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Perioperative Predictors of Morbidity Following Hepatic Resection for Neoplasm

A Multivariate Analysis of a Single Surgeon Experience with 105 Patients

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Objective
Factors that predict mortality or morbidity risk in consecutive hepatic resections for neoplasm were examined, with controlled variables of surgical technique and experience.

Summary Background Data
Hepatic resection has become the therapy of choice for the management of metastatic or primary neoplasms of the liver. Although mortality for this procedure has steadily decreased, associated morbidity remains high.

Methods
One hundred five patients undergoing hepatic resection for malignancy over a 4-year period by a single surgeon to identify preoperative, intraoperative, or postoperative predictors of morbid outcomes were studied. Variables were analyzed using multiple regression in a stepwise, logistic model.

Results
Sixty-day hospital mortality was 2.8%, with morbidity occurring in 33%. A significant preoperative predictor of morbidity was serum bilirubin ($p > 0.005$). Notably, preoperative renal function, or medical illness, did not increase morbid risk. Operative variables increasing risk included extent of resection, blood loss, and operative time ($p > 0.005$).

Conclusions
Complex hepatic resection can be performed with low mortality, and serum bilirubin is the single most powerful predictor of postoperative complication.

Hepatic resection is used with increasing frequency in the management of metastatic or primary neoplasms of the liver. Experience in institutions has demonstrated that elective resection can be performed with a low mortality rate in carefully selected patients.[1–3] Typically, hepatic resection for benign disease has been reported to have minimal risk of mortality. Mortality following resection for malignant disease has fallen from 15% 30 years ago to 2%–5% today,[4–7] and the risk for resection for benign disease is even less.[8] Risk factors for perioperative mortality have been determined and include cirrhosis, chronic obstructive pulmonary disease, and diabetes.[3,9]

Despite this salutary reduction in mortality, there re-

mains a significant risk of morbidity with hepatic resection. The reported incidence of complications range from 25% to 50%.[1-6] Most of these complications are related to either excessive blood loss, hepatic failure, or infection. However, no recent studies have examined perioperative predictors of increased morbidity in a well-selected patient population undergoing resection for malignant tumors. The present study explores the work of a single surgeon and, therefore, eliminates the variables seen in series that reflect the work of several surgeons with varying techniques.

METHODS

One hundred five patients undergoing major hepatic resection for malignancy, from 1986 to 1990, were studied to identify potential preoperative, intraoperative, or postoperative predictors of morbid outcome. All variables were analyzed univariately using the chi-squared or Student's t-test, as appropriate.[10] Variables found to be significant at a level of $p \leq 0.10$ were considered eligible for multiple regression analysis. Using BMDP statistical software,[11] multiple regression was performed with the logistic model in a stepwise fashion with a significance level of $p < 0.10$ required for keeping variables in the final equation.

Hepatic resections consisting of formal lobectomies, segmentectomies, and nonanatomic resections were performed. In the lobectomies, hepatic tissue was resected to the interlobar fissure. Nonanatomic resections were defined as free-hand resection of a lesion without regard for segmental or lobar anatomy. A few nonanatomic resections (6 out of 105) conformed to the classically defined "wedge resection,"[4] but most resembled "limited resection."[12] Segmentectomies were either left lateral or left medial, and were divided into three groups: simple resections, including wedge, single nonanatomic, or single left lobectomies; right lobectomies; and complex resections, including trisegmentectomies, complex, involving multiple nonanatomic, or segmentectomies plus nonanatomic resections.

All lobar (with the exception of caudate) and segmental resections were performed with complete control of the portal venous system, hepatic arterial inflow, and hepatic venous outflow before parenchymal resection. Caudate lobe and nonanatomic resections were performed similarly without prior control of lobar or segmental vascular supply. All parenchymal dissections were performed using the ultrasonic aspirator (Cavitron, Boulder, CO). Intraoperative cholangiography was used only when there was a specific question about biliary anatomy (two patients).

