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

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

Abstract

Colorectal cancer (CRC) is one of the commonest cause of death from cancer. Lung seeding occurs in approximately 10% of patients surgically treated for primary CRC with radical intent: the lung is indeed the most common site of metastases after the liver. While surgical treatment of liver metastases is widely accepted affecting long-term outcomes, more controversial and not standardized is the therapy for colorectal patients developing lung metastases. Several experiences suggest 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 are far to be defined. This review focused on the uncommon scenario of single pulmonary metastases from CRC. We explored pertinent literature and provided an overview on epidemiology, clinical characteristics and imaging. 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

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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 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 among the most three common cancer types over the world and 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 between 25%–35%[3]. In particular, lung metastasectomy presents a long history, and since the 1950's, specific indications were provided with the aim to identify patient subsets who might beneficiate from surgical resection[3]. The management of mCRC patients with lung disease requires a multidisciplinary approach and the evaluation of several factors related to patients and tumor characteristics might affect prognosis. The lack of strong scientific evidence makes it challenging to choose the most appropriate strategy. National and International guidelines recommend radical resection of lung metastases whenever possible and recommend perioperative or postoperative chemotherapy evaluating prognostic factors on a case-by-case basis. One of the most considered parameters is the number of lung metastasis to predict therapy type, which might be systemic in case of multiple spreading or ablative in limited or oligo-metastatic disease. However, nowadays multiple ablative approaches are available consisting 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 to identify the most appropriate diagnostic and therapeutic approach.

The aim of this review is to describe treatment possibilities and survival outcomes in patients with single lung metastases from CRC to support the physicians in decision-making how 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, in the United States, about 150000 new cases of CRC occurred[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 for CRC, approximately 25% of CRC patients have distant metastases at diagnosis[8,9]. Among mCRCs, 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 an advanced disease[11] but only 10% are isolated without liver metastasis[12].

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

In a systematic analysis performed by Parnaby *et al*[13], the incidence of pulmonary metastases for rectal cancer during initial staging ranged from 10%-18%. For colon cancer patients, the incidence of pulmonary metastases at time of initial staging ranged from 5%-6%. Instead, Tan *et al*[14] analyzed data of a large cohort from 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 because 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[15]; in approximately 20%-30% of the CT scans for CRC staging, indeterminate lesions have been found, but only 10%-20% are malignant[15,16].

Grossmann, in an observational cohort study[17], included preoperative staging CT of chest and abdomen for 200 patients with CRC, 5 patients had pulmonary metastases and 50 (25%) had indeterminate nodules (8 metastases diagnosed as true at the follow up). Considering the low incidence of pulmonary metastases and the relative minimal impact on treatment plans, authors concluded that routine staging based on chest CT in CRC patients is not recommended[17], and the presence of indeterminate lung nodules should not delay surgery for CRC[15].

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 a 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 because it detects approximately 20%-25% more nodules, as small as 2 to 3 mm[18]. Similarly, an isolated pulmonary nodule presenting as subsolid lesion (so called ground-glass opacity) are highly more suggestive for a primary lung tumor rather than metastatic lesion[19]. At the same time, if a single pulmonary nodule is detected during oncological follow-up in a patient with previous CRC history, the probability of its 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 extrapulmonary cancer, had a malignant tumor[20].

In particular, the probability that a solitary pulmonary was cancer ranged from 67% for nodules ≤ 1 cm to 91% for nodules > 3 cm nodule 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 in traditional radiological imaging, fluorodeoxyglucose (FDG)-positron emission tomography (PET)-CT has a valuable role because it improves staging accuracy to select the appropriate treatment. A study by Jess *et al*[21] demonstrated that the discovery of an indeterminate lung nodule during staging by means of a CT scan, a PET-TC after three months from the previous CT is able to identify a malignant nodule However, PET has limited sensitivity for lesions < 1 cm in size, passing from 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[22]. Moreover, 18F-FDG PET CT scan is not particularly effective to distinguish primary lung tumors from solitary pulmonary metastases and CRC[23], considering that those diseases usually present with an increased metabolic uptake. On the contrary, a negative result at PET scan 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, a surgical resection can be indicated for diagnostic and potentially therapeutic purposes.

