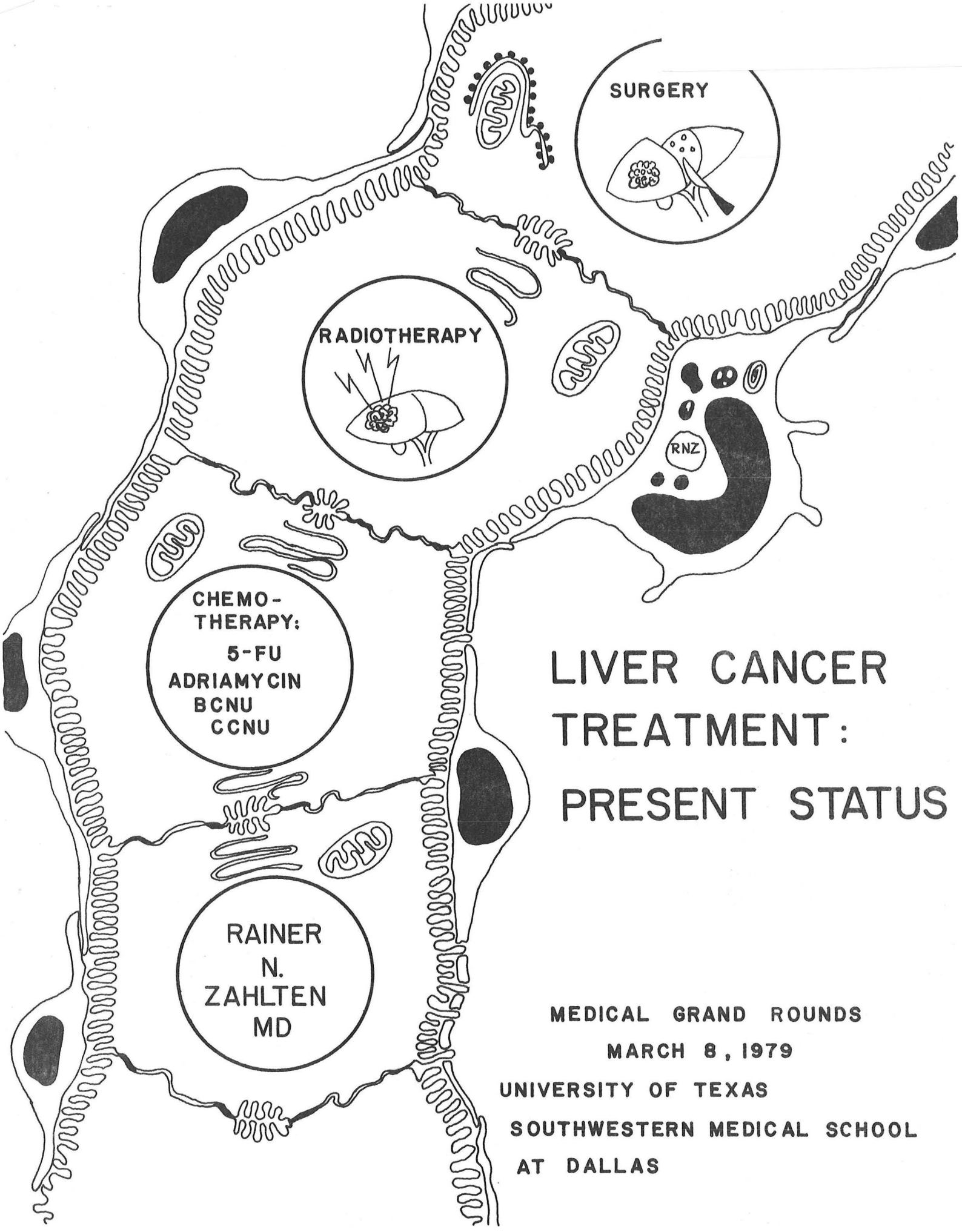



# LIVER CANCER TREATMENT: PRESENT STATUS

MEDICAL GRAND ROUNDS
MARCH 8, 1979
UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL SCHOOL
AT DALLAS

INDEX

## Acknowledgement

I am grateful to Mrs. Jo Shockley for the skillful preparation of this protocol.

## I. Introduction

Treatment of liver cancers (either of primary or secondary nature) by means of surgery, radiation, or chemotherapy has still a long way to go until it reaches the Hall of Fame of medical achievements. Because of the obviously slow progress the subject of current treatment of these neoplastic diseases continues to attract little more than rather disenchanted interest and a feel of resignation in many clinical medical circles. But future advances in the area of early cancer diagnosis and superselective chemotherapy should be expected to add significantly to increase of survival and hopefully cure. Nevertheless, in anticipation of future improvements in the care of hepatic neoplasm it seems to be appropriate to attempt a critical analysis of the current status of liver cancer treatment and discuss its presently still significant limitations. The discussion will be limited to primary hepatic carcinomas and metastatic liver involvement. Extrahepatic bile duct tumors will not be explicitly discussed.

### 1. Primary hepatic tumors

#### a. Epidemiology

Worldwide epidemiological studies revealed cancer incidence statistics which specified several African countries as high incidence areas for primary liver carcinomas such as Mozambique, Rhodesia, Uganda, and South Africa (Bantu) whereas North America, Western Europe and Australia are designated as low incidence areas (Table I, Ref. 1).

TABLE I

Highest and Lowest Cancer Morbidity Rates for Primary Liver Cancer

(Age-adjusted; No./100,000/year)

| Male | | Female | |
|---|---|---|---|
| Highest | Lowest | Highest | Lowest |
| 103.8 | 0.3 | 34.2 | 0.1 |
| (Mozambique) | (Japan) | (Rhodesia) | (Newfoundland) |

In the United States the incidence of hepatocellular carcinoma (HCC) has risen from 1964-1974 from 1.3/100,000 population to 4.0/100,000 (1,2). In this country there is no significant difference in total liver tumor incidence between males and females when all primary liver tumors are taken into account. For HCC the male:female ratio is approximately 2:1 as in most parts of the world. In areas of high primary

liver cancer incidence such as Mozambique, Nigeria, Singapore and Hawaii, the ratio is over 3:1 (male:female). In the African countries such as Mozambique there is also a characteristic shift of the rising age-incidence curve for HCC towards the younger age group. In the 25-34 year age range the HCC incidence in Mozambique is 500 times higher than in the U.S. where the highest incidence occurs between 40-60 years of age (1). In some of the African regions HCC accounts for over 50% of all malignancies in men and over 20% for all malignancies in females (3). Current cancer statistics published by the American Cancer Society (4) show the new estimates for cancer and cancer related death of all sites as well as for liver and biliary passages for 1978 (Tables II, III).

TABLE II

Estimated New Cancer Cases by Sex for All Sites as Well as for Liver and Biliary Passages (1978)

| | Liver and Biliary Passages | All Sites |
|---|---|---|
| Male | 5,800 | 352,000 |
| Female | 6,000 | 348,000 |
| Total | 11,800 | 700,000 |

TABLE III

Estimated Cancer Deaths by Sex for All Sites as Well as for Liver and Biliary Passages (1978)

| | Liver and Biliary Passages | All Sites |
|---|---|---|
| Male | 4,600 | 213,000 |
| Female | 5,000 | 176,500 |
| Total | 9,600 | 390,000 |

Large autopsy series have revealed (5) that in the U.S. 90% of the primary hepatic tumors are represented by hepatocellular carcinoma (HCC), the rest being cholangiocellular carcinoma and other rare entities. The ratio of primary to secondary carcinomas of the liver has been estimated by one author as 1:13 to 1:65 (6).

b. Pathological features of primary hepatic tumors

The tumorous liver weight is often increased to 2,000-3,000 gm. The tumor is either massive (30% of all cases), nodular or diffuse. Hobnail surface of the liver is frequent but surface nodules are rarely umbilicated in contrast to metastases. The right liver lobe is preferentially affected (80-90%). Two-thirds of all HCC present as nodular masses and may occasionally replace the whole liver. The diffuse form of the neoplasm is present in 5% of the cases.

c. Metastases from primary hepatic tumor

When clinically diagnosed or found at autopsy HCC as well as cholangiocellular carcinoma show a high degree of dissemination with an incidence of pulmonary metastases between 41-82% (5,7,8,9).

d. Cirrhosis and primary hepatic tumors

Pathologists very early recognized the association between HCC and cirrhosis. The degree of association varies geographically and is remarkably different between high and low HCC incidence regions. A survey of the international pathological literature shows that the incidence of HCC in cirrhotic livers is low in Europe and the U.S. but high in Africa and Southeast Asia (10-15). In reverse, the incidence of cirrhosis in livers with HCC is extremely high throughout the world and fairly uniform (5,16,17) and shown in Table IV.

TABLE IV

Association of Cirrhosis and Hepatocellular Carcinoma (HCC)
(Data from Autopsies)

| Geographic Area | % HCC in Cirrhosis | % Cirrhosis in HCC |
|---|---|---|
| Africa, Southeast Asia | 40-50 | 80-90 |
| Europe, USA | 5-10 | 80-90 |

e. HCC, cirrhosis, alcohol and hepatitis B infection

Purtilo et al. (14) compared large autopsy series at Boston City Hospital from the period 1917-1954 (23,114 autopsies) with the period from 1955-1968 (14,000 autopsies). He concluded that cirrhosis and HCC at Boston City Hospital have progressively increased in frequency, especially cirrhosis associated with alcoholism. This author suggested that chronic alcoholism and hepatitis B virus (HBV) could probably

act synergistically to produce a type of cirrhosis which is associated with a higher incidence of HCC. An analysis of 294 patients in Great Britain who died with cirrhosis showed that 24% had developed HCC. Hemochromatosis and $HB_sAg$ positive chronic active hepatitis were high risk groups (36% and 42% respectively) (17a).

French and American investigators postulated that the high incidence of HCC in Africa and Southeast Asia is related to the high prevalence of HBV infection and macronodular ("posthepatitic") cirrhosis in those areas (18,19).

Prince and co-workers (20) tested 165 patients with HCC in Senegal against 154 controls with other cancers (closely matched with respect to age, sex, ethnic group and time of hospitalization) and 328 similarly matched controls without cancers. The radioimmunoassay (RIA) was used for $HB_sAg$ detection. Essentially all of the HCC patients with positive $HB_sAg$ were chronic carriers (Table V).

TABLE V

Incidence of $HB_sAg$ in HCC, Other Cancers and Controls in Senegal (Africa)

| | HCC | Other non-liver Ca | Controls |
|---|---|---|---|
| $HB_sAg$ | 61.2% | 11.7% | 11.3% |

Maupas (21) determined the anti-$HB_c$-antibody as a marker of active or recent infection with HBV as shown in Table VI.

TABLE VI

Incidence of Anti-$HB_c$ in HCC Patients versus Controls

| Geographic Area | Anti-$HB_c$ in HCC | Anti-$HB_c$ in Controls |
|---|---|---|
| Senegal | 87% | 34% |
| Hong Kong | 70% | 36% |
| USA | 24% | 4% |

In addition to the above findings, Kubo et al. (22) reported a 72.6% incidence of anti-$HB_c$ of HCC patients compared to 30.1% of controls.

Peters et al. (Amer. J. Clin. Pathol. 68:1, 1977) reinvestigated autopsy tissues of patients with HCC during the period of 1969-1974 with orcein stain for $HB_sAg$. They found in 73% of non-alcoholic cirrhotic patients a positive reaction for $HB_sAg$ in liver tissue. The same group recently updated their findings until 1977, confirming that in HCC patients with non-alcoholic chronic liver disease in the U.S. the prevalence for HBV infection is as high as in Africa and Asia. The previously low incidence for HBV infection of HCC patients in the U.S. as presented in Tables IV and VI is probably due to dilution of the patient population of HBV and non-alcoholic chronic liver disease with the massive number of alcoholic cirrhotic patients with HCC (23a). All the above results support a strong association of HBV and cirrhosis with the development of HCC, but do not prove a cause relationship. Other environmental factors, still unknown, may contribute to the development of primary hepatic neoplasms.

f. Natural history of HCC and survival rates

Average duration of life from the onset of symptoms without treatment has been reported to be between 4.5-7 months (23,24). Other authors found in their patient population with HCC a mean* survival time of 6.5 months (25), 6 weeks for cholangiocarcinoma and up to 8 months in HCC (26), 7 months from onset of symptoms (27), 3 months without specific therapy (28) and 1 month with or without laparotomy (23). Median** survival of untreated patients after diagnosis varies from 1 month in Asia (29), 1 month in Africa (30) to 4 months in this country (31).

2. Metastatic liver cancer

a. Characteristics of hepatic metastases from other primary tumors

The incidence of cancerous involvement of the liver by metastases from other primary tumors is significantly higher than the incidence of primary hepatic tumors. The liver is one of the most common sites of metastatic tumor growth disseminated from other primary carcinomas. Splanchnic bed tumors (gastric, pancreatic, colo-rectal) produce hepatic metastases disproportionately often (32).

Metastatic liver disease generally presents as a nodular growth pattern with visible umbilication of tumor nodules over the liver surface. Rapid expansion with dramatic hepatomegaly is often the course of liver involvement. It has been recognized for a long time that blood supply of hepatic tumors, both primary or secondary, is predominantly by branches of the hepatic artery. The percentage of patients with liver metastases found during laparotomy or autopsy is demonstrated in Table VII (33).

*mean survival: arithmetic mean of times of survival.
**median survival: the value on the numerical scale of classification in a frequency distribution below which and above which half of the observations fall.

TABLE VII

% of Patients with Liver Metastases at Laparotomy and Autopsy, Depending on Localization of the Primary Tumor

| Primary Tumor | At Laparotomy (%) | At Autopsy (%) |
|---|---|---|
| Stomach | 20 | 45 |
| Pancreas | 49 | 63 |
| Colon | 25 | 65 |
| Rectum | 23 | 47 |

Liver metastasis from breast cancer at time of diagnosis of the primary tumor has been estimated between 15-35% and at autopsy 35-65% (33). At the diagnosis of carcinoid, 96% of patients are found to have metastatic liver disease. Median survival is approximately 23 months (34). To demonstrate the superior quantitative importance of metastatic hepatic tumors, a rough estimation can be made of the incidence of metastatic liver involvement as expected for 1978 for several selected tumors. This is demonstrated in the following Tables (4,33).

TABLE VIII

Estimated New Cases of Liver Metastases From Various Tumors for 1978 (USA)

| Primary Tumor | Hepatic Metastases | |
|---|---|---|
| | Laparotomy or Liver Scan | Autopsy |
| Colo-rectal | 18,360-25,500 | 16,584-36,798 |
| Breast | 13,605-31,745 | 4,177-22,165 |
| Pancreas | 4,818-10,731 | 12,600-14,800 |
| Stomach | 2,760- 5,980 | 4,672 |

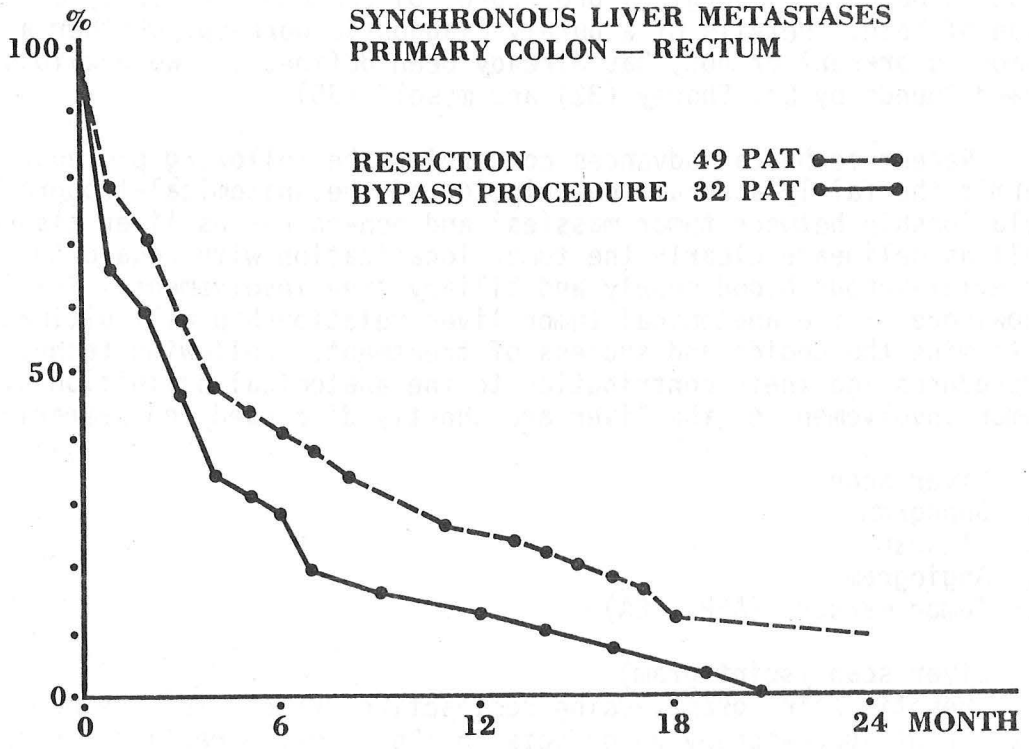
The total expected liver metastases incidence for 1978 related to four primary cancers only (Table VIII) is therefore between 77,576-152,391 cases. The ratio of liver metastases from these extrahepatic primary tumors to the incidence of primary hepatic tumors is between 6.5 to 12.9. Including metastasis from all extrahepatic tumors this ratio has been estimated to be approximately 1:13 to 1:65 (6). The mean and median survival of patients with liver metastases, with or without resection of the primary tumor, is shown as an example in Table IX for colorectal cancer (33).

