



Lung metastases from colorectal cancer: a multidisciplinary approach and role of local treatment: a narrative review

Ka Lun Mak, Michael Kuan Yew Hsin

Department of Cardiothoracic Surgery, Queen Mary Hospital, Hong Kong, China

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Correspondence to: Ka Lun Mak. Department of Cardiothoracic Surgery, Queen Mary Hospital, Hong Kong, China. Email: klmakmak1020@gmail.com.

Objective: To review current available options of local treatment for colorectal lung metastases.

Background: Colorectal cancer is one of the leading malignancies worldwide. Despite advances in screening policy and early surgical treatment, a significant number of patients are suffering from colorectal metastatic disease, including the lung. Local treatment for pulmonary metastatic colorectal cancer has made significant progress in the last few decades. Survival benefit and procedure related morbidity are widely studied.

Methods: PubMed database is searched for articles related to local treatment of colorectal lung metastases including pulmonary metastasectomy, radiofrequency ablation, radiotherapy, isolated lung perfusion.

Conclusion: Local treatment for colorectal lung metastases is widely prescribed for purported survival benefit, although evidence is based on retrospective studies only. With advances in technique and technology, approaches such as minimally invasive thoracoscopic surgery and percutaneous radiofrequency ablation can minimize trauma and procedure related morbidity. New modalities of radiotherapy like stereotactic body radiation therapy (SBRT) can reduce radiation related toxicity to surrounding structures. Isolated lung perfusion can maximize the dose of chemotherapeutic agents that can be safely delivered to the lung parenchyma; however, this is at the expense of significant associated morbidity. The role of local treatment to colorectal lung metastases needs further randomized controlled trials to define the survival benefit. Multidisciplinary meetings, involving oncologists, thoracic surgeons and interventional radiologists, are advisable before offering local treatment to patients with colorectal lung metastases.

Keywords: Local treatment; colorectal lung metastases; multidisciplinary approach

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Introduction

Colorectal cancer is a common malignancy causing morbidity and mortality. Despite advances in screening and early surgical treatment of colorectal primary tumor, metastases to different organs, including the liver and lung, is still prevalent. Treatment options for colorectal lung metastases, including systemic chemotherapy, targeted therapy, radiotherapy, surgical resection of lung metastases, tumor ablation, have been studied widely in

the hope of improving patient survival. This review article will focus on local treatment of colorectal lung metastases. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://asj.amegroups.com/article/view/10.21037/asj-21-59/rc>).

Methods

A review of literature was performed in PubMed database with key word “colorectal lung metastases”, “pulmonary

metastasectomy”, “radiotherapy”, “radiofrequency ablation” and “isolated lung perfusion” is performed. Meta-analysis, randomized controlled trial, retrospective studies, case reports related to outcome of local treatment of colorectal pulmonary metastases are included for review. Non-English written articles and review articles are excluded.

Discussion

Pulmonary metastasectomy

Surgical resection of colorectal lung metastases is a frequently performed procedure around the world. According to the different national registry data and retrospective studies, 5-year overall survival of pulmonary metastasectomy for colorectal cancer is around 40% to 70% (1-10). The evidence supporting pulmonary metastasectomy for survival is largely based on retrospective studies and registry data, which are inevitably limited by selection bias. The patient demographics and treatment protocols are heterogenous from study to study. According to the International Registry of Lung Metastases in 1997, the 5-year survival of patients with colorectal lung metastases without resection was around 10% despite systemic treatment (11). With recent advances of chemotherapy regimen and targeted therapy, patients with systemic treatment are having better survival and quality of life. In the year 2020, Treasure analyzed the data from the incomplete randomized controlled trial Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) and showed that in patients with pulmonary metastases who did not undergo resection received systemic treatment, a 5-year survival of 29% was achieved. For patients with pulmonary metastasectomy performed, 5-year survival is 38% but the sample size is too small to draw conclusion (12,13). Although the study was terminated because of poor patient recruitment, this is the most contemporary outcome data on patient with colorectal lung metastases. There are prospective study and national registry data suggesting that pulmonary metastasectomy confers no benefit in survival and patient reported quality of life (14-16). Survival benefits of pulmonary metastasectomy for colorectal lung metastases should be further studied in randomized controlled trials with adequate power.

Indication and patient selection of pulmonary metastasectomy

Lung metastases are usually indolent and asymptomatic. The goal of pulmonary metastasectomy is to improve patient

survival. It is paramount to balance the risks and benefits of pulmonary metastasectomy, and judicious patient selection can improve the outcome of pulmonary metastasectomy. According to the International Registry of Lung Metastasis (11), factors to consider when offering pulmonary metastasectomy should include tumor resectability, operability of the patient with particular attention to the lung function, whether control of the primary tumor has been achieved, the lack of alternative treatment and the absence of synchronous extra-thoracic disease.

