Therapeutic Strategies for Resectable Stage-IIIA N2 Non–Small Cell Lung Cancer Patients: A Network Meta-Analysis

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ABSTRACT

BACKGROUND: The National Comprehensive Cancer Network (NCCN) guidelines did not give an explicit comparison of the efficacy between surgery and radiotherapy in treating Stage-III N2 non–small cell lung cancer (NSCLC) patients, leaving a paucity for clinical reference. Through this study, we try to locate the optimum treatment strategy including surgical type for these patients.

METHODS: A systematic literature search was performed from PubMed, Cochrane Library, Embase, and Google Scholars. The endpoints were overall survival (OS), mean OS, and progression-free survival (PFS). The treatments comprised radiotherapy, lobectomy, and pneumonectomy. Network meta-analysis was carried out for calculating the odds ratio (OR) for binary variants. All the analyses implemented Stata 17.0 MP.

RESULTS: Eight clinical trials reporting 1756 patients met the inclusion criteria. Radiotherapy and surgery were equivalent in improving patients' OS (OR = 0.842, 95% confidence interval [CI]: [0.645, 1.099]). The mean OS of patients were similar in terms of radiotherapy, lobectomy, and pneumonectomy. Besides, radiotherapy and surgery had equivalent effects in improving PFS (OR = 0.896, 95% CI: [0.718, 1.117]).

CONCLUSIONS: Since lobectomy and pneumonectomy following neoadjuvant treatments had equivalent efficacy in prolonging OS for patients with stage-IIIA N2 NSCLC compared with definitive radiotherapy, young patients with favorable performance status (0) should try surgery to pursue better prognosis while elderly patients with unfavorable PS or radiosensitive pathology types should accept definitive radiotherapy. More high-quality clinical trials are needed to support our findings.

KEYWORDS: Locally advanced lung cancer, efficacy, network meta-analysis, lobectomy, prognosis

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Introduction

Stage-III non–small cell lung cancer (NSCLC) is a hardly curable disease often with a poor prognosis, which accounts for 20% to 25% of new diagnoses of NSCLC.[1] Approximately 50 000 patients are diagnosed with stage-III NSCLC in the United States annually.[2]

Despite prominent advances in cancer treatments, the 5-year survival rate of stage-III NSCLC patients remains at 18%, which is dismal, yet.[3,4] One reason contributing to the poor cure rate in stage-III NSCLC is the poor local control caused by heterogeneity among patients rather than definitive radiotherapy.[5,6]

Owing to the disparity in the size and localization of the primary tumor and metastasis to the distant lymph node, patients are recommended to receive personalized treatment strategies according to National Comprehensive Cancer Network (NCCN) guidelines.[7,8] Stage-IIIA N2 NSCLCs include T1N2M0 NSCLCs and T2N2M0 NSCLCs according to the tumor node metastasis (TNM) staging system. Currently, patients newly diagnosed with stage-IIIA N2 NSCLC mainly start with two different treatments: definitive chemoradiotherapy or neoadjuvant chemotherapy with or without radiotherapy preceding surgery.[9,10]

However, which treatment strategy is superior in the long run remains opaque, nor is the preponderance of different surgery types. Therefore, by network meta-analysis and conventional meta-analysis, we tried to explore the optimum treatment for Stage-IIIA N2 NSCLC patients and generated evidence for clinicians.

Methods

Searching strategy

We initiated our study by searching medical databases including PubMed, Embase, Cochrane Library, and Google Scholar with the following mesh terms and free words: ("Non-Small-Cell

Lung Carcinoma" OR "Non-Small Cell Lung Cancer") AND ("surgery" OR "lobectomy" OR "bronchopulmonary segments" OR "resection" OR "pneumonectomy") AND ("radiotherapy" OR "neoadjuvant radiotherapy" OR "Concurrent Radiotherapy" OR "radical radiotherapy") AND ("versus" OR "vs" OR "compared with") AND (N2) AND (Stage-IIIA). This meta-analysis was guided by the PRISMA guideline (Preferred Reporting Items for Systematic Reviews and Meta-analysis). The last search was done on November 15, 2021.

