Peer Review File

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Reviewer A

The authors conducted a meta-analysis investigating postoperative radiotherapy in phase III N2 non-small cell lung cancer after resection followed by adjuvant chemotherapy. It poses an interesting clinical question regarding the effectiveness of radiotherapy in the perioperative period for NSCLC patients. However, this study has several flaws.
Major Comment 1:
The authors should provide more information about the enrolled patients, including the ratio of historical types, the regimen used, and the timing of radiotherapy (concurrent or continuous). This additional information would help readers better understand the study.

Reply: Thank you for your valuable comment. We have added some data as per your suggestions. (see Page 16, Table 1)

Changes in the text: Please refer to the table below.

Table 1. Baseline characteristics of included studies.

Study (year)	Time duration	Country of origin	Study design	No. of patients	Histology	No. of patients (PORT)	No. of patients (non-PORT)	RT technique	RT dose	RT timing	Type of surgery	Chemotherapy Regimen	Outcomes (PORT vs non-PORT)
CALGB 9734 (2007)	1998-2000	America	Phase III single center RCT	37	NR	19	18	NR	50 Gy	Continuous (2~4 weeks after CTx)	Lob/Bil/ Pne	4 cycles of paclitaxel(200mg/m^2) /carboplatin (AUC<6)	1yr OS: 74% vs. 72% median DFS 33.7m vs. 16.8m
Shen (2014)	2004-2009	China	Phase III multicenter RCT	135	SCC: 59 (43.7%) NSCC: 76 (56.3%)	66	69	3D	50 Gy	Concurrent	Lob/Bil/ Pne	4 cycles of paclitaxel(175mg/m^2) /cisplatin(60mg/m^2)	5yr OS: 37.9% vs. 27.5% median OS: 40m vs. 28m 5yr DFS 30.3% vs. 18.8% median DFS: 28m vs. 18m
Sun (2017)	2009–2014	Korea	Phase II single center RCT	101	SCC: 20 (19.8%) NSCC: 81 (80.2%)	51	50	3D	50 Gy	Concurrent	Seg/Lob /Bil/Pne	PORT: 5 cycles of weekly paclitaxel(50mg/m^2)/ cisplatin (25mg/ m^2) +2 cycles of paclitaxel(175mg/m^2) /cisplatin(60mg/m^2) non-PORT: 4 cycles of paclitaxel(175mg/m^2) /carboplatin (AUC=5.5)	median OS: 74.3m vs. 83.5m median DFS: 24.7m vs. 21.9m
Lung-ART (2021)	2007-2018	Europe	Phase III multicenter RCT	501	SCC: 108 (21.6%) NSCC: 393 (78.4%)	252	249	3D (89%), IMRT (11%)	54 Gy	Continuous (2~6 weeks after CTx)	Sub/Lob /Pne	platinum-based doublets (neoadjuvant or adjuvant)	3yr OS 66.5% vs. 68.5% 3yr DFS 47.1% vs. 43.8% median DFS 30.5m vs. 22.8m
PORT-C (2022)	2009-2017	China	Phase III Multicenter RCT	364	SCC: 59 (16.2%) NSCC: 305 (83.8%)	184	180	3D (11%) or IMRT (89%)	50 Gy	Continuous (< 6weeks after CTx)	Lob/Bil	4 cycles of platinum-based doublet regimen	3yr OS 78.3% vs. 82.8% 3yr DFS 40.5% vs. 32.7% median DFS 22.1m vs. 18.6m

PORT, postoperative radiotherapy; RT, radiotherapy; RCT, randomized controlled trial; NR, not reported; SCC, squamous cell carcinoma; NSCC, non-squamous cell carcinoma; 3D, three-dimensional conformed radiotherapy; IMRT, intensity-modulated radiotherapy; CTx, chemotherapy; Lob, lobectomy; Bil, bilobectomy; Pne, pneumonectomy; Seg, segmentectomy; Sub, sublobar resection; AUC, area under the curve; OS, overall survival; DFS, disease–free survival; m, months

Major Comment 2:
Is it possible to conduct a subgroup analysis to identify whether radiotherapy would be effective in specific combinations, such as regimen, historical types, timing of radiotherapy, etc.?

Reply: We appreciate your critical and valuable comments.

Among the five studies included in this study, only two provided results of subgroup analysis. A subgroup analysis performed in the Lung-ART study compared 3-year DFS in the PORT and control groups. There were no differences based on histology [for SCC (HR 0.71, 95% CI 0.41-1.21), for non-SCC (HR 0.89, 95% CI 0.69-1.14)] and number of mediastinal lymph node sites involved [for 0 (HR 0.22, 95% CI 0.02-2.11), for 1 (HR 0.93, 95% CI 0.69-1.26), and for ≥ 2 (HR 0.78, 95% CI 0.53-1.13)].

