Original Article

Randomized controlled trials of induction treatment and surgery versus combined chemotherapy and radiotherapy in stages IIIA-N2 NSCLC: a systematic review and meta-analysis

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Background: The efficacy of induction treatment plus surgery for improving postoperative survival in patients with non-small-cell lung cancer (NSCLC) in stages IIIA-N2 is controversial, especially compared with the combined chemotherapy and radiotherapy. We therefore performed a systematic review and meta-analysis of the published phase III randomized clinical trials (RCTs) to quantitatively evaluate the survival benefit of preoperative induction treatment vs. combined chemoradiotherapy.

Methods: We systematically searched for trials that started after January, 1980. We excluded relevant studies using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards. Our primary endpoint, overall survival (OS), was defined as the time from randomisation until death (any cause). Secondary endpoint was progression free survival (PFS). PubMed, EMBASE and Cochrane library were used for the study search. All analyses were by intention to treat.

Results: Three studies (1,084 patients) were centrally selected and analyzed for the present meta-analysis. Combination of the three randomized controlled trials showed that there was no significant benefit of induction treatment plus surgery compared to combined chemoradiotherapy on 2-year OS [risk ratio (RR) =1.00; 95% CI, 0.85-1.17; P=0.98] and 4-year OS (RR =1.13; 95% CI, 0.85-1.51; P=0.39). However, from the subgroup analysis, it showed a significant PFS benefit (RR =1.78; 95% CI, 1.08-2.92; P=0.02) regarded chemoradiotherapy as preoperative induction treatment, compared with chemotherapy alone for induction treatment (PFS) (RR =1.05; 95% CI, 0.61-1.81; P=0.86).

Conclusions: There was no significant OS benefit of induction treatment plus surgery compared with combined chemoradiotherapy in patients with NSCLC (stages IIIA-pN2) at 2 and 4 years. However, we could conclude PFS could be improved when radiation therapy was added into preoperative induction treatment. Given the potential advantages of adding radiation preoperatively, clinicians should consider using this treatment strategy in the stage IIIA-N2 disease after fully assessment of the patients.

Keywords: Induction treatment plus surgery; combined chemoradiotherapy; stages IIIA-N2 NSCLC

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Introduction

Lung cancer is the leading cause of cancer-related deaths. Worldwide, roughly 1.5 million new cases of lung cancer are diagnosed annually (1) with about 85% being non-small-cell lung cancers (NSCLCs) (2). For stage IIIA-N2 NSCLC, which is defined as involvement of the ipsilateral mediastinal or subcarinal lymph nodes (3), neoadjuvant chemotherapy followed by surgery has been shown to lengthen survival in selected patients with stage IIIA NSCLC (4-7). Also, combined chemotherapy and radiotherapy has been proven that it can improve the outcome for these patients compared with radiotherapy alone (5,8-12). Whereas, there remains discussion whether induction treatment followed by surgery is the best option compared with combined chemoradiotherapy for stage IIIA-N2 NSCLC.

Examination and synthesis of the limited available data comparing induction treatment plus surgery and combined chemoradiotherapy may allow physicians to determine the optimal treatment for patients with IIIA-N2 disease. Recently, three large phase III randomized clinical trials (RCTs) was published their results to evaluate the survival benefit of induction treatment plus surgery compared with combined chemoradiotherapy (13-15). However, the efficacy of preoperative induction treatment in improving postoperative survival in patients with stages IIIA-N2 NSCLC remains controversial. We therefore conducted a systematic review and meta-analysis of the published phase III RCTs to quantitatively evaluate survival benefit of patients who underwent these two kinds of treatments.

