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SYSTEMATIC REVIEW AND META-ANALYSIS

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Is There a Survival Benefit in Patients With Stage IIIA (N2) Non-small Cell Lung Cancer Receiving Neoadjuvant Chemotherapy and/or Radiotherapy Prior to Surgical Resection

A Systematic Review and Meta-analysis

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Abstract: Optimal management of clinical stage IIIA (N2) non-small cell lung cancer (NSCLC) is controversial. This study is a systematic review and meta-analysis of published randomized control trials of multimodality management strategies for NSCLC.

We conducted a comprehensive literature search of the Pubmed, Embase, Medline, and CENTRAL databases for relevant studies comparing patients with stage IIIA (N2) NSCLC undergoing surgery alone, chemotherapy and/or radiotherapy alone, or surgical resection after neoadjuvant treatment with chemotherapy and/or radiotherapy. We estimated hazard ratios, odds ratios (ORs), and 95% confidence intervals (CIs) for survival data.

Seven trials involving 1049 patients were included in this study. There was no significant difference in overall survival (OS) or progression-free survival (PFS) in stage IIIA (N2) NSCLC patients who received neoadjuvant chemotherapy or chemoradiotherapy prior to surgical resection compared to those who received neoadjuvant chemotherapy or chemoradiotherapy prior to radical radiotherapy. There was a significant increase in pathological complete remission in the mediastinal lymph nodes in stage IIIA (N2) NSCLC patients who received neoadjuvant chemoradiotherapy prior to surgical resection compared to those who received neoadjuvant chemotherapy (OR 3.61; 95% CI 1.07–12.15; $P = 0.04$), but no difference in tumor downstaging, OS, or PFS.

Neoadjuvant chemotherapy and/or radiotherapy prior to surgical resection do not appear to be clinically superior to neoadjuvant chemotherapy and/or radiotherapy prior to definitive radiotherapy in IIIA (N2) NSCLC patients. Neoadjuvant chemoradiotherapy does not improve survival compared to neoadjuvant chemotherapy alone.

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Abbreviations: CALGB = Cancer and Leukemia Group B, CENTRAL = Cochrane Central Register of Controlled Trials, CIs = confidence intervals, DFS = disease-free survival, EFS = dvent-free survival, HRs = hazard ratios, NCCN = National Comprehensive Cancer Network, NSCLC = non-small cell lung cancer, ORs = odds ratios, OS = overall survival, pCR = pathological complete response, PET = positron-emission tomography, PFS = progression-free survival, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trials, SEER = Surveillance, Epidemiology, and End Results.

INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancer cases.[1] The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program estimated the incidence of NSCLC in 2011 in the SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta) was 45.29 per 100,000 population, and the 2004 to 2010 5-year relative survival was 21.7%.[2] Approximately 30% of patients who are newly diagnosed with NSCLC are classified as N2 stage IIIA on the basis of metastasis to the mediastinal lymph nodes. For such patients, outcomes following surgical resection alone are poor, and chemotherapy and radiotherapy have limited effects.[3–5] Although it is generally accepted that surgery is more effective for IIIA (N2) NSCLC removal than radiotherapy, the 5-year survival rate of surgical patients varies greatly, and the surgical approach is associated with substantial morbidity and mortality. Therefore, the most effective treatment strategy for patients with IIIA (N2) NSCLC remains controversial. There is some consensus about the indication for multimodality therapy in most patients with locally advanced NSCLC; however, there is no clear agreement about which therapy should be applied to patients with N2 disease.

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Y-PX carried out the studies and data analyses and drafted the manuscript. BL carried out the samples analyses. X-LX participated in the design of the study and performed the statistical analysis. W-MM conceived the study, and participated in its design and coordination and helped draft the manuscript. All authors read and approved the final manuscript.
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Previous reports have demonstrated that neoadjuvant chemotherapy and/or radiotherapy followed by surgical resection provides better progression-free survival (PFS) than definitive chemoradiotherapy for patients with stage IIIA (N2) NSCLC.[6,7]

Neoadjuvant chemotherapy followed by surgery improves absolute survival at 5 years by 5% in all NSCLC patients including those classified as stage III.[8] However, publications describing the role of chemoradiotherapy as a neoadjuvant treatment are limited, and benefits of induction chemoradiotherapy have not been demonstrated.[9] A randomized phase III trial showed that the addition of neoadjuvant radiotherapy to chemotherapy did not improve event-free survival (EFS) or overall survival (OS), nor did it reduce the local failure rate in patients with IIIA (N2) NSCLC.[10] Therefore, the value of neoadjuvant chemoradiotherapy for NSCLC patients remains to be elucidated.

