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METASTATIC CANCER IN THE LIVER

James Shorey M.D.

OUTLINE

I. Metastatic Cancer in the Liver: General Considerations

A. Introduction

The liver is one of the organs most commonly involved in metastasis of primary cancers. When present, such hepatic involvement is often the proximate cause of death. Although in Western countries metastatic cancer in the liver (MCL) is many times more common than primary liver cell cancer (hepatoma), the latter, perhaps because of interesting clinical and epidemiologic considerations, has been reviewed more extensively in the medical literature.

The present survey concerns the secondary involvement of the liver by metastases from extrahepatic solid tumors. Primary liver cancers, although themselves prone to spawn intrahepatic metastases, are discussed only with regard to the differential diagnosis of MCL.

B. The Liver as a Favored Site of Tumor Metastasis

The liver is among the most common sites of cancer metastasis (Table 1). As shown in Table 2, this is true whether venous blood from the primary tumor first enters the portal vein or a systemic vein, although splanchnic bed tumors (gastric, pancreatic, colo-rectal) produce hepatic metastases disproportionately often (Table 3) (3,4). These data, plus the findings in animal studies (5,6) in which the passage of tumor cells through capillary beds has been demonstrated, indicate that the location of metastatic tumor growth is not determined simply by the trapping effect of the first capillary bed encountered by the blood-borne cancer cell.

Table 2

—Metastases in Liver and Lungs Grouped According to Relation of Primaries to Circulation. 910 Cancers from 6,047 Necropsies at U.C.H. over 20 Years (2)

Site of Primary Cancer	No. of Primary Cancers	Percentage Showing Metastases in	
		Lungs	Liver
Blood Flow Passes to Lungs First			
Breast	49	45	64
Uterus	37	11	24
Ovary	27	11	48
Kidney	19	31	40
Thyroid	10	70	20
Prostate	23	17	9
Blood Flow Passes to Liver First			
Lung	302	—	38
Stomach	144	15	68
Large intestine ..	129	12	40
Pancreas	48	15	58
Gall-bladder and bile ducts ..	31	19	45
Small intestine ..	6	—	33

Table 3

COMMON LOCATION OF METASTASES OF CARCINOMAS ARISING FROM EIGHT DIFFERENT PRIMARY SITES (3)

Listed in Order of Frequency

*Site, metastasis**	*Primary site of carcinoma*							
	Breast	*Lung*	*Stomach†*	*Colon*	*Rectum*	*Ovary*	*Kidney‡*	*Pancreas*
Liver	4	2	1	1	1	3	3	1
Lung	1	1	3	2	2	5	1	3
Pleura	3	5	5	6	6	6	—	—
Bone	2	4	—	—	4	—	2	5
Adrenal	5	3	6	4	5	—	4	4
Peritoneum	—	—	2	3	3	1	—	2
Pericardium	6	6	—	—	—	—	—	—
Kidney	—	—	—	—	—	—	5	—
Pancreas	—	—	4	—	—	—	—	—
Ovary	—	—	—	5	—	—	—	—
Diaphragm	—	—	—	—	—	2	—	—
Uterus	—	—	—	—	—	4	—	—

Table 1

LOCATION OF TUMOR METASTASES

500 CONSECUTIVE AUTOPSIES OF CANCER PATIENTS

(Willis, 1952) (1)

Primary Tumors	Number of Cases	Number of Cases with Metastases in: Liver	Lungs	Bones	Adrenal Glands	Kidneys	Brain	Spleen
Carcinomas								
Head and Neck	64	14	19	5	5	8	1	2
Esophagus	17	7	3	1	-	1	2	-
Stomach	85	39	19	6	4	-	1	-
Colon/Rectum	65	33	8	1	3	3	1	1
Biliary Tract/Liver	18	8	3	2	-	2	-	-
Pancreas	11	8	2	2	1	-	1	-
Breast	45	22	28	21	9	7	7	4
Uterus	30	6	6	1	-	1	-	-
Ovary	9	1	2	-	-	-	-	-
Prostate	15	3	6	3	1	-	-	1
Kidney	10	5	8	4	2	4	3	-
Lung	27	15	9	8	12	4	9	1
Thyroid	6	2	6	3	2	3	-	-
Other	18	10	9	2	3	2	1	3
Sarcomas	26	2	11	6	1	-	1	-
Melanoma	4	2	3	1	3	1	2	-
Other Metastasizing Tumors	5	3	5	2	-	2	-	2
Non-Metastasizing Tumors	45	-	-	-	-	-	-	-
Totals	500	180	147	68	46	38	29	14
Percentages of Total	100%	36	29	14	9	8	6	3

Eighty-seven years ago Paget (7) observed the high frequency of breast cancer metastases to the liver and the relative "immunity" to secondary implants of other organs with a comparable arterial blood supply such as the spleen and kidney. He emphasized the concept that the liver offered a better "soil" for secondary tumor growth than did these other tissues in which cancer cells were as likely to lodge. The observation that various types of liver injury in experimental animals promote the development of metastases (8,9) does not necessarily contradict the "favorable soil" concept.

In addition to mechanical trapping of tumor cells and favorable "soil," a third factor in determining where a circulating cancer cell takes root and grows may be tumor cell membrane properties which promote attachment to capillary endothelium in one tissue in preference to another. Such membrane properties are exhibited, for example, by a mouse tumor line, developed by Fidler, which exhibits a selective propensity to form pulmonary metastases (10). Starting with the B16 melanoma tumor which causes multi-organ metastases when injected intravenously, lung implants were removed and injected into other mice. The procedure was repeated for several "generations." With each repetition of the cycle an increasing proportion of metastases appeared in the lungs. Nicholson (11) demonstrated that Fidler's "pulmonary metastasis" cell lines, in tissue culture, caused greater aggregation of suspended lung cells than did the parent tumor cells, and the degree of aggregation was progressively less in earlier generations of the lung tumor line (F13>F10>F5>F1). Bosmann (12), studying the same tumors, observed significant differences in cell surface proteases and glycosyltransferases as well as in electrophoretic mobilities between cells of the lung-specific tumor and the parent tumor.

At present, therefore, there is reason to believe that factors relating to tumor cell membranes ("seed"), local tissue environment ("soil"), and mechanical tumor cell trapping all may contribute to the relatively high frequency of metastatic tumor development in the liver (6).

C. Gross and Microscopic Patterns of MCL

Liver metastases most often develop as nodular growths scattered randomly throughout both lobes of the liver (13). Those on the surface may be umbilicated. Most are pale in color but melanoma metastases may be brown or black. Occasionally the majority of implants are in just one lobe of the liver. Such a selective distribution of implants, at least in the case of splanchnic bed primary tumors, has been explained on the basis of "streamlining" of portal blood flow so that venous blood from a given abdominal organ consistently enters only one hepatic lobe (14,15); others find no evidence of streamlining in humans (16,17). Alternatively, Willis (1) has suggested that clustered metastases may represent "second generation" tumors derived from cancer cells shed into the portal vein by a more proximally located "primary" metastasis (Figure 1).

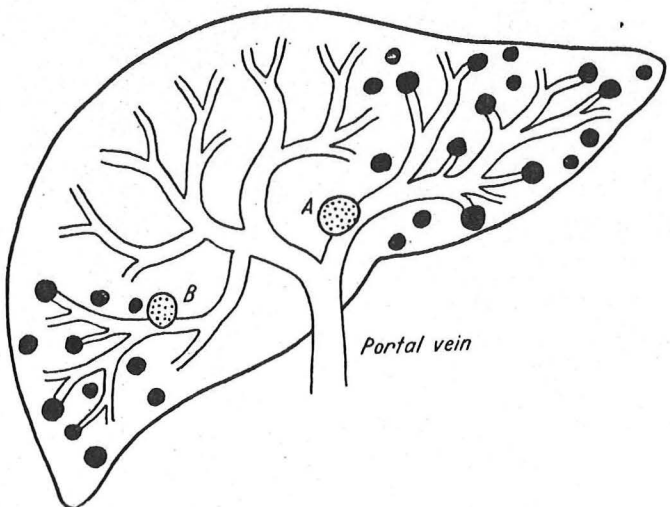


FIG. 1.—Diagram of intrahepatic metastasis. At *A* an initial metastatic (or primary) growth has invaded a main branch of the portal vein and produced daughter metastases throughout the corresponding lobe. At *B* an initial metastasis has invaded a peripheral branch vein and produced daughter metastases in a correspondingly restricted region of liver. (1)

Metastatic tumors typically grow as expanding masses, progressively replacing surrounding liver tissue. Arteries and bile ducts are more resistant to destruction than parenchymal cells (1). Uncommonly metastases may grow instead by infiltrating widely within the sinusoids without destroying the parenchymal cells. This growth pattern, leading to massive hepatomegaly, has been observed most often with metastatic melanoma and carcinomas of the breast, lung, and stomach (18).

It has long been recognized that the blood supply of hepatic tumors, both primary and metastatic, comes almost exclusively from the hepatic artery. This has been demonstrated repeatedly in patients (19-21) as well as in experimental animals (20,22). Venous drainage from liver tumors is most often into the portal vein, rather than the hepatic vein (23).

D. Cirrhosis and MCL

Several earlier reports in the literature had indicated that metastatic cancer is less likely to be found in the cirrhotic than in the non-cirrhotic liver (24-28), but this has been denied in more recent reports (29-32). When viable tumor cells are injected into the portal vein of experimental animals, those with cirrhotic livers actually develop a strikingly larger number of hepatic implants than occur in non-cirrhotic animals (32,33). Several autopsy studies of this issue have suffered from a lack of proper controls, considering age at death, sex, and type of primary tumor. The best controlled series, in which no difference was found in the frequency of MCL in cirrhotic and non-cirrhotic subjects with cancer, was weakened (perhaps inevitably in view of the necessary subgrouping) by the small numbers of subjects in each group (31).

