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

Authors:

Introduction

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 significantly increased incidence of CRC in the elderly population, it is assumed that the global incidence will double by 2035, with a more considerable spread in less developed countries (3).

Despite therapeutic improvements, more than 50% of patients undergoing surgical resection for localized CRC expect disease recurrence (4-5). In this context, the liver represents the most common site of metastases, followed by the lung, with a rate of 10-25% (6-7). 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 (8).

As supported by robust retrospective studies, lung metastasectomy is considered the treatment of choice for metastatic colorectal cancer (mCRC), where the 5-year survival rate of patients is 13%. In selected patients with mCRC, curative resection of isolated LM leads to long-term survival benefits, with 5-year overall survival (OS) rates ranging from 27% to 68% (7, 9-18). 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 (19). 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 (1). In contrast, other prospective randomized trials have demonstrated a benefit in progression-free survival (PFS) and OS with local radical ablative treatment in CRC, lung, breast, and other cancers (20-24).

International oncological and surgical guidelines recommend lung metastasectomy when an R0 resection can be achieved, proposing relative contraindications related to tumour biology, comorbidities, and personal patient expectations (25). The recurrence rate after lung metastasectomy is 68% and residual lung parenchyma is the most reported site (7).

Moreover, the benefit of chemotherapy is still unclear after metastasectomy. Major international guidelines recommend adjuvant therapy after lung metastasectomy, as in treating liver metastases, despite differences in the biological behaviour of liver and lung metastases (25-26). LM grow slowly and have a better overall prognosis than liver metastases. Therefore, it is difficult to conform the treatment model of liver metastases from CRC to lung localisations.

For these reasons, identifying prognostic factors in CRC patients with localized lung disease is mandatory. In particular, detecting specific subgroups that might benefit from surgery or upfront chemotherapy would be helpful.

The number and size of lung lesions, age of patients, stage of the primary tumour and its histology, molecular profile of the tumour, history of liver resection, disease-free survival (DFS), and carcinoembryonic antigen (CEA) concentration seem to be associated with the prognosis of patients with mCRC undergoing lung metastasectomy (7, 27-29).

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 tumour, disease-free interval from primary tumour diagnosis to metastasis <12 months, number of liver MTS >1, largest liver MTS >5 cm, and carcinoembryonic antigen (CEA) level >200 ng/ml. Using these criteria in a preoperative scoring algorithm was highly predictive of surgical outcome, showing that patients with up to two positive factors may be candidates for early metastasectomy (30).

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.

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 metastasis 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. Patients with extrathoracic metastases were not included in this study, 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 mainly based on total body computed tomography (CT) and fluorodeoxyglucose (FDG)-positron emission tomography (PET). The preferred surgical approach were video-assisted thoracic surgery (VATS), reserving thoracotomy or conversion to open surgery for cases where manual palpation of the lung and 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 favored parenchyma-sparing resections, such as segmentectomy and wedge resection

during surgery. Lobectomy was performed for large and centrally located metastases, while pneumonectomy was carried out when the lesion was not accessible to less extensive resection and in case of centrally located lesions or intraoperative complications. Mediastinal and hilar lymphadenectomy was performed according to the surgeon's preference and the intraoperative findings.

Complete resection was defined as no palpable 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 metastatic CRC lesions by pathologists.

Baseline demographic and clinical characteristics, surgical and medical treatments, and survival information were collected. Pathological and molecular characteristics were obtained from histological reports. The following data were collected: sex, age, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) at diagnosis of metastatic lung disease, and patients' comorbidity reported with Charlson Comorbidity Index (CHC). Regarding the primary tumour, data were collected on location, histology, degree of tumour differentiation, BRAF/RAS mutational status, MSI/MMR status, and stage. In the study, right and left primary CRC tumours were described as proximal or distal to the splenic flexure, respectively. Time of diagnosis and location of lung metastases, disease free interval between the primary tumour 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.

Statistical Analysis

Data quality was assessed in terms of accuracy, completeness, and missing information. Descriptive analyses were performed to evaluate the baseline distribution of each variable for all patients undergoing lung metastasectomy. The association between qualitative variables was estimated by the Fisher 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. The independent role of statistically significant variables in the univariate analysis was assessed with a logistic regression analysis. Overall survival (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 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 looked for 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 favourable 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 version 14.10.2 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014) was used for the analysis.

Results

Data from 260 consecutive CRC patients who underwent lung metastasectomy between 2002 and 2022, were reviewed retrospectively.

