Systematic Review and Meta-Analysis

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The effect of induction chemotherapy in patients with locally advanced nonsmall cell lung cancer who received chemoradiotherapy

A systematic review and meta-analysis

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Abstract

Background: The efficacy and toxicity of induction chemotherapy followed by concurrent chemoradiotherapy (CCRT) in patients with locally advanced nonsmall cell lung cancer (NSCLC) is unclear, we performed a systematic review and meta-analysis of published papers to quantitatively evaluate the potential benefit of induction chemotherapy.

Methods: Eligible studies of induction chemotherapy and chemoradiotherapy were retrieved through extensive searches of the PubMed, Science Direct, Embase, and Cochrane library databases from 1994 to 2015. We excluded studies that using non-English. Our primary endpoint was overall survival (OS), secondary end point was toxicity.

Results: Two studies of induction chemotherapy followed by CCRT versus CCRT alone and 5 studies of induction chemotherapy followed by CCRT versus CCRT followed by consolidation chemotherapy published in the same period were selected and analyzed. Our results showed that there was significant benefit of induction chemotherapy plus CCRT compared to CCRT alone on 5-year OS without 1, 2, 3, and 4 years OS. Our analysis also indicated that induction chemotherapy was as effect as consolidation chemotherapy for patients who received CCRT on overall response and OS. Treatment-related toxicity was similar between the 2 group; however, leucopenia was significant decreased in patients treated by induction chemotherapy (odds ratio [OR] = 0.43; 95% confidence interval [CI], 0.30–0.62; $P < 0.00001$).

Conclusion: Five year OS could be improved when induction chemotherapy was added into CCRT for patients of NSCLC. Except low rate of leucopenia, induction chemotherapy was no difference compared to consolidation chemotherapy in patients with NSCLC treated by CCRT.

Abbreviations: CCRT = concurrent chemoradiotherapy, CI = confidence interval, NSCLC = nonsmall cell lung cancer, OR = odds ratio, ORR = objective response rate, OS = overall survival, RTOG = radiation therapy oncology group.

Keywords: concurrent chemoradiotherapy, consolidation chemotherapy, induction chemotherapy, meta-analysis, nonsmall cell lung cancer

1. Introduction

Lung cancer remains the most fatal disease worldwide. For these newly diagnosed, about 85% being nonsmall cell lung cancer (NSCLC).[1] Patients with NSCLC who present at early stages can achieve long-term survival benefit from single modality therapy of either surgery or stereotactic body radiotherapy. Clinical stage III disease occupied approximately 8% to 20% of

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these patients and 60% of which eventually die from their disease.[2] The treatment for patients of locally advanced NSCLC is challenging which including unresectable stage III NSCLC according to the 7th edition TNM-staging classification in most guidelines.[3,4] Locally advanced NSCLC should be treated with multimodality approach, including surgery, chemotherapy, and radiotherapy.[5] Several studies have proved concurrent chemoradiotherapy (CCRT) in superior to sequential chemoradiotherapy, including a meta-analysis based on individual patient data.[6–8]

Despite many clinical trials, the use of induction therapy and CCRT for locally advanced NSCLC remains controversial. This topic is most easily understood by considering the management of stage IIIA (N2) disease and T3-4 N0-1 tumors separately. In addition, an experience with induction therapy for earlier stage NSCLC has begun to emerge. Induction therapy has potential benefits in comparison with postoperative adjuvant therapy, including the assessment of systemic therapy in vivo, improved delivery of drugs to the tumor, earlier treatment of micrometastatic disease, an increased likelihood of patients receiving the planned regimen, and down staging of disease before local therapy. Some of these, such as better drug delivery, are well accepted, whereas others, such as improved overall survival (OS) or progression-free survival, remain unproven.

Given the widespread use of induction chemotherapy in the treatment of NSCLC and the potential benefits, we sought to summary all clinical studies and determine the survival outcomes of NSCLC patients receiving induction chemotherapy.

2. Material and methods

Ethical approval and patient written informed consent are not required due to that this is a systematic review and meta-analysis of previously published studies. This study was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[9]

2.1. Inclusion and exclusion criteria

We identified all publications that studied survival outcomes in NSCLC patients treated with induction chemotherapy and CCRT. Exclusion criteria included noninduction chemotherapy, articles with no control group, a lack of data sufficient for odds ratio (OR) determination, and non-English language studies. In situations of insufficient data, attempts to contract primary authors were made.

