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Pulmonary metastases from colorectal cancer: 25 years of experience

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Objective: To examine the experience of pulmonary resections for colorectal metastases at the McGill University Health Centre. **Design:** A chart review. **Patients:** Forty-nine patients treated surgically between 1975 and 1998 for pulmonary metastases from colorectal cancer. **Intervention:** Thoracotomy with pulmonary resection. **Outcome measures:** Survival of patients with various preoperative and postoperative clinical variables. **Results:** The perioperative death rate was 4%. Overall 5- and 10-year survival rates were 55% and 40% respectively. The mean interval between the initial colonic resection and resection of pulmonary metastases (disease-free interval) was 36 months. The 7 patients who also underwent resection of extrapulmonary metastases had a 5-year survival rate of 52%. Significant preoperative variables that carried a poor prognosis included the following: more than one pulmonary lesion, a disease-free interval of less than 2 years, and moderately or poorly differentiated colorectal cancer. The 16 patients who received chemotherapy after their thoracotomy had a 5-year survival rate of 51% compared with 54% for the 33 patients who did not receive chemotherapy. Recurrent resections of pulmonary lesions did not reduce survival. **Conclusions:** Pulmonary resection for metastatic colorectal cancer is both effective and safe. Resectable extrapulmonary metastases and pulmonary recurrence should not preclude lung resection. Postoperative chemotherapy has no survival benefit. Preoperative variables should guide the clinician when considering surgical intervention.

Objectif : Examiner l'expérience de résections pulmonaires de métastases colorectales réalisées à l'Université McGill. **Conception :** Étude de dossiers. **Patients :** Quarante-neuf patients traités par chirurgie entre 1975 et 1998 pour des métastases pulmonaires issues d'un cancer colorectal. **Intervention :** Thoracotomie avec résection pulmonaire. **Mesures de résultats :** Survie des patients présentant diverses variables cliniques préopératoires et postopératoires. **Résultats :** Le taux de mortalité périopératoire s'est établi à 4 %. Dans l'ensemble, les taux de survie à 5 et 10 ans ont atteint 55 % et 40 % respectivement. L'intervalle moyen entre la résection initiale du côlon et la résection de métastases pulmonaires (intervalle sans maladie) s'est établi à 36 mois. Pour les 7 patients qui ont subi une résection de métastases extrapulmonaires, le taux de survie à 5 ans s'est établi à 52 %. Les variables préopératoires significatives présageant d'un mauvais pronostic étaient notamment les suivantes : plus d'une lésion pulmonaire, intervalle sans maladie de moins de deux ans et cancer colorectal moyennement ou mal différencié. Les 16 patients ayant reçu une chimiothérapie après leur thoracotomie présentaient un taux de survie à cinq ans de 51 % comparativement à 54 % chez les 33 patients n'ayant pas reçu de chimiothérapie. Réséquer de nouveau des lésions pulmonaires n'a pas réduit le taux de survie. **Conclusions :** La résection pulmonaire d'un cancer colorectal avec métastases est à la fois efficace et sûre. La présence de métastases extrapulmonaires résécables ne devrait pas exclure une ablation du poumon. La chimiothérapie après une thoracotomie n'améliore pas la survie. Les variables préopératoires devraient guider le clinicien qui envisage une intervention chirurgicale.

S urgical resection of pulmonary metastases has been widely accepted as standard treatment for patients with isolated pulmonary metastases. Autopsy of patients who died of metastatic colorectal cancer demonstrated that 20% had isolated pulmonary lesions.[1] The first reported pulmonary metastasectomy from a colorectal primary tumour was performed by Blalock in 1944.[2] Retrospective studies have demonstrated an

increased survival when compared with historical patients without resection. Pulmonary resection remains controversial because of conflicting studies regarding prognostic factors, repeat thoracotomies for recurrent pulmonary lesions, and management of patients with extrapulmonary metastases. Also, no study has addressed the use of chemotherapy after resection. The purpose of this study was to review our experience at McGill University and attempt to answer these questions.

