Perioperative Blood Transfusion and Determinants of Survival After Liver Resection for Metastatic Colorectal Carcinoma

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The authors reviewed their institutional experience with liver resection for metastatic colorectal carcinoma to (1) determine whether perioperative blood transfusion affects survival; (2) identify prognostic determinants; and (3) estimate the patient requirement for a prospective randomized trial designed to demonstrate efficacy of liver resection. Two hundred eighty consecutive patients treated by potentially curative liver resection between 1960 and 1987 were included. Data were obtained for all but 10 patients for at least 5 years after operation or through 1990. Actuarial survival curves related to potential prognostic determinants were analyzed with the log-rank test. Overall, survival was 47 ± 3% at 3 years and 25 ± 3% at 5 years, including 4% 60-day operative mortality rate. Eighty-one patients who did not receive blood 7 days before to 14 days after operation had 60 ± 6% 3-year and 32 ± 6% 5-year survival compared with 40 ± 4% and 21 ± 3% survival rates for 183 patients who received at least one unit (p = 0.03, operative deaths excluded). Extrahepatic disease (p = 0.015), extrahepatic lymph node involvement (p = 0.002), satellite configuration of multiple metastases (p = 0.0052), and initial detection by abnormal liver enzymes (p = 0.0005) were associated with poor survival rates. Synchronous presentation of metastatic and stage B primary disease was associated with a favorable prognosis (p = 0.003). The requirement for a prospective randomized trial estimated by an exponential survival model would be 36, 74, 168, or 428 patients if 5-year survival without resection were 1, 5, 10, or 15%. We conclude that (1) perioperative blood transfusion may be adversely associated with survival; (2) extrahepatic disease, extrahepatic lymph node involvement, satellite configuration, and initial detection by clinical examination or a liver enzyme abnormality portend a poor prognosis; and (3) a prospective randomized trial of liver resection is impractical because of the large patient requirement, at least by a single institution.

RESECTION IS THE only treatment for colorectal carcinoma metastatic to the liver that has resulted in long-term patient survival.[1] Approximately 20% to 45% of patients treated by liver resection benefit from the operation, and 5-year survival is between 20% and 35% in most series.[2] Nevertheless, controversy persists as to whether survival is directly attributable to the operation or to patient selection.[3,4] Indeed, a recent survey of surgeons found no consensus as to whether or not patients with metastatic colorectal carcinoma benefit from liver resection, and fewer than one third of patients with potentially resectable metastases undergo operation.[5]

Many surgeons, including ourselves, have attempted to increase patient survival through refinements in patient selection for operation. If clinical factors with consistent prognostic value were identifiable, operation could be encouraged for those patients with a better chance for success and avoided for patients with a poor prognosis. Although several such prognostic determinants have been identified, only extrahepatic lymph node involvement and unresectable disease have been widely applied in clinical practice as contraindications for operation. The prognostic value of many of these determinants varies considerably between studies. In addition to patient, tumor, and interventional features, recent experiences have suggested that perioperative blood transfusion may affect patient survival by having an adverse effect on tumor behavior.[6,7]

We thus wanted to update our institutional experience with liver resection for metastatic colorectal carcinoma. Our specific aims were to (1) determine whether perioperative blood product transfusion was associated with patient survival; (2) identify patient, primary tumor, metastatic disease, and interventional characteristics that may

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have prognostic value; and (3) estimate the patient requirement for a prospective randomized trial designed to demonstrate efficacy of liver resection.

Methods

We conducted a retrospective analysis of all patients treated at the Mayo Clinic between 1960 and 1987 with potentially curative liver resection for metastatic colorectal carcinoma. Potentially curative liver resection was defined as an operation during which all known tumor was thought to be removed by the operating surgeon. Patients with unresectable persistent or recurrent primary disease, unresectable extrahepatic metastases, gross involvement of the resection margin, or previous liver surgery for metastases were excluded from analysis. Data were collected from patient histories, operative and pathology reports, and outside records when necessary (particularly to obtain information on the primary tumor and the operation for the primary tumor if it had been performed elsewhere). Follow-up information was obtained from clinical visits, correspondence, or telephone interviews for nearly all living patients through mid-1990.

Actuarial patient survival was calculated by the Kaplan-Meier method.[8] Comparisons of patient survival curves were made with the log-rank test.[9] Associations of continuous variables with patient survival and the simultaneous associations of multiple variables with survival were assessed with Cox's proportional hazards model.[10] The patient requirement for a prospective trial designed to determine the efficacy of liver resection for metastatic disease was determined by an exponential survival model.

Blood product transfusion data were obtained from the Mayo Blood Bank data files. A record of all blood products transfused during the perioperative period was obtained for every patient in the study. The perioperative period was defined as the interval of time beginning 1 week before and ending 2 weeks after the liver resection.

Demographic and clinical characteristics of the patients, pathologic and staging features of the primary tumors and metastases, and interventional factors were subjected to univariate analysis to identify possible associations with patient survival. Patient-related characteristics analyzed were gender and malignant predisposition, such as previous malignancy, inflammatory bowel disease, or colonic polyposis. Primary tumor features analyzed included primary tumor stage by the Astler-Coller classification[11] (without regard to metastatic disease); primary tumor location, including proctoscopic level (distance from the anal verge) for rectal tumors; regional lymph node status; local extension of tumor to adjacent organs; primary tumor size; and histologic grade (Broder's classification). Metastatic disease features analyzed included: the temporal relationship between the diagnoses of the primary tumor and liver metastasis (synchronous metastasis if detected within 3 months of the primary tumor and metachronous metastasis if detected at least 3 months after diagnosis of the primary tumor); method of detection of the metastatic disease; number, size, configuration, and histologic grade of metastases; whether or not metastases were located on the surface of the liver; extrahepatic lymph node involvement; and presence of extrahepatic disease such as resectable lung metastasis or local recurrence. Features of intervention that were subjected to analysis included the decade of the liver operation; whether or not biopsy of metastasis was performed before liver resection; the type of liver resection performed; the margin of liver resection obtained during operation; and administration of adjuvant chemotherapy or radiation therapy directed toward either the primary tumor or metastatic disease.

