Clinical score for colorectal cancer patients with lung-limited metastases undergoing surgical resection: Meta-Lung Score

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Abstract

Background
Radical resection of isolated lung metastases (LM) from colorectal cancer (CRC) is debated. Like Fong's criteria in liver metastases, our study was meant to assign a clinical prognostic score in patients with LM from CRC, aiming for better surgery selection.

Methods
We retrospectively analyzed data from 260 CRC patients who underwent curative LM resection from December 2002 to January 2022, verifying the impact of different clinicopathological features on the overall survival (OS).

Results
At the univariate analysis: higher baseline CEA levels ($p = 0.0001$), disease-free survival less than or equal to 12 months (m) ($p = 0.0043$), LM size larger than 2 cm ($p = 0.0187$), multiple resectable nodules ($p = 0.0083$), and positive nodal status of the primary tumor ($p = 0.0011$) were associated with worse prognosis. In a Cox regression model, these characteristics retained their independent role for OS ($p < 0.0001$) and were chosen as criteria to be assigned one point each for clinical risk score. The 5-year survival rate in patients with 0 points was 88%, while no patients with a 5-point score survived at 2 years. Based on the 0–1 vs. 2–5 score range, we obtained a significant difference in median OS: not reached vs. 40.8 months (95 %CI 36 to 87.5), respectively ($p < 0.0001$) stratifying patients into good and poor prognosis. The prognostic role of the score was also confirmed in terms of median RFS: not reached in 0–1 scored patients vs. 30.5 months (95 %CI 19.4 to 42) in patients with 2–5 scores ($p = 0.0006$).

Conclusions
When LM from CRC is resectable, the Meta-Lung Score provides valuable prognostic information. Indeed, while upfront surgery should be considered in patients with scores of 0 to 1, it should be cautiously suggested in patients with scores of 2 to 5, for whom a prognosis comparison between preventive surgery and other treatments should be investigated in prospective randomized clinical trials.

Keywords: Lung-limited metastases - Clinical score - Colorectal cancer - Lung metastasectomy.

Highlights

- Radical resection of isolated lung metastases from colorectal cancer is still debated.
- Five clinical features act independently in the prognostic outcome of CRC patients.
- The Meta-Lung Score is an outcomes predictor-tool in CRC lung metastasectomy.
- Upfront surgery could be considered in patients scoring 0 and 1.
- Prospective randomized clinical trials are needed in patients with a score from 2 to 5.

1. Background

Colorectal cancer (CRC) is the third most diagnosed cancer and the second most lethal [1], being the cause of approximately 9.4% of cancer-related deaths worldwide in 2020 [2]. Considering the increasing incidence of CRC, it is assumed that globally it will double by 2035, with a more considerable spread in less developed countries [3].

Despite the diagnostic and therapeutic improvements, more than 50% of patients undergoing surgical resection for localized CRC expect disease recurrence [4], [5], [6], [7], [8]. In this context, the liver represents the most common site of metastases, followed by the lung, with a rate of 10–25% [9], [10]. Isolated lung metastases (LM) are rare (1.7%–7.2%) and occur more frequently in patients with rectal carcinoma than in CRC. In most cases, lung and liver metastases appear synchronous [11].

The 5-year overall survival (OS) rate in stage IV CRC patients is 13.8% when metastases surgery is not feasible. In selected subjects, the curative resection of isolated LM leads to long-term survival benefits, with 5-year OS rates ranging from 27% to 68%, as supported by robust retrospective studies [10], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21]. However, the first prospective study on pulmonary metastasectomy in patients with mCRC (Pulmonary Metastasectomy in Colorectal Cancer - PulMiCC trial) showed no survival benefit for patients undergoing surgical resection compared to systemic therapy alone [22]. Although the study was abruptly terminated due to a lack of recruitment, the survival rate observed in the chemotherapy group was far better than expected after four years, standing at 47%. Therefore, it is crucial to speculate on the potential benefit of pulmonary metastasectomy in specific subgroups of patients (1). On the contrary, prospective randomized clinical trials (RCT) have demonstrated a benefit in progression-free survival (PFS) and OS following local radical ablative treatment in CRC, lung, breast, and other cancers [23], [24], [25], [26], [27].

International oncological and surgical guidelines recommend lung metastasectomy when an R0 resection can be achieved, conferring relative contraindications related to tumor biology, comorbidities, and personal patient expectations [28]. The recurrence rate after CRC lung metastasectomy is 68%, and residual lung parenchyma is the most reported site [10]. Many uncertainties exist regarding the indication for pulmonary metastasectomy, such as its timing versus systemic therapy, multimodal treatment, number of lesions, whether both hepatic and lung potentially resectable localizations are present, to operate first liver then lung, or vice versa. Moreover, the benefit of chemotherapy is still unclear after metastasectomy. Major international guidelines recommend adjuvant therapy after lung metastasectomy, as dictated following liver metastasectomy, despite notable differences in the biological behavior of liver and lung metastases [28], [29]. LM grows slowly and has a better overall prognosis than liver metastases. Therefore, conforming the treatment model of liver metastases from CRC to lung localization is difficult.