Inclusion criteria

1. Clinical trials or randomized controlled trials comparing surgery with radiotherapy after neoadjuvant chemotherapy or chemoradiotherapy in Stage-IIIA N2 NSCLC patients were retrieved.
2. Initial staging procedures of all patients should include CT or fiber bronchoscopy.
3. The neoadjuvant chemotherapy should be platinum-based chemotherapy, while the dose of induction radiation should be around 45 Gy.

Exclusion criteria

1. Potentially unresectable patients were included.
2. Performance status (PS) of included patients was not assessed.
3. Studies had no direct comparison of the surgery group and the radiotherapy group.
4. Cohorts with Newcastle-Ottawa scale (NOS) score less than 5 or random controlled trials (RCTs) are defined as high risk by the Cochrane risk of bias tool (Cochrane ROB).

Data extraction and quality assessment

Two independent investigators (ZYS and YL) searched studies and assessed the quality utilizing the NOS score for cohort studies or the Cochrane ROB tool for RCTs. Author name, year of publication, study region, the gender distribution of participants, sample sizes, median and range of age, hazard ratio (HR) for the association between two treatments (surgery and radiotherapy), and overall survival (OS) along with progression-free survival (PFS), median and range of OS months plus the number of patients for three treatment subtypes (radiotherapy, lobectomy, and pneumonectomy) were collected. Cohorts with NOS scores higher than 5 or RCTs defined as low risk of bias using the Cochrane ROB tool were considered high quality. Any discrepancy was arbitrated by the senior reviewer (JFF).

Endpoints

The primary endpoint was OS and mean OS for different treatments.

The secondary endpoint was PFS for different treatments.

Statistical analysis

The odds ratio (OR) and 95% CIs (confidence intervals) were generated as effect sizes for binary variants. Conventional meta-analysis was performed for analyzing both OS and PFS from direct comparisons between surgery and radiotherapy with statistical heterogeneity set as $I^2 > 50\%$ and $P < 0.01$ for the random-effect model, otherwise, the fixed-effect model would be utilized. Network meta-analyses were executed according to the frequentist framework in Stata software version 17.0 by the random-effects model to compare the mean OS among radiotherapy, lobectomy, and pneumonectomy, which were presented as network forest (shown as OR and 95% CI) to show the pairwise comparison. To enhance the stability of the results, the assessment of both gross and loops inconsistency between direct and indirect comparison was performed. A network funnel plot was performed to detect the small sample effect. $P < .05$ was considered to be statistically significant.

Results

Study characteristics

We retrieved a total of 666 articles through initial search strategies. After scrupulous inspection of the articles, a total of 8 cohorts reporting 1756 participants were included.[11-18] The process of study selection was presented in the flow diagram (Figure 1). Newcastle-Ottawa scale score of cohorts and Cochrane ROB tool for RCTs suggested all studies enrolled are of high quality (Supplement Figure 1 and Supplement Table 1). Two studies were conducted in America, another two studies were conducted in German, and the rest four studies were conducted in Canada, Belgium, Netherland, and Spain, respectively. The median age of patients ranged from 52 to 71 years. The proportion of male patients exceeded 50% in each arm of all studies except one. All the participants in eight studies were White clinically and radiologically diagnosed with Stage-III N2 NSCLC. All patients from each arm of the eight studies received neoadjuvant chemotherapy which was platinum-based or chemoradiotherapy before randomization. Most studies applied platinum-based doublets as chemotherapy. Cisplatin was used in three studies conducted by Shepherd et al,[16] Albain et al,[18] and Eberhardt et al,[13] respectively. The type of platinum agent used was not mentioned in the rest studies. Postoperative radiotherapy for a total dose of 45 Gy was given to patients along with chemotherapy only in Albain et al's[18] study and Couñago et al's[12] study. Only patients defined as partial response, complete response, or stable disease after neoadjuvant treatment received further treatments. The main characteristics of the included studies were shown in Table 1.