TABLE IX

Mean and Median Survival for Patients with Liver Metastases from Colorectal Cancer When Primary Tumor Is Resected or Diversion Procedure Is Performed

| | Diversion Procedure | | | Resection | | |
|---|---|---|---|---|---|---|
| | No. | Mean | Median | No. | Mean | Median |
| Stearns & Birkley, 1954 | 28 | 8.4 | 8 | 22 | 18 | 11 |
| Jaffe et al., 1963 | 80 | | 4.5 | 60 | | 8 |
| Bengmark & Hafström, 1969 | 12 | | 2 | 22 | | 5 |
| Oxley & Ellis, 1969 | 25 | | 3 | 76 | | 10 |
| Nielsen et al., 1971 | 50 | 5.0 | | 38 | 12.3 | |
| Baden & Anderson, 1974 | | | | 105 | | 10 |

These results are verified (33) for patients who had either resection or bypass procedure for colorectal cancer (Fig. 1).




Survival for patients with synchronous liver metastases from colorectal carcinoma subjected to bypass procedure or resection of primary.

Figure 1

In the past, once the diagnosis of cancer in the liver was established, generally no further treatment was initiated except the usual terminal care. For clinical trials of liver cancer therapy, a zero control has to be utilized to evaluate true therapeutic success. A zero control is either "no treatment" or "standard treatment". "No treatment" represents the natural course of the disease which has made the physicians aware of the extremely poor prognosis for these patients and should encourage them in the future to defend controlled clinical trials. But since nowadays in all hospital settings the natural course of the disease is influenced by standard therapy, only patients under standard therapy are acceptable controls for the evaluation of new therapeutic protocols.

From the previous data it is obvious that the majority of hepatic tumors are metastatic liver tumors and primary hepatic tumors are relatively rare compared to this patient population. In the following chapter, currently available diagnostic procedures and their recent advances will be discussed. They will determine which, or if any, therapeutic approaches such as surgery or chemotherapy will be feasible for a particular patient.

## II. Specific diagnostic techniques

If the certain diagnosis of either primary HCC or metastatic liver tumor has been made by a combination of clinical signs and symptoms, palpation, abnormal laboratory findings, peritoneoscopy and liver biopsy, then further diagnostic procedures are intended to clearly define treatibility of the hepatic neoplasm. The decision to be made is between a) surgical procedure, b) chemotherapy or c) combination of both. Details of a purely diagnostic work-up, whether a tumor is present or not, has already been defined in two previous Grand Rounds by Dr. Shorey (32) and myself (35).

Recent technical advances concerning the following procedures permit the fairly accurate description of the anatomical-topographical relationship between tumor mass(es) and non-cancerous liver tissue as well as delineate clearly the tumor localization with regard to arterial-venous blood supply and biliary tree involvement. Precise knowledge of the anatomical tumor-liver relationship will ultimately determine the choice and success of treatment. Following technical procedures and their contribution to the anatomical definition of tumor involvement of the liver are shortly discussed and summarized:

1. Liver scan
2. Sonogram
3. CT scan
4. Angiograms
5. Tumor markers (AFP, CEA)

### 1. Liver scan (scintigram)

Hepatic scintigrams, using radioactive tracers for the demonstration of space-occupying defects in the liver, were first described in 1954 (36). The isotopes utilized over the years include Rose bengal iodine-131 ($^{131}I$), radioactive gold ($^{198}Au$), gallium-72 ($^{72}Ga$)

and technitium-99 ($^{99}Tc$). Technitium-99 has emerged to be superior to the other radioisotopes because of improved counting statistics, reduced scanning time, lower radiation dose and better spatial resolution. Approximately 80% of the technitium radioactivity is located in the liver, 10-15% in the spleen, and 5% in the bone marrow (37).

During evaluation of patients with suspected single tumor or significant metastatic disease, only 74-90% of those with documented liver lesions had abnormal scans (38). If accuracy rate of liver scans was evaluated in combination with plasma carcinoembryonic antigen (CEA) or standard liver function tests for the detection of hepatic metastases from carcinoma of the breast, it was found that the liver scan as a single test had a true-positive rate of 89% and a false-positive rate of 14%. When composite tests were performed requiring two individual tests being positive, a positive liver scan and abnormal CEA levels yielded 74% true-positive results with no false-positive outcomes (39).

A single tumor or metastasis have to be large to be detected on liver scan. The minimum size lesion that can be seen on the hepatic scintigram is 2.0-2.5 cm diameter where the tissue is 10 cm thick. Where the tissue is only 5 cm thick, a lesion of 1.5 cm can be seen (40,41). There is no question that liver scanning is still quite non-specific for tumor evaluation. Intra-observer errors of 15-20% (42), motion artefacts, anatomical variants of intrahepatic duct and vessel structures, conditions such as cirrhosis, benign tumors, large kidneys, congenital cysts, liver abscesses and dilated bile ducts all contribute to difficulties in interpretation. If one summarizes the current literature, liver scan accuracy for evaluation of metastatic liver disease ranges from 74-84% with false-positive rates as low as 13% and as high as 42%. False-negative rates vary from 10% to 25% (43,44).

In summary, one can conclude that liver scanning, although benign, has still too many false-positive findings to be utilized in routine preoperative liver screening of patients with operable extrahepatic solid tumors. It is also by itself not accurate enough in most instances to clearly define the intrahepatic, anatomical relationships of tumor to hepatic tissue as a preoperative requirement to define and guide a possible surgical intervention.

2. Sonography (ultrasonic echography)

Primary hepatic tumor

Ultrasonic echography is valuable for the general localization of liver mass lesions and it may be used to demonstrate the solid nature of the lesion as well as to confirm the presence or absence of necrosis within the tumor. In a careful study a group of investigators (45) described four specific patterns of liver tumors responding to sonographical examination: a) large, highly echogenic nodules representing metastasis from the gastrointestinal tract, b) trans-sonic nodules surrounded by a band of echoes caused by

necrotic metastases, c) a trans-sonic area within an echogenic parenchyma representing neoplasm within a cirrhotic liver and d) a trans-sonic hepatomegaly representing diffuse infiltration of the liver by primary neoplasm. Most investigators agree that ultrasonography still requires considerable individual experience to distinguish between cysts, abscesses, necrotic tumors or patterns related to the presence of cirrhosis (46). One advantage which sonography has developed through further recent technical improvements is its precise application with regard to sonographically guided biopsy of liver mass lesions (47,48).

Changes in the acoustic appearance of tumors (changes of size) in response to therapy may also permit the use of this technique to assess the efficacy of specific therapeutic agents. But at present, sonography can only be useful as an adjuvant diagnostic procedure for defining the presence and general localization of a liver tumor or metastatic lesion as well as facilitate percutaneous biopsy. Its usefulness for the precise description of the tumor-hepatic tissue is therefore limited by its rather confined sensitivity to exclude metastases of small size in presence of cirrhosis. Currently, there are no well controlled studies available which have compared systematically the sensitivity and accuracy of liver sonography for tumor diagnosis with scintigraphy, CT scanning or angiography.

3. Computed tomography (CT)

a. Indications for CT scanning

Computed tomography has rapidly gained recognition as a non-invasive technique for the evaluation of various organ systems. Though still in the state of great flux and rapid technical improvements, its present performance as well as known limitations promise further real contributions towards diagnostic evaluation and definition of hepatic tumors. At present, the following indications for CT scanning of the liver have been established (49).

1. Cystic diseases of the liver
2. Intrahepatic and perihepatic abscesses
3. Primary tumors of the liver
4. Metastatic disease of the liver
5. Differential diagnosis of jaundice
6. Differentiation of contour and focal defects on the isotope scan
7. Localization for percutaneous biopsy

CT studies of the liver are conducted without or with contrast enhancement by intravenous contrast agents. Intravenous injection of meglumine diatrizoate and sodium diatrizoate (Renografin) will raise the density of normal liver parenchyma. Intrahepatic abscesses, cysts or metastatic disease may subsequently become more clearly delineated. Intravenous injection of iodipamide methylglucamine (Cholografin) may be important for the recognition of intrahepatic tumors that are isodense as well as for the recognition of regenerating nodules.

In the normal CT anatomy the liver appears homogeneous in density with the exception of the biliary and intrahepatic venous system. The longitudinal fissure between the right and left liver lobe, the porta hepatis, the major biliary radicles and the intrahepatic venous system can be identified. This allows a fairly good delineation of the topographical anatomy of liver lesions.

b. CT scanning of primary benign tumors

These are very rare tumors and include cavernous hemangiomas, fibromas, leiomyomas, benign adenomas and regenerative nodules. As a rule benign liver tumors cannot be differentiated from malignant or metastatic liver tumors on the basis of the CT scan.

c. CT scanning of primary malignant tumors

The major representatives are the HCC, cholangiocarcinoma or the mixed type. They may occur as solitary mass, scattered nodules, or as diffuse infiltrating tumors. The use of intravenous, iodinated contrast material usually enhances the density differences between normal liver parenchyma and primary liver carcinoma. But on the bases of appearance and density it is so far impossible to differentiate diffuse or multinodular types of hepatocarcinomas from metastatic disease (49).

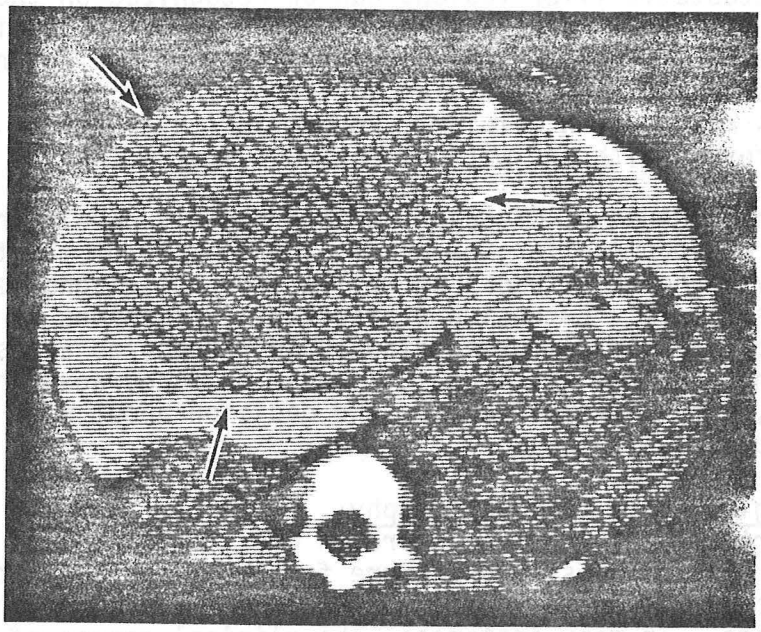


Figure 2. Large hepatoma replacing the entire right lobe of the liver.

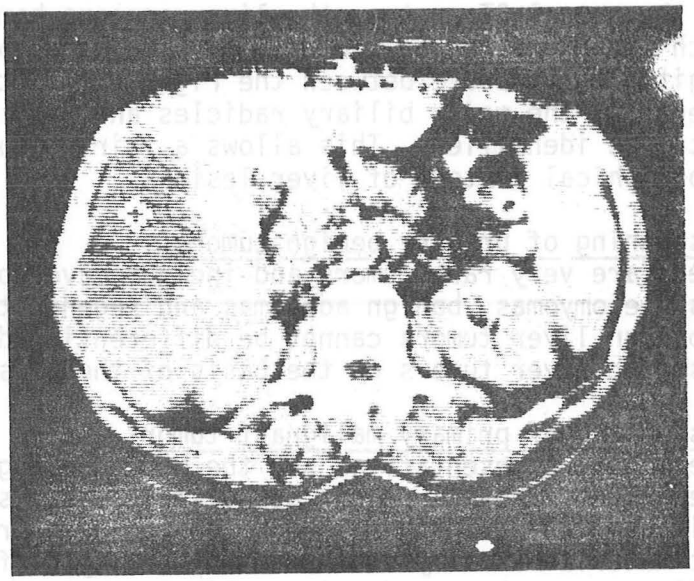


Figure 3. Metastatic, mucinous adenocarcinoma of the colon.

d. CT scanning and metastatic liver disease

Metastatic liver lesions can be recognized on the CT scan because of liver contour changes and alteration in density. Most liver metastases are solid but mucinous lesions of the colonic or ovarian carcinomas may display fluid consistency. Sometimes, metastatic lesions may contain calcium. For optimal evaluation, studies should be performed with and without contrast medium (49).

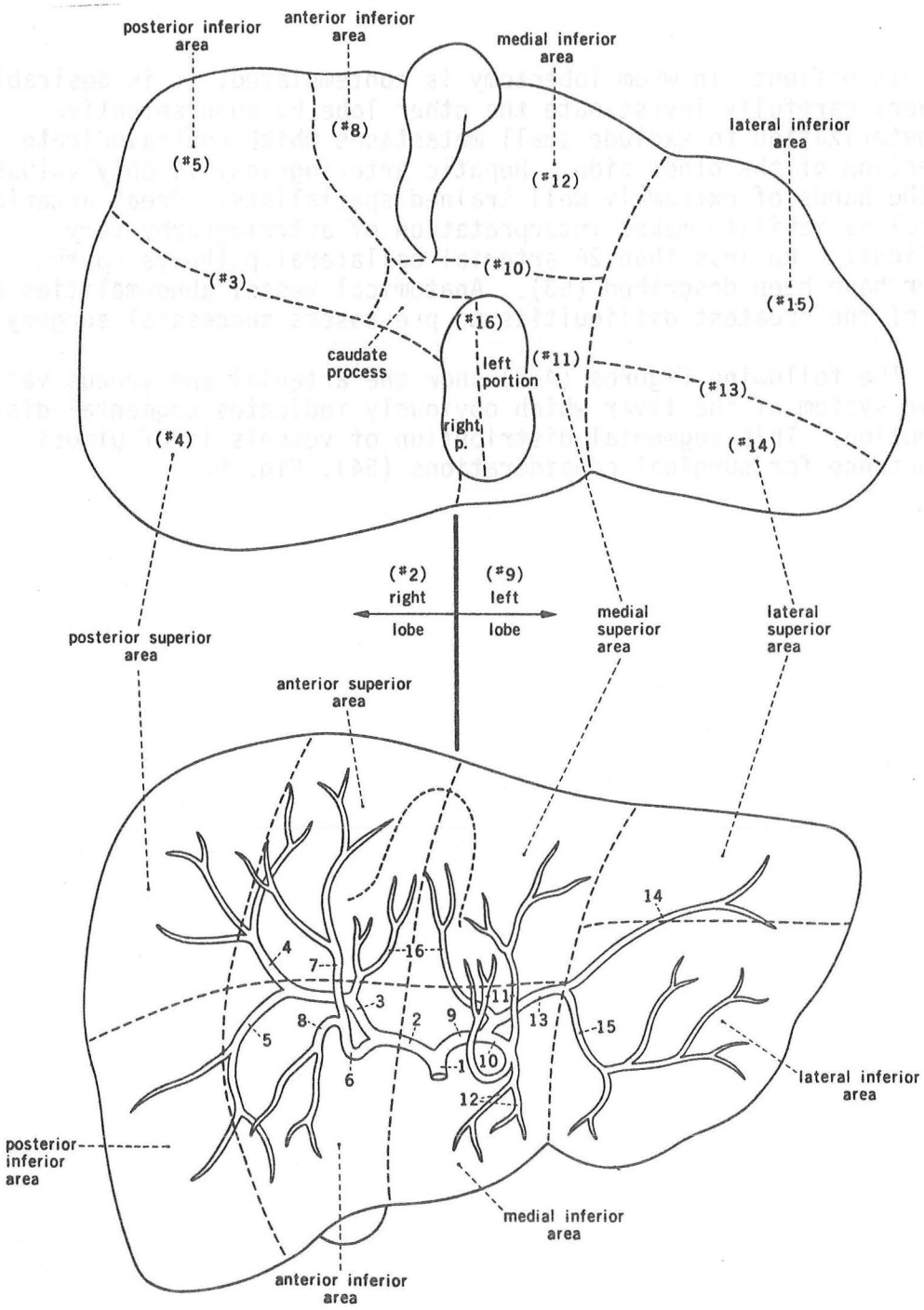
In conclusion, CT scanning is a rapidly developing technique with great promise for the precise definition of the topographical anatomy of hepatic tumors as well as for the diagnosis of the tumor species itself. Extensive statistical evaluations in comparison to other previously discussed diagnostic procedures are still lacking. Nevertheless, its availability should be encouraged whenever additional, vital information for the decision about mode of therapy is needed.

