Original Article

Results of intention-to-treat pulmonary metastasectomies in northern Finland revealing significant number of new lung primary carcinomas: time to move on from wedge resections?

Topias Karjula[1,2]^, Anne Niskakangas[1,2], Olli Mustonen[1,2], Iiris Puro[1,2], Juha P. Väyrynen[2], Olli Helminen[1,2], Fredrik Yannopoulos[1,3]

[1]Surgery Research Unit, Medical Research Center, Oulu University Hospital and University of Oulu, Oulu, Finland; [2]Cancer and Translational Medicine Research Unit, Medical Research Center Oulu, Oulu, Finland; [3]Department of Cardiothoracic Surgery, Oulu University Hospital, Oulu, Finland

Contributions: (I) Conception and design: O Helminen, F Yannopoulos; (II) Administrative support: O Helminen, F Yannopoulos; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: T Karjula, O Helminen, F Yannopoulos; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Topias Karjula, MD. Surgery Research Unit, Medical Research Center, Oulu University Hospital and University of Oulu, Aapistie 5A, 90220, Oulu, Finland; Cancer and Translational Medicine Research Unit, Medical Research Center Oulu, Oulu, Finland. Email: topias.karjula@oulu.fi.

Background: A considerable proportion of intended pulmonary metastasectomies is known to turn out as new incidental primary lung cancers in final pathology. We aimed to analyse the trends and results of pulmonary metastasectomies using the intention-to-treat approach with an emphasis on final histopathological findings.

Methods: All intention-to-treat pulmonary metastasectomies performed in Oulu University Hospital between 2000 and 2020 were included in the study. Long term survival was analysed with the Kaplan-Meier method and log-rank tests. A binary logistic regression analysis was performed to calculate odds ratios for incidental primary lung cancer in final histology.

Results: A total of 154 intended pulmonary metastasectomies were performed to 127 individual patients. There was an increasing trend in pulmonary metastasectomies during the study period. Despite the increasing trend in comorbidities of the operated patients, the length of hospital stays decreased, and the postoperative complication rates remained stable. In final pathology reports, 9.7% were new primary lung cancers and 13.0% were benign nodules. A long disease-free interval (≥24 months) and smoking history were associated with incidental primary lung cancer in final histology. The short-term 30- and 90-day mortalities after pulmonary metastasectomy were 0.7%. The 5-year survival after pulmonary metastasectomy from all histologies was 52.8%, and from colorectal cancer metastasectomies (n=34) it was 73.5%.

Conclusions: The significant amount of new primary lung cancer lesions in pulmonary metastasectomy specimens highlight the diagnostic importance of pulmonary metastasectomy. A segmentectomy could be considered as a primary procedure in pulmonary metastasectomy in patients with a long disease-free interval and a heavy smoking history.

Keywords: Pulmonary metastases; pulmonary metastasectomy; intention-to-treat; pathology

Submitted Nov 29, 2022. Accepted for publication May 12, 2023. Published online Jun 13, 2023.
doi: 10.21037/jtd-22-1647
View this article at: https://dx.doi.org/10.21037/jtd-22-1647

^ ORCID: 0000-0002-2342-6034.

Introduction

The lungs are the second most frequent site of metastases in extrathoracic malignancies. The most common sources of pulmonary metastases are colorectal cancer (CRC), urogenital cancers, sarcomas, breast cancer and malignant melanoma (1). Pulmonary metastasectomy is generally considered in patients with a controlled primary cancer, absence/control of extrathoracic metastases and tolerance for surgical treatment. During the past decades, pulmonary metastasectomies have been performed increasingly. Alongside the primary cancer histology, factors such as disease-free interval (DFI), the size of the largest metastatic nodule, the number of metastases and the completeness of resection are proven prognostic factors of pulmonary metastasectomy (2,3). Quite recently, Expert Consensus guideline was published by The Society of Thoracic Surgeons (4), which underlines the multidisciplinary assessment in the treatment of pulmonary metastases. 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. Surgical treatment is advised in carefully selected patients offering survival benefit, especially, in patients with controlled primary cancer site, absence/control of extrathoracic metastases, an achievable complete resection and tolerance for surgery.

Highlight box

Key findings

- 9.7% of intention-to-treat pulmonary metastasectomies represented primary lung cancer in final pathology reports.

What is known and what is new?