The main value of PET is its high level of sensitivity to detect extrathoracic 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, positive extrathoracic or mediastinal uptake is insufficient to exclude a patient from metastasestomy. All suspicious extrathoracic sites should be investigated, if possible also with a biopsy, before surgery.

Further improvements on 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[24].

THERAPY

Surgery

Colorectal neoplasms are the commonest epithelial lesion for which pulmonary metastasectomy is indicated and they are the only type of primary metastatic cancer in the lungs in which survival advantages of pulmonary metastasectomy were demonstrated, in a randomized clinical trial, despite limited by several pitfalls and controversies[25].

In current clinical practice, pulmonary metastasectomy, in the context of controlled primary tumor sites, is performed with curative intent, since rewarding survivals have been reported in colorectal patients with complete resection of pulmonary metastases by several authors[26-29]. This seems to be particularly evident in single pulmonary metastases where complete resections are easier 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[30], provided some strict criteria are met:

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

Feasibility: patients might tolerate pulmonary resection at 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). The 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, 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[31], even if mini-invasive approaches have been proposed in the last two decades[32,33], 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*[33] compared the results of 8 studies showing that no difference between video-assisted thoracic surgery (VATS) *vs* open thoracotomy metastasectomy were detected in either the overall survival 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 authors, further large prospective studies are needed to identify the indications for VATS in patients with pulmonary metastases. At the same time, it is logical to assume that in solitary pulmonary lesion VATS procedures are more frequently feasible compared with multiple pulmonary lesions, since completeness of resection it is more easily to be achieved. Based on these assumptions, we may 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 several reasons: (1) The extent of resection is not related to the survival outcome; (2) Wedge resection seems to be associate with a better short term outcome compared to segmentectomy/lobectomy[33,34]; 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[34]. Therefore, when technical feasible, wedge resection or segmentectomy should be preferred to lobar resection and surgeons should attempt this strategy as much as possible.

Regarding the surgical technique for nodule resection, the standard method consists of stapler use, also if laser-assisted lung resection emerged as an alternative option. Regardless of the laser type adopted, this technique demonstrated similar early and long-term results after pulmonary metastasectomy[35], and is also associated to a lower local recurrence rate in some studies compared with stapler resection[36]. Moreover, laser resection may avoid the need of performing a lobectomy in selected cases[37] 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)[38]

Radiotherapy and other loco-regional approaches

About 70% of CRC metastases are un-resectable and radiotherapy represents a very promising and rapidly evolving non-invasive treatment modality, particularly with stereotactic body radiation therapy (SBRT)[1]. In fact, SBRT can result as potentially equally effective and less toxic than surgery, especially in elderly or patients with important comorbidities[39]. More in detail, SBRT is a treatment technique with very

sharp radiation dose gradients, which allows the delivery of high doses per fraction in 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, radiation dose and fractionation schedule is chosen based on several factors, such as tumor size, tumor location and neighboring organs at risk dose constraints. In most of the clinical trials, SBRT was delivered in 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 fraction 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[40,41].

Four-dimensional (4D)-CT delineates the internal target volume contouring a gross tumor volume, which includes tumor position in all respiratory cycles and then is 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 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[42]

Treatment accuracy can be implemented with respiratory gating techniques, with the benefit to reduce the mean radiation dose received by the lungs avoiding pulmonary acute toxicity, but also pulmonary, cardiac, and esophageal late toxicities[43,44]. In addition, magnetic resonance guidance provides excellent visualization of non-bony structures during radiotherapy.

In terms of results, Filippi *et al*[41] demonstrated similar overall survival 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*[40] performed a systematic review among oligometastatic patients (average number of lesions per patients = 1.5) and showed that SBRT offers high local control rates (up to 90%) and satisfactory overall survival rates (up to 70% at 2 years) with a PFS lasting from 9 up to 34.4 mo and a relative low toxicity burden. These data are similar to those obtained by Franzese *et al*[45], who showed an LC rate of 95% at 1 year and of 73% at 3 years in 270 patients with maximum 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 a more careful selection of patients must be performed[46]. In fact, SBRT is often offered to patients who are usually not eligible for other treatment modalities[1,2,38].