Radiotherapy, surgery, and the primary endpoint in Stage-IIIA N2 NSCLC

Seven out of eight studies including 1674 patients presented information about chemotherapy, radiotherapy, and surgery

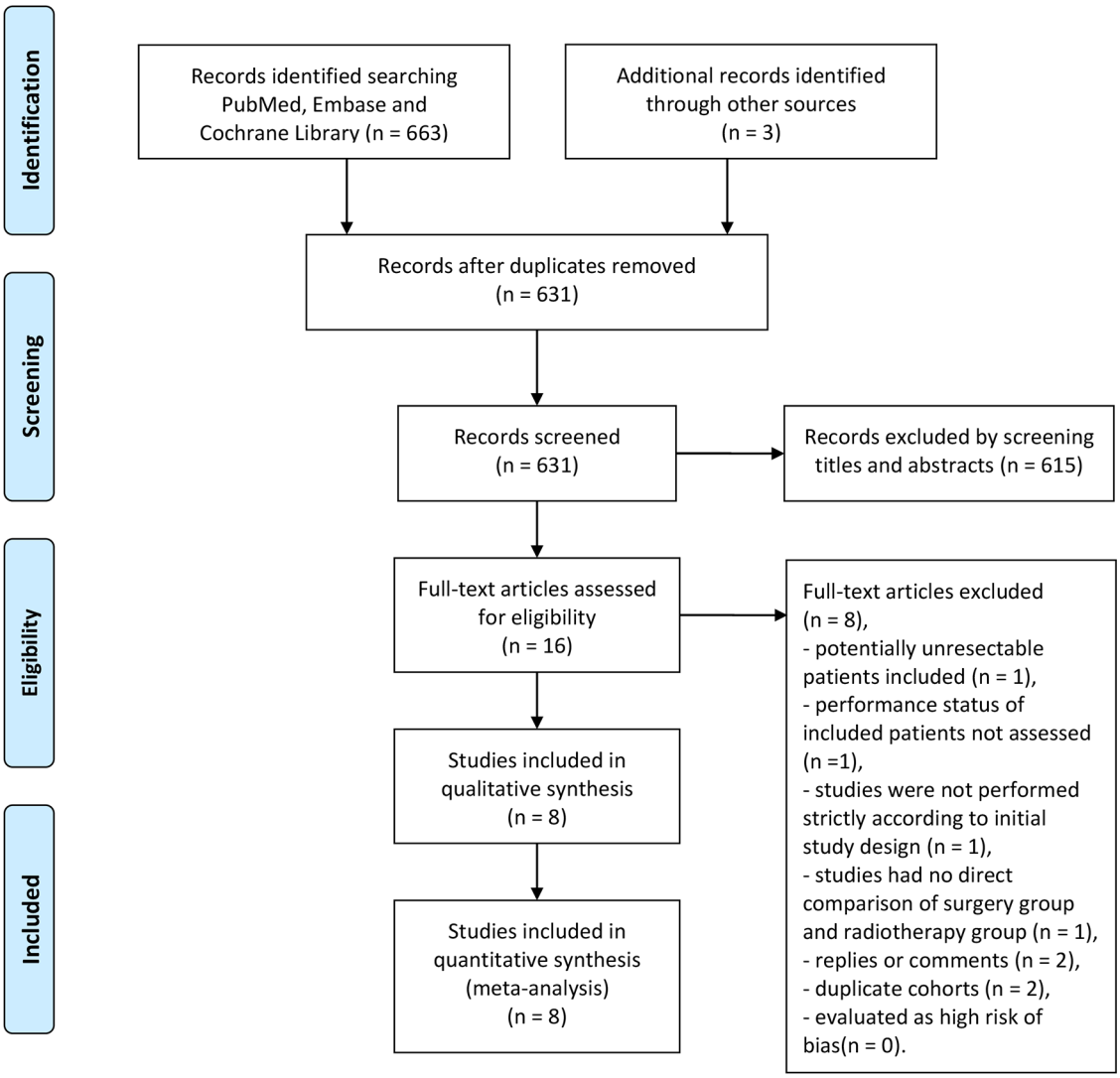

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study search and selection for the Meta-analysis (adapted from *Moher et al*).

performed on Stage-IIIA N2 NSCLC patients. Hazard ratio for OS was used as the primary endpoint in these 7 studies. Three of 8 studies reporting 473 patients presented data of radiotherapy, lobectomy, pneumonectomy, and mean OS in NSCLC patients. All 3 studies compared lobectomy with pneumonectomy;[12,14,17] two of 3 studies compared radiotherapy with lobectomy;[12,17] two of 3 studies compared radiotherapy with pneumonectomy.[12,17] Most patients received radiotherapy (n = 243), followed by lobectomy (n = 129) and pneumonectomy (n = 101). For the primary endpoint, compared with radiotherapy, surgery reached equivalent OS with pooled OR of 0.842 (95% CI: [0.645, 1.099], $P = .205$; Figure 2). Compared with radiotherapy, lobectomy and pneumonectomy had no statistical difference in prolonging mean OS while treating Stage-IIIA N2 NSCLC patients. The network map and the network forest plot are shown in Figures 3 and 4.

