

Pulmonary Metastasectomy for Colorectal Cancer: A Brief Review

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Abstract

The performance of pulmonary metastasectomy is a widely disseminated practice for the treatment of advanced neoplasms with lung metastases. Since 1944, when this type of operation was first described, several reports, case series and cohort studies have been published; however, no randomized clinical trial has been carried out on the subject to date. This makes our current practice controversial in many ways. The objective of this study is to review the medical literature, discuss several aspects of the controversial points and present the current evidence, or lack of it, behind surgical practice in the resection of lung metastases in patients with colorectal adenocarcinoma.

Keywords: Pulmonary Metastasectomy; Colorectal Cancer; Lung metastasectomy

Introduction

Among the surgical procedures for lung cancer treatment, lung metastasectomy is the most often performed in most thoracic surgery departments. According to Treasure, *et al.* 2014, lung metastasectomies represent 15% - 50% of cancer procedures performed in thoracic surgery departments in Europe [1].

Traditionally, pulmonary metastasectomy for the treatment of colorectal carcinoma is the most frequent indication of that surgical procedure; however, this practice is not supported by any randomized clinical trial and, to date, the accumulated knowledge has been obtained from series of cases and cohort studies [1]. Nevertheless, this therapeutic modality is currently considered a potentially curative treatment, capable of prolonging survival in a selected group of patients [2].

Therefore, our aim is to review the literature emphasizing publications in the last three years, and discussing the most controversial topics.

Historical Aspects

In 1944, Blalock published the first successful case of pulmonary metastasis resection. In his article, he reported performing a pneumonectomy for treatment of pulmonary metastases in a patient that had been surgically treated for colon cancer four years before [3]. After this report, other surgeons started to perform pulmonary metastasectomies and between the 50s and 70s, several case series studies appeared, supporting this surgical procedure. At the same time, there were reports of successful cases of resection of liver metastases of colorectal tumors, allowing the increase in knowledge on metastasectomies [4,5].

In 1997, Pastorino, *et al.* published one of the most relevant studies on overall pulmonary metastasectomy. In his study, he assessed 5,206 cases of lung metastasectomies from different primary sites, in 18 thoracic surgery departments in the US, Canada and Europe. Of these procedures, 4,572 (88%) were considered as complete surgical resection.

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On the one hand, the patients submitted to complete pulmonary resection had a median survival of 35 months; on the other hand, who not submitted to complete surgical resection had a median survival of 15 months. Guidelines for the performance of lung metastasectomies as we know today were designed based on this work [6].

The large series and cohort studies, which are currently the highest level of evidence available regarding pulmonary metastasectomies, emerged since then and reinforced the impact on these patients' survival, with relatively low morbidity and mortality rates.

Rodriguez-Fuster, *et al.* assessed 532 patients from 32 centers for cancer treatment, totaling 1,050 resections of pulmonary metastases and the surgical-related mortality rate was < 1% and the morbidity related to treatment was 16% [7].

In 2009 Younes, *et al.* published a study with 529 that were submitted to lung metastases resection from different primary sites. This consists in total of 776 thoracotomies. Median follow-up time across all patients was 21.6 months (range: 0 - 192 months). The postoperative complication rate was 9.3%, and the 30-day mortality rate was 0.2%. The ninety-month overall survival rate for all patients was 30.4% [8].

In 2010 Sardenberg, *et al.* studied 77 patients that were submitted to 122 thoracotomies for 273 metastases resection of soft tissue sarcoma. According to the authors the median follow-up time of all patients was 36.7 months (range: 10 - 138 months). The postoperative complication rate was 9.1%, and the 30-day mortality rate was 0%. The 90-month overall survival rate for all patients was 34.7% [9].

