

Surgical Treatment and Other Regional Treatments for Colorectal Cancer Liver Metastases

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ABSTRACT

The liver is the most common site of distant metastasis from colorectal cancer. About one-fourth of patients with liver metastases from colorectal cancer have no other sites of metastasis and can be treated with regional therapies directed toward their liver tumors. Surgical resection of colorectal cancer liver metastases can result in a 24%-38% five-year survival, but only a minority of patients are candidates for resection. Other

regional therapies such as cryosurgery, radiofrequency ablation, and hepatic intra-arterial chemotherapy may be offered to patients with unresectable but isolated liver metastases. The efficacy of these treatments is still being determined. For most patients with spread of metastatic colorectal cancer beyond the liver, systemic chemotherapy rather than regional therapy is a more appropriate option. *The Oncologist* 1999;4:197-208

INTRODUCTION

Colorectal cancer remains a common and frequently fatal disease. In 1998, an estimated 131,600 persons in the United States were diagnosed with colorectal cancer, and 56,500 persons died of colorectal cancer [1]. Colorectal cancer is the fourth most commonly diagnosed cancer and the second leading cause of cancer death [1]. Treatment of primary colorectal cancer with surgical resection, combined in certain cases with chemotherapy or radiation therapy, is curative in many patients. However, nearly half of patients will develop liver metastases during the course of their disease, with 15%-25% having liver metastases at the time of primary diagnosis and another 20% of patients developing metachronous liver metastases [2].

As with many types of cancer, death from colorectal cancer is often a result of metastatic disease. Over one-half of patients who die of colorectal cancer have liver metastases at autopsy, and the majority of these patients die as a result of their metastatic liver disease [3]. But unlike many other types of cancer, the presence of distant metastases from colorectal cancer does not preclude curative treatment. About 25% of patients with colorectal cancer liver metastases have no other sites of metastasis [4], and of these patients, 10%-25% are candidates for surgical resection [5].

Five-year survival following resection of isolated colorectal cancer liver metastases can be as high as 38% [6]. For the 75%-90% of patients with isolated colorectal cancer liver metastases who are not amenable to surgical resection [5], several newer but less proven therapies are being developed.

This article will describe the surveillance of patients following curative therapy for primary colorectal cancer, natural history of untreated colorectal cancer liver metastases, surgical resection of these metastases, and other regional therapies, including cryosurgery, radiofrequency ablation, and hepatic intra-arterial chemotherapy.

SURVEILLANCE

Two-thirds of patients who undergo curative surgery for colorectal cancer will develop local, regional, or distant recurrence [7]. Eighty-five percent of tumor recurrences are detected within 2.5 years of surgery for the primary colorectal cancer, and the remaining 15% are detected within the next 2.5 years [7]. Surveillance following curative resection for colorectal cancer is intended to discover recurrences early in their course in hopes of optimizing the results of subsequent therapy. A reasonable surveillance schedule following curative treatment of colorectal cancer includes a history and physical examination, digital rectal examination, and Hemoccult stool testing.

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Carcinoembryonic antigen (CEA) levels may be monitored every three months in patients with stage II or stage III disease, in whom resection of liver metastases would be clinically indicated. A chest x-ray should be obtained every 12 months for the first five years. A pelvic computed tomography (CT) scan may be obtained three to four months after resection of rectal carcinoma to establish a baseline and then yearly for three years, although the benefit of this surveillance remains controversial. Colonoscopy should be performed after one year and then every three years if no abnormalities are observed. All patients with a history of colorectal cancer are at risk for metachronous primary tumors making life-long follow-up essential.

There are no rigid guidelines regarding the intensity of surveillance after treatment of primary colorectal cancer because there is no definitive evidence that intense surveillance improves survival. *Kjeldsen et al.* prospectively followed 597 patients after assigning these patients to frequent or infrequent follow-up. Patients who received frequent follow-up had recurrences diagnosed earlier and underwent more operations, but there was no difference in overall survival or cancer-related survival [8]. This study did not include CEA monitoring. *Moertel et al.* retrospectively studied 1,216 patients in whom 84% had CEA monitoring [9]. CEA levels rose above 5 ng/ml in 76% of patients who had recurrence only in the liver. Only 2.9% of patients with CEA elevations who underwent salvage surgery for curative intent were alive and disease-free one year after salvage surgery. The authors concluded that CEA monitoring infrequently led to cancer cures. A subsequent meta-analysis, however, showed that intensive follow-up including CEA monitoring may lead to a 9% better five-year survival than infrequent follow-up [10]. Thus, the intensity of surveillance following curative treatment of colorectal cancer remains an individual decision.

