

## Peer review file

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### Reviewer A

Endoh and colleagues reported on a study of pulmonary metastasectomy for pulmonary metastasis of breast cancer. In the manuscript, the authors described 253 breast cancer patients who underwent lung resection. The 10-year survival rate was 50.4%. Based on this data, they concluded that pulmonary metastasectomy has limited efficacy in breast cancer.

This is an interesting paper which addresses a controversial topic. The strength of this paper is that it contains a large number of patients when compared with other papers of similar topic. However, there are several major issues which make the paper weak. 1) Study period. The study spanned 36 years and during this time, so many new treatments in breast cancer have emerged. Patients in modern era will undoubtedly have a better survival than those in old era. As such, at least the year of surgery needs to be included in the multivariable analytic model to account for the effect of time. Furthermore, it remains unclear if the study findings are similar across eras. Therefore, a separate analysis which can serve as a sensitivity analysis can be performed exclusively for patients treated in modern era e.g. 2000-2017.

### Reply 1:

Thank you for your valuable comment. We agree with the reviewer and have added the following additional analysis according to your thoughtful remarks.

The data were divided into two periods, 1982 to 1999 and 2000 to 2017, and univariate and multivariate analyzes for overall survival (OS) and cancer-specific survival (CSS) were performed with reference to the period between 2000 to 2017. The period of pulmonary metastasectomy (PM) <2000 was a significant poor prognostic factor in univariate analysis of OS and CSS, however not in multivariate analysis.

As a prognostic factor for OS, in addition to disease-free interval (DFI) shown in

the original manuscript, tumor diameter and lymph node metastasis were significant worse prognostic factors. As a favor prognostic factor for CSS, complete resection was present as a significant prognostic factor in addition to the DFI and tumor diameter shown in the first manuscript. Because complete resection was not a prognostic factor for OS, without modification of the original article, we conservatively described that pulmonary metastasectomy from breast cancer was an option in limited patients.

We conducted a sensitivity analysis of the patient background between the two periods of 1982-1999 and 2000-2017. There were significant differences in the period of PM, DFI, number of tumors, tumor diameter, surgical procedure, lymph node dissection and lymph node metastasis. However, no difference was found in the resection margin of metastasectomy, the ratio of preoperative and postoperative therapies. These results indicated that a part of the patient's background changed with addition of the period factor, but no difference was observed in the ratio of the resection margin for PM from breast cancer, which was associated the objective of this study. Also, in multivariate analysis, the period of PM was not a prognostic factor for OS and CSS. From above results, the conclusion was in agreement with the original manuscript.

These data are ready to be re-submitted as supplemental data. If the editor wishes, we would like to accept re-correction to present those data in the revised manuscript. Changes in the text:

**Changes in the text:**

**(ABSTRACT)**

- (1) We changed “Univariate analyses revealed that a disease-free interval <36 months, lobectomy/pneumonectomy, large tumor size and lymph node metastasis were predictive of a worse prognosis. In the multivariate analysis, a disease-free interval <36 months remained significantly related to overall survival. (Page 4, Line 57-61)” to the following sentences.

P4, Line 57-61:

Univariate analyses revealed that the period of pulmonary metastasectomy before 2000, a disease-free interval <36 months, lobectomy/pneumonectomy, large tumor size and lymph node metastasis were predictive of a worse prognosis. In the multivariate analysis, a disease-free interval <36 months, large tumor size and lymph node metastasis remained significantly related to overall survival.

- (2) We changed “Univariate analyses revealed that a higher age, disease-free interval <36 months, lobectomy/pneumonectomy, large tumor size, lymph node metastasis and incomplete resection were predictive of a worse prognosis. Multivariate analysis confirmed that a disease-free interval <36 months and large tumor size were significantly related to cancer-specific survival. (Page 4, Line 63-67)” to the following sentences.

P4, Line 63-67:

Univariate analyses revealed that the period of pulmonary masestasectomy before 2000, disease-free interval <36 months, lobectomy/pneumonectomy, large tumor size, lymph node metastasis and incomplete resection were predictive of a worse prognosis. Multivariate analysis confirmed that a disease-free interval <36 months, large tumor size and incomplete resection were significantly related to cancer-specific survival.

## **(RESULT)**

- (3) We added the following sentence.

P10, Line 160-163:

We conducted a sensitivity analysis of the patient background between the two periods of 1982-1999 and 2000-2017. There were significant differences in age, DFI, number of tumors, tumor diameter, surgical procedure, lymph node dissection, and lymph node metastasis between the periods. However, resection margin of metastasectomy showed no difference in the ratio of preoperative and postoperative therapy outcomes (Supplementary Table 1).

