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Qualitative and quantitative efficacy assessment of CT-imaging of liver lesions using Imeron 400 vs. Imeron 300 in a randomised blinded study

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To my beloved family,

particularly my three angels

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αFP	Alpha (α) - Fetoprotein
AH	Hepatic Artery
AJCC	American Joint Committee on Cancer
Alb	Albumin
ALP	Alkaline Phosphatase
AP	Arterial Phase
ASC	Ascites
BCLC	Barcelona - Clinic Liver Cancer
Bili	Bilirubin
CA	Cryoablation
Ca	Carcinoma
CCC	Cholangiocarcinoma
CIN	Contrast-Induced Nephrotoxicity
CLIP	Cancer of Liver Italian Program
cm	Centimeter
CPS	Child - Pugh Score
CRC	Colorectal Carcinoma
CRF	Case Report Form
CT	Computer Tomography
cTACE	Conventional Transarterial Chemoembolisation
CUPI	Chinese University Prognostic Index
D	Drop-outs
DD	Double Drop-outs
DEB-TACE	Transarterial chemoembolisation with chemotherapeutically loaded beads
dl	Deciliter
EC	Esophageal Carcinoma
ECOG	Eastern Cooperative Oncology Group
EHE	Hemangioendothelioma
EPS	Eastern Cooperative Oncology Group Performance Status
FLC	Fibrolamellar Carcinoma
FLT3	Fms-Like Tyrosine kinase 3

FNA	Fine-Needle Aspiration
FNH	Focal nodular hyperplasia
g	Gram
GCP	Good Clinical Practice
GRETCH	GRoupe d'Etude et de Traitement du Carcinoma Hépatocellulaire
HA	Hepatocellular adenoma
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C Virus
HIFU	High-Intensity Focussed Ultrasound ablation
HU	Hounsfield Units
INR	International Normalised Ratio
IRE	Irreversible Electroporation
ITT	Intend-To-Treat
IVC	Inferior Vena Cava
JIS	Japan Integrated Staging
KPS	Karnofsky Performance Scale Index
LA	Laser Ablation
LGA	Left Gastric Artery
LN	Lymph Nodes
M	Metastasis
MA	Mesenteric Artery
MACA	Mamma Carcinoma
MELD	Model for End-stage Liver Disease
MELD-Na	Model for End-stage Liver Disease - sodium
MESO	Model for End-stage Liver Disease to serum sodium ratio
mg	Milligram
ml	Millilitre
mm	Milimeter
MPS	Main Portal Scissura
MRI	Magnetic Resonance Imaging
MWA	Microwave Ablation

N	Node
NaCl	Natrium Chloride
NASH	Non-alcoholic Steatohepatitis
NET	Neuroendocrine Tumour
p	Probability of extreme data arising by chance
P	Performance
PACS	Picture Archiving and Communication System
PDGFR	Platelet-Derived Growth Factor Receptor
PEI	Percutaneous Ethanol Injection
PET	Positron Emission Tomography
PET/CT	Positron Emission Tomography/ Computer Tomography
PP	Per Protocol
PSC	Primary Sclerosing Cholangitis
PV	Portal Vein
PVE	Portal Vein Embolisation
PVP	Portal Venous Phase
PVT	Portal Vein Thrombosis
RAF	Rapidly Accelerated Fibrosarcoma
RFA	Radiofrequency Ablation
ROI	Regions of Interest
Sec	Second
SEG	Segment
SI	Signal Intensity
SIRT	Selective Internal Radiation Therapy
T	Tumour
TAE	Transarterial Embolisation
TAS	Trans-Axial Scissura
THI	Tissue Harmonic Imaging
TNM	Tumour/ Node/ Metastasis
TS	Transverse Scissura
TSH	Thyroid-Stimulating Hormone
UKELD	United Kingdom model for End-stage Liver Disease
US	Ultrasonography

VCM	Vinyl Chloride Monomer
VEGFR2	Vascular Endothelial Growth Factor Receptor 2
VH	Hepatic Veins
VS	Vertical Scissura

1. Introduction

1.1. Anatomy of the liver

1.1.1. Macroscopic structure of the liver

The liver (Greek word for liver: hepar - ἡπαρ, hence the adjective hepatic) represents the largest gland in the human body, possessing an exocrine as well as an endocrine function, as well as its largest solid organ and second-largest overall after the skin. It has a weight of 1200 to 1500 g and a width of 7 to 10,5 cm for adults, depending on sex and body size.[1]

Anatomically, the liver is divided by fissures (fossae) into four lobes: the left (lobus hepatis sinister), the right (lobus hepatis dexter), the quadrate (lobus quadratus) and the caudate lobe (lobus caudatus).[2]

It is the only human organ that has the remarkable property of self-regeneration following damage of up to 75%.[3,4] If a part of the liver is resected or destroyed, the remaining parts can grow back to the liver's original size in approximately three to six months, regaining its original function within two to three weeks, provided that no other damage or complications arise.[5]

The liver's various functions are performed by the liver cells, the hepatocytes, which account for approximately 80% of the liver's cytoplasmic mass and play a vital role in the physiopathology of the liver.[6]

The liver's role in metabolism is significant; it is the main site in the body for gluconeogenesis and has a number of complex functions, such as glycogen storage, protein (inter alia plasma protein) synthesis, storage and secretion, the synthesis of cholesterol, phospholipids and bile salts, decomposition of erythrocytes, production of hormones and detoxification. Hepatocytes have the ability to metabolise and inactivate exogenous and endogenous compounds such as drugs and steroids, respectively, while also being able to modify ammonia into urea for excretion (urea cycle). The liver also induces the production and secretion of bile and, thus, participates in the emulsification of lipids and digestion.[7,8]

1.1.2. Segmental anatomy of the liver

The Couinaud classification is the most commonly used to describe the hepatic functional anatomy. According to it, the liver is divided into eight functionally independent segments (SEG) (Table 1). Every SEG possesses a vascular inflow via the portal vein's (PV, Latin: vena portae) and hepatic artery's (AH, Latin: arteria hepatica) branches, which are located in the centre of the SEG, outflow via the hepatic veins (VH, Latin: venae hepaticae) at the margins of the SEG and biliary drainage through the bile duct at the centre of the SEG.[9,10]

Table 1. Hepatic segments based on the Couinaud classification[9]

I	Caudate or Spigel lobe	
II	Lateral SEG	Superior subsegment
III		Inferior subsegment
IVa	Medial SEG	Superior subsegment
IVb		Inferior subsegment
V	Anterior SEG	Inferior subsegment
VIII		Superior subsegment
VI	Posterior SEG	Inferior subsegment
VII		Superior subsegment

The liver is divided into a functional left and right side, namely the left and right liver (also known as the left and right hemiliver), via the main portal scissura (MPS) or Cantlie's line. The MPS contains the middle VH and spans from the posthepatic inferior vena cava (IVC), along the anterosuperior (diaphragmatic) surface of the liver, to the centre of the gallbladder fossa. The right vertical scissura (VS) contains the right VH and subdivides the liver's right lobe into anterior (SEGs V and VIII) and posterior SEGs (SEGs VI and VII). The SEG V is divided from the SEG VIII and, respectively, the SEG VI from the SEG VII by the transverse scissura (TS), which contains the main right PV. The SEGs V and VI

are located inferior at the anterior and posterior sectors, respectively, while VIII and VII are located superior to this plane. The left VS, which contains the left VH, subdivides the left lobe of the liver into lateral (SEGs II and III) and medial (SEG IV) sectors. According to Bismuth, the medial SEG (SEG IV) of the left liver can be divided into two subsegments by the trans-axial scissura (TAS) containing the left PV (SEGs IVa and IVb). From the external surface of the liver, the SEGs IVa and IVb are separated from the SEGs II and III by the falciform ligament. The SEGs II and III are also divided by the TAS containing the left PV. The SEG I (Caudate or Spigel lobe) is divided by the SEGs II and III by the ligamentum venosum. SEGs I, VI and VII are located posteriorly and are not visible on a frontal view. The lateral part of the left hemiliver is formed by the SEGs II and III and the medial part is formed by the SEGs IVa and IVb. The right hepatic border is formed by the SEGs V and VIII (Figure 1).[9,11,12]

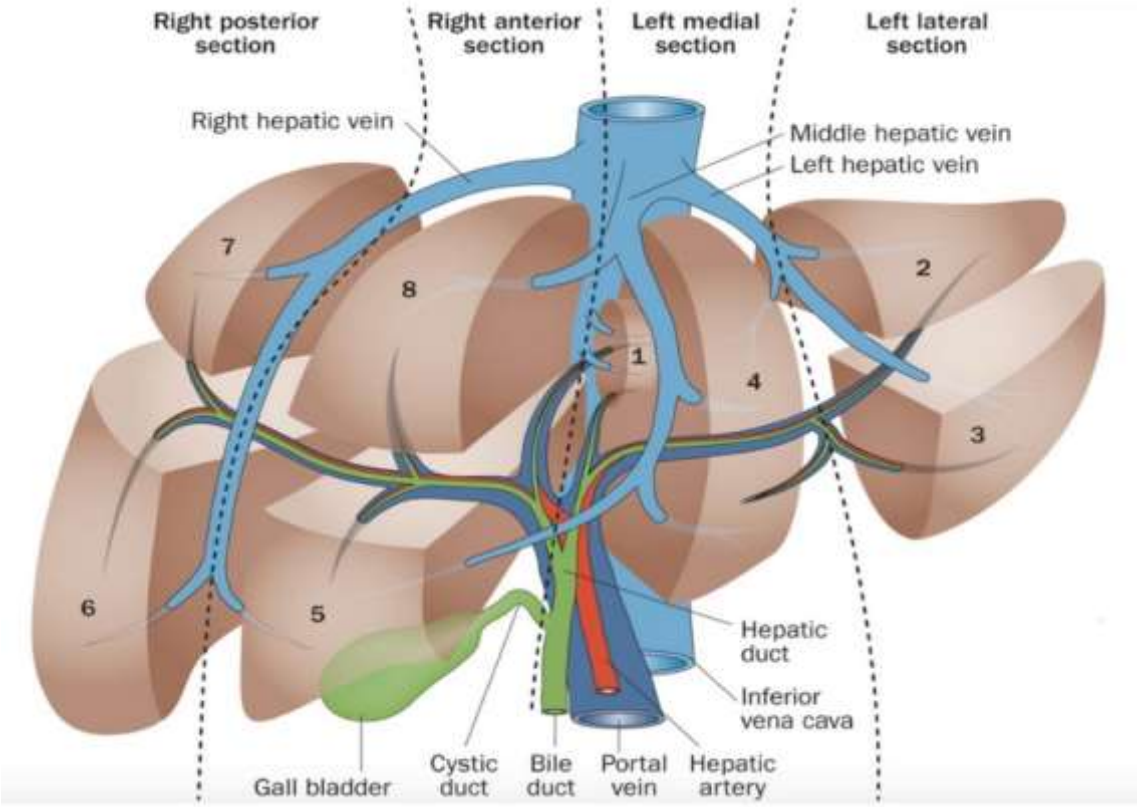


Figure 1. Couinaud's Segmental Anatomy of the Liver. Reproduced from López-Terrada D, Alaggio R, de Dávila MT, et al.[12] Copyright licence number: 5170650928363.

Since the liver is divided into self-contained SEGs, each of them can be resected without affecting the others, as long as the resections proceed along the vessels that demarcate the borders of the SEGs.[9]

SEG 1 (Caudate or Spigel lobe) differs anatomically from all the other SEGs as its portal inflow originates from the left and right branches of the PV and also short VHs are frequently present, connecting it directly to the IVC. Due to this unique blood supply, it is isolated and can be saved from a disease process; it can also undergo hypertrophy in order to compensate for the destruction of the liver parenchyma caused by a disease.[9]

Resecting specific liver SEGs is particularly useful in patients with hepatocellular carcinoma. The main quest in these cases is to resect the entire tumour-affected liver tissue whilst retaining all healthy liver in order to prevent further loss of the liver properties and functions. It has been proved that non-SEG based resections provide operative mortality of 20 - 60%, while SEG based resections provide operative mortality of 0 - 16%, minimising also the postoperative liver dysfunction and also offering a long-term outcome similar to a major liver resection.[10,11]

1.1.3. Liver's blood circulation

The hepatic blood supply is unique, since it is derived not only from the heart, but also from the digestive track via the AHs and the PV, respectively. The AHs supply the liver with oxygenated blood, which represents 20 - 25% of the liver's blood, while the remaining 75 - 80% of the liver's blood is supplied by the PV. However, only half of the liver's oxygen supply originates from the hepatic PV, while the other half originates from the AHs.[13-15]

The patterns of the liver's arterial blood supply are variable; in 25% to 75% of cases, deviations of the main pattern in which the liver receives its arterial blood supply are found.[16]

There are multiple AH variations and classifications. In some cases, there also exist aberrant AH, known as accessory AH, which contribute to the hepatic arterial blood supply; these are even capable of providing the main arterial supply to hepatic parts, in which case they are termed as "replacing AHs". Being familiar

with the conventional anatomy and its variations is of utmost importance for the radiologist, as well as the surgeon, in order to plan the best therapeutic approach and to reduce the intra- and postoperative complications.[17-22]

The common AH arises in most cases from the coeliac trunk. It divides into the gastroduodenal arteries and the proper AH, which, within the hepatoduodenal ligament, bifurcates into right and left branches, termed the right and left branches of the AH, respectively, each supplying the right and left lobes, respectively.[17-20]

The most commonly used classification of the liver vascularisation is that of Michel from 1955. Michel described ten types, with type I being the most common, as described above. In 10% of cases, a left AH starts from the left gastric artery (LGA) and supplies the left liver while a middle AH supplies the right liver; this represents Michel's type II. In 11% of cases, a right AH starts from the superior mesenteric artery (MA) and supplies the right liver, while a middle AH supplies the left liver, respectively: this is Michel's type III. In type IV, which represents 1% of cases, the common AH originates from the gastroduodenal artery and produces a right and left AH, which supply the right and left liver, respectively. In 8% of cases, there is an accessory left AH starting from the LGA and this represents type V. In type VI, which occurs in 7% of cases, an accessory right AH starting from the superior MA is present. Michel's type VII is a combination of types V and VI, namely there is an accessory right, as well as an accessory left AH, starting from the left gastric and superior MA, respectively. The type VIII refers to the cases where there is an accessory left AH, starting from the LGA and a middle AH which both supply the left liver, while the right liver is supplied from the right AH. Types IX and X are rare; in type IX, the common AH starts from the superior MA, while in type X it starts from the LGA.[19,20]

The segmental vascularisation of the liver also has many variations. Branches from both the left and right AH supply SEG 1 of the liver, namely the caudate lobe; this is also the case for SEG 4, although there exists much controversy on this matter in the literature. Most commonly, the left AH supplies SEGs 2 and 3, while the right AH supplies the SEGs 5, 6, 7 and 8.[21,22]

The portal system consists of all the veins which drain the blood from the spleen, pancreas, gallbladder and nutrient-rich venous blood from the abdominal part of

the gastrointestinal track, except for that from the lower part of the rectum. The blood is brought to the liver by the PV which, in the liver, branches like an artery and terminates in the sinusoids from which the blood is delivered via the VHs to the IVC.[23-32]

The average length of the PV in adults is 8 cm, its diameter is of between 1 and 1,5 cm and it is devoid of valves. The splenic and the superior mesenteric veins unite behind the neck of the pancreas to form the PV; the latter also receiving blood from the inferior mesenteric, gastric and cystic veins. At the hilum, which is also called the porta hepatis or transverse fissure, the PV ramifies into two branches, right and left, before entering the liver. There are also variations of the liver vascularisation; the left branch usually supplies SEGs II, III and IV, while the right branch supplies SEGs V and VIII (anterior branch) and VI and VII (posterior branch). In the hepatic lobules and SEGs, the PVs are typically found behind the AHs and the bile ducts. The branches of these veins pass between the lobules and conclude in the sinusoids.[23-25]

The sinusoids are small blood vessels, approximately 10 – 15 µm in diameter, with a fenestrated endothelium between the rows of the hepatocytes. The hepatocytes are separated from the sinusoids by the perisinusoidal space (space of Disse), which is filled with plasma. In the sinusoids, oxygen from the AHs and nutrients from the intestines, which arrive via the PV, diffuse through the capillary walls into the liver cells. At the walls of the sinusoids are located special cells, the Kupffer cells (also referred to as Browicz-Kupffer cells or stellate macrophages), which are part of the mononuclear phagocyte or reticuloendothelial system and whose function is the removal of particulate materials and the destruction of microorganisms from the blood, before in enters the circulation. The blood from the sinusoids drains into the central veins of the lobules which merge into the VHs.[26-29]

The VHs are differentiated into two groups, namely the upper and lower groups. The upper group, which mostly consists of three veins, arises from the posterior part of the liver and drains the quadrate and left lobes. The lower group, which consists of a varying number of veins that are usually smaller than the ones of the upper group, arises from the caudate and right lobes. The VHs lack valves

and drain the deoxygenated, cleaned and detoxified blood from the liver directly into the IVC.[30,31]

The inferior or posterior vena cava forms by the union of the right and left common iliac veins and drains blood from the lower half of the body (below the diaphragm) into the right atrium of the heart.[32]

In the normal resting situation, 10 - 15% of the total blood volume is in the liver, with approximately 60% of that being in the sinusoids. When a haemorrhage occurs, the liver adjusts its blood volume and is able to send blood into the circulation in order to compensate for a moderate blood loss.[33]

