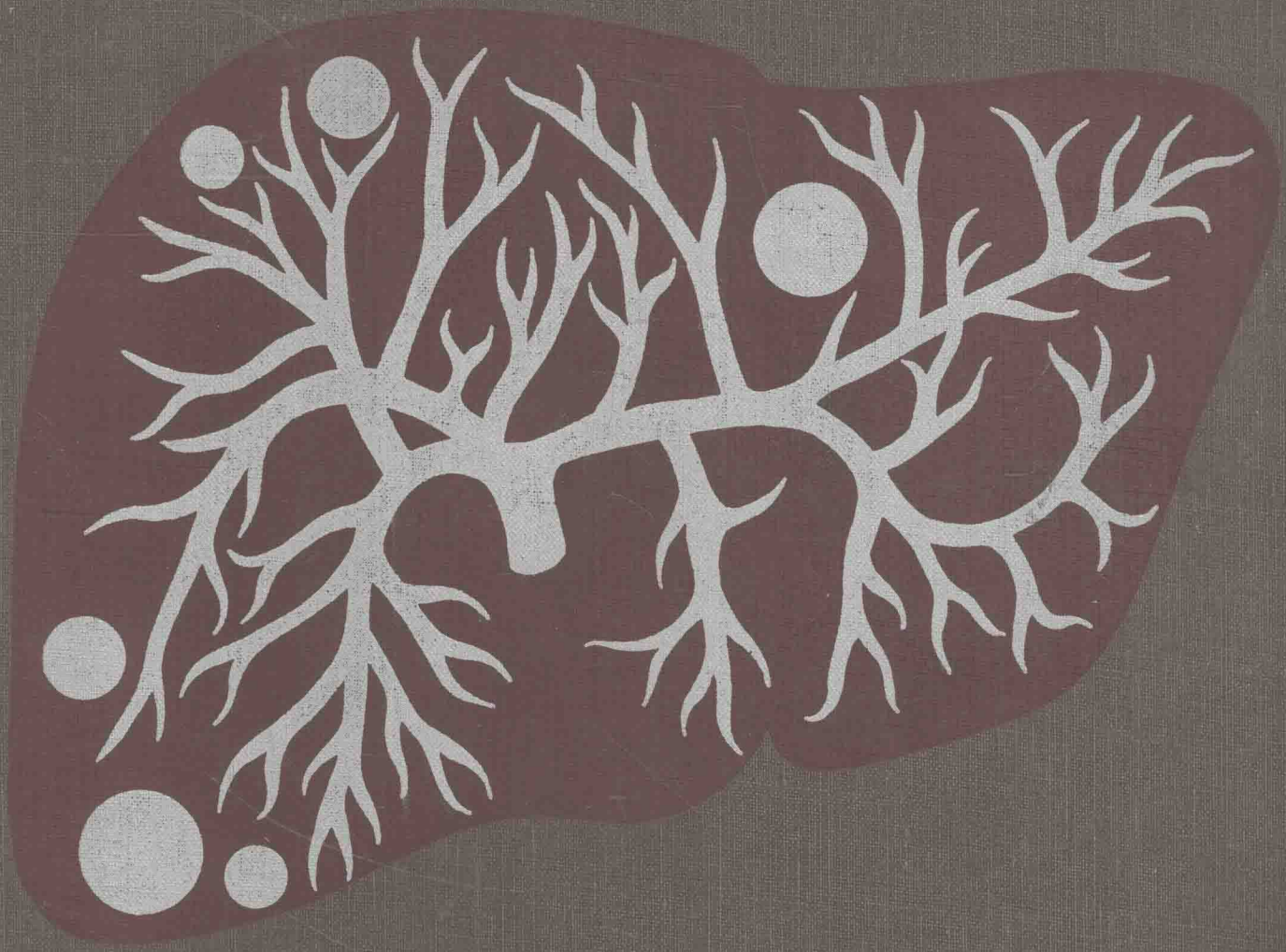

Liver Metastasis

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Preface

In this fifth volume of the series on metastasis by site, the liver is the target organ. We have focused on various aspects of liver metastasis as distinct from the usual approach of emphasis on primary cancers that may or may not give rise to metastases in the liver. As in the previous volumes, we have covered various basic aspects of liver metastasis and some aspects of metastasis in general that have not been dealt with previously in this series. In the diagnostic section, in addition to descriptions and discussions of specified techniques, we have included chapters concerned with critical comparisons of these techniques. In the therapy section, we have encouraged as many different viewpoints as possible on this controversial topic, at the price of some unavoidable overlap between chapters.