Results

Two hundred eighty patients underwent potentially curative liver resection for metastatic colorectal carcinoma at the Mayo Clinic between 1960 and 1987. There were 173 men and 107 women with a mean (± standard deviation) age of 59 ± 12 years. Data were incomplete for 11 patients operated on before 1985, who were lost to follow-up before 5 years had elapsed since operation. When data collection was completed, 85 of the 280 patients were alive. Sixty-four patients were disease free at a mean of 65 ± 59 (median, 51) months after operation; 19 had recurrent disease at a mean of 41 ± 29 (median, 35) months after operation; and the status of two patients could not be determined at a mean of 31 ± 20 (median, 31) months after operation.

Overall survival (± standard error) was 84 ± 2% at 1 year, 47 ± 3% at 3 years, and 25 ± 3% at 5 years. Median survival was 2.8 years. One hundred seventy-four of 195 patient deaths (89%) were due to clinically recurrent disease. Five patients died within 30 days of operation, and 10 patients (eight without disease, two with disease) died within 60 days of operation, resulting in 30- and 60-day operative mortality rates of 2% and 4%, respectively. Five patients remained free of disease and died 192, 147, 59, 50, and 40 months after liver resection. The disease status at death for the remaining eight patients was unknown.

Perioperative Blood Transfusion

Mean and median transfusion requirements (Table 1) were 2.6 and 2 units of whole blood and packed red blood cells, 1.0 and 0 units of fresh frozen plasma, and 0.3 and 0 units of platelets. To assess the possible adverse tumor response to transfusion and to eliminate the obvious relationship between technical complications resulting in blood loss and culminating in patient death, those patients who died or were lost to follow-up within 60 days of op-

TABLE 1. *Perioperative Transfusion Associated With Patient Survival*

	No. of Patients	Probability of Survival (% ± SE) 1 yr	3 yr	5 yr	Log-rank Test
Whole blood and packed RBCs					
None	81	85 ± 4	60 ± 6	32 ± 6	
>1 unit	183	81 ± 3	40 ± 4	21 ± 3	p = 0.03
Whole blood only	120	87 ± 3	46 ± 5	25 ± 4	
Packed RBCs only	41	85 ± 6	35 ± 8	—	
WB and packed RBCs	22	82 ± 8	45 ± 11	21 ± 11	
Platelets					
None	257	82 ± 2	45 ± 3	24 ± 3	
≥1 unit	7	86 ± 13	69 ± 19	46 ± 22	NS
Fresh-frozen plasma					
None	221	81 ± 3	44 ± 3	24 ± 3	
≥1 unit	43	86 ± 5	54 ± 8	25 ± 9	NS

eration were excluded from survival analysis. Remaining were 264 patients. Eighty-one of these patients did not receive any whole blood or packed red blood cells during the perioperative period. One hundred eighty-three patients received a total of 607 units. Eighty-six per cent of transfusions were administered during the operation, and 6% and 5% were administered during the preoperative week or the first 2 postoperative weeks for symptomatic anemia.

The group of 81 patients who did not receive any whole blood or packed red blood cells had significantly greater survival than the group of 183 patients who received at least one unit ($p = 0.03$) (Fig. 1). The proportion of patients whose metastases were detected by symptoms, physical examination, or a liver enzyme abnormality was higher in the transfusion group, 25% *versus* 5% ($p < 0.01$, chi square test). Also, a higher proportion of patients in the transfusion group underwent major liver resections (right hepatectomy, segments 5, 6, 7, 8; left hepatectomy, segments 2, 3, 4; or other), 53% *versus* 26% ($p < 0.01$). Other patient, primary tumor, metastatic disease, and interventional features were comparable between the two groups of patients (Table 2).

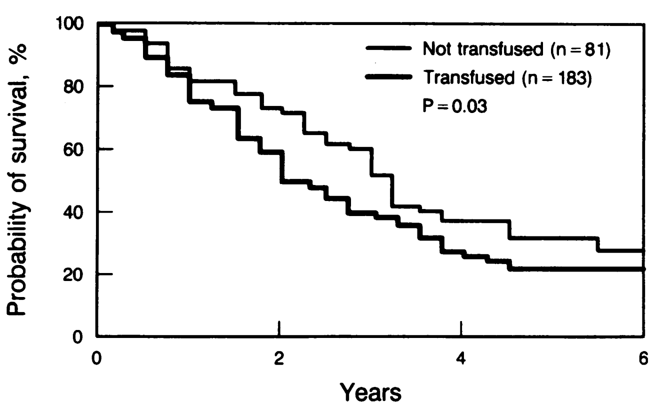

FIG. 1. Perioperative blood transfusion and probability of survival after liver resection.

Of the 183 patients who received at least one unit of blood, 120 patients received only whole blood, 41 patients received only packed red blood cells, and 22 patients received at least one unit of each. As our institution gradually shifted from whole blood to packed red blood cell administration between 1980 and 1985, the time of operation and duration of follow-up differed between these three subgroups of patients. Nevertheless, survival for transfused patients did not seem to be affected by whether the patients received whole blood, packed red blood cells, or both.

An attempt was made to determine whether the decrease in survival was associated with the volume of transfused whole blood and packed red blood cells (*i.e.*, a dose effect). The distribution of transfusion volume was not linear nor linear after log or log-log transformations of transfusion volume. Thus, transfusion volume was not evaluated as a continuous variable in a Cox proportional hazards model.

There were no significant associations between transfusions of fresh frozen plasma or platelets and survival, but the numbers of patients who received these blood components were small.

Patient and Primary Tumor Features

None of the patient and primary tumor features (Table 3) that were subjected to univariate analysis were associated with patient survival. Although primary tumor stage by itself was not associated with survival, there was an association for patients with synchronous presentation of primary tumor and liver metastasis, as described later. Proportional hazards analyses using a continuous variable were applied to primary tumor size and primary tumor regional lymph node involvement (number of involved lymph nodes) to reduce the chance of missing a significant

TABLE 2. *Comparison of Patients With and Without Perioperative Blood Transfusion (Excluding 16 Patients Who Died or Were Lost to Follow-up Within 60 Days of Operation)*