The patient characteristics were consistent with 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%).

As of the data cut off, 31 January 2022 167 (64.2 %) patients were alive.

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 analysed the impact of different clinicopathological features on OS. At the univariate analysis (table 2), the clinicopathological features associated with poor prognosis were: altered baseline CEA levels (p=0.0001), disease free survival (DFS) less than or equal to 12 months (p=0.0043), lung metastasis size larger than 2 cm (p=0.0187), multiple resectable nodules (p=0.0083), and positive lymph node status of the primary tumour (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, at the univariate analysis, although underrepresented in this population (3%), the BRAF mutation is confirmed to be associated with a poor prognosis. Other variable evaluated did not show a significant correlation with OS.

The five clinical criteria, significant on univariant and multivariant analysis (lymph node-positive of primary tumour, DFS ≤ 12 months, multiple metastatic lesions, altered preoperative CEA level, and metastasis 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 patient's clinical outcome after metastasis resection. The score was found to be highly predictive for long-term outcome (p< 0.0001) (Fig. 2). The 5-year survival rate in patients with 0 points was 88%, while no patients with 5-points score survived at 2 years (table 4). In order to stratify favourable and poor prognosis patients, we compared the categories with scores 0-2 versus those with scores 3-5, obtaining a significant difference in median OS. We found a median OS of 101.7 months

(95%CI 64.6 to 101.7) in good prognosis group versus 39.5 months (95%CI 27.3 to 87.5) in poor prognosis patients ($p<0.0001$) (Fig.1).

Discussion

This retrospective multicentre study provides interesting information on data collected from 260 patients with CRC undergoing surgery for pulmonary metastasectomy with curative intent.

In the lack of specific recommendations on managing lung metastases from CRC, most of the therapeutic recommendations that have been discussed for liver metastatic disease are also applicable to the treatment of lung metastases, despite differences in their biological behaviour. A number of retrospective studies support lung metastasectomy as the standard of care in mCRC, but some do not present a clear survival benefit (7, 9-18, 31-33). Therefore, for many CRC patients with metastases limited to the lung, the benefit ascribable to surgery should be clarified. Without clear evidence-based data, a consensus needs to be achieved on selecting patients who may benefit most from the surgical strategy.

Consistent with the percentage range described in the literature (27%-68%) (7, 9-18, 31-33), 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 tumour lymph nodes, DFS less than or equal to 12 months, metastatic lesion exceeding 2 cm, multiple lung lesions, and high 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 poor survival in patients with mCRC undergoing lung metastasectomy. Indeed, as described in a 2013 meta-analysis and more recent analysis, DFS ≤12 months is one of the most critical factors for a worse prognosis in lung metastasectomy patients with CRC (17-18). It is probable that early metastatic spread biologically represents a more aggressive manifestation of the disease. Contrasting data on the prognostic role of the largest resected lung metastases of CRC have been gathered in several retrospective studies (27-34). Other analyses documented superior survival rates for patients with solitary LMs compared to multiple LMs (27, 35-43). However, as long as 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 poor prognosis (27, 35-41). The serum CEA level is a strong marker of the total tumour mass and the capacity of tumour 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. It is essential to carefully monitor CEA levels after LM resection, as its level should revert to normal after lung metastasectomy.

In our study, the lymph node status of the primary tumour 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 (0.09), while the degree of tumour differentiation was not predictive of outcome.

Therefore, more than a single clinical criterion is needed to select patients as candidates for surgical treatment. According to the clinical management of liver metastases (30), 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 simplicity and greater utility.

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 behaviour and high tumour burden (44-45), 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 solid prognostic value in predicting the outcome of CRC patients with lung-limited disease who are candidates for metastasectomy. Patients with scores from 0 up to 2 have a favourable outcome (5-year survival rate of 60%). 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 of 3 or 4. In these patients, delaying the metastasectomy in favour of upfront chemotherapy allows a better assessment of tumour biology and an appropriate selection of patients for surgery. Patients with a score of 5 have a very poor 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 themself. The surgical option could then be reserved for patients who respond to systemic therapy.

This work is a retrospective analysis of outcomes from patients treated at different Institutions. Although the surgical and oncological approach is standardized, it may differ in extent and accuracy from center to center. A further possible source of bias is differences concerning the assessment and treatment of CRC metastatic disease according to the longtime of data reached in our study.

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.

