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Efficacité et sécurité de la thermoablation percutanée du carcinome hépatocellulaire chez les patients porteurs de TIPS : une étude monocentrique rétrospective contrôlée

Antoine Dumoutier

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FACULTÉ DE MÉDECINE

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pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

D.E.S de Radiologie et d'Imagerie Médicale

par

Antoine DUMOUTIER

né le 24 août 1994 à Saint-Sébastien-sur-Loire

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**EFFICACITE ET SECURITE DE LA THERMOABLATION PERCUTANEE DU
CARCINOME HEPATOCELLULAIRE CHEZ LES PATIENTS PORTEURS DE TIPS :
UNE ETUDE MONOCENTRIQUE RETROSPECTIVE CONTROLEE**

Président : Monsieur le Professeur Éric FRAMPAS

Directeur de thèse : Monsieur le Docteur Aymeric NICOLAS

Membres du jury : Monsieur le Professeur Yann TOUCHEFEU

Monsieur le Docteur Arthur DAVID

Monsieur le Docteur Jérémie MEYER

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LIST OF ABBREVIATIONS

AAV2 : Adeno-Associated Virus 2
AFP : Alpha-Feto-Protein
Akt : Protein kinase B
ALAT : Alanine Aminotransferase
ALP : Alkaline Phosphatase
ASAT : Aspartate Aminotransferase
APOE : Apolipoprotein E
BCLC : Barcelona Clinic Liver Cancer
CD : Cluster of Differentiation
CI : Confidence Interval
CT : Computed Tomography
DAMP : Damage-Associated Molecular Patterns
DFS : Disease Free Survival
EASL : European Association for the Study of the Liver
EFNA1 : Ephrin A1
ENT : Ear, Nose, Throat
GGT : Gamma-glutamyltransferase
GI : Gastro-Intestinal
GST : Glutathione S-Transferase
HBV : Hepatitis B Virus
HCV : Hepatitis C Virus
HCC : Hepatocellular Carcinoma
HDL : High Density Lipoprotein
HSD_{17B13} : 17 β -Hydroxysteroid dehydrogenase type 13
HVPG : Hepatic Venous Pressure Gradient
IL : Interleukin
INR : International Normalized Ratio
IRE : Irreversible Electroporation
LDL : Low Density Lipoprotein

LIRADS : Liver Imaging Reporting And Data System
MELD : Model for End-Stage Liver Disease
MRI : Magnetic Resonance Imaging
NAFLD : Non-Alcoholic Fatty Liver Disease
NASH : Non-Alcoholic Steato-Hepatitis
NO : Nitric Oxyde
OECD : Organisation for Economic Co-operation and Development
OR : Odds Ratio
OS : Overall Survival
PACS : Picture Archiving and Communication System
PAMP : Pathogen-Associated Molecular Patterns
PAPm : Mean Pulmonary Artery Pressure
PDGF : Platelet-Derived Growth Factor
PEIT : Percutaneous Ethanol Injection Therapy
PI3K : Phosphoinositide 3-Kinase
PNPLA3 : Patatin-like phospholipase domain-containing protein 3
PRR : Pattern Recognition Receptor
PS : Performance Status
PT : Prothrombin Time
PTFE : Poly-Tetra-Fluoro-Ethylene
SIR : Society of Interventional Radiology
TACE : Trans-Arterial ChemoEmbolization
TARE : Trans-Arterial RadioEmbolization
TGF : Transforming Growth Factor
TIPS : Transjugular Intrahepatic Portosystemic Shunt
TNF : Tumor Necrosis Factor
TNM : Tumor Node Metastasis
US : UltraSound
VEGF : Vascular Endothelial Growth Factor
Wnt : Wingless and Int-1

PREAMBLE

I – Cirrhosis

I – 1. Epidemiology

Liver cirrhosis is a worldwide preoccupation and a heavy burden in both low-income countries and high-income countries. Mortality has been increasing in the last decades causing more than 1.3 million deaths in 2017¹. The Global Burden of Disease Study 2017 estimated over than 120 million prevalent cases of cirrhosis worldwide¹. Poynard and *a*² have estimated a prevalence of around 2.8% concerning advanced fibrosis in a general population aged 40 years or older in France.

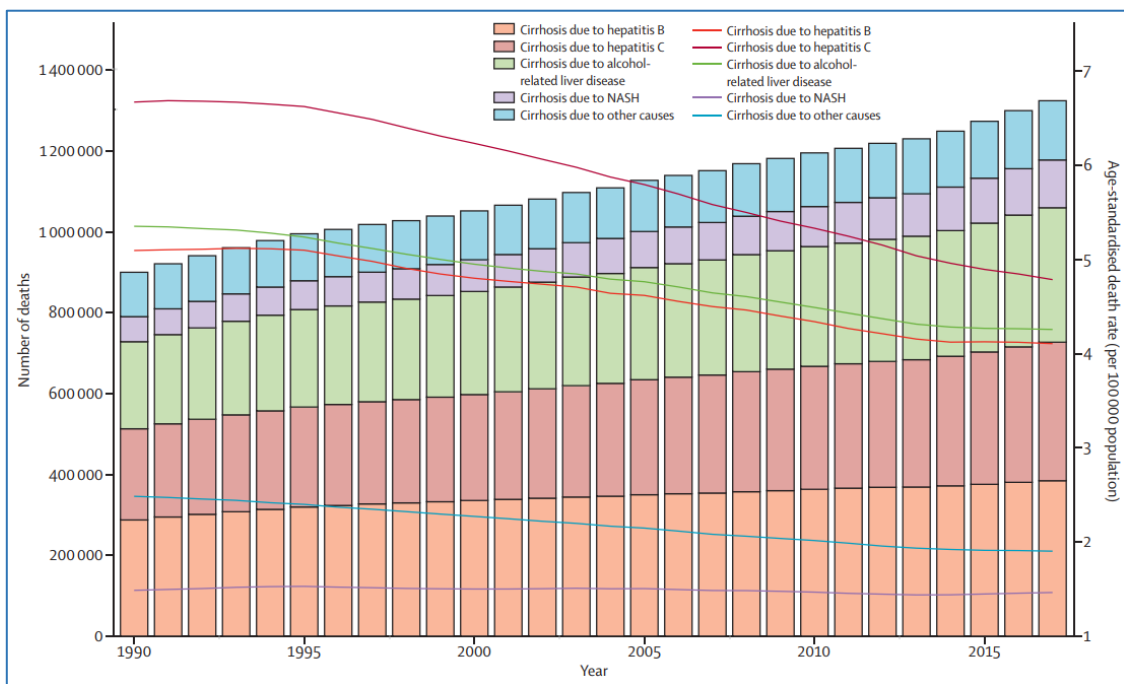


Figure 1 : Number of deaths and age-standardised death rates at the global level by cause of cirrhosis, 1990–2017

Bars refer to number of deaths in each year. Lines refer to age-standardised death rate in each year
From GBD 2017 Cirrhosis Collaborators¹

To our knowledge, there are very few medico-economic data on the impact of cirrhosis. Spanish authors encountered a difference of nearly 700 € per year of medical expense between an early fibrosis stage patient and an advanced fibrosis stage patient known for Non-Alcoholic Fatty Liver Disease (NAFLD)³. We also know that 7614 liver transplantations were performed in 2017 in Europe, more than half due to cirrhosis, and a liver transplantation

cost is estimated over 100 000 U\$ in OECD countries⁴ (only costs related to the liver transplantation and the initial hospital stay following transplantation).

In 2019 in France, 120 million euros were dedicated to beating addictions related to psychoactive substances, including 8.9 million in the fight against alcohol⁵. Alcohol misuse represents an annual medical cost of 8.6 billion euros and an estimated social cost of 120 billion euros in 2010⁶.

1 – 2. Etiologies

The etiologies of cirrhosis are extremely broad although dominated by 3 main causes : alcohol misuse, viral hepatitis, and Non-Alcoholic SteatoHepatitis (NASH).

Alcoholic cirrhosis is a complication that affects between 5 to 10% of patients with alcohol misuse (the risk increases substantially above 3 drinks per day), while patients with a metabolic syndrome have a risk of progression to cirrhosis of 1 to 2%. Very often these two risks co-exist and potentiate each other¹.

Viral hepatitis will be responsible for a chronic infection in 5 to 90% of cases depending on the age of the patient for hepatitis B, and in nearly 80% of cases of hepatitis C. Progression to cirrhosis occurs in up to 40% of untreated patients with hepatitis B and up to 20% with hepatitis C¹.

Other causes are based on genetic predisposition, such as hemochromatosis, which causes iron overload, particularly in the liver, and which can cause cirrhosis in 2 to 4% of cases; Wilson's disease, which causes copper overload; and alpha-1 antitrypsin deficiency. A small percentage of cirrhosis is also induced by dysimmune causes, such as autoimmune hepatitis, primary biliary cirrhosis or sclerosing cholangitis.

However, the risk of progression to cirrhosis differs in each individual and genetic factors could influence the hepatic response to these various aggressions. Indeed, several single-nucleotide polymorphisms have been identified⁷, the I148M variant of PNPLA3 has the largest effect, increasing the risk of non-alcoholic fatty liver disease, NASH, alcoholic cirrhosis, and hepatocellular carcinoma by two to three times^{8,9}. Few variants, for example in the HSD17B13 gene, EFNA1 gene or APOE gene seem to be protective against cirrhosis^{7,10}.

In Western Europe, almost 48% of male patients who died from cirrhosis were affected by alcohol intoxication¹, while 21% were related to a hepatitis C viral infection, 9% to a hepatitis B viral infection and 12% to NASH (This data is expected to increase as NAFLD is now considered the principal liver disease¹¹). Almost 15% of cirrhotic patients died from another cause of liver disease.

These percentages are very heterogeneous at an international level : according to global data, hepatitis B and C as well as alcohol are each responsible for about 25% of death due to cirrhosis, while in West Africa hepatitis B accounts for nearly 50% of cases and in East Asia hepatitis C is responsible for over 40% of cases¹.

1 – 3. Physiopathology

The different etiologies responsible for cirrhosis generate hepatic aggression, both parenchymal and vascular, resulting in inflammatory phenomena. This inflammation is at the origin of hepatocyte destruction but also the remodelling of sinusoidal vascularisation associating defenestration or capillarization¹²⁻¹⁴, which leads to hypoxaemia and then fibrogenesis¹⁵ and vasoconstriction¹⁶⁻¹⁸.

Hepatocyte destruction is one of the factors responsible for hepatocellular insufficiency, which is clinically expressed, for example, by hepatic encephalopathy. The various elements of sinusoidal remodelling are responsible for an increase in vascular resistance within the portal network, which is called portal hypertension. This leads to angiogenesis which allows the opening of intrahepatic but also extrahepatic porto-systemic shunts.

Once the cirrhosis stage is reached, several elements such as chronic inflammation, immunosuppression and a modification of gut microbiota¹⁹ conducive to bacterial translocations will reinforce the above-mentioned phenomena by promoting splanchnic vasodilatation.

1 – 3.a. Hepatic sinusoid

The liver sinusoid is a vascular structure that can be considered as the hepatic capillary. Nevertheless, it has many differences from a "classical" capillary. The liver sinusoid is a vascular bed where the portal flow and the hepatic arterial flow meet. It is bordered by a barrier comprising an endothelium which is made up of sinusoidal endothelial cells which have the particularity of being riddled with "cytoplasmic holes" allowing exchanges with the hepatocytes. This is what confers the hepatic sinusoid the property of a fenestrated/discontinuous capillary. This barrier is also made up of Kupffer cells, which adhere to the endothelium within the sinusoidal lumen. Below this endothelium there is a space called the space of Disse which separates the endothelium and the hepatocytes. Within the space of Disse are star cells also called Ito cells.

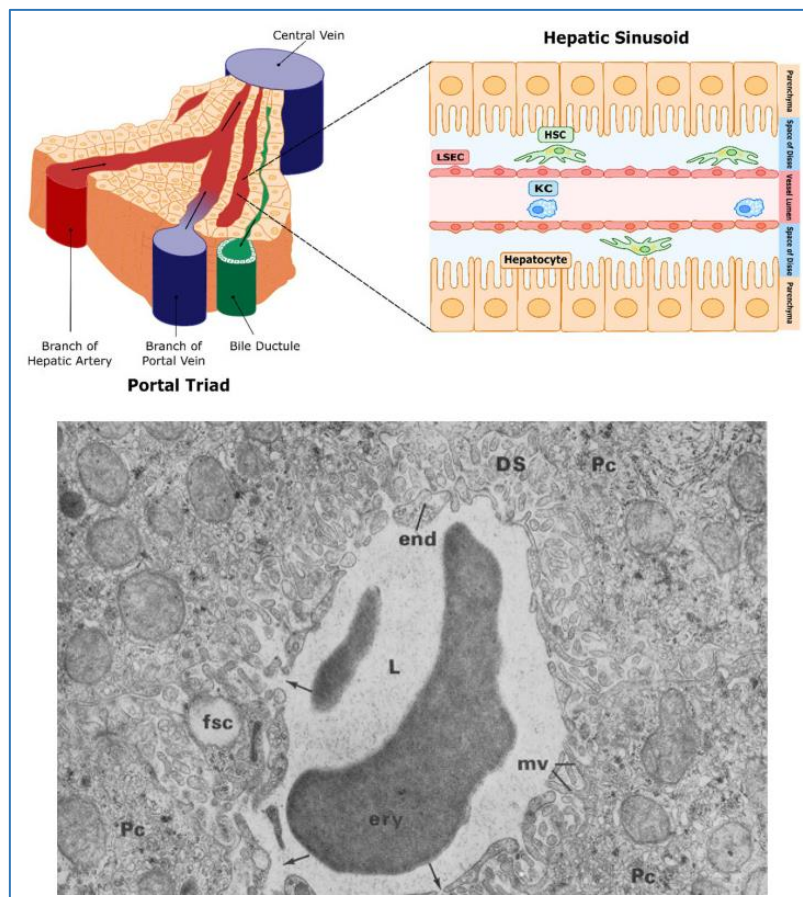


Figure 2 (top) : Representation of an hepatic acinus (left) and an hepatic sinusoid (right), from Gibert-Ramos and al²⁰

HSC : Hepatic stellate cell; LSEC : Liver sinusoidal endothelial cell; KC : Kupffer cell

Figure 3 (bottom) : Electron microscopic study of an hepatic sinusoid (x16 000), from Wisse and al¹⁴

L : Sinusoid lumen; ery : Erythrocyte; end : Liver sinusoidal endothelial cell; mv : Microvilli from hepatocyte ; DS : Space of Disse; Pc : Parenchymal cell (hepatocyte)

Sinusoidal endothelial cell

Sinusoidal endothelial cells contain pores or windows measuring approximately 100 nm and occupying 20% of the cell surface, these pores are not randomly arranged on the cell surface but grouped together in the form of “sieve plates”¹⁴.

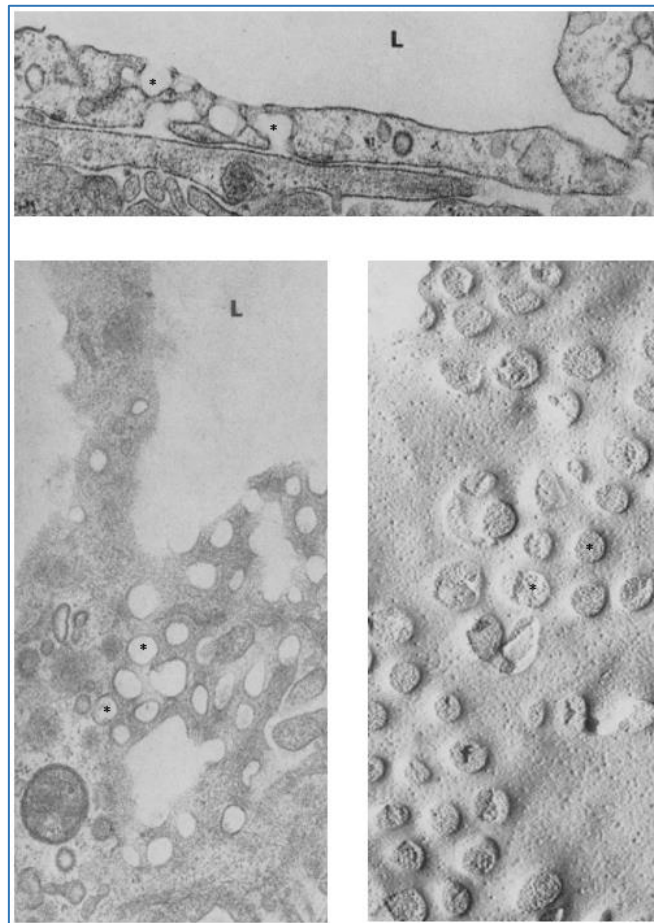


Figure 4 (top) : Electron microscopic study of an hepatic sinusoid (x37 000), longitudinal view of pores(*) and sieve plates on an hepatic endothelial cell

Figure 5 (bottom left) : Electron microscopic study of an hepatic sinusoid (x40 000), transversal view of pores(*) and sieve plates on an hepatic endothelial cell

Figure 6 (bottom right) : Electron microscopic study of an hepatic sinusoid (x41 500), transversal view of pores(*) and sieve plates on an hepatic endothelial cell
From Wisse and al¹⁴

These cells have multiple roles, the first being the patency of certain molecules allowed by the fenestration and the absence of a basement membrane. This includes lipid clearance and that of molecules such as chylomicrons, HDL or LDL, or thus many nanoparticles and metabolites²¹⁻²³.