In our center, all patients referred to us for pulmonary metastasectomy are properly worked up with positron emission tomography-computerized tomography (PET-CT) scan and pulmonary function test. Patients’ performance status and co-morbidities are assessed by thoracic surgeon. These patients are discussed in multidisciplinary meeting with oncologist case by case. Pulmonary metastasectomy will be considered in patients with no extra-thoracic metastases, good performance status, pulmonary metastases which can be resected completely, predictive postoperative forced expiratory volume and diffusing capacity of carbon monoxide greater than 40%.

Retrospective studies and case series have been performed to identify factors associated with better survival following pulmonary metastasectomy. A longer disease free interval (17-19), a lower carcinoembryonic antigen (CEA) level before pulmonary metastasectomy (20,21), a smaller number of pulmonary metastases (18,22,23) are features that have been associated with better survival after pulmonary metastasectomy identified in retrospective studies. A meta-analysis of retrospective studies was performed in 2012 and showed that a disease-free interval of less than 36 months, a pre-thoracotomy CEA level greater than 5 ng/mL, and more than one metastatic lesion, are factors associated with worse survival in pulmonary metastasectomy. A prognostic model was designed to assess the risk of pulmonary metastasectomy. If a patient exhibited all 3 risk factors, the 5-year survival was 26.8% while it increased to 68.2% in a patient with zero or only one risk factor ($P<0.001$) (24).

Circulating tumor cells (CTCs) have been well studied as biomarkers for prognosis of patients with colorectal cancers. In a retrospective study performed in Germany, if patients had circulating tumor cells in the pulmonary vein detected during pulmonary metastasectomy, this was associated with increased thoracic lymph node metastases (25). Another retrospective study performed in Japan showed that the presence of circulating tumor cells in peripheral blood during metastasectomy was associated with worse

overall and disease-free survival (26). Both studies are retrospective studies and the role of circulating tumor cells in the decision making for pulmonary metastasectomy is still under investigation.

Primary tumor location has been investigated as a prognostic marker for pulmonary metastasectomy. According to a retrospective study performed by MD Anderson Pulmonary Metastasectomy Study Group, patients with left colon cancer were associated with better overall survival after pulmonary metastasectomy when compared with patients with right colon cancer and rectal cancer (27). Another retrospective study performed in Germany also showed similar findings (28).

However, there is significant heterogeneity among these studies in terms of patient demographics, follow up protocol and adjuvant chemotherapy protocol, and extrapolation from these studies needs to be done with caution.

A prior history of colorectal liver metastases was associated with worse prognosis in patients with pulmonary metastasectomy performed as reported in meta-analysis and retrospective studies (29-32). Nevertheless, for patients with previous colorectal liver metastases, pulmonary metastasectomy was associated with better survival in selected patients with long disease-free interval, normal carcinoembryonic antigen level, fewer tumor nodules and absence of mediastinal lymph node involvement (33-47).

The molecular status of colorectal lung metastases also has been studied in relation to survival after pulmonary metastasectomy. Survival in patients after pulmonary metastasectomy for colorectal lung metastases with tumors harboring RAS, BRAF and TP53 mutations were found to be worse than patients with wild type of RAS, BRAF and TP53 gene (48-50). On the other hand, APC gene and low expression of RNA-binding motif protein 3 expression were associated with better survival after pulmonary metastasectomy (51). Tumor biology appears to play a significant role in the survival of colorectal cancer (CRC) patients with metastatic disease.

In selected patients who developed pulmonary recurrence after pulmonary metastasectomy, repeated pulmonary metastasectomy may have survival benefit (52-55). Advanced age, male sex, increasing size and number of pulmonary metastatic nodules, high pre-thoracotomy carcinoembryonic antigen level, mediastinal lymph node involvement, high grade primary tumor, previous liver metastases were factors associated with worse survival (56-61). Careful patient selection is appropriate before offering repeated pulmonary metastasectomy to patients

with pulmonary recurrence.

Chemotherapy in patient with pulmonary metastasectomy

With advances in systemic chemotherapy, aggressive multimodality treatment for colorectal lung metastases has been the focus of study in retrospective series (62). Aggressive multimodality treatment includes systemic chemotherapy, radical resection of primary colorectal cancer, and hepatic and pulmonary metastasectomy. In selected patients, aggressive multimodality treatment was associated with improved survival when compared with patients without perioperative chemotherapy. The reduction in mortality risk was greatest in patients receiving colorectal radical resection, chemotherapy and liver/lung resection (63).