1.1.4. Liver's lymph circulation

Approximately 25 - 50% of the lymph flowing through the thoracic duct is produced in the liver. The lymphatic vessels of the liver are portal, sublobular and superficial, also named capsular, according to their location. At least 80% of the hepatic lymph flows into the portal lymphatic vessels. Hepatic lymphatic fluid and cells from the sinusoids reach the lymphatic vessels through the liver sinusoidal endothelial cells into the space of Disse.[34-36]

The majority of the lymphatic vessels accompany the blood vessels in the hepatic hilum and the lesser omentum and reach the coeliac lymph nodes (LN), which, in turn, drain into the thoracic duct, although hepatic lymph can also drain into the mediastinal LN. Of clinical importance is the fact that metastases can reach the liver from all the organs which are drained by the PV.[36,37]

1.2. Liver tumours

1.2.1. Benign tumours

The more common benign tumours of the liver include:

- Liver or cavernous haemangioma
- Hepatocellular adenoma (HA)
- Focal nodular hyperplasia (FNH)

- Hepatic cysts
- Hepatic lipoma
- Bile duct hamartoma[38-40]

1.2.1.1. Liver or cavernous haemangioma

The cavernous haemangiomas are the commonest benign hepatic tumours, with an incidence of 5 – 7%.[41] Their etiopathogenesis is unknown; however, female hormones might contribute to their development as the prevalence in females is 4,5 times greater than in men.[42,43] They are usually solitary and consist of blood vessels' masses that are aberrant and uneven in size and pattern.[44] The haemangiomas of the liver are usually small and asymptomatic, typically being incidental findings when the liver is imaged or examined for other reasons, although larger haemangiomas may produce symptoms.[43]

Goodman reported that only 40% of haemangiomas measuring 4cm in diameter are symptomatic, whereas 90% of 10 cm diameter haemangiomas produce symptoms.[45] The spontaneous rupture of a haemangioma is a very rare occurrence and until now has been described only for haemangiomas of very large dimensions (giant haemangiomas); however, this rupture does have a high mortality rate of 36 - 69% of the patients.[46,47]

The diagnosis of the haemangiomas is a challenging task for the radiologist as they resemble other hypervascular hepatic lesions, which can be both benign or malignant in nature, such as focal nodular hyperplasia, hepatocellular adenoma or hepatocellular carcinoma and metastasic tumours of the liver.[40]

On non-enhanced CT scans they appear hypoattenuating in contrast to the surrounding hepatic parenchyma and calcifications are not common. In enhanced CT scans, it is typical to observe a nodular, discontinuous, peripheral enhancement during the arterial phase (AP) and a progressive peripheral enhancement with a centralising fill-in during the portal venous phase (PVP).[48]

1.2.1.2. Hepatocellular adenoma (HA)

Hepatocellular adenomas, also referred to as hepatic or liver cell adenomas, are rare benign tumours of the liver. It has been suggested that they are associated with glycogen storage disease, as well as the use of oral contraceptive pills and steroids, although the main cause is the former. The complication of the tumour can be acute haemorrhage into the peritoneum, which in 25 - 30% of the cases with large tumours can be lethal. The risk of malignant transformation is yet to be clarified.[49-51]

In the late AP of CTs, the majority of adenomas present as lesions with homogeneous enhancement, which usually remain isodense in later stages in comparison to the liver, a characteristic which helps the radiologist to distinguish them from haemangiomas and small HCCs. Adenomas usually have sharp, defined margins, sometimes demonstrating a pseudocapsule of lower attenuation and they are not lobulated. Haemorrhage within the lesions can also be observed and it appears as an area of high attenuation. Calcifications can also exist in one third of cases.[52]

1.2.1.3. Focal nodular hyperplasia (FNH)

The FNH is the second commonest hepatic benign tumour and is typically encountered in young adult females.[53,54] FNH is a, mostly, asymptomatic hyperplastic process and has no malignant potential. In most cases it is found incidentally on imaging. In 20% of cases the patients feel pain in the right upper abdomen. In contrast to hepatic adenomas, spontaneous rupture and haemoperitoneum are not common for FNH.[55,56]

FNH displays three characteristic features: aberrant nodular architecture, vessel malformation and cholangiolar proliferation. FNH is divided into two histologic types: the classic, in which all three characteristic features of FNH are present, representing 80% of the cases and the non-classic, in which two characteristics are present, representing the remaining 20%. The non-classic type of FNH is further subdivided into three variants: the telangiectatic, the mixed hyperplastic and adenomatous variant and the variant with cytologic atypia.[57]

FNH usually appears iso- or hypoattenuating on non-enhanced CT scans, with the exception of cases involving fatty liver, where the lesions may appear hyperattenuating in contrast to the surrounding tissue. A central scar is often present and this appears hypoattenuating. In the AP, the lesion becomes hyperattenuating with the exception of the scar, when present, which remains hypoattenuating, although it can show enhancement in the delayed scans, in which the lesion is usually isoattenuating.[58]

1.2.1.4. Hepatic cysts

The hepatic cystic lesions include, among others, simple and multiple cysts (polycystic liver disease). The other types of liver cysts are beyond the purpose of this study and, therefore, will not be discussed further.[59]

Hepatic cysts rarely produce symptoms (only 10-15% of the cases). The symptoms can include pain and swelling of the upper abdomen. It is estimated that they are present in 5% of the population and, while their pathogenesis is not known, they are considered to be congenital.[60] Treatment is indicated only when symptoms are present. The therapy of choice is the laparoscopic deroofing for non-infected cysts or percutaneous drainage for cysts when they are infected.[59]

Hepatic cysts appear hypoattenuating with sharp borders on the CT and they do not enhance after contrast medium intravenous application.[61]

1.2.1.5. Hepatic lipoma

Hepatic lipomas are uncommon, asymptomatic and are usually found accidentally. They represent benign tumours with a good prognosis. Hepatic lipomas are divided in pure lipomas, which are round in shape and surrounded by the hepatic parenchyma and pseudolipomas or capsular lipomas, which originate from the Glisson's capsule. Hepatic lipomas consist of mature adipocytes in the hepatic parenchyma with peripheral blood vessels. Their imaging appearance on the ultrasonography, CT and MRI is characteristic and, thus, unnecessary surgical procedures can be avoided.[62-64]

On CT scan, hepatic lipomas present as homogeneous lesions, isodense to fat tissue.[65]

1.2.1.6. Hepatic leiomyoma

Leiomyomas are smooth muscle tumours, which originate primarily from the intestinal muscularis or blood vessels' tunica media and are common in the gastrointestinal and genitourinary tracts. Primary hepatic leiomyomas are extremely uncommon[66]. A histological clarification, by means of excision biopsy, of these lesions is necessary in order to exclude malignancy and it is, simultaneously, the therapy of choice.[67,68]

Hepatic leiomyomas display on the CT a bright peripheral enhancement in the AP and a constant uniform attenuation in the PVP and delayed phases.[69]

1.2.2. Malignant tumours

The most common types are:

- Hepatocellular carcinoma (HCC)
- Fibrolamellar carcinoma (FLC)
- Cholangiocarcinoma (CCC)
- Metastatic tumours
- Tumours of blood vessels in the liver[70]

1.2.2.1. Hepatocellular carcinoma (HCC)

The HCC, also known as malignant hepatoma and primary liver cell carcinoma, represents the commonest hepatic primary malignant tumour, accounting for approximately 85 - 90% of primary liver cancers.[71,72] It is the fifth most frequent malignant disease, its incidence constantly increasing, and its mortality in developed countries ranks third among all malignancies, after lung and colon cancer.[73-75] There is a strong correlation between hepatic cirrhosis, as well as

Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) infections and the development of HCC.[76-82]

The malignant cells are similar to normal hepatocytes in appearance as well as histologic pattern (trabecular, pseudoglandular, compact and undifferentiated). The growth patterns of HCC are three: large solitary masses (focal) exist in 50% of the total cases, nodular HCC (multifocal) in about 40% and diffuse infiltration (infiltrative) occurs in about 10% of cases. In one-third of cases occurs PV invasion.[54]

1.2.2.1.1. Epidemiology of HCC

There are two main patterns regarding the epidemiology of HCC: one in Western Europe and North America (the so-called Western countries) and another in central and Southeast Asia, as well as sub-Saharan Africa and the Amazon basin; the disease being more common in the non-Western countries. The rising incidence of HCC, however, is common for all countries.[75-85] Males are affected more than females. The age of the patients also varies in different parts of the world.[78-80] For the Western countries, its prevalence increases with increasing age, whereas in Africa and Southeast Asia, there is a shift towards younger age groups.[80] These epidemiological differences and variability are, in part, due to the various risk factors found in the different countries. Infection with HBV or HCV around or at the time of birth, for example, predisposes a person to earlier malignancies than if infected later. In sub-Saharan Africa and Southeastern Asia, HCC is the commonest malignant disease. Half of the worldwide annual deaths due to HCC occur in China, where HBV infection is present in 90% of the total HCC cases, whereas in Japan, chronic HCV infection is present in the same percentage (90%) of the total HCC cases.[78,82,86] In Germany, it represents the seventh to eighth most frequent malignant disease but has the highest increase of incidence.[81]

1.2.2.1.2. Pathogenesis of HCC

The pathogenesis of HCC is a multifactorial, multistage, complex process. Viral, environmental, habitual and hereditary factors are involved in its development. HCC occurs in almost 80% of the total cases on the base of a cirrhotic liver, mostly due to chronic HBV and HCV infections, long-term alcoholism and non-alcoholic steatohepatitis (NASH).[87,88] The leading cause of HCC worldwide is HBV infection, with the highest prevalence in China and Africa.[89-91] Alcohol can indirectly lead to liver cancer, as it represents the predominant cause of hepatic cirrhosis, mainly in the Western countries.[92] Infection of food with Aspergillus flavus or Aspergillus fumigatus (for example in grain products stored for long periods in wet environments), which results in the production of aflatoxin, can also induce HCC, especially in areas where fungal contamination of food happens often, such as in tropical areas.[89,90] Acute and chronic hepatic porphyrias and tyrosinemia type I also pose as risk factors for HCC.[93-95]

1.2.2.1.3. Demonstration of HCC on CT

HCC can have a variety of appearances on CT according to the growth pattern. Focal HCC presents as a large mass, which might include fat, necrosis and calcifications. Multifocal HCC presents as multiple masses with nonhomogeneous attenuation, with or without necrosis. Diffuse HCC resembles cirrhosis and its detection is usually challenging.[96,97]

For the identification of HCC, the enhancement pattern is critical. Since its main blood supply comes from AH branches, it typically demonstrates an early AP enhancement with a subsequent, rapid wash-out, becoming isoattenuating or hypoattenuating in the PVP. However, 10% of the HCCs present as hypovascular lesions.[48,52,98]

Invasion of vessels, mainly the PV, the VHs and the IVC, can often be seen. PV tumor thrombi can also be present and they show enhancement.[96,97]

1.2.2.1.4. Treatment and Prognosis of HCC

Treatment options in the management of HCC include surgical, locoregional, radiation, systemic treatment or a combination of the above. The decision of choosing the optimum treatment and its prognosis depend on a variety of factors, the most important being the tumour size, grade and staging. Early diagnosis and treatment of HCC improve the prognosis essentially; however, it is typically diagnosed at later stages, since it is usually asymptomatic in the early stages. HCC patients should be carefully evaluated in order for the optimal treatment option to be chosen, but the presence of underlying liver disease makes this task even more difficult.[99]

1.2.2.1.4.1. Surgical treatment options

1.2.2.1.4.1.1. Hepatectomy

Resection represents the gold standard in the therapy of early stage small tumours with good liver function[100-103]. The outcome of a partial hepatectomy for carefully selected patients is very promising and, due to the improvement of surgical methods and the optimising of staging systems in the last decades, the patients' 5-year survival rates after curative resection is approximately 50 - 70%.[104-108]

In the last few decades, perioperative mortality has decreased dramatically and some centres even claim to have no cases of deaths due to surgical complications of hepatectomy.[100,109]

The ideal candidates are patients with early-stage small HCCs, but there have also been good results after surgical resection reported for patients with more advanced stages.[110-112]

Contraindications for partial hepatectomy are the presence of multiple or bilobar tumours, the existence of extrahepatic metastases, main bile duct involvement and thrombosis of the main PV or the vena cava.[113]

Factors that influence the prognosis after hepatic resection are the tumour's size, the existence of tumour nodules, the remnant liver volume, the residual hepatic function and the presence of portal hypertension.[105,114-117]

The tumour's complete resection is of great importance to decrease the chances of recurrence, however, it is at the same time vital that not too much liver tissue is removed, as this could lead to liver failure.[118] Nevertheless, the resection of up to 70 - 75% of a non-cirrhotic and 50% of a cirrhotic liver is possible, without resulting in liver failure, as the liver has the unique ability to regenerate and regain its mass and functions following resection or destruction.[5,119,120]

When the estimated mass of the liver after the resection is less than these values, there is evidence that preoperative PV embolisation (PVE) is of advantage.[121] It has also been shown that preoperative PVE decreases the postsurgical complications in cirrhotic patients, but it has not been proved to be an advantage for non-cirrhotic patients.[122]

The main reason of death within the first five years after HCC resection is recurrence of the tumour or a de-novo tumour growth, mainly on the base of cirrhosis; cirrhosis playing a significant role in the recurrence of HCC.[12-126] Vascular infiltration and intrahepatic spread of the resected HCC, as well as chronic persistent hepatitis and HCV infection are usually to blame for the early (within the first 24 months after resection) recurrence of the cancer, while precancerous lesions in the liver that remain after the resection are considered to be responsible for later (more than 24 months after resection) recurrences. The early recurrences have generally a worse prognosis than the late recurrencies.[126,127]

Renewed resection and radiofrequency ablation (RFA) are potential therapy options for a recurrence, although the 5-year survival rates following these treatments are not high, namely about 35,2% and 29,1% respectively.[128] A further treatment possibility for strictly selected patients with a recurrence, who also meet the Milan criteria, is salvage liver transplantation.[129] For this treatment option, the 5-year survival rate is about 70%.[130]

Adjuvant therapies to prevent recurrence, such as the use of interferon, chemotherapy, chemoembolisation, radiation, retinoids, vitamin K and immunotherapies, have also been suggested, but, up to the present time, research for all these suggested methods have had either negative or contradictive results, or no statistical significance, thus, they are not recommended.[131-141]

1.2.2.1.4.1.2. Liver transplantation

Regarding patients with underlying hepatic disease and simultaneous early resectable HCC, liver transplantation has proved to provide better disease-free survival and, at the same time, subsiding of the underlying disease. Although HCC might reoccur in the transplanted liver, it still represents the best therapeutic option for these patients.[142] The one-year survival following liver transplantation for all indications is about 85%, the ten-year survival is 61% and the twenty-year survival is 43%.[143] The various etiologies of HCC affect the host liver differently and this influences the treatment responses and outcomes.[99]

Indications for liver transplantation are end-stage liver disease, primary liver tumours with the main representative being the HCC, cholestatic disease and acute liver failure. The most frequent transplantation indication is decompensated cirrhosis, due to viral infection mainly by HCV and HBV or alcohol abuse. Metastatic or benign tumours and other liver diseases represent a very small percentage of the indications for transplantation.[143,144]

Due to the lack of adequate donor organs, the candidates for transplantation must be chosen very carefully in order to be given to the patients who will benefit the most. The Milan criteria are a set of criteria which have been developed to address this problem and to assess the suitability of the patients for transplantation.[145,146]

1.2.2.1.4.1.2.1 Milan criteria for liver transplantation

The Milan criteria are a set of characteristics to evaluate whether patients with HCC and cirrhosis are suitable for liver transplantation. They were first introduced in 1996 by Mazzaferro et al., who proved that setting specific, strict standards for the selection of liver transplantation candidates, had, as a result, improved the overall and disease-free, four-year survival following transplantation, without any further anticancer treatment. The name of the criteria originated from the fact that the patients were treated at the “Division of Gastrointestinal Surgery of the National Cancer Institute” in Milan, Italy.