It also has an immune role through its participation in viral and antigenic clearance as well as that of certain immunoglobulins such as IgG^{24,25}. This immune valence is also reflected in the expression of PRR (Pattern Recognition Receptor) allowing the recognition of PAMP (pathogen-associated molecular patterns) and DAMP (damage-associated molecular patterns) and thus the initiation of mechanisms related to innate immunity. Endothelial cells also play a key role in adaptive immunity by acting as antigen-presenting cells or by participating in the activation of CD4⁺ and CD8⁺ T cells^{26,27}.

Kupffer cell

Kupffer cells adhere to endothelial cells on their endoluminal side and are part of the macrophages whose main role is to phagocytose foreign debris and particles from the portal system as they pass through the liver. They assist endothelial cells in their role of lipid, protein and nanoparticle clearance. They are also involved in the phagocytosis of apoptotic cells in the circulation such as erythrocytes. These cells naturally play an anti-inflammatory role by filtering the passage of immunoreactive substances from the gastrointestinal tract but also by producing anti-inflammatory molecules such as IL-10²⁸.

Hepatic stellate cell

Hepatic stellate cells, also known as Ito cells, are located in the space of Disse. Their basal function is not well understood, but it seems that they play a role of antigen presenting cells. Their role in the pathophysiology of hepatic fibrosis is much better identified as they are one of the key elements²⁹.

Hepatocyte

Hepatocytes are the main hepatic parenchymal cells, accounting for about 80% of liver mass. They are cubic cells of about 30µm on a basal side and have multiple villi to increase their exchange surface.

They have a central role in the production and storage of certain proteins, including albumin, fibrinogen and certain coagulation factors. They metabolise numerous lipid or carbohydrate structures from the portal network to produce cholesterol, fatty acids and bile salts. Finally, hepatocytes have a fundamental role in the metabolism and detoxification of

certain exogenous molecules such as drugs, but also of many endogenous molecules such as steroids or the transformation of ammonia into urea prior to its elimination.

1 – 3.b. Cellular remodelling

Sinusoidal endothelial cell

The changes associated with liver disease, particularly cirrhosis, result in a reduction in cytoplasmic pores, which is referred to as defenestration or capillarisation. In addition, patients with cirrhosis develop a subendothelial basement membrane³⁰. During aggression, endothelial cells are also capable of secreting a pro-fibrosing substance, IL-33, which initiates the activation of star cells³¹. These phenomena lead to impaired substrate exchange and are considered major contributing factors for hepatic dysfunction in liver cirrhosis³².

Kupffer cell

Kupffer cells can be stimulated by many phenomena, such as alcohol, liver infections or high-fat diets which polarize phenotype Kupffer cell production from M2-cells (anti-inflammation) to M1-cells (pro-inflammation). This results in the production of substances such as TGF- β , TNF- α or Fas ligand that will attack hepatocytes, initiate star cell activation and promote an overall inflammatory atmosphere conducive to fibrinogenesis³³⁻³⁵.

Hepatic stellate cell

Under the action of multiple substances, such as TGF- β , TNF- α , IL-1 or PDGF, stellate cells will go from a quiescent state to an activated state which is characterised by cell proliferation, a transformation into myofibroblasts and the production of collagen and other extra-cellular matrix building blocks³⁶.

Hepatocyte

Hepatocytes are the target of multiple hepatotoxic agents which, regardless of their origin, will promote hepatocyte apoptosis and trigger cell regeneration phenomena. Hepatocytes undergoing damage will be at the origin of the synthesis and release of oxidative and pro-fibrosing substances participating in the activation of star cells³⁷.

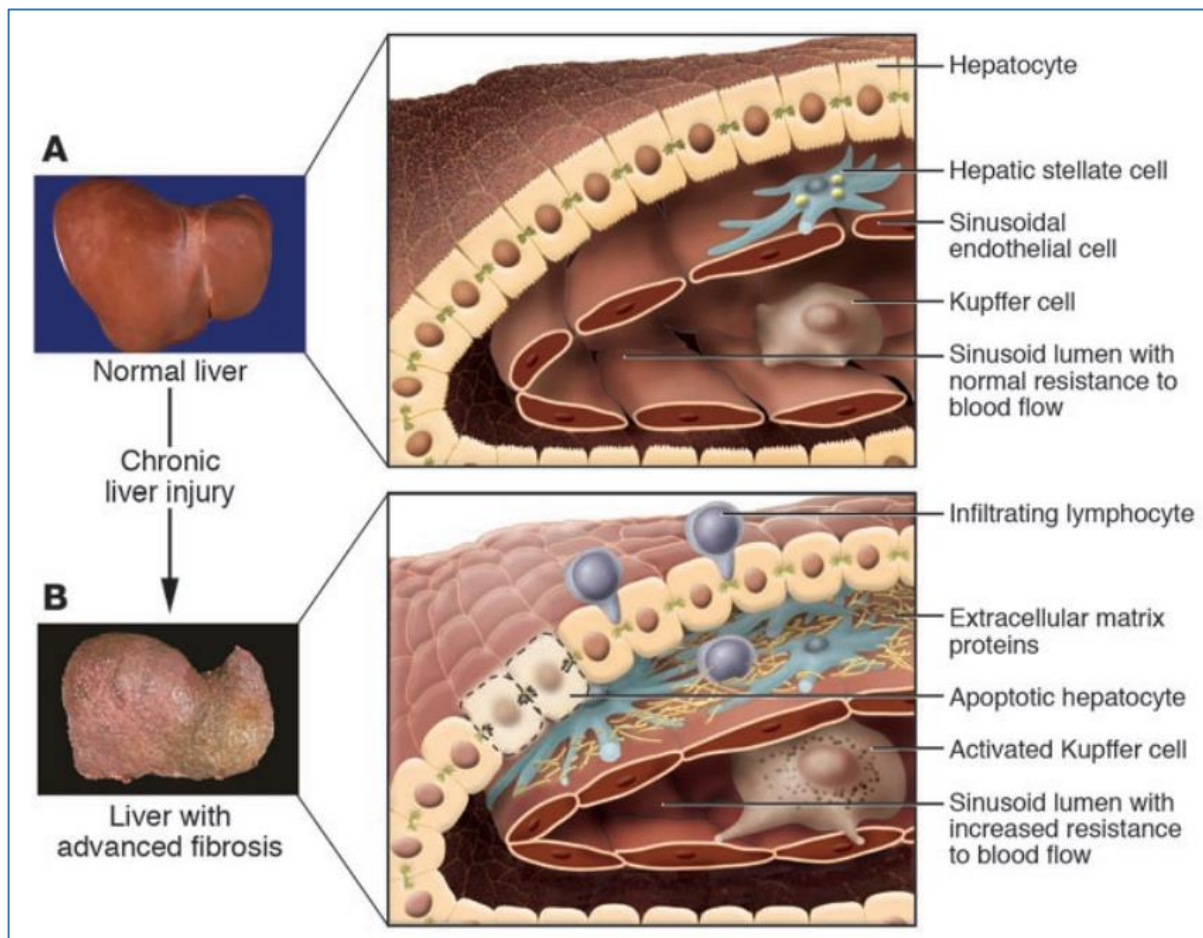


Figure 7 : Modification in an hepatic sinusoid architecture in a liver with fibrosis, from Brenner and al³⁸

I – 4. Hepatic insufficiency

Hepato-cellular insufficiency is a set of symptoms reflecting the failure of hepatocytes, which may be haematological, neuro-psychological, mucocutaneous or endocrine.

I – 4.a. Haematological manifestations

Clinically they are not always noticeable but can be expressed for example, by ecchymosis, haematomas or epistaxis. They are most often part of a context of a lowered prothrombin level, itself secondary to the decrease in the concentration of coagulation factors, primarily factor V which is the only non-vitamin K-dependent factor of the extrinsic path.

[1 – 4.b. Neuropsychological manifestations](#)

The most represented neuro-psychological disorder is hepatic encephalopathy, secondary to the accumulation of neurotoxic substances insufficiently metabolised by the hepatocytes. It is distinguished in 4 clinical stages, ranging from flapping tremor to coma, passing through stages of confusion.

[1 – 4.c. Mucocutaneous manifestations](#)

Stellate angiomas with a thoracic tropism are common. The extremities are also affected, with palmar erythrosis and onychonychia being described. These symptoms may also be associated with foetor hepaticus and mucocutaneous jaundice.

[1 – 4.d. Endocrine Manifestations](#)

Cirrhosis causes disorders in the metabolism of steroidal molecules, resulting in changes in secondary sexual characteristics : gynecomastia, hypogonadism, and depilation in men; breast atrophy and secondary amenorrhea in women.

[1 – 5. Portal hypertension](#)

A portal venous system is considered to be the accumulation of blood from one capillary system to a second capillary system, through the veins, without passing through the heart.

The largest in the human body is the portal-hepatic system, which is often referred to as the portal system, although it is not the only one. The portal venous system is responsible for carrying much of the blood from the gastrointestinal tract (from stomach to upper third of the rectum) to the liver. It is also responsible for splenic, pancreatic, vesicular and mesenteric fat venous drainage. Anatomically, the portal vein consists in the confluence of the superior mesenteric vein and the spleno-mesenteric confluence, which corresponds to the union of the inferior mesenteric vein and the splenic vein. Other smaller veins join these venous confluences, such as the right and left gastric veins, the para-umbilical vein and the cystic vein.

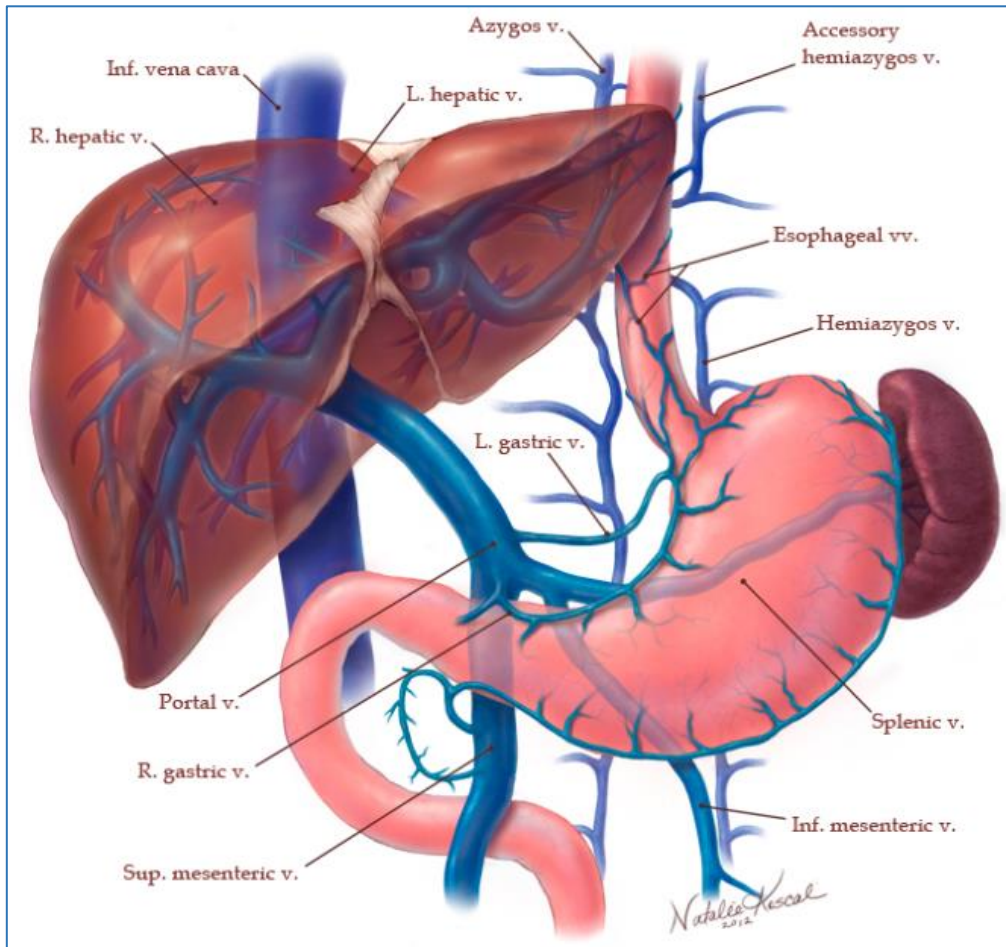


Figure 8 : Portal anatomy, from medicalart.johnshopkins.edu, by Natalie Koscal

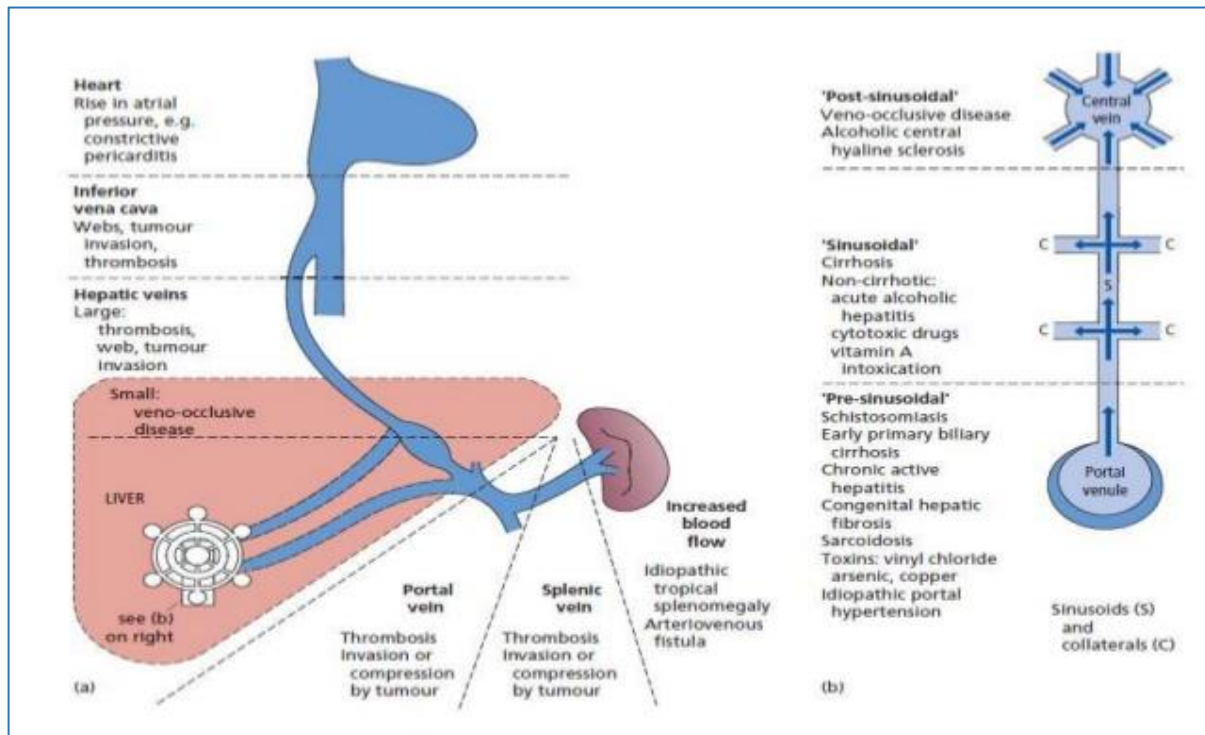
Portal hypertension results in an increase in the pressure gradient between the inferior vena cava and the portal vein, which is known as the porto-systemic pressure gradient. This gradient is normally between 1 and 5 mmHg. The clinical repercussions of portal hypertension can be expressed over 12 mmHg³⁹.

1– 5.a. Etiologies

The causes of portal hypertension can be divided into 3 groups :

- Suprahepatic block : This is most often due to the occlusion of the suprahepatic veins, often as a result of thrombosis, known as the Budd-Chiari syndrome. Portal hypertension secondary to stenosis/occlusion of the superior vena cava, right heart disease or constrictive pericardial damage may also be present;

- Infrahepatic block : This is most often due to thrombosis or compression of the portal vein;
- Intrahepatic block : Within intrahepatic blocks, the most frequent cause by far is cirrhosis with sinusoidal involvement. However, there are pre-sinusoidal (bilharzia, granulomatosis, primary biliary cirrhosis, idiopathic portal hypertension) and post-sinusoidal (veno-occlusive disease) disorders;



*Figure 9 : Etiologies of portal hypertension, from humanbodyanddiseases.com
(a) Suprahepatic and Infrahepatic etiologies
(b) Intrahepatic etiologies*

1 – 5.b. Physiopathology

For a long time, the mechanism of portal hypertension in cirrhosis was explained by an increase in portal pressure secondary to hepatic fibrosis and regenerative nodules. However, this increase in pressure now appears to be multi-factorial, combining fibrosis remodelling, contraction of activated hepatic star cells⁴⁰ and endothelial dysregulation with changes in the secretion of vasoactive substances (decrease in the vasodilator substance NO and increase in vasoconstrictor substances such as endothelin, thromboxane and VEGF)^{18,41}.

Portal hypertension is also involved in the vasodilatation of the splanchnic network, resulting in increased portal flow. Variations of systemic flow in cirrhosis is still debated, first theories claimed that cirrhosis was associated with peripheral vasodilatation and a hyperdynamic circulation^{42,43}. Nonetheless, decreased blood flow has been demonstrated in the peripheral limbs, renal and cerebral macrovasculature of patients with liver disease^{44,45}. Newby and Hayes propose a contrary theory according to which splanchnic vasodilatation would be responsible for "arterial steal" and porto-systemic shunts would be responsible for "venous steal". The whole would generate the activation of peripheral vaso-constrictive phenomena such as the renin-angiotensin-aldosterone system, notably responsible for tissue hypoperfusion⁴⁶, which can lead to failure, as seen in the hepato-renal syndrome. It will also result to hydro-sodium retention.