To the best of our knowledge, there are no recently published systematic reviews investigating survival benefit in patients with stage IIIA (N2) NSCLC receiving neoadjuvant chemotherapy and/or radiotherapy prior to surgical resection. The objectives of this systematic review and meta-analysis were to determine the survival benefit of multimodality therapy including surgery to stage IIIA (N2) NSCLC patients and to determine if neoadjuvant chemoradiotherapy is superior to neoadjuvant chemotherapy in stage IIIA (N2) NSCLC patients.

METHODS

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Zhejiang Cancer Hospital, China.

Study Selection

Two review authors independently searched the PubMed, Embase, Medline, and Cochrane Central Register of Controlled Trials (CENTRAL) databases using the following key words: non-small cell lung cancer AND neoadjuvant therapy AND N2. Additional information was retrieved through a manual search of the reference lists from relevant articles. The search results were collated in a spreadsheet, and the titles and abstracts of potentially relevant studies were screened to select eligible studies. The full texts of potentially eligible studies were retrieved and examined to determine which studies met the inclusion criteria.

Inclusion criteria were randomized controlled trials (RCTs); trials comparing the efficacy of neoadjuvant therapy prior to surgical resection versus. neoadjuvant therapy prior to radical radiotherapy, or neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy alone; patients with pathologically confirmed stage IIIA (N2) NSCLC; trials that included survival data as endpoints; and full-text articles published in English.

Exclusion criteria were nonrandomized controlled trials; patients with stage IIIA (N2) NSCLC confirmed only by imaging; trials that did not include survival data as endpoints; and trials that were only published as an abstract.

Disagreement about study selection was resolved by discussion and consensus with another author.

Data Extraction

Two review authors independently extracted information from eligible studies. Data included title, source, publication year, authors, numbers of patients, interventions, and outcomes. Primary outcome measures were hazard ratios (HRs) and 95% confidence intervals (CIs) for OS, PFS/disease-free survival (DFS), pathological complete response (pCR) in the mediastinal lymph nodes, and tumor downstaging. Secondary outcome measures were adverse events. Disagreement about data extraction was resolved by discussion and consensus with another author.

Risk of Bias in Individual Studies

Risk of bias in individual studies was assessed independently by 2 authors. Characteristics assessed by the 2 authors included concealment of randomization sequence and proportion of patients lost to follow-up.

Statistical Analysis

Statistical analyses were performed using Review Manager v5 software (RevMan, The Cochrane Collaboration). HRs and 95% CIs for survival data were calculated and verified as previously described.[11] A P value <0.05 was considered statistically significant. Heterogeneity was evaluated with the χ^2-based Q test. For outcome data with evidence of low heterogeneity ($P < 0.10$), a fixed-effect model was used; for outcome data with evidence of significant heterogeneity ($P > 0.10$), a random-effects model was selected. Sensitivity analysis was conducted to confirm whether the results were robust and reliable.

RESULTS

Search Strategy

The searches identified 985 articles, and 48 studies were considered potentially eligible for inclusion. After analyzing the full text articles, 41 studies were excluded, and 7 were found eligible for inclusion according to our criteria for considering studies in this review[7,12–17] (Figure 1). The characteristics of all 7 included trials are shown in Table 1.

Neoadjuvant Therapy Prior to Surgical Resection Versus Neoadjuvant Therapy Prior to Radical Radiotherapy

Characteristics of Included Studies

The searches identified 4 RCTs of neoadjuvant chemotherapy or chemoradiotherapy prior to surgical resection (n = 414) versus neoadjuvant chemotherapy or chemoradiotherapy prior to radical radiotherapy (n = 406) in NSCLC patients.[12–15] Of these, 2 were large RCTs (INT 0139 [n = 396][12] and EORTC 08941 [n = 332][14]) and 2 were small RCTs (n = 61[13]; n = 31[15]). The trials were published between 1998 and 2009. One was conducted at multiple academic and community hospitals in the USA and Canada,[12] 1 was conducted in the Netherlands,[14] and 2 were conducted in North America.[13,15] In 1 trial (INT 0139), patients received chemoradiotherapy before being randomly assigned to a surgery or radiotherapy group, while in the other 3 trials patients received induction chemotherapy. All patients had T1, T2, or T3 primary NSCLC tumors and pathological proof of N2 involvement based on endobronchial ultrasound-guided procedures, mediastinoscopy, or thoracoscopic procedures. The 2 large trials reported HRs and 95% CIs for PFS and OS. The 2 small trials reported HRs and 95% CIs for OS. The minimum follow-up in the 4 trials ranged from 30 to 48 months.

