Colorectal Hepatic Metastases

Resection, Local Ablation, and Hepatic Artery Infusion Pump Are Associated With Prolonged Survival

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Background: Treatment of metastatic colorectal cancer to the liver is not uniform. We describe the management of metastatic colorectal cancer of the liver at a single institution during a 10-year period.

Methods: From January 1, 1990, through December 31, 1999, 174 patients were identified from the tumor registry at the University of Alabama at Birmingham with a diagnosis of metastatic colorectal cancer to the liver. Patient, tumor, laboratory, operative, and adjuvant therapy factors were analyzed, with overall survival as the endpoint. Log-rank tests were used for univariate analysis, Cox proportional hazards model for multivariate analysis, and Kaplan-Meier curves were used for graphical representation of survival. Significance was defined as P < 0.05.

Results: Median age was 60 years (age range, 18-92 years). Seventy-nine percent of patients had synchronous liver metastases at the time of diagnosis of the primary colorectal tumor. The primary tumor was in the colon and rectum 75% and 25% of the time, respectively. Of the 89 patients who underwent operation, 73 received definitive surgical treatment for their liver metastases. Fifty-two patients underwent lobectomy or wedge resection, 5 underwent cryotherapy, and 16 had a hepatic artery infusion pump (HAIP) inserted. Median follow-up duration of surgically treated patients was 26 months. Operative mortality was 1.3%. The 3-year actuarial survivals for patients who underwent resection, HAIP, or those with unresectable disease were 70 months, 32 months, and 3 months, respectively (P < 0.001). By multivariate analysis, surgical intervention, a carcinoembryonic antigen level less than 200 µg/L, or a low T stage of the primary tumor were associated with prolongation of survival.

Conclusions: Surgical resection should be attempted for hepatic colorectal metastases, as this is associated with prolonged overall survival. Hepatic artery infusion pump insertion seems to prolong overall survival for those with unresectable hepatic metastases, but it is not equal to resection. Aggressive surgical management of patients with hepatic colorectal metastases is safe, may prolong overall survival, and therefore should be considered in all patients with metastases confined to the liver.

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MANAGEMENT of patients with metastatic colorectal cancer to the liver is not uniform. Current treatment options include surgical resection,1-3 local ablation by cryotherapy4 or radiofrequency ablation5 hepatic artery infusion pump (HAIP),6,7 and preoperative systemic chemotherapy.8 Surgical resection, if performed by experienced surgeons, with low morbidity and mortality, seems to provide the best chance for long-term survival.2,9 Despite the absence of randomized trials comparing resection with observation or other options, studies of the natural history of untreated isolated colorectal metastasis to the liver suggest that there are few long-term survivors.10 This study was performed at a single institution to document the treatment modalities in all patients with metastatic colorectal cancer to the liver and to determine the important factors from both the primary tumor and metastatic disease associated with overall survival. In addition, patients undergoing definitive surgical resection were separately analyzed to determine the factors associated with prolonged posthepatectomy survival.

Table 1 presents the frequency distribution of various clinicopathologic factors, including patient, primary tumor, metastatic tumor, laboratory, operative, and adjuvant therapy factors for the whole group (N = 174) and the resection group (n = 52).
PATIENTS AND METHODS

From January 1, 1990, through December 31, 1999, 174 patients were identified from the tumor registry at the University of Alabama at Birmingham (UAB) with a diagnosis of metastatic colorectal cancer to the liver. They included patients with synchronous, extrahepatic metastasis, as well as those patients with disease confined to the liver, in an effort to evaluate the full spectrum of disease. Patient factors included age in years, sex, race, and family history of colorectal cancer.