NATURAL HISTORY

Understanding the natural history of colorectal cancer liver metastases sets a framework from which to assess the value of various treatments. Numerous studies conducted primarily in the 1960s and 1970s examined the natural history of patients with untreated colorectal cancer liver metastases. Median survival for these patients was found to be between five and nine months [11-16]. However, in these older studies, the majority of patients had advanced disease diagnosed without the advantage of modern-day imaging techniques.

Patients selected for surgical resection of their liver metastases represent a subset of patients with more limited disease. Accordingly, several studies have retrospectively determined the survival of patients with potentially resectable colorectal cancer liver metastases that were left untreated.

Wilson et al. found a 0% five-year survival for patients with untreated but potentially resectable liver metastases compared with a 28% five-year survival for patients with resected liver metastases [17]. A subsequent study found five-year survival rates in similar groups of patients to be 2% and 25%, respectively [18]. In another study, patients with untreated but potentially resectable liver metastases had a mean survival of 21.3 months, with only 1 of 13 patients surviving five years [19]. *Wanebo et al.* found that patients with an untreated single liver metastasis had a median survival of 19 months, with no patients surviving five years, while patients with a resected single liver metastasis had a median survival of 36 months with 25% of patients surviving five years [20]. All of these studies are limited because of their retrospective analysis and relatively insensitive methods for assessment of extent of disease. However, it is now generally accepted that resection of colorectal cancer liver metastases improves long-term survival.

PREOPERATIVE ASSESSMENT

In patients with colorectal cancer, synchronous liver metastases may be detected during preoperative testing or identified intraoperatively during colectomy. Suspicious liver lesions may be biopsied during colectomy to confirm metastatic disease. Metachronous liver metastases may be suspected at some point after colectomy based on the surveillance described above and confirmed on follow-up radiological imaging.

Further evaluation of patients with colorectal cancer liver metastases is based on anticipated treatment. If the considered options are observation or systemic chemotherapy, confirmation of the presence of metastatic disease by ultrasound or CT scan is sufficient. In patients who are candidates for surgical resection of their liver metastases, the goals of preoperative assessment are: A) to exclude the presence of extrahepatic disease; B) to delineate the anatomy of the metastases, and C) to determine the ability of the patient to tolerate hepatic resection.

Candidates for surgical resection of colorectal cancer liver metastases should undergo a detailed history and physical examination, hematology and chemistry panels, liver function tests, chest x-ray, and abdominal and pelvic CT scans. Chest CT scans are of marginal benefit in patients with normal chest x-rays. A recent study demonstrated that in patients with colorectal cancer liver metastases with no evidence of lung metastases on chest x-ray, chest CT had a positive yield of only 4% and a positive predictive value of 36% for lung metastases [21]. Patients should undergo colonoscopy if they have not already done so within the past 12 months, to rule out recurrence of the original primary colorectal cancer or development of a second primary

colorectal cancer. About 5% of patients with colorectal cancer develop a metachronous primary colorectal cancer [22]. Further radiological imaging studies are based on surgeon preference.

Transabdominal ultrasound is a relatively inexpensive modality but misses up to 50% of liver metastases [23]. It has essentially no role in the preoperative evaluation of potential liver resection candidates.

Abdominal CT scans remain a commonly used modality for the assessment of liver metastases. The liver is the most highly attenuated of all the abdominal organs on CT scan, and colorectal cancer liver metastases on CT images are usually hypoattenuated relative to normal liver. The addition of i.v. contrast increases the detection of liver metastases. While normal liver is perfused primarily by the portal vein, liver metastases are perfused principally by the hepatic artery [24]. Therefore, on CT images obtained during the portal venous phase following i.v. contrast administration, hypoattenuated liver metastases are more easily recognized [25].

A more sensitive but invasive test is CT arteriportography (CTAP), which involves the placement of a catheter into the superior mesenteric artery and the capture of CT images during the portal venous phase following contrast injection. Overall sensitivity for detection of liver metastases with helical CTAP exceeds 90% [26], compared with 80% for helical CT scans with i.v. contrast [27, 28]. However, perfusion abnormalities and pseudolesions are frequently observed with CTAP, thereby significantly reducing the specificity of this test [29].

Magnetic resonance imaging (MRI) is being increasingly utilized for the diagnosis and characterization of liver lesions, particularly now that liver-specific contrast agents and dynamic scanning have been incorporated. One liver-specific contrast agent, manganese-pyridoxal diphosphate (Mn-DPDP), is a paramagnetic agent taken up preferentially by hepatocytes and excreted in the bile. Normal liver parenchyma is markedly enhanced on T1-weighted images, while metastases do not enhance [30]. Superparamagnetic iron oxide (SPIO) particles, another contrast agent, are taken up by the reticuloendothelial system and cause a reduced signal on T2-weighted images [31]. A recent study found that MRI with SPIO-enhancement was as sensitive as CTAP in detecting liver metastases [32].