Materials and methods

Eligibility criteria

RCTs comparing preoperative induction treatment plus surgery with combined chemoradiotherapy were conducted using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards (16) as the basis for reporting the materials and methods of this study, and aimed to include the patients with stages IIIA-pN2 NSCLC if they started after Jan 1, 1980. The following criteria for eligibility into this meta-analysis were set before collecting the articles: (I) the trials had to be phase III RCTs comparing the survival between a groups receiving preoperative induction treatment plus surgery and another group receiving combined chemoradiotherapy; (II) the studies involved patients with stages IIIA-pN2 NSCLC based upon international staging criteria (17); (III) the hazard ratios (HRs) and confidence intervals (CIs) of the patients who underwent preoperative induction treatment plus surgery and those who received combined chemoradiotherapy could be calculated at specified time intervals after surgery from the survival rates in the article; (IV) the median follow-up time of the study exceeded at least 2 years; (V) published and unpublished trials were sought, with no language restriction, using randomised trial search filters for PubMed, EMBASE and Cochrane library.

Data collection

Two investigators independently searched eligible trials, and discrepancies were resolved by discussion between them. Non-English publications were evaluated based on their English abstract and the translation of their main text. The keywords "IIIA-N2 Non-small-cell lung cancer + chemotherapy plus radiotherapy", "IIIA-N2 NSCLC + radiotherapy plus chemotherapy with or without surgical resection", totally hit 280 citations. The relevant clinical studies were manually selected based on summary analyses. Articles reporting studies unrelated to our question were excluded, and finally only three studies (13-15) were found to fulfill all of our eligibility criteria (*Table 1*).

Validity assessment

We conducted the validity assessment referred to the meta-analysis performed by Wright *et al.* (18). Two reviewers evaluated the quality of the studies independently with disagreements resolved by consensus. Using the Cochrane approach to allocation concealment, trials were described as having adequate, unclear, or inadequate concealment (19). The reviewers assessed whether there was blinding of outcome assessment and adequate description of withdrawls (20). The adequacy of the method of randomization was also assessed as described by Jadad *et al.* (20). Finally, an assessment was made as to whether the trial results used intention to treat analysis (21,22). The authors of included studies were asked to verify assessments of study methodology where possible.

Statistical analyses

Statistical analyses for the meta-analysis were performed with RevMan (Review Manager Version 5.3 for Windows, Cochrane Collaboration. Oxford, UK, 2014), and a pooled relative risk was calculated with 95% CIs. The methods

Table 1 Characteristics of phase III randomized clinical trials of preoperative induction treatment plus surgery vs. combined chemoradiotherapy

First author	Accrual years	Patients registered	TNM	Induction treatment used (dose per cycle)	Patients randomized	Intervention (surgery)	Control (radiotherapy)	Postoperative consolidation treatment	Median follow-up years
Johnstone *et al.* (13)	1990-1994	73	IIIA-N2 (T1-3N2M0)	Cisplatin (120 mg/m^2; D1, 29), vinblastine (4.5 mg/m^2; D1, 15, 29, and 43), and mitomycin-C (8 mg/m^2; D1, 29)	61	Surgery (n=29): exploratory thoracotomy; complete resection	Radiotherapy (n=32): (50 Gy to the primary and regional nodes, the completion of induction chemotherapy for a total 64 Gy	75% patients consolidation chemotherapy completed	At least 4 years
van Meerbeeck *et al.* (14)	1994-2002	582	IIIA-N2 (T1-3N2M0)	3 cycles of cisplatin (at least 80 mg/m^2/cycle), or carboplatin (AUC = 5/cycle, combined with at least one other chemotherapy drug)	332	Surgery (n=167): exploratory thoracotomy; radical resection	Radiotherapy (n=165): (60-62.5 Gy primary tumor and involved mediastinum and the uninvolved mediastinum of 40-46 Gy)	40% patients postoperative radiotherapy administered	6 years
Albain *et al.* (15)	1994-2001	429	IIIA-N2 (T1-3pN2M0)	2 cycles of cisplatin (50 mg/m^2 on days 1, 8, 29, and 36) and etoposide (50 mg/m^2 on days 1-5 and 29-33) plus radiotherapy (45 Gy)	396	Surgery (n=202): thoracotomy; complete resection; incomplete resection	Radiotherapy (n=194): induction thoracic radiotherapy (45 Gy); continued to 61 Gy	55% patients consolidation chemotherapy completed	69.3 months