Hemostasis was achieved primarily in all patients who were treated with open and closed suction drains. In addition, all patients were explored through a right, subcostal incision extending to the sternum medially and into the right flank laterally. Four patients had thoracic extensions (three sternotomies, one thoracotomy) when a tumor involved the supra-hepatic vena cava and required resection. Sternotomy was the preferred method for chest exposure. The patient who had a right anterior thoracotomy had a previous sternotomy and mediastinitis treated with a pectoralis flap closure. In all patients, all known disease was resected with 1-cm or greater margins. Three patients had concurrent placement of hepatic arterial infusion pumps.

Morbidity was defined as any complication that prolonged hospital stay or affected outcome. This broad definition was used for statistical analysis, as most complications were related to infection. All patients had a routine computed tomography scan 1 week after surgery to document the presence or absence of perihepatic fluid collection. Mortality was defined as death occuring in the hospital or within 30 days after operation.

RESULTS

Patient Population

A profile of the patient population is shown in Table 1. The average age of the group was 56 years (13–78); 60% were male and 40% were female. Metastatic colon cancer represented 50% of disease; hepatocellular carcinoma, 40%; and sarcomas or cholangiocarcinoma, 10%. Sixty-nine percent of patients had prior abdominal surgery, 10% had undergone previous hepatic resections, 24% had been treated preoperatively with hepatic radiation therapy, and 25% had a pre-existing major illness. Three patients had diabetes, four had coronary artery disease requiring medical therapy, two had prior cerebral-vascular accidents, and three had chronic obstructive pulmonary disease requiring bronchodilator therapy. Histograms of the preoperative serum bilirubin, albumin, alkaline phosphatase, and creatinine are shown in Figure 1.

Operative Procedures

The distribution and summary statistics for the operative procedures is detailed in Table 2. Nineteen patients had simple resections, including wedges, nonanatomic resections, or left lobectomies (Group 1); 47 undergoing right lobectomies (Group 2); and 39 who had complex

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Table 1. CLINICAL PROFILE OF 105 HEPATIC RESECTION PATIENTS

Age (yr)	
Mean	56.0
Range	13–78
Gender	
Male	63 (60)
Female	42 (40)
Tumor	
Colorectal	52 (50)
Hepatoma	41 (39)
Sarcoma/cholangiosarcoma	10 (9)
Other	2 (2)
Medical history	
Prior surgery	72 (69)
Prior hepatectomy	11 (10)
Prior radiation	25 (24)
Medical illness	
DM	3 (2.8)
CAD	4 (3.8)
CVA	2 (1.9)
COPD	3 (2.8)

DM: diabetes mellitus; CAD: coronary artery disease; CVA: cerebral vascular accident; COPD: chronic obstructive pulmonary disease.
Values in parentheses are percentages.

or extensive resections, including trisegmentectomies, multiple-segmentectomies, or nonanatomic resections (Group 3). Simple right or left lobectomies were performed in 40 patients. Lobectomy, combined with contralateral lobe nonanatomic resections, were performed in nine patients. Trisegmental resections (right lobe plus left medial, left lateral segment, or left lobe with right anterior resection) were performed in 14 patients. Caudate lobe resections were performed in two patients, single nonanatomic resections were performed in 11, and complex nonanatomic (two or more resections) were performed in 11. Seven patients had diaphragm resections, two had diaphragm and pericardial resections, four had inferior vena cava resections, and one had a partial right atrial resection and reconstruction. The mean volume of resected tissue was 604 cm^3.

Perioperative Management

The operative time averaged 4.1 hours, with a range of 1–9 hours (Table 2). Estimated blood loss (EBL) was calculated by the anesthesiologist and correlated with the amount of blood transfused. The average EBL was 3.1 L, with a range of 0.1–30.0 L and a median of 2.0 L; the median number of red blood cell transfusions was 3.5, with a range of 0–60. Twenty-five percent of the patients received no blood transfusions. Total fluid administration ranged from 1.4–70 L with a median of 6 L.

Morbidity

Thirty-four patients (33%) had some complications relating directly or indirectly to perihepatic sepsis, and most responded to antibiotics alone (Table 3). Two patients required percutaneous abscess drainage and one eventually died.

Statistical Analysis

All available perioperative variables were analyzed univariately with multiple logistic regression analysis to search for predictors of complications related to perihepatic sepsis (Table 4).