Younes, *et al.* published in 2012 an multivariate analysis of 440 patients submitted to lung metastasectomies from different primary sites. The average follow-up time was 43.2 months (range: 0-192) and the 60-month Overall Survive (OS) was 43.7%. Univariate analysis: patients with adenocarcinoma presented the highest 5-year survival rates (53.4%, $P = 0.0001$); Disease Free Interval (DFI) > 36 months ($P < 0.0001$), number of nodules on CT scan ($P = 0.0052$), number of malignant nodules resected ($P = 0.0252$) and the size of the largest resected nodule ($P < 0.0001$) were also significant. Multivariate analysis: number of malignant nodules resected ($P = 0.01$), size of the largest nodule resected ($P = 0.001$), DFI > 36 months ($P < 0.001$) and histology of the primary tumour ($P = 0.017$) had significant impact on survival [10].

Finally, Younes, *et al.* reported on a series of 120 patients with lung metastases from colorectal carcinoma submitted to metastasectomy [11]. According to the authors, these patients had a median survival of 34.7 months with a median estimated five-year survival of 24.3%, showing that there really is a gain in survival for these patients, considering that survival with exclusive chemotherapy does not exceed a median value of 5% in five years [11].

According to previous information mentioned above in this text, pulmonary metastasis resection in general are feasible and seems to have an impact in OS of these patients.

Selection of candidate patients for pulmonary metastasectomy for treatment of colorectal carcinomas

Currently, to indicate resection of pulmonary metastases in general, we use criteria that have been well established in the literature, based on THE International Registry of Lung Metastasis study [6].

These criteria are:

1. The primary site should be controlled or controllable
2. Absence of other metastatic extrapulmonary lesions
3. No other method of treatment rather than surgery may be available
4. The patient must be in clinical conditions to withstand surgery
5. Complete resection of all metastases must be possible.

Similarly as with the resection of pulmonary metastases, liver metastasectomy also has no randomized clinical trials to support it as the ideal treatment [12,13]. However, this treatment is widely used and supported by cohort studies and has become the treatment of choice recommended by American and British guidelines [14-16].

Given these facts, one can infer that it is possible to operate on patients with synchronous lung and liver metastases, provided that the other premises for metastasectomy indication are respected [16]. The site to be addressed first is the one defined as having a higher chance to become unresectable.

If we have a patient with unilateral pulmonary metastases, is it necessary to explore the two lungs? To answer this question we can remember the article published by Younes, *et al.* in 2002. In this prospective study 267 patients were followed from 1990 to 1997. This includes 179 patients that had initial diagnosis of unilateral lung metastases from different primary sites and 88 patients had bilateral metastases. Ipsilateral thoracotomy was performed on all patients with unilateral disease. Bilateral thoracotomy was performed on all patients with bilateral lung metastases. Median follow-up was 17 months. The two groups of patients with confirmed bilateral metastases (synchronous or metachronous) were compared. Actuarial overall 5-year survival was 34.9%. Contralateral recurrence-free 6-month, 12-month, and 5-year survival were 95%, 89%, and 78%, respectively. Patients who experienced recurrence in the contralateral lung within 3, 6, or 12 months had an overall 5-year survival rate of 24%, 30%, and 37%, respectively. When patients with recurrence in the contralateral lung were compared to patients with bilateral metastases on admission, there was no significant difference in overall survival ($p < 0.05$) [17].

Staging is crucial to identify patients with extrapulmonary and extrahepatic metastases. The use of positron-emission tomography (PET-CT) is recommended. According to Ozis, *et al.* (2014), the use of PET-CT for the staging of colorectal cancer patients provides additional findings, when compared to classical staging techniques using tomography. According to this author, the use of PET-CT changed the staging in 14.4% of patients with colorectal tumors, resulting in treatment changes [18].

Artiko, *et al.* published a prospective study of 75 patients undergoing surgical treatment of primary site colorectal carcinoma and submitted to PET-CT. To detect recurrence, sensitivity was 96.6% and specificity was 82.4%; for detection of disease stage 3 and 4, sensitivity was 94.9% and specificity was 87.5% [19]. According to this information the PET-CT has a great sensitivity and an acceptable specificity to detect local disease recurrence at the primary site and metastatic disease. We use it at daily clinical practice to evaluate patients that are potential surgical candidates in our surgical department.

