The Influence of Intraoperative Hypotension and Perioperative Blood Transfusion on Disease-free Survival in Patients with Complete Resection of Colorectal Liver Metastases

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An increased interest in surgical treatment of liver metastases from colorectal origin has evolved recently. However not all patients benefit from this approach, with early recurrence and death still being encountered. To evaluate clinical as well as perioperative factors that might significantly affect the outcome of patients with completely resected colorectal liver metastases, we examined 116 patients who underwent resection between September 1987 and August 1989. Median follow-up time was 13.2 months (0.6 to 31.4 months). The overall survival rate was 91% at 1 year and 75% at 2 years. Median survival was not reached. Median disease-free survival time was 11.5 months, with 49.4% and 21.2% of the patients being free of disease at 1 and 2 years, respectively. By univariate analysis, site of primary colorectal cancer, preoperative carcinoembryonic antigen (CEA) level, size of metastases, number of metastases, length of operation time, percentage mean arterial pressure, number of hypotensive episodes, duration of hypotensive episodes, and whole blood transfusion significantly affected recurrence rate following resection. However only site of primary tumor, CEA, number of metastases, and number of hypotensive episodes remained significant in the multivariate analysis. The most significant single factor that affected recurrence rate was the number of hypotensive episodes during the operative procedure. It is concluded that hypotensive episodes, even when well controlled, should be avoided during operation to maximize the chances of cure and prolong disease-free survival of patients with colorectal liver metastases.

SURGICAL RESECTION OF metastatic liver disease has recently become widely accepted, with reports of low operative morbidity and mortality rates for this procedure, along with its efficacy in affecting long-term survival of the patients.[1] However it has become clear that the improvement in survival is not wide spread, making it fundamental to identify the patients most likely to benefit from resection. Many reports that have discussed the influence of clinical prognosticators on the outcome of patients with liver metastases of colorectal cancer are controversial, mainly because of the small number of patients, the long interval between the time the first and last patients were entered, and the heterogeneity of the patients and their management.

In the present study we report a single institution experience with patients undergoing complete resection of colorectal liver metastases during a short period, September 1, 1987 to August 31, 1989. We evaluate preoperative clinical prognostic determinants as well as perioperative factors that could affect disease recurrence and survival.

Materials and Methods

During the period from September 1987 to August 1989, 133 patients underwent complete hepatic resection for colorectal metastases. Complete information in the medical records was not available for 17 patients and thus they were excluded from the analysis. We examined 116 patients for whom comprehensive data were available. Nine patients did not have complete information on all the variables analyzed (Table 1). All patients underwent resection after a preoperative workup and intraoperative surgical confirmation of the absence of discontiguous extrahepatic tumor. After the operation the patients were followed routinely. Median follow-up time was 13.2 months (range 0.6 to 31.4 months).

The following factors were considered for prognostic effect: age, site of primary colorectal cancer, Duke's stage of primary tumor, preoperative carcinoembryonic antigen

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TABLE 1. *Patient Characteristics and Distribution*

Variable	n	Mean	SD	Minimum	Maximum
Age (years)	116	59.3	11.5	29	87
CEA	109	97.1	341.5	0	3190
Number of metastases	116	1.8	1.4	1	8
Size of metastases (cm)	110	5.7	3.95	0.5	29
Interval from primary (months)	116	19.8	20.2	0	99.7
Operative time (min)	116	231.9	86.6	75	590
Baseline MAP (mmHg)	116	98.0	11.4	73.3	140
Minimum MAP (mmHg)	116	71.6	8.4	50	96.6
Per cent MAP	116	73.8	10.6	44.1	96
Duration hypotensive episodes (min)	116	30.1	28.4	0	120
Number hypotensive episodes	116	2.1	1.9	0	9
Blood loss (mL)	116	1964.0	1447.0	100	7000
Whole blood (U)	116	0.6	1.4	0	8
Packed cells (U)	116	2.9	4	0	26
Plasma (U)	116	5.9	7.5	0	48
Site of primary					
Rectum	30				
Sigmoid	29				
Left	24				
Right	24				
Stage of primary					
A	1				
B	32				
C	83				
Operation type					
Wedge	24				
Segmentectomy	28				
Left lobectomy	10				
Right lobectomy	47				
Trisegmentectomy	7				
Distribution of metastases					
Unilobar	99				
Multilobar	17				

CEA, carcinoembryonic antigen; MAP, mean arterial blood pressure; SD, standard deviation; U, units.