Because the multiple regression analysis was undertaken to determine preoperative predictors of complications, variables that could not be determined preoperatively were excluded from the multiple regression equation (Table 5). The admission bilirubin was found to be a significant predictor ($p = 0.005$), and the operative group as defined above was marginally significant ($p = 0.084$). When analyzed as a categorical variable, preoperative bilirubin more than 1.0 increased the odds of

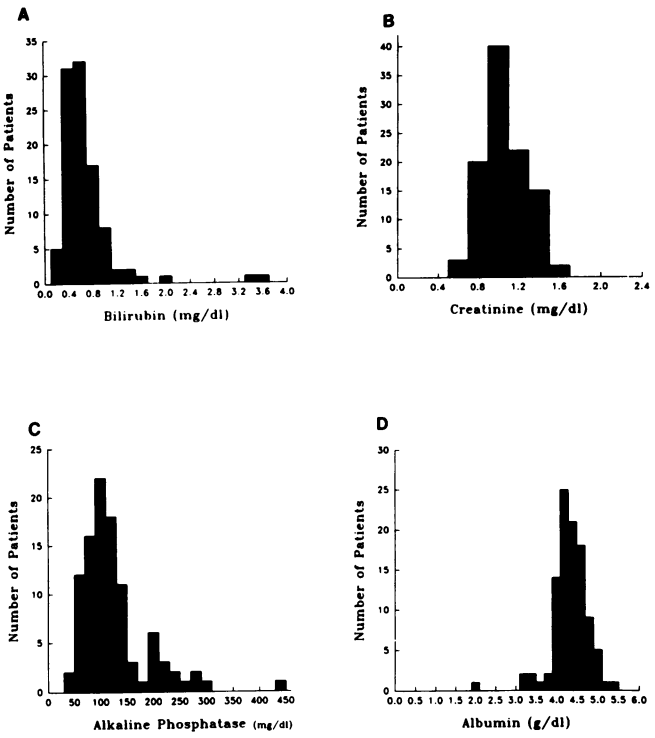

Figure 1. The histograms for liver and renal function tests in patients undergoing resections for malignancies. (A) Serum bilirubin showing 80% of patients with a bilirubin of 1.2 or less. (B) Serum creatinine with 90% of patients having a normal serum creatinine. (C) Alkaline phosphatase with more than 20% of patients having abnormal elevations in alkaline phosphatase. (D) Serum albumin with only 10% of patients having albumins less than 3.5 mg/dL.

Table 2. OPERATIVE PROFILE OF 105 HEPATIC RESECTIONS

Procedure	
Group 1	19
Group 2	47
Group 3	39
Operative time (hrs)	
Mean	4.1 ± 0.14
Range	1.0–9.0
Blood loss (L)	
Mean	3.1 ± 0.4
Range	0.1–30.0
Red blood cell transfusions (units)	
Mean	5.1 ± 0.8
Range	0–60
Intraoperative fluid (L)	
Mean	7.7 ± 7.8
Range	1.4–70.0

Group 1: simple resections including wedge, single nonanatomic, or left lobe resections; Group 2: right lobectomies; Group 3: complex resections including trisegmentectomies, multiple nonanatomic, or combined resections.
All means are shown with standard error.

complications by a factor of 6.45 (95% confidence interval for the odds ratio 1.23–33.4). The average admission bilirubin was 0.56 in the group without complications and 1.0 in the group with complications.

Several operative variables were significantly predictive of postoperative complications. The estimated blood loss was 2529 mL in those without and 3983 mL in those with postoperative complications ($p = 0.08$). Patients who avoided complications required a mean of 4.0 red blood cell transfusions, and those with complications required 6.9 units ($p = 0.07$). The overall operative time averaged 3.8 hours for those without and 4.6 hours for those with postoperative complications ($p = 0.005$).

The length of stay was markedly different for those who did and those who did not have complications. The mean length of stay was 10.3 days in those without and 23.5 days in those with postoperative complications. When multiple linear regression was used to search for predictors of either length of stay or the log-length of stay (to "normalize" the distribution of length of stay), the only significant predictive variables were admission bilirubin and operative score.

