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Giuseppe Maria Ettorre *Editor*

Hepatocellular Carcinoma

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Hepatocellular Carcinoma

Springer

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To my wife Micaela and my children
Federico, Giulio, and Elisa
To my father Domenico, teacher of the discipline of surgery

Foreword

It is a pleasure to introduce to the surgical community the present work of Prof. Giuseppe Maria Ettorre and the authors, who made a fantastic effort to summarize and, at the same time, deeply analyze all the important updates related to hepatocellular carcinoma. Starting from molecular advancements, pathogenesis, pathophysiology, up to the latest diagnostic advancements and therapeutic tools, the book takes us on a fascinating journey through all the possible therapeutic options, providing the reader with the highest possible analysis of the literature and the scientific evidence supporting all the argumentations and choices.

This monograph represents the most up-to-date work on hepatocellular carcinoma, maintaining the traditional high standards of the Italian Society of Surgery biannual scientific appointment. The book chapters address all aspects of surgery, from the significance of R0-R1 resections to the role of minimally invasive surgery (laparoscopy and robotic), from ALPPS to liver transplantation, defining a space for each option and reformulating each one on the currently complex scenario of sequential or even simultaneous integration and recombination of two or more of these tools.

Looking at the general structure, the level of scientific documentation, the quality of iconographic material, and the completeness of the work, I can only strongly recommend that readers enjoy the discovery of this book and express my deep gratitude to the authors for their excellent accomplishment.

Catania, Italy
September 2022

Francesco Basile
Italian Society of Surgery

Foreword

The Italian Society of Surgery has chosen a highly prestigious topic for the 2022 biennial talk, hepatocarcinoma (HCC), and has entrusted it to Giuseppe Maria Ettorre, who is certainly one of the greatest experts on the subject. This disease affects mainly patients in the Far East and sub-Saharan Africa and determines a high number of deaths, estimated between 500,000 and one million per year, being a common cause of cancer-related death. The disease is also highly prevalent in Western countries and especially in Italy.

HCC is one of the few neoplasms whose origin has a certain etiological agent, namely hepatitis viruses. It is estimated that 15 years after the infection, due to the cirrhotic evolution of the liver, the incidence of this neoplasm is very high, at least five times higher than in a healthy liver.

The hepatitis B virus causes continuous cell death and consequently the reproduction of hepatocytes to compensate for the losses. This compensation can result in a somewhat disordered growth, representing the origin of the tumor. But oncogenesis can also derive from penetration of the viral DNA into the genome of the hepatocyte, causing oncogenic mutations. Also, the hepatitis C virus penetrates the hepatocyte through the "core" protein. slowing down its apoptosis and thus favoring oncogenic mutations in the genome.

It should be noted that this is a tumor with variable biology and evolution, not only in relation to the multiple histological characteristics (trabecular, compact, pseudoglandular forms, etc.) but also because the clinical evolution varies from solitary and even giant forms to multifocal forms up to the so-called cancer-cirrhosis.

Many paradigms in place in the twentieth century have fallen; for example, that isolated forms with a diameter greater than ten centimeters or cases with vascular invasion regularly have a poor prognosis even if operated on. However, there has always been much skepticism about bringing cirrhotic patients into the operating room.

Over the past four decades, in parallel with the development of biological knowledge, diagnostics and therapies have also made great strides. Imaging (CT, MRI, angiography, etc.) with virtual reconstructions has created safety conditions for the surgeon, and the instruments available in open, laparoscopic, and robotic surgery have allowed a meticulous and almost bloodless surgery with greatly improved results.

One cannot fail to mention the many therapeutic proposals that have been put forward: radiofrequency, ultrasound, radioembolization, and other minimally invasive procedures that are useful remedies for palliation for inoperable cases but destined to fail over time. Chemotherapy is ineffective on the tumor and toxic to the hepatocytes.

In the future, the light of treatment with direct-acting anti-virals has come on. The effectiveness in destroying the virus represents the prevention of posthepatitis cirrhosis and therefore of HCC. Today the costs of these treatments are very high and preclude large-scale use, but over the years this will become possible.

As far as surgery is concerned, it is ascertained that adequately studied cirrhotic patients, that is, with accurate assessment of cirrhosis severity, could undergo even greater liver resections for HCC with a good safety margin. Finally, for those in whom hepatic resection is contraindicated, hepatic transplantation is established. In Italy 20 years ago the national average of transplants for HCC, in compliance with the Milan criteria, was 10%. In our transplant center at the Regina Elena Oncological Institute in Rome, it was 30%: that group of surgeons and anesthetists was extraordinary and included Massimo Carlini, Giuseppe Maria Ettorre, Giovanni Vennarecci, Pasquale Lepiane, Roberto Santoro with Mario Antonini's anesthesiology group, who currently represent a heritage of Italian surgery. Now the allocation of organs according to the MELD has raised the percentage of liver transplants for HCC in all Italian centers, with favorable results.

This book represents the sum of our 30 years of experience and that of many hepatobiliopancreatic surgery centers that, with high professionalism and admirable enthusiasm, deal with this disease and this surgery with extraordinary professionalism. The gratitude of the Italian Society of Surgery, the Italian surgical community, and my staff goes to them all.

Rome, Italy
September 2022

Eugenio Santoro
Italian Society of Surgery

Preface

Hepatocellular carcinoma (HCC) is a rising disease. The etiology of this tumor depends on its geographical distribution, and in most cases it is strictly related to diseased parenchyma, with fewer tumors growing on normal liver. As a young student, I remember when anti-viral therapies were being studied as a potential solution for patients with liver disease and the discussion among scientists on the expected drop in the incidence of HCC, given the efficacy of these drugs. *Mutatis mutandis*, the issue has now shifted to other types of liver disease and HCC is still an impactful problem around the world, with not only virus-related parenchymal changes but also the metabolic syndrome being a growing entity.

Nowadays, the management of patients affected by HCC is multidisciplinary. I remember attending the multidisciplinary meetings at Hôpital Beaujon under the supervision of my mentor Prof. Jacques Belghiti, an expert in the field of HCC who had absorbed influences from Western and Eastern surgical cultures. It was the beginning of a 360° approach to the patient, considering both the oncological point of view and the liver disease. In this setting, Italy has a strong tradition: indeed, in recent decades, several surgical schools around our country have contributed to the development of new insights into the treatment of HCC. Among others, I'd like to mention the schools of Prof. Capussotti in Turin, Prof. Gennari in Milan, Prof. D'Amico in Padua, Prof. Gazzaniga in Genoa, Profs. Cavallari and Mazziotti in Bologna, Profs. Nuzzo, Santoro, and Tersigni in Rome, Profs. Calise and Cuomo in Naples. All the above and others allowed us to create and develop what is nowadays considered the best practice for patients affected by HCC, possibly improving their quality of life and oncological outcomes.

The book I am honored to have been invited to edit on behalf of the Italian Society of Surgery (SIC) aims to summarize all the fundamental aspects of the epidemiology, etiology, multidisciplinary approach, and treatment of HCC. I apologize if some of the experts have been involuntarily excluded and if you might notice some minor imperfections that are unfortunately impossible to avoid in such a huge editorial effort.

Before wishing you a good reading, I would finally like to thank my team—Drs. Marco Colasanti, Roberto Meniconi, Stefano Ferretti, Nicola Guglielmo, Giammauro Berardi, Germano Mariano, and Mariolina Pascoli—without whom none of this would have been possible.

Rome, Italy
September 2022

Giuseppe Maria Ettorre

Contents

Part I

Overview

Epidemiological Aspects of Hepatocellular Carcinoma

1

Diego Serraino, Lucia Fratino, and Pierluca Piselli

1.1 Incidence and Mortality

The World Health Organization (WHO) estimates that, worldwide, approximately 900,000 individuals develop each year hepatocellular carcinoma (HCC), the most common form of liver cancer [1]. Overall, 69.8% of all HCC cases occur in males, with a male-to-female ratio of 2.66. Accordingly, HCC is the fifth most frequent incident cancer type in men, the ninth in women, and the sixth in the two sexes combined (Table 1.1). From a geographical perspective, the incidence of HCC shows very wide variations. According to the Global Cancer Observatory (GCO), part of the International Agency for Research on Cancer (IARC), 72.5% of all new cases of HCC occur in Asia, where standardized incidence rates peak to 11.6 cases per 100,000 inhabitants/year. In Africa, HCC is the fourth most common incident cancer, with an 8.8 standardized yearly incidence rate of new cases per 100,000 individuals (Table 1.1). In Oceania, Northern America, and Europe, HCC is less common than in Asia or Africa, with the lowest incidence rate being documented in Europe (5.2 new cases per 100,000 individuals per year) where HCC ranks thirteenth overall among incident cancer types.

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Table 1.1 Hepatocellular carcinoma incidence, mortality, and prevalence in 2020

	New cases (rank[a])	Incidence rate[b]	Deaths (rank[a])	Mortality rate[b]	Prevalence (proportion[c])
Asia	656,992 (5)	11.6	608,898 (2)	10.7	732,048 (15.8)
Africa	70,542 (4)	8.8	66,944 (3)	8.5	83,201 (6.2)
Oceania	4419 (12)	7.2	3539 (6)	5.5	4845 (11.4)
Latin America and the Caribbean	39,495 (9)	4.8	37,566 (6)	4.6	39,580 (6.1)
Northern America	46,599 (13)	6.8	34,818 (6)	4.7	49,746 (13.5)
Europe	87,630 (13)	5.2	78,415 (7)	4.4	85,119 (11.4)
Worldwide	905,677 (6)	9.5	830,180 (3)	8.7	994,539 (12.8)
Males	632,320 (5)	14.1	577,522 (2)	12.9	693,917 (17.7)
Females	237,357 (9)	5.2	252,658 (6)	4.8	300,622 (7.8)

Source: International Agency for Research on Cancer [1]

[a] Hierarchical position in cancer incidence or mortality rates among all cancer types

[b] Incidence or mortality rates per 100,000 persons/year are age-standardized on the world population

[c] Proportion of people living with hepatocellular carcinoma within 5 years since diagnosis per 100,000 persons

With regard to mortality, HCC is, worldwide, the third most common oncological cause of death: more than 830,000 persons die because of HCC every year. Most of these deaths (69.6%) occur among males, with a peak in mortality rates of 12.9 deaths per 100,000 people per year: HCC is the second cause of oncological deaths in males and the sixth among females (Table 1.1). Deaths caused by HCC are particularly frequent in Asia, where HCC is the second cause of cancer death. HCC mortality is also very frequent in Africa, with a mortality rate of 8.5 deaths per year per 100,000 individuals (HCC is the third cause of oncological deaths in the continent), whereas it is less common in Oceania, Northern America, and Europe, where HCC ranks seventeenth among oncological death causes, with a mortality rate (8.5 deaths per year per 100,000 individuals) 2.4 times lower than that registered in Asia (Table 1.1).

1.2 Prevalence

Prevalence is a statistical parameter that indicates the number of people living, in a specific geographic area and period, after a cancer diagnosis dating back one or more years. The prevalence of cancer patients is strictly related to the frequency (i.e., incidence) and the prognosis (i.e., survival) of the disease, and, to a lesser

extent, to various factors like population aging, time trends in cancer incidence and survival [2]. In general, about 5% of the population is living after a diagnosis of all cancer types combined. The number of prevalent cases has increased at an annual mean rate of approximately 3%, an increase largely attributable to long-term survivorship of patients with cancers like, among others, breast, prostate and colon-rectum carcinomas [2–4]. Worldwide, it is estimated that 995,000 people are living after a diagnosis of HCC, i.e., 12.8 cases per 100,000 individuals. Most of these prevalent cases are males (69.8%) and from Asia (73.6%) while the proportion ranges from 6.1/100,000 in Latin America and the Caribbean to 15.8/100,000 in Asia (Table 1.1).

Long-term prevalence has been used as a surrogate for cancer cure, denoting disease-free survivors with mortality patterns resembling those of a population group without cancer of the same sex and age. Patients living after a cancer diagnosis include individuals under treatment, relapse-free ones at excess risk of recurrence or death, and patients who have the same death rate as the corresponding general population—they also represent the so-called "cured cancer patients" [5]. For European cancer patients diagnosed in 2000, the cure fraction widely varies according to cancer type and sex. Among men, the cure fraction ranges from 94% of those with testicular cancer to 4% of men with pancreatic carcinoma while, among women, it ranges from 87% for thyroid cancer to 5% for pancreatic cancer. Prevalent cancer patients with HCC show the second lowest cure fraction, i.e., 5% among men and 7% among women [6].

1.3 Survival of Patients Diagnosed with Hepatocellular Carcinoma

Overall, HCC is the second most lethal tumor after pancreatic cancer. In the United States, data from population-based cancer registries collected by the Surveillance, Epidemiology and End Results (SEER) Program estimated a 20.3% 5-year relative survival for people diagnosed with HCC. Relative survival is an estimate of the percentage of patients who would be expected to survive the effects of their cancer after excluding the risk of dying from other causes [7]. No difference emerged in survival rates at each time interval between men and women.

Survival substantially depends on cancer stage at diagnosis, which determines treatment options and has a strong influence on the length of survival. In general, a cancer is deemed *localized* when it is found only in the part of the body where it started (also called *stage 1 cancer*). If a cancer has spread to a different part of the body, the stage is deemed *regional* or *distant*. The earlier HCC is discovered, the better is the chance of a person surviving five years after being diagnosed. Table 1.2 shows the distribution of liver cancer cases according to stage of disease at diagnosis, and the corresponding relative survival probability. In the United States, 45% of HCC are diagnosed at local stage, 26% at regional stage, and 18% at distant stage; the corresponding percentages of 5-year relative survival range from 35.3% to 2.7%.

Table 1.2 Distribution of hepatocellular carcinoma cases by stage and corresponding 5-year relative survival in the United States, 2011–2017

Stage	Percent of cases	5-Year relative survival (%)
Localized	45	35.3
Regional	26	12.3
Distant	18	2.7
Unknown	11	7.4

Source: NIH National Cancer Institute [7]

Table 1.3 One- and five-year relative survival for liver cancer in England, 2013–2017

Sex	1-Year relative survival (%)	5-Year relative survival (%)
Men	34.6	10.7
Women	40.0	13.7
Total	38.1	12.7

Source: Cancer Research UK [9]

At a population level, in Europe the survival probability of cancer patients has been evaluated by EUROCARE—a large cooperative study of population-based cancer survival. Overall, the results from EUROCARE indicates that cancer survival is improving over time although differences among countries persist. EUROCARE data from 107 cancer registries for more than 10 million cancer patients diagnosed up to 2007, and followed up to 2008, have shown that 5-year relative survival generally increased steadily over time for all European regions. However, improvements in survival for liver cancer and other rapidly fatal cancers (e.g., esophagus, pancreas, and pleura) were limited. For liver cancer, 5-year survival was approximately 12% [8].

Similarly, population-based survival probabilities for patients with liver cancer have been documented for England by the Cancer Research UK [9] for the period 2013–2017. As shown in Table 1.3, 38.1% of patients survived one year after diagnosis—a percentage drastically reduced to 12.7% after 5 years. It is worth stressing the substantial survival advantage of women as compared to men (13.7% vs. 10.7% at 5-year survival).

In Italy, the relative 5-year survival of Italian patients with liver cancer appears to be higher than the European average, i.e., 20%, without significant differences between men (20–21%) and women (19–22%), or among geographic areas. Interestingly, HCC patients who survive one year after diagnosis show a 33% probability of surviving an additional five years [10].