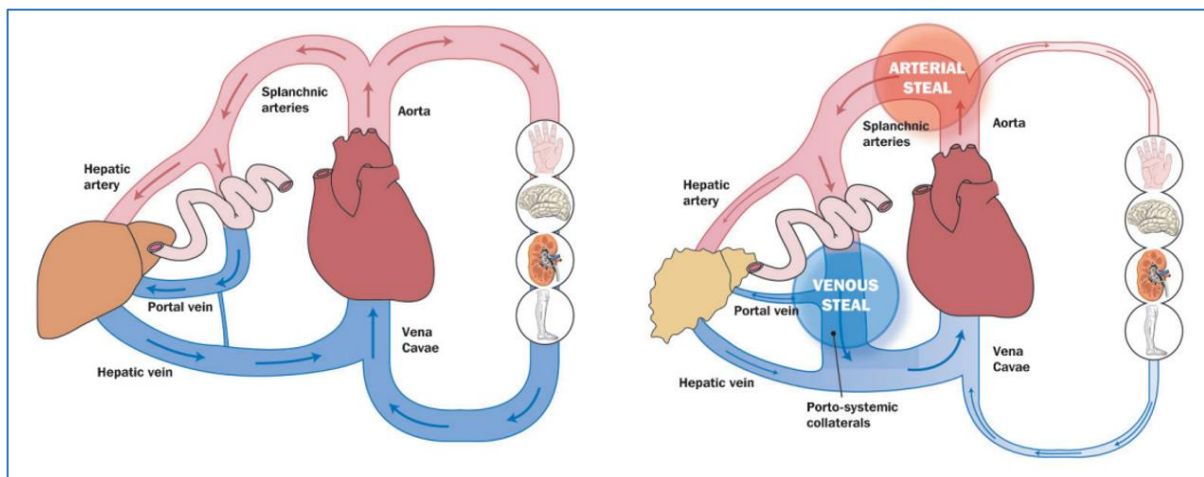


Figure 10 : Representation of splanchnic steal phenomena according to Newby and Hayes theory, with normal circulation (on the left) and steal phenomena in patients with cirrhosis and portal hypertension (on the right), from Newby and al⁴⁶

1 – 5.c. Symptoms and complications

One of the main symptoms is ascites, which is intraperitoneal transudate that can result in an increase in abdominal circumference.

One of the main consequences of portal hypertension is also the appearance of porto-systemic venous shunts, due to the hyperpressure but also to the secretion of substances such as VEGF allowing angiogenesis³⁹. Clinically this can be seen in the form of subcutaneous shunts, or endoscopically by oesophageal varices.

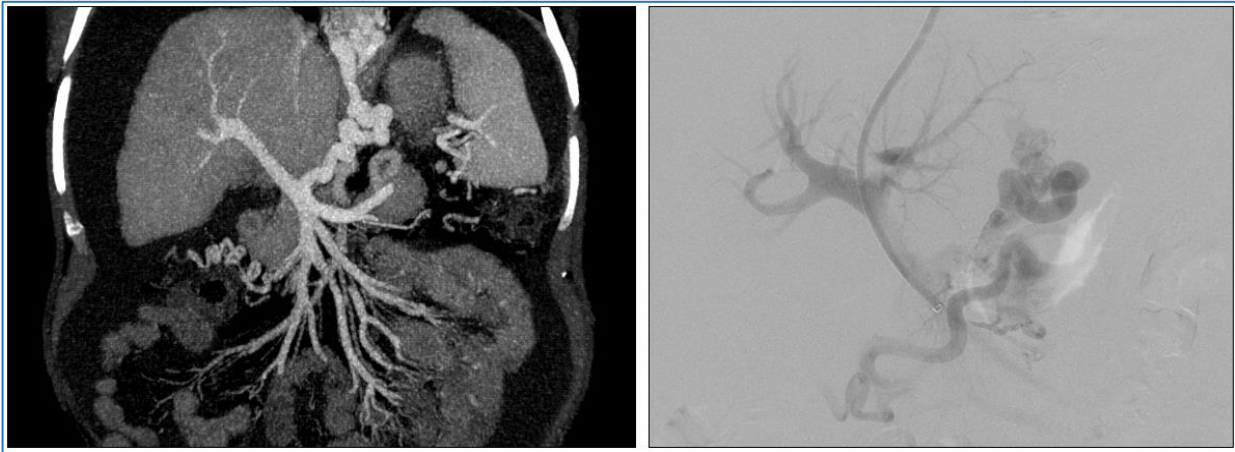


Figure 11 : Portal hypertension : Porto-systemic venous shunts via gastric and oesophageal varices seen in CT (left) and portography (right).

Venous congestion is also responsible for an increase in splenic volume, regularly resulting in splenomegaly. The latter may be the cause of cell and platelet consumption, known as hypersplenism, which can lead to anaemia and/or thrombocytopenia.



Figure 12 : Portal hypertension : Pre-TIPS scan of one of the patients in our cohort showing right hydrothorax (arrowhead), diffuse ascites (asterisks) and splenomegaly (arrow).

The complications can be just as diverse :

- Thrombotic, primarily involving the portal trunk, it is favoured by a disequilibrium of Virchow's triad with venous stasis and potential endothelial damage.
- Haemorrhagic, in most cases related to ruptures of oesophageal varices.
- Neuro-psychological, in addition to hepatocellular insufficiency, porto-systemic shunts contribute to the increase in ammoniaemia.
- Finally, nephrological, since the activation of the renin-angiotensin-aldosterone system contributes to water retention and hyponatremia. But above all, when the adaptive mechanisms are exceeded, renal arterial and arteriolar vasoconstriction can lead to failure and hepato-renal syndrome.

Management of these complications includes preventive and active therapies such as β -blockers, diuretics, lactulose, embolisation or ligation of oesophageal varices, TIPS.

II - Hepatocellular carcinoma

II – 1. Epidemiology

According to the 2020 GLOBOCAN report, liver cancer is the 7th most common cancer in terms of incidence and the 2th most common in terms of mortality, causing around 830,000 deaths annually⁴⁷. Hepatocellular carcinoma (HCC) accounts for approximately 90% of primary liver cancers⁴⁸.

The main risk factors for HCC are well-defined, with cirrhosis as the main risk factor, but also alcohol abuse, viral infections such as HBV, HCV⁴⁹ or adeno-associated virus 2 (AAV2)⁵⁰, metabolic syndrome, smoking and inhalation of aflatoxin B1 (a fungal carcinogen). The risk of developing HCC at 5 years in a cirrhotic patient varies from 4 to 30% depending on the etiology of the cirrhosis⁵¹.

Many articles dealing with the subject show that adult patients with HCC are almost exclusively sporadic, with the presence of at least one non-genetic risk factor for HCC, such as alcohol abuse or chronic infection with HCV or HCV. Nevertheless, some susceptibility genes for encoding glutathione S-transferases (GSTs) such as GSTM1 and GSTT1 may be over-represented in patients with HCC⁵².

II – 2. Carcinogenesis

Several mechanisms affecting carcinogenesis in HCC are suspected :

Carcinogenesis seems to be induced by changes in the microenvironment. Indeed, the activation of hepatic star cells leads to the production of pro-inflammatory and oxidative molecules that can alter hepatocyte proliferation and promote tumour formation.

The cirrhotic state is therefore responsible for a decrease in the proliferation capacity of hepatocytes, and certain studies in animals show that the molecules responsible for the decrease in proliferation accelerate carcinogenesis^{53,54}. Indeed, the molecule p21 is overexpressed in cirrhotic patients and interferes with p53 inducing cell cycle arrest and senescence in response to telomere shortening^{53,55}.

Telomere shortening limits the capacity of cell proliferation and regeneration resulting in the presence of multiple senescent hepatocytes. When telomeres reach a limit in length, chromosomal damage can therefore be the cause of senescence but also cell cycle arrest and apoptosis^{53,56,57}.

Finally, there are also hypotheses based on changes in the macro-environment, according to which the liver mass must match the available space in the abdomen. Thus, the loss of liver mass observed in cirrhosis should be compensated for and would be associated with the secretion of growth factors that could promote carcinogenesis⁵³.

These modifications are involved in both the activation and the removal in inhibition of carcinogenic pathways such as Wnt/ β -catenin or PI3K/Akt^{53,58}.

II – 3. Screening

The diagnosis of HCC can be made in three ways. Firstly, by an incidental finding on imaging performed in another indication; secondly in a symptomatic context (abdominal pain, altered general condition, deterioration in liver function); and thirdly, more frequently as part of regular surveillance in patients with cirrhosis or chronic HBV infection.

Indeed, several studies have demonstrated survival benefit in association with HCC surveillance, early detection, and the possibility of curative treatment. One of the most significant studies is a Chinese study of more than 18,000 patients which found a 37% reduction in mortality in a population receiving regular imaging follow-up^{59,60}.

Thus, after analysis of several studies regarding the benefit for the patient but also the annual cost of examinations, the recommendations have agreed on ultrasound imaging monitoring of cirrhotic patients⁶¹. Regarding the frequency of monitoring, it has been clearly demonstrated that there is a gain in survival when monitoring is performed every 6 months compared to annual monitoring, whereas monitoring every 3 months does not show any impact on survival.

However, these recommendations are regularly challenged by new data in the literature, in particular the relevance of sonography monitoring whose sensitivity, in addition to being operator-dependent, is very much reduced in obese and poorly echogenic patients who are over-represented in NASH patients. Thus, although it seems clear that cross-sectional

imaging techniques such as CT or MRI outperform sonography in terms of sensitivity^{62,63}, their inclusion in recommendations is tempered by their accessibility, exposure to ionising radiation and the injection of a contrast agent as well as by certain medico-economic studies.

Today the European recommendations are therefore : biannual US-imaging monitoring, for cirrhotic patients, non-cirrhotic HBV patients at intermediate or high risk of HCC²⁶ and non-cirrhotic F3 patients.

One of the major areas of research concerns the improvement of screening using blood biomarkers. Currently, the measurement of a marker called alpha-feto-protein has become a frequent practice. Indeed, in association with ultrasound screening, it would increase diagnostic performance between 6 and 18%⁶⁴. However, it is also associated with an increase in false positives and an 80% increase in the economic cost of HCC diagnosis⁶⁵, which thus makes it impossible to establish recommendations for AFP analysis in all patients according to the EASL.

Johnson and *al*⁶⁶ proposed the development of a new score called GALAD composed of 5 factors : gender (G), age (A), AFP-L3 (L), AFP (A) and des-gamma-carboxy prothrombin (D), which, according to their statistics, allows the detection of early HCC with a sensitivity of 86% and specificity of 89%. Several studies confirm this high diagnostic performance which could allow a more important place for these biological markers in HCC screening as a replacement or complement to current radiological strategies⁶⁷⁻⁶⁹. Nonetheless, at present, none of these tests can be recommended for surveillance of patients at risk of developing de novo HCC⁷⁰.

II – 4. Diagnosis

The role of imaging in the diagnosis of HCC has been central since the early 2000s when the non-invasive diagnosis of HCC was accepted in response to a well-defined and typical diagnostic pattern^{71,72}. This non-invasive diagnosis is validated exclusively in cirrhotic patients based on a higher pre-test probability of developing HCC than in the general population but also on histological and pathophysiological data regarding hepatic vascular and tumour changes^{73,74}.

Non-invasive diagnosis of HCC now requires injected imaging, which, regardless of the modality, generally finds the same pattern, *i.e.* a hypervascular nodule at the late arterial time (wash-in), followed by wash-out at the portal or late time (EASL criteria).

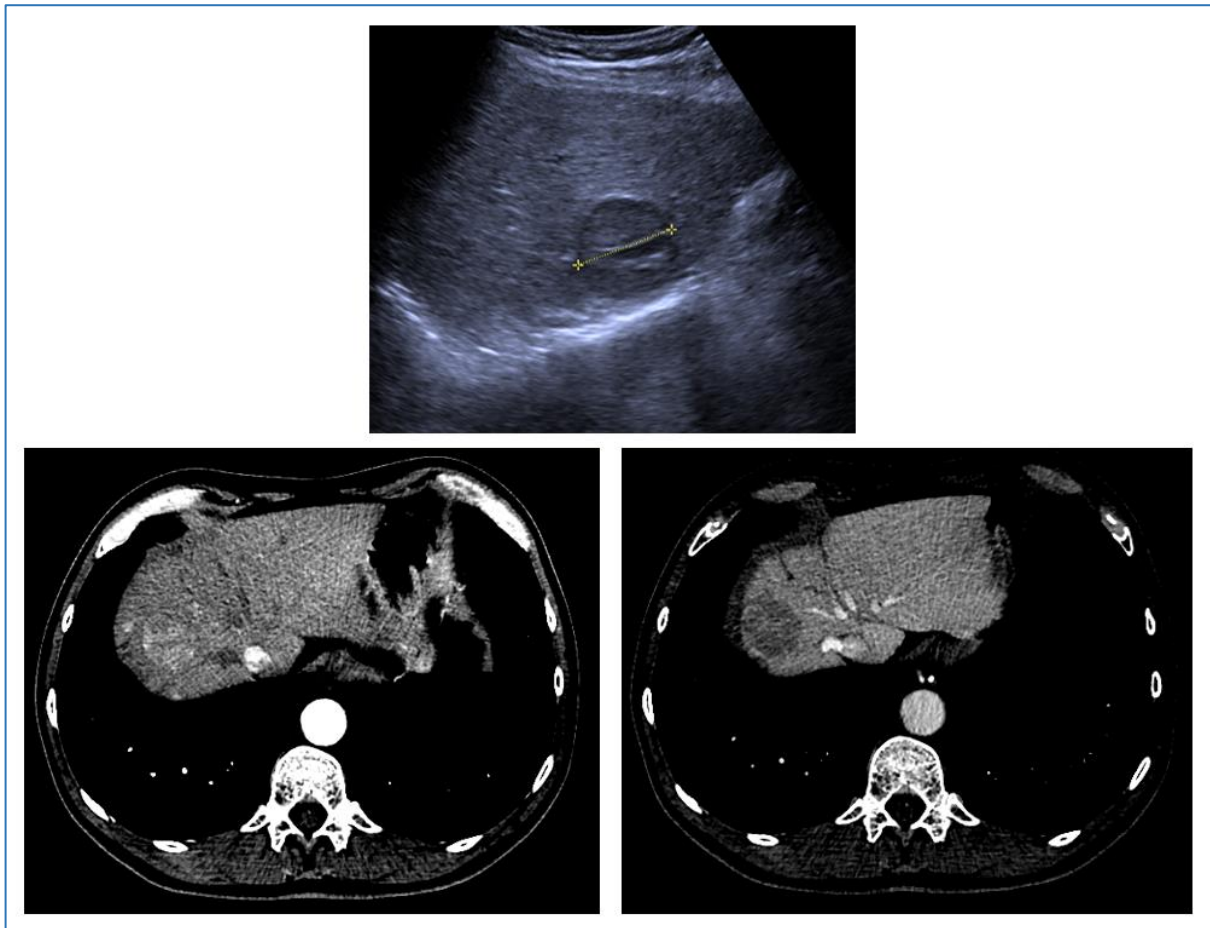


Figure 13 : 66-year-old patient known for alcoholic cirrhosis: Discovery of a hypoechoic nodule >10mm during ultrasound surveillance (top) which justified a multiphase CT scan showing a hypervascular liver nodule in arterial time (bottom left), with a washout in portal time (bottom right) This nodule is highly suspicious of HCC.

Although CT has a natural place in the diagnosis, this is considered even more so for MRI which has a slightly higher sensitivity⁷⁵, while providing additional semiological elements in favour of HCC (T2 hypersignal, Diffusion hypersignal). In addition, MRI allows the use of hepatobiliary contrast products which provide additional diagnostic elements in the hepatobiliary phase where HCC nodules are supposed to appear in hyposignal. Several studies report better sensitivity of the latter compared to conventional contrast agents^{76,77}. Nevertheless, some of these contrast agents appear to be associated with respiratory motion artefacts during the arterial phase resulting in degraded image quality⁷⁸.