The impressions gotten from review of these reports are: First, that patients with cirrhosis are less likely to have cancer at the time of death. This appears to be due largely, perhaps entirely, to the earlier mean age of death in cirrhotic patients as compared to cancer patients generally (28,30,32,33). Second, that at the time of death cirrhotic patients with primary extrahepatic cancers may have liver metastases less often than non-cirrhotic cancer patients (28,29), due to a tendency for shorter survival of the cirrhotic subjects after onset of cancer (28,31,32). But, finally, at a comparable stage of tumor advancement, as indicated by the number of different organ sites of metastasis, MCL is found as commonly (28), or more so (32), in the cirrhotic, as in the non-cirrhotic patient.

E. Clinical Features

The clinical manifestations of MCL were reviewed by Fenster and Klatskin (34) in a series of 81 patients whose hepatic tumors were diagnosed by needle biopsy. These authors emphasized that most of their patients were evaluated at an advanced stage of tumor progression, a point to be considered with respect to the percentage data in Tables 4 and 5.

Table 4

SYMPTOMS REFERABLE TO THE LIVER
IN 81 PATIENTS WITH PROVEN MCL

(Fenster and Klatskin, 1961)

	Number of Patients (Percent)	
Hepatic Pain	29	(36)
Ascites	25	(31)
Jaundice	22	(27)
Palpable Mass	6	(7)
No Hepatic Symptoms	27	(33)
Non-specific Complaints Suggestive of Tumor	77	(95)

The major symptoms presented by these patients are listed in Table 4. Two-thirds of them had complaints referable to the liver, the most frequent being pain in one-third of the cases, followed by ascites, jaundice, and a mass noted by the patient. In addition, 95% of the patients had non-specific symptoms suggestive of cancer including weight loss (80%), anorexia (69%), gastrointestinal symptoms (62%), and fever (23%).

Pain was localized in the right upper quadrant of the abdomen in most cases, was sharp and intermittent in character, and often radiated to the right infrascapular area or into the right flank. The pain tended to worsen with deep breathing, coughing, and postural changes. Local tenderness was often present in the area of the pain.

Fever was present in almost a quarter of patients, in whom evidence of infection was absent. Indeed, this was the initial complaint in 6 of the 81 patients, which had led to medical evaluation. Generally, the fever was low grade, but in 4 patients temperatures ranged between 102° and 106° F. Four patients had night sweats. All types of primary tumors were represented among the febrile patients.

A small proportion of patients with MCL may present a combination of features including right upper quadrant abdominal pain, fever and leukocytosis, apparently reflecting tumor necrosis, which may raise the suspicion of intra-abdominal sepsis. On occasion, the intensity of these findings may be sufficient to suggest the development of an acute abdominal emergency (35).

F. Physical Findings

Abnormalities on physical examination noted in Fenster and Klatskin's patients are listed in Table 5. The high frequency of hepatomegaly (89%) is a further reflection of the far advanced disease in this series of patients. The liver was abnormally firm in the majority of these cases, including all those with palpable but normal-sized livers. Variations in consistency on palpation of different areas

of the liver were occasionally noted. Hepatic tenderness was diffuse in some patients and localized, especially in areas of palpable nodules, in others. A friction rub was heard over the liver in 10% of the patients, most often just beneath the costal margin. Four of the 8 patients with an audible rub also had severe right upper quadrant abdominal pain. The frequency of hepatomegaly in patients with MCL has been lower (60% (4), 52% (36), 70% (13)) in other reported series. Massive hepatomegaly is particularly associated with metastases from melanoma and colonic carcinoma (1, 37), as well as tumors manifesting diffuse intrasinusoidal growth, as discussed above (18).

Table 5

LIVER ABNORMALITIES ON PHYSICAL EXAMINATION IN 81 PATIENTS WITH PROVEN MCL

(Fenster and Klatskin, 1961)

	Number of Patients (Percent)
Abnormalities of Liver — Total	77 (95)
Hepatomegaly	72 (89)
6 - 10 cm Below Costal Margin	48
> 10 cm Below Costal Margin	24
Induration	62 (77)
Tenderness	52 (64)
Nodularity	43 (53)
Friction Rub	8 (10)

It is important to recognize that hepatomegaly, accompanied by abnormal liver function tests, is occasionally seen in patients with renal cell carcinomas in the absence of metastases (38). Following resection of the primary tumor the liver function abnormalities and liver enlargement may subside. A similar phenomenon is recognized in some patients with localized Hodgkin's disease remote from the liver (39-41). Primary tumors causing extrahepatic biliary tract obstruction may cause hepatomegaly by this mechanism in the absence of liver metastases.

II. Diagnosis of Metastatic Tumor in the Liver

The diagnosis of MCL becomes an issue under various circumstances: First, as a differential diagnostic consideration in the patient with evidence of liver disease of undetermined nature; second, in the patient with known primary tumor for which treatment and prognosis will differ according to whether or not metastasis has occurred; and third, in the patient who has undergone past resection of a primary tumor with intent of cure and in whom there is reason to suspect development of "metachronous" metastatic tumor in the liver.

The mistaken diagnosis of MCL may deprive the patient of potentially curative primary tumor treatment, while, on the other hand, failure to detect liver metastases when present could lead to unnecessarily extensive surgery without prospect of increased benefit.

Among the rare cases of successful resection of hepatic tumor metastases, several have occurred in persons found to have a solitary implant or a small number of adjacent metastases recognized months to years after excision of the primary cancer.

Many possible sources of information are available for diagnosis of MCL including physical examination, blood tests, radionuclide imaging (liver "scanning"), percutaneous liver biopsy, peritoneoscopy, angiography, and sonography. These measures are discussed individually in the following pages, after which their rational application is considered.

A. Laboratory Tests for Diagnosis of Metastatic Cancer in the Liver

The value of a laboratory test for the diagnosis of a particular disease can be described in terms of the test's sensitivity, specificity, and overall accuracy (Table 6). Sensitivity refers to the likelihood that the test will be positive when the disease is present; specificity concerns the probability that the test, when positive, actually reflects the disease in question rather than some other condition.

Table 6

DIAGNOSTIC ACCURACY OF LABORATORY TESTS

	Disease Present	Disease Absent	
Test Positive	A True Positive	B False Positive	A + B
Test Negative	C False Negative	D False Positive	C + D
	A + C	B + D	Total

$$\text{Sensitivity} = \frac{A}{A + C} \qquad \text{Specificity} = \frac{A}{A + B}$$

$$\text{Overall Accuracy} = \frac{A + D}{\text{Total}}$$

While the "overall accuracy" figure has the apparent advantage of expressing the value of a test as a single number, and is often cited in the literature dealing with laboratory tests, its weakness lies in the possibility of its having a deceptively high value, even for a very weak test, when a relatively large control group is employed. Table 7 provides an example of a test whose poor sensitivity and specificity would make it virtually useless in clinical practice but whose "overall accuracy" is an apparently respectable 88%.

Table 7

HYPOTHETICAL DATA ILLUSTRATING THE POTENTIAL WEAKNESS OF THE "OVERALL ACCURACY" TERM

	Disease	No Disease	
Test Positive	2	5	7
Test Negative	8	95	103
	10	100	110

Sensitivity $\frac{2}{10}$ = 20% Specificity $\frac{2}{7}$ = 29%

Overall Accuracy $\frac{97}{110}$ = 88%

For quantitative tests, as well as tests subject to graded interpretation, such as liver scans, one can maximize specificity by raising the threshold of positivity, but obviously this is done at the cost of reduced sensitivity. However, since even the best non-histologic tests for MCL are generally not considered sufficient proof for or against liver tumor to be the basis of a therapeutic decision, these "inferential tests" (42) must be regarded as screening tests, and as such their threshold of positivity must be set low enough to favor sensitivity above specificity.

B. Blood Tests

The serum alkaline phosphatase test (AP) has been the single most popular test for detection of MCL for several years (43-52). Several different methods have been employed for measurement of this enzyme, but the choice of method apparently has little effect on the diagnostic strength of the test.

The combined data from the series of studies cited above, in which the accuracy of AP for detection of hepatic tumor metastases was tested, reveal an overall sensitivity rate of 65% and specificity of 76% (Table 8). The high specificity figure reflects the fact that the majority of the patients in these reports had known primary tumors, rather than their presenting the spectrum of acute and chronic liver diseases which the clinician is ordinarily obliged to distinguish from MCL.

Table 8

Accuracy of the Alkaline Phosphatase Test as an Indicator of MCL
Data from 6 Studies (47-52)

Total Number of Patients	True Positive	False Positive	True Negative	False Negative
1001	251	78	526	146
Sensitivity	63%		Specificity	76%

The leucine aminopeptidase (LAP) and 5-nucleotidase (5-NT) tests are useful alternatives to AP in attempting to determine whether an elevated serum AP level is due to bone or liver disease, but they otherwise offer no additional information for the diagnosis of MCL (53-55).

Another alternative test to AP, gamma glutamyl transpeptidase (GGT) may be more sensitive than AP for detection of liver metastases (Figures 2 and 3), and this possibility deserves further investigation (55-59).