(4) We changed “Univariate analysis revealed that a DFI <36 months, lobectomy or pneumonectomy, large tumor size and lymph node metastasis were predictive of a worse overall survival (Table 3). Incomplete resection of the pulmonary metastasis was not related to overall survival. Multivariate analysis confirmed that a DFI <36 months was significantly related to overall survival. (Page 11, Line 178-183)” to the following sentences.

P13, Line 218-223:

Univariate analysis revealed that the period of PM before 2000, a DFI <36 months, lobectomy or pneumonectomy, large tumor size and lymph node metastasis were predictive of a worse overall survival (Table 3). Incomplete resection of the pulmonary metastasis was not related to overall survival. Multivariate analysis confirmed that a DFI <36 months, large tumor size and lymph node metastasis was significantly related to overall survival.

(5) I changed “Univariate analysis revealed that a higher age, DFI <36 months, lobectomy or pneumonectomy, larger tumor size, lymph node metastasis and incomplete resection were predictive of a worse cancer-specific survival (Table 4). A DFI <36 months and larger tumor size remained significant in the multivariate analysis. As with overall survival, incomplete resection was not significantly related to cancer-specific survival in the multivariate analysis. As with overall survival, incomplete resection was not significantly related to cancer-specific survival in the multivariate analysis. (Page 11, Line 185-190)” to the following sentences.

Page 11, Line 185-190:

Univariate analysis revealed that the period of PM before 2000, DFI <36 months, lobectomy or pneumonectomy, large tumor size, lymph node metastasis, and incomplete resection were predictive factors of a worse cancer-specific survival (Table 4). A DFI <36 months, large tumor size, and incomplete resection remained

significant in the multivariate analysis. Differing from overall survival, incomplete resection was found to be significantly related to cancer-specific survival in the multivariate analysis.

## (DISCUSSION)

(6) We changed “In the present study, multivariate analysis revealed that a DFI <36 months was significantly associated with worse overall survival, and a DFI <36 months and the size of the pulmonary metastatic nodule were significantly associated with worse cancer-specific survival. (Page 15, Line 245-249)” to the following sentence.

P15, Line 245-249:

In the present study, multivariate analysis revealed that a DFI <36 months, large tumor size and lymph node metastasis were significantly associated with worse overall survival, and a DFI <36 months, the size of the pulmonary metastatic nodule and incomplete resection of PM were significantly associated with worse cancer-specific survival.

(7) We changed “We revealed that the DFI was predictive of both overall survival and cancer-specific survival. (Page 15, Line 252-253)” to the following sentence.

P15, Line 252-253:

We revealed that the DFI and tumor diameter were predictive of both overall survival and cancer-specific survival.

(8) We changed “Incomplete resection was not identified as a prognostic factor (Page 15, Line 253-258)” to the following sentence.

P14, Line 253-258:

Incomplete resection was identified as a poor prognostic factor for cancer-specific

survival in this study, however it was not a significant prognostic factor for overall survival in both univariate and multivariate analyses. Therefore, complete resection was not a significant prognostic factor contributing to survival, and the resection of breast cancer lung metastases was considered to be controversial, as in some previous reports.

**(Limitations)**

Regarding the length of the study period and its influence, we have stated "Third, our multi-institutional database covers a period of 36 years, during which chemotherapy, hormone therapy and supportive care have improved rapidly. Thus, the results of this study might not reflect real-world metastatic breast cancer patients. (P 19, Line 314-317)" in the "**Limitations**" section.

**(Table 1)**

We changed the part of "table1" to match the era breaks.

P22, Line 366: **(Pre) Table 1. Characteristics of the patients who underwent pulmonary metastasectomy**

Characteristics	n (%) or median (range) <sup>a</sup>
Period of pulmonary metastasectomy	
1982–2000	98 (39)
2001–2009	66 (26)
2010–2017	89 (35)

P26, Line 399: **(Post) Table 1. Characteristics of the patients who underwent pulmonary metastasectomy**

Characteristics	n (%) or median (range) <sup>a</sup>
Period of pulmonary metastasectomy	
1982–1999	88 (35)
2000–2009	76 (30)
2010–2017	89 (35)

**(Table 3)**

We have revised "table3" by adding the factor for period of metastasectomy.

