Resection of Liver Metastases: State of the Art

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In this article, we present current surgical perspectives on the management of liver metastases, with a focus on state-of-the-art resection, by drawing on clinical data provided in the medical literature. Metastases from

*Aside from serving as a primary organ for the maintenance of metabolic homeostasis, the liver is unfortunately also known for its propensity to harbor tumor metastases. It has been noted that the liver is surpassed only by regional lymph nodes as the most common site of metastases, and that hepatic metastases can be found in 25% to 50% of all patients dying of cancer.[1] These figures, in part, reflect the wide spectrum of primary tumors that may use the liver as a reservoir for their metastases. Although the majority of hepatic metastases originate from colorectal cancer, primary tumors from the lung, breast, kidney, pancreas, ovaries, uterus, stomach, and esophagus, as well as neuroendocrine tumors, sarcomas, and melanoma, also metastasize to the liver.*

In this article, we present current surgical perspectives on the management of liver metastases by critically evaluating the clinical data provided in the medical literature. The focus of the discussion is on the current status of patient selection, techniques, and resection of liver metastases from a select group of primary sites wherein it is applicable. Because metastases from colorectal cancer are the most amenable to resection when considering long-term benefit, we highlight the evidence-based rationale for surgical resection and provide a succinct comparison of all treatment modalities for liver metastases from colorectal cancer. The results of surgical resection of metastases originating from sites other than the colon and rectum are also discussed.

**Surgical Approach to Hepatic Metastases**

Although a wide variety of primary cancers are known to metastasize to the liver, there is a paucity of reliable data to guide resection of many such tumors. To date, colorectal cancer and neuroendocrine tumors of the gastrointestinal tract constitute the only two histologic types for which a liver-directed surgical approach has been well substantiated in the literature. This discrepancy may be due to the fact that liver metastases from other cancers typically occur in the setting of widespread systemic failure, whereas tumors arising within the portal system possess a greater proclivity for establishing truly isolated hepatic metastases. Currently, surgical management of hepatic metastases primarily involves interventions that center on achieving potential cure; therefore, patient selection is limited to those in whom the liver is the only site of failure or the dominant site of disease.

Neuroendocrine tumors of gastrointestinal origin comprise a diverse group that includes malignant gastrinomas, carcinoid tumors, insulinomas, glucagonomas, somatostatinomas, and vasoactive intestinal peptide-secreting tumors (VIPomas). When neuroendocrine liver metastases can be completely removed, aggressive surgical resection should be undertaken, because the 5-year survival rates in this setting are typically greater than 50%.[2-4] Unfortunately, these metastases are most often discovered when they are diffuse and usually beyond curative resection. At this point, they are often associated with disabling or life-threatening symptoms, and their initial management should consist of medical therapy aimed at alleviating such manifestations. In contrast to the management of most hepatic metastases, surgical therapy of neuroendocrine liver metastases can be advocated even if complete resection is not possible. The goal in such a case becomes improvement in quality of life as opposed to potential cure. Especially in the case of carcinoid metastases, significant palliation of symptoms seen secondary to these functional endocrine tumors has been achieved with 90% debulking.[5] Moreover, the indolent nature of neuroendocrine metastases may allow for surgical re-resection to provide long-term symptomatic disease control and exceptionally long survival rates.

Although reports are largely anecdotal, several authors have noted variable success using a surgical approach to "noncolorectal, nonneuroendocrine" metastases. Many reports collectively group these
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Table 1 compiles reported hepatic resections for a wide variety of noncolorectal nonneuroendocrine liver metastases. As a general tenet, most surgeons would consider resection of certain lesions if the procedure yielded a 5-year survival rate > 10%. The first eight histologic types of primary tumors listed in the table might meet this benchmark, but the limited numbers of cases make accurate outcome analysis difficult. At present, the lack of data on the natural history of these subtypes makes general recommendations for resection premature, but the trends we have begun to see are promising.

Although the surgical management of hepatic metastases may infrequently encompass an exotic presentation from a multitude of primaries, the majority of cases mandating resection are derived from colorectal cancer. Therefore, the remainder of this article will focus on the management of these metastatic cancers. It should be noted, however, that aside from colorectal cancer-specific chemotherapy, the underlying principles and practices guiding surgical management are applicable to most liver metastases, regardless of histologic type.

Liver Metastases From Colorectal Cancer

Epidemiology
In the year 2002, an estimated 148,300 people will be diagnosed with colorectal cancer and approximately 56,600 will die of the disease in the United States alone.[9] Despite well-promulgated screening recommendations and improving treatment regimens, approximately 40% of all patients diagnosed with primary colorectal cancer will develop liver metastasis. With regard to timing, 15% to 20% of colorectal cancer patients present with synchronous liver metastases at the time of initial diagnosis and another 20% will later present with metachronous liver metastases.[10,11] This translates roughly into more than 50,000 patients with colorectal cancer-derived liver metastases in a given year.

Natural History of Colorectal Cancer
"I will proceed with my history, telling the story as I go along of small cities no less than of great. For most of those which were great once are small today; and those which used to be small were great in my own time. Knowing, therefore, that human prosperity never abides long in the same place, I shall pay attention to both alike."
—Herodotus

The state of any art represents a dynamic glimpse at the ongoing spectrum of improvement. As noted by Herodotus, in order to frame the advances to be garnered tomorrow, one must have an accurate appraisal of the past. The state of the art for the resection of hepatic metastasis should therefore reflect first on the natural history of untreated disease.