Radiotherapy, surgery, and the secondary endpoint in Stage-IIIA N2 NSCLC

Three of 8 studies reporting 661 patients presented data of radiotherapy, surgery, and PFS in Stage-IIIA N2 NSCLC patients. Compared with radiotherapy, surgery reached similar PFS with pooled OR of 0.896 (95% CI: [0.718, 1.117], $P = .327$; Figure 5).

Consistency and inconsistency

Inconsistency did not exist in either gross analysis or loops analysis.

Small sample effect

The network funnel plot shows no small sample effect in any study of any endpoint.

Table 1. Main characteristic of all the studies included in conventional meta-analysis and network meta-analysis.

STUDY COHORT	STUDY REGION	FOLLOW-UP (MONTHS) (MEDIAN AND RANGE)	NUMBER OF PATIENTS		AGE (YEARS)		ENDPOINTS		NOS SCORE
			ARM CTS/CRTS	ARM CT/CRT	ARM CTS/CRTS	ARM CT/CRT	ALL PATIENTS	SURGERY SUBTYPES	
Shepherd et al[16]	Canada	NR	16 (12/4)	15 (10/5)	61 (49-70)	52 (44-72)	OS	NR	8
van Meerbeeck et al[17]	Belgium	NR	167 (119/48)	165 (127/38)	61 (29-78)	62 (33-76)	OS/PFS	OS	8
Albain et al[18]	America	22.5 (0.9-125.1)	202 (131/71)	194 (121/73)	59 (31-77)	61 (32-78)	OS/PFS	NR	9
Kappers et al[14]	Netherland	54 (13-129)	38 (21/17)	44	NR	NR	NR	OS	9
Aggarwal et al[11]	America	NR	146 (63/83)	103 (64/39)	61	64	OS	NR	8
Eberhardt et al[13]	German	78	81 (56/25)	80 (53/27)	58 (33-72)	59(42-74)	OS/PFS	NR	8
Koryllos et al[15]	German	NR	156 (103/53)	102 (76/26)	71 (40-81)	69(39-78)	OS	NR	7
Couñago et al[12]	Spain	33.4 (2-134)	118 (94/24)	129 (113/16)	62 (41-48)	65 (37-82)	OS	OS	9

Abbreviations: CT/CRT, chemotherapy/chemoradiotherapy; CTS/CRTS, chemotherapy and surgery/chemoradiotherapy and surgery; NOS, Newcastle–Ottawa Scale score; NR, not reported; OS, overall survival; PFS, progression-free survival.

Discussion

To the best of our knowledge, this is the first network meta-analysis comparing the efficacy of radiotherapy, lobectomy, and pneumonectomy in Stage-IIIA N2 NSCLC patients in terms of OS, mean OS, and PFS, which is of great importance to provide novel evidence to the potentially amended recommendation by NCCN guideline.

An early meta-analysis published in 2015 had already investigated the efficacy of surgery compared with radiotherapy in terms of OS, and PFS in Stage-IIIA N2 NSCLC patients.[19] However, it only included 3 random controlled trials.[17,18,20] We made an update to the conventional meta-analysis on the efficacy of surgery, and radiotherapy concerning OS in Stage-IIIA N2 NSCLC patients, which incorporated more high-quality clinical trials, especially three new studies published after 2015. With these studies included, the changes in current lung cancer treatments and expanded sample size made our analysis much closer to the reality and more precise data compared with the previous one. According to our results, compared to radical radiotherapy, neoadjuvant chemotherapy or chemoradiotherapy followed by surgery showed no superior OS in Stage-IIIA N2 NSCLC patients.

In addition, we performed the first network meta-analysis investigating the mean OS of patients respectively accepted radiotherapy, lobectomy, and pneumonectomy. However, despite lobectomy displaying superiority over pneumonectomy in included studies,[12,14,17] our network meta-analysis disclosed that radiotherapy, lobectomy, and pneumonectomy have no statistical difference in prolonging mean OS of Stage-IIIA N2 NSCLC patients after neoadjuvant treatment.