It is a pleasure to offer our sincere thanks to the contributors and publisher for their efforts in making this volume a fair record of the state of the art of diagnosis and treatment of liver metastasis; we hope it will be of interest not only to clinicians concerned with this common manifestation of cancer, but also to basic researchers in the general field of oncology.

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Chapter 1
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Introduction

Liver metastases are a common occurrence in patients with cancer and constitute a major oncologic problem. The Roswell Park Memorial Institute data on 9700 consecutive autopsies on patients with 10,736 primary cancers, which are analyzed by Pickren and his colleagues (chapter 1), show that of 8055 primary cancers metastasizing to one or more organs, liver metastases were present in 4444 cases. The incidence of liver metastasis (41.4%) was exceeded only by that of the lymph nodes (57%), but exceeded that of the lungs (39.7%). The primary sites that most commonly metastasize to the liver are eye (77.8%), pancreas (75.1%), breast (60.6%), gallbladder and extrahepatic bile ducts (60.5%), colon and rectum (56.8%), and stomach (48.9%). In absolute numbers, analysis of 4444 primary sites reveals liver metastases from cancers of bone marrow in 643 cases, breast in 635, lung and trachea in 593, lymph nodes in 525, and colon and rectum in 383 cases.

The patterns of metastasis are next examined by Gilbert and his colleagues (chapter 2), extending the principles previously developed in this series of books by Viadana, Bross, and Pickren (1978) and Bross (1980), in which certain organs were identified as generalizing sites from which metastases spread. It is concluded that the liver is a primary target organ in gastrointestinal cancers, some urologic cancers, neuroblastomas, some melanomas, and lung cancers. It is less often a primary target organ in breast cancer. "Liver-only" involvement, when liver metastasis is the main disease to be treated, occurs almost exclusively in patients with colonic, and less commonly, rectal cancers, hepatocarcinomas, and endocrine tumors. Patients selected from this group are expected to benefit most from local therapy.

Some of the ultrastructural details of establishment of metastases in the liver and some microanatomic bases for invasion are discussed by Warren (chapter 3), with particular emphasis on microcirculation, the size of tumor emboli in relation to arrest site, and the local lymphatic system. Normally, blood flowing over intact vascular endothelium tends to keep it free of emboli; however, the presence of fenestrations, exposure of underlying collagen, and any form of damage promotes arrest. Kupffer cells, which are associated with platelets, also tend to promote arrest by obstructing blood flow through the sinuses. Warren notes that extravasated cancer cells arrested in the liver move to an immediately subendothelial position, or between plates of liver cells that are only two to four cells thick, implying that at least initially the cancer cells cannot be far from diffusible nutrients. This may contribute to making the liver good metastatic "soil."

Ultrastructural aspects of liver invasion are also discussed by Dingemans and Roos (chapter 4), who stress differences between the liver

and other organs. The fenestrations in the sinusoidal linings make this potential initial barrier to penetrating cancer cells more permeable than the capillary endothelium of the lung, for example. Furthermore, over 90% of the liver parenchyma consists of hepatocytes with few connective tissue elements, in contrast to other tissues where connective tissues are thought to modify invasion. Finally, the reticuloendothelial elements peculiar to the liver are thought to have tumoricidal activities. Like Warren, Dingemans and Roos emphasize the differences in interactions between liver cells and different types of cancer cells.

The destruction of host tissues by invasive cancers and their metastases is due partly to a variety of proteinases present in tumor tissues. In their discussion of proteolytic mechanisms of tissue destruction, Recklies and Poole (chapter 5) note that although the tumor thiol proteinase described by them has not yet been identified in nonmalignant tissues, it is unlikely that only one specific tumor proteinase can be responsible for not only destructive effects, but also for modification of cell interactions by virtue of nonlethal autolysis of the cell periphery (Weiss 1967). The control of both proteinase secretion from tumors and proteinase activity by naturally occurring inhibitors is also discussed, and the need for more detailed study in this area is stressed.

