8. Lung metastases of colorectal cancer: Focus on surgery

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Abstract. The natural history of colorectal cancer (CRC) progresses from localised to metastatic stages and lung metastases are one of the most important locations.

Lung metastasis appear mainly in the parenchyma and to a lower extent and generally later, grow endobronchially.

The International Registry of Lung Metastases study (IRLM) sets two reference parameters for metastasis surgery: risk factors and prognosis groups. Nowadays, these factors are clinical, histopathological and immunohistochemical. They may specify the prognosis and surgical indication.

Surgical treatment of lung metastases from CRC is not new. Extensive experience has confirmed that it can prolong survival in some patients. The fundamental goal of this surgery is to achieve a complete resection, universally acknowledged as a consistent prognostic factor because it is the only one in which we can truly have an influence on improving survival in these patients.

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However, collaboration between thoracic surgeons and oncologists is needed to offer this surgery only to patients for whom it may improve survival and quality of life. A review of these topics will be performed in this chapter.

**Introduction**

The natural history of CRC progresses from localised stage to metastatic one. In the majority of cases, stage IV disease is beyond the reach of curative surgery; however, in some situations surgery is considered the best treatment option. This is the case for isolated or a small number of lung metastases.

CRC metastases to the respiratory system are fairly infrequent. In most cases, metastases enter the lungs through haematogenous dissemination (via the portal and inferior vena cava) and less frequently through lymphatic dissemination. Metastases to the bronchial system can also occur. According to different published series, lung metastases appear in 10% to 30% of CRC patients (1-3), and most are diagnosed 5–60 months after primary tumour treatment (4, 5). These metastases can appear as the only metastatic lesions (2–4% of cases) (6), but they can also sometimes appear subsequently to liver metastases.

Intrabronchial lesions are rare and can present with dyspnea, cough, fever or repeated infections. In these cases, bronchoscopy is the best method to diagnose the metastasis. By contrast, lung metastases are asymptomatic and incidental radiographic findings. Mediastinal or hilar adenopathies arise from lymphatic spread or a nearby lesion. Their real frequency is unclear because surgical analyses of nodal status are not usually performed (7). Despite this, studies have recorded incidences of mediastinal node metastasis ranging from 3.5% to 16.7% (8, 9). All occurrences of mediastinal node metastases have a negative impact on survival.

Surgical treatment of lung metastases is not new. The first metastasectomy was performed in 1885, and Blalock (1) performed the first CRC lung metastasectomy in 1944. After this procedure was first carried out, several studies were conducted on the topic, but patient heterogeneity led to controversial results. In general, surgical treatment for metastatic disease was thought to hold the potential to extend overall survival. In 1991 the International Registry of Lung Metastases (IRLM) was created, and an analysis of long-term metastasectomy results in 5206 patients with lung metastases from different primary tumours treated at European and American Hospitals was published in 1997 (10). This study focused on risk factors of lung cancer metastases and prognostic groups, although the results could not be validated due to sample heterogeneity. Other prognostic factors were subsequently introduced, such as type of lung surgical resection, completeness
of surgery, tumour histology and nodal involvement. On the other hand, several immunohistochemical factors are also currently being considered to individualise effective treatments.

The IRLM study changed the paradigm of surgical treatment in patients with lung metastases. Its results confirmed surgery as an effective treatment in terms of survival. In fact, although chemotherapy has improved the median survival to 2 years, the 5-year survival rate of patients who do not undergo a surgical procedure is less than 5% (11). However, when surgery is not able to completely remove the whole tumour, median survival is 9–15 months (4, 10). Surgery carries a risk of complications, which can be very significant, particularly if procedures are bilateral, repeated, or combined with systemic or radiotherapeutic treatments. Knowing which patients are likely to benefit most from this decision is critical.

1. Preoperative evaluation

Just 1–8% of patients with CRC lung metastases can undergo metastasectomy. Surgical resection of lung metastases is determined by two essential factors: the surgical risk and the extent of metastatic disease.

Evaluation of general health and respiratory function to assess surgical risk

The surgical risk evaluation is a complex process. It should be individualised and must include the patient’s performance status, comorbidity, cardiopulmonary function and the extent of lung resection (20,21). Although most planned resections are minor, in many cases the resection may be more extensive than anticipated, or the patient may require multiple resections. These two factors should be kept in mind during evaluation to predict the respiratory functional status after the surgical procedure.

A number of published series have shown that concomitant diseases such as arterial hypertension (diastolic pressure > 110 mmHg), diabetes mellitus, hypoalbuminemia (serum albumin < 2.5 g/dL), renal failure, weight loss > 10%, body mass index < 18.5 kg/m² or > 30 kg/m², ECOG > 2 or Karnofsky index < 50%, EPOC and neoadjuvant treatment have a negative impact on postsurgical mortality. On the other hand, patient age should not be considered a negative prognostic factor (22) and thus, by itself, should not preclude surgical resection. The mortality rate among elderly people treated with surgical resection of lung metastases is more closely related to their comorbidities than to age itself, so a select group of these patients can undergo the procedure after proper support treatment.
The most determinant factors to predict surgical risk are cardiovascular and/or respiratory status. The mortality rate secondary to lung metastases resection is directly related to heart or respiratory complications, indicating the need for a very thorough evaluation of these two functions prior to surgery.