Identifying prognostic factors in CRC patients with localized lung disease sounds mandatory in this scenario. In particular, detecting those subgroups that might benefit from upfront surgery rather than preventive chemotherapy would be helpful.

The number and size of lung lesions, age of patients, stage of the primary tumor, its histology and molecular profile, history of liver resection, disease-free survival (DFS), and carcinoembryonic antigen (CEA) concentration have been associated with the prognosis of patients with mCRC undergoing lung metastasectomy by several studies [10], [30], [31], [32].

The Fong criteria, first developed in 1999, are a valuable tool in the clinical practice of mCRC with liver metastases. They consist of seven factors, including lymph node positivity on the primary tumor, the disease-free interval from primary tumor diagnosis to metastases < 12 months, number of liver MTS >1, largest liver MTS >5 cm, and CEA level >200 ng/ml. Using these criteria in a preoperative scoring algorithm highly predicted surgical outcomes, showing that patients with up to two positive factors may be candidates for early metastasectomy [33].

Our study also proposes the identification of a score that correlates with clinical outcomes in mCRC patients undergoing pulmonary metastasectomy, aiming to better select patients for surgery and the most appropriate treatment strategy.

2. Materials and methods

This observational retrospective study was approved by the Institutional Review Board of Cagliari (Reference Ethics Committee No. PG/2021/7091) and conducted according to the Helsinki Declaration (as revised in 2013). Informed written consent was obtained from all the patients. We retrospectively analyzed the medical records of 260 patients with lung metastases secondary to CRC. All patients underwent metastases resection with curative intent from December 2002 to January 2022 at three authoring Italian institutions: the Division of Thoracic Surgery at "A. Businco Cancer Center" in Cagliari, the Division of Thoracic Surgery at "Città della Salute e della Scienza" in Tourin, and the Department of Thoracic Surgery at "IRCCS Azienda Ospedaliero-Universitaria" in Boulogne. Locoregional control of the primary disease was confirmed in all patients considered for lung resection. This study did not include patients with extra-thoracic metastases except for previously resected liver metastases or synchronous resectable liver metastases. Other eligibility criteria included age between 18 and 85 years and no history of previous oncological disease.
The preoperative surgical evaluation was based on total body computed tomography, and when indicated by oncological assessment, it was integrated by fluorodeoxyglucose-positron emission tomography. The preferred surgical approach was video-assisted thoracoscopic surgery (VATS), reserving the thoracotomy when conversion to open surgery was needed and for cases where manual palpation of the lung and the identification of infra-radiological lesions was necessary. The choice between a single-port or multiport VATS approach depended on each surgeon's preference and patients' acceptance. We preferred parenchyma-sparing resections, such as segmentectomy and wedge resection during surgery. Lobectomy was performed for large and centrally located metastases. At the same time, pneumonectomy was carried out when the lesion was not accessible to less extensive resection and in case of intraoperative complications. Thoracic lymphadenectomy was performed according to the surgeon's preference and the intraoperative findings (Table 1).
Complete resection was defined as no palpable residual macroscopic lesion in the lung and the absence of microscopic invasion of acceptable wide section boundaries (at least 2 cm or the equal diameter of the lesion) on histopathological examination. All resected specimens were confirmed as CRC metastases by pathologists.
Baseline demographic and clinical characteristics, surgical and medical treatments, and survival information were collected. Pathological and molecular characteristics were obtained concurrently with the histological reports. The following data were collected: sex, age, Eastern Cooperative Oncology Group Performance Status at diagnosis of metastatic lung disease. Concerning the primary tumor, data were collected on location, histology, degree of tumor differentiation, BRAF/RAS mutational status, MSI/MMR status, and stage. The study described right and left primary CRC tumors as proximal or distal to the splenic flexure, respectively. Time of diagnosis and location of lung metastases, disease-free interval between the primary tumor and the lung metastases (Disease Free Survival DFS), the date and surgical approach for lung metastases, the date and location of any recurrence, and chemotherapy treatment for metastatic disease were also collected.