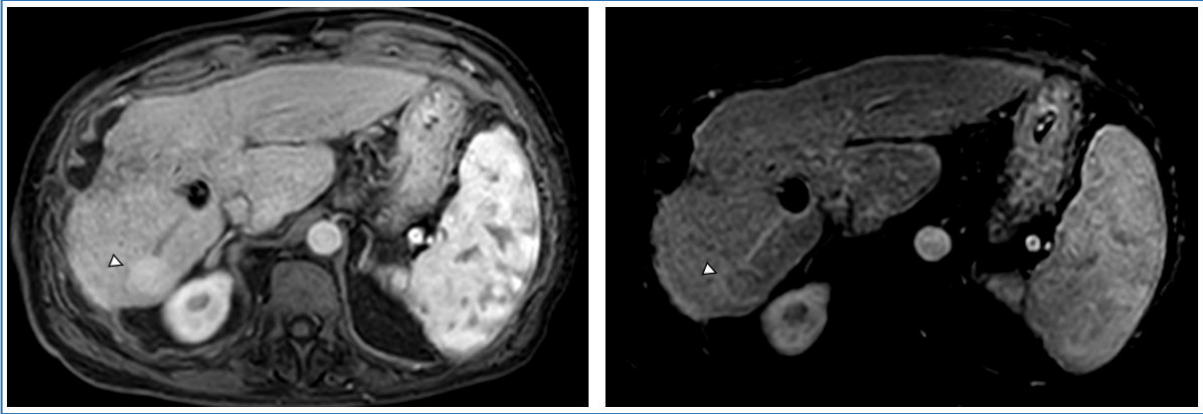


Figure 14 : 68-year-old patient followed for alcoholic and dysmetabolic cirrhosis: MRI discovery of a hypervascular liver nodule (arrowhead) at arterial time (left) with washout at portal time and capsular enhancement (right)

While the place of morphological cross-sectional imaging is well codified, that of contrast sonography is still under debate. Indeed, the EASL has long tempered its use due to increased diagnostic confusion between HCC and cholangiocarcinoma than that with cross-sectional imaging. However, more recent studies have established diagnostic criteria appropriated to the modality, namely a later and more moderate washout in HCC than in cholangiocarcinoma^{79,80}. Thus, while the EASL includes it in its diagnostic algorithm as a second-line modality, several national scientific societies adopt this modality in their algorithms at the same level as cross-sectional imaging (with regard to characterisation and not detection).

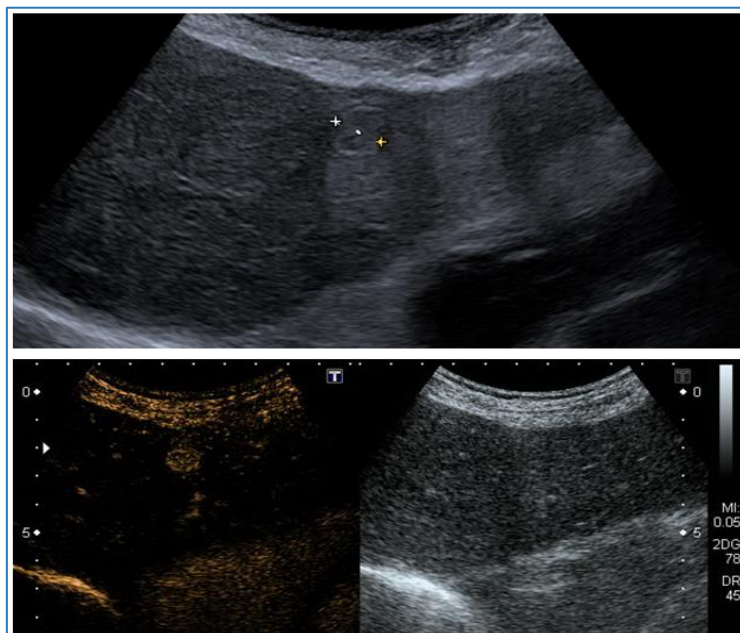


Figure 15 : A 63 year old patient with viral cirrhosis, whose ultrasound revealed a hypoechoic nodule >10mm (top). In the absence of a contributory result on cross-sectional imaging, a contrast ultrasound was performed and found a hypervascular nodule (bottom) without typical washout. Biopsy will provide histological evidence of HCC.

Of course, histopathological diagnosis remains important in the diagnosis of HCC, especially in non-cirrhotic patients but also in cases of non-typical HCC features on imaging⁷⁰.

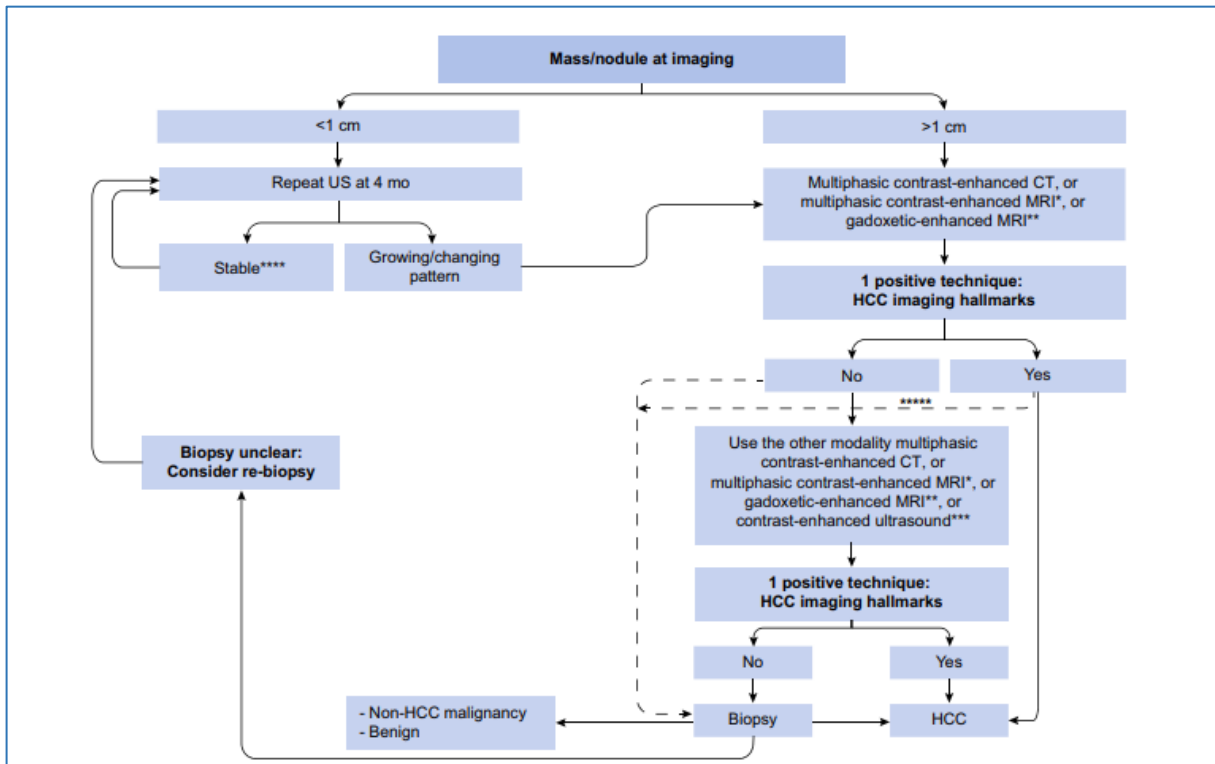


Figure 16 : Diagnostic algorithm for HCC in cirrhotic liver referring to EASL 2018 recommendations, from EASL Clinical Practice Guidelines⁷⁰

This algorithm is based on EASL criteria (wash-int/wash-out), however a different classification, entitled LI-RADS, is increasingly found in current practice. This classification also uses the hypervascularisation criterion and the (non-peripheral) wash-out criterion in addition to three other diagnostic criteria, namely the size of the nodule, the presence of capsular enhancement and growth above a progression threshold. These criteria are not recognised by the EASL, which therefore does not recognise the use of the LI-RADS classification whilst defining recommendations⁸¹. The LI-RADS classification also includes ancillary criteria, some of which are malignant (nodule-in-nodule appearance, mosaic appearance, moderate T2 hypersignal), and others benign (intense T2 hypersignal, stability in size at 2 years); these criteria may weight the classification of a nodule favourably or unfavourably. Thus, we obtain a LI-RADS classification ranging from LR-1 (definite benignity) to LR-5 (definite HCC). In addition to these differences in classification, there are also differences of opinion regarding the need for treatment or monitoring. Thus, according to the EASL only typical HCC nodules are eligible for immediate treatment, otherwise histological evidence is required.

CT/MRI Diagnostic Table						
Arterial phase hyperenhancement (APHE)		No APHE		Nonrim APHE		
Observation size (mm)		< 20	≥ 20	< 10	10-19	≥ 20
Count additional major features: • Enhancing "capsule" • Nonperipheral "washout" • Threshold growth	None	LR-3	LR-3	LR-3	LR-3	LR-4
	One	LR-3	LR-4	LR-4	LR-4 LR-5	LR-5
	≥ Two	LR-4	LR-4	LR-4	LR-5	LR-5

LR-4 / **LR-5** Observations in this cell are categorized based on one additional major feature:
 • LR-4 – if enhancing "capsule"
 • LR-5 – if nonperipheral "washout" OR threshold growth

Ancillary features favoring malignancy	Ancillary features favoring benignity
Favoring malignancy in general, not HCC in particular <ul style="list-style-type: none"> • US visibility as discrete nodule • Subthreshold growth • Restricted diffusion • Mild-moderate T2 hyperintensity • Corona enhancement • Fat sparing in solid mass • Iron sparing in solid mass • Transitional phase hypointensity • Hepatobiliary phase hypointensity 	<ul style="list-style-type: none"> • Size stability > 2 yrs • Size reduction • Parallels blood pool • Undistorted vessels • Iron in mass, more than liver • Marked T2 hyperintensity • Hepatobiliary phase isointensity

Favoring HCC in particular

- Nonenhancing "capsule"
- Nodule-in-nodule
- Mosaic architecture
- Blood products in mass
- Fat in mass, more than adjacent liver

Figure 17 : Li-Rads classification (2018), using major and ancillary criteria to classify nodule from LR-1 to LR-5, from ACR Li-Rads V2018 core.

According to LI-RADS, a multidisciplinary discussion in a treatment perspective is suggested for nodules classified as LI-RADS 5, but also for LR-4 nodules (probable HCC) for which biopsy is optional.

For LR-3 nodules (intermediate probability of malignancy), LI-RADS recommends repeat imaging between 3 and 6 months, whereas for nodules >1cm the EASL considers biopsy.

II – 5. Treatment

The different treatments for HCC depend on a prior staging of the disease, where the extent of the HCC, the liver function and the general condition of the patient all impact on the patient's survival.

Unlike most solid tumours, the TNM classification is not used in current practice, particularly as it is defined by the presence or absence of microvascular invasion, which can only be assessed in the event of surgical resection of the tumour⁷⁰.

From these different criteria derives the BCLC (Barcelona Clinic Liver Cancer) classification⁸², updated in 2022⁸³, which is intended as an aid to therapeutic decision-making. A distinction is therefore made between :

- Very early stage (BCLC 0) : This is a single HCC, 20 mm or less, without macrovascular invasion, without extrahepatic extension, with preserved liver function and PS-0.

These patients are eligible for curative treatment : if the patient is not eligible for liver transplantation, ablation will be offered; if eligible, surgical resection or transplantation will be offered.

- Early stage (BCLC A) : This is a single HCC of any size, or up to 3 HCC nodules with none larger than 3cm, with no macrovascular invasion, no extrahepatic extension, preserved liver function and PS-0.
 - For single nodules : Ablation is an important option for nodules less than or equal to 30 mm, beyond this size, its indications are still under discussion. Transplantation and surgical resection are also major treatments, the presence of clinically detectable portal hypertension is a major decision criterion, its absence is in favour of surgical resection while its presence is in favour of liver transplantation⁸⁴.
 - For multiple nodules (≤ 3 nodules each ≤ 3 cm) : Priority is given to liver transplantation due to a high risk of recurrence after surgical resection or ablation, however the latter two options are considered in case of contraindication to transplantation.

- **Intermediate stage (BCLC B)** : This is multifocal HCC that does not meet the definition of BCLC A, with no macrovascular invasion, no extrahepatic extension, preserved liver function and PS-0.

For patients eligible for liver transplantation, this is the first-line treatment option.

For patients not eligible for liver transplantation :

- In case of well-defined nodules, accessible to selective treatment, with preservation of portal patency, treatment with trans-arterial chemoembolisation (TACE) is preferred.
- In the case of diffuse, infiltrative, extensive HCC, the treatment option is systemic therapies.

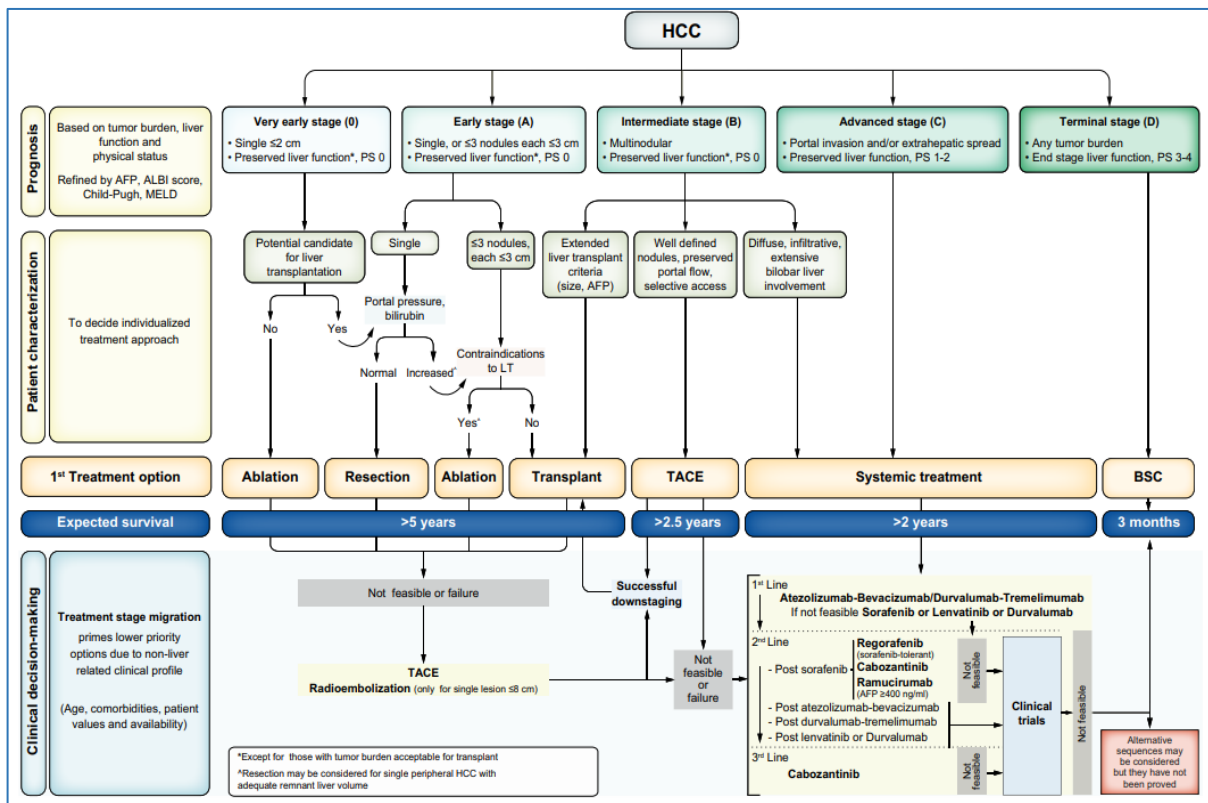


Figure 18 : BCLC staging and treatment strategy in 2022 concerning HCC.

- **Advanced stage (BCLC C)** : These are HCCs with macrovascular progression, often portal or extrahepatic extension, with relatively preserved liver function and a PS≤2.

Treatment is based on systemic therapies : Atezolizumab-Bevacizumab combination is now recommended as first-line due to a survival benefit compared to Sorafenib^{83,85} in eligible patients : preserved liver function and low risk of upper GI bleeding. The combination of Tremelimumab and Durvalumab also shows a survival benefit compared to Sorafenib^{83,86}. These two combinations are now the first line of treatment for BCLC C - HCC. Sorafenib is indicated as a second-line treatment, or as a first-line treatment in cases where the above-mentioned therapeutic combinations are contraindicated.

- End stage (BCLC D) : These are patients with severely impaired liver function and/or a PS>2, not eligible for liver transplantation.

In these patients no treatment has any survival benefit. Only symptomatic treatments are considered within a palliative management.

Certain therapeutic options, such as radioembolization (TARE), stereotactic radiotherapy or irreversible electroporation (IRE), also seem to have a role to play in the management of patients with HCC.

Although the role of radiotherapy has yet to be defined, it is sometimes carried out in cases of BCLC 0 or A HCC that cannot benefit from conventional therapies, although the current scientific data do not allow it to be included in the recommendations^{87,88}.

Concerning Yttrium-90 radioembolization, for now, its indication is recognised in patients who should benefit from TACE but who present a portal thrombosis. In this population survival after TARE is superior to that after TACE⁸⁹. In its latest publication, BCLC also proposes treatment by radioembolization in BCLC 0 and A patients in the context of a single nodule, when patients are unable to benefit from conventional therapies, in the same way as TACE, with the only constraint being a tumour size ≤ 8 cm^{83,90}.

