Choice of Surveillance After Hepatectomy for Colorectal Metastases

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Hypothesis: By review of a reported series, is outcome related to surveillance after hepatectomy?

Design: We reviewed English-language literature indexed on MEDLINE from January 1, 1990, through December 31, 2002. Indexing terms were combinations of hepatectomy, colorectal metastases, and recurrence with prognostic, repeat, follow-up, or surveillance.

Study Selection: Studies containing any of the following data fields were included: recurrence after hepatectomy, rates of repeat hepatectomy, 5-year survival (overall or disease free) after hepatectomy (initial or repeat), posthepatectomy surveillance protocol, and detection of recurrence by surveillance modality.

Data Extraction: Data were taken directly from a small number of articles and pooled across studies for analysis. We highlighted difficulties in assessing data quality and validity as a caveat to the interpretation of the results.

Results: The rate of recurrence after hepatectomy was 58%, and the rate of hepatic recurrence was 30%. Repeat hepatectomy was performed in 9.6% of cases. Five-year survivals after initial and repeat hepatectomy were 29% and 38%, respectively. Many studies did not report their surveillance protocols. For those that did, computed tomography or ultrasonography with carcinoembryonic antigen measurement most commonly formed the basis of surveillance. No data related surveillance techniques to the outcomes of recurrence detection, repeat hepatectomy, or survival.

Conclusions: This review confirmed the value of repeat hepatectomy for recurrent disease, but uncovered no direct evidence supporting any surveillance modalities. Further studies are clearly needed, and approaches to these are discussed.

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When possible, surgical resection is the treatment of choice for hepatic colorectal metastases. With resection, 5-year survival rates of up to 58% are reported, whereas without treatment median survival is only 6 months, and with chemotherapy this is only extended to 20 months.

However, in most series reported, disease recurs in up to 80% of patients after hepatectomy. The recurrence usually involves the liver and is confined to the liver in approximately half of these cases. As with initial hepatectomy, the feasibility of repeat resection depends not only on the disease being confined to the liver but also on the distribution of hepatic disease permitting curative resection. Overall, only 23% to 33% of hepatic recurrences are resectable. However, when possible, repeat hepatectomy is associated with 5-year survival rates equivalent to those reported for first hepatectomy, and therefore detecting hepatic recurrence at a resectable stage would significantly improve prognosis for this selected group of patients.

The first aim of this study was to examine follow-up protocols described for the surveillance of patients who have undergone hepatectomies for colorectal metastases and any evidence presented for their impact on the detection of recurrent hepatic disease, repeat hepatectomy rate, and most important, patient survival. Second, from this review of the evidence, we hoped to derive a suggested protocol for surveillance after hepatectomy for colorectal metastases.

Methods: A search of English-language literature indexed on MEDLINE was performed for recent references pertaining to hepatic resection for colorectal metastases. Studies reporting on repeat hepatic resections and also potential prognostic indicators and adjuvant treatments after hepatic resection were included. Series published from January 1, 1990, through

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December 31, 2002, were considered and included if they reported data for any of the fields that we analyzed. Series were excluded if they appeared to be entirely a subset of a later series included in the study, to prevent duplication. Studies were also excluded if they contained none of the desired data fields.

The data fields drawn from these studies, when available, were the number of patients undergoing initial hepatectomy, the overall recurrence rates, the rate of recurrence confined to the liver, the number of repeat hepatectomies, and the overall and disease-free 5-year survival rates after the initial hepatectomy and repeat resection. The follow-up regimen after hepatectomy was also recorded, with any information provided on how recurrence was detected. The data for each field were pooled for all studies reporting that field so that we could estimate average rates of a particular event. We investigated the possibility of relating follow-up to outcome. The outcome measures used included patient survival, recurrence rates, hepatic recurrence rates, and rates of repeat resection.

RESULTS
STUDIES REVIEWED

Twenty-five studies published from 1990 through 2002 were found to contain relevant data fields. The number of patients undergoing hepatectomy for colorectal metastases in these studies ranged from 32 to 1818, and the total number of patients for all studies was 5745.1,9,12-34 The total number of patients for each data field to be analyzed was smaller than this in each case, as no report covered all data fields. There was a relative paucity of information for some of the areas under review. This is made clear by the number of patients in these subsets of the reports reviewed.

