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THORACIC

Multicentre retrospective analysis on pulmonary metastasectomy: an European perspective

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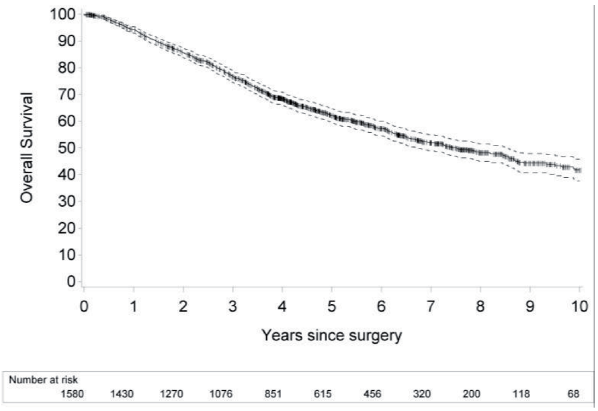
Multicentre retrospective analysis on pulmonary metastasectomy

Summary

- 1,647 patients who underwent curative-intent pulmonary metastasectomy
- 15 European institutions
- Inclusion period: 01/2010-12/2018

Results:
- VATS in 54.9% cases
- Wedge resections in 67.1% cases
- Lymph node dissection in 41.4% cases
- Solitary metastasis in 69.9% cases
- 30-day postoperative morbidity: 14.5%
- 5-year overall survival: 62.0%
- 5-year recurrence-free survival: 29.6%



Abstract

OBJECTIVES: To assess the current practice of pulmonary metastasectomy at 15 European Centres. Short- and long-term outcomes were analysed.

METHODS: Retrospective analysis on patients ≥18 years who underwent curative-intent pulmonary metastasectomy (January 2010 to December 2018). Data were collected on a purpose-built database (REDCap). Exclusion criteria were: previous lung/extrapulmonary metastasectomy, pneumonectomy, non-curative intent and evidence of extrapulmonary recurrence at the time of lung surgery.

RESULTS: A total of 1647 patients [mean age 59.5 (standard deviation; SD = 13.1) years; 56.8% males] were included. The most common primary tumour was colorectal adenocarcinoma. The mean disease-free interval was 3.4 (SD = 3.9) years. Relevant comorbidities were observed in 53.8% patients, with a higher prevalence of metabolic disorders (32.3%). Video-assisted thoracic surgery was the chosen approach in 54.9% cases. Wedge resections were the most common operation (67.1%). Lymph node dissection was carried out in 41.4% cases. The median number of resected lesions was 1 (interquartile range 25–75% = 1–2), ranging from 1 to 57. The mean size of the metastases was 18.2 (SD = 14.1) mm, with a mean negative resection margin of 8.9 (SD = 9.4) mm. A R0 resection of all lung metastases was achieved in 95.7% cases. Thirty-day postoperative morbidity was 14.5%, with the most frequent complication being respiratory failure (5.6%). Thirty-day mortality was 0.4%. Five-year overall survival and recurrence-free survival were 62.0% and 29.6%, respectively.

CONCLUSIONS: Pulmonary metastasectomy is a low-risk procedure that provides satisfactory oncological outcomes and patient survival. Further research should aim at clarifying the many controversial aspects of its daily clinical practice.

Keywords: Lung metastases • Lung metastasectomy • Pulmonary metastasectomy • Prognosis • Real-world practice

ABBREVIATIONS

ASA	American Society of Anesthesiology
DFI	Disease-free interval
ESTS	European Society of Thoracic Surgeons
IQR	Interquartile range
OS	Overall survival
PM	Pulmonary metastasectomy
REDCap	Research Electronic Data Capture
RFS	Recurrence-free survival
SD	Standard deviation
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
VATS	Video-assisted thoracic surgery

INTRODUCTION

Lungs are the most frequent site of metastases of primary tumours located outside the chest cavity [1]. Over the last decades, pulmonary metastasectomy (PM) with curative intent has become part of a multidisciplinary treatment strategy for (oligo)metastatic disease, and currently represents an established therapeutic option for carefully selected patients [2], with proven survival benefits and minimal postoperative morbidity.

In the 2023 annual report of the European Society of Thoracic Surgeons (ESTS), PM accounts for 9.3% of all lung resections performed from 2007 to 2022 in 130 European units [3].

Despite the vast number of articles published on the topic, however, high-quality evidence on the outcomes of PM in

scientific literature is lacking [4]. Due to the scarcity of guidelines and recommendations to support daily clinical practice, there is a broad international and interinstitutional variability in indications, timing and modalities to perform PM [5].

Multidisciplinary oncology care teams are increasingly confronted with a multitude of potential treatment combinations for lung metastases, and the role of PM in this evolving landscape is not defined. Furthermore, the population of PM candidates is extremely heterogeneous in terms of tumour histology and biological behaviour, disease-free interval (DFI), size and number of lung metastases, metastases-directed systemic treatments, etc. [4].

As a consequence of the relevant differences in therapeutic approaches, surgical techniques and patient characteristics, PM remains a non-standardized practice [6].

In order to offer a comprehensive overview of the current practice of PM in Europe, we designed and conducted a multicentre retrospective study, with the support of a fellowship from the ESTS Biology Club.

PATIENTS AND METHODS

The results of the present study are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. A STROBE checklist is provided as Supplementary Material, File S1.

Ethical statement

The Ethics Committee of the promoter centre (European Institute of Oncology, Milan, Italy) approved the study (ref. IEO 1438, 13 January 2021) in agreement with the General Data Protection Regulation. The local Ethics Committees of all the satellite centres also approved the study. Due to the retrospective nature of the study, written patients informed consent was waived.