4. Angiography, portovenography

Arteriography has been proven over many years to likely be the single best diagnostic procedure for the detection and precise description of primary, and to a lesser degree, secondary hepatic neoplasms. In many instances, the clinical course of HCC or metastases and the therapeutic measure of choice depend on the gross anatomical type (50,51) which varies significantly from patient to patient along with histopathology of the tumor and the liver parenchyma (52). As long as arteriography defines the gross pathology of HCC or metastases in relation to the noncancerous portion of the liver, this procedure serves important clinical purposes. But even though the tumor is small and resectable by itself, if the noncancerous portion is highly cirrhotic, surgery proves catastrophic.

In patients in whom lobectomy is contemplated, it is desirable to very carefully investigate the other lobe by superselective catheterization to exclude small metastases which contraindicate resection of the other side. Hepatic arteriography is only valuable in the hands of extremely well trained specialists. Great arterial vessel variability makes interpretation of arteriography very difficult. No less than 26 arterial collateral pathways to the liver have been described (53). Anatomical vessel abnormalities are one of the greatest difficulties to pre-assess successful surgery.

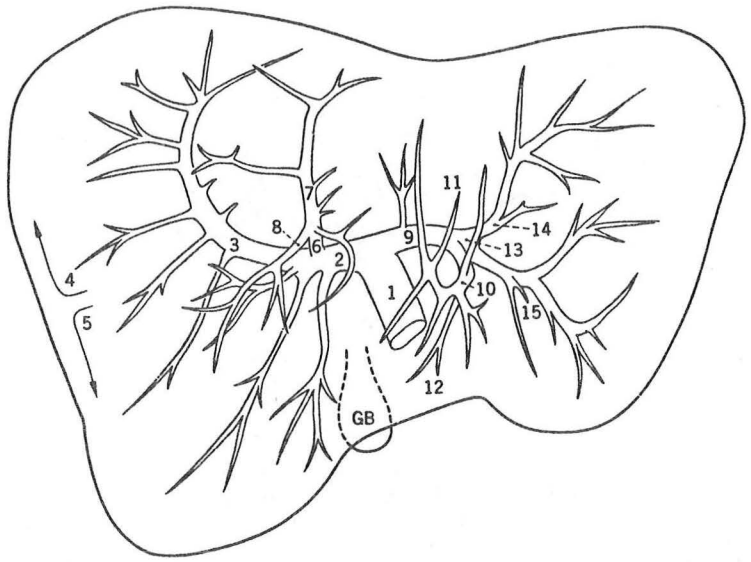
The following figures (4-7) show the arterial and venous vascular system of the liver which obviously indicates segmental distribution. This segmental distribution of vessels is of utmost importance for surgical considerations (54), Fig. 5.




Intrahepatic arterial distribution and liver segments. The true dividing line between the right and the left is the one that connects the gallbladder bed and the hepatic vein at its opening into the vena cava, being different from the falciform ligament or the anatomical line, which divides the lateral and the medial segment.

The numbers of the arteries are not the same as those in Figure 2-1. They are; 1: hepatic proper. 2 and 9: right and left hepatics, respectively, both sending off branches 16 to the caudate lobe. 3: posterior segmental artery. 4 and 5: arteries of the posterior superior and posterior inferior areas. 6: anterior segmental artery. 7 and 8: anterior superior and anterior inferior arteries. 10: medial segmental artery. 11: two arteries of the medial-superior area. 12: two arteries of the medial-inferior area. 13: lateral segmental artery. 14 and 15: arteries of the lateral superior and lateral inferior areas (Adapted from HEALEY, J.E., JR., SCHROY, P.C. and SORENSEN, R.J.: J. Intern. Coll. Surgeons **20**: 133, 1953).

Figure 4




The prevailing pattern of branching of the portal vein. 2 and 9 are the right and left main branches of the portal vein (PV) or 1; 3 is the posterior segmental vein, 4 and 5 are the veins for the postero-superior and postero-inferior areas, respectively; 6 is the anterior segmental vein, 7 and 8 are the veins for the antero-superior and antero-inferior areas. Of the branches of the left portal vein (9), 10 is the medial segmental vein, 11 and 12 are the veins for the medial-superior and medial-inferior areas; 13 is the lateral segmental vein, 14 and 15 are the veins for the lateral-superior and lateral-inferior areas (Adapted from Grant's Atlas of Anatomy). GB: gallbladder. They will be schematically represented as follows:

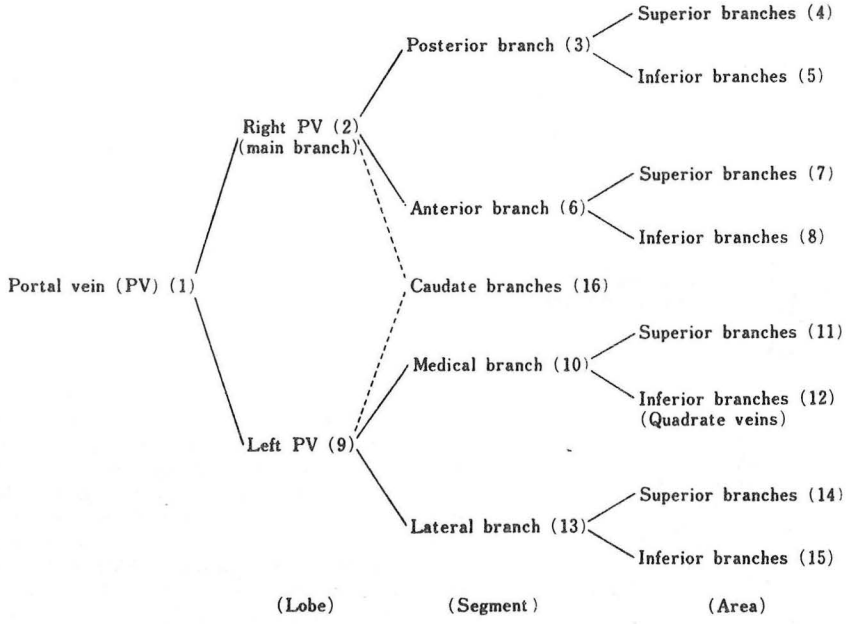
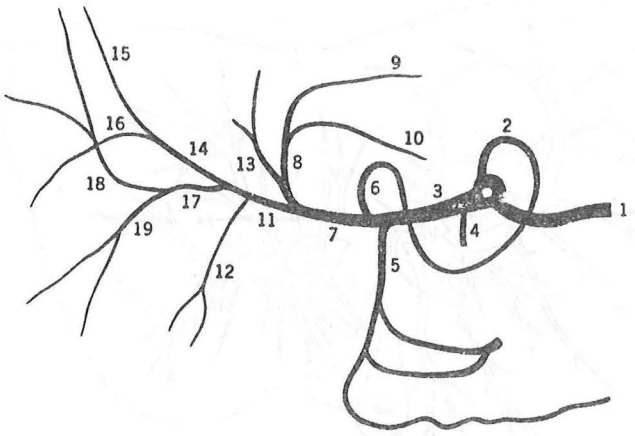
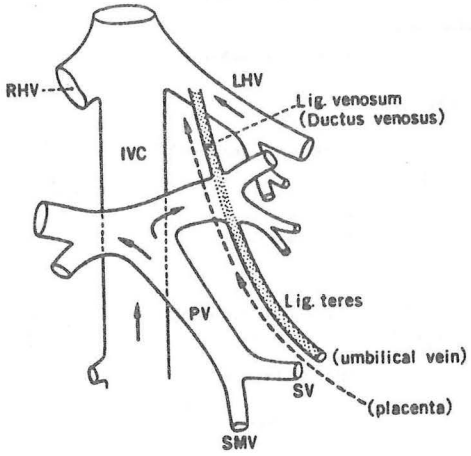



Figure 5




a. Schematic representation of the typical celiac arteriogram.
1: splenic. 2: left gastric. 3: common hepatic. 4: superior (dorsal) pancreatic. 5: gastroduodenal. 6: right gastric. 7: hepatic proper. 8: left hepatic. 9: lateral superior area branches. 10: lateral inferior area branches. 11: right hepatic. 12: cystic. 13: middle hepatic. 14: posterior segment arteries. 15: posterior superior area branches. 16: posterior inferior area branches. 17: anterior segment arteries. 18: anterior superior area branches. 19: anterior inferior area branches.

Figure 6




The anatomy of the Ligamentum teres and Lig. venosum in their relationship to the blood vessels, and the fetal circulation through the umbilical vein and Ductus venosus (dotted lines). In the fetus, the blood coming from the placenta bypasses the liver and enters the heart without going through the sinusoids. PV: portal vein. SMV: superior mesenteric vein. SV: splenic vein. IVC: inferior vena cava. RHV, LHV: right and left hepatic veins.

Figure 7

Basic angiographic changes which occur in liver tumors are (55):

1. Arterial displacement
2. Vessel encasement
3. Tumor vessels demonstrated in the arterial phase
4. Tumor stain
5. Zones of radiolucency
6. Halo effects in the capillary phase
7. Displacement of the portal vein
8. Visualization of the hepatic vein
9. Portal block with retrograde flow in the venous phase

Primary carcinomas are generally more hypervascular than secondary tumors.

a. Arteriography in hepatocellular carcinoma (HCC)

Some of the rather characteristic angiographic features which may enable a differential diagnosis between primary and secondary tumors are the 1) rich arterial supply of HCC and 2) the formation of new arteries which accompanies its growth. Early metastasis of HCC within the liver may be demonstrated as small discrete poolings of the contrast medium. The primary tumor types, defined by angiography, which appear to be resectable, are a) the solitary massive type of hepatocellular carcinoma, b) the confluent massive type and c) the encapsulated, slow growing type (54). Cholangiocarcinomas are rather hypovascular.

b. Arteriography in metastatic carcinomas

The effective diagnosis of metastatic liver carcinomas depends largely on the vascularity of the tumor. Hypovascular metastases are from lung, esophagus and pancreas, whereas hypervascular metastases are disseminated from renal cell carcinoma, leiomyosarcoma, hemangiosarcoma, thyroid carcinoma, malignant carcinoid and islet-cell carcinoma. Hypervascular tumors are visualized in the early arterial phase down to lesions as small as 1 cm diameter. Central radiolucency and the halo or rim sign are common in metastasis. There are many other additional features which cannot be discussed here.

Representative results of celiac angiography in livers with HCC (52) (Table X) and metastatic carcinomas (55) (Table XI) are shown below.

TABLE X

Celiac Angiography in Hepatocellular Carcinoma—Angiographic Findings *vs.* Gross Anatomical Types

| Gross Anatomical Type | No. of Cases | Frequency of Various Abnormalities (Per Cent) | | | | | | | | | Average Diameter of Hepatic Artery Proper (mm)* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Hypervascularity | Arterial Tumor Vessels | Displaced Large Vessels | Encasement of Arteries | Arterioportal (A-V) Shunts | Portal Regurgitation | Vascular Lake & Channel | Tumor Blush (Stain) | Coronary Lucent Rim | |
| Diffuse | 8 | 87 | 50 | 25 | 25 | 50 | 25 | 13 | 100 | 0 | 7.5 |
| Multinodular | 15 | 100 | 47 | 40 | 40 | 73 | 20 | 47 | 87 | 8 | 6.2 |
| Cirrhotic oligonodular | 11 | 64 | 0 | 27 | 9 | 9 | 0 | 0 | 91 | 7 | 4.7 |
| Encapsulated | 15 | 100 | 87 | 93 | 40 | 40 | 13 | 93 | 100 | 80 | 6.3 |
| Solitary | 26 | 100 | 77 | 85 | 62 | 46 | 19 | 69 | 88 | 0 | 6.6 |
| Confluent | 11 | 100 | 55 | 45 | 82 | 82 | 27 | 45 | 91 | 0 | 7.3 |
| Nodular massive | 14 | 100 | 86 | 79 | 64 | 71 | 36 | 79 | 100 | 0 | 7.1 |
| Average | Total 100 | 95 | 62 | 66 | 49 | 52 | 20 | 56 | 93 | 13 | 6.6 |

* Measurement on films.

TABLE XI

Alterations in celiac angiograms in primary and metastatic liver carcinomas.

| Type | No. of cases | A-V shunt | Hypervascularity & tumor vessels | Tumor stain | Dilatation of large arteries | Displacement of large vessels | Portal vein regurgitation |
|---|---|---|---|---|---|---|---|
| Primary | 92 | 81.5% | 90.2% | 100% | 59.2% | 43.4% | 14.1% |
| Secondary | 62 | 0 | 40.4 | 72.6 | 15.5 | 29.4 | 0 |

c. Contraindications and complications of celiac angiography

Heart disease, dehydration, renal failure, hepatic failure, aneurysms, advanced atherosclerosis, obliterative vascular disease, bleeding tendencies and a severely debilitated state have been recognized as contraindications for celiac angiography. Major complications include reactions to the contrast agent, hematoma formation at site of needle or catheter insertion and arterial thrombosis which occurs in about 0.5% according to Lang (55).

d. Splenoportography

Splenoportography is primarily indicated in the diagnosis of portal hypertension and only plays a minor role in cancer diagnosis. However, this technique has been successfully applied to define tumor growth in the portal vascular bed (56,57).

e. Umbilico-portography (transumbilical portography, Fig. 5) has also mostly been utilized for the diagnosis of portal hypertension as well as for tumor diagnosis in the portal venous branches. This technique, compared to splenoportography, results in "hepatograms" of greater density since a large volume of contrast media can be injected rapidly into the main portal vein near the liver. Using this technique, tumors as small as 1 cm in diameter can be seen as filling defects (58).

f. Conclusion

In experienced hands, angiography of the liver (especially in conjunction with scintigraphy) leads in over 95% of liver tumor cases to precise diagnosis and anatomical-topographical description of the cancer-noncancerous tissue relationship (59). Therefore, this diagnostic technique is clinically essential for cases which may be possible candidates for surgical therapy or hepatic artery infusion with chemotherapeutic agents.

5. Serum tumor markers

Serum tumor markers such as α-fetoprotein (α-FP) or carcinoembryonic antigen (CEA) have been considered for a long time as important information for 1) tumor diagnosis, 2) therapeutic success and 3) therapeutic follow-up.

a. Alpha-fetoprotein (AFP)

Bergstrand and Czar (60) found in 1956 an alpha-1 globulin in human fetal serum which was noted by Tatarinov (61) in 1964 to be

significantly elevated in sera of patients with hepatocellular carcinoma. Prior to Tatarinov's discovery, another team of Russian investigators had observed the production of alpha-1 fetoprotein by experimental hepatoma tissue (62). AFP is a glycoprotein of the approximate molecular weight of 72,000 (63). At polyacrylamide electrophoresis it appears as a distinct band between albumin and alpha-1 antitrypsin (64) and it contains about 4% carbohydrate of which three residues are terminal sialic acid (65). At least four different isoproteins have been uncovered (65) and no difference has been found between fetal and hepatoma-derived AFP (66).

The human fetus synthesizes AFP until about the 32nd week of gestation with a rapid fall of serum levels from thereon. Maternal serum AFP concentrations rise during gestation, presumably by fetal-maternal transfer (67). AFP reaches its normal, very low serum level as observed in adulthood during the first year of postnatal life.

Elevations of AFP have been observed in infants and adults with viral hepatitis, biliary atresia, neonatal hepatitis, congestive hepatomegaly from cardiac defects, hepatoblastoma, teratomas, ataxia telangiactasia and hereditary tyrosinosis (68), but serum levels are usually far below concentrations seen in the presence of hepatic tumors.

AFP-positivity rates in established primary liver cell cancer

AFP-positivity rates show apparent geographical differences. The highest AFP-positivity rates reported are 87% in Indonesia, 78% in Senegal, 73% in Taiwan, 59% in Hong-Kong and 66-71% in Uganda (69).

The lowest AFP-positivity rates are in Britain, 29%; and USA, 28-50%. The Chinese Co-ordinating Group for Liver Cancer, in screening nearly half a million people, found an AFP-positivity rate of 75.6% in liver cancer cases (69). Ten to 20% of HCC in various ethnic populations are not AFP producers.