(CEA) levels, size of metastases (sum of the greater diameter of each individual nodule), number of metastases, distribution of nodules (uni- or multilobar), disease-free interval (time from primary to resection of hepatic metastases), type of hepatic resection (wedge, segmentectomy, left lobectomy, right lobectomy, trisegmentectomy), operative time, intraoperative blood loss, blood transfusion (whole blood, packed red blood cells, fresh frozen plasma) during the perioperative period (the day of surgery and the 72 following hours), and intraoperative hypotension.

Intraoperative hypotension was evaluated by determining the mean arterial pressure (MAP) from the anesthesia chart. The MAP was calculated by the following equation: (systolic pressure + 2x diastolic pressure)/3. Baseline MAP was defined as the pressure when the surgeon started the operation. Minimum MAP is the lowest MAP reached during the operation. This value (minimum MAP) is then expressed as a percentage of the baseline (percentage MAP). We defined hypotension in this study when MAP decreased to levels lower than 80% of baseline MAP. Subsequently we determined the number of hypotensive episodes (less than 80% baseline MAP) during the operation, as well as the total duration (in minutes) of the hypotensive episodes. From these determinations we evaluated the following parameters as prognostic factors: baseline MAP, minimum MAP, percentage MAP, number of hypotensive episodes, and overall duration of hypotensive episodes.

Statistical Analysis

To assess the dependence of death or recurrence on the variables analyzed, overall and disease-free survival rates were estimated for each variable by the Kaplan and Meier product-limit method.[2] Log rank test[3] was used to check dependence of overall and disease-free survival rates on each variable. Proportional hazard regression[4] was used to incorporate all of the explanatory variables in the same model. Forward stepwise procedure and likelihood ratio tests were used to select the variables with the greatest prognostic value. Cumulative hazard plots were generated to check visually the assumption of the proportionality of the hazard rates. Statistical analysis was performed using the BMDP computer software package.[5] The critical significance level of A = 0.05 was chosen.

Results

The distribution of patients by each variable analyzed is displayed in Table 1. Median blood loss was less than two units (Fig. 1), with approximately 25% of patients requiring no blood transfusion. Most patients did not receive whole blood (Fig. 2) or packed red blood cell transfusion (Fig. 3), but a few patients had major blood and blood product restoration (Table 1).

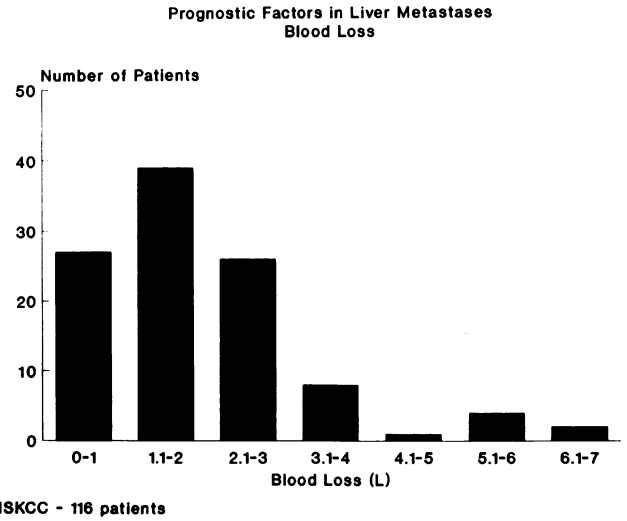

FIG. 1. Blood loss in patients undergoing complete hepatic resection for colorectal metastases. Median blood loss was less than two units.