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 progression free survival PFS was 53% at 1 year and 28% at 2 years. Failure at irradiation site was 7.5% (it occurred in 3 of 56 patients) and the time to progression after SBRT was similar to surgical series; the typical pattern of failure was intrathoracic progression[42].

Thus, SBRT for CRC oligometastases may be a very good tool to maintain high local control and good overall survival rates, especially if the radiation dose is escalated. Previous studies demonstrate 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 overall survival. Comito *et al*[47] demonstrated a correlation between overall survival and cumulative tumor volume greater than 3 cm.

However, SBRT is a treatment resulting in toxicities. Particularly, pulmonary SBRT has a safety profile expressed in moderate acute effects and a characteristic late toxicity pattern—appearing more than 6 mo after the end of treatment—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 of rib fractures). Despite, 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 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[48], ESMO[1],and NCCN[49]) agree that radical surgery represents the only potentially curative treatment for lung metastases, also if 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 neither on the best timing nor on the preferred drug regimen.

Based on literature and clinical experience, the choice of chemotherapy treatment can be assessed on 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* un-resectable)[50,51]. Especially 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)[52,53]. 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 an 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 overall survival (OS) improvement. 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 a 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 this result (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, $P < 0.05$)[54].

The role of postoperative therapy is also debated because no randomized study compared postoperative therapy after lung metastasectomy *vs* surgery alone. A meta-analysis of 18 cohort studies with 3885 patients with colorectal lung metastases evaluated postoperative chemotherapy role 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 studies retrospective nature and the high heterogeneity, which can negatively affect these results[55].

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 habitually adopted regimen is monotherapy with fluoropyrimidine or the combination with oxaliplatin (FOLFOX/XELOX). Such recommendations are mainly derived from data on mCRC patients with the liver-only disease[56].

In the case of potentially resectable lung metastases, induction chemotherapy has, as the main objective, maximal tumor shrinkage to achieve a 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. The analysis of the liver met survey registry evaluated 9619 mCRC patients divided into three groups: group 1 (9185 patients with the 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 of group 1 and 2 (51.5% and 44.5%, respectively) and worse for patients of group 3 (14.3%) (P = 0.001)[57].Thus confirms 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[58,59], others report disadvantages after AT administration[60,61].

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 needs clarification in appropriate prospective studies.

Regarding its potential use in patients with operated single metastases, very few data are present in literature. Rapicetta *et al*[62] al did not report any survival advantage when AT was administered, while Guerrera *et al*[63] reported a better outcome when adjuvant chemotherapy was performed in patients with multiple metastases suggesting that no robust data on single metastases were available. The authors confirmed their theories in a recent best evidence topic that showed that AT may improve the prognosis in specific subject pf patients with advanced disease or particular molecular pattern[64].

Based on these reports, a 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 are 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, determining worse prognosis in patients with CEA levels > 4-5 ng/mL (Table 1). The primitive tumor site seem not to be associated with prognosis, with only the study of dr Cavallaro *et al*[65] reporting a better survival rate in case of right side tumors *vs* left sided rectum neoplasms. Conversely, the primitive CRC stage resulted an important prognostic factor, with a poor prognosis in 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 case of mediastinal involvement, with various authors reporting that thoracic nodal involvement could be an important prognostic factor for worse long-term outcome[48,66]. Welter and co-workers[67] report significantly poorer median survival for patients with nodal involvement than for patients without (≈ 30 mts *vs* 86 mts). This may also be an element of the decision-making process to decide if a patient is suitable for a surgical intervention or not[68], although the same authors caution that even some patients with intra-thoracic lymph node metastases have a longer overall survival with surgery than with chemotherapy alone[67].

On the other hand, mediastinal lymphadenectomy during lung metastasectomy is infrequently performed, resulting as one of the most common missing analyzed variable[69].

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

Tumor dimension, with a cut of 2 cm, is another well analyzed parameter in these patients, valid in presence of single but also multiple metastases[62].

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 also in previous paragraphs, multidisciplinary evaluation is fundamental, especially in case of multi-organ involvement. In particular, patients with history of extrathoracic metastases[62,69-71] presented a worse prognosis similarly to patients with synchronous or bilateral lung involvement[72].