Figure 2 (57)

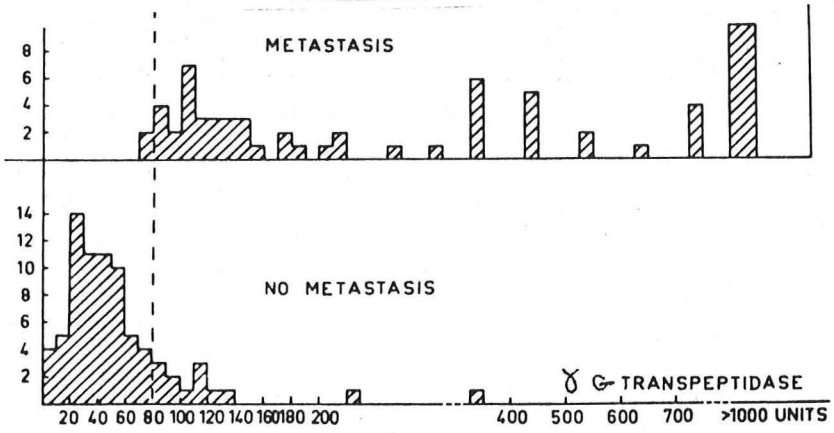
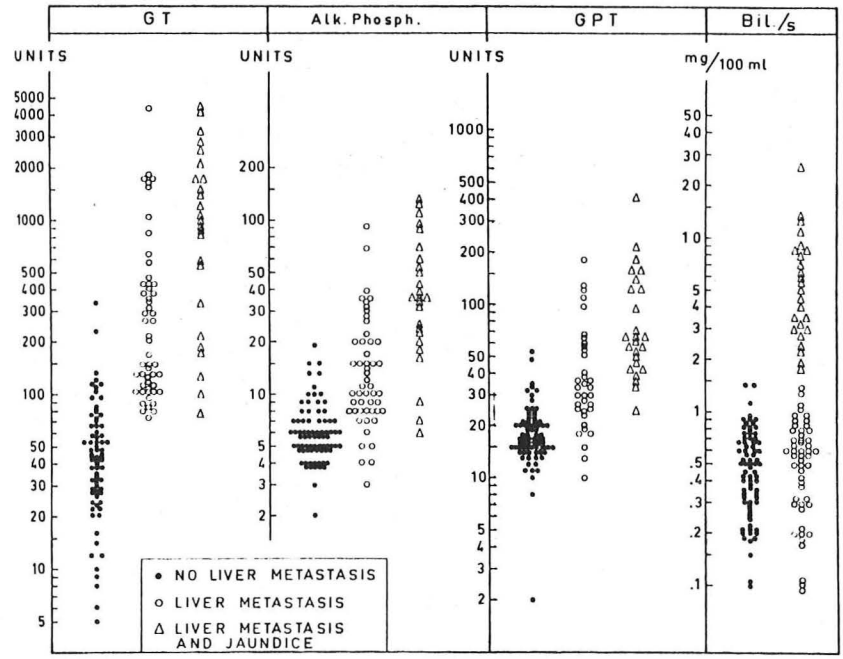


Figure 3



GT, APh, GPT and bilirubin in the groups without and with liver tumour. The latter group is subdivided into anicteric and icteric cases. Logarithmic scale. (57)

Aronsen studied the distribution of AP and GGT in hepatic tumors and the surrounding liver tissue using histochemical techniques (60). He observed that,while no tumors contained AP, 8 of 25 had demonstrable GGT activity. Both enzymes were increased in liver tissue, especially in the vicinity of the tumor. The strong AP stain in the walls of dilated sinusoids close to the tumor was thought to be related to tumor vascularization.

A variety of other liver function tests, including the transaminases (49,50,61), total and direct-reacting bilirubin (45,52,57), lactic dehydrogenase (50), and bromsulphalien (BSP) retention (43,45,48) have all been reported to have some diagnostic capacity for MCL but, even when used in combination with AP, contribute no more than a minor improvement to the diagnostic power of the AP test alone (48,49,52,61,62).

Alpha-fetoprotein, when present in the serum in high concentration, is strong evidence for the presence of primary hepatocellular carcinoma. The test might be useful when hepatoma is a differential diagnostic consideration in a patient with suspected MCL. Its usefulness in such a case is lessened, however, by the observation that a positive alpha-fetoprotein test has been reported in a few cases of gastric and bronchogenic carcinomas and carcinoid tumors metastatic to the liver (63,64).

C. Hepatic Artery Angiography

Arteriography may be helpful in distinguishing hepatic tumor from other lesions such as cysts, abscesses, or cirrhosis in patients with hepatomegaly

and abnormal liver function tests (65-69). Hepatomas tend to be highly vascular, as do hepatic metastases from carcinoid tumors, islet cell carcinomas, renal cell carcinomas, and leiomyosarcomas (Table 9). In tumors such as these, implants of 1 cm or less in diameter may be demonstrable by arteriography (66). On the other hand, certain other tumors are more likely to have relatively avascular liver metastases; these include adenocarcinomas of the pancreas, bile ducts and gallbladder, and squamous cell carcinomas of the lung and esophagus (66,67,70-75). In series of unselected cases, liver metastases were most often (approximately 70%) fairly avascular, and such metastases may escape detection by angiography if they are less than 3 cm in diameter (69).

Table 9

HEPATIC TUMOR VASCULARITY AS DETERMINED BY ARTERIOGRAPHY (74)

(Watson *et al.*, 1971)

	Degree of Vascularity (Number of Patients)				
	Least Vascular 0	1	2	3	Most Vascular 4
Hepatoma	0	0	5	9	10
Cholangiocarcinoma	1	2	3	0	0
Metastatic Carcinoma	1	12	18	6	0

Angiographic evidence of hepatic tumor includes macroscopic tumor neovasculature, tumor stain or "blush," puddling or pooling of contrast medium, arteriovenous shunting, vessel encasement, arterial stretching and displacement (usually by relatively large tumors) and, with avascular tumor, lucencies in the hepatogram phase when normal liver tissue is diffusely opacified. (65,67,69,71,72,74,76).

Some authors (65,71,72) but not others (73) report better visualization of hepatic tumors with infusion of epinephrine prior to injection of contrast medium. Using this technique, improved contrast may result from the relative insensitivity of tumor vessels, as compared to normal hepatic vessels, to the vasoconstrictive effect of the drug.

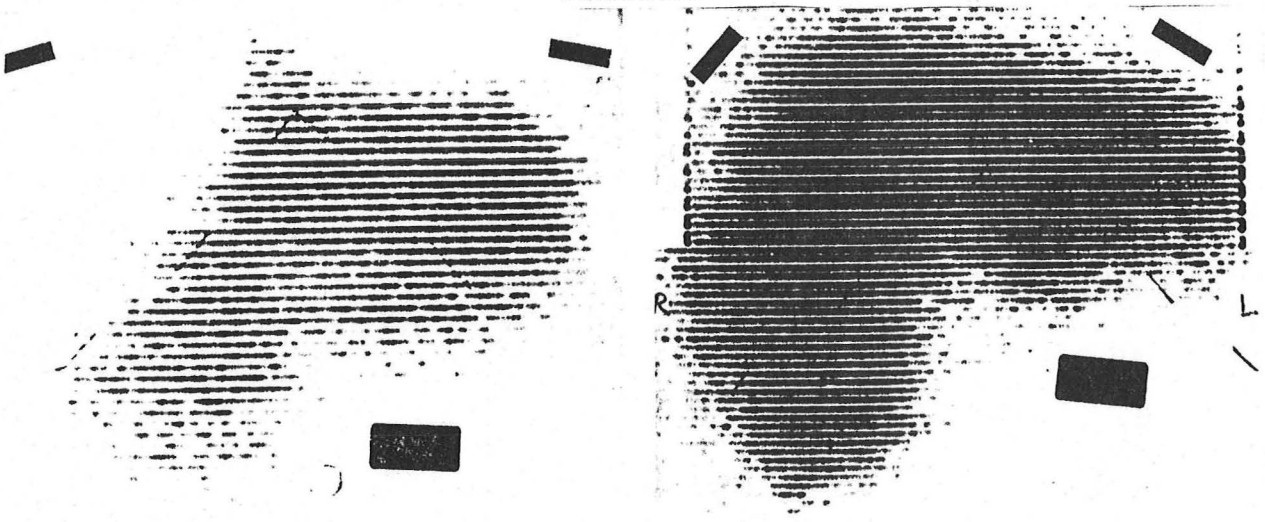
Although celiac axis arteriography may permit visualization of MCL (74), superselective hepatic artery catheterization is generally preferred (72).

Since angiography is an invasive procedure involving a certain small risk to the patient (77), is relatively expensive and time-consuming (78), and in general may be no more sensitive than simpler tests for diagnosis of MCL, its use should be confined to selected cases: for the differential diagnosis of hepatic disease, especially when there is suspicion of hepatoma, or where evidence of liver metastasis is present in patients with primary tumor types associated with highly vascular metastases (70,79).

D. Radionuclide Liver Scanning

During the past decade radionuclide scanning, as much as any other single test, has been relied upon for detection of hepatic tumor metastases. Liver scanning offers the advantages of a non-invasive procedure which can be performed quickly and at reasonable cost, without causing excessive discomfort to the patient. It has the potential of demonstrating the size and location of intrahepatic lesions, allowing, in some cases, direction of the percutaneous biopsy needle to a tumor site (80,81). With sequential scans, the response of intrahepatic tumor to therapy can be assessed more objectively (82,83) (Figure 4). Periodic re-scanning at six-twelve month intervals after apparently curative resection of a primary tumor has been advocated as a means for identifying potentially resectable "metachronous" liver metastases (84), although the benefit to the patient of such early tumor discovery is generally dubious.

Figure 4



. On left is liver scan of woman with metastatic sarcoma (proven at laparotomy). Radiation therapy was given. Scan on right was taken 8 months later. For size determination, date marker is 3.8 cm long. Costal margin is marked.

Technetium (^{99m}Tc) sulfur colloid, the radionuclide preparation currently used most often, is taken up by phagocytic sinusoidal cells of normal liver tissue. Tumor implants, being deficient in such phagocytic cells, fail to trap radionuclide and thereby become identifiable as "filling defects" against the background of more normal tissue.

The accuracy of hepatic scanning for detection of MCL has been the subject of a large number of reports in recent years. Data gathered from 22 papers, in which sensitivity, specificity, and overall accuracy could be determined, are given in Table 10 (49-52,69,85-101). These studies are not all comparable because of the use of various radioisotopes (^{198}Au, ^{131}I-Rose Bengal, ^{99m}Tc) and imaging techniques (rectilinear scanner, gamma camera scintigraphy), differing patient populations (all patients referred for scanning, or only patients with known primary tumor; patients with or without strong evidence of MCL such as hepatomegaly and abnormal liver function tests; general hospitals versus specialized tumor centers), and differing interpretation of equivocal scan patterns as either positive or negative for MCL. For these reasons, the figures in Table 10 are offered as an approximation, rather than as a precise indication of the accuracy of this method of tumor diagnosis. Wherever data on equivocal scans are given in the reports reviewed, these are recorded arbitrarily in this tabulation as "positive for MCL," tending to maximize *sensitivity* at the expense of *specificity*. This approach would appear to be a reasonable routine practice in scan interpretation since the basic purpose of such screening procedures is to alert the physician to the possible presence of metastatic tumor, which is ultimately to be proven or excluded by other means such as percutaneous needle biopsy, peritoneoscopy, or laparotomy (96). While none of these measures can absolutely exclude the existence of liver metastases, the results of these inferential tests, including the scan, will influence the degree of vigor with which histologic proof of tumor is pursued.