A known history of cardiopathy significantly increases mortality risk (23), so its evaluation is strongly recommended (24). With this aim, all patients should undergo a thorough medical history and physical examination, electrocardiogram (ECG) and careful evaluation of Revised Cardiac Risk Index (RCRI) (25, 26). RCRI values > 2, or the presence of either cardiopathy requiring medication, suspicion of undiagnosed cardiopathy or trouble breathing when climbing stairs should be more carefully evaluated following the American Heart Association (AHA) and American College of Cardiology (ACC) criteria (25). If detected, unstable coronary syndrome, untreated cardiac congestive failure, significant arrhythmia or severe valve disease should be treated and corrected before planning a surgical resection. Patients with a low cardiac risk or with these problems successfully solved cardiopathy should undergo a routine respiratory function evaluation with spirometric testing and lung diffusion capacity for carbon monoxide (DLCO).

Several series have shown that reduced forced respiratory volume at the first second (FEV1) and DLCO have prognostic significance related to postsurgical mortality and other complications. Either FEV1 or DLCO > 80% indicates that a pneumonectomy is possible, in contrast to cases with FEV1 or DLCO < 80%.

In the former cases, a cardiopulmonary exercise test (CPET) to measure the maximum oxygen consumption rate (VO2 max) is necessary to understand the cardiopulmonary system reaction to stress and estimate the physiological capacity after surgery. In institutions that lack the capacity to perform a CPET, an exercise test such as climbing stairs or the shuttle walk test, although less preferred, can be used as an alternative. Those unable to climb 22 metres of stairs should be candidates to perform a regular CPET (24).

VO2 max < 35% or 10 mL kg⁻¹ min⁻¹ indicates high risk; thus, lobectomy or pneumonectomy are not recommended. On the other hand, VO2 max > 75% or 20 mL kg⁻¹ min⁻¹ would allow a pneumonectomy to be performed. When VO2 max values are between these two limits, postoperative FEV1 (ppoFEV1), DLCO (ppoDLCO) and VO2 max (ppoVO2 max) values must be estimated. Various techniques may be used to evaluate the number of functional segments to be resected, such as radionuclide pulmonary perfusion scanning, anatomic quantification, computed tomography (CT) or bronchoscopy. All result in a similar estimation, although radionuclide scanning is preferred for the estimation of
postpneumonectomy function because the anatomic quantification methods underestimate these values. The postoperative values can then be calculated by the following equation: 

\[ \text{ppo values} = \left( \frac{\text{preoperative value}}{T} \right) \times R, \]

where \( T \) is the number of obstructed lung segments and \( R = T - \) the number of segments that will be resected.

When \( \text{ppoFEV1} \) and \( \text{ppoDLCO} \) are less than 30% and \( \text{ppoVO2 max} \) is less than 35% (<10 mL/kg/min), resection should be precluded because the estimated risk is too high. Caution is necessary in borderline cases, because these figures predict the functional status at 3–6 months after surgery and could be approximately 30% lower in the days immediately following surgery (27). Those patients selected for surgery who cannot undergo cardiopulmonary tests due to comorbidity should be considered high risk, and their treatment and support should be provided in advanced care units.

**Oncological evaluation: New diagnostic tests**

It is widely accepted that one of the most important criteria when considering lung metastases surgery is the global extent of the disease. Good control of the primary tumour, no detected extrapulmonary metastases, and the possibility of complete resection are absolutely necessary.

Among patients who underwent primary colorectal tumour surgery, 14.4% presented with local recurrence, 3.2% with intraluminal recurrence in the anastomotic point and 1.3% with a metachronous cancer (28). Colonoscopy is considered the best method to diagnose these recurrences (29). However, this technique is unable to detect extraluminal recurrence, leading some authors to prefer the use of virtual colonography (30). Virtual colonography allows the examination of colonic, pericolonic and abdominal organs, with a negative predictive value of 97% to 100% depending on the lesion (31).

The use of FDG-PET provides a sensitivity of 93% in detecting local recurrence, compared to 53% using conventional CT (32). However, PET findings may have different interpretations related to intestinal physiological absorption, lesion size, poor anatomical definition and previous treatment, which can induce inflammation leading to a false-positive result (33). Combining these two techniques could improve results by reducing the rate of false-positive and -negative findings. A recent study of FDG-PET/CT reported a significantly higher sensitivity and specificity than multidetector CT (MDCT) in the diagnosis of locoregional recurrence (98.1% and 75% versus 66.7% and 62.5%, respectively). Therefore, PET/CT should be considered as an elective diagnostic method before using invasive techniques.
In the search for occult metastases, FDG-PET (Fig. 1) has proven to be a more effective tool than conventional imaging (thoracic and abdominal CT).

