Hypothesis: The purpose of this study was to examine the validity of the clinical risk score (CRS), a prognostic tool developed by Fong et al, when translated to another center.

Design: This study assesses 5 independent preoperative prognostic criteria, nodal status of the primary lesion, disease-free interval, number of hepatic metastases, size of the largest metastasis, and preoperative carcinoembryonic antigen level, to determine a preoperative CRS for each patient included in the study.

Setting: The hepatobiliary unit of The Queen Elizabeth Hospital, Adelaide, South Australia.

Patients: Medical records of patients admitted to The Queen Elizabeth Hospital undergoing potentially curative hepatic resection for colorectal metastases during the period of July 1993 to April 2003 were included in the study.

Main Outcome Measure: The primary outcome measure of the study was survival. The calculated CRS was analyzed with respect to patient postoperative survival.

Results: During the 10-year period, 77 patients underwent hepatic resection. Overall survival rates for 1, 3, and 5 years were found to be 80.9%, 57.5%, and 42.3%, respectively. One- and 5-year survival rates for CRSs of 0 and 1 were found to be 93.8% and 72.5%, respectively; for scores of 2 and 3, 76.6% and 31.2%, respectively; and for scores of 4 and 5, 75% and 0%, respectively. No patient with a CRS greater than 3 survived more than 2 years.

Conclusion: This study validates the CRS, finding it to be highly predictive of patient outcome and survival.

Arch Surg. 2004;139:1168-1172

Surgical resection of hepatic metastases from colorectal cancer offers the only chance of cure. Reported 5-year survival rates range between 28% and 58% in comparison with median survival of between 12 and 20 months achieved with palliative chemotherapy. It has received general acceptance as a safe procedure, with surgical mortality rates less than 3%. Because increasing numbers of these operations are therefore being performed, there is an emerging need for prognostic criteria to identify patients most likely to benefit from such invasive therapy. Several previous attempts have been made at this. Most notably, Fong et al published a large, single-institutional database study in 1999, incorporating data from 1001 patients. They found 5 independent preoperative prognostic criteria, which they combined into a clinical risk score (CRS) and determined to be highly predictive of the outcome (P<.001). These criteria were (1) nodal status of the primary lesion, (2) disease-free interval from diagnosis of the primary lesion to discovery of liver metastases greater than 12 months, (3) number of hepatic metastases greater than 1, (4) size of largest metastasis >5 cm, (5) preoperative carcinoembryonic antigen (CEA) level >200 ng/mL.

Our study examined the validity of this CRS when translated to another center, the hepatobiliary unit of The Queen Elizabeth Hospital, Adelaide, South Australia.

METHODS

All patients admitted to The Queen Elizabeth Hospital undergoing potentially curative hepatic resection of metastases from colorectal cancer during the period of July 1993 to April 2003 were identified from the Department of Surgery liver database. Selection criteria for patients to undergo hepatic resection included medical fitness for surgery; preoperative evi-
dence of resectable metastatic disease, confined to the liver on chest and abdominal computed tomography (CT), occasionally supplemented by laparoscopy and more recently positron emission tomography; and the ability to preserve sufficient liver parenchyma. The database, hospital records, and pathology reports were used to extract the following data: (1) demographics (age, sex); (2) pathologic features of the primary colorectal lesion, including nodal status; (3) characteristics of liver metastases, including size, number of lesions, and disease-free interval; (4) preoperative CEA level prior to hepatic resection; and (5) outcome.

Per the protocol outlined in the Fong et al30 article, a preoperative CRS was calculated for each patient. One point was assigned for each of the following criteria, creating a minimum CRS of 0 and a maximum of 5: (1) positive lymph node status of the primary colorectal lesion; (2) disease-free interval from the diagnosis of the primary lesion to discovery of liver metastases less than 12 months; (3) number of hepatic metastases greater than 1 on preoperative imaging; (4) size of the largest hepatic metastases >5 cm on preoperative imaging; and (5) preoperative CEA level >200 ng/mL.

These factors were each individually assessed for their effect on survival, and the CRS was then analyzed with respect to the postoperative survival. Deaths within 30 days of the hepatic resection were considered surgical mortality and were excluded from analysis. Patients were followed up by 6-month CT scans of their abdomens and CEA level estimations. Elevated CEA levels, new lesions on CT scans, or new symptoms were investigated further, as appropriate.

STATISTICS

Statistics were performed using SPSS version 9.0 (SPSS Inc, Chicago, Ill). All data are expressed as median values and ranges. Kaplan-Meier survival curves were constructed and compared by the log-rank test. \( P \) values <.05 were considered significant.

RESULTS

PATIENT DEMOGRAPHICS

Seventy-seven patients underwent hepatic resection for colorectal metastases during the 10-year period from July 1993 to April 2003. Forty-three (55.8%) were male, and 34 (44.2%) were female. The median age at hepatic resection was 67 years (range, 39-92 years). Thirty-five patients (45.5%) had died at the time of last follow-up. Median time from hepatic resection to death was 14.5 months (range, 0.2-98.0 months). The 30-day surgical mortality rate was 2.6% (n=2). The overall survival rates for 1, 3, and 5 years were 80.9%, 57.5%, and 42.3%, respectively.