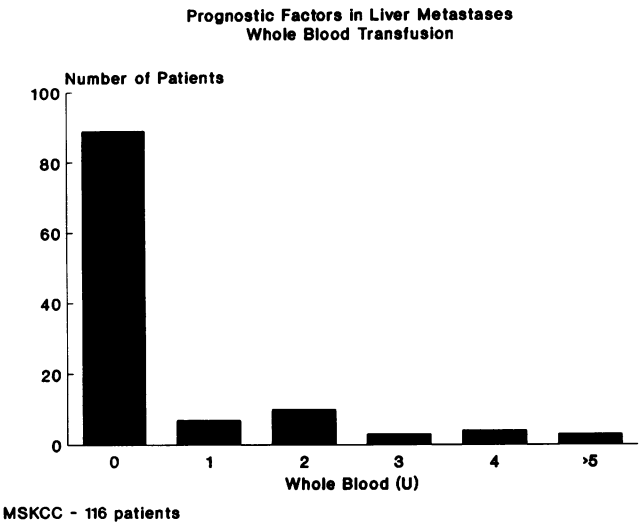

FIG. 2. Approximately 25% of patients required blood transfusion.

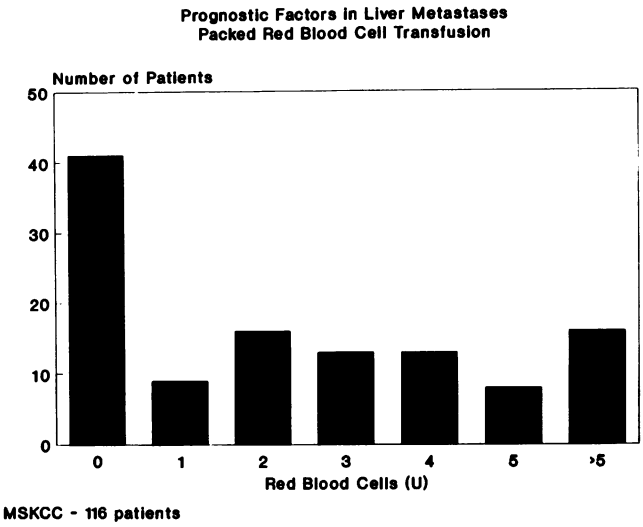

FIG. 3. Most patients did not receive packed red blood cell transfusion.

The median time to second recurrence after resection was 9.03 months (range, 1.1 to 27.4 months). Median disease-free survival time was 11.5 ± 2.5 months. Overall disease-free survival rate of the patients was 49.4% ± 5% at 1 year and 21.2% ± 5% at 2 years. The median survival after resection was not reached, with a 1-year survival rate of 91.3% ± 3.4%, and a 2-year survival rate of 74.7% ± 6.8%.

Twelve patients of 116 died during follow-up; consequently none of the variables significantly affected overall survival rate. The significance of each variable on disease-free interval (second recurrence) was analyzed in more detail and the results are displayed in Tables 2 and 3. By univariate analysis, site of primary colorectal cancer, preoperative CEA level (Fig. 4), size of metastases, number of metastases, length of operation time, percentage MAP, number of hypotensive episodes (Fig. 5), duration of hypotensive episodes (Fig. 6), and whole blood transfusion significantly affected recurrence rate after resection. By multivariate analysis, only site of primary, CEA, number of metastases, and number of hypotensive episodes remained significant (Table 2). The most significant single factor that affected recurrence rate was the number of hypotensive episodes during the operation (Fig. 5).

An equation derived from the analysis was determined to predict the relative risk of recurrence after hepatic resection of metastases:

Risk of Recurrence

$$= e\,[(\#\text{ of episodes} * 0.31) + (\#\text{ of metastases} * 0.21) + (\text{CEA} * 0.001) - (\text{Sigmoid/left} * 0.76)]$$

where: e = base of natural logarithm

CEA = Carcinoembryonic antigen level in ng/mL

Sigmoid/left: If primary is in sigmoid or left colon, enter 1.

If primary is in other site, enter 0.