Table 10

ACCURACY OF LIVER SCANNING FOR DIAGNOSIS OF HEPATIC METASTASES (Combined data from 22 studies)

	MCL	No MCL	
Positive Scan	1366	534	1900
Negative Scan	382	2105	2487
	1748	2639	4387

Sensitivity	78.1%
Specificity	71.9%
Overall Accuracy	79.1%

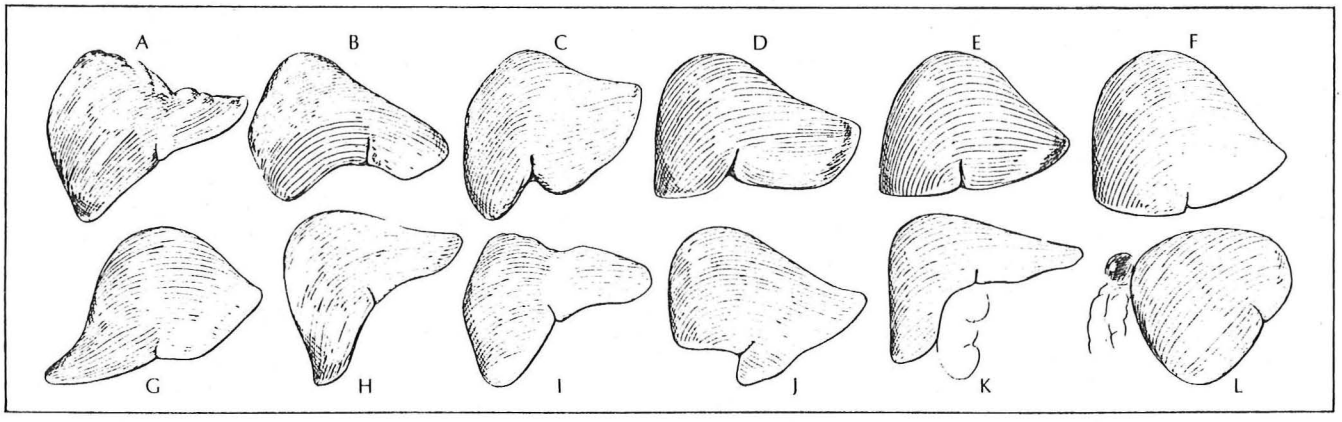
Evidence for MCL on liver scan includes (a) focal "filling defects" which are the most characteristic abnormality, and (b) diffusely abnormal isotope uptake, which is the most common pattern for hepatic lymphoma (41, 102) and multiple small carcinomatous implants, and (c) hepatomegaly. The

diffusely abnormal uptake pattern and/or hepatomegaly are considerably less specific indicators of MCL than are focal defects. Hodgkin's disease and other lymphomas in the liver may cause focal scan defects but more often are associated with diffuse abnormality, hepatomegaly and often splenomegaly (36,41,102). Hepatomegaly and at least moderate splenomegaly both may be present in lymphoma patients without actual tumor infiltration into these organs (39,41).

False positive scans for metastatic liver tumor are most often due to one of the following factors (49,103,104):

(a) anatomic variations in liver shape and silhouette (Figure 5),
(b) other space-occupying lesions, such as cysts or abscesses (105),
(c) diffuse parenchymal liver diseases such as cirrhosis, fatty liver, or hepatitis (106,107) especially when these conditions produce focal scan defects. The presence of splenomegaly often with increased splenic isotope concentration, and "shunting" of radionuclide to the bone marrow, strongly suggest the presence of cirrhosis (91); however, it is important to keep in mind that these changes, reflecting portal hypertension, may be due to MCL alone (108-110), and also to recognize that, as discussed above, the cirrhotic liver is not "immune" to metastatic tumor invasion,
(d) defects due to extrahepatic masses (pressure causing diminished local perfusion?) such as tumor or a distended gallbladder,
(e) recent trauma, including liver biopsy (111), hepatic infarction (112),
(f) primary hepatic tumors (hepatocellular carcinoma, cholangiocarcinoma) (113).

Figure 5



The liver also has widely variant normal configurations: (A) typical triangular shape, 41%. (B) triangular with concave inferior border, 6%. (C) definite hilar indentation, 15%. (D) square liver, 12%. (E) "gendarme's hat" associated with high diaphragm, 14%. (F) globular liver, 3%. (G) hornshaped, with concave right lateral corner due to rib cage, or (H) downward extension of right lobe, 4%-5%. (I) superior accessory lobe, or (J) absent or notched inferior tip, 1%-2%. (K) indented inferior margin due to right kidney, or (L) congenital interposition of colon between the liver and the lateral abdominal wall, rare.

False negative scans, contributing to a reduced sensitivity for detection of MCL, are most often attributed to the presence of metastatic tumors less than 2 cm in diameter, the limit of resolution for present equipment (36,49,66). Resolution may be further reduced by excessive respiratory or other movement of the patient (13). Deep-seated lesions may not be recognized. Several cases are reported, however, where fairly large tumors, located at the liver surface, are undetected for unknown reasons (49, 90).

An additional factor affecting liver scan accuracy is observer error (Table 10.1). For diagnosis of space-occupying lesions (a majority of which, on statistical grounds, will be tumor metastases) inter-observer variability is reported to be about 20% (114) and intra-observer variability (*i.e.*, lack of consistency on re-interpretation of individual scans by a given interpreter at a later date) is said also to be roughly 20% (80,96). Conceivably, such inconsistency could be minimized by an initial descriptive evaluation of the scan without benefit of clinical information, followed, in the same report, by an overall interpretation made with knowledge of all data concerning the patient. In this way it will be apparent to the primary physician how much of the scan interpretation derives from information on the scintigram itself, and how much reflects the nuclear physician's (perhaps subconscious) interpretation of additional data, recognizing that the latter interpretation may contribute substantially to assessment of the patient (80).

Table 10.1

OBSERVER VARIATION FOR IDENTIFICATION OF SPACE-OCCUPYING LESIONS* IN 99 LIVER SCANS (96)

(Ludbrook *et al.*, 1972)

Observer	Scan Interpretation					
	Without Clinical Data			With Clinical Data		
	False Positive	False Negative	Total Error	False Positive	False Negative	Total Error
A. Nuclear Physician	8	19	27	7	13	20
B. Nuclear Physician	1	21	22	1	16	17
C. Nuclear Physician	5	21	26	6	17	23
D. Nuclear Physician (Trainee)	3	19	22	3	14	17
E. Internist	11	15	26	13	12	25
F. Surgeon	12	21	33	11	15	26
G. Surgeon	2	27	29	0	21	21
Averages	6.0	20.4	26.4	5.9	15.4	21.3

*The majority of the space-occupying lesions (36/42) were tumor metastases.

While Technetium (^{99m}TC) sulfur colloid has replaced radioactive gold (^{198}Au) and radioiodinated Rose Bengal ^{131}I-RB) as the preferred radionuclide for liver scanning, this change has not substantially affected the accuracy of scanning for detection of MCL (49,92). Likewise, although use of the gamma camera, as compared to the rectilinear scanner, might be expected on theoretical grounds to improve detection of focal lesions in the liver such an advantage has not been demonstrated (115).

Recognizing that ^{99m}Tc (or ^{198}Au and (^{131}I-RB) scans identify hepatic tumors as areas of reduced isotope uptake, *i.e.*, "negative" images with their inherent non-specificity, "positive" tumor imaging has been considered a desirable goal. A few instances of positive ^{131}I scans for liver metastases from well-differentiated thyroid carcinomas have been reported (116,117). Gallium citrate (^{67}Ga) tends to concentrate in certain tumors as well as in abscesses and other inflamed tissues (118-125) (Table 11). Although most metastatic tumors fail to take up sufficient ^{67}Ga to become identifiable against the rather high background uptake of uninvolved liver tissue, primary hepatocellular carcinoma (hepatoma) does frequently produce a positive image, and such information is useful in the differential diagnosis of MCL. In addition, positive ^{67}Ga imaging of a "cold area" on a ^{99m}Tc scan, with appropriate supporting evidence, may lead to the diagnosis of a pyogenic abscess rather than metastatic tumor.

Table 11

^{67}GALLIUM SCANNING FOR HEPATIC TUMOR

Literature Survey by James *et al.*, *Gut* 15:404, 1974 (124)

	Number of Reports Cited	Number of ^{67}Ga Scans		Percent Positive
		Positive	Negative	
Metastatic Carcinoma in the Liver	7	51	38	57
Primary Liver Cell Carcinoma	7	40	5	89
Lymphoma in the Liver	7	13	3	81
Pyogenic Liver Abscess	4	16	0	100
Cirrhosis	6	1	44	2

In order to obtain additional information from the liver scanning procedure, "flow studies" or dynamic hepatic scintiangiography has been

developed (126-129). The technique involves obtaining polaroid scintigrams of the liver area with a gamma camera over 2-4 second intervals for 30-40 seconds after injecting ^{99m}Tc sulfur colloid. Static scans are then also obtained in the usual fashion. In normal subjects isotope appears in the liver 6-12 seconds after its appearance in the aorta. Under conditions where hepatic arterial blood flow is increased, as in MCL (including lymphoma) as well as primary liver tumors and cirrhosis, there is earlier appearance of radionuclide in the liver. While MCL cannot be readily distinguished from cirrhosis by this method, hepatoma or highly vascular tumor metastases may be suspected when there is high early isotope concentration in a focal area ("tumor stain") which appears later on the static scan as a "cold" defect. This presumably indicates that isotope is delivered early to such tumors because of their abundant arterial blood supply but fails to become fixed there due to a relative paucity of phagocytic cells. Hepatic abscesses may be distinguished by normal isotope appearance in the liver generally but with absence of radioactivity from the area of the lesion in both the dynamic and static scans. Primary and metastatic tumors not detected by standard scans or radiopaque arteriography have been demonstrated with this technique (128).

