INTRODUCTION

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Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver, with an annual incidence of more than 1 million worldwide. There are multiple risk factors, including viral infection and alcohol abuse; hepatitis C viral infection accounts for many cases in the United States[(1)].

The liver is also a common site of metastatic disease. For instance, more than 145,000 cases of colorectal cancer are diagnosed each year, and hepatic metastases develop in approximately half of those cases[(1,2)]. The liver is a frequent site of metastases from colorectal cancer because of portal venous drainage of bowel. In most patients, metastases from colorectal cancer affect only the liver. Unfortunately, because of the size and number of the lesions at the time of diagnosis, few such patients are candidates for surgical resection or localized therapies such as percutaneous thermal ablation[(2,3)] and cryotherapy[(4)]. The first-line therapy for advanced colorectal cancer therefore is systemic chemotherapy[(4)].

Because of the high mortality associated with untreated primary and secondary hepatic malignancies, an increasing number of innovative therapies are being tested. Transarterial therapies take advantage of the dual blood supply of the liver: The hepatic artery predominantly supplies hepatocellular carcinoma and metastatic deposits, whereas normal liver parenchyma depends primarily on portal venous blood[(5)].

Traditional transarterial therapies are based on the infusion of chemotherapeutic drugs into the hepatic artery either intermittently or through a surgically implanted hepatic artery pump. Such therapies also may include the use of bland embolization to induce tumor ischemia. For example, transarterial chemoembolization (TACE) is a catheter-based technique that combines both regional chemotherapy and embolization to increase the dwell time of cytotoxic agents and induce ischemic necrosis in the tumor[(6)].

The use of drug-eluting microspheres in a new variation of the trans-arterial chemo embolization (TACE) method is designed to improve the precision of drug delivery. Another recent advance, a form of brachytherapy, involves the administration via the hepatic artery of yttrium-90 (Y^{90}) microspheres, which preferentially are deposited within hypervascular tumors and emit beta radiation. Experimental techniques in gene therapy also are being tested[(6)].

Anatomy of the liver

The liver is the largest abdominal organ occupying most of the right upper quadrant. It varies considerably among individuals in size and configuration[(7)].

The hepatic profile

The upper limit corresponds to a line through the xiphisternal joint joining a point below the right nipple to a point infero-medial to the left nipple. ***The right border*** corresponds to a curved line, convex to the right, running from the right end of the upper border to a point 1 cm below the costal margin at the tip of the tenth costal cartilage. ***The lower limit*** corresponds to a line completing this triangle, crossing the midline at the trans-pyloric plane[(8)].

Shape, surfaces and peritoneal coverings

The liver is wedge-shaped rather rounded organ, its narrow end pointing left and its anterior edge directed downwards. It has ***5 surfaces****:* superior, anterior, right, posterior and inferior surfaces. No definable border separates superior, anterior, right lateral and right posterior aspects of the liver and it would be more appropriate to group these as the diaphragmatic surface, mostly separated from the visceral surface by the sharp inferior border[(7)]. The liver is ***covered by peritoneum*** except for the bare area *(surface between the superior and inferior coronary ligaments)* and is attached to the diaphragm anteriorly by the falciform ligament and posteriorly by the superior and inferior coronary ligaments that come together laterally to form the left and right triangular ligaments[(9)].

Relations

Superiorly, laterally and anteriorly: The liver conforms to the diaphragm.

Medially: The stomach, duodenum, and transverse colon.

Inferiorly: The hepatic flexure of the colon.

Posteriorly: The right kidney *and* ***Posterio-superiorly****:* the right adrenal gland[(8)].

Hepatic lobes

The liver is customarily apportioned by anatomists into a larger right and a much smaller left lobes by the lines of attachment of the falciform ligament ***anteriorly*** *and* the fissures for the ligamentum teres and ligamentum venosum ***inferiorly***[(8)]. The right lobe is further divided into a quadrate lobe and a caudate lobe by the presence of the gall bladder, the Inferior vena cava ***(IVC)*** and the porta hepatis[(7)].

Caudate lobe

The caudate lobe is a pedunculated portion of the liver extending medially from the right lobe between the IVC and the portal vein. Functionally, it may be considered an autonomous part of the liver as it has separate blood supply, venous and biliary drainage from the rest of the liver parenchyma[(9)].

Segmental anatomy

The classical division of the liver into right and left lobes based on surface anatomical markings does not really describe the internal organization of this organ[(7)]. Corrosion specimens of the portal structures have shown that the liver is divisible functionally into almost 2 equal halves *(the right and left lobes)* demarcated by a plane passing through the gall bladder fossa and the fossa for the ***IVC***[(8)]. This is based on the primary divisions of the triadic system *(The right and left portal veins, hepatic arteries and bile passages divide and subdivide with a common pattern with no evidence of significant intra-hepatic anastomosis in these dendriform systems).* Their branching patterns create a system of lobes and further subdivisions into segments[(7)].

With recent developments in surgery, especially liver transplantation and the introduction of powerful imaging methods which can be used before and during operations, it has become vital to understand the liver segmental anatomy for appropriate localization of hepatic neoplasms as well as identification of the vascular and biliary territories which can be isolated as units for partial hepatectomy and other local surgical or radiological interventions[(10)].

Confusion regarding segmentation is related to differences between the American system of nomenclature proposed by Goldsmith and Woodburne and the European systems proposed by Couinaud and later modified by Bismuth[(9-11)]. Table (I). Fig. (1). According to ***The European System***, the hepatic segments, except for the caudate lobe and medial segment of the left lobe, are defined by the three vertical scissurae described by the major *(right, middle and left)* hepatic veins and by a transverse scissura described by the right and left portal vein branches[(10)]. The European system is preferred as it is easily applicable to cross-sectional imaging techniques as computed tomography ***(CT)***, magnetic resonance imaging ***(MRI)*** and ultrasound ***(US)***. Figs. (2, 3). It also provides adequate information for the surgical planning of sub-segmental hepatic resections[(11)].

Table (I): Anatomic segments of the liver and corresponding nomenclature[(11)].

Anatomic Sub-segment	**Nomenclature**		
	Couinaud	**Bismuth**	**Goldsmith and Woodburne**
Caudate lobe	I	I	Caudate lobe
Left lateral superior subsegment	II	II	Left lat. Seg.
Left lateral inferior subsegment	III	III	
Left medial subsegment	IV	IVa, IVb	Left med. Seg.
Right anterior inferior subsegment	V	V	Right ant. Seg.
Right anterior superior subsegment	VIII	VIII	
Right posterior inferior subsegment	VI	VI	Right post. Seg.
Right posterior superior subsegment	VII	VII	

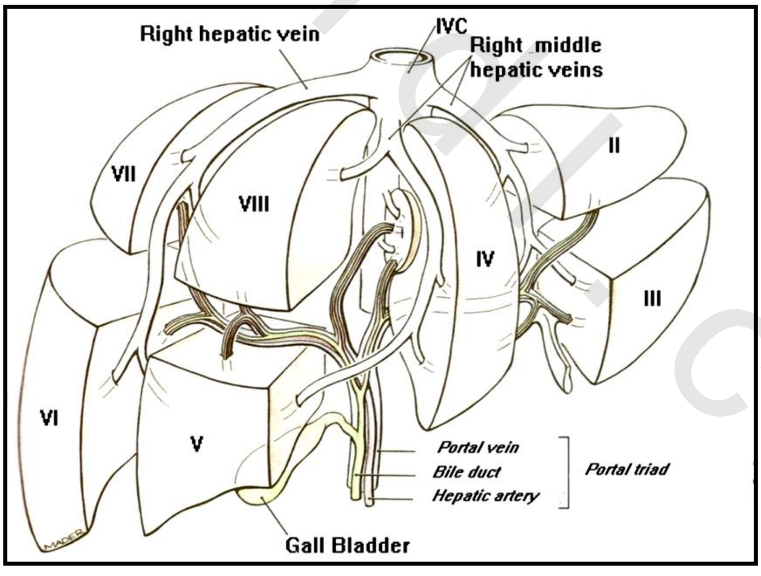


Fig. (1): Diagrammatic illustration of hepatic segmental anatomy[(12)].
The liver consists of **8 functional hepatic segments** numbered in a clockwise direction when the liver is viewed from its ventral aspect. Each segment has a precise arterial supply, venous drainage, and biliary drainage.

