First-Round Peer Review

Reviewer A

The manuscript by Karjula and colleagues represents a mono-centric experience of Results of Intention-to-treat Pulmonary Metastasectomies in Northern Finland. The authors performed a retrospective analysis of 154 intended pulmonary metastasectomies between 2000 and 2020. The authors retrospectively reviewed the surgical outcomes and survival data. The study design is good and the manuscript is well-written.
My questions/Concerns:
Comment 1: Was surgical resection the only used therapy for metastases or additive chemotherapy was used in some patients?

Reply 1: Additive chemotherapy was used in 69 metastasectomies (53.1%), however, there was missing data in 24 cases (15.6%).
We have added this to the text as follows: "Of all pulmonary metastasectomies, 53.1% received adjuvant chemotherapy and 4.6% radiotherapy. Excluding remetastasectomies, 46.1% received adjuvant chemotherapy and 4.8% radiotherapy. There was no trend in the use of adjuvant therapy during the study period."
(See page 6, lines 19-22)

Comment 2: Did you routinely performed lymph node sampling/dissection?

Reply 2: Routine lymph node sampling was not performed. Two thirds of the lymph node samplings (n=27) were performed after 2010; however, there was no trend of the lymph node samplings during the study period.
We have added this to the text as follows: "Lymph node sampling was performed in 18% (n=27) of all intended pulmonary metastasectomies. A systematic thoracic N2 lymph node sampling was performed in 5 cases."
(See page 6, lines 17-18)

Comment 3: What was the lymph node status among the patients?

Reply 3: Unfortunately, as only 18% of all patients had a lymph node dissection, the data on the lymph node status was not collected. We apologize for this shortcoming in our study.

Comment 4: Renaud et al* showed an improved survival after anatomical resection of lung metastases of Colorectal Cancer harbouring KRAS Mutations but the current state of art is the Parenchymal-sparing resections. The sublobar resection may offer, as you showed, a good alternative. Can you try to identify the predictor factors for a primary lung cancer in your cohort (for example, Solitary nodule? Age of patients? History of smoking? Timing

(synchronous/metachronous))

Reply 4: We performed a binary logistic regression analysis predicting primary lung cancer in final histology. Odds ratios for incidental primary lung cancer were calculated for age, tobacco history, timing of suspected pulmonary nodule, and the number of pulmonary nodules. Synchronicity was not an independent risk factor in the regression model, nor tobacco history, age, or number of pulmonary nodules. However, when timing was measured as disease free interval with a cut-off of 24 months, it was an independent risk factor for incidental primary lung cancer in the regression model.

We added text in the edited manuscript as follows:

"A binary logistic regression model was constructed to predict primary lung cancer in final histology. In the multivariable analysis, adjusted odds ratios (ORs) for incidental primary lung cancer were calculated for age (<65years/≥65years), history of smoking (no/yes), DFI (<24months/≥24months), and solitary pulmonary nodule (no/yes). In model 1, all intended pulmonary metastasectomies were included in the analysis. In model 2, only first pulmonary metastasectomies were included in the analysis." (See page 5, lines 10-14).

"In the binary logistic regression analysis predicting final histology, in all intended pulmonary metastasectomies in model 1, a DFI of over 24 months was suggestively associated with incidental primary lung cancer in final histology (adjusted OR=6.45, 95% CI 0.95-43.92, p=0.057; Table S1), whereas age (≥65 years) or number of pulmonary nodules (1/≥2) were not associated with incidental primary lung cancer. Additionally, a history of smoking had an adjusted odds ratio of 5.42 (95% CI 0.73-40.07, p=0.097), however the result was statistically insignificant. In model 2, excluding re-metastasectomies, a DFI over 24 months was significantly associated with incidental primary lung cancer in final histology (adjusted OR 8.48, 95% CI 1.09-66.03, p=0.041, Table S1)." (See page 6, line 29 to page 7, line 5)

"A long DFI and a heavy history of smoking might also be predictive factors for incidental primary lung cancer in final histology, as shown in the logistic regression analysis in our study. Thus an increased segmentectomy rate instead of non-anatomical resections in these patient groups could be beneficial." (See page 9, lines 2-4)

Comment 5: Can you please compare the postoperative complications and the survival between patients underwent wedge resections and anatomical resections

Reply 5: We compared the postoperative complication rates and survival between anatomical resections and wedge resections as requested. The wedge resections had a lower complication rate.