This finding may change the therapeutic strategy in about one-third of patients (35), decreasing the number of futile surgeries. Due to its discriminatory ability in the context of distorted anatomy, combination PET/CT is particularly useful in the diagnosis of recurrence after completion of hepatectomy, showing a sensitivity of 100% compared to 50% obtained with CT alone (36). However, its effectiveness may decrease in patients who have undergone neoadjuvant chemotherapy (37) and those with mucinous adenocarcinomas (38). The detection of metastases in abdominal lymph nodes can be difficult when they are small. The sensitivity of FDG-PET in these cases hardly reaches 30%, and its interpretation is affected by the activity of neighbouring structures. In these cases the combination of PET and CT improves reliability.

A basic requirement in the resection of pulmonary metastases is the possibility of complete resection. Mapping the number and anatomic arrangement of metastases as accurately as possible is therefore essential. In this regard, the identification of millimetric nodules may be underestimated by conventional imaging, leading a significant number of surgeons to prefer final confirmation by palpation in open surgery. The use of helical CT underestimates the presence of metastatic nodules in approximately 20% of pulmonary metastasectomies, with a false positive rate of 29% (39). However, the recent introduction of MDCT technology offers a sensitivity of 97% for non-sarcomatous nodules (40) (Fig. 2), similar to that of combined FDG-PET for nodules smaller than 1 cm (41).

Figure 1. TC-PET imaging: lung metastases from CRC.
2. Prognostic factors

Since Thomford and colleagues (42) established the basis for the surgical treatment of pulmonary metastases, various clinical factors have been described whose presence appears to alter patient prognosis or further define the indication for surgical treatment. Multiple determinants of survival have been recognised with varying degrees of evidence, and always with the uncertainty resulting from the absence of comprehensive, prospective and homogenous studies. In a large study, Kanemitsu and colleagues (43) identified five predictors of poor prognosis: prethoracotomy CEA level, number of lung metastases, neoplastic involvement of hilar and mediastinal lymph nodes, primary tumour histology and presence of extrathoracic disease. Factors such as disease-free interval (DFI), the multilateral and/or synchronised nature of injuries, lung tumour burden, the previous stage of primary tumour, liver metastases or recurrent metastases may also reduce survival.

Lymph node involvement

Mediastinal or hilar lymph node involvement is generally considered a poor prognostic factor in the overall context of pulmonary metastases. However, despite being present in between 12% and 19.2% of patients with lung metastases of colorectal carcinoma (44), few studies have addressed their impact. This may be the result of these patients not being considered
amenable to surgery, since the disease has overtaken the lung station, and the fact that mediastinal node dissection is not performed routinely in many thoracic surgery centres. Various publications stress that if preoperative evidence indicates mediastinal lymph node metastases, diagnosis should be confirmed prior to considering treatment with metastatic resection. Most series that analysed the impact of lymph node metastases were based on intraoperative findings of lymph node involvement, either through "sampling" or by formal lymph node dissection. These studies (8, 13, 14, 45) have established a relationship between the presence of hilar or mediastinal lymph node involvement and poor prognosis, with 5-year survival ranging from 0–19%.

**Carcinoembryonic antigen**

Elevated CEA level is a consistent factor of poor prognosis in most series (44). Higashiyama and colleagues (46) found a significant association between elevated prethoracotomy CEA levels and extrathoracic metastases, especially in the brain. In one study, 5-year survival was 18.9% (range 0–36%) in patients with CEA values higher than 5–10 ng/mL and 59.3% (range 42.7–86.9%) in patients with normal CEA levels. This prognostic difference was more pronounced in patients with CEA levels greater than twice the reference value (14).

**Disease-free interval**

In the study of 5026 cases of lung metastases conducted by IRLM, Pastorino and colleagues (10) found significant prognostic differences according to the disease-free interval (DFI) between primary tumour resection and metastasis. These findings were confirmed by Rena and colleagues (12), who observed 5-year survival rates of 22.6%, 38.6% and 55% in patients with DFI of 0–11 months, 12–35 months and >36 months, respectively. In the same vein, one study (47) found that the synchronised nature of the metastasis was a prognostic factor, while other authors reported the predictive value of DFI in partnership with intrapulmonary tumour load and number of metastases (17).

