**Name of Journal:** *World Journal of Gastrointestinal Oncology*

**Manuscript NO:** 66351

**Manuscript Type:** MINIREVIEWS

**Management of single pulmonary metastases from colorectal cancer: State of the art**

Chiappetta M *et al*. Management of single pulmonary metastases from CRC

Marco Chiappetta, Lisa Salvatore, Maria Teresa Congedo, Maria Bensi, Viola De Luca, Leonardo Petracca Ciavarella, Floriana Camarda, Jessica Evangelista, Vincenzo Valentini, Giampaolo Tortora, Stefano Margaritora, Filippo Lococo

**Marco Chiappetta, Maria Teresa Congedo, Leonardo Petracca Ciavarella, Jessica Evangelista, Stefano Margaritora,** **Filippo Lococo,** Department ofThoracic Surgery, Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Università Cattolica del Sacro Cuore, Rome 00168, Italy

**Lisa Salvatore, Maria Bensi, Floriana Camarda, Giampaolo Tortora,** Oncologia Medica Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Università Cattolica del Sacro Cuore, Rome 00168, Italy

**Viola De Luca, Vincenzo Valentini,** Department of Radiation Therapy, Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Università Cattolica del Sacro Cuore, Rome 00168, Italy

**Author contributions:** Chiappetta M wrote the paper; Congedo MT, Petracca Ciavarella L, Bensi M, De Luca V and Camarda F collected the bibliography and supported manuscript drafting; Evangelista J supported manuscript drafting; Salvatore L and Lococo F revised and edited the manuscript; Margaritora S, Tortorta G and Valentini V supervised the manuscript.

**Corresponding author: Filippo Lococo, MD, Assistant Professor,** Department ofThoracic Surgery, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Largo Agostino Gemelli 8, Rome 00168, Italy. filippo.lococo@policlinicogemelli.it

**Received:** March 26, 2021

**Revised:** May 26, 2021

**Accepted: March 4, 2022**

**Published online:**

**Abstract**

Colorectal cancer (CRC) is one of the most common causes of death from cancer. Lung seeding occurs in approximately 10% of patients surgically treated for primary CRC with radical intent: the lung is the most common site of metastases after the liver. While surgical treatment of liver metastases is widely accepted to affect long-term outcomes, more controversial and not standardized is the therapy for CRC patients developing lung metastases. Experience suggests the potential curative role of pulmonary metastasectomy, especially in oligometastatic disease. However, the optimal strategy of care and the definition of prognostic factors after treatment still need to be defined. This review focused on the uncommon scenario of single pulmonary metastases from CRC. We explored pertinent literature and provide an overview of the epidemiology, clinical characteristics and imaging of single pulmonary metastases from CRC. Additionally, we identified the best available evidence for overall management. In particular, we analyzed the role and results of locoregional approaches (surgery, radiotherapy or ablative procedures) and their integration with systemic therapy.

**Key Words:** Colorectal cancer; Pulmonary metastases; Oligometastases; Chemotherapy; Surgery; Radiotherapy

Chiappetta M, Salvatore L, Congedo MT, Bensi M, De Luca V, Petracca Ciavarella L, Camarda F, Evangelista J, Valentini V, Tortora G, Margaritora S, Lococo F. Management of single pulmonary metastases from colorectal cancer: State of the art. *World J Gastrointest Oncol* 2022; In press

**Core Tip:** Single pulmonary metastasis from colorectal cancer is an uncommon scenario in which diagnostic pitfalls should be considered. Locoregional approaches (surgery more than radiotherapy or ablative procedures) might have a potential curative role with rewarding long-term results. However, since recurrences are common, the best long-term results might be expected by integrating loco-regional with systemic treatment. Moreover, despite limited evidence, different factors seem to influence prognosis in this subset of patients and should be considered when planning a tailored care strategy.

**INTRODUCTION**

Colorectal cancer (CRC) is one of the three most common cancer types worldwide and is responsible for more than 10% of all cancer deaths in men and women, respectively[1]. Pulmonary metastases occur in 15% of metastatic CRC (mCRC) patients, and the lung is the second site of metastases occurrence after the liver[2]. Many therapeutic options are available, ranging from target therapies to surgical resection. Pulmonary metastases surgery, when feasible, is the best treatment showing a 5-year overall survival (OS) between 25% and 35%[3]. In particular, lung metastasectomy has a long history, and since the 1950s, specific indications were provided with the aim of identifying patient subsets who might benefit from surgical resection[3]. The management of mCRC patients with lung disease requires a multidisciplinary approach and the evaluation of several factors related to patient and tumor characteristics might affect prognosis. The lack of strong scientific evidence makes choosing the most appropriate strategy challenging. National and international guidelines recommend radical resection of lung metastases whenever possible and recommend perioperative or postoperative chemotherapy by evaluating prognostic factors on a case-by-case basis. One of the most considered parameters is the number of lung metastases to predict therapy type, which might be systemic in the case of multiple spreading or ablative in limited or oligo-metastatic disease. However, multiple ablative approaches are currently available and consist of surgical resection, stereotaxic radiotherapy, crio or radiofrequency ablation.

Prognostic factors in single lung metastasis are still undefined, and a better stratification could be fundamental in identifying the most appropriate diagnostic and therapeutic approach.

The aim of this review is to describe possible treatments and survival outcomes in patients with single lung metastases from CRC to support physicians’ decision-making on how best to manage these patients.

**EPIDEMIOLOGY AND CLINICAL PRESENTATION**

***Incidence and demographic characteristics***

CRC represents the second most common cancer in females and the third in males[4] and almost 700000 people die every year due to CRC, making it the world's fourth most deadly cancer (after lung, liver and stomach cancer)[5]. In 2020, there were approximately 150000 new cases of CRC in the United States[6]. Despite these relevant numbers, the incidence of CRC decreased from 60 per 100000 people in the 1970s to 38 in 2016[7]. This evidence is substantially attributable to screening programs, early CRC detection and better treatment modalities. Although the implementation of screening allows early diagnosis of CRC, approximately 25% of CRC patients have distant metastases at diagnosis[8,9]. Among patients with mCRC, the lung is the most common extra-abdominal site of metastases[10]. In particular, lung metastases occur in about 10%-30% of all patients diagnosed with advanced disease[11], but only 10% are isolated without liver metastasis[12] .

In a 30-year population-based study, synchronous lung metastases were seen in approximately 10% of patients often associated with liver metastases, while synchronous isolated lung metastases were only seen in around 3% of patients and most often in rectal cancer patients[10].

In a systematic analysis performed by Parnaby *et al*[13], the incidence of pulmonary metastases from rectal cancer during initial staging ranged from 10%-18%. For colon cancer patients, the incidence of pulmonary metastases at the time of initial staging ranged from 5%-6%. Tan *et al*[12] analyzed data from a large cohort in Singapore (754 patients over 4 years) and estimated that isolated pulmonary metastases (no other evidence of metastases elsewhere) develop at any point in the follow-up period, not just at initial staging. The incidence of isolated pulmonary metastases in patients with rectal cancer *vs* colon cancer was 12% *vs* 6%.

***Radiological presentation and diagnostic approach***

Since the introduction of spiral computed tomography (CT) scanners, smaller lesions can be detected at the time of preoperative staging. The significance of indeterminate lung lesions is an open question as the presence of pulmonary metastases during staging CT could change the treatment pathway. Several studies concluded that only a small rate of indeterminate lung lesions are metastases[14]; in approximately 20%-30% of CT scans for CRC staging, indeterminate lesions have been found, but only 10%-20% were malignant[14,15].

Grossmann, in an observational cohort study[16], included preoperative staging CT of the chest and abdomen in 200 patients with CRC, 5 patients had pulmonary metastases and 50 (25%) had indeterminate nodules (8 metastases diagnosed as true at follow-up). Considering the low incidence of pulmonary metastases and the relative minimal impact on treatment plans, the authors concluded that routine staging based on chest CT in CRC patients is not recommended[16], and the presence of indeterminate lung nodules should not delay surgery for CRC[14].

Even if some radiological characteristics can suggest the metastatic nature (well-circumscribed nodules, smooth margins, subpleural or peripheral localization, cavitation or vascular sign), no pathognomonic radiographic features exist that discern metastasis from a primary lung cancer or from benign processes. When multiple nodules are present, the probability of metastatic disease increases significantly. High-resolution helical CT is better than conventional CT as it detects approximately 20%-25% more nodules, as small as 2 to 3 mm[17]. Similarly, an isolated pulmonary nodule presenting as a subsolid lesion (so called ground-glass opacity) are highly suggestive of a primary lung tumor rather than metastatic lesion[18]. In addition, if a single pulmonary nodule is detected during oncological follow-up in a patient with previous CRC history, the probability of malignancy is higher. In a retrospective cohort study including 1104 patients resected at a single institution from 1989 to 1998, 63% of patients with a resected solitary nodule and without previous cancer, 82% with a history of lung cancer, and 79% with a history of extra-pulmonary cancer, had a malignant tumor[19].