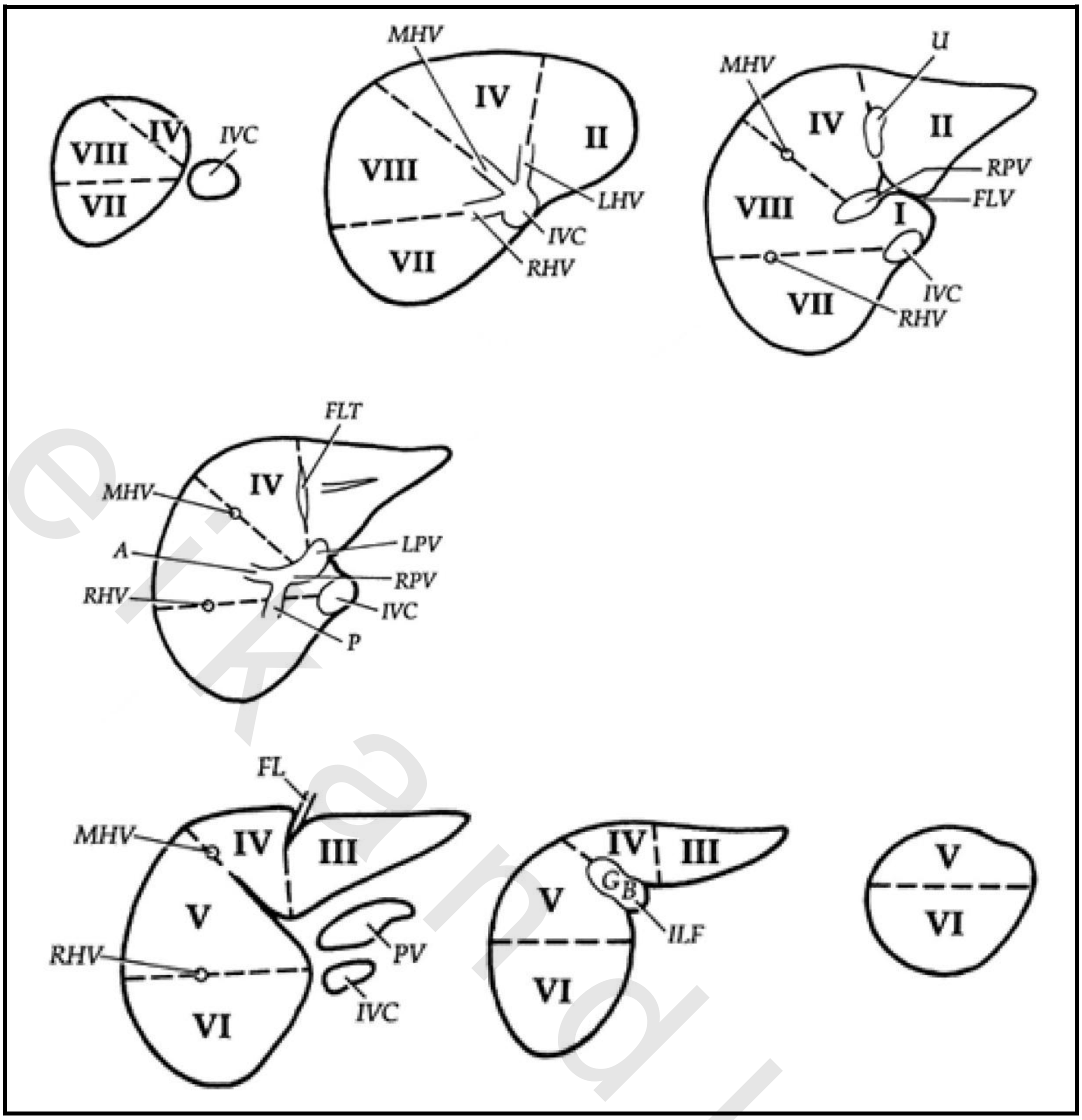


Fig. (2): Diagrammatic illustration of hepatic segmental anatomy as viewed in the trans-axial planes through the liver[11].
The transverse scissura described by the left and right portal vein branches demarcates the cranially located segments **(II, VII, and VIII)** from the caudally located segments **(III, VI, and V, respectively)**. **RHV**: right hepatic vein, **MHV**: middle hepatic vein, **LHV**: left hepatic vein, **PV**: portal vein, **IVC**: inferior vena cava, **FLT**: fissure for the ligamentum teres, **FLV**: fissure for the ligamentum venosum, **RPV**: right portal vein (**A**: anterior branch, **P**: posterior branch), **LPV**: left portal vein, **U**: umbilical segment, **FL**: falciform ligament, **ILF**: interlobar fissure, **GB**: gall bladder.

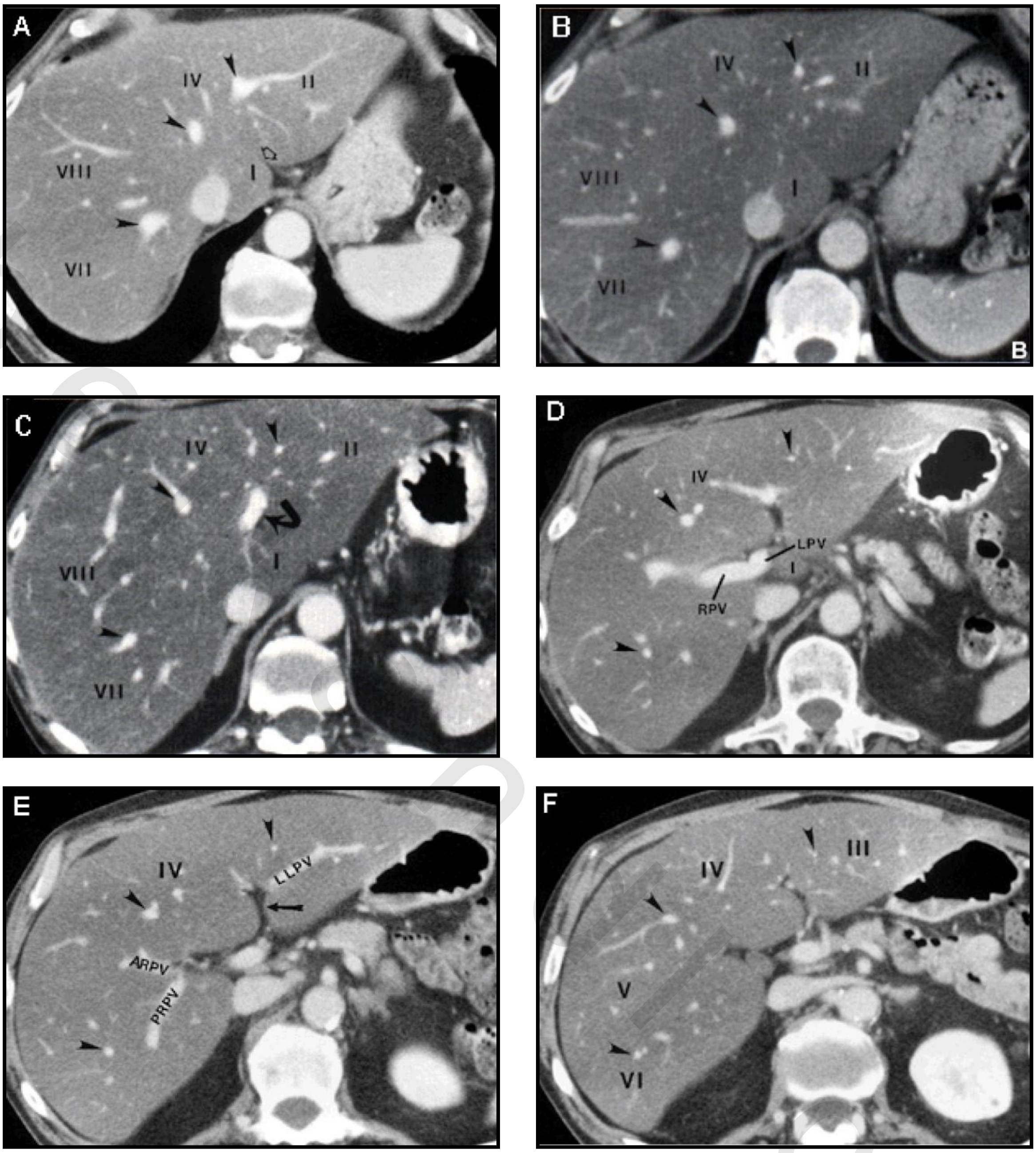


Fig. (3): Hepatic cross-sectional anatomy by CT[11].