P26-28, Line 372-374: **(Pre) Table 3.** Prognostic factors for overall survival after pulmonary metastasectomy

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>p</i> -value	HR	95% CI	<i>p</i> -value
Age	0.98	0.96-1.00	0.202			
Disease-free interval						
<36 months	2.10	1.35-3.25	0.001	2.14	1.32-3.42	0.002
≥36 months	1.00					
Surgical procedure						
Lobectomy or pneumonectomy	1.79	1.15-2.85	0.010	1.41	0.77-2.62	0.265

Wedge resection or segmentectomy	1.00					
Number of pulmonary metastases						
Multiple	0.93	0.47-1.69	0.823			
Solitary	1.00					
Tumor diameter	1.22	1.06-1.38	0.006	1.20	0.95-1.48	0.124
Lymph node metastasis						
Positive	2.01	1.27-3.12	0.003	1.54	0.91-2.58	0.107
Negative	1.00					
Resection status of pulmonary metastasectomy						
Incomplete	1.93	0.27-1.12	0.091			
Complete	1.00					
Preoperative therapy before pulmonary metastasectomy						
+	1.18	0.66-1.99	0.557			
-	1.00					



Postoperative therapy after pulmonary

metastasectomy

+	1.09	0.69-1.74	0.722
-	1.00		

**P26-28, Line 372-374: (Post) Table 3. Prognostic factors for overall survival rate after pulmonary metastasectomy before and after 2000**

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>p</i> -value	HR	95% CI	<i>p</i> -value
<b>Period of metastasectomy</b>						
1982 - 1999	1.82	1.16-2.90	0.009	1.52	0.96-2.44	0.077
2000 - 2017	1.00					
Age	0.99	0.96-1.00	0.209			
<b>Disease-free interval</b>						
<36 months	2.09	1.34-3.24	0.001	2.17	1.39-3.37	<0.001
≥36 months	1.00					
<b>Surgical procedure</b>						

Lobectomy or pneumonectomy	1.79	1.15-2.85	0.010	1.05	0.60-1.85	0.864
Wedge resection or segmentectomy	1.00					
Number of pulmonary metastases						
Multiple	0.93	0.47-1.68	0.821			
Solitary	1.00					
Tumor diameter	1.22	1.06-1.37	0.006	1.21	1.02-1.41	0.031
Lymph node metastasis						
Positive	2.01	1.27-3.12	0.003	1.75	1.06-2.86	0.028
Negative	1.00					
Resection status of pulmonary						
metastasectomy						
Incomplete	1.90	0.88-3.65	0.097			
Complete	1.00					
Preoperative therapy before pulmonary						
metastasectomy						
+	1.18	0.66-1.98	0.568			

-	1.00		
Postoperative therapy after pulmonary metastasectomy			
+	1.09	0.70-1.75	0.705
-	1.00		

**(Table 4)**

We have revised "table 4" by adding the factor for period of metastasectomy.

P29-31, Line 375-377: **(Pre) Table 4. Prognostic factors for cancer-specific survival after pulmonary metastasectomy**

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>p</i> -value	HR	95% CI	<i>p</i> -value
Age	0.97	0.95-1.00	0.037	0.98	0.95-1.00	0.074
Disease-free interval						
<36 months	2.20	1.39-3.49	<0.001	2.31	1.45-3.69	<0.001
≥36 months	1.00			1.00		
Surgical procedure						
Lobectomy or pneumonectomy	1.61	1.01-2.60	0.045	0.98	0.52-1.86	0.960

Wedge resection or segmentectomy	1.00			1.00		
Number of pulmonary metastases						
Multiple	0.93	0.45-1.74	0.840			
Solitary	1.00					
Tumor diameter	1.24	1.07-1.40	0.005	1.30	1.08-1.53	0.006
Lymph node metastasis						
Positive	1.81	1.11-2.88	0.018	1.59	0.93-2.67	0.087
Negative	1.00			1.00		
Resection status of pulmonary metastasectomy						
Incomplete	2.18	1.00-4.21	0.049	2.18	0.96-4.51	0.062
Complete	1.00			1.00		
Therapy before pulmonary metastasectomy						
+	1.25	0.68-2.15	0.446			
-	1.00					

Therapy after pulmonary

metastasectomy

+	1.49	0.91-2.54	0.115
-	1.00		

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**P29-31, Line 375-377: (Post) Table 4. Prognostic factors for cancer-specific survival after pulmonary metastasectomy before and after 2000**