Some oncologists advocate the use of radioimmunodetection (RAID) with labeled antibodies to CEA antigen as a preoperative imaging study to exclude extrahepatic metastases in candidates for liver resection [33]. This examination involves the i.v. infusion of technetium-99m labeled anti-CEA antibodies followed 2-24 h later by either planar scintigraphy or single-photon emission computed tomography (SPECT) [34].

A study by *Moffat et al.* examined patients with known or suspected recurrent or metastatic colorectal cancer with RAID using anti-CEA antibodies. They reported sensitivities of 55% in the extrahepatic abdomen and 69% in the pelvis, and these sensitivities were superior to conventional diagnostic techniques. Overall specificity, however, was only 62.5% [34]. A subsequent study of 100 patients with colorectal cancer liver metastases revealed that RAID with anti-CEA antibodies correctly assessed liver resectability in 17 of 36 patients (47%) and nonresectability in 23 of 57 patients (40%), compared with 44% and 25%, respectively, for abdomen and pelvic CT scans [35].

At the Massachusetts General Hospital, MRI with Mn-DPDP has replaced CTAP as the study of choice to delineate colorectal cancer liver metastases for potential resection. MRI or CT-guided biopsy of lesions deemed critical to the diagnosis of nonresectability is performed if imaging studies are not conclusive. RAID with anti-CEA antibodies is not routinely performed to exclude extrahepatic disease due to the low specificity of this test. Angiograms are obtained for patients who may require placement of a hepatic artery infusion pump. Inferior vena cavagrams have largely been replaced by MRI in patients with possible inferior vena cava invasion.

Laparoscopy, sometimes combined with laparoscopic ultrasound, is increasingly used for preoperative evaluation of metastatic disease. Laparoscopy with laparoscopic ultrasound may be the most sensitive imaging technique for detection of liver metastases and can change the intraoperative treatment plan [36]. In one study of 24 patients with liver tumors judged preoperatively to be resectable by conventional imaging studies, laparoscopy combined with laparoscopic ultrasound identified six patients who were, in fact, unresectable, preventing laparotomy in these patients [37]. The authors have found a much lower incidence of unresectable metastases during laparotomy when MRI with Mn-DPDP is used as the primary preoperative imaging study and often place hepatic artery infusion pumps in patients with unresectable but isolated liver metastases. Thus, at our institution, laparoscopy with laparoscopic ultrasound would prevent laparotomy in a small minority of cases and is not routinely used.

SURGICAL RESECTION OF COLORECTAL CANCER LIVER METASTASES

Based upon preoperative assessment, patients with colorectal liver metastases are candidates for surgical resection if: A) they have no extrahepatic disease; B) all liver metastases can be resected with at least a 1-cm tumor-free margin, and C) adequate residual liver parenchyma can be spared. In the absence of underlying liver dysfunction, up to 75% of the liver can be removed without subsequent hepatic failure [38].

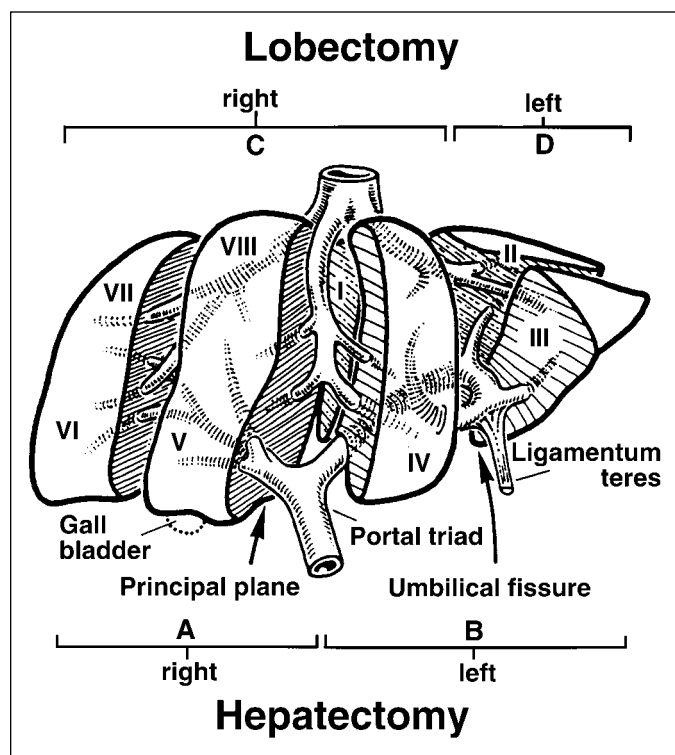


Figure 1: Functional anatomy of the liver. A schematic view of the liver demonstrates sectors or segments I-VIII, as described by Couinaud. Adapted from [40].