2.2. Search strategy for identification of studies

All studies were searched from January 1994 to December 2015 from PubMed, Science Direct, Embase, and Cochrane Library. The following search terms were used: "nonsmall cell lung cancer," "NSCLC," "lung cancer," "induction chemotherapy," "neoadjuvant chemotherapy," "chemoradiotherapy," and "concurrent chemoradiotherapy." The relevant reviews and meta-analysis regarding the role of induction chemotherapy of patients with NSCLC were examined for potential inclusive studies. A summary of the search strategy is provided in Fig. 1.

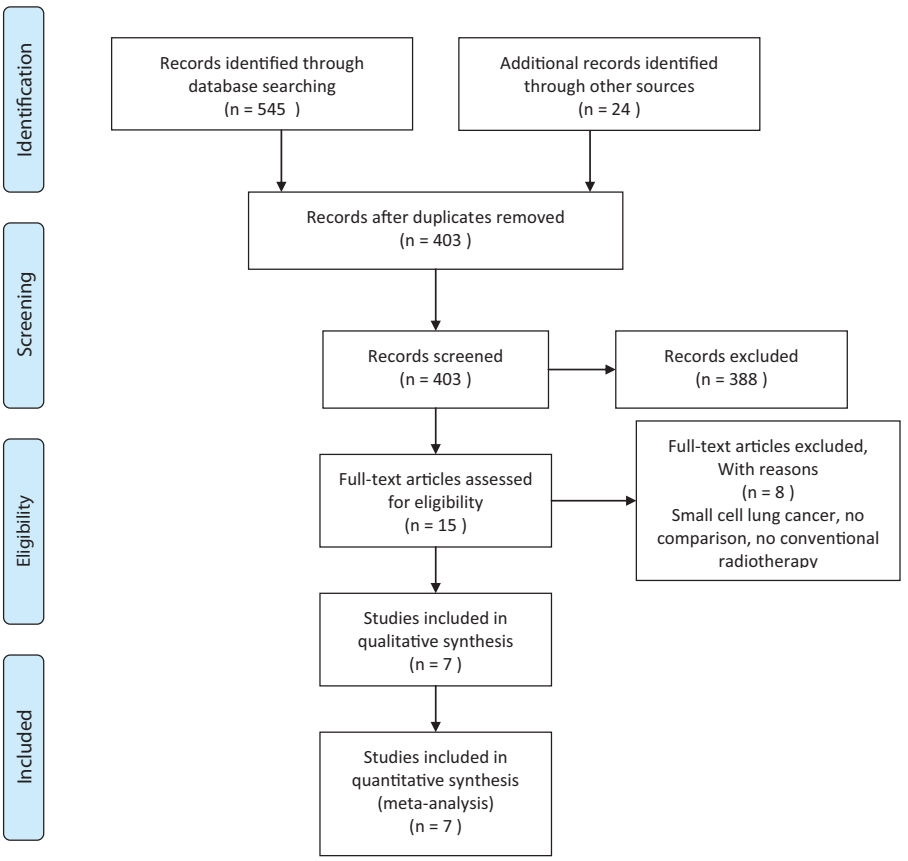

Figure 1. Search process of meta-analysis on induction chemotherapy for patients of NSCLC who received CCRT. CCRT = concurrent chemoradiotherapy, NSCLC = nonsmall cell lung cancer.

Table 1

Characteristics of the included studies for induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone.

First author	Years	Patients	TNM stage	Induction chemotherapy regimens (3 weekly cycles)	Concurrent chemotherapy	Concurrent radiotherapy	Median follow-up, months
Huang et al	2007	265	IIA–IIIB	Platinum and taxane-based (n = 121) Cisplatin and etoposide (n = 1) Cisplatin and gemcitabine (n = 2) Gemcitabine and vinorelbine (n = 3)	Weekly Platinum and taxane-based (n = 165) Cisplatin and etoposide (n = 18) Cisplatin/gemcitabine/taxane (n = 19) 3 weeks Cisplatin and etoposide (n = 63)	3D-CRT Daily 1.8–2.0 Gy (n = 183) Twice-daily 1.2 Gy (n = 82)	19.0
Vokes et al	2007	366	IIIA–IIIB	Carboplatin and paclitaxel (n = 170)	Weekly Paclitaxel and carboplatin	3D-CRT Daily 2.0 Gy (n = 183)	38.0

3D-CRT = 3-dimensional conformal radiation therapy.

2.3. Data extraction and quality assessment

Each of eligible articles were independently reviewed by 2 of the authors who extracted data on the following categories: dates over which the study was conducted, the details of the NSCLC, induction chemotherapy agent and dosing regimen, and radiotherapy treatment including dose and fraction. The extracted data were then crosschecked between the 2 authors to rule out discrepancy. In the situation of disagreement, a 3rd reviewer(c) extracted the data once more after referring to the original articles.