- A considerable proportion of suspected pulmonary metastases are revealed as new primary lung cancers. These patients are generally later re-operated with greater margins, causing a delay in the definitive procedure.
- According to our study, 23.4% of pulmonary nodules resected as metastases represented other histologies than pulmonary metastases from solid malignomas. 9.7% of all intended pulmonary metastasectomies were new primary lung cancers.

What is the implication, and what should change now?

- A segmentectomy could be considered as a primary procedure in pulmonary metastasectomies in patients with a tobacco history and a long disease-free interval when a computed tomography-guided biopsy is not feasible.

Pulmonary metastasectomy in CRC has been disputed by a recent randomized controlled trial (5), raising discussion of the effectiveness of the procedure on survival. However, it is well known that a proportion of intended pulmonary metastasectomies are revealed to be primary lung cancers in final histology reports. Generally, these patients are re-operated accordingly with a greater margin if only a wedge resection was performed causing a delay in the acquired operative procedure.

The aim of this study was to analyse trends and results of pulmonary metastasectomy in northern Finland. The cohort was analysed with an intention-to-treat approach with an emphasis on the final histopathological findings. The secondary aim was to analyse the short-term complications and long-term survival. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1647/rc).

Methods

Design

All patients receiving surgical treatment with curative intent for pulmonary metastases in Oulu University Hospital during 2000–2020 were included in this population-based cohort study. This was an intention-to-treat analysis. Patients were considered for pulmonary metastasectomy if there were no widespread or uncontrolled metastases, curative treatment and a R0-resection was achievable, and patient could tolerate anaesthesia and surgical treatment. For short-term complication profile comparison, all pathological stage I primary lung cancer patients (n=415) operated in the study hospital during the study same study period were selected as a reference group.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Oulu University Hospital Ethics Committee (No. EETTMK 81/2008). Due to the retrospective nature of the study, the need for informed consent was waived by Finnish National Authority for Medicolegal Affairs (VALVIRA).

Data collection

All relevant clinical data was retrospectively collected from a prospectively maintained electronic patient record system used in the study hospital. The ability to tolerate surgery was classified with the American Society of Anaesthesiologists (ASA) physical status classification system. Bilateral metastases operated as a same-day procedure were considered as separate cases. All cancers were restaged according to AJCC/UICC 8th edition of TNM classification (6). The follow-up and cause-of-death information was received from Statistics Finland and Finnish Cancer Registry up to December 31, 2019, with 100% coverage. In patients operated during 2020, follow-up ended 30-days after surgery. Since 98.1% of deaths were cancer related, only overall survival is presented in the study.

Definitions and outcomes

Charlson Comorbidity Index (CCI) was used for comorbidity classification (7). The cancer under treatment was included as one comorbidity. DFI was defined as time from treatment of primary cancer to the date of first clinical or radiological relapse of disease. Metastases detected under 6 months after primary cancer surgery were determined as synchronous, and metachronous when detected after 6 months after primary cancer treatment. Postoperative complications were graded using the Clavien-Dindo (CD) Classification (8) and were limited to be occurring within 30 days of surgery. Of complications requiring specific criteria, pneumonia had to be radiologically confirmed with a chest X-ray, prolonged air leak was defined as lasting over 5 postoperative days, prolonged demand for mechanical ventilation was defined as lasting over 24 hours and atelectasis was assessed separately as a complication if it had effect on treatment or required an intervention to rectify.

Primary outcome was final histology of resected pulmonary nodule. Secondary outcomes were short-term and long-term cancer specific and overall mortality.

Statistical analysis

Chi-squared test and Fisher's exact test was used for categorical variable group comparison. For continuous variable comparison, Student's *t*-test and Oneway-ANOVA were used. 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 (<65/≥65 years), history of smoking (no/yes), DFI (<24/≥24 months), 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. Kaplan-Meier (K-M) survival curves were constructed visualize survival after first pulmonary metastasectomy. Missing data was not imputed.

Statistical analysis was performed using IBM SPSS Statistics Version 28.