In order for a patient to be considered as suitable, all following criteria shall be met:

- - one lesion smaller than five cm or

  - up to three lesions, each smaller than three cm
- absence of extrahepatic manifestations
- absence of gross vascular invasion evidence[145]

Additional criteria, such as advanced hepatic disease, may also affect transplantation suitability; thus, prognostic models for chronic liver disease are used for the evaluation.[146-150]

1.2.2.1.4.2. Locoregional treatment options

Other less invasive treatment alternatives are also used, mainly in cases where a surgical procedure is not possible, is too risky or the patient lacks eligibility. Locoregional transarterial therapies, such as local ablation, embolisation, chemoembolisation, transcatheter therapies and combinations of these, have been intensively forced in the last decades and, although up to now they have often only palliative or neoadjuvant character, they do show promising results, provided that there is a careful selection of cases. However, more scientific proof is required, as well as the development of standard protocols for these therapies.[151-153]

1.2.2.1.4.2.1. Local ablation

Local ablation therapies are guided procedures that use chemical methods, thermal energy or a combination of both in order to destroy the tumour tissues locally. This treatment category includes the following treatment modalities:[103,154,155]

- In **Percutaneous Ethanol Injection** (PEI), alcohol is injected into the tumour causing its coagulative necrosis. PEI is an inexpensive and well-tolerated procedure from the patient's perspective, with few side effects[103,156]. According to a study, the five-, ten- and twenty-year survival rates for cases with up to three tumours less than 3 cm in diameter and with a Child-Pugh score of A or B, were 49.0%, 17.9% and 7.2%, respectively.[157]
- **Percutaneous radiofrequency ablation** (RFA) has been used in the treatment of small, unresectable hepatocellular carcinomas. Its combination with locally delivered chemotherapeutic substances is also suggested for tumours greater than 3 cm and as neoadjuvant therapy to delay the progression of the disease until the orthotopic liver transplantation takes place[158]. A study reported that the five-year survival rate for patients with HCC after RFA treatment was 60,2% and the ten-year survival rate 27,3%, while RFA is a safe procedure.[159]
- **Microwave ablation** has the advantage that the vascularisation near the tumour affects it less compared to radiofrequency ablation. However, the few existing studies have shown controversial results regarding its superiority; thus, more research needs to be conducted.[151,160]
- **Cryoblastation, laser ablation, high-intensity focussed ultrasound ablation and irreversible electroporation** are relatively new techniques and there is, up to now, limited research and not enough scientific information on their roles in the treatment of HCC.[103]

1.2.2.1.4.2.2. Transarterial (chemo)embolisation

Bland transarterial embolisation (TAE) causes coagulative tumour necrosis by blocking the blood flow to the tumour using embolic agents; these are usually lipiodol and polyvinyl alcohol particles. The survival rates of the combined treatment of TAE and ablation are similar to the survival rates of hepatectomy.[161,162]

Conventional transarterial chemoembolisation (cTACE) is the mainstay treatment for patients with multinodular asymptomatic HCC in the stage B of the Barcelona staging system (BCLC), without vascular invasion and metastases, as well as for hepatic metastases from other primaries. It has also been used as neoadjuvant and palliative treatment. In addition to the effect of the embolisation by means of various embolic agents and the subsequent tumour necrosis, as also happens in the bland TAE, there is a chemotherapeutic effect from the chemotheurapetic agents which are simultaneously selectively or superselectively administered and act locally, thus, sparing the healthy liver.[103,161,163,164-172]

Transarterial chemoembolisation with chemotherapeutically loaded beads (DEB-TACE) uses microspheres loaded with chemotheurapetics, mainly Doxorubicin. This has the same indications as cTACE and has shown comparable therapeutic results to cTACE but with fewer adverse effects and also has a better pharmacokinetic profile; the drug release is sustained and occurs under certain ionic conditions.[161,173-177]

Selective internal radiation therapy (SIRT), also termed radioembolisation, involves the administration of radioactive substances, such as Yttrium-90 or Iodine-131, to the tumour through an arterial catheter. It is indicated for patients with HCC in stage B of the BCLC staging system. SIRT has few adverse effects and has shown positive results; however, it is relatively expensive and laborious.[103,161,178-180]

1.2.2.1.4.2.3. Molecular targeted therapies

Sorafenib tosylate (Nexavar) is an oral multikinase inhibitor directed, among others, against the rapidly accelerated fibrosarcoma (RAF) kinase, vascular endothelial growth factor receptor 2 (VEGFR2), platelet-derived growth factor receptor (PDGFR), Ret, fms-like tyrosine kinase 3 (FLT3) and c-Kit. It represents the first systemic therapeutic approach of HCC that has shown positive results and is indicated for patients with good hepatic function and advanced tumours.[103,181]

A great number of other molecular agents are currently being tested.[103]

1.2.2.1.4.3. Other therapeutic attempts

Chemotherapy and radiation have also been used in the treatment of HCC but with suboptimal results.[103]

1.2.2.1.5. Prognostic models for chronic liver disease

1.2.2.1.5.1. Child-Pugh or Child-Turcotte-Pugh score

The Child-(Turcotte-) Pugh scoring system was introduced by Dr. Child and Dr. Turcotte in 1964 and was modified by Pugh and his colleagues in 1972 (Table 2). Pugh substituted the criterion of prothrombin time or INR for nutritional status and appointed scoring points of 1 to 3 to each laboratory value, namely total serum bilirubin, albumin, prothrombin time, ascites and hepatic encephalopathy.[182-184]

Table 2: Child-Pugh scoring system[a]

Clinical and biochemical measurements	Points scored for increasing abnormality		
	1	**2**	**3**
Encephalopathy (according to the grading of Trey, Burns and Saunders[184])	None	Grade 1 and 2	Grade 3 and 4
Ascites	Absent	Slight	At least moderate
Total serum bilirubin (mg/dl)	1 - 2	2 - 3	> 3
Total serum bilirubin (mg/dl) for primary biliary cirrhosis	1 - 4	4 - 10	> 10
Serum albumin (g/dl)	> 3,5	2,8 - 3,5	< 2,8
Prothrombin time (sec. prolonged)	1 - 4	4 - 6	> 6

a) Adapted from Pugh et al.[184]

According to the score resulting from adding the points, chronic hepatic disease is categorized into Child-Pugh classes A to C (Table 3).[182,184]

Table 3. Child-Pugh classes and operative risk[a]

Points	Class	Operative risk
5-6	A	Good
7-9	B	Moderate
10-15	C	Poor

a) Modified from Cholongitas and Pugh[182,184]

1.2.2.1.5.2. MELD (Model for End-stage Liver Disease) score

The Model for End-stage Liver Disease (MELD) score is used to evaluate chronic hepatic disease severity. It incorporates laboratory values for serum creatinine, bilirubin and INR in order to predict the three-month mortality of patients, mainly with cirrhosis. For these patients, the increase of the MELD score represents a deterioration of the hepatic function and reduced three-month survival.[185-187]

The MELD score is calculated with the following formula:

MELD = 9,57 [$\log_e$ serum creatinine (mg/dl)] + 3,78 [$\log_e$ serum bilirubin (mg/dl)] + 11,2 [$\log_e$ INR] + 6,43[188]

and according to the score the three-month mortality for hospitalized patients is:

- ≥ 40: 71,3% mortality
- 30 - 39: 52,6% mortality
- 20 - 29: 19,6% mortality
- 10 - 19: 6,0% mortality
- < 9 - 1,9%: mortality[187,188]

1.2.2.1.5.2.1. Modifications of the MELD Score

In order to overcome some of the MELD score's weaknesses (such as the fact that MELD predicts short-term survival even though the liver transplantation candidates must often wait for a long time on the transplantation list and the fact that it does not take into account other serious conditions of the patients, such as renal failure, cholestasis, persistent ascites or hyponatremia), some modifications of the MELD score have been suggested. These modifications include:

- the MELD-sodium (MELD-Na) score, which integrates the serum sodium levels into the formula
- the MELD to serum sodium ratio (MESO), which also takes into account the serum sodium levels
- the Integrated MELD score, which incorporates the serum sodium levels and the age of the patients to the formula
- the United Kingdom MELD (UKELD) score, which includes the serum sodium, creatinine, bilirubin levels and INR.[150, 189-192]

The MELD-Na and integrated MELD scores are proven to be the best prognostic models to predict the drop-out rates of candidates for liver transplantation and, thus, to evaluate patients with decompensated cirrhosis as suitable candidates. However, a study suggests that the UKELD prognostic model is superior to the MELD-Na.[189,192]

1.2.2.1.6. Hepatocellular carcinoma staging

The staging of HCC is of utmost importance because it determines the prognosis and the most suitable treatment option. Due to its biological heterogeneity, the staging of HCC is complicated and every staging system has its drawbacks. For this reason, apart from the most common TNM classification system, several other staging systems have been introduced internationally in the last decades.[193]

1.2.2.1.6.1. TNM staging system

The TNM (Tumour/ Node/ Metastasis) staging system provides information only on the tumour characteristics and was introduced by the American Joint Committee on Cancer (AJCC). The following tables (Tables 4 and 5) demonstrate the revised edition as published in the 8th Edition of the AJCC Cancer Staging Manual in 2017.[194]

Table 4. TNM classification of HCC[a]

Primary tumour (T)	
TX	Assessment of primary tumour is not posible
T0	There is no primary tumour evidence
T1	Single tumour < 2 cm or ≥ 2 cm, absence of vascular invasion
T1a	Single tumour < 2 cm
T1b	Single tumour ≥ 2 cm, absence of vascular invasion
T2	Single tumour ≥ 2 cm, presence of vascular invasion or multiple tumours < 5 cm
T3	Multiple tumours, at least one ≥ 5 cm
T4	Tumours of any size, which involve a major branch of the hepatic or PV or tumours with invasion of adjoining organs (except from the gallbladder) or with visceral peritoneum perforation
Regional lymph nodes (N)	
NX	Assessment of regional LN is not possible
N0	Absence of regional LN metastasis
N1	Presence of regional LN metastasis
Distant metastasis (M)	
M0	Absence of distant metastasis
M1	Presence of distant metastasis

a) Adapted from the 8th Edition of the AJCC Cancer Staging Manual[194]

Table 5. Staging of HCC according to TNM classification[a]

Stage	T	N	M
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
IIIa	T3	N0	M0
IIIB	T4	N0	M0
IVA	Any T	N1	M0
IVB	Any T	Any N	M1

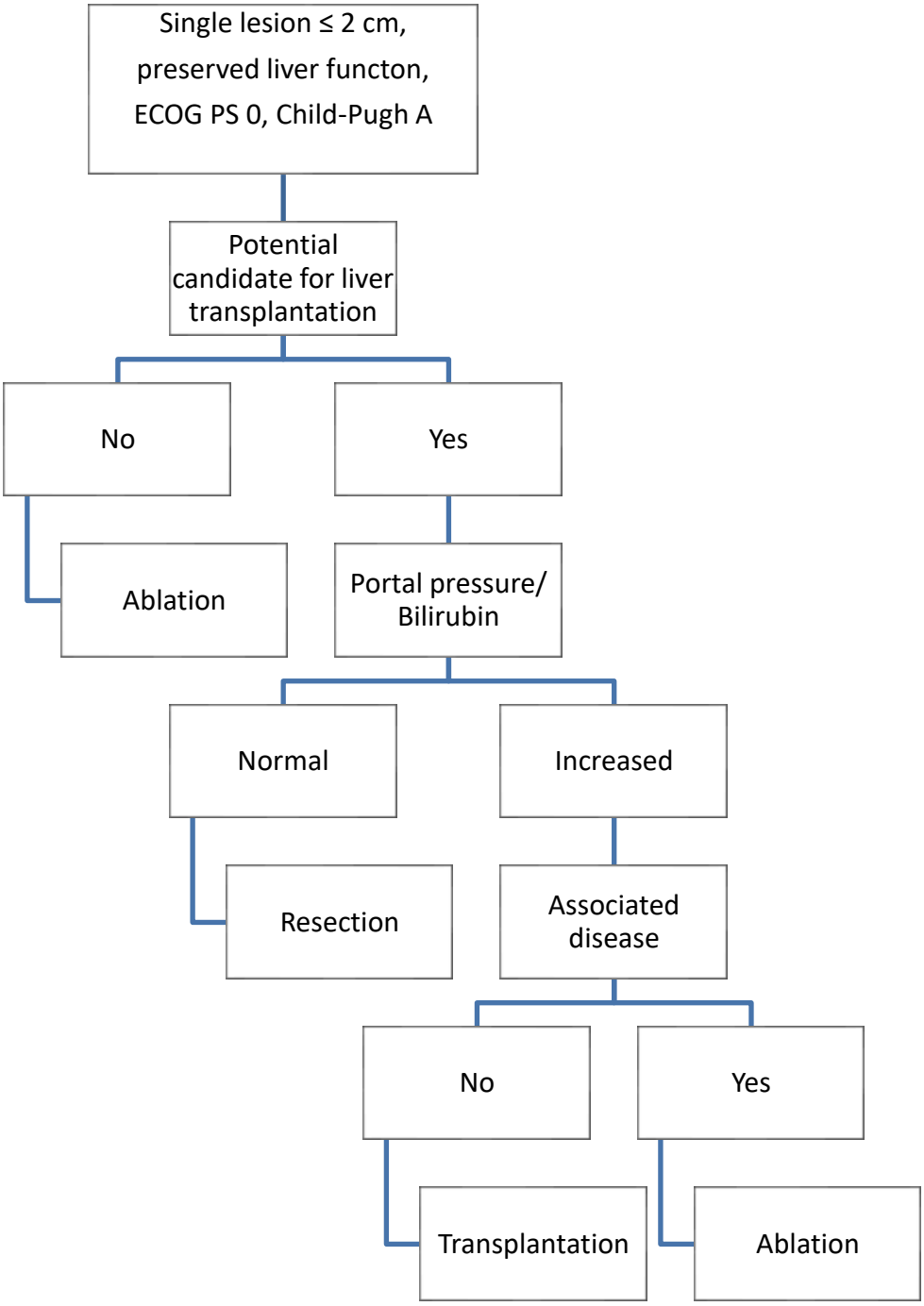
a) Reproduced from the 8th Edition of the AJCC Cancer Staging Manual[194]

1.2.2.1.6.2. Barcelona-Clinic Liver Cancer (BCLC) staging system

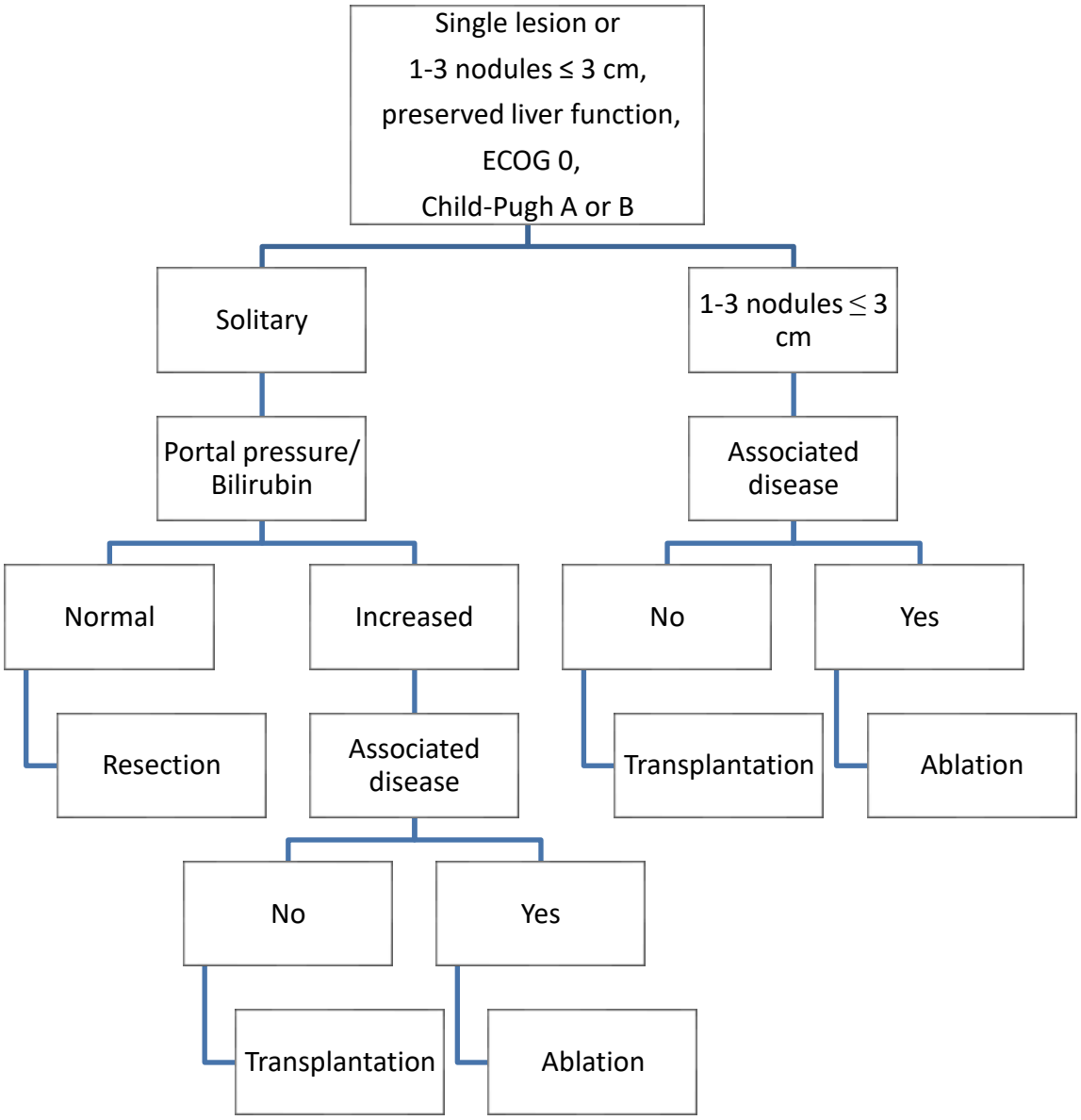
The BCLC staging system was introduced by Llovet and his team in 1999 and was modified by the same author in 2008. It classifies HCC into five stages, namely very early, early, intermediate, advanced and end-stage, depending on the number and size of the tumours, the extent and spreading of the disease, the liver function, the ECOG performance status and the Child-Pugh score, although the latter is now considered obsolete. The BCLC staging system is also the sole system that proposes evidence-based treatment options for each stage (Figure 2). Survival times with the suggested treatments according to the stages, are estimated for the very early stage (0) and early stage (A) to be over 5 years, for the intermediate stage (B) to be over 2,5 years, for the advanced stage to be over 1 year and for the terminal stage to be 3 months.[195-198]

HCC

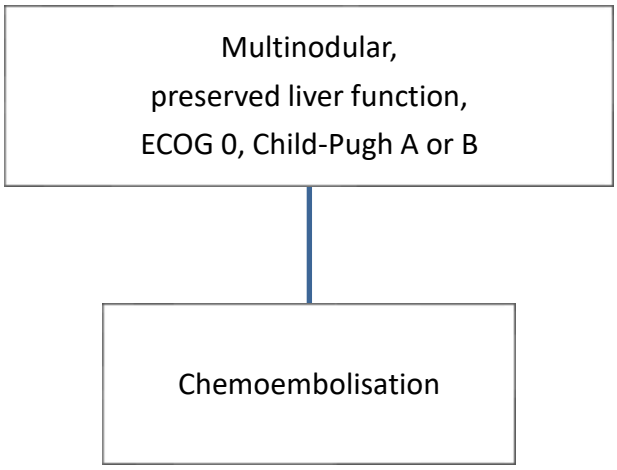
Very early stage (0)