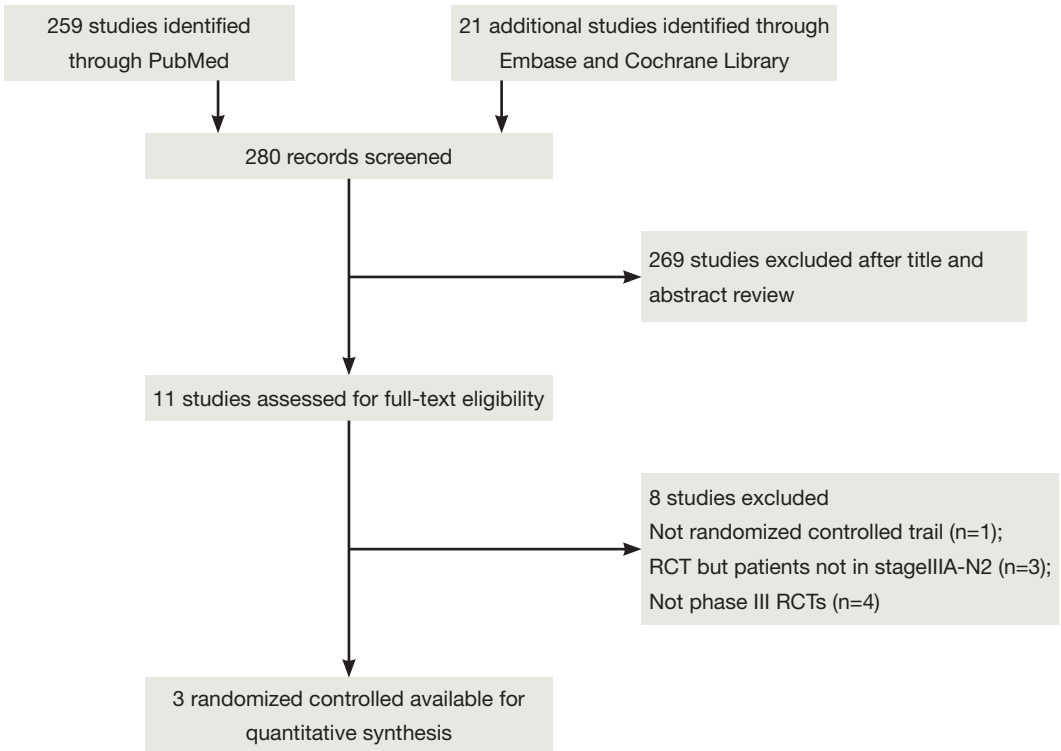

Figure 1 Flow diagram of patients included in systematic review and meta-analysis.

described by Parmar *et al.* were used to estimate the HRs and variance indirectly from CIs or P values for the log rank test (23). To undertake a random effects meta-analysis, the standard errors of the study-specific estimates are adjusted to incorporate a measure of the extent of variation, or heterogeneity, among the treatment effects observed in different studies. The survival rates were derived from the published survival curves when not provided explicitly in the text or tables. Data extraction from the survival curves was done by two researchers independently, and the mean measured values were used for the analysis. Heterogeneity was evaluated with the χ^2 distribution test with rejection region equal to 0.1; and the I^2 test whereby I^2=0% indicated no heterogeneity, I^2=0-40% indicated low heterogeneity, I^2=40-60% indicated moderate heterogeneity, and I^2=50-90% indicated high heterogeneity, I^2=75-100% indicated maximum heterogeneity (19).