2.3.1. Statistical analyses. For dichotomous outcomes, the OR was calculated with a 95% confidence interval (CI) using the Mantel–Haenszel method. Several studies report only Kaplan–Meier survival analysis. In those cases, ORs were extracted from the survival curves or rates using methods recommended by the Cochrane Handbook.[10] Meta-analyses were performed to calculate the pooled ORs from each clinical outcome, and a level <5% was assumed statistically significant. Heterogeneity among the studies was evaluated by the chi-test and the I^2 test. Statistically significant heterogeneity was defined as P less than 0.1 or an I^2 statistic greater than 50%, I^2 values of 25 to 50% were deemed to represent low heterogeneity.[11] When there was no statistically significant heterogeneity, a pooled effect was calculated with fixed-effects model; if not, a random-effects model was used. ORs and 95% CI for time-to-event outcomes were estimated as described by Parmar et al[12] and pooled according to Peto method. A 2 tailed $P < 0.05$ showed statistical significance. Statistical analyses were performed using Revman 5.3 (Cochrane Collaboration, Copenhagen).

3. Results

3.1. Trial flow and characteristics of the eligible trials

Seven studies met the inclusion criteria and were incorporated in the review, accounting for 1143 patients.[13–19] The studies selected were all either prospective or retrospective cohort studies. The flow chart of our study is shown in Fig. 1. Consequently, 2 trials[13,14] involving 596 patients and 5 studies[15–19] of 547 patients with advanced NSCLC were ultimately analyzed. Main characteristics of the selected trials are described in Tables 1 and 2.

A total of 7 researches were eligible for analyzing that included 5 randomized phase III trials[15–19] and 2 retrospective studies.[13,14] With a range for each trial (1.3–6.0 years), the median follow-up time was 3.3 years. The primary endpoints were detailed in all studies. Tables 1 and 2 showed the details of radiotherapy and chemotherapy in the selected researches. There were 4 trials investigated cisplatin-based chemotherapy regimens which include taxane, etoposide, gemcitabine, vinorelbine, and docetaxel. Carboplatin combined with paclitaxel chemotherapy regimens were used in 2 studies and only 1 research consisted of gemcitabine with docetaxel. Conformal radiotherapy was most used and there was a variety of radiation dosed in the studies included in the analysis. The most common radiotherapy regimen was a total dose of 66 Gy in 33 fractions of 2.0 Gy per fraction.

3.2. Overall survival

3.2.1. Induction chemotherapy followed by CCRT versus CCRT alone. There were 2 studies involving 596 patients included in this comparison.[13,14] The statistical heterogeneity

Table 2

Characteristics of the included studies for induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy with consolidation chemotherapy.

First author	Years	Patients	TNM stage	Induction chemotherapy regimens (dose per cycle)	Consolidation chemotherapy regimens (dose per cycle)	Concurrent radiotherapy (5 fractions per week)	Median follow-up, months
Berghmans et al	2008	49	IIB–IIIB	Two cycles cisplatin, gemcitabine, and vinorelbine	Two cycles cisplatin, gemcitabine, and vinorelbine	66 Gy daily 2.0 Gy	51.0
Senan et al	2011	70	IIIA–IIIB	Two cycles cisplatin and docetaxel	Two cycles cisplatin and docetaxel	66 Gy in 33 daily 2.0 Gy	15.1
Belani et al	2005	166	IIIA–IIIB	Two cycles carboplatin and paclitaxel	Two cycles carboplatin and paclitaxel	63 Gy daily 1.8–2.0 Gy	39.6
Garrido et al	2013	139	IIIA–IIIB	Two cycles gemcitabine and docetaxel	Two cycles gemcitabine and docetaxel	60 Gy daily 2.0 Gy	57.0
Fournel et al	2015	127	IIIA–IIIB	Two cycles cisplatin and docetaxel	Two cycles cisplatin and docetaxel	66 Gy daily 2.0 Gy	76.8

was moderate to high in 1, 2, and 4 year OS and a random effect model used (I^2=0.89, P=0.002; I^2=0.55, P=0.14; and I^2=0.67, P=0.09, respectively). No difference of OS at 1, 2, and 4 year were found between these 2 groups (P=0.23, P=0.18, P=0.09, respectively).