Regarding IRE, this non-thermal ablation technique causes cell apoptosis by perforating the lipid membranes with electrical impulses. Thus, this ablation technique avoids the heat-sink effect and preserves adjacent structures at risk (biliary and vascular structures)^{91,92}. Although the results concerning feasibility and safety are satisfactory, the results concerning effectiveness are still few but encouraging^{93,94}. It is now a therapy that is

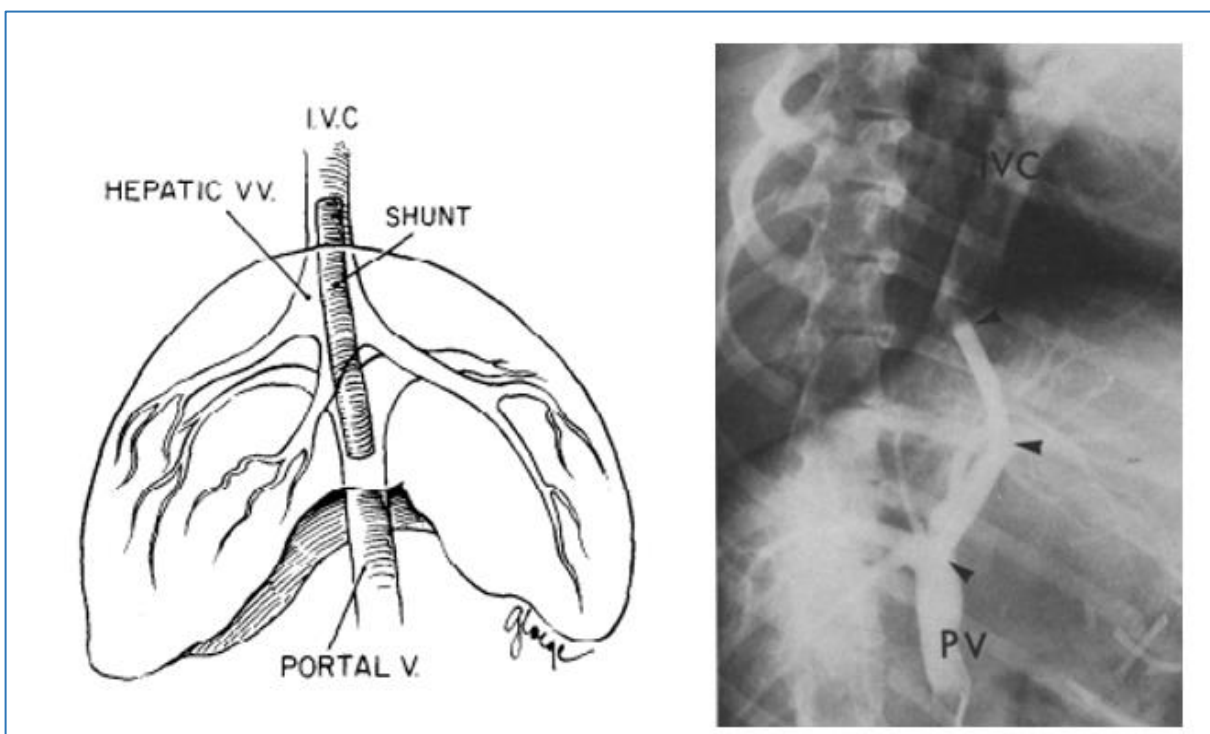
attracting the interest of many teams for the treatment of HCCs that are not accessible to a thermal ablation technique, often because of their proximity to large vascular or biliary structures (typically the hepatic hilum) but which remains absent from international recommendations to this day. In addition, several animal studies suggest that IRE induces an anti-tumour adaptive immune response, which, in combination with immunotherapy, increases tumour necrosis and the immune response both within and outside the treated area^{95,96}.

In addition, although transplantation is the theoretical treatment for some patients, the limited availability of transplants leads to significant delays, which encourages patients to be offered alternative treatments in the meantime in order to keep them within the Milan criteria : they are known as bridge-to-transplant treatments.

III – TIPS

III – 1. Background

At the end of the 1960s, the management of symptomatic portal hypertension, in particular its haemorrhagic complications was already a concern. Surgical porto-caval shunts were practised but the morbidity and mortality were significant⁹⁷. Therefore, certain surgical shunt techniques were developed, such as the veno-venous shunt between the umbilical vein and the saphenous vein or the jugular vein^{98,99}.



*Figure 19 : TIPS : Diagram of an internal porto-caval shunt in a dog (left) and a portal phlebography after the placement of an internal porto-caval shunt (arrowheads) in a dog (right), from Rösch and al¹⁰⁰
PV : Portal Vein ; IVC : Inferior Vena Cava ;*

In the early 1970s, a new technique was developed by Rosch from an animal model and cadavers. This technique, involved the creation of a porto-caval shunt by an endovascular, transjugular route, between a hepatic vein and a portal branch¹⁰⁰. The first attempts were carried out using a non-expandable prosthesis and were frequently complicated by thrombosis¹⁰¹. The performance of TIPS was subsequently improved by multiple technical revolutions, such as balloon angioplasty during the 1970s¹⁰², which was often iterative, and

then by the arrival of self-expanding metal prostheses in the 1980s, which provided better haemodynamic and therefore clinical characteristics¹⁰³. Finally, in the early 2000s, the material innovations and the development of expanded-polytetrafluoroethylene (e-PTFE) that covered stents further reduced the rate of TIPS dysfunction^{104,105}.



Figure 20 : Evolution of TIPS : Spring coil tubing coated with silicone-based co-polymer used by Rösch in animal experimentation (left) and Gore Viatorr expanded polytetrafluoroethylene covered stent (right), from Rösch and al¹⁰⁰ and Gore Medical internet website.

III – 2. Indications

III – 2.a. Acute bleeding of varicose origin

- Rescue TIPS : While the treatment of upper GI bleeding of varicose origin relies primarily on drug therapy and/or endoscopic treatment, TIPS is indicated for acute variceal bleeding when the above treatments fail¹⁰⁶⁻¹⁰⁸.
- Early-TIPS : The Baveno VII conference and several British scientific societies recommend TIPS within 72 hours of oesophageal or gastric variceal bleeding in patients with CHILD C10 to C13 or Child-Pugh class B >7 with active bleeding at initial endoscopy or HVPg >20 mmHg at the time of haemorrhage¹⁰⁸.

TIPS also has a place in the secondary prevention of variceal bleeding in patients with recurrent bleeding despite treatment with beta-blockers and endoscopic variceal ligation¹⁰⁸.

[III – 2.b. Ascites](#)

The Baveno VII conference has recently expanded the indications for TIPS in patients with refractory ascites and now recommends TIPS in patients with at least 3 large volume paracenteses per year, even if they have no history of varicose veins or bleeding.

[III – 2.c. Bleeding related to portal hypertension gastropathy](#)

There is some low-level evidence to support the use of TIPS in patients with portal hypertension gastropathy, whose bleeding complications require repeated blood transfusions despite beta-blocker and endoscopic therapies¹⁰⁸.

[III – 2.d. Budd-Chiari](#)

In patients with unimproved Budd-Chiari despite anticoagulant therapy and in whom angioplasty, stenting, thrombectomy or thrombolysis are not feasible, TIPS appears to be a legitimate option for operators with some experience of Budd-Chiari^{108,109}.

[III – 2.e. Other indications](#)

Several potential indications are recurrently mentioned in the literature, but the lack of data or contradictory results means that they are still subject to discussion. These include bleeding from ectopic varices¹¹⁰, hepatic hydrothorax¹¹¹, hepatic chylothorax¹¹², chylous ascites¹¹³, hepato-renal syndrome¹¹⁴, hepato-pulmonary syndrome¹¹⁵ and portal occlusion¹¹⁶.

III – 3. Contraindications¹¹⁷

Absolute

- Severe pulmonary arterial hypertension (PAPM >45 mmHg)
- Hepatic encephalopathy grade 2 or higher (West-Haven score), persistent or recurrent despite well conducted medical treatment
- Uncontrolled sepsis
- Untreated biliary obstruction

Relative

- Age >70 years : Strongly increases the risk of death at 90 days after TIPS¹¹⁸
- Sarcopenia : Increases risk of hepatic encephalopathy¹¹⁹
- Pulmonary arterial hypertension (PAPM >35 mmHg)
- Portal thrombosis with portal cavernoma
- Severe hepatic, renal or cardiac failure
- Severe coagulopathy
- Polycystic hepatic disease (technical limitation)
- No vascular access for TIPS placement
- Hepatocarcinoma (technical limitation if central)

The decision to perform TIPS must be taken jointly by a hepatologist and an interventional radiologist, and when possible, in a multidisciplinary meeting. Indeed, its indication is based on a hepatological (liver function, encephalopathy), cardiac (electrocardiogram, echography, or even right catheterisation) and radiological (tumour, permeability and vascular anatomical variations) assessment.

III – 4. Technique and complications

III – 4.a. Technique

TIPS is performed in an angiographic suite under general anaesthesia. Under sterile conditions, the right internal jugular vein is punctured and a large-calibre introducer (usually 10-French) is inserted under ultrasound control. This is followed by catheterisation of a hepatic vein, usually the right hepatic vein, and then the need to cross the liver parenchyma, with a Rösch-Uchida set, in order to puncture a portal structure, usually the right portal branch. While in the early days of TIPS, portal puncture was performed under fluoroscopic guidance, it is now recommended to perform it under imaging control, as many guidance methods have been described. Among these, real-time ultrasound guidance appears to be a technique that is both feasible and safe^{117,120}. Once the liver pathway has been established, it is pre-dilated with a balloon prior to the placement of an 8- or 10-mm poly-fluoro tetra-ethylene (PFTE) covered self-expanding prosthesis which is then post-dilated with a balloon. The result of the procedure is considered satisfactory when the porto-systemic pressure gradient measurement is lowered below 12 mmHg.

This procedure may be combined with embolisation of large varicose veins, particularly gastric or oesophageal, using various embolic agents, such as coils, plugs or a long-lasting synthetic biodegradable cyanoacrylate basis glue (Glubran, GEM, Viareggio, Italy).

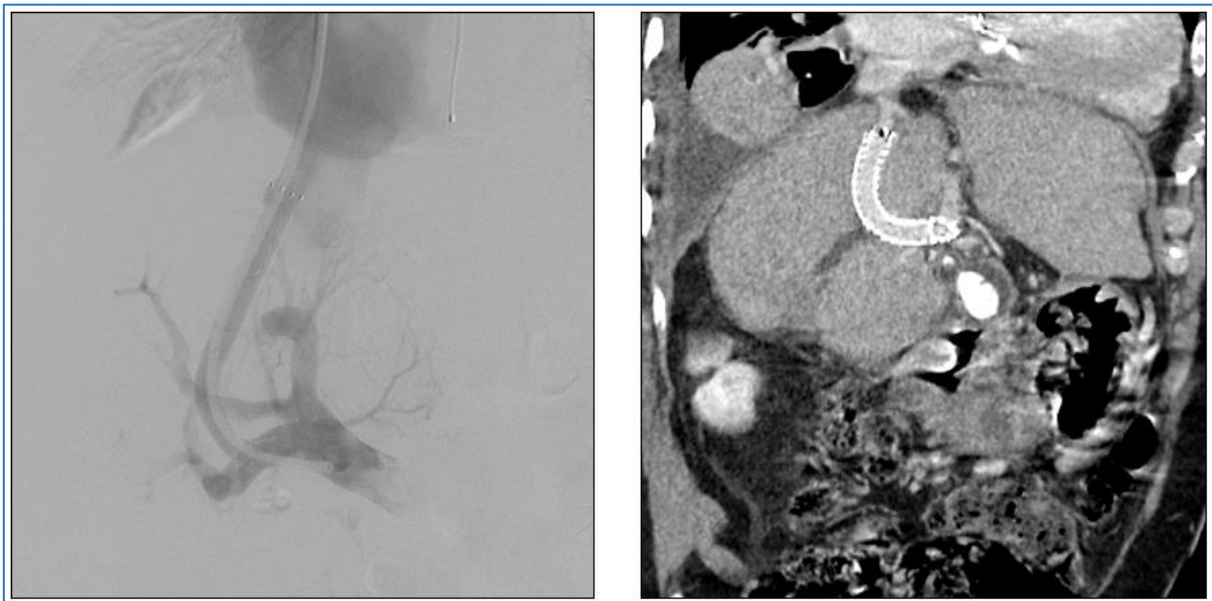


Figure 21 : TIPS: On the left, opacification of the TIPS, the portal network and the right heart cavities by portography. On the right, opacification of the TIPS on a CT scan acquired at portal time.

III – 4.b. Complications

- Per-procedure : These are mainly complications related to the portal puncture where other structures are sometimes punctured (bile ducts, hepatic artery) with a risk of haemobilia, fistula, or subcapsular haematoma. It is also important to puncture an intra-hepatic portal structure to avoid any risk of haemoperitoneum.

These complications are reduced by echo-guided portal puncture, in the same way as accidental carotid puncture. Anecdotally, prosthesis migration and right atrial perforation can also be mentioned.

- Post-procedure : The main complications are TIPS thrombosis, hepatic encephalopathy and liver failure.

III – 5. Physiological changes

The opening of the porto-sus-hepatic shunt via TIPS results in a decrease in pressure and congestion within the porto-mesenteric system. The terminology of shunt also indicates that portal blood is no longer delivered, or in small amounts, to the hepatocytes, and this can be considered as a deportalization of the liver. Several studies have looked at other circulatory changes that occur with the creation of the TIPS. These show a compensatory increase in hepatic arterial flow^{121,122}. It is also noted that deportalization causes the opening of intrahepatic arterioportal shunts¹²³.

This results in an overall increase in extrahepatic haemodynamics, as well as changes in regulation of the renin-angiotensin system and local-regional vasoactive phenomena leading to improved renal function, reduced systemic inflammation and bacterial translocation¹²⁴.

In addition, the placement of a porto-systemic shunt, surgical or TIPS, has raised suspicions since its early days of a role in intrahepatic carcinogenesis. Some authors have demonstrated in animal models an increase in the level of Aflatoxin B1, known for its carcinogenic effects, as well as an increase in dysplastic nodules^{125,126}. Subsequently, some studies have demonstrated an increased risk of HCC development in humans^{127,128}, the mechanisms of which remain unknown, with hypotheses focusing on an increase in hepatic

iron concentration, an increase in growth factors or the impact of vascular changes, either through deoxygenation or compensatory hyperarterialisation. More recent studies contradict these results by not showing an increased risk of HCC in patients with TIPS¹²⁹⁻¹³², however, all the studies available in the literature are retrospective with small numbers and there is a need for large prospective studies to clarify this point.

IV - Percutaneous ablation

IV – 1. Background

The first known use of a thermoablation technique in an oncological situation dates back to 1979, when Hornback et al. attempted to treat several skin and ENT tumours with microwave application¹³³. Percutaneous thermoablation of HCC took off in the 1990s, when surgery became a major part of the treatment of localised HCC, but was only applicable to patients with unilobar involvement, sometimes at the cost of significant morbidity and mortality.

Other alternatives such as chemoembolisation are already in use but pose the problem of treating certain tumour areas that do not bind lipiodol.

Percutaneous ethanol injection therapy (PEIT) under ultrasound guidance has been evaluated, but the heterogeneity of the intra-tumour distribution of ethanol seemed to be an obstacle to this technique.

Several Japanese teams then reported microwave treatment of HCC nodules with good efficacy and fewer complications than surgery, thus opening the discussion of the position of percutaneous ablation in the management of HCC^{134,135}.

Already used for some twenty years in neurosurgery¹³⁶, McGahan et al.¹³⁷ report on their research concerning hepatic radiofrequency in a bovine model, which was shortly afterwards applied by Rossi et al.¹³⁸ for the treatment of human HCC.

IV – 2. Physical principles

Both radiofrequency and microwave ablation involve destroying tumour cells by exposing cancer cells to high temperatures and causing their necrosis. However, the physical principles leading to this temperature rise differ depending on the technique used :

- Radiofrequency requires an electric current produced by a generator and conducted to the ablation probe. The presence of scatter plates on the patient's skin is necessary to close the electrical circuit. The body acts as a resistance within this circuit, allowing

the energy to be dispersed in the form of heat when it encounters the probe (Joule effect). In this way, thermoablation causes cell necrosis by thermocoagulation.

- Microwaves are based on the principle of dielectric heating, which consists of the application of an electromagnetic field produced by a generator and emitted at the end of an ablation probe. This electromagnetic field excites the water molecules, which release some of this energy in the form of heat.

IV – 3. Technique and complications

IV – 3.a. Technique

Percutaneous hepatic thermal ablations are performed in a dedicated room, usually under general anaesthesia.

The first step is to identify the lesion to be treated, either by ultrasound or CT scan. Once the target is defined, one or more needles (depending on the technique used) are positioned within the lesion under the control of imaging. Once the needles are in place, the generator connected to the needles is switched on to initiate heating.

In the case of radiofrequency, according to needle constructors, the heating time can be predefined or can proceed until a significant increase in impedance is achieved, therefore the size of the ablation zone always depends on the needle size in case of monopolar ablation. In the case of microwaves, the heating time is defined beforehand according to the size of the desired ablation zone.

The ablation zone was not only defined to circumscribe the volume of the nodule, but also to include margins of 5-10 mm to match the surgical equivalence of R0 resection. Once the ablation has been carried out, the needle can be withdrawn with a track ablation allowing both the risk of swelling on the puncture path to be limited and the hepatic path to be cauterised to limit the risk of bleeding.

IV – 3.b. Complications

Complications associated with percutaneous hepatic thermoablation procedures are mainly of three types :

- Haemorrhagic : Usually subcapsular haematomas and haemoperitoneum.
- Biliary : The main complication is post-ablation bile duct stenosis. There is also a risk of bilioma or even bilioperitoneum formation.
- Infectious : Usually infection of the necrosis of the ablation area or of a bilioma, equivalent to a liver abscess.

With less frequency, portal thrombosis or complications on neighbouring organs (gallbladder, digestive tract) are observed.



Figure 22 : Radiofrequency thermoablation procedure using two straight needles. The needles are positioned within the nodule to be treated; in this case the nodule is positioned near a TIPS.