In particular, the probability that a solitary pulmonary nodule was cancer ranged from 67% for nodules ≤ 1 cm to 91% for nodules > 3 cm in patients with prior malignancy. Lung cancer was more common than metastasis if the nodule was > 3 cm.

To clarify the significance of indeterminate nodules in patients with CRC discovered by traditional radiological imaging, fluorodeoxyglucose (FDG)-positron emission tomography (PET)-CT has a valuable role as it improves staging accuracy to select the appropriate treatment. A study by Jess *et al*[20] demonstrated that the discovery of an indeterminate lung nodule during staging by means of a CT scan, was identified as a malignant nodule following a PET-CT scan three months after the previous CT scan. However, PET has limited sensitivity for lesions < 1 cm in size, with a sensitivity of 0.405 for metastases of 5-7 mm in diameter to 0.784 for lesions of 8-10 mm and to 0.935 for lesions measuring 11-29 mm in diameter[21]. Moreover, an 18F-FDG PET-CT scan is not particularly effective in distinguishing primary lung tumors from solitary pulmonary metastases and CRC[22], considering that these diseases usually present with an increased metabolic uptake. On the contrary, a negative PET scan result should not be the only determinant when planning the strategy of care. Indeed, if a lung nodule grows, even if the PET scan is negative, surgical resection can be indicated for diagnostic and potentially therapeutic purposes.

The main value of PET is its high level of sensitivity in the detection of extra-thoracic disease. If on the one hand, resection for lung metastasis should not be performed, unless all known disease areas are being treated, on the other hand, positive extra-thoracic or mediastinal uptake is insufficient to exclude a patient from metastasectomy. All suspicious extra-thoracic sites should be investigated, if possible also with a biopsy, before surgery.

Further improvements in radiological differential diagnosis (primary lung tumor *vs* mCRC) could be obtained from radiomics and its application on chest CT-scan or PET-CT scan.

Finally, carcinoembryonic antigen (CEA) could be a useful marker to detect metastasis and recurrence, and current guidelines recommend following up serum CEA regularly to detect recurrent disease. An increased CEA level could be indicative of mCRC when a pulmonary nodule is detected. Moreover, baseline CEA could be a good prognostic factor after recurrence[23].

**THERAPY**

***Surgery***

Colorectal neoplasms are the most common epithelial lesions for which pulmonary metastasectomy is indicated and they are the only type of primary metastatic cancer of the lungs in which the survival advantages of pulmonary metastasectomy were demonstrated in a randomized clinical trial, despite being limited by several pitfalls and controversies[24].

In current clinical practice, pulmonary metastasectomy, in the context of controlled primary tumor sites, is performed with curative intent, as favorable survival has been reported in CRC patients with complete resection of pulmonary metastases by several authors[25-28]. This seems to be particularly evident in single pulmonary metastases where complete resections are achievable. The surgeon's approach should be modulated considering various parameters pertaining to safety margins including local growth properties, size, spread and location of lung metastases. It clearly emerges that a strategy of care should be discussed on an individual, interdisciplinary basis to offer the best possible oncological and surgical results and to maximize long-term patient survival rates.

**Oncologic principles and indication for surgery:** As reported above, a limited subset of CRC patients may benefit from a potentially curative lung metastasectomy[29], provided some strict criteria are met:

Radicality: All pulmonary lesions are technically resectable. In single pulmonary metastases radicality is always achievable, despite the fact that it sometimes requires an anatomical resection instead of the most commonly performed non-anatomical wedge resection.

Feasibility: Patients might tolerate pulmonary resection following evaluation of pulmonary reserve.

Oncological control of disease: The primary CRC site is controlled and extra-thoracic lesions are undetectable (with the exception of resectable liver metastases). General disease control is imperative before performing lung resection and often re-staging imaging (whole body CT-scan or PET-CT scan) is recommended.

Despite that, the presence of solitary pulmonary metastases from CRC ideally represents the best scenario for surgery, and the patient’s oncological history needs to be carefully evaluated during a multidisciplinary tumor board encompassing the presence of a thoracic surgeon. In particular, the timing of lung metastases appearance (synchronous with primary CRC, after liver metastasis treatment, recurrence of lung metastases) should always be considered in the treatment plan.

**Type of approach, type of resection and other technical aspects:** For many decades, radical pulmonary resection *via* thoracotomy has been a standard treatment for metastatic lung tumors[30], even though mini-invasive approaches have been proposed in the last two decades[31,32], resulting in likely similar clinical survival outcomes. However, robust evidence-based data are lacking and no focused analysis has been conducted investigating only CRC patients with solitary pulmonary metastases. A recent meta-analysis performed by Meng *et al*[32] compared the results of 8 studies and showed that no difference between video-assisted thoracic surgery (VATS) *vs* open thoracotomy metastasectomy were detected in terms of the OS rate (HR, 0.72; 95%CI: 0.50-1.04) or the recurrence-free survival rate (HR, 0.79; 95%CI: 0.59-1.08). Nevertheless, as correctly remarked by the authors, further large prospective studies are needed to identify the indications for VATS in patients with pulmonary metastases. In addition, it is logical to assume that in solitary pulmonary lesions VATS procedures are more frequently feasible compared with multiple pulmonary lesions, as completeness of resection it is more easily achieved. Based on these assumptions, we can state that VATS pulmonary resection may be efficacious in most CRC patients with single pulmonary metastases, when two conditions substantially coexist: (1) experience with minimally invasive pulmonary resection; and (2) patient selection (especially anatomical location of the lesion); the interval from chest CT-scan and surgery should be limited to avoid occult pulmonary lesions during VATS procedures.

Concerning the extension of resection, a parenchymal-sparing approach is always recommended for the following reasons: (1) The extent of resection is not related to the survival outcome; (2) Wedge resection seems to be associated with a better short-term outcome compared to segmentectomy/lobectomy[32,33]; and (3) Sparing lung parenchyma is pivotal for eventual re-do surgery. However, segmentectomy seems to be associated with lower relapse rates compared to wedge resection, due to a lower resection-margin recurrence[33]. Therefore, when technically feasible, wedge resection or segmentectomy should be preferred to lobar resection and surgeons should attempt this strategy as much as possible.

With regard to the surgical technique for nodule resection, the standard method consists of stapler use; however, laser-assisted lung resection has emerged as an alternative option. Regardless of the laser type adopted, this technique demonstrated similar early and long-term results after pulmonary metastasectomy[34], and is also associated to a lower local recurrence rate in some studies compared with stapler resection[35]. Moreover, laser resection may avoid the need to perform a lobectomy in selected cases[36] and, owing to recent technological improvements, laser-assisted lung resection may be feasible (especially in single pulmonary metastases) even *via* uniportal VATS (the least invasive approach available today)[37].

***Radiotherapy and other loco-regional approaches***

Approximately 70% of CRC metastases are unresectable and radiotherapy represents a very promising and rapidly evolving non-invasive treatment modality, particularly stereotactic body radiation therapy (SBRT)[1]. In fact, SBRT can potentially be equally effective and less toxic than surgery, especially in elderly patients and those with important comorbidities[38]. In detail, SBRT is a treatment technique with very sharp radiation dose gradients, which allows the delivery of high doses per fraction in a few days (less than or equal to 8), corresponding to consistently higher biologically equivalent doses in comparison with standard radiotherapy resulting in highly targeted treatment, with good surrounding healthy organ sparing, relative non-invasiveness and good tolerance.

On the other hand, the radiation dose and fractionation schedule are chosen based on several factors, such as tumor size, tumor location and neighboring organs at risk of dose constraints. In most of the clinical trials, SBRT was delivered in a few fractions (3-10), while single fraction SBRT has been less investigated and, in general, the dose administered is between 24 and 65 Gy in total. Moreover, the low number of treatment fractions may also play a role in the activation of an anti-tumor immune response because, in addition to damaging and killing cancer cells, radiation can destroy the adjacent tumor protective stromal microenvironment[39,40].

Four-dimensional (4D)-CT delineates the internal target volume contouring a gross tumor volume, which includes the tumor position in all respiratory cycles and is then expanded with a 3 mm isotropic margin to create the planning treatment volume (PTV); finally, a volumetric modulated arch therapy is planned with a specific treatment planning system. Stereotactic radiotherapy is delivered using a linear accelerator with an energy ranging from 6 to 10 MV photons. During each treatment session, cone-beam CT are performed to verify correct positioning of the patient and the correspondence of the PTV with the target volume identified during the simulation and planning phases[41].

Treatment accuracy can be implemented with respiratory gating techniques, with the benefit of reducing the mean radiation dose received by the lungs to avoid pulmonary acute toxicity, but also pulmonary, cardiac, and esophageal late toxicities[42,43]. In addition, magnetic resonance guidance provides excellent visualization of non-bony structures during radiotherapy.