1.4 Main Risk Factors for Hepatocellular Carcinoma

The types and distribution of risk factors largely reflect the wide geographic variations documented in incidence and mortality rates across countries, and the higher frequency of HCC in men as compared to women.

Most HCC cases occur in individuals with a pre-existing liver disease, in particular liver cirrhosis or fatty liver disease. Worldwide, infection with hepatitis B virus

(HBV) or hepatitis C virus (HCV) are the most frequent causes of HCC [11]. With regard to HBV infection, it should be stressed that in high endemic areas—i.e., in Asia or in some sub-Saharan African countries—about 8% of individuals are chronically infected, and approximately 80% of HCC cases are recorded in people who are HBsAg-positive [12]. In contrast, HCV infection is the predominant risk factor for HCC in the USA, North America, Europe, and Japan [9], especially in HCV-infected patients with advanced fibrosis. Maucort-Boulch et al. [13] used data on the prevalence of HBV and HCV infection among 119,000 people with HCC from 50 countries worldwide to extrapolate data to countries without prevalence data. Globally, they estimated that 56% of the 770,000 cases of HCC that were recorded worldwide in 2012 were attributable to HBV and 20% to HCV. HBV is thought to be the cause of two out of three cases of HCC in less developed countries, and of one in four cases in more developed countries [13]. Antiviral therapies are effective in reducing the incidence of HCC, but do not eradicate the risk. Among patients with HCV infection who have a sustained virologic response to interferon-based treatment regimens, the risk of HCC is reduced from 6.2% to 1.5%, as compared with patients who do not have a response [14]. Promising results are progressively emerging from the use of direct-acting antivirals to treat and cure HCV infections, which are associated not only with a reduced mortality but also with a decreased risk of HCC development [15].

Alcoholic cirrhosis is the second most important risk factor for HCC in Europe and North America, the USA included. Alcoholic liver disease negatively impacts on liver metabolism and the risk of HCC increases with duration and quantity of alcohol consumption, starting from very low doses (<10 g/day). A statistically significant increased risk of 4% (from 2% to 6%) for every 10 g/day of alcoholic beverages has been estimated by the World Cancer Research Fund [16]. It is worthy of note that the alcohol-related risk of developing HCC substantially increases in association with several conditions, including HBV or HCV infection, older age, and obesity [17]. Smoking and coinfection with the human immunodeficiency virus can also contribute to the development of HCC.

1.5 Conclusion

Epidemiological data on HCC are an important tool to set priorities for liver cancer prevention. High-coverage of HBV vaccination will be transformational in HBV-endemic countries, but the prevention of HCV transmission and the treatment of chronic carriers of both viruses require actions toward new scalable solutions. In western countries, the reduction of alcohol consumption remains an essential step for HCC prevention.

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Molecular and Genetic Mechanisms of Hepatocellular Carcinoma

2

Michele Valiante and Paola Grammatico

2.1 Introduction

The process promoting the development of hepatocellular carcinoma (HCC) is similar to that underlying other types of cancer. It is a multistep mechanism involving a mixture of genetic and environmental factors. Several exogenous risk factors are implicated in the development and progression of HCC, notably hepatitis infections, alcohol abuse, metabolic syndrome, obesity, diabetes and many others. All these conditions favor a chronic inflammatory state leading to the deposition of fibrotic tissue and playing a crucial role in the onset of liver cirrhosis, which frequently precedes the development of the tumor. It is indeed well known that dysplastic hepatocytes grow inside the regenerative nodules progressively acquiring multiple genetic mutations leading to the neoplasm [1].

2.2 Genetic Landscape of Hepatocellular Carcinoma

The understanding of the genetic landscape of HCC has improved over the past few years as a result of massive advances in genomic technologies. Next-generation-sequencing techniques have allowed us to obtain an in-depth picture of the most frequently mutated genes in HCC. Pathogenic variants in several genes have been found in HCC samples. The genes most frequently mutated in this tumor, ordered according to the mutation rate, are: *TERT*, *TP53*, *CTNNB1*, *AXIN1*, *LAMA2*, *ARID1A*, *ARID2*, *WWP1*, *RPS6KA3*, *ATM*, *CDKN2A*, *KMT2D*, *NFE2L2*, *ERRFI1*,

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ZIC3, *ALB*, *KMT2C*, *IRF2*, *BAZ2B*, *UBR3*, and others [2]. A recent study showed that alterations in these genes can be detected also in plasma cell-free tumor DNA of patients with HCC [3].

- ***TERT***

  The *TERT* (telomerase reverse transcriptase; MIM *187270) gene pathogenic variants are found in more than 68% of HCC samples and they involve the promoter region in 44–59% of cases, representing the most frequently occurring point mutations in HCC [4] and the earliest alterations in hepatocarcinogenesis related to cirrhosis [5, 6]. *TERT*, the catalytic subunit of the telomerase complex, plays a fundamental role in maintaining the length of telomere caps. Pathogenic variants in its promotor, through recruitment of the transcription factor *GABP* [7], upregulate both telomerase promoter activity and *TERT* transcription. While the reduced length of telomere caps at the ends of chromosomes is responsible for DNA double-strand breaks, genomic instability and cell senescence, increased telomerase expression is involved in carcinogenesis [8].
- ***TP53***

  Mutations in the *TP53* (tumor protein p53; MIM *191170) gene are detected in about 35–50% of HCC cases. The transcription factor p53, a tumor suppressor known to be involved in several malignancies, regulates cell cycle arrest, apoptosis, senescence, DNA repair and changes in metabolism, maintaining genomic integrity. *TP53* alterations are responsible for the survival of aneuploid cells, and they can cause centrosome amplification and chromosome instability [9]. High chromosome instability has been reported in HCC patients diagnosed with *TP53* pathogenic variants. The same patients also presented poor differentiation status of neoplasms [10], correlating with a poor prognosis [11]. A large number of *TP53* missense mutations detected in HCC cases are localized in the DNA-binding domain of *TP53*, leading to a lower affinity in binding target genes [4].
- ***CTNNB1***

  The *CTNNB1* (catenin, beta-1; MIM *116806) gene encodes β-catenin, an adherens junction protein, acting as a signaling molecule in the wingless-type (Wnt) pathway. Mutations in this gene cause an aberrant activation of the Wnt β-catenin pathway occurring in 20–40% of HCC samples [12]. β-catenin and Wnt-signaling activation can determine genomic instability, which becomes more evident in association with increased DNA damage or mismatch repair defects, frequently appearing in HCC development. Transient activation of the Wnt/β-catenin pathway can also induce *TERT* mRNA expression and an elevated telomerase activity in different cell lines, supporting the hypothesis that these genes interact in the process of hepatocarcinogenesis [13]. It is interesting to note that mutations in *CTNNB1* are reported to be mutually exclusive with *TP53* pathogenic variants [14].
- ***AXIN1***

  AXIN1 (axis inhibitor 1; MIM *603816) is a gene mutated in 5–10% of HCC cases. Its contribution to tumor growth is related to the activation of the Wnt β-catenin pathway [14]. Genetic alterations in *CTNNB1* and *AXIN1* are mutually

exclusive, probably due to their opposite roles. *AXIN1* is in fact a negative regulator of this cascade.

- ***LAMA2***

  LAMA2 (laminin, alpha-2; MIM *156225) encodes laminin-α2, a crucial component of the muscle basement membrane. It is expressed in skeletal muscle myoblasts and myotubes, where it promotes cell survival, myoblast fusion and myotube formation [15] and it seems to play a role in tumor suppression [2]. Biallelic germinal pathogenic variants of this gene have been reported in multiple types of muscular dystrophy. Somatic mutations of *LAMA2*, more frequently associated with other cancers, are reported in 5–12% of HCC patients [16].

- ***ARID1A* and *ARID2***

  ARID1A (AT-rich interactive domain-containing protein 1, MIM *603024) and *ARID2* (AT-rich interactive domain-containing protein 2, MIM *609539) are mutated in up to 20% of tumoral tissue samples in patients with HCC. *ARID1A* is part of the BRG1-associated factor (BAF) complex [17] that regulates the chromatin structure mobilizing nucleosomes by sliding, expelling or inserting histones, modulating the accessibility of DNA to other systems involved in DNA transcription, replication and repair [4]. It is considered a tumor suppressor that is involved in the mismatch repair mechanism. The reduced expression of this gene is associated with a poor prognosis and facilitates HCC metastasis development. Hepatocyte-specific *ARID1A* knockout mice present with steatohepatitis and HCC [18].

- ***WWP1***

  WWP1 (WW domain-containing protein 1; MIM *602307) is an E3 ubiquitin ligase that plays a pivotal role in HCC tumorigenesis due to its function in regulation of signaling involving Smad4 and EGFR. *WWP1* aberrant expression in HCC is associated with a poor prognosis [19].

- ***RPS6KA3***

  RPS6KA3 (ribosomal protein S6 kinase A3; MIM *300075) encodes a member of the ribosomal S6 family of serine/threonine kinases. Constitutional mutations of this gene cause Coffin–Lowry syndrome (MIM #303600), a rare X-linked dominant disease characterized by mental retardation, facial dysmorphisms, tapering fingers, small fingernails, hypotonia and skeletal anomalies. Ribosomal S6 kinase tumoral alterations interfere with p53 pathways implicated in DNA repair and in maintaining genomic stability [20].

- ***ATM***

  The ataxia telangiectasia mutated gene (ATM serine/threonine kinase; MIM *607585) is involved in DNA damage checkpoint and repair, together with p21, and its mutation rate amounts to 7% of HCC cases.

- ***CDKN2A***

  Mutations in the *CDKN2A* (cyclin-dependent kinase inhibitor 2A; MIM *600160) gene are detected in 6–30% of HCC cases. *CDKN2A* encodes two distinct proteins involved in the *p53* and *RB1* pathways, respectively, and represented by p16(INK4A), a cyclin-dependent kinase inhibitor and tumor suppressor that downregulates cell cycle progression, and p14(ARF), which plays a role

in *MDM2* stabilization. The impaired function of p16 can produce genomic instability, especially in tumors where defects in DNA checkpoint control and in repair mechanisms are already present [21].

- ***KMT2D***

  The *KMT2D* (lysine-specific methyltransferase 2D; MIM *602113) gene product methylates the Lys-4 position of histone H3 and it is considered a tumor suppressor due to its involvement in gene expression regulation. The mutation rate in HCC is around 6%. *KMT2D* seems to be involved in transcript elongation associated with histone H3K4 methylation [22]. Its mutations lead to genomic instability in genomic regions where early replicating fragile sites are located. Constitutional heterozygous pathogenic variants in *KMT2D* have been shown to cause Kabuki syndrome 1 (MIM #147920), a chromatinopathy characterized by peculiar facial dysmorphism, mental retardation, postnatal growth retardation, congenital heart disease and other anomalies [23].

- ***NFE2L2***

  NFE2L2 (nuclear factor erythroid 2-like 2; MIM *600492) represents a leucine zipper transcription factor that binds to the antioxidant response element (ARE) [24], preventing cancer development. Dysregulation of the *NFE2L2* gene alters its antineoplastic activity. Somatic pathogenic variants are detected in about 5% of HCC. The combination of mutation in other genes, such as *ATM* or *TP53*, together with *NFE2L2* alterations, has an additive effect in causing HCC genomic instability.

- ***ERRFI1***

  ERRF11 (ERBB receptor feedback inhibitor 1; MIM *608069) gene mutations are found in around 5% of HCC samples. This gene encodes a cytoplasmic protein that binds and inhibits growth factor receptor kinases and their related signaling. The EGRF-mitogen-inducible gene 6 (MIG6) signal is involved in the inhibition of the EGFR and HGF pathways and its defective activity can induce genomic instability, facilitating the onset of HCC.

- ***ALB***

  ALB (albumin; MIM *103600) encodes the most common protein in human blood, which is produced in the liver and acts as the main regulator of colloid osmotic pressure and as a carrier for multiple molecules. Mutations in *ALB* have been reported in 5% of HCC samples. Experimental studies have proposed that *ALB* alterations can contribute to oxidative stress, while decreased serum albumin might have a role in HCC prognosis [25].

- ***KMT2C***

  KMT2C (lysine-specific methyltransferase 2C; MIM *606833) pathogenic variants had been reported in around 4% of HCC samples. This gene encodes a tumor suppressor member of the myeloid/lymphoid or mixed-lineage leukemia family and it mediates histone H3 methylation at lysine 4 [26], being part of the ASC-2/NCOA6 histone–methyltransferase complex (ASCOM). It acts as a transcriptional coactivator, playing a key role in epigenetics [27], especially in genomic instability [28].

- ***IRF2***

  Somatic mutations of the *IRF2* (interferon regulatory factor 2; MIM *147576) gene had been reported in HCC with a mutation rate of about 4%. *IRF2* is an antagonistic repressor of α and β interferon transcriptional activation (an *IRF1*-mediated process). It is known that *IRF2* upregulation is involved in neoplasm development in mice [29], by promoting cell transformation and genomic instability.
- ***BAZ2B***

  Mutations in the *BAZ2B* (bromodomain adjacent to zinc finger domain, 2B; MIM *605683) gene have been found in around 3% of HCC samples. The function of the corresponding protein remains not well known, but it is thought to be part, as the majority of bromodomain-containing proteins, of the chromatin-dependent regulation of the transcription complex [30].
- ***UBR3***

  The *UBR3* (ubiquitin protein ligase E3 component N-recognin 3; MIM *613831) gene function consist in regulating molecules involved in DNA repair and transcription. In animal models, this gene seems to upregulate the Hedgehog signaling pathway [31], the alterations of which have been extensively studied in cancer. It is known that haploinsufficiency of *Patched-1*, an antagonist of Hedgehog activation, induces genomic instability, promoting carcinogenesis. *UBR3* alterations can be detected in around 2% of HCC patients.

2.3 Hepatocellular Carcinoma and Mendelian Disorders

HCC is not frequently encountered in hereditary cancer predisposition syndromes. At the same time, multiple mendelian diseases are known to confer an increased risk for developing HCC. The principal monogenic disorders associated with HCC are: alpha-1 antitrypsin deficiency (*SERPINA1* gene), tyrosinemia (*FAH* gene), glycogen storage disease type I (*HNF1A* gene), acute intermittent and cutanea tarda porphyria (*HMBS* and *UROD* genes), hereditary hemochromatosis (*HFE*, *HAMP*, *HJV*, *TFR2*, and *SLC40A1* genes) and Wilson's disease (*ATP7B* gene) [32]. Similarly, settings of medium/low penetrance single-nucleotide polymorphisms (SNPs) can represent a significant risk factor for HCC. Various SNPs in different genes, identified through genome-wide association studies, have been shown to have a possible role in HCC development (*DEPDC5*, *GRIK1*, *KIF1B*, *STAT4*, *MICA*, *DLC1*, *DDX18*, *PNPLA3*, and *TM6SF2* genes). In particular, the role of specific SNPs of *PNPLA3* and *TM6SF2* has been confirmed in studies conducted in a sample of individuals with alcoholic liver disease but also in patients with otherwise healthy liver [33].

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Role of the Immune System in Hepatocellular Carcinoma

3

Chiara Taibi, Laura Vincenzi, and Gianpiero D'Offizi

3.1 General Aspects

Liver cancer is the second leading cause of cancer-related deaths worldwide. Hepatocellular carcinoma (HCC) accounts for approximately 90% of liver cancer-related deaths [1, 2]. The liver has considerable capacity to remove gut-derived microbial compounds and pathogens from the circulation and is involved in the detection and clearance of blood-borne infectious organisms [3].