IV – 4. Radiofrequency vs Microwaves

IV – 4.a. Radiofrequency

The heating zone produced by this technique is relatively limited to a few millimetres around the electrode, the heating of the more distant zones is more uncertain as it depends on the physical properties of the tissue and in particular its thermal conductivity. It is therefore considered that the heating within the radiofrequency thermoablation zone may be more heterogeneous for larger volumes^{139,140}.

Indeed, one of the main factors influencing thermal conductivity is tissue perfusion. In fact, at the end of the 1980s, several studies showed that the large vessels were responsible for perivascular tissue cooling during thermal ablation treatments¹⁴¹⁻¹⁴⁴. Subsequent work has shown that the overall perfusion of an organ interferes with thermal conductivity and that the greater the perfusion, the smaller the ablation area¹⁴⁵⁻¹⁴⁸. It is now accepted that this effect appears significant around vessels whose diameter exceeds 3 mm : this is the heat-sink effect^{143,149}, potential vector of treatment insufficiency.

Thermal conductivity can also be a problem if it is too high, causing tissue to char too quickly, not allowing sufficient thermal conductivity to the periphery.

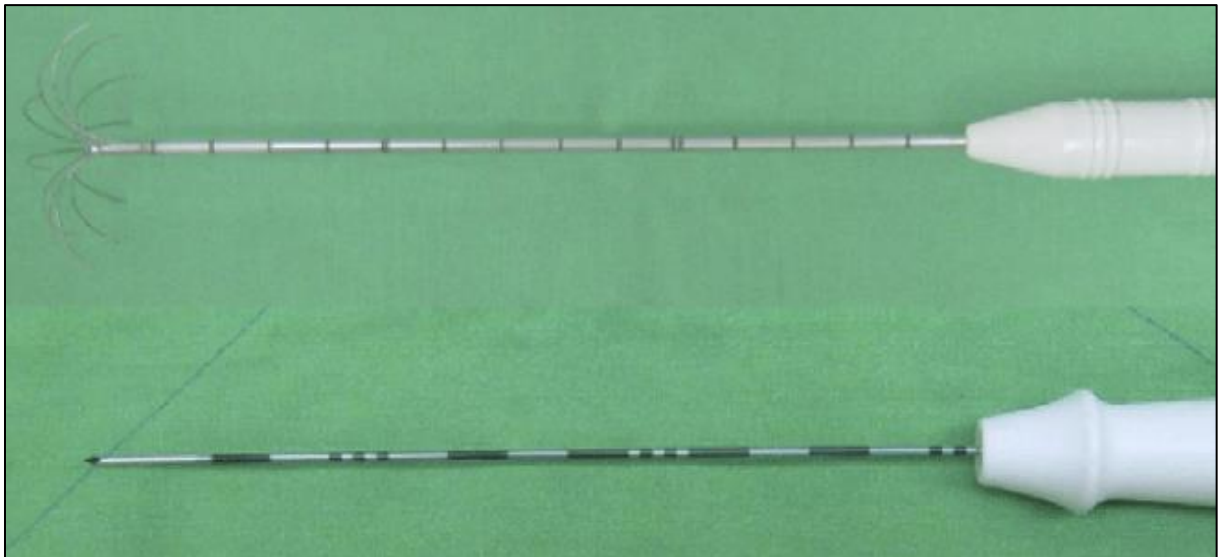


Figure 23 : Radiofrequency ablation needles : Leveen umbrella-shaped (up) and Cool-tip straight (down), from Chen and al¹⁵¹

Nevertheless, radiofrequency has the advantage of being used via two types of needles, umbrella-shaped and straight, with the diameter of the ablation zone perpendicular or parallel to the needle axis respectively. In addition, multipolar radiofrequency ablation techniques (several needles) are being investigated in order to overcome some of the shortcomings of the monopolar technique (larger ablation area, less sensitivity to the heat-sink effect)¹⁵⁰.

IV – 4.b. Microwaves

The physical principle of heat emission through microwaves allows the creation of a potentially larger and more uniform heating volume than radiofrequency. Similarly, the ablation zone appears to be less affected by the heat-sink effect and the rate and maximum temperature of heating is superior to radiofrequency¹⁵².

Multiple studies and meta-analyses have investigated the performance of the two techniques mentioned. While the above evidence suggests a superiority of microwave ablation over radiofrequency ablation, corroborated by some authors¹⁵³, many teams fail to demonstrate a significant difference in survival or recurrence^{139,154,155}. There is some evidence to suggest a lower local recurrence rate with microwave treatment for HCC $\geq 3\text{cm}$, but scientific evidence on this is variable¹⁵⁶⁻¹⁵⁸.

The prioritisation of one technology over another is still open, and must be adapted to each situation (vascular or biliary proximity, number of lesions to be treated). In the absence of solid scientific evidence, it may also be based on medico-economic arguments which are now rebalancing the debate¹⁵⁹.

IV – 5. Thermoablation vs Surgery

Several studies have looked at the comparison between the management of HCC, through surgical resection and by percutaneous ablation.

While the data argue in favour of the surgical option for single HCC $\geq 3\text{cm}$ ^{160,161}, it is more difficult to conclude for smaller HCC. Some authors report better overall survival and recurrence-free survival in patients treated with surgical resection with HCC meeting the Milan criteria^{162,163}, including patients aged over 70 years¹⁶². Nevertheless, these studies

consider nodules up to 5 cm with proportions of nodules ≥ 3 cm close to 50%. One of the strongest meta-analyses shows equivalent overall survival at 1 and 3 years but less at 5 years in patients treated with radiofrequency¹⁶³. Thus, other authors report similar survival and recurrence-free survival between patients treated with radiofrequency and surgical resection concerning nodules ≤ 3 cm¹⁶⁴, and even higher considering radiofrequency for nodules ≤ 2 cm¹⁶⁵.

However, all these results must be put into perspective because of the often-limited comparability. Patients treated by surgery are often more selected, with preserved liver function and nodules of favourable topography. Whereas patients treated by thermoablation are often patients for whom the surgical option is not retained because of the severity of their liver disease or an unfavourable nodular topography and in which thermoablation is finally the best therapy to be offered.

Therefore, percutaneous thermoablation treatment is particularly valuable when surgical resection is not possible in cases of marked portal hypertension or multiple nodules (BCLC A) with the aim of parenchymal sparing.

The different studies agree on a lower complication rate and length of hospitalisation for percutaneous thermoablation treatments¹⁶⁰⁻¹⁶⁵.

IV – 6. Combined therapy : TACE and thermoablation

The idea of therapies combining thermoablation and TACE came first of all from the unsatisfactory results of thermoablation alone for HCC larger than 3 cm. Complete necrosis is obtained in only 50 to 70% of nodules between 3 and 5 cm and even less than 30% for nodules larger than 5 cm¹⁶⁶.

In addition, several physiopathological hypotheses reinforce the interest in this combined therapy : firstly, the ischaemia induced by TACE would make the tumour cells more sensitive to thermal damage, thus allowing a synergy between the techniques; moreover, the vascular occlusion induced by TACE would allow a reduction in the heat-sink effect and thus a reduction in thermal dispersion, which means an increased thermal ablation surface¹⁶⁷.

Some authors have studied on its interest for nodules smaller than 3 cm, for which no

benefit on survival or recurrence-free survival has been demonstrated in comparison with thermoablation alone, but an increase in minor complications¹⁶⁸.

Most authors have worked on the benefit of the technique for nodules of 3 to 5 cm for which the results appear favourable, with a significant improvement in survival, recurrence-free survival and local control, both in comparison with thermoablation alone and TACE alone^{167,169-171}.

Results for nodules larger than 5 cm with this combined technique are still few^{172,173} but seem to be limited by the ablation zones allowed by the needles used in monopolar ablation. To our knowledge, the combination of TACE and multipolar ablation has not yet been evaluated but could potentially address some of the constraints observed for the combined treatment of HCC over 5 cm.

EFFICACY AND SAFETY OF
PERCUTANEOUS THERMOABLATION OF
HEPATOCELLULAR CARCINOMA IN
PATIENTS WITH TIPS : A SINGLE-CENTRE
RETROSPECTIVE CONTROLLED STUDY

I - Introduction

Cirrhosis is a disease whose prevalence is constantly increasing, in particular due to the rise of NAFLD and NASH in Western populations^{1,174}, because of better detection, but also thanks to a better management of cirrhotic patients which increases their survival.

This pathology is a breeding ground for hepatocellular carcinoma, which is also on the rise according to the latest epidemiological reports^{47,175}. In addition to the neoplastic complication, cirrhosis is an important morbidity and mortality factor because of the symptoms it causes, whether on the side of liver failure or portal hypertension.

In patients with HCC classified as BCLC 0 or A, thermoablation appears to be a treatment of choice, alongside surgical resection and transplantation, particularly when the latter is not an option. Thermoablation can also be considered as a bridge-to-transplant treatment or as a treatment for viable tumour residues after TACE.

In patients in whom portal hypertension becomes symptomatic, and for which medical and/or endoscopic treatments are no longer sufficient to control bleeding or ascites, the implementation of a porto-systemic shunt appears to date as the best therapeutic alternative, which in almost all cases involves the installation of an intra-hepatic prosthesis via a trans-jugular route, putting a portal branch and a hepatic vein in communication : the TIPS.

The use of TIPS is increasing year by year, participating in the better management of cirrhotic patients and this trend should continue due to an extension of its indications recommended by the Baveno VII conference¹⁰⁸.

All these factors suggest that the management of HCC in patients carrying TIPS, especially by thermoablation, is likely to become increasingly common.

Nevertheless, there are still many grey areas in this management, particularly in the relationship between TIPS and HCC, where although the excess risk of de novo HCC appears to be questionable in these patients^{127,131}, the excess risk of recurrence remains to be determined in the absence of study on the subject.

There are also questions about the detection of HCC in livers that have been deportalized by portal thrombosis or TIPS. Indeed, although studies differ on this point, some authors report a change in the radiological characteristics of HCC, potentially associated with less detection by imaging¹⁷⁶⁻¹⁷⁹ and a possible impact on the initial staging of the disease but

also on the capacity for early detection of recurrence, which, in both cases may have a negative impact on survival.

Local treatment of HCC in patients with TIPS is not recent, but is still relevant from the point of view of efficacy and safety in patients whose liver function is more often precarious with a definite impact on their survival.

Due to limited data on thermoablation, the most discussed topic in the literature is the treatment of these patients with TACE, where the questioning concerned particularly the incidence of complications on a deportalized liver, potentially at greater risk of ischaemia. Although often performed selectively, several studies give very different figures on the safety of TACE, sometimes with significantly greater complications, particularly biliary complications¹⁸⁰⁻¹⁸⁶.

It also seems essential to put forward certain questions more specific to thermoablation, as the potential increase of the haemorrhagic risk because of hepatic puncture on a hyperarterialised liver, which is based on a physiopathological reflection but has not been explored in the literature to our knowledge; on the heat-sink effect, a potential vector of treatment insufficiency on nodules located near the TIPS; and on the risk of TIPS thrombosis, although the current data, which are few in number, are reassuring on this last point. The latter elements are indeed sufficiently important concerns to motivate some teams to consider ablative treatments by non-thermal methods such as IRE¹⁸⁷ or thermal treatments under cover of transient occlusion of the TIPS¹⁸⁸.

Finally, the key issue is the efficacy of thermoablation treatment on nodules near and far from the TIPS. However, this parameter seems to be more accepted than proven since it is based on a small number of non-controlled studies, with small number of patients^{179,186,189}.

Thus, to the best of our knowledge, this is the first comparative study of focal HCC treatment by thermoablation in the TIPS patient.

Our aim was to evaluate the efficacy and the safety of thermoablation in patients with HCC and history of TIPS intervention compared to a similar treatment in TIPS-naive patients by analysing survival and complication rates.

II - Methods

- Study and population

This is a single-centre retrospective longitudinal study carried out at the Nantes University Hospital, after a favourable opinion from the Nantes Council of Ethics in the Health Sector.

We screened all patients who were treated by hepatic thermoablation at the Nantes University Hospital between December 2008 and September 2020.

Inclusion criteria were treatment of a lesion suspected of being HCC on imaging criteria or with a histologically proven diagnosis in an adult patient. Exclusion criteria were non cirrhotic patients, clinical or imagery suspicion of another histology than HCC, histological evidence that the treated lesion was neoplastic with a histology other than HCC.

HCC were suspected according to the LI-RADS imaging criteria evaluated on cross-sectional imaging, CT or MRI, with injection of contrast agent and multiphase acquisition. Decision of treatment remained to multidisciplinary discussion.

All patients who met the above criteria and had a TIPS implanted before thermoablation were included in a group called TIPS. We chose to create a control group equal to the TIPS group in number of patients. We included each treated patient consecutively to the patients of the TIPS group meeting same previous criteria and not carrying TIPS in a group called n-TIPS.

- TIPS

All the patients followed up underwent TIPS at the University Hospital of Nantes, in an angiography room with a plane sensor (Innova 4100, General Electric Medical System, Waukesha, Wisconsin, USA), by five interventional radiologists with at least two years of experience in TIPS. The procedures were performed under general anaesthesia using the Rösch-Uchida set (Cook, Bloomington, IN, USA) after puncture of the right internal jugular vein. The portal puncture was performed under ultrasound control in almost all cases. This

procedure allowed for the placement of an 8- or 10-mm self-expanding prosthesis Viatorr covered with PTFE (Gore, Flagstaff, Arizona, USA).

- Thermoablation

Patients underwent thermoablation at the Nantes University Hospital, under general anaesthesia. The guidance could be ultrasound using a 5 MHz convex probe of a GE LOGIC E9 device (GE Healthcare, Hatfield, UK) and/or CT using a SIEMENS SOMATON scanner (Siemens Healthcare SA, Zurich, Swiss) and was performed either by radiofrequency, using Cooltip needles (Medtronic, Brampton, Ontario, Canada) or Leveen needles (Boston Scientific, Marlborough, MA, USA); or by microwave using Amica needles (Mermaid Medical HQ, Stenløse, Denmark).

The operators belonged to an interventional radiology team consisting of six interventional radiologists with at least two years of experience in hepatic thermoablation.

- Follow-up

Part of the follow-up of the patients was radiological with an imaging at 1 month, 3 months, 6 months and 1 year after the intervention, by cross-sectional imaging (MRI or CT) with injection of contrast agent and multiphase acquisition. These examinations were interpreted by radiologists with 1 to 20 years' experience in digestive and/or interventional imaging.

The other part of the follow-up was clinical through a consultation with a hepatogastroenterologist of the Nantes University Hospital department in the majority of cases.

- Data collected

All data were collected retrospectively using Powerchart Millennium (Oracle Cerner, Austin, Texas, USA), Clinicom and Carestream PACS (Carestream Health, Rochester, New York, USA) software.

Firstly, the age and sex of the patients; the etiology(ies) of their liver disease; their diabetes status; clinical data (jaundice, encephalopathy) and biological data from a blood sample taken the day before the intervention (bilirubinemia, albuminemia, creatinemia, PT, INR, ASAT, ALAT, GGT, ALP and AFP);

Others through the last abdomino-pelvic cross-sectional imaging before the operation available on the PACS : splenomegaly, ascites, dilatation of the bile ducts, diameter of the portal trunk and the hepatic artery.

CHILD-PUGH and MELD scores were calculated using Microsoft Excel (Redmond, Washington, USA).

The characteristics specific to the TIPS and its placement were also collected : the degree of urgency at the time of placement, the indication, the portal branch and the hepatic vein put in communication, the pre-TIPS and post-TIPS gradient as well as the diameter of the prosthesis.

Via the same software, characteristics specific to the nodules were collected : size; LI-RADS (classification carried out by a senior radiologist with particular expertise in digestive and/or interventional imaging); its location according to Couinaud's segmentation; whether a prior biopsy had been performed, and, if so, whether histological evidence of HCC was present; the distance between the nodule and the wall of the TIPS; possible vascular and/or biliary proximity of the nodule (less than or equal to 5 mm for a structure of 3 mm or more); prior therapeutic management of HCC (surgery, thermoablation, chemoembolization, radioembolization, external radiotherapy).

In the same way, several data were extracted concerning the procedure performed : the type of thermoablation (radiofrequency or microwaves); the surface area treated, measured on the immediate post-procedure images or the first imaging control if the previous option was not feasible (measurement performed by the surface area measurement tools integrated in the Carestream PACS); the type of needle used; the need for dissection whether hydric or gaseous; the need for a pleural pathway; the type of guidance (ultrasound and/or CT), the use of jet ventilation; the duration of the procedure and the duration of the general anaesthesia.

The occurrence of intra-procedural and immediate complications was recorded, as well as their type : TIPS complication, vascular thrombotic or haemorrhagic complication, biliary complication, and their severity was assessed according to the SIR score.

Clinical and biological follow-up were performed at 1, 3, 6 and 12 months. Jaundice, ascites and encephalopathy were investigated in consultation with the hepatogastroenterologist.

On imaging, the permeability of the TIPS was sought, as well as possible complications (thrombotic, haemorrhagic, biliary, other), always classified according to the SIR score; signs of recurrence were reported by distinguishing between local recurrence (thermoablation edges), hepatic recurrence (non-local) and distant recurrence (metastatic).

Thus, survival and recurrence-free survival were determined at each stage of follow-up. Cause of death was also sought where appropriate.

All data were collected in Microsoft Excel, and the collection was completed in April 2022.

- Statistical methodology

The characteristics of the populations were described using means and standard deviations for quantitative variables; the statistical test used was the Student's t test with calculation of the 95% confidence interval where appropriate. For qualitative variables, proportions were used; the statistical tests used were the Fisher and Chi-square tests with expression of the Odds ratio and the 95% confidence interval where appropriate.