In terms of results, Filippi *et al*[40] demonstrated similar OS outcomes between SBRT and surgery (89% *vs* 96% at 1 year and 77% *vs* 82% at 2 years, *P* = 0.134) in 142 patients with lung metastases, including 78 (55%) with single metastases. Moreover, a higher rate of local and distant recurrences occurred in the SBRT cohort, whereas a similar death rate was demonstrated. This retrospective study also showed a worse prognosis in terms of progression-free survival (PFS) in the SBRT cohort, but it cannot be excluded that this was influenced by different follow-up protocols and different sample sizes.

Kobiela *et al*[39] performed a systematic review of oligometastatic patients (average number of lesions per patients = 1.5) and showed that SBRT offers high local control rates (up to 90%) and satisfactory OS rates (up to 70% at 2 years) with a PFS of 9 to 34.4 mo and a relatively low toxicity burden. These data are similar to those obtained by Franzese *et al*[44], who showed a local control rate of 95% at 1 year and 73% at 3 years in 270 patients with a maximum of 5 lung metastases, 59% of the patients had a single disease location. However, disease progression outside the irradiation field still remains the main issue in metastatic CRC patients treated with SBRT. In the oligometastatic setting, SBRT can potentially ablate the whole burden of disease, but more careful selection of patients must be performed[45]. In fact, SBRT is often offered to patients who are usually not eligible for other treatment modalities[1,2,37].

Another retrospective analysis showed excellent promising results in a cohort of 40 patients including 26 with single lung metastases (65%), especially in terms of OS (88% at 1 year, 73% at 2 years), while PFS was 53% at 1 year and 28% at 2 years. Failure at the irradiation site was 7.5% (3 of 56 patients) and the time to progression after SBRT was similar to the surgical series; the typical pattern of failure was intrathoracic progression[41].

Thus, SBRT for CRC oligometastases may be a very good tool for maintaining high local control and good OS rates, especially if the radiation dose is escalated. Previous studies have demonstrated that a higher biologically equivalent dose seems to correlate with higher local control. On the other hand, a higher number of lesions may correlate with lower local control and OS. Comito *et al*[46] demonstrated a correlation between OS and cumulative tumor volume greater than 3 cm.

However, SBRT can result in toxicities. In particular, pulmonary SBRT has a safety profile expressed as moderate acute effects and a characteristic late toxicity pattern, appearing more than 6 mo after the end of treatment, which can be radiologic, secondary to radiation-induced fibrotic changes, and clinical, especially cutaneous erythema and chest wall toxicity (more frequently in terms of chronic neuropathic pain, more rarely as rib fractures). However, various retrospective data have shown that toxicity above grade 3 is extremely rare (mostly G1-G2). In conclusion, stereotactic radiation therapy appears to be a safe and efficient way to treat lung metastases, with very high local control rates, low toxicity and promising PFS in selected oligometastatic patients not suitable for surgical resection.

***Systemic therapy***

**General principles:** National and international guidelines (AIOM[47], ESMO[1], and NCCN[48]) agree that radical surgery represents the only potentially curative treatment for lung metastases, and these recommendations are based on retrospective data only. However, guidelines do not clearly define the role of chemotherapy in this setting. In particular, there is no unanimous consensus on the best timing or on the preferred drug regimen.

Based on the literature and clinical experience, the choice of chemotherapy treatment can be assessed using several variables: patient (performance status, age, comorbidities) and tumor characteristics (RAS/BRAF status, site of the primary tumor right *vs* left, synchronous *vs* metachronous disease), and resectability status of metastases (resectable *vs* potentially resectable *vs* unresectable)[49,50]. In the scenario of single pulmonary metastases from CRC, the multidisciplinary team, composed of oncologists, thoracic surgeons, radiologists, and radiotherapists, plays a crucial role in outlining adequate personalized treatment planning.

In the context of single resectable pulmonary metastases, the “perfect” timing of the surgical approach is debated. “Oncological” prognostic criteria and “technical” surgical criteria should define the adequate strategy (upfront surgery eventually followed by postoperative chemotherapy or perioperative chemotherapy)[51,52]. Based on such results, patients with unfavorable prognostic factors could be considered for perioperative or postoperative chemotherapy to improve their outcome. In contrast, the presence of positive prognostic factors can allow upfront surgery.

The role of perioperative chemotherapy for single resectable pulmonary metastases is controversial due to the absence of prospective randomized trials. Perioperative therapy aims to increase the R0 metastasectomy rate and decrease the possibility of postoperative relapse, with a subsequent improvement in OS. A meta-analysis of eight retrospective studies investigated the role of perioperative chemotherapy in mCRC patients with radically resected lung metastases. Out of 1936 patients with colorectal lung metastases, 926 underwent surgery alone, while 1010 patients also received perioperative chemotherapy. This meta-analysis demonstrated the benefit of perioperative treatment both in terms of OS (HR 0.83, 95%CI: 0.75-0.92, *P* < 0.05) and PFS/recurrence-free survival (RFS)/disease-free survival (DFS) (HR 0.67, 95%CI: 0.53-0.86, *P* < 0.05) compared with surgery alone. Multivariate analysis also confirmed these results (OS: HR 0.56, 95%CI: 0.36–0.86, *P* < 0.05; PFS/RFS/DFS: HR 0.64, 95%CI: 0.46–0.87, *P* < 0.05)[53].

The role of postoperative therapy is also debated as no randomized study has compared postoperative therapy after lung metastasectomy *vs* surgery alone. A meta-analysis of 18 cohort studies involving 3885 patients with colorectal lung metastases evaluated the role of postoperative chemotherapy after radical lung resection compared to surgery alone. Postoperative treatment did not improve OS (HR 0.78; 95%CI: 0.60-1.03, *P* = 0.077) and DFS (HR 0.91; 95%CI: 0.74-1.11, *P* = 0.339) in comparison to surgery alone. However, it is necessary to underline the important limits of this meta-analysis, mainly the retrospective nature of the studies and the high heterogeneity, which may have negatively affected these results[54].

Despite the lack of randomized prospective trials and limited evidence, perioperative or postoperative chemotherapy to treat patients with resectable lung metastases is generally used in clinical practice, particularly for those with unfavorable prognostic factors. The most commonly adopted regimen is monotherapy with fluoropyrimidine or the combination with oxaliplatin (FOLFOX/XELOX). Such recommendations are mainly derived from data on mCRC patients with liver-only disease[55].

In the case of potentially resectable lung metastases, induction chemotherapy has, as the main objective, maximal tumor shrinkage to achieve radical resection. In this setting, the preferred treatment regimen corresponds to the most effective first-line therapy for mCRC, which is established based on patient and tumor characteristics. Patients should be re-evaluated regularly every 8-12 wk during therapy and discussed at multidisciplinary meetings to identify the best response and the most appropriate timing of surgery.

In the setting of oligometastatic disease, mainly involving lung and liver, a surgical approach can be considered, especially when the pulmonary parenchyma is minimally involved. Analysis of the liver in a survey registry evaluated 9619 mCRC patients divided into three groups: group 1 (9185 patients with liver-only disease, radically resected), group 2 (149 patients with liver and lung disease, both radically resected), and group 3 (285 patients with liver and lung disease, only liver resected). The 5-year OS was similar for patients in group 1 and 2 (51.5% and 44.5%, respectively) and worse for patients in group 3 (14.3%) (*P* = 0.001)[56]. Thus, these findings confirm the importance of radical surgery of both liver and lung metastases, when achievable.

**Adjuvant therapies in single metastases:** As described in the previous paragraph, the role of adjuvant therapies after lung metastasectomy is a debated and interesting issue, but presents discordant data and remarkable bias in patient selection. Indeed, some studies are in favor of adjuvant therapy (AT) administration[57,58], and others report disadvantages after AT administration[59,60].

The focal point is that it is difficult to consider a homogeneous population, considering the primitive tumor site, number of lung or extra-pulmonary surgically treated metastases and previous administered treatments. Moreover, the lack of clear prognostic factors may lead to a case-by-case decision on AT in advanced stage patients, and its role remains debated and requires clarification in appropriate prospective studies.

Regarding its potential use in patients with operated single metastases, very few data are present in the literature. Rapicetta *et al*[61] did not report any survival advantage when AT was administered, while Guerrera *et al*[62] reported a better outcome when adjuvant chemotherapy was performed in patients with multiple metastases suggesting that no robust data on single metastases are available. The authors confirmed their theories in a recent best evidence topic which showed that AT may improve the prognosis in specific patients with advanced disease or a particular molecular pattern[63].

Based on these reports, clear evidence of AT benefits in patients who underwent lung metastasectomy for single localization is not present, suggesting this therapy especially in patients with multiple metastases. However, further planned research is needed for a better definition of this issue.

**OUTCOMES**

***Prognostic factors and long-term survival***

Different prognostic factors have been analyzed in patients with lung metastases from CRC, including factors linked to primitive tumors but also patients’ oncological history. The main considered prognostic factors are reported in Table 1, even if detailed analyses in patients with single metastasis are very rare.