In the study by Sun et al., chemotherapy was favored in non-smokers and the multi-station N2 subgroups. Furthermore, in adenocarcinoma, chemotherapy was favored with HR 2.01 and 95% CI 0.972-4.160, though this result did not reach statistical significance.

While we acknowledge the potential benefits of performing subgroup analyses to assess the effectiveness of PORT in specific combinations, the diverse study protocols and presented information precluded the performance of the subgroup analysis requested by the reviewers.

Major Comment 3:
The results of Shen/2014 are challenging to understand. The trend shows that radiotherapy is not effective in improving progression-free survival (PFS), but it is effective in improving overall survival (OS), which is difficult to explain in clinical practice. The authors should reevaluate the data for accuracy.

Reply: We have reevaluated the paper based on your comments. Unlike other studies, Shen et al. suggested that radiotherapy not only suppresses local recurrence but also improves survival outcomes. They reported that the postoperative concurrent radiochemotherapy (POCRT) group exhibited a disease-free survival (DFS) of 28 months with a 5-year DFS rate of 30.3%, while the postoperative chemotherapy (POCT) group had a DFS of 18 months with a 5-year DFS rate of 18.8%. The recurrence hazard ratio in the POCT group was 1.49 (95% CI: 1.008–2.204, P = 0.041). In addition, the POCRT group had a median survival (MS) of 40 months and a 5-year overall survival (OS) rate of 37.9%, while the POCT group exhibited an MS of 28 months with a 5-year OS rate of 27.5%. The hazard ratio for death in the POCRT group was 0.69 (95% CI: 0.457–1.044, P = 0.073).

They reported that radiotherapy was an independent prognostic factor that increased DFS in patients with stage III-N2 NSCLC who underwent surgical resection and adjuvant chemotherapy (HR = 0.67, P = 0.041). However, it was not a prognostic factor for increasing OS (HR = 0.69, P = 0.073). The authors discussed that the relatively small sample size of the study might be related to these results.

Furthermore, they suggested that radiotherapy could eliminate residual small tumors and prevent distant metastasis. In addition, they suggested that, unlike other studies, this study used concurrent radiotherapy, which may have had a synergistic effect with adjuvant chemotherapy to suppress both loco-regional and distant metastasis.

Reviewer B

The authors, Dr. Kim et al., have made meta-analysis evaluating the efficacy of postoperative radiation therapy for patients with completely resected p-N2 positive NSCLC. Overall, the meta-analysis was well conducted and described in their manuscript, and I consider their manuscript has valuable information for physicians to treat patients with NSCLC. However, I consider some context may be inadequate in Introduction section and Discussion section, thus, I recommend authors to make minor revision.

First, they described their opinion for the worse prognoses of patients with pIII-N2 NSCLC as “This is mainly attributed to the high risk of locoregional recurrence, even after complete resection”, in Page 4, Line

64-65. However, I consider the main cause of worsen prognoses of patients with pIII-N2 NSCLC are distant metastases, not locoregional recurrence. The study they referred to as ref.#3 also showed that the main recurrence pattern of patients with completely resected p-N2 NSCLC was distant, consist of 75.5% of all recurrent patients, while loco-regional recurrence (including patients with both distant and loco-regional) was found in 24.5% of all recurrent patients. The stage III diseases should be thought as "nearly systemic disease", and according to such theory, postoperative systemic therapy such as adjuvant chemotherapy has been widely introduced in clinical practice. Thus, their opinion seemed to be slightly inadequate, and I recommend authors to revise the context described in their Introduction Section.

Reply: Thank you for your comment. As you have mentioned, we agree that N2 disease is "nearly systemic disease." In this study, we sought to discuss the clinical implications of PORT and therefore focused on local recurrence. We acknowledge that the sentences used in the introduction may be misleading. We have revised this in the text. (see Page 4, line 64)

Changes in the text: The prognosis for patients with pathological stage III-N2 (pIII-N2) non-small cell lung cancer (NSCLC) remains poor, with 5-year survival rates ranging from 19.2% to 30% (1, 2). Although this is mainly due to the high risk of distant metastasis, locoregional recurrence rates remain high even after complete resection. Multimodal therapy is thought to offer the best chance for 66 improving the prognosis of pIII-N2 NSCLC (3, 4).

