



Pulmonary metastasectomy in colorectal carcinoma

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Abstract: Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths worldwide. It is estimated that 50% of all patients with CRC develop metastases, most commonly in the liver and the lung. Lung metastases are seen in approximately 10–15% of all patients with CRC. A large number of these patients with metastatic CRC can only receive palliative treatment due to invasion of other organs and disseminated disease. However, a subset of these patients present with potentially resectable metastases. Pulmonary metastasectomy is considered to be a potentially curative treatment for selected patients with resectable metastatic CRC. Current data suggest that patients that undergo pulmonary metastasectomy have 5-year survival rates of approximately 40%. However, the majority of data published regarding lung metastasectomy is based on small, retrospective case series. Due to this lack of prospective data, it is still unclear which subset of patients will benefit most from curative-intent surgery. Furthermore, there is also controversy regarding which prognostic and genetic factors are related to survival outcomes and whether there is a difference between open and thoracoscopic approaches in terms of overall and disease-free survival. In this review, we aim to summarize the latest data on prognostic factors and survival outcomes after pulmonary metastasectomy in patients with metastatic CRC.

Keywords: Colorectal cancer; metastasectomy; lung; surgical outcomes

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Introduction

Colorectal carcinoma (CRC) is one of the leading causes of cancer-related deaths in Europe and in the United States (1,2). It is estimated that a quarter of all patients with CRC are diagnosed in an advanced stage with either regional or distant metastases. Furthermore, approximately 50% of all patients will develop metastatic disease, with the liver and the lung being the most common sites of metastases for CRC (3,4). Around 10–15% of all CRC patients develop pulmonary metastases (5). Left untreated, metastatic CRC has a very poor prognosis with reported 5-year survival

rates of less than 5% (6). A large number of patients with pulmonary metastases receive palliative treatment, often with chemotherapy, due to frequent invasion of other organs and the presence of disseminated disease (7). However, a subset of CRC patients with pulmonary metastases present with potentially resectable pulmonary metastases. In this patient group, curative resection of lung metastases can lead to long-term survival (8-11). In 1997, the publication of the International Registry of Lung Metastases reported that lung metastasectomy is a safe and potentially curative procedure, leading to a significant increase in pulmonary metastasectomy procedures being performed worldwide (12).

Several case series in the following years have substantiated this and reported excellent 5-year survival rates, with some studies reporting rates up to 68% at 5 years (6,13-15). Due to these promising results, pulmonary metastasectomy is nowadays considered an established treatment option for metastatic CRC (8,9). However, a number of strict selection criteria should be met before patients are referred for surgery: all pulmonary metastases must be resectable technically; the patient must be able to tolerate pulmonary resection; the primary CRC site must be controlled; no extra-thoracic lesions may be detectable on imaging (except for possible resectable liver metastases) (16).

Despite being an established treatment option, the majority of studies that have been published in support of metastasectomy for CRC lung metastases are from single institutions with relatively small sample sizes. Furthermore, these studies often based on data acquired over prolonged study intervals where information bias can be introduced due to changes in clinical practice and staging patterns (17). Although the majority of reported results are promising, it is still not clear why metastasectomy would be beneficial against haematogenous metastatic disease or which patients will benefit most from curative-intent surgery (13,18). The lack of clear evidence regarding this matter is mainly due to the varying disease course of CRC with pulmonary metastases. Currently, there is no data on whether there is a difference in overall survival between patients presenting with lung metastases synchronous with the CRC, with lung metastases after treatment for CRC, with synchronous liver and lung metastases, or with recurrent lung metastases (19,20). In this study, we aim to summarize the latest and most important data on pulmonary metastasectomy in CRC.