This is reflected in the multitude of innate and adaptive immune cells in the liver.

Dysregulation of immunological networks plays a key role in the development and progression of chronic liver diseases and HCC. In chronic viral hepatitis, alcoholic and metabolic liver disease, chronic inflammation and an altered immune response are all associated with the development of HCC [4–6].

Hepatocarcinogenesis can arise from various different factors promoting tumor antigen tolerance, such as decreased recognition of malignant cells, suppression of immunity and chronic inflammation [7–8].

In necroinflammation, altered survival and proliferation signals are generated and these result in cellular DNA damage. The proliferation of damaged hepatocytes leads to neoplastic transformation [5, 9–11].

Pro-inflammatory cytokines, such as IL-6 and TNF which activate transcription factors, play an important role in the development and progression of HCC. Moreover, the innate and adaptive immune systems are important in the detection and elimination of transformed cells; their alteration is associated with disease progression (Fig. 3.1).

The liver is a major immunomodulator, its protective function being liver-modulated immune tolerance. Liver immune tolerance results from complex

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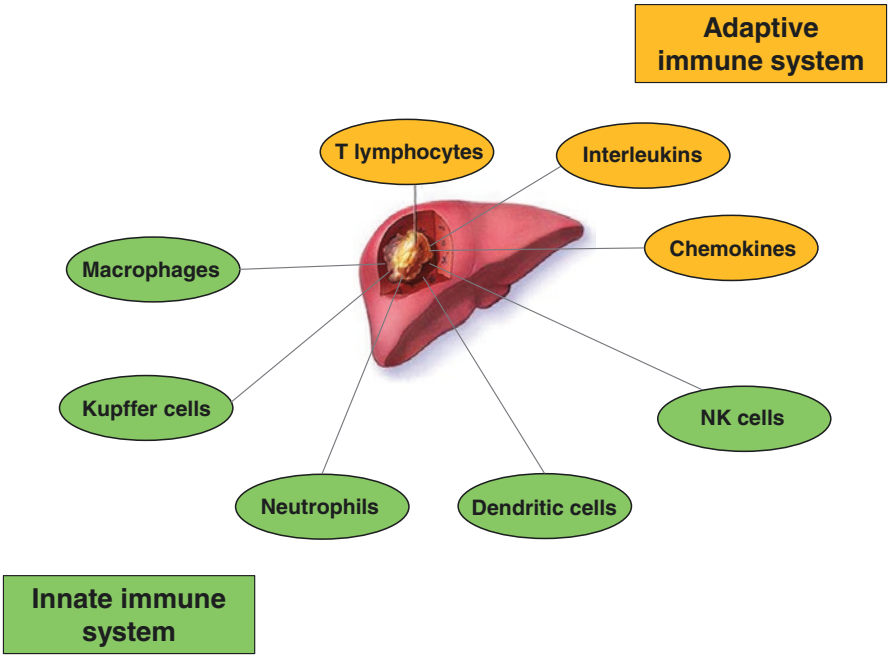

Fig. 3.1 Role of immune cells in hepatocellular carcinoma

interactions between liver-resident cells and peripheral leukocytes. The interactions are maintained by pro-inflammatory cytokines (IL-2, IL-7, IL-12, IL-15 and IFN-γ) and anti-inflammatory cytokines (IL10, IL-13 and TGF-β) [8]. Thus, understanding this immunological network is crucial to identifying new and increasingly effective treatments.

3.2 Innate Immune System

Several immune cells are involved in the mechanism of hepatocarcinogenesis: macrophages, myeloid-derived suppressor cells, Kupffer cells (KCs), neutrophils, dendritic cells (DCs) and natural killer cells (NKs).

3.2.1 Macrophages

Macrophages exert a phagocyte function and play a critical role in pro-inflammatory response and pathogen clearance. They also induce the cytotoxicity of target cells, critical for anticancer immunity.

Tumor-associated macrophages (TAMs) are mainly derived from monocytes, from the bone marrow and spleen and they constitute the main inflammatory cells

[12–15]. In infiltrating tumors, TAMs develop an M2 phenotype characterized by expression of immunomodulatory cytokines (IL-10 and TGF-β) and poor antigen presentation capacity. M2 macrophages produce tumor-promoting and immunosuppressive cytokines and growth factors related to tissue regeneration and angiogenesis. In particular, in HCC IL-6 and TGF-β promote tumor growth, IL-1, TNF-α and IL-6 are involved in invasion and metastasis and TGF-β and IL-20 reduce the anti-tumor immune response. TAMs M2 increase the recruitment and development of regulatory T cells (Tregs) through the activation of a T helper type 2 immune response [16–18].

3.2.2 Myeloid-Derived Suppressor Cells

In HCC, monocyte-derived macrophages contribute to the recognition and clearance of senescent hepatocytes, preventing tumor development. When, however, these cells acquire a myeloid-derived suppressor cell phenotype, they support tumor growth. They suppress T cell infiltration in the tumor and dendritic cell function and promote the expansion of Tregs through the up-regulation of free radicals, arginase activity and production of TGF-β [18, 19].

3.2.3 Kupffer Cells

Kupffer cells (KCs), the liver's resident macrophages, are involved in chemical carcinogenesis-induced hepatocarcinogenesis. They are central to pathogen capture as they clear bacteremia and recruit immune cells to the liver. KCs express an array of scavenger receptors in order to internalize pathogens. At later stages of disease, dying hepatocytes may release danger signals (danger-associated molecular patterns, DAMPs) triggering activation of KCs through Toll-like receptors. Activated KCs produce anti-inflammatory cytokines in response to bacterial endotoxins and downregulate the action of antigen-presenting cells [20, 21]. In addition, KCs can be activated by hypoxic conditions stimulating inflammation also by production of IL-6.

3.2.4 Neutrophils

Neutrophils are the most common tumor-infiltrating immune cells and, when in large numbers, they are predictive of a poorer outcome. Neutrophils can promote hepatocarcinogenesis by enhancing cell growth, angiogenesis and metastasis through production of growth factors HGF and VEGF. Moreover, neutrophils suppress anti-tumor immunity by producing many pro-oncogenic ligands. In HCC, tumor-associated neutrophils interact closely with KCs and recruit Tregs and macrophages, resulting in immune tolerance [22, 23].

3.2.5 Natural Killer Cells

Natural killer (NK) cells are a key part of the innate immune response against viruses and tumors. They exert cytotoxic activity and regulate immune cell functions through cytokine release (IFN-γ in particular) [24]. Their role is similar to that of cytotoxic T lymphocytes (CTLs); however, NK cells react more quickly during the immune reaction and they can also recognize target cells in the absence of MHC. This potential is especially important because cancer cells missing MHC I molecules can only be killed by NK cells [25]. More recently it has been shown that NK cells participate in the adaptive immune response through crosstalk with dendritic cells and T cells. In HCC patients, there is a reduced presence of NK cells with impaired activity in the liver. There is also a depletion in peripheral blood with reduced levels of IFN-γ secretion.

3.2.6 Dendritic Cells

Dendritic cells (DCs) act as a messenger between the innate and the adaptive immune systems. DCs recognize, process and present tumor antigen and are thus essential for the immune response against tumor. Failed HCC-associated antigen presentation by DCs can lead to a weak T cell immune response. This lack of function of DCs may be due to a decreased expression of human leukocyte antigen class-I molecules and maturation defects determining an alteration in cytokine production, in particular a reduction of IL-12 production and an increased release of IL-10 and TGF-β [26, 27]. Thus, defects in DCs promote immune tolerance and are associated with the initiation and progression of HCC. There are fewer activated DCs in the liver tissues of patients with HCC and these are unable to infiltrate cancer nodules, resulting in a reduced recruitment of specific lymphocytes. In addition, DCs indirectly promote proliferation of transformed hepatocytes through their inhibitory effect on $CD8^+$ T cells.

3.3 Adaptive Immune System

Immune cells, such as T lymphocytes, are present in HCC and are crucial in the surveillance and clearance of tumor cells. An abundance of both $CD4^+$ T helper cells and $CD8^+$ cytotoxic T cells correlates with a favorable prognosis in many cancers. $CD8^+$ CTLs recognize tumor antigens carried by antigen presenting cells (APCs) via MHC class I molecules, and kill them by direct lysis or by secretion of cytokines (IFN-γ and TNF-α). Many studies report a significant decrease in $CD4^+$ T cells and an exhausted phenotype of CTLs in HCC patients; these findings are associated with poor prognosis. Continuous antigen presentation in the liver in the absence of $CD4^+$ cells and monocytes derived IL-10 induces antigen-specific tolerance. A memory-like virus-specific $CD8^+$ T cell subset with features of T cell exhaustion has been observed during chronic infection with HCV, persisting even after chronic antigen stimulation ended [28].

A decrease in the ratio of T helper/T suppressive cells is seen in the peripheral blood of patients with cirrhosis and HCC, while a high $CD4^+/CD8^+$ T cell ratio is significantly associated with lower recurrence of HCC after liver transplant. A subset of T helper cells, the follicular T-helper cells (Tfh), supports in-germinal center B-cell activation and maturation in plasma cells. Impairment in these cells appears to be associated with disease progression in HBV-related HCC.

The presence of Tregs, a small sub-population of $CD4^+$ T cells in the tumor microenvironment, is involved in tumor cells escaping immune surveillance and clearance. Tregs inhibit effector B and T cell function after antigen response. Infiltrating Tregs gradually increase during the progression of carcinogenesis.

We can therefore say that the progression of liver diseases correlates with a dysregulated cellular immune response [29, 30].

3.3.1 Interleukins and Chemokines

Immune suppression in the liver is predominantly mediated by cytokines. Liver immune tolerance results from interactions between liver resident cells and peripheral leukocytes. This environment is maintained by pro-inflammatory cytokines (IL-2, IL-7, IL-12, IL-15, IFN-γ) and anti-inflammatory cytokines (IL-6, IL-10, IL-13, TGF-β). As long as HCC is a typical inflammation-related cancer, interleukin molecules can play crucial roles in the development and progression of the disease [31].

Interleukins (ILs) are cytokines that regulate inflammatory and immune responses. They activate and regulate immune cells and participate in an inflammatory cascade. Th1 cells are involved in cell-mediated immune responses, the Th2 cells in humoral-mediated immunity. Hepatocytes express receptors for several cytokines, rendering them susceptible to their action.

In the presence of IL-12 and IFN-γ, naïve $CD4^+$ cells (activated through MHC class II recognition) differentiate into Th1 cells, and activated $CD8^+$ cells. In the presence of IL-4, $CD4^+$ T cells differentiate in Th2 cells. Expression of the Th1 cytokine (IL-1, IL-2, IFN-γ) in tumor tissue is associated with a good prognosis, whereas expression of the Th2 cytokine (IL-4, IL-5, and IL-10) is associated with vascular invasion or metastases. In liver cancer cells, the cytokine milieu often switches to a Th2 profile, which inhibits the tumor-specific CD8 T-cell response, boosts anti-inflammatory cytokines and lowers pro-inflammatory ones. The causative factor of this shift is still unknown. In spite of these findings, we often find overexpression of Th1 cytokines in HCC.

The best known anti-inflammatory cytokines in HCC are IL-6 and IL-10. They suppress T-cell activation and their levels often result increased in HCC. These higher levels seem to correlate with disease progression and a poor prognosis. Specifically, IL-10 downregulates the major histocompatibility complex, facilitating T cell tolerance. IL-6 and TNF, which activate HCC progenitor cells, are mostly produced by resident macrophages [7, 16, 18]. IL-17, a pro-inflammatory mediator,

has pro-tumorigenic effects, promoting cirrhosis progression and HCC development. It is associated with a poor prognosis. IL-22, released by Th 22 cells, is high in HCC patients, a finding which correlates to disease progression.

The roles of chemokines and their receptors in HCC range from promoting to inhibiting tumor growth.

A family of small soluble proteins, chemokines by regulating the recruitment of white blood cells play a crucial role in many events, including angiogenesis, Th1/Th2 development, inflammatory diseases and tumor. They seem to be strictly associated with HCC and correlate with distant organ and lymph node metastasis, even though the exact mechanism is still unknown.

High expression of CXCL12-CXCR4 is found in HCC and surrounding tissues. The CXCL12-CXCR4 axis is implicated in angiogenesis, promoting growth, invasion and metastasis, while the CCL21-CCR7 axis correlates with lymph node metastasis. The CCL20-CCR6 axis is associated with tumor progression; in particular, HCC cell lines with high expression of CCR6 correlate with formation of pseudopodia, augmented intrahepatic metastasis and poor disease-free survival. The expression levels of some chemokine receptors, such as CXCR3 in tumor-infiltrating cells, is higher than in peripheral lymphocytes, suggesting a role in addressing migration of effector T cells into the tumor.

Not all chemokines promote tumor growth. High expression of fractalkine/CX3CL1 in particular correlates with better prognosis in HCC patients, probably by the direct killing of tumor cells [32].

3.4 Conclusions

HCC is the most common type of liver cancer. It occurs in the setting of chronic liver inflammation and is most closely linked to chronic viral hepatitis infection (hepatitis B or C) or exposure to toxins such as alcohol, aflatoxin, or pyrrolizidine alkaloids. Certain diseases, such as hemochromatosis and alpha 1-antitrypsin deficiency, markedly increase the risk of developing HCC. Metabolic syndrome and NASH are also increasingly recognized as risk factors for HCC. Deregulation of controlled immunological network inevitably leads to liver disease, including chronic infection, autoimmunity and tumor development. Persistent upregulation of inflammatory signals due to chronic liver damage leads to necroinflammation (activation of immune cells, altered immunological, survival and proliferation signals and promotion of liver fibrosis) and, subsequently, the induction of tumorigenesis.

The innate and adaptive immune systems are important for the detection and elimination of transformed cells. However, this process is dysregulated in necroinflammation, and anti-inflammatory cytokines (e.g., IL-10 and TGF-β) suppress proper anti-tumor immune responses. The study of these mechanisms is crucial, as early and sustained elimination of the underlying chronic liver damage is key to reducing the risk of HCC and end-stage liver disease. Furthermore, the highly immunotolerant environment and tightly controlled protective mechanisms in the liver make the development of effective immunotherapies for HCC challenging [5].

The identification and validation of immunological biomarkers in HCC and the clinical characterization of patients will be crucial for the generation of favorable responses to novel immunotherapies.

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Underlying Liver Disease

4

Adriano Pellicelli

4.1 Introduction

Hepatocellular carcinoma (HCC) is an increasing form of cancer: it is estimated that, by 2025, more than one million individuals will be affected by HCC annually [1]. HCC represents the sixth most common cancer worldwide and the third most common cause of cancer-related mortality. HCC typically develops on a background of chronic liver disease or cirrhosis in 70–90% of all cases, but about 20% of cases can develop in the non-cirrhotic liver [2]. All risk factors for liver cirrhosis play a role in hepatocellular carcinogenesis, and liver cirrhosis "per se" is a precancerous condition. In patients affected by HCC, chronic liver disease or cirrhosis due to hepatitis C virus (HCV), hepatitis B virus (HBV), hemochromatosis, non-alcoholic steatohepatitis (NASH), alcoholic hepatitis, autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cholangitis are the most common underlying diseases that predispose to the development of HCC. Certain drugs and toxins are also risk factors for HCC. Furthermore rare monogenic syndromes, such as alpha 1-antitrypsin deficiency, glycogen storage disease type I, hemochromatosis, acute intermittent and porphyria cutanea tarda, as well as hereditary tyrosinemia type I are associated with a high risk of HCC.