Finally, the DNA fragmentation index (DFI) between the CRC treatment and lung metastases appearance resulted another validated prognostic factor, even if a universal

cut-off is not present in literature. Indeed, a better prognosis stratification is present considering a DFI > 6[73], > 12[62,74], or 36 mo[68,75,76] 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 that resulted as significant prognostic factor in the paper of Rapicetta *et al*[62] and Davini *et al*[77]. In detail, Davini *et al*[77] reported that PET negativity was a protective factor for overall survival (HR 0.46; P = 0.001; 95%CI: 0.29–0.72) and DFI after lung metastasectomy, while Rapicetta *et al*[62] 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.

Concerning long-term outcome, 5-year OS after single metastasis resection ranged between 32% and 62%[62,72,78], but it is interesting to note that the best survival rates (around the 60% at 5 years) are reported in recent studies[62,72] suggesting a progressive improvement in terms of therapeutic strategies but also regarding a more accurate patients selection. The presence of a single metastases resulted as one of the most important prognostic factors in surgically treated patients (Table1), which was also confirmed in a meta-analysis by Gonzalez *et al*[79], who demonstrated a favorable prognostic role for numbers of resected metastases, which resulted 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 case of multiple metastases: HR 2.04, 95%CI: 1.72-2.41. On the other hand, very few information are present regarding prognostic factors in this class of patients with a single metastases.

Metastasis dimension seems to be significantly related with survival in these patients, with a survival improvement in patients with metastasis dimension less than 2 cm. In particular, Nanji *et al*[80] reported unadjusted 5-year CSS and OS of 57% and 55% for single lesions smaller than 2 cm, 33% a single lesion exceeding 2 cm, in agreement with previous published results[62].

Only Rapicetta *et al*[62]performed a more accurate survival analysis in these patients demonstrating that advanced age and elevated pre-thoracotomy CEA levels were also associate with poor survival. Moreover, the authors analysed prognostic factors for DFS after metastasectomy showing that a short DFI between colorectal resection and lung resection (cut off 12 mo) increased PET uptake and presence of synchronous lung metastasis were predictive for short DFS. A long DFS was detected as protective factor also by Davini *et al*[77], but including also multiple metastases.

The goal of CRC metastasectomy remains to obtain a R0 resection[1,2] , and few evidences are present regarding the prognostic role of the resection margin distance. Indeed, only Davini *et al*[77] reported a significant difference in survival comparing a free resection margin > *vs* > 2 cm, while in other studies it was not investigated or did not present statistical significance[62,63]. 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 is performed.

Finally, Cavallaro *et al*[65]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 result poor and a careful advantages/disadvantage 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%[63,71,74,81] with lung involvement present in about the 50% of cases[82] and with a redo surgery rate of about 50%[74].

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 the 49% and the 76.3%[63,70,79].

In 26 patients with recurrence, Fukada *et al*[70] reported 5-year OS of the 76.9%, while Menna *et al*[83] did not reported survival difference comparing patients who underwent single or repeated lung metastasectomy. Ogata reported a significantly better survival in patients who underwent repeated resection in case of single metastases without extrathoracic disease[81], but also CEA level, number of pulmonary metastases, mediastinal lymph node metastasis, and DFI seems to be related with survival after repeat pulmonary metastasectomy[81,84-86].

However, the excellent survival outcome might be linked to a 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 trial and limited data availability does not permit to draw any definitive conclusions. Chemotherapy, including timing and drug regimen, should be evaluated on a case-by-case basis by the multidisciplinary team considering tumor and patient characteristics.

The best long-term results may be expected when integrating loco regional with systemic treatment. Despite evidences are 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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PRIMARY SOURCES

1	Matthieu Zellweger, Etienne Abdelnour-Berchtold, Thorsten Krueger, Hans-Beat Ris, Jean Yannis Perentes, Michel Gonzalez. "Surgical treatment of pulmonary metastasis in colorectal cancer patients: Current practice and results", Critical Reviews in Oncology/Hematology, 2018 Crossref	107 words — 2%
2	J. Kobiela, P. Spychalski, G. Marvaso, D. Ciardo et al. "Ablative stereotactic radiotherapy for oligometastatic colorectal cancer: Systematic review", Critical Reviews in Oncology/Hematology, 2018 Crossref	80 words — 1%
3	CN Parnaby. "Pulmonary staging in colorectal cancer: a review", Colorectal Disease, 03/2011 Crossref	62 words — 1%
4	www.siftdesk.org Internet	62 words — 1%
5	Andrea R. Filippi, Serena Badellino, Alessia Guarneri, Mario Levis et al. "Outcomes of Single Fraction Stereotactic Ablative Radiotherapy for Lung Metastases", Technology in Cancer Research & Treatment, 2014 Crossref	59 words — 1%
6	P. Jess, M. Seiersen, H. Ovesen, H. Sandstrøm, N. Maltbæk, A.A. Buhl, O. Roikjær. "Has PET/CT a role in	43 words — 1%