Besides, the conventional meta-analysis of these two independent treatments showed that surgery has no statistical difference in improving PFS of Stage-IIIA N2 NSCLC patients compared to radiotherapy. The outcomes of the conventional meta-analysis were consistent with those of the previous study of Ren et al.[19]

According to the latest NCCN guidelines, the recommended treatment for Stage-IIIA N2 NSCLC is radical concurrent chemoradiotherapy followed by durvalumab or neoadjuvant chemotherapy with or without radiotherapy followed by surgery. The guideline did not point out which treatment was premium and left it to clinicians' own decision.

Our results disclosed that neither surgery as a whole compared to radiotherapy, nor surgery subtypes compared to radiotherapy had a statistical difference in improving patients' OS. This is significant because our study gives clinicians more freedom in choosing appropriate treatments for Stage-IIIA N2 NSCLC patients. Considering humanistic care for Stage-IIIA N2 NSCLC patients, our study could help them prioritize radiotherapy.

The reason why surgery failed to improve prognosis compared with radiotherapy in patients with Stage-IIIA N2 NSCLC after response to neoadjuvant chemotherapy probably

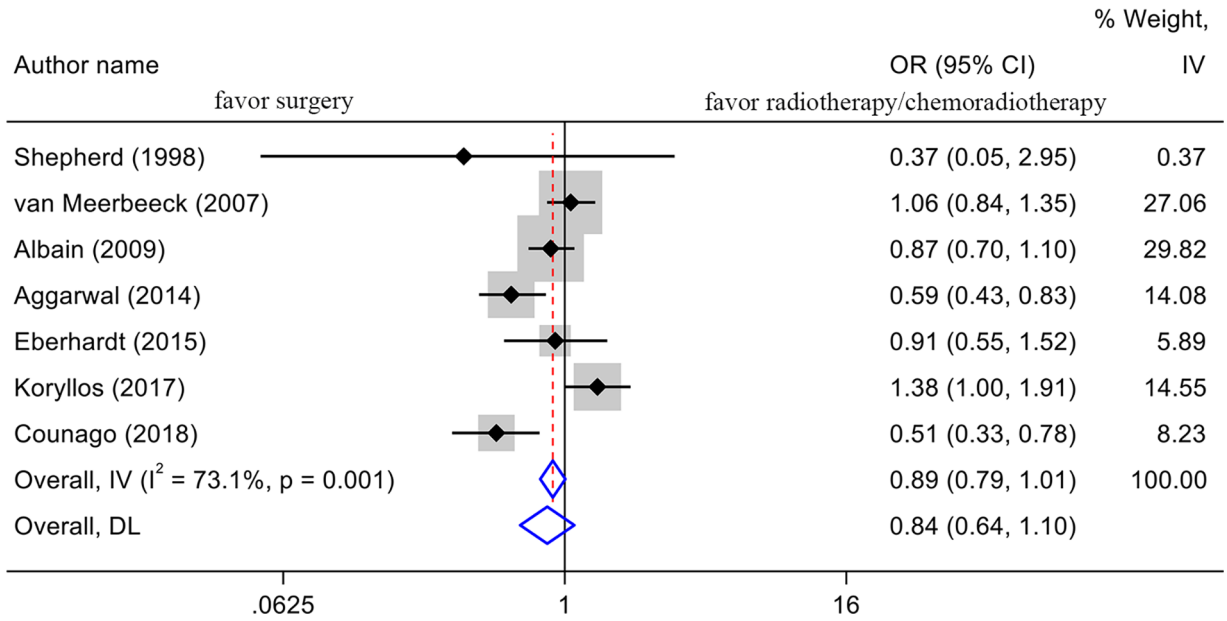

Figure 2. Forest plot of OR for the association between OS and two different treatments (surgery versus radiotherapy/chemoradiotherapy).
OR indicates odds ratio; OS, overall survival.