Study design

A retrospective multicentre analysis was performed on a comprehensive database of patients who underwent PM from 2010 to 2018 at the designated centres. To address the variability in clinical practice across Europe, 21 centres from 9 European countries were invited to participate in the study. Finally, 15 centres from 7 countries obtained Ethics Committee approval.

Relevant data were retrieved from individual medical records of patients and collected in a purpose-built Research Electronic Data Capture (REDCap) database.

When possible, information on events after discharge was collected by subsequent medical records and e-mail and/or phone interviews. Follow-up was closed in December 2022. The designated participant European Centres are listed in the Supplementary Material, File S2.

Definitions and classification systems

The anatomical sites of the primary malignancy were categorized as follows: head and neck (ear, nose, tongue, pharynx, larynx, salivary glands/parotid, thyroid and other), digestive system (oesophagus, stomach, small bowel, colon and rectum, liver, gallbladder and biliary ducts, pancreas and other), urogenital and male reproductive system (kidney and ureters, urinary bladder and urethra, prostate and seminal vesicles, testicle and other), breasts and female reproductive system (breasts, uterus and adnexa, ovary, vagina and other), skin, nervous system, bone, muscles, vessels and soft tissues, and others.

The histologies of the primary tumour were categorized as follows: adenocarcinoma, squamous cell carcinoma, sarcoma, germ cell tumour, melanoma and others.

The American Society of Anesthesiologists (ASA) Physical Status Classification System [7] was used for perioperative patient assessment.

The Clavien–Dindo classification [8] was employed for grading postoperative complications occurring within 30 days from PM.

Hilar-mediastinal lymphadenectomy was defined as the systematic lymph node dissection of:

- $\geq$3 mediastinal stations, including subcarinal lymph nodes, at least 1 upper mediastinum lymph node station (paratracheal, prevascular, subaortic and/or paraaortic), and at least 1 lower mediastinum lymph node station (paraoesophageal, pulmonary ligament);
- $\geq$1 hilar station, including hilar lymph nodes and/or interlobar lymph nodes.

DFI was defined as the time interval between primary tumour diagnosis and diagnosis of lung metastases or PM. Overall survival (OS) was defined as the time interval between PM and death or the last follow-up visit/interview date. Patients with no information on OS were removed from the analyses.

Recurrence-free survival (RFS) was defined as the time interval between PM and detection of any recurrence or death. Patients alive without recurrence were censored at last follow-up. Patients without information on recurrence were removed from the analyses.

Patient selection

The inclusion criteria were as follows: patients aged 18 years or older; patients who underwent PM (at the designated centres) between 2010 and 2018; patients who received PM as their 1st metastasectomy; PM performed with potentially curative intent; PM performed for extrathoracic solid tumour metastases (including oesophageal tumours); PM achieving macroscopic complete resection of all lung metastases; clinical, radiological and/or histological evidence of loco-regional control of the primary malignancy.

The exclusion criteria were as follows: patients who underwent pneumonectomy for PM; patients who received a metastasectomy of other anatomical sites prior to PM; PM performed for thoracic tumours (except oesophageal tumours); PM performed for non-solid tumours (haematologic malignancies); PM performed with diagnostic intent (i.e. not achieving macroscopic complete resection of all lung metastases); clinical, radiological and/or histological evidence of loco-regional recurrence of the primary malignancy at the time of lung surgery; clinical, radiological and/or histological evidence of extrapulmonary recurrence at the time of lung surgery; patients who underwent surgery for extrapulmonary metastases prior to PM.

Statistical analyses

Quantitative variables were expressed as mean with standard deviation (SD) or median with interquartile range (IQR) 25–75%,

whereas frequencies and percentages were given for nominal variables. Kaplan–Meier estimates and 95% confidence intervals were reported for OS and RFS. A 5-year estimate for disease recurrence was obtained using Nelson–Aalen cumulative incidence estimates, treating death without disease as a competing risk. Analyses were performed using SAS software, version 9.4 of the SAS System for Windows.

RESULTS

A total of 1867 subjects who underwent PM were included in the database. After exclusion of 220 subjects (reasons for exclusion are detailed in Table 1), the data of 1647 patients were analysed.

Mean age at primary tumour diagnosis was 59.5 (SD = 12.9) years, and mean age at PM was 62.9 (SD = 12.6) years. Median length of follow-up was 6.1 (IQR 25–75%=4.2–8.1) years.

The most common site of the primary malignancy was the digestive system (52.9%), and the most common histology was adenocarcinoma (61.0%).

Treatments for the primary tumour were administered to 99.1% patients; the therapeutic strategy included surgery and/or endoscopic removal for 97.7% cases. Mean DFI was 3.4 (SD = 3.9) years.

At the time of PM, relevant comorbidities were observed in 53.8% patients: the most frequent comorbidities were dyslipidaemia (13.7%), diabetes (10.2%) and history of previous cancer (other than the tumour causing lung metastases) (8.8%). Median preoperative ASA score was 2 (IQR 25–75%=2–3). Mean forced expiratory volume in 1 s (%) and diffusing lung capacity of carbon monoxide (%) were 93.4 (SD = 29.7%) and 87.0 (SD = 19.6%), respectively.

Before PM, 154 patients (9.4%) underwent induction treatments, mainly chemotherapy (90.9%) (Table 2). Right-sided PMs were more common (49.5%) than left-sided operations (40.2%), while bilateral procedures were performed in 10.3% cases (71.6% sequential, and 28.4% concurrent).

The preferred approach to perform PMs was video-assisted thoracic surgery (VATS) (54.9%), followed by open (thoracotomy, sternotomy or clamshell) (43.2%) and robot-assisted thoracic surgery (2.9%).

