**Hypothesis:** Interval reevaluation for resectability of hepatic colorectal metastases aids patient selection.

**Design:** A retrospective review.

**Setting:** A tertiary care medical center.

**Patients and Methods:** From January 1, 1985, to July 1, 1998, 318 patients with colorectal hepatic metastases were identified. Resectable lesions (N = 73) were divided into synchronous (n = 36) or metachronous (n = 37) and retrospectively reviewed for immediate resection or interval reevaluation. Kaplan-Meier survival curves of treatment groups were compared by the log-rank test.

**Results:** Survival curves of patients with synchronous and metachronous lesions undergoing interval reevaluation vs immediate resection were not significantly different (P = .74 and P = .65, respectively). No lesions from patients who underwent interval reevaluation became unresectable due to growth of the initial metastases. After interval reevaluation, 8 (29%) of 28 patients with synchronous metastases were spared the morbidity of laparotomy because of distant or an increased number of metastases and 10 (36%) of 28 patients were spared the morbidity of hepatic resection at the time of interval laparotomy. Actuarial median and 5-year survival of patients after delayed hepatic resection (51 months and 45%, respectively) were significantly improved compared with those of all other patients with resectable metastases (23 months and 7%, respectively) (P = .02). For patients with metachronous lesions who underwent interval reevaluation, 4 (29%) of 14 patients were spared the morbidity of laparotomy because of an increased number of hepatic or distant metastases.

**Conclusions:** Delaying hepatic resection for metastatic colorectal cancer does not impair survival. Potentially, two thirds of patients can avoid major hepatic surgery. For synchronous metastases, delaying hepatic resection appears to select patients who will benefit from hepatic resection.

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Surgical resection provides the only potentially curative therapy for patients with liver metastases from colorectal carcinoma. Historical evidence shows that only one third of patients with liver metastases from colorectal cancer will be candidates for surgical resection, with the median survival of resected patients ranging between 24 and 40 months and 5-year survival between 16% and 45%. Given the substantial morbidity and mortality of hepatectomy, great effort has been made to elucidate the most significant prognostic factors of long-term survival and establish criteria to aid in selection of candidates for surgical resection. Many studies have shown a dismal prognosis in the presence of extrahepatic disease, and this is generally accepted as a contraindication to hepatic resection. Studies have also shown that the number, size, and distribution of metastases; an elevated carcinoembryonic antigen level; and a higher stage of the primary tumor may significantly affect survival after hepatic resection. Even when multiple prognostic indicators are used in retrospective analyses to select the most favorable subgroups, greater than 60% of patients experience disease recurrence. This is particularly true for patients with synchronous metastases, whose long-term survival, 20% or less, is worse than that in patients with metachronous lesions.

Some believe that the survival benefit from hepatic resection is determined by the biological features of the tumor rather than by early detection. Particularly for synchronous hepatic metastases, some researchers recommend “a test of time” to assess the biological behavior of the metastatic tumor. They theorize that by delaying hepatic resection 3 to 6 months, occult metastases will become evident. In this way, patients who would not be cured by hepatic resection are identified and spared noncurative exploration or resection. While this is intellectually appealing, and practiced by some surgeons, to our knowledge, there is little published evidence to support this theory. The objec-
PATIENTS AND METHODS

The medical records of all patients with the diagnosis of hepatic metastases from colorectal cancer in the database at Dartmouth-Hitchcock Medical Center, Lebanon, NH, between January 1, 1989, and July 1, 1998, were reviewed. Patients were considered to have synchronous hepatic metastases if a lesion was discovered no later than 3 months after the diagnosis or resection of the primary tumor. Any metastatic hepatic lesion discovered more than 3 months after the diagnosis of a nonresectable primary neoplasm or the resection of the primary tumor was considered metachronous. All hepatic metastases were then categorized as resectable or unresectable. Candidates for resection were defined as patients with 4 or fewer metastases in a distribution believed to be resectable with intent to cure by the attending surgical oncologist. In general, lesions in patients with extrahepatic disease were considered unresectable.

All patients with resectable hepatic disease were then categorized as having undergone an immediate hepatic resection or an interval reevaluation for possible hepatic resection. The decision to proceed with immediate surgery or wait and reevaluate was made by the individual treating surgeon. Immediate resection occurred concurrent with or within 3 months of resection of the primary tumor. The interval reevaluation category included any patient with resectable hepatic metastases who was reevaluated for resectability 3 or more months after diagnosis.