REQUIRENCE AND REPEAT RESECTION RATES

Thirteen of the 25 studies reported overall recurrence rates, which ranged from 40% to 78%.8 The total number of patients in these 13 studies was 3020, and 1743 of these had recurrences, giving an average rate of recurrence of 58%.

Hepatic recurrence rates were reported in 12 of the studies and ranged from 20% to 49%.† After combining the results of these studies, hepatic recurrence was reported in 940 of 3078 patients, to give an average rate of 30%. Only 4 studies specifically documented the rates of hepatic-only recurrences, ranging from 16% to 28%.1,16,20,28,32 With a total 795 patients, the estimated 5-year disease-free survival for all these studies was 25%. The 5-year survival after repeat hepatectomy was reported for only 5 studies and ranged from 32% to 100%,12,15,23 with an estimated 5-year survival of 38% for the 264 patients studied. Only 3 studies quoted a 5-year disease-free survival after repeat hepatectomy, from 15% to 86%,12,15,23 estimated at 26% for these studies, with a combined total of 112 patients. The data summarized herein are presented for individual studies in Table 1.

SURVIVAL

Five-year overall survival after first hepatectomy was reported for 14 studies and ranged from 11% to 58%.†,1,9,17,24,28,30,32,34, for the total of 3618 patients, the estimated 5-year survival was 29%. Only 5 studies reported specifically on 5-year disease-free survival, ranging from 16% to 28%.1,16,20,28,32 With a total 795 patients, the estimated 5-year disease-free survival for all these studies was 25%. The 5-year survival after repeat hepatectomy was reported for only 3 studies and ranged from 32% to 100%,12,15,23 with an estimated 5-year survival of 38% for the 264 patients studied. Only 3 studies quoted a 5-year disease-free survival after repeat hepatectomy, from 15% to 86%,12,15,23 estimated at 26% for these studies, with a combined total of 112 patients. The data summarized herein are presented for individual studies in Table 2.

SURVEILLANCE

Ten of the studies did not report their follow-up protocols,§ including 5,12,16,20,32 of the 8 studies that report 5-year disease-free survival rates after hepatectomy,¶ so no information can be drawn from these as to which investigations or protocols detected recurrent disease. For the remainder, a variety of different screening modalities were used. These modalities are considered in turn in the following subsections.

Carcinoembryonic Antigen Levels

Measurement of carcinoembryonic antigen (CEA) levels was the most commonly included test in the studies reporting surveillance protocols, used in 13 studies† at a frequency of once every month to once every 6 months in the first 2 years after hepatectomy (where the interval is specified). One study reported the use of CEA level measurement for surveillance when the CEA level was elevated at the time of the diagnosis of the primary tumor, but regarded the remainder of subjects as nonsecretors and therefore relied on other modalities to follow up this subset of patients.25

Radiology

The commonly used radiological screens for hepatic recurrence were computed tomography (CT) and ultra-

References

†References 1, 9, 12, 14-16, 19, 20, 23, 24, 27, 31, 32, 34.
‡References 1, 12, 16, 19, 24, 28-30, 32, 34.
§References 9, 13, 15, 17, 18, 20-22, 25, 26, 27, 31.

*References 1, 9, 13-17, 20-23, 25, 26, 28, 33.
†References 9, 12, 15, 17, 18, 20-23, 25, 26, 33.

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sonography (US). Five studies reported the use of CT as the only imaging modality, and 4 reported US alone. Four additional studies described the use of CT or US in the follow-up protocols, and one described the use of both routinely. In addition, 1 study reported the use of CT of the abdomen and chest to screen for pulmonary metastases, although the latter were more commonly screened for by means of chest x-ray.

Other Less Commonly Reported Screening Modalities

Four protocols included clinical evaluation; 2 performed liver function tests; 4 described annual colonoscopy; and 3 measured levels of tumor marker carbohydrate antigen 19.9 (CA19.9). There were isolated instances of the use of bone scans and carbohydrate antigen levels otherwise unspecified, possibly CA19.9.