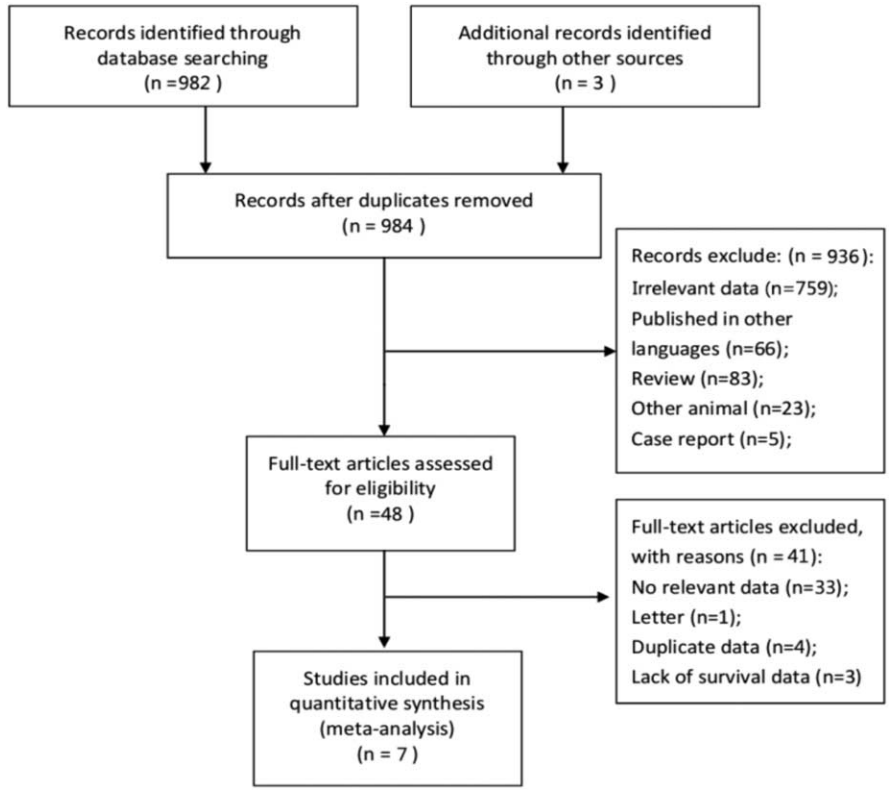

FIGURE 1. Flow chart of article screening and selection process. On the basis of the search strategy, 982 articles were identified by the initial search of the medical literature databases, and 48 required further assessment. Finally, 7 articles were included in this review.

Primary Outcome Measures

Data reporting OS are described in 4 trials (n = 820).[12–15] The meta-analysis revealed no significant difference in OS in stage IIIA (N2) NSCLC patients who received neoadjuvant chemotherapy or chemoradiotherapy prior to surgical resection compared to those who received neoadjuvant chemotherapy or chemoradiotherapy prior to radical radiotherapy (HR 0.95; 95% CI 0.81–1.10; $P = 0.49$; Figure 2). There was no evidence of significant heterogeneity between trials ($\chi^2 = 2.20$, $P = 0.53$, $I^2 = 0.0\%$).

Data reporting PFS are described in 2 trials (n = 728).[12,14] The meta-analysis revealed no significant difference in PFS in

TABLE 1. Trial Characteristics

First Author	Accrual Years	Group	Treatment	Number of Patients	Median OS	3-y OS	*P*	Median DFS/PFS	3y-DFS/PFS	*P*
Albain et al[12]	1994–2001	S	Neo-ChRT + S	202	23.6	37.9	0.24	12.8	27.3	0.017
		ChRT	ChRT alone	194	22.2	33.9		10.5	17.3	
Johnstone et al[13]	1990–1994	S	Neo-ChT + S	29	19.4	33	0.46	-	-	-
		ChRT	ChT + RT	32	17.4	22		-	-	
Van Meerbeeck et al[14]	1994–2002	S	Neo-ChT + S	167	16.4	24.9	0.596	9	17.2	0.605
		ChRT	ChT + RT	165	17.5	27.8		11.3	15.8	
Shepherd et al[15]	––	S	Neo-ChT + S	16	18.7	-	>0.05	-	-	-
		RT	RT alone	15	16.2	-		-	-	
Katakami et al[16]	2000–2006	ChRT	Neo-ChRT + S	29	39.6	51.7	0.397	12.4	34.5	0.187
		ChT	Neo-ChT + S	29	29.9	39.3		9.7	17.9	
Thomas et al[7]	1995–2003	ChRT	Neo-ChRT + S	55	19	31	0.21	9	-	0.69
		ChT	Neo-ChT + S	70	17	18		10	-	
Girard et al[17]	2003–2007	ChRT	Neo-ChRT + S	32	-	51.8	-	17.2	25	-
		ChT	Neo-ChT + S	14	24.2	25.4		12.5	38.5	

ChRT = chemoradiotherapy, ChT = chemotherapy, DFS = disease free survival, neo-ChRT = neoadjuvant chemoradiotherapy, neo-ChT = neoadjuvant chemotherapy, OS = overall survival, PFS = progression free survival, S = surgery.

