

Review Article

Resection of non-hepatic colorectal cancer metastasis

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KEY WORDS Cancer; colorectal; non-hepatic; metastasis

J Gastrointest Oncol 2012;3:59-68. DOI: 10.3978/j.issn.2078-6891.2012.007

Introduction

Colorectal cancer (CRC) continues to be one of the leading causes of significant health problems and cancer-related death in the world. Each year about one million people are diagnosed with CRC worldwide with an estimated 140,000 individuals being diagnosed in the United States (1). About one-half of patients will either present with colorectal liver metastasis (CLM) or develop them during the course of their disease (2,3). While roughly 20% of all patients will present with synchronous liver metastasis, another 25-30% will present with metachronous disease (4-7). Common sites of extra-hepatic metastatic disease include the lung, hilar/peri-hepatic lymph nodes, as well as the peritoneum (8-12). While systemic chemotherapy remains the cornerstone of therapy for patients with stage IV colorectal disease, some patients are optimally managed with the addition of surgical therapy (13-17).

Previous data on patients with extrahepatic disease (EHD) and CLM have suggested that these patients have a poor prognosis (18-20). As such, in most instances, EHD was traditionally considered a strong relative or absolute contraindication to surgical resection. However, more recently our group, as well as others, have reported

long-term survival after resection of EHD (9-12,21-25). As a consequence, resection of EHD from a colorectal primary has increasingly become accepted over the last decade. We herein review the management of patients with EHD metastatic disease from a colorectal primary tumor. Specifically, we highlight the data on the surgical management of patients with metastatic disease at the most common EHD sites (e.g. lung, hilar/peri-hepatic lymph nodes, peritoneum), as well as define general oncological principles for treating this challenging cohort of patients.

CRC Metastasis: Implication of Number and Anatomic Site

There has been controversy regarding the relative importance of total number of EHD metastatic tumors versus location of the specific metastatic site (23,24,26). Some investigators have suggested that the total number of metastatic lesions is the dominant factor that predicts outcome following surgical resection (24,26). In a provocative paper by Elias *et al.*, the authors argued that the site of the metastatic disease did not matter - only the number of metastatic lesions (26). In this study, the total number of tumors impacted survival, but the location of the metastatic disease did not. However, data from this study were difficult to interpret due to the small number of patients included in each subset analysis. More recently, our group published a large, international series looking at resection of extra-hepatic CRC metastases (8). In this study, both the total number of metastases and the location of the metastatic disease were associated with prognosis. Survival was strongly associated with overall tumor burden (Figure 1). We noted, however, that among patients with a large tumor burden (>6 metastatic lesions) the relative prognostic impact of anatomic location was less (Figure 2). Of note, among patients with a lower burden of disease, anatomic

No potential conflict of interest.

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Submitted Dec 06, 2011. Accepted for publication Jan 13, 2012.

Available at www.thejgo.org

ISSN:2078-6891

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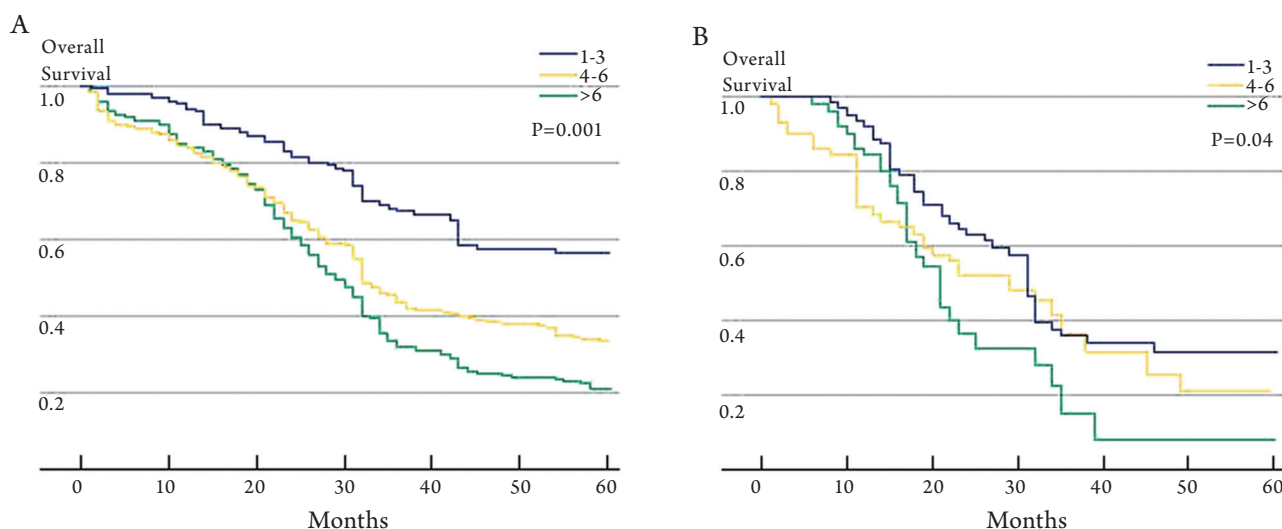