The blood supply of metastases is of great importance, not only because it determines much of their biology, but also because numerous diagnostic and therapeutic techniques that are discussed in later chapters are essentially dependent on tumor vascularization patterns. In discussing these and other related issues, Ackerman (chapter 6) states that the intermingling of (hepatic) arterial and portal vasculatures creates a more complicated system for nourishment of the tumors than occurs in most other organs. In addition, systemic portal and arteriovenous shunting, particularly in association with tumor growth or regression, or after vessel occlusion, may further complicate the picture. Ackerman considers various therapeutic techniques related to tumor blood supply, including hepatic artery infusion and ligation in various combinations. The results of these procedures are discussed by others in the treatment section.

As many patients with cancer ultimately die with metastases, metastasis is often thought to be a remorselessly efficient process in which the patient is overwhelmed by sheer metastatic bulk. In chapter 7, Weiss presents data indicating that dying *with* metastases is distinct from dying *from* metastases; in terms of cancer cells, metastasis is an inefficient process. In some respects, many cancer cells are ill-equipped to survive the process. Metastatic inefficiency is defined and discussed in terms of possible metastatic subpopulations of cancer cells, circulatory trauma, the arrest and subsequent release of circulating cancer cells, first-organ encounters, dormancy, and "seed and soil" factors. Although patients do not usually die as a result of metastatic bulk, the fact that metastases are so often in some way responsible for death emphasizes the repetitious nature of the disease: even inefficient processes succeed if repeated often enough.

The second part of this book is concerned with the diagnosis of liver metastases by ultrasound, computed tomography, radionuclide imaging,

and peritoneoscopy. These techniques are critically compared, and laboratory tests are discussed. Thomas (chapter 8) describes a recent "breakthrough"—the detection of hepatic metastases by routine ultrasonography. This was made possible over the last five years with the development of gray scale signal-processing that permitted textural assessment of organs, improvements in transducer design, and associated technology that has improved resolution and the introduction of "real time" techniques. In comparing ultrasonography with other diagnostic methods, it is important to note the major causes of technically suboptimal liver imaging, such as large body size, bowel gas, and the liver lying high under the costal margin. When allowances are made for these limitations, ultrasonography is reliable. Ultrasonic radiation at the levels used in diagnostic equipment is generally considered to be nonhazardous and, in addition, is a low-cost procedure, making it an excellent technique for initial screening and follow-up studies.

The computer-assisted tomographic diagnosis of hepatic metastases is discussed by Bernardino (chapter 9). The increased use of this procedure has been characterized by its rapid rate of technical improvement. Thus, first-generation equipment that required 2.5 minutes for a liver scan was generally inadequate because of degradation of images by peristalsis. This is no longer the case, however, since third-generation equipment has scanning speeds of less than 10 seconds. By the use of iodine-containing media, the density of normal liver may be increased, thereby making metastases more visible. At present, computed tomographic (CT) examinations are used to confirm lesions that are questionable on ultrasound or radionuclide scans, to monitor the size of lesions in response to therapy, and in the evaluation of patients for partial hepatectomy. Although CT findings in liver metastasis lack specificity, accurate diagnoses may be obtained when they are correlated with the patient's clinical history. Young, Turner, and Castellino (1980) provide some helpful diagnostic suggestions:

1. Preliminary CT scans should be performed prior to contrast enhancement.
2. A control scan should be performed on any equivocal area, followed by a dynamic series of scans without moving the patient, after an intravenous injection of contrast material. (Lesions have been found during the dynamic phase that disappear on a delayed scan.)
3. Lesions tend to become isodense three to five minutes after contrast injection.
4. If the CT number does not change in the first minute of a dynamic scan, then the lesion is avascular (i.e., cyst, hematoma).