Aside from the admission bilirubin, none of the other indices of medical illness, such as admission blood urea nitrogen (BUN), creatinine, history of hypertension, di-

Table 3. PERIOPERATIVE COMPLICATIONS

Complication	No. of Patients
Abscess/collection	20
Biliary fistula	4
Drain site infection	3
Liver ischemia	1
Pneumonia	8
Total perihepatic sepsis	36
Hemorrhage	1
Deep vein thrombosis	3
Pulmonary embolus	1
Small bowel obstruction	1

Table 4. RESULTS OF UNIVARIATE ANALYSIS FOR RISK OF COMPLICATION

Variable	p Value
Male	0.15
Age	0.28
Colon cancer	0.73
Hepatoma	0.69
Prior surgery	0.37
Prior hepatectomy	0.61
Prior radiation	0.50
Major medical illness	0.21
Operation before 1987	0.46
Group 1 *versus* 2 or 3	0.06
Admission alkaline phosphatase	0.48
Admission bilirubin	0.02
Admission SGOT	0.29
Admission PT	0.10
Admission platelet count	0.14
Admission creatinine	0.35
Admission SUN	0.56
Admission albumin	0.94
Admission protein	0.38
Admission hematocrit	0.65
Admisson white blood cell count	0.86
Operative time	0.005
Estimated blood loss	0.08
Transfused units of blood	0.07
Total intravenous fluid	0.14
Postoperative hematocrit	0.44
Volume of liver resected	0.10
Blood pressure <80 mmHg during case	0.53
Postoperative pH	0.13
Postoperative weight gain	0.08
Postoperative temperature	0.09

Group 1: simple resection; Group 2: lobar resection; Group 3: complex resection.

Table 5. MULTIPLE LOGISTIC REGRESSION ANALYSIS

Variable	Coefficient	Improvement p Value
Admission bilirubin	1.02	0.005
Operative group	0.54	0.084

abetes, or heart disease, predicted an increased risk of complication.

Mortality

Three patients (2.8%) died following resection. One death occurred intraoperatively because of hemorrhage during attempted partial caval resection, one occurred 40 days postoperatively because of hepatic failure after trisegmentectomy, and one occurred in a diabetic patient 35 days postoperatively because of sepsis from an intra-abdominal abscess.

DISCUSSION

Major hepatic resection for malignant disease is increasing in large part because of the decreasing morbidity and mortality of the procedure.[1-6] Mortality rates from reports in the 1960s range from 10% to 20%.[7] Recent series report mortalities from 0 to 10%.[1-4] Despite these reductions in mortality, the morbidity of the procedure remains high, with a 27% to 47% postoperative complication rate.

Previous studies have addressed the issue of identifying factors that influence morbidity and mortality. Most have identified amount of blood loss, presence of parenchymal liver disease, and associated medical illnesses as correlating well with perioperative mortality. All prior series have reflected the work of multiple surgeons performing procedures of varying complexity and have extended over time periods of up to 10 years, during which time there were dramatic changes in surgical technique. The present study was intended to analyze a carefully selected group of patients operated on by a single surgeon with consistent technique to determine if, within a well-selected patient population, there may be significant predictors of increased risk of morbidity. Of note, the patients in the first half of the series were found not to have any increased risk of complication over the patients in the second half of the operative series.

The variety of different liver resections made classification for analysis difficult. The operative score on a scale of 1–3 was selected in an attempt to quantitate the magnitude and complexity of the operation, as this remains a very logical predictor of postoperative problems. With careful preoperative radiologic evaluation, this operative score should be predictable before operation. To this end we have included it as a preoperative risk factor.

Although indices of preoperative health and previous medical illness were analyzed, only the admission bilirubin was found to be significant (average of 0.56 *vs.* 1.04). This supports the common impression of many surgeons that hepatic function is an extremely important determinant of surgical outcome.[3,4,9,13] Admission prothrombin time, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, serum albumin, total protein, and a history of prior cirrhosis were not predictors of postoperative complication. Because this group of patients was carefully selected to include only those thought to have reasonable hepatic function, this suggests that admission bilirubin is an extremely potent predictor of perioperative complications. The lack of influence of other predictors, such as the indices of renal function, may largely be due in large part to the careful selection process of operative candidates.

The results of this analysis indicate that complex hepatic resections can be performed with low perioperative mortality but increased risk of postoperative complications. Also, preoperative hepatic function as assessed by the serum bilirubin level is a potent predictor of postoperative complication.

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