(A-E) Black arrowheads: The main hepatic veins form the major vertical scissurae that divide the hepatic segments. **(A) open arrow:** fissure for the ligamentum venosum, **(C) curved arrow:** umbilical segment of left portal vein, **(E) straight arrow:** fissure for the ligamentum teres, **(D):** The right and left portal veins form the transverse scissura, **LPV:** left portal vein, **RPV**: right portal vein, **(E) LLPV**: left lateral segment portal vein branch, **ARPV**: anterior branch of right portal vein, **PRPV:** posterior branch of the right portal vein. **The Latin numbers** in all images correspond to the hepatic segments according to the system of Couinaud.

Vascular anatomy

Three different systems are responsible for the blood supply and the venous drainage of the liver:

I. The portal venous system provides 75-80% of the hepatic inflow.
II. The hepatic arterial system provides 25% - 30% of the hepatic inflow *(however, it carries approximately 50% of available oxygen).*
NB: Terminal branches of both systems drain into the hepatic sinusoids.
III. The hepatic venous system provides the entire venous outflow of the liver into the **I VC** *(the systemic circulation)*[7,10].

I. The portal tree

The portal vein (PV) originates posterior to the neck of the *pancreas (level of lumbar vertebral LV_2)* at the confluence of the superior mesenteric and splenic veins. It measures about 8 cm long and 1.5 cm in caliber[7]. It passes posterior to the common bile duct ***(CBD)*** and hepatic artery ***(HA)*** within the free edge of the lesser omentum as it proceeds towards the porta hepatis where it divides into **right and left main branches** coursing alongside the right and left hepatic arteries and bile ducts. **The initial portion of the right *PV*** courses rightward and cranially, giving off several branches that supply the porta hepatis and caudate lobe. The right ***PV*** divides within the substance of the right lobe into **anterior and posterior branches** that supply the corresponding hepatic segments. Each of these vessels divides again into superior and inferior branches that supply the superior and inferior subdivisions of their respective segments. **The initial portion of the left *PV* (pars transversa**) passes horizontally to the left, giving off branches that supply segments II and III before turning to join the obliterated umbilical vein within the fissure for the ligamentum teres. **This intra-fissural portion (umbilical segment)** of the left ***PV*** extends cranially, terminating in ascending and descending branches that supply the superior and inferior divisions of segment IV (IVa and IVb)[10].

II. The arterial tree

Embryology

Both dorsal aortae provide ventral segmental omphalo-mesenteric arteries to the viscera. These give rise to the vitelline arteries. About the 4th week, fusion of the ventral roots and reduction in the number of segmental arteries leads to the formation of the three main ventrally oriented vessels: The celiac artery to the infra-diaphragmatic portion of the foregut, the superior mesenteric artery (***SMA***) to the midgut and the inferior mesenteric artery to the hindgut. The ventral segmental roots are connected longitudinally via a ventral anastomosis. Persistence of this ventral anastomosis between the ***SMA*** and celiac arteries and/or partial regression of another segment accounts for complete or partial replacement of the celiac artery branches to the ***SMA*** and vice versa. Persistence of the ventral anastomosis between the tenth and thirteenth vitelline arteries also gives rise to the persistent embryonic connection between the proximal celiac and superior mesenteric arteries, known as the arc of Buhler[13].

The Celiac Trunk arises anteriorly from the abdominal aorta at the dorsal vertebra 12-Lumbar vertebra 1 interspace. Its course is usually inferiorly directed but can be horizontal or cranial[9]. Its length averages 1 to 2 cm prior to branching into the left gastric (***LGA)***, common hepatic and splenic arteries[13]. Table (II).

The hepatic artery is intermediate in size between the left gastric and splenic arteries. It arises as a branch of the celiac axis, coursing anteriorly and to the right to enter the free border of lesser omentum where it lies anterior to the (***PV***) and left of the (***CBD)***. Branches: 1. Right gastric artery. 2. Gastro-duodenal artery ***(GDA)***. 3. Right Gastro-epiploic artery. 4. Superior pancreatico-duodenal Arteries 5. Supra-duodenal artery. 6. Cystic Artery[12]. **The artery may be subdivided into:** ***the common hepatic artery (CHA)***, from the celiac trunk to the origin of the ***GDA*** and ***the proper hepatic artery (PHA)***, from that point to its bifurcation[14].

The Proper Hepatic Artery divides within the porta hepatis into right ***(RHA)*** and left ***(LHA)*** main hepatic arteries, the ***RHA*** crosses posterior occasionally anterior) to the common hepatic duct[15]. Within the liver, the right and left main branches divide in a fashion similar to that of the ***PV*** branches to supply their corresponding segments[16]. Fig(4).

The **(*SMA)*** origin is located around L1 (2 mm to 2 cm) below the celiac trunk[13]. It provides **branches** to the distal duodenum, small and large intestine, to the splenic flexure and to the head and body of the pancreas. In 18-20%, it gives origin to the common or right hepatic arteries[14].

This classical branching pattern is seen in only 65 - 75 % of individuals, with **up to 35% having variations** involving one or more vessels[17]. **Table (II, III, IV)**.

III. The hepatic veins

The three main *(right, middle, and left)* hepatic veins lie within the postero-superior aspect of the liver and drain into the ***IVC*** just below the diaphragm[9]. In about 90% of cases, the middle and left hepatic veins join to form a common trunk before emptying into the ***IVC***[13]. In addition, a variable number of smaller dorsal hepatic veins drain the posterior aspect of the right lobe and caudate lobe directly into the ***IVC***[10].

The right vein lies between the right anterior and posterior hepatic segments, drains segments V, VI and VII.

The middle vein lies in the inter-lobar plane, drains primarily segments IV, V, and VIII. **The left vein** courses in the sagittal plane between the medial and lateral segments of the left lobe, drains segments II and III[13].

Hepatic parenchyma

Normal hepatic parenchyma appears homogeneous on both CT and MR images. **On unenhanced CT**, the attenuation value of normal liver parenchyma is from 40 to 70 Hounsfield units ***(HU)*** consistently higher than the spleen, with a mean difference of 8 HU[10]. This is attributed to the high concentration of glycogen within the liver. However, **after IV contrast injection**, the liver attenuation value often becomes less than that of the spleen, with the amount of difference between the hepatic and the splenic attenuation depending on the timing of the scans and the injection rate[18].