Liver resections are performed based on the liver's functional anatomy as described by Couinaud [39], who divided the liver into eight sectors or segments (Fig. 1). The commonly performed major hepatic resections are shown in Figure 1 and include right hepatectomy, left hepatectomy, right trisegmentectomy (sparing segments II and III), left trisegmentectomy (sparing segments VI and VII), and left lateral segmentectomy (resection of segments II and III) [40, 41]. There is no advantage to performing a major resection when removal of one or more segments can eradicate all metastases with an adequate margin. In fact, one or more segmental resections can often spare more normal liver than a major resection or allow resection of metastases not encompassed by a traditional major resection. With the use of intraoperative ultrasound, the anatomic segments of the liver can be clearly delineated, and removal of individual segments can be readily performed.

The surgical resection of colorectal cancer liver metastases first involves an exploratory laparotomy through a right subcostal incision. The abdominal cavity is explored for signs of

extrahepatic disease, and suspicious areas are biopsied. The liver is then fully mobilized by dissection of its supporting ligaments and palpated to identify lesions. Intraoperative ultrasound is used at this point to identify nonpalpable lesions and delineate vascular anatomy [42]. Whether a traditional major resection or one or more segmental resections is performed, the goal of the operation is complete removal of all metastases with at least a 1 cm tumor-free margin. There are various methods of dividing hepatic parenchyma, and the authors prefer a combination of an ultrasonic surgical aspirator and clamp fracture. Small vessels are controlled with electrocautery or hemoclips, and larger vessels are controlled with sutures. An argon beam coagulator can also be used to achieve hemostasis. Transient portal inflow occlusion and maneuvers to reduce hepatic venous pressure help minimize blood loss.

The operative mortality for major hepatic resections has declined with improved operative techniques and postoperative care, but morbidity remains significant. Table 1 summarizes the operative mortality, morbidity, median survival, and five-year survival in seven surgical series published in the 1990s [6, 43-48]. Operative mortality in these studies ranged from 0% to 7%, and causes of death included hemorrhage, sepsis, and hepatic failure. Morbidity was between 22% and 39%, and common causes of morbidity included hemorrhage, biliary leak or fistula, hepatic failure, perihepatic abscess, wound infection, pneumonia, and myocardial infarction. Median survival ranged from 28 to 46 months, and five-year survival was between 24% and 38%.

The five-year survival following surgical resection of colorectal cancer liver metastases has remained stable in published series for the past decade. In 1987, Hughes *et al.*

Table 1. Results of resection of CRC liver metastases

Study	Number of patients	Operative mortality (%)	Operative morbidity (%)	Median survival (months)	5-year survival (%)
Schlag [43] 1990	122	4	34	28	
Docì [44] 1991	100	5	39		30
Rosen [45] 1992	280	4		33.6	25
Gajowski [46] 1994	204	0		33	32
Scheele [47] 1995	434	4.4	22		33
Wanebo [48] 1996	74	7	38	35	24
Fong [6] 1997	456	2.8	24	46	38

Table 2. Negative prognostic factors after surgical resection of colorectal cancer liver metastases [6, 44-48, 50]

Primary colorectal tumor characteristics	Metastases characteristics	Surgical resection characteristics
Advanced stage	Lymph node involvement	Less than 1 cm tumor-free margin
High grade	Extrahepatic metastases	Extensive resection
	Larger size	
	Increased number	
	Satellitosis	
	Bilobar distribution	
	Short disease-free interval	
	Synchronous metastases	
	Elevated CEA level	

published a multicenter retrospective review of 859 patients who had undergone resection of colorectal cancer liver metastases. The overall actuarial five-year survival was 33% [49]. Many studies have examined prognostic factors to determine which patients benefit most from hepatic resection. In the *Hughes et al.* study, no patients with portal or lymph node metastases or with extrahepatic disease survived five years, and few patients with four or more metastases survived five years. Other less significant negative prognostic factors were resection margins less than 1 cm, advanced stage of the primary colorectal cancer, and short disease-free interval [49].

Several surgical series have subsequently examined prognostic factors following surgical resection of colorectal cancer liver metastases. Table 2 summarizes the negative prognostic factors found in seven surgical series [6, 44-48, 50]. The factors are divided into those associated with the primary colorectal tumor, the metastases, or the surgical resection, and are only listed if at least two of the seven studies found the factor to be statistically significant. Each of these studies used slightly different cut-off points to analyze continuous variables such as CEA level, size of hepatic metastases, and number of liver metastases. Patient characteristics such as age or sex were not significant prognostic factors in the majority of studies. Patients with liver metastases from primary colorectal advanced-stage or high-grade cancers had decreased survival. Nearly all studies found that the presence of lymph node involvement and extrahepatic metastases were associated with dramatically reduced survival. Characteristics of liver metastases associated with decreased survival included large size, increased number, satellitosis, and bilobar distribution. Liver metastases that were discovered after a short disease-free interval, synchronous metastases (as opposed to metachronous metastases), and metastases associated with elevated CEA levels also predicted shorter survival. Surgical resections with less than a 1 cm tumor-free margin and extensive resections were associated with decreased survival.