No statistical heterogeneity were found in 3 and 5 year OS (I^2=0.00, P=0.49; I^2=0.00, P=0.40, respectively). Although the P value of 3 year OS was 0.07 without statistical significance, it showed a favor of induction chemotherapy. The result of 5-year OS suggested that induction chemotherapy was a positive factor in locally advanced NSCLC (OR 1.98, 95% CI 1.24–3.17; P=0.004) (Fig. 2).

3.2.2. Induction chemotherapy followed by CCRT versus CCRT followed by consolidation chemotherapy. With 5 eligible trials of induction chemotherapy followed by CCRT compared to CCRT followed by consolidation chemotherapy included in the analysis were available of 1, 2, and 3-year OS.[15–19] No statistical heterogeneity was found in the outcomes. The results showed no statistically significant in OS with induction chemotherapy (P>0.05) (Fig. 3). The 4 and 5-year OS were also reported in 3 studies and it revealed no statistical significance (Fig. 4). The finial outcomes indicated that chemotherapy before or after CCRT were both effective. Data on objective response rate (ORR) were available from the 5 included studies of 547 patients using standard World Health Organization. The test for heterogeneity was no significant (P=0.52; I^2=0%), so the fixed-effects model was used. The ORR in induction chemotherapy arm was similar to consolidation chemotherapy arm, 71.3% versus 68.0%, respectively. (OR 1.25; 95%CI, 0.86–1.83; P=0.25) (Fig. 5).

3.2.3. Toxicity. Methods for reporting toxicity were consistent among the 5 researches of induction chemotherapy followed by CCRT compared to CCRT followed by consolidation chemotherapy.[15–19] The most frequently reported toxic events (grade III to IV) are summarized. The statistical heterogeneity was low and a fixed-effect model was used. Both chemotherapy and