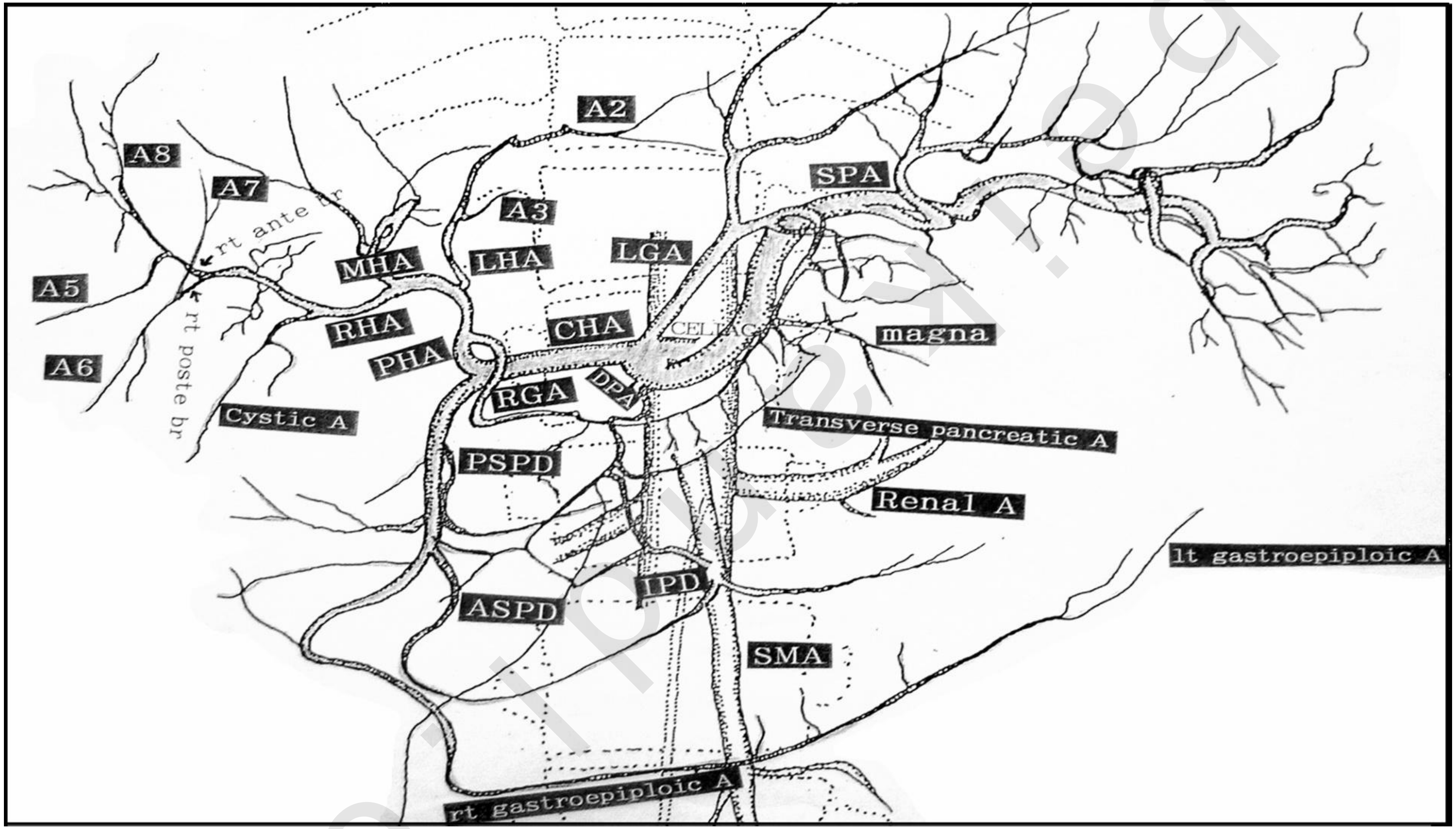


Fig. (4): Diagrammatic illustration of the hepatic arterial supply[13].
C.T: Celiac Trunk, **SMA:** Superior Mesenteric A. **CHA:** Common Hepatic A. **PHA**: Proper Hepatic A., **LGA**: Left Gastric A. **RGA**: Right gastric A. **RHA**: Right Hepatic A. **MHA**: Middle Hepatic A. **LHA**: Left Hepatic A. **A2**, **A3**, **A4**, **A5**, **A6**, **A7** and **A8**: arteries to segments **II**, **III**, **IV**, **V**, **VI**, **VII** and **VIII** respectively.

Table (II): Celiac Artery: Normal and Variant Anatomy[13].

1.	**Classic anatomy**: three branches	
	• Left gastric arteries (usually 1st branch) • CHA • Splenic artery	65-75%
	True trifurcation	25%
2.	**Four branches:** as above plus • Dorsal pancreatic **or** middle colic artery	5-10%
3.	**Two branches**	
	CHA and splenic artery	2%
	LGA and splenic artery	3%
	LGA and CHA	<1%
4.	**All branches arise independently**	<1%
5.	**Celiaco-mesenteric trunk**	<1%
6.	**Miscellaneous**	
	CHA off SMA	2.5%
	CHA off aorta	2%
	Splenic artery off SMA	<1%

Table (III): Superior Mesenteric Artery - Variant Anatomy of the hepatic Arteries[13].

Overall incidence of hepatic branches from SMA	18-20%
Right hepatic artery from SMA	14-18%
• Replaced right hepatic	10-12%
• Accessory right hepatic	4-6%
CHA from SMA	2.5%

Table (IV): Hepatic arteries (normal and variant anatomy) from celiac origin[13].

All hepatic branches off celiac artery	**App. 75%**
Replaced or aberrant hepatic arteries	**41%**
One vessel	31%
Two or more vessels	10%
CHA	
Classic pattern: all hepatic branches off common hepatic	55%
Common hepatic off SMA	2.5%
Early division of the CHA	Approx. 2%
CHA off aorta	2%
Entire common hepatic off left gastric artery	<1%
Aberrant right hepatic artery	**24-26%**
Replaced:	17-18%
Accessory:	7-8%
Accessory right hepatic artery from gastro-duodenal artery	2%
Accessory right hepatic artery from SMA	4-6%
Replaced right hepatic artery from superior mesenteric artery	10-12%
Replaced right hepatic artery off aorta	<2%
Aberrant left hepatic artery	**23-25%**
Replaced	15-18%
Accessory	7-8%
Replaced left hepatic (off left gastric artery)	11-12%
Replaced left hepatic off SMA	2.5%
Accessory left gastric off LHA	7%
Accessory left hepatic off LGA	11-12%
Left gastric/left hepatic trunk from aorta	1-2%
Middle hepatic artery	
From left hepatic artery	45%
From right hepatic artery	45%

Differential diagnosis of hepatic metastatic lesions

I. Congenital hepatic cysts

- Simple cysts- Polycystic liver disease[18].

II. Benign neoplasms

- Cavernous haemangiomas.
- Hepatic adenoma.
- Focal nodular hyperplasia.
- Lipoma.
- Hamartoma (mesenchymal - bile duct hamartomas)[18,19].

III. Malignant neoplasms

- HCC[19,20].
- Peripheral cholangiocarcinoma.
- Angiosarcoma.
- Hepatoblastoma and cystic hepatoblastoma[18].
- Lymphoma

IV. Infectious diseases

Pyogenic abscess - Amebic abscess - Chronic granulomatous disease -Hydatid disease[18].

V. Diffuse liver disease

Focal fatty infiltration - Hepatic fibrosis - Regenerating nodules[18].

Imaging of liver metastases

Hepatic resection is the only potentially curative treatment for these metastases and in selected groups; the 5-year median survival has been reported to be up to 30% (range 15%-67%)[21,22]. Patients with untreated but potentially resectable metastases show a median survival of 8 months and the 5-year survival rate of these patients is less than 5%[23]. Eligibility for surgical treatment requires strict criteria. Besides an adequate clinical condition, all liver lesions have to be completely resectable. The diagnosis of liver metastases relies first and totally on imaging to decide which patients may be surgical candidates. Thus, the imaging technique able to demonstrate the exact number, regional distribution, size of metastases and the volume of the remaining liver is crucial to determine respectability[24].

Imaging modalities

Ultrasound (US) and Contrast Enhanced Ultrasound (CEUS)

The development of CEUS has dramatically increased the potential of sonography in the assessment of focal liver lesions. The use of contrast agents allows perfusion mapping of focal lesions, thus enabling characterization of focal lesions. [25] .In investigations about the diagnostic yield of CEUS versus helical CT in the detection of liver metastases (no histological diagnosis), CEUS showed 97% of lesions seen by CT[25].

Although CEUS is widely used to assess the liver, it has some limitations: it needs considerable operator expertise and often reveals equivocal results in patients with (chemotherapy-induced) fatty infiltration of the liver. Due to the limitations in the visualization of segmental distribution and 3D-shape of metastases, it is limited in the preoperative assessment of patients with liver metastases[24].

A **B**

Fig. (5): Contrast enhanced ultrasound. A) A representative liver metastasis after 13 s of contrast agent injection with early contrast enhancement; B) A representative liver metastasis after 29 s of contrast agent injection with loss of contrast enhancement[26].

Multi-detector computed tomography (MDCT)

Nowadays MDCT is the mainstay of staging and follow-up of these patients, because it provides good coverage of the liver and the complete abdomen and the chest in one session. MDCT scanner has the capability for high-resolution studies with sub-millimeter slice thickness resulting in isotropic pixel sizes, which enable images to be reformatted in various planes that still have the same resolution as the axial images. This may improve detection of small lesions. High-resolution scans with maximum intensity technique and volumetric three-dimensional rendering enable accurate segmental localization and delineation of hepatic tumors[27]. Vascular reconstruction enables the demonstration of the hepatic arterial and portal venous anatomy obviating the need for conventional angiography in surgical planning of tumor resection[28]. Volumetric measurement of tumor size and normal liver is also more accurate[29].