Primary tumor data included individual American Joint Committee on Cancer T, N, and M status, as well as the overall stage as a separate prognostic factor. Also included were location of the tumor (colon or rectum) and the microscopic differentiation, defined as well, moderate, or poorly differentiated. If 2 of the above descriptions were used to describe the differentiation, the worse of the 2 was recorded for statistical evaluation. Laboratory data included serum alkaline phosphatase, with abnormal being defined as levels greater than 120 U/L; serum lactate dehydrogenase, with abnormal being defined as levels greater than 240 U/L; and carcinoembryonic antigen (CEA), with levels greater than 200 µg/L being defined as significantly elevated. This value was chosen because it has been used in previous studies of prognostic factors.1

Secondary tumor factors included the presence or absence of liver only disease, the lobar distribution (unilobar vs bilobar), and the number of liver lesions at the time of diagnosis. Surgical factors included the type of operative procedure, operative blood loss, and the surgical microscopic margin. Resection was defined as wedge (nonanatomical resection) or lobectomy (including multiple anatomic segments and trisegmentectomy). Cryotherapy was defined as multiple freeze-and-thaw cycles of a given tumor, with the residual iceball left in situ. Cryoassisted resection of liver tumors11 was included in the resection category. Hepatic artery infusion pump was defined as a subcutaneously implanted pump that provided long-term infusion of floxuridine through the hepatic artery.6 A small number of patients received combinations of therapeutic modalities, in which case, the patient was recorded to be part of only one group. For example, 1 patient underwent laparotomy and HAIP. In the absence of residual cancer at the time of operation, this patient would be scored as a resection. Similarly, 2 patients underwent wedge resection of lesions by left lateral segmentectomy, and then had cryoablation of other lesions in the right lobe, which were left in situ. This patient was recorded in the cryotherapy group. Patients who did not undergo any form of surgical therapy were originally separated into patients with liver only disease (50 patients) and patients with liver and other distant sites of metastatic disease (51 patients). The overall survival of both of these groups of patients were virtually identical, and therefore, the 2 groups were combined in the analyses. Adjuvant therapy factors were primarily the receipt of chemotherapy after definitive decisions regarding surgical therapy were determined. Chemotherapy during this period primarily took the form of 5-flourouracil and levocovirin, though we do not have specific data or regimens for the majority of patients analyzed since many of them received this form of therapy at institutions closer to home. Chemotherapy received as part of adjuvant therapy for a primary tumor was not included in this analysis.

Data are presented as numbers (percentages). Clinopathologic factors of the whole group (N=174), which included all patients followed up during this period, was contrasted with the resection-only group (n=52) undergoing definitive liver resection. This was done to identify prognostic factors with as complete a denominator as possible, and then to compare these with those patients who ultimately were candidates and underwent surgical resection. The date of last follow-up was December 31, 1999; median follow-up duration of the resected group was 26 months. The follow-up period began at the date of diagnosis of liver metastases. Overall survival was recorded as the time to death regardless of cause, with patients who had no evidence of disease or who were alive with disease censored at the time of last follow-up. Univariate analyses of prognostic factors associated with survival were performed by log-rank test.12 Multivariate analyses were determined using the Cox proportional hazards model,13 and stepwise regression in the SPSS computer software package (Statistical Product and Service Solutions 7.0; SPSS Inc, Chicago, Ill). The method of Kaplan and Meier was used for graphical representation of the survival data.14

