Treatment of Colorectal Hepatic Metastases by Intrahepatic Chemotherapy Alone or as an Adjuvant to Complete or Partial Removal of Metastatic Disease

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Because of the wide variation in reported benefits from the use of intrahepatic chemotherapy for colorectal hepatic metastases, the authors performed their own phase II studies comparing the use of intrahepatic chemotherapy alone and intrahepatic chemotherapy as an adjuvant to complete or partial removal of metastatic colorectal cancer to the liver. Techniques for partial removal included unilateral and bilateral wedge resection, peripheral presinusoidal embolization of the liver, and portal vein branch ligation. Patients were staged using the per cent hepatic replacement method of Pettavel and Taylor, and patients with bilateral metastases were included in the study. Twenty-seven patients, mean age 60.3 years, were examined. There were 19 males, mean age 60.4 years, and eight females, mean age 60 years. The patients were divided into four groups. Group A had an implantable pump only; Group B had an implantable pump and resection; Group C had an implantable pump and arterial embolization and portal vein branch ligation; and Group D had an implantable pump, partial resection, arterial embolization, and portal vein branch ligation. Kaplan-Meyer survival curves were calculated for all of these groups. A separate analysis was carried out for each of the stages, and a comparison was made. The study indicated that the overall median survival time was 18 months and that the more radical the treatment in addition to chemotherapy, the better the results. Such results were not totally dependent on the staging of the tumor volume but were dependent on the degree of extirpation of the tumor. In Group C, consisting primarily of Stage IIa, IIIa, and IV patients (*i.e.*, unresectable patients), a doubling of expected median survival to 12 months could be achieved, compared to those in Group A, which achieved a median survival of only 6 months.

SINCE 80% of the 55,000 patients who die each year from colorectal cancer have hepatic metastases and the median survival time is only 6 months after diagnosis, an aggressive approach is rational.[1-8] Bolus systemic chemotherapy with fluorouracil (5FU®) has not had any significant effect on survival time.[9] Continuous intravenous chemotherapy given percutaneously has only slightly better results.[10] Intra-arterial hepatic chemotherapy was initiated in the 1950's but technical problems initially outweighed the slightly increased benefits of this approach.[11,12] Use of the Silastic® catheter and the Infusaid® pump has been very popular for intra-arterial chemotherapy with over 5000 implantations to date. However, the initial claimed responses of over 80% have not been upheld in more recent publications.[13,14]

Since 1980 we have been performing phase II studies comparing the use of intrahepatic chemotherapy alone and intrahepatic chemotherapy as an adjuvant to complete or partial removal of metastatic colorectal cancer to the liver. Techniques for partial removal have included unilateral and bilateral wedge resection,[15] peripheral presinusoidal embolization of the liver,[16] and portal vein branch ligation.[17]

Because correlation is only possible after staging, as pioneered by Pettavel[18] and Taylor,[19] we have not excluded patients with bilateral metastases but have calculated stage by tumor volume.

Material and Methods

Twenty-seven patients with hepatic metastases from colorectal cancer treated at the Westchester Medical Center, New York Medical College, from April 1980 to May 1985, were entered into the study. The age range of the studied patients was 40–70 years (mean: 60.3 years), and there were 19 males, age range 40–71 years (mean: 60.4 years), and eight females, age range 48–70 years (mean: 60 years). All patients were ambulatory with an Eastern

This work was supported in part from the Lucile and Everett Smith Surgical G.I. Foundation.

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Submitted for publication: November 15, 1985.

TABLE 1. *Treatment Groups*

Group	Pump	Resection	Arterial Embolization	Portal Vein Branch Ligation
A	+			
B	+	+		
C	+		+	+
D	+	+	+	+

TABLE 2. *Distribution of Patients by Gender and Stage*

				Stage				
Group	Total	Male	Female	II	IIa	III	IIIa	IV
A	6	3	3		4			2
B	11	8	5	6	3			2
C	4	4			1		2	1
D	6	2	4		2		1	3

Cooperative Oncology Group (ECOG) performance score of three or less and could withstand laparotomy. None of the patients were jaundiced as a result of tumor volume, and none of the 27 patients had ascites. Only one patient was thought before operation to have extrahepatic disease. Appropriate scans and radiologic studies were carried out, and then transarterial hepatic angiography was done in all patients. When possible, a dynamic hepatic computerized tomography (CT) scan was performed during the portal phase of a selective superior mesenteric artery injection. This maximized the differences in attenuation between normal parenchyma and tumor, improving localization of metastatic deposits. Carcinoembryonic antigen levels and liver chemistry values were obtained.