^{99m}Tc-Bleomycin, like Gallium, is being employed as a "tumor-seeking" agent but appears to have no advantage over ^{67}Ga for diagnosis of liver tumors (130).

E. Sonography

By ultrasonic scanning hepatic metastases may be demonstrated as diffusely scattered echoes when the liver is extensively invaded or, in other cases, as more discrete, nodular foci (131). The diffuse pattern is essentially indistinguishable from that produced by cirrhosis (132). Nodular foci may appear as solid collections of echoes, or as ring-like images which are caused by tumors of homogeneous consistency (133). Lesions of this pattern may be distinguished from fluid-filled cystic masses by increasing the gain setting of the equipment, which leads to a progressive "filling in" of the sonolucent tumor center with echoes (131).

B-mode sonography, the technique most commonly used currently, appears to be no more sensitive for detection of hepatic tumor than radioisotope scanning, offering only the advantage of distinguishing solid from cystic masses (132,134-136). Implants less than 2 cm in diameter, and some considerably larger, are not identified. The more recently developed gray-scale modification, in which echoes are visually displayed in five different grades of brightness according to the strength of the echo signal, appears to result in substantially improved image resolution (137-139). Intra-hepatic masses as small as 5 mm in diameter have been demonstrated by this technique, but how consistently this can be accomplished in the tumor-invaded liver, and with what degree of specificity, is yet to be determined.

It has been suggested, without extensive supporting evidence, that sonography may be an especially useful method of observing hepatic tumor response to therapy (140). In some cases the intensity of echoes from tumor implants increased abruptly following initiation of chemotherapy, possibly indicating a positive therapeutic response to the drugs (139). Sonography may have an advantage over radioisotope scanning for this purpose, since the latter is dependent on phagocytic cell trapping of colloidal isotope, and the function of these cells may be impaired following therapy.

A specially designed sonographic transducer incorporating a central canal through which an aspirating needle may be passed has been employed for puncture of hepatic masses under direct sonographic guidance (141,142). While lesions as far as 15 cm from the surface of the body have been punctured by this means, the studies, to date, have employed a fine bore needle (0.6 mm) capable only of obtaining a cellular suspension suitable for cytologic studies but not for direct histologic examination.

Computerized Axial Tomography

Computerized axial tomography, a radiologic technique used with impressive results for brain scanning, has more recently been modified for transverse scanning of the trunk. Whether this technique will be of value for identification of hepatic metastases has not yet been discussed in the literature.

F. Liver Biopsy

1. Percutaneous "Blind" Needle Biopsy

Among the various diagnostic tests for MCL only a positive biopsy can be regarded as proof of tumor*. The simplest approach for liver biopsy is by the percutaneous needle technique.

In earlier years there was considerable concern among some clinicians about the increased risk of biopsing a liver invaded by metastatic tumor. In a review of over 20,000 percutaneous liver biopsies performed prior to 1953, there were 17 deaths, including 5 patients with MCL who died of intraperitoneal hemorrhage (143). One of these patients had a prothrombin content of 40%, which currently would be regarded as a contraindication to the procedure; another patient, who had no coagulation studies before biopsy

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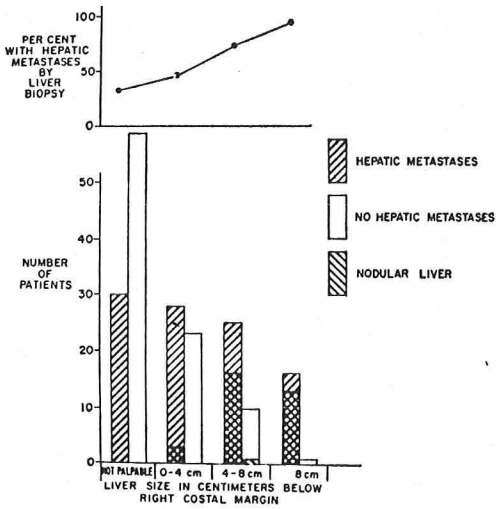
*On occasion tumor tissue recovered with the percutaneous liver biopsy needle has come from an extrahepatic tumor site such as diaphragm or pleura. However, apart from the rare case of a primary tumor in this area, the practical implication of this finding, *i.e.*, that a primary tumor has metastasized, will be essentially the same as for actual MCL.

was said to have breathed while the needle was in the liver and was noted at autopsy to have a 1 cm rent in the liver capsule. A third patient, curiously, was described as "moribund" at the time of biopsy. Fisher and Faloon (144) reported 5 deaths, all due to hemorrhage, among 341 patients undergoing liver biopsy. Four of these 5 patients were among the 33 patients with MCL in this series.

The biopsies in these older studies were performed with the Vim-Silverman or similar type needles. Over the past decade the majority of liver biopsies have been obtained using the simpler, quicker and safer Menghini needle. Lindner surveyed the Menghini needle biopsy experience of 99 centers, involving 79,381 patients (145). Twelve deaths occurred in this series (0.015%) including one in a patient with MCL. With appropriate precautions regarding coagulation tests and patient cooperation, Menghini needle biopsy for diagnosis of MCL, even when the presence of a highly vascular hepatoma is also a possibility, is considered to be an acceptably safe procedure. Faloon, an author of the alarming report cited above (144), has recently expressed agreement with this opinion (Personal communication).

The accuracy (more accurately, sensitivity) of "blind" needle biopsy for diagnosis of MCL has often been quoted as being about 75% based on several studies (34,43,146,147). In the majority of patients in these studies, the liver biopsy simply confirmed an existing suspicion of MCL based on the presence of hepatomegaly and abnormal liver function tests. A better test of the value of liver biopsy comes from the work of Conn and Yesner (4,44). Two hundred patients who had died with cancer capable of metastasis were subjected to percutaneous liver biopsy prior to autopsy. Two specimens were obtained, one by intercostal and one by subcostal puncture. Single specimens were positive for tumor in 45% (intercostal) or 49% (subcostal), and one or both specimens positive in 58% of cases with MCL. In cases with small numbers of tumor implants, as would be the case in patients with a normal-sized liver and normal liver function tests, single biopsies were positive in 15% and double biopsies in 20% of cases (Figure 6).

Figure 6



The relationship of liver size to the presence of palpable hepatic nodules, hepatic metastases, and the incidence of positive liver biopsies. Eight patients with underlying non-neoplastic liver disease were excluded from this graph.

In order to maximize the yield of needle biopsy for diagnosis of MCL these authors recommended, in addition to routine procurement of two biopsies, serial sectioning of all specimens not showing tumor on a single section. They observed that this increased the rate of tumor identification by 4% among their cases.

As noted above the diagnostic yield of needle biopsy was improved about 10% by obtaining two specimens rather than one. Although two separate puncture sites were used in this study, it is commonly believed that multiple (two or more) biopsies through the same anesthetized intercostal space also improves the tumor yield, but this remains to be documented.

It is suggested that directing the liver biopsy needle toward a "cold" area on liver scan (frontal and lateral) will also increase the likelihood of demonstrating intrahepatic tumor (42,81). As discussed above (see Sonography), a method has been described for directing a liver biopsy needle (for cytology) to suspected tumor sites identified by sonography under guidance of a specially designed ultrasound transducer.

It has been reported that the diagnostic accuracy of liver biopsy can be increased further by use of cytologic studies of the fluid collected with the biopsy and of a touch preparation of the biopsy specimens itself (148,149). While no false positive cytologic interpretations occurred in these studies, such a problem arose in the experience of Enriquez and Conn (257) who were unable to confirm the presence of hepatic tumor in 9 of their 11 patients who had positive cytologies and negative liver biopsies, making the reliability of this approach uncertain.

Histology of Liver Biopsy Specimens

Histologic examination of liver tissue obtained by needle or surgical wedge biopsy may provide certain evidence indicating the nature of the primary tumor of origin (34,150). Primary hepatocellular carcinoma (hepatoma) can usually be distinguished from metastatic tumor. Hodgkin's disease and other lymphomas are often specifically identified. A metastatic focus containing mucus secreting epitheloid cells is most likely derived from a primary tumor in the gastrointestinal tract, while an implant with an "oat-cell" pattern suggests that the primary tumor is a bronchogenic carcinoma. If iron or bile pigment can be excluded, pigmented cells can be identified as malignant melanoma. Overall, however, a major proportion of cancer metastases in the liver give insufficient information to permit determination of the site and nature of the parent tumor.

Histologic changes in the non-neoplastic tissue of livers containing tumor metastases have been described by Fenster and Klatskin (34). The most common observations by these authors included a mononuclear cell ("chronic") inflammatory infiltrate in the portal tracts (79%), mild to moderate periportal fibrosis (60%), fatty infiltration - usually minimal - (45%), bile duct proliferation (31%), and scattered areas of sinusoidal congestion in the absence of congestive heart failure. Interestingly, histologic evidence of bile stasis, with "bile plugs" in dilated canaliculi and

sometimes larger collections of bile surrounded by degenerating parenchymal cells ("bile infarcts"), was observed in 36% of biopsies, even in the absence of extrahepatic biliary tract obstruction and in some patients with normal serum bilirubin levels. Hepatic tissue immediately adjacent to tumor foci manifested compression atrophy and necrosis and occasionally frank infarction.

2. Peritoneoscopy

Peritoneoscopy is a procedure of increasing popularity in this country which has been used for several years in Europe and elsewhere. Under some circumstances this technique may be of great value for the detection of hepatic tumors (52,63,151-155). For this purpose, it has the advantage over blind percutaneous needle biopsy of permitting guided biopsy of suspicious areas on the hepatic surface under direct vision. The added capability of coping with excessive capsular bleeding by direct tamponade, if necessary, permits the safer procurement of multiple biopsies.

The yield of positive biopsies for tumor may be considerably better with peritoneoscopic guidance than with the blind technique. By use of guided biopsy, Jori (152) found metastatic tumor in 19 of 20 patients, only 14 of whom had positive blind biopsies. Tumor was demonstrated by blind biopsy in one of his patients with negative peritoneoscopic findings. In a cadaver study Czaja (154) found MCL in 4 of 5 subjects who were later shown to have hepatic metastases at autopsy. Blind biopsy was positive in only one of these cases.