Since no future clinical trial will include an untreated control arm, an examination of the data from the 1960s through the early 1980s is necessary in order to determine the natural history of this disease. Special attention is paid to patient survival rates because these statistics serve as the backdrop against which all subsequent treatment strategies must be compared. The data from this time period can be stratified into two groups (Table 2).[12-22] The studies conducted during the 1960s and 1970s typically represent symptomatic patients accrued during the pre-computed tomography (CT) era, and the 1980s data reflect asymptomatic patients in the post-CT era. As a result, some debate continues over whether the advent of CT imaging improved detection significantly enough to produce a lead-time bias in the survival rates of the latter group. Despite these differences, both sets of studies clearly demonstrate that untreated disease is uniformly fatal, with a median survival ranging from 5 to 12 months. Even the cohort that had potentially resectable liver metastases demonstrated a median survival of approximately 18 months and a 5-year survival rate ranging from only 2% to 8%.[12]

Comparison of Treatment Modalities
Table 3 compares survival rates achieved with different treatment modalities. At present, surgical resection is associated with superior survival rates compared to any other modality and, therefore, remains the treatment of choice for hepatic colorectal metastases. However, in most patients, surgical resection is not an option either due to extrahepatic disease or due to regionally advanced tumors; in the latter group, there is a growing impetus toward multimodality therapy. Therefore, systemic treatments merit a succinct discussion.

Systemic Chemotherapy
Chemotherapeutic approaches to the treatment of metastatic colorectal cancer have met with only
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modest success, at best. Due to poorer outcomes, chemotherapy is conventionally reserved for patients who are not candidates for curative surgical resection. Unfortunately, approximately 80% to 90% of colorectal cancer patients with liver metastasis comprise this group. The origin of effective chemotherapy for colorectal cancer dates back to the early 1950s. Following Rutman’s observation that rat hepatoma cells utilized uracil to a greater extent than normal intestinal cells, Heidelberger’s development of fluorouracil (5-FU) was subsequently applied to the treatment of gastrointestinal cancers.[23,24] Nearly 20 years later, in the late 1970s/early 1980s, the use of 5-FU-based systemic chemotherapeutic regimens began, leading to the current standard of intravenous 5-FU plus leucovorin for the treatment of unresectable disease.

Other systemic agents shown to have significant antitumor effects against colorectal cancer are the topoisomerase I inhibitor irinotecan (CPT-11, Camptosar) and the platinum-based guanine alkylator oxaliplatin. Recent emphasis has been on examining these agents in combination. The most active of these combinations produce response rates ranging from 20% to 50% but only rare complete responses and a median survival of 10 to 16 months (Table 4).[25-27]

**Regional Chemotherapy**

Approximately 15% of patients with unresectable colorectal liver metastases have detectable disease confined only to the liver. In this group, regional chemotherapy represents an improved option. Current regional chemotherapies comprise hepatic artery infusion of floxuridine, based on a study by Breedis et al that illustrated preferential perfusion of tumor cells by the hepatic artery in contrast to the predominantly portal supply of normal hepatic tissue.[28] Another benefit afforded by hepatic artery infusion includes a high 90% first-pass extraction of floxuridine by the liver when administered slowly. This allows for decreased systemic drug toxicity and intrahepatic drug concentrations that are 100- to 400-fold higher than those seen in systemic venous controls.[29]

The seven randomized trials of hepatic artery infusion compared with either systemic therapy or ad libitum controls are well analyzed in the report published by the Meta-Analysis Group in Cancer.[25] Their multivariate analysis showed that hepatic artery infusion results in a three- to fourfold increase in tumor response rates (40%-62%), compared to standard systemic chemotherapy (15%-21%), and lengthens time to progression.[25] However, hepatic artery infusion demonstrated only a marginal increase in survival; ie, the overall and progression-free survival rates were significantly longer for hepatic artery infusion when analyzed against all studies of systemic therapy and ad libitum controls combined, but only a handful of patients survived for 5 years (comparable to natural history controls). In fact, in this meta-analysis report covering several hundred patients, only two survived beyond 5 years.[25]

**Surgical Ablation**

Unlike surgical resection, the goal of which is en bloc removal of tumor with clean margins, regional ablative therapy strives to destroy colorectal cancer metastases in situ. Two forms of surgical ablation are currently used in the treatment of unresectable disease[cryoablation and radiofrequency ablation. Both employ destructive energy applied intratumorally to cause cell death through thermal mechanisms. Cryoablation entails the use of probes equipped with liquid nitrogen or argon gas refrigerant to achieve probe tip temperatures as cold as -160°C. Cell death is enhanced by rapidly freezing the tumor to a peripheral tumor zone temperature of at least -50°C, followed by slow thaw, and subsequent repetition of this freeze/thaw cycle. Radiofrequency ablation causes cell death by application of an alternating electrical current at a frequency of ~400 kHz. This stimulus leads to frictional heating of tissues by ionic agitation. Heating above the 50°C threshold allows for disruption of cellular membranes and induction of protein denaturation, culminating in tumor cell death.

Results following cryoablation are promising for patients with unresectable but liver-isolated metastases. Several investigators have shown survival rates after cryotherapy to be superior to those seen in natural history controls and systemic/regional chemotherapeutic cohorts (Table 5).[30-35] Long-term survival is typically achieved in 10% to 20% of patients. Because the majority of recurrences are limited to the liver, we have initiated a prospective phase II trial of cryoablation followed by 12 months of adjuvant hepatic artery infusion. This combination yields a median survival of about 34 months and a 5-year disease-free survival rate of 17%.