Protocols Combining Different Screening Modalities

With the exception of the study differentiating between CEA secretors and nonsecretors and a retrospective study on the role of CT in detecting hepatic recurrence for which full surveillance details were not available, all of the protocols reported used multiple modalities to improve the sensitivity of detecting recurrence early. Most commonly, CEA measurement was combined with CT or US examination. These combinations occurred in 12 of the 15 studies reporting protocols.

THE RELATIONSHIP OF SCREENING PROTOCOL TO DETECTION OF RECURRENCE

In their study of 106 patients with hepatic resection for colorectal metastases, Griffith et al reported that, of the 9 patients who proceeded to a second hepatectomy, 6 of the recurrences were diagnosed by elevated CEA levels, and 3 by CT scanning. One retrospective study of the detection of hepatic recurrences by CT was unable to differentiate between CT scans performed routinely for surveillance and those prompted to confirm suspicion of recurrence due to clinical findings or rising CEA levels, and so was also unable to define the use of screening CT in detecting recurrent disease. No other information in the studies reviewed related the detection of recurrence to the tests used in surveillance.

SUMMARY OF RESULTS

This review of recent publications on hepatectomies for colorectal malignancy has found that the follow-up pro-

#References 9, 13-15, 17, 18, 20-22, 26, 27, 31.
tocol after hepatectomy was often not described. When the protocols were described, they most often involved a combination of CEA level measurement with CT or US of the abdomen, with or without a variety of further investigations. The rates of recurrence and repeat hepatectomy were similar to those previously reported, as were the results of repeat hepatectomy. The most striking finding was the almost complete absence of data relating surveillance protocol, but at present no evidence clarifies what investigatory, enabling more effective treatment. In this case the target population is clearly defined. In the studies reviewed herein, recurrence amenable to a repeat resection will develop in 9.6% of patients after hepatectomy. The benefits of a repeat resection for these patients are substantial. Because the 5-year disease-free survival after repeat hepatectomy was almost the same as that achieved at initial hepatectomy (26% vs 25%), the clock is effectively reset for these patients in terms of their likely survival. Without repeat resection, the treatment is palliative and the median survival for palliatively treated hepatic metastases of the same stage as those suitable for resection is 20 months. Therefore, surveillance may be regarded as having accomplished these first 2 objectives, which essentially audit the effectiveness of the treatment for the benefit of future patients.

The third objective of surveillance is to screen for recurrent disease in the liver, as this is potentially treatable with repeat hepatectomy if detected early, but likely to remain asymptomatic until late. However, surveillance modalities that may detect recurrence elsewhere have also been included, as recurrence of the primary tumor or pulmonary metastases may also be treated curatively. Hence the inclusion of colonoscopy and chest x-rays where mentioned. It is possible that we underestimated these in our review, as the follow-up protocols described may also be primarily focused on detecting hepatic recurrence. For example, it is possible that surveillance colonoscopy is organized and performed by colorectal surgeons who treated the primary disease rather than by the hepatobiliary surgeons responsible for the hepatectomy.

### Table 2. Overall and Disease-Free 5-Year Survival Rates After Initial and Repeat Hepatectomy by Study

<table>
<thead>
<tr>
<th>Source</th>
<th>5-Year Survival After Initial Hepatectomy, %</th>
<th>5-Year Survival After Repeat Hepatectomy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Disease Free</td>
</tr>
<tr>
<td>Yamaguchi et al, 1994</td>
<td>NS</td>
<td>26</td>
</tr>
<tr>
<td>Nordlinger et al, 1994</td>
<td>26</td>
<td>NS</td>
</tr>
<tr>
<td>Yamada et al, 1997</td>
<td>46</td>
<td>NS</td>
</tr>
<tr>
<td>Crowe et al, 1999</td>
<td>31</td>
<td>NS</td>
</tr>
<tr>
<td>Malas et al, 2002</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Figueras et al, 2001</td>
<td>36</td>
<td>21</td>
</tr>
<tr>
<td>Ambiru et al, 1999</td>
<td>26</td>
<td>NS</td>
</tr>
<tr>
<td>Wang et al, 1996</td>
<td>25</td>
<td>NS</td>
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<tr>
<td>Petrovsky et al, 2002</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Rees et al, 1997</td>
<td>37</td>
<td>NS</td>
</tr>
<tr>
<td>Wanebo et al, 2001</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>Gruenberger et al, 1999</td>
<td>NS</td>
<td>NS</td>
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<td>Strasberg et al, 2001</td>
<td>NS</td>
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<td>Suzuki et al, 2001</td>
<td>NS</td>
<td>32</td>
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<td>Griffith et al, 1990</td>
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</tr>
<tr>
<td>Sasaki et al, 2002</td>
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<td>Brind et al, 1994</td>
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<td>Schlag et al, 1990</td>
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<td>Riesener et al, 1996</td>
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<td>Harmed et al, 1994</td>
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<td>Ilies et al, 1993</td>
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<tr>
<td>Chou et al, 2002</td>
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<tr>
<td>Bakalaras et al, 1999</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Adam et al, 1997</td>
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Abbreviation: NS, not stated.