The impact of chemotherapy, whether it is given before and after pulmonary metastasectomy, has been reported in different retrospective studies, and both strategies have been associated with improved disease-free survival by 6 to 20 months in the chemotherapy group (64-66). But in 2019, there is a retrospective study with propensity score matching performed by Imanishi *et al.* suggesting that adjuvant chemotherapy after curative resection of lung limited metastases showed no survival benefit. Further randomized controlled trial is needed to define the survival benefit from adjuvant chemotherapy.

Amongst the chemotherapeutic agents for preoperative chemotherapy, oxaliplatin-based therapy was associated with improved OS when compared with irinotecan, capecitabine, or alternate regimen (67). No comparative study has been reported to study the timing of chemotherapy relative to pulmonary metastasectomy.

Patients who were most likely to benefit most from systemic chemotherapy were those with high value of pre-operative CEA, hypermetabolism on the PET CT scan, previous extra-thoracic resected metastasis, and short (<12 months) DFI, all of which were features associated with increased risks of disease recurrence (68).

Further prospective studies are needed to study the survival benefit and timing of systemic chemotherapy in selected patient undergoing pulmonary metastasectomy (53).

Approaches to pulmonary metastasectomy (thoracotomy or video assisted thoracoscopic surgery or trans-diaphragmatic approaches)

Video-assisted thoracoscopic surgery, thoracotomy and

median sternotomy are commonly performed surgical approaches for pulmonary metastasectomy. The best approach for pulmonary metastasectomy remains controversial. Both retrospective and prospective studies suggested thoracotomy had advantages over video assisted thoracoscopic surgery because non-imaged tumor nodules could be detected by bimanual palpation during thoracotomy (69-71). With advances in the technology of computed tomography and improved imaging, recent large retrospective comparative studies and meta-analysis of observational studies showed clinical outcome of video assisted thoracoscopic surgery was comparable to thoracotomy. There was no difference in ipsilateral recurrence and disease-free survival. Overall survival was better in patients who underwent VATS approach (72-77). There is no randomized controlled trial to compare the oncological outcome between VATS and thoracotomy approach.

In highly selected groups of patients, transdiaphragmatic approach has been reported where pulmonary metastasectomy was performed in the same setting as the resection of the colorectal primary or hepatic metastasis. This has the advantage of avoiding a separate operation requiring general anesthesia. However, in the published reports, the number of patients who received this approach was small and no comparative study was performed to establish the clinical or oncological benefit of this approach (78-80).

Extent of resection (anatomical resection or not)

Sub-lobar resection for colorectal lung metastases should be performed in a manner which can preserve as much respiratory function as possible while adhering to the principle of resection which is to obtain a clear margin. Retrospective studies showed that higher local recurrence occurred in patients where the resection margin was involved (81). According to Welter *et al.*, 7 mm margin is needed to remove satellite tumor cells and floating cancer cell clusters around the pulmonary metastases (82). Wedge resection, segmentectomy and lobectomy have been reported in the literature for pulmonary metastasectomy (83,84). Pneumonectomy for colorectal lung metastases with survival in terms of years has been reported also (85,86) but it is considered too aggressive for patients with systemic metastatic disease and this is not recommended by the European Society of Thoracic Surgeons (87). In our center, wedge resection with margin greater than 1cm is performed for pulmonary metastasectomy if possible. Lobectomy will be performed if wedge resection cannot provide adequate

margin. Patients are counselled during consent process that there is a possibility of primary lung cancer. Completion lobectomy is performed if histology showed primary lung cancer instead of colorectal pulmonary metastases.

Wedge resection of colorectal lung metastases can be performed with surgical staplers, laser resection or the cut-and-sew technique. The result of pulmonary metastasectomy with laser is a relatively new technique with encouraging results according to retrospective comparative studies. In patients who underwent laser assisted surgery for metastasectomy, there was an association with improved survival, while the rates of complications including atrial fibrillation, pneumonia, prolonged chest tube placement and empyema were not increased compared to patients who underwent non-laser resection. Laser assisted surgery can minimize tissue damage and preserve respiratory function according to an animal study (88), and complete resection of all the pulmonary metastases was possible in a retrospective clinical series in patients who had adequate lung function (89).