Results

Patient characteristics and preoperative evaluation

A total of 154 pulmonary metastasectomies were performed on 127 patients. Of these, 27 operations were re-metastasectomies. There was an increasing frequency in metastasectomies during the study period in 5-year intervals, the numbers were 24, 25, 32, and 73, respectively. The trends of pulmonary metastasectomy patients in 5-year intervals are presented in *Table 1*. The comorbidity load increased during the study period: the proportion of patients with a CCI ≥2 increased from 25.0% in 2000–2005 to 54.8% in 2016–2020 (P=0.006). The mean age increased consistently from 54 years in 2000–2005 to 64 years in 2016–2020 (P=0.002). Of all patients, 59.1% had a smoking history. The median of pack years was 25 (IQR, 15–40). Positron emission tomography (PET) was used in selected cases. The use of PET in clinical staging during the study period increased significantly, reaching 58.9% in 2016–2020 (*Table 1*). Preoperative invasive staging was rarely performed: three patients had a mediastinoscopy and an endobronchial ultrasound was performed to one patient. Histological confirmation via computed tomography (CT)-guided biopsy of suspected metastatic nodules was not performed to any of the study patients.

CRC pulmonary metastases

The median age of CRC pulmonary metastasectomy patients was 65 years, 53.8% of patients had CCI ≥2 and the maximum CCI was 3. A proportion of 50% of metastasectomies were of rectal origin and 26.9% of patients had synchronous pulmonary metastases, 32.4% had bilateral metastases, 70.6% of patients had a solitary lung metastasis at the time of diagnosis and the median of diameter of the largest metastatic nodule was 12 mm, 69.6% of CRC pulmonary metastasectomy patients had a single metastasectomy and 30.4% had remetastasectomies; the median amount of metastasectomies was 1.

Table 1 Patient characteristics and trends of intention-to-treat pulmonary metastasectomies (n=154)

Measure	2000–2005 (n=24)	2006–2010 (n=25)	2011–2015 (n=32)	2016–2020 (n=73)	P value
Gender, n (%)					0.034
Female	10 (41.7)	18 (72.0)	12 (37.5)	30 (41.1)	
Male	14 (58.3)	7 (28.0)	20 (62.5)	43 (58.9)	
Age, years, mean	54	58	59	64	0.002
BMI, kg/m^2, mean	22.7	25.57	28.38	29.08	0.004
Former tobacco history, n (%)					0.485
No	10 (52.6)	11 (52.4)	7 (33.3)	19 (39.6)	
Yes	9 (47.4)	10 (47.6)	14 (66.7)	29 (60.4)	
WHO, n (%)					0.438
0	14 (63.6)	17 (77.3)	19 (61.3)	45 (64.3)	
1	7 (31.8)	5 (22.7)	12 (38.7)	26 (35.7)	
≥2	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	
CCI, n (%)					0.006
0	2 (8.3)	1 (4.0)	1 (3.1)	1 (1.4)	
1	16 (66.7)	19 (76.0)	14 (43.8)	32 (43.8)	
≥2	6 (25.0)	5 (20.0)	17 (53.1)	40 (54.8)	
ASA, n (%)					0.019
1	4 (16.7)	6 (24.0)	3 (10.0)	9 (12.3)	
2	18 (75.0)	13 (52.0)	11 (36.7)	40 (54.8)	
≥3	2 (8.3)	6 (24.0)	16 (53.3)	24 (32.9)	
Imaging, n (%)					<0.001
CT	24 (100.0)	20 (80.0)	21 (65.6)	30 (41.1)	
PET-CT	0 (0.0)	5 (20.0)	11 (34.4)	43 (58.9)	

ASA, American Society of Anesthesiologists physical status classification; BMI, body mass index; CCI, Charlson Comorbidity Index; CT, computed tomography; PET, positron emission tomography; WHO, World Health Organization performance status classification.

Operative approach

The trends in the operative approach are shown in *Table 2*; the use of video-assisted thoracoscopic surgery (VATS) increased after 2008. During 2016–2020, 78.1% of intended metastasectomies were performed by VATS. Anatomical resections showed a slightly increasing trend towards the last quartile of the study period (*Table 2*). In total, 78.6% (n=121) were non-anatomical resections, wedge resections. Twenty-nine cases were anatomical resections, of which 19 were lobectomies, 6 segmentectomies, and the remaining 4 were pneumectomies. Four cases had an extended wedge resection alongside an anatomical resection. Thirty-five of total cases had more than one suspected metastatic nodule removed, and the maximum number of nodules removed in a single operation was 8. In total, our cohort included 19 bilateral pulmonary metastases, defined as bilateral suspected metastatic nodules simultaneously. Same-day bilateral metastasectomies (13 cases) were enrolled as separate cases. The rest of bilateral metastases (6 cases) were operated on separate occasions and enrolled as separate cases. Lymph node sampling was performed in 18% (27 cases) of all intended pulmonary metastasectomies. A systematic thoracic N2 lymph node sampling was performed in 5 cases.