Prognostic factors

Earlier studies have found a number of different prognostic factors related to poor survival rates, including the presence of multiple metastatic nodules, metastatic nodule size, elevated carcinoembryonic antigen (CEA) levels, and short progression-free intervals between primary tumour resection and pulmonary metastasis occurrence (17,21). Several other prognostic factors have been proposed as well; however, a number of these are controversial and still under debate. In a study by Kim *et al.*, survival rates of CRC patients with a history of lung metastasectomy and liver metastasectomy were compared to patients with a history of lung metastasectomy alone. The authors reported no difference in 5-year overall survival (OS) rates between

the two groups (22). Similar results were found in a study by Mineo *et al.* regarding long-term results after resection of simultaneous and sequential lung and liver metastases from CRC. In their series of 29 patients, simultaneous or sequential lung and liver metastasectomy was deemed feasible with acceptable treatment outcomes. Furthermore, reported median survival from the second metastasectomy was 41 months with a 5-year OS rate of 51.3% (23). Conversely, several other studies have shown that a previous history of liver metastasectomy was associated with poor survival in patients undergoing pulmonary metastasectomy. In a retrospective study by Landes *et al.*, patients with lung metastases and an earlier history of hepatic metastases had higher risks of tumour recurrence and decreased survival compared to patients without previous liver metastases (24). Similar results were found by Ampollini *et al.* in their retrospective study of 54 patients which showed that patients with extra-pulmonary metastases had significantly worse 10-year survival rates compared to patients with pulmonary metastases alone (0% *vs.* 55%, respectively) (21).

In a recent, relatively large retrospective study of 420 patients, Nanji *et al.* analysed a number of possible predictors of survival after pulmonary metastasectomy for CRC. The authors found that, in addition to greater number of metastases and a size of the largest pulmonary metastasis exceeding 2 cm, intrathoracic lymph node involvement was a negative predictor of outcome in their patient population. Compared to patients with a negative lymph node status, patients with positive lymph node status had significantly worse 5-year OS (47% *vs.* 19%, respectively; $P < 0.001$) and CSS (49% *vs.* 19%, respectively; $P = 0.001$). In addition, the authors further stratified the patients with positive lymph node disease by anatomic location of nodal metastases. In patients with regional (hilar and intra-pulmonary) lymph node involvement, 5-year CSS and OS both were 24%. In contrast, no patients with mediastinal (paratracheal and subcarinal) lymph node disease survived to 5 years (17). Several studies have corroborated the association of lymph node involvement with considerably worse outcomes (25-28). Despite this widespread understanding, systematic lymph node sampling is not normally performed in CRC patients with pulmonary metastases. Furthermore, it is not known whether thoracic lymph node dissection has any therapeutic benefit or whether it only provides prognostic information (17). In a study by Pages *et al.*, absence of mediastinal lymph node dissection was predictive of recurrent pulmonary disease (29). Conversely, Hamaji and colleagues showed that systematic mediastinal lymph node

dissection was not associated with improved survival rates in patients with positive lymph node status, thus concluding that lymph node sampling has no therapeutic advantage (26). Due to these inconsistencies, there is no consensus at the moment regarding systematic lymph node sampling in CRC patients, which has resulted in a wide range of different practice patterns (30).

Regarding the location of the primary tumour, evidence suggests that rectal cancers have poorer DFS rates and higher risks of developing lung metastases compared to colon cancers (22,31). In a study by Cho *et al.*, outcomes after pulmonary metastasectomy were analysed in 346 patients with colon cancer and 280 patients with rectal cancer. The reported 5-year DFS was poorer in the rectal cancer group compared to the colon cancer group (60.1% compared to 67.2%) (32). Similar results were found by Kim *et al.* in their retrospective study of 129 patients (38 patients with colon cancer and 91 patients with rectum cancer). Their data revealed a large difference in 3-year DFS after pulmonary metastasectomy between patients with rectal cancer (42.6%) and colon cancer (72.5%) (22). Reasons for the differences in metastatic patterns between colon and rectal cancers are likely multifactorial. Factors such as the vascular anatomy surrounding the tumour and the histological subtype have been proposed by several authors (33,34). However, despite these differences in metastatic spread, no difference in OS rates have been found between colon and rectal cancers in these studies.