NODAL STATUS OF THE PRIMARY LESION

Histological reports from the primary tumor demonstrated no lymph node involvement in 28 patients (37.3%). Positive lymph nodes were present in 47 (62.7%). Log-rank analysis demonstrates survival to be significantly reduced in node-positive primary lesions (\( P = .002 \)) (Figure 1). Five-year survival rates for node-negative and node-positive primary lesions were 69.7% and 19.7%, respectively.

Figure 1. Survival after hepatic resection for positive lymph node status (\( n=47 \)) and negative lymph node status (\( n=27 \)) from colorectal primary lesions (\( P = .002 \)).

DISEASE-FREE INTERVAL

The median disease-free interval was 2.75 months (range, 0-56 months). Tumor was found synchronously with the primary lesion in 31 patients (40.3%), either by preoperative imaging or at laparotomy. Recurrence was found within 12 months of the primary lesion in an additional 17 patients (22.1%). Disease-free interval was not found to have a significant effect on the postresection survival, whether using the 12-month cutoff as per the CRS (\( P = .73 \)), a synchronous vs metachronous cutoff (\( P = .38 \)), or at points in between (3 months, \( P = .95 \); 6 months, \( P = .73 \)).

NUMBER OF LIVER METASTASES

The median number of hepatic metastases was 1 (range, 1-5). Forty-two patients (54.5%) had a solitary liver metastasis. Number of hepatic metastases was not found to correlate with survival grouped into 1 or more than 1 (\( P = .59 \)) or when each number of metastases was compared individually (\( P = .90 \)).

SIZE OF LARGEST LIVER METASTASIS

The median diameter of the largest liver metastasis per patient was 4.5 cm (range, 1-13 cm). Thirty-two patients (41.6%) had tumors larger than 5 cm; 4 (5.2%) had tumors larger than 10 cm. Tumor diameter significantly correlated with survival when grouped into less than 5 cm and greater than 5 cm (\( P = .006 \)). Larger tumors were associated with worse survival; 5-year survival rates for patients with tumors less than 5 cm and greater than 5 cm were 51.6% and 27.0%, respectively (Figure 2).

PREOPERATIVE CEA LEVEL

The median preoperative CEA level was 14 ng/mL (range, 1-2934 ng/mL). Twenty-seven patients (35.1%) had a normal CEA level (<10 ng/mL); 7 (9.1%) had a CEA level >200 ng/mL. Twelve patients (16%) did not have a pre-
operative CEA level determined. Grouping patients into preoperative CEA levels < or > 200 ng/mL was found to be predictive of survival (P = .002) (Figure 3). Five-year survival rates for patients with preoperative CEA levels < 200 ng/mL and > 200 ng/mL were 48.9% and 0.0%, respectively; no patient with a preoperative CEA level > 200 ng/mL survived more than 2 years. Grouping patients into preoperative CEA levels < or > 15 ng/mL (using the median value to determine the cutoff) was even more predictive of survival (P < .001) (Figure 4), producing 5-year survival rates of 64.2% and 19.4%, respectively.

**CLINICAL RISK SCORE**

The individual CRSs were found to be highly predictive of long-term outcome (P = .006). Clinical risk score remains highly predictive of survival when grouped into scores of 0 to 2 and 3 to 5 (P < .001); 5-year survival rates were 52.3% and 20.2% and 1-year survival rates were 88.2% and 64.1%, respectively (Figure 5). Indeed, it appears possible to further stratify CRS into 0 and 1, 2 and 3, and 4 and 5 (P < .001). Five-year survival rates were CRS 0 and 1, 72.5%; CRS 2 and 3, 31.2%; and CRS 4 and 5, 0.0%; 1-year survival rates were 93.8%, 76.6%, and 75.0%, respectively (Figure 6). No patient with a CRS higher than 3 survived more than 2 years.

**COMMENT**

In this study, nodal status of the primary lesion, a preoperative CEA level greater than 200 ng/mL, and tumor diameter greater than 5 cm were found to be predictive of survival. Disease-free interval less than 12 months and number of tumors greater than 1 were not found to be predictive. The CRS, stratified as in the Fong et al study (CRS scores 0-2 and 3-5), was found to be predictive of survival, with 5-year survival rates of 32.3% and 20.2%, respectively.