Of all pulmonary metastasectomies, 53.1% (69 cases) received adjuvant chemotherapy and 4.6%

Table 2 Trends in operative results of pulmonary metastasectomy (n=154)

Measure	2000–2005 (n=24)	2006–2010 (n=25)	2011–2015 (n=32)	2016–2020 (n=73)	P value
Clavien-Dindo, n (%)					0.562
No complications	18 (75.0)	20 (80.0)	28 (87.5)	59 (80.8)	
Minor (I–II)	4 (16.7)	2 (8.0)	4 (12.5)	9 (12.3)	
Major (III–V)	2 (8.3)	3 (12.0)	0 (0.0)	5 (6.8)	
Operative approach, n (%)					<0.001
VATS	13 (54.2)	8 (32.0)	17 (53.1)	57 (78.1)	
Thoracotomy	11 (45.8)	17 (68.0)	15 (46.9)	16 (21.9)	
VATS (n=95), n (%)					0.270
Anatomical	0 (0.0)	0 (0.0)	2 (11.8)	11 (19.3)	
Non-anatomical	13 (100.0)	8 (100.0)	15 (88.2)	46 (80.7)	
Thoracotomy (n=59), n (%)					0.584
Anatomical	2 (18.2)	6 (35.3)	5 (33.3)	3 (18.8)	
Non-anatomical	9 (81.8)	9 (52.9)	10 (66.7)	11 (68.8)	
Combination	0 (0.0)	2 (11.8)	0 (0.0)	2 (12.5)	
Extent of resection					0.368
Anatomical	2 (8.3)	6 (24.0)	7 (21.9)	14 (19.2)	
Non-anatomical	22 (91.7)	17 (68.0)	25 (78.1)	57 (78.1)	
Combination	0 (0.0)	2 (8.0)	0 (0.0)	2 (2.7)	

VATS, video-assisted thoracoscopic surgery.

Table 3 Final histological diagnosis of pulmonary metastasectomy

Histology	n	%
Colorectal carcinoma	34	22.1
Renal cancer	17	11.0
Sarcoma	14	9.1
Urothelial cancer	11	7.14
Head and neck cancers	9	5.8
Metastatic lung cancer	8	5.2
Breast cancer	6	3.9
Endometrial cancer	6	3.9
Melanoma	5	3.2
Pancreatic cancer	2	1.3
Other malignancies	7	4.5
New primary lung cancer	15	9.7
Benign	20	13.0
Total	154	100.0

(6 cases) radiotherapy. Excluding remetastasectomies, 46.1% (48 cases) received adjuvant chemotherapy and 4.8% (5 cases) radiotherapy. There was no trend in the use of adjuvant therapy during the study period. Of all cases, 15.6% had missing data on adjuvant therapy.

Histological results

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. Twenty cases (13.0%) turned out to be benign nodules and 1 case (0.6%) was a lymphoma. Excluding the above, the remaining 118 cases consisted of pulmonary metastases from CRC (n=34), genitourinary cancers (n=28), sarcoma (n=14) and other malignancies. The histological diagnoses are summarized in *Table 3*. Of all patients with incidental primary lung cancer, none had bilateral nodules.

In the binary logistic regression analysis, in all intended pulmonary metastasectomies in model 1, a DFI of over

Table 4 Post-operative outcome comparison between pulmonary metastasectomy and stage I primary lung cancer resection

Measure	Metastasectomy (n=154)	Stage I primary lung cancer (n=415)	P value
LOS, days (median)	3	5	<0.001
Dischargement[†], n (%)			<0.001
Home	124 (81.0)	207 (50.7)	
Another hospital or rehabilitation center	29 (19.0)	201 (49.3)	
Clavien-Dindo, n (%)			<0.001
No complications	125 (81.2)	250 (60.4)	
Minor	19 (12.3)	117 (28.3)	
Major	10 (6.5)	47 (11.4)	
VATS-conversion, n (%)			0.264
No	143 (92.9)	371 (89.4)	
Yes	11 (7.1)	44 (10.6)	
Reoperation, n (%)			0.004
No	138 (89.6)	391 (94.2)	
During hospital stay	1 (0.6)	12 (2.9)	
Later	15 (9.7)	12 (2.9)	
30-d mortality, n (%)	1 (0.7)	3 (0.7)	0.939
90-d mortality, n (%)	1 (0.7)	9 (2.2)	0.303
1-year mortality, n (%)	11 (7.1)	22 (5.3)	0.404

[†], patients deceased during hospital stay not included. LOS, length of hospital stay; VATS, video-assisted thoracoscopic surgery.