AFP levels do not correlate with any tests for liver function, they do not assist in predicting the outcome of a liver cancer case and there is no apparent correlation of serum AFP level with tumor size (70). Nodular and poorly differentiated tumors had higher AFP levels than well-differentiated or anaplastic and diffuse or massive tumors. By the time liver cancers are seen in Southern Africa, they are nearly fully evolved and AFP levels increase by only 50% in the few months between diagnosis and death (71). Successful hepatic surgery leads to rapid fall of AFP levels and reappearance of AFP correlates to recrudescence of the disease (72). Somewhat unexpectedly Alpert and Feller (73) presented recent evidence that liver regeneration does not induce AFP synthesis.

Various attempts of mass screening for primary HCC with AFP determinations in various ethnic populations have not fulfilled the expectations that this method could be of preventive medical importance. Only rarely have primary HCC's been discovered on the basis of AFP testing alone. Most patients with positive AFP levels were already

clinically symptomatic and would have been diagnosed anyway by other means. This problem was more pronounced in African patients than in Chinese. It probably correlated to a more rapid tumor growth in Africa than in Taiwan (69). One can therefore conclude that AFP measurements with the sensitive radioimmunoassay (RIA) will help in most instances to confirm the diagnosis of primary HCC and represent a potent test to monitor cancer recurrence after successful hepatic resection. But this assay has not been shown to be of value in massive screening programs.

b. Carcinoembryonic antigen and the liver

Another "tumor marker" which has occasionally been implicated in being of some value in monitoring tumor involvement of the liver is carcinoembryonic antigen (CEA). CEA was first isolated from human colonic carcinoma by Gold and Freedman in 1965 (74). CEA is a β-migrating glycoprotein with a molecular weight of approximately 200,000. It contains roughly 50% carbohydrate and 40% protein. Carbohydrate constituents include N-acetylglucosamine, sialic acid, fucose, mannose and galactose (75). The specificity of CEA levels for the diagnosis of gastrointestinal malignancies as well as subsequent metastatic disease in the liver is limited by the findings that increased circulating levels of CEA may be associated with a variety of other liver conditions besides cancerous involvement. CEA can be elevated on the basis of alcoholic cirrhosis (88% of cases), chronic active hepatitis (22% of cases) and primary biliary cirrhosis (50%) (75).

Patients with hepatic metastasis from carcinoma of the stomach or colon showed in 71% of cases elevation of CEA whereas only 46% with nonhepatic metastasis had elevated CEA levels (76). Serum CEA concentrations were found to be raised in 28 of 72 black Africans with confirmed HCC (77). No significant correlation could be demonstrated in individual patients between serum CEA concentration and various liver function tests. There was also no correlation between serum CEA and AFP levels. These uncertainties about the clinical specificity and relevance of CEA in aiding diagnosis of liver malignancies rule out at present the routine clinical application of CEA testing when liver tumors are suspected.

## III. Therapy

### Introduction

More often than not, primary and secondary tumors of the liver, when found, are beyond the bounds of cure by resection. Radiotherapy, systemic chemotherapy, regional infusion of the liver with chemotherapeutic agents through the hepatic artery or portal vein, and hepatic de-arterialization have all been recommended and tried for these unfortunate patients. In the late stage of tumor involvement with significant compromise of liver functions, any therapy which may cause further injury to the hepatocytes may be contraindicated (78).

### 1. Radiotherapy

It has been recognized that the liver is quite radiosensitive. Doses of more than 3,000 rads at a rate of 1,000 rads per week may

produce radiation hepatitis. This syndrome is expressed as hepatomegaly and ascites which is the result of radiation injury to the hepatic venules and induces a syndrome similar to Budd-Chiari. Also the kidneys may be damaged with whole-field irradiation of the liver. Nevertheless, radiation therapy was attempted in a variety of patients who were believed not to be accessible to any other successful form of therapy. As early as 1956, Ariel reported rather optimistically about symptomatic responses lasting from 9 months to 50 months in 5 of 10 patients with primary liver cell cancer who were treated with external radiation (79).

Phillips and Murikami (80) recorded the response to radiation therapy in 26 patients with primary hepatic carcinoma during 1933-1959. Mean survival after therapy with less than 2,000 rads was 2 months but tumor regression was observed with doses higher than 2,000 rads (mean survival 12 months). Only a small percentage of these patients (including 5 children with probable hepatoblastoma) came to autopsy not allowing an interpretation of results related to tumor type.

Cohen et al. (81) in South Africa treated 9 patients with primary hepatic carcinoma with doses between 2500-4000 rads. One patient died shortly after treatment and 8 survived for 3-34 weeks. Autopsies showed disappearance of all liver tissue comparable to a total hepatectomy on basis of radiotherapy.

In 1971, El-Domeiri reported his results with 31 patients who received radiotherapy of 1000-3600 rads for primary liver tumors. Seventy percent of the patients were dead in less than 6 months and one lived more than one year (82).

Lin (83) reported poor results from radiotherapy in 28 collected cases, but Plengvanit et al. (84) described relief of pain in 40% and objective remission (>2 months) in 35% of 32 patients with primary liver cancer who were treated with at least 4,000 rads.

A comprehensive report (85) from members of the Primary Liver Cancer Research Unit (PLCRU) in South Africa (Falkson et al. 1967-1975) included the results of 59 patients who were randomly allocated to receive radiotherapy (Table XII). Also these data seem to imply that external radiation of different dose schedules had little to offer for patient survival.

TABLE XII

Radiotherapy

| Group No. | No. of Patients | Treatment | Median Survival in Days |
|---|---|---|---|
| I | 8 | 250-400 rads, alternate days, total 3,000 rads to whole liver | 125 |
| II | 7 | 250-400 rads, alternate days, total 3,440 rads, mainly tumor | 78 |
| III | 27 | Telecobalt | 90 |
| IV | 7 | 10 fractions for 14 days, total 800 rads; Procarbazine 300 mg daily p.o. | 59 |
| V | 8 | 250-400 rads twice weekly, total 2,900 rads; hydroxyurea 50 mg/kg p.o. daily | 86 |

In 1976, Ong and Chan (86) reported that of 11 of 81 patients with inoperable carcinoma of the liver, randomized to receive radiotherapy, one survived 5 weeks, 3 patients died within one month and 7 died within 3.5 months. This was not different from 15 patients who had no treatment.

All the above reports strongly suggest that radiotherapy (with and without chemotherapy (87)) in general does not contribute in any significant way to overall patient survival. But nevertheless in a more recent report, Weichselbaum et al. (88) present strong evidence that palliative radiation for pain in metastatic liver (metastases from various origins), given in 300 rads fractions for a total of 2,100 rads, led to complete pain relief in 25 of 28 patients. Since pain in liver cancer patients is the most frequent and most imposing symptom, this beneficial effect should be truly appreciated.

2. Chemotherapy

a. Introduction

Most patients who are diagnosed at the present time with a hepatic malignancy have unresectable tumor mass(es). This often advanced stage of hepatic tumor involvement is symptomatic with upper abdominal pain or mass, loss of appetite, nausea, vomiting or jaundice. Since in the majority of these cases hepatic surgery is not indicated, chemotherapy has emerged as the primary treatment

modality over the last 20 years. A survey of the available literature reveals that the validity of many uncontrolled clinical studies, often involving small patient numbers, is severely limited by the continuing controversy about properly selected control groups. Concurrent, closely matched, randomized control groups within a clinical trial of cancer chemotherapy evaluation have seldom been used because of the limited number of patients available with the rather rare tumors to be evaluated. Most previous cancer treatment trials have utilized either a non-responding group of patients as control compared to treatment-responders or have accepted "historical controls" as a valid approach to clinical trials. The majority of clinical liver cancer trials have utilized such "historical controls" which represent the natural course of the disease (not necessarily though under standard clinical treatment conditions). Unless the numbers in the "historical controls" are large and the prognostic variables well matched, this approach should be viewed cautiously by the physician.

b. Clinical trials in cancer therapy

The evaluation of a new drug thought to be potentially suitable for cancer therapy goes through a series of well defined steps (89).

1. Acquisition of materials for evaluation.
2. Evaluation and selection (screening) of material for further development.
3. Preclinical studies-formulation, toxicology, pharmacology.
4. Clinical phase I, II and III trials.
5. Introduction into medical practice (Phase IV).

Step 4 in the drug evaluation program, starting with Phase I trials and the administration of a new drug to man, is the most dramatic and critical single step in the evolution of a new drug. Phase I, II and III trials have the following end points (89).

PHASE I STUDY

1. Establishment of a maximum (safely) tolerated dose on a given schedule and route of administration.
2. Establishment of the toxicity patterns and a determination of whether the toxicity is predictable, tolerable and reversible.
3. Evidence of anti-tumor activity.

The Phase II studies are investigations that determine whether a new drug has anti-tumor activity worthy of further clinical evaluation. Practically all available clinical trials evaluating modalities of liver cancer chemotherapy are Phase II studies. The important end points are:

PHASE II STUDY

1. Measurable and reproducible decrease in the size of a lesion in a specified period of time.
2. In general, the duration of a partial or complete response must be at least one month.
3. Measurement of survival.

With regard to the first end point of the Phase II trial, Moertel (90) has recently shown that a 50% change in the products of the longest perpendicular diameters of a measurable lesion is a reasonably accurate and reproducible measurement. The commonly used criteria of objective response and disease progression in solid tumors, which are adhered to by most authors, are shown in the following table (89).

TABLE XIII

Commonly Used Criteria for Objective Tumor Response

| | |
|---|---|
| Complete Response: | Complete disappearance of all demonstrable disease. |
| Partial Response: | ≥ 50% reduction in the sum of the products of the longest perpendicular diameters of discrete measurable disease, with no demonstrable disease progression elsewhere. |
| No Response: | No change in the size of any measurable lesion or < 50% reduction of measurable disease as defined above. |
| Progression: | > 50% increase in the sum of the products of the largest perpendicular diameter of any measurable lesion. |

End point 3 of the Phase II trial (measurement of survival) is mostly defined as mean or median survival calculated from the day of treatment initiation. These terms have already been defined on page 5. Within the Phase II studies there are two predominant designs: The first is a drug-oriented approach in which a large number of patients with a variety of diseases are treated with a particular drug. This has been the classical Phase II investigation through which the active drugs such as 5-fluorouracil, cyclophosphamide, methotrexate and, more recently, adriamycin, have been detected. The second major type of Phase II trial is the disease-oriented study. The critical factor in this approach is that the prognostic variables which may affect response are accounted for in the study design. These studies

are either being performed in a controlled randomized fashion or a non-randomized sequential manner. This second major type of the Phase II trial is mostly utilized in the studies of current liver cancer treatment programs.

And finally, a Phase III trial for a new drug is a study in which the drug is given to large numbers of patients to determine the following end points (89).

PHASE III STUDY

1. Confirmation of efficacy seen in Phase II.
2. Occurrence of unexpected events, such as new types of efficacy or adverse effects.
3. Value of the drug in relation to other potential therapies for the tumor.

c. Common drugs utilized in liver cancer therapy

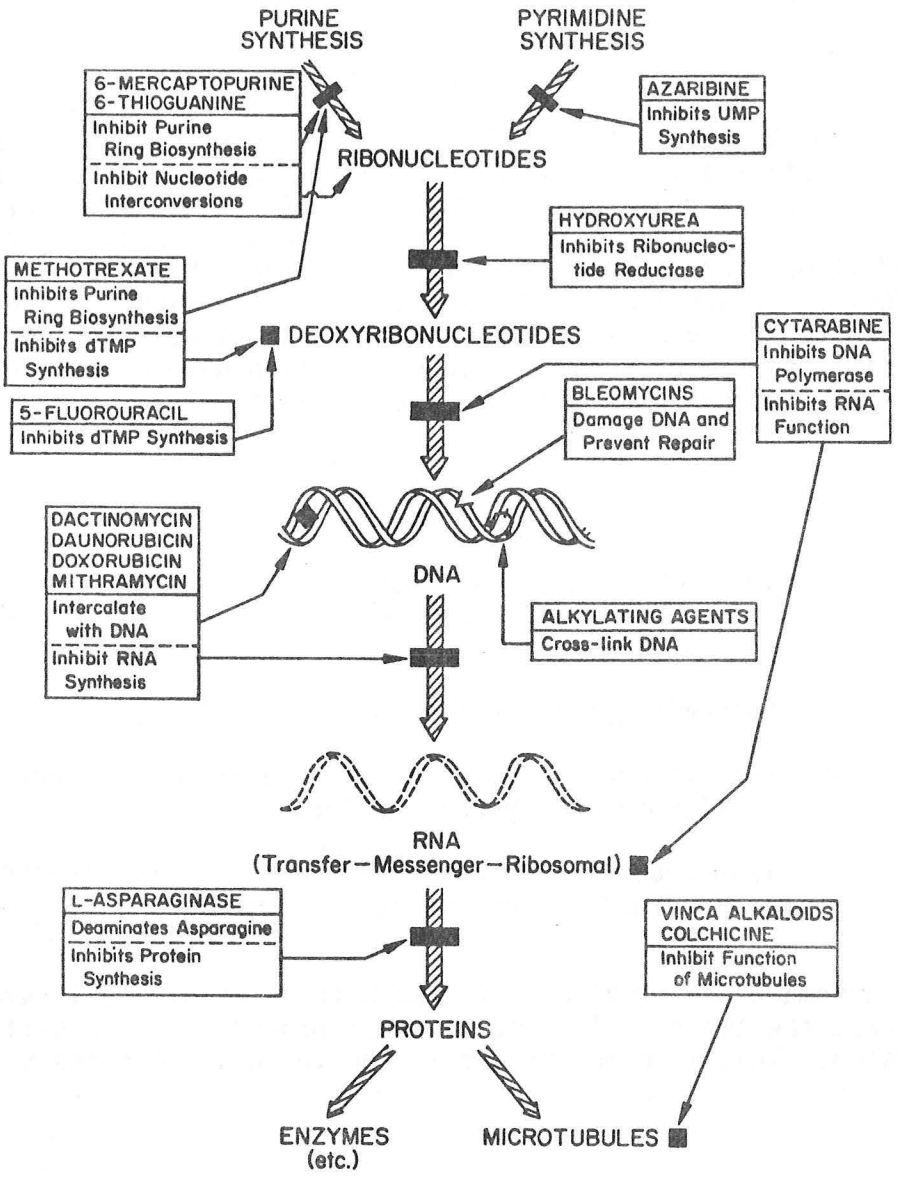
Almost all chemotherapeutic drugs which have shown some effectiveness in the treatment of other than hepatic malignancies have been applied to the treatment of primary or secondary hepatic tumors. These drugs are shown in the following table where they are specified by "class" and "type of agent".

TABLE XIV

Chemotherapeutic Agents for Liver Cancer Treatment

| Class | Type of Agent |
|---|---|
| **A. Antimetabolites** | |
| Fluorouracil (5-Fu) | Pyrimidine analogs |
| Fluorodeoxyuridine (FUDR) | |
| Cytosine Arabinoside (Cytarabine) | |
| Methotrexate (Amethopterine) | Folic acid analog |
| **B. Alkylating Agents** | |
| Carmustine (BCNU) | Nitrosoureas |
| Lomustine (CCNU) | |
| Semustine (Methyl-CCNU) | |
| Streptozotocin | Antibiotic |
| Mitomycin C | |
| Dacarbazine (DTIC) | Triazenes |
| **C. Natural Products** | |
| Vincristine (Velban) | Vinca Alkaloid |
| Bleomycine (Blenoxane) | Antibiotics |
| Doxorubicin (Adriamycin) | |
| **D. Miscellaneous Agents** | |
| Hydroxyurea (Hydrea) | Substituted Urea |

A summary of the mechanisms and sites of action of chemotherapeutic agents useful in neoplastic diseases is presented in Fig. 8 (91).




*Summary of the mechanisms and sites of action of chemotherapeutic agents useful in neoplastic disease.*

Figure 8

d. Techniques of drug application

The early experiences with systemic treatment of primary or secondary hepatic tumors with chemotherapeutic agents have been rather disappointing. This was probably the result of rather ineffective drugs or drug schedules than the route of application. Subsequently administration of chemotherapeutic agents into an artery was first described by Bierman et al. (92) and Klopp et al. (93). Their idea was soon applied to the chemotherapy of liver malignancies by utilizing the technique of hepatic artery catheterization by way of the brachial (94) and the femoral arteries (95). Direct transabdominal catheterization was also carried out by Miller and Griman (96) which has since been used extensively.

