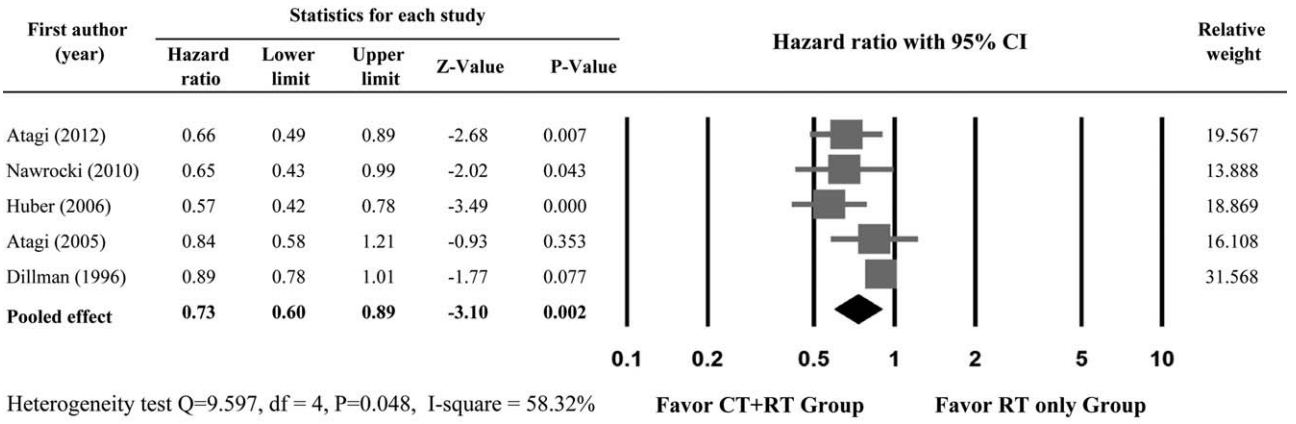

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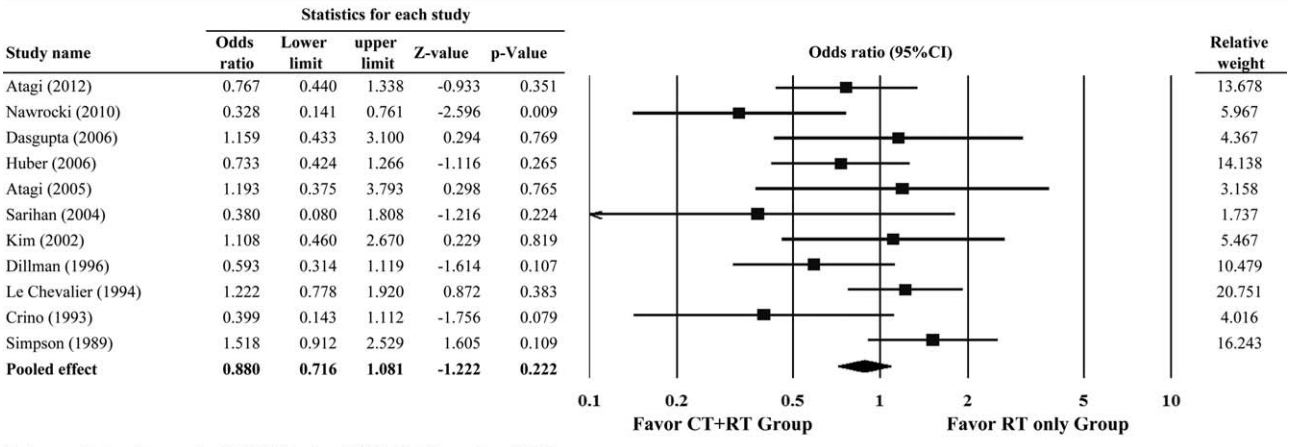

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Figure 2. Results of meta-analysis for (A) overall survival; (B) progression-free survival and (C) objective response rate. CT = chemotherapy, RT = radiotherapy, CI = confidence interval, df = degree of freedom.

compared RT versus concurrent RT+CT in treating patients with stage III NSCLC, and found that RT+CT showed greater benefit for OS, PFS, and ORR (P values $\leq$ .007). Sensitivity analysis indicated the data were robust for OS and PFS, but the study by Simpson et al[30] may have overly influenced the finding for ORR. Our results support the use of CT+RT compared with radiotherapy alone in treating locally advanced stage III NSCLC.

Two prior meta-analyses evaluated the efficacy of radiotherapy alone or combined with chemotherapy in patients with NSCLC.[14,15] Marino et al[14] included 14 trials comprising

Table 3

Sensitivity analysis of included studies.

First author (year)	Statistics with study removed				
Overall survival	**Hazard ratio**	**Lower limit**	**Upper limit**	***Z* value**	***P* value**
Atagi (2012)	0.73	0.62	0.86	−3.76	<.001
Nawrocki (2010)	0.74	0.63	0.86	−3.76	<.001
Huber (2006)	0.71	0.6	0.84	−3.93	<.001
Atagi (2005)	0.73	0.62	0.85	−4.06	<.001
Dillman (1996)	0.7	0.57	0.85	−3.62	<.001
Progression-free survival	**Hazard ratio**	**Lower limit**	**Upper limit**	**Z value**	***P* value**
Atagi (2012)	0.75	0.59	0.94	−2.45	.014
Nawrocki (2010)	0.74	0.59	0.93	−2.59	.01
Huber (2006)	0.79	0.67	0.94	−2.68	.007
Atagi (2005)	0.71	0.55	0.9	−2.81	.005
Dillman (1996)	0.66	0.56	0.79	−4.67	<.001
Objective response rate	**Odds ratio**	**Lower limit**	**Upper limit**	***Z* value**	***P* value**
Atagi (2012)	0.90	0.72	1.12	−0.94	.35
Nawrocki (2010)	0.94	0.76	1.16	−0.61	.54
Dasgupta (2006)	0.87	0.70	1.07	−1.31	.19
Huber (2006)	0.91	0.73	1.13	−0.87	0.39
Atagi (2005)	0.87	0.71	1.07	−1.30	.20
Sarihan (2004)	0.89	0.73	1.10	−1.07	.28
Kim (2002)	0.87	0.70	1.07	−1.31	.19
Dillman (1996)	0.92	0.74	1.14	−0.74	.46
Le Chevalier (1994)	0.81	0.64	1.02	−1.82	.07
Crino (1993)	0.91	0.74	1.12	−0.89	.37
Simpson (1989)	0.79	0.63	0.99	−2.04	.04