Variable	No Transfusions *N* (% of 81)	1 + Transfusions *N* (% of 183)
Categorical variables		
Sex		
Male	47 (58)	117 (64)
Female	34 (42)	66 (36)
Primary tumor stage		
A	0 (0)	0 (0)
B1	6 (7)	20 (11)
B2	31 (38)	63 (34)
C1	2 (2)	7 (4)
C2	36 (44)	86 (47)
Unknown	6 (7)	7 (4)
Primary tumor grade		
1	2 (2)	3 (2)
2	50 (62)	112 (61)
3	13 (16)	29 (16)
4	0 (0)	2 (1)
Unknown	16 (20)	37 (20)
Temporal relationship		
Synchronous	33 (41)	72 (39)
Metachronous	48 (59)	111 (61)
Initial detection		
Symptoms	0 (0)	26 (14)
Physical examination	2 (2)	6 (3)
Liver enzyme abnormality	2 (2)	6 (3)
Operative	37 (46)	79 (43)
High CEA	29 (36)	47 (26)
Imaging	9 (11)	18 (10)
Other	2 (1)	1 (1)
Configuration		
Single	61 (75)	113 (62)
Scattered	13 (16)	49 (27)
Satellite	7 (9)	21 (11)
Extrahepatic lymph nodes		
Normal	70 (86)	157 (86)
Negative	8 (10)	20 (11)
Positive	3 (4)	6 (3)
Grade		
1	0 (0)	0 (0)
2	56 (69)	130 (71)
3	24 (30)	51 (28)
4	1 (1)	2 (1)
Preresection biopsy		
None	54 (67)	125 (68)
Operative	19 (23)	45 (26)
Percutaneous	8 (10)	13 (7)
Operation		
Wedge (single)	51 (63)	73 (40)
Segments 2, 3	9 (11)	13 (7)
Segments 2, 3, 4	1 (1)	6 (3)
Segments 5, 6, 7, 8	8 (10)	54 (30)
Other	12 (15)	37 (20)
Margin of resection		
None	6 (7)	16 (9)
0–1 mm	2 (2)	14 (8)
1 mm–1 cm	35 (43)	82 (45)
≥1 cm	11 (14)	17 (9)
Indeterminant	27 (33)	54 (30)
Decade of operation		
1960s	5 (6)	27 (15)
1970s	15 (19)	35 (19)
1980s	61 (75)	121 (66)
Continuous variables*		
Age	63 ± 11 (63)	58 ± 11 (60)
No. of metastases	1.6 ± 1.4 (1)	1.8 ± 2.8 (1)
Size of largest metastasis	3.9 ± 2.8 (3.5)	6.3 ± 4.1 (5.0)

* Values for continuous variables are mean ± SD.

association due to inadequate sample size or inappropriate categorization. There were no significant associations between these features and patient survival.

Metastatic Disease Features

Of all the features of metastatic disease that were subjected to univariate analysis (Table 4), only clinical presentation, configuration of metastases, extrahepatic lymph node status, and extrahepatic disease were associated with patient survival.

The clinical presentation of liver metastasis was found to have a significant association with patient survival after liver resection. Patients with metastatic disease first suspected on the basis of symptoms (28 patients), physical examination (eight patients), or a liver enzyme abnormality (usually an elevation of the serum alkaline phosphatase level, nine patients), had a significantly lower probability of survival than patients with metastases detected as a result of an operative finding (119 patients), an elevation of the serum carcinoembryonic antigen level (84 patients), or surveillance imaging (29 patients) (Fig. 2, $p = 0.0005$).

Colorectal tumor metastases to the liver occasionally occur in a satellite configuration, which was defined as two or more lesions located in close proximity within the liver, that is, the same segment by Couinaud's nomenclature. Thirty-two patients had metastases in a satellite configuration. Their probability of survival was significantly worse than that for 182 patients with solitary lesions or 66 patients with multiple lesions arising in remote locations in the liver (Fig. 3, $p = 0.0052$).

Extrahepatic lymph node involvement was associated with a poor prognosis. Probabilities of survival to 1 and 3 years were 56 ± 17% and 11 ± 10% for nine patients with biopsy-proven extrahepatic lymph node involvement, and there were no survivors beyond 3½ years despite "potentially curative resection" (Fig. 4). In addition, probability of survival for patients without extrahepatic lymph node involvement as demonstrated by biopsy tended to be better than that for patients with apparently uninvolved lymph nodes that were not studied by biopsy.

Extrahepatic disease, even though resectable, was associated with a poor prognosis ($p = 0.015$) (Fig. 5). Twelve patients had resection of locally recurrent disease before or during liver resection, and the probability of survival was 18 ± 12% at 5 years. Two patients were long-term survivors. One patient died of recurrent disease more than 5 years after liver resection. The other patient had a true anastomotic recurrence, that is, intraluminal and intramural tumor, and remained disease free 4 years after liver resection. Five patients had pulmonary metastases resected before or during liver resection. One patient was lost to follow-up, and the other four all died between 12 and 22 months after liver resection. Fourteen patients had metastases to other or multiple extrahepatic sites. Despite resection, the probability of survival was only 8 ± 8% at 5 years.

TABLE 3. *Patient and Primary Tumor Features Associated With Patient Survival*

	No. of Patients	Probability of Survival (% ± SE) 1 yr	3 yr	5 yr	Log-rank Test
Gender					
Male	173	83 ± 3	46 ± 4	22 ± 4	
Female	107	85 ± 4	48 ± 5	29 ± 5	NS
Malignant predisposition					
Yes	36	83 ± 6	42 ± 8	18 ± 8	
No	244	84 ± 2	48 ± 3	26 ± 3	NS
Location					
Right colon	66	75 ± 5	49 ± 6	24 ± 6	
Transverse colon	22	82 ± 8	59 ± 10	34 ± 12	
Left colon	29	90 ± 6	57 ± 10	32 ± 10	
Sigmoid colon	103	87 ± 3	43 ± 5	23 ± 5	
Rectum	55	87 ± 5	41 ± 7	24 ± 6	
Unknown	5	80 ± 18	40 ± 22	—	NS
Stage (Astler-Coller)					
B1	28	89 ± 6	53 ± 10	34 ± 11	
B2	100	88 ± 3	49 ± 5	24 ± 5	
C1	9	89 ± 10	56 ± 17	56 ± 17	
C2	130	78 ± 4	44 ± 4	22 ± 4	
Unknown	13	100 ± 0	54 ± 14	27 ± 13	NS
B1 and B2	128	88 ± 3	49 ± 5	27 ± 5	
C1 and C2	139	79 ± 4	44 ± 4	24 ± 4	NS
Local extension					
Yes	25	76 ± 9	38 ± 10	19 ± 8	
No	234	84 ± 2	47 ± 3	26 ± 3	
Unknown	21	90 ± 7	58 ± 11	29 ± 11	NS
Size					
≤4 cm	72	79 ± 5	43 ± 6	22 ± 6	
≥4 cm–≤6 cm	91	86 ± 4	51 ± 5	26 ± 5	
≥6 cm	31	81 ± 7	47 ± 9	27 ± 9	
Unknown	86	87 ± 4	45 ± 6	27 ± 6	NS
Grade (Broder's)					
1	5	100 ± 0	25 ± 22	—	
2	175	84 ± 3	47 ± 4	24 ± 4	
3	43	74 ± 7	45 ± 8	33 ± 8	
4	1	100 ± 0	0	0	
Unknown	56	90 ± 4	52 ± 7	29 ± 8	NS

There was not a significant difference in the probabilities of survival between 109 patients with synchronous diagnoses of the primary tumor and liver metastasis and 170 patients with metachronous diagnoses. Patients with stage B primary tumors and a synchronous diagnosis of metastatic disease, however, fared better than the other patients (Fig. 6).

