Peer Review File

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Response to Reviewer A:

Comment 1:

In the review article, the authors evaluated the effect of salvage therapy in the setting of patients having received a radiochemotherapy (RCT) for a stage III non-small cell lung cancer (NSCLC). Nine studies were selected. Despite the high rate of pneumonectomies (28%) the mortality was low and the outcome was good. The authors insisted on the value of time since RCT until salvage surgery as an indicator of better prognostic and suggest that surgery might be proposed for patients who have been sensitive to RCT or who experience local recurrence.

The review is well-written and the figure one explicated well the setting of this manuscript. However, the conclusions go too far beyond what can be said considering the nine studies included in this analysis: these nine reports are only retrospective series of cases and are not formal studies; the numbers of patients by study are small; the TNM status of the patients at time of initial RCT is not well established and one can suspect that it is heterogeneous.

Response: We appreciate the reviewer's constructive suggestion. We agree that these nine reports were only retrospective series of small number of cases and heterogeneous regarding the TNM status of the patients at the time of initial RCT. However, we have already described the limitation of this study in the conclusion section as follows: However, it is difficult to establish the role of salvage surgery in this setting because of the lack of phase III studies, considerable heterogeneity of patients, and the high level of patient selection. Considering this, the accumulation of empirical evidence, preferably in a prospective fashion, is warranted. (Page 13, Lines 213-217)

Comment 2:

The other main weakness, belongs to the selection of the studies in this review. The authors should indicate what MeSH terms were used to detect the different studies and should give a flow chart of selected and rejected studies.

Response: In accordance with the reviewer's comment, we have reconsidered and revised this section as seen below.

Page 6, Lines 102-110

Before

We searched PubMed for studies published from 2000 to 2019 regarding salvage

surgery after definitive CRT for patients with NSCLC. After careful screening, nine retrospective studies were extracted for this review (1-4, 13-17). All nine were single-center studies consisting of a small number of patients (median, 24 patients; range 8 to 35) (Table 1).

After

We searched PubMed for studies published from 2000 to 2019 regarding salvage surgery after definitive CRT for patients with NSCLC. Search terms included controlled terms (MeSH in PubMed and Emtree in Embase) as well as free text terms. Search terms expressing 'non-small cell lung cancer' were used in combination with 'chemoradiotherapy' and 'recurrence'. Only full-length English-language articles were included in this review. Salvage surgery after stereotactic body radiation therapy, review articles and duplicate articles were excluded. After careful screening, nine retrospective studies were extracted for this review (1-4, 13-17). All nine were single-center studies consisting of a small number of patients (median, 24 patients; range 8 to 35) (Table 1).

Comment 3:

It is surprising that the study by Eberhardt et al. (ref) does not figure in the selected study. This is, to my knowledge, the largest study that has investigated post RCT surgery versus definite RCT. In this study, with a median follow-up after random assignment of 78 months, 5-year OS and progression-free survival (PFS) did not differ between arms. The authors should explain why they have excluded this study that have evaluated the value of salvage surgery in patients who achieved CR or PR, insofar as the fig. 1 of their manuscript indicates this setting.

Response: In our review, we defined salvage surgery as lung resection for the local control of a tumor, which was not planned initially, occurring after failure or insufficient treatment of the initial chemoradiotherapy. Since the ESPATUE trial was for planned surgery for potentially resectable patients and did not use definitive RT dose, we did not regard it as a trial of salvage surgery.

Comment 4:

There are cases of T3N0 that need RCT prior to surgery such as Pancoast's tumors.

Response: Since this article is focused on "Multimodal management of locally advanced N2 non-small cell lung cancer," we did not consider the cases of T3N0 that needed RCT prior to surgery.

Comment 5:

The durvalumab is restricted to PD-L1 positive tumors (EMEA).

Response: In accordance with the reviewer's comment, we have reconsidered and changed this as seen below.
Page 5, Lines 83-87
Before
Following these reports, this regimen became the standard of care for those patients (6).
After
Following these reports, this regimen became the standard of care for those patients irrespective of PD-L1 expression (6). However, the European Medicines Agency suggested that durvalumab should be used for the patients who have tumors expressing PD-L1 on ≥1% of tumor cells, based on the results of post hoc analyses (12).