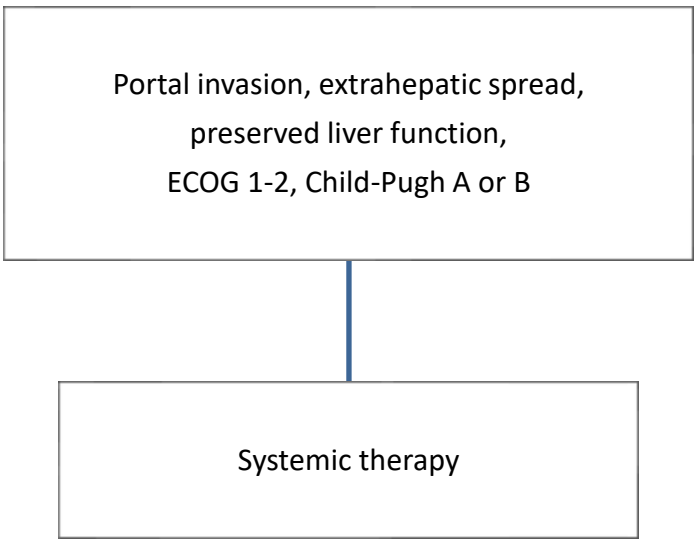
Early stage (A)



Intermediate stage (B)



Advanced stage (C)



End stage (D)

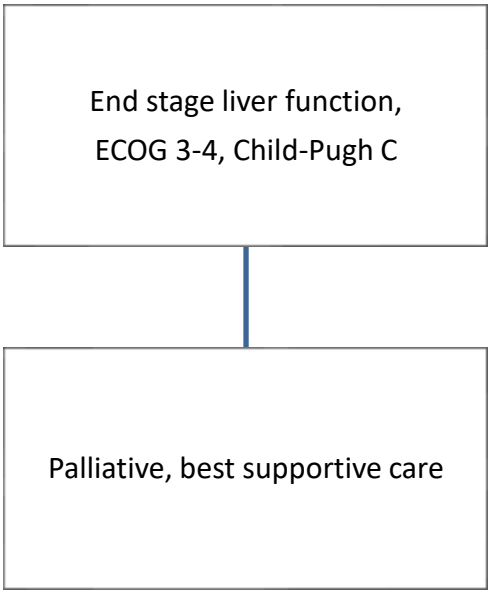


Figure 2. BCLC Staging System: Treatment Algorithm. Adapted from Llovet et al.[195]

1.2.2.1.6.3. Okuda staging system

The Okuda staging system provides information on tumour characteristics, as well as liver function and includes four criteria and three stages.[199]

1.2.2.1.6.3.1. Okuda system´s criteria

- disease involving > 50% of hepatic parenchyma
- ascites
- serum albumin ≤ 3 mg/dL
- serum bilirubin ≥ 3 mg/dL

1.2.2.1.6.3.2. Okuda system´s stages

- stage I: 0 criteria
- stage II: 1 - 2 criteria
- stage III: 3 - 4 criteria

1.2.2.1.6.4. Other staging systems

The **CLIP (Cancer of Liver Italian Program) scoring system** involves the Child-Pugh stage, the morphology of the tumour, the serum AFP and the existence of PV thrombosis.[200]

The **JIS (Japan Integrated Staging) system** takes into account the TNM staging system and the Child-Pugh score.[201] In order for the system to be optimised, other researchers have proposed the incorporation of biomarkers, as well as modifications to the system.[202-204]

The **CUPI (Chinese University Prognostic Index)** was developed based on a Chinese population with mainly HBV-associated HCC. The CUPI is based on the TNM staging system but incorporates more clinical parameters, namely the total serum bilirubin, serum alkaline phosphatase, α-fetoprotein, the presence of ascites and the absence of symptoms on presentation. Every parameter has a minus or plus weighting and, according to the score which results from adding these weightings, the patients are categorised into three groups: low risk, intermediate and high risk groups with respect to three months' survival.[205]

The **French classification or GRETCH (GRoupe d'Etude et de Traitement du Carcinoma Hépatocellulaire) system** includes four stages and takes into account the Karnofsky Performance Scale Index, liver function (serum bilirubin and alkaline phosphatase), serum α-fetoprotein and the presence of portal obstruction detected by sonography.[206]

1.2.2.1.6.5. Comparison of parameters used in the most common HCC staging systems

The following table (Table 6) illustrates the most common HCC staging systems and the parameters that each involves.[206]

Table 6. Comparison of parameters used in the most common HCC staging systems[a]

SYSTEM	S	N	M	Asc	EPS	KPS	CPS	Alb	Bili	αFP	ALP	PVT	P
TNM	x	x	x										
BCLC	x		x		x		x		x			x	x
Okuda	x			x				x	x				
CLIP	x						x			x		x	
JIS	x	x	x				x						
CUPI	x	x	x	x					x	x	x		
GRETCH						x			x	x	x	x	x

S: Size, N: Node, M: Metastasis, Asc: Ascites, EPS: ECOG Performance Status,
KPS: Karnofsky Performance Scale Index, CPS: Child - Pugh Score,
Alb: Albumin, Bili: Bilirubin, αFP: α-Fetoprotein, ALP: alkaline phosphatase,
PVT: PV thrombosis, P: Performance

a) Adapted from Subramaniam et al.[206]

1.2.2.1.7. Performance indexes

Performance indexes estimate how a disease influences a patient's daily activities and living abilities and they are, among others, used as criteria in staging systems. The Eastern Cooperative Oncology Group (ECOG) performance status is incorporated into the BCLC staging system and the Karnofsky Performance Scale Index into the GRETCH system.

The table below (Table 7) describes the scoring for both indexes and their comparison.[207,208]

Table 7. Scoring and comparison of Performance indexes[a]

ECOG PERFORMANCE STATUS		KARNOFSKY PERFORMANCE SCALE INDEX	
Score	**Description**	**Score**	**Description**
0	Fully healed, no evidence of disease, no restrictions of activity.	100	Healthy, no symptoms
		90	No restrictions of activity, trivial complaints
1	Physical constraint in vigorous activities but ambulant and capable of light work	80	Mild complaints and restrictions of activity
		70	Capable of personal care and sedentary work
2	Ambulant most of the day, capable of personal care but impaired to work	60	Mostly capable of personal care
		50	Needs regular medical aid and support for daily activities
3	Immobile most of the day, disability of personal care	40	Impaired, needs nursing care
		30	Need to be hospitalised
4	Immobile and impaired	20	Need for supportive care in hospital
		10	Death imminent
5	Deceased	0	Deceased

a) Modified from Oken et al.[207]

1.2.2.2. Fibrolamellar Carcinoma (FLC)

The fibrolamellar carcinoma was originally considered to be a histologic variant of the HCC[209], but its relatively good prognosis (the one-year survival-rate being 73% and the five-year being 32%), the young age of onset (with a median age of 33 years) and the fact that the pathogenesis of FLC is not related to viral infection, hepatic inflammation, cirrhosis or fibrosis, have led to its acknowledgement as being a distinct clinical entity.[210-213] Its etiology is not yet clarified, but there is suspicion that it is associated with gene mutations.[214,215] The treatment options for FLC are surgical resection or transplantation. Trans-arterial chemo-embolisation (TACE) is applied to patients not eligible for resection or transplantation.[216,217]

On CT scans, fibrolamellar carcinomas are usually single tumours with a central scar and resemble FNH. Small calcifications can also be present. They demonstrate mostly arterial enhancement, which is prolonged at the central scar.[218]

1.2.2.3. Cholangiocarcinoma (CCC)

Cholangiocarcinoma is a rare adenocarcinoma, originating from the biliary tract's epithelial cells. It may occur at any site along the intrahepatic or extrahepatic (perihilar, occurring at the bifurcation of the right and left hepatic ducts, or distal extrahepatic) biliary trees. Perihilar cholangiocarcinomas, also called Klatskin tumours, are the most common, while intrahepatic are the least common.[219,220]

Its reported annual incidence in Western countries is one to two cases per 100000 patients,[221,222] but its incidence is constantly rising globally.[223,224] The exact pathogenesis of cholangiocarcinoma is unknown, but it usually occurs following primary sclerosing cholangitis (PSC). Most patients are older than 65 years old and they typically present at advanced stages. For this reason, even with aggressive therapy, the cure rates are low. The treatment options include hepatic resection and transplantation. Adjuvant therapies, such as chemotherapy, radiation and chemoradiation have essentially not improved the survival of the patients. Palliative measures, such as biliary drainage and

photodynamic therapy, are also used in order to increase the quality of life, reduce the symptoms and to extend the survival of the patient.[225] The majority of patients with untreated disease die in less than 12 months following diagnosis; the death cause usually being hepatic failure or complications due to infection, caused by the biliary obstruction.[226]

The appearance of cholangiocarcinoma on CT varies according to the growth pattern. Mass-forming cholangiocarcinoma demonstrates a slight peripheral enhancement at the borders, which gradually moves towards the centre. Dilatation of the distal bile ducts is usually present. Periductal infiltrating cholangiocarcinoma, which typically develops at the hilum of the liver, demonstrates either as a thickening of the bile duct wall or condensation of the parenchyma surrounding the bile duct. A bile duct ectasia is commonly present. Intraductal cholangiocarcinoma generally demonstrates as a bile duct dilatation with or without the presence of a mass.[227]

1.2.2.4. Metastatic tumours in the liver

In Western countries, where hepatitis is not endemic, the majority of the malignant hepatic cancers are metastatic tumours, representing 91% of the hepatic malignant tumours. The primary tumours are bronchopneumonal in 27% of cases, colorectal in 15%, pancreatic in 10%, breast in 9% and gastric in 8% of cases, as well as melanomas, adrenal and oesophageal tumour types.[216]

Metastatic tumours in the early stages are usually asymptomatic, but later various symptoms can arise, including abdominal pain, fever, nausea, confusion and jaundice. They can be diagnosed with various tests which will be discussed later. They are mostly hypovascular and often have at their periphery a hypervascular border, known as edge enhancement.[228]

The primary cancer site, the number of tumours, the spread of metastatic tumours to other organs and the patient's general health condition determine the treatment decision. In most cases, chemotherapy is used and sometimes also radiotherapy. If the tumours are few and localised, resection is considered, whereas when larger areas are involved, embolisation with injection of chemotherapeutics

directly into the liver can be applied.[229] Transplantation has also been proposed as a therapeutic alternative, but only under strict criteria.[230-232]

Liver metastases can be hyper- or hypovascular. The majority of them are hypovascular and demonstrate a hypoenhancement on the CT at the AP, however other metastases from certain primaries, such as primary thyroid carcinoma, mamma carcinoma, renal cell carcinoma, melanoma, neuroendocrine tumours, leiomyosarkoma and choriocarcinoma, are hypervascular and show a hyperenhancement at the AP on the CT which gradually fades out in the delayed phase.[98]

1.2.2.5. Tumours of blood vessels of the liver

Tumours of blood vessels of the liver occur rarely. They are very aggressive, spread quickly and by the time of diagnosis, it is usually too late for a successful therapy. These tumours are usually very difficult to treat.[233, 234]

1.2.2.5.1. Angiosarcoma

Angiosarcomas of the liver are rare, malignant, fatal tumours, that can develop from either the endothelium of the blood vessels (haemangiosarcomas) or lymph vessels (lymphangiosarcomas) in the liver. They are associated with chronic haemochromatosis, exposure to radiation, arsenic-containing insecticides, Thorotrast (a former radioactive contrast agent) and vinyl chloride monomer (VCM). Its prognosis is very poor, with only 3% of cases surviving more than two years.[233]
On the CT, they present either as multiple or single hypoattenuating masses with hyperattenuation at the presence of hemorrhage and they usually show nodular enhancement.[235]

1.2.2.5.2. Hemangioendothelioma (EHE)

Hemangioendotheliomas are tumours of vascular origin that occur very rarely, show subcapsular distribution and whose pathogenesis is not yet clarified.[234]

Three types of EHE have been identified and its appearance on CT depends on its type. The solitary and multifocal nodular types are hypoattenuating and demonstrate sharp margins. The peripheral enhancement gradually progresses to the centre in the AP and is even in the PVP. The diffuse type shows low density or heterogeneous signal intensity. The “strip-like sign” (coalescence of lesions) and the “lollipop sign” (gradual enhancement of central vessels) are characteristic for EHE and facilitate its identification.[236]

1.3. Diagnostic imaging

Diagnostic imaging, such as ultrasound, hepatic arteriography, computerised tomography (CT) scan, CT hepatic arteriography, CT arterio-portography and magnetic resonance imaging (MRI), are necessary on suspicion of tumour formation or malignancy in the liver.

1.3.1. Abdominal ultrasonography

Ultrasonography is the primary screening test for the detection of pathological lesions of the upper abdomen. It represents a fast, non-expensive and side-effect-free method of examination and can be performed as often as required (usually every three to six months). However, its sensitivity is variable, ranging from 33 - 96% for the detection of HCC in cirrhotic liver, while its sensitivity for the identification of dysplastic nodules and small HCC is relatively low, with rates of 0 - 1,6%. Sonographic contrast agents and tissue harmonic imaging (THI) in combination with sonographic contrast media can facilitate the detection of these tumours. However, every small hyperechoic mass seen with the sonography requires further evaluation as they may represent a metastatic tumour or other type of carcinoma. The CT or MRI can further characterise many non-specific masses observed during the sonography.[237-239]

1.3.2. Hepatic arteriography

The conventional arteriography of the coeliac and superior MAs has been used in the diagnosis of a wide variety of hepatic diseases. In order to set the diagnosis,

one must be able to recognise the overlapping vascular patterns encountered in the normal and abnormal liver. The diagnostic value of angiography for small HCC is relatively high, however, false positive diagnoses do occur due to the similar imaging appearance with other lesions. The differential diagnosis between stains due to tumours and those due to hyperplastic nodules of cirrhosis, for example, is difficult.[240,241]

1.3.3. Computed tomography scan (CT scan)

The contribution of the non-invasive CT in the clarification of abdominal pathological conditions and staging of abdominal cancer has been established for a long time. Multiphasic dynamic helical CT facilitates the characterisation of nodular lesions in the cirrhotic liver. The appearance of hepatocellular carcinomas at the CT scan varies according to the tumour size and the imaging phase.

The distinct dual hepatic blood supply via the AHs and the PV enables the imaging for the detection and clarification of hepatic lesions to be performed in two distinct phases; the hepatic AP and PVP. For the detection of HCC, AP imaging is more useful as HCCs are mainly supplied with blood from the AH. Still, it is less sensitive in detecting small HCCs and dysplastic nodules, because they demonstrate the same density as the surrounding hepatic parenchyma due to mainly being supplied from the PV.

The new advancements in helical CT enable liver imaging during arterial and portal venous contrast enhancement, separately. Hypervascular hepatic lesions (haemangiomas, adenomas, focal nodular hyperplasia and hepatocellular carcinomas) appear denser in the early-AP than the hepatic parenchyma and can, at this stage, be detected, while the hypovascular metastatic tumours can be detected better in the PVP. Furthermore, the main arteries of the upper abdomen, such as the coeliac trunk and the splenic artery, can be depicted more clearly and any tumour invasion from hepatic, pancreatic or gallbladder cancer can be visualised, which may improve the staging compared to conventional CT. False-negative CT imaging can occur and small lesions can, in some cases, remain undetected. Detection rates of 59% for tumours and 37% for tumour

nodules have been reported, while sensitivity and specificity rates of up to 90% have been demonstrated.[98, 242]

1.3.4. CT hepatic arteriography and CT arterial portography

CT hepatic arteriography and CT arterio-portography represent invasive procedures, by which the injection of the contrast agent is applied by means of a catheter, directly into the AH for the hepatic arteriography and into the MA or lineal artery, so as to reach the PV, for the hepatic arterio-portography. These are the gold standards for the preoperative detection of small liver tumours, even of a diameter of 0,2 cm, as they have proved to be the most sensitive imaging methods for detecting these tumours. However, the false positive detection rate of malignances, in cases of benign tumours, is relatively high. For this reason and as they are very invasive techniques, their application should take place only under strict indication.[243,244]

1.3.5. Magnetic resonance imaging (MRI)

For the lesions that are difficult to differentiate using the CT, the radiologist can be assisted further by the MRI. The appearance of the tissues can vary on the MRI depending on the extent of fibrosis or necrosis, the existence of haemorrhage, the histological pattern and the amount of fatty deposits. Some studies proved the superiority of the MRI, in comparison with the CT, in detecting and characterizing focal hepatic lesions.[244]

1.3.6. Positron emission tomography scan (PET)

The positron emission tomography (PET) scan is an imaging examination that requires the intravenal application of a radioactive substance, the tracer, in order to assess the function of an organ. The PET scanner detects signals from the tracer and, thus, a pathological condition is suspected in the areas where there is an accumulation of the tracer.[245]

According to Kinkel, the PET scan is the most sensitive, non-invasive imaging method for diagnosing liver metastases from colorectal, gastric and oesophageal primary tumours. It also has a high sensitivity for detecting extrahepatic foci of metastases[245]. It has been demonstrated in the literature that PET scans can produce some false-negative results in cases of hepatocellular carcinomas and false-positive results in cases of abscesses or of patients with diabetes mellitus, as blood sugar or insulin levels may affect the test results.[246]

PET scans and CT scans can also be combined (PET/CT scan) in order to obtain a more accurate diagnosis with excellent results. However, due to their relatively high cost and limited availability, PET and PET/CT scans are not applied for the routine abdominal examination.[246]

1.4. Biopsy

In some cases, when the diagnosis by means of non-invasive methods remains unclear, a liver biopsy cannot be avoided. In these cases, hepatic tissue may be obtained for biopsy either by puncture with a needle through a lower intercostal space or by surgery and resection of the hepatic tissue.[247-249]

Hepatic material for the biopsy can be acquired either by means of percutaneous fine-needle aspiration (FNA) for the cytologic evaluation or through core needle biopsy or open surgical biopsy for histologic examination. The combination of US-guided or CT-guided FNA and liver core biopsy improves the diagnostic precision with a sensitivity rate of 96% and a specificity rate of 95%. These rates are higher than any other technique used in diagnosing HCC and are far less traumatic and dangerous than open surgical biopsy. The latter is nowadays rarely performed and only in cases where it is impossible to precisely locate the lesions by radiographic means.[250]

In general, a liver biopsy takes place when the laboratorial or radiographic findings do not fulfil the criteria required in order for the clinician to be certain that the lesion is HCC or on occasions before resection of a small liver lesion (an incidental finding in the lack of symptoms of young patients), as in these cases there occur a lot of false positive HCC diagnoses.[251-254]

A fine-needle biopsy of focal liver lesions is an advantage for the above clinical scenarios, as its accuracy is, according to Caturelli et al., 95,6% for lesions up to 2 cm and, thus, unnecessary operations can be avoided.[255] The latter is crucial considering the risks and complications of hepatectomy, the most common of them being a postoperative liver failure, intra-abdominal infection and sepsis, biliary fistulae and extensive bleeding. Doci et al. report that the postoperative morbidity after liver resection in their study was 35%, while mortality was 2,4%. However, the rates were lower the later the surgeries were performed and the smaller the lesion and, thus, the smaller the resected area were.[256,257] In the study of Virani et al., 22,6% of the patients had complications within the first thirty days after the surgical procedure, of whom 9% eventually died.[258]

On the contrary, complications related to percutaneous liver biopsy are rare, mainly being severe haemorrhage and infection or even sepsis. Another potential complication is the needle tract metastasis, due to the spread of the tumour cells, whose prevalence in most studies is around 1%, while the mortality rate is in most studies under 0,3%.[259-263]

1.5. Computed tomography scan of the liver

1.5.1. Attenuation

The difference in the attenuation between the lesion and the liver tissue is critical for detecting and diagnosing the lesion. Cysts, calcifications, fat and blood, such as in haemorrhage, help the radiologist identify a lesion; however, these features are rarely present in a tumour. Liver lesions on non-enhanced CT-scans are usually hard to distinguish from the surrounding liver parenchyma since their contrast is low. For this reason, the use of a contrast agent is necessary.