Other features of metastatic disease, such as the number of metastases, the size of the metastases, including the largest and smallest lesions if multiple, and the histologic grade of the metastases, were not associated with survival by univariate analyses. When these same features were subjected to proportional hazards analyses employing a continuous variable, only the number of metastases was related to patient survival. Indeed, initial analysis employing a categorical variable suggested that patients with 2 to 3 or 4 or more liver metastases fared worse than the patients with solitary lesions, but the p value was 0.17 (Fig. 7). This tendency was found to be significant by proportional hazards analysis, with a p value of 0.001.

Interventional Features

There were no differences in the probability of patient survival that could be related to whether or not a percutaneous or operative biopsy of the liver metastasis was performed before liver resection, the extent of the liver operation, the margin of resection obtained at operation, nor the decade in which the liver resection was performed (Table 5). The administration of adjuvant chemotherapy and radiotherapy for both primary and metastatic disease was too variable to allow meaningful analysis of a potential effect on patient survival.

Multivariate Analysis

Several factors, including those associated with patient survival by univariate analysis were analyzed multivariately with Cox's proportional hazards model. An initial model analyzed primary tumor stage, method of initial detection, configuration of metastases, extrahepatic lymph node status, and extrahepatic disease. A second model

TABLE 4. *Metastatic Disease Features Associated With Patient Survival*

	No. of Patients	Probability of Survival (% ± SE) 1 yr	3 yr	5 yr	Log-rank Test
Temporal relationship of diagnoses					
Synchronous	109	89 ± 3	49 ± 5	23 ± 4	
Metachronous	170	80 ± 3	46 ± 4	27 ± 4	
Other	1	100 ± 0	100 ± 0	100 ± 0	NS
Temporal relationship and primary tumor stage					
Synchronous B	52	100 ± 0	62 ± 7	30 ± 7	
Synchronous C	53	77 ± 6	37 ± 7	16 ± 5	
Metachronous B	75	79 ± 5	39 ± 6	24 ± 6	
Metachronous C	86	78 ± 4	49 ± 6	30 ± 6	p = 0.003 (synch B *vs.* C)
Clinical detection/ presentation					
Operative finding	119	89 ± 3	50 ± 5	25 ± 4	
Imaging	29	93 ± 5	50 ± 10	26 ± 10	
CEA elevation	84	79 ± 5	55 ± 6	34 ± 6	
Symptoms	28	78 ± 8	30 ± 9	17 ± 8	
Physical examination	8	63 ± 17	16 ± 14	—	
Liver enzyme elevation	9	67 ± 16	0	0	
Other	3	100 ± 0	67 ± 27	0	p = 0.0005
Configuration					
Single*	182	87 ± 3	51 ± 4	30 ± 4	
Multiple, scattered	66	80 ± 5	50 ± 7	18 ± 6	
Satellite	32	77 ± 8	16 ± 7	11 ± 6	p = 0.0052
Surface location					
Yes	25	72 ± 9	41 ± 10	27 ± 10	
No	77	79 ± 5	53 ± 6	21 ± 6	
Unknown	178	88 ± 2	46 ± 4	27 ± 4	NS
Histologic grade					
2	196	86 ± 3	46 ± 4	23 ± 4	
3	81	79 ± 5	47 ± 6	26 ± 6	
4	3	67 ± 27	67 ± 27	—	NS
Extrahepatic lymph node involvement					
Yes – biopsy+	9	56 ± 17	11 ± 10	0	
No – biopsy–	31	90 ± 6	54 ± 10	37 ± 12	
No – no biopsy	240	84 ± 2	48 ± 3	25 ± 3	p = 0.002
Number					
1*	185	86 ± 3	50 ± 4	29 ± 4	
2, 3	72	79 ± 5	43 ± 6	17 ± 6	
≥4	23	76 ± 9	32 ± 10	13 ± 8	NS
Size (largest diameter, lesion if >1 cm)					
≤2.9 cm	68	91 ± 4	53 ± 6	26 ± 6	
3.0–4.5 cm	71	83 ± 5	42 ± 6	24 ± 6	
4.6–7.5 cm	65	86 ± 4	49 ± 6	27 ± 6	
≥7.6 cm	67	77 ± 5	44 ± 6	26 ± 6	NS
Extrahepatic disease (resected)					
None	249	86 ± 2	49 ± 3	27 ± 3	
Local recurrence	612	55 ± 15	27 ± 13	18 ± 12	
Lung metastases	5	100 ± 0	0	0	
Multiple/other	14	71 ± 12	42 ± 13	8 ± 8	p = 0.015

* The discrepancy between the number of patients listed in Number (1) and Configuration (Single) is due to three patients with multilobulated solitary lesions, suggesting satellite fusion.

was applied to the 261 patients with follow-up beyond 60 days and included perioperative blood transfusion. In both models, extrahepatic lymph node status, method of initial detection, and configuration of metastases appeared to be significant predictors of survival. Only nine patients had extrahepatic lymph node involvement, and five of these

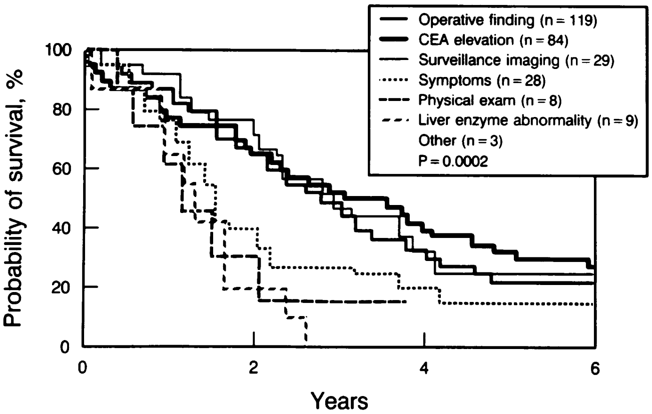

FIG. 2. Presentation of metastatic disease and probability of survival after liver resection.