**Number, size and distribution of metastases**

A significant number of published case series involved predominantly single metastases. Although some authors (8, 43, 48) found better survival in cases of solitary metastasis compared to multiple lesions, the real impact of the number of metastases on survival has not yet been established. In a recent
study, Onaitis and colleagues (49) reported a significant relationship between the existence of three or more metastases and the possibility of recurrence, especially when associated with a DFI less than 1 year. Surgery was not curative in any of these patients, indicating non-surgical treatment. Few studies have investigated the size of metastases as a prognostic factor, probably due to the diversity of samples. In this respect, assessment of total tumour burden may be more appropriate (17). Only two series to date (48, 50) have reported a significant relationship between tumour size and 5-year survival, which may fall below 11% in patients with tumours larger than 3.75 cm. With respect to the distribution of metastases, non-conclusive evidence indicates that bilateral distribution is, by itself, an adverse prognostic factor.

**Primary cancer stage**

The initial state of the primary tumour is a factor rarely considered in most studies of pulmonary metastasis resection, and few have reported it to influence survival. However, Melloni and colleagues (51) observed a better prognosis in stage T1-T2 primary colorectal carcinoma compared to T3-T4 tumours, with 5-year survival rates of 63% and 34% respectively. These results are similar to those of Inoue and colleagues (14) using Dukes’ staging, who reported 5-year survival rates of 68.7% for stage A primary tumours compared to 32.8% for stages B–D. The anatomical location of the primary tumour has also been speculated to influence outcome. Several studies have demonstrated a greater tendency for lung metastases to originate from rectal cancers, which are associated with an inferior survival compared to tumours of colonic origin (52, 53).

**Liver metastases**

The liver and lung are the most common sites of CRC metastasis. Approximately 5–10% of CRC patients will develop liver and lung metastases (44), of which 6.9–30.8% will be synchronous respect to the primary tumor. In patients with both lung and liver metastases, the overall 5-year survival after the first metastasectomy (liver or lung) was between 74% and 30% (52), with no significant differences between patients with lung only as the first site of metastases compared to those with both lung and liver involvement. The prognosis associated with the synchronous occurrence of both lesions still remains unclear. While some large studies have reported no prognostic significance (54, 55), Kobayashi and colleagues (56) observed a 5-year survival rate of 22% among patients with synchronous metastases compared with 50% in patients with metachronous metastases. The results of other
studies (52, 57) appear to be in line with these results, in that they associate the concomitance of lesions or a DFI < 1 year with poorer survival rates.

**Recurrence**

Insufficient experience is available to determine the prognostic role of metastatic recurrence in the lung. Some series (8, 58) have shown that in select patient groups, repeated resection of lung metastases can lead to survival rates ranging from 29% to 53.8%. However, further studies are needed to determine what types of patients may benefit from surgical treatment, since early recurrence (DFI < 6 months) (59) and number of metastases may be poor prognostic factors (58).

**3. Pathological prognostic factors**

The formation of lung metastases is a multifactorial process. Factors related to the original tumour and other genetic factors, such as the activation of genes that promote metastasis or inactivation of genes that inhibit it, are not yet well understood. Metastases reach the lungs through the blood and also via the lymphatic system, and once confirmed, the metastatic nature of a lung tumour nodule can be defined by a number of these factors.

The clinical behaviour of CRC pulmonary metastases is unpredictable. Although adverse prognostic factors have been identified, they have not been conclusive (51). Exhaustive studies are necessary, with larger groups and selected patient series. The molecular profile of aggressive CRC with high metastatic potential includes the expression and overexpression of proteins due to alteration of the p53, K-ras, DCC and nm23 genes, among others (60,61,62). The elevation of proteolytic enzymes (metalloproteinases 2 and 9 and cathepsin B), adhesion molecules, and a high rate of angiogenic factor expression can lead to increased vascular endothelial growth and a high density of microvessels. All these factors and others are promising sources for new antiangiogenic and targeted therapies. New prognostic factors determined using immunohistochemistry or molecular biology, which may also help in the selection of patients more or less likely to be susceptible to these new therapies, are currently in the early stages of investigation and remain still controversial.

**Histopathology**

Histopathological factors that may be related to tumour behaviour, and therefore to prognosis, include aerogenous spread with floating cancer cell
clusters (ASFC) to alveoli in areas near the site of infiltration, vascular invasion in the tumour (63), lymphatic invasion and pleural invasion. These are all poor prognostic factors regarding tumour behaviour, particularly the association of the first two, which some studies have identified as independent prognostic factors (19, 60).

**Immunohistochemical**

No definitive prognostic immunohistochemical marker has been identified to date, but many can be informative.

E-cadherin is a glycoprotein with a significant role in modulating the invasiveness of tumour cells (Fig. 3).

![Image](Image)

**Figure 3.** Expression of the E-cadherina.

Its low expression in tumour cells is associated with increased tumour invasion and worse behaviour, also expressed by primary tumours of the colon (60). Although not supported by all authors, E-cadherin expression may help to select patients for chemotherapy.