Data regarding survival from the time of the diagnosis of hepatic metastases and characteristics with potential prognostic value, including number and distribution of hepatic metastases and stage of the primary tumor, were recorded. For metachronous lesions, the disease-free interval following resection of the primary tumor was also recorded. In patients with lesions that were found to be unresectable on follow-up evaluation, the reason for unresectability was determined and classified as increased size of original metastases, increased number of metastases, or distant metastases. Statistical analyses were performed using a log-rank test and Kaplan-Meier actuarial survivor curves.

RESULTS

PATIENT CHARACTERISTICS

A total of 318 patients with hepatic metastases from colorectal cancer were identified. Overall, 198 (62.3%) were men and 120 (37.7%) were women. Their mean age was 64 years (range, 24-87 years). Synchronous hepatic metastases were diagnosed in 193 (60.7%) of the patients, while 126 (39.6%) had metachronous metastases. (One patient had a synchronous and a metachronous lesion.) Of the 193 patients with synchronous lesions, 36 (18.7%) were initially identified as candidates for curative hepatic resection. Of the 126 with metachronous lesions, 37 (29.4%) were considered resectable. Overall, 49 patients underwent hepatic resection, with only 1 perioperative death; this patient was included in the survival analysis. Characteristics of the patients with resectable hepatic metastases are listed in Table 1.

Table 1. Characteristics of Patients With Resectable Hepatic Colorectal Metastases

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Synchronous (n = 36)</th>
<th>Metachronous (n = 37)</th>
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TREATMENT OF PATIENTS WITH SYNCHRONOUS HEPATIC METASTASES

Figure 1 shows the distribution by treatment of patients with resectable, synchronous, hepatic metastases. Eight patients underwent immediate hepatic resection (5 wedge resections and 3 lobectomies), while 28 underwent interval reevaluation.

For the 28 patients who underwent interval reevaluation, the mean interval to the final decision regarding therapeutic intervention was 6 months (median, 5 months; range, 3-15 months). Thirteen patients underwent chemotherapy with fluorouracil during this interval. Interval reevaluation consisted of performing a physical examination and obtaining a medical history, a computed tomographic (CT) scan of the abdomen and pelvis, and either a chest CT scan or an x-ray film for all patients. Of the patients considered candidates for hepatic resection by the previous studies, 22 (79%) of 28 also underwent CT portography. Two recent patients were examined by magnetic resonance imaging in addition to CT portography. As shown in Figure 1, at the time of reevaluation, 8 patients were no longer considered surgical candidates. Five patients developed an increased number of hepatic metastases to greater than 4, while 2 others were found to have distant metastatic disease. Representative CT scans of a patient with lesions that were considered unresectable at the time of reevaluation because of an increased number of intrahepatic metastases are shown in Figure 2. This patient had 3 metastases initially evident on a CT scan (Figure 2, left panel). On interval reevaluation 6 months later, 4 new hepatic metas-
The mean survival of all 36 patients with synchronous, resectable, hepatic metastases (5-year survival, 27 months) was significantly better than that of all other patients with resectable synchronous metastases (mean survival, 22 months). Those patients who, after interval reevaluation, had a successful hepatic resection survived an average of 37 months. Within this group, 6 of 10 patients were still alive at 9, 20, 24, 25, 80, and 86 months, compared with 3 of 18 patients still living (at 4, 7, and 16 months) who did not undergo hepatic resection after reevaluation.

To determine whether interval reevaluation identified a subgroup of patients with improved survival, the survival of patients undergoing interval hepatic resection was compared with that of all other patients with resectable synchronous metastases. As shown in Figure 4, the survival of patients who underwent hepatic resection after interval reevaluation was significantly better than that of the rest of the patients with resectable, synchronous, hepatic metastases (5-year survival, 45% vs 7%; P = .02).

**Figure 3** shows the distribution by treatment of patients with metachronous hepatic metastases. Twenty-three of the patients with metachronous lesions underwent exploration for immediate hepatic resection, while the remaining 14 underwent interval reevaluation. Four of the 23 patients undergoing immediate surgical intervention had wedge resections only, while 17 underwent formal lobectomy or trisegmentectomy. Two patients were found to have unresectable disease at the time of laparotomy secondary to an increased number of hepatic lesions.