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Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>p</i> -value	HR	95% CI	<i>p</i> -value
Period of metastasectomy						
1982 - 1999	1.86	1.15-3.07	0.011	1.61	0.99-2.66	0.055
2000 - 2017	1.00					
Age	0.98	0.95-1.00	0.051			
Disease-free interval						
<36 months	2.27	1.42-3.61	<0.001	2.36	1.47-3.77	<0.001
≥36 months	1.00			1.00		
Surgical procedure						

Lobectomy or pneumonectomy	1.57	0.98-2.55	0.059			
Wedge resection or segmentectomy	1.00					
Number of pulmonary metastases						
Multiple	0.95	0.46-1.77	0.878			
Solitary	1.00					
Tumor diameter	1.24	1.08-1.41	0.004	1.27	1.08-1.45	0.004
Lymph node metastasis						
Positive	1.74	1.06-2.79	0.029	1.53	0.93-2.46	0.093
Negative	1.00			1.00		
Resection status of pulmonary						
metastasectomy						
Incomplete	2.21	1.02-4.26	0.046	2.33	1.07-4.51	0.035
Complete	1.00			1.00		
Therapy before pulmonary						
metastasectomy						
+	1.28	0.70-2.19	0.415			

-	1.00		
Therapy after pulmonary metastasectomy			
+	1.57	0.95-2.70	0.080
-	1.00		

**(Supplementary table 1):**

P35, Line 385-387

We added the supplementary table a as reviewer's suggestion.

Patient characteristics for lung metastasectomy in breast cancer before and after 2000

(N = 253)

Variable	Period of pulmonary metastasectomy		<i>p</i> -value
	1982-1999, (n=88, 35%) n(%) or median (range)	2000-2017, (n=165, 65%) n(%) or median (range)	
Age, years	54 (35-74)	58 (32-82)	0.009
Disease-free interval, years	3.5 (0-18.4)	5.6 (0-31.2)	0.024
Number of metastases	1 (1-7)	1 (1-5)	0.031
Tumor diameter, cm	2.0 (0.5-9.0)	1.4 (0.3-7.0)	0.002
Procedure			<0.001
Wedge resection	25 (28)	88 (53)	
Segmentectomy	14 (16)	8 (5)	
Lobectomy	48 (55)	68 (41)	
Pneumonectomy	1 (1)	1 (1)	
Lymph node dissection			0.027

None	31 (41)	98 (59)	
Hilar	17 (22)	26 (16)	
Mediastinal	28 (25)	41 (25)	
Lymph node metastasis			0.016
None	60 (68)	137 (83)	
Hilum	19 (22)	15 (9)	
Mediastinum	9 (10)	13 (8)	
Resection status of metastasectomy			0.539
Complete	81 (92)	148 (90)	
Incomplete	7 (8)	17 (10)	
Preoperative therapy			0.121
Yes	15 (17)	42 (25)	
No	73 (83)	123 (75)	
Postoperative therapy			0.932
Yes	49 (56)	92 (56)	
No	38 (44)	73 (44)	

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2) Lack of clear eligibility criteria. The study aims to include only patents with metastatic breast cancer to lung. However, it is quite likely that some patients with primary lung cancer without metastatic breast cancer were mistakenly included in the database. This very important because primary lung cancer can be cured while metastatic breast cancer cannot be cured. The authors should provide an explanation of what measures or criteria have been used to separate primary lung cancer from breast cancer. For example, primary adenocarcinoma of the lung is typically TTF-1 positive. How many of these patients have positive TTF-1? Furthermore, breast cancer usually metastasizes to multiple organs including bone, brain, liver etc. Patients who have metastases in other organs than lung at the date or before the date of lung surgery will be more likely to be those who did not have primary lung cancer. It will be relevant to know how many of those patients were and what organs of metastases were. How many patients had hormone receptor analyzed from the lung resection specimens and were the results congruent with the primary breast specimen?



**Reply 2:**

Thank you for your attention to the details. As you pointed out, the distinction between lung metastases originating from primary breast cancer and primary lung cancer is important for this study. In the text, “From the database, we selected 387 patients with histologically proven pulmonary metastases originating from breast cancer between December 1982 and March 2017. (Page 9, Line 132-133)”, but currently it is inadequate and misleading to the reader. “From the database, based on immunohistochemical and histopathological studies of breast cancer-specific markers such as hormone receptors and lung cancer-specific markers such as TTF-1, we enrolled 387 patients diagnosed with pulmonary metastases originating from breast cancer between December 1982 and March 2017.” was changed to the description. By improving the points you indicated, the meaning of the sentence has become easier to convey to the reader. Thank you for pointing out.