WHOLE GROUP

One hundred twenty-one patients (70%) died during the follow-up period, with the majority dying of disease-related causes. By univariate analysis, significant factors associated with shorter survivals were no surgical procedure, a CEA level at or greater than 200 µg/L, a tumor grade of or worse than T3, synchronous presentation, bilobar disease, a lactate dehydrogenase level at or greater than 240, patients being nonwhite, more than 1 liver lesion, poor differentiation of the primary tumor, alkaline phosphatase levels at or greater than 120 U/L, and older age (>60 years) (Table 2). Three unfavorable characteristics were selected into the final Cox model: no surgical procedure, CEA level at or above 200 µg/L, and a T3 or worse primary tumor stage. Once the prognostic value of these factors were considered, no other value offered additional prognostic importance. Figure 1 demonstrates that surgical resection provides the most significant prolongation of overall survival, followed by HAIP and cryotherapy (P<.001). Three-year actuarial survival rates for resection, HAIP, or those with unresectable disease were 70%, 32%, and 3%, respectively (P<.001), with only patients undergoing surgical resection surviving for more than 5 years. To date, none of the cryotherapy patients have survived 3 years; however, small numbers and short follow-up durations in this group preclude more definitive statements about survival patterns. The nonsurgical group contains both patients with liver only disease and those with extrahepatic disease. There was no difference between these 2 curves, so the groups were combined into one curve as stated in the “Patients and Materials” section. Figure 2 demonstrates the unfavorable effect of CEA levels at or greater than 200 µg/L (P<.001) and Figure 3 demonstrates the unfavorable effect of a worse than T3 pri-
mary tumor on the overall survival of the whole group ($P = .03$). No patient with either an elevated CEA or T4 primary tumor survived longer than 40 months.

**RESECTION GROUP**

Nineteen patients (37%) have died during the follow-up period, with all but 1 patient dying of disease. Univariate analysis demonstrated factors significantly associated with a shorter overall survival: a CEA level higher than 200 µg/L, a primary tumor stage higher than T3, and being of the male sex. Trends toward statistical significance were seen with poorly differentiated primary tumors, more than 1 liver lesion, and a positive microscopic margin (Table 3). Figure 4 demonstrates the importance of a CEA level greater than 200 µg/L, where no patient with an elevated CEA level lived longer than 30 months. Figure 5 demonstrates the significance of increasing primary tumor T stage.

**PATTERNS OF FAILURE IN PATIENTS WHO UNDERWENT RESECTION**

To date, of the 52 patients who underwent hepatic resection, 21 (40%) have developed recurrent disease, with 1 dying of disease during the follow-up period, and 2 undergoing repeat hepatic resections and/or ablation of their recurrent disease. Of the 21 patients who have developed recurrent disease, 13 (62%) have sustained distant recurrence, with 3 of these having liver recurrence in conjunction with their distant disease.
Eight (38%) of the 21 recurrences were liver only, of which 2 were able to be successfully treated with further surgical intervention.

**COMMENT**

This study demonstrated that proper selection of patients for resection, cryotherapy, and/or HAIP are associated with prolonged survival compared with...
those patients undergoing no surgical intervention. While many other studies have examined surgical resection, cryotherapy, and/or HAIP separately, this study attempted to evaluate each of these interventions from a single institution and compare them to the populations that either were not referred for surgical resection or were evaluated and were not candidates. Understanding that there is a selection bias, nonrandomized comparison of these survival curves with survival curves of our own patients (those who were not candidates for surgical intervention [liver only disease] as well as those patients who may have been acceptable surgical candidates but who were not offered operation) suggests that surgical intervention has a favorable effect on survival. In our entire cohort, the factors associated with prolonged survival by multivariate analysis were surgical intervention, lower T stage of the primary tumor, and a lower serum CEA level. Analyzing the surgically resected group separately to determine the factors associated with prolonged survival demonstrated that lower serum CEA, lower T stage of the primary tumor, and being of the female sex were the most important factors.

Surgical resection, while never compared in a randomized trial with observation, remains the procedure of choice in selected patients. Multiple series have demonstrated prolonged survival in patients with metastatic colorectal cancer, with more than 1000 patients recently reported from Memorial Sloan-Kettering Cancer Center, New York, NY. Throughout approximately 13 years, this study evaluated prognostic factors in 1001 patients who underwent hepatic resection for metastatic colorectal cancer. Other than extrahepatic disease and positive microscopic margin, which often are not able to be determined preoperatively, the most important factors were node-positive primary tumors, disease-free interval shorter than 12 months, more than 1 tumor, the largest tumor being larger than 5 cm, and a serum CEA level higher than 200 µg/L. Weighing each of these factors equally, we suggest that 2 or fewer factors would produce the greatest chance for long-term survival. Our data is in rough agreement with these factors, showing advanced primary tumor stage and elevated CEA as poor factors. As in the present study, female sex has been demonstrated to be an important factor; the possible cause of this finding is yet unexplained. The durability of hepatic resection on 10-year disease-specific survival was demonstrated in a recent article by D’Angelica et al, in which there was a 78% chance of being alive at 10 years if one survived the initial 5 years posthepatectomy.