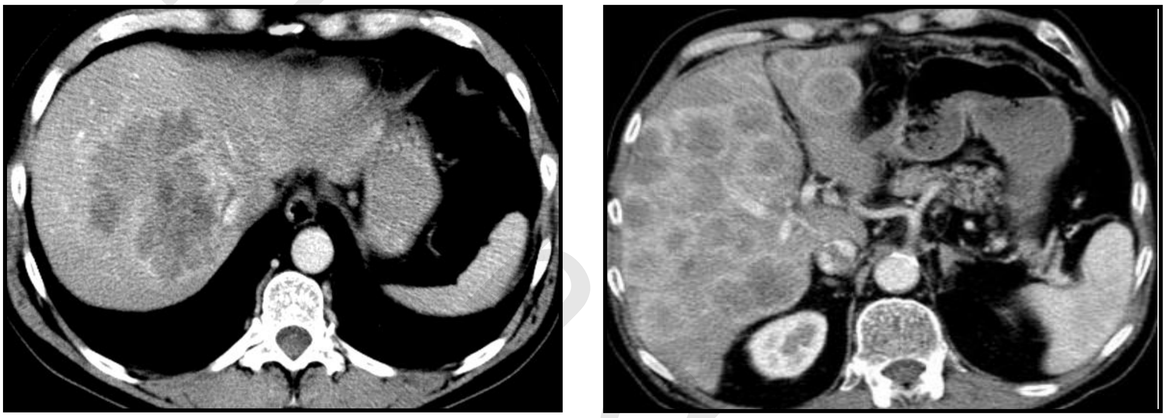
How many scans are necessary for a CT examination of the liver? For the evaluation of liver metastases, the use of triple-phase multidetector CT and /or contrast material–enhanced MR imaging is suggested to establish a baseline, which can help assess disease extent and allow post treatment comparison. In patients with colorectal cancer, for example, liver metastases are calcified in 11% at initial presentation[30]. These lesions with calcification are much better seen on unenhanced scans than on portal-venous phase scans. Small colo-rectal liver metastasis (CRLM) often are hyperattenuating during the hepatic arterial phase whereas larger lesions will often show a hyperattenuating rim during the hepatic arterial phase and a hypoattenuating center representing diminished vascularity and/or tumor necrosis[31], and larger lesions usually are detected as hypoattenuating lesions during the portal venous phase[32]. However the vascularity and therefore enhancement characteristics can be widely variable for reasons that are poorly understood[32].

Many studies found Arterial and equilibrium phase have no incremental value compared to hepatic venous phase CT in the detection of *hypo vascular LM*. Venous phase is still the most significant timing to detect hypo vascular liver metastases[33,34].

In patients with *hyper vascular hepatic deposits*, neuro endocrine tumors for example , the lesions are avidly enhancing in the hepatic arterial phase of the study with or without hypo dense center representing central breaking down[35,36].

Several studies have assessed the value of using thin slices to improve detection of small metastases.2.5 mm or 1.25 mm thick slices were significantly superior to 5, 7.5 and 10 mm thick slices[37]. When the slice thickness is decreased to 1 mm, no further improvement in lesion detection is seen, but there is a considerable increase in image noise with subsequent degradation of image quality. Therefore a slice thickness of 2-4 mm is recommended for axial viewing[38].

Although MDCT is the modality of choice to rule out metastatic disease in colorectal cancer, up to 25% of liver metastases may still be missed. Extra care has to be taken for patients with contrast allergies or with renal impairment[39].



A **B**

Fig. (6): A) Axial contrast-enhanced CT scan of a 58-year-old patient with colon cancer shows a lobulated and ill-defined liver metastasis. B) Axial contrast-enhanced CT scan of a 74-year-old patient with rectal cancer shows confluent liver metastases[40].

CT with arterioportography

In CT with arterioportography (CTAP), CT scanning of the liver is performed during contrast agent injection into either the superior mesenteric artery or hepatic artery *via* a percutaneously placed catheter. It provides maximum tumor-to-liver contrast by enhancing the liver parenchyma alone as in the portal phase and depicts tumor deposits as areas of perfusion defects. This is based on the fact that metastases are almost exclusively fed *via* the hepatic artery. CTAP was usually reserved for imaging candidates prior to surgical hepatic resection as it provided an accurate segmental localization of liver metastases and excellent depiction of liver vasculature. This invasive technique is less routinely performed with the advent of MDCT and MRI with liver-specific contrast agents, which are as accurate in lesion detection but with much lower false positive rates[41].

MRI (Magnetic Resonance Imaging)

The standard MRI protocol should always include unenhanced T1- and T2-weighted and contrast-enhanced pulse sequences. In liver MR imaging a set of T1-weighted in-phase and opposed-phase gradient-recalled echo images is acquired to assess the parenchyma for the presence of fatty infiltration or focal sparing of diffuse fatty infiltration. For T2-weighted imaging, the turbo-spin echo (TSE) or the fast spin echo with fat suppression are preferred over the single-shot TSE pulse sequences. In addition, heavily T2-weighted pulse sequences with a time of echo of approximately 160-180ms may help in differentiation between solid [metastasis, hepatocellular carcinoma, *etc.*] and non-solid lesions (e.g., haemangioma, cyst)[(42)].

After the acquisition of unenhanced pulse sequences, contrast-enhanced pulse sequences are always obtained. Nowadays, two different groups of MR contrast agents for liver imaging are available: first, the non-specific gadolinium chelates and second the liver-specific MR contrast agents. The latter group can be divided into two subgroups, the hepato-biliary contrast agents, and the reticulo-endothelial (or Kupffer cell) contrast agents[(43)].

Diffusion weighted sequence tests the mobility of water molecules in tissues and provides insight into the tumor microstructure. Most tumors are highly cellular, and cell membranes restrict the motion of water molecules, resulting in a decrease in tumor ADC. An increase in ADC has been noted in responding lesions in in vitro studies, animal studies, and previous clinical studies **.**It is believed that an increase in ADC is a consequence of cellular damage caused by the therapeutic agent leading to necrosis[(42,43)].

Non-specific gadolinium chelates

The liver and liver-lesion enhancement patterns obtained with non-specific gadolinium chelates (extracellular contrast agents) are similar to those obtained with iodinated contrast agents used in CT. Several agents with similar properties are on the market, including gadopentetate dimeglumine (Schering, Berlin, Germany), Gd-DTPA-BMA (GE Healthcare, Oslo, Norway), and Gado-teridol (Bracco, Milan, Italy).

Extracellular gadolinium chelates are used extensively for liver MRI. Following intravenous injection of a gadolinium-based agent, typically three phases of contrast enhancement are imaged: the arterial, portal venous phase and the equilibrium phase. During the arterial phase, most of the liver does not enhance as the majority of the liver's blood supply is *via* the portal vein. Enhancement patterns of liver lesions are similar to those demonstrated on CEUS and contrast-enhanced CT. The equilibrium phase or delayed phase is useful for helping with lesion differentiation (e.g., haemangioma *vs* metastasis). In addition, washout of contrast from HCC and peripheral or heterogeneous washout from liver metastases are characteristic findings on delayed imaging[(44)].

Liver-specific contrast agents

Hepatobiliary agents

Hepatobiliary agents represent a heterogeneous group of paramagnetic molecules of which a fraction is taken up by hepatocytes and excreted into the bile. Mangafodipir trisodium (Teslascan®, GE Healthcare) is taken up by hepatocytes and results in signal intensity increase on T1-weighted images (a so-called "T1 enhancer"), and a fraction is also taken up by the pancreas, which has been used for pancreatic MR imaging [45]. Focal non-hepatocellular lesions (i.e., metastases) do not enhance post-contrast, resulting in improved lesion conspicuity Mangafodipir-enhanced MRI has been shown to be superior to unenhanced MRI and helical CT for detection of liver metastases[45].

Reticuloendothelial agents

All reticuloendothelial system (RES) agents are super-paramagnetic iron oxide-based contrast agents (SPIO). SPIO particles are taken up by RES cells (so-called Kupffer cells) of normal liver parenchyma, as also by macrophages of the spleen and lymph nodes. They shorten T2 relaxation times in the liver tissue, and resulting in a loss of signal intensity in normal liver parenchyma. Despite of this, malignant liver lesions do not have a substantial number of RES cells and appear as hyper intense lesions with distinct borders in contrast to the hypo intense liver parenchyma after application of SPIO on T2-weighted MR study images[46].

There are some published studies comparing some methods reporting varying sensitivity. Some have reported that SPIO-enhanced MRI has better diagnostic efficacy for liver lesions over that of Gadolinium-enhanced MRI, and dynamic CT imaging with high sensitivity values[47]. Another study has claimed equal sensitivity between SPIO-enhanced MRI and Gd-DTPA-enhanced MRI in the delayed hepatocyte phase for the detection of liver metastases[48]. Gd- and SPIO-enhanced MRI had equal performance and were shown to perform significantly better than the other modalities on a per lesion basis in some studies[49]. These data were similar to previous studies comparing Gd- and SPIO-enhanced MRI each other ***or*** with MDCT or PET/CT[50-52].