There is geographic heterogeneity in the etiologic factors for HCC, which vary across countries worldwide. HCV infection and alcoholic liver disease are the main cause of liver cancer in developed countries and the predominant causative factors in Western Europe, whereas HBV infection is the primary risk factor in most developing countries and particularly in most parts of Asia, South America and Africa. HCC related to NASH is increasing worldwide. Some studies report different prevalence rates of NASH as the underlying cause of HCC, ranging between 4% and 22% in developed countries, as reported by Michelotti et al. [3]. In another population-based

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study, in the United States, non-alcoholic fatty liver disease (NAFLD) accounted for 59% of HCC cases, with a cumulative incidence rate of 0.3% over a 6-year follow-up [4]. NAFLD/NASH is an increasing cause of HCC in developed countries.

4.2 Viruses and Hepatocellular Carcinoma

Chronic HBV, HCV and hepatitis delta virus (HDV) infections are the traditional viral risk factors associated with the development of HCC. HCV-related HCC pathogenesis is thought to occur indirectly via chronic inflammation and oxidative stress with subsequent cirrhosis, while HBV can have also a direct oncogenic mechanism, sometimes independent from the development of liver cirrhosis.

4.2.1 Hepatitis B Virus

HBV infection is the cause of 60% of HCC cases in Africa and East Asia while it is the underlying cause of HCC in about 20% of cases in Western Europe. HBV can integrate into the host cell genome causing insertional mutagenesis and leading to the activation of oncogenes. For this reason HBV is associated with an increase risk of developing HCC even in the absence of liver cirrhosis.

HBV is a double-stranded circular DNA virus. The incorporation of the virus into the human gene causes inactivation of protein p53, a transcription factor that suppresses tumor growth. The HBx protein of HBV can bind to p53 forming a protein complex and inactivating many functions of p53, including apoptosis. A p53 mutation is present in 30–60% of HCC patients. Furthermore, HBx sequesters p53 in the cytoplasm and prevents it from entering the nucleus. Inactivation of p53 is one of the factors implicated in oncogenesis of HBV-related HCC. An abnormal activation of the B catenin signaling pathway has been observed in more than 60% of patients with HCC [5]. The activation of this pathway is related to the occurrence of the stemness and drug resistance of HCC cells [6].

Levels of reactive oxygen species (ROS) are increased in the blood and liver of patients with hepatitis B. ROS has an important role, as demonstrated in several studies, in promoting HBV-related liver fibrosis and cancer [7]. The risk of HCC among patients with HBV infection is approximately 2–5% and the disease can develop even in the absence of liver cirrhosis. The risk of developing HCC is reduced by approximately 50–60% in patients treated with antiviral therapy with virological response (VR) [8]. But VR seems not to significantly reduce the overall incidence of HCC when a patient has already progressed to liver cirrhosis [9].

4.2.2 Hepatitis C Virus

Chronic HCV is the most common underlying disease in Europe, North America and Japan. HCV is an RNA virus that does not integrate in host cell genome and for this reason the risk of developing HCC is more common in patients with liver

cirrhosis. The risk of developing HCC is lower but persistent in cirrhotic patients who have reached a sustained virological response (SVR) after therapy with direct-acting antiviral (DAA). The relationship between HCV infection and HCC has been widely studied. HCV infection causes inflammation and necrosis of hepatocytes. Cell turnover due to inflammation induces, through poorly differentiated hepatocytes, dysplastic foci and lastly HCC [10]. HCV infection leads to endoplasmic reticulum (ER) stress and seems to alter calcium homeostasis, inducing oxidative stress. Some studies showed that excessive ER stress due to HCV replication, degrades p53 in the lysosomes so HCV infection disrupts p53 function through activation of a protein kinase [11]. Reduction of p53 tumor suppression can favor development of HCC. High intracellular ROS levels, as in HBV infection, seem to promote hepatocarcinogenesis [12].

HCV infection and in particular HCV core and NS5 proteins can activate telomerase reverse transcriptase (TERT) expression and reverse transcriptase activity. The increased TERT activity has been found to be associated with HCC [13].

HCV can also activate the Wnt/beta-catenin and subsequent activation of pro-survival genes, a pathway that has been shown to promote HCC.

In conclusion, HCV infection and in particular liver cirrhosis due to HCV can predispose indirectly to the development of HCC, but other direct mechanisms of HCV-related HCC oncogenesis exist and can add to the risk for HCC development.

4.2.3 Hepatitis Delta Virus

HDV has not yet been included in the list of carcinogenic viruses, but evidence suggests that the risk of developing HCC is higher in patients with chronic hepatitis D compared to those infected with HBV. HDV replicates in the nucleus of hepatocytes and interacts with several cellular proteins, modulating their expression.

HDV may alter multiple cellular signaling pathways involved in inflammation, oxidative stress, apoptosis, and cellular proliferation. HCC associated with HDV was shown to be characterized by the upregulation of genes involved in the control of DNA replication, and DNA damage and repair. Genome instability due to HDV infection is an important mechanism of hepatocarcinogenesis [14]. This genomic profile is peculiar to HDV and distinct from that of HBV-associated HCC, suggesting that these two viruses promote hepatocarcinogenesis by different mechanisms.

4.3 Non-alcoholic Fatty Liver Disease and Non-alcoholic Steatohepatitis

Over the last decade, NAFLD has become an increasing cause of HCC. NAFLD is considered as the hepatic manifestation of the metabolic syndrome and is closely associated with obesity and diabetes. NAFLD is not always associated with an evolution towards liver cirrhosis, but at least 20–30% of patients develop liver disease with necroinflammation and fibrosis. This condition is known as non-alcoholic steatohepatitis (NASH). Patients with NASH have an increased risk of developing HCC.

NAFLD is characterized by excessive lipid accumulation (steatosis) with evolution in some cases into NASH. Liver cirrhosis and HCC are complications of NASH when this condition is not properly treated. It is interesting to note that HCC is reported also in non-cirrhotic NASH patients [15].

A meta-analysis has demonstrated that patients with diabetes mellitus have a higher risk of developing HCC compared to non-diabetic patients [16]. Overweight patients in a similar way have an increased risk for HCC. NAFLD/NASH, as reported before, are the expression of a metabolic syndrome characterized by diabetes mellitus, insulin resistance, obesity and hypertriglyceridemia.

HCC associated with NAFLD/NASH could have different mechanisms. Hepatic lipid accumulation progresses to necroinflammation leading to hepatocarcinogenesis as a consequence of different conditions such as insulin resistance, hyperinsulinemia, dyslipidemia, oxidative/endoplasmic reticulum (ER) stress, genetic predisposition, dysbiosis in the gut microbiome and altered response of the immune system. Insulin resistance leads to an increase in intracellular free fatty acids (FFA). Elevated FFA β oxidation induces oxidative stress and the release of ROS and of various inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and leptin. There is a link between oxidative/ER stress and progression to HCC. Oxidative stress promotes carcinogenesis by activation of JNK kinase and inactivation of the p53 tumor suppressor gene (*TP53*) [17]. Iron overload is frequently observed in NASH patients and is related to insulin resistance. Intracellular iron overload due to increased production of hepcidin can induce DNA damage that may predispose to HCC [18]. Other studies have also identified the role of the immune system and, in particular of $CD8^+$, $CD4^+$ and Kupfer cells and of altered intestinal gut microbiome in hepatocarcinogenesis in patients with NASH/cirrhosis.

4.4 Alcoholic Fatty Disease

The prevalence of alcoholic fatty liver disease (AFLD) is increasing throughout the world. About 26–30% of HCC can be attributed to alcohol. Central and Eastern Europe and tropical Latin America have a higher incidence of drinkers. There is some evidence that females are more susceptible to the toxic effects of alcohol than males. It was demonstrated that women have lower levels of gastric alcohol dehydrogenase activity and for this reason they are more susceptible to the hepatotoxic effects of alcohol. Furthermore, some studies have demonstrated that Whites have lower ethanol metabolizing enzymes in the liver, compared to Blacks and Hispanics [19]. Progression to cirrhosis and mortality is higher in AFLD (36%) compared to NAFLD (7%). AFLD has a similar mechanism of liver damage compared to NAFLD. Alcohol is metabolized into acetaldehyde by alcohol dehydrogenase (ADH), the CYP2E1 enzyme represents the major pathway involved in the metabolism of ethanol. High cell concentrations of acetaldehyde and ROS are formed in the cell. Acetaldehyde is a potent carcinogen driving the tumorigenesis by the alteration of DNA while concomitant high concentrations of ROS can activate JNK kinase with subsequent induction of carcinogenesis [20].

Ethanol is also involved in "*de novo* cellular lipogenesis" with following steatosis and excess of intracellular FFA. Excess FFA, as observed in NAFLD, determines oxidative/ER stress, increase intracellular ROS levels with progression to HCC [20].

In conclusion AFLD induces cirrhosis and promotes HCC through a similar mechanism to NAFLD.

4.5 Hereditary Hemochromatosis

Hereditary hemochromatosis (HH) is an autosomal recessive disorder of iron metabolism, with elevated iron deposition in most organs including the liver, leading to progressive liver dysfunction and cirrhosis. HCC is a complication of HH nearly always occurring in liver cirrhosis. About 80–85% of individuals with HH are *C282Y* homozygotes and are at risk of developing liver cirrhosis. Other mutations in the high iron gene are *C282Y*/*H63D* compound heterozygosis. Excessive iron in the liver may act both directly and indirectly to induce carcinogenesis. Free intracellular iron, which is present when iron binding capacities of the plasma transferrin or intracellular ferritin are surpassed, interacts with H_2O_2 with formation of Fe^{3+}. Superoxide anions can reduce Fe^{3+} back to Fe^{2+}. Increased accumulation of Fe^{2+} in the cytosol enhances generation of ROS, whose toxic effects on proteins and DNA promote carcinogenesis. HH patients have higher rates of *TP53* gene mutations and decreased p53 protein activity in the liver, thus facilitating hepatocarcinogenesis [21]. Increased intracellular iron is also present in chronic liver diseases such as AFLD, NAFLD, and viral infections, contributing to the pathogenesis of HCC in other liver diseases.

4.6 Autoimmune Hepatitis and Primary Biliary Cholangitis

In autoimmune hepatitis (AIH), chronic liver inflammation and interface hepatitis are present which cause liver inflammation and fibrosis. While early diagnosis and treatment avoid progression to cirrhosis, the persistence of damage leads to liver fibrosis. A major risk factor for HCC in AIH is cirrhosis, and cirrhosis appears as "a sine qua non" condition for the development of HCC in AIH patients. A similar risk for hepatobiliary cancer is present in primary biliary cholangitis (PBC). The incidence of HCC in AIH is 3.06 per 1000 person-years while it is 4.1 per 1000 person-years for PBC. These data support the importance of regular monitoring of disease severity in AIH and PBC, with initiation of HCC screening in patients who progress to cirrhosis [22].

4.7 Wilson Disease

Wilson disease is caused by accumulation of copper in the liver, brain or other organs due to mutation of *ATP7B* gene that encodes a protein that helps in excretion of copper in the bile canaliculus. This results in toxic levels of copper in the

hepatocytes. Hepatocyte apoptosis and mitochondrial oxidative injuries is the mechanism of copper injury in hepatocytes. Due to the availability of chelating agents, life expectancy of these patients has now increased. In some studies the risk of HCC was low even in cirrhotic patients and this leads the authors to state that regular surveillance for HCC is not required. It has been postulated that a high hepatic copper level is protective against hepatic oncogenesis. Based on animal studies, it has been suggested that excessive copper accumulation might have a protective effect on hepatocarcinogenesis. On the other hand, in the Long-Evans Cinnamon rat model for Wilson disease, persistent copper accumulation resulted in an increased risk of HCC which could be prevented by administration of D-penicillamine [23]. Therefore carcinogenesis is thought to be the result of liver injury leading to chronic inflammation and cirrhosis due to chronic copper accumulation [23].

4.8 Alpha 1-Antitrypsin Deficiency

Alpha 1-antitrypsin (A1AT) is the most abundant liver-derived glycoprotein in plasma. Hereditary deficiency of A1AT in plasma leads to an accumulation of polymers of A1AT mutants in the ER of hepatocytes. One of the clinical manifestations of A1AT deficiency is liver disease in childhood and cirrhosis and/or HCC in adulthood. Mutations of A1AT results in two pathologic genotypes called PiZZ and PiSZ. The PiZZ A1AT genotype is associated with liver damage and high risk for HCC. Accumulation of A1AT variants in ER may potentially induce multiple signaling events related to ER stress. ER stress induces an altered regulation of several genes driving proliferation and tumorigenesis; furthermore there is a secondary activated mitochondrial autophagy. The final results are liver inflammation and carcinogenesis [24].

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Part II

Diagnosis

Imaging of Hepatocellular Carcinoma

5

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5.1 Role of Ultrasound and Contrast-Enhanced Ultrasound

Ultrasound (US) every 6 months is universally recommended for hepatocellular carcinoma (HCC) surveillance in all guidelines [1, 2].

The detection of any new focal lesion during US surveillance should directly require a diagnostic "recall strategy" that varies according to the size of the lesion. Lesions <1 cm should be admitted into a non-enhanced follow-up program based on US repetition at 3–6 months; if the size remains stable over a 2-year period, the 6-month surveillance can be restored. The "recall strategy" for lesions ≥1 cm is based on contrast-enhanced imaging techniques with use of vascular contrast agent, such as computed tomography (CT) or magnetic resonance imaging (MRI).

Contrast-enhanced US (CEUS) has been observed to improve the characterization of focal liver lesions with enhancement patterns generally similar to CT and MRI and can be useful in the case of renal impairment. US contrast agents (microbubbles) comprise an albumen or phospholipid shell containing a stable perfluorocarbon or sulphur hexafluoride gas. CEUS is not recommended as a first-line imaging technique or for recall strategies in terms of cost-effectiveness, because CT or MRI will be needed for staging, but it can be utilized when both CT and MRI are contraindicated and/or inconclusive [1].

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5.2 Computed Tomography Technique

Contrast-enhanced CT (CECT) or contrast-enhanced MRI play an essential role in the diagnosis of HCC and do not require histopathologic confirmation. According to the Liver Imaging-Reporting and Data System (LI-RADS), the use of a multidetector-row CT with a minimum of 8-detector rows is recommended, with an axial slice thickness ≤5 mm [3]. The scanning protocol should include an unenhanced phase (to detect hemorrhage/treatment sequelae) and three enhanced phases of study. For CECT, an extracellular intravenous iodinated contrast agent is used, possibly with moderate/high iodine concentration (≥350 mgI/mL), administered at high injection rates (>3 mL/s), with dose adjusted according to body size indexes [3]. According to LI-RADS v2018, the multiphase dynamic study of the liver consists of a first late hepatic arterial phase (25–30 s after contrast agent injection with bolus tracking), a portal venous phase (60–80 s after contrast agent injection) and an equilibrium phase (2–5 min after contrast agent injection) [3].