The positive rate of TTF-1 in lung cancer is 63% to 83% in adenocarcinoma, but rarely it is also positive in breast cancer (reference-1).

Twenty-six participating research institutes including ours are specialized in cancer treatment, and not only HE staining but also TTF-1, Napsin-A, estrogen receptor, etc. were used for pathological definitive diagnosis. However, this study protocol did not prescribe the collection of these immunostaining results, so the number of TTF-1 positive patients cannot be reported. Moreover, it is difficult to collect it newly in practice. In fact, patients who are TTF-1 positive are diagnosed with primary lung cancer and will not be enrolled in this study.

The number of patients with metastatic lesions at other sites at the time of detection of lung metastasis from breast cancer is unknown. Six patients (2%) had Stage 4 at the time of treatment for the primary lesion of breast cancer in this study. These patients may have metastatic lesions in addition to lung metastases, but it was not possible to make a judgment because there were no collected data. Most of the other patients are considered to be patients without lesions of other parts before surgery for lung metastasis from breast cancer.

Regarding the analysis of status of hormone receptors in pulmonary metastases and primary breast specimens, the present study did not collect data of status of hormone receptor for pulmonary metastatic specimens. It is difficult to compare the two and present the percentage of results where the two matches. Moreover, it is difficult to collect it newly in practice.

Of the 16 references cited by Fan et al. in meta-analysis, 7 reported that hormone receptors were prognostic factors (reference-2). Planchard et al. reported the most 125 cases among these 7 papers, but reported only the status of hormone receptors in the primary lesion of breast cancer, and 77 cases (62%) were unknown (reference- 3). Welter et al. only reported the status of hormone receptors in the resected lung metastases, in 11 cases (26%) there was a discrepancy between the pulmonary metastatic lesion and the primary breast lesion, and in 5 cases (11%), it was unknown (Reference-4). Among the patients enrolled at my institution, which is one of the institutions participating in this study, a concordance in the status of hormone receptor was shown in 8 out of 12 patients (67%), and the expression had disappeared in 4 patients (33%). In terms of hormone receptor status, if the primary breast cancer is positive and the metastatic tumor is positive, it will be helpful in diagnosing metastasis from breast cancer, however if the primary tumor is negative or unknown, it is considered difficult to utilize. Of the 253 cases analyzed in this study, estrogen receptor status was positive in 75 patients (30%), negative in 69 patients (27%), and unknown in 109 patients (43%) at primary breast cancer.

From the database, immunohistochemical examination of breast cancer-specific markers such as hormone receptors and lung cancer-specific markers such as TTF-1 and morphological histopathological analysis of lung metastases from primary breast cancer It is intended for diagnosed patients. However, reporting that real number in the text was as difficult as in previous reports.

#### (References)

- 1) Voutsadakis, I.A.; Mozarowski, P. Expression of TTF-1 in breast cancer independently of ER expression: A case report and pathogenic implications. *Breast Dis.* 2017, 37, 1–6.
- 2) Fan J, Chen D, Du H, et al. Prognostic factors for resection of isolated pulmonary metastases in breast cancer patients: a systematic review and meta-analysis. *J Thorac*

Dis. 2015;7:1441-51.

- 3) Planchard D, Soria JC, Michiels S, et al. Uncertain benefit from surgery in patients with lung metastases from breast carcinoma. *Cancer* 2004;100:28-35.
- 4) Welter S, Jacobs J, Krbek T, et al. Pulmonary metastases of breast cancer. When is resection indicated? *Eur J Cardiothorac Surg* 2008;34:1228-34.

### **Changes in the text:**

We changed “From the database, we selected 387 patients with histologically proven pulmonary metastases originating from breast cancer between December 1982 and March 2017. (Page 8, Line 125-126)” to the following sentence.

Page 8, Line 125-126: From the database, based on histopathological studies, we enrolled 387 patients diagnosed with pulmonary metastases originating from breast cancer between December 1982 and March 2017.

(Limitations)

Regarding the length of the study period and its influence, we have stated "Since our database was established by thoracic surgeons, it lacked sufficient information on breast cancer. We recognize this as the greatest limitation of our study. (P 15, Line 268-270)” in the “**Limitations**” section.

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3) The conclusion of limited efficacy. Because there is no comparison group that underwent no metastasectomy, it remains unclear whether the observed results are good or bad. Whether the efficacy is limited or not cannot be determined based on the data presented. At best, one can say which group of patients the treatment is less useful for.