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 =8.45, 95% CI: 1.09–66.03, P=0.041, Table S1). The median time between diagnosis of extrathoracic cancer and incidental primary lung cancer was 24.6 months (IQR, 11.8–166.7 months). 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).

Short-term outcomes

Short-term outcomes after pulmonary metastasectomy are presented in *Table 4*. The median length of stay (LOS) in hospital was 3 days (IQR, 2–5 days). In 5-year intervals, the median length of hospital stay decreased from 5 to 3 days (P<0.001). A proportion of 18.8% of metastasectomies presented overall complications (CD I–V) and 6.5% had major complications (CD III–V). One patient (0.6%) was reoperated during the hospital stay due to haemorrhagic complications. Seventeen patients were reoperated later, 15 of which due to the finding of a primary lung cancer and the remaining 2 due to local recurrence of the metastasis. Of all patients, 81.0% were discharged directly to home and 19.0% to another hospital or other rehabilitation centre. There was no statistically significant difference in short-term mortality between the pulmonary metastasectomy and stage I primary lung cancer patients (30-day mortality 0.66% *vs.* 0.72%, P=0.939; 90-day mortality 0.66% *vs.* 2.17%, P=0.303; *Table 4*). The patient characteristics

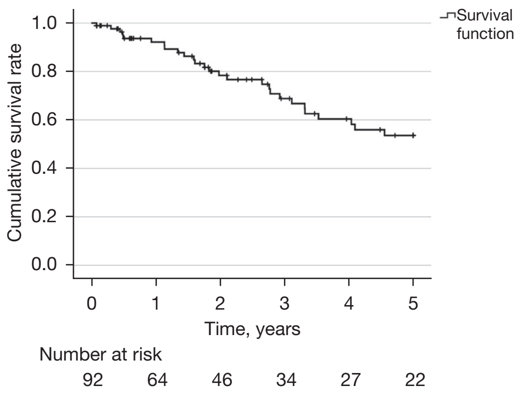

Figure 1 The 5-year overall survival of pulmonary metastasectomy patients from all histology.

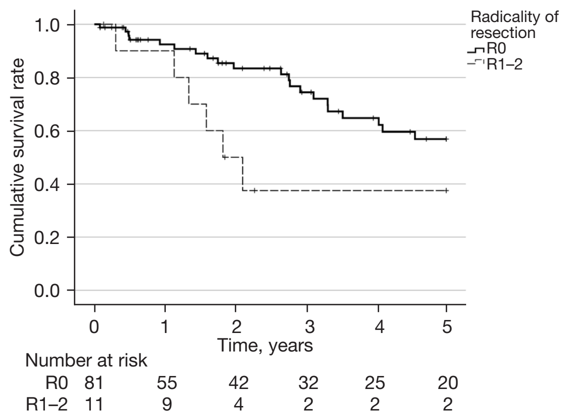

Figure 2 The 5-year overall survival of pulmonary metastasectomy from all histology stratified by the resection radicality of pulmonary metastasectomy. Log rank P=0.027.

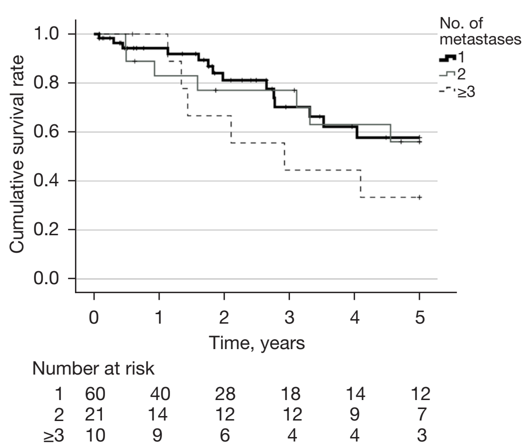

Figure 3 The 5-year overall survival of pulmonary metastasectomy patients with malignant histology stratified by the number of metastases. Log rank P=0.351.

of operated stage I primary lung cancer patients are presented in supplementary Table S2.

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).

Long-term outcomes

The 1-year survival after the first intended pulmonary metastasectomy was 92.5%. In all metastasectomy patients with a survival time of under 1 year, the cause of death was metastatic cancer. 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; Table S3).