Surgical Technique

Considering that patients with pulmonary metastatic lesions have the risk of additional lesions arising after metastasis resection and that these patients often require more than one surgical approach, one should always aim at performing such resections while preserving as much healthy lung parenchyma as possible; that is, one should, whenever possible, make “economic resections” (segmentectomy or wedge resection), removing the lesions with disease-free margins [20]. However, when facing central lesions that affect the pulmonary hilum structures, large lesions or multiple lesions in the same lobe or lung, it is often necessary to perform a lobectomy or eventually, a pneumonectomy [6]. The access route can be attained through lateral thoracotomy, median sternotomy previous bi-thoracotomy with transverse sternotomy (clamshell) or video-thoracoscopy [20].

Lateral thoracotomy is the classic access route for this procedure. It allows access to all lobes of the operated lung, as well as allowing the surgeon to perform the complete palpation of the organ to detect any additional lesions that might have been undetected on imaging studies. With the advent of the muscle-sparing thoracotomy in the 90s, it was possible to make this access route less harmful from a functional point of view, reducing lesions in muscles and nerves [21].

The median sternotomy is an access route that results in less damage to the chest wall than the lateral thoracotomy, as there is no need to violate muscles, as well as preventing the pain caused by thoracotomy. This access route allows both lungs to be addressed at the same time; however, this type of incision can hinder the approach of the posterior portions of the lungs [22].

The anterior bi-thoracotomy and transverse sternotomy (clamshell) is an access route that allows full and bilateral access to the pulmonary hila, in addition to allowing access to all regions of both the right and the left lungs. The major disadvantage of this approach is that causes great destruction with functional impairment of the chest wall muscles [23].

In the last decades of the 20th century, video-assisted thoracoscopy surgery (VATS) gained ground and popularity among surgeons worldwide, allowing smaller incisions and, consequently, less postoperative pain [20]. However, it is a consensus that pulmonary metastasectomy is a procedure performed with curative intent and for this to be achieved, it is necessary that all pulmonary lesions be removed. Would it be possible to accomplish that using only video-assisted surgical access? Eckardt, *et al.* (2012) elected 37 patients candidates for metastasectomy. These patients had 55 suspected metastatic lesions seen on CT. Patients were first operated by VATS, with 51 lesions (92%) being identified intraoperatively. After VATS, the same patients underwent thoracotomy during the same surgical procedure, using the same anesthesia, and 29 additional nodules were identified. Of these, six (21%) were metastases, 19 (66%) were benign nodules, 3 (10%) were subpleural lymph nodes and 1 was a second primary lung tumor. Thus, one can conclude that it is technically possible to perform metastasectomies by VATS; however, when this is performed, some lesions might go undetected and a significant percentage of these lesions have neoplastic etiology [24].

However, Migliore, *et al.* recently published a systematic review of the literature on this subject to assess the role of video-assisted surgery compared to conventional open techniques for pulmonary metastasis resection in general. In their results, the authors observed that the choice of access route did not have an impact on patient survival; they also affirm that this subject remains controversial and it is not possible to conclude which access route would be considered the gold standard for this type of surgical procedure [25].

Prognostic factors

When evaluating a patient with lung metastases that is a potential surgical candidate, it is interesting to know the clinical, laboratory and radiological characteristics that are predictive of poor oncologic and postoperative prognosis. This knowledge helps us to determine whether there really is a positive association between risk and benefit, so that the procedure can be indicated for patients that can really benefit from it [20]. For this purpose, some cohort studies have been published in an attempt to provide answers to this question.

In 2014, Vodicka, *et al.* published a retrospective cohort study of 75 patients undergoing pulmonary metastasectomy for the treatment of colorectal carcinoma over a period of 12 years. A total of 95 surgical procedures, with resection of 133 metastases were performed. Approximately 28% of the patients were alive with no signs of disease recurrence five years after the surgical procedure and the five-year survival rate after the procedure was 45%. Patients with two or more metastases had a risk of death 2.7-fold higher; elevated serum CA19-9 and tissue polypeptide-specific antigen (TPS) concentration increased mortality by 3.2- and 5.5-fold, respectively, when compared to patients that did not have these alterations [2].