MRI is a highly sensitive method of pre-operative imaging of colorectal liver metastases and should be considered the "gold standard". Except contraindications to MRI which include pacemakers, implantable cardiac defibrillators, cochlear implants and metallic orbital foreign bodies, MR imaging is still limited in the anatomic coverage, although the recent introduction of multi-channel MR coils with wider coverage and the moving-table MR technique has re-established the "competitiveness" of MR with MDCT with regard to patient throughput. One of the advantages of MR in liver imaging is the better soft tissue contrast, which reveals better characterization of focal liver lesions in question. The development of a liver-specific MR contrast agent has further improved the diagnostic yield of MRI in lesion detection and characterization[53,54].

Positron Emission Tomography (PET/CT)

The recent introduction of PET/CT hybrid scanners enables seamless and accurate fusion of the high resolution anatomic localization of CT with the functional data of fluorodeoxyglucose (FDG-PET). A combination of FDG-PET and CT scanning characteristics seems promising, and integrated PET/CT is becoming more widely available, although the exact clinical value and efficacy is not yet fully established. Due to restricted availability, high cost and an additional radiation exposure, PET/CT can be used in selected patients where the diagnosis is not clear following conventional diagnostic modalities[24].

(FDG-PET) can detect occult metastases in 32% of the patients, and thereby change the course of treatment in more than one-fourth of the cases. In addition, the role of FDG PET / CT as a problem-solving tool in patients on follow-up for a treated LM has been increasing in the setting of unexplained elevation of carcinoembryonic antigen and equivocal findings on conventional imaging modalities[55,56].

Which imaging modality is the best model in detection of LM? The issue of when to use which imaging method is still not solved. The answer likely depends on local equipment, availability, and operator expertise[57].

Clearly, continuing improvements in imaging are allowing metastases to be identified at an earlier stage but a different approach is needed to improve the detection of smaller metastases. A multi-modality strategy is recommended since no single modality can accurately detect all liver metastases[57-59].

Therapeutic approaches for liver metastases

Resectable tumors

Surgery

Surgery is the treatment of choice in certain malignancies and the only modality which may be considered as curative. However, only 10-25% of patients with hepatic metastases are eligible for curative surgical resection. Postoperative mortality is lower than 5%, especially in medical centers with high expertise, due to better knowledge of liver anatomy, efficient bleeding control during the operation and wide use of intra operative ultrasonography. Five year survival ranges from 25-39%[60].

The following criteria define a potential curative operation[61]: a) Ro resection (no microscopic residual tumor after the surgical procedure) with surgical margins ≥ 1cm, b) residual liver volume ≥30% of total liver parenchyma c) No presence of extra hepatic disease, d) Patients with adequate cardiopulmonary function[61,62].

1. Partial hepatectomy

Partial hepatectomy is a relatively safe procedure and is the treatment of choice for eradication of malignant hepatic lesions in non-cirrhotic patients as it is associated with a 5-year survival in more than 30% of patients. However, definitive surgical intervention is not feasible in most cases *(70-85% of the patients are not candidates for hepatectomy)* **because of:**

- Large tumor volume, inaccessible locations, multiplicity of tumor foci and extreme tumor extension[63].
- Extra-hepatic metastases are present in many cases[63].

2. Surgical ligation or dearterialization

Has been used but it was complicated by considerable morbidity[64]. Its effect on tumor regression and symptomatic improvement was temporary because of the rapid development of collateral circulation[64].

3. Total hepatectomy and liver transplantation

The donor availability limits this procedure[65,66]. Liver transplantation (LT) is now established as the only definitive treatment for end stage liver disease (ESLD). Liver transplantation can be divided to living donor liver transplantation, and cadaveric liver transplantation. Also it can be divided to **Left lobe transplantation** in pediatric recipients cases and **Right lobe transplantation** for adult recipients, as a larger piece of the liver is required[67,68]. Both Pre operative assessment including parynchmal, vascular and biliary assessment as well as post operative follow up for the donor and recipient are required for better outcome[69,70].

Strategies to convert non-resectable liver metastases to resectable status

Chemotherapy

Preoperative or conversion chemotherapy has become the primary treatment approach for non-resectable LM. This therapy helps to downstage liver disease, allowing more patients to undergo curative hepatectomy with a > 30% non-tumoral liver parenchyma remnant. The chemotherapy regimens used include fluorouracil, leucovorin, oxaliplatin, irinotecan, and monoclonal biologic agents (cetuximab/bevacizumab). Modern chemotherapy allows 12.5% of patients with initially unresectable LM to be rescued by liver surgery. Current data suggest that the perioperative combination of a monoclonal biologic agent with cytotoxic chemotherapy regimens can significantly increase progression-free survival in resected metastatic patients[71]. Despite a high recurrence rate and the requirement for repeat hepatectomies and extrahepatic resections, 5-year survival rate of 33% has been reported, approaching that of patients diagnosed with operable disease[72,73].

Portal Vein Embolization (PVE)

Preoperative portal vein embolization (PVE), first described in 1986[74], and then used in the setting of hepatic resection of hilar cholangiocarcinomas, is an effective means of inducing hypertrophy of the future liver remnant (FLR), thus allowing safe hepatic resection[75]. The underlying principle involves blocking portal venous flow to the side of the liver ipsilateral to the lesion in order to induce hypertrophy of the contralateral side and increase the volume of the FLR. In patients with an otherwise normal liver, current guidelines recommend preoperative PVE when the ratio of the remnant liver volume is < 30%. Patients submitted to prolonged chemotherapy with a high risk of induced hepatic lesions should benefit from this method when this ratio is less than 40%. The optimal time interval necessary to induce maximum hypertrophy after PVE has not been established, although some Japanese teams perform resection as early as 2 weeks after PVE. The majority of groups, however, use a 4–6 week interval between PVE and surgery. Long-term survival has been comparable to that after resection without PVE[76].

Local thermal ablation techniques

Ablation is destruction of a body part, this could be obtained by heat (for examples: radiofrequency ablation (RFA), Microwave ablation, LASER induced thermotherapy), cold (cryotherapy), chemicals (ethanol, acetic acid)[77].

RFA is the most commonly used technique, it has been applied mainly as a complementary procedure to surgery, allowing more effective disease clearance in selected patients with otherwise unresectable hepatic tumors[77,78].

RFA probes are inserted into the tumor under **US**, **CT** or **MRI** guidance and effect tumor necrosis by hyperthermia[77].

The use of RFA is limited because:

- **Three or fewer lesions** only can be treated, each <4 cm as charring of tissues decreases the conduction of heat leading to limitation in the tumors size completely ablated by current instruments (within 2–4 cm)[77].

- The RFA lesion is **difficult to follow radiographically**.
- The lesions **adjacent to the gall bladder** cannot be ablated as this could potentially lead to perforation or cholecystitis[79].
- Tissues **adjacent to large vessels** are protected from being thermally damaged because of the detrimental effect of the blood flow[79].
- Lesions **adjacent to diaphragmatic surface** can not be ablated for fear of diaphragmatic injury[80].
- Thermal damage and perforation of the gastrointestinal wall was reported with lesions located **within 1 cm of the liver capsule**[81].

Adding RFA to hepatic resection has been reported to be well tolerated; perioperative morbidity and mortality have been comparable to that after resection alone[82]. For patients with metastases considered unresectable, local thermal ablation combined with hepatic resection can achieve a median survival up to 37 months[83,84].

Results from the European Organization for Research and Treatment of Cancer (EORTC) trial have also demonstrated that local thermal ablation is superior to chemotherapy alone in treating patients with colorectal metastases that could not be managed by resection alone. In patients with extensive bilobar disease, recurrence rates are high, but long-term survival is encouraging and may be improved with aggressive postoperative chemotherapy[85-87].

In some patients with multiple hepatic LM, a complete metastatic clearance cannot be achieved by a single hepatectomy, even when downstaged by chemotherapy, after portal embolization, or combined with a locally destructive technique (RFA or microwave ablation or cryotherapy). In two-stage hepatectomy, the tumor clearance of one hemiliver is obtained first (as a non-curative intervention) and the remaining tumor lesions of the contralateral hemiliver are resected in a second operation, after a period of liver regeneration. This approach has yielded good outcomes in patients with multiple, bilateral LM[88-90].

Non-resectable liver metastases

There are some contraindications for the resection of hepatic metastases, which are generally accepted (Table V)[90,91].

Table V: Absolute contraindications for the resection of hepatic metastases.