2.1. Statistical analysis

Data quality was assessed in terms of accuracy, completeness, and missing information. Descriptive analysis were performed to evaluate the baseline distribution of each variable for all patients undergoing lung metastasectomy. The association between qualitative variables was estimated by Fisher's exact test for categorical binomial variables or by the chi-square test in all other instances. Survival probability over the time was estimated by the Kaplan–Meier method. Significant

differences in survival probability between strata were assessed with the log-rank test. A logistic regression analysis assessed the independent role of statistically significant variables in the univariate analysis. OS was defined as the time interval between the date of surgery for lung metastases and death or the last follow-up visit for patients lost to follow-up. Recurrence-free survival (RFS) was defined as the time interval between the date of surgery for lung metastases and the death, or the first sign of clinical progression or the last follow-up visit for patients who were lost to follow-up.
In this study, we investigated clinical factors assessed at the time of diagnosis of lung metastases from CRC, which correlated with outcomes and allowed us to stratify patients into good or poor prognosis categories. To detect a difference in 5-year OS between patients with a favorable prognosis (estimated to be around 60%) and those with a poor prognosis (estimated to be around 40%), assuming an alpha probability of 0.1 and beta probability of 0.1, the required sample size was at least 145 patients, using a 'comparison proportion test'. A p-value < 0.05 was considered statistically significant. The statistical software MedCalc® Statistical Software version 20.008 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021) was used for the analysis.

3. Results

3.1. Patient characteristics

Data from 260 consecutive CRC patients who underwent lung metastasectomy between 2002 and 2022 were reviewed retrospectively.
The patient characteristics were consistent with the oligometastatic CRC population (Table 1). The median age was 66 years (range, 37–85), 150 were male (57.7%), and 110 were female (42.3%). Most patients had a left-sided primary tumor, 121 patients (46.5%) with rectal cancer, and 98 (37.7%) with left colon cancer. The remaining 41 patients (15.8%) had right-sided colon cancer. Seventy-seven patients (29.6%) had previously resected liver metastases; lung metastasis was the first location of metastatic disease for the remaining 183 patients (70.4%).
The minimally invasive thoracoscopic approach was the treatment of choice, although open surgery was more widely used in the early time-lapse of our case history (Table 1). The thoracic lymphadenectomy following lung metastasectomy was performed in 76.2% of patients and showed no statistically significant impact on OS (Table 1, Table 2). The mean postoperative length of stay was 6.7 days, and no postoperative 30-day mortality rate was reported.
Regarding the molecular profile, 125 patients (48.1%) had a RAS Wild Type (WT) tumor, while 83 patients (32.7%) had a RAS mutated tumor. For 50 patients (19.2%), this data was not available. In addition, seven patients (2.7%) had a BRAF mutated tumor, 176 patients (67.7%) were BRAF WT, and for 77 patients (29.6%), this data was not available.
As for chemotherapy treatment, 33 patients (12.7%) received neoadjuvant fluoropyrimidine-based doublet chemotherapy, six of them in combination with biologic drugs (5 anti-VEGF and 1 anti-EGFR). One hundred twenty-one patients (46.5%) received adjuvant chemotherapy; the schedule was reported for 78 patients: 16 patients (6.1%) received fluoropyrimidines as monotherapy, while the remaining 62 (23.8%) received a doublet chemotherapy.
Having defined the cut-off date as 31 January 2022, 167 (64.2 %) patients were alive.

3.2. Treatment outcomes

At a median follow-up of 33.4 months (95% Confidence Interval [CI] 29.8 to 36.7), the median OS was 75.6 months (95% 57.6 to 101,7).
We analyzed the impact of different clinicopathological features on OS. In the univariate analysis (Table 2), the clinicopathological features associated with poor prognosis were: altered baseline CEA levels (p = 0.0001), DFS less than or equal to 12 months (p = 0.0043), lung metastases size larger than 2 cm (p = 0.0187), multiple resectable nodules (p = 0.0083), and positive lymph node status of the primary tumor (p = 0.0011) (Fig. 1). In a COX regression model, these five features maintained

their independent role for OS ($p < 0.0001$) (Table 3). Interestingly, in the univariate analysis, although underrepresented in this population (3%), the BRAF mutation is confirmed to be associated with a poor prognosis. Other variables evaluated did not show a significant correlation with OS.
The five clinical criteria, significant on univariant and multivariant analysis (lymph node-positive of the primary tumor, DFS ≤ 12 months, multiple metastatic lesions, altered preoperative CEA level, and metastases size larger than 2 cm), were chosen as criteria for a clinical risk score. We assigned one point for each criterion, and the resulting score was compared with the patient's clinical outcome after metastases resection. Thus, the median OS was not reached for patients with a score of 0–1, while it declined from 45.9 months reached by patients with a score 2 up to 12.3 months in patients with a score 5. The 5-year survival rate in patients with 0 points was 88%, while no patients with a 5-points score survived at 2 years (Table 4).
In order to stratify favorable and poor prognosis patients, we compared the categories with scores 0–1 versus those with scores 2–5, obtaining a significant difference in median OS. We found that median OS was not reached for the good prognosis group compared with 40.8 months (95 %CI 36 to 87.5) for the poor prognosis patients ($p < 0.0001$) (Fig. 2). The prognostic role of the score was also confirmed in terms of RFS. In the subgroup of patients with 0–1 score the median RFS was not reached, versus 30.5 months (95 %CI 19.4 to 42) in patients with 2–5 scores ($p = 0.0006$) (Fig. 3).
Interestingly, adjuvant chemotherapy would not appear to give a statistically significant OS benefit ($p = 0.3$). Likewise, by splicing the population according to the enrollment date (2002–2012 vs 2013–2022), no statistically significant differences in OS ($p = 0.3$) and RFS ($p = 0.5$) were described. In a multivariate analysis, only the Meta-Lung score maintained its independence (Table 5), considering OS and RFS as the outcomes for the two different decades.