Anatomical resections were performed in 376 patients (22.8%): 257 lobectomies (or bilobectomies), 115 segmentectomies and 4 combined (segmentectomies/lobectomies).

Non-anatomical resections were carried out in 1271 patients (77.2%): 1103 wedge resections, 52 precision tumourectomies (including laser ablations) and 116 combined (wedge resections/precision tumourectomies).

In 40.0% patients, the resected lung lesions were located exclusively in the upper-middle lobe(s), in 37.0% cases only in the lower lobe(s) and in 23.0% cases in both upper-middle and lower lobe(s).

Table 1: Reasons for exclusion from analysis

Reasons for exclusion from analysis	*N*
Missing information on type of resection	7
Inconsistencies	36
Subjects not fulfilling inclusion criteria	185

Table 2: Demographic and baseline characteristics

Variable	Statistic	Result
Gender		
Female	*n*/*N* (%)	710/1645 (43.2)
Male	*n*/*N* (%)	935/1645 (56.8)
Age at primary tumour diagnosis (years)	*N*	1615
	Mean (SD)	59.5 (12.9)
	Median (IQR)	60.8 (51.8–69.0)
DFI (years)	*N*	1602
	Mean (SD)	3.4 (3.9)
	Median (IQR)	2.0 (1.0–4.0)
Age at PM (years)	*N*	1647
	Mean (SD)	62.9 (12.6)
	Median (IQR)	64.5 (55.1–72.5)
Year of surgery (1st PM if bilateral)		
2010	*n*/*N* (%)	105/1647 (6.4)
2011	*n*/*N* (%)	115/1647 (9.0)
2012	*n*/*N* (%)	139/1647 (8.4)
2013	*n*/*N* (%)	166/1647 (10.1)
2014	*n*/*N* (%)	182/1647 (11.1)
2015	*n*/*N* (%)	232/1647 (14.1)
2016	*n*/*N* (%)	227/1647 (13.8)
2017	*n*/*N* (%)	230/1647 (14.0)
2018	*n*/*N* (%)	251/1647 (15.2)
Treatment of the primary tumour	*n*/*N* (%)	1630/1645 (99.1)
Completeness of resection of the primary tumour		
R0	*n*/*N* (%)	1317/1383 (95.2)
R1	*n*/*N* (%)	66/1383 (4.8)
Anatomical site		
Head and Neck	*n*/*N* (%)	99/1647 (6.0)
Digestive system	*n*/*N* (%)	871/1647 (52.9)
Urogenital and male reproductive system	*n*/*N* (%)	224/1647 (13.6)
Breasts and female reproductive system	*n*/*N* (%)	185/1647 (11.2)
Skin	*n*/*N* (%)	124/1647 (7.5)
Nervous system	*n*/*N* (%)	5/1647 (0.3)
Bone, muscles, vessels, and soft tissues	*n*/*N* (%)	118/1647 (7.2)
Other	*n*/*N* (%)	21/1647 (1.3)
Histology		
Adenocarcinoma	*n*/*N* (%)	1001/1642 (61.0)
Squamous cell carcinoma	*n*/*N* (%)	77/1642 (4.7)
Sarcoma	*n*/*N* (%)	159/1642 (9.7)
Germ cell tumour	*n*/*N* (%)	12/1642 (0.7)
Melanoma	*n*/*N* (%)	124/1642 (7.6)
Other	*n*/*N* (%)	269/1642 (16.4)
Major comorbidities at the time of PM	*n*/*N* (%)	883/1646 (53.6)
Atrial fibrillation and/or dysrhythmias	*n*/*N* (%)	98/1646 (6.0)
Myocardial ischaemia and/or infarction	*n*/*N* (%)	91/1646 (5.5)
Carotid artery stenosis and/or cerebrovascular events	*n*/*N* (%)	70/1646 (4.3)
Heart valve disease	*n*/*N* (%)	48/1646 (2.9)
Thromboembolism and/or chronic obliterative vascular disease	*n*/*N* (%)	91/1646 (5.5)
Heart failure	*n*/*N* (%)	26/1646 (1.6)
Chronic obstructive pulmonary disease	*n*/*N* (%)	104/1646 (6.3)
Asthma and/or obstructive sleep apnoea syndrome	*n*/*N* (%)	44/1646 (2.7)
Pulmonary hypertension	*n*/*N* (%)	4/1646 (0.2)
Pulmonary fibrosis	*n*/*N* (%)	3/1646 (0.2)
Diabetes	*n*/*N* (%)	168/1646 (10.2)
Obesity	*n*/*N* (%)	100/1646 (6.1)
Dyslipidaemia	*n*/*N* (%)	226/1646 (13.7)

Continued

Table 2: Continued

Variable	Statistic	Result
Hypoalbuminemia and/or liver disease	*n*/*N* (%)	38/1646 (2.3)
Other cancer(s)	*n*/*N* (%)	144/1646 (8.8)
ASA score		
1	*n*/*N* (%)	75/1619 (4.6)
2	*n*/*N* (%)	852/1619 (52.6)
3	*n*/*N* (%)	675/1619 (41.7)
4	*n*/*N* (%)	17/1619 (1.1)
FEV_1 (l)	*N*	1090
	Mean (SD)	2.7 (0.8)
	Median (IQR)	2.6 (2.1; 3.2)
FEV_1 (%)	*N*	1245
	Mean (SD)	93.4 (29.7)
	Median (IQR)	99.0 (82.0; 111.0)
DLCO (%)	*N*	990
	Mean (SD)	87.0 (19.6)
	Median (IQR)	86.0 (74.3; 99.0)
Induction therapy before PM	*n*/*N* (%)	154/1646 (9.4)
Chemotherapy	*n*/*N* (%)	140/1646 (8.5)
Radiation therapy	*n*/*N* (%)	11/1646 (0.7)
Hormone therapy/ immunotherapy/targeted therapy	*n*/*N* (%)	13/1646 (0.8)
Treatment interruption due to toxicity	*n*/*N* (%)	2/1646 (0.1)

ASA: American Society of Anaesthesiologists; DFI: disease-free interval; DLCO: diffusing lung capacity of carbon monoxide; FEV_1: forced expiratory volume in 1 s; IQR: interquartile range; PM: pulmonary metastasectomy; SD: standard deviation.