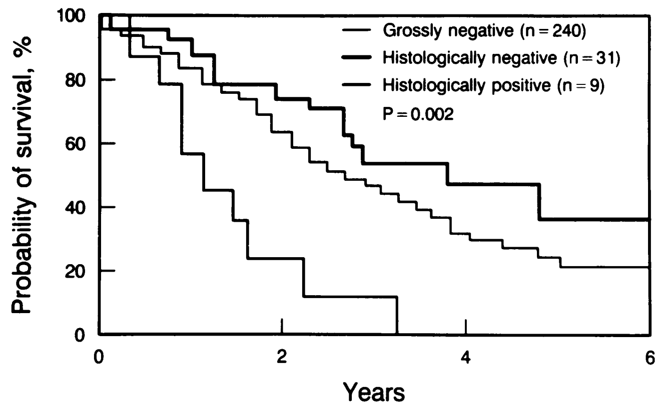

FIG. 4. Extrahepatic lymph node involvement and probability of survival after liver resection.

patients presented with symptoms, signs, or a liver enzyme abnormality due to liver metastases. Thus, extrahepatic lymph node involvement could not be considered a predictor of survival independent of method of initial detection. A model considering only method of initial detection and configuration of metastases demonstrated initial detection by symptoms, signs, or a liver enzyme abnormality ($p < 0.002$) and satellite configuration ($p < 0.01$), but not multiplicity of scattered lesions ($p = 0.38$) to be independent predictors of a poor prognosis.

Prospective Randomized Trial Requirement

Using an exponential survival model, the patient requirement was estimated for a prospective randomized trial (Table 6) designed to demonstrate efficacy of liver resection for metastatic colorectal carcinoma. If such a trial were designed with a 90% chance of demonstrating a significant difference between two randomized patient groups, assuming 25% 5-year survival for the group of patients selected to undergo liver resection, and that all patients could be accrued during the first year of the study, then the patient requirement would be 36 if 5-year survival were 1% without resection, 74 if 5-year survival were 5% without resection, and 168 or 428 if 5-year survival were 10% or 15% without resection.

Discussion

This retrospective study of our institutional experience with treatment of metastatic colorectal carcinoma by potentially curative liver resection was conducted to (1) determine whether perioperative blood product transfusion was associated with patient survival; (2) identify prognostic determinants; and (3) estimate the patient requirement for a prospective randomized trial designed to demonstrate efficacy of liver resection. We found perioperative transfusion of whole blood and packed red blood cells to have an adverse association with patient survival. Extrahepatic disease, extrahepatic lymph node involvement, satellite configuration of metastases, and detection of metastases by clinical examination or a liver enzyme abnormality were each significantly associated with a poor probability of survival. Multivariate analysis demonstrated satellite

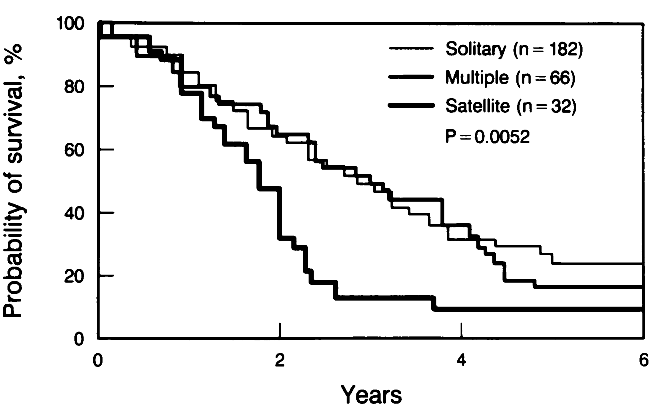

FIG. 3. Configuration of metastases and probability of survival after liver resection.

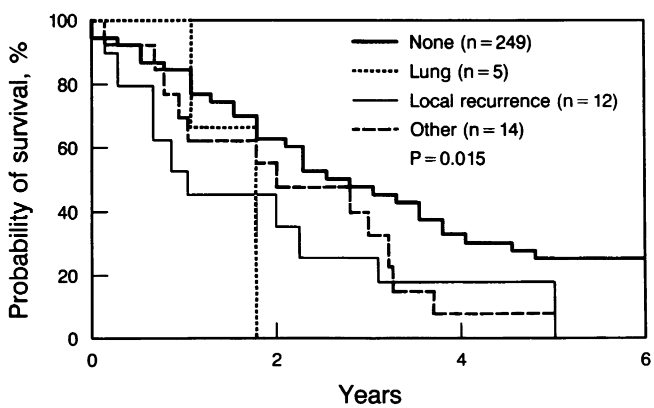

FIG. 5. Extrahepatic disease (resected) and probability of survival after liver resection.

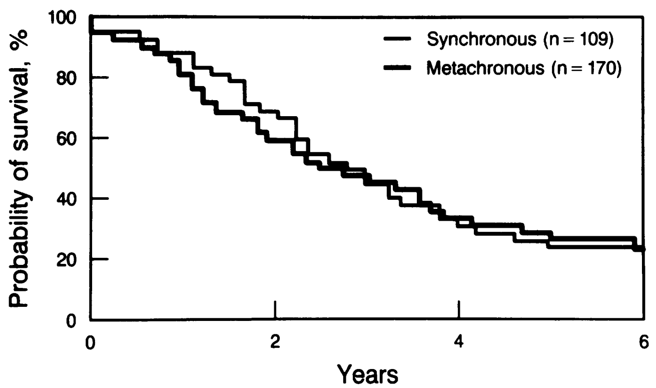

FIG. 6. Primary tumor stage with respect to the temporal relationship of diagnoses and probability of survival after liver resection.

configuration and clinical detection of metastases to be significantly associated with poor survival independent of the other factors. The patient requirement for a prospective randomized controlled trial of liver resection was estimated to be between 36 and 408 patients, depending on 5-year survival without resection, which would be expected to be between 1% and 15%.