- The transcription factor CDX-2 is expressed in normal colonic epithelium and in the majority of adenocarcinomas of the colon. CDX-2 can potentially be used for diagnosis but has no prognostic value (64,65). This antibody is also specific for the identification of neuroendocrine tumours of intestinal origin and/or diagnosis of their metastases.
- Cathepsin B belongs to a family of lysosomal enzymes and is involved in the regulation of certain growth factors in malignancies including breast cancer and CRC. Cathepsin B could be an acceptable tumour marker, as it can also be quantified in the blood and may be valuable, especially in cases of remote metastases (66).

- The insulin-like growth factor 1 receptor (IGF1_R), B catenin, viral oncogene homolog B FBJ murine osteosarcoma (FOS-B), melanoma antigen (MAGE) and other proteins have not demonstrated statistically significant prognostic value (60).

- Vascular endothelial growth factor (VEGF) is a glycoprotein related to lymphangiogenesis (and thus metastasis via the lymphatic system). Additionally, higher VEGF levels in tumour tissue have been associated with poorer prognosis. This factor identified by immunohistochemistry may be an independent prognostic marker of tumour behaviour and used to indicate poor prognosis (67,68), although other studies have not confirmed these results (69).

- Epidermal growth factor receptor (EGFR) overexpression and/or amplification, as determined by immunohistochemistry and molecular biology, respectively, correlates with advanced tumour stages and metastasis development.

Genetic factors

Many genes are involved in the molecular profile of CRC, either via the activation of oncogenes involved in the process of neoplastic proliferation (MYC, RAS) or inactivation of oncogene suppressors (APC, P53, DCC, nm23) (60, 61).

Among tumour suppressors, p53 (located on chromosome 17p) plays an essential role in tumour angiogenesis. The p53 gene (Fig. 4) encodes a protein that acts as a tumour suppressor. Its mutation occurs in 70–80% of CRC. Overexpression of p53 protein, detected immunohistochemically, is used as a marker for p53 mutations and associated with a poorer prognosis in terms of lower DFI, but has not been shown to affect survival (60).

The nm23 gene is regarded as a suppressor of the metastasis process. The expression of two proteins, nm23-H1 and nm23-H2, and its significance in CRC is controversial (61). While some authors found that reduced expression of nm23 was associated with advanced stages of disease and metastasis, others found that nm23 overexpression was associated with recurrence, liver metastasis and decreased survival. This apparent contradiction was explained by Berney and colleagues (61), who suggested that nm23 protein overexpression was due to a mutant nm23 protein resulting from deletion of
the nm23 gene. However, other recent studies have failed to relate the expression of nm23 with staging and/or prognosis.

Mutation or loss of the DCC (deleted in colorectal cancer) gene, which is related to adhesion molecules, is also involved in the progression of adenoma to carcinoma in primary tumour development and associated with more advanced tumour stage and poorer prognosis. Mechanisms related to the C4.4A gene may also be associated with tumour invasion (70).

K-ras is currently the most important CRC biomarker. K-ras belongs to a family of oncogenes that encode a protein with a key role in EGFR signalling. K-ras mutations are found in 30% to 40% of CRC patients. They are highly correlated with both primary tumours and metastatic disease, and observed more frequently in metastasis. Patients with K-ras-mutated tumours have a lower DFI after lumpectomy, suggesting a worse prognosis. Patients with the mutated gene also do not respond to targeted anti-EGFR drug treatment (62).

4. Surgical treatment

Surgery for lung metastases from colorectal carcinoma is universally accepted as one of the main therapeutic strategies in these patients, although, to date, no studies have assessed the precise benefit of this treatment. However, the surgical approach to these lesions carries a low morbidity and virtually non-existent mortality and also occasionally leads to the discovery of a second
primary tumour, with the possibility of providing correct oncological treatment thereof.

The fundamental goal of this surgery is to achieve a complete resection. Complete resection is universally acknowledged as a consistent prognostic factor, and it is the only one in which we can truly have an influence on improving survival in these patients. When resection is complete, surgical treatment of patients with metastases has reported survival rates ranging from 30% to 63% (2, 12, 61) at 5 years and 18% at 10 years. By contrast, median survival after incomplete surgery is only 9 to 15 months (3, 4, 7), emphasising the need for careful collaboration between thoracic surgeons and oncologists to offer this surgery only to patients for whom it may improve survival and quality of life.

Resection criteria indications

Excluding the occasional diagnostic surgery, surgery for metastases should be considered a therapy for local control of extensive disease. Indications and surgical techniques have been modified with respect to the improved diagnoses provided by imaging techniques and the precise use of cancer treatments in the context of multimodal therapy, indirectly leading to a greater number of candidates for resection (48, 71) as well as a gradual improvement in survival.

In general, surgical treatment to remove a solitary metastasis, especially if it is peripheral, is usually considered favourable. Indications for the surgical removal of bilateral multiple metastases and repeat metastasectomy of lung recurrences are more controversial. In this regard, the National Comprehensive Cancer Network (NCCN) has released NCCN Colon Cancer Guidelines Version 1.2011, which states the criteria for resectability of metastases and locoregional therapies within surgery (Table 1).