Results of radiofrequency ablation for hepatic metastases are not as well substantiated in the literature. In published series to date, most data contain both primary and mixed metastatic tumors.[36-47] Only one series involved more than 40 patients with metastatic tumors. Results have varied, and most reports do not provide long-term survival statistics. One concern regarding this treatment modality is the issue of recurrence as a
function of the size of treated tumors (Table 6). One of the largest studies of radiofrequency ablation analyzed predictors of failure.[47a] These include (1) lack of increased lesion size on contrast-enhanced CT scan at 1 week, implying ineffectively treated margins, (2) poorer outcome for colorectal cancer vs a better outcome for hepatocellular carcinoma, neuroendocrine cancer, and other metastases, and (3) larger tumor volume (failure if tumor size > 18 cm³; success if ≤ 9.2 cm³; P = .015). Possibly contributing to treatment failure is the fact that intraoperative (real-time) ultrasound monitoring is not as effective in delineating ablation margins during radiofrequency ablation as for cryoablation, making the estimation of complete tumor destruction less than optimal. Recent evidence suggests that improved modes of radiofrequency delivery may yield better results in the future.[48] We have initiated a prospective randomized multicenter phase II trial of radiofrequency ablation as part of a multimodality regimen for unresectable liver metastasis from colon cancers. The trial will systematically examine overall survival, quality of life, and patterns of failure for radiofrequency ablation followed by either systemic chemotherapy alone or hepatic artery infusion plus systemic chemotherapy.

Surgical Resection

Although liver surgery was performed as early as the turn of the century, resection of liver metastases was not in vogue until the 1970s. Much of the early skepticism regarding a surgical approach was due to the high morbidity and mortality associated with these procedures, as well as the debatable therapeutic benefit of local surgery in what was considered widely disseminated disease. Several factors have since led to safer liver resections. These include surgical application of the principles of liver anatomy, enhancement of preoperative imaging, optimization of cardiopulmonary monitoring, the advent of intraoperative staging, technical advances leading to "bloodless" surgery, and better postoperative metabolic support. These improvements have led to numerous publications highlighting the safety of liver resection. An examination of the literature from major centers illustrates that mortality typically ranges from 2% to 4% (Table 7).[49-58] The operative mortality is usually related to the magnitude of the liver resection and is commonly attributable to complications from hemorrhage or liver failure.[59] Reports from several authors illustrate that complications due to liver failure occur in about 1% to 4% and due to hemorrhage in 1% to 3% of all resections.[60,61] Although overall morbidity ranges from 20% to 40%, close supervision and rapid intervention preempt most mortality. At our institution, the low incidence of major complications from resection is best reflected by a current perioperative mortality of well under 1% and median hospital stay of less than 6 days. By the 1970s, the emerging strategy of focusing on the specific subset of patients with "liver only" metastases began to demonstrate the possible therapeutic benefit of resection.[62-64] By the late 1970s, the number of surgeons reporting on liver resection in colorectal cancer patients increased dramatically, and has since led to the publication of several large series with 100 or more patients (Table 7).[49-58] These investigations have uniformly demonstrated that surgical resection can result in long-term survival for a substantial portion of patients. The reported 5-year survival rates in these studies range from 25% to 37%, and the median survivals range from 24 to 42 months. Although not listed in Table 7, three studies included 10-year follow-up statistics. Both Scheele and Jamison[53,54] documented 10-year survival rates of 20%, and Fong[55] reported a 22% 10-year survival. Although randomized prospective trials are lacking, these results clearly demonstrate that surgical resection produces survival rates superior to other modalities and is the only treatment associated with a considerable potential for cure.

Hepatic Resection of Colorectal Cancer Metastases

Perioperative Evaluation

Perioperative evaluation is imperative for proper stratification of patients, in order to identify candidates for curative surgical resection. As such, this assessment has three goals: (1) to exclude the presence of disseminated extrahepatic disease, (2) to quantify and localize metastases with regard to anatomic and vascular structures, and (3) to assess whether a given patient is healthy enough to tolerate this invasive surgical procedure.

Assessment Goal #1
To achieve the first aim, the conventional work-up includes CT scans of the chest, abdomen, and pelvis. Most authorities also advocate performing a colonoscopy (if one has not been performed within the previous 12 months) to rule out recurrence of the primary colorectal cancer or the
presence of a second primary. Whole-body positron-emission tomography (PET) scanning using fluorine-18-fluorodeoxyglucose (FDG) has received a substantial amount of attention recently. This imaging technique is based on the observation that neoplastic cells undergo an accelerated rate of metabolism and, therefore, process glucose at much higher levels than normal tissues. By administering a tagged analog of glucose (FDG) that is readily taken up by active tumor cells, but not processed by them, this marker accumulates and appears as a hyperintense focus following subsequent PET scanning (Figure 1).