The patients were staged using a combination of radiography and direct exploration at laparotomy. The staging system used by us was a refinement of the Percent Hepatic Replacement (PHR)[18,19] system.

Stage I PHR less than 25%

Stage II PHR 25–75%

Stage III PHR more than 75%

Stage IV Extrahepatic disease

Each stage had a subset "a," which denoted that the situation of one of the tumors was such that it was deemed unresectable. This was usually because the tumor was contiguous with the hepatic veins or the inferior vena cava.

After staging, patients were allocated to one of four treatment groups (Table 1), which was dependent on the anatomical location of tumor. The aim was to remove or debulk tumor whenever possible and then treat by intrahepatic chemotherapy.

All but two patients received an Infusaid pump (Model 400, Infusaid Corp., Norwood, MA). These two patients had intra-arterial catheters placed, and an external pump was used to give continuous chemotherapy. This regimen consisted of floxuridine, starting at a dose of 0.1 mg/kg per day and working up to 0.3 mg/kg per day over a period of 14 days each month. Mitomycin C was used as an adjuvant therapy later in the patient's course if failure to maintain response from floxuridine was demonstrated.

Table 2 indicates the distribution of our patients by gender and stage in the various groups. In Group B complete resection was achieved in all Stage II patients. Partial resection (debulking) was carried out in the remainder.

Results

The survival curve for all 27 patients is shown in Fig. 1. The median survival time was 18 months from the time of our initial treatment.

In Table 3, the distribution of patients by stage, following laparotomy, is analyzed. We had no patients in this study with small lesions, that is no Stage I or Ia patients. Also, there were no patients with Stage III disease who were resectable. The performance status of all our patients was good, although nearly three-quarters of them had bilateral hepatic metastases. Average survival of Stage II patients was over 2½ years after we initiated treatment, but for Stage IIa and IIIa disease it was similar at 10 months. When extrahepatic disease existed, survival was reduced to 6 months.

In Table 4, the Stage II patients are analyzed in more detail. Eighty-three per cent of them had synchronous liver metastases, and they were referred for treatment on an average of 3 months after diagnosis. Two-thirds of them were still alive at the time analysis for this paper closed.

In Table 5, the Stage IIa patients are analyzed. Sixty per cent of them had synchronous metastases, and the average survival of these people after primary cancer re-

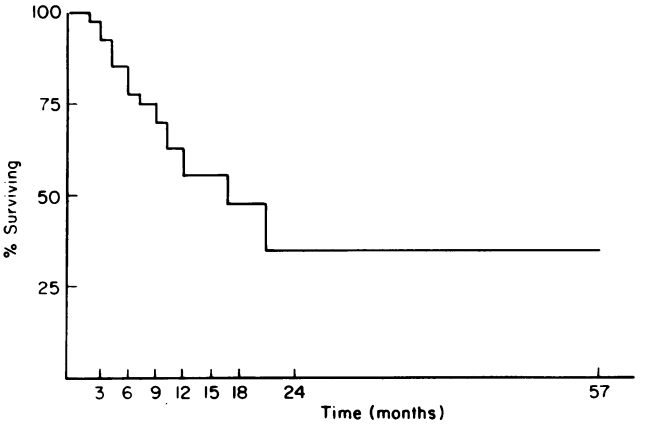

FIG. 1. Kaplan-Meyer survival curve for all patients in the study.

TABLE 3. *Distribution of Patients by Stage, Following Laparotomy*

Stage	# of Patients	Mean Performance	Bilateral %	Average Survival (months)
I	0			
Ia	0			
II	6	0	66.6	31
IIa	10	0.6	75	9.3
III	0			
IIIa	3	1	0	10
IV	8	0.75	66.6	6

section is 8 months less than Stage II patients. These patients also waited a mean of 1 year before being referred for aggressive management by us. Over half of these patients were alive at the end of the study.

Table 6 demonstrates that all our Stage IIIa patients had metachronous disease and were referred fairly soon after diagnosis. They achieved a 4-year survival from the time of primary cancer resection.