The 5-year overall survival of pulmonary metastasectomies from all malignant histologies was 52.8% (*Figure 1*) with a median follow-up time of 25.2 months (IQR, 7.1–56.6). The overall survival of pulmonary metastasectomy in CRC were 100%, 88.2% and 73.5%, at 1-, 3-, and 5-years respectively. The median follow-up time of CRC pulmonary metastasectomies was 23.2 months (IQR, 2.7–48.0 months). The 5-year overall survival stratified by histology is shown in the Figure S1. 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). Of all deceased metastasectomy patients, 98.1% died of metastatic cancer, 2 patients died of ischemic heart disease and 1 patient of subarachnoid haemorrhage.

Of the total 91 patients with a malignant metastatic histological finding, 80 patients (87.9%) had a complete R0 resection in primary pulmonary metastasectomy. Three operations were enucleations and were considered as R1 resection. The 5-year survival rate of R0 resected patients was 56.9%, whereas patients with R1–2 resection had a 5-year survival of 37.5% (P=0.027; *Figure 2*). Sixty (65.9%) patients had a solitary pulmonary metastasis, 21 (23.1%) patients had 2 metastases, and 10 (10.9%) patients had ≥3 metastases. There was no statistical difference between the 5-year survival of patient groups based on the amount of lung metastases (P=0.351; *Figure 3*).

Discussion

We performed a study on the results and trends of pulmonary metastasectomies in a 20-year study period in a single institution in northern Finland which is the main treatment centre for all surgically treated pulmonary cancer cases, both metastasectomies and primary lung cancer. A significant proportion of 9.7% of intended pulmonary metastasectomies were new primary lung cancers in final pathology. Pulmonary metastasectomies had an increasing trend. Despite the increasing trend of co-morbidity load of operated patients, the complication rates remained steady.

There is limited amount of literature on the final pathological diagnosis of intended pulmonary metastasectomies from all primary cancer types. The PulMiCC trial reported a proportion of 2.5% of primary lung cancers and 0.2% of benign hamartomas in the recruited CRC pulmonary metastasectomy patients (9). However, this is not comparable to our study, as it includes only CRC patients; our data included all intention-to-treat metastasectomies irrespective of the primary cancer histology. Additionally, Kathuria *et al.* reported an 8% proportion of non-neoplastic histological findings in intended pulmonary metastasectomies; no primary lung cancer cases were reported (10). Another study from 2012 reported 3% of VATS pulmonary metastasectomies turning out as primary lung cancers in the final pathology reports; however, the study included only patients with pulmonary metastases operable by VATS (11). Several studies have evaluated the clinical problem of the differential diagnosis of solitary pulmonary nodules in patients with an earlier malignancy, reporting highly variable proportions (17–76%) of primary lung cancer in the final histopathological results (12,13). However, the surgical studies on solitary pulmonary nodules also include patients treated as a suspected primary lung cancer and a history of an earlier primary cancer and are therefore not comparable with our results. Our result of the significant proportion of primary lung cancers in intended pulmonary metastasectomies underlines the diagnostic challenges of pulmonary metastasectomy, especially in patients with a single pulmonary nodule with a malignant suspicion and a history of an earlier malignancy. 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.

The result of the increasing trend of pulmonary metastasectomies in this study was expected and is compatible with the literature from the past decades (20). We speculate that the increase in the frequency of pulmonary metastasectomy is due to several reasons. The incidence of several cancers most commonly presenting with pulmonary metastases has been increasing (21). Also, the frequency of pulmonary metastases and the synchronicity of pulmonary metastases has been increasing (22). Additionally, treatment guidelines on pulmonary metastases have changed during the last decades since, only in 2004, NICE guidelines on CRC included surgical treatment of pulmonary metastases (23). In our study, the first CRC pulmonary metastasectomy was performed in 2005. Despite the increase in the comorbidity of the operated patients, there was a decrease in the length of hospital stay during the study period, which is concordant with the literature (20). Nevertheless, regardless of this trend there was no statistically significant trend in postoperative complications. The decreasing trend of the length of hospital stay is at least partly due to the increasing use of VATS (24). In short-term complication comparison with stage I primary cancer patients, pulmonary metastasectomy patients had shorter hospital stays and had a lighter complication profile, as expected.