Genetic mutations in metastatic CRC

In recent years, developments in the field of oncogenetics have resulted in the identification of several genetic mutations associated with colorectal carcinogenesis and prognosis. The BRAF gene encodes the B-Raf protein, a member of the Raf kinase family of growth signal transduction protein kinases that plays a role in regulating the MAP kinase/ERKs signalling pathway. This pathway transduces growth signals from the cell surface to the nucleus (35). Mutations in the BRAF gene occur in approximately 8–12% of all CRC cases and have been associated with a number of clinicopathological features such as sex, tumour location, and clinical stage. Furthermore, it is known that BRAF mutation status are important mediators in the epidermal growth factor receptor (EGFR) signalling pathway inhibitors (36,37). In a meta-analysis by Li *et al.*, patients with a BRAF mutation were shown to have a 5.8-fold increase in female

gender, poor differentiation, more advanced histological stages, proximal tumour site, and size >5 cm compared to patients with no BRAF mutations (38). However, there are conflicting reports regarding the correlation between BRAF mutations and clinical stage in patients with CRC (39,40).

Another genetic mutation which is known to play a role in colorectal carcinogenesis is the RAS mutation (41). The RAS protein, similar to the B-Raf protein, is a crucial factor in regulating intracellular signalling networks and activates several pathways such as the MAP kinase cascade. Activating mutations in the RAS gene cause an amplification of expression and activity (42). The KRAS and NRAS mutations are the most important mutations in the RAS family (43). KRAS mutations occur in approximately 40% of all metastatic CRC cases, especially in exon 2, codons 12 (70–80%) and 13 (15–20%) (44–46). NRAS mutations are less common and occur in approximately 3–5% of all CRC patients, with the most common mutations being in exons 2, 3 and 4 of the NRAS gene (47). There are data that suggest that these RAS-mutant CRCs are also correlated with the occurrence of pulmonary metastases, possibly explaining why data from studies regarding CRC with pulmonary metastases occasionally have greater proportions of RAS mutations (48). Furthermore, it is suggested that these RAS mutations are associated with poorer OS and DFS rates in patients with metastatic CRC (49–52). In a large population-based analysis from the ‘Surveillance, Epidemiology, and End Results’ (SEER) registries, KRAS mutations were associated with an increased risk of death in patients with CRC (53). Despite all of the data exploring the impact of genetic mutations on CRC, the exact role of RAS mutations after pulmonary metastasectomy has not been elucidated. The limited data that is published so far is mostly based on demonstrating the role of KRAS mutations in predicting death after lung metastasectomy. The role of RAS family mutations, however, have not been evaluated comprehensively. In a recent retrospective study by Corsini *et al.*, 130 patients who underwent pulmonary metastasectomy were analysed for mutational status in order to identify predictors of OS and DFS. The authors found that RAS mutations were present in 82 patients (63.1%), with multivariable analysis showing that RAS mutations were significantly associated with poorer rates of OS ($P=0.006$) and DFS ($P=0.001$). The authors concluded that RAS mutations play an important prognostic role in determining survival and disease recurrence in CRC patients after pulmonary metastasectomy (54). These findings are consistent with results found in studies regarding the

prognostic significance of these mutations in primary CRC and CRC with hepatic metastases. Data from these studies have shown poorer OS and DFS for CRC patients with KRAS mutations, both with and without metastatic disease (55,56). Treatment modalities directed at mutant CRC are currently still limited, as therapies with anti-EGFR receptor antibodies are usually aimed at patients with KRAS wild-type disease. However, there is some evidence to suggest that these treatments also have therapeutic anti-tumoural activity in KRAS-mutant CRC (57,58).