The patients were equally distributed into four groups (each group containing approximately 25% of the patients) according to the calculated risk of recurrence: A < 1.23; B 1.23–1.81; C > 1.81–< 3.16; D ≥ 3.16. There was a significant difference in the recurrence rate among the four groups (Fig. 7).

Discussion

Colorectal carcinoma frequently metastasizes to the liver. Up to 35% of patients have apparent or occult me-

TABLE 2. *Significance of Evaluated Variables on Disease-free Survival (Critical Significance Level of A = 0.05)*

Variable	Probability Value: Univariate Analysis	Probability Value: Multivariate Analysis	Coefficient	SE
Age (years)	0.7827			
Site of primary	0.0269	0.0033	−0.7579	0.2596
Stage of primary	0.1393			
Disease-free interval	0.7320			
Carcinoembryonic antigen	0.0256	0.0232	0.0009	0.0003
Size of metastases (cm)	0.0467			
Number of metastases	0.0056	0.0213	0.2086	0.0835
Distribution	0.1800			
Type of operation	0.8793			
Operation time (min)	0.0198			
Blood loss (mL)	0.7436			
Mean arterial pressure (mmHg)				
Baseline	0.1773			
Minimum	0.0808			
Percentage MAP	0.0084			
Number of episodes	0.0001	<0.00001	0.3097	0.0708
Duration (min)	0.0006			
Whole blood (U)	0.0462			
Packed cells (U)	0.4809			
Plasma (U)	0.2337			

SE, standard error; MAP, mean arterial blood pressure; U, units.

TABLE 3. *Pearson Correlation Coefficients Among Variables-Coefficient Value (Probability Value)*

Variable	Site	CEA	No. Metastases	No. Episodes
Age (years)	0.1086	0.2022	−0.1048	−0.0114
	(0.2456)	(0.0349)	(0.2758)	(0.9030)
Stage of primary	−0.2182	0.1172	0.1126	0.0967
	(0.0220)	(0.2248)	(0.2413)	(0.3147)
Size of metastases	0.0387	0.2049	0.4520	0.1415
	(0.6875)	(0.0326)	(0.0001)	(0.1402)
Distribution of metastases	0.0407	−0.0817	0.4268	0.1205
	(0.6727)	(0.3980)	(0.0001)	(0.2097)
Interval from primary	0.2075	−0.0616	−0.1345	−0.0175
	(0.0304)	(0.5265)	(0.1631)	(0.8563)
Type of operation	0.0911	0.1213	0.2024	0.1270
	(0.3307)	(0.2088)	(0.0339)	(0.1740)
Time of operation	−0.0024	−0.0416	0.1521	0.3906
	(0.9792)	(0.6672)	(0.1126)	(0.0001)
Baseline MAP (mmHg)	0.2648	0.0570	0.0725	0.5145
	(0.0041)	(0.5560)	(0.4513)	(0.0001)
Minimum MAP (mmHg)	−0.0471	0.1126	0.0801	−0.4582
	(0.6154)	(0.2436)	(0.4051)	(0.0001)
Percentage MAP	−0.2533	0.0336	−0.0104	−0.7743
	(0.0060)	(0.7287)	(0.9136)	(0.0001)
Duration of hypotensive episodes (min)	0.1471	−0.0490	0.0820	0.8866
	(0.1558)	(0.6125)	(0.3940)	(0.0001)
Blood loss (mL)	0.1883	−0.0781	0.1182	0.2843
	(0.0429)	(0.4193)	(0.2185)	(0.0020)
Whole blood (U)	0.0447	−0.0122	0.0216	0.1504
	(0.6331)	(0.8993)	(0.8222)	(0.1069)
Packed cells (U)	0.0921	−0.0520	0.1349	0.2028
	(0.3254)	(0.5910)	(0.1598)	(0.0289)
Plasma (U)	0.0784	−0.0776	0.1535	0.1635
	(0.4020)	(0.4220)	(0.1094)	(0.0795)

CEA, carcinoembryonic antigen; MAP, mean arterial blood pressure; U, units.