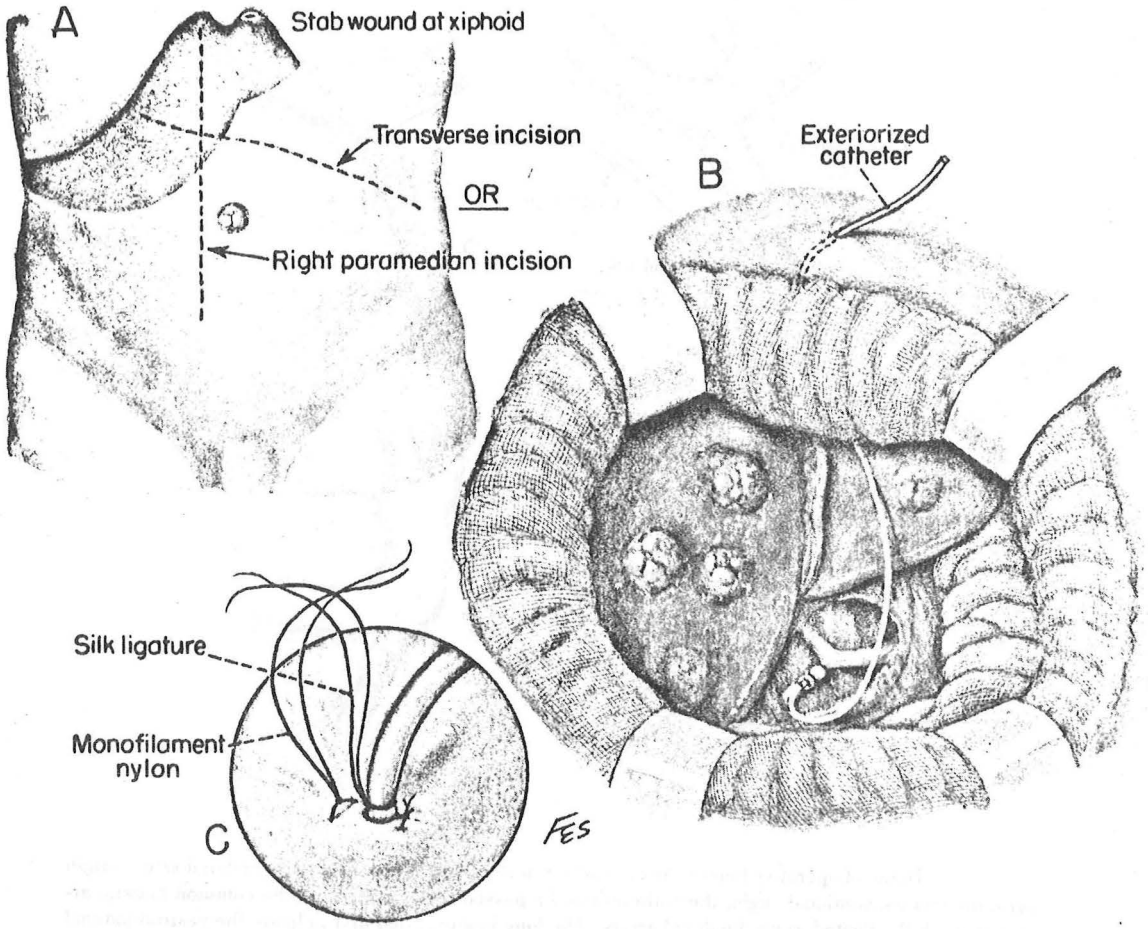
A technique of temporary occlusion of the hepatic artery with intermittent oncolytic drug infusion has recently been described by Bengmark and Fredlund (97). Considerable theoretical rationale exists for hepatic artery infusion. The normal hepatocyte has a low mitotic rate and is nourished by a dual vascular supply (portal vein and hepatic artery). Neoplastic disease in the liver should theoretically have higher mitotic activity than the hepatic parenchyma. In addition, both primary as well as secondary hepatic tumors are predominantly supplied by the hepatic artery. Higher, localized drug concentrations within the tumor tissue as well as less systemic toxicity because of hepatic drug elimination have been favored arguments of proponents for hepatic artery infusions.

TABLE XV

Modes of Antineoplastic Drug Administration in Liver Tumors

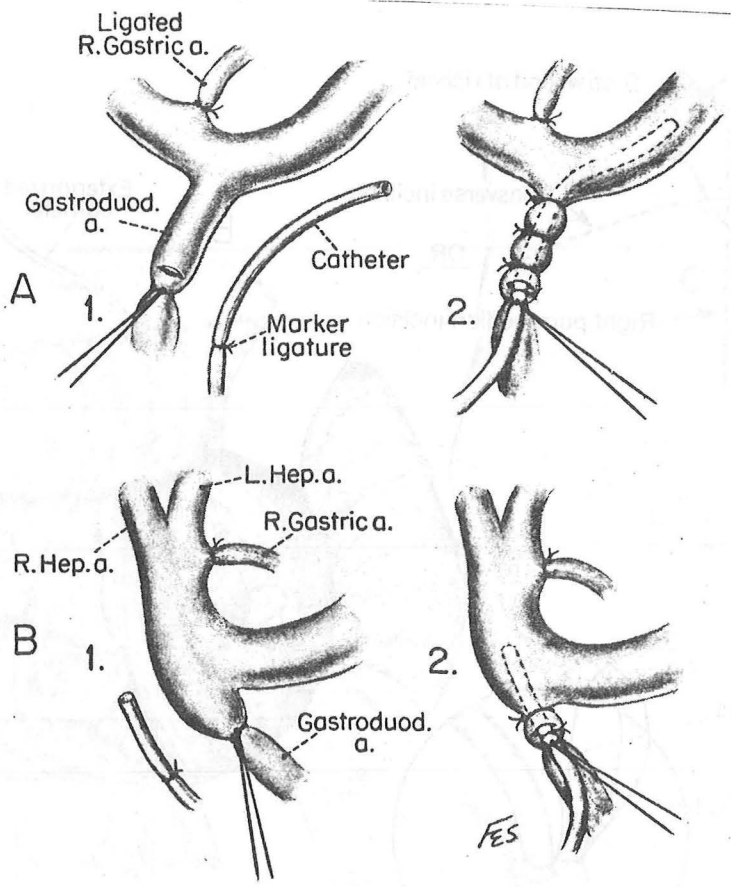
1. Systemic (peripheral veins)
2. Percutaneous arterial catheter into hepatic artery (femoral or brachial artery)
3. Transabdominal catheter placement through gastroduodenal or gastroepiploic artery

Bengmark and Fredlund (97) and Watkins et al. (98) have recently reviewed the technically most advanced procedures of hepatic artery infusion. This is demonstrated in the following Figures 9-13.



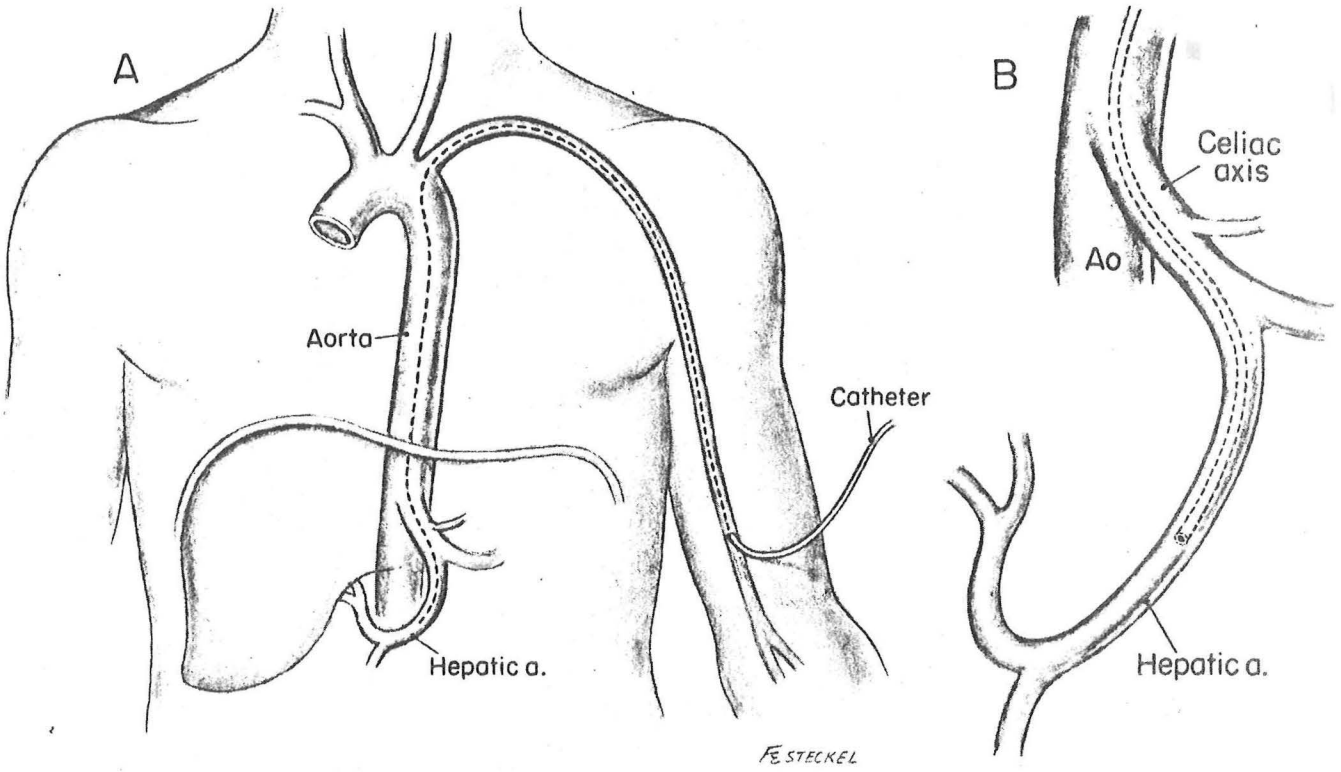

Operative placement of arterial infusion catheter. (A) Either a transverse incision or a right paramedian incision may be employed according to the preference of the operating surgeon. (B) Exposure of the hepatic artery and gastroduodenal artery with retrograde placement of the catheter in the unobstructed common hepatic artery through the ligated gastroduodenal artery. (C) Detail of securing exteriorized catheter at the skin surface. A silk ligature grooving the wall of the Teflon infusion catheter is tied to a monofilament nylon skin suture.

Figure 9



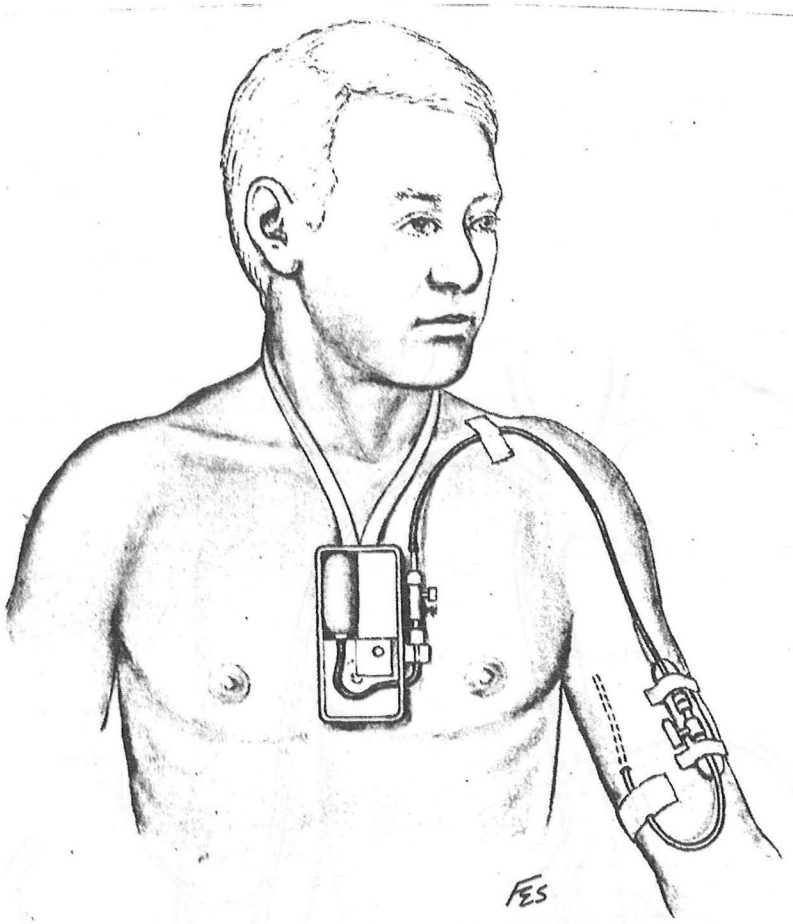

Detail of operative hepatic artery catheterization. (A) When the gastroduodenal artery origin presents this conventional angle, the catheter can be passed retrogradely into the common hepatic artery through the ligated gastroduodenal artery. The long ligature, tied first to ligate the gastroduodenal artery (A.1), is then tied firmly to groove the wall of the Teflon infusion catheter to hold it in position (A.2). (Encircling ligatures about the gastroduodenal artery will not hold the catheter in the correct position.) (B) When the gastroduodenal artery takeoff presents this unconventional angle, passage of the Teflon catheter into the hepatic artery in the retrograde direction predisposes to the hazard of vessel wall erosion. The catheter must be directed downstream in the hepatic artery, with the catheter tip at least 1 cm proximal to the anatomic bifurcation of the common hepatic artery.

Figure 10



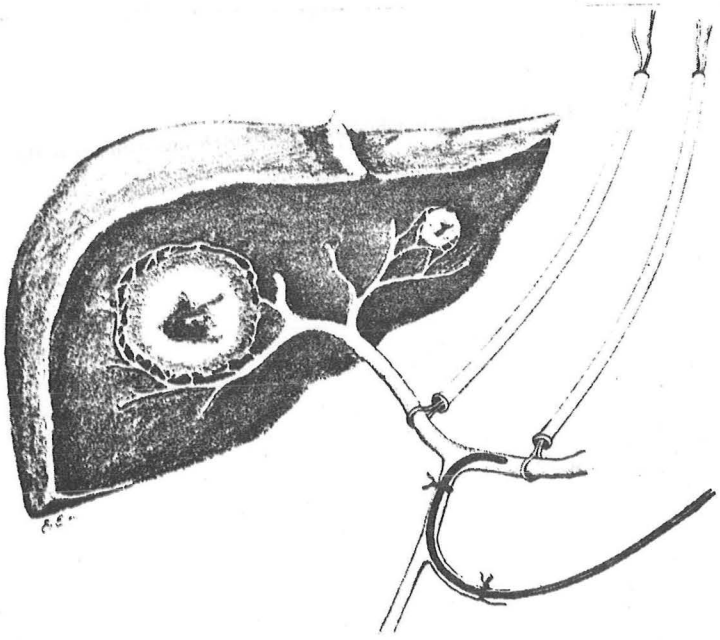

Localization of brachial artery percutaneous catheter in the common hepatic artery.

Figure 11




Method of attachment of chronometric infusion pump to brachial artery catheter for protracted ambulatory outpatient infusion.

Figure 12



Temporary occlusion of the hepatic artery can be produced by tightening the strangulating catheters placed proximal and distal to the gastroduodenal artery. Oncolytic drugs may be infused intra-arterially through a catheter inserted in the gastroduodenal artery.

Figure 13

Catheter placement into arteries for infusion of cytotoxic drugs creates conditions for potential complications. Such complications may include the following.

TABLE XVI

Potential Complications of
Intra-Arterial Infusions

1. Percutaneous Puncture Site

   Infection-local and systemic

   Leakage and cracks

   Hemorrhage

   Thrombosis-embolism

2. Catheter Tip

   Dislodgment

   Blockage

   Thrombosis-arterial occlusion; retrograde propagation

   Embolization

   Bleeding

   Migration of catheter tip and perforation

3. Systemic Toxicity

   Catheter dislodgment

   Incomplete drug absorption or inactivation

Several new modifications have recently been advocated to further improve arterial infusion of oncolytic agents. Kaplan et al. (99) infused prior to chemotherapy radiotracers ($^{99m}$Tc-sulfur colloid) at flow rates approximating those attained with infusion pumps into the catheter. They believe to be able to predict more reliably the potential flow distribution of the chemotherapeutic agents within the tumor vascular bed.

Another group suggested the use of vasoconstrictors concomitant with intra-arterial chemotherapy (100). The aim of this technique is to divert the flow of cytotoxic drugs from the vasoconstrictor

sensitive arterial bed of normal liver tissue towards the rather vasoconstrictor-insensitive vascular bed of tumor tissue. The possible benefit of any of these modifications has still to be evaluated.

e. Results of liver cancer treatment with chemotherapy

A great number of studies have been published utilizing almost every available anti-neoplastic agent in various concentrations and combinations. Most studies deal with insufficient patient numbers, do not adequately define possible prognostic indicators and tumor status, and make critical evaluation an almost impossible task. The following account will list some of these studies as a basis for further discussion.