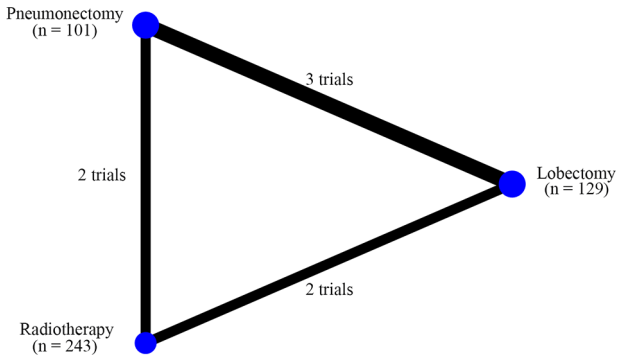

Figure 3. Network comparison of mean OS after three different types of treatments.
OS indicates overall survival.

lies in that the mortality rate within the following 3 months after surgery is much higher than that of radiotherapy.[21-23] Mortality that occurred within 90 days after treatment is presumably predominantly caused by the tumor's biological behavior or the effect of radiotherapy but owing to pulmonary complications when it comes to surgery.[24] According to the study by Kim et al,[24] pulmonary complications account for half of the perioperative deaths and 40% of 90-day mortality. As the main cause of death in pulmonary complications, bronchopleural fistula needs concern from clinicians ceaselessly.[25]

While surgery after neoadjuvant chemotherapy has modest overall mortality, right (morphological right) pneumonectomy is considered to be highly associated with an increased risk of mortality.[26] Considering the high mortality of right pneumonectomy, especially among the elderly, benefits come from it diminished.[27] Thus, the clinicians should be cautious while turning to surgery for Stage-IIIA N2 NSCLC patients, especially right pneumonectomy.

Since patients from the surgery group paused to accept the additional preoperative examination,[28] their treatment may be noncontinuous, which may reduce the curative effect of comprehensive treatment. The indications of surgery in Stage-IIIA N2 NSCLC remain vague, more randomized clinical trials with a large sample size and specified for Stage-IIIA N2 NSCLC patients are needed to further evaluate the pros and cons of various surgery subtypes.

With the advances in clinics and more consensuses gradually reached among clinicians, we hope more high-quality clinical trials which are unified in operation mode and neoadjuvant chemotherapy regimen will be conducted to discover the best treatment strategy for Stage-IIIA N2 NSCLC patients. We will make new updates to our studies at the time. Recently, the immunotherapy represented by utilizing immune checkpoint inhibitors is being tried as a neoadjuvant treatment and has reached remarkable preliminary outcomes. We plan to compare neoadjuvant immunotherapy followed by surgery with traditional neoadjuvant treatments followed by surgery when the relative studies published are sufficient in the near future.

Limitations

First, the major limitation of our research is the relatively small quantity of included studies; therefore, we did not evaluate the potential publication bias.

Second, given the limited included trials, we could not perform subgroup analysis according to the age or the pathologic types, resulting in potential bias.

Third, the form of the present research is an analysis based on literature, which may lead to the marginal significance of publication bias in HR for OS or PFS.