5.3 Magnetic Resonance Imaging Technique and Contrast Agents

MRI improves the detection and characterization of focal hepatic lesions, in comparison to a CT scan. In addition, MRI performs better compared to CT in the detection of HCC in patients with liver cirrhosis, especially when a hepatobiliary phase (HBP) is added [4]. In particular, a HBP was found to be superior to CECT also in guiding the correct treatment decisions for HCC [5]. MRI of the liver is best performed at 1.5 T or higher field strength [3]. The MRI protocol includes T1-weighted in-/out-of-phase gradient echo (GRE) images, T2-weighted images without and with fat suppression, diffusion-weighted images with at least two b values acquired (0–50 s/mm^2 and 400–800 s/mm^2) [6]. The dynamic contrast-enhanced MRI scan can be performed both with gadolinium-based extracellular contrast agents or with hepatobiliary contrast agents [3]. The multiphasic MRI study is essential for identification of the typical imaging features and vascular hallmarks, which are defined according to LI-RADS v18 as “arterial phase hyperenhancement”, “washout appearance” and “enhancing capsule” [4, 6, 7]. Hepatobiliary contrast agents make it possible to investigate the vascular characteristics of HCC lesions and to assess hepatocellular function in a single examination [6]. The most commonly used hepatobiliary contrast agents include two gadolinium-based compounds: gadoxetate disodium (Gd-EOB-DTPA) and gadobenate dimeglumine (Gd-BOPTA).

5.4 Imaging Features of Hepatocellular Carcinoma

HCCs are generally arterial hypervascular tumors. However, hyperenhancement (“wash-in”) in the arterial phase alone is poorly specific for HCC. When hypoenhancement in the portal venous or delayed phases (“wash-out”) is added, both the

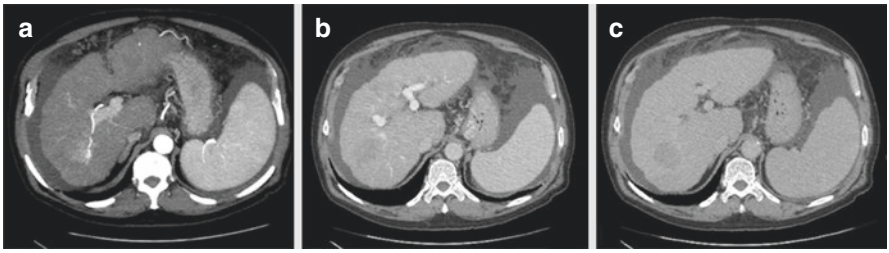

Fig. 5.1 Typical CT imaging features for hepatocellular carcinoma. (**a**) Axial plane, arterial phase CT scan demonstrates arterial wash-in associated with afferent arteriole on maximum intensity projection reconstruction. (**b**, **c**) Portal and delayed phases respectively show the progressive wash-out of the lesion. The figure is published with the patient's authorization

specificity and sensitivity increase (Fig. 5.1) [8]. Early HCCs are, however, characterized by a hypo- or isoenhancement in arterial phase imaging, due to their incomplete neoangiogenesis [7]. Another characteristic imaging feature included by LI-RADS among the major criteria for HCC diagnosis is the presence of a peripheral "capsule appearance", histologically composed also by fibrous tissue, which explains its late enhancement due to retention of gadolinium in the extracellular interstitial spaces [6, 9]. Another characteristic feature of HCC, included in the "ancillary criteria" of LI-RADS, is the "nodule-in-nodule" appearance (Fig. 5.2) [10]. Vascular invasion is more frequent in progressed HCC. It can be microvascular, if it is only appreciable on microscopy, or macrovascular (Figs. 5.3 and 5.4) which refers to macroscopically visible tumor in vein (LR-TIV) [11]. Both of them are indicators of a poor overall survival and an aggressive biologic behavior [6]. The presence of intralesional fat is very specific for HCC and this is well evaluable on MRI T1-weighted GRE dual-echo sequences, with loss of signal in the out-of-phase images (Fig. 5.5) [10].

5.5 Liver Imaging Reporting and Data System (LI-RADS)

The LI-RADS system aims to standardize terminology, technique, interpretation, reporting and data collection in liver imaging for HCC surveillance and is promoted by the American College of Radiology and developed by an international committee of radiologists, hepatologists, pathologists and surgeons. US LI-RADS v2017 is limited to screening or surveillance in patients at risk for HCC, to identify HCC at an early stage, when it is potentially curable. CEUS LI-RADS v2017, as well as CT and MRI LI-RADS, should be applied in patients at high risk of HCC, including in this category adult cirrhotic patients, patients with chronic HBV, and patients with current or prior HCC.

The LI-RADS v2018 algorithm is articulated in successive diagnostic steps directed first to the identification of diagnoses other than HCC (LR-1, LR-2, LR-TIV, LR-M [malignancy other than HCC] or LR-NC [non-categorizable]) and

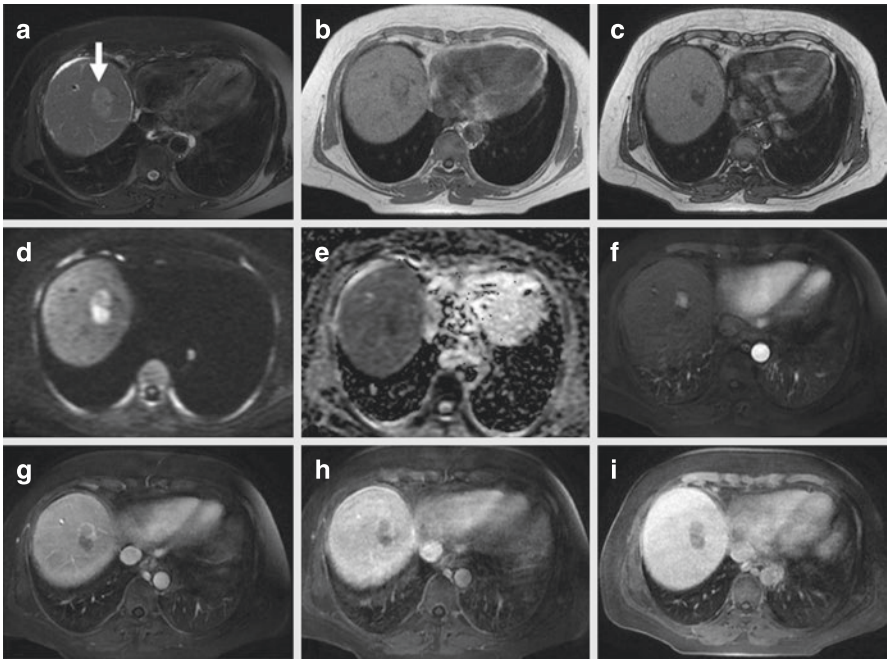

Fig. 5.2 Small hepatocellular carcinoma nodule-in-nodule appearance. (**a**–**c**) A 3-cm nodule is appreciable on segment 8 (white arrow), mildly hyperintense on axial T2-weighted fat saturated (**a**), partially hyperintense on T1-weighted in-phase gradient echo (GRE) (**b**) with a partial signal drop-out on axial out-of-phase GRE (**c**) as expression intralesional fat. (**d**, **e**) Diffusion-weighted imaging (**d**), and apparent diffusion coefficient map (**e**) show lesion restriction related to hypercellularity. (**f**–**i**) Axial T1-weighted fat-saturated sequence in the arterial phase shows intense arterial wash-in of the upper portion of the nodule (**f**), with wash-out in the portal venous (**g**) and delayed (**h**) phases and lack of contrast agent uptake in the hepatobiliary phase (**i**). The figure is published with the patient's authorization

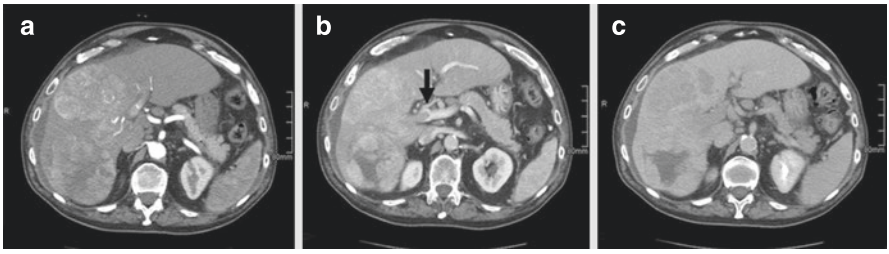

Fig. 5.3 A voluminous lesion subverts the structure of the right liver, with imaging compatible with hepatocellular carcinoma appreciable on the CT axial images in the arterial (**a**), portal venous (**b**) and delayed (**c**) phases. Macrovascular invasion is observed with neoplastic thrombosis causing occlusion of the right portal vein, subocclusion of the left portal vein and the common portion of the mesenteric splenic confluence (black arrow). The figure is published with the patient's authorization

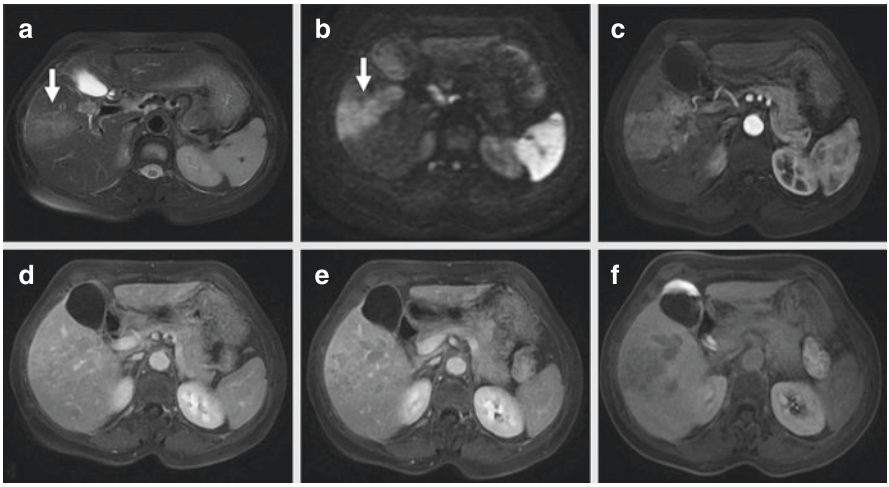

Fig. 5.4 Hepatocellular carcinoma with macrovascular invasion on MRI: between hepatic segments 5 and 6 a poorly defined mass associated with neoplastic thrombus in the anterior right portal vein branch. (**a**) Lesion with intermediate signal on the axial T2-weighted fat saturated image. (**b**) Restriction on diffusion-weighted imaging (white arrows). (**c**) Axial T1-weighted fat saturated image during the arterial phase with lesion wash-in. (**d**, **e**) Axial T1-weighted fat saturated images during the portal venous (**d**) and delayed (**e**) phases, with lesion wash-out. (**f**) Contrast-enhanced MRI axial T1-weighted fat suppressed image in the hepatobiliary phase with lesion hypointensity

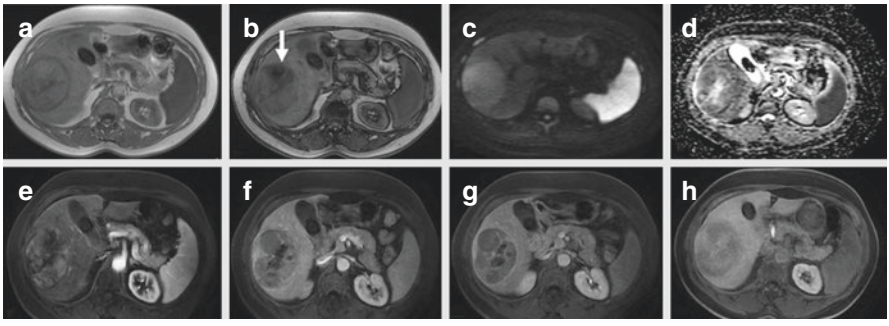

Fig. 5.5 Hepatocellular carcinoma with fat metaplasia at segment 5 and 6. (**a**) Axial T1-weighted gradient echo (GRE) in-phase sequence where the lesion is heterogeneously isointense to liver parenchyma. (**b**) Axial T1-weighted GRE out-of-phase sequence with signal drop-out due to intracellular fat component (white arrow). (**c**) Axial diffusion-weighted images with diffusion restriction of the lesion, (**d**) also appreciable on apparent diffusion coefficient map. (**e**–**g**) After contrast agent administration, the lesion shows slight hyperintensity on the axial T1-weighted fat saturated sequence in the arterial phase (**e**), with progressive wash-out in the portal venous (**f**) and delayed (**g**) phases. (**h**) Hypointensity of the lesion on axial T1-weighted fat saturated sequence, in the hepatobiliary phase

then to a diagnostic table that helps to distinguish LR-3, LR-4 and LR-5 [7]. The classification from LR-1 to LR-5 is intended as growing probability of HCC malignancy, where LR-1 and LR-2 are considered respectively "certainly benign" and "probably benign".

5.6 Treatment Response: mRECIST and LI-RADS

Some HCC treatment strategies act by induction of tumor necrosis or reduction in vascularity, which is not necessarily accompanied by tumor reduction. The World Health Organization and Response Evaluation Criteria in Solid Tumors (RECIST) criteria do not address measures of antitumor activity other than tumor dimensional reduction [12]. In 2010, Lencioni et al. proposed a modified version of the RECIST (mRECIST) for HCC, in which tumor necrosis represents a treatment effect [13]. The mRECIST for HCC has introduced a classification in the determination of tumor response based on disappearance of tumoral arterial enhancement and changes in the sum of diameters of target lesions; it includes complete response, partial response, progressive disease, stable disease, or not evaluable disease.

5.6.1 LI-RADS Treatment Response Algorithm

The LI-RADS includes a treatment response algorithm that can be applied to patients with HCC treated by ablation, intra-arterial therapies, or external beam radiation therapy. The algorithm is based on the visual assessment of tumor viability defined as nodular, mass-like, or thick, irregular tissue in or along the treated lesion showing APHE or wash-out appearance. The LI-RADS algorithm expands on the mRECIST approach not only by defining viable disease but also by providing non-evaluable, equivocal, and nonviable treatment response categories. Unlike mRECIST, the LI-RADS treatment response categories are assigned on a lesion-by-lesion basis [7].

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Pathology of Hepatocellular Carcinoma

6

Andrea Baiocchini, Lucia Rosalba Grillo,
and Giuseppe Maria Ettorre

6.1 Introduction

Hepatocellular carcinoma (HCC) is a primary malignant tumor of the liver consisting of neoplastic hepatocytes. Our understanding of this neoplasm has evolved in recent years and new histological variants and new molecular alterations have been described. By means of new immunohistochemical staining it is now possible to evaluate the response to immunotherapy making the pathologist instrumental in the development of personalized therapies. HCC can affect any age and both sexes. It arises in cirrhotic and non-cirrhotic livers, the former being more frequent. Common risk factors are viral hepatitis C and B, chronic vascular diseases of the liver, alcohol consumption, non-alcoholic steatohepatitis, primary hemochromatosis and malignant transformation of an adenoma. Fibrosis is certainly one of the key factors in the development of HCC, but numerous other factors are yet unknown. The discovery of new molecular signatures in HCC, associated with distinct macroscopic growth patterns, have allowed a molecular classification of this neoplasm.

6.2 Main Gross Pattern of Hepatocellular Carcinoma

The size of HCC can vary greatly, ranging from a diameter of less than 2 cm to very large tumors with a diameter greater than 20 cm that can replace an entire lobe of the liver.

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There are essentially three main macroscopic patterns: nodular, massive, and diffuse or cirrhotomimetic. Related to the hepatectomy specimens, the Liver Cancer Study Group of Japan (LCSGJ) proposed to divide the nodular type into two subclasses: distinctly nodular and vaguely nodular [1]. The former has been further divided by Shimada et al. into simple nodular, simple nodular with extranodular growth (Fig. 6.1) and confluent multi-nodular [2].