tastases at the time of laparotomy for the resection of a primary colon cancer.[6] Metachronous tumors occur within 2 years of resection of the primary disease in approximately 50% of all patients who develop hepatic metastases,[7] while more than 65% of the patients will have liver involvement by the time they die. Untreated patients have a poor prognosis, with median survival time between 4.5 and 15 months, with rare exceptions surviving more than 3 years.[8]

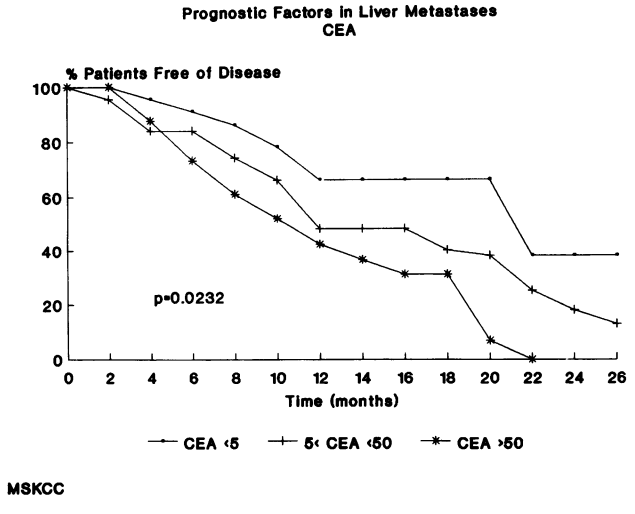

FIG. 4. Preoperative carcinoembryonic antigen levels.

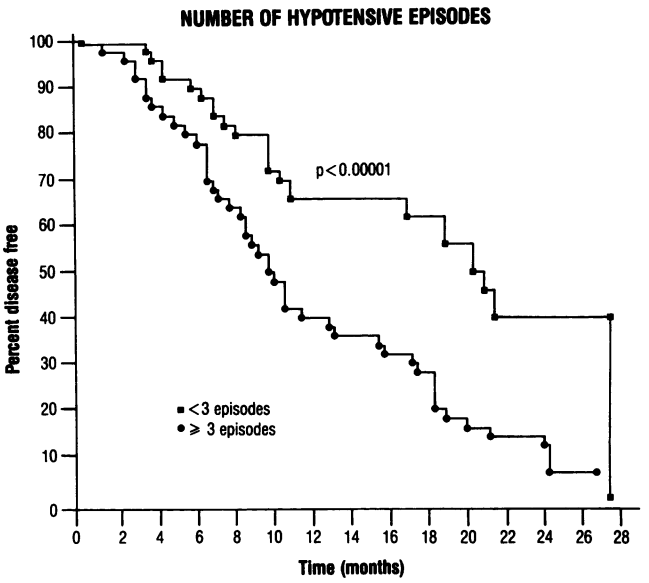

FIG. 5. The most significant single factor that affected recurrence rate was the number of hypotensive episodes ($p < 0.00001$).

Growing evidence suggests that surgical resection is currently the only effective treatment for selected patients with liver metastases of colorectal origin. However it is clear that not all patients benefit from resections because early postoperative recurrence is observed in many patients.[8] Detection of clinical factors that could predict the outcome after operation would improve the selection of patients.

The present study was undertaken primarily to investigate factors in the perioperative management of selected patients that could have prognostic influence. The predictive value of treatment variables was compared with that of clinical factors to identify the optimal treatment strategy for patients with colorectal liver metastases. Due to the relatively short follow-up and to the low mortality rate in our series, only disease-free survival (second recurrence) is discussed in depth in the present study. Overall survival in our patients was 91.3% and 74.7% at 1 and 2 years, respectively, after resection. These results compare favorably with previously reported series[1] but emphasize the considerable disparity between disease-free and overall survival.