When a contrast agent is intravenously applied, the dual blood supply to the liver by the AH and PV assists the radiologist in diagnosing the lesion. This happens because there is a difference between the blood supply to the hepatic parenchyma and hepatic tumours. The blood supply to the liver tissue is 80% provided by the PV and 20% by the AH, while hepatic tumours are supplied solely

by the AH. As a result, contrary to the normal liver tissue enhanced in the PVP, most liver tumours are enhanced in the AP.

Hypervascular tumours enhance in the AP and appear as hyperdense lesions surrounded by a comparatively hypodense hepatic parenchyma. The late AP (approximately 35 seconds after the contrast agent's injection) is the optimal time for detecting hypervascular lesions, as this is the time required by the contrast agent to journey from the peripheral vein to the liver tumour via the AH.

Hypovascular tumours, on the contrary, are detected in the PVP, when the maximal enhancement of the liver tissue takes place and they present as hypodense lesions surrounded by a comparatively hyperdense hepatic parenchyma. The best time for detecting hypovascular lesions is the late portal venous or hepatic phase (approximately 75 seconds postinjection).

In the equilibrium phase (approximately four minutes postinjection), the contrast agent gradually flushes away from the liver and there is a decrease in the hepatic parenchyma's density. Some tumours have special characteristics in this phase and this fact helps the radiologists in their diagnosis; examples of these tumours are the hepatocellular carcinoma, which demonstrates a fast washout of the contrast agent and the haemangioma, which retains the contrast agent for longer. The best time for this phase is at 10 minutes post contrast agent injection.

Practically, the first step to characterise a focal liver lesion on CT is determining its density. For example, if the lesion's density resembles water density and at the same time is homogeneous, with clear margins and demonstrates no enhancement, it is almost certainly a cyst.[98, 264, 265]

1.5.2. Liver lesions' demonstration on the CT

Liver lesions are categorised into hypervascular and hypovascular, according to their enhancement pattern. Hypervascular liver lesions can either be primary liver pathologies, mainly benign, or secondary (metastases).

As mentioned above, primary liver tumours are, in their majority, hypervascular. The most common malignant hypervascular primary liver lesion is the hepatocellular carcinoma, but it can also present as hypovascular.[48,52,98]

Hypovascular liver lesions, contrary to the hypervascular, are in their majority malignant. Hypovascular tumours are also more common than hypervascular,

with metastases from other primaries being their main representative. Although, as stated above, most primary liver tumours are hypervascular, there are exceptions, such as the cholangiocarcinoma, which presents as a hypovascular lesion, often with delayed enhancement.[98]

Lesions that show no enhancement and have, centrally, a near-water density, can be cystic lesions, which can also be malignant in some cases, as well as abscesses or metastases with central necrosis.[61,98]

1.6. Contrast agents in the diagnostic of hepatic tumours

The significant improvements in the composition of contrast agents in the past decades have made them safer and better tolerated by patients. They are indispensable for the detection of abdominal lesions as they allow for a better and morphological demarcation of the complicated abdominal topography, increase the conspicuity of the lesions and enable a better assessment of dynamic processes, such as the blood circulation. As stated above, the distinct dual hepatic blood supply enables the imaging of the liver for the detection and clarification of its lesions in the hepatic arterial and the PVPs separately, enabling the detection of both hyper- and hypovascular lesions. This has become much easier with the use of contrast media.

Most of the currently available contrast media used for the CT are water-soluble, iodinated, non-ionic and have a low molecular weight. They are metabolised in the kidneys and their circulatory half-life is, for healthy individuals, usually 1 - 2 hours.[266, 267]

1.6.1. Adverse reactions of iodinated contrast agents

The administration of iodinated contrast agents can cause adverse reactions, such as physiochemotoxic and hypersensitivity reactions, which can be mild, intermediate and severe; even lead to death. Commonly reported physiochemotoxic adverse reactions are heat sensation, pruritus, erythema, nausea, hypertension, arrhythmia, angina and vasovagal symptoms. The physiochemotoxic reactions present more often than hypersensitivity reactions.

The latter can be acute, taking place within an hour after injection and ranging from simple urticaria to full anaphylaxis, or delayed, typically occurring between an hour and one week after injection. The most common delayed adverse reactions are skin rashes and flu-like symptoms.[268-272]

Administration of larger volumes of contrast agents enhances the risk of adverse reactions; in fact, the cardiac pump function of patients with cardiovascular disease might, in some cases, not be capable of transporting larger volumes of contrast agents within one heartbeat, even leading to heart failure.[273, 274] Furthermore, there is evidence that greater volumes and higher administration rates of iodinated contrast agents increase the probability of hypersensitivity reactions.[275]

Contrast-Induced Nephrotoxicity (CIN) represents impairment in renal function due to the administration of contrast agents and occurs in 2 – 7 % of cases.[268-271, 276, 277] Other rare adverse reactions to iodinated contrast agents are extravasation of the contrast agent, air embolism, iodinated contrast medium-induced thyrotoxicosis in patients with hyperthyroidism and metformin accumulation leading to lactic acidosis in cases of concomitant metformin therapy.[269-271, 278-280]

1.6.2. Imeron

The active ingredient of Imeron is Iomeprol. It is a non-ionic, water-dissolvable, low osmolar, dialysable iodinated contrast agent.

It is manufactured in the dosages 100, 250, 300, 350 and 400, which contain 100 mg/ml, 250 mg/ml, 300 mg/ml, 350 mg/ml and 400 mg/ml iodine respectively. They all have a pH value of 6,9 to 7,2.

100 ml Imeron 100 contain 30,62 g Iomeprol with an osmolality of 301 +- 14 mosmol/kg water and a viscosity of 1,4 +-0,1 mPa s at 37 C.

100 ml Imeron 250 contain 51,03 g Iomeprol with an osmolality of 435 +- 20 mosmol/kg water and a viscosity of 2,9 +-0,3 mPa s at 37 C.

100 ml Imeron 300 contain 61,24 g Iomeprol with an osmolality of 521 +- 24 mosmol/kg water and a viscosity of 4,5 +-0,4 mPa s at 37 C.

100 ml Imeron 300 contain 71,44 g Iomeprol with an osmolality of 618 +- 29 mosmol/kg water and a viscosity of 7,5 +- 0,6 mPa s at 37 C.

100 ml Imeron 400 contain 81,65 g Iomeprol with an osmolality of 726 +- 34 mosmol/kg water and a viscosity of 12,6 +- 1,1 mPa s at 37 C.[281-283]

2. Objectives of the clinical study

The aim of this study was the optimisation of the strength and injection rate of the contrast agent Imeron in the Multislice Spiral-CT of the upper abdomen. The contrast agent dose schedule for Multislice Spiral-CT had to be adjusted to the speed of the examination.

One possibility for reducing the time of the examination and X-ray exposure would be to increase the injection rate up to 5 ml/sec. However, in many patients the cardiac pump function does not allow for the transportation of such a large volume of contrast agent within one heartbeat.[274] This leads to a decrease of the maximum enhancement and a flattening of the contrast concentration curve in the abdominal arteries. With a contrast agent of higher iodine concentration, the injection rate may be reduced without decreasing the iodine delivery rate, which makes it possible to reduce the volume load of the heart. A greater volume and faster injection rate of a contrast agent also leads to greater haemodynamic disturbances and other acute hypersensitivity reactions to contrast agents.[275,284] Several studies have also shown that higher contrast agent injection rates lead to increased extravasation rates.[285-293]

Furthermore, a medium injection rate in comparison to a higher rate has been shown to produce less false positive results in the detection of small hypervascular hepatocellular tumours in patients with cirrhosis.[294]

It is estimated that the injection of a higher concentrated contrast agent (Imeron 400) with a lowered flow rate and lower total administered volume of contrast would equalise the attenuation and contrast values of a lower concentrated contrast agent (Imeron 300) with higher flow rates and higher total value of contrast. It is known from daily clinical practice that the first mentioned profile is better tolerated by patients and, thus, there is expected to be a benefit concerning CT examinations.

The primary criterion was the maximum absolute contrast of lesions to their backgrounds (difference $SI_{lesions}$ minus $SI_{surrounding\ tissue}$) of arterial and venous phase scans.

Secondary criteria were quantitative evaluations of the signal intensities in different regions, as well as a group of qualitative criteria, including an evaluation of the accuracy in comparison to a gold standard. The patients' sensation and comfort at the administration of the contrast agent were also taken into account.

The secondary criteria were more analytically the following:

- Signal intensities:
    - Normal liver tissue
    - Pancreatic tissue
    - Abdominal aorta
    - Portal vein
    - Lesions
    - Tissues surrounding the lesions
- Maximum absolute contrast of lesions to their backgrounds separately in arterial and venous phases, broken down to types of lesions
- Technical quality
- Image quality
- Overall contrast quality

3. Materials and method

3.1. Study design

The present exploratory pilot study was designed as a prospective single centre (Johann Wolfgang Goethe University Frankfurt), parallel-group, double blinded, randomised, interindividual comparison.

3.2. Patients

3.2.1. Number of patients

In the study participated a total of 50 patients. 25 of them belonged to group 1 and 25 belonged in the group 2.

Up to this study, no data was available about the influence of the planned iodine strengths and injection rates of Iomeprol (Imeron) on the maximum of contrast and, therefore, no sample size calculation could be carried out. The present study was explorative in nature. A number of 25 patients per group was considered to be sufficient to describe possible trends for differences between the treatment groups.

3.2.2. Study groups

The patients of group 1 received a total of 120 ml Imeron 300 at dual phase injection and 30 ml NaCl at mono phase injection. The patients of group 2 received a total of 90 ml Imeron 400 at dual phase injection and 23 ml NaCl at mono phase injection.

3.2.3. Inclusion criteria

Included were all the patients of both genders who were referred to multidetector CT for pretherapeutic tumour staging for one of the following indications:

- Primary liver carcinoma
- Extent of liver spread (hypervascularised metastasis)

- Cholangiocarcinoma
- Pancreatic carcinoma
- Gastric carcinoma

The patients should also fulfill the following criteria:

- Adult (age> 18 years)
- Conscious and cooperative
- must have given written informed consent

3.2.4. Exclusion criteria

- Hyperthyreosis (TSH decreased)
- Hypersensitivity to iodinated contrast agents
- Alcohol or drug abuse
- Pregnant or nursing women
- Female patient, for whom the possibility of a pregnancy could not be excluded for the following reasons:
    - Postmenopausal for 3 years
    - Surgical sterilisation
    - Pregnancy test
- Participation in a clinical trial within the past 14 days or previous enrolment in this study
- Circumstances that would significantly decrease the chance of attaining reliable data or of achieving the study objectives according to investigator's final opinion

3.3. Materials

3.3.1. Investigation product

3.3.1.1. Description

Iomeprol in different iodine concentrations, namely Imeron 300 with concentration 300 mg Iod/ml (120 ml) or Imeron 400 with concentration 400 mg Iod/ml (90ml) according to random list.

Imeron 300 and 400 are registered for the most common radiologic urologic and cardiologic indications and in clinical use in Germany.

3.3.1.2. Labeling and packaging

Each medication set was composed of a box containing one bottle of 200 ml of Imeron 300 or Imeron 400 according to the randomisation list. The labeling was obtained by the local chemistry.

3.3.1.3. Administration, use and disposal of the compound during and at the end of the study

The test solution was administered intravenously using an automated power injector (Spectris; Medrad, Pittsburgh, PA). The injection volume, as well as the injection rate was determined by a randomisation list, which was in the hand of the drug dispensing person.

A new medication set had to be used for each patient. At the end of the study, the overall used study medication was given to the local chemistry.

3.3.2. Administration procedure

Bolus triggering: Care Bolus technique

Dual phase injection:

Group 1: First phase: 80 ml Imeron 300 at 5 ml/sec

Second phase: 40 ml Imeron 300 at 2,5 ml/sec

Saline flushing: 30 ml NaCl at 2,5 ml/sec

Group 2: First phase: 60 ml Imeron 400 at 3,7 ml/sec

Second phase: 30 ml Imeron 400 at 1,9 ml/sec

Saline flushing: 23 ml NaCl at 1,9 ml/sec

3.3.3. Technical parameters

3.3.3.1. CT equipment

Sensation 16 (Siemens, Forchheim, Germany)

3.3.3.2. Imaging protocols

Table 8. Imaging protocols

Scan	Care bolus	Arterial phase	Portal-venous phase
Collimation	2 x 2,5 mm	16 x 1,75 mm	16 x 1,5 mm
Pitch	-	1	1
Table feed/ rotation	-	12 mm	24 mm
kV	120	120	120
mAs	~50	150-180	150-180
Time of rotation	0,5 sec	0,5 sec	0,5 sec
Direction	-	cranio-caudal	cranio-caudal

Location	aorta (truncus coeliacus)	diaphragm to great gastric curvature	diaphragm to great gastric curvature
Scan duration	-	~9 sec	~5 sec
Reconstruction			
Slice width/ increment	- -	1 mm/ 0,5 mm	2mm/ 1mm
MPR	-	coronal	coronal

3.4. Method and study schedule

3.4.1. Admittance to the study

Each patient fulfilling the eligibility criteria, as defined in chapters 3.2.3 and 3.2.4, was offered to participate in the study. After obtainment of the patient's written informed consent, his demographic and anthropometric data, medical anamnesis, concomitant therapies and indications, he was recorded in the case report form (CRF).

3.4.2. Distribution in study groups

After entering the study, the patients were randomly assigned to groups 1 and 2, which determine the iodine concentration, the injection volume and the injection rate, as defined in chapter 3.3.2.

The randomisation list was computed using the ProcPlan procedure of the statistical software package SAS, version 8.02.

The contrast agent was administered via bolus injection. Post injection of the contrast agent, saline flushing with NaCl with the corresponding flow rate of the portal-venous phase, respective to the randomisation group, was also performed.

As the basic parameter of the study was time of administration (equal iodine administration rate per group), the overall administration time for total injection (contrast medium and NaCl) had to be the same for both groups.

The above-mentioned volumes of saline solution, namely 30 ml for group 1 and 23 ml for group 2, ensured that the overall volume of the contrast agent was implemented to the patient. In order to equalise the time of the total injection, since we did not want the overall injection time of the contrast agent to influence the outcome of our study, the volume of NaCl was different for each group.

3.4.3. Data handling

The data was handled according to the good clinical practice (GCP) guidelines:

- Before the start of the data entry procedures: checks of completeness and legibility of the CRF, as well as plausibility check
- Data entry procedure: double entry mode using a plausibility - controlling data entry form
- After data entry: cross checks within and between the cases, complete data listings, scatter plots, check of the minimum and maximum values, control of plausibility using data cleaning macro-procedures.

3.4.4. Randomisation

The patient's assignment to one of the study groups was randomised. The randomisation list was computed with the use of the ProcPlan procedure of the statistical software package SAS, version 8.02.

3.4.5. Replacement policy

The present study was planned to be carried out on a total of 50 per-protocol patients.

Patients who discontinued the study due to reasons that were not related to the study were considered drop-outs. Withdrawals are patients who discontinued the

participation due to reasons that were directly related to the study, such as adverse events. Drop-outs and withdrawals were replaced.