the characterization of indeterminate lung lesions on staging CT in colorectal cancer? A prospective study", European Journal of Surgical Oncology (EJSO), 2014
Crossref

7	academic.oup.com Internet	41 words —	1%
8	A. Brent, R. Talbot, J. Coyne, G. Nash. "Should indeterminate lung lesions reported on staging CT scans influence the management of patients with colorectal cancer?", Colorectal Disease, 2007 Crossref	37 words —	1%
9	Sulaiman Nanji, Safiya Karim, Ephraim Tang, Kelly Brennan, Anna McGuire, C.S. Pramesh, Christopher M. Booth. "Pulmonary Metastasectomy for Colorectal Cancer: Predictors of Survival in Routine Surgical Practice", The Annals of Thoracic Surgery, 2018 Crossref	32 words —	1%
10	Cecilia Menna, Giammauro Berardi, Simone Maria Tierno, Claudio Andreetti et al. "Does Repeated Surgery For Recurrent Colo-Rectal Lung Metastases Results In Improved Survival?", The Annals of Thoracic Surgery, 2018 Crossref	31 words —	1%
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14 Marcello Migliore, Semih Halezeroglu, Michael R Mueller. "Making precision surgical strategies a reality: are we ready for a paradigm shift in thoracic surgical oncology?", Future Oncology, 2020
Crossref
24 words — < 1%

15 Ciro Franzese, Tiziana Comito, Davide Franceschini, Mauro Loi et al. "Recursive partitioning model-based analysis for survival of colorectal cancer patients with lung and liver oligometastases treated with stereotactic body radiation therapy", Journal of Cancer Research and Clinical Oncology, 2020
Crossref
23 words — < 1%

16 C. Alberto, R. Snchez, F. Piniella, D. Pescador, G. Borobio, A. Garca, C. Cano. "Chapter 9 Management of Non-Hepatic Metastatic Disease in Colorectal Cancer", IntechOpen, 2014
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17 f1000.com
Internet
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18 www.researchsquare.com
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18 words — < 1%

19 Meng, Di, Linhai Fu, Luming Wang, Yining Dai, Wang Lv, Jieping Zhang, and Jian Hu. "Video-assisted thoracoscopic surgery versus open thoracotomy in pulmonary metastasectomy: a meta-analysis of observational studies", Interactive Cardiovascular and Thoracic Surgery, 2016.
Crossref
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21 www.nature.com

Internet

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22 Yuting Li, You Qin. "Peri-operative chemotherapy for resectable colorectal lung metastasis: a systematic review and meta-analysis", Journal of Cancer Research and Clinical Oncology, 2020
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23 K.L. Nash, J.D. Collier, J. French, D. McKeon, A.E.S. Gimson, N.V. Jamieson, J. Wallwork, D. Bilton, G.J.M. Alexander. "Cystic Fibrosis Liver Disease: To Transplant or Not to Transplant?", American Journal of Transplantation, 2007
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26 Nozawa, Hiroaki. "Synchronous and metachronous lung metastases in patients with colorectal cancer: A 20-year monocentric experience", Experimental and Therapeutic Medicine, 2011.
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27 ecancer.org
Internet

9 words — < 1%

28 Lin, J.C.. "Diagnostic and therapeutic video-assisted thoracic surgery resection of pulmonary metastases", Surgery, 199910
Crossref

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29	Michel Gonzalez, Matthieu Zellweger, Marco Nardini, Marcello Migliore. "Precision surgery in lung metastasectomy", Future Oncology, 2019 Crossref	8 words — < 1%
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31	dica.nl Internet	8 words — < 1%
32	www.jove.com Internet	8 words — < 1%
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