Patients and methods

Between 1975 and 1999, 49 patients underwent curative pulmonary resection for metastases from colorectal carcinoma. The resections were considered curative because all metastatic lesions were removed. Patients who had incomplete resections were excluded. The charts of all patients were reviewed with respect to demographic characteristics, operative and pathology reports of the colorectal and pulmonary resections and any extrapulmonary resections. The use of post-thoracotomy chemotherapy was noted.

The resected pulmonary tissue was compared histologically with the primary colorectal cancer to ensure that the lesion was not a primary lung cancer.

Operative death was defined as death within the same hospitalization. Survival, with the date of the thoracic surgery as the starting point, was estimated using the Kaplan–Meier method.

Demographic characteristics

There were 17 women and 32 men, and the mean age was 67 years. The primary colorectal neoplasm was always an adenocarcinoma. Fourteen (29%) patients underwent low anterior resection, 10 (20%) had a sigmoid resection, 8 (16%) had a left hemicolectomy, 8 (16%) had an abdominal perineal resection and 9

(18%) had a right hemicolectomy. Six percent of patients had a Dukes' stage A primary colorectal adenocarcinoma, 57% had a Dukes' stage B, 27% had a Dukes' stage C. The stage was not described in 10% of the patients. The degree of differentiation was commented on in 23 patients: the tumour was well differentiated in 10, moderately differentiated in 10 and poorly differentiated in 3. Most patients (82%) had their pulmonary lesions detected on routine follow-up chest radiography. However, a chest radiograph obtained because of a rise in the carcinoembryonic antigen (CEA) level revealed a pulmonary nodule in 8% of patients. The remaining patients presented either with dyspnea or cough.

Before thoracotomy, extrapulmonary sites were evaluated for recurrence of the primary colorectal cancer. Colonoscopy, barium enemas and abdominal computed tomography were used frequently to insure that the lungs were the only site of metastases. Patients having any neurologic symptoms underwent CT of the head. Bone scans were obtained for acute bony pain.

The median interval between the initial colon resection and the pulmonary resection was 36 months. Lobectomy was performed in 17 (35%), wedge resection in 21 (43%), pneumonectomy in 5 (10%), bilobectomy in 3 (6%) and lobectomy with a wedge resection in 3

(6%). Two patients (4%) died of respiratory failure while in the intensive care unit after thoracotomy. One had undergone a pneumonectomy and the other a right upper lobectomy.

Thirty-seven patients had a solitary nodule; 7 patients had 2 lesions and 5 patients had 3 metastatic lesions. Forty-seven patients had unilateral lesions; the other 2 had bilateral lesions. The diameter of the pulmonary lesion was greater than 2 cm in 28 patients.

After pulmonary resection, 16 patients underwent intravenous chemotherapy with serial doses of 5-fluorouracil (5-FU) and leukovorin. The remaining patients did not receive chemotherapy. Four patients underwent a second resection and 2 of these patients underwent a third pulmonary resection.

Extrapulmonary metastases were managed by resection in 7 patients; 2 from the bowel anastomosis, 2 from the liver and 3 from the brain.

Results

Follow-up was complete in all patients.

Seven patients suffered a complication after resection: postoperative atrial fibrillation in 2, hematoma in 2, pneumothorax in 2, and an empyema in 1 patient.

Overall survival rates at 5, 10 and 15 years were 55%, 40%, and 25% respectively (Fig. 1). Survival was not
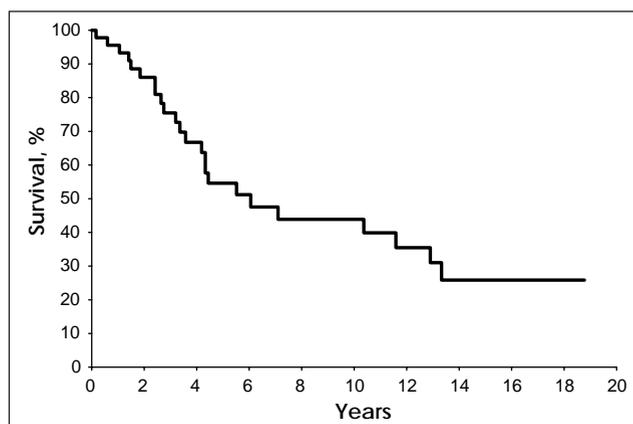
FIG. 1. Overall survival after thoracotomy and resection for pulmonary metastases from colorectal carcinoma.

significantly affected by age, sex, tumour site or Dukes' stage of the colorectal primary. The diameter of the pulmonary lesion, the location and the pre-operative CEA and AP levels also had no affect on survival.