The CEA levels are routinely analyzed during follow-up in CRC patients, and it is interesting to note that they may also have a prognostic role in patients with lung metastases, by determining the worse prognosis in patients with CEA levels > 4-5 ng/mL (Table 1). The primitive tumor site does not seem to be associated with prognosis, with only the study by Cavallaro *et al*[64] reporting a better survival rate in the case of right sided tumors *vs* left sided rectal neoplasms. Conversely, the primitive CRC stage resulted in an important prognostic factor, with a poor prognosis in the case of advanced T-stage, presence of neighboring organ invasion or metastases to the loco-regional lymph nodes (Table 1).

It is interesting to note that lymph node spreading seems to be a significant prognostic factor in the case of mediastinal involvement, with various authors reporting that thoracic nodal involvement could be an important prognostic factor for worse long-term outcome[47,65]. Welter and co-workers[66] reported significantly poorer median survival for patients with nodal involvement than for patients without (≈ 30 mo *vs* 86 mo). This may also be a factor in the decision-making process to decide whether a patient is suitable for a surgical intervention or not[67], although the same authors caution that even some patients with intra-thoracic lymph node metastases have a longer OS with surgery than with chemotherapy alone[66].

On the other hand, mediastinal lymphadenectomy during lung metastasectomy is infrequently performed, and is one of the most common missing analyzed variable[68].

Despite no robust evidence being available on this topic to date, hilo/mediastinal lymph node sampling (at least) is advisable during pulmonary metastasectomy from CRC, especially when enlarged lymph nodes (at CT-scan) or uptake (at 18F-FDG PET-CT scan) by lymph nodes are detectable. There are no articles specifically focused on single pulmonary metastases, but oncological principles and indications are also applicable and valid in this scenario.

Tumor dimension, with a cut-off of 2 cm, is another well analyzed parameter in these patients, valid in the presence of single but also multiple metastases[61].

Another interesting argument is the outcome considering the patient’s oncological history, which may be extremely various considering the timing of lung metastases appearance, concomitant liver involvement and disease-free intervals after CRC treatment. As we reported in previous paragraphs, multidisciplinary evaluation is fundamental, especially in the case of multi-organ involvement. In particular, patients with a history of extra-thoracic metastases[61,68-70] had a worse prognosis similar to patients with synchronous or bilateral lung involvement[71].

Finally, the DNA fragmentation index (DFI) between CRC treatment and lung metastases appearance is another validated prognostic factor, even if a universal cut-off is not present in the literature. Indeed, a better prognosis stratification is present when the DFI is evaluated at > 6[72], > 12[61,73], or 36 mo[67,74,75] confirming that a long DFI is an important factor when considering treatment for lung metastases from CRC.

A promising factor may be the metabolic activity of the nodule which was found to be a significant prognostic factor in the study by Rapicetta *et al*[61] and Davini *et al*[76]. In detail, Davini *et al*[76] reported that PET negativity was a protective factor for OS (HR 0.46; *P* = 0.001; 95%CI: 0.29–0.72) and for DFI after lung metastasectomy, while Rapicetta *et al*[61] reported that PET positivity in single CRC metastases (RR: 2.702, 95%CI: 1.041-7.013, *P* = 0.041) was a negative independent prognostic factor only for DFI.

With regard to long-term outcome, 5-year OS after single metastasis resection ranged between 32% and 62%[61,71,77], but it is interesting to note that the best survival rates (around 60% at 5 years) were reported in recent studies[61,71] suggesting a progressive improvement in terms of therapeutic strategies, but also regarding more accurate patient selection. The presence of a single metastases was one of the most important prognostic factors in surgically treated patients (Table 1), which was also confirmed in a meta-analysis by Gonzalez *et al*[78], who demonstrated a favorable prognostic role for the number of resected metastases, which was a significant favorable factor associated with CEA levels, DFI, and presence of lymph node involvement. In detail, the authors reported a significantly increased mortality risk in the case of multiple metastases: HR 2.04, 95%CI: 1.72-2.41. On the other hand, very few data are available regarding prognostic factors in this class of patients with single metastases.

Metastasis dimension seems to be significantly related with survival in these patients, with survival improvement in patients with a metastasis dimension less than 2 cm. In particular, Nanji *et al*[79] reported an unadjusted 5-year CSS and OS of 57% and 55%, respectively, for single lesions smaller than 2 cm, and 33% for a single lesion exceeding 2 cm, in agreement with previously published results[61].

Only Rapicetta *et al*[61] performed a more accurate survival analysis in these patients and demonstrated that advanced age and elevated pre-thoracotomy CEA levels were also associated with poor survival. Moreover, the authors analyzed prognostic factors for DFS after metastasectomy and showed that a short DFI between colorectal resection and lung resection (cut-off 12 mo) increased PET uptake and the presence of synchronous lung metastasis were predictive of a short DFS. A long DFS was also found to be a protective factor by Davini *et al*[76], but also included multiple metastases.

The goal of CRC metastasectomy is to obtain a R0 resection[1,2], and there is little evidence regarding the prognostic role of the resection margin distance. Indeed, only Davini *et al*[76] reported a significant difference in survival when comparing a free resection margin > *vs* > 2 cm, while in other studies it was not investigated or did not show statistical significance[61,62]. However, considering the integrated treatments that may follow surgical resection, it is possible that the resection distance did not influence survival when a complete resection was performed.

Finally, Cavallaro *et al*[64] reported a significantly better survival rate when lung metastases were not associated with liver metastases.

Based on these reported studies, CEA pre-thoracotomy levels and short DFI may be evaluated when treating these patients, considering that the prognosis may be poor and a careful advantages/disadvantages analysis should consider the patient’s general condition and surgical risks.

***Incidence of recurrence and its management***

Recurrence after lung metastasectomy is common, ranging between 32.9% and 72%[62,70,73,80] with lung involvement present in about 50% of cases[81] and with a redo surgery rate of about 50%[73].

When technically feasible and in patients able to tolerate a repeated lung resection, the surgical approach seems to ensure interesting results in terms of survival, with 5-year OS ranging between 49% and 76.3%[62,69,78].

In 26 patients with recurrence, Fukada *et al*[69] reported a 5-year OS of 76.9%, while Menna *et al*[82] did not report a survival difference when comparing patients who underwent single or repeated lung metastasectomy. Ogata reported a significantly better survival in patients who underwent repeated resection in the case of single metastases without extra-thoracic disease[80]; however, CEA level, number of pulmonary metastases, mediastinal lymph node metastasis, and DFI also seem to be related to survival after repeat pulmonary metastasectomy[80,83-85].

However, this excellent survival outcome might be linked to careful patient selection indicating that the surgical approach in patients with limited lung involvement and good performance status may reduce the risks of redo-surgery in these patients. Conversely, repeated surgery may be carefully considered in patients with nodal or extra-thoracic metastases and sub-optimal clinical conditions.

**CONCLUSION**

Single pulmonary metastasis from CRC is an uncommon scenario with diagnostic pitfalls to be considered. Loco-regional approaches (surgery more than radiotherapy or ablative procedures) may have a potential curative role with rewarding long-term results. However, the absence of randomized prospective trials and limited data availability does not permit definitive conclusions. Chemotherapy, including timing and drug regimen, should be evaluated on a case-by-case basis by the multidisciplinary team by considering both tumor and patient characteristics.

The best long-term results may be expected when integrating loco-regional with systemic treatment. Despite evidence being limited, different factors seem to influence prognosis in this subset of patients and should be considered when planning a tailored care strategy.

**ACKNOWLEDGEMENTS**

We would like to thank Franziska M Lohmeyer, PhD, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, for her support revising our manuscript language.