Figure 1. A: Overall survival among patients with colorectal liver metastasis (CLM) only stratified by number of CLM treated; B: Overall survival among patients with CLM + extrahepatic disease (EHD) stratified by number of CLM + EHD metastasis treated. Used with permission: Pulitano C, Bodingbauer M, Aldrighetti L, *et al.* Liver resection for colorectal metastases in presence of extrahepatic disease: results from an international multi-institutional analysis. *Annals of Surgical Oncology* 2011;18(5): 1380-8.

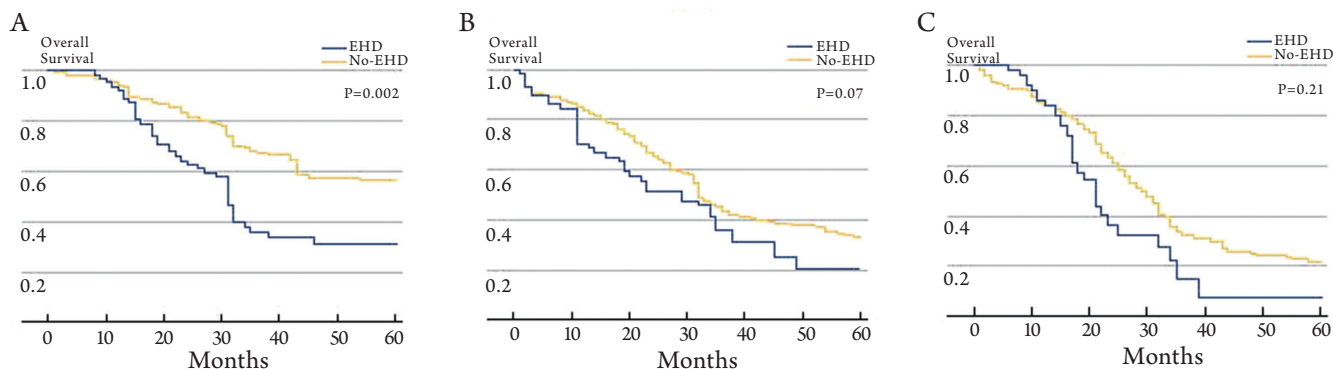


Figure 2. Overall survival rates when the total number of metastases (CLM + EHD) was (A) 1-3 (B) 4-6 (C) >6 stratified by the presence or absence of EHD. Used with permission: Pulitano C, Bodingbauer M, Aldrighetti L, *et al.* Liver resection for colorectal metastases in presence of extrahepatic disease: results from an international multi-institutional analysis. *Annals of Surgical Oncology* 2011;18(5): 1380-8.

location of the metastatic disease had a strong influence on survival (Table 1). As such, both total number of EHD metastases and the location of the metastases should be considered when assessing patients for surgery.

Pulmonary Metastasis

The lung is one of the most common metastatic sites for colorectal carcinoma. About 2-7% of patients with primary CRC will present with isolated lung metastasis, while about 10% of patients will have synchronous pulmonary and

CLM. The lung is the most accepted EHD site managed with surgical resection. In 1944, Blalock reported the first successful resection of pulmonary metastasis from colorectal carcinoma. Subsequently, Thomford in 1965 defined specific criteria for resection of metastatic colorectal disease to the lung (27). Today, resection of pulmonary metastasis is well-established, although the evidence for the effectiveness of metastasectomy largely comes from retrospective studies (28-35). Similar to surgical management of all patients with metastatic disease, patient selection is critical in identifying the best candidates for

Table 1. Survival statistics by location of extrahepatic disease. Used with permission: Pulitano C, Bodingbauer M, Aldrighetti L, *et al.* Colorectal Liver Metastasis in the Setting of Lymph Node Metastasis: Defining the Benefit of Surgical Resection. *Annals of surgical oncology* 2011.

