Annie Toja. *Provence, France*. Acrylic.

*Guidelines are being developed regarding surgical resection of hepatic metastases.*

# Resection of Colorectal Liver Metastases: Current Perspectives

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**Background:** *Metastases to the liver is the leading cause of death in patients with colorectal cancer.*

**Methods:** *The authors review the data on diagnosis and management of this clinical problem, and they discuss management options that can be considered.*

**Results:** *Complete surgical resection of metastases from colorectal cancer that are localized to the liver results in 5-year survival rates ranging from 26% to 40%.*

**Conclusions:** *By adding modalities such as targeted systemic therapy and other "local" treatments for liver metastases, further gains in survival are anticipated.*

## Introduction

Colorectal cancer is the fourth leading cancer in the United States and ranks second in cancer-related deaths. It is estimated that in 2005, over 146,000 new patients were newly diagnosed with colorectal carcinoma and over 56,000 died of this disease.[1,2] Of the 146,000 new cases with colorectal cancer, 50% (73,000 patients) developed liver metastases, and 30% (44,000 patients) had metastatic disease confined to the liver. In the past, only 5% of patients who developed liver metastases from colorectal cancer were considered eligible for surgical directed therapies.[3] With improved surgical techniques, reduced postoperative mortality, and better systemic therapy, indications for surgery have broadened so that nearly one third of patients with colorectal liver metastases (14,000 patients) undergo hepatic tumor resections each year in the United States.[4-6]

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*Abbreviations used in this paper:* CT = computed tomography, RFA = radiofrequency ablation.

## Outcomes of Liver Metastasis Resection

Historically, liver tumor resection from the liver was associated with a high operative mortality rate. In 1898, Keen et al[7] reported a 15.5% operative mortality rate for liver resection performed in 59 cases from 1886 to 1897.

**Table 1. — Results of Colorectal Liver Metastasis Resection**

| Reference (year) | No. of Patients | Operative Mortality (%) | Survival (%) | | | | Median Survival (mos) |
|---|---|---|---|---|---|---|---|
| | | | 1-yr | 3-yr | 5-yr | 10-yr | |
| Foster[8] (1974) | 168 | 5.0 | – | – | 20 | – | – |
| Wilson[3] (1976) | 60 | – | – | – | 25 | – | – |
| Wagner[9] (1984) | 116 | – | – | – | 25 | – | – |
| Adson[10] (1984) | 141 | 3.0 | 82 | 40 | 25 | – | 24 |
| Hughes[11] (1986) | 859 | – | – | – | 33 | – | – |
| Scheele[12] (1990) | 173 | 5.5 | – | – | 40 | 27 | – |
| Schlag[13] (1990) | 122 | 4.0 | 85 | 35 | 25 | – | 32 |
| Rosen[14] (1992) | 280 | 4.0 | 84 | 47 | 25 | – | – |
| Gayowski[15] (1994) | 204 | 0.0 | 91 | 43 | 32 | – | – |
| Scheele[16] (1995) | 434 | 4.0 | 85 | 45 | 23 | 18 | 40 |
| Jamison[17] (1997) | 280 | 4.0 | 84 | – | 27 | 20 | 33 |
| Fong[18] (1999) | 1001 | 2.8 | 89 | 57 | 37 | 22 | 42 |
| Choti[19] (2002) | 226 | 1.0 | 93 | 57 | 40 | 26 | 46 |
| Abdalla[20] (2004) | 190 | – | – | 73 | 58 | – | 21 |
| Mutsaerts[21] (2005) | 102 | 3.0 | 71 (2-yr) | | 29 | – | – |