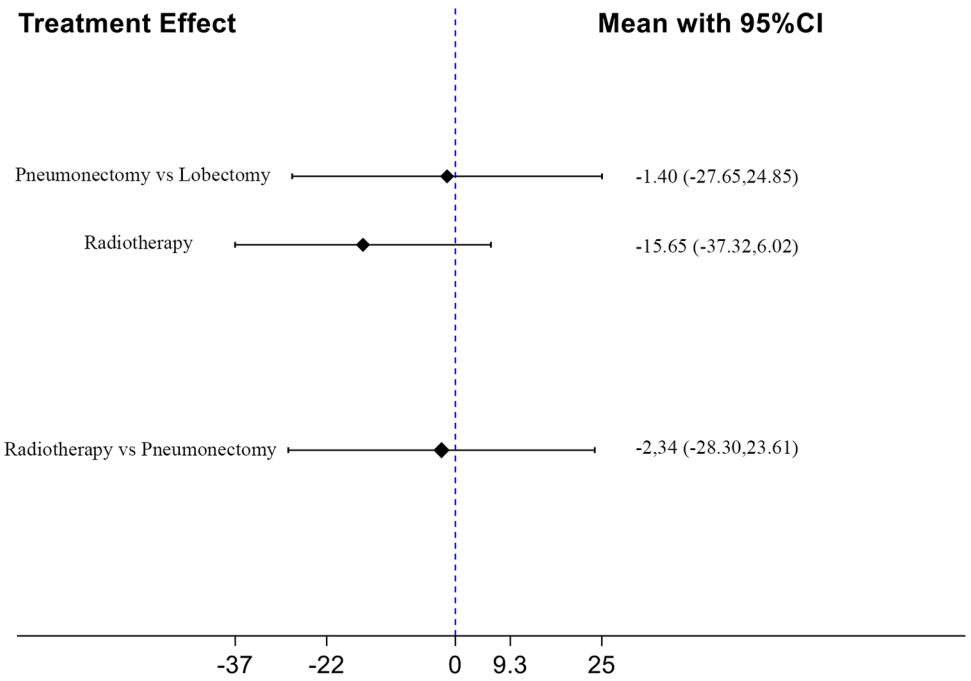

Figure 4. Forest plot of each comparison on mean OS in the network meta-analysis.
OS indicates overall survival.

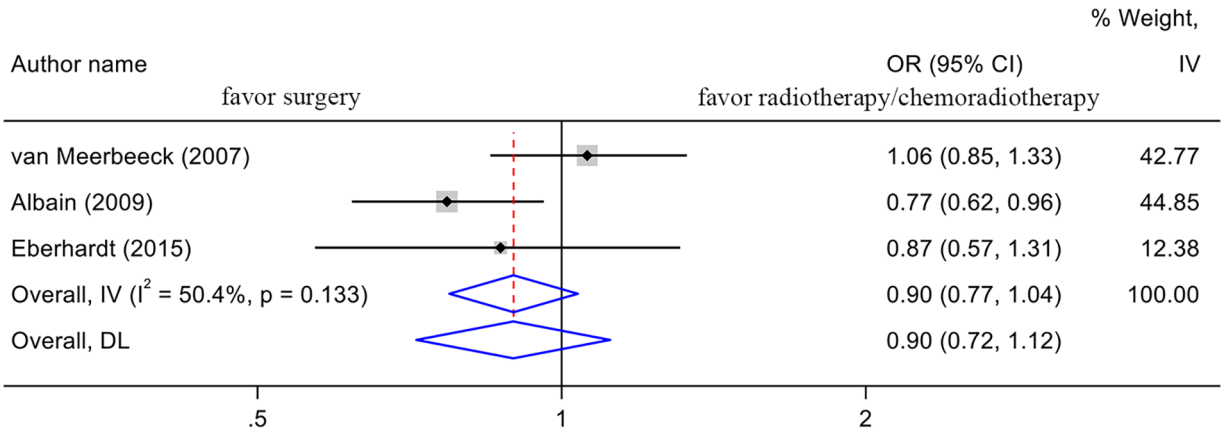

Figure 5. Forest plot of OR for the association between PFS and two different treatments (surgery versus radiotherapy/chemoradiotheraphy).
OR indicates odds ratio; PFS, progression-free survival.

Fourth, we did not include any studies from Asia due to the low quality of studies screened, which could result in potential bias.

Fifth, the first-line chemotherapy and radiotherapy for Stage-IIIA N2 NSCLC patients keep updating over the years. Considering the treatments in studies done at different times differed from each other, the potential of bias could not be excluded.

Conclusion

In summary, radical concurrent chemoradiotherapy is comparable to neoadjuvant chemoradiotherapy plus surgery in improving Stage-IIIA N2 NSCLC patients' OS or PFS. Radiotherapy, lobectomy, and pneumonectomy had similar efficacy in prolonging Stage-IIIA N2 NSCLC patients' mean OS. We suggest that clinicians give young patients with favorable PS (PS = 0) lobectomy or pneumonectomy following neoadjuvant chemotherapy, and recommend elderly patients with less favorable PS (PS ranks from 1 to 2) to accept definitive radiotherapy. More high-quality clinical trials are needed to support our findings.

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Author Contributions

ZS, YL, and SF gathered and analyzed the data and wrote the article; ZS, YL, and YS performed the quality evaluation and analyzed the data. JZ checked all the statistical methods used

and helped polish the language. JF conceived and designed this study. All authors contributed to revising the manuscript. All authors reviewed the article. All authors read and approved the final manuscript.

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Supplemental Material

Supplemental material for this article is available online.

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