Site	n(%)	Median survival (mo)	3-Year survival (%)	5-Year survival (%)
Lung	62(36.2)	46	60	33
Peritoneum	25(14.6)	32	32	26
Hepatic Pedicle lymph nodes	41(23.9)	29	43	27
Aortocaval lymph nodes	14(8.1)	13	22	7
Other	11(6.5)	_a	_a	_a
Multiple sites	18(10.5)	15	26	14

^aNumber of patients too small for survival calculations.

Table 2. Selection criteria for pulmonary metastasectomy. Used with permission: Villeneuve PJ, Sundaresan RS. Surgical Management of Colorectal Lung Metastasis. *Clin Colon Rectal Surg* 22(4):233-41, 2009.

Colorectal primary controlled, or If present, is considered resectable
Absence of extrathoracic disease, or If present, is resectable or ablatable
Pulmonary metastases are completely resectable An R ₀ resection is the goal
Patient has adequate cardiopulmonary reserve

Adapted from Greelish, Friedberg²⁵ and Pfannschmidt *et al.*⁵⁴

resection.

Clinical practice guidelines for the management of patients with pulmonary metastasis have been established (36). Specifically, general recommendations for the surgical resection of pulmonary metastasis include: (I) metastasis are technically resectable with microscopically negative (R₀) margins (II) general and functional risks are tolerable (III) primary tumor is controlled, and (IV) no extra-thoracic lesions are present (with the exception of hepatic lesions in which complete removal of both hepatic and pulmonary metastasis is feasible) (Table 2). The presence of concomitant clinically positive disease in the mediastinal or hilar lymph nodes is a strong contraindication to pulmonary metastasectomy, as this is an ominous prognostic factor associated with prohibitively poor long-term survival (31-34,37,38).

Surgical resection for pulmonary metastasis is associated with a reported 5-year survival ranging from 20% to 60% (28-30,32,39). Several factors have been associated with prognosis following surgical resection of pulmonary CRC metastasis. Specifically, high preoperative carcinoembryonic antigen (CEA) has been shown to be an independent factor associated with worse long-term survival (40-43). The number of pulmonary lesions is also associated with long-term outcome. Multiple studies have noted that tumor number is an important independent predictor of long-term outcome (43,44). In one of the largest registry studies examining long-term results of lung metastasectomy among 5206 cases, the reported 5-year survival was 43%

for patients with single lesions versus 27% for patients with four or more lesions (45). Another factor that impacts outcome is whether the patient presents with synchronous or metachronous disease, as well as the disease-free interval between resection of the primary tumor and the pulmonary metastasis. Several studies have noted that a disease-free interval of greater than 1 year between the time of the diagnosis of the primary tumor and the pulmonary metastasis was associated with improved outcomes (37,45).

Patients whose disease pattern includes both pulmonary and hepatic metastases may benefit from either simultaneous or sequential lung and liver resections (39,46-50). In general, patients who present with synchronous pulmonary and CLM can undergo either simultaneous or staged resections. Among patients who need an extensive liver resection, a staged approach may be preferable. In other circumstances where the disease is more limited a simultaneous approach can be performed with low morbidity and perioperative mortality (51). When undertaking a staged approach, outcome appears comparable regardless of whether the lung or liver resection is undertaken first (51). As such, the approach should be individualized. For patients with metachronous metastasis, a longer time interval between the detection of the lung and liver metastasis has been associated with a better prognosis (46-50).