To evaluate patient outcome, several variables were analyzed. Age was not a significant factor. Site of primary was shown to be a significant prognosticator in our series, with primary tumor originating in the left or sigmoid colon being associated with lower recurrence rates than primary

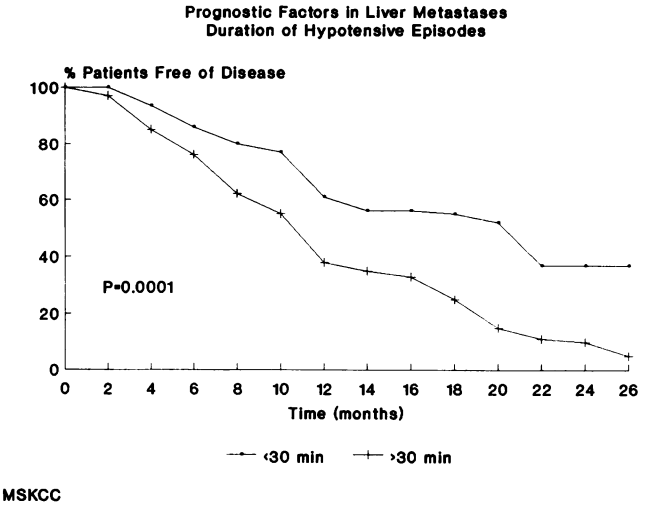

FIG. 6. Duration of hypotensive episodes (p = 0.0001).

tumor in other locations. These findings are in accordance with other studies,[9,10] but most series do not show any significant effect of site on outcome.[1,11-13]

In our study the risk of recurrence was not significantly affected by the stage of the primary colorectal cancer. Authors have reported conflicting results regarding the significance of Duke's classification on the outcome of patients with resected colorectal cancer metastatic to the liver, with some reports showing significant effect[1,9,12] while others show no effect.[10,13-15]

In our experience a short disease-free interval between the primary and liver recurrence did not significantly increase the likelihood of recurrence. Similar results have been shown in other reports.[1,12,16] However some investigators have suggested that patients with longer disease-free intervals between the primary occurrence and metastasis did better than patients with a shorter disease-free interval.[9,11] By univariate analysis the number of metastases and the size of the metastases (both used to quantify tumor burden) were shown to be significant predictors of recurrence in our study, but they were found to be interdependent. The coefficient of correlation between number of metastases and size of metastases was high (coefficient = 0.452, p = 0.0001). By multivariate analysis, however, only the number of metastases was selected as a significant determinant of outcome. This is an indication that tumor burden is an important factor. A higher number of metastases implies more diffuse spread of the disease, which theoretically increases the likelihood of other microscopic metastases being present in other sites, intra- or extrahepatic, with delayed growth and recurrence.[8,11] In a study by Nordlinger et al.,[17] the number of liver metastases resected did not affect postoperative outcome and survival for patients with less than four liver metastases resected was not different from survival in those with more than four resected.

Carcinoembryonic antigen is a valuable laboratory test for detecting hepatic metastatic disease in patients with colorectal cancer.[18] Preoperative CEA levels significantly affected the outcome of patients in our study. It was analyzed as a continuous variable and progressively higher levels were associated with increased incidence of recurrence. Other studies, however, do not show any significance of CEA as a prognostic determinant.[1,13]

As other studies have found, the type of resection *per se* did not influence survival in our patients. The extent of resection is dictated by the number, distribution, and size of metastases. Flanagan and Foster[16] noted that overall survival rate of 39% at 5 years following lesser operations of wedge resection and 'partial lobectomies' compared quite favorably with more extensive resections. Other authors[9,13,15] also have found that the simpler procedures offered better median survival time.

Recurrence was not affected significantly by the distribution of liver metastases in our study. Patients with uni- or multilobar involvement did not have a significantly different risk of recurrence after resection. When patients were stratified for tumor burden (number and size of metastases), the effect on recurrence and survival was independent of the distribution of the hepatic nodules, as long as the operative procedure encompassed all the disease with clear margins. Some authors, however, advocate that only those patients with solitary or unilobar metastases should be considered to be candidates for liver resection.[11,19]

To evaluate the second aspect of our study, the prognostic influence of patient management factors, we concentrated on factors that affect the response of the patient to microscopic neoplasia present after completion of liver