A critical comparison between ultrasonography and CT in the detection of liver metastases is made by Peetrons, Osteaux, and Jeanmant (chap-

ter 10). They discuss the difficulties of comparing two diagnostic methods that are still in a state of active development; their own comparisons are based on a four-year study, beginning in 1976, of 67 patients subjected to both examinations at an interval of less than six weeks and in whom the diagnosis was confirmed independently. Relatively equal diagnostic scores lead to the conclusion that the techniques are competitive, but that a combination of the two procedures resulted in the correct diagnosis in 62 of 67 patients. Peetrons and his colleagues consider ultrasonography to be the initial screening method of choice, with CT scanning as the final noninvasive step in the diagnosis of liver metastases.

The current 30 years' experience with radioisotope scanning permits Blau (chapter 11) to provide a balanced, definitive appraisal of the role of nuclear medicine in the detection of liver metastases. Blau discusses the terms *sensitivity* (true positive ratio) and *specificity* (true negative ratio) that together can project the accuracy of a test in populations with different prevalences of diseases. When this analysis is applied to patients with breast cancer, it is concluded that radioisotope scanning of the liver is virtually useless in the management of these patients because of the high ratio of false to true positive results. Blau considers the present slow rate of improvement in the technique to be due partly to inherent difficulties—including scatter, collimation, and patient motion, and partly because of the failure to adopt recent technical advances such as tomography, scintiangiography, tumor specific radiopharmaceuticals, and patient motion correction circuitry.

Bouvard and Bouvard (chapter 12) compare scintigraphy and ultrasonography in the detection of liver metastases, and conclude that with the present state of the art, ultrasound is the most accurate method for demonstrating or excluding liver metastases. In addition, while use of both techniques may be useful in some cases, scintigraphy alone is inadequate.

The development of new optical systems warrants a review and reassessment of peritoneoscopy, a procedure regarded as midway between invasive and noninvasive procedures. Riemann (chapter 13) draws on the considerable experience of his group using peritoneoscopy in association with biopsy under direct vision, and describes the characteristic appearances of liver metastases that, if present, are pathognomonic. False negative findings sometimes occur as a result of location of metastases at the dorsal parts of the liver or from metastases not involving the liver surface; thus, other techniques may be required to increase the diagnostic accuracy above 87%. In addition to gaining information on the liver, peritoneoscopy permits direct examination of the abdominal cavity, and the procedure is of relatively low risk and causes minor discomfort to the patient.

The ultimate diagnostic tests for liver metastasis would be those made on blood or other easily obtainable specimens. Chu (chapter 14) discusses the present reliability of such tests in relation to liver metastasis. It is clear from his comments that many physicians ordering a number of tests are unaware of their limitations. At a conference held at the National Institutes of Health on 29 September 1980, the consensus was that although carcinoembryonic antigen (CEA) radioimmunoassay is used extensively in the

diagnosis and monitoring of cancer, its usefulness for this purpose requires considerable qualification. In conjunction with other tests, however, it is useful in patient follow-up, particularly in relation to therapy and prognosis. The plasma level of CEA associated with a localized primary cancer will rise as the tumor metastasizes, and it is of interest in the present context that liver metastases are associated with particularly high CEA levels, although approximately 20% of patients with proven metastases maintain stable plasma CEA concentrations. CEA assay provides an extremely useful method of postoperative monitoring in cases of colorectal cancer. The failure of circulating CEA levels to fall usually indicates residual cancer; slowly rising levels tend to indicate local recurrence; and sudden increases often point to metastasis to the liver and bones.

The presence of hepatic metastases in a patient raises difficult questions of patient treatment and whether specific treatment should be initiated. The section on treatment begins with a discussion by Bengmark and Jeppsson (chapter 15) of a key issue, the staging of liver metastasis. Accurate staging is not only of value in assessing prognosis and response to treatment, but also in selection of patients for resection and other forms of therapy. Accurate staging is essential for comparison of data. In one staging scheme, stage I corresponds to less than 20% of the liver being replaced by tumor and is associated with a mean postoperative survival of nine months, compared with stage II disease with 20% to 70% replacement and 4.1-month survival, and stage III disease with more than 70% replacement and 3.2-month survival. Bengmark and Jeppsson consider accurate staging to be accomplished only at laparotomy, although computed tomography may improve preoperative staging. Liver function tests also have severe limitations.