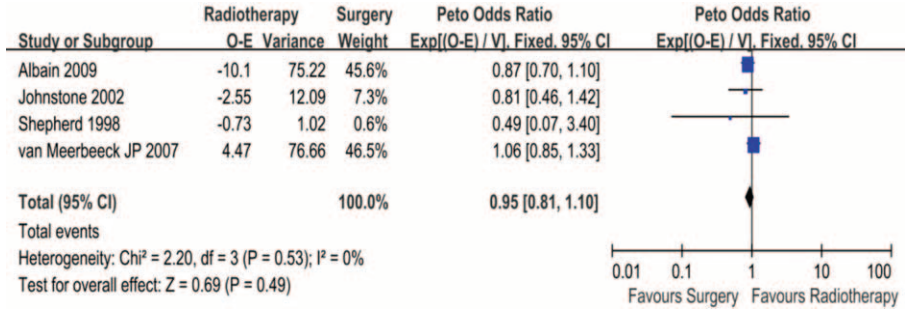

FIGURE 2. Neoadjuvant chemoradiotherapy or chemotherapy prior to surgical resection compared with neoadjuvant chemoradiotherapy or chemotherapy prior to definitive radiotherapy in stage IIIA (N2) NSCLC: overall survival.

stage IIIA (N2) NSCLC patients who received neoadjuvant chemotherapy or chemoradiotherapy prior to surgical resection compared to those who received neoadjuvant chemotherapy or chemoradiotherapy prior to radical radiotherapy (HR 0.90; 95% CI 0.77–1.05; $P = 0.19$; Figure 3). There was evidence of significant heterogeneity between trials ($\chi^2 = 4.01$, $P = 0.05$, $I^2 = 75\%$).

The method of stratification was identified as a possible source of heterogeneity between these trials. In the North American Intergroup Study (INT0139) trial,[12] patients received induction chemotherapy (cisplatin and etoposide) with concurrent radiotherapy, and regardless of the response, they were randomly assigned to a surgery or radiotherapy group. In the EORTC 8941 trial,[14] patients received induction chemotherapy (platinum/gemcitabine [40%] or platinum/taxane combination [21%]) only, and patients were stratified for type of response, histological subtype, and institution before being randomly assigned to a surgery or radiotherapy group.

Secondary Outcome Measures

Adverse events included grade 3 or 4 neutropenia and esophagitis in patients treated with neoadjuvant chemotherapy or chemoradiotherapy prior to surgical resection or radical radiotherapy. Grade 3 pneumonitis was observed in patients treated with neoadjuvant chemoradiotherapy. Postoperative complications associated with surgery included arrhythmia, prolonged ventilation, and prolonged air leak. Mortality was higher in surgical patients compared to those treated with radical radiotherapy. Adverse events and mortality are shown in Table 2.

Neoadjuvant Chemoradiotherapy Versus Neoadjuvant Chemotherapy Prior to Surgical Resection

Characteristics of Included Studies

The searches identified 3 RCTs of neoadjuvant chemoradiotherapy prior to surgical resection versus neoadjuvant chemotherapy prior to surgical resection in NSCLC patients[7,16,17] (n = 229). The trials were published between 2009 and 2012 and were conducted at multiple academic and community hospitals in Germany,[7] Japan,[16] and France.[17] In 1 trial,[7] the intervention group (neoadjuvant chemoradiotherapy) received 3 cycles of cisplatin and etoposide, followed by twice-daily radiation with concurrent carboplatin and vindesine, and surgical resection. The control group (neoadjuvant chemotherapy) received 3 cycles of cisplatin and etoposide, followed by surgery, and then further radiotherapy. In 2 trials,[16,17] patients were randomized to receive either induction chemotherapy plus concurrent radiation therapy followed by surgery (neoadjuvant chemoradiotherapy) or induction chemotherapy followed by surgery (neoadjuvant chemotherapy). NSCLC patients in 2 trials had pathological proof of N2 involvement. In 1 trial (n = 13), pathological proof of N2 involvement was not possible to obtain due to lymph node location, but 18-fluorodeoxyglucose position-emission tomography (PET) scan showed increased uptake corresponding to N2 involvement.