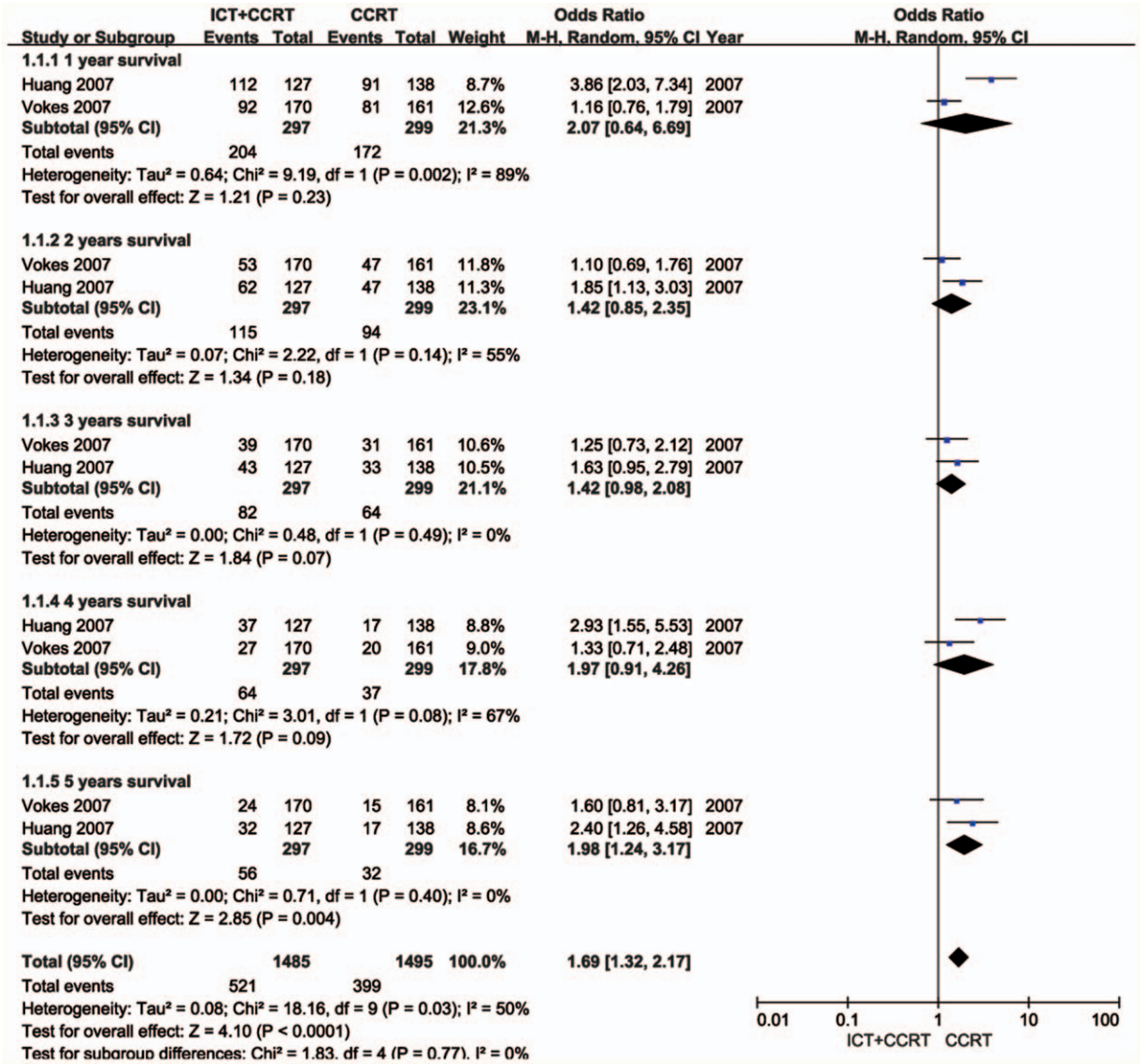

Figure 2. Forest plot of OR of 1, 2, 3, 4, and 5-year overall survival in induction chemotherapy followed by CCRT group versus CCRT alone group. CCRT = concurrent chemoradiotherapy, OR = odds ratio.

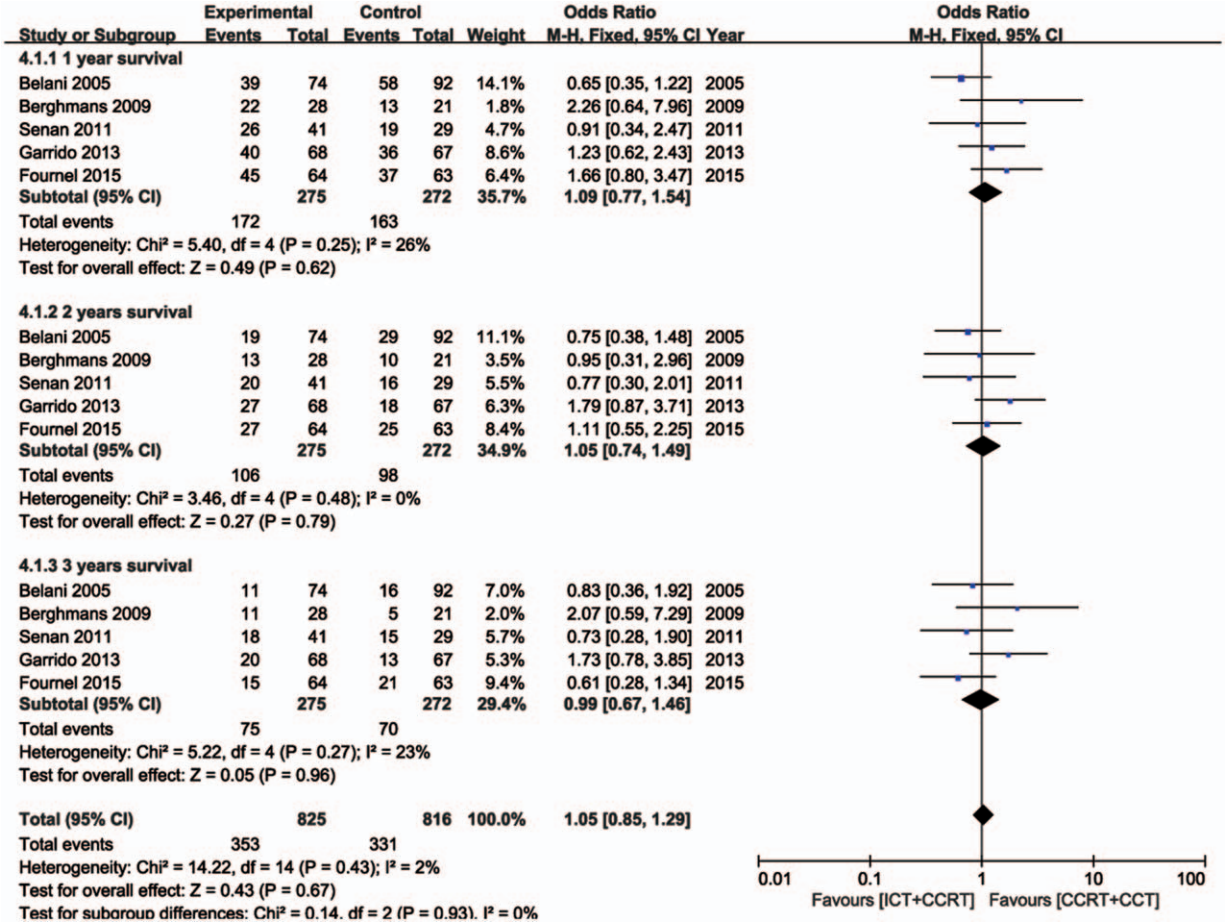

Figure 3. Forest plot of OR of 1, 2, and 3-year overall survival in induction chemotherapy followed by CCRT group versus CCRT with consolidation chemotherapy group. CCRT = concurrent chemoradiotherapy, OR = odds ratio.