TABLES

	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 tumour	
• Sx	98 (37.7%)
• Dx	41 (15.8%)
• Rectum	121 (46.5%)
Primary Tumour	
• pT1-3	224 (86.2%)
• pT4	19 (7.3%)
• NA	17 (6.5%)
Primary Tumour	
• Node-negative	103 (39.6%)
• Node-positive	155 (59.6%)
• NX	2 (0.8%)
Primary Tumour 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%)
Metastases Lung Size	
• ≤ 2 cm	177 (68.1%)
• > 2 cm	80 (30.8%)
• NA	3 (1.2%)
Previous Metastases	
• Yes	183 (70.4%)
• No	77 (29.6%)
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%)
Clinical involvement of thoracic lymph nodes	
• Yes	248 (95.4%)
• No	12 (4.6%)

Table 1. Patient's characteristic. Abbreviations: ECOG PS= Eastern Cooperative Oncology Group Performance Status; K-RAS= Kirsten Rat Sarcoma Viral Oncogene Homologue; N-RAS= Neuroblastoma RAS viral oncogene homolog B1; NA= Not Available; DFS= Disease Free Survival.

Variable	**OS P-Value**
Gender M vs F	p=0.6
Age < 70 vs ≥ 70	p=0.8
ECOG PS 0-1 vs 2	p=0.7
Site of primary tumour DX vs SN	p=0.09
Primary Tumour pT1-3 vs pT4	p=0.5
Primary Tumour pN0 vs pN+	**p=0.0011**
Primary Tumour Grade G1-2 vs G3	p=0.9
Metastases Lung sites Single vs multiple nodules	**p=0.0083**
Metastases Lung Size ≤ 2 cm vs > 2 cm	**p=0.0187**
Previous Metastases No vs Yes	p=0.8
DFS >12 m vs ≤ 12 months	**p=0.0043**
CEA baseline levels Normal vs High	**p=0.0001**
K-RAS/N-RAS mutational status WT vs MUT	p=0.5
B-RAF mutational status WT vs MUT	**p=0.02**
Clinical involvement of thoracic lymph nodes cN0 vs cN+	p=0.8

Table 2. Univariate predictors of adverse outcomes. Abbreviations: 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; NA= Not Available; 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
Metastases Lung > 2cm	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 tumour	0.0137	1.9677	1,1489 to 3,3700
Significance level= p<0.0001			

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

	Survival (%)					
Score	**1-yr**	**2-yr**	**3-yr**	**4-yr**	**5-yr**	**Median OS (m)**
0	97%	91%	88%	88%	88%	NR
1	97%	90%	78%	71%	60%	NR
2	97%	80%	65%	54%	46%	45.9 (95%CI36.1 to 75.5)
3	90%	74%	58%	45%	34%	41.7 (95%CI 29 to 87.5)
4	73%	72%	41%	27%	27%	29.3 (895%CI 8.8 to 62.2)
5	34%	0	0	0	0	12.3 (95%CI 4.6 to 19.5)
Total	**95%**	**83%**	**70%**	**60%**	**55%**	**75.6 (95% 57.6 to 101,7)**