Primary Outcome Measures

Data reporting pathological complete remission (pCR) in the mediastinal lymph nodes and tumor downstaging after treatment are described in 2 trials (n = 102).[16,17] The meta-analysis

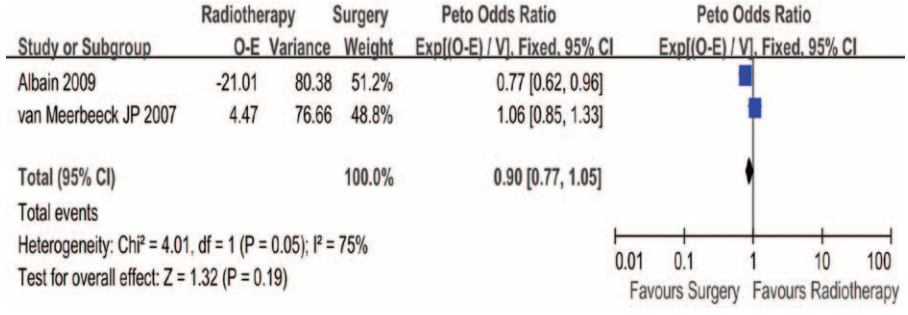

FIGURE 3. Neoadjuvant chemoradiotherapy or chemotherapy prior to surgical resection compared with neoadjuvant chemoradiotherapy or chemotherapy prior to definitive radiotherapy in stage IIIA (N2) NSCLC: progression-free survival.

TABLE 2. Main Complications and Mortality in the Included Trials

First Author	Complications	Mortality
Albain et al[12]	Grade 3 or 4 neutropenia: 77 (38%) in the surgical arm and 80 (41%) in the radiation arm; grade 3 or 4 esophagitis: 20 (10%) patients in the surgical arm and 44 (23%) in the radiation arm ($P = 0.0006$).	16 (8%) patients died in the surgical arm, 4 (2%) patients in the radiation arm.
Johnstone et al[13]	Only 1 patient in each group had acute nonhema tologic toxicity greater than grade 3 (nausea and vomiting). This was equivalent across the treatment arms.	2 (6.9%) patients died in the surgical arm (1 of late pulmonary toxicity and 1 of pulmonary embolus), and 1 (3.1%) patient in the radiation arm (radiation pneumonitis).
Van Meerbeeck et al[14]	Surgical arm: 2 cases of grade 3 acute esophagitis and 1 case of grade 4 acute pneumonitis. Radiation arm: acute grade 3/4 esophageal and pulmonary toxic effects were observed in 1 patient (<1%) and 5 patients (4%), late pulmonary and esophageal fibrosis occurred in 11 (7%) patients and 1 (<1%) patient.	Surgical arm: 6 (3.6%) died within 30 days following surgery. Radiation arm: 1 (0.6%) patient died of radiation pneumonitis.
Shepherd et al[15]	Radiation arm: 1 patient had grade 3 radiation pneumonitis. None had grade 3 or 4 esophagitis. Surgical arm: Postoperative complications included arrhythmia (3 patients), prolonged ventilation (2 patients), prolonged air leak, infection, and a telectasis (1 patient in each arm).	NR
Katakami et al[16]	Grade 3 or 4 leukopenia in 26 patients (92.9%) in the neo-ChRT arm and 13 patients (46.4%) in the neo-ChT arm ($P = 0.075$). Grade 3 or 4 neutropenia in 25 patients (89.3%) in the neo-ChRT arm and 21 patients (75.0%) in the neo-ChT arm ($P = 0.313$). Grade 3 or 4 thrombocytopenia in 2 patients (7.1%) in the neo-ChRT arm but in no patients in the neo-ChT arm.	No treatment-related deaths were reported through out the trial in either arm.
Thomas et al[7]	20 patients (10%) in the neo-ChRT group and 1 patient (0.5%) in the control group showed substantial hematotoxicity ($P < 0.0001$). Esophagitis (grade ≥3) was significantly more pronounced in the neo-ChRT group (39 of 206 [19%] vs 7 of 187 [4%]; $P < 0.0001$). Pneumonitis (CTC grade ≥3) was the predominant side effect in the control group (3 of 206 [1%] vs 13 of 187 [7%]; $P = 0.0006$).	5 patients died from fatal events after neutropenia, resulting in a mortality rate with chemotherapy of 0.8% (the neo-ChRT group: 2 of 264) and 1.2% (the control group: 3 of 26).
Girard et al[17]	10 patients experienced postoperative complications, consisting of grades 1–2 fever (n = 3), grade 3 infection (n = 1), grade 4 thrombosis or pulmonary embolism (n = 3), grade 3 intestinal obstruction (n = 1), grade 2/4 pneumopathy (n = 2), and grade 1 emphysema (n = 1). Surgical morbidity rate was not significantly different between patients treated with induction chemora diotherapy vs induction chemotherapy ($P = 0.231$).	NR

CTC = common terminology criteria, neo-ChRT = neoadjuvant chemoradiotherapy, neo-ChT = neoadjuvant chemotherapy, NR = not reported.

revealed a significant 15% increase in pCR in the mediastinal lymph nodes in stage IIIA (N2) NSCLC patients who received neoadjuvant chemoradiotherapy prior to surgical resection compared to those who received neoadjuvant chemotherapy (OR [odds ratio] 3.61, 95% CI 1.07–12.15; $P = 0.04$; Figure 4). There was no evidence of significant heterogeneity between trials ($\chi^2 = 0.04$, $P = 0.84$, $I^2 = 0\%$).

