Tumor Vascularity as a Prognostic Factor for Hepatic Tumors

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The prognostic and therapeutic significance of tumor vascularity was studied in 36 patients with hepatoma or metastatic colon cancer in the liver. All patients had nonresectable tumor and were treated by hepatic artery ligation and hepatic arterial infusion chemotherapy. Chemotherapy consisted of methotrexate, actinomycin-D, 5-fluorouracil and cyclophosphamide. Hepatic tumors were categorized into Grades I to III in the order of increasing vascularity as determined by preoperative hepatic angiography. Tumor vascularity of 15 patients with hepatoma was Grade III in 11 (73%) and Grade II in 4 (27%). No patient with hepatoma had a Grade I tumor. The median survival of patients was 10 and 6 months for Grade III and II hepatomas, respectively, after hepatic artery ligation, and 18 and 8.5 months for Grade III and II, respectively, from the time of diagnosis of hepatoma. Tumor vascularity of 21 patients with metastatic colon cancer was as follows: Grade III in 3 (14%); Grade II in 10 (48%); and Grade I in 8 (38%). The median survival was 11, 10.5 and 4 months for Grades III, II and I, respectively, after hepatic artery ligation, and 17, 14.5 and 7.2 months for Grades III, II and I, respectively, from the time of diagnosis of hepatic metastases of colon cancer. The results indicate that the more vascular the hepatic tumor on angiogram, the better the prognosis following hepatic artery ligation and infusional chemotherapy.

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MALIGNANT TUMORS of the liver derive their blood supply almost exclusively from the hepatic artery.[1,3] Based upon this observation, hepatic artery ligation and infusional chemotherapy has evolved as a treatment for nonresectable hepatic tumors.[2] A major portion of hepatic tumor is destroyed by ischemic necrosis immediately following ligation of the hepatic artery. The residual disease is treated by postoperative infusional chemotherapy delivered selectively in high concentration through a catheter in the hepatic artery. In our experience, however, preoperative hepatic angiography has disclosed a gradation in vascularity of hepatic tumors in different patients. The significance of this finding in the treatment of hepatic tumors was evaluated in the present study. The data were obtained from the records of 36 patients who either had hepatoma or metastatic colon cancer in the liver; and who were treated by hepatic artery ligation and infusional chemotherapy.

Submitted for publication March 3, 1976.

Materials and Methods

Since 1970, 232 patients have been treated for malignant tumors of the liver by the gastric and mixed tumor service at Memorial Sloan-Kettering Cancer Center. Of those 232 patients, 69 had hepatic resection, 91 hepatic artery ligation and infusional chemotherapy, 72 laparotomy only or other procedures. Of 91 patients who were treated by hepatic artery ligation and chemotherapy, 53 had hepatoma or metastatic colon cancer and form the basis of this study. Among those, 17 patients were not suitable for the study because either their angiographic films were not available for re-examination, or their postoperative period was shorter than 6 months. The remaining 36 patients, 15 with hepatoma and 21 with metastatic colon cancer, were analyzed in the present study.

Hepatic angiography was performed preoperatively via the celiac axis and superior mesenteric artery. Tumor vascularity was graded by degree of neovascularity in the phase of optimal arterial visualization. The gradation is as follows: Grade I—the vascularity similar to or less than that of the normal liver; Grade II—the vascularity that is slightly more in degree than that of the normal

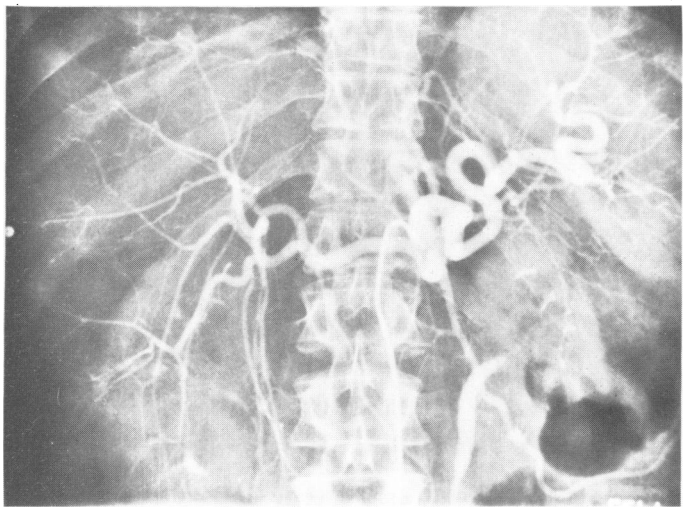

FIG. 1. Grade I tumor vascularity.

liver; Grade III—the vascularity that is much more than that of the normal liver (Figs. 1–3).