1887 patients that assessed radiotherapy and chemoradiotherapy in patients with unresectable stage IIIa and IIIb NSCLC. In contrast to our study, their study also included trials that evaluated sequential use of radiotherapy and chemotherapy. They evaluated survival at one, two, three, and 5 years.[14] Marino et al found that in patients treated with cisplatin-based therapy plus radiation, the estimated pooled OR of death at 1 and 2 years was 0.76 and 0.70 (ORs of <1 show benefit for the combined therapy compared with radiotherapy alone), respectively, and the reduction in mortality was 24% and 30%. For patients who received non-cisplatin-based chemotherapy plus radiation, the pooled OR at 1 year was 1.05 and at 2 years was 0.82, with a reduction in mortality of 5% and 18%, respectively. Marino et al found no significant difference in survival at three and 5 years after receiving radiotherapy alone and combined radiotherapy with chemotherapy. Similar to our results, the findings of Marino et al favor the use chemotherapy (particularly cisplatin-based chemotherapy) plus radiation. We did not evaluate long-term survival. In addition, due to the small number of studies included in our meta-analysis, we were unable to perform subgroup analysis that evaluated the efficacy of different types of chemotherapy (e.g., carboplatin-based vs paclitaxel).

Another meta-analysis evaluated the effectiveness of concurrent chemoradiotherapy with radiotherapy alone in patients with NSCLC by evaluating OS, tumor control, and treatment-related morbidity.[15] Unlike our study, which focused on patients with unresectable stage III NSCLC, the study of O'Rourke et al[16] included RCTs in patients with stage I-III NSCLC undergoing radical radiotherapy and who were randomized to receive radiotherapy alone or chemoradiotherapy administered either concurrently or sequentially. Their study included 19 studies with 2728 patients. Consistent with our results, O'Rourke et al found chemoradiotherapy significantly reduced the overall risk of death (HR, 0.71; 95% CI, 0.64 to 0.88) and showed benefit for PFS (HR, 0.69; 95% CI, 0.58 to 0.81). O'Rourke et al did not evaluate ORR or long-term survival.

O'Rourke et al also found that the incidence of acute esophagitis, neutropenia, and anemia was greater with concurrent chemoradiotherapy compared with radiotherapy alone. Although we did not evaluate the difference in toxicity between radiation therapy and concurrent chemoradiotherapy, the included studies reported that the combination therapy had consistently a higher incidence of certain toxicities, such as grade 3–4 leukocytopenia, neutropenia, anemia, and esophagitis.[12,26–28] The findings of increased toxicity with concurrent chemoradiotherapy highlight the importance of patient selection when considering treatment choice.

One limitation of this study is that the age range of the participants in the included studies is broad (average age, 54–77 years). Elderly patients have more comorbidities and experience more frequent life-threatening toxicity from chemotherapy that can preclude treatment completion. Studies investigating outcomes of chemoradiotherapy for NSCLC in elderly patients report conflicting results. Elderly patients in one such study appeared to gain a survival advantage from combined RT and chemotherapy compared with RT alone.[36] However, the authors noted that, as is the case with younger patients, this benefit came at the cost of additional toxicity. Similarly, Davidoff et al concluded that survival benefits associated with chemoradiotherapy in clinical trials can extend to the elderly, but that gradual strategies are beneficial to reducing mortality risk.[37] In contrast, patients over 70 years of age were identified as a subgroup with significantly lower median survival times after chemoradiotherapy for NSCLC.[38] To further complicate this

debate, data describing outcomes of chemoradiotherapy for NSCLC in the elderly is limited by their under-representation in such studies, likely due to physician biases regarding the tolerability of such treatment in older patients.[39] In light of this uncertainty, the results of our study should be interpreted with caution as they relate to elderly patients.

To our knowledge, only one other meta-analysis, that of Marino et al, which was performed over 10 years ago, has specifically evaluated the benefit of radiotherapy alone compared with chemoradiotherapy in treating patients with unresectable N2 stage III NSCLC. The strength or our study is that it included only RCTs. However, our findings are limited by the small number of studies included. Also, the small sample size and the data reported in the studies precluded us from performing subgroup analyses that evaluated different treatment regimens or histological subtypes of NSCLC.

Our study is also limited by the heterogeneity of treatment regimens used in the studies. However, despite particular heterogeneity in chemotherapy regimens, the heterogeneity of OS, PFS, and ORR was low to moderate. These results suggest that the heterogeneity in chemotherapy regimens did not have a large impact on survival analysis. Further studies are needed to evaluate the effects of different chemotherapy regimens on other outcome measures such as health-related quality of life, an accurate predictor of survival[40] for which data remain scarce for NSCLC.[41]

In summary, the combination of concurrent chemoradiotherapy offers greater benefit with regard to OS, PFS, and ORR than radiation therapy alone in patients with inoperable, locally advanced stage III NSCLC. However, potential toxicities associated with concurrent chemoradiotherapy warrant further investigation and more quality studies.

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