### **Reply 3:**

Thank you for your review opinion. Our analysis showed that complete resection was not a prognostic factor for overall survival in pulmonary metastasectomy (PM)

from breast cancer. This indicates that surgical treatment for this target did not affect the prognosis. Therefore, I had to say conservatively that PM for breast cancer was one of the options. Beneficiaries of this option may be expected to benefit if DFI  $\geq$  3 years and no effective treatment other than surgery.

Therefore, in “Conclusion” section, we used a conservative expression to avoid identifying the beneficiaries of this optional treatment as you pointed out.

**Changes in the text:** none

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4) Factors such as comorbidity, FEV1, smoking history can influence survival after lung surgery and should be included in multivariable analysis.

**Reply 4:**

Data collection of comorbidities, FEV1, and smoking history were not included in the study protocol, making analysis using them difficult. In addition, it is necessary to obtain the IRB approval for the new data collection and then to collect information from all institutions. Even if it could be done, there is a possibility that some medical records are lost due to the 36-year registry. Therefore, it seems difficult to deal with it in reality.

Fan et al. reported a meta-analysis on prognostic factors of pulmonary metastasectomy from breast cancer (reference-2), and among the 16 papers covered, univariate analysis revealed that the prognostic factors were comorbidities. , FEV1, smoking history was not recognized.

No references describing respiratory function and comorbidities were found in the literature on lung metastasis resection of breast cancer. Regarding smoking history, Planchard et al. reported that 24 out of 125 cases had smoking history, 36 were nonsmokers, and 65 were unknown, which was not a significant prognostic factor for overall survival (p=0.211) (reference-3).

Comorbidities may be associated with death from other illnesses. Therefore, we performed univariate and multivariate analyzes on prognostic factors for cancer-

specific survival in order to exclude the effects of death from other diseases (Table 4).

(Reference)

2. Fan J, Chen D, Du H, et al. Prognostic factors for resection of isolated pulmonary metastases in breast cancer patients: a systematic review and meta-analysis. *J Thorac Dis.* 2015;7:1441-51.

3. Planchard D, Soria JC, Michiels S, et al. Uncertain benefit from surgery in patients with lung metastases from breast carcinoma. *Cancer.* 2004;100:28-35.

**Changes in the text:** none

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5) Curability. This has been mentioned throughout the paper. Please define the word curability. Since metastatic lung cancer is an incurable disease, perhaps other terminology should be used.

**Reply 5:**

Thank you for suggesting the important matter. I support your opinion. “Curability” means that the complete resectability of the pulmonary lesions without remnant lesions in this manuscript. However, as you pointed out, the term “curability” was considered inappropriate because the lung metastasis of breast cancer is a systemic disease and an incurable disease. I changed "Curability" in the text and tables to "resection status of pulmonary metastasectomy".

**Changes in the text:**

I changed “Data for the following parameters ... type of surgery, **disease curability**, date of metastasis, ... date of recurrence. (page8, Line 118-122)” and words in Table 1,3 and 4 to the following sentence and words.

P page8, Line 118-122: Data for the following parameters were collected: sex, age, primary tumor histology, primary tumor stage, primary tumor treatment, hormone

receptor status, date of surgery for the primary tumor, type of surgery, resection status of pulmonary metastasectomy, date of metastasis, DFI, laterality of the pulmonary metastasis, tumor size, number of resected metastases, date of PM, other treatments, and site and date of recurrence.

P 22-23, Line 366-367 (Table 1): I changed "Curability" to "Resection status".

Resection status

Complete	229 (91)
Incomplete	24 (9)

P 26-28, Line 372-374 (Table 3): We changed "Curability of pulmonary metastasectomy" to "Resection status of pulmonary metastasectomy".

Resection status of

pulmonary metastasectomy

Incomplete	1.93	0.27-1.12	0.091
Complete	1.00		

P 29-31, Line 375-377 (Table 4): We changed "Curability of pulmonary metastasectomy" to "Resection status of pulmonary metastasectomy".

Resection status of

pulmonary metastasectomy

Incomplete	2.18	1.00-4.21	0.049	2.18	0.96-4.51	0.062
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Complete

1.00

1.00

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6) Table 2: Stage of breast cancer. Since this paper is reporting on metastasectomy of breast cancer. Only patients with stage IV breast cancer should be included.