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

Figures

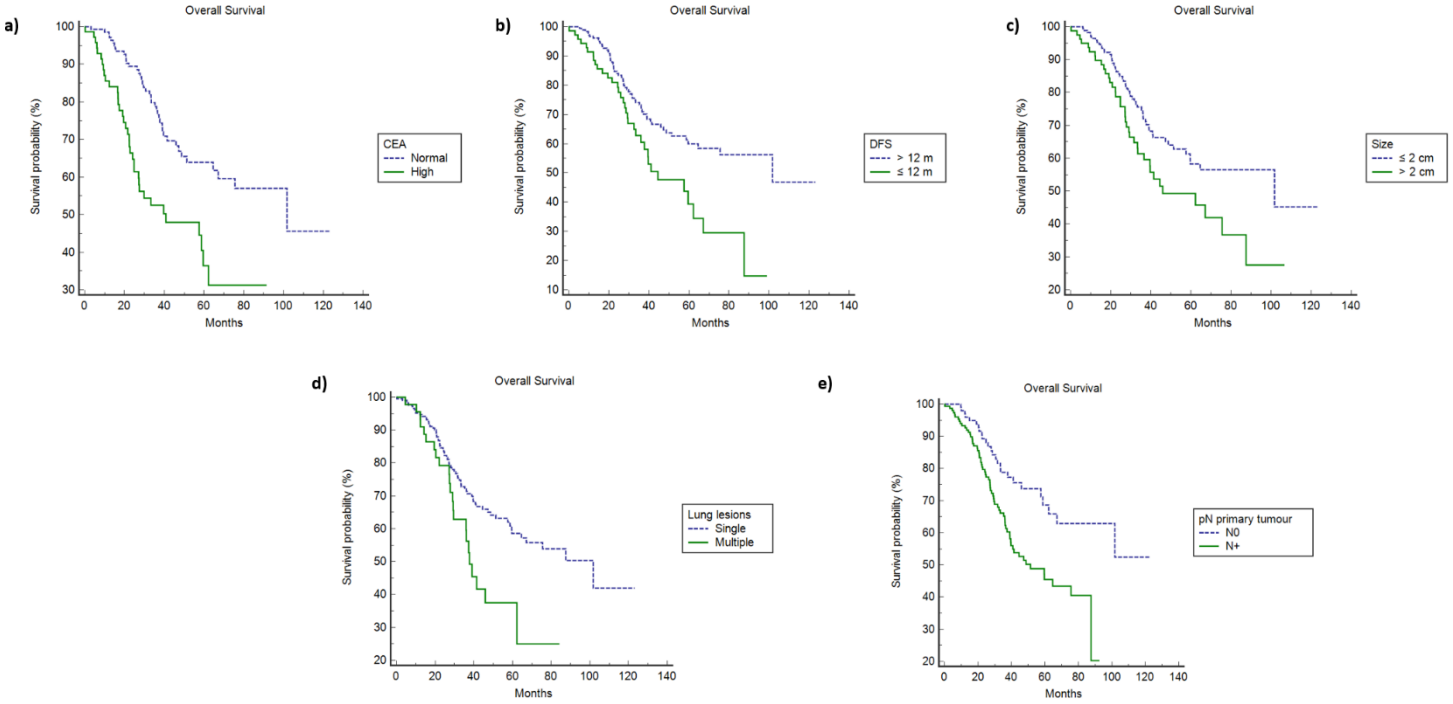

Fig. 1. Clinicopathological features associated with median Overall Survival (mOS) at the univariate analysis: altered baseline CEA levels (p=0.0001), disease free survival (DFS) less than or equal to 12 months (p=0.0043), lung metastasis size larger than 2 cm (p=0.0187), multiple resectable nodules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

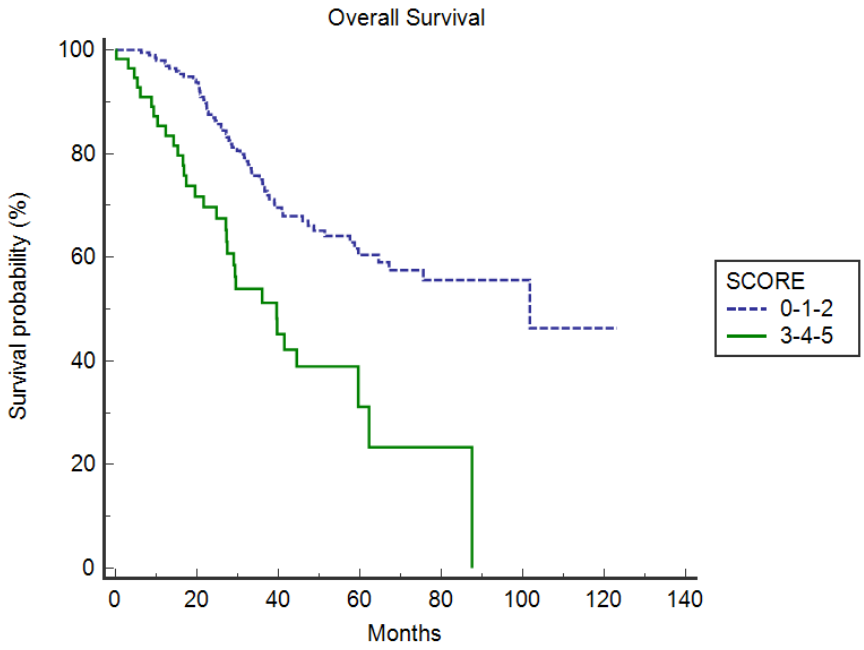

Fig. 2. Median Overall Survival in CRC patients after lung metastasis resection, based on Meta-Lung score. In the subgroup of patients with 0-2 score, the median OS was 101.7 months versus 39.5 months in patients with 3-5 scores (p<0.0001)