- **Early/small HCC** (E-HCC) is defined as a hepatocarcinoma ≤2 cm with distinct margins. The concept of small size emphasizes the diameter of the neoplasm and not an early stage of hepatocarcinogenesis. Macroscopically, they can be single nodular, single nodular with extracapsular growth, confluent multinodular and vaguely nodular [3]. Microscopically, E-HCCs are characterized by a population of well-differentiated neoplastic cells of small or medium hepatocyte-like size; increase in the density of the nuclei (crowding); thin trabecules; pseudoglands with or without bile. E-HCCs can contain poorly differentiated areas that influence the prognosis (nodule-in-nodule). E-HCCs are potentially invasive malignant neoplasms that infiltrate the adjacent parenchyma, invade blood vessels, and metastasize. Compared to the classic HCC they have better differentiation and the disease-free interval is longer with a low recurrence rate. Main risk factors for relapses are the absence of a capsule, vascular microinvasion, and poor cellular differentiation.
- **Nodular HCC** is a well-circumscribed neoplasm of spherical or ovoid shape, characterized by well-defined margins and expansive growth pattern. This HCC often arises in the context of a cirrhotic liver and is often formed by several juxtaposed nodules that can have different colors from yellowish, reddish, to green (Fig. 6.2). This color variation may be due to various factors such as bile content, areas of necrosis and hemorrhages. The texture can range from soft, crumbly, to firm and depends on the extent of necrosis and on stromal reaction.

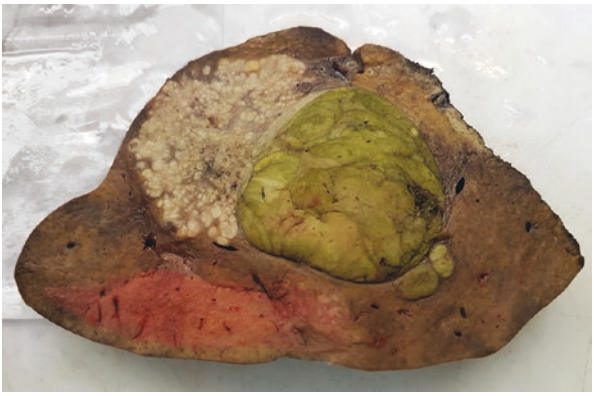

Fig. 6.1 Nodular hepatocellular carcinoma (HCC) with dominant encapsulated nodule with bile accumulation and extracapsular growth with adjacent confluent multinodular HCC

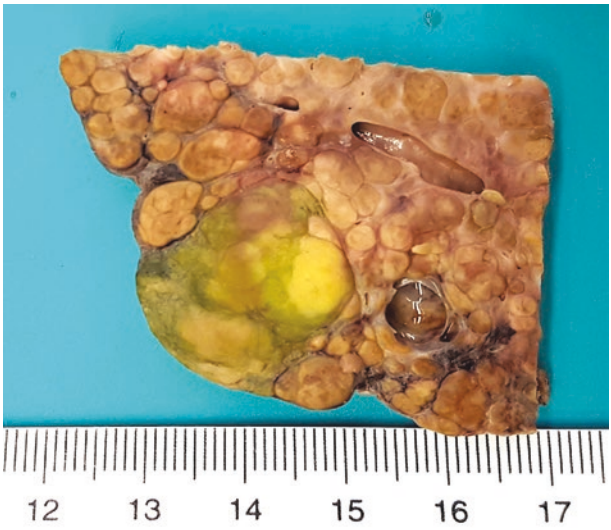

Fig. 6.2 Subcapsular nodular hepatocellular carcinoma in a cirrhotic liver with expanding growth pattern and bile accumulation

- **Massive HCC** causes a marked increase in liver volume that appears to be mostly replaced by large tumor masses that can occupy an entire lobe. On cut surface, massive HCC has a soft consistency and variegated appearance due to the presence of necrosis and hemorrhagic areas.
- **Diffuse or cirrhotomimetic HCC** is characterized by the presence of numerous nodules, similar to each other in size and shape, which can reach several hundred and fill the entire liver. Tumor nodules can be confused with the regenerative nodules of cirrhosis. The presence of numerous satellites around a dominant nodule is not considered a cirrhoticomimetic carcinoma.

In addition, there are at least two other variants represented by the pedunculated type and by the so-called icteric-type HCC.

- **Pedunculated HCC** protrudes from the liver; it is often solitary and can reach a huge diameter. In relation to the presence of a peduncle (hanging lesions) or its absence (sessile forms) it is sometimes sub-classified into type I and type II, respectively. The tumor may also have a long stalk and appear as a free polypoid mass in the abdominal cavity. Sessile forms have a dome-shaped appearance and are covered by the liver capsule (Fig. 6.3).
- **Icteric-type HCC** have the tendency to invade the main bile ducts with occlusion of the lumen and the onset of jaundice. On gross examination these tumors appear nodular with a tumor mass in the lumen of a dilated intrahepatic bile duct. Intraductal growth does not seem to have a different prognosis than other HCCs although the rate of portal venous invasion is higher.

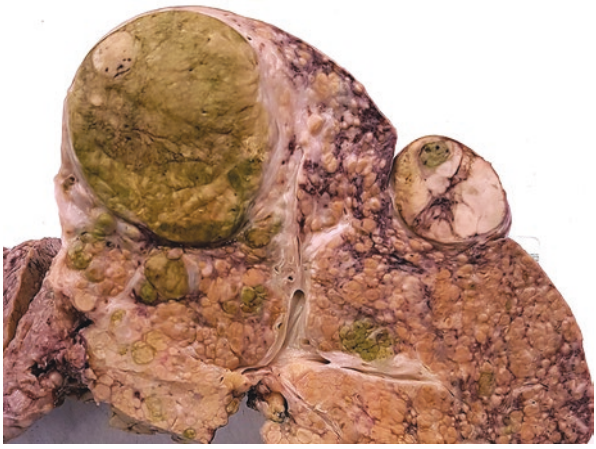

Fig. 6.3 Nodular hepatocellular carcinoma (HCC) in a cirrhotic liver. On the right a lesion that protrudes from the liver surface with a sessile form is visible (pedunculated HCC, sessile type)

6.3 Histology

The microscopic features of HCC reflect its biological complexity and change according to differentiation. Two key aspects of the morphology of these tumors are the absence of portal tracts and the presence of aberrant arteries. HCC shows architectural changes and cytological alterations. The main tumor architectural changes consist in a trabecular, solid or compact, pseudoglandular or acinar, and macrotrabecular (more than 10 cells thick) pattern (Fig. 6.4). Some HCCs show a pelioticlike appearance and many HCCs can have mixed architecture. The tumor stroma is usually not very prominent but cases with stromal reaction (scirrhous HCC, sclerosing HCC, and fibronodular HCC) have been recorded. The stromal reaction plays a decisive role in the growth, spread and even differentiation of the neoplasm. HCCs are highly vascularized neoplasms and show two patterns of microvessels: sinusoidlike and capillary-like microvessels [4] that affect the biological behavior of the neoplasm. E-HCC and distinctly nodular HCC are generally surrounded by a variable thickness fibrous pseudocapsule (FPC) that can be complete or incomplete. FPC influences the biological behavior of the neoplasm [5].

The cytological alterations of neoplastic hepatocytes are as follows:

- In well-differentiated HCC they appear very similar to normal hepatocytes, and in these cases the diagnosis is often based on nuclear crowding and increase in cytoplasmic basophilia.
- In poorly differentiated HCC the cells are characterized by irregular nuclei, cellular pleomorphism and giant cells with highly atypical nuclei.

In all HCCs numerous inclusions in the cytoplasm of tumor cells are frequent. They include eosinophils globules, hyaline globules, pale bodies and Mallory-Denk bodies (MDBs). Some tumoral hepatocytes can store glycogen or fat and contain bile, the latter specially in biliary canaliculi.

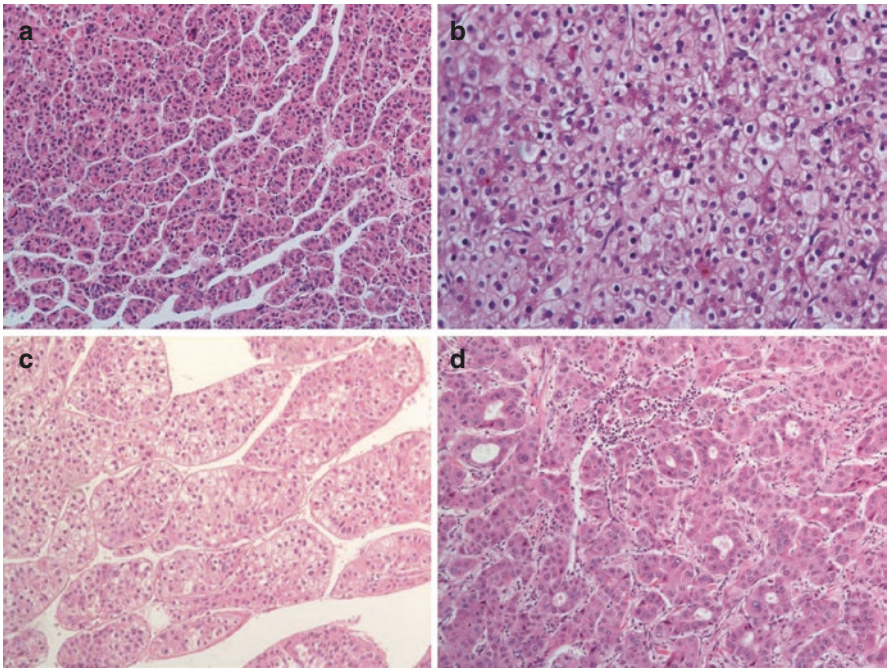

Fig. 6.4 Main histological pattern of hepatocellular carcinoma: (**a**) trabecular; (**b**) solid; (**c**) macrotrabecular; (**d**) pseudoglandular

6.4 Grading, Staging, and Metastases

An important prognostic factor is tumor grade. It predicts patient survival and disease-free interval after HCC resection and liver transplantation. A well-defined, reproducible, and widely accepted grading system has yet to be developed. From a strictly clinical point of view, grading based on architectural and cytological features in a three-tiered system is preferred: well-differentiated, moderately differentiated and poorly differentiated tumors [6], in contrast to the four-tiered grading system by Edmondson and Steiner [7], which is more appropriate for clinical research.

The main factors in HCC staging are: tumor size, multifocality, tumor grade and angiolymphatic invasion. Staging is essential to indicate optimal treatment. The AJCC/UICC (American Joint Committee on Cancer/Union for International Cancer Control) system is very useful for predicting the outcome after surgical resection and transplantation.

The most common sites of HCC metastases are the lung, bone, abdominal lymph nodes and adrenal glands. Peritoneal carcinosis is rare but may be present. Direct invasion of the diaphragm is also possible.

6.5 Immunohistochemistry

Immunohistochemistry (IHC) has to answer two questions: whether the lesion of hepatocellular origin is benign or malignant and whether the neoplasm is an HCC or another malignant tumor. In the non-cirrhotic liver, if the lesion has a clear hepatocellular differentiation, it is necessary to evaluate whether it is a focal nodular hyperplasia, an adenoma or an HCC. In the cirrhotic liver one must differentiate between a macroregenerative nodule, a dysplastic nodule (low or high grade) and HCC. The following immunostains are commonly used for major differentiation diagnosis: glypican-3, alpha-fetoprotein (AFP), HepPar1, arginase-1, polyclonal CEA and CD10 (both canalicular pattern).

6.6 Variants

Several histological subtypes of HCC have been recognized. The subtypes or variants of HCC have a distinct histological morphology, distinct immunohistochemical and molecular markers, a different clinical correlation and a different prognosis [8].

Combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CCA) is a distinct molecular lesion that can originate in cirrhotic and non-cirrhotic livers and its frequency is estimated at around 2–5% of primary liver tumors. Prognosis is intermediate between HCC and CCA, lymph node metastases are frequent and it has higher risk of recurrence after surgical resection and higher risk of relapse after orthotopic liver transplantation (OLT). A neuroendocrine component in HCC or CCA is very rare. These tumors belong to the group of *mixed neuroendocrine-non-neuroendocrine tumors* (MiNENs). In *clear-cell HCC* we have more than 50% of clear cells. The prognosis is better than non-clear HCCs and the main differential diagnosis is with renal cell carcinoma metastases and other clear-cell tumors.

Other peculiar variants of HCC are *granulocyte-colony-stimulating factor producing HCC*, *lymphocyte-rich HCC*, *scirrhous HCC*, and *steatohepatitic HCC*. The latter subtype often arises in the context of steatohepatitis and shows macrovesicular steatosis, ballooned cells, Mallory-Denk bodies, intratumoral inflammation and fibrosis. The amount of fat needed to qualify a steatohepatitic HCC must be greater than 33%. There seems to be no difference in survival from ordinary HCC.

Fibrolamellar HCC is a distinct subtype that arises in young patients without cirrhosis and no underlying liver disease, with distinct clinical features, as well as unique morphologic, immunohistochemical, and molecular findings. After surgical resection, approximately 55% of cases has intrahepatic recurrence within the first 5 years. Macroscopically, it is a voluminous neoplasm with central scar and calcifications. The neoplastic cells are polygonal, eosinophilic, with macronucleoli, immersed in an abundant collagen stroma with a lamellar appearance. Pale bodies are frequent but not specific. These tumors are HepPar1+ and arginase 1+. Eosinophilic granular cytoplasm is CD68 positive and tumor cells express CK7 and CK19. The *DNAJB1-PRKACA* fusion gene is considered to be pathognomonic [9].

A recently described subtype of HCC is termed *macrotrabecular/massive HCC* (MTM-HCC). MTM-HCC is characterized by large trabeculae with a thickness greater than 10 cells affecting at least 50% of an HCC. It frequently originates in non-cirrhotic livers and it is often associated with high levels of AFP. These tumors are large in size and have frequent angioinvasion with poor prognosis.

Other variants are: *chromophobe HCC*, *fibronodular HCC*, and *myxoid HCC*.

6.7 Differential Diagnosis

The main differential diagnosis of HCC is with benign and malignant neoplasms in cirrhotic and non-cirrhotic livers. In the latter the differential diagnosis is made with focal nodular hyperplasia and adenoma, while in cirrhotic livers with macroregenerative nodules and with low- and high-grade dysplastic nodules. The most suggestive aspects for the diagnosis of HCC are stromal invasion and sinusoid arterialization, well highlighted with immunostain for CD34. The use of a panel of IHC markers (glypican 3, glutamine-synthetase, and HSP70) can help in the differential diagnosis between benign and malignant nodules. A clear positivity of at least two out of three markers strongly supports HCC.

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Hepatological Evaluation and Biomarkers

7

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7.1 Introduction

Most patients with hepatocellular carcinoma (HCC) have underlying liver disease [1]. The need to predict the risk of post-hepatectomy liver failure (PHLF) should be of greater interest before performing a liver resection in a cirrhotic patient, especially if the indication is hepatocellular carcinoma (HCC), which can be treated with other options, including liver transplantation, thermoablation or effective palliative techniques, such as chemoembolization or radioembolization.