Patients who do not meet these criteria may have to try alternative treatments for local disease control such as cryotherapy, stereotactic radiotherapy or radiofrequency ablation. Radiofrequency ablation, indicated firstly for metastases of less than 5 cm and not hilar, is an effective treatment even at the expense of non-negligible morbidity (mainly pneumothorax) and high recurrence requiring repeated ablation (72). The existence of affected lymph nodes is another point of controversy. Most authors (8, 44, 73, 74) consider lymph node involvement to negatively impact survival, regarding it as one of the most important prognostic factors. One study reported a 5-year survival of 0% for patients with mediastinal lymph node involvement (8), leading these authors to consider it a contraindication for extensive excision.
### Table 1. NCCN Guidelines™ Version 1.2011 Colon Cancer. Principles of surgery: Criteria for respectability metastases and locoregional therapies within surgery.

<table>
<thead>
<tr>
<th>Lung</th>
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<tbody>
<tr>
<td>- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required</td>
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<tr>
<td>- The primary tumor must have been resected for cure (R0)</td>
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<td>- Resectable extrapulmonary metastases do not preclude resection</td>
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<tr>
<td>- Re-resectin can be considered in selected patients</td>
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<tr>
<td>- Ablative techniques can be considered when unresectable and amenable to complete ablation</td>
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<tr>
<td>- Patients with respectable synchronous metastases can be resected synchronously or using a staged approach</td>
<td></td>
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<tr>
<td>- Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgical respectable</td>
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**Evaluation for conversion to resectable disease**

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<td>- Re-evaluation for resection should be considered in otherwise unresectable patients after 2 months of preoperative chemotherapy and every 2 months thereafter</td>
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<tr>
<td>- Disease with a higher likelihood of being converted to resectable are those with initially convertible disease distributed within limited sites</td>
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<tr>
<td>- When considering whether disease has been converted to resectable, all original need to be amenable to resection</td>
<td></td>
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<tr>
<td>- Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease</td>
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The optimal timing of resection is also an important consideration, and the best time to resect pulmonary metastases has been a source of some controversy. Most authors state that metastasectomy should be performed when metastasis is diagnosed, if patients meet requirements. However, in a retrospective study, Tanaka and colleagues (75) observed that after potentially curative metastasectomies, new lesions appeared in 50% of patients due to further growth of previously undetected lesions, and found increased survival in patients in whom surgery was delayed more than 3 months. It is important to remember that smaller lesions have a shorter doubling time and therefore a shorter growing time. However, other tumour characteristics, mainly the number, size and aggressiveness of metastases and the type of surgical approach, must also be considered before deciding upon surgery.

A metastasis that increases rapidly in size can produce both parenchymal spread and adenopathy, but can reduce the chances of a lesser resection. Waiting 3 months to conduct the metastasectomy may be indicated for no peripheral lesions smaller than 1 cm because this allows us to assess the presence of metastases initially hidden or absent, as well as their best display in radiological images and subsequent palpation. On the other hand, from a purely technical standpoint, the resection of a solitary peripheral metastasis using video-assisted thoracoscopic surgery (VATS) has minimal risk and generates few adhesions that interfere with subsequent resection in case of recurrence. By contrast, the need for open surgery due to central and/or multiple nodes poses a greater risk of adhesions, morbidity and increased recovery time. In these cases, the decision to wait may be particularly favourable.

Another issue surrounding surgical indications is with the presence of liver metastases. Although some reports (77) consider these a negative prognostic factor of survival and recurrence, their synchronous or metachronous appearance should not be a contraindication. Several studies indicate that 5-year survival is around 30% and can reach 74% (13, 16, 52, 54, 56, 58). These results are comparable to surgery for lung metastases only, confirming the benefits of resection treatment in these patients (76). Recent studies (56, 78) have indicated better survival in metachronous metastases compared to synchronous metastases. The strategy for surgical intervention is controversial: sequential, simultaneous, or dependent on the severity of their location. Most groups favour a sequential process dealing first with liver metastases (1).

**Approaches**

The surgical approach must meet two requirements: it should be the less aggressive as possible and allow all metastases to be resected. The information provided by imaging is becoming more detailed and accurate, but
recent studies have emphasised that these methods still demonstrate low sensitivity to millimetric injury (39). Thus, another requirement in this type of surgery is manual palpation.

Several factors determine the type of approach in this type of surgery, including the number, size and anatomical location of metastatic lesions and positive lymph nodes, as well as the functional status of the patient and the preferences and personal experience of the different surgical teams. Regardless of preference per se, each approach has its advantages and disadvantages (Table 2).