Data reporting tumor downstaging after treatment are described in 1 trial (n = 58).[16] The results showed no significant tumor downstaging after treatment in stage IIIA (N2) NSCLC patients who received neoadjuvant chemoradiotherapy prior to surgical resection compared to those who received neoadjuvant chemotherapy (OR 2.53, 95% CI 0.71–9.01; $P = 0.15$).

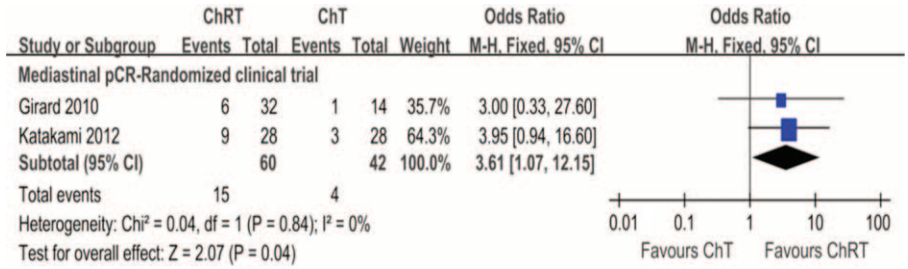

FIGURE 4. Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy prior to surgical resection in stage IIIA (N2) NSCLC: pathological complete remission in the mediastinum.

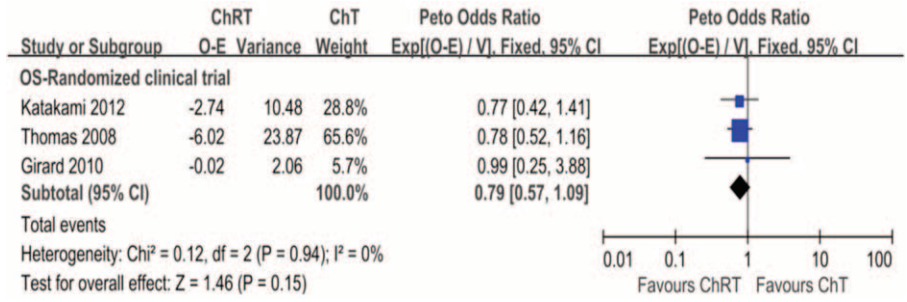

FIGURE 5. Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy prior to surgical resection in stage IIIA (N2) NSCLC: overall survival.

Data reporting OS are described in 3 trials (n = 229).[7,16,17] The meta-analysis revealed no significant difference in OS in stage IIIA (N2) NSCLC patients who received neoadjuvant chemoradiotherapy prior to surgical resection compared to those who received neoadjuvant chemotherapy (HR = 0.79, 95% CI 0.57–1.09; Figure 5). There was no evidence of significant heterogeneity between trials ($I^2 = 0\%$).

Data reporting PFS are described in 2 trials (n = 104).[16,17] The meta-analysis revealed no significant difference in PFS in stage IIIA (N2) NSCLC patients who received neoadjuvant chemoradiotherapy prior to surgical resection compared to those who received neoadjuvant chemotherapy (HR = 0.67; 95% CI 0.39–1.15; Figure 6). There was no evidence of significant heterogeneity between trials ($I^2 = 0\%$).

Secondary Outcome Measures

Adverse events included grade 3 or 4 neutropenia, grade 3 or 4 thrombocytopenia, pneumonitis, and hematotoxicity in both the chemotherapy and chemoradiotherapy groups. Esophagitis was more pronounced in the chemoradiotherapy group compared to the chemotherapy group. Postoperative complications consisted of grades 1 and 2 fever, grade 3 infection, grade 4 thrombosis or pulmonary embolism, grade 3 intestinal obstruction, grade 2/4 pneumopathy, and grade 1 emphysema. Surgical morbidity rate was not significantly different between patients treated with induction chemoradiotherapy versus induction chemotherapy. Adverse events and mortality are shown in Table 2.