Results

Three randomized phase III trials, with a total of 1,084 patients, were included for survival analysis (*Figure 1*). The trial characteristics and the treatment schedules used are listed in *Table 1*. The two studies reported by Johnstone *et al.* (13) and van Meerbeeck *et al.* (14) merely used the platinum based regimen for preoperative induction treatment, which differs from the trial reported by Albain *et al.* (15) received the platinum based regimen plus radiotherapy (45 Gy) for preoperative induction treatment. After induction treatment was completed, patients registered who were response to the induction treatment can be randomized into next step. Thus, the results were based on three randomized controlled trials (789 patients), and then preoperative induction treatment followed by surgery was assigned to a total of 398 patients, while combined chemotherapy and radiotherapy without surgery was assigned to 391 patients. The overall classification of histologic types was 283 (36.9%) squamous cell carcinomas (surgery: non-surgery =137:146), 291 (36.9%) adenocarcinomas (153:138, respectively), 146 (18.5%) large cell carcinomas (73:73, respectively), 69 (8.7%) miscellaneous types (35:34, respectively). There was no clear evidence of a difference in the effect on survival by chemotherapy regimen or scheduling, number of drugs, platinum agent used, or whether postoperative chemo or

Table 2 Methodological quality of included trials

Study	Allocation concealment	Method of randomization	Blinded assessment of outcome	Description of withdrawals	Intention to treat analysis
Johnstone *et al*. (13)	Unclear	Adequate	None described	Yes	Yes
van Meerbeeck *et al*. (14)	Unclear	Adequate	None described	Yes	Yes
Albain *et al*. (15)	Inadequate	Adequate	None described	Yes	Yes

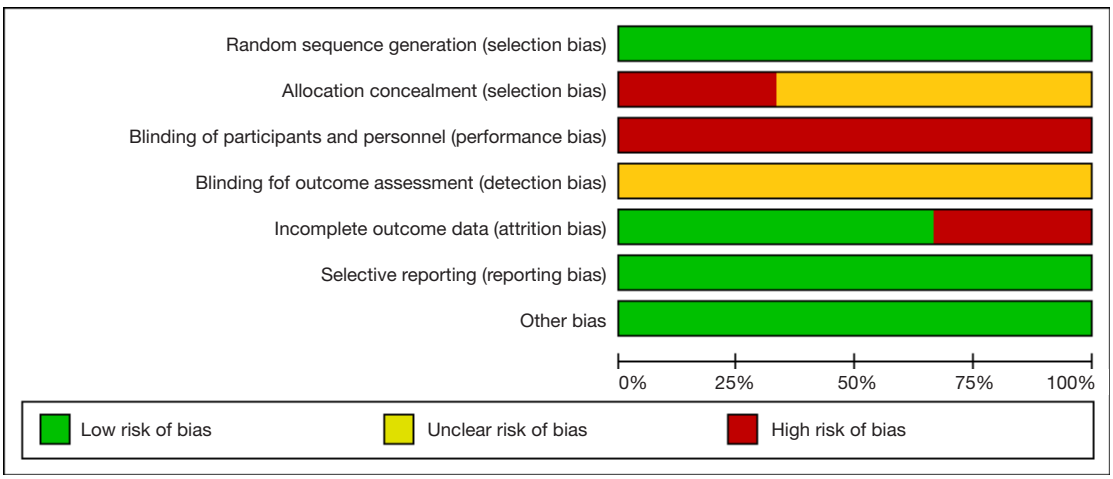

Figure 2 Risk of bias graph: each risk of bias item presented as percentages across all included studies.

radiotherapy was given. There was no clear evidence that particular types of patient defined by age, sex, performance status, histology, or clinical stage benefited more or less from both of them.

The quality of included trials was shown (*Table 2*). Intergroup trial 0139 (15) was found to be inadequate in allocation concealment. All of the included studies contained a clear statement that they had conducted method of randomization and intention to treat analysis. Further quality details of the trials are shown in the *Table 2*. According to the three trials' methodological quality, we reviewed authors' judgements about each risk of bias item presented as figure (*Figure 2*).