Fong et al. recently published a large retrospective study of 456 consecutive patients with colorectal cancer liver

metastases who underwent resection at Memorial Sloan-Kettering Cancer Center [6]. Perioperative mortality was only 2.8%, perioperative morbidity was 24%, median hospital stay was 10 days, median survival was 46 months, and five-year survival was 38%. The authors concluded that the only factors which are absolute contraindications to resection are the presence of extrahepatic metastases and tumors larger than 10 cm in diameter. These factors were associated with only 13% and 14% five-year survival rates, respectively. A reasonable percentage of patients with other negative prognostic factors, such as bilobar tumor distribution and four or more tumors, survived five years, and thus the authors concluded that these factors should not be considered absolute contraindications to surgical resection.

Many oncologists consider four or more tumors in the liver to be a contraindication to surgical resection. This likely stems from the *Hughes et al.* study, which stated that four or more metastases “might by [itself]...be considered [a] contraindication to hepatic resection” [49]. However, in this study, the number of patients with four or more metastases was too small to achieve statistical significance. In the *Fong et al.* study, patients with four or more metastases experienced a reasonable 24% five-year survival [6]. Thus, the authors do not consider four or more metastases as an absolute contraindication to surgery.

Despite careful selection, a majority of patients who undergo resection of colorectal cancer liver metastases will have recurrence of their cancer. The most common sites of recurrence following resection of colorectal cancer liver metastases are the liver and lung [6]. Repeat liver resections for colorectal cancer liver metastases have been reported by several groups [51-60]. In a recent series of 170 patients, median survival following repeat hepatic resection was 34 months, and five-year survival was 32%. The only significant negative prognostic factor was an incomplete resection. Median follow-up, however, was only 25 months [60].

Some groups have reported broader criteria and more aggressive approaches to liver resection than those outlined above. One alternative for patients with isolated liver and lung metastases from colorectal cancer is resection at both sites, and this approach has been reported in several small series [51, 61-63]. These studies included a total of 52 patients, and survival ranged between 3 and 64 months from the time of resection of the metastases. A few groups have reported on the resection of initially unresectable colorectal cancer liver metastases following tumor regression from chemotherapy given either by systemic administration or hepatic intra-arterial administration [64-66]. In a recent series of 53 patients with a mean follow-up of greater than two years, five-year survival was 40%, with

15 cases of repeat liver resection for liver recurrence [66]. The survival benefit from these strategies has not been definitively demonstrated.

HEPATIC CRYOSURGERY

Unlike surgical resection, regional therapies for liver metastases, such as hepatic cryosurgery, attempt to destroy tumors in situ. Hepatic cryosurgery involves the freezing and thawing of liver tumors by means of a cryoprobe inserted into the tumor. During freeze/thaw cycles, intracellular and extracellular ice formation occurs in an area termed "the iceball," leading to tumor destruction [67].

Hepatic cryosurgery is performed by first making an abdominal incision, followed by exploration of the abdomen to search for extrahepatic metastases. Intraoperative ultrasound is used to identify and assess intrahepatic lesions. For superficial lesions, a cryoprobe can be placed into the center of the lesion under direct vision. For deeper lesions, a Seldinger-type technique is used whereby a needle is inserted into the center of the lesions under ultrasonic guidance. Following dilation of the tract over a guidewire, a cryoprobe is passed. Liquid nitrogen is circulated through the cryoprobe, and the subsequent iceball formation is observed by ultrasound. Freezing is continued until the iceball is at least 1 cm beyond the tumor. Some centers perform two or three freeze/thaw cycles or combine freezing with hepatic inflow occlusion to increase tumor destruction and iceball size [67, 68].

Hepatic cryosurgery is generally reserved for patients with colorectal cancer liver metastases in whom one or more lesions are not surgically resectable, although certain centers offer hepatic cryosurgery as an alternative to surgical resection [69]. Cryosurgery can treat multiple lesions and salvages more uninvolved liver parenchyma than surgical resection. Cryosurgery may also be used to treat tumors intimately associated with major blood vessels, but large blood vessels may serve as "heat-sinks" and prevent adequate freezing of immediately adjacent tumor [70]. Hepatic inflow occlusion or hepatic vein occlusion may reduce the incidence of inadequate freezing of tumor adjacent to blood vessels [71], but recurrence of tumor adjacent to large blood vessels remains a problem [72]. In addition, many surgeons avoid hepatic inflow occlusion for fear of blood vessel wall destruction and subsequent hemorrhage. Cryosurgery may help in treating patients that are left with a positive surgical margin after hepatic resection as well as patients in whom underlying illness or hepatic insufficiency precludes surgical resection.