In a recent meta-analysis of 11 articles in the literature, FDG-PET was shown to possess an overall sensitivity of 97% and an overall specificity of 76% (both at a 95% confidence level [CL]) in detecting recurrent colorectal cancer throughout the body. The analysis also found the overall FDG-PET-directed change in management to be 29% (95% CL). Our experience with FDG-PET has resulted in a management change in 16% of cases. Five articles have tried to directly compare FDG-PET to CT in the perioperative evaluation of patients. All five found in favor of FDG-PET, but only the last two included a sizable comparison. Whiteford et al compared the records of 105 patients who underwent 101 CT scans and 109 FDG-PET scans for suspected metastatic or recurrent colorectal adenocarcinoma. They found the sensitivity of FDG-PET in detecting extrahepatic metastases exclusive of regional recurrence was higher than for CT and other conventional diagnostic studies (94% vs 67%). Interestingly, the sensitivity of FDG-PET in detecting mucinous cancer was lower (58%; n = 16) than for nonmucinous cancer (92%; n = 93).

In addition to FDG-PET, scans utilizing various radiolabeled antibodies directed against colorectal tumor antigens have been employed over the past 15 years in an attempt to improve sensitivity and specificity. However, these scans have typically produced high false-positive results. Nevertheless, if more specific antibodies are developed, this method may further enhance the diagnostic accuracy of extrahepatic disease in the future.

Assessment Goal #2

A "bolus, dynamic, triphasic" helical CT scan of the upper abdomen provides excellent definition of the number of liver lesions, the vascular relationship with those tumors, and any variations in the hepatic arterial anatomy. Because the hepatic artery primarily perfuses liver metastases, most lesions will show hypoattenuation relative to normal liver during the portal venous phase of the scan. Some authors advocate the use of CT arterioporationography, which has been shown to possess an overall sensitivity of 94%. However, given the increased cost, invasiveness, and high false-positive rates associated with this type of imaging, we find it difficult to advocate its routine use. Furthermore, on the occasions when the "bolus, dynamic, triphasic" helical CT scan proves inadequate, MRI with mangafodipir trisodium or superparamagnetic iron oxide contrast agents can provide supplemental information. These imaging techniques are especially helpful in discerning metastatic tumors from a variety of benign liver lesions, and are at least as accurate as CT arterioporationography.

Another popular mode of perioperative evaluation is laparoscopy and laparoscopic ultrasound. This method is minimally invasive and usually involves the placement of only three transabdominal ports (Figure 2). After routine surveillance to rule out extrahepatic disease, a modified flexible ultrasound transducer fitted to a telescopic shaft is introduced intra-abdominally to survey the liver for previously undetectable lesions and to assess whether curative resection is feasible. Several authors have demonstrated that laparoscopy and laparoscopic ultrasound can provide evidence of unresectability better than conventional imaging studies, and have advocated its use to prevent unnecessary laparotomy. In these studies, laparoscopy and laparoscopic ultrasound determined unresectability in 25% to 64% of patients. In a study by Jarnagin et al, 104 patients were staged laparoscopically and were compared prospectively to 82 patients undergoing exploration without laparoscopy. The authors found that 83% of patients subjected to laparotomy after laparoscopic staging underwent a potentially curative resection, compared to 66% of those who were not so staged. Furthermore, they showed that, although the yield of laparoscopy and laparoscopic ultrasound was exceptional in detecting additional hepatic tumors (10 of 12) and unsuspected advanced cirrhosis (5 of 5), it often failed to identify unresectability because of lymph node metastases, vascular involvement, or extensive biliary involvement.

Assessment Goal #3

To determine the ability of a patient to tolerate hepatic resection, we commonly obtain a full panel of blood tests. Because a biochemical profile demonstrating reasonable liver function is necessary to ensure a satisfactory outcome, these tests typically include aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, prothrombin time, albumin, and bilirubin levels. A serum albumin of less than 3 g/dL, elevated transaminases, or a prolonged prothrom-
bin time that does not respond to the administration of vitamin K often signifies extensive hepatic involvement and poor functional reserve.[78] Patients undergo a cardiopulmonary assessment in an effort to reduce the postoperative risk of pneumonia, pleural effusion, pulmonary embolism, or myocardial infarction. The Eastern Cooperative Oncology Group (ECOG) functional rating is commonly used in most oncology trials. Patients meeting a classification of 0 to 2 are considered good candidates for surgical resection.

**Indications for Surgical Resection**

**Standard Criteria**

In 1986, Ekberg et al described specific surgical criteria that must be met to achieve acceptable survival rates following hepatic resection.[79] Readily adopted as standard dogma for hepatic resection of colorectal cancer metastases, Ekberg’s contraindications were (1) the presence of more than four lesions, (2) extrahepatic disease (portal lymph node metastases), and (3) the inability to obtain clear margins > 1 cm.[79]

**Maximum Number of Lesions**

Despite the fact that Ekberg’s conclusions were based on a small number of patients and a substantial portion of the cases (19%) showed positive margins on histologic examination, several surgeons subsequently promulgated the first of these caveats—regarding the maximum number of colorectal cancer metastases that should be treated with curative resection—to guide patient management.[80,81] The results from several subsequent publications have given some credence to this conclusion.