For the whole groups, there was no improvement in 2-year overall survival (OS) [risk ratio (RR) =1.00; 95% CI, 0.85-1.17; P=0.98] and 4-year OS (RR =1.13; 95% CI, 0.85-1.51; P=0.39) compared with the combined chemoradiotherapy arm (*Figure 3A,B*). From the subgroup analysis, when we performed a meta-analysis on the two studies reported by Johnstone *et al.* (13) and van Meerbeeck *et al.* (14), the pooling data from both studies (n=393) indicated that there was no significant difference in 3 years progression free survival (PFS) (RR =1.05; 95% CI, 0.61-1.81; P=0.86) (*Figure 3C*) regarded the preoperative chemotherapy as induction treatment. However, according to the sub-meta-analysis on the study reported by Albain *et al.* (15), it showed a significant PFS between the intervention arm and control arm (RR =1.78; 95% CI, 1.08-2.92; P=0.02) (*Figure 3C*). Thus, when the radiotherapy was added into preoperative induction treatment, compared with only preoperative chemotherapy as induction treatment, it could improve PFS. Heterogeneity testing indicated that the study at 3 years PFS was low heterogeneity [I^2=0%; P for χ^2 test =0.37 (>0.1)] and at 2 years OS and 4 years OS were also low heterogeneity [I^2=15%; P for χ^2 test =0.31 (>0.1); I^2=0%; P for χ^2 test =0.99 (>0.1)], respectively.

Discussion

In many centers, they have demonstrated that stages IIIA-N2 NSCLC patients have significant survival advantage benefited from preoperative induction treatment plus surgery compared with surgery or radiotherapy alone (4-7,24). In addition, it has been proven that combined