The patients who underwent hepatic artery ligation had nonresectable tumors involving both lobes of the liver. Ligation of the hepatic artery was performed at the level of the common hepatic artery. The distal portion of the ligated artery was cannulated through the gastroduodenal artery by using a silastic catheter. Postoperatively, the catheter was kept patent by continuously infusing heparinized saline with a portable infusion pump (Sigmamotor Co., New York). Chemotherapy consisted of: actinomycin-D 0.02 mg/kg body weight and methotrexate 0.2 mg/kg body weight weekly via the hepatic artery catheter; 5-fluorouracil 10 mg/kg body weight weekly by intravenous injection; cyclophosphamide 1 mg/kg body weight daily by mouth. Chemotherapy was usually started within two weeks of surgery and continued as long as patients tolerated the chemotherapy. When the hepatic arterial catheter was occluded, usually within 3 to 4 months after surgery, chemotherapy was administered intravenously using the same dosages. The patients were followed by weekly examination and blood counts. The blood was analyzed monthly for liver and renal function studies. Liver scan using Technetium-99 sulfur colloid was obtained once every 4 months.

Results

Hepatoma. Tumor vascularity of 15 patients with hepatoma was revealed as Grade III in 11 (73%) and Grade II in 4 patients (27%). None of these tumors was found to be a Grade I lesion. Four patients died of acute renal failure postoperatively. Extensive tumor necrosis appeared to be the principal cause for this complication. Of particular interest is that all of those patients with renal failure had hepatoma with Grade III vascularity. Excluding 4 postoperative mortalities, the median survival was 10 months (ranging from 4 to 27 months) for patients with Grade III hepatoma and 6 months (ranging from 4–10 months) with Grade II hepatoma following hepatic artery ligation (Table 1). Three patients are presently alive and well with Grade III hepatoma at 27, 10 and 9 months after operation and one is alive with a Grade II hepatoma at 10 months postoperatively. When the median survival was computed from the time of diagnosis of hepatoma, it was 18 months (ranging from 10–29 months) with Grade III hepatoma and 8.5 months (ranging from 6–34 months) with Grade II hepatoma.

Metastatic Colon Cancer. Tumor vascularity of 21 patients with this tumor was Grade III in 3 (14%), Grade II in 10 (48%), and Grade I in 8 patients (38%). None of these patients died postoperatively. The median survival was 11 months (ranging from 10–12 months) for Grade III cancer; 10.5 months (ranging from 1–12 months) for Grade II cancer; and 4 months (ranging

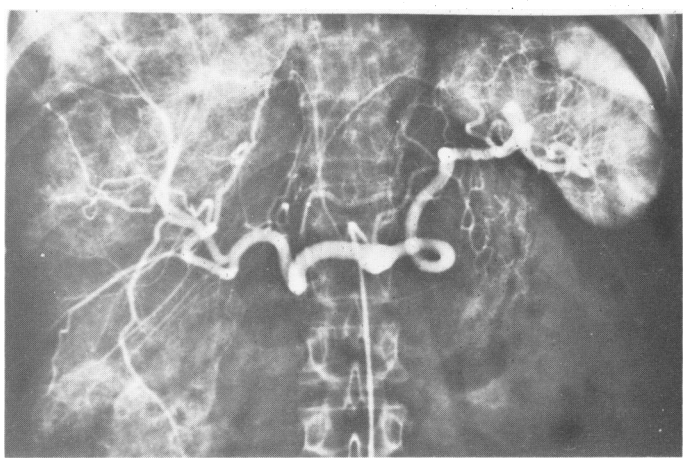

FIG. 2. Grade II tumor vascularity.

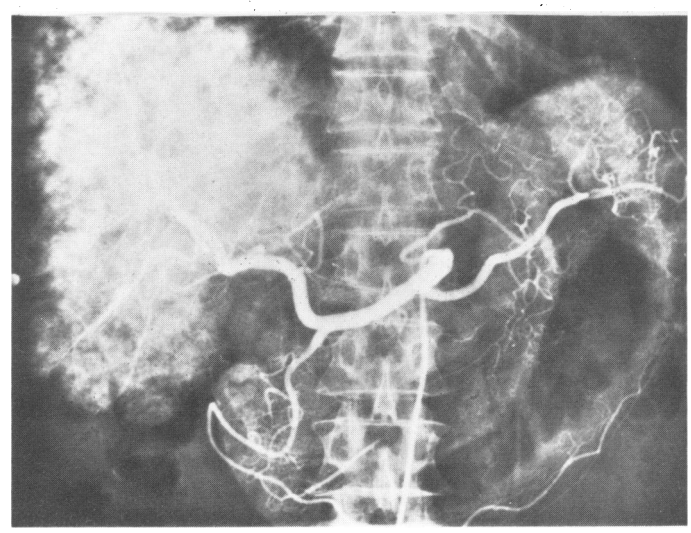

FIG. 3. Grade III tumor vascularity.

from 1–13 months) with Grade I cancer following hepatic artery ligation (Table 2). Two patients are presently alive and well with Grade III cancer at 10 and 12 months, and one is alive with Grade II cancer at 10 months postoperatively. No patient is alive with Grade I cancer. When the median survival was computed from the time of diagnosis of hepatic metastases, it was 17 months (ranging from 15–22 months) with Grade III cancer; 14.5 months (ranging from 11.5–21 months) with Grade II cancer; and 7.2 months (ranging from 2.5–19 months) with Grade I cancer.