Matsui, *et al.* published a cohort study of 186 patients submitted to metastasectomy procedures for colorectal cancer, it includes pulmonary metastasectomy (61), liver metastasectomy (100) and hepatic and pulmonary metastasectomies (25). In this study it was observed that the presence of synchronous metastases was a significant prognostic factor and that patient survival was approximately 30% at 5 years, a value below the 60% of patients submitted to pulmonary metastasectomy exclusively or 50% of patients undergoing liver metastasectomy alone. This study also considers rectal carcinoma and multiple liver metastases as poor prognosis factors, with a hazard ratio in the multivariate analysis of 6.99 ($p = 0.02$) for multiple liver metastases and 0.02 ($p = 0.004$) for the primary site in the colon [26].

However, Cho, *et al.* in 2014, published a cohort study with a sample of 698 patients. In their study, no differences in survival were observed regarding primary tumor site location, i.e., patients with rectal tumors had the same survival of patients with colon tumors after completion of pulmonary metastasectomy, being disease-free survival of 67.2% for colon cancer compared with 60.1% for rectal cancer ($p = 0.04$) [27].

Some authors report the size of lung metastases as a prognostic factor for this type of surgical procedure. According to Javed, *et al.* (2014) the presence of higher-volume lung metastases represented a poor prognostic factor. Among the 66 patients who underwent pulmonary metastasectomy between the years 2004 to 2010, it was verified that the patients whose resected lesions were < 20 mm had a median survival of 47 months, whereas the median survival of those with resected lesions > 20 mm was 25 months (p = 0.04) [28].

Another factor that seems to be directly related to these patients' prognosis is the involvement of mediastinal and hilar lymph nodes. Renaud, *et al.* published a review of 320 patients submitted to surgery in 2 centers for the treatment of colorectal cancer between 1992 and 2011. According to this study, patients that had hilar and mediastinal lymph node involvement showed 50% lower survival than patients with disease-free lymph nodes; moreover, the presence of synchronous liver metastases and multiple lung metastases, once again had a negative impact on survival [29]. In another study, the same authors stressed that the presence of lymph node involvement is a poor prognostic factor, in addition to finding a correlation between the presence of liver metastases, elevated pre-operative levels of carcino-embryonic antigen (CEA) and disease-free interval < 24 months with shorter survival [30].

Another retrospective analysis of 120 patients undergoing metastasectomy for treatment of colorectal neoplasia identified, through multivariate analysis, that the presence of unilateral metastases, neoadjuvant chemotherapy to metastasectomy and complete lesion resection were favorable prognostic factors [11]. Subbiah, *et al.* assessed 229 patients with colorectal carcinoma who underwent pulmonary metastasectomy. Of these, 114 were submitted to neoadjuvant chemotherapy. Of these, 32% had received oxaliplatin, 46%, irinotecan, 16% capecitabine and 6% other medications.

In the multivariate analysis, patients that received irinotecan had lower survival than patients submitted to surgical treatment only (hazard ratio = 1.8 p = 0:02), patients undergoing oxaliplatin-based treatment showed no conclusive results when compared to patients who underwent surgery only (hazard ratio = 0:57 p = 0:21), and the same occurred with capecitabine therapy (hazard ratio = 1.45 p = 0.16) [31].

Despite of the controversies involving this practice, the use of induction chemotherapy for patients that are submitted to lung or liver metastasectomy is recommended by the National Comprehensive Cancer Network internacional guidelines for colon and rectal cancer treatment [14-16].