After pulmonary metastasectomy, 50-75% of patients will recur, both with pulmonary as well as other EHD sites (35). Local or intra-pulmonary recurrence can be due to an incomplete resection, lymphangitic spread, or "floating"

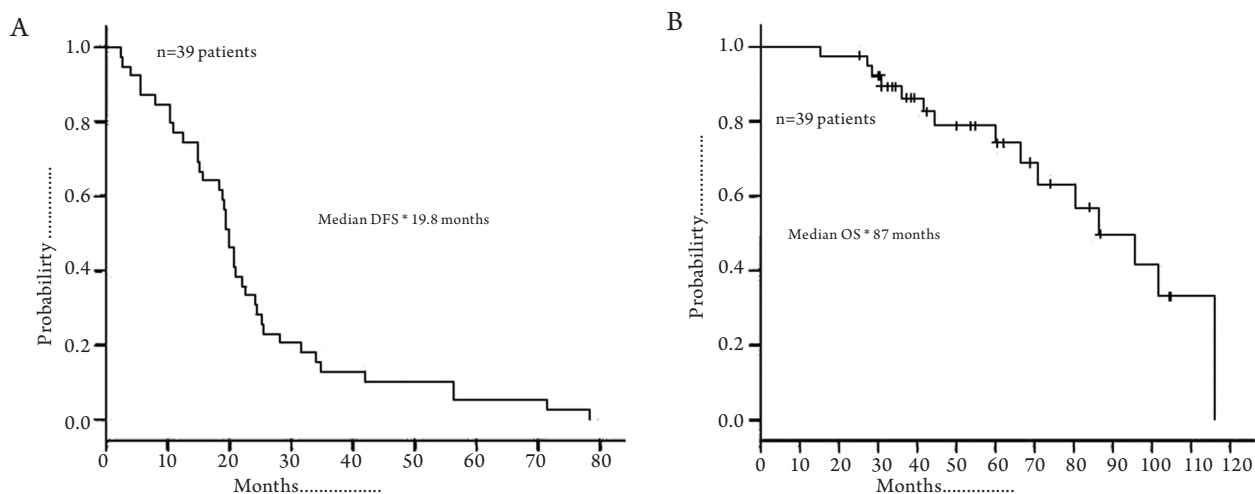


Figure 3. Disease-free (A) and overall survival (B) after initial pulmonary metastasectomy for CRC lung metastasis. Used with permission: Shah SA, Haddad R, Al-Sukhni W, *et al.* Surgical resection of hepatic and pulmonary metastases from colorectal carcinoma. *Journal of the American College of Surgeons* 2006;202(3): 468-75.

cancer cells (52,53). Despite the relatively high incidence of recurrence, the overall survival associated with pulmonary metastasectomy ranges from 48-60% (Figure 3) (37,39-50,54). In a meta-analysis incorporating 14 studies and 1684 patients, most of whom underwent a unilateral wedge resection for limited disease (53%), the overall 5-year survival was 48% (54). Of note, 5-year survival was only 17% among patients with peri-bronchial/hilar lymph nodes and no patient with mediastinal lymphadenopathy survived to 5 years (38). In contrast, patients who had no nodal disease had a 5-year survival of 60%. The authors noted a median survival of 29 months overall; however, among those patients with a disease-free interval of 3 years or more between the primary tumor treatment and the diagnosis of the pulmonary metastasis median overall survival was 49 months (45).

Given the relative high incidence of recurrence following pulmonary metastasectomy, there has been interest in repeat pulmonary resection (Table 3). Park *et al.* reported a 79.3% 5-year survival after second metastasectomy and a 5-year survival of 77.8% after a third resection (50). Other studies have shown similar results with 5-year survival ranging from 42-61%, suggesting that second and third resection of recurrences are viable options for patients with recurrent disease and can lead to long-term survival in a subset of patients (53,55,56).

Extrahepatic Lymph-Node Metastases

In addition to loco-regional nodal basins, CRC may metastasize to peri-hepatic, hilar, or para-aortic lymph

nodes. Nodal metastasis outside the regional CRC basin may represent “metastasis from metastasis” as a subset of patients who do not have regional lymph node metastasis can subsequently be found to have peri-hepatic or hilar lymph node metastasis (57-59). While the overall incidence of lymph node metastasis in the setting of CLM is hard to define, most studies have reported a range of 1-10% (21,60-63). Traditionally, metastatic disease in the hilar or para-aortic lymph nodes has been considered a strong relative contraindication to surgery due to poor long-term survival among this group of patients. With more effective chemotherapy, as well as the recent publication on improved outcomes for patients with non-regional lymph node metastasis, the role of resection of CLM in the setting of lymph node metastasis has been reconsidered (8,11,22,64,65).