4. Discussion

This retrospective multicenter study provides fascinating information on data collected from 260 patients with CRC undergoing surgery for pulmonary metastasectomy with curative intent.
In the lack of specific recommendations about managing CRC lung metastases, most of the therapeutic recommendations that have been discussed for liver metastatic disease are also applicable to treating LM, despite differences in their biological behavior. Several retrospective studies support lung metastasectomy as the standard of care in mCRC, but some do not present unambiguous survival
benefits [10], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [34], [35], [36]. Therefore, the benefit ascribable to surgery should be clarified for many CRC patients with metastases limited to the lung. With precise evidence-based data, a consensus could be achieved on selecting patients who may benefit most from the surgical strategy [37].
Consistent with the percentage range described in the literature (27%-
68%) [10], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [34], [35], [36], our study found a five-year OS of 55%. Five pre-surgical criteria emerged as significant predictors of an adverse outcome after pulmonary metastasectomy: positive primary tumor lymph nodes, DFS less than or equal to 12 months, metastatic lesion exceeding 2 cm, multiple lung lesions, and elevated pre-surgery CEA levels. On the contrary, previously resected metastases did not reach statistical significance.
In previous reports, these prognostic factors have already been associated with worse survival in patients with mCRC undergoing lung metastasectomy. Indeed, as described in a *meta*-analysis in 2013 and in a more recent analysis, DFS ≤ 12 months is one of the most critical factors for a worse prognosis in lung metastasectomy patients with CRC [20], [21]. Early metastatic spread probably represents a more aggressive manifestation of the disease's biology. Though contrasting and not directing, other studies have also documented findings on the prognostic role of resected larger lung metastases of CRC [38], [30], [31], [32], [33], [34], [35], [36].

In several retrospective studies, thoracic lymphadenectomy is a prognostic factor associated with reduced survival after pulmonary metastasectomy from CRC. Since our study focused on validating a preoperative score, we did not extend the role of intraoperative ilo-mediastinal nodal resection. Despite this, patients who underwent thoracic lymphadenectomy resulting in pathologic nodal localization showed a statistically significant shortened OS compared with disease-free lymph nodes ($p < 0.0001$), according to data from other retrospective studies in the literature [39], [40].
Other analysis documented superior survival rates for patients with solitary LMs compared to multiple LMs [30], [41], [42], [43], [44], [45], [46], [47], [48]. However, if an R0 resection is achievable, denying surgery to patients with multiple lesions seems unreasonable. The literature has reported that an elevated serum CEA level before thoracic surgery is an important prognostic indicator associated with a worse prognosis [30], [38], [41], [42], [43], [44], [45], [46]. The serum CEA level represents a notable marker of the total tumor mass and the capacity of its cells to express CEA. Though an elevated CEA level is an important prognostic factor, its finding should not be an absolute criterion for a formal exclusion from lung surgery if radical resection is feasible. Monitoring CEA level after LM resection is paramount, as its level should revert to normal after lung metastasectomy.
In our study, the lymph node status of the primary tumor also showed a negative prognostic value. However, the 5-year survival rate for the lymph node-positive group was still attractive at 45%. Sidedness seemed to affect prognosis without statistically significant ($p = 0.09$), while the degree of tumor differentiation was not predictive of outcome.
Therefore, more than a single clinical criterion is required to select patients as candidates for surgical treatment. According to the clinical management of liver metastases [33], we proposed a prognostic score, the Meta-Lung Score, which includes as many prognostic factors as necessary to allow a comprehensive stratification of outcomes. In this current analysis, five criteria were found to be independent prognostic factors for outcome. Although the relative risk of death from cancer varied marginally for these five criteria, we decided to assign each criterion one point for clarity and smart applicability.
Our analysis confirmed that the BRAF mutation is also associated with a worse prognosis. As expected, the BRAF mutation was underrepresented in this population. Indeed, BRAF-mutated CRC exhibits distinctive molecular, pathological, and clinical features of aggressive behavior and high tumor burden [49], [50], a distant pattern from our study population. For such reasons, the BRAF mutation was not included in the Meta-Lung Score. In contrast, RAS did not influence the prognosis of CRC patients undergoing lung metastasectomy.
The Meta-Lung Score shows substantial prognostic value in predicting the outcome of CRC patients with lung-limited disease who are candidates for metastasectomy. Patients with scores 0–1 had a favorable outcome (5-year survival rate of 68%). These patients are good candidates for lung resection, and prompt surgery should be considered. However, the perspective is more cautious in patients with a score ranging 2–4. In these patients, a multidisciplinary discussion might be helpful to assess the role of metastasectomy in favor of upfront chemotherapy, allowing a better study of tumor biology and an appropriate selection of patients for surgery. Patients with a score of 5 have a worse prognosis, with a 0% survival rate at 24 months. For this reason, an initial surgical approach is highly questionable in these patients, considering the related surgical morbidities themselves [51]. The surgical option could then be reserved for patients who respond to systemic therapy. Notably, this investigation aligns with other retrospective literature analysis about the unclear benefit of adjuvant chemotherapy after metastasectomy [52].
The main limitation of our work is its retrospective nature, and therefore these data cannot be considered definitive due to biases arising from an unselected population, different schemes and timing between centers, which were rarely disclosed during data collection. A further possible source of bias is differences concerning the assessment and treatment of CRC metastatic disease according to the long-time data reached in the study, although OS and RFS showed no statistically significant changes when compared temporally between the two consecutive decades. The