Table 3: Operative and histopathological characteristics

Variable	Statistic	Result
Side of surgery		
Right	*n*/*N* (%)	816/1647 (49.5)
Left	*n*/*N* (%)	662/1647 (40.2)
Bilateral	*n*/*N* (%)	169/1647 (10.3)
Bilateral concurrent	*n*/*N* (%)	48/169 (28.4)
Bilateral sequential	*n*/*N* (%)	121/169 (71.6)
Type of surgical approach		
VATS	*n*/*N* (%)	904/1647 (54.9)
RATS	*n*/*N* (%)	48/1647 (2.9)
Open	*n*/*N* (%)	712/1647 (43.2)
Extension of resection		
Anatomical resections	*n*/*N* (%)	376/1647 (22.8)
Lobectomy (or bilobectomy)	*n*/*N* (%)	257/1647 (15.6)
Segmentectomy	*n*/*N* (%)	115/1647 (7.0)
Combined	*n*/*N* (%)	4/1647 (0.2)
Non-anatomical resections	*n*/*N* (%)	1271/1647 (77.2)
Wedge resection	*n*/*N* (%)	1103/1647 (67.0)
Precision tumourectomy (including laser ablation)	*n*/*N* (%)	52/1647 (3.2)
Combined	*n*/*N* (%)	116/1647 (7.0)
Location of the resected lung lesions		
Lower lobe(s)	*n*/*N* (%)	604/1633 (37.0)
Upper-middle lobe(s)	*n*/*N* (%)	653/1633 (40.0)
Both	*n*/*N* (%)	376/1633 (23.0)
Total number of resected lung lesions	*N*	1455
	Mean (SD)	2.4 (3.8)
	Median (IQR)	1.0 (1.0; 2.0)
Hilar-mediastinal lymph node dissection	*n*/*N* (%)	681/1647 (41.4)
Intraoperative adverse events	*n*/*N* (%)	9/1647 (0.6)
Number of confirmed metastases		
0–1	*n*/*N* (%)	1147/1641 (69.9)
2–4	*n*/*N* (%)	392/1641 (23.9)
>4	*n*/*N* (%)	102/1645 (6.2)
Size of confirmed metastases (mm)		
<10	*n*/*N* (%)	335/1610 (20.8)
10–30	*n*/*N* (%)	1095/1610 (68.0)
>30	*n*/*N* (%)	180/1610 (11.2)
Negative resection margin (mm)	*N*	915
	Mean (SD)	8.9 (9.4)
	Median (IQR)	6.0 (3.0; 10.0)
Completeness of resection		
R0	*n*/*N* (%)	1411/1474 (95.7%)
R1	*n*/*N* (%)	63/1474 (4.3%)

IQR: interquartile range; PM: pulmonary metastasectomy; RATS: robot-assisted thoracic surgery; SD: standard deviation; VATS: video-assisted thoracic surgery.

The median number of resected lesions was 1 (IQR 25–75%=1–2), ranging from 1 to 57. Solitary lung metastases were diagnosed in 1147 patients, who underwent PM mostly through minimally invasive techniques (65% cases). Multiple metastases (494 patients) were more frequently resected through an open approach (62.6% cases, rising to 90.2% when the number of resected lesions was ≥4).

Hilar and mediastinal lymph node dissection was performed on 681 patients (41.4%), and consisted in lymph node sampling in 65.9% cases, and lymphadenectomy in 34.1% cases. The most frequently resected lymph node station was the subcarinal, in 21.9% cases.

Intraoperative adverse events occurred in 9 (0.6%) cases: among these, the most common event was intraoperative parenchymal air leakage (5 cases).

At histopathological analyses, the median number of confirmed lung metastases was 1 (IQR 25–75%=1–2). The mean size of the metastases (or size of the largest one, in case of multiple metastases) and mean negative resection margin were 18.2 (SD = 14.1) and 8.9 (SD = 9.4) mm, respectively. A R0 resection of all lung metastases was performed in 95.7% cases (Table 3).

The 30-day postoperative morbidity was 14.5%. The most frequent complications were prolonged air leaks and atelectasis and/or pneumonia (2.9% and 2.8%, respectively). In 79.4% cases, complications were graded as mild/moderate (Clavien–Dindo grade I–II). Thirty-day mortality was 0.4%.

The mean length of stay was 5.0 (SD = 3.7) days, and 2.4% patients experienced an intensive care unit stay longer than 24 hours (Table 4). Adjuvant treatments were administered to 29.9% patients who had undergone PM.

OS at 1, 3 and 5 years were 94.2%, 76.7% and 62.0%, respectively (Table 5, Fig. 1). Tumour progression was the reported cause of death for 66.1% patients. The analyses showed a trend towards longer OS for patients who underwent lymph node dissection, albeit not statistically significant ($P = 0.0733$). Similarly, OS did not significantly differ between patients who received adjuvant treatments those who did not ($P = 0.6330$).