Several studies have examined the impact of lymph node metastasis through the use of empiric routine lymphadenectomy at the time of liver surgery (21,59,63,66). In a study by Elias *et al.*, lymph node dissection of the hepatic pedicle was undertaken in 100 consecutive patients undergoing curative hepatectomy for CLM in whom lymph node involvement of the hepatic pedicle was not macroscopically detectable (63). Microscopic lymph node involvement was found in 14 patients. In a separate study by the Strasbourg group, among 160 patients who had routine lymphadenectomy, the authors reported an 11% incidence of microscopic disease in the lymph nodes (59). Laurent *et al.* reported an incidence of 15% for microscopic disease in the peri-hepatic/hilar lymph nodes (21). Early reports from these centers noted a poor survival among patients with

Table 3. Survival following pulmonary metastasectomy stratified according to the number of resection. Used with permission: Park JS, Kim HK, Choi YS, *et al.* Outcomes after repeated resection for recurrent pulmonary metastases from colorectal cancer. *Annals of oncology* 2010;21(6): 1285-9.

Survival	Initial metastasectomy	Second metastasectomy	Third metastasectomy
Overall 5-year survival (%)	71.17	79.32	77.78 ^a
DFS			
Median survival (months)	27.43	42.8	Not calculated ^a
5-year survival (%)	33.30	48.69	Not calculated ^a

^a The number of patients that underwent third metastasectomy was too small for statistical analysis. OS, overall survival; DFS, disease-free survival.

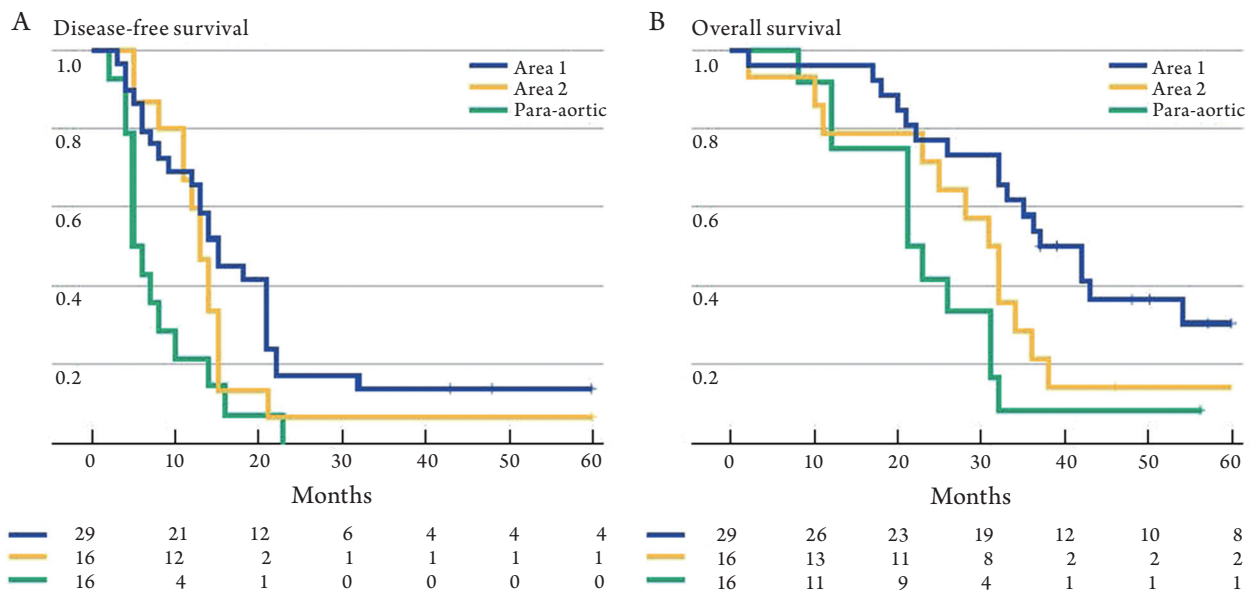


Figure 4. Disease-free (A) and overall survival (B) stratified by the location of lymph node metastasis. Used with permission: Pulitano C, Bodingbauer M, Aldrighetti L, *et al.* Colorectal Liver Metastasis in the Setting of Lymph Node Metastasis: Defining the Benefit of Surgical Resection. *Annals of surgical oncology* 2011.

microscopic lymph node metastasis, with 5-year survival in the range of 5-18%. More recently other groups reported more favorable long-term survival, noting that the specific site of the metastatic lymph node disease is important in stratifying patients with regards to prognosis (11,22,67).