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Today, the operative mortality rate for liver resections is less than 5% (Table 1).[3,8-21] In 1963, Woodington and Waugh[22] reported long-term outcomes from tumor resection for colorectal cancer metastases in the liver. This landmark article from the Mayo Clinic included the outcomes of a personal series of 25 patients treated from 1938 to 1959. Four of 20 patients with long-term follow-up were alive at 5 years. In 1976, Wilson and Adson[3] reported the outcomes of 60 patients with tumor resections from the liver for colorectal metastases. Of the 36 patients eligible for follow-up, 15 were alive at 5 years and 8 were alive at 10 years. An overall 25% 5-year survival rate was again observed in patients who had undergone complete resection of solitary liver lesions. These outcomes in patients with metastatic colorectal cancer challenged the prevailing paradigm of the natural history of this disease. It was counterintuitive that systemic disease could be controlled by local therapy. These studies were initially criticized for potential stage migration bias. This issue was addressed by Wagner et al[9] who reported outcomes of similar patients who underwent surgical exploration without resection at the same institution during the same time period. In this study, only 2% of 70 patients who had potentially resectable liver metastases but did not undergo resection were alive at 5 years. These findings were consistent with other studies that evaluated potentially resectable tumors that were removed compared to those with no resection (Table 2).[9,12,23-31] For example, Scheele et al[32] reported a 5-year survival rate of 40% in patients who underwent tumor resections compared to 0% in 62 patients who had potentially resectable tumors but did not undergo resection. In a similar study, Wood et al[27] reported an 8% 5-year survival rate in 13 patients who were deemed resectable yet did not undergo an operation.

Despite the small numbers and nonrandomized format, the findings from these early studies changed the clinical approach to patients with colorectal liver metastases. An important oncologic question is whether the recently improved systemic therapies can achieve the same results as resection of colorectal liver metastases; this seems unlikely. The natural history of colorectal cancer metastasis in the majority of patients is dismal.[33] Historically, the median survival is 6 to 12 months if untreated.[34,35] Even with newer therapeutics such as irinotecan or oxaliplatin, the 5-year survival rate with nonsurgically treated hepatic metastases is low.[36-38] In contrast, those who undergo a complete resection have 5-year survival rates of 25% to 40%. It can be argued that the patients who undergo resection are selected and may have better outcomes because they

**Table 2. — Results of Nonsurgically Treated Colorectal Cancer Metastasis**

| Reference (year) | No. of Patients | Median Survival (mos) | 5-yr Survival (%) |
|---|---|---|---|
| Pestana[23] (1964) | 353 | 9.0 | 3 |
| Cady[24] (1970) | 269 | 13.0 | 1 |
| Lahr[25] (1983) | 175 | 6.1 | 1 |
| Wagner[9] (1984) | 252 | 19.0 | 2 |
| Adson[26] (1987) | 70 | – | <5 |
| Wood[27] (1976) | 113 | 10.6 | – |
| Scheele[12] (1990) | 921 | 6.9 | 0 |
| Stangl[28] (1994) | 677 | 7.5 | 1 |
| Rougier[29] (1995) | 318 | 5.7 | – |
| Scheele[30] (1995) | 964 | – | 0 |
| Kato[31] (2003) | 178 | – | 3.4 |

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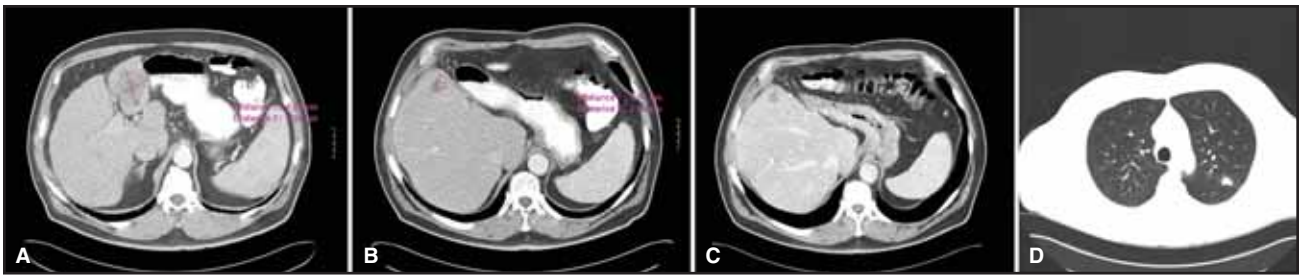


Fig 1. — (A) A 65-year-old man with a single 5-cm lesion to the left lobe with 3 additional lesions in the right lobe. (B) At 4-month follow-up after left hepatectomy, ablation demonstrates evidence of recurrence and stable ablation sites. (C) At 18-month follow-up, there is no change in ablation site and no evidence of liver disease. (D) At 18-month follow-up, a new biopsy-proven metastasis is seen in the left upper lobe.