Postoperative complications following cryosurgery include arrhythmia, cracking of frozen liver with subsequent hemorrhage, right-sided pleural effusion, subphrenic or hepatic abscess, bile collection, biliary fistula, thrombocytopenia, myoglobinuria, acute renal failure, and cryoshock

phenomenon (multisystem organ failure and disseminated intravascular coagulation) [69, 71, 73, 74]. Measures to reduce complications include packing the cryoprobe site with Gelfoam to prevent hemorrhage and postoperative administration of Lasix, mannitol, and sodium bicarbonate to promote diuresis and alkalize the urine. Overall morbidity rates range widely from 6% [69] to 49% [74] with aggressive treatment. Mortality rates range from 0%-8%, with an overall mortality rate in reported series of 1.6% [72]. Median survival in reported series has ranged from 8 to 33 months [72].

The long-term survival following hepatic cryosurgery for colorectal cancer liver metastases is unclear. Published studies suffer from varied patient selection, small numbers, and lack of long-term follow-up. *Onik et al.* reported on 69 patients with metastatic liver tumors with 82% of metastases from colorectal cancer. After a mean follow-up of 12-15 months, 60% of patients were alive, and 40% of patients were disease free. Local failure rates were not reported [75]. In another study of 32 patients with liver tumors, including 24 patients with colorectal cancer liver metastases, 28% of patients remained disease-free after a median follow-up of 24 months [69]. Of the patients with recurrence, 32% failed in the liver only, 54% failed in the liver and another site, and 14% failed outside the liver. Of the patients with recurrence only in the liver, 9% recurred at the treatment site. Finally, *Weaver et al.* reported on 47 patients with liver metastases from colorectal cancer treated with cryosurgery with or without surgical resection [73]. After a median follow-up of 26 months, overall survival was 62%, and 11% of patients had no evidence of disease after a median follow-up of 30 months. There were no documented recurrences at the cryosurgery site in 22 patients who were alive at the end of the study, but the incidence of cryosurgery site recurrence in the other 23 patients was not reported.

Hepatic cryosurgery is an option for patients with isolated colorectal cancer liver metastases that are not surgically resectable but limited enough to allow cryoablation of all lesions. These patients' tumors usually have unfavorable tumor biology, and it is unclear whether cryoablation improves survival. It is also unclear whether hepatic cryosurgery will lead to equivalent survival in patients with more limited disease who currently undergo surgical resection. Well-controlled studies are required to address these questions.

RADIOFREQUENCY ABLATION

Among the more promising experimental therapies for colorectal cancer liver metastases is radiofrequency (RF) ablation. This technique involves percutaneous or intraoperative insertion of an RF electrode into the center of a hepatic tumor under ultrasonic or CT guidance. RF energy is then emitted from the electrode and absorbed by the surrounding

tissue. This process generates extreme heat, leading to coagulative necrosis of treated tissue [76]. The initial limitation of this therapy was the small (1.5 cm) diameter of necrosis achievable with a single RF electrode. Strategies to increase this treatment area include multi-probe arrays [76], saline infusion with RF application [77], and internal cooling of the tip of the RF electrode [76].

In a recent study conducted at the Massachusetts General Hospital, liver tumors were treated with RF ablation, either through percutaneous insertion or through laparotomy, and subsequently surgically resected 0-7 days after RF ablation. Tumors treated intraoperatively and resected immediately after RF ablation were found to have irreversible cellular damage, while tumors resected on days 3-7 after RF ablation showed coagulative necrosis. CT scans obtained between RF ablation and surgical resection accurately estimated the area of coagulative necrosis in resected specimen (*Goldberg et al.*, submitted for publication).

Several small series have reported results of patients with metastatic liver tumors treated with RF ablation. *Solbiati et al.* reported a series of 16 patients with 31 metastatic liver tumors from various gastrointestinal cancers [78]. Four patients ultimately underwent resection and residual viable tumor was found in all four liver specimens. In the remaining 12 patients, 18 of 27 lesions remained stable or decreased in size for at least nine months. Eight of 12 patients achieved disease-free survival after a mean of 16.6 months. *Solbiati et al.* also reported on 29 patients with 44 liver metastases, most from colorectal cancer [79]. Disease-free survival was 33% at 18 months, and overall survival was 89% at 18 months. Localized progression of disease was seen in 34% of treated lesions. *Livraghi et al.* reported on RF treatment of 14 patients with 24 liver metastases in which 52% of lesions (all smaller than 3.5 cm) had complete necrosis six months following treatment [77].