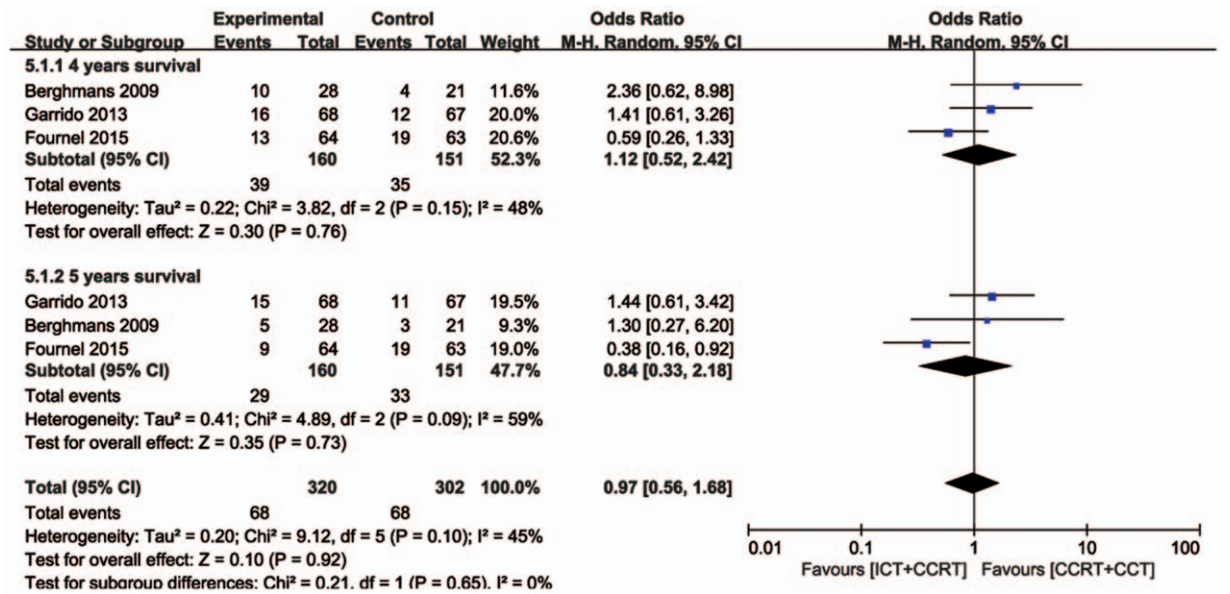

Figure 4. Forest plot of OR of 4 and 5-year overall survival in induction chemotherapy followed by CCRT group versus CCRT with consolidation chemotherapy group. CCRT = concurrent chemoradiotherapy, OR = odds ratio.

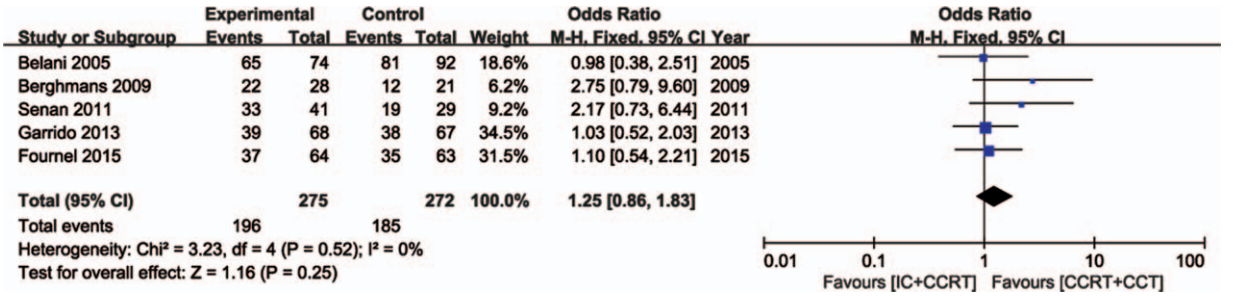

Figure 5. Forest plot of overall response rate in induction chemotherapy followed by concurrent chemoradiotherapy (CCRT) group versus CCRT with consolidation chemotherapy group.