RFS at 1, 3 and 5 years was 64.1%, 38.4% and 29.6%, respectively (Table 5, Fig. 2). After PM, 5-year recurrence rate (at any site) was 61.9%. In the majority of cases (78.4%), the diagnosis of tumour recurrence was only radiological. Further lung lesions

Table 4: Postoperative course

Variable	Statistic	Result
ICU stay longer than 24 hours	*n*/*N* (%)	38/1612 (2.4)
Complications occurring within 30 days from PM	*n*/*N* (%)	239/1647 (14.5)
Fever >38°C	*n*/*N* (%)	37/1647 (2.3)
Atrial fibrillation and/or dysrhythmias	*n*/*N* (%)	29/1647 (1.8)
Myocardial ischaemia/infarction	*n*/*N* (%)	2/1647 (0.1)
Thromboembolism	*n*/*N* (%)	6/1647 (0.4)
Prolonged air leaks (>5 days)	*n*/*N* (%)	47/1647 (2.9)
Atelectasis and/or pneumonia	*n*/*N* (%)	46/1647 (2.8)
Respiratory failure	*n*/*N* (%)	8/1647 (0.5)
Broncho-pleural fistula with or without empyema	*n*/*N* (%)	5/1647 (0.3)
Chylothorax	*n*/*N* (%)	5/1647 (0.3)
Vocal fold dysfunction	*n*/*N* (%)	7/1647 (0.4)
Anaemia requiring blood transfusions and/or haemothorax	*n*/*N* (%)	34/1647 (2.1)
Gastrointestinal complications	*n*/*N* (%)	14/1647 (0.9)
Neurological complications	*n*/*N* (%)	5/1647 (0.3)
Urogenital complications	*n*/*N* (%)	16/1647 (1.0)
Complication grading according to the Clavien–Dindo classification		
I	*n*/*N* (%)	88/238 (37.0)
II	*n*/*N* (%)	101/238 (42.4)
III	*n*/*N* (%)	40/238 (16.8)
IV	*n*/*N* (%)	8/238 (3.4)
V	*n*/*N* (%)	1/238 (0.4)
Length of postoperative stay	*N*	1528
	Mean (SD)	5.0 (3.7)
	Median (IQR)	4.0 (3.0; 6.0)

ICU: intensive care unit; IQR: interquartile range; PM: pulmonary metastasectomy; SD: standard deviation.

Table 5: Kaplan–Meier estimates for overall survival and recurrence-free survival

Years since PM	OS (95%CI)	RFS (95%CI)
1	94.2 (92.9–95.2)	64.1 (62.1–66.1)
2	85.6 (83.9–87.2)	46.4 (44.6–48.2)
3	76.7 (74.7–78.5)	38.4 (36.8–40.0)
5	62.0 (59.9–64.0)	29.6 (28.3–31.0)
10	41.7 (39.1–44.3)	21.7 (20.4–23.0)

CI: confidence interval; OS: overall survival; PM: pulmonary metastasectomy RFS: recurrence-free survival.

after PM were detected in 60.6% patients with recurrence. Recurrences were treated in 787 (83.0%) patients, including surgical/endoscopic/thermal ablation in 57.4% cases. The OS and RFS of patients stratified based on the anatomical site and histology of the primary malignancy are shown in Fig. 3.

DISCUSSION

The cumulative incidence of lung metastases in cancer patients ranges from 20 to 50% [9]. Surgical resection of lung metastases with curative intent is widely accepted as a valid therapeutic option for carefully selected patients, as part of a multimodal treatment

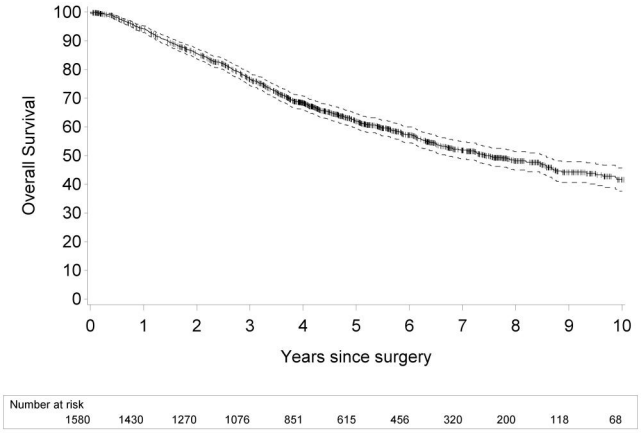


Figure 1: Overall survival. Due to lack of information, 67 subjects were excluded from the analysis: for 1 patient the status was unknown, for 25 deceased patients, the date of death was unknown and for 41 patients alive, the date of last follow-up could not be calculated.

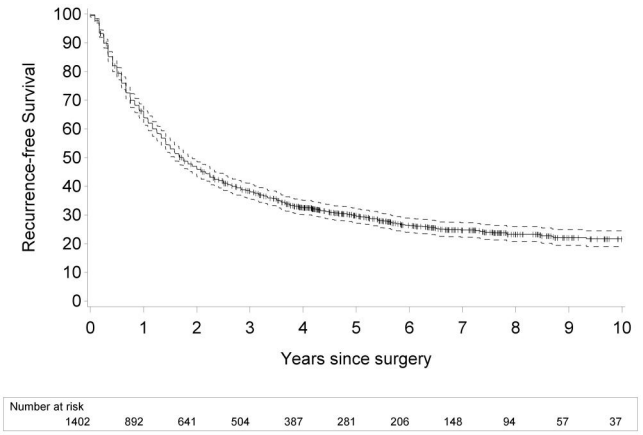


Figure 2: Recurrence-free survival. Due to lack of information, 245 subjects were excluded from the analysis: for 187 patients, the recurrence status was unknown, for 2 deceased patients without recurrence, the date of death was unknown and for 56 patients with recurrence, the date of recurrence was unknown.

approach. Eligibility criteria for PM commonly include control of the primary malignancy, absence of extrapulmonary metastases, completely resectable pulmonary lesions and low surgical risk [4, 10].