In a 1989 multicenter series by Hughes et al, the disease-free survival (14%) and total 5-year survival (18%) were reduced following resection of four or more metastases, compared to the results seen with resection of one to two lesions.[82] Nevertheless, these authors maintained that the only absolute contraindication was the impossibility of a radical removal of tumor—ie, the assumption that residual disease will remain after the hepatic resection. Reporting on 68 patients with more than four metastases, Fong et al demonstrated a 5-year survival of 24%, compared to 23% for 140 patients with up to three lesions and 47% for the 240 patients with one lesion.[83] Likewise, Ohlsson et al found a 28% 5-year survival in patients with one to three resected lesions, compared to a 15% 5-year survival in the group with four or more lesions.[84]

**Extrahepatic Disease**

The second contraindication reiterates that the goal of resection is aimed at potential cure. Once metastases have disseminated beyond the liver, it makes little sense to provide exclusively regional treatment. Numerous studies have substantiated this view. In a study by Adson et al, the presence of extrahepatic disease resulted in no 5-year survivors and dramatically reduced 2- and 3-year survival rates.[85] More recently, Gayowski et al reported on 204 patients who underwent curative hepatic resection for metastatic colorectal cancer. After examining 14 clinical and pathologic determinants previously reported to influence outcome, they found that lymph node involvement and direct invasion to adjacent organs were significant indicators of poor prognosis (P < .05).[86]

**Size of Resection Margins**

The third contraindication above is probably the most important determinant that surgeons ultimately have control over. With respect to the size of the resection margin, several authors have agreed that margins greater than 10 mm yield substantially improved results.[84-87] Cady et al noted that one of the main features separating patients who survive from patients who die is the attainment of resection margins of at least 1 cm.[87] Scheele et al reported on 266 patients who underwent resection of colorectal metastases to the liver with curative intent, and in their analysis, found a decreased crude survival associated with limited resection margins of less than 10 mm (P = .019). [61] Finally, in describing their 25 years of experience with resecting hepatic colorectal cancer metastases, Ohlsson et al showed a 30% 5-year survival rate for resections with greater than 10-mm margins, compared to a 20% 5-year survival for resection margins less than 1 cm.[84]

**Extended Criteria**

Emerging challenges to the above dogma are appearing with greater frequency. This is especially apparent regarding the maximum number of lesions that may be treated with curative resection. One of the earliest disputes to the "rule of 4" came from results published by Nordlinger et al in 1987.[88] Among the 80 patients in this study, 14 underwent curative resection of five or more metastases. Survival rates, compared to those of the two- to four-lesion group, were found to be similar. Although largely anecdotal, Kawasaki et al reported on five patients with bilateral multiple...
metastatic liver lesions from colorectal cancer, four of whom were alive and free of cancer between 36 and 74 months after hepatectomy.[89] Interestingly, this cohort included a patient with 12 metastases that were widely distributed throughout the liver. Minagawa et al published mixed results concerning the effect of multiple lesions on survival.[90] They reported that the 10-year survival rate of patients with four or more nodules (29%) was better than that of patients with two or three nodules (16%) and was similar to that of patients with a solitary lesion (32%). In this cohort, one patient underwent removal of 13 metastases and was alive beyond 5 years. The authors concluded that, although multiple metastases impaired the prognosis relative to solitary lesions, the life expectancy of patients with four or more nodules mandates surgical removal. These seemingly contradictory results bring us to an important observation discussed by Scheele and Altendorf-Hofmann.[91] In their review, they suggest that survival is not predicated upon number of metastases per se, but rather, on the ability to achieve "true R0" resections (radical resections with clear margins that completely circumscribe the specimen). Although their data clearly substantiate this point, there is a tendency for more disseminated hepatic distribution with an increasing number of lesions. Therefore, the technical threshold of curative resectability becomes an issue with increasing number and distribution. In our opinion, this fact should not preclude an operative approach toward four or more lesions. Instead, an individualized feasibility approach to every patient is warranted to ensure a clear margin of 1 cm or more. Another area in which convention has been challenged involves the question of whether any extrahepatic disease precludes surgical intervention. These exceptions generally refer to "contained" extrahepatic disease and not a widely disseminated picture, typically including local recurrence, direct tumor invasion to adjacent structures, and solitary lung metastasis. Although lymph node metastasis at the liver hilum has been closely associated with poor prognosis, reports of anecdotal success are found in the literature.[92]

Techniques

Historical Background
In 1957, Couinaud described a functional anatomy of the liver based on its vascular subdivision.[93] Following Starzl’s emphasis, most hepatic resections have traditionally followed this functional anatomic schema in an attempt to reduce the risk of major intraoperative hemorrhage and accidental gas embolism. As illustrated in Figure 3A, the Couinaud classification divides the liver into eight independent segments, each of which has its own vascular inflow, outflow, and biliary drainage. Because the liver is divided into self-contained units, each segment can be resected without damaging the remaining segments. To accomplish this, resections must proceed along the vessels that define the peripheries of these segments. In general, this establishes anatomically based resection lines parallel to the hepatic veins. Nonanatomic resections do not follow these guidelines and are usually reserved for small lesions located on or adjacent to the liver’s surface. These procedures are also often used to spare residual hepatic tissue when extensive resections are required. Although many authors have failed to demonstrate statistical differences in the results achieved with anatomically based vs nonanatomically based approaches, this may, in fact, indicate the presence of other confounding variables. It has been suggested that anatomically based procedures reduce the incidence of negative margins and that the slight advantage seen (by some authors) with nonanatomic resections may reflect less difficult cases with lower operative risk and/or a reduced tumor load. Rather than compromise resection margins, a wiser approach to ensuring good margins and sufficient residual hepatic function involves preoperative selective portal embolization. This procedure can induce hypertrophy and regeneration in healthy liver parenchyma and has been used by several authors prior to extensive resections.[89,90,94]

Access and Exposure
To gain the necessary wide exposure required for hepatic resection, a bilateral subcostal incision (two finger widths below the costal margin) is made, extending to the xiphoid process. Exposure is enhanced with the aid of self-retaining subcostal retractors, which lift the superior margin of the incision up and away from the liver underneath. Next, the liver is mobilized by dividing its attachments to the lesser omentum, the ligamentum teres/falciforme, and the triangular ligaments. Routine palpation, surveillance, and a complete exploration of the abdominal cavity follows, with any suspected extrahepatic lesions being biopsied and sent for histologic confirmation. After confirming the absence of extrahepatic disease, the
gallbladder is usually removed (or dissected and left attached by cystic duct, to serve as a handle for right hilar structures) before resection is begun, unless a segmental resection is planned.