The long-term survival of CRC pulmonary

metastasectomies in our data was significantly better than the reference literature data on CRC pulmonary metastasectomies (25-33). The reference data is summarized in supplementary Table S4. Concerning DFI, our data showed a shorter median DFI of 9.9 months (IQR, 0–33 months), whereas reference cohorts showed median DFI values ranging from 12 to 27.5 months with 5-year survivals ranging from 45.5% to 64.7% (22-27,29). Also, the median size of the largest metastatic nodule in our cohort seems to be smaller than several reference cohorts (24,25,29). This better survival in our data might be partly due to patient selection. However, a large proportion of all our pulmonary metastasectomy patients presented with bilateral metastases. Additionally, nearly a third of our CRC metastasectomy patients underwent re-metastasectomies. Therefore, our patient selection cannot be deemed too conservative or risk aversive. On the other hand, the smaller size of the largest pulmonary metastasis and shorter DFI could imply a more effective control after treatment of the primary cancer compared to the reference data.

Our study has a few strengths as a population-based intention-to-treat analysis of pulmonary metastasectomies. The selection bias is restricted to surgical patient selection, as all pulmonary metastases in the northern Finland are operated in the study hospital. Additionally, the follow-up data for mortality was 100% complete. The most significant limitations of this study are the small sample size and the single-institution basis of the study. 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. 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.

Conclusions

A significant proportion of pulmonary metastasectomies turned out to represent primary lung cancer in final pathology reports. 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. Larger or easily to-reach suspected nodules should be considered for invasive biopsies more often to reach and accurate diagnosis and accurately treat the patient in one procedure correctly streamlining the surgical treatment process.

Acknowledgments

The study benefited from samples/data from Northern Finland Biobank Borealis, Oulu, Finland (https://oys.fi/biopankki/).
Funding: This study was supported by State Research Funding (VTR), Instrumentarium Science Foundation and Mary and Georg C. Ehrnrooth Foundation. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1647/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1647/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1647/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1647/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Oulu University Hospital Ethics Committee (No. EETTMK 81/2008). Due to the retrospective nature of the study, the need for informed consent was waived by Finnish National Authority for Medicolegal Affairs (VALVIRA).

References

1. Cheung FP, Alam NZ, Wright GM. The Past, Present and Future of Pulmonary Metastasectomy: A Review Article. Ann Thorac Cardiovasc Surg 2019;25:129-41.
2. Younes RN, Fares AL, Gross JL. Pulmonary metastasectomy: a multivariate analysis of 440 patients undergoing complete resection. Interact Cardiovasc Thorac Surg 2012;14:156-61.
3. Pfannschmidt J, Dienemann H, Hoffmann H. Surgical resection of pulmonary metastases from colorectal cancer: a systematic review of published series. Ann Thorac Surg 2007;84:324-38.
4. Handy JR, Bremner RM, Crocenzi TS, et al. Expert Consensus Document on Pulmonary Metastasectomy. Ann Thorac Surg 2019;107:631-49.
5. Milosevic M, Edwards J, Tsang D, et al. Pulmonary Metastasectomy in Colorectal Cancer: updated analysis of 93 randomized patients - control survival is much better than previously assumed. Colorectal Dis 2020;22:1314-24.
6. Bierley JD, Gospodarowicz MK, Wittekind C. editors. TNM classification of malignant tumours. 8th ed. Chichester: Wiley, 2017
7. Armitage JN, van der Meulen JH; Royal College of Surgeons Co-morbidity Consensus Group. Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score. Br J Surg 2010;97:772-81.
8. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
9. Treasure T, Farewell V, Macbeth F, et al. The Pulmonary Metastasectomy in Colorectal Cancer cohort study: Analysis of case selection, risk factors and survival in a prospective observational study of 512 patients. Colorectal Dis 2021;23:1793-803.
10. Kathuria K, Jambhekar NA, Pramesh CS, et al. A clinicopathologic analysis of 88 lung resections of suspected metastatic carcinomas with proven primaries. Indian J Cancer 2013;50:356-60.
11. Eckardt J, Licht PB. Thoracoscopic versus open pulmonary metastasectomy: a prospective, sequentially controlled study. Chest 2012;142:1598-602.
12. Kanzaki R, Fukui E, Kanou T, et al. Preoperative evaluation and indications for pulmonary metastasectomy. J Thorac Dis 2021;13:2590-602.
13. Bellier J, Perentes JY, Abdelnour-Berchtold E, et al. A plea for thoracoscopic resection of solitary pulmonary nodule in cancer patients. Surg Endosc 2017;31:4705-10.
14. Marchevsky AM, Changsri C, Gupta I, et al. Frozen section diagnoses of small pulmonary nodules: accuracy and clinical implications. Ann Thorac Surg 2004;78:1755-9.
15. Pütz K, Engels M, Vollbrecht C, et al. Indications and limitations of fresh frozen sections in the pulmonary apparatus. Pathologe 2012;33:402-6.
16. Wallace MJ, Krishnamurthy S, Broemeling LD, et al. CT-guided percutaneous fine-needle aspiration biopsy of small (< or =1-cm) pulmonary lesions. Radiology 2002;225:823-8.
17. Tsukada H, Satou T, Iwashima A, et al. Diagnostic accuracy of CT-guided automated needle biopsy of lung nodules. AJR Am J Roentgenol 2000;175:239-43.
18. Kagimoto A, Tsutani Y, Shimada Y, et al. Segmentectomy for clinically early-stage primary squamous cell carcinoma of the lung. Thorac Cancer 2022;13:3477-85.
19. Hattori A, Matsunaga T, Fukui M, et al. Oncologic outcomes of segmentectomy for stage IA radiological solid-predominant lung cancer >2 cm in maximum tumour size. Interact Cardiovasc Thorac Surg 2022;35:ivac246.
20. Bartlett EK, Simmons KD, Wachtel H, et al. The rise in metastasectomy across cancer types over the past decade. Cancer 2015;121:747-57.
21. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
22. Chen H, Stoltzfus KC, Lehrer EJ, et al. The Epidemiology of Lung Metastases. Front Med (Lausanne) 2021;8:723396.
23. Treasure T, Milošević M, Fiorentino F, et al. History and present status of pulmonary metastasectomy in colorectal cancer. World J Gastroenterol 2014;20:14517-26.
24. Numan RC, Baas P, Klomp HM, et al. Optimal surgical management of pulmonary metastases: VATS versus thoracotomy. Respirology 2016;21:188-90.
25. Ratnayake CBB, Wells CI, Atherton P, et al. Meta-analysis of survival outcomes following surgical and non surgical treatments for colorectal cancer metastasis to the lung.