have less virulent disease. A trial designed to compare resection vs systemic therapy is unlikely until more efficacious systemic therapy regimens are discovered. Currently, the survival rates reported after curative hepatic resections are 25% to 39% for 5 years and 22% to 23% for 10 years.[3,9,13,39]

Among patients with colorectal cancer who have undergone "curative" hepatic metastasectomy, 60% will develop local, regional, or distant recurrence. Eighty-five percent of recurrences occur within the first 30 months of the original resection.[40,41] Of those that recur, 30% are confined to the liver, allowing for consideration of repeat hepatic resections or ablation procedures.[11,42-52] Of note, repeat resections are associated with a 5-year survival rate of 20% to 30%.[42,44,45,48,52-54] Thus, current outcomes data indicate that there is a subset of patients with colorectal cancer in whom local directed therapies result in long-term control of hepatic metastatic disease.

## Current Patient Selection Approaches for Surgery

The complex decisions required to determine resectability are best made in the setting of an interdisciplinary team that includes surgeons experienced in liver surgery. Preoperative evaluation requires a complete medical evaluation to determine the patient's suitability for surgery as well as detailed anatomic imaging to determine the location of the liver tumors and to exclude extrahepatic metastasis. Radiologic evaluation is needed not only to identify extrahepatic disease but also to assess the adequacy of liver parenchyma after surgery. In addition to the patient evaluation, liver function tests are evaluated to assess the synthetic function of the liver; combined with radiologic findings, these tests can aid in the decision-making process. Patients with a history of liver cirrhosis or liver steatosis may not tolerate liver resection. If liver function is normal, as much as 75% to 80% of the liver can be resected safely.[4,14-16,32,55-58]

The 2006 National Comprehensive Cancer Network guidelines suggest that colonoscopy should be performed if more than 6 months have elapsed since the previous colonoscopy or since prior colorectal surgery to evaluate for metachronous lesion or recurrence at the primary site.[59]

## Imaging

The evolution of imaging of the liver has produced remarkable improvements over the decades (Fig 1). CT scan of the liver evaluates for metastases prior to surgery.[60] The quality of imaging has improved, and the modality effectively characterizes liver lesions during different contrast enhancement phases. Test sensitivity for detecting metastatic lesions in the liver approaches 80%.[61,62] In the arterial phase, metastases can appear as well- or ill-defined hypodense lesions, occasionally with peripheral rim enhancement. In the portal venous phase, metastases may appear as a hypodense lesion compared to surrounding liver parenchyma. Some lesions may demonstrate a washout of the peripheral enhancement during arterial and portal venous phases that then disappear in the delayed phase.[63]

CT arterioportography has a sensitivity of close to 90% in identifying hepatic lesions, but this is an invasive procedure. Lesions are best seen on the portal phase of imaging.[64-66] The addition of CT angiography can be used to map the liver vasculature and to better define liver and tumor volume.[67]

A contrast-enhanced CT is the initial modality most often chosen for assessing the liver for metastases. With fast acquisition of images, the liver can be evaluated in several contrast-enhanced phases. These images can then be reconstructed three-dimensionally to provide improved evaluation of the vasculature. In the postoperative follow-up, CT is the imaging of choice to assess for recurrence or for tumor response after ablation or intra-arterial chemotherapy.[63] CT scan has several limitations. In patients with renal insufficiency or iodine contrast allergies, the contrast agent may need to be eliminated, thus compromising the quality of the imaging. Patients are also exposed to radiation during the examination. Furthermore, the sensitivity in detecting lesions less than 1 cm in diameter is poor.[63]

Magnetic resonance imaging (MRI) is currently the most effective imaging modality in detecting and char-

acterizing liver lesions.[68] MRI is most often ordered prior to tumor resection to characterize indeterminate lesions on CT scan or to identify lesions not seen on CT. Due to the high lesion-to-liver contrast, MRI has a higher sensitivity to detect and characterize small lesions compared to CT. On T1-weighted images, metastases appear hypointense, whereas on T2-weighted images, they are hyperintense. Using a liver-specific contrast agent, MRI has equivalent sensitivity to CT angiography.[69,70] The advantages of MRI over CT scan to identify liver lesions include the lack of radiation, high spatial resolution, better lesion detection and characterization, and improved contrast sensitivity. Drawbacks include the high financial cost, a long procedure time, and a longer time required by patients to hold their breath.[63]