For the 14 patients who underwent interval reevaluation, the mean interval to the final decision regarding therapeutic intervention was 6 months (median, 4 months; range, 3-29 months). As shown in Figure 5, at the time of interval reevaluation, 4 patients were no longer considered surgical candidates. One patient had developed an increased number of metastases, while 2 were found to have distant metastatic disease. One patient did not undergo laparotomy because of a significant clinical decline. Ten patients underwent exploratory laparotomy for intended hepatic resection, and all underwent resection. The surgical

**Table 2** shows a comparison of the number of liver metastases, distribution of the intrahepatic lesions, and the stage of the primary tumors for those patients with resectable, synchronous, hepatic metastases undergoing immediate resection vs interval reevaluation. The patients who underwent interval reevaluation had a greater number of poor prognostic indicators, particularly a higher average number of metastases (2.0 vs 1.4) and a higher percentage of stage III primary tumors (68% vs 37%).
resections included 4 left lobectomies, 4 right lobectomies, 1 left lobectomy with a right wedge resection, and 1 right lobectomy with a left wedge resection.

SURVIVAL OF PATIENTS WITH METACHRONOUS HEPATIC METASTASES

The number of liver metastases, the distribution of the intrahepatic lesions, and the stage of the primary tumors for patients with resectable, metachronous, hepatic metastases undergoing immediate resection vs interval reevaluation are compared in Table 3. Overall, these prognostic indicators are comparable. Although the patients undergoing immediate resection had a higher percentage of stage II or III primary tumors (82% vs 57%), they enjoyed a longer disease-free interval from the time of resection of the primary tumor (26 vs 19 months). The mean survival of all 37 patients with resectable, metachronous, hepatic metastases was 32 months. Patients who underwent immediate exploratory laparotomy had

Figure 2. Left panels. Computed tomographic scans of a patient initially diagnosed as having 3 synchronous hepatic metastases. Arrows indicate 3 metastases that were initially identified. Right panels. Interval reevaluation at 6 months detected 4 new metastases. Arrows indicate 3 of the 4 new lesions. R indicates right; L, left.
a mean survival of 32 months and a 5-year survival of 22%. Of the patients undergoing immediate surgery, those with successful hepatic resections experienced a mean survival of 34 months. For the 2 patients found to have unresectable lesions at the time of exploration, the mean survival was 24 months. Patients undergoing interval re-evaluation had a mean survival of 31 months and a 5-year survival of 20%. As shown in Figure 6, there was no significant difference in survival between patients with metachronous metastases who underwent immediate surgery and those who underwent interval re-evaluation (P = .65), indicating that interval re-evaluation did not impair survival.

For the patients who underwent interval re-evaluation, those who did not undergo surgery after the re-evaluation had a mean survival of 18 months. All patients in this group who underwent surgery underwent hepatic resection and had a mean survival of 36 months, with a 5-year survival of 27%. To determine whether interval re-evaluation of patients with resectable, metachronous, hepatic metastases identified a subgroup of patients with improved survival, the survival of patients undergoing interval hepatic resection was compared with that of all other patients with resectable, metachronous, hepatic metastases. As shown in Figure 7, the survival of patients who underwent hepatic resection after interval re-evaluation was not significantly different from that of the rest of the patients with resectable metastases (P = .57).

**COMMENT**

With an estimated mortality risk for hepatic resection of 5% and a morbidity of 20% to 50%, preoperative identification of patients with hepatic metastases from colorectal carcinoma who are likely to benefit from this treat-
Able.1,19 In this manner, patient selection for hepatic resection will not provide any survival benefit if occult disease becomes clinically detectable. In theory, delaying hepatic resection may also help to select a subgroup of patients who experience a significant survival benefit. In particular, identifying patients with synchronous hepatic metastases who can achieve survival benefit through hepatic resection presents an even greater challenge. Despite the appearance of resectability at the time of initial diagnosis of hepatic metastases, hepatic resection will not provide any survival benefit if occult metastases are present. In theory, delaying resection of synchronous hepatic metastases for 3 to 6 months may allow occult disease to become clinically detectable.1 In this manner, patient selection for hepatic resection can be facilitated since patients who become unresectable during the interval to reevaluation (and, therefore, would not benefit from hepatic resection) can be spared the morbidity and mortality of major surgery. In addition, for patients with synchronous hepatic metastases, delaying hepatic resection may also help select a subgroup of patients who experience a significant survival benefit.

One concern regarding this approach is that additional metastases found at the time of reevaluation represent new metastatic lesions occurring during the interval to reevaluation. There are multiple reasons why additional metastatic lesions found at the time of reevaluation are unlikely to represent new metastases occurring during the waiting interval. First, complete resection of the primary tumor removes the principal source of any new metastases. Second, the doubling time of metastases from colorectal cancer is approximately 14 weeks, and it is estimated that at least 30 doublings are required for a tumor to become clinically detectable from the level of a single cell. Therefore, it is more likely that any additional metastases detected at the time of an interval reevaluation at 6 months represent previously occult disease that has grown to a detectable size rather than new metastases that occurred during the interval to reevaluation. Third, if these lesions represented new metastases occurring during the diagnostic interval, the expected survival of the interval reevaluation group would be less than that of the immediate resection group. In our group of patients, this was not the case, as shown in Figures 4 and 6.