**Reply 6:**

Regarding Table 2 and the results (p10, Line 163-164), it was stated in the text as "Table 2 shows the characteristics of the primary breast cancers in the patients." Certainly, as the comment says, the current description is not sufficient and the expression is misleading to the reader. We changed it as shown below. By improving the points you pointed out, the meaning of the sentence has become easier to convey to the reader. Thank you for your guidance.

**Changes in the text:**

We changed "Table 2 shows the characteristics of the primary breast cancers in the patients. (p10, Line 163-164)" and words in Table 2 to the following sentence and words.

p10, Line 163-164: Table 2 shows the characteristics of the primary breast cancers **during breast surgery** in the patients.

P 24-25, Line 369-370 (Table 2): We changed "Stage" to "Stage at breast surgery" according to your opinion.

**Stage at breast surgery**

I	40 (16)
II	126 (50)
III	25 (10)
IV	6 (2)
NA	56 (22)

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**Reviewer B**

Pulmonary metastasectomy for breast cancer is very rarely indicated (only salvage treatment of single lesion not responding to previous treatment); considering pneumonectomy or Greater resection is absolutely contraindicated.

**Reply B:**

Thank you for reviewing. We fully support your opinion.

This study included a retrospective analysis for 36-year analysis, so total patients underwent pneumonectomy was included in 2 of 253 cases (1%) (Table 1). For both overall and cancer-specific survival rates, pneumonectomy was indicated a poor prognostic factor in univariate analysis (Table 3 and 4). This is described in the Abstract (p4, Line 57-61; p4, Line 63-65) and Results (p11, Line 178-180; p11, Line 185-187).

**Changes in the text:** No additional notes.

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**Reviewer C**

Many thanks for submitting your manuscript entitled „Pulmonary metastasectomy for pulmonary metastatic breast cancer has a limited prognostic impact: a multi-institutional retrospective analysis“ for consideration for publication in the Journal of Thoracic Disease.

In this multicenter retrospective observational study, you present the outcomes of pulmonary metastasectomy (PM) performed over a 35-year period on the group of 253 female patients with pulmonary metastatic breast cancer. You describe and analyze postoperative overall survival (OS) and cancer-specific survival after PM as well as statistically analyses the tumor and treatment related factors, which may influence the survival. You identify one independent prognosticator for the OS (DFI <



36 months) and two independent prognosticators related to the cancer-specific survival (DFI < 36 months and larger tumor size). You conclude that PM for metastatic breast cancer has limited efficacy and is considered an optional treatment. The manuscript is well structured and the study objective is defined. The results of the statistical analysis are well presented. You reflected well on the limitations of the study.

However:

1) The role of a curative-intent PM for metastatic breast cancer, due to ongoing development of modern systemic treatment strategies has been continuously decreasing. Therefore, the relevance of the presented topic is not too high for the thoracic surgeons performing lung metastases surgery. For this reason, the objective of the study should be better specified.

#### **Reply C1:**

We changed "indication" to "implication" according to your opinion.

#### **Changes in the text:**

P4, Line 50-51: The purpose of this study was to assess the prognostic factors and indications **implication** for pulmonary metastasectomy for metastatic breast cancer using a multi-institutional database.

P7, Line 99-101: The purpose of this study was to assess the prognostic factors and indications **implication** for PM for pulmonary metastasis of breast cancer using a Japanese multi-institutional database.

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2) In the „Patient and Methods“ section you did not describe the patient selection criteria. The data regarding preoperative diagnostics, operative standards (e.g. VATS vs. open, lymph node dissection), frequency of follow up, is lacking.

#### **Reply C2:**

We changed following your suggestion in the “Patients and Methods” section.

### **Changes in the text:**

(1)

We changed “The surgical indications and procedures were determined at each institution’s discretion. (P7, Line 109-110)” to the following sentence.

P7, Line 109-114:

The indication, procedure, and approach of surgical resection for PM were independently determined by each institution. As reported in a previous study (19), general indications for surgical resection of pulmonary metastasis followed the criteria of Thomford et al. (20): the primary lesion was under control or was planned to be under control; there were no metastases to other organs; and the patient’s general condition was good enough to withstand surgery.

(2)

P20, Line 351-354: We added two references in “References” section according to the above sentence.

19. Kawamura M, Nakajima J, Matsuguma H, et al. Surgical outcomes for pulmonary metastases from hepatocellular carcinoma. *Eur J Cardiothorac Surg* 2008;34:196 –9.

20. Thomford NR, Woolner LB, Clagett OT. The surgical treatment of metastatic tumors in the lungs. *J Thorac Cardiovasc Surg* 1965;49:357– 63.