Positron emission tomography (PET) can be useful for detecting metastatic lesions, especially when combined with CT scanning. However, it is no more sensitive than MRI in detecting liver metastasis, and it lacks the spatial resolution and the ability to characterize lesions.[71] Truant et al[72] correlated PET and CT findings in 53 patients with final pathologic diagnoses. They found that PET detected significantly more extrahepatic, intraperitoneal metastases than CT detected, with a sensitivity of 63% vs 25%. PET is most useful for identifying extrahepatic and possibly unresectable metastases. The detection rate for lesions less than 1 cm is 21%.[73-76]

Laparoscopic evaluation is used for selected patients who have no contraindications for resection based on noninvasive testing. Grobmyer et al[77] suggested that patients should be considered for laparoscopic evaluations if they have two of the following characteristics: a lymph node-positive primary tumor, a CEA level greater than 200 ng/mL, more than 1 hepatic tumor, disease-free interval less than 12 months, and a hepatic tumor greater than 5 cm. Patients with two or more of these findings have a 30% chance of having occult extrahepatic intraperitoneal disease.

Intraoperative ultrasound is very sensitive in detecting liver lesions not identified preoperatively. It can detect more lesions than a preoperative MRI can detect. Between intraoperative ultrasound and palpation, additional lesions have been found in the liver at the time of surgery in over 40% of patients.[63] The relationships between tumor and important vessels can also be evaluated by this technique.[62,78]

## Principles of Surgical Technique

The gold standard for treating isolated colorectal metastasis in the liver is surgical resection. The first step in assessing resectability is determining anatomically which lesion or lesions can be resected safely. Adequate hepatic tissue to allow normal hepatic function postoperatively is critical. Liver metastases resection surgery began to enter the therapeutic arsenal after the clinical results of Waugh and Adson were reported.[3] Evaluation of the liver initially focused on the location of the metastases, the number of lesions, and disease-free intervals. Prior contraindications for resection included more than 4 lesions, extrahepatic disease, large tumors, or multilobar lesions.[79,80] With consistent reports of 5-year survival rates greater than 30%, the surgical evaluation now focuses on whether a complete resection ($R_0$) can be safely performed.

**Table 3. — Characterization of Results of Resection of Hepatic Metastases**

| | |
|---|---|
| $R_0$ | No macroscopic of microscopic disease remains after surgical resection |
| $R_1$ | Microscopic disease remains after surgical resection |
| $R_2$ | Macroscopic (visible) disease remains after surgical resection |

Regardless of the resection technique, a 1-cm tumor-free margin is required (Table 3). Less than a 1-cm margin leads to an increased rate of recurrence.[81] Survival is better with fewer lesions resected and a resection margin greater than 1 cm,[16,82,83] but overall survival remains better for those with inadequate resection margins than for those with no resection at all.[84] Positive margins (68%) or bilobar disease (64%) results in an increased risk for recurrence after surgery.[84] Other studies confirm that a resection margin less than 1 cm, metastasis greater than 5 cm, and synchronous lesions are associated with a higher recurrence rate and poorer prognosis.[15,32,55]

Portal vein embolization can be considered preoperatively to allow hypertrophy of the unaffected liver parenchyma. The increased liver reserve prior to major liver resections theoretically enlarges the remaining functional liver parenchyma. There is minimal evidence, however, that this procedure affects the resectability rate or improves survival.[85,86]

Approximately 25% of patients will present with metastases at the time of diagnosis. Thirty percent of these patients will have disease isolated to the liver.[87-89] In selected patients, a procedure combining both a liver resection and colorectal resection of the primary tumor can be considered. Martin et al[90] evaluated 134 patients who had undergone a combined procedure compared to 106 patients undergoing staged procedures. The overall survival was similar, but the complication rate for the combined procedure was significantly less than a staged procedure. However, the combined procedures tended to include more right colectomies and more limited hepatic resections. Difficult low anterior or abdominal perineal resections or liver lobectomies were more often performed as staged procedures. A combined colorectal resection with a liver resection can be considered in a physically ideal patient, but most often the procedures are staged.