DISCUSSION

The Role of Surgery in Multimodality Therapy for NSCLC

In the era before the use of computed tomography, lung cancer patients without symptoms, biochemical abnormalities, or mediastinal widening on plain chest radiography were treated with surgery as an optimal therapy. Complete surgical excision of tumors by lobectomy or pneumonectomy combined with

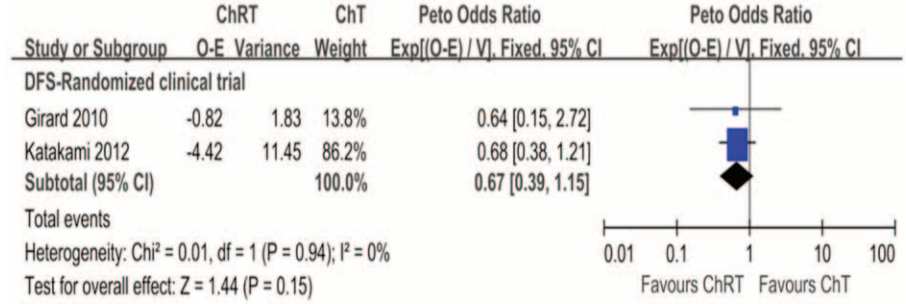

FIGURE 6. Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy prior to surgical resection in stage IIIA (N2) NSCLC: disease-free survival.

mediastinal lymph node dissection was the standard procedure. However, NSCLC patients with clinically obvious N2 exhibited poor survival following primary surgery.[5,18–20]

During the last 3 decades, the use of surgery for the treatment of advanced NSCLC has evolved from primary therapy to its current role as an important component in multimodality management strategies. Our meta-analysis investigated the survival benefit of multimodality therapy including surgery for stage IIIA (N2) NSCLC patients. The results indicated that neoadjuvant chemoradiotherapy or chemotherapy prior to surgical resection does not provide a significant survival benefit to IIIA (N2) NSCLC patients compared to neoadjuvant chemoradiotherapy or chemotherapy prior to definitive radiotherapy. Previous studies showed that patients who underwent lobectomy had better OS than those who received chemotherapy plus radiotherapy, and patients who underwent resection had longer PFS than those who continued radiotherapy uninterrupted up to 61 Gy after concurrent chemoradiotherapy.[12] In other reports, postoperative radiotherapy versus surgery alone did not improve OS in patients with IIIA (N2) NSCLC,[21] and lobectomy provided better long-term survival than pneumonectomy after induction chemotherapy, with no increase in postoperative complications or recurrence rate.[22,23] Taken together, these observations suggest that not all patients with locally advanced NSCLC are suitable candidates for resection; however, surgery may be beneficial for a subpopulation of patients with downstaging after chemotherapy/radiotherapy or those that are suitable for lobectomy.

Neoadjuvant Chemoradiotherapy Versus Neoadjuvant Chemotherapy

In the past 2 decades, chemoradiotherapy was proven superior to chemotherapy alone in nonoperable locally advanced NSCLC. Several phase II trials investigated the safety and efficacy of preoperative chemoradiotherapy delivered sequentially or concurrently for N2 patients.[24,25] The Cancer and Leukemia Group B (CALGB) trial 8935 explored the feasibility of a sequential trimodality approach in patients with N2 disease.[24] In that trial, 74 patients were initially treated with 2 cycles of induction chemotherapy consisting of cisplatin and vinblastine. Surgical resection was performed in patients with response or stable disease after sequential adjuvant chemoradiotherapy. Sixty-three patients in CALGB 8935 underwent an exploratory thoracotomy with 46 (75%) having resectable lesions. The complete resection rate was less than 40% after 2 cycles of induction chemotherapy, and only a small fraction of patients had pathologic downstaging. The Southwest Oncology Group (SWOG) conducted the largest multi-institutional trial (n = 126) with a concurrent chemoradiotherapy strategy.[25] Biopsy proof of positive N2 nodes (IIIA, N2) was required. Induction treatment included 2 cycles of cisplatin and etoposide plus concurrent chest radiotherapy with 45 Gy. Surgery was performed if patients exhibited a response or stable disease after induction treatment. Radiotherapy was given to patients with unresectable disease or positive margins or nodes. Results from these studies indicated that, compared to induction chemotherapy alone, concurrent chemoradiotherapy improved nodal downstaging (CALGB 8935, 22%; SWOG 8805, 53%) and yielded a higher percentage of pCRs (21% vs 0%); however, the 3-year OS rates were similar (CALGB 8935 23%, SWOG 27%).