We added text to the revised version of the manuscript as follows:

"When comparing short-term outcomes between wedge resections and anatomical resections, patients who had a wedge resection had a lower overall complication rate in comparison to patients who received an anatomical pulmonary resection (11.7% vs. 27.6%, p=0.03; Table S3). There was no difference in VATS conversion rates, reoperation rates or short-term 30- or 90-day mortality between wedge resections and anatomical resections (Table S3)." (See page 7, lines 19-22)

"Wedge resections were associated with better 1-year survival in comparison to anatomical resections (anatomical resection 82.3% vs. wedge resection 93.4%, p=0.046)." (See page 7,

lines 25-27)

"The anatomical resections of the suspected pulmonary metastases compared to wedge resections did not affect 5-year overall survival (anatomical resection 43.4% vs. wedge resection 53.3%, p=0.392; Table S3)." (See 8, lines 2-4)

"Although wedge resections have a lower complication rate in comparison to the anatomically resected metastases, the extension to anatomical resections did not affect short-term mortality or long-term survival in our cohort." (See page 9, lines 8-9)

*Ann Surg. 2019 Dec;270(6):1170-1177. doi: 10.1097/SLA.0000000000002829.

Reviewer B

As the authors found a lung cancer incidence of approximately 9% in their metastasectomy patients, the authors are recommending that an anatomic sublobar resection should be performed instead of a wedge resection for metastasectomy.

I have some remarks:

Comment 1: It is known that not every lung nodule is a metastasis. For this reason, if possible, histological confirmation should be sought before surgery, e.g. via CT-guided puncture. In how many patients was histological confirmation sought preoperatively?

Reply 1: Due to lack of resources in the public healthcare system and challenges in the specificity of the CT-guided puncture, it has rarely been performed in suspected pulmonary metastases in our institution. None of our patients had a CT-guided puncture preoperatively. The evolvement of the diagnostic protocols during the relatively long study period might partly account for the lack of histological confirmation in our data.

We added text as follows:

"Histological confirmation via CT-guided biopsy of suspected metastatic nodules was not performed to any of the study patients." (See page 5, lines 28-29)

Comment 2: Regarding the patients with lung cancer, how many of the patients with incidental lung cancer had bilateral nodules?

Reply 2: None of our patients with incidental lung cancer had bilateral nodules.

We have added text to the edited manuscript as follows:

"Of all patients with incidental lung cancer, none had bilateral nodules." (See page 6, lines 27-28).

Comment 3: Line 29: 30.4% of the patients had a re-metastasectomy, are these patients taken out of the cohort because patients with re-metastasectomy have up to 100% a metastases so it is unlikely that these patients have a benign finding or a lung cancer.

Reply 3: We thank the reviewer for this notion. Initially, the re-metastasectomies were included in the final histology analysis. However as requested by reviewer A, a binary logistic regression

analysis predicting incidental primary lung cancer was performed wherein an additional model 2 excluding re-metastasectomies was constructed. In model 2, DFI with a cut-off of 24 months had an adjusted odds ratio of 8.48 (95% CI 1.09-66.03). The predictive value of DFI increased in model 2 compared to model 1 which included all intended pulmonary metastasectomies. We added text to the revised manuscript as follows: "In model 2, excluding re-metastasectomies, a DFI over 24 months was significantly associated with incidental primary lung cancer in final histology (adjusted OR=8.48, 95% CI 1.09-66.03, p=0.041, Table S1)." (See page 7, lines 3-5)

Comment 4: Did all patients had initially (in time of diagnosis of the primary cancer) a chest ct scan?

Reply 4: Unfortunately, we did not collect the data on diagnostics of the primary cancer of the suspected pulmonary metastases. However, since the first diagnosis of the primary cancer of the pulmonary metastases in our cohort has occurred in 1989, it is likely that chest ct-scanning in search of pulmonary metastases and clinical staging was not yet part of routine diagnostics. We added text to the revised manuscript as follows: "The lack of comprehensive clinical data on the primary cancers of the pulmonary metastases in our cohort can also be seen as a limitation in our study." (See page 10, lines 6-7)

Comment 5: Regarding the patients with lung cancer, how long was the median time between the diagnosis of the extrathoracic cancer and the lung cancer diagnosis.