Peritoneoscopy with liver biopsy has been especially useful in the staging of Hodgkin's disease (63) and non-Hodgkin's lymphomas (155). A positive biopsy in these cases, establishing the existence of Stage IV disease, usually makes subsequent staging laparotomy unnecessary.

3. Diagnosis of MCL at Laparotomy

Inspection of the liver at laparotomy frequently becomes the ultimate means of excluding MCL, often at a time when this determination will influence the nature of the therapy applied to the primary tumor. Examination of the liver by direct vision as well as palpation has been considered very accurate for this purpose. Hogg and Pack (156) reviewed the autopsy findings of 100 patients, who died within three days after abdominal surgery for gastrointestinal tract cancer, whose livers, at operation, had been carefully inspected and found free of metastases. Liver metastases were identified at autopsy in 5 of these cases (5%). Three of the 5 cases, however, had tumor recognizable only on microscopic sections. In a similar study by Bengmark (157) of 26 patients found free of hepatic tumor at laparotomy who died postoperatively, 3 (11%) had hepatic metastases at autopsy. The importance of documenting the neoplastic character of apparent metastatic implants by histologic examination, including study of frozen sections at the time of surgery if a therapeutic decision depends on this diagnosis, is emphasized by Bengmark's observation of 2 patients said to

have MCL by inspection at surgery, in whom no liver tumor was present at subsequent autopsy (157).

Ozarda and Pickren (13) studied the distribution of metastases in 150 autopsy cases with MCL. In 16 of these cases all metastatic implants were within the hepatic parenchyma with none at the liver surface. When these were combined with the (unstated) number of cases wherein the only surface metastases found were in subdiaphragmatic and posterior locations and essentially inaccessible to the surgeon, more than 15% of cases with liver metastases would have escaped detection at exploratory laparotomy.

Several years ago Wangensteen and associates (158) advocated "second-look" laparotomy at defined intervals following "curative" resection of abdominal cancers, in hope of identifying early local recurrences as well as focal metastases at a stage when they might be completely resectable. This approach has never become widely accepted (159). Ellis (160) has emphasized the value of re-exploration in such patients when evidence of tumor recurrence arises because, in addition to identifying resectable locally recurrent tumor, several instances of a second, independent primary cancer were observed, and other cases of benign lesions such as anastomotic strictures and adhesive bands causing bowel obstruction or deep-seated chronic abscesses were identified. However, no resectable hepatic metastases were found in this series of 100 re-operated patients.

G. Specific Comments Concerning Hepatic Involvement in Hodgkin's Disease and Other Lymphomas

In patients with Hodgkin's disease (HD) or lymphoma, recognition of liver involvement provides evidence of disseminated (Stage IV) disease and indicates the need for chemotherapy (161,162) or possibly, in the case of lymphoma patients, for total body irradiation (163). Demonstration of hepatic tumor obviates the need for staging laparotomy, which some, but not all, authorities feel is indicated for all HD and lymphoma patients except those with existing proof of Stage IV disease or with medical contraindications to surgery (164,165).

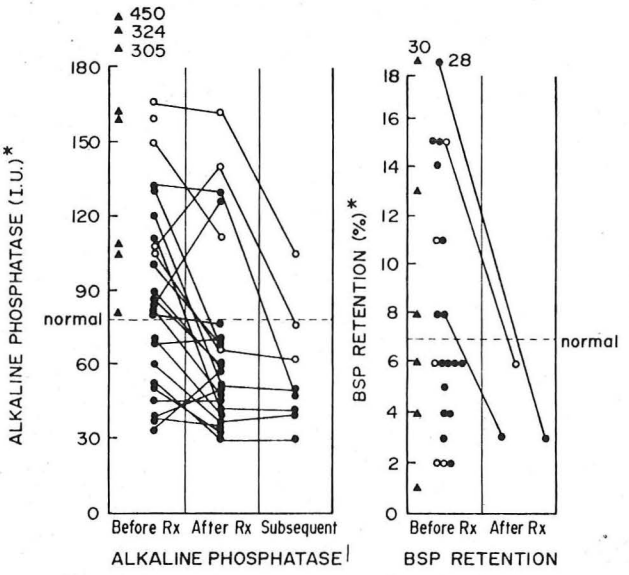
In patients with these diseases, non-histologic tests are even less useful than they are for identifying carcinomatous liver metastasis. On physical examination, moderate hepatomegaly (39) and cholestatic jaundice may be observed in patients without hepatic tumor (166). Jaundice is, of course, most often due to actual hepatic tumor or, less often, to extra-hepatic biliary tract obstruction due to lymphadenopathy, or to hemolysis (39,167,168). Marked splenomegaly, on the other hand, substantially increases the likelihood of both splenic and hepatic tumor infiltration (40,169). In HD splenic involvement almost alway precedes hepatic disease (170,171), but this is less often true for other lymphomas (155).

If one accepts the concept that all HD and lymphoma patients without already proven Stage IV disease should undergo exploratory laparotomy, it is reasonable that percutaneous liver biopsy be done first in such cases.

If the "blind" biopsy contains no tumor, peritoneoscopy may offer a further low-risk alternative to laparotomy, permitting biopsy of suspicious hepatic lesions under direct vision, as well as multiple undirected punctures with the ability to treat any capsular bleeding with direct tamponade (63).

Demonstration of Reed-Sternberg (R-S) cells on liver biopsy is the best proof of HD in the liver. Lesions lacking R-S cells but containing atypical histiocytes and having a pattern otherwise consistent with HD have been tentatively regarded as positive for tumor by some authors, especially if splenic involvement is also proven (39). A variety of other histologic features including granulomas, lymphocytic portal tract infiltrates, fatty infiltration, cholestasis, and hemosiderosis may be seen in livers which are free of tumor and are the apparent cause of abnormal liver function tests in many of these patients. These abnormalities are frequently reversed following effective radiation therapy of lymph nodes remote from the liver (166,172,173) (Figure 7).

Figure 7



* Average given when more than one determination done

Alkaline phosphatase values and sulfobromophthalein (BSP) retentions in 8 untreated patients with positive liver biopsies and in 24 untreated patients with true negative biopsies. Solid triangles = positive biopsy; solid circles = true negatives aged 20+ years; open circles = true negatives aged 0 to 19 years.

H. Rational Application of Tests for the Diagnosis of MCL

Diagnostic Procedure	Indications
I. Known Primary Tumor	
A. Inferential Tests	
1. Clinical Evaluation	
2. Blood Tests (especially Alk. Phosphatase and GGT)	Routine
3. Liver Scan	
4. Gray-Scale Sonography?	
5. Angiography	(a) if hepatoma is a diagnostic possibility, or primary tumor is of a type likely to be highly vascular (b) prior to anticipated hepatic artery ligation and/or hepatic artery infusion chemotherapy.
B. Liver Biopsy	
1. "Blind" Biopsy	(a) if clear evidence of tumor metastasis is not present elsewhere and (b) if laparotomy were not to be done irrespective of liver biopsy findings.
2. Peritoneoscopic Biopsy	(a) if clear evidence of tumor metastasis is not present elsewhere and (b) blind biopsy is negative and (c) sufficient concern remains that MCL may be present, based on abnormal inferential tests (IA,1-3, above) and/or the presence of a primary tumor with recognized high propensity for metastasis.
3. Liver Biopsy at Laparotomy	(a) patients with Hodgkin's disease and possibly other lymphomas not already proven to have Stage IV disease by other means

Diagnostic Procedure	Indications
	(b) patients with intra-abdominal cancer for which surgical treatment, either palliative or curative, is indicated. (Operative liver biopsy probably indicated regardless of how characteristic the gross appearance may be for hepatic metastases, to exclude a rare false positive diagnosis of MCL.)

II. MCL as a Differential Diagnostic Possibility in a Patient without a Recognized Primary Tumor

In such a patient, with unexplained liver abnormalities, the evaluation is best pursued according to the same plan as outlined above, with the exception that if a satisfactory alternative explanation for the abnormality is found by the stage of percutaneous liver biopsy and no evidence of an extrahepatic primary tumor has been found, probably no further studies are indicated.

III. Therapy

A. Introduction

With rare exception, metastatic cancer is an incurable form of disease. Therapy of MCL is directed primarily at relief of symptoms and prolongation of satisfactory life. While the importance of detecting primary cancers at an early stage when they may be curable has been demonstrated for many tumors, the same cannot be said for early detection of metastases. Even when metastases are apparently restricted to a single confined area such as the liver, there is little evidence that early detection and treatment are of ultimate advantage to the patient in terms of possible cure, more effective palliation, or extended survival. This is not to deny, however, that detection of early MCL and other metastases is important in planning therapy of a primary tumor, as discussed above.

The vigor with which the physician attempts to prolong the survival of a patient with a painful and debilitating disease obviously requires careful thought, attempting to extend only *worthwhile* life, as defined by the patient and his family. The quality of the patient's remaining life must not be diminished by the imposition of painful, expensive, and complicated therapy without firm evidence that such treatment is to his ultimate benefit.

Local palliative resection of already disseminated primary cancers in such sites as breast, stomach, and colon, and biliary diversion surgery for tumors causing obstructive jaundice are good examples of useful palliative therapy, significantly reducing the eventual misery of the dying cancer patient (174-178).

Other forms of therapy such as systemic and intra-arterial chemotherapy, hepatic artery ligation, or irradiation are best reserved for the patient with distressing symptoms, since there is no increased long-term benefit from their use in asymptomatic patients.

It is of great importance that evaluation of any new method of tumor therapy be carried out in prospective trials in which carefully matched control patients are treated with standard (presumably somewhat effective) therapy. Such studies are difficult, time-consuming and expensive and are best performed by well-coordinated multi-center cooperative tumor study groups.