**Common Examples of Hepatic Resection**

Up to 85% of healthy liver may be removed with impunity. This rule of thumb does not apply in cases of compromised hepatic functioning, and one should err on the side of caution to prevent postoperative hepatic failure. Depending on the number and distribution of hepatic metastases, five major hepatectomies are commonly performed (Figure 3B). These procedures include (1) right lobectomy (removal of segments V, VI, VII, and VIII), (2) right trisegmentectomy (removal of segments IV, V, VI, VII, and VIII), (3) left lateral segmentectomy (removal of segments II and III), (4) left lobectomy (removal of segments II, III, and IV), and (5) left trisegmentectomy (removal of segments II, III, IV, V, and VIII).

**Technical Advances**

Several intraoperative technical advances have helped increase the safety and effectiveness of hepatic resection. Even with the adoption of anatomically based procedures, major hemorrhage remained a serious complication. In addition, several studies highlighted the impact of blood loss and transfusion on poor outcomes.[95,96] With the advent of effective hemostatic equipment and an increasing emphasis by the surgical community on "bloodless" techniques, the potential for severe blood loss has been significantly reduced (Figure 4). The following methods have helped establish practically "bloodless" resections.

**Cell-Saver Machine**

One innovation responsible for reduced risk of homologous transfusion is the cell-saver machine, which collects blood lost during surgery and allows it to be recycled back to the patient, thereby minimizing the total amount of blood loss.[97] With regard to hepatic surgery, there has been concern that the processing of blood may initiate lipid peroxidation and the release of hepatotoxic products. However, one recent study addressed this issue and found insufficient evidence of a postoperative liver disorder induced by toxic metabolites of lipid peroxidation.[98]

**Vascular Isolation**

Inflow occlusion and total vascular isolation are other methods of reducing blood loss during hepatic resection. This strategy involves the placement of atraumatic clamps on the afferent and efferent blood supply to the liver. If combined with low central venous pressure (< 5 cm H2O), this approach can significantly reduce blood loss. Investigational data support the belief that intermittent clamping is superior to continuous clamping.[99-101] For example, Uchinami et al observed that free-radical production and subsequent liver damage is significantly less severe with intermittent pedicle clamping than with continuous clamping.[101]

**Cavitron Ultrasonic Aspiration**

The Cavitron Ultrasonic Aspirator for transection of liver parenchyma has been shown to have a beneficial effect on hepatic resection.[102] This device is a handheld instrument with a hollow titanium tip that vibrates along its longitudinal axis at 23 kHz (23,000 times per second). When the tip is brought in contact with tissue, mechanical energy is transferred, creating high- and low-pressure areas. When pressure drops below the vapor pressure of tissue, vapor-filled vacuoles form within the cells. These vacuoles expand and collapse as pressure rises and falls with each cycle, generating forces that fragment the cells. Another attractive feature of the Cavitron Ultrasonic Aspirator is the limited extent of damage to adjacent tissues. The fragmentation is confined to an area of about 25 to 50 µm from the tip, with minimal thermal injury and protein denaturation. Typically, the use of a scalpel or laser results in greater amounts of tissue damage; with electrocautery, the extent of tissue damage can exceed 1,000 to 4,000 µm. Yet another major advantage of the system in hepatic resection is the selectivity of its dissection. Because the device’s rate of cavitation activity is proportionate to the water content of the cells (ie, tissues with high water content are fragmented more readily), dissection can be performed leaving blood vessels and biliary structures behind for individual ligation. This device allows for precise resection planes and helps eliminate fracturing of the hepatic tissue (a common occurrence of blunt dissection). Therefore, the likelihood of achieving clear margins > 1 cm increases. A recent retrospective comparison showed that simultaneous use of the Cavitron Ultrasonic Aspirator and hepatic inflow occlusion had a major impact on reducing intraoperative blood loss, transfusion requirement, operative time, mortality and morbidity rates, and length of hospital stay.[103]

**Argon-Beam Coagulator**

The argon-beam coagulator is another effective hemostatic device. Known also as the argon plasma beam, this instrument uses laser technology. To create the beam, an electric current is passed
through an inert gas (argon). The thermal emission of the beam is then used to coagulate bleeding tissue. The argon-beam coagulator employs a noncontact method; the probe is positioned close to the bleeding tissue and heats it from a small distance. The device can coagulate up to a depth of 2.4 mm and needs a gas flow of up to 12 L/min. Argon-beam coagulation is rapid and effective, and has been shown to provide potent hemostasis even in the face of anticoagulative therapy.[104] It has been suggested that this technique poses a theoretical possibility of tumor spread by gas flow and air embolization. A recent publication addressed this possibility and found the opposite to be true. Yamagata et al performed companion studies, which determined that an exposure of 10 seconds with argon-beam coagulation is sufficient to destroy any microscopic residue of malignant cells near the resection line.[105] Thus, an argon-tissue coagulator could be of value for prophylaxis against recurrence near the resected surface.