Chemotherapy of primary hepatic carcinoma

Falkson (101) recently summarized his as well as the experience by the PLCRU with the randomized controlled clinical trials of more than 500 Bantu patients with primary liver cell cancer, of whom only 7 survived more than one year. At the PLCRU, 28 patients randomized to receive vitamin C as placebo had a median survival time of 89 days from admission to the hospital and a median survival time from the start of treatment of only 64 days. Falkson believes that this is the only randomized control group reported in the literature until 1976 and is therefore a standard for comparison with other forms of chemotherapy. Falkson and the PLCRU utilized a great variety of alkylating agents, antimetabolites, anti-tumor antibiotics and chemotherapy combinations which until 1975, gave no satisfactory results and did not significantly improve survival of these patients.

Lee (102) reviewed the state of the art of systemic and regional treatment of primary carcinoma of the liver until 1977. Systemic chemotherapy with various chemotherapeutic agents, before the availability of adriamycin, showed only modest benefit. Despite unquestionable objective evidence of tumor regression in a few instances, chemotherapy was not found to significantly prolong survival time of primary carcinoma of the liver. The following table summarizes a few of the results reported in the literature with regard to systemic drug treatment.

TABLE XVII

Response of Primary Hepatic Carcinoma to Systemic Chemotherapy

| Study | Drugs | Median Survival (Months) |
|---|---|---|
| Plengvanit (103) | Nitrogen mustard ± prednisone | 6.1-7.4 (4.1-untreated) |
| Chan (104) | 5-Fu | 2.4 (1.6 controls) |
| Olweny (105) | Adriamycin | 8 (Range 1-13 mos.) |
| Moertel (106) | 5-Fu + BCNU | Objective response in 7 of 19 patients; complete remission for 3.4 and 6 years in 3 patients. |

After the initial data by Olweny (105) were reported showing significant improvement of median survival as well as tumor regression in his African patients treated with adriamycin, a prospective randomized clinical trial was initiated by the Eastern Cooperative Oncology Group (ECOG, 1974-1978). The results of their 168 patients (North American and South African) with unresectable primary liver cancer treated with four different drug schedules were published in November 1978 by Falkson et al. (107). This representative study will be analyzed in more detail.

Patients were randomized to receive treatment with oral 5-Fluorouracil (5-Fu), oral 5-Fu plus streptozotocin, oral 5-Fu plus methyl-CCNU or adriamycin alone. The single agent treatments (oral 5-Fu and adriamycin) were associated with less gastrointestinal toxicity than were the oral 5-Fu treatment combinations. Toxicity was mostly related to the hematologic or gastrointestinal system and occurred in more than 60% of all patients evaluated for toxicity. A total of 15 partial responses were reported. Adriamycin appears to be the most active agent and responsible for 9 of the 15 responses. The 48 patients randomized to oral 5-Fu alone showed no responses. The survival associated with oral 5-Fu alone was significantly shorter than the survival time associated with the remaining 3 treatment programs among both North American and South African patients. Covariates of prognostic significance were treatment, initial performance status and sex. South African black patients had a shorter survival time than North American black patients. If one excludes oral 5-Fu from consideration, prognostic variables appeared to dominate any differences between the remaining treatments under study.

All patients had histologically confirmed hepatocellular carcinoma or cholangiocellular carcinoma. From the 168 patients entered into the study, 156 cases could be analyzed for toxicity, response and survival. All patients were stratified by presence and absence of active heart disease, jaundice (presence or absence), cirrhosis (presence or absence) and performance scale. The performance scale was as follows:

0 = fully active

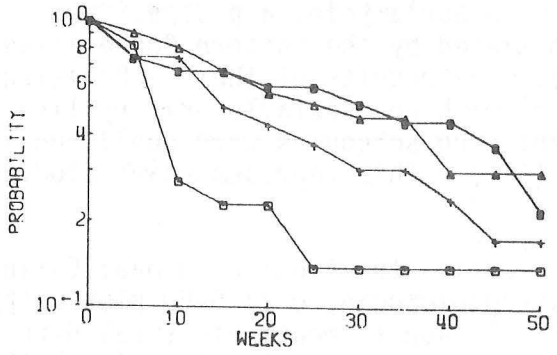
1 = ambulatory, capable of light work

2 = in bed <50% of time, capable of self-care but not of work activities

3 = in bed >50% of time, capable of only limited self-care

4 = ineligible for study

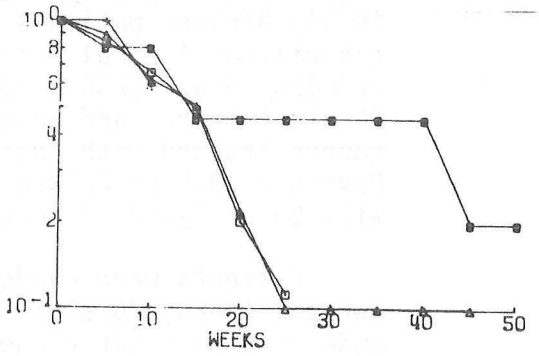
The following figures (14-17) (107) display the relationship between treatment and survival for North American white patients, North American black patients and South African black patients as well as the influence of performance status on survival. Median survival with oral 5-Fu was 7 weeks in North American white patients, 15 weeks in North American black patients and 4 weeks in South African black patients.




| TREATMENT | ALIVE | DEAD | TOTAL | MEDIAN |
|---|---|---|---|---|
| □ Oral 5-FU | 0 | 22 | 22 | 7.3 |
| ● Oral 5-FU + Streptozotocin | 2 | 13 | 15 | 31.1 |
| △ Oral 5-FU + Methyl CCNU | 1 | 20 | 21 | 26.1 |
| + Adriamycin | 1 | 15 | 16 | 15.0 |

Survival by initial treatment–North American whites (patients with no prior chemotherapy).

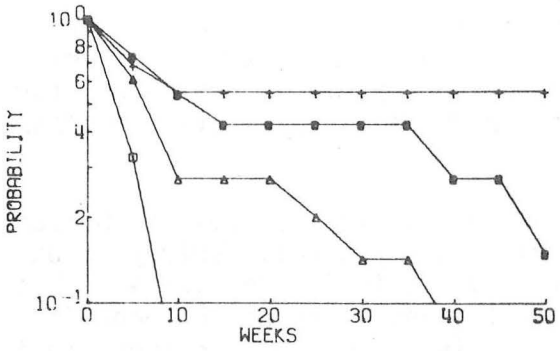
Figure 14




| TREATMENT | ALIVE | DEAD | TOTAL | MEDIAN |
|---|---|---|---|---|
| □ Oral 5-FU | 0 | 6 | 6 | 14.7 |
| ● Oral 5-FU + Streptozotocin | 0 | 5 | 5 | 14.2 |
| △ Oral 5-FU + Methyl CCNU | 1 | 8 | 9 | 15.1 |
| + Adriamycin | 0 | 1 | 1 | UNDEF |

Survival by initial treatment–North American blacks (patients with no prior chemotherapy).

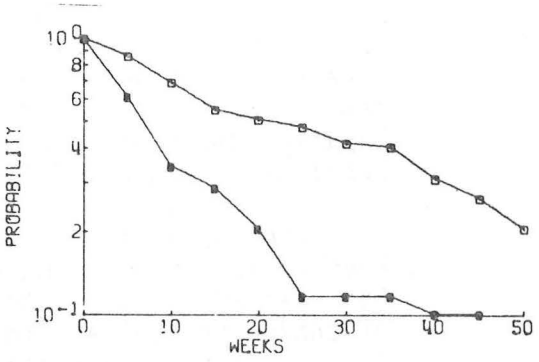
Figure 15




| TREATMENT | ALIVE | DEAD | TOTAL | MEDIAN |
|---|---|---|---|---|
| ▫ Oral 5-FU | 0 | 14 | 14 | 3.1 |
| ▪ Oral 5-FU + Streptozotocin | 2 | 9 | 11 | 11.5 |
| ▲ Oral 5-FU + Methyl CCNU | 0 | 13 | 13 | 6.3 |
| + Adriamycin | 6 | 6 | 12 | 60.5 |

. Survival by initial treatment–South African blacks (patients with no prior chemotherapy).

Figure 16




INITIAL PERF. STATUS

| PS AT STRT OF T | ALIVE | DEAD | TOTAL | MEDIAN |
|---|---|---|---|---|
| ▫ ECOG 0-1* | 7 | 67 | 74 | 20.9 |
| ▪ ECOG 2-3* | 6 | 70 | 76 | 6.7 |

*ECOG Performance Status:
0 = fully active
1 = ambulatory, capable of light work
2 = in bed < 50% of time, capable of self-care but not work activities
3 = in bed > 50% of time, capable of only limited self-care
4 = ineligible for study

Survival by initial performance status (patients with no prior chemotherapy).

Figure 17

Adriamycin-treated South African black patients had a median survival of 61 weeks.

Figure 17 illustrates the effects of performance status at the start of treatment, related to survival, and shows that the worse the performance status the shorter the median survival. The survival times for each group were as follows: North American white patients 28 weeks for patients with a better performance status and 9 weeks for patients with a poorer performance status; North American black patients 15 weeks for those with better performance status and 10 weeks for those with poorer performance status; and South African black patients 14 weeks for those with better performance status and 4 weeks for those with poorer performance status. Survival was therefore affected by treatment and patient risk factors.

## Conclusion

The above study delineates several important points. Oral 5-Fu has no further justification in the treatment of hepatocellular carcinoma. This is similar to the poor results obtained with this drug in other gastrointestinal malignancies. Further studies are warranted with the other drug combinations as well as with the single agent adriamycin. The results also demonstrate significant differences between South African black patients and black patients treated elsewhere. Excluding oral 5-Fu from consideration, prognostic variables (initial performance status, sex and institution) appear to dominate any differences between the remaining treatments under study. The results demonstrate the importance of pretreatment characteristics in determining survival and possibly affecting chemotherapeutic response in patients with primary liver cancer.

The general experience had been in the past, that primary liver cancer was less sensitive to the available systemic chemotherapy (before the introduction of adriamycin) than the treatment of metastatic carcinomas to the liver. Responses to systemic chemotherapy for primary hepatic tumors of 11.5% compared to 20.0% in metastatic neoplasm have previously been cited (108).

The early disappointing experiences with systemic chemotherapy have obviously been one of the reasons why hepatic artery infusion has claimed so much interest of many clinical investigators as a method of choice in contrast to systemic therapy. The aim of hepatic artery infusion, as we have stated before, is to improve the therapeutic index of the chosen agent by increasing drug exposure for hepatic tumor without increasing exposure for sensitive host tissue such as bone marrow and gut (109).

In contrast, Moertel (110) has stated, rather bluntly, his belief that there is no evidence that the more expensive and difficult hepatic-artery infusion techniques make any contribution to the survival of patients with gastrointestinal carcinoma when metastasis is apparently limited to liver.

Nevertheless, because of the great number of studies performed with hepatic artery infusion in primary as well as secondary hepatic tumors and the frequent claims of significant increases of median survival in various patient populations, the next paragraph will summarize a selected number of the published reports.

f. Hepatic artery infusion in chemotherapy of primary or secondary hepatic carcinomas

The modern techniques of hepatic artery infusions and catheter placement have already been discussed in a previous section. Recently, Lundberg (111) and also Lee (112) have summarized hepatic artery perfusion data with regard to primary hepatic carcinomas and liver metastasis. Lundberg's summary is shown in Table XVIII and Lee's in Table XIX. These summaries cover experiences from 1963-1976.

## TABLE XVIII

*Reported Results in Selected Studies of the Use of the Fluorinated Pyrimidines by Intrahepatic Arterial Infusion*

| Reference | Catheter placement method[a] | Drug | Dose and duration | Patients evaluable | Response | | | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | Rate | Median survival of responders (months) | In colorectal | |
| Sullivan and Zurek (1965) | IO | 5-FU<br>FUDR | 5.0–7.5 mg/kg · day *or*<br>0.3 mg/kg · day | 73 | 58% | 9.4 | 61% | |
| Rochlin and Smart (1966) | IO+PC | 5-FU | 10 mg/kg · day × 2 wk | 51 | 44% | 6.0 | 50% | |
| Burrows *et al.* (1967) | PC | 5-FU | 40 mg/kg × 5 *or* | 29 | 58% | | | |
| | | 5-FU | 20 mg/kg × 10 days | 39 | 73% | 6.2 | 59% | |
| | | FUDR | 1 mg/kg × 10–40 days | 22 | 25% | | | |
| Labelle *et al.* (1968) | IO+PC | 5-FU<br>FUDR | 10–40 mg/kg × "months"<br>0.1–0.7 mg/kg × "months" | 66 | 47% | ? | 60% | |
| Donegan *et al.* (1969) | IO | 5-FU | 500 mg × 14 days or more | 13 | 39% | 7.7 | 50% | No response; portal vein |
| Massey *et al.* (1971) | PC | 5-FU | 15–30 mg/kg × less than 21 days | 38 | 60% | 10.8 | 60% | |
| Tandon *et al.* (1973) | PC | 5-FU | 25–30 mg/kg × 7–9 days | 95 | 64% | ? | 67% | Prior Rx c̄ 5-FU |
| Cady and Oberfield (1974*b*) | IO | FUDR | 0.1–0.3 mg/kg · day for 6–9 months | 51 | 71% | 16 | 71% | |
| Fortuny *et al.* (1975) | PC | 5-FU | 25 mg/kg × 12 days | 12 | 84% | 12.5 | 84% | Mitomycin C 46% |
| Ansfield *et al.* (1975) | PC | 5-FU | 20–30 mg/kg × 4 days; then 15 mg/kg × 17 days | 293 | 55% | 7.3 | | Prior Rx c̄ 5-FU |

[a] IO: intraoperative; PC: percutaneous.

TABLE XIX

**Hepatic artery infusion chemotherapy for adenocarcinoma of the liver and biliary tract**

| Author | Year | Pt. no. | Liver cell | Biliary tract | Gall-bladder | Infusing agents | Infusing duration (days) | Results |
|---|---|---|---|---|---|---|---|---|
| Herter *et al.* (46) | 1963 | 2† | — | 2 | — | Mtx (25–50 mg/day) | 1–30 | 1 objective response |
| Ariel (9) | 1965 | 4 | | | | Radioactive (RA) micro-sphere | | Shrinkage 3–5 months, 1 died at 1.5 year |
| Ariel & Pack (10) | 1967 | 5‡ | 3 | — | 2 | 5FU, Mtx & RA micro-sphere | 5–20 | 4 objective responses |
| Gorgun & Watne (39) | 1967 | 2† | | | | Mtx | 4–29 | Tumor regressed 2, 3 months |
| Chan (24) (Singapore) | 1967 | 13 | | | | 5FU (20–25 mg/kg/day) | 7–10 | Mean survival 3.3 months *vs.* 1.6 months symptomatically treated |
| Labelle *et al.* (57) | 1968 | 7‡ | | | | 5FU (10–40 mg/kg/day) or FUDR (0.1–0.7 mg/kg/day) | | Overall 66 pts. (primary and metastatic cancer) 47% responded |
| Donegan *et al.* (28) | 1969 | 3† | 1 | — | — | Mtx (50 mg/day) | 10–197 | No response |
| | | | — | — | 2 | 5FU (0.5 gm/day) | | |
| Geddes *et al.* (37) (S. Africa) | 1970 | 9† | | | | 5FU or Mtx | 75–247 | Mean survival 87–291 *vs.* 64 days of control |
| Watkins *et al.* (102) | 1970 | 21† | 10 | 5 | 6 | FUDR (10–20 mg/day) | 90–180 | 75% (9/12) of those with satisfactory Rx had favorable response |
| Massey *et al.* (69) | 1971 | 6 | 3 | 3 | — | 5FU | 4–21 | 2 bile duct patients responded |
| El-Domeiri *et al.* (30) | 1971 | 6† | | | | Mtx and/or 5FU | | 2 survived 2, 3 years |

TABLE XIX (cont.)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Ansfield *et al.* (8) | 1971 | 14 | 9 | — | — | 5FU (20–30 mg/kg/day | 21 | 66% (6/9) improved |
| | | | — | 1 | — | × 4, 15 mg/kg/day × 17) | | No response |
| | | | — | — | 4 | | | 50% (2/4) improved |
| Davis *et al.* (27) | 1974 | 24 | 9 | — | — | 5FU (20–30 mg/kg/day × 4, | 21 | Better than systemic therapy |
| | | | — | 9 | — | 15 mg/kg/day | | Worse than systemic therapy |
| | | | — | — | 6 | × 17) | | Same as systemic therapy |
| Stehlin *et al.* (97) | 1974 | 14† | 10 | 3 | 1 | 5FU mainly | | Median survival 3 *vs.* 1 month for untreated patients |
| Cady & Oberfield (23) | 1974 | 18† | | | | FUDR (0.3 mg/kg/day) | 14–532 | Over half had substantial improvement, median survival = 14.5 months |
| Ramming *et al.* (91) | 1976 | 7† | | | | 5FU (10 mg/kg/day) | 30–315 | 6 symptomatic reliefs, all alive (median survival = 14 months) |
| Matsumoto *et al.* (70) (Japan) | 1976 | 8 | | | | Mitomycin-C (2 mg/kg/wk) | 28–64 | 75% (6/8) had regression of tumor |
| Ong & Chan (83) (Hong Kong) | 1976 | 19† | | | | 5FU | | 47% (9/19) died in 1 month, maximum 73 days |

† All direct placement of catheter at exploratory laparotomy.
‡ Some catheters placed directly, some percutaneously.