outcomes analyzed might be investigated in prospective RCT, particularly in patients with scores between 2 and 4, for whom a prognosis comparison between preventive surgery and other treatments is mandatory.
The Meta-Lung Score appeared to be an exciting prognostic tool in selecting CRC patients' candidates for radical surgical treatment when metastatic lung disease is diagnosed. One of the key issues is the manageability of this score in the current clinical practice, considering the importance of a rigorous patient selection to avoid unnecessary risks of surgery. Although the value of a score in the setting of lung metastatic CRC patients is deemed suitable for surgical resection with curative intent, the results offered by the Meta-Lung Score need to be confirmed by future prospective studies.

CRediT authorship contribution statement

Pina Ziranu: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration. Paolo Albino Ferrari: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration. **Francesco Guerrera:** Investigation, Data curation, Writing – review & editing, Visualization. **Pietro Bertoglio:** Investigation, Data curation, Writing – review & editing, Visualization. **Alessandro Tamburrini:** Investigation, Data curation, Writing – review & editing, Visualization. **Andrea Pretta:** Investigation, Data curation, Writing – review & editing, Visualization. **Paraskevas Lyberis:** Investigation, Data curation, Writing – review & editing, Visualization. **Giulia Grimaldi:** Investigation, Data curation, Writing – review & editing, Visualization. **Eleonora Lai:** Investigation, Data curation, Writing – review & editing, Visualization. **Massimiliano Santoru:** Investigation, Data curation, Writing – review & editing, Visualization. **Fabio Bardanzellu:** Investigation, Data curation, Writing – review & editing, Visualization. **Laura Riva:** Investigation, Data curation, Writing – review & editing, Visualization. **Francesca Balconi:** Investigation, Data curation, Writing – review & editing, Visualization. **Eleonora Della Beffa:** Investigation, Data curation, Writing – review & editing, Visualization. **Marco Dubois:** Investigation, Data curation, Writing – review & editing, Visualization. **Matteo Pinna-Susnik:** Investigation, Data curation, Writing – review & editing, Visualization. **Clelia Donisi:** Investigation, Data curation, Writing – review & editing, Visualization. **Enrico Capozzi:** Investigation, Data curation, Writing – review & editing, Visualization. **Valeria Pusceddu:** Investigation, Data curation, Writing – review & editing, Visualization. **Alessandro Murenu:** Investigation, Data curation, Writing – review & editing, Visualization. **Marco Puzzoni:** Investigation, Data curation, Writing – review & editing, Visualization. **Federico Mathieu:** Investigation, Data curation, Writing – review & editing, Visualization. **Sabrina Sarais:** Investigation, Data curation, Writing – review & editing, Visualization. **Aiman Alzetani:** Investigation, Data curation, Writing – review & editing, Visualization. **Luca Luzzi:** Investigation, Data curation, Writing – review & editing, Visualization. **Piergiorgio Solli:** Investigation, Data curation, Writing – review & editing, Visualization. **Piero Paladini:** Investigation, Data curation, Writing – review & editing, Visualization. **Enrico Ruffini:** Investigation, Data curation, Writing – review & editing, Visualization. **Roberto Cherchi:** Investigation, Data curation, Writing – review & editing, Visualization, Supervision, Project administration. **Mario Scartozzi:** Investigation, Data curation, Writing – review & editing, Visualization, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements
We thank all the investigators and patients for participating in this study.