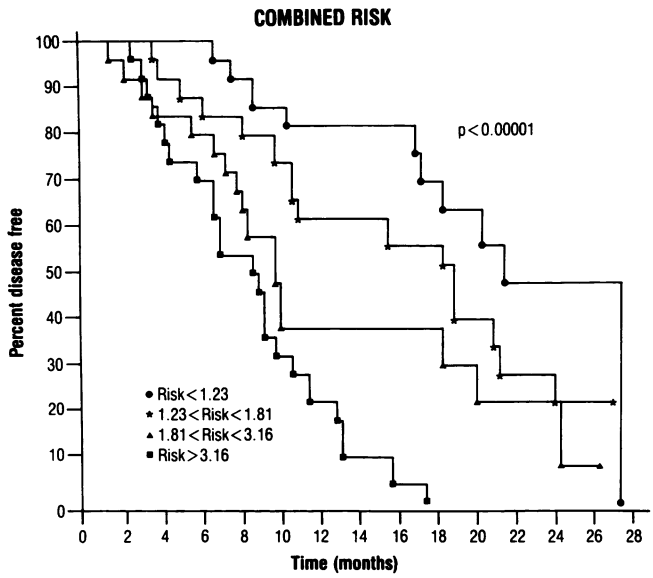

FIG. 7. Disease-free survival in patients separated into combined relative risk groups. Risk was calculated using the equation described in Results.

resection. It is known that immunocompetence of the patient is important in the development and rate of growth of tumors. Two factors that occur during management of patients with liver metastases are classically shown to be modulators of immunity: transfusion of blood-derived products and hypovolemia.

The administration of blood reduces the incidence and severity of graft rejection in kidney transplant recipients.[20] Transfusions exert an immunosuppressive effect on the host through yet unknown mechanisms. Blood transfusion in animal studies diminishes cell-mediated immunity, decreases macrophage migration, and increases the production of immunosuppressive prostaglandin E.[21] Recently blood transfusions were shown to have detrimental effects on patients harboring malignant tumors. Reports have shown that in patients with various malignancies,[22–24] there was a higher rate of tumor recurrence in those that received transfusion. However these findings are not uniformly observed.[25] A previous study by Stephenson et al.[26] showed a significant influence of blood transfusion on the outcome of 59 patients with colorectal liver metastases operated on during a 10-year period. Our study, like theirs, showed that only transfusion of whole blood significantly affected recurrence. This effect, however, was seen only in the univariate analysis. By multivariate analysis, none of the blood products transfused affected disease-free survival. There was no multivariate analysis in the study of Stephenson et al.[26]

One other factor analyzed in our study surprisingly has been completely overlooked in the majority, if not all, the studies that evaluate the effect of transfusion on tumor growth and recurrence. This was the occurrence of intraoperative hypotension. We observed that the number of hypotensive episodes was the single most significant prognosticator. The duration of hypotension also was a significant factor by univariate analysis, but it was highly correlated with the number of hypotensive episodes (correlation coefficient = 0.886, $p = 0.0001$). Consequently multivariate analysis selected only the number of episodes, rather than the duration of hypotension, as the significant factor.

Blood loss and hypovolemic shock have been shown to affect the immune system significantly.[27,28] These events depress mitogen-induced lymphocyte proliferation[29] as well as the production of interleukin-2.[30] In an experimental study performed in our laboratory, hypovolemic events significantly enhanced tumor growth independent of blood transfusion.[31] These results emphasize that careful hemodynamic management of the patient to avoid hypovolemic episodes during treatment is fundamental. Following careful selection of the patients with the highest potential of curability, the surgeon must avoid detrimental variables that are preventable.

Our results demonstrate that some variables (number of metastases, CEA level, site of primary tumor) can help the surgeon to identify patients with a greater likelihood of recurrence and other treatment variables (*e.g.*, number of hypotensive episodes) that could further affect recurrence rate. Prospective clinical studies, although difficult to conduct, should be designed to define management optimization, perhaps including patients with clinically unfavorable factors in preoperative neoadjuvant treatment, and patients with unfavorable treatment variables (*e.g.*, hypotension) in postoperative adjuvant treatment.

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