radiotherapy most frequently led to grade III or more of leucopenia (OR = 0.43; 95%CI: 0.30–0.62; $P < 0.00001$), thrombocytopenia (OR = 0.66; 95%CI: 0.33–1.30; $P = 0.23$), radiation pneumonitis (OR = 0.49; 95%CI: 0.23–1.06; $P = 0.07$), and esophagitis (OR = 0.71; 95%CI: 0.46–1.11; $P = 0.14$) (Fig. 6). Only leucopenia was significantly higher in consolidation group than induction group. No significant difference in the number of treatment-related severe pulmonary, neurological, infection, cardiovascular, liver, and renal toxicity was observed between the 2 modalities.

4. Discussion

Our meta-analysis provides a summary of induction chemotherapy on the prognostic in locally advanced NSCLC patients who received CCRT. The difference of survival between the patients who received induction chemotherapy compared to those that did not receive induction chemotherapy is significant at 5-year OS. However, the 1, 2, 3, and 4 years OS are not achieved statistical significant. This outcome reflects that induction chemotherapy may be an important factor which affecting long-term survival but not short-term survival. For several decades, the survival rate of NSCLC has not been significantly improved for the reasons given below: both loco-regional recurrence and distant metastasis were easy to occur, and loco-regional failure being the primary culprit. Induction chemotherapy has been proved to reduce the size of local and regional lesions to improve local disease control while preserving normal structure and function as much as possible in locally advanced NSCLC patients.[20,21] Induction chemotherapy has a number of putative advantages including down staging, reduced tumor volume, delivery of treatment conveniently, and achieved high rates of treatment response. Induction chemotherapy, most importantly, may also facilitate selection for CCRT of patients with favorable tumor biology, patients who achieved treatment response prior to CCRT or who do not with progress disease can obtain a better survival. Moreover, it can avoid the morbidity of fruitless CCRT for patients with poor tumor biology who underwent disease progression after induction chemotherapy.[22–24] With the mechanisms above, patients of locally advanced NSCLC could

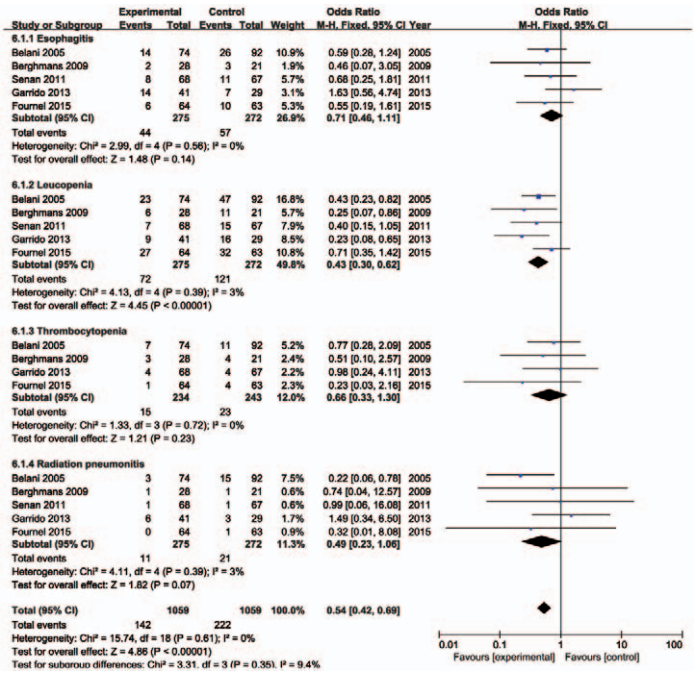

Figure 6. Forest plot of adverse effects in induction chemotherapy followed by concurrent chemoradiotherapy (CCRT) group versus CCRT with consolidation chemotherapy group.

obtain better long-term survival in induction chemotherapy group than those who only treated by CCRT only. Marquez-Medina et al[25] reported that for patients treated by induction chemotherapy, the lower presence of angiolymphatic invasion and tumor necrosis were associated with a good survival. Further analysis should be conducted to improve the prognosis of patients with locally advanced NSCLC.

Although long-term OS benefit was identified from the induction chemotherapy regimen, the optimal sequencing of chemotherapy and CCRT in the management of locally advanced NSCLC has remained a subject of intense debates. Against this background, we present a meta-analysis to evaluate the efficacy and toxicity of induction chemotherapy followed by CCRT versus CCRT followed by consolidation chemotherapy in the treatment of locally advanced NSCLC.