In this subset of patients, PM has shown remarkable survival benefits, with low postoperative morbidity [5].

However, despite being integrated into daily clinical practice worldwide, PM is not substantiated by strong scientific evidence. The few prospective trials on PM do not provide unequivocal answers [2, 11], while the numerous retrospective studies suffer from lack of control groups (the no-PM cohort) and selection bias [12], in addition to the many intrinsic differences (notably regarding primary tumour histology) that prevent adequate comparisons of outcomes.

Consequently, the practice of PM is remarkably variable in terms of patient selection, surgical technique and associated pre- and postoperative systemic therapies.

In our study, to adjust for the heterogeneity of the selected population, we excluded patients who had undergone any metastasectomy prior to PM. Due to the high perioperative morbidity and mortality (∼19%) associated with the procedure [4, 5], pneumonectomies were also excluded.

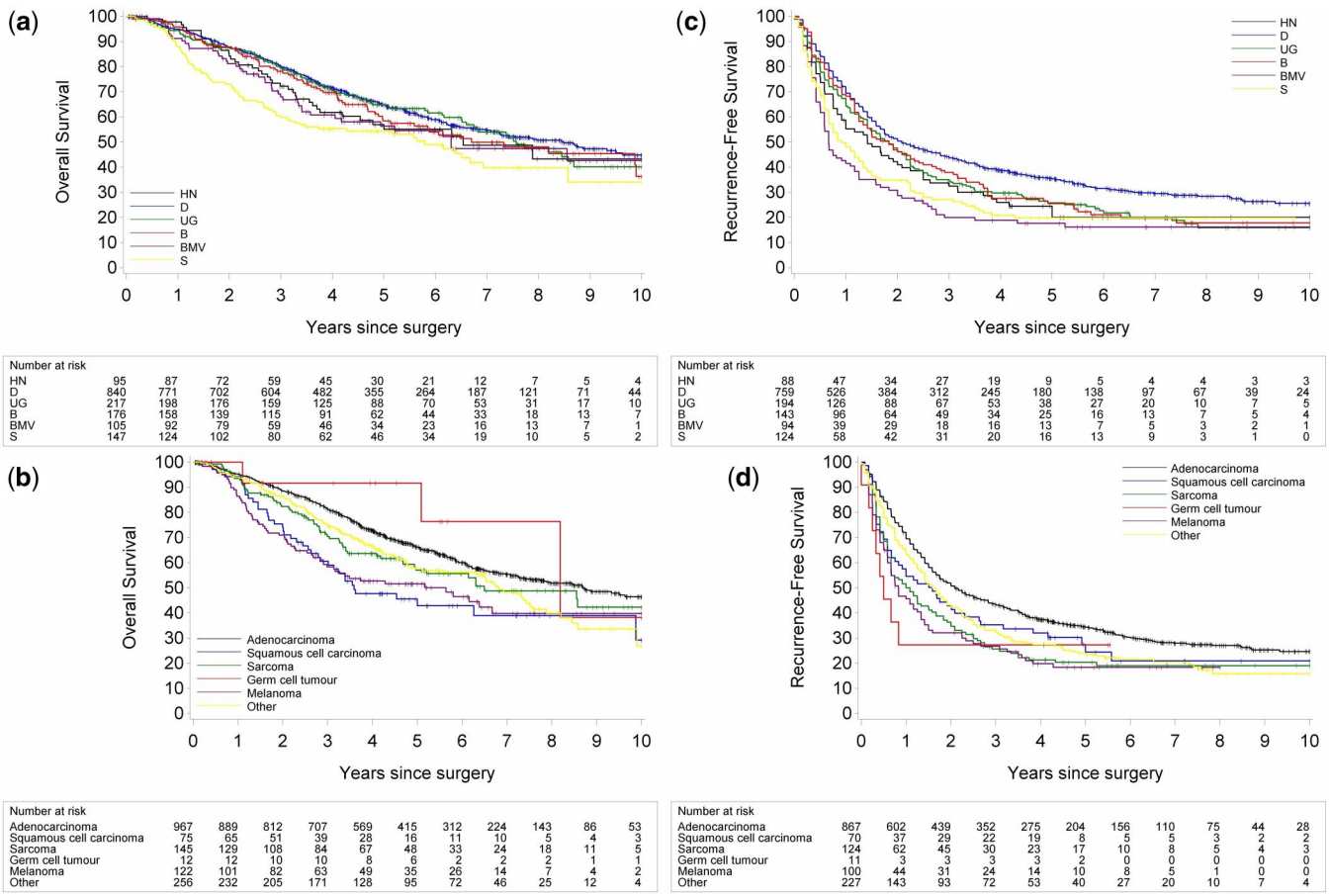


Figure 3: Overall survival depending on anatomical site (**a**) and histology (**b**) of primary tumour. Recurrence-free survival depending on anatomical site (**c**) and histology (**d**) of primary tumour. B: breasts and female reproductive system; BMV: bone, muscles, vessels and soft tissues; D: digestive system; HN: head and neck; S: skin; UG: urogenital and male reproductive system.

In agreement with the existing literature, patients who underwent PM were mostly male, ∼60 years old at the time of primary tumour diagnosis, and 63 years old at the time of PM [13]. The mean DFI before PM was ∼3 years, ranging from 0 (synchronous lung metastases) to 50 years. DFI is a crucial prognostic factor for PM [2, 5, 10, 14]: a longer DFI may reflect lower disease aggressiveness, and is therefore associated with prolonged survival after PM, albeit currently a 'DFI threshold' cannot be implemented in clinical decision-making to assess eligibility to surgery [4]. In the 2008 ESTS survey on PM, 47% respondents considered synchronous lung metastases as a relative contraindication to surgery; a DFI shorter than 12 months was also indicated as a relative contraindication by 35% of the surveyed population [6].