Other attempts in the literature at staging are summarized by us in table 1; it is evident that histologic grade and percentage of the liver parenchyma involved are highly predictive of survival. Most of these series documented the survival in patients with untreated liver metastasis. Other factors that appear critical in determining survival and treatment response are

1. Original stage of the colon cancer; Duke's stage A patients live longer than Duke's C patients from the time they develop liver metastasis.
2. Level of CEA at the time of liver metastasis diagnosis (in colon cancer patients) (Martin et al. 1979).
   a. 16 nanograms or less = excellent response to treatment of liver disease with good survival.
   b. 40 to 50 nanograms = stabilization or modest response to treatment.
   c. 50 nanograms = progression of tumor and short survival.

3. Level of performance on the Karnofsky index; the higher the performance status at the time of treatment of liver metastasis, the better the response and survival. Favorable responses to treatment are rarely obtained for patients with Karnofsky status below 70 (Webber et al. 1978).
4. Histologic type of primary; patients with colon and carcinoid tumors metastatic to the liver have the longest survival. Melanoma, lung, pancreatic, and stomach cancers rarely respond to local treatment of the liver (chapter 16).
5. Assessment of vascularity of the metastasis by arteriography helped predict survival and response to therapy by hepatic artery dearterialization. Survival in patients with high vascularity was 11 months; patients with low vascularity of their tumor survived only 4 months (Kim et al. 1977).
6. Low serum albumin is potentially symptomatic for extrahepatic metastasis; a score greater than 80 on a test for serum glutamic-oxaloacetic transaminase (SGOT) indicates portal hypertension (chapter 16).
7. Poor arterial anatomy feeding the liver (chapter 23).

The question of whether patients with liver metastasis benefit from systemic chemotherapy is indeed complex. The difficulty in attributing survival benefit to treatment in diseases that "respond" to treatment in fewer than 30% of cases is magnified by an apparent survival benefit only in those patients responding to treatment when compared with nonresponders. Are the patients in both groups biologically the same, or are the responders a more favorable group with an inherent biologic survival advantage in spite of treatment? Thus, the 70% of patients not responding might be dying even earlier because of treatment toxicity; a decrease in tumor size may not be the reason for prolonged survival in the responders.

It is generally accepted that patients with liver metastases resulting from lymphoma, seminoma, and nonseminomatous testicular cancer, childhood cancers (Wilms' tumor and rhabdomyosarcoma), breast cancer, and oat cell cancer of the lung have a prolonged survival with chemotherapy. The question of efficacy of chemotherapy arises with patients with gastrointestinal, lung, and genitourinary cancers.

In a review of 1300 cases of recurrent colorectal cancer with and without hepatic metastases, a number of critical findings were noted by Lavin and associates (1980):

1. In terms of patient survival and objective tumor response, no systemic chemotherapy regimen (intensive multiple drugs) used in previously untreated patients was more effective than oral or intravenous 5-fluorouracil. The authors did not study hepatic artery infusion (HAI) of drugs.

Table 1

NATURAL HISTORY OF UNTREATED LIVER METASTASIS

Investigator	Primary Site	Description	Survival (Months) Mean (Range)
*Pettavel and Morgenthaler (1978)	Colon	Stage I: liver functions and liver size; both normal	15.0
New Staging System		Stage II: liver functions and liver size; one abnormal	4.7
		Stage III: liver functions and liver size; both abnormal	1.4
Nielsen, Balslev, and Jensen (1971)	Colon	Few metastatic nodules	18.0
		Several metastatic nodules	9.0
		Numerous metastatic nodules	5.0
Wood, Gillis, and Blumgart (1976)	Colon	Solitary metastasis	16.7
		Many metastases (1 lobe)	10.6
		Many metastases (both lobes)	3.1
Pettavel and Morgenthaler (1970)	Colon	Stage I: (solitary or small); not obvious on clinical examination	21.5 (15–52)
		Stage II: (< 2 cm); liver functions normal and not obvious on clinical examination	10.7 (7–15)
Old Staging System		Stage III: numerous, small or medium nodules; liver either enlarged or having abnormal chemistries	4.7 (2.7–7)
		Stage IV: enlarged liver and abnormal chemistries	1.4