A retrospective study showed that patients who had segmentectomy for pulmonary metastases harboring RAS mutation had a better overall survival and longer time to pulmonary recurrence when compared with patients undergoing wedge resection. But in patients with wild type RAS, the overall survival and time to pulmonary recurrence between segmentectomy group and wedge resection group was similar (90). Genetic analysis showed that pulmonary metastases and colorectal primary usually shared the same genetic RAS mutation and pulmonary metastases was common in patient with RAS mutation (91). Anatomical resection for pulmonary metastasectomy should be considered if the primary tumor harbored the RAS mutation. Tissue diagnosis before pulmonary metastasectomy for genetic status is not needed since high concordance between colorectal primary and colorectal pulmonary metastases.

The role of mediastinal lymph node sampling

Mediastinal lymph node involvement of colorectal cancer was associated with worse survival when compared with patients who did not (92-94). Although mediastinal lymph node dissection could not improve the survival of patients with mediastinal lymph node metastases from colorectal cancer (95), mediastinal lymph node sampling or dissection during pulmonary metastasectomy could provide important prognostic information. The sensitivity of positron emission tomography detecting mediastinal lymph node metastases

was only 35% (95). The location of lymph node involvement, be it hilar or mediastinal, did not affect survival (96).

The European Society of Thoracic Surgeons advocates systematic lymph node sampling or dissection during pulmonary metastasectomy with curative intent (87).

Ablation of pulmonary metastases

Since the application of radiofrequency ablation in the treatment of primary lung cancer in 2000, ablative therapy of colorectal lung metastases has been studied also. A large case series in Japan showed the 5-year survival of patients treated with percutaneous radiofrequency ablation of colorectal lung metastases was similar to pulmonary metastasectomy (97). Also, radiofrequency ablation is technically less demanding, and can be performed regardless of whether there has been any previous thoracic surgery procedures, is associated with less pain and does not require a general anesthesia. However radiofrequency ablation may cause complications including pneumothorax (98), pleural effusion, abscess (99), bronchopleural fistula and injury to nerves (100).

Radiofrequency ablation of colorectal lung metastases is limited by the size of the tumor. The risk of local recurrence increases with the size of the lung metastases (97). No randomized controlled trial has been performed to compare surgery and radiofrequency ablation. Currently, radiofrequency ablation of colorectal lung metastases is reserved for patients with high general anesthetic risks who are not fit for operation.

Stereotactic body radiotherapy to pulmonary metastases

Stereotactic body radiotherapy (SBRT) is emerging as an alternative modality of local control therapy for colorectal lung metastases. It is offered to patients with suboptimal lung function or high surgical risks who are not fit for pulmonary metastasectomy. Although colorectal lung metastases are more radio-resistant when compared to lung metastases from other primaries (101), a meta-analysis showed that patients receiving SBRT with escalated doses for colorectal lung metastases had improved local control and overall survival with minimal toxicity (102). The reported rates of grade 3 toxicity is less than 10% and in most series less than 5%; grade 4 or greater toxicity was rare with no cases documented in the reports (103-105).

Retrospective study by Nelson *et al.* showed that 2-year risk of local recurrence after SBRT (29.4%) is higher than

that after wedge resection (14.1%) for colorectal lung metastases (106). But this retrospective study is limited by selection bias and the relationship between local recurrence and survival is not well defined. Further randomized controlled trial is needed to be performed to establish the relationship between local control and survival.

In vivo isolated lung perfusion

With the experience of isolated limb perfusion for melanoma and soft tissue sarcoma (107), *in vivo* isolated lung perfusion has been developed to deliver higher doses of chemotherapy to pulmonary tissue (108,109). Pulmonary recurrence after pulmonary metastasectomy is common, up to 60% (108) according to retrospective studies. The theory of micro-metastases in pulmonary tissue has been postulated to account for this high recurrence. Isolated lung perfusion theoretically can deliver much higher doses of chemotherapy to the pulmonary tissue, while avoiding the dose limiting toxicity from systemic chemotherapy.

Animal experimental study has shown the safety of isolated lung perfusion (110). Nevertheless, the clinical use of isolated lung perfusion is not yet established, and this is an area which is still under active investigation. The morbidity related to isolated lung perfusion is not insignificant- thoracotomy is required to allow access to control the major pulmonary vessels. The benefit of *in vivo* isolated lung perfusion needs to be established with larger clinical trials.

Summary

Local treatments for colorectal lung metastases are advancing rapidly but the survival benefits from them remain to be determined. Even though local treatments for colorectal lung metastases are mostly safe with the advances in technology, they are not free from procedure related mortality or morbidity. Large randomized controlled trials are needed to guide our future management of colorectal lung metastases.

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