The primary advantages of RF ablation over cryosurgery lie in the low incidence of complications and the ease of performing the procedure percutaneously under CT or ultrasound guidance. Two series have reported no complications in a total of 45 patients [80, 81]. In three other studies, two cases of self-remitting bleeding [78, 79] and one case of transient ascites [77] were reported. RF ablation can also be performed percutaneously, thus avoiding laparotomy. At the Massachusetts General Hospital, over 100 liver tumors have been treated percutaneously or intraoperatively with RF ablation with only two minor complications (*Goldberg et al.*, manuscript in preparation). The efficacy of RF ablation in destroying liver tumors as compared with cryosurgery is unclear, and RF ablation cannot be used to treat relatively large tumors. Thus, further studies and technological advances are needed.

HEPATIC ARTERIAL INFUSION CHEMOTHERAPY

For the subset of patients with isolated colorectal cancer liver metastases that are not amenable to surgical resection, hepatic arterial infusion (HAI) chemotherapy can also be considered. HAI chemotherapy is based upon two primary concepts: A) liver metastases larger than a few millimeters derive most of their blood supply from the hepatic arterial circulation, while the normal liver derives most of its blood supply from the portal circulation [82], and B) clearance of chemotherapeutic agents by first-pass through the liver can increase drug level in the liver and limit systemic toxicity [83]. Floxuridine (FUDR) is the most commonly used agent for HAI chemotherapy. In one study, hepatic venous levels of FUDR were four times higher following intra-arterial administration than following systemic administration, and systemic FUDR levels following intra-arterial administration were one-fourth the FUDR levels following i.v. infusion [84]. It is estimated that intra-arterial administration of FUDR allows a level of liver exposure 100-400 times greater than with i.v. administration [85].

HAI chemotherapy is generally reserved for patients without evidence of extrahepatic metastases. Rare exceptions are made for patients with a good performance status who have minimal extrahepatic metastases but substantial liver tumor burden. Patients considered for HAI chemotherapy first undergo a preoperative angiogram to define arterial anatomy, since about 37% of patients have variant arterial anatomy [86]. Subsequently, an operation is performed in which a cannula is placed into the hepatic arterial circulation and attached to an infusion pump. The pump is implanted into a subcutaneous pocket in the abdominal wall. During the operative procedure, the gallbladder is removed to prevent chemical cholecystitis, and careful dissection is performed to prevent inadvertent perfusion of the stomach, duodenum, and pancreas with chemotherapeutic agents. On postoperative day 3 or 4, radiolabeled macroaggregated albumin is injected into the infusion pump, and a scintillation scan is obtained to verify full hepatic perfusion and exclusion of extrahepatic perfusion [86]. A lung window following this study can also determine the degree of intrahepatic vascular shunting, which occasionally is a problem with extensive liver involvement. Once appropriate hepatic perfusion is verified and the patient has recovered from the operative procedure, HAI is initiated. A typical infusion regimen involves a 14-day continuous infusion of FUDR at a dose of 0.15 mg/kg/day, leucovorin 8 mg/m²/day, and Decadron 20 mg/14 days followed by a 14-day continuous infusion of heparinized saline. The cycle is then repeated.

Hepatic toxicity is not uncommon with HAI FUDR. Liver function tests should be obtained every two weeks to allow dose adjustments that will reduce the chances of biliary

sclerosis. One guideline is to withhold FUDR infusion for any liver function test that exceeds twice the baseline value, and to resume treatment at one-half or one-third the original dose when the liver function tests return to baseline. After three cycles of HAI chemotherapy, an abdominal CT scan should be performed to assess response. In patients with stable disease or disease regression, cycles can be continued and re-evaluated periodically for response. Patients with disease progression during therapy should have treatment discontinued.

Early experience with HAI chemotherapy revealed many potential technical complications, which may have had a negative impact on the results of earlier studies. Better knowledge of the technical aspects of HAI cannula and pump placement has led to fewer complications and may translate into better future results. In one series of 180 patients, there was only a 5.5% early surgical complication rate, but the late surgical complication rate remained high at 28.8%. Late complications included pump pocket collections, catheter and arterial thrombosis, gastritis, and duodenitis [86]. FUDR-related complications include biliary sclerosis [87], chemical hepatitis [87], and proper hepatic duct strictures.