Some studies describes the use of isolated lung perfusion (ILuP) with chemotherapy in patients submitted to lung metastases resection. The first studies were performed using pig model [32,33]. Meanwhile recent study described this kind of therapy in human. In this paper 20 patients with sarcoma lung metastases and 30 patients with colorectal carcinoma lung metastases were submitted to ILuP with melphalan followed by complete resection of all palpable lung lesions. According to the authors the 3-year overall survival and disease-free survival were 57% ± 9% and 36% ± 8%, respectively. Operative mortality was 0%, and 90-day morbidity was mainly respiratory (grade 3: 42%, grade 4: 2%) [34]. But is not possible to conclude the real value of this practice based in this study, its clear that more studies are needed to answer this question.

In summary, According to the results of the articles mentioned previously in this revision there are some prognostic factors that appears in two or more different studies (tables 1 and 2) showing relevance as predictive of bad outcome (disease free interval, presence of two or more lung lesions, synchronous hepatic lesions and presence of mediastinal lymph node metastases).

Authors	Year of Publication	Number of Patients	CEA	TPS	CA19-9	Short disease free interval
Vodicka, <i>et al.</i>	2014	75	-	+	+	-
Matsui, <i>et al.</i>	2014	186	-	-	-	-
Cho, <i>et al.</i>	2014	698	-	-	-	+

Javed., <i>et al.</i>	2014	66	- +	-	-	-
Renaud., <i>et al.</i>	2014	320	-	-	-	-
Renaud., <i>et al.</i>	2015	106	+	-	-	+
Younes., <i>et al.</i>	2013	120				+
Subbiah., <i>et al.</i>	2014	229	-	-	-	-

Table 1: Prognostic factors studied in previous colorectal lung metastectomy papers. At the lines, we have (+) for that prognostic factors that show statistical relevance and (-) for the ones that do not show relevance.

Authors	Sincronous hepatic lesions	Rectal Cancer	Size of Lesions	Bilateral Disease	Absence of Induction Chemotherapy	Mediastinal Disease
Vodicka., <i>et al.</i>	-	-	-	-	-	-
Matsui., <i>et al.</i>	+	+	-	-	-	-
Cho., <i>et al.</i>	-	-	-	-	-	-
Javed., <i>et al.</i>	-	-	+	-	-	-
Renaud., <i>et al.</i>	+	-	-	-	-	+
Renaud., <i>et al.</i>	+	-	-	-	-	+
Younes., <i>et al.</i>					+	
Subbiah., <i>et al.</i>	-	-	-	-	-	-

Table 2: Prognostic factors studied in previous colorectal lung metastectomy papers. At the lines we have (+) for that prognostic factors that show statistical relevance and (-) for the ones that do not show relevance.

Future perspectives

To date, no randomized clinical trial has been carried out to compare the performance of surgical treatment with chemotherapy alone. In 2010 an international multicenter clinical trial called “Randomised trial of pulmonary metastectomy in colorectal cancer (PulMiCC)” was started, sponsored by the Cancer Research of the United Kingdom. The objective of this study is to compare the outcome of patients undergoing metastectomy with patients undergoing chemotherapy alone. We hope that with this study, which is still in progress, questions such as the actual impact of surgery on the treatment of these patients and how best to select patients will be elucidated.

Conclusions

Currently, surgical treatment of pulmonary metastases is a relevant and safe option in the treatment of colorectal cancer. However, there are no randomized controlled trials to support this treatment. Cohort and case series studies also suggest that there are some prognostic factors that can help in clinical decision-making, especially in patients for whom the indication may not be so clear. Randomized trials are necessary to confirm the actual benefits of pulmonary metastectomy. Despite of the absence of clinical trials, we recommend the practice of:

- 1-Pre operatory evaluation using a PET – CT
- 2-Perform the operation using video assisted technique that allow the surgeon to use the high definition images of the video equipment at the same time that is possible to palpate the entire lung to detect the nodules.
- 3-Prior to execute the pulmonary metastectomy, evaluate each patient considering the prognostic factors: short disease free interval, presence of two or more lung lesions, synchronous hepatic lesions and presence of mediastinal lymph node metástases.

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