Parameter	Characteristics that contraindicate resection
Lesions	Extrahepatic
Liver Tumors	>10
Liver segments involved	>6
Cardiopulmonary status	Bad
Necessary Liver resection	>70%
Ro resection	Not feasible

Many strategies are applied for management of unresectable liver metastasis including:

I. Systemic chemotherapy
II. Trans arterial approaches

III. Immunotherapy
IV. Radiotherapy

I- Systemic chemotherapy

In case of extensive and unresectable metastases, systemic chemotherapy is the standard treatment. For hepatic deposits from colorectal cancer Nowadays, the combination of 5-FU and leucovorin (LV) achieves a 20-30% 5 year overall survival[92].

Irinotecan is a camptothecin derivative and acts as a topoisomerase I inhibitor. Topoisomerases are enzymes located in the cell nucleus which unwind DNA before replication. Inhibition of their action causes DNA strand breaks and failure of replication and the cell dies. As topoisomerase I is overexpressed in colorectal cancer, irinotecan seems a potentially effective drug. Oxaliplatin on the other hand is a platinum compound, which inhibits DNA replication by forming intra- and interstrand platinum- DNA crosslinks[93].

Newer chemo- therapeutic agents have also been added and the triple regimen, (which involves 5-FU, LV and irinotecan or oxaliplatin) is the preferred standard treatment today[94].

Newer drugs, like cetuximab or bevacizumab are also used in combination with first line therapy with good results. Bevacizumab in combination with FOLFIRI (5-FU, leucovorin and irinotecan) or 5- FU+LV is licensed in the UK as a first line treatment of colorectal cancer metastases[95].

II- Intra-arterial Approaches

(Infusion, Chemoembolization, Radioembolization)

Techniques for regional hepatic therapy for metastatic cancer to the liver include hepatic arterial infusion chemotherapy, chemoembolization, radio-embolization with yttrium-90 labeled particles, and isolated hepatic perfusion.

Trans-catheter arterial embolization for HCC was first reported by Doyon et al in the early 70s[96]. Chemoembolization using gel-foam and anticancer drugs was reported by Yamada et al in the early 1980s[96,97].

Recent advances in catheter manufacture and increased quality of digitally subtracted imaging devices allowed more superselective transarterial approaches beyond second and third-order vascular branches with greater depth, precision, and dependability thus allowing higher success rates, lower dose of chemotherapeutic agents and lower rate of complications[98,99].

While these approaches have been available for a long time, their role in the management of metastatic cancer continues to evolve. Recent improvements in systemic chemotherapy for metastatic cancer should force oncologists to re-evaluate the role of regional hepatic therapy. It is essential to evaluate the indication and timing for these approaches [99,100].

III- Immunotherapy

Immunotherapy is mainly used in advanced diseases which have failed to respond to conventional therapy. Levamisole, a non-specific immune stimulate, was used in adjunctive treatment with 5-FU as an immune modulator. More exploration of different combinations may provide new adjuvant regimens. Some scientists have recently reported a phase I-II clinical trial of neoadjuvant immonotherapy with interlukin 2 before hepatectomy for liver metastases. Clinical trials in 2006 have also shown that the monoclonal antibody 17-1A was effective in increasing the survival following resection of Dukes C primary colorectal tumors. It can also be used as an adjuvant treatment before or after liver resection for liver metastases from colorectal cancer[100,101].

IV- Radiotherapy

Traditional external beam irradiation has found little place in the management of liver tumors because of the particularly radiosensitive nature of normal liver tissues, which limits the total dosage to 30-35 Gy. Selective internal radiation therapy (SIRT) is a new modality that may be valuable in colorectal cancer liver metastatic patients which was not suitable to resection, RFA and cryotherapy[101].

Stereotactic radiation therapy (SRT) allows radiation beams to be given to a very specific area, Stereotactic radiotherapy (SRT) gives smaller doses of radiation over a number of treatment sessions (called multiple fractions), until the desired total dose is given[101].

Transarterial therapies for treatment of liver metastases

The first-line treatment for unresectable hepatic metastases is chemotherapy, which may be administered systemically or with a hepatic arterial route. Because the progression of hepatic disease contributes significantly to morbidity and mortality, transarterial therapies may be used for palliative or adjuvant therapy, to help stabilize disease or to reduce the hepatic tumor burden[102]. Transarterial therapies take advantage of the dual blood supply of the liver. Approximately 80% of the blood supply to hepatic metastases arrives via the hepatic artery, whereas three-fourths of the blood supply to normal hepatic parenchyma is portal venous. Hence, cytotoxic agents that are infused selectively into the hepatic artery preferentially target tumor cells over normal hepatic tissue (Table VI)[103].

Rational

1. The liver receives a **dual blood supply** from the hepatic artery and the ***PV***. Approximately 1/3 of the normal hepatic blood flow comes from the hepatic artery and the other 2/3 from the ***PV*** [96]. About 1/2 of the oxygen required by the normal hepatic parenchyma is supplied by the ***PV***. On the other hand, HCC and most hepatic metastatic deposits are almost exclusively supplied by the hepatic artery[96]. This dual vascular supply provides a unique opportunity to explore intra-arterial therapies for hepatic malignancies since the tumor can be made ischaemic while uninvolved liver is spared[104].
2. **The pharmacokinetic advantage of loco-regional drug administration** enhances their effect as many drugs exhibit preferential extraction when delivered intra-arterially rather than intravenously and they can achieve quite favorable liver/systemic drug concentration ratios *(up to 40 times)*, thus minimizing the systemic toxicities associated with chemotherapy[105].

3. These two partially effective therapies act synergistically leading to prolonged dwell time of the drug *(persisting for several months):*
   - The ischaemia resulting from the embolization might actually enhance the drug cytotoxic action.
   - Many drugs are actively expelled from tumor cells due to the action of the trans-membrane pump **P-glycoprotein** and it is conceivable that tissue hypoxia induced by chemoembolization inhibits the active efflux of the drugs [104].

Chemoembolization has been increasingly used in the last few years

- As a mean of palliation for unresectable or recurrent tumors [96].
- Reducing the size of the neoplasm.
- Relieving pain or bleeding[106].
- Prolong survival.

Table VI: Options for transarterial therapies[100,107].

Traditional methods Without embolization • Intermittent chemotherapy infusion into the hepatic artery • Continuous infusion with a hepatic artery pump With embolization • Bland embolization • Transarterial chemoembolization (TACE)
Recent advances Embolization with drug-eluting microspheres Embolization with radiation-emitting microspheres
Experimental methods Gene therapy

A- Hepatic arterial infusion chemotherapy

Traditional transarterial therapies are based on the infusion of chemotherapeutic drugs into the hepatic artery either intermittently or through a surgically implanted hepatic artery pump[103]. The concept of hepatic artery infusion (HAI) dates back to the early 1960s when it was tried in a few patients with gastrointestinal tumors metastatic to the liver and was associated with favorable outcomes. The rationale for HAI is to expose the metastases to high chemotherapy concentrations while minimizing systemic toxicity. The other rational is the high first pass hepatic extraction of the drug used for this approach. Both factors cause high local drug concentrations with reduced systemic toxicity and allow relatively higher dosages as compared with intravenous treatment[108]. Some studies comparing intra-arterial chemotherapy with conventional systemic chemotherapy have demonstrated consistently higher response rates in patients receiving intra-arterial chemotherapy[109].

Multiple agents such 5-FU, mitomycin, cisplatin, and doxorubicin have been infused. Infusing in the hepatic artery is achieved through an implantable subcutaneous infusion pump connected to a surgically placed hepatic artery catheter, which delivers the chemotherapeutic agent at a slow fixed rate, usually for 2 weeks[110,111].

Complications related to hepatic artery thrombosis, catheter displacement, hematomas, infections, and liver perfusion are all reported as pump-related complications(110). The technical complications are closely associated with surgeon experience and arterial anatomy. Treatment-related toxicities include chemical hepatitis, biliary sclerosis, and peptic ulceration. Chemical hepatitis, which is the most common (42%), presents with elevation in liver enzymes or bilirubin. Liver function monitoring, dose reduction, or treatment cessation are recommended based on the severity of the clinical presentation. Although most cases are reversible, biliary sclerosis can develop in 3% to 26% of patients(112). Response rate and survival also improve with the addition of dexamethasone. Contraindications include portal vein thrombosis, more than 70% liver replacement by tumor, significant impairment of liver function, or a hepatic artery anatomy that would preclude perfusion of the entire liver(113). The utilization of HAIP unfortunately has lost its adoptability secondary to a small number institutions seeing benefit,and significantly high pump related complications(112,113).