Overall prognosis is negatively affected by synchronous presentation of liver metastases with the primary lesion, elevated CEA levels, positive lymph nodes, and serosal invasion.[18,83] Mutsaerts et al[21] demonstrated that long-term survival is also negatively affected by a shorter interval in appearance of a metachronous lesion as well as the number of lesions seen on CT scan preoperatively. Many of these prognostic factors, including the disease-free interval — especially if less than 1 year from the time of resection of the primary tumor — were thought to portend a worse prognosis after hepatic resection. More recent studies have found no significant difference in overall survival after hepatic resection when comparing metachronous vs synchronous hepatic metastases and also no significant difference in the time interval between the onset of the primary and the metastatic lesion.[20] These patients, regardless of the interval, still have a better outcome if they undergo a complete ($R_0$) tumor resection.[55] Overall survival is worse in patients who present with a short recurrent interval or synchronous metastasis. However, if patients are selected for a surgical resection and if a complete resection can be performed, their survival after surgery is no longer influenced by their disease-free interval (Table 4).[83,90-98]

The number of lesions in the liver holds prognostic significance. Originally, the presence of 4 or more lesions in the liver was thought to render the tumors unresectable. Follow-up studies have since shown no significant difference in 5-year survival in patients with more or fewer than 4 lesions if an adequate $R_0$ surgical resection was performed.[55,99] Currently, many institutions recommend surgery if a metastasis can be resected with sufficient remaining liver reserve regardless of the number or the size of the lesions.[4,55,100,101] Newer recommendations define as unresectable tumor as involving more than 70% of the liver or involvement of greater than 6 segments.[102-104]

Bilobar disease was initially reported to be an absolute contraindication to resection. With the advent of ablative techniques, including radiofrequency ablation (RFA) and cryotherapy, resection of hepatic metastases can be combined with ablation of a contralateral lobar lesion. Survival is shorter if resection is combined with ablation of a contralateral lobar lesions compared to an $R_0$ resection alone. Abdalla et al[20] reported a 4-year survival rate of 65% in patients treated with resection only compared with 36% in those with resection plus RFA and 22% in those treated with RFA alone. Thus, bilobar disease alone is no longer an absolute contraindication to surgical resection. To ensure an adequate resection, RFA or cryotherapy can be used to ablate the margins of poorly localized lesions, especially if the surgical resection margins will be less than 1 cm.[85,86,105]

The size of the lesion, even if it exceeds 5 cm, is no longer a contraindication to resection. Again, the current emphasis is on rendering the patient tumor-free with a complete $R_0$ resection. Overall survival is worse for lesions greater than 5 cm; however, if the lesion can be completely resected, the tumor size is no longer significant in determining overall survival.[20]

Overall morbidity and postoperative mortality are lower in high-volume centers.[104,106] The postoperative morbidity rate has been reported to be between 22% and 39% due to hemorrhage, sepsis, biliary leak or fistula, liver failure, wound or intraabdominal abscess, and pneumonia. In high-volume centers, mortality rates are between 0% and 7%.[19,96,104,107]

**Table 4. — Results of Simultaneous vs Staged Resections**

| Reference (year) | No. of Patients | Type of Resection | Morbidity (%) | Mortality (%) |
|---|---|---|---|---|
| Vogt[91] (1991) | 36 | 19 simultaneous<br>17 staged | 5.2<br>17.6 | 0 |
| Scheele[92] (1991) | 98 | 60 simultaneous<br>38 staged | –<br>– | 2 |
| Jenkins[93] (1997) | 46 | 22 simultaneous<br>24 staged | –<br>– | – |
| Elias[94] (1995) | 53 | 53 simultaneous | 19 | 0 |
| Jaeck[95] (1996) | 41 | 20 simultaneous<br>21 staged | 20<br>10 | 0 |
| Nordlinger[83] (1996) | 1008 | 115 simultaneous<br>893 staged | –<br>– | 7<br>2 |
| Bolton[96] (2000) | 165 | 50 simultaneous<br>115 staged | –<br>– | 12<br>4 |
| Fujita[97] (2000) | 97 | 83 simultaneous<br>14 staged | 58<br>– | 0 |
| Lyass[98] (2001) | 112 | 26 simultaneous<br>86 staged | 27<br>35 | 0<br>2.3 |
| Martin[90] (2003) | 240 | 134 simultaneous<br>106 staged | 49<br>67 | 4<br>4 |