Overall and disease-free survival analyses were performed using Kaplan-Meier curves and a log-rank test.

Overall survival, recurrence-free survival and complication statistical analyses were performed per-nodules. Treatment of lost to follow-up was done per-protocol. Survival and complication per-patient were treated only in a descriptive way.

The various statistical tests were carried out with the help of the BiostaTGV interface using the R software. Statistical significance was set a $p < 0.05$.

III - Results

- Flow chart

The Nantes University Hospital database contained 617 patients who underwent hepatic thermoablation between December 2008 and September 2020. Within this population 371 thermoablations were performed for histologically proven or suspected HCC on imaging criteria. Of these patients, 36 had TIPS and 335 did not.

Two of the 36 patients with TIPS had exclusion criteria related to a histological finding of an etiology other than HCC demonstrated after thermoablation.

The 34 patients meeting the criteria formed the TIPS group, in which there were 66 nodules treated in 51 procedures.

We selected the 34 patients treated consecutively to the TIPS group and meeting the criteria from the 335 patients mentioned above to form the n-TIPS group in which there were 84 nodules treated in 67 procedures.

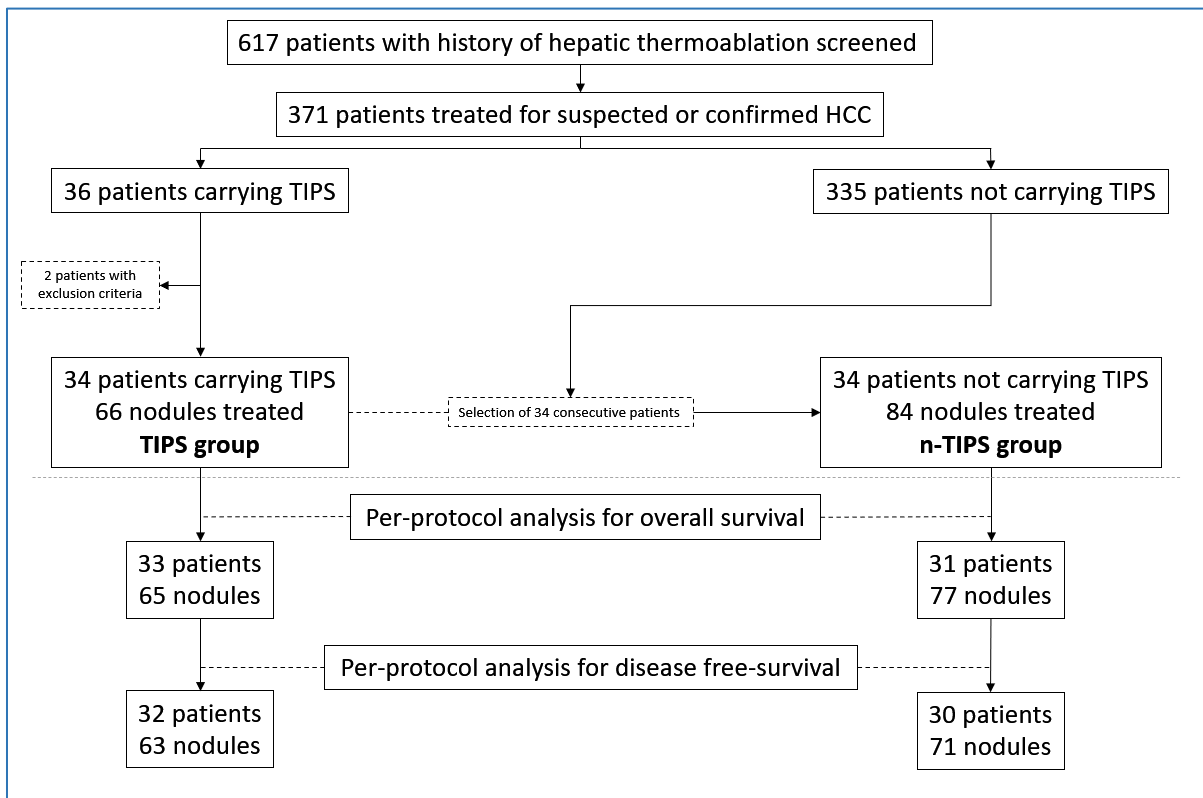


Figure 24 : Flow chart
TIPS : Transjugular intrahepatic porto-systemic shunt; HCC : Hepatocellular Carcinoma

The data set was processed to establish statistics on patient characteristics, nodules, thermoablation procedures, TIPS and complications.

In accordance with per-protocol analysis and management of missing data, the overall survival analysis was based on data from 33 patients and 65 nodules in the TIPS group and 31 patients and 77 nodules in the n-TIPS group. Following the same requirements, the analysis of recurrence-free survival is based on data from 32 patients and 63 nodules in the TIPS group and 30 patients and 71 nodules in the n-TIPS group.

- Population characteristics

Both populations showed a clear male predominance estimated at 95% in the TIPS group and 99% in the n-TIPS group ($p : 0.32$; OR : 0.25; 95% confidence interval (CI 95) [0.004; 3.26]). Regarding the etiology of cirrhosis, HBV and HCV infections were observed, with a prevalence of 4% and 8% respectively in the TIPS group and 4% and 10% in the n-TIPS group ($p : 0.51$ and 0.35 respectively). The n-TIPS group contained one patient with cirrhosis related to haemochromatosis, for whom 4 nodules were treated.

Concerning the biological data, AFP levels averaged 104 ng/mL in the TIPS group and 35 ng/mL in the n-TIPS group.

Regarding clinical data, for jaundice and hepatic encephalopathy, there were 1 and 3 cases respectively in the TIPS group versus none in the n-TIPS group (Jaundice : $p : 0.44$; Encephalopathy : $p : 0.08$).

Concerning radiological data, 1 patient in the TIPS group treated for 2 nodules had dilated intrahepatic bile ducts, compared to none in the n-TIPS group.

The mean age was 65 years in the TIPS group and 69 years in the n-TIPS group ($p < 0.05$; 95% confidence interval [-6.11; -1.80]). There was a higher proportion of alcoholic cirrhosis in the TIPS group estimated at 95% ($p < 0.05$), while there was a higher proportion of patients with NASH (39%) in the n-TIPS group ($p < 0.05$). There was also a higher proportion of diabetic patients in the n-TIPS group : 56% versus 30% in the TIPS group ($p < 0.05$).

Clinically, there were more patients with ascites and splenomegaly in the TIPS group, respectively 23% and 82% compared to 10% and 40% ($p < 0.05$ for these two factors).

Criteria		TIPS	n-TIPS	p-value	Odds-Ratio	CI 95
Population						
Age	n	65.03	68.98	0.0004*		[-6.11 ; -1.80]
Sex (M)	%	95	99	0.32	0.25	[0.004 ; 3.26]
Diabetes	%	30	56	0.002*		
Cirrhosis						
OH	%	95	73	0.0002*		
HBV	%	4	8	0.51	0.53	[0.08 ; 2.42]
HCV	%	4	10	0.35	0.45	[0.07 ; 1.99]
NASH	%	27	39	0.03*		
CHILD						
CHILD	Score	6.75	5.63	1.18 ⁻⁶ *		[0.69 ; 1.55]
CHILD A	%	67	89			
CHILD B	%	29	10			
CHILD C	%	4	1			
MELD	Score	11.32	9.40	0.0001*		[0.93 ; 2.91]
AFP	ng/mL	103.69	35.05			
Biological						
Total bilirubin	µmol/L	27,33	16,62			
ALAT	UI/L	33,83	57,18			
ASAT	UI/L	61,03	66,90			
GGT	UI/L	110,68	285,85			
APL	UI/L	130,48	106,12			
Clinical and Radiological						
Jaundice	%	1	0	0.44		[0.03 ; INF]
Encephalopathy	%	4	0	0.08		[0.56 ; INF]
Ascites	%	23	10	0.02*		
Splenomegaly	%	82	40	3.32 ⁻⁷ *		
Portal trunk diameter	mm	18.21	14.71	1.62 ⁻¹³ *		[2.69 ; 4.30]
Hepatic artery diameter	mm	7.22	5.33	3.92 ⁻¹⁵ *		[1.48 ; 2.31]

Figure 25 : Clinical, biological and radiological characteristics of patients in the TIPS and n-TIPS groups

This difference is also visible in the Child-Pugh and MELD scores, Child score being estimated at 6.75 in the TIPS group versus 5.63 in the n-TIPS group ($p < 0.05$; CI 95 [0.69; 1.55]), while the latter is estimated at 11.32 in the TIPS group versus 9.40 in the n-TIPS group ($p < 0.05$; CI 95 [0.93; 2.91]).

From a radiological point of view, the diameter of the portal trunk and the hepatic artery were more pronounced in the TIPS group, respectively 18.21 and 7.22 mm versus 14.71 and 5.33 mm ($p < 0.05$; Portal trunk : CI 95 [2.69; 4.30]; Hepatic artery : CI 95 [1.48; 2.31]).

- TIPS data

TIPS was performed as an emergency procedure in 9 of 34 patients. In 15 patients the indication was related to a bleeding complication of portal hypertension, while in the other 19 patients TIPS was performed because of ascites refractory to medical treatment. Only one patient had a portal thrombosis prior to TIPS placement.

The prosthesis connected the right portal branch with the right hepatic vein in 28 cases, the right portal branch with the middle hepatic vein in 5 cases and the left portal branch with the middle hepatic vein in 1 case.

The average pre-TIPS gradient was 17 mmHg and 6 mmHg for the post-TIPS gradient. In 7 cases the prosthesis used was an 8-mm Viatorr and in 27 cases a 10-mm Viatorr prosthesis.

TIPS		
Emergency procedure	n (%)	9(26%)
Scheduled procedure	n (%)	25(74%)
Indication		
Bleeding	n (%)	15(44%)
Ascites	n (%)	19(56%)
Path		
Right portal branch - Right hepatic vein	n (%)	28(82%)
Right portal branch - Middle hepatic vein	n (%)	5(15%)
Left portal branch - Middle hepatic vein	n (%)	1(3%)
Mean gradient		
Pre-TIPS	mmHg	17
Post-TIPS	mmHg	6
Prosthesis diameter		
8-mm	n (%)	7(20%)
10-mm	n (%)	27(80%)

Figure 26 : TIPS characteristics in TIPS group

- Data on treated nodules

The diagnosis of HCC occurred on average 34 months after TIPS procedure.

The largest diameter of the nodules was on average 18.75 mm in the TIPS group versus 17.29 mm in the n-TIPS group (p : 0.21; CI 95% [-0.82; 3.76]); concerning the proximity of nodules to biliary structures, there were 4 nodules at risk in the TIPS group compared with none in the n-TIPS group (p : 0.08). In terms of Li-Rads classification, the mean in the TIPS group was 4.45 versus 4.57 in the control group (p : 0.26), with 57% and 64% LR-5 nodules respectively. Histological evidence of HCC was obtained in 10 cases in the TIPS group versus 13 cases in the n-TIPS group (p : 0.96).

Concerning the proximity of nodules to vascular structures, it was 30% in the TIPS group and 15% in the n-TIPS group ($p < 0.05$).

There was a higher proportion of prior therapy in non-TIPS patients (67% vs. 19% in the TIPS group : $p < 0.05$). We considered as previously treated all nodules treated in a non-naive patient, even if the previous treatment did not target the nodule included in our study: the latter could correspond to a local recurrence but also to a de novo HCC at a distance from the former. Thus, 38 nodules in the n-TIPS group were treated in patients with a history of prior thermoablation compared with 7 in the TIPS group (45% vs. 11% : $p < 0.05$), 31 nodules in the n-TIPS group were treated in patients with a history of prior chemoembolisation versus 4 in the TIPS group (37% versus 6% : $p < 0.05$), similarly, 14 nodules in the control group were treated in patients with a history of surgical resection versus 2 in TIPS carriers (17% versus 3% : $p < 0.05$). Furthermore, in the n-TIPS group, 1 patient treated for a nodule had a history of previous treatment with radioembolisation, the same is true for previous treatment with stereotactic radiotherapy; no patient in the TIPS group had been previously treated with such techniques.

Nodule		TIPS	n-TIPS	p-value	CI 95
Mean size	mm	18.75	17.29	0.21	[-0.82 ; 3.76]
Nodule >3cm	%	1.5	1		
Li-Rads	Score	4.45	4.57	0.26	[-0.35 ; 0.09]
LR-5 nodule	%	57	64	0.34	
Vascular proximity	%	30	15	0.03*	
Biliary proximity	%	5	0	0.08	[0.53 ; INF]
Histological evidence	%	15	16	0.96	
Prior therapy	%	19	67	3.20 ⁻⁹ *	
Thermoablation	%	11	45	4.33 ⁻⁶ *	
Chemoembolisation	%	6	37	9.27 ⁻⁶	
Surgery	%	3	17	0.007*	

Figure 27 : Nodules characteristics in TIPS and n-TIPS groups

- Data on thermoablation procedures

Nodules were mainly treated by radiofrequency, used in 75% of cases for the TIPS group and 74% of cases in the n-TIPS group (p : 0.78). The ablation area was 895 mm² in the n-TIPS group versus 825 mm² in TIPS group (p : 0.30).

Ablation required the use of hydrodissection in 12% of cases in the TIPS group and 7% of cases in the n-TIPS group (p : 0.31) and carbodissection in 4% of cases in the former group and 2 cases (2%) in the control group (p : 0.65). A trans-pleural passage was necessary for the treatment of 5 nodules in the TIPS group (7%) and 9 nodules in the n-TIPS group (11%) (p : 0.51).

Ablation was mainly CT-guided, used in 75% of cases in the TIPS group and 73% of cases in the n-TIPS group (p : 0.66), while US-guidance was used in 35% of cases in each group (p : 0.97).

Thermoablation		TIPS	n-TIPS	p-value	CI 95
RF	%	75	74	0.78	
MWA	%	25	26		
Ablation area	mm ²	825	895	0.30	[-203,95 ; 63.05]
CT-guidance	%	75	73	0.66	
US-guidance	%	35	35	0.97	
Multiple nodule procedure	%	27	23	0.52	
Hydrodissection	%	12	7	0.31	
Carbodissection	%	4	2	0.65	[0.21 ; 23.63]
Trans-pleural passage	%	7	11	0.51	
Jet-Ventilation	%	59	70	0.15	
Average procedure time	mn	68	57	0.06	[-0.26 ; 21.52]
Average anaesthesia time	mn	141	133	0.28	[-6.48 ; 22.50]

Figure 28 : Thermoablation procedures characteristics in TIPS and n-TIPS group

Regarding anaesthetic parameters, jet ventilation was used in 59% of nodules treated in the TIPS group and 70% in the n-TIPS group (p : 0.15). The average procedure time was 68 minutes in the TIPS group and 57 minutes in the control group (p : 0.06) for a general anaesthesia time of 141 minutes versus 133 minutes (p : 0.28).

- Complications

Complications were classified according to Society of Interventional Radiology SIR Score.

Regarding immediate complications, there were 3 complications in the TIPS group and 4 in the n-TIPS group (p : 1; Odds Ratio : 0.95; CI 95 [0.13; 5.85]). In the TIPS group there were two complications classified as SIR B corresponding to two per-procedural liver bleeds, which did not require active management and did not prolong hospitalisation. The third complication, also classified as SIR B, corresponded to a haemothorax during a radiofrequency procedure, of small abundance, which also did not require active management. In the n-TIPS group, there was two hepatic bleeds classified as SIR B for the same reasons as mentioned above; there were also two per-procedure pneumothoraxes requiring drainage (SIR C).

Complications

Minor

- A. No therapy, no consequence
- B. Nominal therapy, no consequence; includes overnight admission for observation only

Major

- C. Require therapy, minor hospitalisation (<48h)
- D. Require major therapy, unplanned increase in level of care, prolonged hospitalisation (>48h)
- E. Permanent adverse sequelae
- F. Death

Figure 19 : SIR Score : Score established by the Society of Interventional Radiology for the classification of complications related to interventional radiology procedures according to their severity.

Two post-procedure complications were identified in the TIPS group at 1 month : one was thrombotic concerning a segmental portal branch (SIR C); the second was a bilioma that formed on a radiofrequency scar of the hepatic dome and then fistulated to the hepatic capsule, pleura and skin with several episodes of infection occurring over several months (SIR D). There was no TIPS thrombosis at 1 month after the operation.

In the control group, a diaphragmatic hernia, asymptomatic, secondary to a radiofrequency procedure was identified on a scan at 6 months (SIR A).

Complications		TIPS	n-TIPS	p-value	Odds-Ratio	CI 95
Immediate complications	n	3	4	1	0.95	[0.13 ; 5.85]
1 month complications	n	2	0			
6 month complications	n	0	1			
Total complications	n	5	5	0.75	1.29	[0.28 ; 5.89]
SIR A	n	0	1			
SIR B	n	3	2			
SIR C	n	1	2			
SIR D	n	1	0			
Bleeding	n	3	2	0.65	1.94	[0.21 ; 23.93]
Biliary complications	n	1	0	0.44		

Figure 30 : Complications characteristics in TIPS and n-TIPS groups

- Survival and recurrence

In terms of local control, local recurrence was observed at 1 year in 8 cases in the TIPS group (13%) as well as in the n-TIPS group (15%). In the 4 patients with TIPS whose treated nodule was located less than 10 mm from the TIPS, there was no recurrence at 1 year, either local or distant.