TABLE 1. *Tumor Vascularity and Survival*: Hepatoma*

Tumor Vascularity	No. Patients	From Hepatic Artery Ligation	From Diagnosis
Grade I	0	—	—
Grade II	4 (27%)	6 (4–10)	8.5 (6–34)
Grade III	11 (73%)	10 (4–27)	18 (10–29)
Overall	15	9 (4–27)	11 (6–34)

* Median survival in months with ranges after exclusion of 4 postoperative deaths.

Discussion

Although not included in this study because of the heterogeneity of disease, we have similarly treated 38 patients who had other types of metastatic cancer of the liver. Of those, 15 patients conformed to the criteria for this study and their results are as follows. There were 4 patients with breast cancer, 3 with melanoma, 3 with leiomyosarcoma of the small bowel, two with gastric cancer, two with carcinoid tumor and one with pheochromocytoma. Five of 15 patients had tumor vascularity of Grade III (33%): two patients with leiomyosarcoma, two with carcinoid and one with pheochromocytoma. The median survival was 20 months (ranging from 6–39 months) from the time of diagnosis of hepatic metastases and 17 months (ranging from 6–34 months) from the time of operation for hepatic artery ligation. Four patients had Grade II tumor (27%) and the median survival was 7 months (ranging from 6–28 months) after diagnosis, and 3 months (ranging from 2–5 months) after operation. Six patients had Grade I tumor (40%) and the median survival was 8.5 months (ranging from 3–23 months) after diagnosis and 3 months (ranging from 2–20 months) after operation. Despite the variety of tumors, those findings are surprisingly in agreement with the results obtained in this study: the more vascular the tumor, the better the prognosis following hepatic artery ligation and infusional chemotherapy.

Results of the study demonstrate a close correlation between angiographic vascularity and arterial dependency of tumor: the more vascular the tumor, the more dependent to the hepatic artery for their survival. Therefore, an effective destruction of very vascular tumors can be achieved by interruption of the hepatic artery and infusion of chemotherapeutic agents through a catheter in the hepatic artery. Chemotherapy is given to treat residual disease which survived ischemic injuries following hepatic arterial ligation. In hypovascular tumors, however, neither ischemic necrosis of the tumor, nor selective delivery of chemotherapeutic agents is suitable by using the hepatic artery. This would explain the poor clinical results in tumors with Grade I vascularity in this study.

Of interest is the high incidence of acute renal failure after ligation of the hepatic artery. Acute renal failure developed in 5 patients and only one survived after 4 weeks of hemodialysis. All 5 patients had very vascular hepatoma. Destruction of tumors following ligation of the hepatic artery in those patients may have been too effective. Hyperuricemia or release of vasoactive substances secondary to massive necrosis of tumors may be important factors contributing to the development of postoperative renal failure.[5]

It appears from this review that the portal vein may be more important than the hepatic artery in nurturing hypovascular tumors. Honjo et al.[4] reported a good response following portal vein ligation in the treatment of hepatic tumors of various origins. Of particular interest in their report is that the result of portal vein ligation for hepatoma is conspicuously opposite to that of ours: average survival of 5.8 months in 5 patients with very vascular tumor and 15.4 months in 4 patients with hypovascular tumor. Although they did not employ infusional chemotherapy, in our experience, postoperative chemotherapy is an essential part of treatment for hepatic tumors following hepatic artery ligation.[2]

It may then be concluded that the treatment of hepatic tumors in the form of circulatory deprivation and infusional chemotherapy should be individualized according to the findings on preoperative hepatic angiogram. Highly vascular tumors may be best treated by ligation of the hepatic artery followed by infusional chemotherapy via the hepatic artery, whereas hypovascular tumors may be treated by ligation of the portal vein followed by in-

TABLE 2. *Tumor Vascularity and Survival*: Metastatic Colon Cancer*

Tumor Vascularity	No. Patients	From Hepatic Artery Ligation	From Diagnosis
Grade I	8 (38%)	4 (1–13)	7.2(2.5–19)
Grade II	10 (48%)	10.5 (1–12)	14.5(11.5–21)
Grade III	3 (14%)	11 (10–12)	17 (15 –22)
Overall	21	7 (1–13)	13 (2.5–22)

* Median survival in months with ranges.

fusional chemotherapy via the portal vein. The portal vein cannot be ligated without producing subsequent portal hypertension. Because of that reason, only the right or left branch of the portal vein correspondent to the location of major neoplastic involvement should be ligated and cannulated. Thereafter, the remaining portal vein branch or the hepatic artery may be cannulated for infusional chemotherapy of residual diseases.

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