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## Role of Neoadjuvant Therapy

Most patients with colorectal liver metastases will present with unresectable disease. Beginning in the 1990s, Bismuth et al[79] reported on a small percentage of patients who had a significant downsizing of their hepatic lesion with neoadjuvant chemotherapy. These patients were then brought to surgery for an attempted $R_0$ resection. The 5-year survival rate was 40%, similar to those resected de novo. These results have been reproduced multiple times (Table 5).[79,108-114] Therefore, those patients initially determined to be unresectable should be reevaluated for resectability after neoadjuvant therapy for

**Table 5. — Results for Neoadjuvant Therapy Prior to Resection**

| Reference (year) | No. of Patients | Chemotherapy Regimen | Resectability | 5-Year Survival |
|---|---|---|---|---|
| Bismuth[79] (1996) | 330 | Oxaliplatin/FU/LV | 46 (14%) | 40% |
| Giacchetti[108] (1999) | 151 | Oxaliplatin/FU/LV | 58 (38%) | |
| Adam[109] (2001) | 701 | Oxaliplatin/FU/LV | 95 (13.5%) | 35% |
| Wein[110] (2001) | 53 | Infusional FU/LV | 6 (11%) | |
| Rivoire[111] (2002) | 131 | Oxaliplatin/FU/LV | 57 (43%) | |
| Adam[112] (2004) | 1104 | Oxaliplatin/irinotecan/FU/LV | 128 (12.5%) | |
| Pozzo[113] (2004) | 40 | CPT/FU/LV | 11 (27.5%) | |
| Delaunoit[114] (2005) | 795 | Oxaliplatin/irinotecan/FU/LV | 24 (3.3%) | |

resectability. More recently, newer effective chemotherapeutic combinations, including FOLFOX or FOLFIRI with bevacizumab, have had more consistent results in downsizing liver metastases from colorectal adenocarcinoma. Adam et al[109] performed a hepatic resection on 95 (13.5%) of 701 patients who were initially deemed to be unresectable but were downsized with neoadjuvant therapy. The overall 5-year survival rate after resection was 35%. Neoadjuvant therapy may also identify patients who would not benefit from surgery due to biologically aggressive disease.[33] Several retrospective studies have demonstrated patients can be treated to the point of becoming resectable. These studies report a 5-year survival rate between 13% and 38% in patients resected to no evidence of disease ($R_0$).[26,32,115] On occasion, a multimodality approach of neoadjuvant chemotherapy combined with surgical resection and/ or ablation can render patients tumor-free.

Approximately 60% to 70% of patients treated with resection will recur. Of those who recur, 30% of recurrences will be isolated to the liver.[18,92] The liver parenchyma will regenerate or hypertrophy to presurgical size in 3 to 6 months, and significant resection can be performed a second time if the patient's physical status will allow repeat procedures.[6] Several studies have demonstrated similar morbidity and mortality compared to primary resection (Table 6).[42-49,52-54] The overall 5-year survival is similar to that of the initial resections and the timetable is reset from the time of the second resection.[29-37,39,97] A recent retrospective study by Petrowsky et al[52] demonstrated similar morbidity and mortality rates compared to primary resection, with a 34% actuarial 5-year survival rate and 15% actual 5-year survivors at the time of follow-up. These results are similar to those published for primary resections and suggest that reintervention is of benefit. Risk factors associated with a worse outcome were similar to those for primary resection and included the number of tumors resected, the size of the largest lesion, positive margins, and bilobar involvement.

## Combination of Resection With Ablative Therapies

Radiofrequency ablation has expanded the indications for patients who can be surgically treated. It is currently the most widely used method of liver ablation and is discussed in detail elsewhere in this issue.[116]