Patients for whom efficacy analysis could not be completely carried out were not replaced.

The CRFs of drop-outs or withdrawals were marked on the cover page with a “D” or “DD” (in case of two consecutive drop-outs). The random list of replacement patient applied also for the replacement patients.

3.4.6. Inclusion of patients for standard analysis

Analyses of safety and efficacy were based on two patient populations, which were defined as follows:

- The intend-to-treat (ITT) population comprised any patient enrolled in the study who received any dose of the study drug. The safety analysis was performed on this population.
- The per-protocol (PP) population comprised all patients who completed the study and adhered strictly to study requirements. The efficacy analysis was performed on this population.

3.4.7. Analysis of demographic and baseline characteristics

Demographic and baseline characteristics were summarised by data listing, summary statistics (extreme values, mean and median values, standard deviation) or frequency distribution tables, as appropriate for each item.

Treatment groups were checked for homogeneity with respect to all possible influences on the key variables.

3.4.8. Course of the study

Seven to one day (days -7 to -1) prior to the examination took place the recruitment, according to the inclusion and exclusion criteria, the patient’s

information and the informed consent, the recording of the demographic data, medical history, concomitant medication and the pre-dose events.

Day 0 was the day of the examination. The CT examination started with a SCOUT scan. A venous access (>18G) was fixed in the antecubital vein of the arm, preferably at the left one. A Care Bolus CT scan followed, which was performed in order to determine the individual delay time between the start of the contrast agent injection and the start of the arterial and PVP CT scans. The threshold for starting CT scanning was fixed to 140 HU. The start of the AP took place immediately post reaching the fixed threshold and the obligatory scanner delay of 6 seconds. The breath-hold command was included in the scanner delay. The contrast agent was administered by means of a power injector (Spectris; Medrad, Pittsburgh, PA). The concentration of Imeron, the administration volume, as well as the injection rates for all scans followed the randomisation list. After the first phase of administration of Imeron, the AP CT scan was followed by the PVP. The delay between arterial and PVP was fixed at 45 seconds, based on data in the at the time current existing literature.

The patient remained for one hour post injection or 30 minutes post end of overall CT scan under the observation of the examining physician.

Twenty-four hours after the administration of the contrast agent (day 1) took place the follow-up, in order to record potential adverse events.

The efficacy evaluation, which included qualitative and quantitative assessments (technical, image and overall contrast quality) and the signal intensity measurements on the basis of CT images, were subsequently carried out by the investigator.

Finally, two independent radiologists, who were not involved in the study previously, assessed the accuracy in consensus. Histological reports or clinical follow-up served for this purpose as the gold standard.

3.4.9. Investigator's assessments

The following criteria were evaluated:

3.4.9.1. Technical quality

The technical quality was assessed in 4 scores:

i. 1= Insufficient = the overall structures of the upper abdomen were not visualised
ii. 2 = Moderate = the overall structures of the upper abdomen were distinctly visualised
iii. 3 = Good = the overall structures of the upper abdomen were good visualised
iv. 4 = Excellent = the overall structures of the upper abdomen were excellently visualised

3.4.9.2. Image quality (presence of contrast artifacts)

The presence of contrast artifacts was assessed in 3 scores:

i. None
ii. Present, minor degradations due to artifacts
iii. Present, major degradations due to artifacts

3.4.9.3. Overall contrast quality

The overall contrast quality was evaluated in 4 scores:

i. 1 = Insufficient = the boundary between the lesion or lesions and the surrounding area was not depicted
ii. 2 = Sufficient = the boundary between the lesion or lesions and the surrounding area was distinctly visualised
iii. 3 = Good = the boundary between the lesion or lesions and the surrounding area was visualised, but the lesion or lesions were not completely delineated
iv. 4 = Excellent = the boundary between the lesion or lesions and the surrounding area was visualised and the lesion or lesions were completely delineated

3.4.9.4. Quantitative assessment (Signal Intensity)

The signal intensity (HU) was measured at arterial and venous enhancement using the ROI technique (operator-defined regions of interest). The difference between the HU measurement in the tumour and the surrounding hepatic normal tissue was assessed through drawing ROIs both in the tumour and in the surrounding hepatic lesion. Tumourous lesions were only measured in solid portions of the tumour.

3.4.10. Image evaluation

Acquired images were saved to a picture archiving and communication system (PACS) and images were reviewed on a dedicated reporting workstation (Centricity™ PACS, GE-Healthcare, Waukesha, WI).

All image evaluations were performed by two radiologists, with 5 and 8 years of experience in abdominal imaging at the time of the study, in consensus.

3.4.11. Data collection and statistical analysis

Results of image evaluations were tabulated to facilitate their analysis. The mean, standard deviation and range of the results of the quantitative assessment were calculated and the difference between both protocols of contrast administration both in the AP and venous phase was tested for statistical significance using the Two-Sample t-Test. The absolute number and percentage of the results of qualitative image evaluation was calculated and the difference in qualitative results between both protocols was tested for statistical significance using the Wilcoxon-Mann-Whitney-Test. Statistical analyses were done with the use of BIAS software for Windows. P values less than 0,05 were considered to indicate statistical significance.

3.4.12. Ethics

The study was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) and was approved by the Ethics Committee of the University Clinic of the J. W. Goethe University Hospital Frankfurt am Main (study protocol number: Imeron 300/400 MDCT Upper Abdomen, study protocol: IOM/16-04, vote of the Ethics Committee reference number: 205/04, date of approval: 10.02.2005).

Informed consent was obtained from all subjects involved in the study prior to their enrollment and data confidentiality has been ensured.

4. Results

4.1. Patient selection

A total of 50 patients fulfilling the eligibility criteria, as defined in chapters 3.2.3 and 3.2.4, were selected.

4.2. Patient withdrawal

None of the 50 patients were withdrawn from the study.

4.3. Patient gender

From the 50 patients who were chosen to be studied 29 were male (58%) and 21 were female (42%).

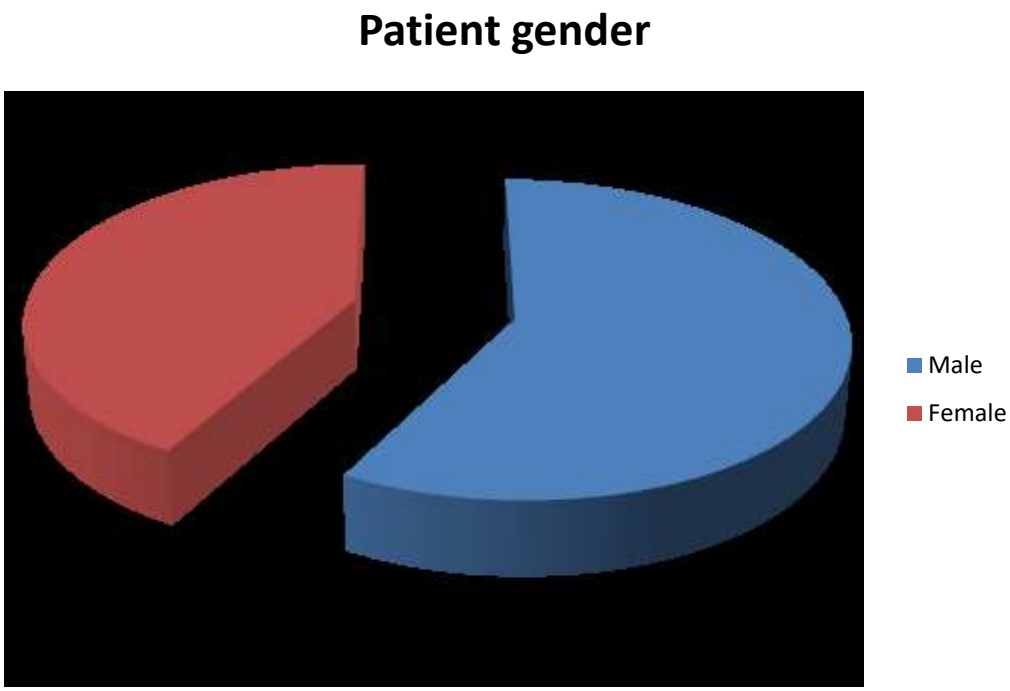


Figure 3. Pie chart of gender distribution

4.4. Patient age

The age of the patients on the examination date ranged from a minimum of 39 to a maximum 80 years with a mean of 63,3 years of age (standard deviation: 9,93).

4.5. Number of lesions pro patient

The mean number of lesions per patient was of 2,44 +/- 1,12 lesions, with a minimum of 1 and a maximum of 5 lesions per patient. The total number of lesions included was 357.

4.6. Diagnosis

19 patients from the 50 who participated in the study (38%) were diagnosed with hepatocellular carcinoma (HCC). 13 patients (26%) had hepatic metastases from a primary colorectal carcinoma (CRC), 9 (18%) from a primary mamma carcinoma (MACA) and 4 (8%) from a primary gastric carcinoma (Gastro-CA). One patient (2%) was diagnosed with each of the following diseases: primary cholangiocarcinoma (CCC), primary esophageal carcinoma (EC), primary pancreatic carcinoma (Pancreas-Ca), primary prostatic carcinoma (Prostata-Ca) and primary neuroendocrine tumour (NET).

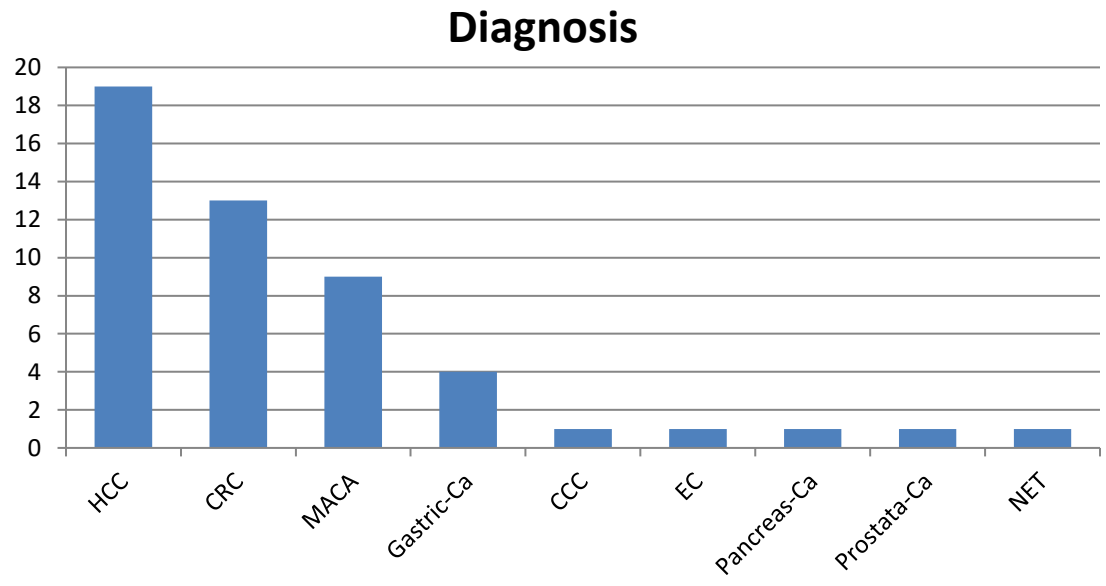


Figure 4. Bar chart of diagnosis

4.7. Diagnosis in relation to gender

From the 19 patients who were diagnosed with HCC, 11 (57,9%) were male and 8 (42,1%) were female. From this group, 13 patients were diagnosed with hepatic metastasis with a primary colorectal tumor; 9 were male patients (69%), while 4 were female (31%). Furthermore, all 9 patients with a primary mamma carcinoma were female, whereas all 4 patients with a primary gastric carcinoma were male. Patients who were diagnosed with hepatic metastases of other primary carcinomas (primary cholangiogarcinoma, esophageal carcinoma, primary pancreatic carcinoma, primary neuroendocrine tumour and primary prostatic carcinoma) were all male.

4.8. Size of lesions

For the Imeron 300 group the mean size of the assessed hepatic lesions was 32,7 +/- 23,7 mm, with a minimum of 5,3 mm and a maximum of 95,7 mm.

For the Imeron 400 group the mean size of the assessed hepatic lesions was 33,3 +/- 26,8 mm, with a minimum of 8 mm and a maximum of 135 mm.

Statistical analysis showed no statistically significant difference between the diameters of the lesions in both protocols (p = 0,90).

4.9. Absolute contrast of lesions to their backgrounds (difference $SI_{lesions}$ minus $SI_{surrounding}$ tissue) of arterial and venous phase scans

For the Imeron 300 group the mean HU measurement of the hepatic lesions in the AP was 63,3 +/- 44,3, with a minimum of 10 HU and a maximum of 238 HU and in the venous phase it was 64,6 +/- 27,3, with a range of 10 HU to 114 HU. The mean HU measurement of the surrounding hepatic tissue in the AP was 72,9 +/- 14,9, with a minimum of 43 HU and a maximum of 108 HU and in the venous phase it was 98 +/- 16,9 with a minimum of 64 HU and a maximum of 139 HU. The mean difference between the hepatic lesion and the surrounding hepatic

tissue was -9,6 +/- 42, with a range of -62 to 133 and in the venous phase -33,4 +/- 24 with a range of -90 to 23.

For the Imeron 400 group the mean HU measurement of the hepatic lesions in the AP was 57,9 +/- 31,1, with a minimum of 5 HU and a maximum of 163 HU and in the venous phase it was 62,4 +/- 31, with a minimum of 5 HU and a maximum of 143 HU. The mean HU measurement of the surrounding hepatic tissue in the AP was 74,4 +/- 12,3, with a range of 49 to 99 HU and in the venous phase 95,4 +/- 18, with a range of 57 to 141 HU. The mean difference between the hepatic lesion and the surrounding hepatic tissue was -16,5 +/- 31,6, with a minimum of -73 and a maximum of 72 and in the venous phase -31,8 +/- 30,8, with a minimum of -104 and a maximum of 28.

There was also no statistical difference between both protocols regarding the difference in HU measurement between the hepatic lesion and the surrounding hepatic tissue both in the AP ($p = 0,36$) and in the venous phase ($p = 0,92$).

4.10. Technical quality

The technical quality achieved for the Imeron 300 group was graded as excellent for 24 of the cases (96%), which means that the overall structures of the upper abdomen were excellently visualised for both the arterial and venous phases; in one of the cases (4%) the quality was insufficient, namely the overall structures of the upper abdomen were not visualised for both the arterial and venous phases.

For the Imeron 400 group, the technical quality was graded for 22 of the cases (88%) as excellent for both the arterial and venous phases; in one case (4%) it was graded as good, namely the overall structures of the upper abdomen were well visualized for both the arterial and venous phases and in one case (4%) it was graded as insufficient for both the arterial and venous phases.

Statistical analysis showed no statistically significant differences between both protocols regarding the technical quality of the images, in both the arterial ($p = 0,46$) and the venous phases ($p = 0,48$).

4.11. Image quality

For the Imeron 300 group, in 24 of the cases (96%) there were no artefacts related to the contrast medium, while in 1 case (4%) there were minor degradations for both the arterial and venous phases, respectively.

For the Imeron 400 group, there were no contrast artefacts in 22 of the cases (88%) and only minor artefacts in 3 of the cases (12%) for both arterial and venous phases, respectively.

Statistical analysis showed no statistically significant differences between both protocols regarding the presence of artefacts related to the contrast medium, in either the AP ($p = 0,46$) or in the venous phase ($p = 0,46$).

4.12. Overall contrast quality

The overall contrast quality was, for the Imeron group 300, excellent for 24 of the cases (96%), meaning that the boundary between the lesion or lesions and the surrounding area was visualised and the lesion or lesions were completely delineated, while in 1 case (4%) the quality was good, which means that the boundary between the lesion or lesions and the surrounding area was visualised, but that the lesion or lesions were not completely delineated; concerning the venous phase, the overall contrast quality was graded as excellent in 23 cases (92%) and in 2 cases as good (8%).

For the Imeron 400 group, the overall contrast quality in the AP was graded as excellent for 24 of the cases (96%) and as good in 1 case (4%), while for the venous phase it was graded as excellent in 22 cases (88%), in 2 cases as good (8%) and in 1 case (4%) as sufficient, namely the boundary between the lesion or lesions and the surrounding area was distinctly visualised.

Statistical analysis showed no statistically significant differences between both protocols regarding the overall contrast quality of the images, either in the AP ($p = 0,50$) or in the venous phase ($p = 0,48$).