The association between perioperative blood transfusion and survival was independent of the obvious relationship between technical complications that result in blood loss and perioperative patient death because those patients who died or were lost to follow-up within 60 days of operation were excluded from the survival analysis. Caution is warranted in interpretation of our results from the univariate analysis, however. Multivariate analysis did not demonstrate a significant association between perioperative transfusion and survival independent of other prognostic determinants. The differences in survival associated with clinical presentation and satellite configuration were much greater than the difference associated with transfusion by univariate analysis, and a transfusion effect on survival may have been overshadowed by the other more significant factors during multivariate analysis. It is also possible that patients with advanced disease were more likely to receive blood transfusions, particularly because the proportion of patients whose metastases were detected by symptoms, physical examination, or a liver enzyme abnormality (which may indicate advanced disease) was significantly higher for the transfused group.

A relationship between blood transfusion and tumor behavior has been suggested by both clinical experience[7,12] and laboratory research.[13-18] Blood transfusion has long been known to afford improved kidney allograft survival,[19] but the actual modulatory mechanisms remain unclear. Blood and blood product transfusions have been shown to increase suppressor T cell activity,[14] inhibit natural killer cell activity,[15] increase levels of alpha-2 macroglobulin[16] (a protease inhibitor that causes nonspecific lymphocyte suppression), and increase levels of prostaglandin E_2[17] (which activates suppressor T cells and inhibits interleukin-2 production) in a dose-dependent fashion for up to 7 days after transfusion. In addition, the mitogenic activity of platelet-derived growth factors increases during blood storage and may stimulate tumor growth after transfusion.[18] Perioperative transfusion thus could stimulate tumor growth directly or by an immunosuppressive effect and could result in an adverse effect on patient survival.

A number of clinical studies have addressed the effect of perioperative blood transfusion on patient survival after surgery for malignant disease. Francis[7] recently reviewed 31 such studies examining the effect of blood transfusion on prognosis after surgical treatment of primary colorectal carcinoma. Transfusion had a significant adverse effect on patient survival in 13 studies (42%), a beneficial effect in one study (3%), and no significant effect in 17 studies (55%).[7] The percentage of patients transfused in the studies ranged from 22% to 86%. Francis noted, however, that transfusion was frequently associated with other factors that may have adversely affected prognosis. He cautioned against attributing transfusion itself to be responsible for a worse prognosis in the presence of confounding variables.

Stephenson et al.[6] from the National Cancer Institute have reported that patients treated by potentially curative liver resection for metastatic colorectal carcinoma who received more than 11 units of blood had significantly shorter disease-free intervals and worse survival than those patients who received 3 to 10 units of blood.[6] Furthermore, they showed by Cox proportional hazards analysis that transfusion of each additional unit of blood increased risk of death by 7% ($p = 0.0013$). Other predictors of survival included the size and the number of metastases. The transfusion effect on survival was not seen for patients with a poor prognosis (*i.e.*, three or more metastases, metastases greater than 3 cm, and resection margin involve-

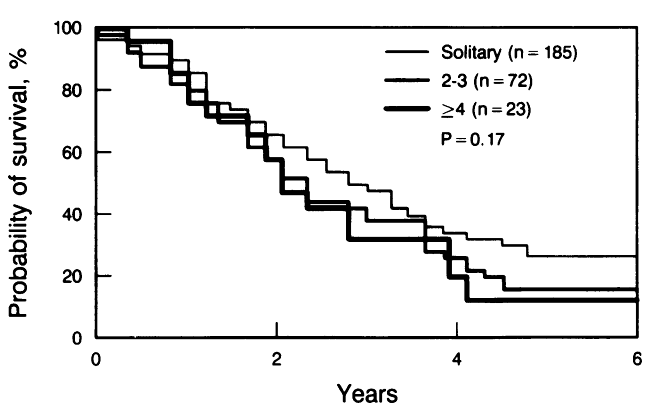

FIG. 7. Number of metastases and probability of survival after liver resection.

TABLE 5. *Interventional Features Associated With Patient Survival*

	No. of Patients	Probability of Survival (% ± SE) 1 yr	3 yr	5 yr	Log-Rank Test
Operation					
Wedge (single)	127	90 ± 3	51 ± 5	26 ± 4	
Segments 2, 3	23	87 ± 7	43 ± 10	29 ± 10	
Segments 2, 3, 4	8	60 ± 8	45 ± 19	—	
Segments 5, 6, 7, 8	71	82 ± 5	43 ± 6	25 ± 6	
Other	51	71 ± 6	46 ± 8	20 ± 7	NS
Margin of resection					
None	24	74 ± 9	36 ± 10	29 ± 11	
0–1 mm	17	88 ± 8	58 ± 12	32 ± 12	
≥1 mm–1 cm	123	86 ± 3	48 ± 5	27 ± 5	
≥1 cm	31	84 ± 7	51 ± 9	36 ± 11	
Indeterminant	85	83 ± 4	45 ± 6	18 ± 4	NS
Preresection biopsy					
None	189	81 ± 3	47 ± 4	25 ± 4	
Operative	66	91 ± 4	51 ± 6	28 ± 6	
Preoperative (percutaneous)	25	75 ± 10	41 ± 11	16 ± 10	
Decade of operation					
1960–1969	32	82 ± 7	41 ± 9	31 ± 8	
1970–1979	51	85 ± 5	41 ± 7	14 ± 5	
1980–1987	197	85 ± 3	50 ± 4	27 ± 4	NS

ment). In contrast, we were unable to determine whether there was a dose-dependent effect of transfusion on survival because the distribution of transfusion volume was not linear or transformable to allow proportional hazards model analysis. The transfusion requirement in the National Cancer Institute experience was considerably higher than in our experience (mean, 7.8 U *versus* 2.6 U; median, 6 U *versus* 2 U; and a minimum of 3 U in seven [13%] patients compared with no transfusion in 81 [31%] of our patients). This difference may explain the greater effect that transfusion had on survival in that study compared with our study. The National Cancer Institute study, however, had no apparent operative deaths, and the 30% overall 5-year survival rate was similar to our experience.

Younes et al.[20] recently reported that transfusion of whole blood during operation and up to 72 hours after operation was associated with a shorter disease-free interval after liver resection for metastatic colorectal carcinoma by univariate, but not multivariate, analysis.[20] Multivariate analysis found that an increasing number of intraoperative hypotensive episodes was most predictive of earlier recurrence, a factor that we did not investigate in our study.