In line with previous studies [4, 5, 15], the most common histology in our cohort was colorectal adenocarcinoma (>50% cases). This is due to the high prevalence of lung metastases in colorectal cancer patients (up to 15%) [16], and to the recent evolution in systemic treatments for stage IV colorectal tumours that have made a greater proportion of patients amenable to surgery with curative intent [17]. Thus, although a (much debated) randomized controlled trial disclosed no survival benefit of PM over non-surgical treatment [11], colorectal adenocarcinoma is considered a favourable histological subtype for PM [5, 6, 10, 14, 15], particularly in a multidisciplinary treatment setting [4].

The annual number of PMs increased over time: 57.2% were carried out in the period 2015–2018, with the highest number of PM/year being performed in 2018 (15.3%).

In candidates for PM, the expected survival gain must be carefully weighted with the inherent surgical risks. Preoperative evaluation is, therefore, critical for an appropriate patient selection, and should be accomplished in a multidisciplinary setting and following the criteria applied to major parenchymal resection for primary lung cancer [4]. The respiratory function should be carefully considered when planning a PM, as it may influence the surgical strategy [6, 13], and potentially compromise patient fitness for further anticancer treatments (both systemic and local, i.e. repeated PMs). Non-anatomical lung resections are typically preferred to minimize parenchymal loss and the subsequent functional impairment [18]: in our cohort, they accounted for 77.2% of all PMs, with a higher prevalence for wedge resections (67.1%). The estimated decrease in forced expiratory volume in 1 s for each wedge resection is 0.58% [19]. Consequently, PM candidates with a limited respiratory function are less likely to receive anatomical resections, curative resections of multiple nodules and bilateral procedures [20]. In the present study mean forced expiratory volume in 1 s and diffusing lung capacity of carbon monoxide were above 80%.

In a previous report from the ESTS database 2019 [13], a 50% preoperative comorbidity rate was disclosed, with the majority of patients presenting an ASA score ≥2. Similarly, in our cohort, more than half the patients had 1 or more comorbidities, with a higher prevalence of metabolic disorders (32.3%). Cardiovascular and respiratory comorbidities were reported in 25.6% and 9.4% cases, respectively. ASA score was ≥2 in 95.3% of the population.

Our results reflect the recent paradigm shift in surgical approach for PM: ∼55% operations were carried out through VATS, while open (mainly thoracotomy) and robot-assisted thoracic surgery procedures were less common. Thoracotomy has long been considered the optimal approach for PM, as it allows adequate digital palpation of the parenchyma and identification of unexpected (preoperatively unknown) nodules [6]. A prospective study on patients undergoing PM showed that only 87% lesions were palpable during VATS, while 67 additional occult nodules were detected by palpation during thoracotomy; however, 43 of these (64%) were benign [21]. Owing to the development of imaging techniques (narrow slices on computed tomography), to the implementation of pre- and intraoperative nodule localization techniques, and to the growing expertise in thoracoscopic procedures, the use of VATS has increased from <20% to >50% of all PMs [13]. Moreover, VATS is associated with lower postoperative morbidity and analgesia requirements, shorter chest tube-dwelling time and hospital stay [13, 22], and is equivalent to thoracotomy in terms of survival outcomes [4, 5, 10, 13]. It should be noted, however, despite the growing preference for minimally invasive PMs, that the choice of the optimal approach is dictated by a number of factors, including the number, size and location of lung metastases, as well as cardiopulmonary function.

A total of 1458 pulmonary lesions were resected in our cohort, with a mean of 2.4 resected lesions per procedure. In the majority of cases, however, surgery was performed for solitary lung metastases, in compliance with the existing recommendations. One patient underwent surgical removal of 57 nodules. The number of lung metastases reflects disease aggressiveness and is a proven negative predictive factor for several metastatic tumours [5, 10]. However, the consensus on the maximum number of resectable lesions is weak [6], and thoracotomy is usually preferred for multiple metastases [14].

Likewise, the size of lung metastases is listed among the prognostic indicators of survival after PM [4, 5], although there is no apparent limit to the diameter of resectable pulmonary lesions. In our series, the mean size of metastases was 18.2 mm and the largest resected metastasis measured 18.5 cm. In case of large lesions, an open approach is recommended [14].

Radical (R0) resection of all lung metastases is the main goal of PM [4]. In our series, the overall R0 resection rate was 95.7%. There is robust evidence that negative resection margins are associated with improved RFS and OS [10], although the minimal 'safety rim' (distance of the surgical margin from the tumour) depends on several factors, including the size of the lesion and the biological features of the primary malignancy. It was demonstrated that that tumour aggressiveness increases with size, and that size >5 mm and resection margins <7 mm correlate with intrapulmonary local recurrence. Hence, broader resection margins should be foreseen for larger metastases [23]. These findings have important implications on the extent of lung resection for PM: laser ablation and precision tumourectomies have, by definition, the smallest resection margins, while stapled parenchymal resections ensure adequate distance from the neoplastic tissue. However, no association between the intrapulmonary recurrence rate and the type of resection was disclosed [23]. Despite being generally recommended [4, 5], hilar and mediastinal lymph node dissection was reported in less than half of our dataset and was mostly limited to nodal sampling. Unfortunately, the preoperative nodal status was not documented in the database. However, the advantage of performing nodal assessment during PM has yet to be clarified [13].