Second, I felt that the sentence "Nonetheless, the meta-analysis in 1998 did not show an adverse effect of PORT in patients with stage III-N2. It implies the possibility that there might be oncological benefits that could compensate for the adverse effect of PORT in stage III-N2 NSCLC", described in Page 9, Line 173-175, which discuss the potential of PORT for patients with stage III-N2 disease, was difficult to understand. Just before the sentence, they described the result of meta-analysis published in 1998 (ref.#29) showing the worsen outcome by addition of PORT for patients with pN0 and pN1 NSCLC, however, the authors did not show the result from pN2 subset in this 1998' study in their manuscript. If the outcome of patients in pN2 subset in the 1998' meta-analysis was favorable for addition of PORT, there may be oncological benefits that could compensate for the adverse effect of PORT. On the other hand, if the outcome of patients in pN2 subset in the 1998' meta-analysis was unfavorable as same as for patients with pN0 and pN1 NSCLC, or even be equivalent to non-PORT patients, the PORT should be harmful due to the adverse event. In summary, we can't evaluate the possibility of PORT in stage III-N2 NSCLC only according to the data concerning to the adverse event, and the evaluating the data concerning outcome is mandatory. So, I recommend the authors to add the findings of the outcome of patients in pN2 subset from the 1998' meta-analysis in the Discussion Section.

Reply: We appreciate your valuable comments. In the 1998 meta-analysis (1), subgroup analysis was performed to assess whether there was evidence of a differential effect of postoperative radiotherapy according to the number of involved lymph node stations. They suggested a tendency for PORT to become increasingly detrimental as the number of involved node status decreased (trend P = 0.016). (see Page 9, line 170)

1. Group PM-aT. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. The Lancet. 1998;352(9124):257-63.

Changes in the text:
Over the past 30 years, the role of PORT in pIII-N2 NSCLC after complete resection has been consistently controversial. Data from RCTs performed in the 1980 to 1990s were incorporated in a meta-analysis published in 1998 that showed worse outcomes for pN0 and pN1 NSCLC (28). Furthermore, it suggested a tendency for PORT to become increasingly detrimental as the number of involved lymph nodes decreased,

with a statistically significant trend observed (P = 0.016). This was thought to be related to outdated radiation techniques and subsequent heart and lung toxicity supported by accumulating evidence from several other studies (29). Nonetheless, the meta-analysis in 1998 did not show an adverse effect of PORT in patients with stage III-N2. It implies the possibility that there might be oncological benefits that could compensate for the adverse effect of PORT in stage III N2 NSCLC.

Reviewer C

This is a meta-analysis based on the publication of 5 randomized trials testing PORT after a complete resection of N2 disease and chemotherapy. The analysis is mainly based on the two large recent randomized trials of China and Europe. Your conclusions is in complete agreement with the two papers: improved local control but no survival benefit. The three other trials included a limited number of patients. Your analysis is correct but I am not sure it add any new information. One problem is that you are not reporting when you start your search.
I am supposing you are using the data published on the individual data of the patients included in those trials.
In the introduction, you are telling us that the poor results was attributed to the high risk of locoregional relapse but this is only one part of the problem: distant failure is also a major concern

Reply: Thank you for your valuable comment. We acknowledge that the results of this meta-analysis have some similarities to those of previous studies. However, radiotherapy is still used as an important treatment modality, and there is still controversy as to what clinical benefits it offers. Therefore, by combining the results of two recently published RCT studies (PORT-C and Lung-ART), we can update the current knowledge on the clinical implications of radiotherapy in patients with III-N2 NSCLC who underwent complete resection.

As you have mentioned, not only local recurrence but also distant failure must be considered. In this study, we wanted to discuss the clinical implications of PORT and therefore focused on local recurrence. We acknowledge that the sentences used in the introduction may be misleading. We have revised this in the text. (see Page 4, line 64)

Changes in the text: The prognosis for patients with pathological stage III-N2 (pIII-N2) non-small cell lung cancer (NSCLC) remains poor, with 5-year survival rates ranging from 19.2% to 30% (1, 2). Although this is mainly due to the high risk of distant metastasis, locoregional recurrence rates remains high even after complete resection. Multimodal therapy is thought to offer the best chance for improving the prognosis of pIII-N2 NSCLC (3, 4).

Reviewer D

This paper is similar to the following paper (*). The following article clearly shows that postoperative radiation therapy improves locoregional progression-free survival (HR 0.64, 95% CI: 0.50-0.81, P=0.0003), but not OS (HR 0.87, 95% CI: 0.71-1.07, P=0.18), DFS HR 0.83, 95% CI: 0.71-0.97, P=0.02).

*Lei T, Li J, Zhong H, et al. Postoperative radiotherapy for patients with resectable stage III-N2 non-small cell lung cancer：a systematic review and meta-analysis. Front Oncol. 2021；11：680615.