Five-year survival for patients who had solitary pulmonary lesions was 60% as opposed to 29% for those with 2 or more lesions (*p* = 0.024) (Fig. 2). Patients who had unilateral lesions had a 5-year survival of 58% whereas those who had bilateral involvement had a survival of 0% (*p* = 0.021). Patients who had a tumour-free interval greater than 2 years had a 5-year survival of 67% compared with 32% for patients whose tumour-free interval was less than 2 years (*p* = 0.037) (Fig. 3).

Sixteen patients who received 5-FU and leukovorin postoperatively had a 5-year survival rate of 51% as opposed to 54% for the 33 patients who did not receive chemotherapy (*p* = not significant) (Fig. 4). The difference remained nonsignificant even when multivariate adjustment was used for the relatively minor differences in the prognostic profile of the untreated and treated groups.

Survival did not differ in patients who underwent more than one operation for pulmonary metastases from those who did not. Patients who underwent extrapulmonary resection before or after their pulmonary resection did not have a significant difference in survival from those who did not require extrapulmonary resection (Fig. 5).

Discussion

The lung is the second most common site of colorectal metastases, developing in 10% to 20% of patients with colorectal cancer.[3] Between 13% and 28% of patients with pulmonary metastases from colorectal cancer have potentially resectable lung metastases.[3,4] The prognosis for patients with pulmonary metastases that remain unresected is poor: 44% within 6 months and only a 9% 2-year survival.[3] To date, there is no effective chemotherapy that significantly improves survival for colorectal carcinoma metastatic to the lungs. Therefore, surgical excision of pulmonary metastases has remained the treatment of choice.

Most patients are asymptomatic when pulmonary metastases are discovered. Regular chest radiography and serial CEA measurement have enabled physicians to detect pulmonary recurrence before systemic dissemination of disease. When a le-
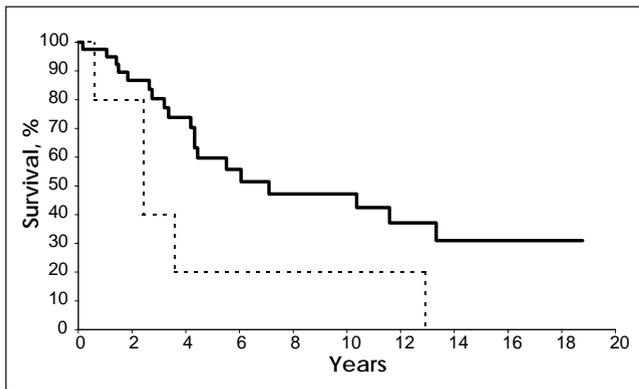

FIG. 2. Survival after thoracotomy and pulmonary resection according to number of pulmonary metastases (dotted line = <2, solid line = ≥2).
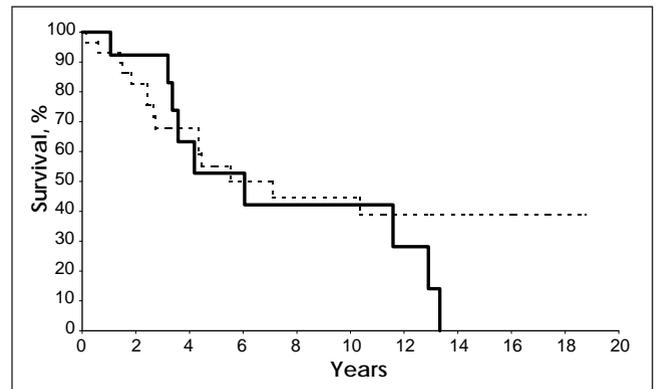