**REFERENCES**

1 **Van Cutsem E**, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D'Hoore A, Diaz-Rubio E, Douillard JY, Ducreux M, Falcone A, Grothey A, Gruenberger T, Haustermans K, Heinemann V, Hoff P, Köhne CH, Labianca R, Laurent-Puig P, Ma B, Maughan T, Muro K, Normanno N, Österlund P, Oyen WJ, Papamichael D, Pentheroudakis G, Pfeiffer P, Price TJ, Punt C, Ricke J, Roth A, Salazar R, Scheithauer W, Schmoll HJ, Tabernero J, Taïeb J, Tejpar S, Wasan H, Yoshino T, Zaanan A, Arnold D. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016; **27**: 1386-1422 [PMID: 27380959 DOI: 10.1093/annonc/mdw235]

2 **Benson AB**, Venook AP, Al-Hawary MM, Cederquist L, Chen YJ, Ciombor KK, Cohen S, Cooper HS, Deming D, Engstrom PF, Garrido-Laguna I, Grem JL, Grothey A, Hochster HS, Hoffe S, Hunt S, Kamel A, Kirilcuk N, Krishnamurthi S, Messersmith WA, Meyerhardt J, Miller ED, Mulcahy MF, Murphy JD, Nurkin S, Saltz L, Sharma S, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Wuthrick E, Gregory KM, Freedman-Cass DA. NCCN Guidelines Insights: Colon Cancer, Version 2.2018. *J Natl Compr Canc Netw* 2018; **16**: 359-369 [PMID: 29632055 DOI: 10.6004/jnccn.2018.0021]

3 **Ehrenhaft JL**, Lawrence MS, Sensenig DM. Pulmonary resections for metastatic lesions. *AMA Arch Surg* 1958; **77**: 606-612 [PMID: 13582418 DOI: 10.1001/archsurg.1958.04370010138013]

4 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

5 **Brody H**. Colorectal cancer. *Nature* 2015; **521**: S1 [PMID: 25970450 DOI: 10.1038/521S1a]

6 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020; **70**: 7-30 [PMID: 31912902 DOI: 10.3322/caac.21590]

7 **Siegel RL**, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2020. *CA Cancer J Clin* 2020; **70**: 145-164 [PMID: 32133645 DOI: 10.3322/caac.21601]

8 **Amin MB**, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR, Winchester DP. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin* 2017; **67**: 93-99 [PMID: 28094848 DOI: 10.3322/caac.21388]

9 **Kattan MW**, Hess KR, Amin MB, Lu Y, Moons KG, Gershenwald JE, Gimotty PA, Guinney JH, Halabi S, Lazar AJ, Mahar AL, Patel T, Sargent DJ, Weiser MR, Compton C; members of the AJCC Precision Medicine Core. American Joint Committee on Cancer acceptance criteria for inclusion of risk models for individualized prognosis in the practice of precision medicine. *CA Cancer J Clin* 2016; **66**: 370-374 [PMID: 26784705 DOI: 10.3322/caac.21339]

10 **Mitry E**, Guiu B, Cosconea S, Jooste V, Faivre J, Bouvier AM. Epidemiology, management and prognosis of colorectal cancer with lung metastases: a 30-year population-based study. *Gut* 2010; **59**: 1383-1388 [PMID: 20732912 DOI: 10.1136/gut.2010.211557]

11 **Li Y**, Zhou Z, Liu D, Zhou M, Tan F, Liu W, Zhu H. Predictive and Prognostic Factors of Synchronous Colorectal Lung-Limited Metastasis. *Gastroenterol Res Pract* 2020; **2020**: 6131485 [PMID: 33299406 DOI: 10.1155/2020/6131485]

12 **Tan KK**, Lopes Gde L Jr, Sim R. How uncommon are isolated lung metastases in colorectal cancer? A review from database of 754 patients over 4 years. *J Gastrointest Surg* 2009; **13**: 642-648 [PMID: 19082673 DOI: 10.1007/s11605-008-0757-7]

13 **Parnaby CN**, Bailey W, Balasingam A, Beckert L, Eglinton T, Fife J, Frizelle FA, Jeffery M, Watson AJ. Pulmonary staging in colorectal cancer: a review. *Colorectal Dis* 2012; **14**: 660-670 [PMID: 21689294 DOI: 10.1111/j.1463-1318.2011.02601.x]

14 **Brent A**, Talbot R, Coyne J, Nash G. Should indeterminate lung lesions reported on staging CT scans influence the management of patients with colorectal cancer? *Colorectal Dis* 2007; **9**: 816-818 [PMID: 17931171 DOI: 10.1111/j.1463-1318.2007.01229.x]

15 **Kronawitter U**, Kemeny NE, Heelan R, Fata F, Fong Y. Evaluation of chest computed tomography in the staging of patients with potentially resectable liver metastases from colorectal carcinoma. *Cancer* 1999; **86**: 229-235 [PMID: 10421258]

16 **Grossmann I**, Avenarius JK, Mastboom WJ, Klaase JM. Preoperative staging with chest CT in patients with colorectal carcinoma: not as a routine procedure. *Ann Surg Oncol* 2010; **17**: 2045-2050 [PMID: 20151212 DOI: 10.1245/s10434-010-0962-y]

17 **Collie DA**, Wright AR, Williams JR, Hashemi-Malayeri B, Stevenson AJ, Turnbull CM. Comparison of spiral-acquisition computed tomography and conventional computed tomography in the assessment of pulmonary metastatic disease. *Br J Radiol* 1994; **67**: 436-444 [PMID: 8193888 DOI: 10.1259/0007-1285-67-797-436]

18 **Ohtaki Y**, Shimizu K, Nagashima T, Nakazawa S, Obayashi K, Azuma Y, Iijima M, Kosaka T, Yajima T, Ogawa H, Tsutsumi S, Arai M, Mogi A, Kuwano H. Clinical and Radiological Discrimination of Solitary Pulmonary Lesions in Colorectal Cancer Patients. *World J Surg* 2018; **42**: 1161-1170 [PMID: 28983707 DOI: 10.1007/s00268-017-4243-9]

19 **Reinhardt MJ**, Wiethoelter N, Matthies A, Joe AY, Strunk H, Jaeger U, Biersack HJ. PET recognition of pulmonary metastases on PET/CT imaging: impact of attenuation-corrected and non-attenuation-corrected PET images. *Eur J Nucl Med Mol Imaging* 2006; **33**: 134-139 [PMID: 16193313 DOI: 10.1007/s00259-005-1901-1]

20 **Jess P**, Seiersen M, Ovesen H, Sandstrøm H, Maltbæk N, Buhl AA, Roikjær O. Has PET/CT a role in the characterization of indeterminate lung lesions on staging CT in colorectal cancer? A prospective study. *Eur J Surg Oncol* 2014; **40**: 719-722 [PMID: 24462549 DOI: 10.1016/j.ejso.2013.11.030]

21 **Benson AB**, Venook AP, Al-Hawary MM, Arain MA, Chen YJ, Ciombor KK, Cohen S, Cooper HS, Deming D, Farkas L, Garrido-Laguna I, Grem JL, Gunn A, Hecht JR, Hoffe S, Hubbard J, Hunt S, Johung KL, Kirilcuk N, Krishnamurthi S, Messersmith WA, Meyerhardt J, Miller ED, Mulcahy MF, Nurkin S, Overman MJ, Parikh A, Patel H, Pedersen K, Saltz L, Schneider C, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Gregory KM, Gurski LA. Colon Cancer, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2021; **19**: 329-359 [PMID: 33724754 DOI: 10.6004/jnccn.2021.0012]

22 **Yu X**, Song X, Zhu L, Chen W, Dai D, Li X, Xu W. Role of 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in the Diagnosis of Newly Found Suspected Malignant Solitary Pulmonary Lesions in Patients Who Have Received Curative Treatment for Colorectal Cancer. *Gastroenterol Res Pract* 2017; **2017**: 3458739 [PMID: 28487728 DOI: 10.1155/2017/3458739]

23 **Cho WK**, Choi DH, Park HC, Park W, Yu JI, Park YS, Park JO, Lim HY, Kang WK, Kim HC, Cho YB, Yun SH, Lee WY. Elevated CEA is associated with worse survival in recurrent rectal cancer. *Oncotarget* 2017; **8**: 105936-105941 [PMID: 29285304 DOI: 10.18632/oncotarget.22511]

24 **Treasure T**, Farewell V, Macbeth F, Monson K, Williams NR, Brew-Graves C, Lees B, Grigg O, Fallowfield L; PulMiCC Trial Group. Pulmonary Metastasectomy versus Continued Active Monitoring in Colorectal Cancer (PulMiCC): a multicentre randomised clinical trial. *Trials* 2019; **20**: 718 [PMID: 31831062 DOI: 10.1186/s13063-019-3837-y]

25 **van Dorp M**, Beck N, Steup WH, Schreurs WH. Surgical treatment of pulmonary metastases in the Netherlands: data from the Dutch Lung Cancer Audit for Surgery. *Eur J Cardiothorac Surg* 2020; **58**: 768-774 [PMID: 32282876 DOI: 10.1093/ejcts/ezaa090]

26 **Rotolo N**, De Monte L, Imperatori A, Dominioni L. Pulmonary resections of single metastases from colorectal cancer. *Surg Oncol* 2007; **16 Suppl 1**: S141-S144 [PMID: 18037287 DOI: 10.1016/j.suronc.2007.10.007]

27 **Kim JY**, Park IJ, Kim HR, Kim DK, Lee JL, Yoon YS, Kim CW, Lim SB, Lee JB, Yu CS, Kim JC. Post-pulmonary metastasectomy prognosis after curative resection for colorectal cancer. *Oncotarget* 2017; **8**: 36566-36577 [PMID: 28402263 DOI: 10.18632/oncotarget.16616]

28 **Gonzalez M**, Zellweger M, Nardini M, Migliore M. Precision surgery in lung metastasectomy. *Future Oncol* 2020; **16**: 7-13 [PMID: 31858825 DOI: 10.2217/fon-2018-0713]

29 **Pfannschmidt J**, Dienemann H, Hoffmann H. Surgical resection of pulmonary metastases from colorectal cancer: a systematic review of published series. *Ann Thorac Surg* 2007; **84**: 324-338 [PMID: 17588454 DOI: 10.1016/j.athoracsur.2007.02.093]