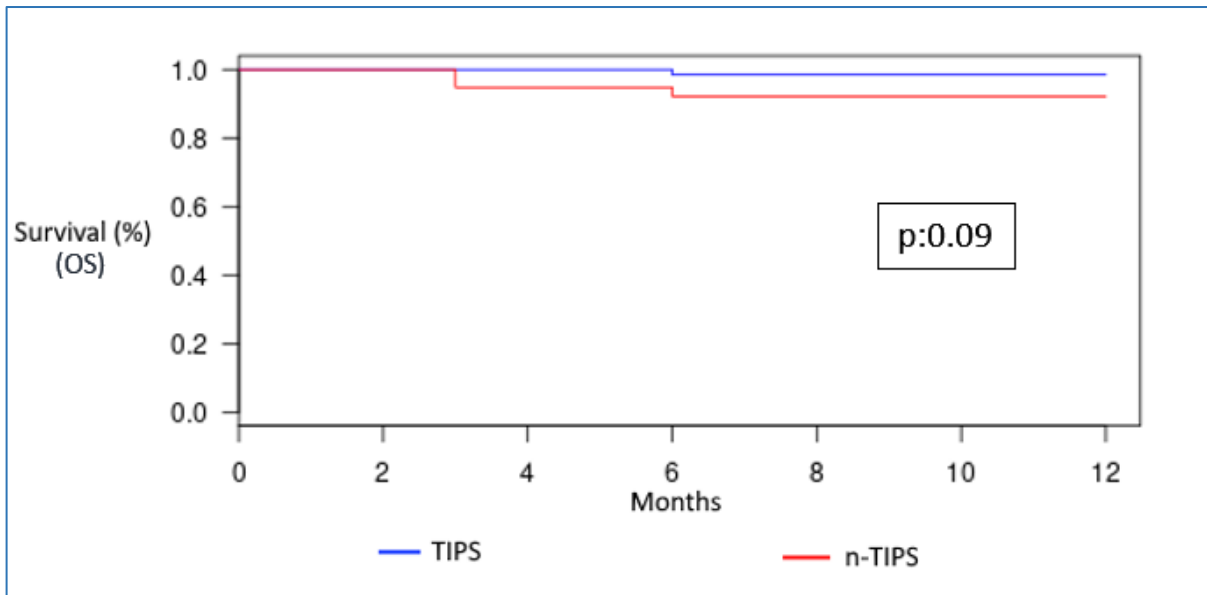


Figure 31 : Per-nodule overall survival in TIPS and n-TIPS groups during 1-year

Regarding 1-year overall survival, there was 1 death in the TIPS group (upper GI bleeding) and 3 in the n-TIPS group (oedema-ascitic decompensation, urinary sepsis and purulent pleurisy), *i.e.* an overall survival per-nodule of 98% and 92% respectively and per-patient of 97% and 90%.

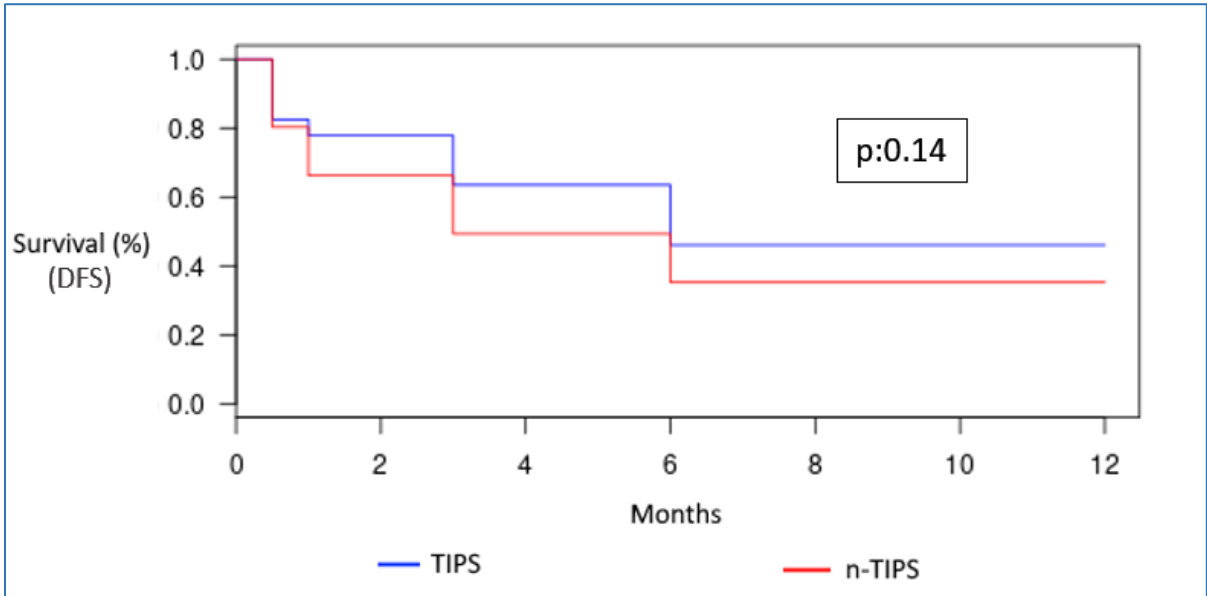


Figure 32 : Per-nodule disease-free survival in TIPS and n-TIPS groups during 1-year follow-up

Regarding 1-year disease-free survival, the rate per nodule was 46% in the TIPS group and 35% in the n-TIPS group and the rate per patient was respectively 59% and 50%.

IV - Discussion

- Comparability of patient characteristics

There is a homogeneity between our two groups concerning viral cirrhosis, whether related to HBV or HCV, which seems essential given that these are the etiologies considered to be the most carcinogenic¹⁹⁰.

Nevertheless, there is also some heterogeneity in other aspects, with a preponderance of ethylic cirrhosis in the TIPS group (95% versus 73% : $p < 0.05$) and a higher proportion of dysmetabolic cirrhosis in the n-TIPS group (39% versus 27% : $p < 0.05$). Similarly, the proportion of diabetic patients was significantly higher in the n-TIPS group. Although the literature does not show any major differences, it does seem that the carcinogenesis associated with dysmetabolic cirrhosis is greater than that associated with ethylic cirrhosis¹⁹¹. In addition, diabetes also appears to be an independent risk factor for HCC¹⁹². The impact of these latter elements may be balanced by some data arguing that non-oncological liver mortality is higher in cirrhotic patients of ethylic origin¹⁹³ and by assumption of increased cancerogenesis in TIPS carriers¹²⁵⁻¹³².

Logically, CHILD and MELD scores are significantly higher in patients with TIPS, since the indications for this device are much more frequent in patients with severe liver disease. It is for the same reasons that a higher proportion of signs of liver failure and portal hypertension are observed, and in particular because certain signs, often radiological, seem to decrease slowly or even incompletely even after reduction of the porto-systemic gradient as suggested by certain publications in transplanted patients¹⁹⁴⁻¹⁹⁶.

The average age of the n-TIPS group was higher (68.98 compared with 65.03 : $p < 0.05$), which could be explained by a potential reluctance to treat elderly patients with TIPS, whose severe liver disease already makes them more fragile and at greater risk of complications.

- TIPS

Concerning TIPS procedure, the data from our study are entirely in line with the standards in the literature, both in terms of the material used, with the use of 8- or 10-mm Viatorr prostheses, the topography of the prostheses with a connection between the right portal branch and the right hepatic vein in 82% of cases, and the results of the procedure with an average porto-systemic gradient estimated at 6 mmHg once TIPS has been put in place^{197,198}.

- Comparability of treated nodules

On many criteria the treated nodules appear comparable between our two groups, first of all concerning their average size, but also concerning their pejorative aspect on imaging with similar mean Li-Rads classifications and a similar rate of nodules classified LR-5.

There was a significant predominance of nodules of perivascular topography in the TIPS group, which are potential vectors of treatment failure and complications.

However, there was a significant difference in prior therapy with only 33% of nodules naïve to treatment in the n-TIPS group versus 81% in the TIPS group ($p < 0.05$) and a trend that was found for each type of management among TACE, thermoablation and surgery. If the hypothesis of sampling variation is the main one, we can try to see other reasons for such differences in proportions.

Regarding surgical resection, it is known that one of the main contraindications is the presence of portal hypertension, which at the same time is one of the main problems in patients requiring TIPS.

Concerning TACE, embolising the arterial network of a liver without portal network has raised questions of safety for several years, especially concerning biliary complications. The data are still discordant in the literature, and although selective TACE appears to be legal, there is still a potential reluctance and a reduction in the theoretical indications for less selective embolisations.

With regard to thermoablation, the indications may have been tempered by the lack of data, as these were published several years after the start of our recruitment.

- Comparability of thermoablation procedures

Thermoablation procedures were comparable in both groups with similar proportions of thermoablation techniques, imaging modalities used for guidance and procedure times.

- Complications

Regarding induced mortality, we did not observe any deaths, neither per-procedurally nor within 30 days after the procedure, in the TIPS group or in the n-TIPS group. This result is in line with what has been observed in the literature, with mortality rates induced by the procedure estimated between 0.15 and 1.4%¹⁹⁹⁻²⁰¹.

Morbidity also appears to be quite comparable between the two groups. Our overall complication rate was 7.5% in the TIPS group and 6% in the n-TIPS group (p : 0.75), which seems to correspond to the average complication rate described in the literature, which is estimated at between 4.1 and 12%²⁰⁰⁻²⁰².

Regarding bleeding complications, there were 3 events in the TIPS group (2 hepatic and 1 thoracic) and 2 hepatic events in the n-TIPS group, *i.e.* rates of 4.5 and 2.5% (p : 0.65). None of these events required active therapy. The comparison of these rates does not show any major difference, despite the predominance of perivascular nodule in TIPS group and global liver hyperarterialisation^{121,122}, but they should obviously be interpreted with caution given the small total number of events.

If we compare our rates with those provided in the literature, they appear to be in the middle range with an estimated bleeding complication rate of between 0.8 and 4.9%^{201,203-208}. This is particularly true as all bleeding complications are recorded in our study, whereas some publications only report bleeding complications considered severe and requiring specific management^{209,210}. Thus, the percentage of haemorrhagic complications requiring embolization or surgical management is estimated at between 0.2 and 2.4%^{211,212}.

Regarding biliary complications, there was one event in the TIPS group, *i.e.* a rate of 1.5%, compared with no cases in the n-TIPS group. Here again, there is no significant

difference between the two groups, despite excess risk of ischemia in a deportalized liver and questions about a potential increased risk of biliary complication. Nonetheless, due to the small number of events, this result should be interpreted with caution.

If we refer to the data in the literature, the rate of biliary complications is estimated to be between 0.5 and 4.2%^{201,207,213-216}, again with disparities between the studies concerning the complications reported, some omitting biliomas and only reporting abscesses for which they observe rates of between 0.3 and 2%^{217,219} and up to 1% of cases of drainage for this complication²¹¹.

Finally, there were no TIPS-related complications, including thrombosis, in the first month post-procedure, which could be reassuring about the risk of damage caused by thermal ablation methods although few nodules were treated close to the TIPS in our study.

- Survival and recurrence

Regarding local control, there was no significant difference between the two groups with a local recurrence rate of 13% in the TIPS group and 15% in the n-TIPS group. This result is consistent with the absence of local recurrence at 1 year in the 4 patients carrying TIPS for whom a nodule located less than 10 mm from the device was treated. This might suggest with great caution that the risk of insufficient treatment and local recurrence induced by the heat-sink effect of TIPS could be put into perspective.

Concerning overall and recurrence-free survival at 1 year, the Kaplan-Meier curves do not appear to differ significantly between the two groups ($p : 0.08$ and $p : 0.14$ respectively). These results appear encouraging concerning the potential risk of excess mortality in patients with TIPS who often have more severe liver disease severity score¹⁰⁸, but also concerning the potential excess risk of recurrence in the latter¹²⁵⁻¹³². Nevertheless, these results must be put into perspective, particularly because of the heterogeneity of our groups with regard to prior treatment which is probably detrimental to the survival and recurrence-free survival of patients in the n-TIPS group.

If the choice of a follow-up by nodule makes it possible to gain in power by an increase in numbers, it is more convenient to express survival per patient rather than per nodule to evaluate our results with the literature. The overall and recurrence-free survival rates at 1 year are respectively 97% and 59% in the TIPS group and 90% and 50% in the n-TIPS group. The literature provides us with an estimated overall survival rate at 1 year of between 87% and 100% while the recurrence-free survival rate is estimated to be between 63.2 and 85.4%^{160,161,165,215,219-223}.

If our rates appear to be lower than those in the literature, it may be due to the fact that the inclusion and exclusion criteria are quite different. Indeed, in our study 25% of our patients underwent thermoablation in a context of multiple nodules (27% in TIPS group and 22% in n-TIPS group ; p : 0.52) whereas many studies only include patients with a single nodule^{161,165,219,220} ; 18% of patients had a CHILD B score (10% in the n-TIPS group) and 3% a CHILD C score (1 patient in the n-TIPS group) whereas many studies only include CHILD A patients and exclude those with signs of portal hypertension^{160,219,220} ; our study did not impose an age restriction whereas some studies select younger patients¹⁶⁰ ; all treated nodules were included regardless of their location, including more unfavourable locations such as perivascular or peribiliary nodules, whereas some studies exclude them or only include nodules that might also be eligible for surgical resection^{160,165,219} ; one study excluded patients with recurrence within 2 months of ablation¹⁶⁰ ; finally, most studies only included patients who were naïve to any treatment for HCC, whereas this represented 54% of the nodules treated in our study (33% in the n-TIPS group)^{161,141,165,219-222}.

V - Conclusion

The management of HCC in patients with TIPS has been the subject of debate for almost 25 years and is expected to become a major issue due to the increasing prevalence of both cirrhosis, HCC and patients with TIPS, especially due to better management of cirrhotic patients.

Hepatic thermoablation is a major radical treatment for BCLC 0- and A-HCC, and our data indicate that it is safe in patients carrying TIPS, including for the device itself.

Fears of undertreatment or early local recurrence in nodules located near the TIPS due to the heat-sink effect do not appear to be verified in this study and thus corroborate the latest data from Yan and *al*²²⁴.

Finally, concerning survival and recurrence-free survival, the efficacy of thermoablation in patients with TIPS does not seem to differ from the efficacy of the same technique in patients without this device.

Thus, this evidence suggests that the management of HCC by thermoablation in patients carrying TIPS should be similar to that in TIPS-naive patients.

Nevertheless, these data need to be confirmed by studies that do not suffer from heterogeneity concerning prior treatments, and, ideally, by larger prospective studies with prolonged follow-up.

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Vu, le Président du Jury,
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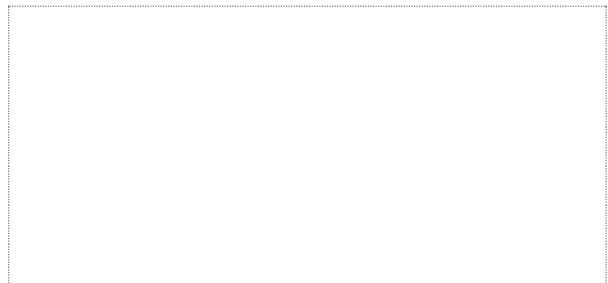
Professeur Éric FRAMPAS

Vu, le Directeur de Thèse,
(tampon et signature)



Docteur Aymeric NICOLAS

Vu, le Doyen de la Faculté,



Professeur Pascale JOLLIET

Titre de Thèse : EFFICACITE ET SECURITE DE LA THERMOABLATION PERCUTANEE DU CARCINOME HEPATOCELLULAIRE CHEZ LES PATIENTS PORTEURS DE TIPS : UNE ETUDE MONOCENTRIQUE RETROSPECTIVE CONTROLEE

RESUME

Introduction : La thermoablation hépatique du CHC chez les patients porteurs de TIPS est une technique qui pose aujourd'hui encore la question de sa sûreté sur un foie déportalisé et hyperartérialisé. Par ailleurs, l'efficacité de la thermoablation du CHC chez les patients porteurs de TIPS n'a jamais été investiguée par des études contrôlées malgré plusieurs hypothèses physiopathologiques pouvant faire suspecter une insuffisance de traitement ou une récurrence exacerbée dans cette population.

Matériel et méthodes : Entre Décembre 2008 et Septembre 2020, 34 patients porteurs de TIPS (66 nodules) et 34 patients non-porteurs de TIPS (84 nodules) ayant été traités par thermoablation hépatique pour un CHC ont été inclus et répartis en deux groupes. Les complications per et post-procédures, la survie et la survie sans récurrence ont été recueillies et analysées rétrospectivement.

Résultats : Le taux de complications était de 7.5% dans le groupe TIPS et 6% dans le groupe n-TIPS (p :0,75). Les courbes de Kaplan-Meier ne montraient pas de différence significative de survie et de survie sans récurrence à 1an entre les deux groupes (respectivement p : 0,09 et p : 0,14).

Conclusion : La thermoablation du CHC chez les patients porteurs de TIPS apparaît comme une technique sûre dont l'efficacité ne semble pas différer de celle observée chez les patients naïfs de TIPS.

MOTS-CLES

CHC (Carcinome Hépatocellulaire) ; TIPS (Transjugular Intrahepatic Portosystemic Shunt) ; Thermoablation percutanée ; Radiofréquence ; Micro-ondes ; Heat-sink effect