(3)

We changed “There was no standard protocol for postoperative follow-up surveillance. (P7-8, Line 115-118)” to the following sentence.

P7-8, Line 115-118:

Patients were followed up with chest CT scan twice a year to detect the recurrence of breast cancer including the pulmonary metastasis, and additional imaging studies were performed at the discretion of the treating physician. Survival outcome surveillance was subsequently conducted at 1-year intervals by the registration center.

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3) A very high rate of performed lobectomy procedures should be better explained.

**Reply C3:**

Thank you for reviewing. We support your opinion.

The rate of performed lobectomy decreased over the years. In 1982-1999, it was 48 patients out of 88 patients (55%), in 2000-2009 it was 37 patients out of 76 patients (49%), and in 2010-2017 it was down to 31 patients out of 89 patients (35%) (P=0.0008). This factor is expected to be due to advances in diagnostic imaging to detect pulmonary metastasis, improvement of surgical procedure, change of surgical indication, etc., but it was not clear in this study.

**Changes in the text:** We added the following sentences.

P 9-10, Line155-157:

The rate of lobectomy decreased over the years: between 1982 and 1999, it was 55% (48/88 patients), between 2000 and 2009, it was 49% (37/76 patients), and between 2010 to 2017, it was 36% (31/89 patients) (P<0.001).

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4) The cause of death in three patients is missing. There is no data regarding postoperative complications or e.g. the length of postoperative hospital stays.

**Reply C4:**

We added the following sentences to explain the causes of death, however we had not collected data on postoperative complications and length of stay.

**Changes in the text:**

We changed “One patient died within 30 days and two patients within 90 days after PM. (P10, Line 167-168)” to the following sentence.

P10, Line 167-168:

One patient died of pulmonary embolism within 30 days after PM and two patients

died of acute exacerbation of interstitial pneumonia within 90 days.

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5) The cut-off value for DFI was adapted from existing literature. Did you consider performing the ROC analysis to estimate the cut-off value for your patient population?

**Reply C5:**

Thank you for your review opinion. We understand that there is a method to utilize a receiver operating characteristic (ROC) curve analysis to determine the cut-off value of disease-free survival (DFI). In this study population, the ROC curve identified an optimal DFI cutoff value of 77 months for overall survival, however the area under the curve was 0.64.

Fan et al. conducted a meta-analysis on the prognostic factors for pulmonary metastasectomy from breast cancer, where DFI was reported as one of the prognostic factors. DFI was reported as a prognostic factor in 9 of the 15 papers covered, and the cut-off value of DFI was 3 years in 8 of the 9 papers (reference-1). The prognostic factor with a cut-off value of DFI <3 years was a pooled hazard ratio (HR) with a hazard ratio (95%CI) of 1.70 (1.21-2.10), which was significantly associated with overall survival.

Based on this, we have decided to perform the analysis with a cut-off value of DFI = 3 years, and we hope to publish the results of this analysis.

(Reference )

1. Fan J, Chen D, Du H, et al. Prognostic factors for resection of isolated pulmonary metastases in breast cancer patients: a systematic review and meta-analysis. J Thorac Dis. 2015;7:1441-51.

**Changes in the text:** none

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6) You describe that the size of metastatic nodules is a negative prognosticator for the cancer-specific survival. What was the cut-off for the diameter of the lung metastasis?

**Reply C6:**

Thank you for your review opinion. As you mentioned, there are certainly ways to set the cut-off value and analyze it. The median tumor diameter of lung metastases was 1.5 cm (range, 0.3-9.0 cm). Since the tumor diameter is a continuous variable, we performed univariate and multivariate analyzes using the Cox proportional hazard model as a continuous variable. No specific cut-off value was set for the analysis of tumor size.

**Changes in the text:** none

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7) You concluded that PM for breast cancer is considered an optional treatment. Could you specify who might benefit from this option?

**Reply C7:**

Thank you for your review opinion. Our analysis showed that complete resection was not a prognostic factor for overall survival in pulmonary metastasectomy (PM) from breast cancer. This indicates that surgical treatment for this target did not affect the prognosis. Therefore, I had to say conservatively that PM for breast cancer was one of the options. Beneficiaries of this option may be expected to benefit if DFI  $\geq$  3 years and no effective treatment other than surgery.

Therefore, in “Conclusion” section, we used a conservative expression to avoid identifying the beneficiaries of this optional treatment.

**Changes in the text:** none