There have been five randomized trials comparing HAI chemotherapy with FUDR to systemic chemotherapy with FUDR or 5-fluorouracil (5-FU) (Table 3) [88-92]. Response rates for HAI chemotherapy ranged from 42% to 62%, compared to 10% to 21% for systemic chemotherapy. The increased response rate for HAI chemotherapy did not translate into significantly increased survival in any of the studies. However, significant drawbacks to the design of each trial preclude a definitive conclusion about which therapeutic approach better prolongs survival. Median survival ranged from 12.6 to 17 months. A meta-analysis of six studies by *Harmantas et al.* [93] demonstrated a statistically significant survival advantage of HAI chemotherapy over systemic chemotherapy, but this analysis included one study in which some patients in the control group received no treatment [94]. These earlier studies of HAI chemotherapy were hindered by

hepatobiliary toxicity related to excessive dosage of HAI FUDR, a high rate of surgical complications, and the allowance of crossover between treatment groups [95]. An ongoing randomized trial by the Cancer and Leukemia Group B (CALGB) may provide more definitive results.

Despite better disease control in the liver, about 56% of patients receiving HAI chemotherapy subsequently develop extrahepatic disease, compared with 37% of patients receiving systemic FUDR [88]. One approach has been to combine HAI chemotherapy with systemic chemotherapy. In one study, 33% of patients receiving both HAI and systemic FUDR developed extrahepatic disease, compared with 61% of patients receiving HAI FUDR alone [96]. However, survival did not differ between the two groups. Several centers are presently exploring the combination of FUDR-based HAI chemotherapy and i.v. CPT-11.

Stagg et al. reported results of an HAI regimen consisting of a lower dose of FUDR (0.1 mg/kg/day) for seven days combined with weekly intra-arterial 5-FU (15 mg/kg) with the goal of reducing hepatotoxicity [97]. Patients receiving this regimen had response rates (50%) equivalent to those obtained with higher doses of FUDR alone and a median survival of 22.4 months, and no patient required treatment termination due to drug toxicity. Other trials have examined combinations of FUDR, dexamethasone, and leucovorin, and response rates between 56% and 78% with median survivals between 23 and 24.8 months have been observed [98-100].

At least three studies have examined whether adjuvant HAI chemotherapy improves survival in patients following surgical resection of liver metastases from colorectal cancer. In one study, patients received HAI of 5-FU following curative resection of colorectal cancer liver metastases [101]. After a median follow-up of 33 months, 50% of patients were alive without recurrence. The authors compared this with historical controls and concluded that adjuvant HAI chemotherapy after resection may decrease disease recurrence. *Wagman et al.* in a randomized prospective study found no difference in survival in patients with a single resectable metastasis who received

Table 3. Prospective randomized clinical trials of HAI chemotherapy versus systemic chemotherapy*

Study	Study size	HAI treatment (sample size)	Systemic treatment (sample size)	Median survival HAI versus systemic (months)	p value	Crossover
<i>Kemeny</i> [88]	99	FUDR (48)	FUDR (51)	17 versus 12	0.424	Yes
<i>Chang</i> [89]	64	FUDR (32)	FUDR (32)	17 versus 12	0.27	No
<i>Hohn</i> [90]	143	FUDR (67)	FUDR (76)	15.45 versus 15.81	NS	Yes
<i>Martin</i> [92]	69	FUDR (33)	5-FU (36)	12.6 versus 10.5	0.53	No
<i>Wagman</i> [91]	41	FUDR (31)	5-FU (10)	13.8 versus 11.6	0.55	Yes

*Adapted from [93]. NS = not significant.

either resection alone or resection plus HAI FUDR, although the number of patients in this study was small [91].

Another approach to extensive isolated liver metastases is isolated hepatic perfusion (IHP) with tumor necrosis factor (TNF) and melphalan. In this procedure, the circulation of the liver is isolated by placing cannulae in the portal vein, hepatic artery, and retrohepatic inferior vena cava, and routing blood from these vessels into an extracorporeal circuit. The liver perfusate is used to increase the liver temperature to about 40°C, and TNF and melphalan are added to the circuit for 60 min. In a series of 35 patients with liver metastases, 75% of patients treated with IHP had a partial or complete response. The mean duration of response in these advanced-stage patients was nine months [102].

CONCLUSION

Patients with isolated colorectal cancer metastases that are potentially resectable should be evaluated by a surgeon

experienced in hepatic resections, because their best hope for long-term survival remains surgical resection. Despite modern surgical techniques, only a minority of patients have limited disease amenable to resection. Patients who do not meet the criteria for surgical resection and do not have extrahepatic disease can be considered for regional therapies such as cryosurgery or radiofrequency ablation, but further studies are needed to demonstrate improvement in survival with these treatments. For patients with more extensive liver metastases, HAI chemotherapy can be considered as an alternative to systemic chemotherapy, but a survival benefit has not yet been convincingly demonstrated.

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