Comment 6:

Consideration regarding minimum restaging before surgery should be added (brain MRI).

Response: In accordance with the reviewer's helpful comment, we have reconsidered and changed the legend to Figure 1 as described below.
Figure legend of Figure 1 (Page 17-18, Lines 328-332)
Before
According to the degree and speed of disease progression and patient factors, treatment modalities are determined for disease progression. Among them, surgeries that are performed for oligometastasis, long-term persistent disease, and locoregional recurrence are also defined as salvage surgery.
After
According to the degree and speed of disease progression and patient factors, treatment modalities are determined for disease progression. Among them, surgeries that are performed for oligometastasis, long-term persistent disease, and locoregional recurrence are also defined as salvage surgery. Needless to say, the indication must be determined based on the careful restaging.

Comment 7:

Modalities of relapses after salvage surgery should be indicated (frequence of brain system relapse).

Response: We have added the site of recurrence after salvage surgery in table 2.

Table 2 (Page 11, Lines 172-178)

Authors (Year)	RFS after salvage surgery			OS after salvage surgery			OS from definitive CRT			Site of recurrence after salvage surgery	Favorable prognostic factor in salvage surgery
	Median (months)	3-year rate	5-year rate	Median (months)	3-year rate	5-year rate	Median (months)	3-year rate	5-year rate		
Bauman (2008)(1)	12 (PFS)	39%† (PFS)	20%† (PFS)	30	47%	24%†	N/A	N/A	N/A	L: 8%, D: 25%, L+D: 13%	N/A
Yang (2015)(3)	10	31%†	23%	33	42%†	31%	N/A	N/A	N/A	L: 13%, D: 23%, L+D: 6%	Pathological CR
Dickhoff (2016)(14)	44 (EFS)	66%† (EFS)	44%† (EFS)	46	68%†	46%†	N/A	N/A	N/A	D: 13%, L+D: 7%	N/A
Shimada (2016)(15)	Not reached†	72%	55%†	Not reached†	78%	78%†	N/A	N/A	N/A	L: 17%, D: 11%, L+D: 6%	N/A
Sawada (2017)(16)	N/A	N/A	N/A	Not reached†	75%†	75%	Not reached†	75%†	75%†	L: 13%	N/A
Casiraghi (2017)(2)	12‡ (DFS)	20%‡ (DFS)	20%‡ (DFS)	13	32%	20%	N/A	N/A	N/A	N/A	Long interval from definitive CRT to salvage surgery (continuous variable)
Schreiner (2018)(17)	22	44%†	44%	30	46%	46%	N/A	N/A	N/A	L: 38%, D: 38%	N/A
Sonobe (2019)(4)	13†	49%†	49%	48†	67%†	51%	75†	77%†	61%	D: 45%	Pathological CR in conversion setting
Vielva (2019)(18)	15 (DFS)	9%† (DFS)	9%† (DFS)	76	58%	53%	N/A	N/A	N/A	L: 15%, D: 30%	Radiological downstaging of T factor

RFS: Recurrence-free survival, OS: Overall survival, PFS: Progression-free survival, EFS: Event-free survival, DFS: Disease-free survival

CRT: chemoradiotherapy, N/A: not available, L: Locoregional recurrence, D: Distant recurrence, CR: complete response

†: We summarized the median survival period, 3-year survival rate, and 5-year survival rate of each study, and if there was no description about these values in their own references, an author (AH) calculated these values from the Kaplan-Meier curve of each study.

‡: DFS data missing for five patients; seven patients who had explorative surgery were excluded.

Response to Reviewer B:

Comment 1:

The manuscript reviewed the role of salvage surgery after CRT. Currently, there is insufficient evidence regarding "salvage surgery", but the authors summarized the published data and discussed the meaning and limitation of salvage surgery. The paper is well written and informative.