30 **Riquet M**, Foucault C, Cazes A, Mitry E, Dujon A, Le Pimpec Barthes F, Médioni J, Rougier P. Pulmonary resection for metastases of colorectal adenocarcinoma. *Ann Thorac Surg* 2010; **89**: 375-380 [PMID: 20103301 DOI: 10.1016/j.athoracsur.2009.10.005]

31 **Greenwood A**, West D. Is a thoracotomy rather than thoracoscopic resection associated with improved survival after pulmonary metastasectomy? *Interact Cardiovasc Thorac Surg* 2013; **17**: 720-724 [PMID: 23832919 DOI: 10.1093/icvts/ivt300]

32 **Meng D**, Fu L, Wang L, Dai Y, Lv W, Zhang J, Hu J. Video-assisted thoracoscopic surgery versus open thoracotomy in pulmonary metastasectomy: a meta-analysis of observational studies. *Interact Cardiovasc Thorac Surg* 2016; **22**: 200-206 [PMID: 26590306 DOI: 10.1093/icvts/ivv309]

33 **Shiono S**, Okumura T, Boku N, Hishida T, Ohde Y, Sakao Y, Yoshiya K, Hyodo I, Mori K, Kondo H. Outcomes of segmentectomy and wedge resection for pulmonary metastases from colorectal cancer. *Eur J Cardiothorac Surg* 2017; **51**: 504-510 [PMID: 27773868 DOI: 10.1093/ejcts/ezw322]

34 **Rolle A**, Pereszlenyi A, Koch R, Richard M, Baier B. Is surgery for multiple lung metastases reasonable? A total of 328 consecutive patients with multiple-laser metastasectomies with a new 1318-nm Nd:YAG laser. *J Thorac Cardiovasc Surg* 2006; **131**: 1236-1242 [PMID: 16733151 DOI: 10.1016/j.jtcvs.2005.11.053]

35 **Lococo F**, Cesario A, Ricchetti T, Rapicetta C, Paci M, Sgarbi G. Erratum to: Lung Tissue Damage Caused by Heat Accumulation from Adjacent Laser Application: Surgical Implications. *Thorac Cardiovasc Surg* 2014; **62**: e2 [PMID: 25415626 DOI: 10.1055/s-0034-1394168]

36 **Stefani A**, Oricchio F, Cinquepalmi A, Aramini B, Morandi U. Is laser-assisted resection preferable to lobectomy for pulmonary metastasectomy? *Lasers Med Sci* 2020; **35**: 611-620 [PMID: 31410616 DOI: 10.1007/s10103-019-02856-8]

37 **Lococo F**, Iaffaldano A, Zanfrini E, Pogliani L, Tabacco D, Sassorossi C, Mazzarella C, Margaritora S. Thulium cyber laser-assisted uniportal thoracoscopic resection of a pulmonary metastasis from colorectal cancer. *Minerva Chir* 2020; **75**: 475-477 [PMID: 33006450 DOI: 10.23736/S0026-4733.20.08416-3]

38 **Ricardi U**, Badellino S, Filippi AR. Clinical applications of stereotactic radiation therapy for oligometastatic cancer patients: a disease-oriented approach. *J Radiat Res* 2016; **57**: i58-i68 [PMID: 26962198 DOI: 10.1093/jrr/rrw006]

39 **Kobiela J**, Spychalski P, Marvaso G, Ciardo D, Dell'Acqua V, Kraja F, Błażyńska-Spychalska A, Łachiński AJ, Surgo A, Glynne-Jones R, Jereczek-Fossa BA. Ablative stereotactic radiotherapy for oligometastatic colorectal cancer: Systematic review. *Crit Rev Oncol Hematol* 2018; **129**: 91-101 [PMID: 30097241 DOI: 10.1016/j.critrevonc.2018.06.005]

40 **Filippi AR**, Guerrera F, Badellino S, Ceccarelli M, Castiglione A, Guarneri A, Spadi R, Racca P, Ciccone G, Ricardi U, Ruffini E. Exploratory Analysis on Overall Survival after Either Surgery or Stereotactic Radiotherapy for Lung Oligometastases from Colorectal Cancer. *Clin Oncol (R Coll Radiol)* 2016; **28**: 505-512 [PMID: 26899780 DOI: 10.1016/j.clon.2016.02.001]

41 **Filippi AR**, Badellino S, Ceccarelli M, Guarneri A, Franco P, Monagheddu C, Spadi R, Ragona R, Racca P, Ricardi U. Stereotactic ablative radiation therapy as first local therapy for lung oligometastases from colorectal cancer: a single-institution cohort study. *Int J Radiat Oncol Biol Phys* 2015; **91**: 524-529 [PMID: 25542308 DOI: 10.1016/j.ijrobp.2014.10.046]

42 **Kini VR**, Vedam SS, Keall PJ, Patil S, Chen C, Mohan R. Patient training in respiratory-gated radiotherapy. *Med Dosim* 2003; **28**: 7-11 [PMID: 12747612 DOI: 10.1016/S0958-3947(02)00136-X]

43 **Giraud P**, Morvan E, Claude L, Mornex F, Le Pechoux C, Bachaud JM, Boisselier P, Beckendorf V, Morelle M, Carrère MO; STIC Study Centers. Respiratory gating techniques for optimization of lung cancer radiotherapy. *J Thorac Oncol* 2011; **6**: 2058-2068 [PMID: 22052228 DOI: 10.1097/JTO.0b013e3182307ec2]

44 **Franzese C**, Comito T, Toska E, Tozzi A, Clerici E, De Rose F, Franceschini D, Navarria P, Reggiori G, Tomatis S, Scorsetti M. Predictive factors for survival of oligometastatic colorectal cancer treated with Stereotactic body radiation therapy. *Radiother Oncol* 2019; **133**: 220-226 [PMID: 30414754 DOI: 10.1016/j.radonc.2018.10.024]

45 **Franzese C**, Comito T, Franceschini D, Loi M, Clerici E, Navarria P, De Rose F, Di Brina L, Mancosu P, Reggiori G, Tomatis S, Scorsetti M. Recursive partitioning model-based analysis for survival of colorectal cancer patients with lung and liver oligometastases treated with stereotactic body radiation therapy. *J Cancer Res Clin Oncol* 2020; **146**: 1227-1234 [PMID: 32056005 DOI: 10.1007/s00432-020-03148-3]

46 **Comito T**, Cozzi L, Clerici E, Campisi MC, Liardo RL, Navarria P, Ascolese A, Tozzi A, Iftode C, De Rose F, Villa E, Personeni N, Rimassa L, Santoro A, Fogliata A, Mancosu P, Tomatis S, Scorsetti M. Stereotactic Ablative Radiotherapy (SABR) in inoperable oligometastatic disease from colorectal cancer: a safe and effective approach. *BMC Cancer* 2014; **14**: 619 [PMID: 25163798 DOI: 10.1186/1471-2407-14-619]

47 **Salvatore L**, Aprile G, Arnoldi E, Aschele C, Carnaghi C, Cosimelli M, Maiello E, Normanno N, Sciallero S, Valvo F, Beretta GD. Management of metastatic colorectal cancer patients: guidelines of the Italian Medical Oncology Association (AIOM). *ESMO Open* 2017; **2**: e000147 [PMID: 28761730 DOI: 10.1136/esmoopen-2016-000147]

48 **Benson AB 3rd**, Venook AP, Cederquist L, Chan E, Chen YJ, Cooper HS, Deming D, Engstrom PF, Enzinger PC, Fichera A, Grem JL, Grothey A, Hochster HS, Hoffe S, Hunt S, Kamel A, Kirilcuk N, Krishnamurthi S, Messersmith WA, Mulcahy MF, Murphy JD, Nurkin S, Saltz L, Sharma S, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Wu CS, Gregory KM, Freedman-Cass D. Colon Cancer, Version 1.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2017; **15**: 370-398 [PMID: 28275037 DOI: 10.6004/jnccn.2017.0036]

49 **Meimarakis G**, Spelsberg F, Angele M, Preissler G, Fertmann J, Crispin A, Reu S, Kalaitzis N, Stemmler M, Giessen C, Heinemann V, Stintzing S, Hatz R, Winter H. Resection of pulmonary metastases from colon and rectal cancer: factors to predict survival differ regarding to the origin of the primary tumor. *Ann Surg Oncol* 2014; **21**: 2563-2572 [PMID: 24668147 DOI: 10.1245/s10434-014-3646-1]

50 **Suzuki H**, Kiyoshima M, Kitahara M, Asato Y, Amemiya R. Long-term outcomes after surgical resection of pulmonary metastases from colorectal cancer. *Ann Thorac Surg* 2015; **99**: 435-440 [PMID: 25499475 DOI: 10.1016/j.athoracsur.2014.09.027]