Among patients with CLM, the location of the lymph node metastasis may dictate the relative survival benefit of surgical intervention. Specifically, Jaeck *et al.* note that liver resection did not offer a survival benefit among patients with lymph node metastasis along the common hepatic artery and celiac axis (area 2), but was beneficial for those patients with lymph node disease restricted to the hepatoduodenal ligament and retro-pancreatic location (area 1) (59). Adam *et al.* similarly noted a difference in outcome when comparing survival of patients with lymph node metastasis in area 1 versus area 2 (22). In a separate multi-institutional

international study from our own group, we found that - while long-term survival may be possible in patients with lymph node metastasis in area 2 - surgery held the most benefit for patients with lymph node disease relegated to area 1 (14% versus 30%) (Figure 4). In contrast to areas 1 and 2, the outcome of surgery for patients with para-aortic lymph node metastasis is particularly dismal. Adam *et al.* reported a median survival of only 17 months for this group of patients and every patient experienced a recurrence. In the report by Pulitano *et al.*, these investigators similarly noted no long-term survivors among patients operated on in the setting of para-aortic lymph node disease (67). Taken together, these data strongly suggest that lymph node location should be taken into consideration when deliberating about whether surgical resection should be undertaken. While overall survival in the setting of lymph

node disease outside the CRC lymph node basin is only in the range of 18-20%, certain subsets of patients such as those with disease restricted to the hepatoduodenal ligament (area 1) may have a 5-year survival up to 30%.

In addition to the location of the lymph node disease, the presence of clinically "positive" macroscopic disease is also a critical factor in outcome. Unlike patients with sub-clinical microscopic disease, patients with clinically evident macroscopic disease almost universally have a poor outcome. As such, most clinicians have concluded that resection of macroscopic lymph node metastasis should be a contraindication to hepatic resection (15,19,20,68). A review by Rodgers and McCall of 15 studies in the literature describing liver resection for CLM reported on 145 patients with macroscopic lymph node involvement, of whom only 5 were alive at 5 years (61). In several separate studies that reported on patients with macroscopic nodal involvement, the authors noted that virtually all patients were dead within 5 years of surgery (62,69,70). As such, patients with clinical macroscopically evident lymph node metastasis should be treated in a multi-modality setting with preoperative chemotherapy with only a well-selected subset considered for eventual surgery.

Peritoneal Carcinomatosis

Peritoneal carcinomatosis is a form of disease progression that affects 30% to 40% of patients with CRC (71,72). Traditionally, peritoneal carcinomatosis has been associated with a median survival of only 6 to 9 months (72-74). Peritoneal carcinomatosis is thought to result from peritoneal spread of cancer cells or seeding of the peritoneum during surgery (75,76). While many consider peritoneal carcinomatosis to be a form of disseminated disease portending an extremely poor outcome, Sugarbaker and colleagues have challenged this concept (76). Specifically, some clinicians have argued that peritoneal carcinomatosis is more akin to loco-regional recurrence/metastasis for which a more aggressive approach may be appropriate in select circumstances (76,77).

Some centers have reported on their experience with cytoreduction surgery (CRS) and intraperitoneal chemotherapy for peritoneal CRC metastasis. Surgery for peritoneal disease usually involves complete CRS with removal of all gross disease in combination with hyperthermic intraperitoneal chemotherapy, usually consisting of the installation of mitomycin C or oxaliplatin for 30-90 minutes after CRS is completed. Using this approach, median survival exceeding 60 months has been reported in a well-selected subset of patients (78). The

approach to patients with peritoneal metastasis from CRC, however, still remains highly controversial. Such therapy remains not the standard of care and is not indicated for most patients, especially those with disseminated carcinomatosis (3). Among those patients with peritoneal disease, patient selection is critical to achieving acceptable outcomes.