Although the data reported in Table XVIII are a collection of selected studies, they nevertheless show a fair number of investigative studies involving a total of 782 patients who have a response in 50-84% of cases treated with fluorinated pyrimidines for colo-rectal liver metastases by intraarterial infusion. The median survival time ranges between 6.0-12.5 months from beginning of treatment. This compares to a median survival (without primary tumor resection) in the absence of chemotherapeutic treatment of 3-8 months (Table IX).

In the data accumulated by Lee (112) in Table XIX there are several encouraging results with regard to objective responses and median survival times of patients who were treated with various chemotherapeutic agents for various primary hepatic and biliary tumors. For example, Cady and Oberfield (113) reported over 50% substantial improvement with a median survival time of 14.5 months (FUDR treatment) and Matsumoto et al. (114) claimed 75% significant tumor regression with mitomycin C treatment.

In addition, a recent report by Bern et al. (115) compared in a limited number of patients the effect of intra-arterially as well as intravenously administered adriamycin on primary hepatocellular carcinoma. Of initially 14 patients entered into the study, 4 of each group were evaluated. The partial response time was 22.5 weeks (range 8-37) for the intra-arterial group and 27.2 weeks (range 16-38.5) for the intravenous group. Mean survival for both treatment groups was 21 weeks for non-responders and 43 weeks for responders. An important finding was that intra-arterial infusion did not protect patients from adriamycin toxicity. Cardiac and liver toxicity were not seen (accumulated dose 450 $mg/m^2$) but marrow and gastrointestinal toxicity developed at $1.2 \times 10^{-7}M$ adriamycin serum levels. Adriamycin disappearance curves after intra-arterial and intravenous therapy were similar for similar bilirubin levels, and prolonged with hyperbilirubinemia. It has been recently reviewed (116) that cardiac toxicity of adriamycin generally develops at cumulative dose levels of above 500 $mg/m^2$.

Since adriamycin has been said to be cleared partially by biliary excretion (45%), the degree of cholestasis may greatly influence serum accumulation and subsequent systemic toxicity. The clinical response data of this study further support the validity and necessity of more extensive, well controlled studies to evaluate adriamycin for liver cancer treatment.

Several other publications should be mentioned which represent some of the greater clinical cancer center studies on the effect of intra-arterial chemotherapy for the treatment of primary or secondary liver tumors.

Watkins and coworkers from the Lahey Clinic Foundation (98) have summarized their experiences with arterial infusion chemotherapy of diffuse hepatic malignancies involving HCC as well as metastatic tumors. Besides developing some of the most modern infusion techniques, these authors applied this treatment procedure to more than

500 patients. Long term followup for up to 12 years in 247 patients was performed. Watkins et al. observed objective response to intra-arterial fluorouracil treatment of hepatic metastasis from colo-rectal cancer of 71% (1961-1967). A minimum of 3 weeks satisfactory infusion chemotherapy was required. The initial postoperative death rate in the early 1960's was as high as 29.9% but fell until 1971 to 5.9%. This improvement involved better techniques and better patient selection. With the drop of postoperative death rates, the overall response rate for all patients catheterized with colo-rectal cancer increased from 55.6% previously to 65.4% in 1971. The authors concluded that they were able to establish a high rehabilitation rate for normal life activities and they were able to prolong survival time by a factor of 3 to 4 when compared to actuarial survival statistics for untreated historical control groups and internal non-responding control groups.

Ansfield and Ramirez (117) from the Wisconsin Clinical Cancer Center studied 528 patients with liver metastases from primary gastrointestinal tumors with 5-Fu infusion (21 day infusion) via the intrahepatic arterial route from 1964 until present. Transabdominal, femoral and brachial artery placements of the catheter were utilized. These authors report important data with regard to toxicity, morbidity and mortality of the intra-arterial treatment technique which should be kept in mind by all clinical investigators considering cancer treatment.

The following table describes the investigators experience with toxic reactions related to the intrahepatic artery infusion with 5-Fu.

TABLE XX

Toxic Reactions to Intrahepatic Artery Infusion (5-Fu), 528 Cases

| Toxic Reactions | No. of Patients |
|---|---|
| Nausea and vomiting | 48 |
| Diarrhea | 78 |
| Significant upper abdominal pain | 35 |
| Stomatitis | 31 |
| Leukopenia, WBC count <2000 | 14 |
| Thrombocytopenia, platelet count <50,000 | 2 |

The various types and instances of morbidity are shown in Table XXI, with catheter displacement (from brachial or femoral approach) the most frequent, having occurred in 62 patients.

TABLE XXI

Morbidity Resulting from Intrahepatic Artery Infusion, 528 Cases

| Morbidity | No. of Patients |
|---|---|
| Catheter displacement | 62 |
| Catheter cracking or leaking | 29 |
| Infection at site of percutaneous catheter entry | 20 |
| Upper GI tract bleeding | 14 |
| Infected mycotic aneurysms or peripheral septic embolization | 5 |
| Clotted catheter | 8 |
| Hepatic artery occlusion | 6 |
| Non fatal stroke | 1 |

Mortality related directly to treatment mode was limited to 5 patients: 2 died from perforation of gastric ulcers, 1 from a massive superior mesenteric thrombosis, 1 from a fatal stroke and 1 from 5-Fu toxicity in a brittle diabetic patient. Table XXII reports the overall clinical results of the 528 treated patients.

TABLE XXII

Clinical Results and Survival Times of the Improved and Unimproved Patients with Intrahepatic 5-Fu Arterial Infusion

| | |
|---|---|
| Total number of patients | 528 |
| Number of study patients | 369 |
| Number improved | 202 (55%) |
| Survival (months)-11.8; Median, 7.5 | |
| Number unimproved | 167 (45%) |
| Survival (months)-mean, 5.7; Median, 2.4 | |
| P value <.001 | |

A significant number of the patients entered into the arterial infusion study had previously been treated intravenously with a loading course of 5-Fu, some of which showed tumor regression or an unchanged status for a number of months to several years. As soon as progression appeared, the patients were treated with intra-arterial infusion. The authors emphasize that other than by infusion with a fluoropyrimidine, there is no relatively innocuous method of reversing progressive liver metastasis of colo-rectal origin after intravenous administration of 5-Fu has failed.

And finally, 3 other recent reports should be mentioned. These studies summarize the experience with prolonged arterial infusions (up to 2 years) in primary and metastatic hepatic tumors (118), the combination treatment of metastatic cancer from colo-rectal primaries with 5-Fu and yttrium 90 isotope microspheres (65 patients) (119) and the combination treatment approach with FUDR plus irradiation in 48 patients with metastatic liver disease (120). In all these studies the authors claim slight increase of median survival and significant objective responses (>60%) with beneficial palliative effects resulting in enhanced quality of life.

One can conclude from the above reports that chemotherapy of primary or metastatic hepatic tumors is entirely a palliative procedure although slight to significant increases in median survival

(especially with adriamycin) have been recorded. Another therapeutic (or rather palliative approach) has been utilized by some more surgically oriented cancer centers, namely Hepatic Artery Ligation. This procedure, which occasionally is combined with concomitant chemotherapeutic arterial infusion, is shortly discussed in the following paragraph.

g. Hepatic artery ligation

Numerous anatomical studies have shown that both primary and metastatic tumors in the liver receive their blood supply almost exclusively from the hepatic arterial system. In the normal liver the hepatic artery supplies 25% of the blood to the liver and 50% of its oxygen. The portal vein provides 75% of the blood volume and 50% of the oxygen to the liver (121). Others demonstrated a 90% decrease in tumor blood flow after hepatic artery ligation as compared to 35-40% decrease in normal liver tissue (122). In animal hepatic tumor systems, hepatic artery ligation produced a selective necrosis of tumor in the liver, with increase of survival time (123).

The concept of treating human liver cancers by interruption of their arterial supply was first suggested by Markowitz in 1952 (124). Two major surgical procedures have been utilized for de-arterialization of the liver. One technique pursues ligation of the main hepatic artery only, whereas the other procedure attempts "complete" hepatic de-arterialization. This latter procedure was first reported by Balasegaram (125) and involves ligation of the hepatic artery distal to gastroduodenal and right gastric branches, detaching falciform, coronary and triangular ligaments and occluding all arterial supply to the liver from the diaphragmatic or abdominal wall. The authors, on the basis of their experience, proposed three indications for this extensive surgical procedure including 1) minimal cirrhosis of the liver with no evidence of thrombosis or tumor infiltration of the portal vein, 2) the absence of severe liver impairment with ascites and significant jaundice and 3) the presence of normal liver tissue between multicentric tumors. Although complete de-arterialization increases the risk of liver necrosis, Almersjö et al. (126) found no correlation between the extent of de-arterialization and survival time. From the experience of several oncologists, regression of primary and secondary liver tumors will occur in 50% or more of patients with de-arterialization, but remission is generally of short duration and may not long exceed the period of postoperative morbidity. The reason for the rather short-lived palliative effect is most likely the remarkable ability of collateral vessels to re-arterialize the liver after surgical interruption of the arterial blood supply (127).

From 1966 to 1976, 130 patients with primary hepatocellular carcinoma of the liver and 166 patients with metastatic malignancy have had deliberate ligation of the hepatic artery in order to produce selective necrosis of the tumor (128). The mortality which was directly related to ligation of the hepatic artery varied significantly from institution to institution and is most likely dependent on the mode of patient selection and the quality of the surgical technique. McDermott et al. (129) reported recently a

0% operative mortality in 5 successive patients with various tumor involvement of the liver. Other reports (130-134) show operative mortalities ranging up to 40%. Hepatic artery ligation produced an immediate rise of LDH and transaminases (up to 5-60 times normal value) and creative phosphokinase (4-15 times normal). All elevated enzymes returned to preoperative levels within a week (128).

Conclusion

Hepatic de-arterialization has been shown in experienced hands to yield in selected patients to a good palliative response with regard to temporary tumor regression and relief of excruciating RUQ pain. Whereas in the occasional individual patient significant increase in survival (more than one year) may occur, the overall median survival data of the published cases in the literature do not justify to propose this procedure as a general therapeutic approach. Evaluation of the published cases is extremely difficult because of the tremendous variability in the natural history of malignant disease of the liver, the relatively small number of cases in all reported series and the variety of types of tumors treated in this way.

h. Hepatic artery ligation and chemotherapy

Because anatomical studies have revealed that the variations of vascular supply of tumors may vary greatly, arterial ligation alone may not irradicate a tumor completely in a significant number of cases. Apparently cells in the outer growth zone of a tumor or tumor nodule may survive a de-arterialization, being also supplied by the portal system, whereas the big mass of cells in the interior of the tumor will succumb to anoxia (97). Since chemotherapy acts mainly on multiplying and growing cells (outer layer of tumor nodules) it would appear rational to combine chemotherapy with de-arterialization.

Several recent studies have been published utilizing either temporary de-arterialization combined with intra-arterial infusion of oncolytic drugs (97) (Fig. 13), intermittent occlusion with a balloon catheter with drug infusion (135) or permanent ligation with infusion therapy (136,137). The rather small number of patients treated with a combined de-arterialization-chemotherapy procedure do presently not allow any definite conclusions about the possible value of this technique.

As we have discussed previously, most hepatic tumor patients will be seen by their respective physicians when tumor growth has already passed the stage of curative resectibility. But a small number of patients, and hopefully more in the future, may be recognized early enough to be subjected to curative partial hepatic resection. To complete the discussion of the currently available treatment modalities for liver cancer, the last section will summarize the technical surgical aspects, patient selection and clinical results of the surgical liver cancer treatment.

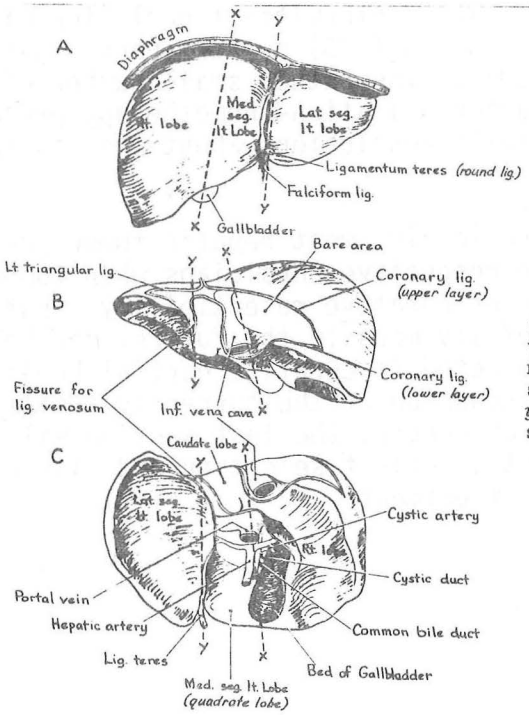
## 3. Surgical treatment of liver carcinomas

### a. Introduction

Langenbuch (138) reported the first successful partial resection of a liver with tumor in 1888. The first right hepatic lobectomy was performed by Wendel (139) in 1911 with the patient surviving for 9 years. But resection of liver tumors has achieved reasonable success only in the last 20 years when advances were made in defining the surgical anatomy of the liver and in understanding surgery related metabolic changes.

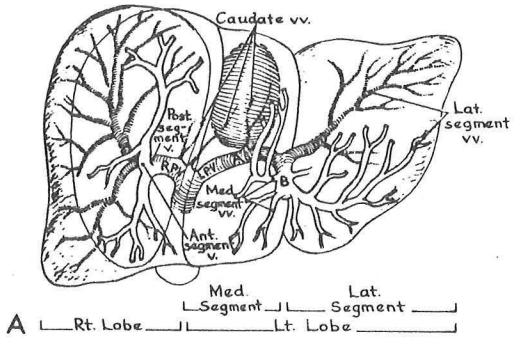
### b. Surgical anatomy

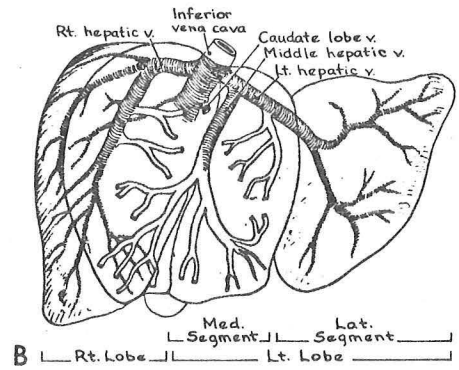
Externally the liver appears as a single organ. However, it can be divided into right and left lobes based on its internal vascular and ductal structures. Conventionally, the falciform ligament has been used as the boundary of the right and the left lobe. However, based on several anatomical studies related to the true distribution of vascular and ductal structures, division between right and left lobes can be identified by the lobar fissures (Cantlie's line), a line connecting the gallbladder fossa anterio-inferiorly with the fossa of the inferior vena cava postero-superiorly. The left lobe of the liver can be further subdivided by the falciform ligament into medial and lateral segments. Similarly, further segmental subdivision of the right lobe has been defined. The vascular and ductal distribution related to segmental divisions has already been reviewed in some detail in the angiography section of this protocol. The following additional figures should serve as a more detailed orientation for the understanding of the major types of hepatic resections which may be possible in the surgical treatment of liver tumors. An enhanced appreciation of surgical anatomy by the internist will certainly strengthen his position in any future discussions related to important diagnostic and therapeutic decisions about individual patients.




The three surfaces of the liver are shown. *A*, The anterior view with the interlobar fissure marked by the line *x-x* and the left segmental fissure marked by the line *y-y*. *B*, Posterior view, showing the same fissures. *C*, Inferior view.

Figure 18




*A*, Intrahepatic branches of the portal vein: *RPV*, right portal vein; *LPV*, left portal vein; *A*, transverse portion; *B*, umbilical portion. *B*, The hepatic venous return, showing intralobar position of middle hepatic vein and intrasegmental portion of the right hepatic vein. (Modified from Healey, J. E., Jr.: Int. Coll. Surg., 22:546, 1954.)