**Table 6. — Results of Repeat Hepatic Tumor Resections for Cure**

| Reference (year) | No. of Patients | Operative Mortality (%) | Median Survival (mos) | Survival (%) | | |
|---|---|---|---|---|---|---|
| | | | | 1-yr | 3-yr | 5-yr |
| Bozzetti[49] (1992) | 11 | 9 | 23 | | 36 | – |
| Vaillant[48] (1993) | 16 | 6.2 | 33 | | 57 | 30 |
| Nordlinger[47] (1994) | 116 | – | – | | 33 | – |
| Fong[46] (1994) | 25 | 0 | 30 | | – | – |
| Fernandez[45] (1995) | 170 | – | 34 | | 45 | 32 |
| Tuttle[44] (1997) | 23 | 0 | 40 | | 55 | 32 |
| Adam[53] (1997) | 64 | 0 | 46 | 87 | 60 | 41 |
| Yamamoto[54] (1999) | 75 | 0 | 30 | 48 | 31 | |
| Muratore[43] (2001) | 29 | 3.4 | – | | 35 | – |
| Suzuki[42] (2001) | 26 | 0 | 31 | | 62 | 32 |
| Petrowsky[52] (2002) | 126 | 1.6 | 37 | 86 | 51 | 34 |

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Overall, RFA is safe and feasible but is less effective than surgical resection in prolonging survival. The overall morbidity is less than a surgical resection and the operative mortality is less than 1%. Complications include symptomatic pleural effusions, fever, pain, subcapsular and subcutaneous hematomas, biliary tree injuries, hepatic abscess, diaphragmatic necrosis, hepatic artery injury, renal failure, liver failure, coagulopathy, and ventricular fibrillation.[117-120]

Cryotherapy is another ablative technique used for liver metastases. Cryotherapy involves the use of a liquid nitrogen-filled cryoprobe. The probe is inserted into a lesion, and alternating freeze/thaw cycles are initiated. Intracellular and extracellular water is turned into ice to create an "ice ball." Cell death is secondary to damage caused by the formation and thawing of ice crystals. Cryotherapy can be used in conjunction with surgical resection, especially if the surgical margins are close.[121] The cryoprobe is often too big to be used percutaneously but can be used laparoscopically. Rivoire et al[111] demonstrated a 37% 4-year survival rate and a 14% morbidity rate after neoadjuvant chemotherapy, partial hepatectomies, and cryotherapy. Major blood vessels can act as a heat sink, inhibiting an adequate freezing cycle in tissue close to the vessels. As with RFA, a 1-cm margin around the lesion should be frozen. Ultrasound guidance is often used to confirm proper placement of the probe and to confirm an adequate region of destruction.[86,122] Ruers et al[123] reported a disease-free survival rate of 7% after 2 years and a 61% 2-year survival rate. They summarized that cryotherapy was a good adjunct for local control but had little impact on overall survival.

Complications occur less frequently with cryotherapy than with surgical resection. Complications include hemorrhage from a cracked and frozen liver, bile leak or fistula, right pleural effusion, thrombocytopenia, myoglobinuria, arrhythmias, acute renal failure, cryoshock from disseminated intravascular coagulation (DIC) and multiorgan shock. The overall mortality rate is 1.6%.[121,123] Cryotherapy has become less popular due to its limitations in controlling lesions over 4 cm and also its higher complication and mortality rate compared to RFA. As with RFA, cryotherapy can be used as an adjunct to surgical tumor resection.

## Follow-up

Postoperative surveillance evaluates the efficacy of treatment as well as screening for recurrence.[124,125] According to the 2006 National Comprehensive Cancer Network guidelines, follow-up includes a physical examination, a CEA measurement, and a CT scan of the chest and abdomen every 3 months for 2 to 3 years, then every 6 months for 5 years. Some clinicians limit the use of CT scan until a measurable CEA level is noted (Fig 2). Most recurrences are identified within the first 2 years of operation. The surveillance begins again if a patient has had a re-resection of a liver lesion. A recurrence beyond 5 years of intervention is rare; therefore,