Nevertheless, two other studies in the literature,[6,20] laboratory studies, and reported experiences with perioperative blood transfusion during surgical treatment of primary colorectal carcinoma[7,12] suggest that there may indeed be an adverse effect of perioperative blood transfusion on patient survival after operation for primary or metastatic colorectal carcinoma. Conceivably, perioperative blood transfusion may have an immunosuppressive effect that encourages growth or spread of residual disease after operation, but further study to corroborate these findings is clearly warranted.

Extrahepatic disease, whether resected before or during liver resection, was associated with a poor prognosis. Corroborative findings have been reported by Scheele et al.,[21] Doci et al.,[22] and Hughes et al.[23] These studies demonstrated a significant decrease in disease-free survival and a tendency toward decreased patient survival when locally recurrent or distant extrahepatic disease was removed before or during liver resection. Nevertheless, several patients have survived for more than 5 years.

Extrahepatic lymph node involvement has been a consistent predictor of poor survival in other studies and earlier reports from our institution. With the exception of a single report by Nakamura et al.,[24] the results obtained with liver resection for metastatic colorectal carcinoma in the presence of extrahepatic lymph node involvement have been dismal. Unless resection with radical regional hepatic lymphadenectomy, as advocated by Nakamura

TABLE 6. *Patient Requirement for Prospective Randomized Trial of Liver Resection*

Estimated 5-yr Survival (%) With Resection	Without Resection	Patient Requirement (No.)
25	1	36
25	5	74
25	10	164
25	10	428

et al.,[24] is proven to be efficacious by further experience, extrahepatic lymph node involvement currently should be considered a contraindication to liver resection.

Patients with apparently uninvolved lymph nodes that were not studied by biopsy did not fare as well as those with biopsy-demonstrated uninvolvement, which suggests that some patients with apparently normal lymph nodes had involvement that went undetected. We therefore now advocate routine extrahepatic lymph node biopsy for all patients before major hepatic resection.

Metastatic disease occurring in a satellite configuration is associated with a poor prognosis. This association also was identified by Scheele et al.[21] and Ekberg et al.[25]

Detection of metastatic disease by clinical signs, symptoms, or liver enzyme elevation (most often serum alkaline phosphatase) was associated with a poor prognosis. This finding is corroborated by results from several studies[26-29] of the natural history of colorectal carcinoma liver metastases; all showed liver enzyme elevation to have an adverse effect on prognosis even without liver resection. Similarly, others have shown survival after liver resection to be dependent on the extent of liver involvement with metastatic disease (*i.e.*, percent replacement), which parallels liver enzyme elevation.

Thus, extrahepatic disease, extrahepatic lymph node involvement, satellite configuration of metastases and clinical manifestation of metastases each are indicators of widespread, extensive metastatic disease or both; and the clinical course is rarely affected by operative intervention.

We were surprised to find that no other patient, primary tumor, metastatic disease, or interventional characteristics had significant prognostic value. Other studies, earlier reports from our institution, and the Registry of Hepatic Metastases study conducted by Hughes et al.[23] (in which our institution participated) have identified numerous prognostic determinants. Advanced primary tumor stage (regional lymph node involvement),[21-23,30] undifferentiated primary tumor histology (high tumor grade),[21] synchronous diagnoses of primary and metastatic disease (or a short disease-free interval),[21,23,31] increasing number of metastases (more than three or four),[23,32] and limited margins of resection[23,27,32] have been associated in several studies with decreased patient survival or disease-free survival.

Our institutional experience was first reported by Woodington and Waugh in 1963.[33] Mean survival was 3.1 years (range, 10 months to more than 9.5 years) for eight patients who underwent liver resection for metastatic colorectal carcinoma between 1938 and 1959. In 1976, Wilson and Adson[34] reported 28% 5-year survival for 60 patients treated between 1949 and 1972. Survival was much better for patients with solitary lesions (42% at 5 years), and no patients with multiple metastases survived 5 years. Women also had a better prognosis. Adson and van Heerden[35] reported the institutional experience with 34 major liver resections in 1980. Excluding two postoperative deaths, survival was 41% at 3 years, and again patients with multiple metastases had a poor prognosis. One hundred forty-one liver resections performed between 1948 and 1982 were reported by Adson et al. in 1984.[36] Extrahepatic lymph node involvement and advanced primary tumor stage (regional lymph node involvement) were found to have an adverse effect on prognosis. Gender had borderline significance, and multiplicity of metastases had less significance. Adson[37] reported an update on the same patients in 1987 and confirmed the earlier findings. Overall survival was 23% at 5 years.

Clearly, the variability of prognostic determinants in our studies attest to the heterogenicity of our patients. The current study, which is twice as large as our previous studies, failed to demonstrate prognostic value for gender. The effect of multiplicity of metastases on prognosis (significant earlier[34,35] but not later[36,37]) was again demonstrated herein, but only by proportional hazards analysis. Because our present survival statistics did not differ with regard to the decade in which the liver operations were performed, it is evident that subtle, unrecognized differences in patient and disease characteristics, referral patterns, and changing indications for operation may have had a profound effect on the identification of prognostic determinants.

We were puzzled by the finding that patients with synchronous diagnoses of metastatic disease and stage B primary disease (no regional lymph node involvement) fared better than the other patients. The large studies by Hughes et al.,[23] Scheele et al.,[21] and Schlag et al.[31] found survival for patients with synchronous diagnoses to be less than that with metachronous diagnoses. Other studies by Doci et al.[22] and Iwatsuki et al.[30] did not find the temporal relationship to have prognostic value. This discrepancy may be related to differences in patient population and referral patterns.

Our results do compliment the other studies that demonstrate the adverse effect of primary tumor regional lymph node involvement on survival after liver resection, but only for patients with synchronous diagnoses of primary and metastatic disease. When primary tumor regional lymph node involvement analysis included all patients, it was not found to have prognostic value. This discrepancy between the current study and other studies may be related also to differences in patient population, referral patterns, and indications for operative intervention.

The remarkably consistent finding in the current study, previous reports from our institution, and other studies is patient survival after potentially curative liver resection. Actuarial 5-year patient survival is consistently between

25% and 45%.[2] Most differences between survival figures are attributable to whether operative and postoperative deaths and patients with gross or microscopic residual disease are included in data analysis and length and success of follow-up. Although many prognostic factors have been identified, the significance of each varies considerably between studies, and the actual differences in survival attributed to these factors are small. Only the presence of extrahepatic lymph node involvement, satellite configuration of metastases, and extensive hepatic disease (as manifest by clinical detection or extent of liver involvement) have consistently been shown to have significant detrimental effects on prognosis.