Ethical approval and consent to participate
This observational retrospective study was approved by the Institutional Review Board of Cagliari (Reference Ethics Committee No. PG/2021/7091). This study was performed in accordance with the study protocol, the ethical principles stated in the Declaration of Helsinki as well as those indicated in the International Conference on Harmonization (ICH) Note for Guidance on Good Clinical Practice (GCP; ICH E6, 1995), and all applicable regulatory requirements. All patients signed a written informed consent before study entry. Adequate information was given to eligible patients by the principal investigator or co-investigators in accordance with local regulations. The declaration of informed consent was personally signed and dated by the subject, and by the investigator/person designated by the investigator to conduct the informed consent discussion.

Consent for publication
Patients signed an informed consent regarding the publication of their data.

Funding information
No external funding was used for the conduct of this study or the preparation of this article.

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Table 1. Patient's characteristic. Abbreviations: N. = numbers; ECOG PS = Eastern Cooperative Oncology Group Performance Status; DFS = Disease Free Survival; K-RAS = Kirsten Rat Sarcoma viral oncogene; N-RAS = Neuroblastoma RAS viral oncogene homolog B1; B-RAF = v-raf murine sarcoma viral oncogene homolog B1; VTS = Video Thoracic Surgery; N0 = no mediastinal lymph nodes clinically involved; N1 = pulmonary hilar nodes clinically involved; N2 = mediastinal nodes clinically involved; R0 = no residual tumor; R1 = microscopic residual tumor; R2 = macroscopic residual tumor; NA = Not Available.

	N. (%)
Gender	
M	150 (57.7%)
F	110 (42.3%)
Age	
< 70 y	173 (66.5%)
≥ 70 y	87 (33.5%)
ECOG PS	
0–1	216 (83%)
2	44 (17%)
Site of primary tumor	
Sx	98 (37.7%)
Dx	41 (15.8%)
Rectum	121 (46.5%)
Primary tumor	
pT1-3	224 (86.2%)
pT4	19 (7.3%)
NA	17 (6.5%)
Primary tumor	
Node-negative	103 (39.6%)
Node-positive	155 (59.6%)
NX	2 (0.8%)
Primary tumor grade	
Well-moderate	183 (70.4%)
Poorly	64 (24.6%)
NA	13 (5%)
Metastases lung sites	
Single site	215 (82.7%)
Multiple site	45 (17.3%)
Metastasis lung size	
≤ 2 cm	177 (68.1%)
> 2 cm	80 (30.8%)
NA	3 (1.2%)
Previous metastases	
Yes	77 (29.6%)
No	183 (70.4%)

	N. (%)
DFS	
≤ 12 months	72 (27.3%)
> 12 months	188 (72.3%)
CEA baseline levels	
Normal	143 (55%)
High	75 (28.8%)
NA	42 (16.2%)
K-RAS/N-RAS mutational status	
Wild type	125 (48.1%)
Mutant	85 (32.7%)
NA	50 (19.2%)
B-RAF mutational status	
Wild type	176 (67.7%)
Mutant	7 (2.7%)
NA	77 (29.6%)
Surgical approach for lung metastases	
VTS	187 (71.9%)
Thoracotomy	68 (5%)
VTS converted to thoracotomy	5 (1.9%)
Type of lung resection	
Wedge resection	194 (74.6%)
Sub-lobar anatomical resection	16 (6.2%)
Lobar resection	49 (18.8%)
Pneumonectomy	1 (0.4%)
Residual tumor after lung metastasectomy	
R0	245 (94.2%)
R1	14 (5.4%)
R2	1 (0.4%)
Clinical involvement of thoracic lymph nodes	
N0	247 (95%)
N1	6 (2.3%)
N2	7 (2.7%)
Thoracic lymphadenectomy	
Yes	198 (76.2%)
No	62 (23.8%)
Pathological involvement of thoracic nodes	
N0	180 (69.2%)
N+	18 (6.9%)
Nx	62 (23.8%)
Postoperative complications (Clavien-Dindo) [53]	
No	224 (86.2%)
Grade I	23 (8.8%)
Grade II	6 (2.3%)

	N. (%)
Grade III	5 (1.9%)
Grade IV	2 (0.8%)
Adjuvant chemotherapy	
Yes	121 (46.5%)
No	139 (53.5%)

Table 2. Univariate predictors of adverse outcomes. Abbreviations: M = male; F = female; ECOG PS = Eastern Cooperative Oncology Group Performance Status; K-RAS = Kirsten Rat Sarcoma Viral Oncogene Homologue; N-RAS = Neuroblastoma RAS viral oncogene homolog B1; WT = Wild Type; MUT = Mutated; B-RAF = v-raf murine sarcoma viral oncogene homolog B1; NA = Not Available; DFS = Disease Free Survival.