Therefore, there is no novelty in this study. I deem it not worthy of publication in this journal.

Reply: Thank you for mentioning this critical point. PORT remains an important treatment modality in clinical practice. To provide patients with optimal treatment plans, I considered it necessary to obtain

updated knowledge by combining the results of two recently published large studies (PORT-C and Lung-ART). Furthermore, because of the development of radiotherapy technology, the radiotherapy techniques used recently are very different from those of the past. Therefore, authors of this study believe that this article is meaningful, including two recently conducted studies.

Reviewer E

First of all, I would like to congratulate authors to carry out meta-analysis of this kind. As we have got into the era of ICI or TKI, we tend to see fundamentals in cancer treatment.

Radiation therapy plays key roles in local control of disease. In terms of patient selection, more would benefit from radiation compared to surgical resection during various stages in lung cancer treatment. As authors described in the manuscript, radiation therapy grew more sophisticated in last couples of decades.

In manuscript
Page 4 line 67
Authors defined chemotherapy applied postoperatively as POCT. I wounder this is a common term in this field. I would prefer adjuvant chemotherapy for this term. Though it might be easier to describe similar to PORT. This is only an opinion.

Reply: Thank you for your comment. We have revised term POCT to adjuvant chemotherapy throughout the text. (line 67, 69, 76, 161, 193, and 206)

Changes in the text: Large clinical trials have demonstrated that adjuvant chemotherapy offers clinical benefits in terms of overall survival (OS) and disease-free survival (DFS) among patients with completely resected pIII-N2 NSCLC.

Line 72
Authors describe ‘damage to the lungs, heart, and other major organs’. Does this mean side effects or toxicity of radiation therapy, which may occur after radiation such as radiation pneumonitis or perhaps later in course of treatment.

Reply: This includes any side effects or toxicities of radiation therapy that may occur immediately or later.

Page 9
Line 169
This part is well discussed and I cannot agree more with authors comments. The delivery methods of radiation definitely improved efficacy. Could you add reference or is this that obvious to us these days?

Reply: Thank you for your agreement with our discussion. We have added a reference in the text. Currently, in radiation therapy, refined radiation delivery such as three-dimensional conformed radiotherapy (3D RT) and intensity-modulated radiotherapy (IMRT) has become common. (see Page 9, line 177)

Changes in the text: Since then, radiotherapy techniques have been developed that are more delicate for target mediastinal tissue and less invasive for normal tissues including lung and heart. (17, 18, 29, 30)

Line 190
This indeed needs more to discuss, perhaps not in this review, though.

Reply: We agree with your suggestion. We currently live in the era of ICIs and TKIs. Various prospective studies on ICIs and TKIs are being conducted. In the future, when the study results are sufficiently mature, we can perform additional study on the relationship with PORT.

Reviewer F

The authors reported a meta-analysis about PORT after complete resection of stage IIIA-N2 NSCLC. This is a well-conducted and written manuscript.

Reply: Thank you for recognizing the value of our study.

Reviewer G

The main objective of this meta-analysis is to evaluate the clinical impact of postoperative radiotherapy (PORT) in non-small cell lung cancer (NSCLC) patients who have undergone complete resection. The study also aims to assess the benefits of adjuvant chemotherapy and PORT in terms of overall survival (OS), disease-free survival (DFS), and local and distant recurrence rates. According to the meta-analysis, adjuvant chemotherapy alone does not significantly reduce the risk of local recurrence in patients with completely resected pIII-N2 NSCLC. However, additional postoperative radiotherapy (PORT) was significantly associated with a reduced local recurrence rate. The pooled analysis of five randomized controlled trials (RCTs) revealed that PORT decreased the local recurrence rate by 47% compared to observation alone.
This information provides valuable insights into the potential benefits of postoperative radiotherapy in NSCLC patients after complete resection. However, it's crucial to consider individual patient factors and preferences when deciding on treatment strategies. Furthermore, ongoing research and advancements in oncology may contribute to refining treatment recommendations for NSCLC.
Although this paper lacks novelty, as a review article, I believe it provides an accurate assessment of postoperative radiotherapy at this point in time.
It would be an excellent paper if there was a discussion of which cases might benefit from PORT based on the results of this study.

Reply: Thank you for your valuable comment. As you have mentioned, although our paper lacks novelty, we can provide the latest knowledge at this point in time by enrolling the result of two recently published large-scale RCTs.

We also agree with the fact that it is important to plan a treatment strategy that considers individual patient factors and preferences.

As described in page 9 lines 184-189 of the manuscript, we cautiously speculate that PORT may have clinical implication in multi-station N2. In addition, we believe that the various oncology studies currently underway can refine which patients may benefit more meaningfully from PORT.