Despite extensive worldwide experience with liver resection for metastatic colorectal carcinoma, the issue of whether the operation is efficacious remains controversial.[3-5] Several retrospective, historically controlled studies have found that the natural history of untreated, but potentially resectable, liver metastases is considerably worse than after liver resection; survival beyond 5 years is exceedingly rare.[34,38,39] Nevertheless, several investigators have proposed conduction of a randomized prospective trial designed to demonstrate efficacy of liver resection. We calculated that such a study would require 36, 74, 168, or 428 patients if 5-year survival in the group denied liver resection were 1%, 5%, 10%, or 15%, respectively. Disregarding ethical considerations, such a study seems to be presently impractical because of the large patient requirement, at least in a single institutional setting.

We remain steadfast in our opinion that liver resection for metastatic colorectal carcinoma affords a better chance for long-term survival (25% at 5 years) for a select group of patients. Improved survival is possible only if complete extirpation of tumor is accomplished at operation. Advanced or aggressive metastatic disease is manifested by clinical presentation, extensive hepatic involvement, and satellite configuration of metastases, which are relative contraindications for liver resection. Even if resectable, distant metastases or locally recurrent disease are also relative contraindications for liver resection. Extrahepatic lymph node involvement remains an absolute contraindication for major liver resection because survival has been uniformly poor in all but one study. Furthermore, extrahepatic lymph node biopsy should be performed before every major liver resection to avoid unnecessary complications for patients with incurable disease. Liver resection should be performed with meticulous technique to avoid blood loss and avert blood transfusion, which may have an adverse effect on tumor behavior and patient survival.

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Discussion

DR. DONALD L. MORTON (Los Angeles, California): I am pleased to have the opportunity to discuss this well-presented large series of patients with metastatic disease to the liver, resected by the group at the Mayo Clinic.

Our own results for resection of liver metastases began in 1972 when I performed my first hepatic lobectomy for metastatic disease from colon cancer; I am happy to report that the patient is still alive today. As a result of this favorable experience, we have been rather aggressive in resecting metastatic disease to the liver. We now implant an Infusaid pump in patients with very large, borderline-resectable lesions, so we can administer intra-arterial chemotherapy to shrink metastases for easier resection.

The John Wayne Cancer Clinic has a 50% rate of 5-year survival for colon cancer that has metastasized to the liver. I think this reflects careful patient selection: we usually do not resect hepatic metastases if there are multiple sites of involvement or extrahepatic disease.

I question the significance of perioperative blood transfusion as an independent prognostic variable, for two reasons. First, the slide shows small differences between patients who received blood transfusion and those who did not. Second, patients who need preoperative, intraoperative, or postoperative transfusions are generally those with large lesions that either require a trisegmentectomy, or are too close to the vena cava for use of the Longmire-Storm clamp. Conversely, patients who do not need blood transfusions tend to have smaller, more peripheral lesions that can be resected under close hemostatic control. This suggests that patients with large metastases (and poor prognosis) are more likely to receive blood.

Although a randomized trial to prove or disprove the role of liver resection in the management of metastatic disease requires a large number of patients, it must be done; otherwise our medical colleagues will continue to deny its usefulness—even though very few patients treated by other means have survived 5 years.

I am convinced that one of the biggest mistakes surgeons make is to yield complete responsibility for treating metastatic disease to their medical colleagues. Looking back over my 30 years of managing cancer patients, I recognize that the only long-term survivors are those who have undergone surgical treatment of their metastases. Few patients treated with chemotherapy for the common solid neoplasms have been long-term survivors.

It seems very short-sighted to consider surgery only for local disease. Instead, we should begin to think about the potential benefit of reducing the tumor burden as part of a synergistic multimodal program of therapy.

DR. JAMES H. FOSTER (Hartford, Connecticut): Is it operative skill or patient selection that gives us these unusually good results? Of those 74 survivors, Dr. Rosen, how many were actually, not actuarially, alive 5 years after their liver resection? Are there patients that have disease at 5 years that are counted as survivors? Finally, of that lucky one-quarter of patients who survived 5 years, how many eventually succumbed to their disease?

DR. BYERS W. SHAW, JR. (Omaha, Nebraska): That was an excellent presentation, Dr. Rosen, and a fascinating series. I wanted to follow up just a little bit more on Dr. Morton's mention of the role of the perioperative transfusions. I wondered if you had taken the time to analyze what the difference was in the causes of death between these patients?

I think if you were going to try to make a point that somehow perioperative transfusion was a prognostic factor, you would have to show us perhaps why these patients with the greater transfusion requirement died to see if it had anything to do with some factor that might be related to transfusion. For instance, did they die of more metastatic disease or did they die more frequently of liver failure or some other perioperative complications?

DR. WILLIAM V. MCDERMOTT, JR. (Boston, Massachusetts): This is, as always, an impressive series from Dr. Adson and his colleagues. We have not looked at our series in terms of of multiplicity of transfusions so I really cannot comment on this, but I must say instinctively I agree with Dr. Morton that probably the other factors that would be associated with multiplicity of transfusions could account for the difference.

The two factors that we have found to be important are (1) multiplicity of metastases; three or more have significantly smaller 5-year survival than one or two; and (2) margin of resection; if it is less than a centimeter, that has been significant in terms of long-term survival.

Conversely, like everyone else, one gets wary in terms of the effectiveness of any treatment on long-term survival. For example, we all have these anomalies. Before the days of resection, I followed one patient 8 years with calcifying liver metastases and he finally died just short of 9-year survival. That would have been considered an excellent result with any form of therapy. We also have current cases who are over 5 years in terms of survival but still have metastatic recurrent disease either in the liver or in other areas of the body.

So there are many complexities in this area; it will take us a lot longer in retrospective review to untangle all these apparently conflicting factors that go into determining the success of the procedure.

Nonetheless, it is always very impressive to hear Dr. Adson and his group and their reports, and I look forward to further reports from them.

DR. ARTHUR H. AUFSES, JR. (New York, New York): Because one of the earliest, if not the first, reports of the role of perioperative transfusion related to primary colon cancer was reported by Dr. Tartter and his associates from the Mount Sinai Medical Center, I feel impelled to make a comment.

We unquestionably believe that perioperative transfusion does have a role to play in increasing recurrence, certainly in primary tumors. And that was true stage for stage, which would tend to be in opposition to what Dr. Morton said regarding the size of the lesions.

We do not have any data on the use of perioperative transfusion in