Local ablation, either with cryotherapy or radiofrequency ablation, remains an alternative for those patients who are deemed unfavorable candidates for hepatic resection. In an institution where an aggressive surgical approach is the standard (including multiple segmental resections or cryotherapy-assisted resection), the patients undergoing these procedures may be biologically worse candidates for achieving long-term survival. Despite this speculation, several studies have demonstrated prolonged survival in patients with metastatic disease to the liver from colorectal cancer. Unfortunately, like the present series, most of these studies have limited numbers of patients and are mixed with other histological entities, both primary and metastatic. Radiofrequency ablation of these lesions is being safely used though laparoscopic, percutaneous, and open applications. A recent multi-institutional report demonstrated a local failure rate of 2% and a distant failure rate of 28%, with relatively short-term follow-up durations, although this represented both primary and metastatic lesions. It remains to be seen whether this will be a durable finding, and which patients are selected to be the best candidates. Optimally, organizing a trial to examine the benefits of one type of local ablation instead of another would be possible.

The role of HAIP in prolonging patient survival remains to be definitively proven. Since one of the original Phase II trials with a fully implantable pump from our institution demonstrated a survival advantage over historical trials, most studies have failed to show such a definitive advantage. A recent metaanalysis has shown a statistically significant survival advantage at 1 year and a trend for prolonged survival at 2 years. Studies like this, as well as other studies examining quality of life and the economics of HAIP vs systemic chemotherapy may be raising the level of enthusiasm for this treatment modality in unresectable patients. One alternative to immediate HAIP is the use of preoperative systemic chemotherapy to select a favorable group of patients who will respond. Bismuth et al reported that 15% of this group of patients ultimately underwent hepatic resection, with an actuarial 5-year survival of 40%. Alternatively, HAIP as an adjuvant to complete surgical resection has been recently reported. This demonstrated a statistically significant survival advantage at 2 years with an impressive reduction in liver only recurrence. Unfortunately, improved overall survival of the HAIP group did not reach statistical significance because of the inability of our current systemic agents to adequately control distant metastases. Obviously, further work in the control of distant metastases remains a major focus of future research.

In summary, our study demonstrated that surgical intervention by resection, cryotherapy, or HAIP in a single institution seems to prolong survival compared with a nonrandomized control group during the same period. Patients who are technically resectable and are able to physically undergo operation should be recommended for surgical intervention. Patients with poor prognostic factors associated with early recurrence after resection should be candidates for investigational systemic and local control measures. If unable to undergo complete primary resection, or in the presence of liver only recurrence after hepatic resection, then cryotherapy or radiofrequency ablation may be viable alternatives. Hepatic artery infusion pump or neoadjuvant systemic chemotherapy may have a role in the clearly unresectable, nonresectable patient with good performance status. Lastly, novel combinations of resection, local ablative measures, as well as regional and systemic therapy need to be continually explored. In conclusion, major surgical resection performed safely, in addition to having the tools to offer alternatives, are important contributions to the
multidisciplinary management of patients with metastatic colorectal cancer to the liver.

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ing PGE$_2$ production in the tumor-bearing host may restore MO immune competence and host immunity.

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Correction

Reference Error. In the first reference of the article titled “Colorectal Hepatic Metastases: Resection, Local Ablation, and Hepatic Artery Infusion Pump Are Associated With Prolonged Survival” published in the March issue of the Archives (2001;136:318-323), the first author, Fong Y, was omitted from the list.