Table 7 demonstrates an even greater survival of nearly 5 years from primary colon surgery. There is an even distribution of synchronous and metachronous disease, and the patients were referred 6 months after diagnosis, but only one-quarter remained alive at the end of our analysis.

Treatment was provided on pre- and perioperative anatomical distribution of tumor and was not dependent on extent or stage. Treatment was based on intrahepatic chemotherapy, but, when possible, tumor was also removed or debulked or devascularized.

Analysis was done by construction of survival curves using the Kaplan-Meyer method[21] and by comparison of results for each group.

Group A patients were treated using the Infusaid pump only. There was one complete responder. Mean survival was 6 months, with only one-third of the patients surviving longer.

When Group B, containing patients who had partial or complete resection and the pump, is analyzed, most

TABLE 4. *Analysis of Stage II Patients*

RX	PCR	DX	SY	M	REF	S
57	59	59	+		2	DWD
46	55	55	+		9	AWD
34	35	35	+		1	AWD
21	24	24	+		3	DWD
20	35	21		+	1	AWD
9	12	12	+		3	ANED

RX = Survival in months from time of our initial treatment; PCR = Survival in months from primary cancer resection; DX = Survival in months from diagnosis of liver metastases; SY = Synchronous liver metastases; M = Metachronous liver metastases; REF = Months between diagnosis of liver metastases and referral; S = Status; DWD = Dead with disease; AWD = Alive with disease; ANED = Alive, no evidence of disease.

TABLE 5. *Analysis of Stage IIa**

RX	PCR	DX	SY	M	REF	S
17	21	21	+		4	DWD
12	36	36	+		24	DWD
11	42	23		+	12	AWD
10	36	13		+	3	AWD
9	37	37	+		28	AWD
9	18	18	+		9	AWD
7	18	18	+		11	AWD
7	9	9	+		2	AWD
6	39	22		+	16	DWD
4	19	12		+	8	DWD

* See Table 4 for definition of abbreviations.

of these patients are in Stage II, but there were two patients who had Stage IV disease. One of them died 2 months after liver surgery, and the other one was alive over 10 months later. Because of prolonged patient survival, a median survival time could not be calculated for this group (Fig. 2). Further, there is clearly a significant difference between Group A and B with the p value of 0.0186 for the Wilcoxon test and 0.0079 for the Savage test. The longest survivor died with disease at 57 months after her first liver resection. A second resection was done 2 years before her death.

In those Group B patients who, because of the anatomical localization of disease, could only undergo partial resection, the median survival was 1 year. This was significantly better than the Group A patients with similar staging who were treated only by intrahepatic chemotherapy. The completely resectable Group B patients did far better with only one death at 21 months and the second at 57 months.

Group C contained those patients who had hepatic artery embolization and portal vein branch ligation in addition to the pump. The staging of the patients in this Group was slightly worse than in Group A. The median survival again could not be calculated, as more than 50% of the patients were still alive at the conclusion of the study, but there was no significant difference in the survival curves for Groups A and C (Fig. 3). Two of these patients were complete responders.

When a further debulking is done by adding partial resection to hepatic arterial embolization, portal vein branch ligation, and the pump, as in Group D, median

TABLE 6. *Analysis of Stage IIIa**

RX	PCR	DX	SY	M	REF	S
12	47	14		+	2	AWD
10	50	15		+	5	DWD
8	46	12		+	4	DWD

* See Table 4 for definition of abbreviations.

TABLE 7. *Analysis of Stage IV**

RX	PCR	DX	SY	M	REF	S
10	27	14		+	4	AWD
9	129	22		+	13	DWD
7	9	9	+		7	DWD
7	47	23		+	16	AWD
6	234	8		+	2	DWD
4	6	6	+		2	DWD
3	4	4	+		1	DWD
2	7	7	+		5	DWD

* See Table 4 for definition of abbreviations.

survival of 12.1 months was achieved (Fig. 4), although the staging of these patients is similar to those in Groups A and C. There were three complete responders. Again, the generalized Wilcoxon and Savage nonparametric methods were used to compare Groups A and D. According to the Wilcoxon test, there was a significant difference with a p value of 0.0994, but this was not confirmed by the Savage method where the p value was 0.2718.