**Table 2.** Characteristic surgical approaches.

<table>
<thead>
<tr>
<th>Surgical approaches</th>
<th>Visual metastases</th>
<th>Lung palpation</th>
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<tbody>
<tr>
<td>Standard thoracotomy</td>
<td>Excellent</td>
<td>Excellent</td>
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<tr>
<td>Lateral thoracotomy</td>
<td>Excellent</td>
<td>Excellent</td>
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<tr>
<td>Sternotomy</td>
<td>Optimal (except posterior lesions)</td>
<td>Excellent</td>
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<tr>
<td>Clamshell</td>
<td>Excellent</td>
<td>Excellent</td>
</tr>
<tr>
<td>Thoracoscopy</td>
<td>Medium-Optimal (IF peripherals)</td>
<td>No</td>
</tr>
<tr>
<td>VATS</td>
<td>Optimal</td>
<td>Medium</td>
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<tr>
<th>Surgical approaches</th>
<th>Pain</th>
<th>Morbidity</th>
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<tbody>
<tr>
<td>Standard thoracotomy</td>
<td>Severe</td>
<td>CRM ++</td>
</tr>
<tr>
<td>Lateral thoracotomy</td>
<td>Moderate</td>
<td>SM + -</td>
</tr>
<tr>
<td>Sternotomy</td>
<td>Moderate</td>
<td>CRM + SM - +</td>
</tr>
<tr>
<td>Clamshell</td>
<td>Intense</td>
<td>CRM + SM +</td>
</tr>
<tr>
<td>Thoracoscopy</td>
<td>Mild</td>
<td>CRM - SM +</td>
</tr>
<tr>
<td>VATS</td>
<td>Mild-moderate</td>
<td>CRM - + SM +</td>
</tr>
</tbody>
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CRM: Cardio-Respiratory Morbidity
SM: Surgical Morbidity
VATS: Video-assisted Thoracoscopic Surgery

Classical posterolateral thoracotomy, previously used widely, is gradually falling into disuse because it is very aggressive and painful. Lateral thoracotomy should be the approach of choice for unilateral lesions. It allows a correct visualisation of parenchymal lesions and proper mediastinal lymph node evaluation. Axillary thoracotomy also has limited applications in specific metastatic sites.

If metastatic disease is present in both hemithorax (Fig. 5), a choice must be made between sequential treatment with bilateral thoracotomy and simultaneous treatment, often with a sternotomy.
Figure 5. Bilateral lung metastases and mediastinal nodal involvement.

Sternotomy, which had its peak in the 1980s, allows the simultaneous exposition of both hemithoraces and is of course indicated for bilateral lesions. Its postoperative management is less complex overall than thoracotomy, and it is thought to be a less painful approach and functionally less aggressive. Its limitations are determined by the difficulty in addressing posterior lesions, especially those in the lower left lobe. A variant of sternotomy is the transverse "clamshell" sternotomy used in lung transplants and also occasionally considered for addressing bilateral lesions. This technique allows proper access to both hemithoraces but is more painful than sternotomy and requires sectioning of the mammary arteries.

Thoracoscopy is also a reasonable surgical approach and its outcome, in terms of survival, is similar to open surgery (44, 57, 80). It provides all of the a priori advantages of minimally invasive surgery: less pain (79), less impairment of lung function (80) and less surgical trauma, with decreased morbidity, reduced hospital stay and improved aesthetics. Thoracoscopy also reduces the possibility of pleuropulmonary adhesions, which is of importance in the event that iterative surgery is indicated for multiple metastases or diagnostic purposes. At the therapeutic level, imaging with PET and high resolution CT was previously required to determine the exact number and location of metastases. Most authors consider thoracoscopy mainly for metastases that are single or double, non-recurring, peripheral and less than 3 cm. For lesions smaller than 1 cm, peripheral, but more than 5 mm of the visceral pleura, the use of CT-guided microcoils as “pointers” is indicated; the added complication rate is very low. Intraoperative ultrasound can also help localise initially undetectable lung nodules. However, it is clear that manual palpation of lung nodules provides
greater security. In this respect, VATS with an additional small minithoracotomy allows the advantages of VATS and open surgery to be combined, and is in principle the approach of choice in most peripheral metastases. However, there are supporters of the VATS approach for the treatment of virtually all pulmonary metastases (81). Additionally, there is always the option, in case of doubt, for conversion to open surgery.

**Type of removal**

The purpose of this type of surgery is to achieve a complete (R0) resection while preserving the lung parenchyma as much as possible. Thus, the excision should be tailored to the lung injury, although in terms of survival, minor and major resections do not significantly differ. In this respect, as in all forms of lung surgery, surgery can be divided into three basic categories: minor resections (wedge resection and atypical), anatomical resections (segmentectomy, lobectomy and pneumonectomy), and extended resections.

In general, the greatest number of resections, approximately 70% (7, 71), correspond to minor resections, due to the peripheral location of most injuries. On the other hand, the minimum margin of resection has not been defined yet, although most surgeons are in favour of limiting it to 1 cm (Fig. 6).

If this limit cannot be assured using an autosuture machine and common endocutter, one must resort to manual suture resection with electrocautery and, more recently, laser cautery (Fig. 7).