Reply 5: The median time between diagnosis of extrathoracic cancer and incidental lung cancer was 24.6 months (IQR 11.8-166.7 months). We added this to the revised manuscript (See page 7, line 6-7)

Comment 6: How many patients had a smoking history? This will influence your lung cancer incidence.
Reply 6: We added this to the revised manuscript: "Of all patients, 59.1% had a smoking history. The median of pack years was 25 (IQR 15-40)." (See page 5, lines 24-25)

Comment 7: Please define "anatomic sublobar resection", do you mean a segmentectomy?
Reply 7: By anatomic sublobar resection we meant a segmentectomy. We corrected this into the revised manuscript.

Second-Round Peer Review

Reviewer A
I would like to thank the authors for addressing all my concerns

Reviewer B
First, I want to thank the authors for their responds to my remarks. But in total, I still have some major remarks on this study.

Comment 1: Conclusion (Abstract and manuscript): I want to congratulate the authors for showing that there is higher incidence in lung cancer than estimated, but I do not agree to the conclusion of the authors. Welter et al. (PMID: 28402510) are showing that we need to have a distance margin of at least 7 mm in the time of colorectal cancer metastases. Renaud et al. are showing that in some patients regarding the RAS status we better perform an anatomic resection. So in case of metastases, a wedge resection might be enough. Furthermore, 13% of their patients had a benign nodule (line 172), also here a wedge resection would be enough. Instead of resecting all lung nodules per segmentectomies like the authors are concluding, a preoperative histology should be taken (e.g. ct-punction). Resecting all patients per segmentectomy would be an overtreatment.

Furthermore, the authors themselves are showing that the segmentectomy group had a significantly higher postoperative morbidity rate (Line 201-203). Also regarding the aspect of recurrent metastases a re-operation after an anatomical resection is more complicated compared to an operation after wedge resection. In total, I can not agree with this conclusion.

Reply 1: We thank the reviewer for this remark. We must admit our conclusion being too straightforward; segmentectomy for all suspected pulmonary metastases indeed can be seen as overtreatment. However, we would like to underline the logistic regression analysis predicting incidental primary lung cancer in final histology and suggest in the conclusion that a segmentectomy should be included as a treatment option in patients with a history of smoking and a long disease-free interval.

We adjusted the text as follows:
"The significant amount of new primary lung cancer lesions in pulmonary metastasectomy patients highlights the diagnostic importance of pulmonary metastasectomy. A segmentectomy could be considered as a primary procedure in pulmonary metastasectomy in patients with a long DFI and a heavy smoking history."
(See page 2, lines 15-17)

"Whereas wedge resections and frozen sections have a good degree of sensitivity and specificity in diagnosing malignant lesions from benign lesions [14] they lack accuracy in differentiating between metastatic and different types of primary lung cancer lesions [15]. Occasionally, a CT-guided biopsy can be taken preoperatively from the suspected malignant nodule. However, there are cases were a CT-guided biopsy is not feasible as the diagnostic accuracy of CT-guided biopsies of pulmonary nodules weakens for example in small nodules or subpleural locations [16,17]. Also, CT-guided biopsies of the pulmonary nodules are not entirely harmless, as the procedure has a morbidity risk with a possibility of severe complications [16]. As our study showed a long DFI and a heavy history of smoking being possible predictive factors for incidental primary lung cancer in final histology in intended pulmonary metastasectomies, these patients could benefit from a segmentectomy and a lymphadenectomy as a primary procedure in treating the suspected pulmonary metastases, especially when a CT-guided biopsy is not feasible or available. Segmentectomies have been shown to have good oncological results in early-stage lung cancer [18,19], and thus if the final histology in pulmonary metastasectomy turns out as primary lung cancer, a reoperation with a required extent of resection could be avoided. Although wedge resections have a lower

complication rate in comparison to the anatomically resected metastases, the extension to anatomical resections did not affect short-term mortality or long-term survival in our cohort."
(See page 9, lines 7-21)

"A segmentectomy could be considered as a primary procedure in patients with a long DFI and a heavy history of smoking when an invasive CT-guided biopsy is not feasible. Performing a segmentectomy and a lymphadenectomy directly on these patients might eliminate the need for additional resection and surgery if the nodule turns out to be a primary lung cancer."
(See page 10, lines 23-26)

Comment 2: Key findings: The authors are writing that patients with lung cancer are later re-operated with a delay in the definitive procedure. How was it in your patients? How long was the time from the first operation to the definitive lung cancer operation? It would be interesting if the delay would have an impact on the overall survival although the cancer is already resected by wedge resection.