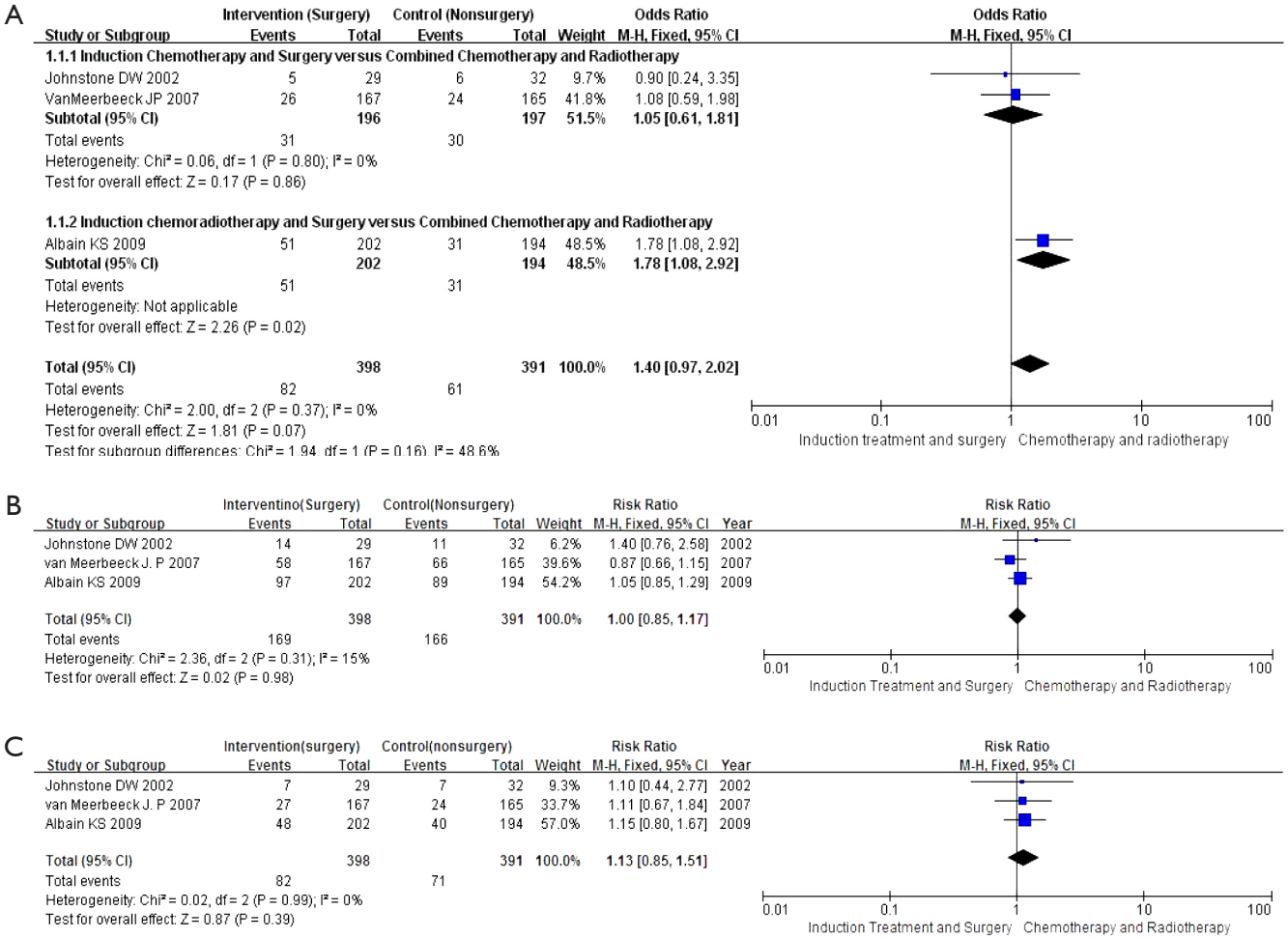

Figure 3 (A) 2-year overall survival; (B) 4-year overall survival; (C) 3-year progression free survival. I^2 test for heterogeneity; P=χ^2 distribution test for heterogeneity with rejection region =0.1; CI, confidence interval. Johnstone *et al.* (13); van Meerbeeck et al. (14); Albain *et al.* (15).

chemoradiotherapy can improve IIIA-N2 NSCLC patients OS compared with radiotherapy or surgery alone (5,8-12). The meta-analysis reported by Wright *et al.* (18) tried to compare chemotherapy followed by surgery with sequential chemotherapy and radiotherapy, but it was inconclusive because of small numbers. Given the failure of numerous clinical trials attempting to answer this question as well as the small sample sizes of individual published studies on this topic, we attempted to evaluate and synthesize the available data to provide clinicians with summarized evidence-based information to guide them in taking care of patients with stage IIIA (N2) disease. Thus, we integrated the three large randomized trials with a total of 1,084 patients to analyze and compare which one is the optimal treatment.

Our meta-analysis pointed out that whether preoperative induction treatment plus surgery or combined chemoradiotherapy was given, it showed no improvement in the stages IIIA-N2 NSCLC patients 2-year OS (RR =1.00; 95% CI, 0.85-1.17; P=0.98) and 4-year OS (RR =1.13; 95% CI, 0.85-1.51; P=0.39). It matches with the finding from the results reported by the three trials (13-15) showed no significant OS benefit in treatment between preoperative induction treatment plus surgery and chemoradiotherapy. This implies that patients in stages IIIA-N2 NSCLC might be received either of the two treatments, and their OS could be no significant difference.

However, although the OS have been demonstrated without any difference between the two treatments, it still need us to make clear its appropriate context of patients with unresectable IIIA-N2 disease what the crucial term

"unresectable" was clearly defined in the article. And another concern is how the assessment of irresectability was performed (25). Because there have different European series who published their 5-year survival rates of 36% (Swiss group) (26), 34% (Essen group) (27), or 30% (Leuven group) (28) among patients with IIIA-N2 disease but resect after induction treatment. The rationale of these studies is to provide surgery as the best local treatment for resectable NSCLC and improve outcome by induction therapy to manage distant micrometastasis. Though the result of our meta-analysis emphasized the OS without significance between the two treatments, this should not lead to the over-interpretation that combined chemoradiotherapy is the best choice for every patient with IIIA-N2 NSCLC. We also concur with the editorial that patients who are good candidates for surgery may still be appropriately managed by using resection rather than radiation (29).