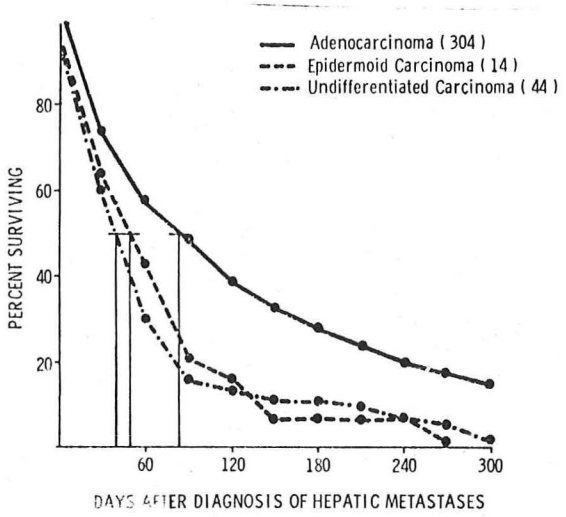
Survival statistics of untreated patients with liver metastases from various types of primary tumor have been reported (157,179-183). Such studies, while useful, cannot be accepted as control data in place of concomitantly studied, matched control patients, as a basis for the claim of efficacy of a given method of treatment.

In many cases, especially among patients with advanced liver involvement, survival appears to be determined by hepatic metastases rather than by the primary tumor or metastases elsewhere (177,184).

Some reports indicate that resection of primary colonic tumors prolongs the survival of patients with liver metastases (174,175), but it is likely that in many such cases the degree of tumor advancement influenced the surgeon's decision regarding excision of the primary tumor; others find no effect on survival (46,177). As discussed above, resection of the primary tumor is justified, nevertheless, by its useful palliative effect.

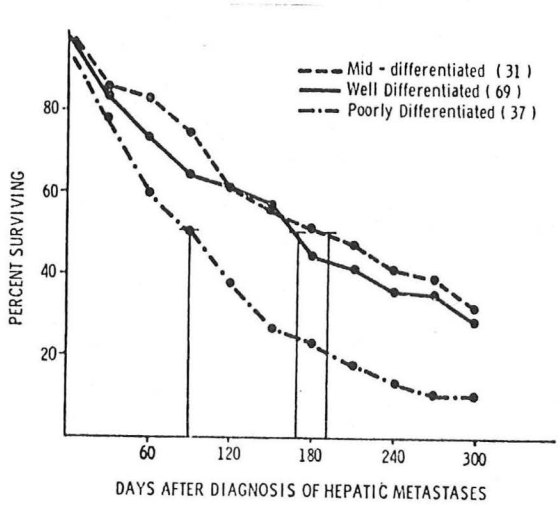
In the detailed study of Jaffe (177), factors shown to influence survival of untreated patients with MCL included the type of primary tumor (colonic carcinoma patients surviving longer than gastric, pancreatic, and biliary tract tumor patients), histologic tumor type (adenocarcinoma > epidermoid and undifferentiated carcinomas [Figure 8], degree of differentiation (poorly differentiated < mid- and well-differentiated [Figure 9], and the degree of functional hepatic impairment as indicated by BSP retention and alkaline phosphatase levels (Figure 10). Factors having little or no effect included the age of the patient, and the coexistence of extrahepatic metastases.

Figure 8



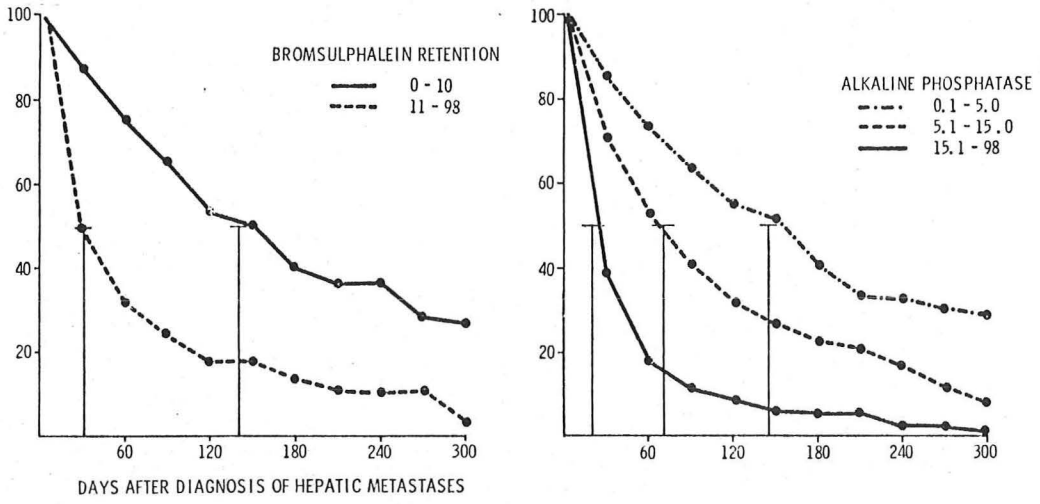
Survival rate of patients with hepatic metastases according to histologic type of carcinoma.

Figure 9



Survival rate of patients with hepatic metastases from colonic carcinoma according to histologic differentiation of the metastases.

Figure 10



Survival rate of patients with hepatic metastases according to alkaline phosphatase and bromsulphalein retention values.

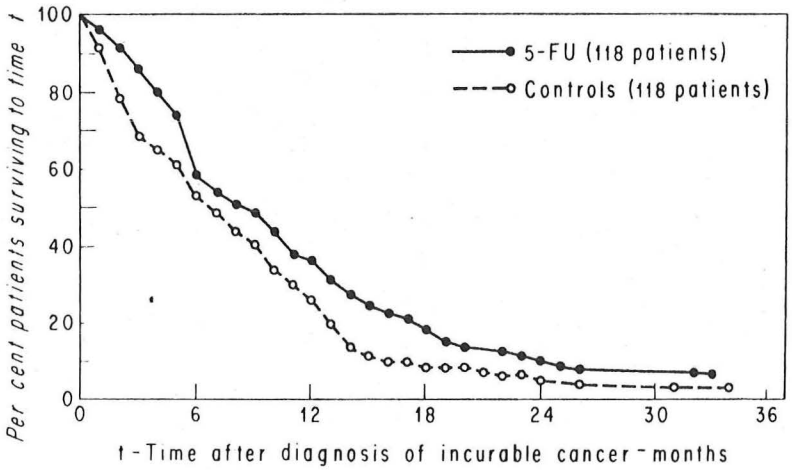
B. Chemotherapy

1. Systemic Chemotherapy

The choice of chemotherapeutic agents for treatment of MCL is determined largely by the nature of the primary tumor of origin, when that is known. The largest group of primary cancers producing liver metastases are adenocarcinomas of the gastrointestinal tract (150,185,186). The drug of choice for these tumors has been 5-Fluorouracil (5-FU) despite the recognition that the overall response rate to this agent, approximately 20%, has been disappointingly low (187) and its efficacy, once hepatic metastases are present, has been even less impressive (188-190). Several alternative agents have been tested but none has matched even the efficacy of 5-FU (187). Various intravenous dosage regimens have been suggested, and that of Horton *et al.* (191) seems to offer the optimal therapeutic/toxic ratio (192). In an attempt to deliver the drug more directly to hepatic implants, as well as to simplify its administration, oral 5-FU therapy had been advocated (193, 194) but the superiority of this approach over intravenous therapy has not been confirmed (195).

The disappointing response of patients with MCL to therapy with single drugs (Figure 11) has stimulated study of multiple-drug regimens. Use of the MOPP regimen (nitrogen mustard, vincristine, procarbazine, and prednisone) has resulted in a dramatic improvement in the response of patients with advanced Hodgkin's disease (161) and lymphomas (196) to treatment. Using this regimen, De Vita and associates at the National Cancer Institute reported the induction of complete remissions in 16 of 18 patients with Stage IV Hodgkin's disease with liver involvement. In 4 of these patients the remission had been sustained to the time of the report for 27-48 months. These investigators have also reported complete and sustained remissions (32-111 months) in 10 of 27 patients with advanced diffuse histiocytic lymphoma who were treated with a regimen similar to that used to treat the Hodgkin's disease patients (196).

Figure 11



5-FU therapy and survival in advanced colorectal cancer (from Moertel, C. G., and Reitemeier, R. J.: Advanced Gastrointestinal Cancer. New York, Harper and Row, 1969, p. 132 (187)

Evidence is accumulating which indicates that, as has been the case for the leukemias, Hodgkin's disease, and the lymphomas, multi-agent chemotherapeutic regimens are capable of producing more frequent and more sustained remissions in patients with disseminated carcinomas and sarcomas than have been possible with the use of single drugs (187). This is one of the most promising areas of current investigation of the therapy of disseminated cancer.

2. Hepatic Artery Infusion Chemotherapy

In the hope of capitalizing on the observations that, first, hepatic tumors are supplied almost exclusively by arterial blood and, second, that 5-FU and related agents are apparently "detoxified" in the liver, direct infusion of these drugs into the hepatic artery has been advocated as treatment of MCL (197-205). It was reasoned that such an approach, as compared with standard "bolus" therapy given by way of a peripheral vein, would permit more prolonged exposure of the tumors to higher concentrations of oncolytic drug for a given degree of systemic toxicity (198). It was intended that the duration of infusion might exceed the tumor "doubling time" so that all tumor cells might be exposed to drug at their most vulnerable phase of growth.

Transbrachial catheter placement has been used by some investigators, while others have implanted the catheter in the hepatic artery at laparotomy. Some patients have been treated in hospital with two to three week periods of infusion, subsequently repeated periodically, while others were treated as outpatients over periods of several months by use of a portable chronometric infusion pump (199).

Certain patients have apparently derived significant symptomatic relief from this type of therapy. Improved median survival of patients treated with hepatic artery infusion as compared either with retrospectively matched patients or with untreated patients reported by other authors has been claimed (180,201,202,204-206). It is disappointing, however, that despite the use of this procedure for more than a decade, no prospective controlled study comparing systemic versus intra-arterial 5-FU administration has yet been reported. There is considerable skepticism among a number of experienced oncologists that the added discomfort and inconvenience imposed by use of this method as compared with systemic chemotherapy is justified by the modest, indeed uncertain, extension of survival afforded (192,207-209).