The task of the hepatologist, in supporting the surgical team, is to help in identifying the cirrhotic patient at greater risk of clinical decompensation of portal hypertension, up to the fearful development of postsurgical liver failure. In this chapter, we explain how the evaluation must go beyond the simple measurement of the well-known parameters of liver function. Over the past decade there has been substantial progress in hepatic resection for hepatocarcinoma (HCC) [2], which can be explained by a better selection of surgical candidates and improvement of pre- and postoperative management [3]. Nevertheless, liver failure after major resection in cirrhosis is still associated with high morbidity and mortality [4], and the fear of such complications therefore continues to limit the therapeutic possibilities of hepatic resection in patients with HCC. Liver surgery for hepatocellular carcinoma (HCC) remains limited by two major aspects: a sufficient remnant of liver volume

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must be preserved [5] and, second, ischemic injury to remnant liver cells should be reduced as much as possible to minimize reperfusion injury. The threshold below which the liver remnant becomes insufficient depends on different variables, the most commonly proposed being age, etiologies of liver disease, grade of hepatic disease and portal hypertension, and hepatic functional reserve [6].

Age alone does not contraindicate liver resection. In previous studies on liver resection for HCC, the age of 70 years was reported as one of the negative predictive factors for postoperative survival. The most recent literature has, however, refuted this result and to date a careful selection of the elderly patient allows one to obtain survivals similar to those of younger patients [6].

7.1.1 Etiologies of Liver Disease: Metabolic-Associated Fatty Liver Disease

Among the different etiologies of liver disease, particular consideration in patients evaluated for liver resection should be given to hepatic steatosis, a constantly increasing cause of liver disease. Growing attention is being paid to advanced steatosis as it seems to compromise or delay liver regeneration after major resection. The risk of resection begins to increase in the case of steatosis involving more than 30% of hepatocytes [7]. Experimental data indicate that macro-type steatosis, rather than micro-steatosis, increases surgical risk. In cases of steatosis involving 30–60% of hepatocytes, larger resections should be carefully evaluated. In cases of steatosis >60% of hepatocytes, the resections should be limited (<2 hepatic segments and preferably an enucleation is advisable) [8].

In the case of a suspicion of advanced steatosis, it is recommended to perform a liver biopsy to exclude a critical burden of steatosis and eventually plan a preoperative medical treatment. The suspicion of hepatic steatosis should go beyond the simple external evaluation of body mass index or composition or the presence of diabetes, as demonstrated in a seminal study on liver resection in metabolic-associated fatty liver disease (MAFLD), where 31.9% of patients with hepatic steatosis did not show any signs of metabolic syndrome nor a history of alcohol abuse and were not treated with steatogenic chemotherapy (i.e., irinotecan) before liver resection [7].

In these patients, histological evaluation allows to assess the presence of non-alcoholic steatohepatitis (NASH) and the degree of fibrosis. Reddy et al. found that patients with NASH had higher 90-day overall mortality (56.9% vs. 37.3%; $p = 0.008$) and any hepatic-related morbidity (28.4% vs. 15.7%; $p = 0.043$), compared with corresponding controls. This includes a higher rate of postoperative hepatic decompensation (16.7% vs. 6.9%; $p = 0.049$) and a higher risk of post-hepatectomy liver insufficiency (6.9% vs. 2.0%; $p = 0.170$). On multivariable logistic regression, resection of four or more segments (OR 9.4; 95% CI: 4.1–21.5; $p < 0.001$), and NASH (OR 2.7; 95% CI: 1.0–6.1; $p = 0.016$) were independently associated with any hepatic-related morbidity. Hence liver inflammation is the key feature to include among the negative predictive factors of liver

resection outcome in patients with MAFLD [7]. A more recent study performed in an Asian cohort of patients also found that liver failure of all grades was higher in the MAFLD group compared with other etiologies (29.5% vs. 9.5% moderate liver failure, and 20.1% vs. 7.2% severe liver failure; $p < 0.0001$). Extrahepatic complications, such as cardiac disease (11.8% vs. 6.8%; $p = 0.02$) and pulmonary embolism (2% vs. 0.4%; $p = 0.01$) were also higher in the MAFLD group compared with other etiologies [9]. A drawback of these studies is the absence of a clear distinction between MAFLD and NASH.

7.2 Methods to Evaluate Liver Function and Hepatic Reserve Before Surgery

The safety of resective liver surgery in patients with cirrhosis has significantly improved in the last decade, but mortality related to surgery is still estimated between 3% and 15% [3]. Post-hepatectomy liver failure (PHLF) is the most feared complication, with a mortality rate of up to 50%. In this chapter, for the definition of PHLF we adopted the classification given by the International Study Group of Liver Surgery in 2011. According to this definition, the parameters to define the three grades (A, B, C) of PHLF are based on hepatic (INR/neurologic symptoms), renal (acute kidney injury criteria) and pulmonary function (arterial oxygen saturation) [10]. For convenience, we will use the definition of "mild" (INR between 1.5 and 2 + grade I–II of hepatic encephalopathy) or "severe" (INR > 2 + grade III–IV hepatic encephalopathy) to mean those PHLF in which there was a deviation from the regular clinical management without or with invasive treatment, respectively.

7.2.1 Predictors of Post-hepatectomy Liver Failure

Invasive portal pressure measurement is one of the most important and more concordantly evaluated indicators of outcome. Moreover, a hepatic venous pressure gradient (HVPG) >6 mmHg indicates the presence of cirrhosis more accurately than liver histology [11]. Also in the case of compensated cirrhosis without esophageal varices, a further stratification is warranted, based on the measurement of portal pressure, which is most commonly assessed by the invasive (transjugular) measurement of HVPG, consisting of the difference between the wedged (or balloon-occluded) hepatic venous pressure and the free hepatic venous pressure. The HVPG accurately reflects portal pressure in sinusoidal causes of portal hypertension [12]. Although it is fairly easy to perform and safe, accurate measurement requires specific training [13]. For this reason, the number of studies conducted to assess the role of the HVPG as a prognostic factor are also limited in number, although the conclusions are fairly solid and concordant [14, 15]. The stratification of compensated cirrhosis has also been based on the HVPG results, with HVPG between 5 and 10 mmHg indicating mild portal

hypertension and above 10 mmHg indicating a clinically significant portal hypertension (CSPH) at risk of ascites, encephalopathy, jaundice and varices [12].

The first reports on HVPG assessment before liver resection were published in 1996 and 1999 by the Barcelona Clinic Liver Cancer group and included a small series of patients applying for hepatic resection (29 and 43 patients, respectively) [12]. Based on these two studies, the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) recommended in their guidelines the use of HVPG in the selection of hepatic resection candidates (indicating HVPG < 10 mmHg and normal bilirubin as key positive predictors of survival in patients undergoing resection). More recently, a French multicenter study on more than 300 patients confirmed that among the 20 patients with PHLF, HVPG was a strong independent predictor of worse outcome. PHLF was 8.3 vs. 50% (p = 0.001) if HVPG was below or above 10 mmHg, respectively. However, the latest published EASL HCC guidelines mitigate the role of HVPG > 10 mmHg as a contraindication to surgery, and suggest that the role of portal hypertension in deciding on eligibility for resection of HCC should not be absolute but always balanced with the extent of hepatectomy and liver function indicators [16]. We also believe that resection decisions must also be taken on the basis of the localization of the hepatic nodule; for instance, the posterior sectors are burdened with greater technical difficulties [17]. The predictive value of HVPG is further enhanced when combined with the MELD score, using for the latter the value of 10 as a cut-off. In patients with HVPG ≥ 10 mmHg but with a MELD score <10, severe PHLF occurred in 14.3% of cases when an enucleation was performed, whereas this percentage increased up to 66.7% in cases of more extended hepatectomies (more than 2 segments).

In patients with an HVPG > 10 mmHg and MELD ≥10, severe PHLF occurred in 87.5%, even in the case of limited resections. Less than 20% of the patients enrolled experienced a normal and uneventful postoperative course in spite of having a pressure gradient ≥10 mmHg [13]. Therefore, the most appropriate approach to avoid excluding patients who might otherwise benefit from a curative HCC resection, or who might otherwise take too high a surgical risk, is to use a multiparametric algorithm as the one recently proposed by Citterio et al. and then endorsed by EASL [18]. According to this hierarchical interaction (portal pressure + extent of resection + MELD score), HVPG > 10 mmHg or indirect evidence of CSPH are no longer an absolute contraindication for HCC resection in patients with cirrhosis, if MELD is below 10 and the resection limited. Other studies which included patients with HVPG > 10 mmHg found an acceptable risk of PHLF of about 5–30%, with an acceptable 36-month survival (about 75%) [19]. In the case of HVPG > 10 mmHg, we should select those with a good performance status (PS 0–1), with preserved liver function (MELD <10), and without any sign of clinical decompensation of liver cirrhosis (only Child A5–6), including the absence of esophageal varices.

7.2.2 Biomarkers and Dynamic Test to Recognize Liver Function and Its Reserve Capacity

Among the various biomarkers used to investigate liver function, certainly the most validated are bilirubin values preresection and coagulation status. The use of hepatic clearance of indocyanine green (ICG) has been widely used in Asian countries for surgical decision making. ICG is a dark bluish-green tricarbocyanine dye that rapidly binds to plasma lipoprotein and is metabolized completely and solely by hepatocytes. ICG clearance can be measured by giving a single intravenous injection (around 0.5 mg/kg) and determining the blood level 15 min later (ICG-R15) [14]. The normal values of the ICG-R15 range between 8% and 14%. Patients with clearance kinetics of less than 14% are considered fit for major hepatectomy, whereas those with >20%, a major hepatectomy should be not recommended. According to some authors, in patients with a retention between 14% and 20%, surgery should be proposed only if the liver remnant is >50% [5]. ICG can be measured directly by using a fingertip optical sensor, which allows a continuous measurement of serum ICG concentration [12]. Much of the experience of using ICG before surgery comes from studies conducted on Asian patients, with a high prevalence of early HBV-related cirrhosis. Makuuchi et al. in a seminal study conducted on a large sample of Asian patients proposed an algorithm based on ICG-R15, ascites, bilirubin levels and the extent of liver resection [20]. However, in a recent French multicenter study on 343 patients, applying the Imamura and Makuuchi criteria, as many as 13 patients would not have been candidate for resection surgery due to a high estimated risk of PHLF, while in the French experience 92% of them were alive at the surveillance after 3 months [15].

7.2.3 MELD Score

Another algorithm to assess the operational risk, elaborated with the intention of having a quick and simple evaluation tool, is based on the use of MELD <10, associated with natremia for those with MELD 9–10. In an external validation, also this algorithm failed its reproducibility.

7.2.4 Fibrosis Biomarkers and Noninvasive Evaluation of Portal Hypertension

With regard to fibrosis biomarkers, no study conducted so far has shown a correlation between their serum levels and the development of clinically significant portal hypertension. Platelet counts also have less than 0.75 accuracy at the AUROC (area under the receiver operating characteristic) curve.

On the other hand, noninvasive tests are increasingly being used to improve prediction of CSPH. Liver stiffness measurement (LSM) is the most validated test for indirect portal pressure measurement, although its correlation with HVPG is not

excellent (AUROC 0.67–0.86) [21]. Our advice is to use, in order to assess patients at risk of HVPG > 10 mmHg a cut-off of LSM equal to 20–25 kPa (AUROC 0.93 for CSPH) [22]. Spleen elastometry (SEM) has been tested in a more limited number of studies, but a cut-off <40 kPa is highly sensitive (98%) to rule out HVPG > 10 mmHg, while SEM > 50 kPa is 90% specific for CSPH. The liver surface nodularity (LSN) score performed at CT or ultrasound [23] predicts HVPG > 10 mmHg in 88%. While the diameter of the spleen as well as that of the portal vein have a lower accuracy. A recent portal hypertension score has been proposed to combine LSM and LSN to improve the detection reliability for CSPH to more than 75% [24].

7.3 Conclusion

In accordance with the recent EASL guidelines on noninvasive liver disease severity and prognosis evaluation methods, we believe that HVPG remains the only validated tool for an exact assessment of portal hypertension severity and cannot be substituted by noninvasive techniques [25].

In conclusion, none of the proposed algorithms based on biomarkers of liver function has entered routine surgical practice. Clinicians and surgeons engaged in resective liver surgery know that portal hypertension is the most important prognostic factor associated with PHLF. In consideration of the logistic difficulty to perform invasive portal pressure measurement on all surgical candidates, our idea is to first study patients with noninvasive methods and to refer to a center with a hepatic hemodynamics team those at high risk of clinically significant portal hypertension. Liver function should obviously not be neglected but integrated in a multiparametric consideration, bearing in mind that in patients with bilirubin between 27 and 33 mmol/L or MELD scores about 10 and portal hypertension, surgical consideration should not be denied *a priori*. A short delay of surgical resection, allowing better clinical management, is recommendable in these cases.

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Part III

Treatment

Percutaneous and Laparoscopic-Assisted Ablation of Hepatocellular Carcinoma

8

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8.1 Introduction

Over the last few decades, percutaneous and laparoscopic ablative techniques have grown as a potentially curative therapeutic option for hepatocellular carcinoma (HCC). Ablation refers to necrosis achieved using chemicals or thermal energy delivered directly to the tumor under image guidance. The seminal technique was percutaneous ethanol injection (PEI). Subsequently, hyper-thermal ablative therapies emerged, including radiofrequency ablation (RFA) and microwave ablation (MWA). Ablation is now considered a valid complement to surgery or even a replacement for resection. It enables sparing of parenchyma, alone or in combination with surgery, and allows treatment of high-risk patients.

8.2 Treatment Indications

Beside thermal ablation, potentially curative therapies for HCC include liver resection (LR) and liver transplantation (LT). Owing to the absence of randomized trials comparing the three approaches, when selecting the best option, it is recommended to evaluate the main independent clinical prognostic factors of HCC: tumor burden, vascular invasion, extrahepatic spread, liver function, portal hypertension, and patient conditions (Eastern Cooperative Oncology Group [ECOG] Performance Status) [1]. Both the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases have endorsed the Barcelona

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Clinic Liver Cancer (BCLC) staging system that incorporates all the above-mentioned items [1, 2].

Currently, thermal ablation may be considered as first-line therapy in very early-stage HCC (BCLC 0: single tumor <2 cm, no vascular invasion/satellites, preserved liver function, ECOG-0) and is the best option for patients with early-stage HCC (BCLC A: single tumor >2 cm or three nodules <3 cm, preserved liver function, ECOG-0) who are not candidates for LR. In selected cases, LR leads to the best outcomes (5-year survival of 60–80%) and represents the treatment of choice for patients without cirrhosis, but LR in the cirrhotic liver should be reserved only for patients with solitary tumors, very well-preserved liver function, no portal hypertension or platelet count ≥100,000/mL [3]. Even though an extension of these criteria could be considered, especially after the promising results obtained in experienced centers with LR in patients who did not satisfy the requirements, a consensus has not been reached yet [4]. To address the issue of patients with small tumors and impaired liver function, with respect to the *therapeutic hierarchy* strategy, ablation can be considered the best option for patients affected by both unresectable BCLC A and B HCC [5].

Ablation therapy may serve to treat LT candidates within the Milan criteria to reduce the drop-out risk due to tumor progression while waiting (*bridging*) or to bring patients within validated criteria for LT (*downstaging*) [6]. Indeed, response to bridging and downstaging treatments affects the rate of post-LT tumor recurrence [7].

8.3 Ablation Techniques

"Percutaneous" refers to any procedure that delivers chemicals or energy by a guided puncture of the tumor through the abdominal wall of the patient under local anesthesia.