**Intraoperative Ultrasound**

Although not directly involved in hemostasis, intraoperative ultrasound can provide essential information and should routinely be performed by a well-trained surgeon. Schmidt et al, in an examination of metastases < 2 cm, found the sensitivity and specificity of intraoperative ultrasound to be 98% and 95%, respectively.[106] They also found that the modality was as adept as spiral CT or CT arterial portography (CTAP) at detecting liver metastases < 10 mm. Thus, intraoperative ultrasound can be especially important in the detection of lesions that may be missed by palpation or other preoperative studies. At our institution, intraoperative ultrasound has detected the presence of small occult lesions in 5% of cases.

With improved ultrasound technology, hepatic resections have also become more precise and safer. For example, pulse and color-flow Doppler provides intraoperative ultrasound examination with detailed views of the architecture of the liver, including real-time mapping of hepatic vessels in relation to focal hepatic lesions. In this way, the surgeon receives an immediate assessment of the lesion and does not have to rely on studies that may be outdated by the time of surgery. Furthermore, intraoperative ultrasound supporting three-dimensional (3D) computed reconstruction can provide a complete and accurate rendering of the lesion as it exists within the tissue (Figure 5). Thus, final assessment of resectability and determination of resection planes according to Couinaud segmental anatomy can be made quickly in the operating room, and with great precision.

**Prognosticators**

In addition to the aforementioned three criteria (number of lesions, extrahepatic disease, and margin of resection), a wide array of factors have been examined to see if they significantly influence patient survival. The major factors that contribute to a worsening prognosis include nodal status of the primary tumor (stage II vs III), primary tumor dedifferentiation (ie, poorly differentiated tumor, tumor ploidy, mucin production), synchronous presentation (no disease-free interval), elevated preoperative carcinoembryonic antigen levels (marker of tumor aggressiveness or tumor load), increased size of resected lesions, and blood loss or transfusions.

More recent prognosticators emerging in the literature include echogenicity on ultrasound examination, and various measures of gene expression. Table 8 lists the proven prognosticators derived from a multitude of studies.[49-56,79,83-86,88,90,92,95, 96,105,107,108] These prognostic factors are subdivided into characteristics of the primary colorectal cancer, metastases, and surgical results, and are listed in decreasing order of significance for each group, based on popular consensus in the literature.

**Patterns of Failure and Management of Recurrence**

A recurrence of colorectal metastases is seen in approximately 66% of patients who undergo liver resection. For the majority of these patients (60% to 70%), tumor relapse usually occurs within 2 years of surgery. The predominant site of recurrence is the liver, but a substantial portion of patients re-present with widely disseminated disease. A percentage breakdown of the sites of first recurrence following hepatic resection for colorectal cancer metastases is provided in Table 9.[83] A variety of alternative approaches have been implemented to further improve patient outcomes. These include repeat resection, neoadjuvant therapy, and adjuvant therapy postresection.

**Repeat Resections**

Increasing levels of safety associated with performing hepatic resections have led to more aggressive approaches to the management of liver-localized recurrences following initial resections. Because the treatment of choice for hepatic metastases remains curative resection, repeat resections have become increasingly popular. Due to the increased number of adhesions and
modified anatomy resulting from the original surgery, these cases typically are more difficult. Despite this, the perioperative mortality remains relatively low when performed by experienced surgeons. A collective review of 10 series involving 484 patients showed a perioperative mortality rate of 1%, a median survival of 24 to 46 months, and a 5-year survival rate of 36%.[109-118]

In cases in which the recurrence is limited to the liver and a curative resection is technically feasible, long-term results largely parallel the survival rates achieved with the initial resection. That said, actual 5-year survivors in these studies are few, and long-term results are needed. Rarely, a third resection for the salvage of recurrence after repeat resection is performed if the patient meets criteria.[117,118]

**Neoadjuvant Therapy**

For the 80% to 90% of patients with liver metastases deemed unresectable upon initial evaluation, survival is poor even after partial response to chemotherapy. Because hepatic resection is the best available option, this form of multimodality treatment entails the use of systemic chemotherapy to convert an unresectable liver metastasis into a resectable one by downstaging the tumor. Although this approach is still considered investigational, preliminary results are promising, and a significant number of patients achieve enough of a response to then undergo resection.

In a study of over 300 patients, Bismuth et al illustrated that the neoadjuvant regimen of 5-FU, leucovorin, and oxaliplatin converted 53 (16%) previously unresectable patients into surgical candidates.[119] They also showed that the survival benefit for this cohort was comparable to that obtained with primary liver resection (40% at 5 years).

Another form of neoadjuvant therapy under investigation involves the immunomodulator interleukin (IL)-2, a known stimulator of T lymphocytes that has been shown to increase response rates of hepatic metastases when administered in combination with chemotherapy.[120] Although no clinical studies of substance have been published to date, IL-2-based immunotherapy may play a potent role in neoadjuvant therapy in the future.

**Postresection Adjuvant Therapy**

Nearly two-thirds of patients who undergo hepatic resection of colorectal cancer metastases subsequently develop recurrent tumors. It has been theorized that chemotherapy administered after resection may improve results by eliminating micrometastases. Studies have examined the role of both systemic chemotherapy and hepatic artery infusion as postresection adjuvant treatments. To date, no studies of systemic chemotherapy as an adjunct after resection have demonstrated an improved survival benefit. Results with hepatic artery infusion as an adjunct to resection have been contradictory.