FIG. 4. Comparison of survival after resection of pulmonary metastases beween those who received chemotherapy (solid line) and those who did not (dotted line).
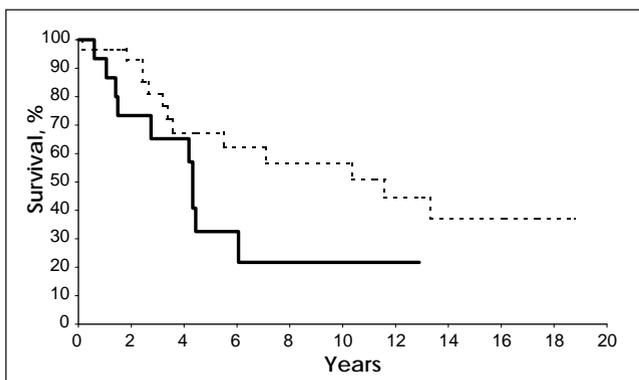

FIG. 3. Survival after thoracotomy and resection for pulmonary metastases according to disease-free interval (solid line = <2 years, dotted line = ≥2 years).
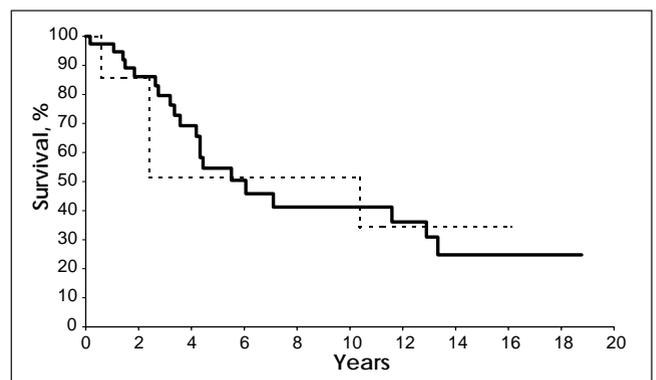

FIG. 5. Survival after thoracotomy and pulmonary resection for those who did (dotted line) and did not (solid line) have extrapulmonary resection.

sion is detected on a chest radiograph, an orderly approach to searching for disseminated disease is warranted. It is not necessary to perform a biopsy to differentiate a primary lung lesion from a metastatic lesion since surgical resection is the treatment for both types if the lesion is localized. It is, however, important to search for extrapulmonary metastases. After a thorough physical examination, seeking signs of metastases to other sites, CEA levels should be obtained to gauge how aggressive the search for extrapulmonary disease should be. To rule out hepatic recurrence, liver function tests along with a CT of the upper abdomen should be performed. Since a CT is not very sensitive for colorectal recurrence contrast enema examination or colonoscopy should be done to rule out a recurrence or a new primary tumour in the gastrointestinal tract. Finally, CT of the chest should be done because CT has demonstrated additional pulmonary nodules in 20% of patients.[5]

Previous studies have demonstrated a 5-year survival of 15% to 61%.[3,5–8] Our study is in the higher part of this range. We have demonstrated that the important preoperative prognostic factors are as follows: number of metastases, disease-free interval, degree of differentiation of the colonic primary, and whether the lesions are unilateral or bilateral. All these factors have a significant impact on survival.

Preoperative CEA and AP levels, the diameter of the lesions, and the stage of the colorectal primary had no significant impact.

Controversy exists on whether resecting pulmonary lesions is beneficial when extrapulmonary lesions have already been resected or are to be resected. Our study demonstrates that these patients do just as well as those who do not have other lesions. Therefore, any patient with a history of extrapulmonary metastatic resection should be considered for pulmonary resection. Even if the 2 lesions present

at the same time, every attempt should be made to resect both.

Some of our patients underwent multiple pulmonary resections. They did not have a shorter survival than those who required only one resection. Therefore, we recommend that close follow-up with chest radiography should be instituted postoperatively to detect any recurrence since another resection can improve survival.

Controversy exists about the benefit of post-thoracotomy chemotherapy. Physicians have no data regarding this question. Our study shows no improvement in survival. The decision to treat a patient was based on the patient's desires, the physician's beliefs and accessibility. The 2 groups had similar preoperative CEA levels and number of metastases, criteria that might influence the oncologist in deciding whether to use chemotherapy. Chemotherapeutic agents are not specific for neoplastic cells, and normally proliferating cells are also affected, accounting for the often serious side effects of treatment. The morbidity of postresection chemotherapy was not assessed in this study because of the subjectivity of the question and the retrospective nature of the study. All patients who received treatment received 5-FU and leukovorin, drugs that act synergistically to increase cytotoxicity. They are associated with myelosuppression and often debilitating diarrhea and gastrointestinal mucositis. Our study showed no benefit for 5-FU and leukovorin, so it is our recommendation that it not be administered following pulmonary resection. Newer agents have not been tested and their value should be assessed in the future.