From the subgroup analysis, when the induction treatment was separated into preoperative chemoradiotherapy and preoperative chemotherapy treatment, and then compared them with combined chemoradiotherapy, it showed some potential advantages for the patients PFS when radiation therapy was added into preoperative induction treatment. The 3 years PFS synthesized by the two studies (13,14) was no significant difference (RR =1.05; 95% CI, 0.61-1.81; P=0.86), and it matches with the results reported by Johnstone *et al.* (13) and van Meerbeeck *et al.* (14) (HR =1.06; 95% CI, 0.85-1.33; P=0.605). Nevertheless, we compared the data reported by the Intergroup trial 0139 (15), and it showed a significant PFS (RR =1.78; 95% CI, 1.08-2.92; P=0.02), which indirectly suggests that induction chemoradiotherapy as a preoperative induction treatment might be superior to induction chemotherapy without radiotherapy. The study WJTOG9903 (30) also tried to ascertain whether induction-concurrent radiotherapy added to chemotherapy could improve the survival of patients undergoing surgery for stage IIIA N2 NSCLC. Although PFS had not been improved in the chemoradiotherapy plus surgery arm *vs.* the chemotherapy plus surgery arm (median, 12.4 *vs.* 9.7 months; HR =0.68; 95% CI, 0.38-1.21; P=0.187), Katakami (30) pointed out that these differences are not statistically significant due to the small sample size. And they demonstrated that the addition of radiotherapy to the induction chemotherapy regimen for stage IIIA (N2) NSCLC appears to confer better local control without adding significant adverse events, and tumor down-staging after induction therapy is an important factor for improving patient survival. The retrospective review published by Martin *et al.* (31), the retrospective study conducted by Darling *et al.* (32) and the results published by Higgins *et al.* (33) also supported potential advantages of an increased pathologic complete response rate and improved local control for adding the radiation into induction therapy, and then improved the PFS.

Although the systematic review and meta-analysis performed by Shah *et al.* (34) to compare induction chemoradiotherapy *vs.* induction chemotherapy alone demonstrated that published evidence is limited but does not support the inclusion of radiation therapy in induction regimens for stage IIIA (N2) NSCLC, it did not affect our result. Because their meta-analysis indeed lacked sufficient data, such as WJTOG9903 (30) and the retrospective study conducted by Darling *et al.* (32), and their meta-analysis, with a total of seven studies, included some low qualified studies and the statistical heterogeneity were deemed imprecise. In addition, we failed to compare the administration of postoperative radiotherapy in the EORTC (14) with the consolidation chemotherapy in the IG trial 0139 (15), which might result in an imbalance of better local control and better PFS in surgery arm of the intergroup trial, but some published studies (35,36) proved that the locoregional relapse rate was higher in the postoperative radiotherapy arm.

The heterogeneity test detected low heterogeneity between the combined studies. The included studies were considered low heterogeneity for the following reasons. Firstly, the ratio of overall classification of histologic types in each study is closed to 1:1, and the ratio of gender in each study is almost equal (13-15). Secondly, three studies included only clinical stage IIIA-N2 NSCLC patients. And the therapeutic regimens were also similar among the studies. As for the Intergroup Trial 0139, radiation therapy was added into preoperative induction treatment, but the subgroup analysis has been given, which turns out to be still very low heterogeneity. Thirdly, all the trials are phase III RCTs and have enough follow-up time. In addition, according to the three trials' methodological quality, we reviewed authors' judgements and figured out each risk of bias item, and it also indicated without serious problem to affect our meta-analysis.

Conclusions

There was no significant OS benefit of induction treatment plus surgery compared with combined chemoradiotherapy

in patients with NSCLC (stages IIIA-N2) at 2 and 4 years. However, from the subgroup analysis, we could conclude PFS could be improved when radiation therapy was added into preoperative induction treatment. Given the potential advantages of adding radiation preoperatively, clinicians should consider using this treatment strategy in the stage IIIA-N2 disease after fully assessment of the patients.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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