Variable	OS P-Value	Hazard ratios (95% Confidence Interval)
Gender		
M vs F	p = 0.6	0.9 (95 %CI 0.6 to 1.4)
Age		
< 70 vs ≥ 70	p = 0.8	0.9 (95 %CI 0.6 to 1.5)
ECOG PS		
0–1 vs 2	p = 0.7	0.9 (95 %CI 0.5 to 1.5)
Site of primary tumor		
DX vs SN	p = 0.09	0.6 (95 %CI 0.3 to 1.0)
Primary tumor		
pT1-3 vs pT4	p = 0.5	0.8 (95 %CI 0.3 to 1.7)
Primary tumor		
pN0 vs pN+	**p = 0.0011**	**0.5 (95 %CI 0.3 to 0.8)**
Primary tumor grade		
G1-2 vs G3	p = 0.9	1 (95 %CI 0.6 to 1.6)
Lung metastases localization		
Single vs multiple nodules	**p = 0.0083**	**0.5 (95 %CI 0.3 to 0.8)**
Lung metastasis size		
≤ 2 cm vs > 2 cm	**p = 0.0187**	**0.6 (95 %CI 0.4 to 0.9)**
Previous metastases		
No vs Yes	p = 0.8	1 (95 %CI 0.7 to 1.6)
DFS		
>12 m vs ≤ 12 months	**p = 0.0043**	**0.5 (95 %CI 0.3 to 0.8)**

Variable	OS P-Value	Hazard ratios (95% Confidence Interval)
CEA baseline levels		
Normal vs High	**p = 0.0001**	**0.4 (95 %CI 0.2 to 0.6)**
K-RAS/N-RAS mutational status		
WT vs MUT	p = 0.5	0.9 (95 %CI 0.5 to 1.4)
B-RAF mutational status		
WT vs MUT	**p = 0.02**	**0.03 (95 %CI 0 to 0.3)**
Clinical involvement of thoracic lymph nodes		
cN0 vs cN+	p = 0.8	1 (95 %CI 0.4 to 2.8)
Thoracic lymphadenectomy		
Yes vs No	p = 0.4	0.8 (95 %CI 0.5 to 1.3)
Pathological involvement of thoracic nodes		
Yes vs No	**p < 0.0001**	**0.09 (95 %CI 0.03 to 0.2)**
Adjuvant chemotherapy		
Yes vs No	p = 0.3	0.8 (95 %CI 0.5 to 1.2)

Table 3. Multivariate predictors of adverse outcomes. Abbreviations: DFS = Disease Free Survival.

Factors	P	Exp(b)	95% CI of Exp(b)
High levels of baseline CEA	0.0019	2.0910	1.3132 to 3.3296
DFS ≤ 12 months	0.0481	1.6418	1.0041 to 2.6845
Metastasis lung > 2 cm	0.0088	1.8787	1.1724 to 3.0103
Multiple lung metastases	0.035	1.7679	1.0410 to 3.0025
pN positive of primary tumor	0.0137	1.9677	1.1489 to 3.3700
Significance level = p < 0.0001			

Table 4. Meta-Lung score, clinical risk score for adverse outcomes. Each risk factor is one point: node-positive primary tumor, disease-free interval ≤ 12 months, multiple lung metastases; metastasis lung size greater than 2 cm; high CEA levels.

		Survival data					
Score	**N. of pts (%)**	**1-yr**	**2-yr**	**3-yr**	**4-yr**	**5-yr**	**Median OS (m)**
0	**39 (15%)**	97%	91%	88%	88%	88%	NR
1	**89 (34%)**	97%	90%	78%	71%	60%	NR

		Survival data					
Score	**N. of pts (%)**	**1-yr**	**2-yr**	**3-yr**	**4-yr**	**5-yr**	**Median OS (m)**
2	**75 (29%)**	97%	80%	65%	54%	46%	45.9 (95 %CI36.1 to 75.5)
3	**43 (17%)**	90%	74%	58%	45%	34%	41.7 (95 %CI 29 to 87.5)
4	**11 (4%)**	73%	72%	41%	27%	27%	29.3 (895 %CI 8.8 to 62.2)
5	**3 (1%)**	34%	0	0	0	0	12.3 (95 %CI 4.6 to 19.5)
Total	**260**	**95%**	**83%**	**70%**	**60%**	**55%**	**75.6 (95% 57.6 to 101,7)**

Abbreviations: N. = numbers; pts = patients; yr = years; m = months.

Table 5. Multivariate analysis predicting on OS and RFS according to the Meta-Lung score for two different decades of treatment.