Figure 1 initial therapy

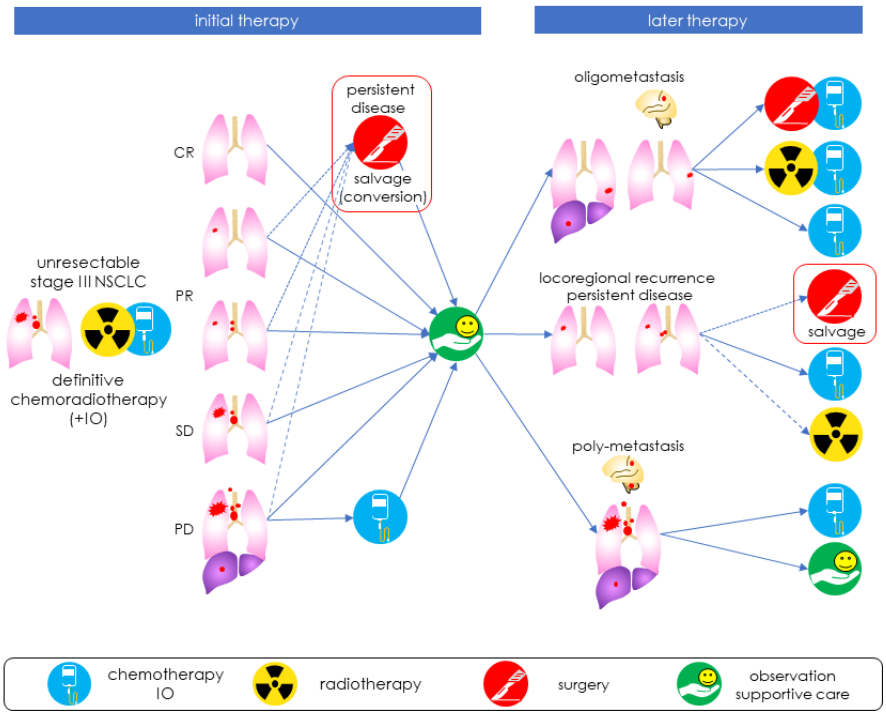
The reviewer feels SD or PD cases after definitive CRT may be a possible candidate for salvage surgery (e.g. the cases that lymph node was disappeared but primary tumors progressed). Please reconsider this point.

Figure 1 later therapy

The authors suggested radiotherapy against locoregional recurrence after definitive CRT. The reviewer feels it is unlikely to perform additional RT after definitive CRT. Please reconsider this point.

Response: We have added the arrows from SD or PD to salvage surgery (conversion surgery) in the initial therapy described in figure 1. Concerning the later therapy, some previous articles reported additional RT after definitive CRT (22-24). However, we think that it is an exceptional treatment. We have changed the solid line under the later therapy to dotted line as shown in the revised figure 1.

Figure 1 (Page 4, Lines 57-59)



Response to Editor's comments:

Please confirm and add the following information to the article.

Response: We wish to express our appreciation to the editor. We have reviewed the information in the COI and we would like to update it as follows.

Before

Dr. Mitsudomi has received grants from Pfizer, Boehringer Ingelheim, MSD, Cho Pharmaceutical, Chugai, Taiho, Eli Lilly, and Daiichi-Sankyo; and has received personal fees from Astra Zeneca, Pfizer, Boehringer Ingelheim, MSD, Ono Pharmaceutical, Chugai, Bristol-Myers Squibb, Taiho, Thermofisher, Roche Diagnostics, and Eli Lilly.

After

Dr. Mitsudomi reports grants and personal fees from AstraZeneca, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Chugai, personal fees from Pfizer , personal fees from Novartis, personal fees from Bristol-Myers Squibb, personal fees from Eli Lilly, personal fees from Merck Sharp and Dohme, grants from Daiichi Sankyo, grants from Taiho, grants from Ono Pharmaceutical, outside the submitted work.

Request to the Editors about additional correction:

After careful reevaluation of this review article, we noticed that we had to update PFS information of supplements which have been reported by Antonia SJ et al in 2018 (N Engl J Med. 2018;379(24):2342-50). Please consider making the following correction.

Page 5, Lines 88-91

Before

However, the difference between the distant-metastasis free survival rate at 18 months of 64% reported in 2018 (10) and the progression-free survival rate of 44% read from the curve reported in 2017 (12) gives an approximation of the proportion of patients who are alive with only loco-regional recurrence, which is about 20%.

After

However, the difference between the distant-metastasis free survival rate at 18 months of 64% and the progression-free survival rate of 50% read from the curve reported in 2018 (10) gives an approximation of the proportion of patients who are alive with only loco-regional recurrence, which is about 15%.