**Hepatic Artery Infusion**

Lorenz et al compared the impact of hepatic artery infusion plus resection on survival relative to resection alone.[121] In this randomized study, 226 patients recruited from 26 hospitals were stratified, based on the number of metastases and site of the primary tumor. Patients were then assigned to undergo either resection of liver metastases followed by adjuvant hepatic artery infusion of 5-FU (1,000 mg/m2/d for 5 days as a continuous 24-hour infusion) plus leucovorin (200 mg/m2/d for 5 days as a short infusion), or liver resection only. Early interim analysis found that this dose and schedule resulted in a significant number of side effects and may have increased the risk of death; the study was prematurely terminated.

**Hepatic Artery Infusion Plus Systemic Chemotherapy**

In contrast, Kemeny et al found in a randomized study of 156 patients that hepatic artery infusion of floxuridine plus systemic 5-FU after resection of colorectal liver metastases resulted in improved survival outcomes, compared to patients receiving systemic chemotherapy alone.[122] At a median follow-up of 62.7 months, the median survival of the hepatic artery infusion/systemic chemotherapy group was 72.2 months, compared with 59.3 months for the monotherapy group. After 2 years, the disease-free survival in patients receiving hepatic artery infusion/systemic therapy was significantly improved over that in patients given systemic therapy alone (90% vs 60%, respectively; P < .001).

**Timing of Postresection Chemotherapy**

Whether the results seen in the earlier studies are attributable to variations in methods (ie, dosing and scheduling) remains to be proven. However, evidence is emerging that such methods (in particular the timing of chemotherapy after resection) may play a significant role in the eventual outcome.

Kooby et al found that adjuvant chemotherapy improved outcome if administered early after resection, but may prove lethal if administered prior to completion of DNA synthesis in regenerating the liver.[123] These authors performed 70% hepatectomies on adult male Fischer rats and
subsequently evaluated the effect of chemotherapy on liver regeneration. Animals treated with floxuridine at the point of hepatic nucleoside triphosphate (NTP) normalization (a measure of hepatic DNA synthesis) showed a significantly improved survival over those that began treatment within this period (75% vs 17%; P = .0005, log-rank test). Although translational studies are required, these authors demonstrated that floxuridine inhibits hepatic DNA synthesis and influences mortality if it is administered too early after hepatectomy. These results bring up interesting questions about the biological changes that occur after resection. We have been aware for some time of the liver’s amazing capacity to undergo hypertrophy and regeneration when stressed. Following hepatic resection, the regenerative milieu responsible for triggering hepatocyte growth induces similar effects in any residual tumor cells.[124]

Immunomodulators
Another form of adjuvant therapy that may be used in the future to combat residual tumor cell growth involves the use of immunomodulators. Investigational studies have shown that the immune status of the liver may be compromised following resection, and this may promote the growth of liver metastases. Jarnagin et al conducted a study addressing the growth of residual microscopic disease in the setting of postoperative host cellular immune dysfunction.[125] Using gene delivery of IL-12 into rat livers prior to surgical resection, they showed that IL-12 secretion elicited an immune response directed at residual tumor and reduced the incidence of recurrence seen after resection. Karpoff et al analyzed the ability of muramyl tripeptide phosphatidylethanolamine (MTP-PE) to stimulate Kupffer cells and protect against tumor growth in Buffalo rats.[126] They showed that animals treated with MTP-PE had fewer tumor nodules than control animals (19 vs 184, P < .005). These results were enhanced by portal delivery of MTP-PE, as the number of nodules observed in this group was significantly less than in the group receiving intravenous MTP-PE (2 vs 36, respectively; P < .05). Although their clinical role has yet to be defined, administration of these and other immunotherapies may prove to be useful as adjuvant therapy for patients who undergo resection of liver malignancies.

Cost-Effectiveness Analysis
The rising costs of health-care delivery in the United States underscore the need to assess the cost/benefit ratio of treatment, especially when multiple options exist. With regard to hepatic resection, increased survival translates into a positive financial benefit. Beard et al, reporting on 100 hepatic resections conducted from 1997 to 1999, used a simple decision-based model to evaluate the marginal costs and health benefits of hepatic resection.[127] Their analysis found that, as survival prognosis increases, the financial benefits offset the costs related to the intervention. Therefore, hepatic resection appears highly cost-effective, compared with nonsurgical treatments for liver metastases from colorectal cancer (Table 10).[127]

Conclusions
Despite the lack of multiple randomized prospective trials with consistent data, the results of prospective/retrospective analysis from multiple centers demonstrate superior results for resection compared to any other treatment modality for liver metastases from colorectal cancer. Hepatic resection for isolated colorectal liver metastases can achieve long-term survival in most patients, and cure in many. Adjunctive chemotherapy following hepatic resection may further improve the long-term prognosis of patients. Ablative techniques are useful tools in the surgeon’s armamentarium for palliation and potential cure of unresectable liver tumors. In addition to liver metastases from colorectal cancer, those from renal, Wilm’s, adrenocortical, breast, ovarian, and testicular tumors, as well as from melanomas and soft-tissue sarcomas, may lend themselves to resection. However, in such circumstances, patient selection is critical to achieving optimal outcome. Prospective trials are needed to validate the role of ablative strategies and to discern the optimal multimodality combinations of resection, ablation, hepatic artery infusion, and systemic chemotherapy. Improved patient selection and tumor discrimination by high-quality imaging methods such as FDG-PET scans may further improve outcomes.

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