Discussion

Although a large number of studies have been published regarding the outcomes of pulmonary metastasectomy in CRC patients, only a small proportion of these data are based on prospective and randomised data. In a meta-analysis of 25 studies by Gonzalez, a total of 2,925 patients were included for further analysis. The authors found that survival rates after complete resection of lung metastases ranged between 27–68% with median survival ranging between 18.5–72 months. Median disease-free interval ranged from 19–39 months in this study (59). In another meta-analysis by Zabaleta *et al.*, data on 3,501 CRC patients from 17 studies were analysed for survival after pulmonary metastasectomy. Their results showed that the overall median survival from lung metastasectomy was 64 months with 3- and 5-year survival rates of 68.6% and 51.9%, respectively (60). Both meta-analyses were based on retrospective case series and did not include any prospective studies. There have been two other meta-analyses that have included randomised trials comparing more with less intensive follow-up strategies after surgical treatment for early CRC. The results from these trials showed that intensive surveillance was associated with earlier detection of metastases. However, early detection and treatment of metastatic CRC did not result in an overall survival benefit (61,62).

In the recently published multicentre randomised ‘Pulmonary Metastasectomy versus Continued Active Monitoring in Colorectal Cancer’ (PulMiCC) trial, the effectiveness of lung metastasectomy was investigated prospectively. Between 2010 and 2016, patients with potentially resectable lung metastases were recruited and assigned to active monitoring with or without metastasectomy. Due to poor accrual, the study was stopped earlier, with only 65 patients included for randomisation. Nevertheless, data analysis was performed which showed an estimated 5-year survival of 38% in the metastasectomy

arm compared to 29% in the well-matched controls. The authors concluded that the survival of patients undergoing pulmonary metastasectomy was similar to the results of earlier observational studies. However, despite the small number of patients, their data suggested that survival rates of the control patients is better than previously reported by other studies (63). Recently, an updated analysis of the PulMiCC trial was published which included an additional 28 patients to reach a total of 93 patients. The median survival after metastasectomy was 3.5 years compared to 3.8 years for the matched controls. The overall median 5-year survival rates were 29.6% for the control arm and 36.4% for the metastasectomy arm. The authors concluded that their results undermined the ‘close to zero’ assumption regarding the survival of CRC patients that do not undergo lung metastasectomy (64). Although these results provide interesting new insights for the treatment of metastatic CRC, clinicians should be careful with adapting treatment guidelines without further evidence from larger, well-powered trials.

Another controversial topic regarding pulmonary metastasectomy is whether video-assisted thoracoscopic surgery (VATS) achieves similar survival outcomes compared to open thoracotomy. It is generally assumed that a thorough lung palpation is necessary to for complete nodule resection as small, non-imaged lung nodules can be missed during VATS (65,66). Althagafi *et al.* reported that non-imaged lung metastases were detected during 36% of pulmonary metastasectomies (67). However, there is a lack of prospective data comparing these two approaches in terms of survival rates and the results from studies are sometimes contradictory. Nevertheless, the majority of recent publications have shown that VATS results in similar OS and DFS compared to open thoracotomy (68-70). In addition to these outcomes, VATS results in less postoperative pain and faster recovery compared with open surgery (71). Furthermore, because of the reduced rate of postoperative intrathoracic adhesions, some authors have suggested that VATS is more suitable for treating pulmonary metastases that may require repeated resections for recurrent disease (71-73). However, (conversion to) open thoracotomy can be necessary when lesions identified on imaging are not found or when surgical margins are compromised due to technical problems during VATS (74).

Future developments in minimally invasive approaches such as robotic-assisted thoracoscopic surgery (RATS) and systemic treatments will very likely change the landscape and treatment guidelines for patients with metastatic CRC.

Treatments such as anti-vascular endothelial growth factor (VEGF) and anti-EGFR molecules, or with programmed cell death (PD) protein 1 immune checkpoint inhibitors have already been integrated in the latest treatment protocols for metastatic CRC (75). New treatments such as oncolytic reovirus, which can be used as an immune stimulant due to its immunomodulatory properties that span the genomic, protein, and immune cell distribution levels, provide promising opportunities for treating metastatic CRC in the near future (76). Experimental surgical techniques such as isolated lung perfusion with melphalan and gemcitabine have also shown promising results for unresectable metastatic CRC in animal and phase I studies (77-83). However, pulmonary metastasectomy still plays a vital role for treating selected patients with CRC and pulmonary metastases. Large, prospective trials are necessary to clarify which patients will benefit most from lung metastasectomy and to determine what these survival outcomes are.

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