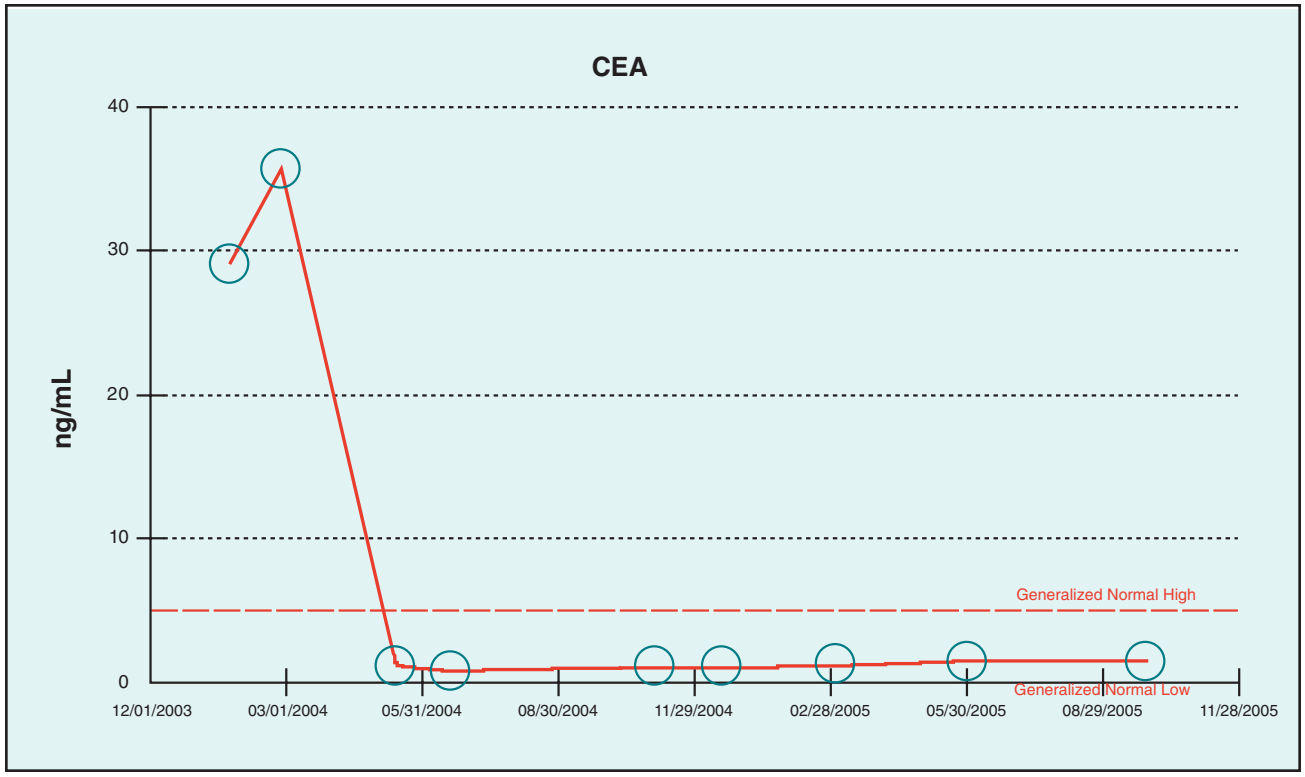


Fig 2. — Carcinoembryonic antigen levels after resection and during follow-up (same patient as Fig 1).

routine imaging and laboratory follow-up other than screening colonoscopy are unnecessary.[124-126]

## Conclusions

Clinical experience suggests that patients with colorectal cancer liver metastases have heterogenous tumor biology. The ongoing trend is to include a surgical approach for more patients with liver metastases from colorectal carcinoma. With the addition of newer chemotherapeutics, survival has improved in patients treated both medically and surgically for metastatic colorectal cancer. The role of neoadjuvant chemotherapy is being clarified. The current approach is upfront surgery unless a lesion is considered unresectable. Neoadjuvant therapy may soon be recommended more frequently, however, as more predictable responses from the intervention occur.

During the preoperative evaluation, attention needs to be focused on considering sufficient liver parenchyma and assessment for extrahepatic disease. Survival benefits in patients undergoing a second liver resection have similar outcomes as those undergoing a primary resection. Regardless of the surgical resection, patients benefit most when tumor-free margins greater than 1 cm are achieved. If the margins are close, RFA or cryotherapy can be added to ensure an adequate depth.

Resection remains a critical treatment modality for patients with colorectal liver metastases since it provides the only significant chance for cure or long-term survival. With the extraordinary advances made in chemotherapeutics as well as newer surgical techniques, metastatic colon cancer remains a potentially curable disease. Patients are best treated in a multimodality environment where a medical oncologist, a radiologist, and those skilled in hepatobiliary surgery plan and execute optimal therapy.

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