Variables	**P**	**Exp(b)**	**95% CI of Exp(b)**
A) Overall Survival (months)			
Meta-Lung score	**<0,0001**	2,8052	1,7947 to 4,3846
2002–2012 vs 2013–2022	0,5604	0,8512	0,4950 to 1,4639
B) Recurrence Free Survival (months)			
Meta-Lung score	**0,0009**	1,8757	1,2958 to 2,7151
2002–2012 vs 2013–2022	0,7486	0,9307	0,6000 to 1,4438

Fig. 1. Clinicopathological features associated with median Overall Survival (mOS) at the univariate analysis: altered baseline CEA levels (p = 0.0001), disease free survival (DFS) less than or equal to 12 months (p = 0.0043), lung metastases size greater than 2 cm (p = 0.0187), multiple resectable lung nodules (p = 0.0083), and positive lymph node status at the primary tumor (p = 0.0011).

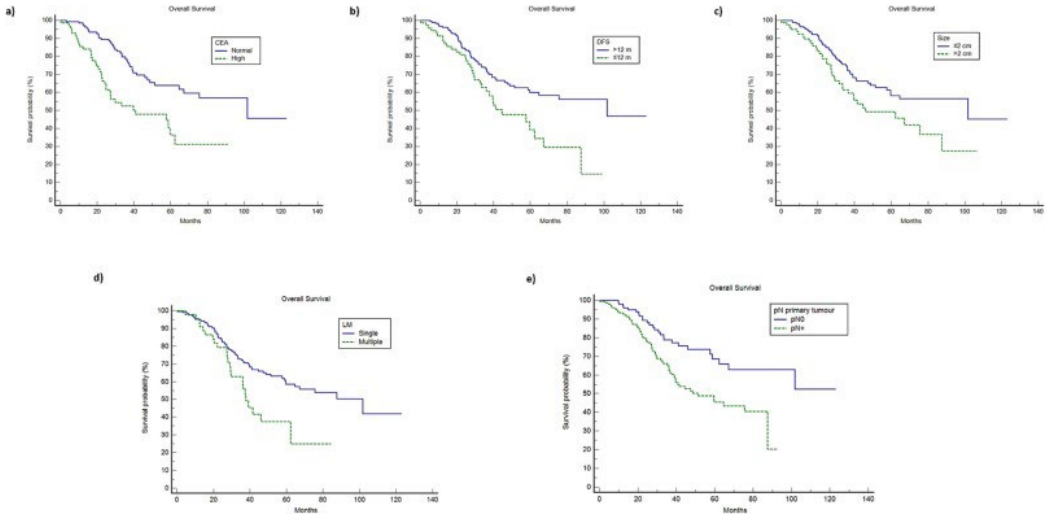

Fig. 2. Median Overall Survival in CRC patients after lung metastases resection, based on Meta-Lung score. In the patients' subgroup with 0–1 score (continuous/blue line), the median OS was not reached versus 40.8 months (95 %CI 36 to 87.5) in patients with 2–5 scores (dotted/green line), (p < 0.0001). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

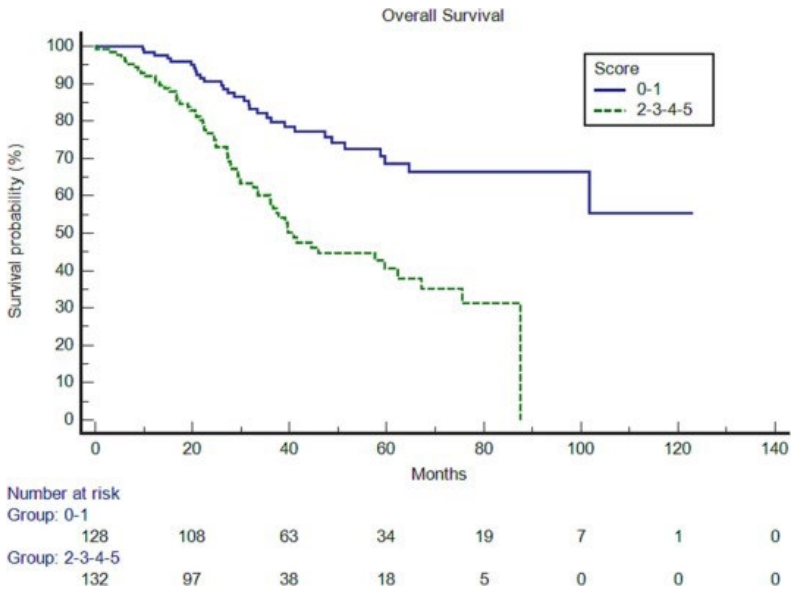

Fig. 3. Median Recurrence-Free Survival in CRC patients after lung metastases resection, based on Meta-Lung score. In the subgroup of patients with 0–1 score (continuous/blue line), the median RFS was not reached versus 30.5 months (95 %CI 19.4 to 42) in patients with 2–5 scores (dotted/green line), (p = 0.0006). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)