ANZ J Surg 2021;91:255-63.
26. Sponholz S, Oguzhan S, Mese M, et al. The impact of primary tumor location on prognosis after colorectal lung metastasectomy. Int J Colorectal Dis 2021;36:1731-7.
27. Gössling GCL, Chedid MF, Pereira FS, et al. Outcomes and Prognostic Factors of Patients with Metastatic Colorectal Cancer Who Underwent Pulmonary Metastasectomy with Curative Intent: A Brazilian Experience. Oncologist 2021;26:e1581-8.
28. Davini F, Ricciardi S, Zirafa CC, et al. Lung metastasectomy after colorectal cancer: prognostic impact of resection margin on long term survival, a retrospective cohort study. Int J Colorectal Dis 2020;35:9-18. Erratum in: Int J Colorectal Dis 2020;35:371-2.
29. Suzuki H, Kiyoshima M, Kitahara M, et al. Long-term outcomes after surgical resection of pulmonary metastases from colorectal cancer. Ann Thorac Surg 2015;99:435-40.
30. Sakamaki Y, Ishida D, Tanaka R. Prognosis of patients with recurrence after pulmonary metastasectomy for colorectal cancer. Gen Thorac Cardiovasc Surg 2020;68:1172-8.
31. Fukada M, Matsuhashi N, Takahashi T, et al. Prognostic factors in pulmonary metastasectomy and efficacy of repeat pulmonary metastasectomy from colorectal cancer. World J Surg Oncol 2020;18:314.
32. Corsini EM, Mitchell KG, Correa A, et al. Effect of primary colorectal cancer tumor location on survival after pulmonary metastasectomy. J Thorac Cardiovasc Surg 2021;162:296-305.
33. Nanji S, Karim S, Tang E, et al. Pulmonary Metastasectomy for Colorectal Cancer: Predictors of Survival in Routine Surgical Practice. Ann Thorac Surg 2018;105:1605-12.

Cite this article as: Karjula T, Niskakangas A, Mustonen O, Puro I, Väyrynen JP, Helminen O, Yannopoulos F. Results of intention-to-treat pulmonary metastasectomies in northern Finland revealing significant number of new lung primary carcinomas: time to move on from wedge resections? J Thorac Dis 2023;15(6):3319-3329. doi: 10.21037/jtd-22-1647