The liver is the most common site of distant metastases from colorectal cancer. Resection remains the only
chance of cure for patients with hepatic colorectal metastases, resulting in prolonged survival compared with those patients treated with palliative chemotherapy.\textsuperscript{20-25} The safety of major hepatic resection has been demonstrated in multiple institutions, encouraging surgeons to pursue more extensive resections.\textsuperscript{1,4,14,16-19,26-28} The current study supports this with a surgical mortality rate less than 3%. The long-term results demonstrate an overall 5-year survival rate of 42.3%. This supports previous studies, which have demonstrated a 5-year survival rate between 28% and 58%.\textsuperscript{1-19}

With a trend toward more radical resections and a more aggressive surgical approach encouraged by improving short- and long-term results,\textsuperscript{1-19,28} the ability to stratify patients’ prognoses preoperatively would have the following benefits: (1) improve patient information when obtaining informed consent; (2) assess the likely need for adjunctive chemotherapy; and (3) facilitate comparative studies and clinical trials. The current study supports previous findings that survival following hepatic resection is multifactorial. Several studies have analyzed determinants of long-term outcome\textsuperscript{1,2,8,10,17,29,31,32} however, the goal of a prognostic preoperative score to guide clinical practice had remained elusive. The CRS proposed by Fong et al\textsuperscript{30} based on a large, single-center experience seemed an excellent candidate for a prognostic index. One recent report has also found the CRS to correlate with outcome,\textsuperscript{31} although their reported 5-year survival rates of 40% in patients with a CRS of 0 to 2 and 12% in patients with a CRS of 3 to 5 are lower than in our study.

Analyzed individually, 3 of the 5 variables listed were predictive of survival: node status of the primary lesion (P = .002), a preoperative CEA level greater than 200 ng/mL (P = .002) and tumor size greater than 5 cm (P = .006). This supports data from previous studies.\textsuperscript{1,3,30-32,34} Disease-free interval less than 12 months (P = .73) and number of tumors greater than 1 (P = .59) were not found to be predictive in this series. This is in contrast to other studies, which have commonly found these 2 factors to be significantly predictive of survival.\textsuperscript{8} A possible explanation for this could be the small numbers in the current study. One previous study, however, found liver parenchymal involvement (total tumor volume in centimeters cubed) to be predictive of survival rather than the number of tumors.\textsuperscript{4} The cutoff value for preoperative CEA level of 200 ng/mL was taken from the Fong et al\textsuperscript{30} article. This seems to be rather high, because the median CEA value in this study was 14 ng/mL. Other studies have used lower threshold values of preoperative CEA (>100 ng/mL, \textsuperscript{33} >30 ng/mL, \textsuperscript{36} >20 ng/mL \textsuperscript{37}) and found them to be highly predictive of survival. If the threshold value in this study was changed to greater than 15 ng/mL, then the discrimination of this variable was increased (P < .001 vs P < .002).

Other prognostic indicators for survival postresection of hepatic colorectal metastases have been identified. Histological factors, including resection margins and infiltrative growth pattern, have been found to be predictive of survival\textsuperscript{12}; however, these are not useful preoperative criteria. Further prognostic indicators include CT determination of pathologic growth pattern,\textsuperscript{38} cell-cycle proteins Rb and p53 expression, thymidylate synthase\textsuperscript{39} and antiapoptotic protein mcl-1,\textsuperscript{40,41} and perioperative detection of circulating cancer cells.\textsuperscript{42} As medical science progresses, these may become more available and be incorporated into any predictive score; however, at present, these sophisticated investigations are unlikely to be readily available in daily clinical practice.

For the purpose of validating the CRS as published, it was decided to include number of tumors greater than 1 and disease-free interval less than 12 months in the CRS, despite our finding them not to be prognostic. Similarly, we used the CEA level cutoff as described by Fong et al.\textsuperscript{30} The current study found the CRS to be highly predictive of outcome (P = .006). When stratified as in the Fong et al\textsuperscript{30} study, those patients with a CRS of 0 to 2 show a favorable outcome, with a 5-year survival rate of 56.3%, compared with those with a CRS of 3 to 5 (25.5%). Resection would therefore be highly acceptable in those with a CRS of 0 to 2. For patients with a CRS of 3 to 5, outcome is not dismal and resection would not be absolutely contraindicated; however, adjunctive therapies may be advisable and patients should be informed appropriately. Perhaps the most striking finding of this study was that when CRS was further stratified, no patient with a CRS greater than 3 survived 2 years postresection. The survival achieved by palliative chemotherapy regimes can be similar,\textsuperscript{20-25} sparing the major insult and risks of surgery. If this experience in the current study were substantiated with larger numbers, it may prove inappropriate to offer resection to patients with a CRS score greater than 3.

The current study validates the CRS, finding it to be highly predictive of outcome (P = .006). The CRS remains a promising prognostic indicator, based on wide preoperative availability of the data. The exact thresholds for the criteria, especially the preoperative CEA value, require further investigation; in our series, the discrimination of preoperative CEA level could be improved by using a lower cutoff value of 15 ng/mL. Furthermore, additional investigation is needed to substantiate the find-

\textsuperscript{8}References 6, 7, 10, 11, 13, 16, 31, 32, 33.
ing that patients with a CRS score greater than 3 are in-appropriate for resection.

Accepted for Publication: March 15, 2004.

Correspondence: Guy J. Maddern, MD, University of Adelaide, Department of Surgery, The Queen Elizabeth Hospital, Woodville Rd, Woodville, SA, 5011, Australia (guy.maddern@adelaide.edu.au).

REFERENCES

20. Chang AE, Schneider PD, Sugarbaker PH, Simpson C, Culnane M, Steinberg SM. A prospective randomised trial of regional vs systemic continuous 5-FU chemo-