In our meta-analysis, neoadjuvant chemoradiotherapy prior to surgical resection significantly increased pCR in the mediastinal lymph nodes compared to neoadjuvant chemotherapy alone in stage IIIA (N2) NSCLC patients. However, neoadjuvant chemoradiotherapy prior to surgical resection did not significantly improve OS or DFS. A cohort analysis showed that resectable N2/N3 after chemoradiotherapy in stage III NSCLC is a risk factor for mortality,[26] and SWOG 8805[25] revealed that the strongest predictor of long-term survival after thoracotomy is the absence of tumors in the mediastinal nodes at surgery (median survival, 30 vs 10 months; 3-year survival rates, 44% vs 18%; $P = 0.0005$). In accordance with our data, a previous meta-analysis demonstrated that neoadjuvant chemoradiotherapy does not provide better survival compared to neoadjuvant chemotherapy alone in stage IIIA (N2) NSCLC undergoing surgical resection.[9] However, the results from clinical trials[16,17] show mediastinal downstaging from cN2/pN2 to pN0 and better outcomes in stage IIIA (N2) NSCLC patients with mediastinal lymph node metastasis treated with neoadjuvant chemoradiotherapy than neoadjuvant chemotherapy alone.

Currently, neoadjuvant chemoradiotherapy is used for potentially resectable locally advanced NSCLC in approximately 50% of National Comprehensive Cancer Network (NCCN) institutions, while neoadjuvant chemotherapy is used in the others,[27] Further studies are required to fully understand the clinical benefits of each approach.

Acute and Late Morbidity, Surgical Complications, and Mortality

Our review demonstrated that neoadjuvant chemoradiotherapy is a tolerable treatment that results in a similar extent of resection and a statistically similar rate of surgical complications compared to neoadjuvant chemotherapy in patients with stage IIIA (N2) NSCLC. Neoadjuvant chemoradiotherapy may eradicate micrometastases with an acceptable toxicity, and it may result in complete surgical resection by reducing the quantity of cancer cells in the primary tumor and metastatic regional nodes.

Currently, it remains controversial whether pneumonectomy or lobectomy should be performed after neoadjuvant chemoradiotherapy in order to reduce surgical complications and mortality in patients with advanced NSCLC. Many studies have reported that pneumonectomy may result in an unacceptably high rate of perioperative mortality.[12,28] In INT0139,[12] pneumonectomy (26%) was associated with a significantly higher mortality rate than lobectomy (1%). However, no obvious survival difference was found between the surgical and nonsurgical arms in the study, because the increased mortality in patients who received pneumonectomy after induction chemoradiotherapy adversely affected the OS of the surgical group. Some reports have shown that pneumonectomy after induction chemoradiotherapy does not increase risk for morbidity and mortality in properly selected patients.[29,30] In these studies, there were no significant differences in 90-day mortality and OS between patients who underwent pneumonectomy and those who received lobectomy, whereas cardiopulmonary morbidity and early mortality occurred more frequently in patients who underwent a pneumonectomy than in those who underwent a lobectomy. Notably, right-sided pneumonectomy after chemoradiotherapy appears to be associated with relatively increased cardiopulmonary risk and may only be performed in selected patients.[31] However, in a phase III clinical trial,[14] a low postoperative mortality was observed, even among patients who underwent right-sided pneumonectomy, although patient selection may have

contributed to this observation (among the 579 eligible patients, 247 patients were excluded for surgery or radiation therapy due to inadequate response).

LIMITATIONS

The current study was subject to several limitations. First, the therapy regimens adopted by the various trials differed, which may have influenced the efficacy of treatment approaches. Second, detailed and individual patient survival data were not directly reported in some included trials; thus, HRs and 95% CIs were collated for analysis during information extraction, leading to a certain degree of measurement bias. Third, there was evidence of significant heterogeneity between the 2 trials included in the analysis of PFS following neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy prior to surgical resection. This heterogeneity may have been due to variability in the participants, interventions, outcomes studied, and study design, and suggests the outcome measure should be interpreted with caution. Fourth, the analyses included a small number of studies, and some studies had relatively small sample sizes. More studies are required to confirm our findings, and studies with a larger sample size are required to minimize interindividual variability, which may cause inconsistency among the results of various studies restricting the generalizability of our data.

CONCLUSION

Neoadjuvant chemotherapy and/or radiotherapy prior to surgical resection do not appear to be clinically superior to neoadjuvant chemotherapy and/or radiotherapy prior to definitive radiotherapy in IIIA (N2) NSCLC patients. Neoadjuvant chemoradiotherapy does not improve survival compared to neoadjuvant chemotherapy alone, but it may increase the rate of pCR in the mediastinal lymph nodes, which has been correlated with better PFS and OS. Neoadjuvant chemotherapy alone or with radiotherapy is not associated with significant postoperative complications and mortality. Further studies should be conducted to determine the subgroups of patients who will benefit from various multimodality management strategies.

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