### RATIONALE FOR SURVEILLANCE

There are 3 principal objectives to follow-up after hepatectomy. The first objective is to evaluate the efficacy of the treatment. The efficacy of hepatic resection is well established, as described in the introduction. The second is to evaluate prognostic factors that may preoperatively predict outcome after resection. Many prognostic factors have been evaluated, and those found to predict prognosis include the stage of the primary disease, the interval between surgery for the primary disease and diagnosis of hepatic metastasis, the number and size of metastases, and CT appearances of the tumor. Some of these have also been found to predict outcome after repeat hepatectomy, including the interval between hepatectomies and the number and size of recurrences. Therefore, surveillance may be regarded as having accomplished these first 2 objectives, which essentially audit the effectiveness of the treatment for the benefit of future patients.

The third objective of surveillance is to screen for recurrent disease, with the intended benefit for the individual patient under surveillance. For this purpose, a screening program should ideally be targeted at an at-risk population, be sensitive and specific, and identify disease at an earlier stage than would present symptomatically, enabling more effective treatment. In this case the target population is clearly defined. In the studies reviewed herein, recurrence amenable to a repeat resection will develop in 9.6% of patients after hepatectomy. The benefits of a repeat resection for these patients are substantial. Because the 5-year disease-free survival after repeat hepatectomy was almost the same as that achieved at initial hepatectomy (26% vs 25%), the clock is effectively reset for these patients in terms of their likely survival. Without repeat resection, the treatment is palliative and the median survival for palliatively treated hepatic metastases of the same stage as those suitable for resection is 20 months. Thus, it is worth identifying those few patients who may be amenable to repeat resection before disease progression renders their disease unresectable.

Therefore, we have made a case of need for a surveillance protocol, but at present no evidence clarifies what surveillance is appropriate to meet the requirement of sensitively and specifically identifying recurrence at an early...
and resectable stage. It could be argued that an intensive multimodality protocol should be used, as this would be most likely to detect recurrence early, until it is possible to derive an evidence-based strategy.

**SUGGESTED SURVEILLANCE PROTOCOL.**

The suggested regimen in the Figure is clearly subject to the caveat that no evidence suggests that it will improve patient survival. Indeed, because of the lack of direct evidence for a beneficial protocol, the regimen is deliberately intensive. In this way it may benefit individuals by detecting resectable recurrence early. It will also gather a large amount of data that may be used to provide evidence that will allow the strategy to be refined for the benefit of future patients and to improve the efficiency of surveillance. The screening tests suggested are relatively readily available, inexpensive, and noninvasive. The primary aim is to screen for hepatic and other potentially resectable metastatic recurrence. It specifically excludes colono-scpic follow-up for recurrent primary disease.

**FURTHER RESEARCH**

There is clearly a need for ongoing effort to elucidate an evidence-based follow-up protocol after hepatectomy for colorectal metastases. There are 2 principle means by which this may be achieved. First, it should be possible to determine retrospectively the trigger for the diagnosis of recurrent disease from some of the series reviewed herein and in other series of hepatectomies not yet published. Therefore, it should also be possible to calculate the relative value of each screening modality in terms of detecting recurrence and resectable recurrence and prolonging survival.

Second, by using a protocol such as that suggested in the Figure, data collected prospectively in a multicenter study of intensive follow-up will indicate which screening modalities could have an impact on survival. As the number of patients who may benefit from repeat hepatectomy is relatively small, multicenter trials will in all probability be needed to provide more definitive information on appropriate follow-up.

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**REFERENCES**