All patients who survived long enough developed chemical hepatitis, which was diagnosed by increases in transaminases that decreased when chemotherapy was stopped. Transient jaundice developed in four patients. Two of these had strictures of the upper portion of the common hepatic duct, but it cannot be proved at this point if these strictures were secondary to treatment, as suggested by Johnson and Rivkin.[14] Unlike Daly et al.,[13] only one patient in this series developed a peptic ulcer, which could not be treated by Tagamet®. This patient had the pump catheter redirected to the subclavian vein.

We have not had to operate for cholecystitis, and we have not made it a routine to remove gallbladders during placement of catheters or before embolization of the right lobe of the liver. We have found that the patient does develop a chronic ischemic cholecystitis in response to

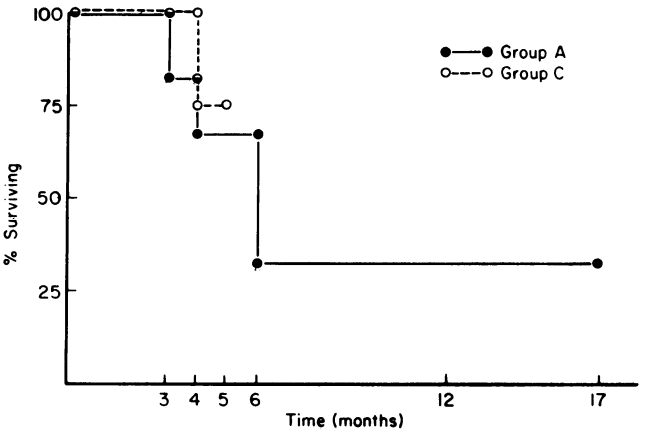

FIG. 3. Survival curves comparing Groups A and C.

embolization, and this may necessitate cholecystectomy during implantation of the pump catheter.

Only the nonresponders clearly died of advancing tumor within the liver. At the time of death, 12 patients had extrahepatic disease. This was commonly in the lung and the bone marrow. One patient died of brain metastases. In those patients who died of extrahepatic disease, two had no evidence of any metastatic cancer in the liver.

Discussion

Implanted pumps for chemotherapy of colorectal metastases to the liver are very popular with patients. However, we have been less than convinced by the early publications in which response rates of 80% were claimed, and the survival time has been difficult to decipher from these papers.[22,23] We prefer to determine survival time from the moment of implantation of the pump. Another difficulty has been in comparing the various papers, because it was not known if patients of comparable staging were being compared. Therefore, the wide variety of re-

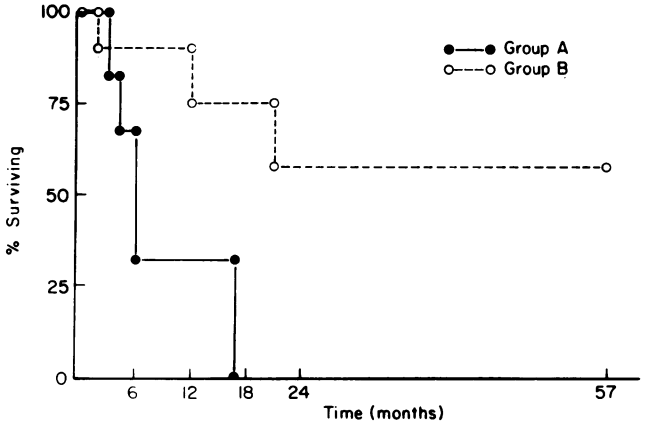

FIG. 2. Survival curves comparing Groups A and B.

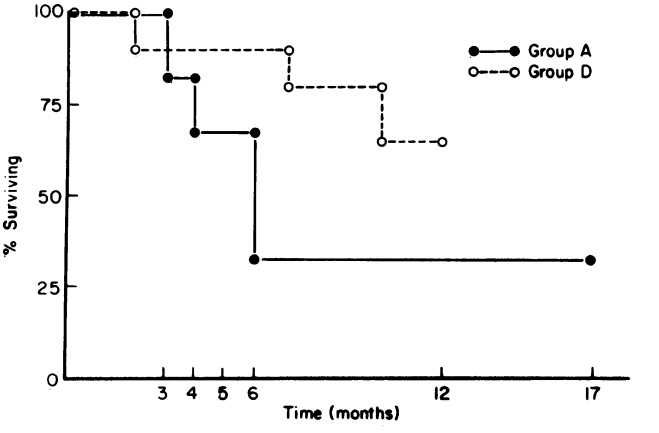

FIG. 4. Survival curves comparing Groups A and D.

sponse noted in the literature may be due to patient selection rather than any benefit from intrahepatic chemotherapy or the use of the pump itself.

