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

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 of Thoracic 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

Corresponding author: Filippo Lococo, MD, Assistant Professor, Department of Thoracic Surgery, Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Università Cattolica del Sacro Cuore, Largo Agostino Gemelli 8, Rome 00168, Italy. filippo.lococo@policlinicogemelli.it

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.

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

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.

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.

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FOOTNOTES

ORCID number: Marco Chiappetta 0000-0002-3807-6911; Lisa Salvatore 0000-0003-3864-0719; Maria teresa Congedo 0000-0001-5563-0331; Maria Bensi 0000-0002-5647-0525; Viola De Luca 0000-0002-9914-0075; Leonardo Petracca Ciavarella 0000-0002-9659-1014; Floriana Camarda 0000-0002-5206-6867; Jessica Evangelista 0000-0001-6707-6120; Vincenzo Valentini 0000-0003-4637-6487; Giampaolo Tortora 0000-0002-1378-4962; Stefano Margaritora 0000-0002-9796-760X; Filippo Lococo 0000-0002-9383-5554.

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