Figure 19

Intrahepatic arrangement of hepatic arteries and bile ducts. *A*, Hepatic arteries, shown in black: (*1*) hepatic artery, (2) right hepatic artery, (3) left hepatic artery, (4) right posterior segment, (5) right anterior segment, (6) left medial segment, (7) left lateral segment. *B*, Corresponding biliary ducts, shown in white. (Modified from Healey, J. E., Jr., Schroy, P. S., and Sorensen, R. J.: J. Int. Coll. Surg., 20:133, 1953.)

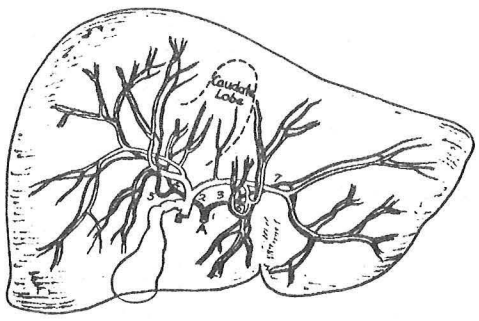
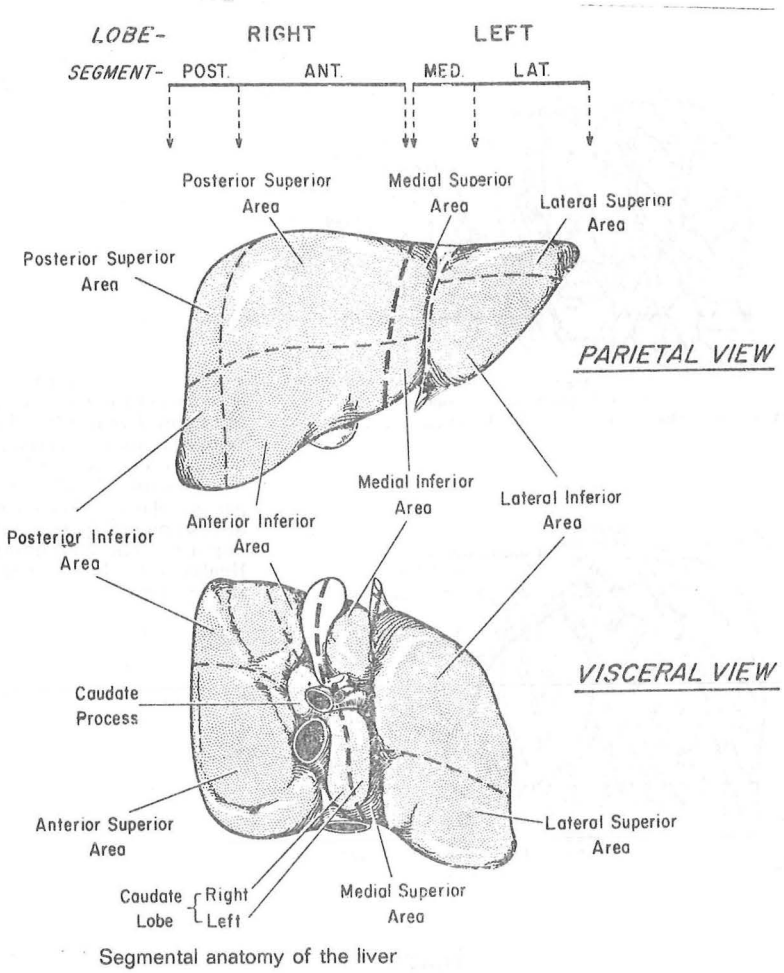
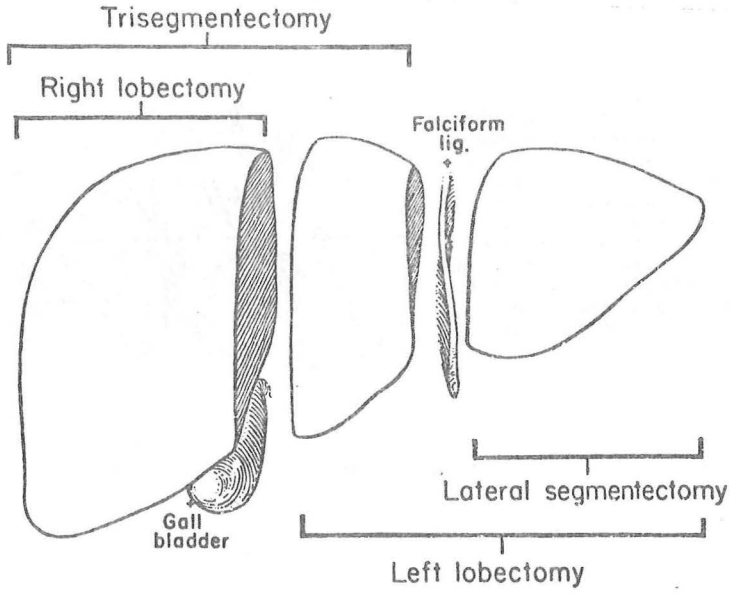



Figure 20




Segmental anatomy of the liver

Figure 21



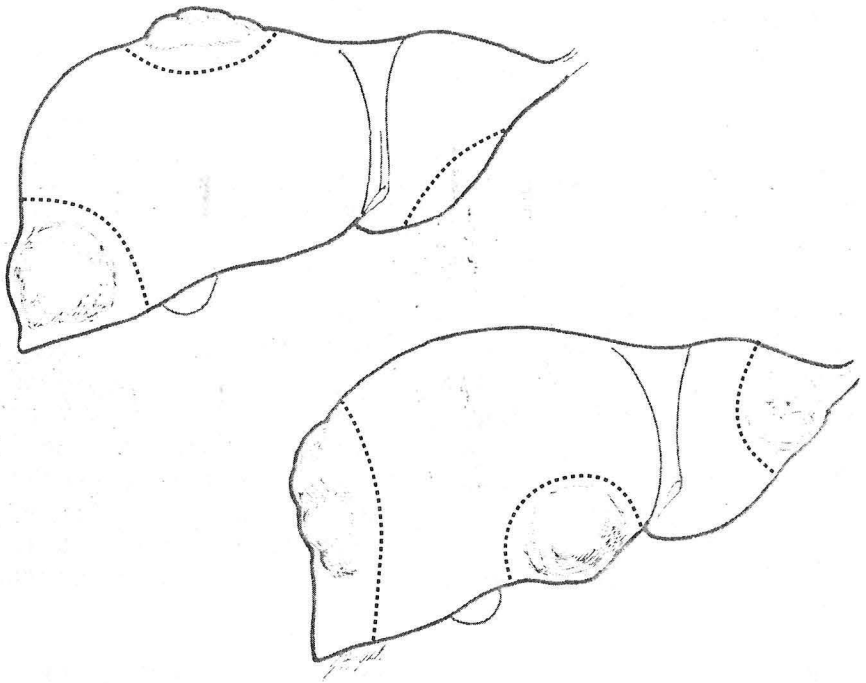

The common hepatic resections, of which there are only four. The most radical procedure, trisegmentectomy, involves removal of the true right lobe plus the medial segment of the left lobe. The least radical procedure, lateral segmentectomy, was incorrectly termed left lobectomy in the older literature.

Figure 22

c. Types of resection

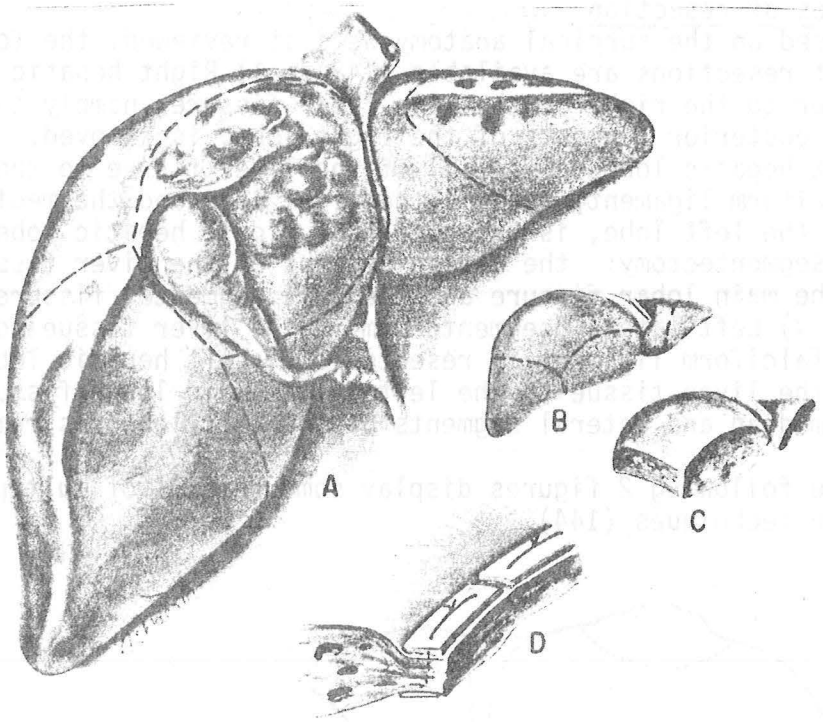
Based on the surgical anatomy we just reviewed, the following types of resections are available (143): 1) Right hepatic lobectomy: the liver to the right of the main lobar fissure, namely the anterior and the posterior segments of the right lobe, is removed. 2) Extended right hepatic lobectomy: all of the liver tissue to the right of the falciform ligament, that is the right lobe and the median segment of the left lobe, is resected. 3) Middle hepatic lobectomy or median segmentectomy: the median segment or the liver tissue between the main lobar fissure and the left segmental fissure is removed. 4) Left lateral segmentectomy: the liver tissue to the left of the falciform ligament is resected. 5) Left hepatic lobectomy: all of the liver tissue to the left of the main lobar fissure, namely the median and lateral segments of the left lobe, is removed.

The following 2 figures display some details of multiple wedge excision techniques (144).



Wedge excisions. Although wedge excision is most useful for small tumors along the free edge of the liver, it also may be done for more bulky disease. Typical large wedge excisions are illustrated. Individual circumstances will dictate whether preliminary hilar control is necessary. The upper diagram illustrates the type of peripheral excision of the lower part of the left lateral segment often done to satisfy the "en bloc" principle in removing a large gastric carcinoma that has invaded adjacent liver.

Figure 23




Multiple wedge excisions to remove 99 per cent of carcinoid liver metastases in a 65-year-old male with fulminant malignant carcinoid syndrome. (Case 3, Table 9–1). Reprinted courtesy of the Reuben H. Donnelly Corporation, New York, N.Y.

Figure 24

d. Pathophysiology of hepatic resection

A patient can survive resection of 80-90% of his liver, but 10-20% of a normal liver could not support life over an extended period of time. Such a patient will always have a period of relative liver insufficiency, and survival is absolutely dependent on the liver's remarkable ability to regenerate rapidly. Careful metabolic support during this time period is of utmost importance. In humans, regeneration of the residual liver is apparent on radioisotope scanning by the third postoperative week. Regeneration of cirrhotic human liver remains equivocal (144).

The most important functional changes after resection involve 1) decrease of protein, albumin and total cholesterol, 2) decrease in bile flow and hyperbilirubinemia, 3) variable hypoglycemia during the first 48 hours, 4) decrease of prothrombin time to about 30% of normal and 5) a rise in SGOT and SGPT. Most of these changes are restored to normal within the third or fourth postoperative week.

Based on pathophysiological observation on liver resection, 80-85% resection seems to be the upper limit for a noncirrhotic liver, and in the presence of moderately severe cirrhosis (with coarse nodular surface) right hepatic lobectomy is deemed as detrimental or even life threatening (145).

e. Indication, patient selection, contraindication and resectability

The indications for resection of primary hepatic carcinoma is

still rather limited because the tumor may be multicentric in origin, involving both lobes of the liver or is associated with cirrhosis, jaundice, ascites and severe liver impairment. The proportion of patients (Lee, Y.-T.N., Cancer Treatment Reviews 4:195, 1977) with resectable lesions is near zero in South Africa and about 7% in Malaysia. The resectability rate is about 20% in Hong Kong and 10% in Lahey Clinic patients with hepatoma for curative treatment. In general, the incidence of concomitant cirrhosis will greatly determine resectability of primary hepatic tumors. Lin (146) reported 72.6% operability and 41.6% resectability among the operable cases based on the afore mentioned general criteria for indications.

The question of resectability in metastatic tumors in the liver (mostly of gastrointestinal origin) is more difficult to evaluate but is basically limited to solitary metastases. Raven (147) studied 818 patients from the Royal Marsden Hospital with primary tumors of stomach, colon or rectum. Twenty-three percent had hepatic metastasis and 5% had metastases that were judged to be resectable on the basis of a solitary nodule or multiple metastases confined to one lobe. He concluded that about one in every 20 patients operated on for cancer of the gastrointestinal tract will have technically resectable hepatic metastases.

f. Operative mortality, surgical mortality, and postoperative complications

Progress in surgical technique has steadily reduced the operative mortality and surgical mortality (death within 30 postoperative days) of hepatic lobectomy. Schweizer and Howland (148) reported a 35.8% surgical mortality in 53 cases and Brunschwig (149) reported 29% in 24 cases. Lin (143) published data from Taiwan University Hospital from a series of 118 hepatic lobectomies for primary carcinoma of the liver with a 4.3% operative mortality and a 15.3% surgical mortality. Ong (150) reported about his vast surgical experience from the University of Hong Kong where he showed a dramatic improvement of operative mortality in hepatic resections from 32% operative deaths to 5% operative deaths during the period from 1964 to 1976.

g. Results and prognosis

1. Primary hepatic carcinoma

The results of treatment and the prognosis for HCC following hepatic lobectomy depend naturally on the extent of the malignancy, the presence or absence of occult intrahepatic or extrahepatic metastasis, as well as of associated liver cirrhosis. In general, the results of treatment are hardly satisfactory.

Of 80 patients reported by Lin (151), who survived hepatic lobectomy, two-thirds died within a year after operation either because of local recurrence (26%) or lung metastasis (18.7%) or hepatic failure (11.9%). But nevertheless, this surgical procedure yielded in the same series survival for 1 to 2 years in ten cases, 2 to 3 years in five cases, 3 to 4 years in three cases and more than 5 years in nine cases (19.1%).

Wang et al. (152) reported pessimistically about two patients only who survived more than 5 years in a series of 130 hepatic lobectomies for HCC collected from 10 teaching hospitals in China over a 20 year period.

More encouraging, El-Domeiri et al. (153) from Sloan-Kettering Hospital reported a 15.6% rate of 5 year survival among 32 hepatic lobectomies for HCC over a 20 year period.

Several other reports in the literature, with some geographic variation in results, more or less confirm the successes and failures of the above discussed studies.

2. Metastatic liver tumors

Flanigan and Foster (154) surveyed the world literature in 1967 and found 32 reports involving 72 patients with primary malignancies of colonic origin in 45 cases. The overall 5 year survival rate for the 72 patients was 24%.

In a later survey of 98 US hospitals in 1974, Foster and Berman (155) described 176 patients who had undergone surgical resection for embolic metastases to the liver of which 126 patients (72%) had primaries in the colon and rectum. Of the 88 patients available for the 5 year evaluation, 16 patients (18%) were alive 60 months after liver resection. Six of these patients developed recurrence, and 4 of the 6 had died. Thus, 10 of the 88 determinate cases seem "cured".

In general, the lure of describing success exceeds the temptation to report failures. Therefore, some of the reports in the literature may be overstatements of therapeutic expectations. But another report from the literature by Wilson and Adson (156) from the Mayo Clinic reported no 5 year survivors in resections for multiple metastases but 42% of 36 patients with a single metastasis lived for more than 5 years. Eight were alive without recurrence 10 years or more after hepatectomy. These positive results leave at least a ray of hope that further improvements in early cancer diagnosis, new combination therapies and proper patient selection may further increase the chances of successful treatment of liver carcinomas.

h. Conclusions and hopes

The value of a review such as this is limited by the overwhelming number of variables which enter into diagnosis, patient selection, treatment modalities and expertise of the treating physicians. Since one can easily recognize all the shortcomings which still restrict successful treatment of liver cancer, some of the more positive aspects should be emphasized again.

1. The rather recent recognition that cirrhosis as well as hepatitis B are strongly associated with the etiology of hepatic carcinoma may open the door to future preventive medical measures such as vaccination against hepatitis B infection.

2. Great advancements have occurred in the area of diagnostic procedures such as computerized tomography, sonography, scintigraphy

and angiographic flow studies which all will contribute to more agressively and decisively isolate the tumor patient who may be subject to curative surgery.

3. Over the next decade, further advancements in early tumor diagnosis by specific tumor marker screening can be expected.

4. New and more specific chemotherapeutic agents may be developed which could further improve medical treatment of liver carcinoma.

5. Liver cancer patients should be entered into controlled, randomized treatment programs on a regional or national level. Only a major effort and interest of all academic and practicing physicians can lead to progressive conversion of palliative to curative treatment of liver carcinoma.

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