51 **Lee WS**, Yun SH, Chun HK, Lee WY, Yun HR, Kim J, Kim K, Shim YM. Pulmonary resection for metastases from colorectal cancer: prognostic factors and survival. *Int J Colorectal Dis* 2007; **22**: 699-704 [PMID: 17109105 DOI: 10.1007/s00384-006-0218-2]

52 **Onaitis MW**, Petersen RP, Haney JC, Saltz L, Park B, Flores R, Rizk N, Bains MS, Dycoco J, D'Amico TA, Harpole DH, Kemeny N, Rusch VW, Downey R. Prognostic factors for recurrence after pulmonary resection of colorectal cancer metastases. *Ann Thorac Surg* 2009; **87**: 1684-1688 [PMID: 19463577 DOI: 10.1016/j.athoracsur.2009.03.034]

53 **Li Y**, Qin Y. Peri-operative chemotherapy for resectable colorectal lung metastasis: a systematic review and meta-analysis. *J Cancer Res Clin Oncol* 2020; **146**: 545-553 [PMID: 32036456 DOI: 10.1007/s00432-020-03142-9]

54 **Zhang C**, Tan Y, Xu H. Does adjuvant chemotherapy improve the prognosis of patients after resection of pulmonary metastasis from colorectal cancer? A systematic review and meta-analysis. *Int J Colorectal Dis* 2019; **34**: 1661-1671 [PMID: 31446479 DOI: 10.1007/s00384-019-03362-7]

55 **Nordlinger B**, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Mauer M, Tanis E, Van Cutsem E, Scheithauer W, Gruenberger T; EORTC Gastro-Intestinal Tract Cancer Group; Cancer Research UK; Arbeitsgruppe Lebermetastasen und–tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO); Australasian Gastro-Intestinal Trials Group (AGITG); Fédération Francophone de Cancérologie Digestive (FFCD). Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; **14**: 1208-1215 [PMID: 24120480 DOI: 10.1016/S1470-2045(13)70447-9]

56 **Andres A**, Mentha G, Adam R, Gerstel E, Skipenko OG, Barroso E, Lopez-Ben S, Hubert C, Majno PE, Toso C. Surgical management of patients with colorectal cancer and simultaneous liver and lung metastases. *Br J Surg* 2015; **102**: 691-699 [PMID: 25789941 DOI: 10.1002/bjs.9783]

57 **Rusch VW**. Pulmonary metastasectomy. Current indications. *Chest* 1995; **107**: 322S-331S [PMID: 7781414 DOI: 10.1378/chest.107.6\_supplement.322s]

58 **Higashiyama M**, Kodama K, Takami K, Higaki N, Yokouchi H, Nakayama T, Murata K, Kameyama M, Ashimura J, Naruse Y, Nagumo S. Intraoperative lavage cytologic analysis of surgical margins as a predictor of local recurrence in pulmonary metastasectomy. *Arch Surg* 2002; **137**: 469-474 [PMID: 11926957 DOI: 10.1001/archsurg.137.4.469]

59 **Higashiyama M**, Tokunaga T, Nakagiri T, Ishida D, Kuno H, Okami J. Pulmonary metastasectomy: outcomes and issues according to the type of surgical resection. *Gen Thorac Cardiovasc Surg* 2015; **63**: 320-330 [PMID: 25836329 DOI: 10.1007/s11748-015-0544-9]

60 **Shiono S**, Ishii G, Nagai K, Yoshida J, Nishimura M, Murata Y, Tsuta K, Kim YH, Nishiwaki Y, Kodama T, Iwasaki M, Ochiai A. Predictive factors for local recurrence of resected colorectal lung metastases. *Ann Thorac Surg* 2005; **80**: 1040-1045 [PMID: 16122482 DOI: 10.1016/j.athoracsur.2004.12.033]

61 **Rapicetta C**, Lococo F, Davini F, Carleo F, Kauppi J, Di Stefano TS, Ricciardi S, Di Martino M, Räsänen J, Paci M, Melfi F, Cardillo G. Is Adjuvant Chemotherapy Worthwhile After Radical Resection for Single Lung Metastasis From Colorectal Cancer? A Multicentric Analysis Evaluating the Risk of Recurrence. *Front Oncol* 2019; **9**: 763 [PMID: 31482063 DOI: 10.3389/fonc.2019.00763]

62 **Guerrera F**, Mossetti C, Ceccarelli M, Bruna MC, Bora G, Olivetti S, Lausi PO, Solidoro P, Ciccone G, Ruffini E, Oliaro A, Filosso PL. Surgery of colorectal cancer lung metastases: analysis of survival, recurrence and re-surgery. *J Thorac Dis* 2016; **8**: 1764-1771 [PMID: 27499967 DOI: 10.21037/jtd.2016.05.98]

63 **Guerrera F**, Falcoz PE, Renaud S, Massard G. Does perioperative chemotherapy improve survival in patients with resectable lung metastases of colorectal cancer? *Interact Cardiovasc Thorac Surg* 2017; **24**: 789-791 [PMID: 28453801 DOI: 10.1093/icvts/ivw389]

64 **Cavallaro P**, Bordeianou L, Stafford C, Clark J, Berger D, Cusack J, Kunitake H, Francone T, Ricciardi R. Impact of Single-organ Metastasis to the Liver or Lung and Genetic Mutation Status on Prognosis in Stage IV Colorectal Cancer. *Clin Colorectal Cancer* 2020; **19**: e8-e17 [PMID: 31899147 DOI: 10.1016/j.clcc.2019.12.001]

65 **Renaud S**, Alifano M, Falcoz PE, Magdeleinat P, Santelmo N, Pagès O, Massard G, Régnard JF. Does nodal status influence survival? Results of a 19-year systematic lymphadenectomy experience during lung metastasectomy of colorectal cancer. *Interact Cardiovasc Thorac Surg* 2014; **18**: 482-487 [PMID: 24442624 DOI: 10.1093/icvts/ivt554]

66 **Welter S**, Jacobs J, Krbek T, Poettgen C, Stamatis G. Prognostic impact of lymph node involvement in pulmonary metastases from colorectal cancer. *Eur J Cardiothorac Surg* 2007; **31**: 167-172 [PMID: 17150367 DOI: 10.1016/j.ejcts.2006.11.004]

67 **Cho JH**, Kim S, Namgung M, Choi YS, Kim HK, Zo JI, Shim YM, Kim J. The prognostic importance of the number of metastases in pulmonary metastasectomy of colorectal cancer. *World J Surg Oncol* 2015; **13**: 222 [PMID: 26205014 DOI: 10.1186/s12957-015-0621-7]

68 **Zabaleta J**, Iida T, Falcoz PE, Salah S, Jarabo JR, Correa AM, Zampino MG, Matsui T, Cho S, Ardissone F, Watanabe K, Gonzalez M, Gervaz P, Emparanza JI, Abraira V. Individual data meta-analysis for the study of survival after pulmonary metastasectomy in colorectal cancer patients: A history of resected liver metastases worsens the prognosis. *Eur J Surg Oncol* 2018; **44**: 1006-1012 [PMID: 29602524 DOI: 10.1016/j.ejso.2018.03.011]

69 **Fukada M**, Matsuhashi N, Takahashi T, Tanaka Y, Okumura N, Yamamoto H, Shirahashi K, Iwata H, Doi K, Yoshida K. Prognostic factors in pulmonary metastasectomy and efficacy of repeat pulmonary metastasectomy from colorectal cancer. *World J Surg Oncol* 2020; **18**: 314 [PMID: 33256771 DOI: 10.1186/s12957-020-02076-3]

70 **Sakamaki Y**, Ishida D, Tanaka R. Prognosis of patients with recurrence after pulmonary metastasectomy for colorectal cancer. *Gen Thorac Cardiovasc Surg* 2020; **68**: 1172-1178 [PMID: 32323124 DOI: 10.1007/s11748-020-01368-5]

71 **Fournel L**, Maria S, Seminel M, Nesci J, Mansuet-Lupo A, Guinet C, Magdeleinat P, Bobbio A, Regnard JF, Alifano M. Prognostic factors after pulmonary metastasectomy of colorectal cancers: a single-center experience. *J Thorac Dis* 2017; **9**: S1259-S1266 [PMID: 29119012 DOI: 10.21037/jtd.2017.04.44]

72 **Hwang MR**, Park JW, Kim DY, Chang HJ, Kim SY, Choi HS, Kim MS, Zo JI, Oh JH. Early intrapulmonary recurrence after pulmonary metastasectomy related to colorectal cancer. *Ann Thorac Surg* 2010; **90**: 398-404 [PMID: 20667318 DOI: 10.1016/j.athoracsur.2010.04.058]

73 **Takakura Y**, Miyata Y, Okajima M, Okada M, Ohdan H. Short disease-free interval is a significant risk factor for intrapulmonary recurrence after resection of pulmonary metastases in colorectal cancer. *Colorectal Dis* 2010; **12**: e68-e75 [PMID: 19843115 DOI: 10.1111/j.1463-1318.2009.02070.x]