The lack of controls and the retrospective design are important limitations of this study. The vigour of patient follow-up differed from patient to patient, resulting in a less than ideal outcome assessment. Also, because our study included patients from 1975, preoperative screening for extrapulmonary metastases was

likely to be significantly less sensitive, resulting in a higher proportion of patients with more widespread metastases. This may result in an underestimation of survival in potentially curative resections during the present era.

Patients with a solitary, unilateral lesion should undergo a standard posterolateral thoracotomy, providing excellent exposure of the hemithorax. Patients with bilateral metastases may be explored safely through either a median sternotomy or staged bilateral thoracotomies.[8] Some surgeons believe a median sternotomy is the best approach for all lesions, even unilateral, to ensure a more complete resection. However, a study by Roth and colleagues[9] comparing median sternotomy with open unilateral thoracotomy demonstrated no difference in patient survival. Presently, the use of video-assisted thoracic surgery (VATS) in the management of pulmonary metastases is being evaluated. McCormack and colleagues[10] performed a prospective trial of 18 patients comparing the sensitivity of VATS and open thoracotomy in detecting pulmonary metastases. Ten patients (56%) had additional malignant lesions found at thoracotomy after VATS was performed. They therefore concluded that a thoracotomy is required to achieve complete resection.[10] With the advent of spiral CT, the sensitivity has increased remarkably, detecting an additional 40% of lesions,[11] which appears to be a similar number to that documented to be found by the open technique in McCormack's study. Despite the findings of this study, one should approach VATS in oncologic surgery with extreme caution. The inability to palpate the lung for smaller, intraparenchymal lesions may prevent complete resection of metastatic disease.

Conclusions

We conclude that resection of

pulmonary metastases significantly improves overall survival and that patients do not benefit from the presently available chemotherapy after pulmonary resection. However, prognostic factors of all patients should be evaluated and a decision should be made regarding the benefit of resection with thoracotomy versus conservative management. Poor prognostic factors like bilateral lesions, multiple lesions, lesions requiring pneumonectomy for complete resection, and lesions that present very soon after colonic resection should be considered in all patients. Patients with a poor prognosis may benefit more from palliative measures than a thoracotomy with pulmonary resection.

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Notices
Avis

American College of Surgeons Clinical Congress

The 2001 Clinical Congress of the American College of Surgeons will be held from Oct. 7 to 12, 2001, in New Orleans. The majority of general and scientific sessions and all scientific exhibits will be held at the Ernest N. Morial Convention Center. The Hilton Riverside will serve as the headquarters hotel.

The program will include 34 postgraduate courses, more than 300 research-in-progress presentations and approximately 175 scientific exhibits. Topics for the general and specialty sessions and listings of postgraduate courses can be found on the American College of Surgeons Web site at **www.facs.org/clincon2001/2001index.html**.

Laparoscopic and gynecologic surgery

The Mayo Clinic Scottsdale is sponsoring the 14th Annual Techniques in Advanced Laparoscopic and Gynecologic Surgery course, from Oct. 24 to 27, 2001, to be held at the Hyatt Regency Maui Resort & Spa, 200 Nohea Kai Dr., Lahaina, Maui, Hawaii. This course will provide an in-depth review of laparoscopic techniques, complications, instrumentation, among other topics and procedures. Course highlights include interactive case presentations, using an audience response system, and Video Festival, which will include a variety of laparoscopic procedures with an interactive discussion by each author. Credits: AMA Category 1 and ACOG — to be decided. Course registration fee is US$680. For further information contact Sarah Dorste, Mayo School of CME, Mayo Clinic Scottsdale, 13400 East Shea Blvd., Scottsdale AZ 85259; tel 480 301-4661, fax 480 301-8323.