To the best of our knowledge, this is the first meta-analysis of induction chemotherapy followed by CCRT in comparison to CCRT with consolidation chemotherapy. Under comprehensively searched literatures, our meta-analysis showed that patients in induction chemotherapy followed by CCRT arm with similar ORR (OR = 1.25, 95%CI 0.86–1.83, $P = 0.25$) compared with CCRT followed by consolidation chemotherapy arm. It indicated that induction chemotherapy is as efficient as consolidation chemotherapy for locally advanced NSCLC. Also, similar OS was obtained in both groups. The concept of induction chemotherapy followed by CCRT or CCRT followed by consolidation chemotherapy has become progressively more popular in an attempt to improve distant disease control.[26] This regimen is practically used in clinical treatment of patients with locally advanced NSCLC. When it comes to toxicities, the final results revealed no significant toxicity in terms of induction chemotherapy versus consolidation chemotherapy except induction chemotherapy with an decreased risk of grade 3 to 4 leukopenia (OR = 0.43, 95%CI 0.30–0.62, $P < 0.00001$). One potential explanation is the toxic effects lead on hematopoietic and immune systems after CCRT, as a result of myelosuppression. Although there is a trend of in favor of consolidation chemotherapy for radiation induced pneumonitis ($P = 0.07$) and esophagitis, both of which did not achieve statistical significance between the 2 cohort, these lower incidences could be interpreted by the use of modern radiation technologies and a less toxic chemotherapy regimen for induction or consolidation to prevent pulmonary as well as esophagus toxicities. Further exploration is needed to identify the potential mechanism.

Three-dimensional conventional radiation therapy is the standard treatment in NSCLC. The famous radiation therapy oncology group 0617 trial has established 60 Gy as the standard dose. It was performed as a randomized, phase III trial assessing a standard dose versus high dose radiation therapy with concurrent and consolidation paclitaxel plus carboplatin with or without cetuximab for patients of unresected stage III NSCLC.[27] Patients were randomly assigned to receive either a standard dose of 60 Gy or a high dose of 74 Gy, radiation dose was prescribed to the planning target volume with 2 Gy daily fractions, median OS was 28.7 months for the standard dose group and 20.3 months for those of high dose group ($P = 0.004$), and high dose group was associated with more treatment-related deaths. Schild and Vokes have discussed pathways to improving combined modality therapy, especially radiotherapy for stage III NSCLC in detail.[28] In the present meta-analysis, most selected studies were similar to the standard dose.

Although various chemotherapy drugs were used among these studies, there was a trend in favor of cisplatin-based therapy. However, we were unable to reach a consensus to recommend any individual chemotherapy regimen due to methodological issues and patient heterogeneity of the studies. In a single institution review by Kocak et al,[29] they analyzed to different chemotherapeutic regimens (group 1: gemcitabine plus cisplatin; group 2: docetaxel and cisplatin) in patients with locally advanced NSCLC who received induction chemotherapy followed by CCRT, the response rate in group 2 was significantly higher than that of group 1 after induction chemotherapy (88.2% vs 64.1%, $P = 0.017$). One month after CCRT, it showed a statistical difference for ORR in group when compared to group 1 ($P = 0.04$). Median OS was 12 months in group 1 whereas 29.9 months in group 2, and median progression-free survival was 8 months in group 1 compared with 12 months in group 2 ($P = 0.043$). Final results suggest docetaxel plus cisplatin superior to gemcitabine and cisplatin in locally advanced NSCLC.[29] Future researches should focus on different chemotherapy regimens.

The limited availability of randomized data has clearly decreased the power of our meta-analysis on induction chemotherapy followed by CCRT compared to CCRT alone, though it is worth that these studies showed a long-term survival benefit to the addition of induction radiotherapy. This highlights the need for caution when interpreting these pooled data. Clinicians who treat lung cancer should strive to develop formal protocols and participate in randomized studies that address this topic in order to address this critical shortage of evidence. In addition, the chemotherapy regimens used in these studies were heterogeneous and these could have an impact on survival. However, most of the included studies were platinum-based and delivered radiation concurrently with chemotherapy.

In conclusion, published evidence is limited but does support the inclusion of induction chemotherapy for locally advanced NSCLC to achieve long-term survival. Both induction chemotherapy and consolidation chemotherapy are efficient for patients of locally advanced NSCLC who treated by CCRT, given the potential toxicities of adding consolidation chemotherapy to CCRT, clinicians should consider using this treatment strategy only in the context of a clinical trial to allow better assessment of its effectiveness.

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