The overall rate of intraoperative adverse event was negligible (0.6%), and the 30-day morbidity and mortality were relatively low (14.5% and 0.4%, respectively), with a mean length of stay of 5 days. Patients experienced more commonly respiratory complications, and less than a fourth presented severe (Clavien–Dindo grade ≥3) adverse events. Our results are in line with the available literature [2, 4, 13], and confirm the low operative risk of PM, with a greater preference for parenchyma-sparing resections and a VATS approach [10, 13].

The benefits of lung-directed perioperative systemic treatments are debated [4], and the therapeutic strategy is generally elaborated by a multidisciplinary team [6] on multiple factors, including patient fitness, disease histology, availability of effective systemic options, control of the primary tumour, number and size of lung metastases [10]. Notably, induction chemotherapy is also employed to predict the effectiveness of PM: disease progression during neoadjuvant therapy is commonly regarded as a negative predictor of complete eradication of the lung metastases through surgery, and a contraindication to PM [6]. The timing of induction treatment should be defined considering on the one hand the risk of disease persistence due to the break of systemic therapy [5], and on the other the potential inhibition of wound healing (for targeted therapies) [4].

In our population, we showed a 5-year OS of 62%. These results are particularly remarkable, considering the typically poor outcomes of stage IV patients. This may be due to the strict eligibility criteria of our study, namely to the exclusion of patients who had extrathoracic metastases at the time of PM, patients who underwent previous metastasectomies and/or patients who received a pneumonectomy. Perioperative systemic treatments may also affect survival, although in our series only a minority of patients received induction and/or adjuvant therapies. We also showed that adjuvant therapies did not significantly affect OS.

In the largest published series on PM, 5-year OS was 36% after complete resection of lung metastases [2], in agreement with current literature, reporting 5-year OS of 20–40% [10]. In a retrospective analysis on PM for solitary metastases, a 5-year OS of 67% was disclosed [23].

Limitations

This study presents several limitations, mainly inherent to its retrospective nature and to the heterogeneity of the population in terms of primary tumour histology, extent of lung resection, perioperative systemic treatments and overall patient management strategy. In a non-negligible number of cases, information on survival or recurrence was missing, which might have induced bias in the estimated survival curves. Similarly, we have no data on the total number of PMs performed at each centre. Our study design does not allow comparisons with non-surgical interventions for lung metastases. The criteria employed for selecting patients to include in the present study are not intended to be used as selection criteria for PM. Larger and, possibly, worldwide studies are needed to provide recommendations on the optimal surgical approach and treatment strategies for lung metastases. While we acknowledge the absence of direct comparisons in the manuscript, we contend that the overarching clinical implications for multidisciplinary tumour boards

take precedence in conveying the importance of PM in appropriate cases. To the best of our knowledge, this is the largest study reporting on short- and long-term outcomes of PM of the last 20 years, and therefore offers an updated overview of the European PM practice.

CONCLUSION

PM remains a heterogeneous practice across Europe, but represents a low-risk, effective treatment for selected patients, with undeniable survival benefits. Further research should aim at clarifying the many controversial aspects of PM in its daily clinical practice, with the goal of offering a valuable patient-tailored approach.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

Elena Prisciandaro: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Validation; Visualization; Writing–original draft; Writing–review and editing. **Luca Bertolaccini:** Conceptualization; Methodology; Supervision; Writing–review and editing. **Steffen Fieuws:** Data curation; Formal analysis; Methodology; Validation; Writing–original draft; Writing–review and editing. **Andrea Cara:** Investigation; Writing–review and editing. **Lorenzo Spaggiari:** Investigation; Writing–review and editing. **Lin Huang:** Investigation; Writing–review and editing. **René H. Petersen:** Investigation; Writing–review and editing. **Marcello C. Ambrogi:** Investigation; Writing–review and editing. **Elisa Sicolo:** Investigation; Writing–review and editing. **Annalisa Barbarossa:** Investigation; Writing–review and editing. **Paul De Leyn:** Investigation; Writing–review and editing. **Diana Sporici:** Investigation; Writing–review and editing. **Ludovica Balsamo:** Investigation; Writing–review and editing. **Abid Donlagic:** Investigation; Writing–original draft. **Michel Gonzalez:** Investigation; Writing–review and editing. **Marta G. Fuentes-Gago:** Investigation; Writing–review and editing. **Clara Forcada-Barreda:** Investigation; Writing–review and editing. **Maria T. Congedo:** Investigation; Writing–review and editing. **Stefano Margaritora:** Investigation; Writing–review and editing. **Yaniss Belaroussi:** Investigation; Writing–review and editing. **Matthieu Thumerel:** Investigation; Writing–review and editing. **Jérémy Tricard:** Investigation; Writing–review and editing. **Pierre Felix:** Investigation; Writing–review and editing. **Nina Lebeda:** Investigation; Writing–review and editing. **Isabelle Opitz:** Investigation; Writing–review and editing. **Angela De Palma:** Investigation; Writing–review and editing. **Giuseppe Marulli:** Investigation; Writing–review and editing. **Cesare Braggio:** Investigation; Writing–review and editing. **Pascal A. Thomas:** Investigation; Writing–review and editing. **Frankie Mbadinga:** Investigation; Writing–review and editing. **Jean-Marc Baste:** Investigation; Writing–review and editing. **Bihter Sayan:** Investigation; Writing–review and editing. **Bedrettin Yildizeli:** Investigation; Writing–review and editing. **Dirk E. Van Raemdonck:** Formal analysis; Supervision; Writing–review and editing. **Walter Weder:** Formal analysis; Methodology; Writing–review and editing. **Laurens J. Ceulemans:** Conceptualization; Formal analysis; Methodology; Supervision; Validation; Writing–review and editing.

Reviewer information

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