The best results occur in patients in whom no more than 30% of the liver is involved, but these patients can often be resected in any case. Further, because the results get worse with increasing involvement of the liver, we have essentially used the pump group as a control, and we have tested the addition of the other modalities against this. Our results indicate no clear benefit in patients treated by the pump alone (Group A), and this was not because they had more extensive disease than the others. In patients staged similarly in Group C, we demonstrated a doubling of survival time by adding arterial embolization and portal vein branch ligation.

In hepatic tumors, measurement of partial responses is difficult, but a yardstick is survival time. Our feeling was that patients who did not survive much beyond 3 months from implantation of the pump did not have the course of their disease changed by this method of management. However, this failure to respond only occurred in four patients out of our total. On the other hand, one patient in Group A did have a total response to treatment with the pump, although, in this group alone, the median survival time was no different from that obtained by conventional management of patients by chemotherapy.

Since the overall median survival time for our study group was 18 months, it appeared that further treatment techniques in addition to the pump were of benefit. When each approach was analyzed, it was clear that the more active the intervention, the better the results. This was particularly notable in Group B, where the volume of disease was similar in those who had complete resection and in those who had partial resection. However, there did not appear any statistical difference in these patients whether they had unilateral or bilateral disease. In fact, in our overall study, two-thirds of the patients did have bilateral disease. Our results, in general, indicated that the median survival times were doubled by the addition of an active method of treatment, but the effect of the pump alone was questionable.

We would therefore recommend that all patients have active intervention, ranging from embolization to complete resection in addition to implantation of the Infusaid pump. This approach was of benefit to our patients who survived longer than 3 months because not only was life prolonged but good quality of life was achieved out of the hospital, with the patient's performance status usually between 0 and 1 on the ECOG scale.

Most patients who presented to us with Stage II disease had timely referral patterns and did well. However, when the tumors were situated in unresectable positions and yet were small in volume, the time from diagnosis of the liver metastases to referral was unacceptably long in nearly half our cases. It seemed that delaying as long as a year removed any chance of a 5-year survival in this group.

In patients with Stage IIIa disease, we found that they all developed metachronous tumor, having survived for nearly 3 years following the primary cancer resection. Again, in the Stage IV patients, a delay in referral appeared to be fatal.

Our results indicate that we did not have significant problems following implantation of the pump. Like other authors, we have paid careful attention to avoid gastrointestinal perfusion; thus, we have not had to be concerned with gastritis and peptic ulcer formation. We have not found a high incidence of hepatic artery thrombosis, and only one of our cases had biliary sclerosis of the junction of the right and left hepatic ducts. Nonetheless, chemical hepatitis did seem to be universal.

We do emphasize that there is high rate of recurrence of metastases in the extrahepatic situation if treatment is stopped in this group of patients. Therefore, at the first sign of chemical hepatitis, we have reimplanted the catheter into the superior vena cava so that systemic chemotherapy can be given. This has reduced the chemical hepatitis and, we hope, will reduce the development of systemic metastases.

Summary

Twenty-seven patients with colorectal cancer metastatic to the liver were treated by intrahepatic chemotherapy using an implanted pump in association with other modalities of treatment. The regional chemotherapy consisted of floxuridine, and this was given for 2 weeks out of 4. Six of the patients (Group A) were treated in this way alone; the other patients had some other form of treatment as well so that in Groups B, C, and D infusional chemotherapy was adjuvant. Our study indicated that the more radical the treatment in addition to chemotherapy, the better the results. Such results were not totally dependent on the staging of the tumor volume but were dependent on the degree of extirpation of the tumor. Even in Groups B and C, which consisted primarily of Stage IIa, IIIa, and IV patients (*i.e.*, unresectable patients), a doubling of expected survival to 12 months could be achieved, compared to Group A.

It is therefore suggested that infusional intrahepatic chemotherapy for colorectal metastases to the liver is inadequate and that the addition of other modalities are required to improve survival.

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