Another concern is that interval reevaluation may result in a missed opportunity if increased size of the original metastases causes lesions in patients to become unresectable. In this study, no patient became unresectable secondary to increased size of an original metastasis. However, this remains a valid concern, particularly in the patient who presents with a metastasis in an unusual location, such that any further growth might technically preclude resection. In this instance, immediate removal might be preferable.

The findings in this study support a test of time for patients with resectable, synchronous, hepatic metastases. We have shown that almost 30% of patients with synchronous and metachronous metastases were spared the morbidity of noncurative surgery. Of the patients with synchronous lesions, an additional 36% of the patients considered eligible for surgical resection after interval reevaluation were spared the morbidity of major hepatic resection at the time of exploratory laparotomy. Furthermore, a subgroup of patients was selected whose survival was significantly better than that of the other patients with resectable, synchronous, hepatic metastases.

We recognize that if a synchronous hepatic lesion is small, peripherally located, and easily removed at the time of primary resection with negligible increase in the morbidity or mortality of the surgery, it is best to do so. In the fortunate circumstance that this proves to be the patient’s only hepatic lesion, this would spare the morbidity of a second laparotomy after an interval reevaluation. However, there are many arguments against performing a major hepatic resection at the time of primary resection. These include the added morbidity and mortality, an insufficient metastatic workup, and the possibility of needing extensive revision of the incision. In addition, this study demonstrates that by delaying hepatic resection, combined with improved preoperative assessments, up to two thirds of patients being considered for major hepatic resection may avoid the significant morbidity and mortality of a major procedure that will not benefit their survival. Most patients in this study were reevaluated by CT scans and CT portograms. Increasing use of ferridex magnetic resonance imaging to detect hepatic lesions may help lower the number of patients found to be unresectable at laparotomy and increase the number avoiding surgery altogether. Routine use of laparoscopy to look for extrahepatic disease before full laparotomy may also help to lower the number of unnecessary explorations. Another potential adjunct is the carcinoembryonic antigen scan, which may help to identify additional intrahepatic or extrhepatic disease not appreciated by the conventional modes of imaging.
Another component requiring consideration is the role of chemotherapy during the interval to reevaluation. Randomized prospective clinical trials have shown that adjuvant fluorouracil-based chemotherapy improves the survival of patients after resection of node-positive colorectal carcinoma, indicating that this treatment can effectively eradicate micrometastases. Since a high proportion of patients with synchronous hepatic metastases will have occult micrometastases, we recommend that they be treated with fluorouracil-based chemotherapy during the interval reevaluation period. In addition to destroying micrometastases, chemotherapy may also create an additional element of rigor to the test of time. For example, patients who remain technically resectable at the time of reevaluation, but who show signs of disease progression while undergoing chemotherapy, may prove to be another subgroup that ultimately does not benefit from hepatic resection. Conversely, patients who respond to chemotherapy may become technically easier to resect, particularly with respect to a larger negative margin. At our institution, the interval reevaluation approach is being prospectively evaluated to confirm the results of our retrospective study.

As in the case of synchronous metastases, there is no impairment to overall survival by delaying resection of metachronous hepatic metastases. Thus, this approach is a reasonable option as it can potentially identify patients for whom a hepatic resection will not offer any survival benefit. However, unlike interval reevaluation for synchronous lesions, it does not appear to select a subset of patients who are more likely to experience a survival benefit after surgical resection.

Patient selection for hepatic resection of colorectal metastases remains challenging. Hepatic resection offers no benefit to patients with resectable, synchronous, hepatic metastases if occult disease is present. This study has shown that interval reevaluation does not impair overall survival. Through interval reevaluation, potentially two thirds of patients with resectable, synchronous, hepatic metastases can be spared the mortality and morbidity of noncurative hepatic surgery. In addition, a subgroup of patients who achieve significant survival benefit can be identified.