A consensus statement published by a consortium of cytoreduction centers noted eight clinical and radiographic variables to select patients. Specifically, an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 , no extra-abdominal disease, up to three small resectable hepatic parenchymal metastases, no biliary or ureteral obstruction, less than one site of small bowel obstruction, small volume mesenteric disease, and minimal disease in the gastro-hepatic ligament (79). The authors noted that these guidelines should allow for improved selection of patients for complete CRS, in turn giving patients a better chance for survival. Complete CRS is perhaps the most critical factor associated with survival, and therefore only patients with low volume peritoneal CRC disease should be considered for resection (77,79,80).

Verwaal *et al.* reported a randomized trial examining patients treated with systemic chemotherapy (5-Fluorouracil and leucovorin) versus operative cytoreduction with intra-peritoneal therapy (81). In this study, cytoreduction with intraperitoneal chemotherapy was shown to be associated with a survival benefit (median survival: systemic chemotherapy, 12.6 months versus cytoreduction and intraperitoneal chemotherapy, 22.4 months). The study is difficult to interpret, however, in light of currently available more efficacious systemic chemotherapy. An update of the trial with a median follow-up of almost 8 years reported a 5-year survival of 43% among patients with no gross residual disease, but no patient who had gross residual disease left at the time of CRS survived to 5 years (82). In more contemporary retrospective studies, other investigators have similarly noted the feasibility of long-term survival in a select group of patients. For example, Glehen *et al.* reported on 506 patients undergoing CRS and hyperthermic intraperitoneal chemotherapy at 28 institutions. The overall median survival was 19.2 months for hyperthermic intraperitoneal chemotherapy with a 5-year survival of 19% (12). Elias *et al.* reported that cytoreduction and hyperthermic intraperitoneal chemotherapy was able to achieve a 5-year survival of 51% among patients with isolated, resectable peritoneal disease (77). More recently Shen *et al.* reported that complete CRS plus hyperthermic intraperitoneal chemotherapy for limited peritoneal CRC disease had a comparable survival to patients undergoing hepatic resection for CLM (83). Specifically, the 1-, 3-, and

5-year overall survival for a complete CRS was 91%, 48%, and 26% versus 87%, 59%, and 34% for patients undergoing resection of CLM. The study has been criticized, however, for the relatively low 5-year survival reported among patients with resected hepatic metastasis - making any true comparison difficult. In a meta-analysis by Cao *et al.* the authors reported a general trend toward a survival benefit for CRS and hyperthermic intraperitoneal chemotherapy versus the control groups (84). While such results are encouraging and provocative, patients with peritoneal CRC disease should still be considered at very high risk of disseminated disease. As such, surgery for this group of patients needs to be extremely selective and done within a multi-disciplinary approach.

Conclusion

It is important to note that in a large series of over 1,600 patients with CLM only 10% underwent resection of non-hepatic CRC metastasis (8). Despite the very select nature of this cohort, the 5-year survival was only 26%. Therefore, based on the high risk of disseminated disease, most patients with non-hepatic metastatic CRC cancer should initially be treated with systemic chemotherapy. While this general approach is particularly warranted for patients with macroscopic lymph nodes or peritoneal disease, some patients - such as those with isolated, solitary pulmonary metastasis - may be appropriate for "up-front" surgical resection. For the majority of patients with non-hepatic CRC metastasis who receive systemic chemotherapy, continued and iterative reassessment with cross-sectional imaging is required. Patients who progress on therapy should receive additional chemotherapy and, in general, not be considered candidates for resection. Patients with responsive or stable disease on systemic therapy should be considered for surgery if a complete resection (R0) of the disease sites is feasible. Both the number and the site of metastatic disease needs to factor into the decision to offer surgery. Specifically, patients with a large burden of disease (6 or more lesions/disseminated peritoneal disease) and those with certain anatomic sites of disease (para-aortic lymph nodes, peritoneal disease) have a very guarded prognosis. As such, surgery should only be undertaken in a very select subset of these patients who have clearly demonstrated responsive or quiescent disease for a prolonged period of time. Patients should be discussed in the context of a multidisciplinary team. While non-hepatic CRC metastasis should no longer be an absolute contra-indication to surgery, careful selection is tantamount to ensuring maximal benefit of surgical resection.

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Cite this article as: Johnston FM, Kneuert PJ, Pawlik TM. Resection of non-hepatic colorectal cancer metastasis. *J Gastrointest Oncol* 2012;3:59-68. DOI: 10.3978/j.issn.2078-6891.2012.007