Hepatic artery ligation followed by hepatic artery (210-212) or portal vein (82,213,214) infusion chemotherapy has been employed in several uncontrolled studies.

C. Hepatic Artery Ligation

Despite the realization that hepatic tumor metastases derive their blood supply almost exclusively from the hepatic artery while surrounding liver tissue is also perfused by portal vein blood, until fairly recently hepatic artery ligation (HAL) has been considered too dangerous for use as

a means of tumor therapy. Indeed, mortality among reported cases of accidental HAL has exceeded 50% (215,216); however, in many fatal cases other complications of surgery such as shock, sepsis, or hemorrhage contributed to mortality (215). It had also long been recognized that experimental HAL in dogs, even under technically optimal conditions, almost invariably caused death of the animal. Wolbach and Saiki (224) first demonstrated that fatal liver damage after HAL in the dog was due to outgrowth of the anaerobic spore-forming organisms normally lying dormant in the canine liver, and subsequently others showed that germfree animals survived HAL, as did those that were treated with antibiotics or hyperbaric oxygen (217,218).

The literature concerning hepatic artery ligation for treatment of human MCL has recently been reviewed by Sparks *et al.* (219). Among the reported series, post-operative mortality has ranged from 0 to 40%, with an average of 15% in a total of 216 cases.

Percutaneous hepatic and superior mesenteric arteriography is commonly performed prior to HAL both to define the arterial vascular anatomy and to document patency of the portal vein. Some authors (212, 220) have emphasized the importance of complete dearterialization of the liver by transsection of the lesser omentum, falciform ligament, and triangular ligament to interrupt all potential routes of collateral arterial blood flow. Completeness of arterial flow interruption can be tested by injection of $Xenon^{133}$ directly into hepatic tumors; absence of "washout" of radioactivity is evidence of effective tumor ischemia (21, 221). The advantage of complete dearterialization over simple HAL has been disputed (219,222).

Cholecystectomy is routinely performed at the time of HAL to prevent complications of post-operative gallbladder necrosis.

Post-operatively various supportive measures have been employed, including use of glucagon to enhance portal blood flow (213); extrapolating from the example of the dog experiments, antibiotics and oxygen therapy have also been used, but since the human liver, unlike that of the dog, is sterile (223) the need for these measures is uncertain.

Fever and abnormal liver function tests, especially a sharp but transient elevation of the transaminases, are usually observed in the first week after HAL, reflecting tissue necrosis.

Although HAL produces a definite increase in survival of experimental animals with hepatic tumor metastases (21,225), there is little evidence that survival of human subjects is extended (213,214,219,226). The procedure is used for its palliative effect, and symptomatic improvement has been reported in roughly 60% of patients so treated (82,219).

A recent preliminary report gives suggestive evidence that infusion of gel emboli into the hepatic artery through a transfemoral catheter may produce effective tumor ischemia more simply and safely than hepatic

artery ligation (227).

Carefully controlled prospective studies comparing hepatic artery occlusion (by ligature or embolization) and/or hepatic artery infusion chemotherapy with simpler means of treatment including systemic chemotherapy (single or multiple drug) and irradiation are urgently needed.

D. Surgical Resection of Hepatic Metastases

Surgical excision of solitary liver metastases, either by local or segmental resection or hepatic lobectomy, has been described in several reports, most involving a small number of patients (159,228-237). Repeated abdominal exploration at six to twelve month intervals following initial surgery to resect newly developed metastases (the "second-look" approach) has been advocated by a few authors (158,159, 232). Removal by local resection of a single hepatic implant found during laparotomy for an abdominal tumor, even considering a certain added risk involved, is probably indicated whenever it is technically feasible if no unresectable tumor is recognized elsewhere. The patient deserves the chance of cure, however small.

In quantitative terms the small probability of curing a patient of cancer by resection of hepatic metastases, assuming that the primary tumor has also been completely removed, is suggested by the data of Ozarda and Pickren (13). In an autopsy study of 150 subjects with hepatic metastases, all but 11 also had extrahepatic metastases, and 7 of these 11 had tumor implants in both lobes of the liver. While it may be argued that these cases were studied at the maximal stage of tumor advancement, and that metastases *might* have been confined to the liver at an earlier stage (certainly not necessarily) and, among these, more *may* have had single lobe involvement, these arguments are far overbalanced by the consideration that in this study the identification of those few cases with potentially resectable liver implants required extensive necropsy dissection to provide information which could not be available at the time of surgery. This, in part, explains the high failure rate of metastasis resection, even in the few instances where this appears feasible to the surgeon.

Wilm's tumor represents a special case in which long term survivals - apparent cures - have been accomplished after excision of hepatic and pulmonary metastases in addition to the primary tumor (238-240).

As discussed below, in patients with symptomatic carcinoid tumors resection, even if incomplete, of massive hepatic implants may provide useful palliation of disabling vasomotor symptoms (241-244).

E. Radiation Therapy

In view of its simplicity and frequent efficacy there has been surprisingly little interest in radiation treatment of symptomatic liver metastases expressed in the literature. This may reflect concern about possible radiation injury to the liver, but it has been demonstrated repeatedly that

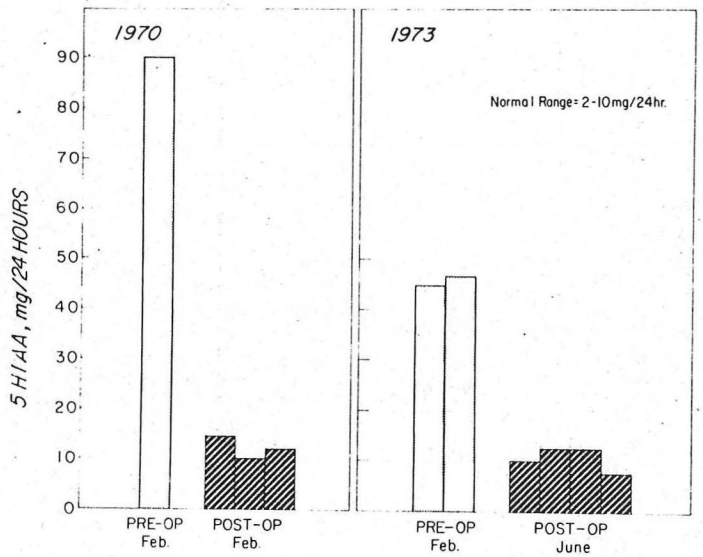
most patients can tolerate up to 3500 rads given over a three and one-half to four week period, and that such treatment may lead to gratifying relief of pain, anorexia, and weakness (245-247). The response is sometimes transitory but, if necessary, further irradiation may be administered after a month's delay (246). Surely this means of treatment deserves careful comparison with other advocated therapeutic modalities.

F. Treatment of Metastatic Carcinoid Tumor in the Liver Associated with the Carcinoid Syndrome

The carcinoid syndrome represents perhaps the best opportunity for useful symptomatic improvement to be derived from treatment of hepatic tumor metastases. This syndrome of striking vasomotor disturbances with flushing and cyanosis, and episodic gastrointestinal and respiratory symptoms is due to high circulating levels of humoral factors including serotonin, 5-hydroxytryptophane, bradykinin, histamine, catecholamines, and possibly prostaglandins. These compounds are produced in large hepatic metastases usually, rather than in the primary tumor itself. Because the tumor is often slow growing the patient may suffer these alarming symptoms for years if untreated. In some instances, pharmacological antagonists to the vasoactive tumor products may provide symptomatic relief (248).

A variety of treatment modalities directed at reduction of the functioning hepatic tumor mass have been employed. Of various systemic chemotherapeutic agents tested, cyclophosphamide appears to be the most consistently effective (248). Smaller numbers of patients appear to have benefited significantly from resection of the bulk of the hepatic tumor mass (237,241-244,249-251) or from hepatic artery ligation (82,219,220,252,253). Reduction of tumor function can be roughly quantitated in these patients by serial measurement of urinary F-hydroxy indole acetic acid (5-HIAA) excretion. At least one reported patient has undergone both resection and, later, dearterialization with worthwhile symptomatic improvement after each procedure (Figure 12) (54).

Figure 12



Levels of 5-hydroxy-indole-acetic acid in the urine on two admissions for partial resection and later for dearterialization.

When resection or hepatic artery ligation is undertaken for treatment of carcinoid liver metastases, there is a risk of precipitating a "carcinoid crisis" due to the massive release of vasoactive factors from injured tumor tissue. Patients should be treated pre-operatively with large dosages of serotonin antagonists (methylsergide or cyproheptadine), with further doses being given at surgery if necessary. Vasopressor therapy may be necessary after surgery to sustain the blood pressure (254). Murray-Lyon has advocated hepatic artery infusion chemotherapy prior to arterial ligation to reduce the risk of such vasomotor crises (82).

G. Liver Transplantation

The results of liver transplantation in patients with primary or secondary hepatic tumors have been generally disappointing, with rapid development of widespread recurrent tumor (255,256). It is considered likely that post-transplant immunosuppressive therapy releases any immunologic repression of latent tumor foci which might have existed pre-operatively.

H. Conclusion

Metastatic cancer in the liver, like widely disseminated cancer generally, has proven frustratingly resistant to therapy. This does not reduce the obligation of the physician to offer the patient the best possible means of symptomatic palliation available, attempting to relieve his physical discomfort as well as the emotional distress both he and his family suffer.

Among the immediate objectives of research in this area should be a clarification of the value of certain promising diagnostic techniques such as peritoneoscopy and gray-scale ultransonic scanning, and a careful assessment in controlled, cooperative studies of the relative value of various therapeutic modalities recommended for MCL, including hepatic artery infusion chemotherapy, hepatic artery ligation, and multiple-drug chemotherapy regimens.

Longer term objectives must include the development of means to identify more primary tumors at a pre-metastatic stage and of methods, thus far largely unsuccessful, to rid the body of microscopic metastatic tumor foci remaining after attempted curative resection of primary cancers.

The impressive progress made in the treatment of Hodgkin's disease and lymphomas in recent years should inspire the pursuit of better means to treat other patients with disseminated cancer.

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