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REFERENCES


DISCUSSION

Kevin S. Hughes, MD, Burlington, Mass: This is an excellent paper looking at a very important question: how do we better select patients for hepatic resection? The test of time, as Dr Blake Cady has often suggested, works very well and has been shown to work well with no detrimental effects. In the synchronous group, the mean survival resected at once is 28 months but if delayed is 37 months. They have obviously teased out a better group and avoided resection in a group that would otherwise have died from occult disease, thus avoiding resection and identifying a better group for resection. In the metachronous population, though, that has not been the case. The 3- to 6-month test of time that they used has not shown improvement in survival for the metachronous group. I would suggest that maybe this group, the metachronous group, has slower-growing tumors, a longer doubling time, and their test of time may not be long enough. That’s supported by their own data. All the patients in the synchronous group have hematogenous spread that’s identified at the time of surgery, and the local regional spread is greater in that group: 61% node positive, 39% T3 or T4, and nobody in the T1-T2 range. The metachronous group has occult disease at most hematogenously, and locally,
has less nodal disease, less T3, T4, and does have some T1, T2. In the short test of time in the synchronous group, 64% of the patients become unresectable in the synchronous group, but in the metachronous group only 29% become unresectable. These are probably slower-growing tumors selected out by the metachronous population. First, do you have the ability now with your radiologic reviews of both of these groups to actually measure doubling time and have you found a difference in doubling time between the synchronous and the metachronous groups, and, second, in looking at the grade of the tumors and other biologic markers, is there a difference in the grade or the aggressiveness of the tumors in the synchronous group vs the metachronous group.

Blake Cady, MD, Providence, RI: It's always nice to have your biases confirmed, but I'd like to say that this points out that in surgical treatment of metastatic disease, the outcome is pattern dependent, not time dependent, as a generality, which is so nicely displayed here. This is true with pulmonary metastases of sarcoma and pulmonary metastases in colorectal carcinoma as well as liver metastases. So your survival benefit in the synchronous lesions that have a resection is a selection process, not from any inherent advantage from the delayed surgery; it's just that you eliminate the unnecessary operations, as you pointed out. But the metachronous appearance is already a selection process; that's why you didn't see the advantage there. But the corollary of this, which we as a profession don't appreciate, is that since this is a pattern process, not a time process, in metastatic disease, anything you do to speed up the time detection such as CEA [carcinoembryonic antigen] screening won't help. That's what your data show. Do you do CEA screening after primary colorectal cancer treatment and if you do, why? Have you instituted a policy so that all patients that present with synchronous lesions now go through a delay process and reevaluation in order to eliminate that 30% or 60% of patients that won't benefit?

William A. Cook, MD, North Andover, Mass: There's something that was unclear to me in this group of patients and that is what else was going on. Did any of these people have chemotherapy? Did they have radiation for local lesions? That sort of thing would otherwise effect what is going on in the different cohorts.

Dr Lambert: We did not specifically measure the doubling time; however, we did consider the possibility that metastases that develop during the interval could be metastases of metastases. However, we did not feel that this was likely. There have been a number of studies on tumor kinetics which show that the doubling time of colorectal metastases is approximately 14 weeks. It is estimated that it takes about 30 doubling times for a single cell to become clinically detectable; we felt that the metastases that we were seeing were most likely occult disease present at the time of initial evaluation which became detectable over the interval. We did not specifically look at the grade of the tumors. We did look retrospectively at the CEA levels that were recorded. Unfortunately, CEA levels were not recorded on a sufficient enough number of patients to make analysis meaningful.

To address Dr Cady's questions, I am happy to be able to be here and to confirm your bias. Our current practice is to check CEA levels before patients are operated on so that we can follow them postoperatively as a marker. Is there a benefit to measuring CEs? A recent study out of Memorial Sloan Kettering, by Dr Fong et al, cited 5 prognostic indicators they feel can be used to provide a prognostic scale for patients with hepatic colorectal metastases. Carcinoembryonic antigen greater than 200 was confirmed in the study of over 1000 patients to have prognostic value. I think that if you were to use a prognostic scale and could identify patients who have a worse prognosis, it would be those patients most likely to benefit more from an interval reevaluation.

We are looking at this prospectively now. It is a treatment algorithm which has been adopted by the surgeons in the gastrointestinal tumor board at Dartmouth. If patients present with synchronous lesions that are resectable, we encourage them to get chemotherapy and then to be reevaluated in 3 to 6 months for resection.

As far as Dr Cook's question, we did look at the number of patients that had chemotherapy. The numbers in our study are on the small side, but 13 patients in the interval reevaluation group did receive chemotherapy. Three of those patients were included in the 4 patients that became unresectable. The 1 patient that had a radiologic regression had received chemotherapy, and of the 20 patients that went to surgery, 4 of the patients who were found unresectable at the time of laparotomy had received chemotherapy and 4 of the patients that went on to be resected had received chemotherapy. So right now the numbers are evenly divided in that group.