74 **Rama N**, Monteiro A, Bernardo JE, Eugénio L, Antunes MJ. Lung metastases from colorectal cancer: surgical resection and prognostic factors. *Eur J Cardiothorac Surg* 2009; **35**: 444-449 [PMID: 19136273 DOI: 10.1016/j.ejcts.2008.10.047]

75 **Yedibela S**, Klein P, Feuchter K, Hoffmann M, Meyer T, Papadopoulos T, Göhl J, Hohenberger W. Surgical management of pulmonary metastases from colorectal cancer in 153 patients. *Ann Surg Oncol* 2006; **13**: 1538-1544 [PMID: 17009154 DOI: 10.1245/s10434-006-9100-2]

76 **Davini F**, Ricciardi S, Zirafa CC, Romano G, Alì G, Fontanini G, Melfi FMA. Correction to: Lung metastasectomy after colorectal cancer: prognostic impact of resection margin on long term survival, a retrospective cohort study. *Int J Colorectal Dis* 2020; **35**: 371-372 [PMID: 31838578 DOI: 10.1007/s00384-019-03485-x]

77 **Pfannschmidt J**, Muley T, Hoffmann H, Dienemann H. Prognostic factors and survival after complete resection of pulmonary metastases from colorectal carcinoma: experiences in 167 patients. *J Thorac Cardiovasc Surg* 2003; **126**: 732-739 [PMID: 14502146 DOI: 10.1016/s0022-5223(03)00587-7]

78 **Gonzalez M**, Gervaz P. Risk factors for survival after lung metastasectomy in colorectal cancer patients: systematic review and meta-analysis. *Future Oncol* 2015; **11**: 31-33 [PMID: 25662325 DOI: 10.2217/fon.14.259]

79 **Nanji S**, Karim S, Tang E, Brennan K, McGuire A, Pramesh CS, Booth CM. Pulmonary Metastasectomy for Colorectal Cancer: Predictors of Survival in Routine Surgical Practice. *Ann Thorac Surg* 2018; **105**: 1605-1612 [PMID: 29518384 DOI: 10.1016/j.athoracsur.2018.02.007]

80 **Ogata Y**, Matono K, Hayashi A, Takamor S, Miwa K, Sasatomi T, Ishibashi N, Shida S, Shirouzu K. Repeat pulmonary resection for isolated recurrent lung metastases yields results comparable to those after first pulmonary resection in colorectal cancer. *World J Surg* 2005; **29**: 363-368 [PMID: 15706447 DOI: 10.1007/s00268-004-7537-7]

81 **Murakawa T**. Past, present, and future perspectives of pulmonary metastasectomy for patients with advanced colorectal cancer. *Surg Today* 2021; **51**: 204-211 [PMID: 32857252 DOI: 10.1007/s00595-020-02119-y]

82 **Menna C**, Berardi G, Tierno SM, Andreetti C, Maurizi G, Ciccone AM, D'Andrilli A, Cassiano F, Poggi C, Diso D, Venuta F, Rendina EA, Ibrahim M. Do Repeated Operations for Recurrent Colorectal Lung Metastases Result in Improved Survival? *Ann Thorac Surg* 2018; **106**: 421-427 [PMID: 29605599 DOI: 10.1016/j.athoracsur.2018.02.065]

83 **Kanzaki R**, Higashiyama M, Oda K, Fujiwara A, Tokunaga T, Maeda J, Okami J, Tanaka K, Shingai T, Noura S, Ohue M, Kodama K. Outcome of surgical resection for recurrent pulmonary metastasis from colorectal carcinoma. *Am J Surg* 2011; **202**: 419-426 [PMID: 21824604 DOI: 10.1016/j.amjsurg.2010.08.016]

84 **Hachimaru A**, Maeda R, Suda T, Takagi Y. Repeat pulmonary resection for recurrent lung metastases from colorectal cancer: an analysis of prognostic factors. *Interact Cardiovasc Thorac Surg* 2016; **22**: 826-830 [PMID: 26920721 DOI: 10.1093/icvts/ivv382]

85 **Chen F**, Sakai H, Miyahara R, Bando T, Okubo K, Date H. Repeat resection of pulmonary metastasis is beneficial for patients with colorectal carcinoma. *World J Surg* 2010; **34**: 2373-2378 [PMID: 20582543 DOI: 10.1007/s00268-010-0695-x]

86 **Shiomi K**, Naito M, Sato T, Nakamura T, Nakashima H, Naito M, Mikubo M, Matsui Y, Watanabe M, Satoh Y. Effect of adjuvant chemotherapy after pulmonary metastasectomy on the prognosis of colorectal cancer. *Ann Med Surg (Lond)* 2017; **20**: 19-25 [PMID: 28702182 DOI: 10.1016/j.amsu.2017.06.026]

87 **Imanishi M**, Yamamoto Y, Hamano Y, Yamada T, Moriwaki T, Gosho M, Okumura T, Boku N, Kondo H, Hyodo I. Efficacy of adjuvant chemotherapy after resection of pulmonary metastasis from colorectal cancer: a propensity score-matched analysis. *Eur J Cancer* 2019; **106**: 69-77 [PMID: 30471650 DOI: 10.1016/j.ejca.2018.10.003]

88 **Tsitsias T**, Toufektzian L, Routledge T, Pilling J. Are there recognized prognostic factors for patients undergoing pulmonary metastasectomy for colorectal carcinoma? *Interact Cardiovasc Thorac Surg* 2016; **23**: 962-969 [PMID: 27572615 DOI: 10.1093/icvts/ivw273]

89 **Zampino MG**, Maisonneuve P, Ravenda PS, Magni E, Casiraghi M, Solli P, Petrella F, Gasparri R, Galetta D, Borri A, Donghi S, Veronesi G, Spaggiari L. Lung metastases from colorectal cancer: analysis of prognostic factors in a single institution study. *Ann Thorac Surg* 2014; **98**: 1238-1245 [PMID: 25106681 DOI: 10.1016/j.athoracsur.2014.05.048]

90 **Tampellini M**, Ottone A, Bellini E, Alabiso I, Baratelli C, Bitossi R, Brizzi MP, Ferrero A, Sperti E, Leone F, Miraglia S, Forti L, Bertona E, Ardissone F, Berruti A, Alabiso O, Aglietta M, Scagliotti GV. The role of lung metastasis resection in improving outcome of colorectal cancer patients: results from a large retrospective study. *Oncologist* 2012; **17**: 1430-1438 [PMID: 22956535 DOI: 10.1634/theoncologist.2012-0142]

91 **Landes U**, Robert J, Perneger T, Mentha G, Ott V, Morel P, Gervaz P. Predicting survival after pulmonary metastasectomy for colorectal cancer: previous liver metastases matter. *BMC Surg* 2010; **10**: 17 [PMID: 20525275 DOI: 10.1186/1471-2482-10-17]

**Footnotes**

**Conflict-of-interest statement:** No conflict-of-interest to declare.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** March 26, 2021

**First decision:** May 3, 2021

**Article in press:**

**Specialty type:** Oncology

**Country/Territory of origin:** Italy

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Kaba E, Turkey **S-Editor:** Zhang H **L-Editor:** Webster JR **P-Editor:** Zhang H

**Table 1 Main prognostic factors in patients with lung metastases from colorectal cancer**

|  |  |  |
| --- | --- | --- |
| **Prognostic factor** | **Overall survival** | **Disease-free survival** |
| **Favorable** | **Negative** | **Favorable** | **Negative** |
| Number of metastases[23,68,71,76-78,86-90] | Single | Multiple  |  |  |
| Preoperative CEA level[61,69,86,87] | < 4-5 ng/mL | > 4-5 ng/mL |  |  |
| pStage of CRC[71,79, 86,87] | Local disease, low Tstage, absence of nodal involvement | Advanced p and T stage, nodal Involvement |  |  |
| Lung metastases appearance[23,61,69-71, 87,91] | Metachronous lung metastases | Bilateral lung synchronous metastasis, past history of extra thoracic metastasis | Long DFI between CRC and first detection of pulmonary metastasis | Synchronous pulmonary metastasis and CRC |
| Pulmonary metastasis derivation from primary site of CRC[64] | Right colon | Left colon or rectum | Not investigated | Not investigated |
| Lung metastasis size (cm)[61,69,78,79] | < 2 cm | > 2 cm | Not investigated | Not investigated |
| Mediastinal lymph node metastasis[23,69,89] | Negative | Positive | Not investigated | Not investigated |
| Metabolic characteristics[61,79] | Lung metastasis PET negative | Lung metastasis PET positive  | Lung metastasis PET negative | Lung metastasis PET positive |
| Distance between lesion and resection margin (cm)[79] | > 2 cm | < 2 cm | Not investigated | Not Investigated |

CRC: Colorectal cancer; CEA: Carcinoembryonic antigen; DFI: DNA fragmentation index; PET: Positron emission tomography.