**Figure 6.** Lung metastases: wedge resection.
These latter methods are also indicated for the resection of multiple small peripheral metastases. In general, as they tend to achieve hemostasis and correct aerostasis.

In the case of larger or more central metastases, multiple metastases in the same lobe, and whenever there is a doubt about the origin of the lesion (second primary tumour vs metastasis), anatomical resection is required (segmentectomy, lobectomy or pneumonectomy). Anatomical resections may also be used for patients with lymph node tumour (N1) between the vessels and segmental bronchi. Pneumonectomy should be considered exceptionally, only if patients meet all indicated requirements for the surgery. Similarly, extended surgery (such as wall and mediastinum) is indicated only if patients meet these requirements and in the absence of response to other cancer treatments.

The role of lymphadenectomy in its various forms is controversial. Most published studies (3, 7) do not involve systematic lymph node dissection, unless there is evidence of enlarged lymph nodes at the time of surgery. However, recent evidence that patients with lymph node involvement have a poorer prognosis (4, 8, 14, 73, 74) may indicate the potential need for systematic selective mediastinal lymph node examination (mediastinoscopy) (82, 84), ideally selectively, for screened patients whose imaging tests (CT, PET) suggest mediastinal lymph node involvement (cN2) associated with metastatic disease. In these situations, surgical resection is not contraindicated, but, particularly in the case of metastatic relapses, other methods such as stereotactic radio frequency radiation may be indicated instead.
Lymphadenectomy associated with metastasectomy ensures consistent complete resection (7). Some authors noted an improvement in survival, (8,84) and others a decrease in recurrences (7, 83). Although at present no randomised studies have confirmed the benefits of lymph node dissection, these current findings suggest that lymphadenectomy associated with surgery for metastases should be considered.

Reoperations

Metastatic disease recurrence is common in colorectal carcinomas, perhaps due to the dubious effectiveness of adjuvant chemotherapy (7,83). Reported rates of both resectable and unresectable recurrences range from 46% to 70% in different series (4, 58). Although specific prognostic factors influencing recurrence have not been assessed in detail, according to some studies, recurrences are more frequent in patients younger than 65, with shorter DFI, and with more than three previous metastases (49). The indication for reoperation has been disputed, particularly in patients with confirmed mediastinal lymph node involvement, but the majority of reports favour reoperation after re-evaluation and in compliance with requirements (17, 58, 83). However, only a minority of patients meet the criteria indicating a second resection. In this selected group of patients, survival rates ranging from 30% to 53% have been reported (8, 12, 16, 17, 58, 82, 83), with acceptable mortality. These results are similar to those after the first metastasectomy, particularly in cases of isolated relapse in the absence of lymph node involvement (83). Similarly, highly select patients may undergo a third metastasectomy, but with a progressively lower benefit in terms of both disease control and survival.

Endobronchial metastases

Endobronchial colorectal metastases are uncommon, but may also be underdiagnosed (85, 86). They are more frequent in advanced stages of disease, often coexist with lung metastases (86), and can be generated via the impact of occasional lymphatic tumour emboli on the bronchial submucosa or, more often, due to progression of parenchymal injury.

A specific feature of this location is its tendency to cause airway obstruction (Fig. 9).

The most common presenting symptoms are dyspnea, cough and hemoptysis, although it may be a radiological finding in asymptomatic patients. Only 55% of endobronchial metastases are detected by CT (86). Bronchoscopy is the ideal method for diagnosis, with sensitivity close to 100% in central lesions. Therefore, bronchoscopy or echobroncoscopy should
perhaps be indicated systematically in patients with lung metastases, with a standard procedure for evaluation.

Laser photoresection, photodynamic therapy, cryotherapy and brachytherapy are palliative methods that can substantially improve pulmonary symptoms. Cryotherapy, photodynamic therapy and even brachytherapy should be considered in central and localised lesions, photocoagulation and laser vaporisation in bleeding injury, and stenting in the case of coexisting extrinsic compression. As in lung metastases, excision surgery is an option, but only in very selected cases. In general, patients’ very advanced disease precludes excision.

**Conclusion**

With the increasing incidence of CRC, the number of patients with distant metastases is also increasing, and for this reason, various treatment methods have been introduced, and treatment protocols have been changed.

The lung is the most frequent extraperitoneal metastatic site and these metastases develop in about 10% of the patients who undergo a curative resection for this cancer. Most lung metastases are disseminated at the time of diagnosis and curative resection is not indicated in these cases, but a conservative treatment or chemotheraphy, are good alternatives we can use.

Although this surgery could be performed for selected cases, getting a 5-year survival rate from 9% to 60%, it would be necessary a close collaboration between thoracic surgeons and oncologists to offer this
treatment only to patients for whom it may improve survival and quality of life.

References

Lung metastases of colorectal cancer: Focus on surgery