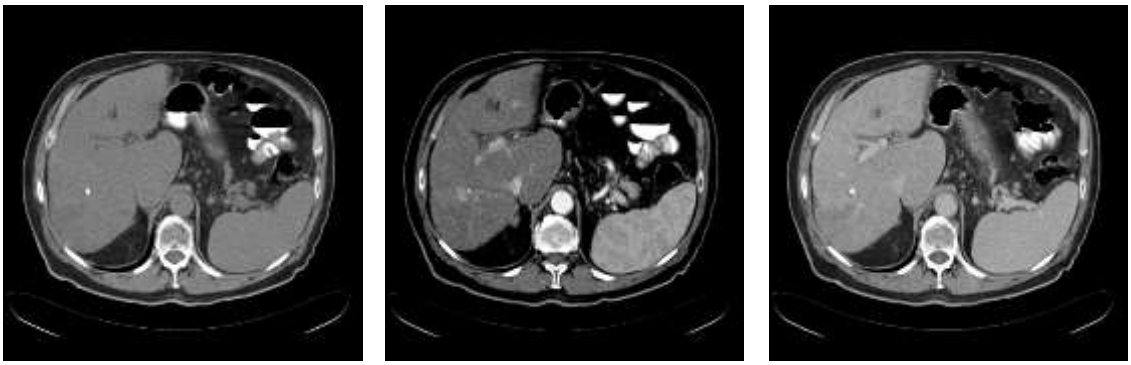


Figure 5. Patient 1: HCC - Imeron 300

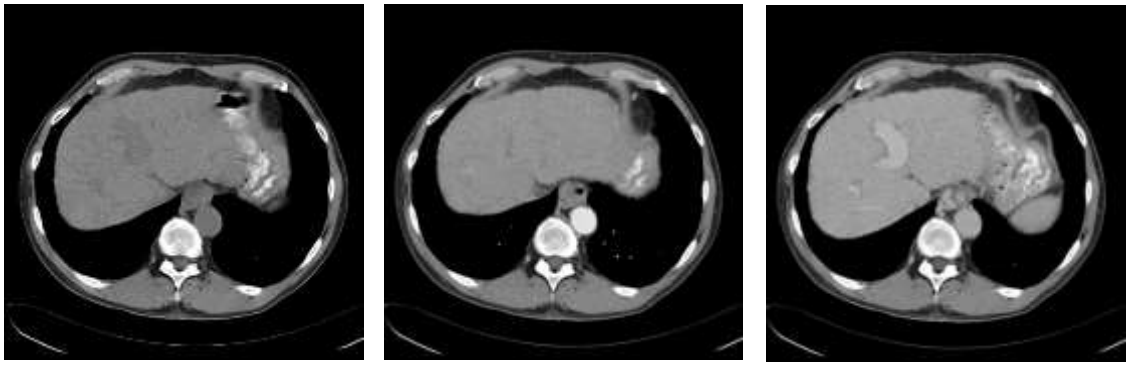


Figure 6. Patient 2: HCC - Imeron 300

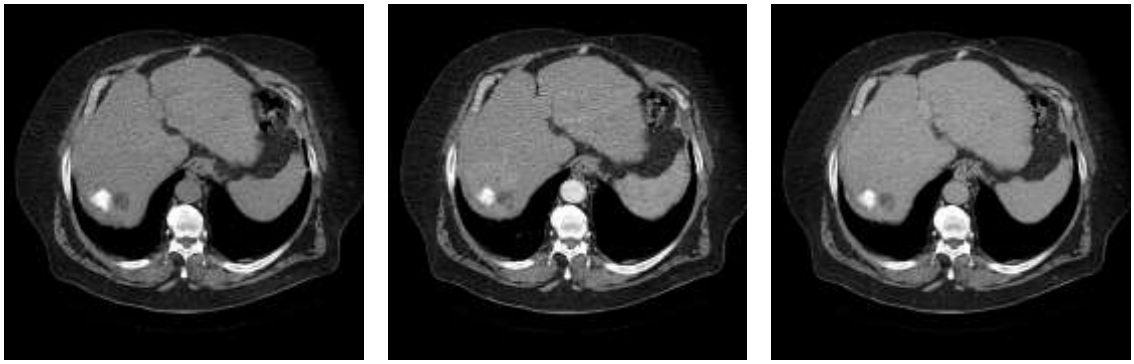


Figure 7. Patient 3: HCC - Imeron 400

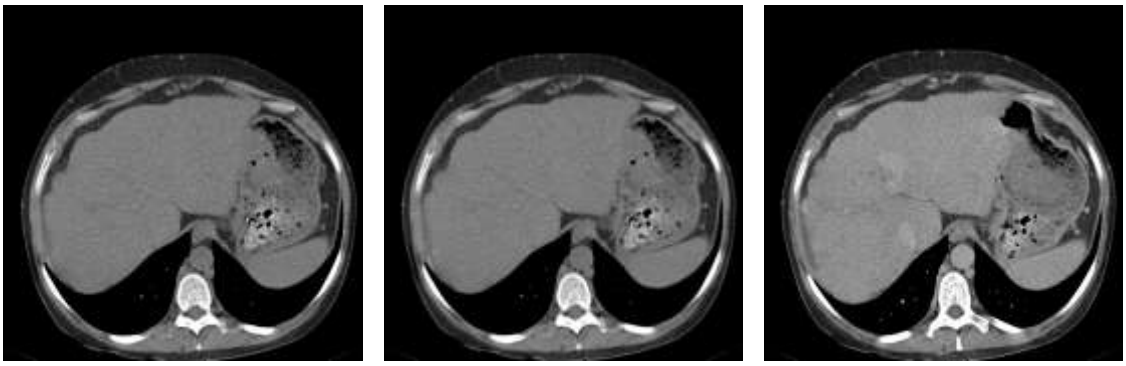


Figure 8. Patient 4: HCC - Imeron 400

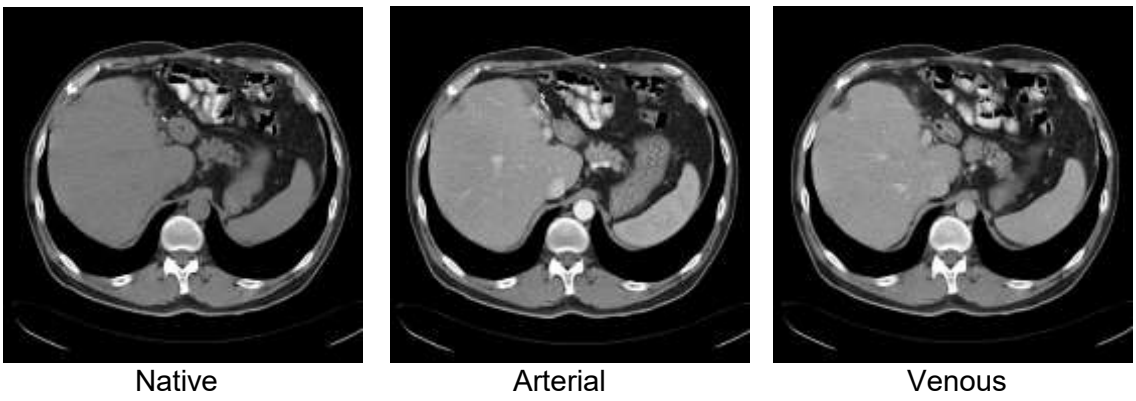


Figure 9. Patient 5: Hepatische Metastasen - Imeron 300

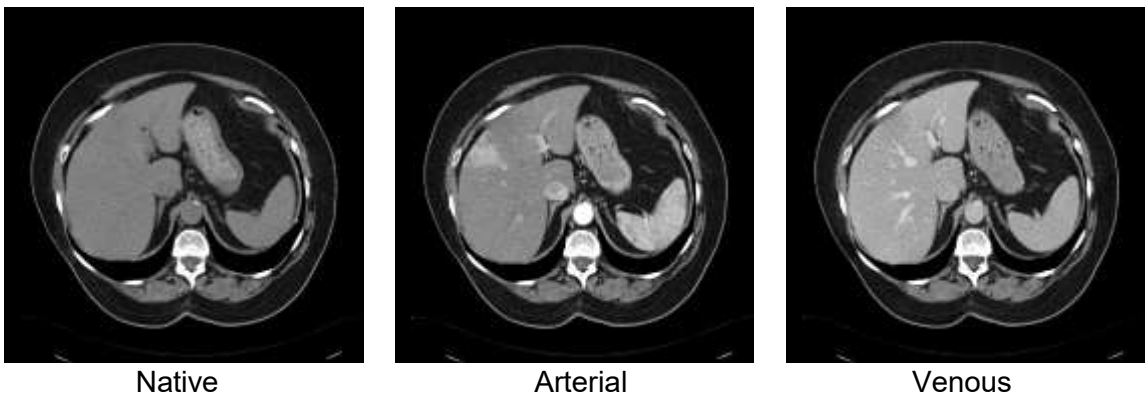


Figure 10. Patient 6: Hepatische Metastasen - Imeron 300

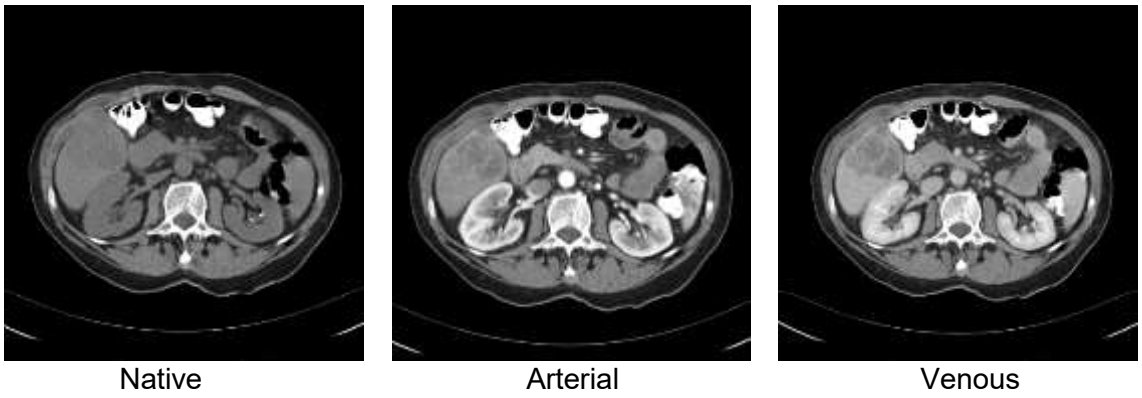


Figure 11. Patient 7: Hepatische Metastasen - Imeron 400

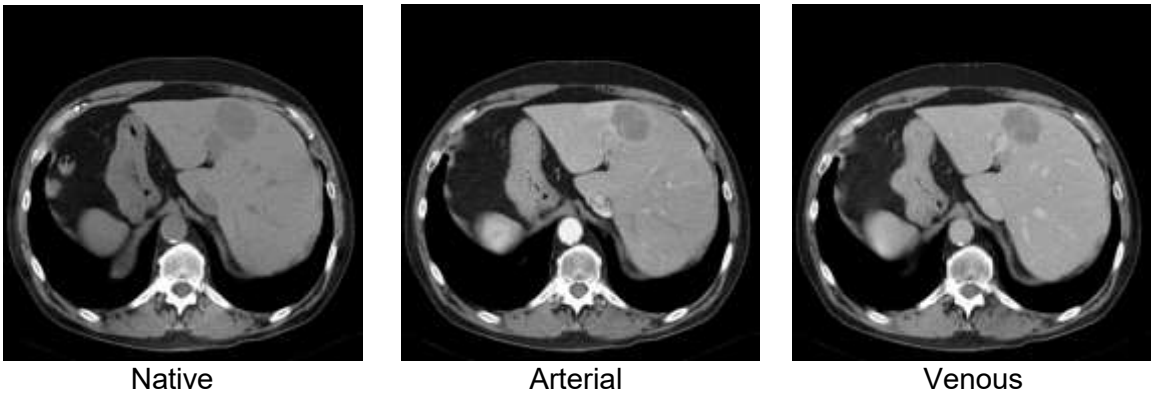


Figure 12. Patient 8: Hepatische Metastasen - Imeron 400

5. Discussion

5.1. Characteristics of the study subjects

In our study 57,9% of the patients with HCC were male and 42,1% female. These percentages differ from the data of the majority of the studies, which have shown a higher prevalence of HCC for men, with the gender ratio varying between 66,66% to 80% for male and 20% to 33,33% for female.[295]

The mean age of the participants was 63,3 years, which correlates with the mean age of diagnosis for Western patients, as referred in numerous studies.[296, 297]

5.2. Comparison of the performance quality of the two protocols

Regarding the absolute contrast of lesions to their backgrounds (difference SIlesions minus SIsurrounding tissue), our study showed that there was no statistical difference between both protocols regarding the difference in HU measurement between the hepatic lesion and the surrounding hepatic tissue both in the arterial phase ($p = 0,36$) and in the venous phase ($p = 0,92$).

Moreover, there was no statistically significant difference between both protocols regarding the technical quality of images both in the arterial phase ($p = 0,46$) and in the venous phase ($p = 0,48$),

In regard to the image quality, there was no statistically significant difference between both protocols regarding the presence of artifacts related to contrast medium both in the arterial phase ($p = 0,46$) and in the venous phase ($p = 0,46$).

The overall contrast quality of images both in the arterial ($p = 0,50$) and in the venous phase ($p = 0,48$) showed no statistically significant difference between both protocols.

5.3. Comparison with the literature

The multiphasic computed tomography (CT) imaging is a very useful tool in the hands of clinicians for the initial assessment and evaluation of patients with

abdominal lesions. It has been proved to have high accuracy in the detection and characterisation of benign and malignant hepatic lesions.[298-306]

The quality of the produced images depends greatly on the injection rate and volume of the contrast medium. An increased injection rate of contrast medium has been shown to produce hepatic images of better quality in the AP, however it was reported that there were also more physiochemotoxic and other adverse reactions to the contrast agents, such as haemodynamic disturbances. Furthermore, the cardiac pump function of many patients is not able to transport a large volume of contrast agent in a heartbeat. As a result, the maximum enhancement decreases and the contrast concentration curve flattens. A higher iodine concentration in the contrast medium enables the reduction of the injection rate and, thus, the reduction of the volume load of the heart, without reducing the iodine delivery rate. In addition, the increase of the injection rate causes an increase in the extravasation rates, as well as to more false positive results in the detection of small hypervascular hepatocellular carcinomas in cirrhotic patients.[275, 285-294, 307, 308]

The aim of the current study was to test whether a reduced flow rate of 3,7 ml/sec in comparison to 5 ml/sec of contrast medium injection, while keeping the iodine injection delivery rate constant by using a higher iodine concentration medium, namely Imeron 400 vs. Imeron 300, would adversely affect the image quality. The parameters used to test the difference in image quality between both groups were qualitative, in the form of an assessment of the overall technical quality addressing organ delineation, the presence of artifacts related to the administered contrast agent and the delineation of the lesion within the liver as compared to the surrounding hepatic tissue. Quantitative assessment was based on the assessment of the difference between the HU measurement of the hepatic lesion compared to the surrounding hepatic tissue which represented the contrast between the lesion and the surrounding tissue. The current study's results showed no statistically significant differences between both groups in all assessed aspects, both qualitative and quantitative.

The subject of the efficacy of different iodine concentrations of the same contrast agent for the enhancement of various organs and anatomical structures on CT

scans has intrigued many scientists and, for this reason, an abundance of relevant studies has been contacted in the last decades. However, most studies cannot be directly compared to our study since they compare the different iodine concentrations of the contrast agents either at constant administration rates or using a fixed volume of both contrast agents, both resulting in the administration of a greater absolute iodine amount with the higher concentration protocol (which had a positive effect on the image quality in this group of patients but at the cost of increased amount of injected iodine), as opposed to our study in which we used a fixed amount of iodine for both protocols.

Romano et al. (2009) have compared two contrast media (Iomeprol) with iodine concentrations of 400 and 320 mg/ml, respectively, in the multidetector CT (MDCT) scan of the abdomen. They determined that the medium with the higher iodine concentration resulted in significantly better image enhancement, both in the arterial (first reader: p = 0,0004, second reader: p = 0,01) and venous phases (first reader: p = 0,04, second reader: p = 0,05), while having the same minor impact on the patient's heart rate and safety as the medium with the lower concentration.[309]

The superiority of contrast agents with higher iodine concentrations in some special cases, has also been demonstrated by Brink et al., who have suggested in two scientific papers (both 2003) that using a high contrast concentration, for instance a 400 mg/ml iodine contrast medium, seems to be of advantage when scanning overweight patients and in cases where there is a necessity for a high-detailed imaging of the vessels via high-resolution CT angiography. This is because rapid imaging, which is more achievable with the higher concentration of contrast medium, is of great importance for the best possible contrast use in CT angiography. The same also applies when using multiphasic CT imaging of the parenchymal organs.[310,311]

Suzuki et al. (2007) have compared, in a blind study, two contrast media of different iodine concentrations, namely 300 and 370 mg/ml, respectively, keeping all other parameters constant. As a result, they observed no significant differences in the visual evaluation of the AHs with 3D-CT-angiography, however, the aortic contrast enhancement at the late AP, as well as of the liver at the PVP,

was significantly higher for the higher iodine concentration medium. They also observed that the aortic and PV's contrast enhancement was at some phases higher in women in comparison to that of men.[312]

Marchianò et al. (2005) have shown in their study that a higher iodine concentration in the contrast medium results in a better healthy liver tissue to lesion contrast in the cirrhotic patient's biphasic spiral CT scans; this could be of great importance in the diagnosis of hepatocellular carcinoma.[313]

Yamashita et al. (2000) have also observed that the higher the concentration of contrast medium used, the better was the quality of the hepatic parenchymal enhancement.[314]

Guerrisi et al. (2011) also observed that a higher iodine concentration of the contrast agent at a constant flow rate leads to a greater aortic enhancement during the hepatic AP and a profound improvement of the conspicuity of hepatocellular tumours in the cirrhotic liver, when using the 64-row multi-detector CT.[315]

In support of this observation, Tsurusaki et al. (2004), also suggested that a higher iodine concentration in multiphasic dynamic CT can achieve better portal and hepatic venous enhancement, as well as better enhancement of the hepatic parenchyma.[316]

The results of Sahani et al. (2007) agree with those of Tsurusaki et al. in the fact that the injection of a contrast medium with a higher iodine concentration results in a better enhancement at the AP in comparison to one having a lower iodine concentration. However, in contrast to Tsurusaki et al., they did not observe significant differences between the two contrast media concentrations concerning the enhancement at the PVP. Sahani et al.'s study also demonstrated that there were no differences in the side effects produced from both concentrations.[317]

Behrend et al. (2009) performed a similar study to our study but in the chest. They compared intravascular contrast enhancement in multidetector computed tomography (MDCT) of the chest using two protocols, with concentrations of 300 and 400 mg iodine/ml, respectively, while using a constant delivery rate of 1,29 g iodine/sec for both protocols. The authors concluded that there was no

statistically significant difference ($p \leq 0,005$) between both protocols regarding the contrast enhancement at all anatomic sites, namely the right and left ventricles, pulmonary trunk, right and left pulmonary arteries and the ascending and descending aortas.[318]