B- Transarterial Chemoembolization (TACE)

Transarterial chemoembolization (TACE) is a catheter-based technique that combines both regional chemotherapy and embolization to increase the dwell time of cytotoxic agents and induce ischemia in the tumor. Conventional TACE therapy, in which arterial inflow is reduced to delay drug washout, enables chemotherapeutic drug concentrations within a tumor that are up to 100 times greater than those achievable with systemic chemotherapy(114). It has been shown that anoxic damage increases vascular permeability and thereby promotes penetration of chemotherapeutic agents into the tumor(115,116).

Though TACE implementation is tailored according to the liver function of each patient as well as the extent of the tumor and portal vein involvement, the use of selective TACE more often can result in a better outcome with less adverse effects(117,118). There is increasing evidence that selective TACE achieves better antitumoral effects and reduces both the dosage of drugs used for TACE and the number of TACE sessions needed to achieve extensive tumor necrosis as compared to the use of conventional TACE(119,120).

C- Drug-Eluting Beads (DEB)

The use of drug-eluting microspheres in a new variation of the TACE method is designed to improve the precision of drug delivery. Drug-eluting microspheres are made of polyvinyl alcohol hydrogel and are biocompatible, hydrophilic, and nonresorbable(121). The primary advantage of using drug-eluting microspheres for chemotherapy is the sustained release of the chemotherapeutic agent over a long period of time, which contrasts with the more rapid release of the agents from the lipiodol solution in standard TACE therapy. With a controlled gradual and local release, contact time of the drugs with the tumor is greater and plasma levels of the drugs are lower than those with standard TACE therapy. Preprocedural planning with cross-sectional imaging and liver function testing is imperative. Accurate staging of disease by assessing the intrahepatic and extrahepatic tumor burden is crucial to exclude the possibilities of surgical therapy, radiofrequency ablation, and cryotherapy. Cross-sectional imaging can be extremely useful for assessing the hepatic arterial anatomy and portal vein patency(121,122).

Pharmacokinetics

Drug loading and elution kinetics are dependent on the particle size. For example, DC Beads (Biocompatibles UK, Surrey, England) are manufactured in various sizes ranging from 100 to 1200 µm (Fig. 7A). For a specific drug concentration, smaller microspheres require less time for drug loading than larger ones do, with a loading efficiency of 99% up to a maximum concentration of 45 mg/mL. Elution kinetics are similarly affected by microsphere size, with smaller microspheres eluting more quickly than larger ones[123,124].

Technique and Administration

Prior to administration via a catheter, the loaded beads are mixed with an equal volume of non-ionic contrast medium to guide the injection. The specific targeting of the drug at the site of the tumor implies enhanced efficacy by a maximized tumor dose and at the same time reduced toxicity due to negligible systemic exposure and toxicity. According to the product information, Irinotecan loaded DC Beads™ or DEBIRI (100mg irinotecan per 2ml DC Beads™) are stable over a period of 14 days when stored refrigerated. After mixing with non-ionic contrast media irinotecan-loaded beads have to be administered immediately. The bead admixture is reported to be stable for a maximum 24h at 2- 8° C or 4h at room temperature.

(A) **(B)**

Fig. (7): A- Different DC beads sizes. B- Yttrium-90 (Y^{90}) bearing microspheres

Baseline angiography of the celiac, superior mesenteric, and hepatic arteries, should be performed to determine the vascular anatomy and assess tumor vascularity. Administration through the proper hepatic artery is feasible for treatment of bilobar disease. In patients with variant arterial anatomy, such as a replaced left hepatic artery or a middle hepatic artery, bilobar disease may be treated incrementally by dividing the drug dose and infusing separate portions into the individual hepatic arteries. After the infusion of drug-eluting microspheres, a solution containing bland microspheres (without drugs) may be administered to achieve complete embolization, which is characterized as the cessation of flow in the catheterized vessel[125].

Follow-up cross-sectional imaging with the same modality that was used at baseline is critical for determining the tumor response. Determinants of tumor response observed at imaging include a reduction in tumor size; a lack of contrast enhancement, which signifies necrosis. In cases of tumor progression or partial necrosis with residual areas of enhancement suggestive of viable tumor cells, therapy with drug-eluting microspheres injection may be repeated[103,123].

D-Yttrium-^{90} radioembolization

The therapeutic use of external-beam irradiation of the liver has been limited because of the vulnerability of the normal hepatic parenchyma to damage by radiation. Approximately 50% of patients who receive a whole-liver radiation dose of 35 Gy (a dose insufficient to induce tumor cell death, develop radiation-induced liver disease)[126,127].

Yttrium-90 (Y^{90}) bearing microspheres(figure 7B), however, act as point sources of radiation that, when delivered via the hepatic artery, are deposited predominantly within tumor tissue. Y^{90} emits beta radiation with a mean energy of 0.94 MeV and mean penetration of 2.5 mm. Y^{90}-bearing microspheres can deliver an intratumoral radiation dose of 100–150 Gy, which is highly effective for tumor destruction. In addition, the preferential deposition of the microspheres within the tumor allows selective irradiation of the target rather than normal hepatic parenchyma and thereby reduces the risk of radiation-induced hepatitis[128].

E- Bland embolization

Using –for example- N-butyl-2-cyanoacrylate, a liquid glue that polymerizes instantaneously on contact with blood or endothelium, as an embolic agent, Primarily used for uncontrolled bleeding or arteriovenous malformations[129], this agent was introduced to treat liver metastasis from malignant neuroendocrine tumors of the pancreas[130,131] Mixed with radiopaque Lipiodol, the polymerization time can be prolonged to 10-15 sec, depending on dilution[132]. Therefore, a peripheral embolization can be achieved leading to almost complete tumor ischemia and prevention of collateral blood supply. Furthermore, cyanoacrylate causes a permanent and complete occlusion of the embolized arteries, whereas vessels occluded with Gelfoam particles were revascularized within 8 days[133].

In many studies, using a mixture of cyanoacrylate and Lipiodol to treat liver metastasis from gastrointestinal neuroendocrine tumors by transarterial embolization without anticancer agents showed a fair response[132,133].

Future directions

The future of trans catheter therapies is promising. Ongoing research in this field incorporates advances in the knowledge of liver cancer biology, new concepts in targeting liver cancer, development of new drugs, improvement of intra-arterial drug delivery techniques, and technological advances in imaging systems[123].

Advances in therapeutics

It is anticipated that delivered agents will become more potent, translating into higher efficacy and survival benefit. Furthermore, new therapies will be developed that may be more tumor specific or potent. These therapies may involve the delivery of genetic information. Recent research has investigated the targeted delivery of gene therapy to the liver by means of isolated hepatic perfusion or via the portal vein.

The delivery of gene therapies and other future therapies will likely use nanotechnology. Nanocomposites could also be tagged to be tumor specific, tumor avid, visible at time of delivery, and carry a specific therapy. Finally, new classes of drugs delivered intraarterially could lead to markedly more potent tumor kill than conventional chemotherapeutic agents. For example, a new class of anticancer drugs, such as 3-bromopyruvate, specifically targeting tumor metabolism could be infused locally by means of transcatheter delivery for increased potency by disrupting the ability of the cancer cell to generate energy, but leaving normal cells intact, this new approach is extremely promising.

Early preclinical testing in the rabbit VX2 tumor model has proved quite effective, leading to significant survival benefit and even cure of the animals[123,134].

Gene therapy

Other experimental therapies that take advantage of a trans-arterial approach are in early stages of development. Gene therapy is based on the transfer of DNA or RNA into host tissues, a procedure that may lead to new protein synthesis or to the deactivation of gene expression, with the ultimate goal of inducing tumor lysis, blocking tumor growth, inducing antitumor immunity, activating a prodrug, or inhibiting tumor angiogenesis[134,135]. These results represent the opening of new avenues for transarterial therapy in patients with an unresectable primary or secondary hepatic malignancy.

Advances in imaging

Transcatheter therapies will be aided by advances in imaging. Because of limitations of conventional digital subtraction angiographic (DSA) imaging in completely targeting tumors, several techniques have been used to more successfully and completely target tumors during transcatheter delivery of a therapeutic agent. CT is performed with an arterial catheter placed selectively into a feeding vessel. Iodinated contrast medium was manually injected via this hepatic arterial catheter while the patient was imaged in the CT scanner[41]. This “catheter-directed CT angiography” successfully assisted superselective radioembolization, facilitating tumor targeting and sparing normal hepatic parenchyma. This technique is easily applicable to other therapies. In fact, several studies have demonstrated similar success with C-arm angiographic CT for chemoembolization and other transcatheter therapies[134].

The utility of combining DSA with MR imaging has also been demonstrated, resulting in catheter repositioning in nearly 50% of cases for better tumor therapy[134].