Reply 2: Patients with incidental primary lung cancer in final histology had a definitive procedure later on with a median delay of 45.5 days (IQR 32.5-55.5 days). There was no survival difference in 5-year overall survival between patients receiving a delayed definitive procedure for incidental primary lung cancer (n=15) and the reference cohort of operated stage I primary lung cancer patients (delayed procedure 70% vs. normal protocol 61.4%; p=0.643).

We added to this to the text as follows:
"These patients were operated later with a definitive procedure with a median delay of 45.5 days (IQR 32.5-55.5 days). Using log rank tests in K-M analysis, the delay in the definitive procedure did not affect 5-year overall survival when comparing to the reference data of operated stage I primary lung cancers (delayed procedure 70.0% vs. standard procedure 61.4%, p=0.643)."
(See page 7, lines 8-11).

Comment 3: In line 64-65 the authors are writing about the importance of a lymph node dissection/sampling. In their study only 18% had a sampling, in addition only 5 cases a systematic lymph node sampling for N2 (Line 1654-165). Regarding this fact the patients are not adequately operated, especially in case of lung cancer. Regarding the extention of the lung resection the authors recommend to operate like in lung cancer patients. Would they now also recommend a sampling/ dissection in all patients with colorectal cancer history and lung nodule?

Reply 3: We thank the reviewer for this critique. We admit that the lymph node resection/sampling rate in our study is relatively low in comparison to reference data. Lines 64-65 about lymph node dissection/sampling in the introduction is part of briefing of the The Society of Thoracic Surgeons (STS) guidelines. In the referred STS consensus document (DOI: 10.1016/j.athoracsur.2018.10.028), authors point out the heterogenous stance towards lymph node dissection/sampling during pulmonary metastasectomy. In 2010, STS guidelines argued that mediastinal N2 nodal involvement in pulmonary metastasis, should be excluded from pulmonary metastasectomy entirely (DOI: 10.1097/JTO.0b013e3181dcf920). Also previously, 32.2% of ESTS members replied not performing any lymph node sampling during pulmonary

metastasectomy (DOI: 10.1097/JTO.0b013e31818bd9da). To the best of our knowledge, the STS expert consensus document is the first to recommend lymph node sampling/dissection during pulmonary metastasectomy, and it is published in 2019, in the end of the study period of our data. These might partly account for the low lymph node resection/sampling rate in our study hospital.

We edited the text as follows:
"The guideline recommends minimally invasive surgery to be preferred over open approaches, and lymph node sampling/dissection concomitant with pulmonary metastasectomy should be considered, as mediastinal lymph node involvement predicts a poor survival."
(See page 3, lines 9-12)

The following text was added to the limitations:
"The lymph node sampling rates in our study are relatively low in comparison to the reference data and thus, the lower lymph node involvement status, via adjuvant therapy stratification, might have affected the survival data in our cohort."
(See page 10, lines 18-20)

Concerning the comment on inadequate lymph node resection in lung cancer treatment, for clarification, as pointed out in our article, in patients with incidental primary lung cancer, a hilar N1 to systematic N2 lymphadenectomy with a required extent of resection (mainly lobectomy), depending on clinical staging of the incidental primary lung cancer, was performed later on.
In pulmonary metastasectomies, we recommend lymph node dissection/sampling to be performed according to STS expert consensus guidelines.

We edited the text as follows:
"In final pathology reports, 15 cases (9.7%) were new primary lung cancers and were later accordingly re-operated with an appropriate anatomical resection and a lymphadenectomy."
(See page 6, lines 26-27)

Segmentectomies are performed as a primary procedure in about 8% of patients in pulmonary metastasectomy cohorts (DOI: 10.1016/S0022-5223(97)70397-0, DOI: 10.1111/ANS.16866). In our study, reconsidering our conclusion, we merely suggest that in addition to obvious justifiable anatomical reasons, segmentectomies, accompanied with a lymphadenectomy, could be also considered in pulmonary metastasis patients with a long DFI and a heavy tobacco history.

We edited our text as follows:
"A segmentectomy could be considered as a primary procedure in pulmonary metastasectomy patients with a long DFI and a heavy history of smoking when an invasive CT-guided biopsy is not feasible. Performing a segmentectomy and a lymphadenectomy directly on these patients might eliminate the need for additional resection and surgery if the nodule turns out to be a primary lung cancer."
(see page 10, lines 23-26)