Hansmann et al. (2013) compared four contrast material injection protocols with different iodine concentrations and different injection flow rates for dual-energy computed tomography pulmonary angiography (DE-CTPA) in patients with suspected pulmonary embolism. In the first two protocols, they used 80 ml iopromide at a concentration of 370 mg/ml with flow rates of 4 ml/sec and 3 ml/sec, respectively, while in the next two protocols they used 98 ml iopromide at a concentration of 300 mg/ml with flow rates of 4,9 ml/sec and 3,7 ml/sec, respectively. The target tract attenuation was highest for the protocols with 80 ml iopromide at a concentration of 370 mg/ml with a flow rate of 4 ml/sec and 98 ml iopromide at a concentration of 300 mg/ml with a flow rate 4,9 ml/sec, With similar findings to our study, Hansmann et al. found that there was no statistically significant difference ($p = 0,3395$) regarding the attenuation in the group of the higher iodine concentration at a slower administration rate, namely 370 mg/ ml at 4 ml/ sec and the group of the lower iodine concentration at a higher rate, namely 300 mg/ml at 4,9 ml/ sec. However, in the group with the higher concentration, there occurred more artefacts on iodine perfusion maps (three versus two). They also confirmed that, the higher the administration rate, the better the attenuation in groups with the same iodine concentration.[319]

Fenchel et al. (2004) compared an iodine contrast medium with two different iodine concentrations, namely 300 and 400 mg/ml, for the multislice CT of the pancreas. Two independent readers came also to the conclusion that the contrast medium with the higher concentration results in a better contrast enhancement of the vessels during the AP and as a result makes the evaluation of potential pathologies more accurate.[320]

Furthermore, Sandstede et al. (2006) also approached the same conclusion, as they demonstrated with their study that the higher iodine concentration in the contrast media when used in the CT of the pancreas leads to a better enhancement at the AP.[321]

Ma et al. (2008) reported that although both contrast media with different iodine concentrations in their study showed similar results with the 16-row multiple-detector CT for the presurgical planning of the pancreas, the medium with the higher concentration resulted in a better enhancement and quality of 3D-images, while also being injected for a shorter time.[322]

Similar results have reported Setty et al. (2006) who have demonstrated that a greater contrast enhancement and image quality is achieved for the chest 16-slice multidetector CT by using contrast media of higher-concentration. Furthermore, there is a financial benefit without an increase in the risk of unwanted adverse reactions when using media with higher concentrations.[323]

Cademartiri et al. (2005) have reported that the higher the iodine concentration of a contrast medium is, the greater the attenuation in the descending aorta and coronary arteries is achieved.[324]

Becker et al. compared, in their 2011 study, two contrast agents with concentrations of 320 and 400 mg/ml, respectively, in coronary CT angiography and also concluded that the higher the concentration of contrast agent used, the higher the coronary arterial enhancement was achieved, which led to a better visualisation of the SEGs.[325]

Honoris et al. (2015) compared contrast agents with four different concentrations in coronary CT angiography and demonstrated that although a high concentration of contrast agents resulted in better vascular enhancement, low concentrations of contrast agents provided a better image quality.[326]

On the contrary, Zheng et al. (2014), concluded that both contrast agents, with concentrations of 270 and 370 mg/ml respectively, provided similar enhancement and image quality in coronary CT angiography.[327]

Achenbach et al.'s (2017) results agree with those of Zheng as they demonstrated that the image quality in coronary CT angiography used for the diagnosis of coronary stenosis was equal for both (lower and higher) iodine concentrations.[328]

Sun et al. demonstrated in their study of 2017 that contrast agents with higher iodine concentrations combined with low tube voltage produce similar image qualities with lower iodine concentrations, while allowing a radiation dose reduction.[329]

Similar results were obtained by Park et al. (2016), who compared two contrast agents with different iodine concentrations and concluded that although the contrast agent with higher iodine concentration produces a better enhancement of the ascending aorta in the coronary CT angiography, the image quality in the ascending aorta, the left main coronary artery and the left ventricle is similar in both groups.[330]

On the contrary, Van Cauteren et al. showed in their study of 2018 that the use of a greater volume of contrast agent with a lower concentration injected at a higher rate, led to a greater and longer clinically relevant maximal enhancement in CT angiography.[331]

The randomised multicentre study of Rengo et al. (2019) has shown that intravascular attenuation, contrast enhancement and heart rate changes in coronary CT angiography are independent of the iodine concentration when the contrast agents are injected at 37 °C and with the same iodine delivery rate.[332]

Two paediatric studies of Wang et al. (2016) and Hou et al. (2017) demonstrated that a lower concentration contrast medium in combination with a low tube voltage does not compromise the image quality, while the iodine load and radiation dose were lower than with the use of a higher contrast agent concentration.[333, 334]

More explicitly, Wang et al. compared two different concentrations of iodinated contrast media in children's abdominal CT scans in combination with 70% adaptive statistical iterative reconstruction (ASIR) for the lower concentration and 50% ASIR for the higher. They concluded that the image quality was comparable for both concentrations, while there was a significant reduction in radiation and iodine load for the lower concentration.[333]

Hou et al. used contrast media with two different iodine concentrations for the cardiac CT of children with congenital cardiac disease and observed that there

was a reduction in radiation and iodine load for the group with the lower concentration, while the quality of the images was similar in both groups.[334]

As stated above, the discrepancy between our results and the results of other studies is mainly due to the fact that in our study we used two different administration rates for each iodine concentration of the contrast agents, as opposed to other studies which used a constant rate. Another reason is that we used a fixed amount of injected iodine for both protocols while other researchers injected a fixed volume of both contrast media, which resulted in a greater absolute quantity of iodine being injected with the higher concentration protocol.

5.4. Limitations of the current study

Limitations of the current study include the relatively small number of patients included and the absence of clinical evaluation of the effect of reduced injection flow rate on the patients' sensation and tolerance of contrast injection, as in the current study we concentrated more on the imaging aspect of the two protocols.

5.5. Conflicts of interest declaration

The author has no conflict of interest to declare.

6. Conclusion

The results of the current study showed no statistically significant differences between both groups in all assessed aspects, both qualitative and quantitative. In addition, most of the relevant studies in the international literature have shown no inferiority of contrast agents with a higher iodine concentration in comparison to those with lower concentrations, with regard to their efficacy for the enhancement of various organs and anatomical structures on CT scans, in fact, some of these have proven to be superior.

In conclusion, the current study has shown that it is possible to reduce the injection rate of iodinated contrast medium from 5 ml/sec to 3,7 ml/sec while keeping the iodine injection flow rate constant by using a high iodine concentration contrast media, without affecting the attenuation or the image quality of the multiphasic CT imaging of the liver.

7.1. Summary

Background: In the Computer Tomography imaging, examinations for the diagnosis of lesions of the upper abdomen currently use water-soluble, iodinated, non-ionic contrast agents with low molecular weight. One possibility to reduce the time of the examination and X-ray exposure is to increase the injection rate. However, higher injections rates lead to increased hypersensitivity reactions and extravasation rates. Furthermore, cardiac pump function does not always allow for the transportation of such a large volume within one heartbeat. With a contrast agent of higher iodine concentration, the injection rate may be reduced without decreasing the iodine delivery rate while reducing the volume load of the heart.

Aim: to compare the performance and image quality of two injection protocols of contrast medium for multiphasic CT imaging of malignant hepatic lesions; one using Imeron 300 at an injection rate of 5 ml/ sec and the second using Imeron 400 at an injection rate of 3,7 ml/ sec, for multiphasic CT imaging of malignant hepatic lesions, in order to optimise the iodine concentration and injection rate of the contrast agent Imeron in the Multislice Spiral-CT of the upper abdomen.

Materials and methods: the current prospective, single centre, double-blinded, randomised and interindividual comparison study included 50 patients (29 males and 21 females) with a mean age of 63,3 years. Patients were randomised to one of the two injection protocols. Image evaluation included qualitative assessment (technical quality, presence of artefacts and overall contrast quality) and quantitative assessment (measuring the difference in HU between the lesion and the surrounding hepatic tissue). The difference between both protocols was tested for statistical significance using the Wilcoxon-Mann-Whitney test and the Two-Sample t-test.

Results: there was no statistically significant difference between both protocols regarding the technical quality of images, both in the AP ($p = 0,46$) and in the venous phase ($p = 0,48$). Additionally, no statistically significant difference was found regarding the presence of artefacts related to the contrast medium, both in the AP ($p = 0,46$) and in the venous phase ($p = 0,46$), as well as regarding the overall contrast quality of images both in the AP ($p = 0,50$) and in the venous phase ($p = 0,48$). Quantitative assessment showed no statistically significant

difference regarding the difference in HU measurement between the hepatic lesion and the surrounding hepatic tissue, both in the AP (p = 0,36) and in the venous phase (p = 0,92).

Conclusion: in the multiphasic CT imaging of the liver, reducing the injection rate of the contrast medium Imeron from 5 ml/ sec to 3,7 ml/ sec while increasing the iodine strength of the agent from 300 to 400 mg/ml, respectively, and thus keeping the iodine injection flow rate constant, produces similar signal intensities and results in similar technical, image and overall contrast qualities..

Keywords: Contrast-medium, injection rate, iodine concentration, hepatic malignancy, multiphasic CT

7.2. Zusammenfassung

Hintergrund: für die Diagnose von Läsionen des Oberbauchs werden in der Computertomographie (CT) wasserlösliche, jodhaltige, niedermolekulare, nichtionische Kontrastmittel angewendet. Eine Möglichkeit, die Untersuchungszeit und Strahlenexposition zu verkürzen, besteht darin, die Injektionsrate zu erhöhen. Höhere Injektionsraten führen jedoch zu häufigeren Überempfindlichkeitsreaktionen und Extravasationsraten. Darüber hinaus ermöglicht die Pumpfunktion des Herzens nicht immer den Transport eines so großen Volumens innerhalb eines Herzschlags. Mit der Verwendung eines Kontrastmittels mit höherer Jodkonzentration kann die Injektionsrate reduziert werden, ohne die Jodrate zu reduzieren. Das ermöglicht, die Volumenbelastung des Herzens zu verringern.

Ziel: Vergleich der Leistung und Bildqualität von zwei Injektionsprotokollen des Kontrastmittels Imeron in zwei Konzentrationen, nämlich von Imeron 300 mit einer Injektionsrate von 5 ml/ sec bzw. Imeron 400 mit einer Injektionsrate von 3,7 ml/s für die multiphasische CT-Bildgebung von malignen Leberläsionen, mit dem Ziel der Optimierung der Jodkonzentration und Injektionsrate des Kontrastmittels Imeron in der Multislice-Spiral-CT des Oberbauches.

Materialien und Methoden: Die Studie ist eine prospektive, monozentrische, doppelblinde, randomisierte und interindividuelle Vergleichsstudie. 50 Patienten haben teilgenommen (29 Männer und 21 Frauen) mit einem Durchschnittsalter von 63,3 Jahren. Die Patienten wurden randomisiert in einem der beiden Injektionsprotokolle. Die Bildauswertung umfasste eine qualitative Auswertung (technische Qualität, Vorhandensein von Artefakten und Gesamtkontrastqualität) und eine quantitative Auswertung (Messung des HU-Unterschieds zwischen der Läsion und dem umgebenden Lebergewebe). Der Unterschied zwischen beiden Protokollen wurde mittels des Wilcoxon-Mann-Whitney-Tests und des Two-Sample-t-Tests auf statistische Signifikanz getestet.

Ergebnisse: Es gab keinen statistisch signifikanten Unterschied zwischen beiden Protokollen hinsichtlich der technischen Qualität der Bilder, sowohl in der arteriellen ($p = 0,46$) als auch in der venösen Phase ($p = 0,48$). Zudem zeigte sich kein statistisch signifikanter Unterschied hinsichtlich des Auftretens von

kontrastmittelbedingten Artefakten, sowohl in der arteriellen (p = 0,46) als auch in der venösen Phase (p = 0,46), sowie hinsichtlich der gesamten Kontrastqualität der Bilder sowohl in der arteriellen (p = 0,50) als auch in der venösen Phase (p = 0,48). Die quantitative Bewertung zeigte keinen statistisch signifikanten Unterschied bezüglich des Unterschieds der HU-Messung zwischen der Leberläsion und dem umgebenden Lebergewebe, sowohl in der arteriellen (p = 0,36) als auch in der venösen Phase (p = 0,92).

Fazit: Die Reduzierung der Injektionsrate des Kontrastmittels Imeron von 5 ml/sec auf 3,7 ml/sec bei gleichzeitiger Erhöhung der Jodkonzentration von 300 auf 400 mg/ml und damit Konstanthaltung der Flussrate von Jod beeinträchtigen die Bildqualität bei der multiphasischen CT-Bildgebung der Leber nicht; es werden ähnliche Signalintensitäten, technische-, Bild- und Gesamtkontrastqualität produziert.

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9.1. Curriculum Vitae

Education

June 2000	High school diploma from Ziridis School, Athens, Greece (Grade: excellent)
June 2007	Doctor of Dental Surgery (DDS) degree from the Dental School of the National and Kapodistrias University of Athens, Greece (Grade: very good)
September 2012	Oral Surgeon degree from the Association of Dentists (Landeszahnärztekammer) of Hessen, Germany
March 2016	Medical Doctor (MD) degree from the Medical School of the National and Kapodistrias University of Athens, Greece (Grade: very good)
December 2021	MSc degree in “Medical Research Methodology”, Aristotle University Thessaloniki

Work experience

July 2007 - Oktober 2008	Dentist at the private practice of DDS Vassiliki Konsologlou-Zantiotou, Athens, Greece
November 2008 - September 2012	Resident oral surgeon, educational assistant and scientific employee of the Department of Oral surgery and Implantology, Dental school

	of the J.W. Goethe University in Frankfurt am Main, Germany
September 2012 - March 2013	Specialist in Oral Surgery and Implantology, educational assistant and scientific employee of the Department of Oral surgery and Implantology, Dental school of the J.W. Goethe University in Frankfurt am Main, Germany
April 2013 - March 2019	Oral surgeon at Eurion private clinic in Frankfurt am Main, Germany
March 2016 - September 2019	Maternity leave for three children
October 2019 - present	Resident dermatologist at the dermatological practice Dres. Jüstel, Frankfurt am Main, Germany

9.2. Lebenslauf

Ausbildung

Juni 2000	Schulabschluss, Ziridis Schule, Athen, Griechenland (Note: ausgezeichnet)
Juni 2007	Doctor of Dental Surgery (DDS) Diplom (Zahnarzt), Zahnmedizinische Fakultät der Nationalen Kapodistrias Universität Athen, Griechenland (Note: sehr gut)
September 2012	Anerkennung zum Führen der Gebietsbezeichnung „Oralchirurgie“, Landeszahnärztekammer Hessen, Deutschland
März 2016	Medical Doctor (MD) Diplom (Arzt), Medizinische Fakultät der Nationalen Kapodistrias Universität Athen, Griechenland (Note: sehr gut)
Dezember 2021	MSc in „Medical Research Methodology”, Aristotle Universität, Thessaloniki, Griechenland

Berufserfahrung

Juli 2007 - Oktober 2008	Zahnärztin, Privatpraxis DDS Vassiliki Konsologlou, Athen, Griechenland

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April 2013 - März 2019	Fachzahnärztin für Oralchirurgie, Eurion Privatklinik, Frankfurt am Main, Deutschland
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11.1. Declaration of authenticity

I hereby declare that the thesis entitled “Qualitative and quantitative efficacy assessment of CT-imaging of liver lesions using Imeron 400 vs Imeron 300 in a randomized blinded study” which I have admitted to the Medical Faculty of the Johann Wolfgang Goethe University of Frankfurt at Main and which was supervised by Prof. Dr.med. Vogl and with the aid of Dr. med. Hammerstingl and Dr. med. Naguib (Institute of Diagnostic and Interventional Radiology of the Johann Wolfgang Goethe University, Frankfurt at the Main), was written, without any further help, by myself with the aid of the quoted material. Moreover, I declare that I have not used the help of a commercial promotion agency.

Hitherto, I have not submitted an application for admission to a doctorate at any university in Germany or abroad. The present work has not yet been submitted as a thesis.

Niedernhausen, 15.12.2021

(Place, Date) (Signature)

11.2. Schriftliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die dem Fachbereich Medizin der Johann Wolfgang Goethe-Universität Frankfurt am Main zur Promotionsprüfung eingereichte Dissertation mit dem Titel „Qualitative and quantitative efficacy assessment of CT-imaging of liver lesions using Imeron 400 vs Imeron 300 in a randomized blinded study“ im Institut für Diagnostische und Interventionelle Radiologie des Johann Wolfgang Goethe Universitätsklinikums Frankfurt am Main unter Betreuung und Anleitung von Herrn Prof. Dr. med. Vogl mit Unterstützung durch Frau Dr. med. Hammerstingl and Herrn Dr. med. Naguib ohne sonstige Hilfe selbst durchgeführt und bei der Abfassung der Arbeit keine anderen als die in der Dissertation angeführten Hilfsmittel benutzt habe. Darüber hinaus versichere ich, nicht die Hilfe einer kommerziellen Promotionsvermittlung in Anspruch genommen zu haben.

Ich habe bisher an keiner in- oder ausländischen Universität ein Gesuch um Zulassung zur Promotion eingereicht. Die vorliegende Arbeit wurde bisher nicht als Dissertation eingereicht.

Niedernhausen, 15.12.2021

(Ort, Datum) (Unterschrift)