PEI was one of the initial ablative techniques employed for treatment of HCC. Ethanol (95–99.5%) induces coagulative necrosis of the nodule because of cellular dehydration, protein denaturation, and chemical occlusion of small tumor vessels. PEI is performed under ultrasound (US) guidance or in combination with computed tomography (CT). A needle is advanced inside the target lesion and 5–10 mL of agent is injected (several times for tumors >2 cm). PEI is fast and cheaper compared to other techniques [8], but it is characterized by insufficient control of ethanol spread, inhomogeneous distribution within the lesions, and inadequate margin treatment due to heterogeneity within the tumor architecture. Almost complete necrosis can be achieved in HCC ≤ 2 cm treated with PEI [9], but for larger nodules local recurrence is common [10], particularly if compared to thermal ablation techniques.

Heat producing coagulative necrosis of hepatocytes is the mechanism behind RFA and MWA.

RFA produces heat by using high frequency alternating current passed through a circuit including a generator, a monopolar electrode needle advanced into the target

lesion, dispersive grounding plates located on the patient's skin, and the tumor, the resistive element. The applied current agitates ions around the tip of the electrode and heat is then conducted deeper into the surrounding tissue. Irreversible cell injury depends on the duration of heat application: the shorter the application the higher the temperatures required [11]. Evidence suggests immediate cell death at temperatures of 60–100 °C or within 5–6 min of heat application >50 °C [12]. Heat allows extension of the necrosis to a safety ring in the peri-tumoral tissue, which might eliminate undetected satellites and might explain the fewer local recurrence compared to PEI. RFA offers increased control over the ablation zone shape, but this is also impacted by increased tissue impedance, which occurs with tissue desiccation and vaporization [11]. This issue has been overcome with the advent of MWA.

Microwaves are generated by applicators in a range between 915 MHz and 2.45 GHz and transmitted by an antenna to polar water molecules, resulting in tissue heating. They penetrate through biologic materials with high impedance, such as dehydrated or charred tissue. In other terms, MWA can deliver high temperatures for longer time, thus improving ablation efficacy by increasing thermal conduction into the surrounding tissue [11] and allowing faster treatments of larger tumors compared to RFA [13].

The efficacy of percutaneous ablation depends on the imaging-guidance tools, given that precise tumor targeting is essential for achieving complete necrosis. Currently, US, computed tomography (CT), and cone-beam CT are the modalities of choice for guidance and result assessment. Fusion imaging is a novel technique that enables the overlay of multiple imaging and is helpful in small tumors to decrease the risk of missing the target [14].

Hyperthermal ablation techniques have drawbacks. Heat applied near large vessels, typically the hepatic veins, undergoes thermodynamic exchange with the blood stream and ablation efficacy is diminished. MWA is less susceptible to this phenomenon (heat sink effect) than RFA [15]. Both RFA and MWA share similar complications including hemorrhage, hepatic abscess, pneumothorax, bowel perforation, biliary injury, and track seeding. Slow retraction of the electrode/antenna (track ablation) is a technical refinement that may reduce hemorrhage and seeding. In any case, major complication rates are 2–10% and the procedure-related mortality rates are <1% [16].

There are several other percutaneous thermal ablation modalities under investigation, such as laser ablation, cryoablation and irreversible electroporation. Results are promising, but these techniques require higher operator skills and are burdened by severe complications. Therefore, their use is not currently recommended in the routine treatment of HCC, but only as part of clinical trials.

Even though less invasive procedures are preferable in cirrhotic HCC patients, the percutaneous approach has major limitations. Thrombocytopenia and portal hypertension expose patients to an unacceptable risk of peri-operative bleeding. Indirect localization of the tumor requires operator expertise and confidence with image-guidance tools. Moreover, target lesions are often in high-risk locations or too deep to be safely reached from the skin surface. Therefore, to increase the number of patients who could benefit from ablative treatment, laparoscopic ablation has

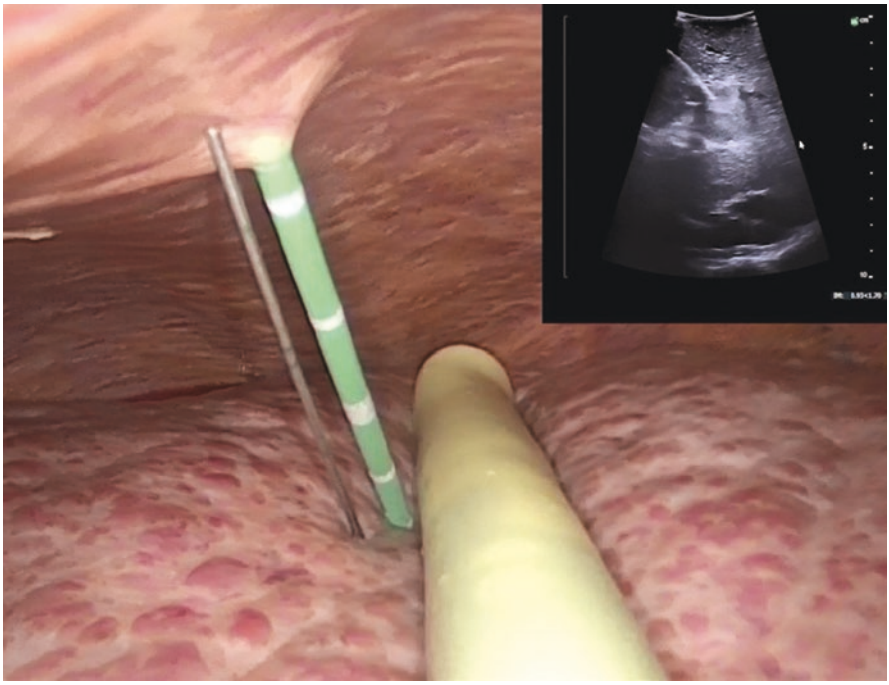

Fig. 8.1 Laparoscopic microwave ablation (Prof. Cillo's personal experience)

been implemented for RFA and MWA assisted by laparoscopic intraoperative ultrasound (LUS) (Fig. 8.1).

Criteria reaching the highest consensus for a laparoscopic approach are: HCC not visible percutaneously (along the diaphragm) or next to the hilum (risk of biliary thermal injuries), HCC near visceral structures, ineligibility for LR and severe coagulopathy [17–19].

LUS is a major advantage compared to the percutaneous approach since it is considered the most effective tool for detecting liver nodules [18]. Clinical experience supports a single-stage approach with immediate ablation of newly discovered HCC [18, 20].

Laparoscopy allows direct visualization of the liver, enhancing the ability to treat HCC located at the dome, peripherally, or in proximity to other organs. In the latter scenario, laparoscopy permits active protection of surrounding structures, reducing the risk of visceral injuries. Moreover, visualization of the entry point of the applicator allows bleeding source control. Severe complications rates are reported to be about 2% [17]. Common complications are pneumonia, pneumothorax, and bleeding from the trocar access. Tumor seeding, peritoneal dissemination, biliary strictures, arterial thrombosis, and liver abscess are reported less frequently.

While remaining minimally invasive, laparoscopic ablation is more flexible compared to the percutaneous approach [18, 19, 21] and, for HCC in difficult locations, it improves success rates [18, 19].

8.4 Oncological Outcomes

Although PEI has been largely replaced by thermoablation, it may still be applied in selected cases or to target part of a tumor located near structures at risk for thermal injury. Metanalyses comparing PEI to RFA have demonstrated the superiority of the latter in terms of overall survival (OS) and recurrence-free survival (RFS). The 3-year survival rate of patients treated with PEI was 48–67%, while for those treated with RFA it was 63–81%. Local tumor recurrence (LTR) was significantly less frequent with RFA [8, 22].

In the absence of randomized trials comparing RFA to surgery in compensated cirrhotic patients with very early HCC, Cho et al. created a Markov model to simulate a randomized trial comparing LR, percutaneous RFA monotherapy and percutaneous RFA monotherapy followed by LR in the case of local residual disease. The expected values for OS were 7.6, 7.4, and 7.6 years, respectively, while the expected 5-year OS rates were 62.5%, 60.3%, and 62.3% [23]. For unresectable candidates, the combination of RFA and transarterial chemoembolization (TACE) has shown benefit in terms of OS and RFS compared to monotherapy with RFA (OS: HR = 0.62; 95% CI 0.49–0.78, $p < 0.001$; RFS: HR = 0.55; 95% CI 0.40–0.76, $p < 0.001$) or TACE alone (2-year OS: 91.1% vs. 60.6%, $p = 0.004$; 2-year LTR: 48.1% vs. 78.2%, $p < 0.001$) [24, 25]. In cases of single HCC < 3 cm, when tumor recurs after RFA, LT should be considered [26].

As for MWA vs. RFA, Cui et al. have recently found no significant difference in 3- and 5-year OS, in 3-year RFS, in 1-year LTR, in technical efficacy, or in major complications. MWA is compared to LR only in two non-randomized studies showing similar 3-year OS (MWA 70–87.7% vs. LR 72–93.6%), but higher LTR (MWA 10.3–16.2% vs. LR 2.8–4.9%) [27].

Laparoscopic ablation achieves total necrosis of the tumor in a single session in more than 90% of the cases, comparable with the expected range of success of percutaneous ablation. Local tumor progression, when looking at the experience gained in the era of laparoscopy, is 2.8–23% [17]. In the earliest years, median OS for patients undergoing laparoscopic RFA for unresectable HCC was 26 months, while RFS was 14 months [28]. More recent analyses in high-volume centers, offering laparoscopic ablation for HCC unsuitable for LR or LT, report 1-, 3-, and 5-year OS of 88%, 55%, and 34%, respectively [18]. A retrospective analysis of 815 laparoscopic MWA on 674 patients treated in the authors' center, one of the most experienced in this field, has reported 1-, 3-, and 5-year OS of 81.9%, 54.9%, and 35.9%, respectively [19]. The updated data are listed in Table 8.1.

In conclusion, laparoscopic thermoablation has been shown to be a safe and effective curative treatment for HCC in those patients at risk of complications or unsuccessful therapy through a percutaneous access.

Table 8.1 Laparoscopic microwave ablations (MWA) performed at Padua University Hospital 2014–2021 (unpublished data)

No. of patients	1273	
No. of laparoscopic MWA	1796	
Child-Pugh score		
• A	762	(59.9%)
• B	260	(20.4%)
• C	24	(1.9%)
• Missing	227	(17.8%)
Milan-out[a]	248	(19.5%)
Postoperative complications		
• Fever	54	(4.2%)
• Nausea/vomiting	4	(0.3%)
• Ascites	110	(8.6%)
• Liver failure[b]	60	(4.7%)
• Hemoperitoneum	1	(0.1%)
• Pleural effusion	10	(0.8%)
• Pneumothorax	5	(0.4%)
Overall survival		
• 1-year	87% (95% CI 85–90)	
• 3-year	60% (95% CI 56–63)	
• 5-year	45% (95% CI 41–49)	

[a]Exceeding the Milan criteria for liver transplantation
[b]According to 50–50 criteria

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Endovascular Treatments of Hepatocellular Carcinoma

9

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9.1 Introduction

Hepatic tumors, in particular hepatocellular carcinoma (HCC), present an almost exclusive arterial supply as opposed to the normal parenchyma, which is vascularized by the portal vein. The neo-angiogenesis creates the possibility of releasing high quantities of drugs or radiation directly into the tumor, minimizing systemic effects.

9.2 Transarterial Chemoembolization

Transarterial chemoembolization (TACE) is an interventional radiology procedure consisting of the concomitant administration, via a transarterial route, of embolic material and anti-cancer drugs into the liver [1].

The indications for TACE in HCC encompass, according to the Barcelona Clinic Liver Cancer (BCLC) group, patients with intermediate stage (BCLC stage B) with a class of recommendation IA [2] and, more recently, with very early and early stage (BCLC stage 0 and A) with a class of recommendation of IB [2].

9.2.1 Technical Variations

From a technical point of view, the TACE technique presents several variations according to embolic material and drugs.

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Concerning embolic material, it is possible to distinguish conventional TACE (c-TACE), drug-eluting microsphere TACE (DEM-TACE) and degradable starch microsphere TACE (DSM-TACE).

c-TACE uses ethyl ester of iodized fatty acids of poppy seed oil (Lipiodol, Guerbet, France) as embolic material, mixed with anticancer drugs [1]. This emulsion is injected selectively into the arterial feeder of the HCC followed by a gelfoam solution for ensuring complete embolization [1]. c-TACE has the most consistent body of evidence regarding clinical results. Two randomized controlled trials (RCTs) showed that the c-TACE group had a relative risk of death ranging from 0.47 (95% CI 0.25–0.91) to 0.49 (95% CI 0.29–0.81) with a better overall survival compared with the control group [3, 4].

DEM-TACE uses microspheres as delivery and embolic material [1]. These microspheres allow slow release of the anti-cancer drugs used. The linkage between the beads and the drugs is based on ionic interaction. There are several different types of bead based on size and intrinsic opacity. The guidelines recommend a standard size of 100–300 μm. Two RCTs tried to demonstrate the superiority of DEM-TACE vs. c-TACE with poor results [5, 6]. In particular, the authors found no oncological benefit, but a better safety profile and drug-eluting toxicity. However, this evidence dates back to the early 2010s. More recently, Yang et al. [7], in a systematic review in 2020, showed a better 2-year overall survival of DEM-TACE vs. c-TACE (relative risk 0.89; 95% CI 0.81–0.99; $p = 0.046$).

DSM-TACE uses a resorbable amylomer (hydrolyzed potato starch) shaped as beads of 45 ± 7 μm in size that can be mixed with different anti-cancer drugs. The beads are enzymatically degraded by amylases, they have a half-life of about 35–50 min and are completely resorbed after approximately 2 h [8]. Very few reports exist on the value of DSM-TACE in HCC treatment. In particular, DSM-TACE was tested as first- and second-line (after kinase inhibitors discharge) treatment with promising results [8, 9]. One report by Auer et al. [10] showed comparable results between DSM-TACE and transarterial radioembolization.

The most used drug, in the USA and Europe, is doxorubicin. A few new drugs have been tested against doxorubicin in TACE. Shi et al. [11], in a RCT, showed that a mix of lobaplatin, epirubicin and mitomycin C has a better overall survival compared with doxorubicin alone. However, two RCTs failed to demonstrate the superiority of epirubicin over doxorubicin [12, 13].

9.3 Transarterial Radioembolization

Transarterial radioembolization (TARE) is based on the transarterial hepatic delivery of a radioisotope, yttrium 90 (^{90}Y), a pure beta-radiation emitter [14]. ^{90}Y is loaded onto microspheres; resin for Sirtex (SIR-Sphere, Sirtex Medical, Australia) and glass for Therasphere (TheraSphere, Boston Scientific, Marlborough, MA, USA), with differences between the two devices [14]. Both devices present potential benefits.

9.3.1 Technical Considerations

All patients must undergo careful pre-treatment angiographic mapping of the vascularization of the tumors less than 2 weeks before the procedure; 185 MBq of ^{99m}Tc-macroaggregated albumin allows single-photon emission computed tomography (SPECT) scanning assessment of pulmonary or digestive shunting. A lung shunt >20% or 30 Gy potentially contraindicates the treatment [14]. The careful search for and embolization of all the suspected vessels for digestive shunting is mandatory to avoid the possibly severe consequences of non-target embolization and can be done in the same treatment session [14]. This phase must possibly include preliminary cone-beam CT to ensure correct and safe delivery of the radio-device. Assessment of the treatment can be done by SPECT (bremsstrahlung photons) or positron emission tomography (PET) (Fig. 9.1). Recently, the possibility of same-day angiography assessment and treatment has been explored with good results.

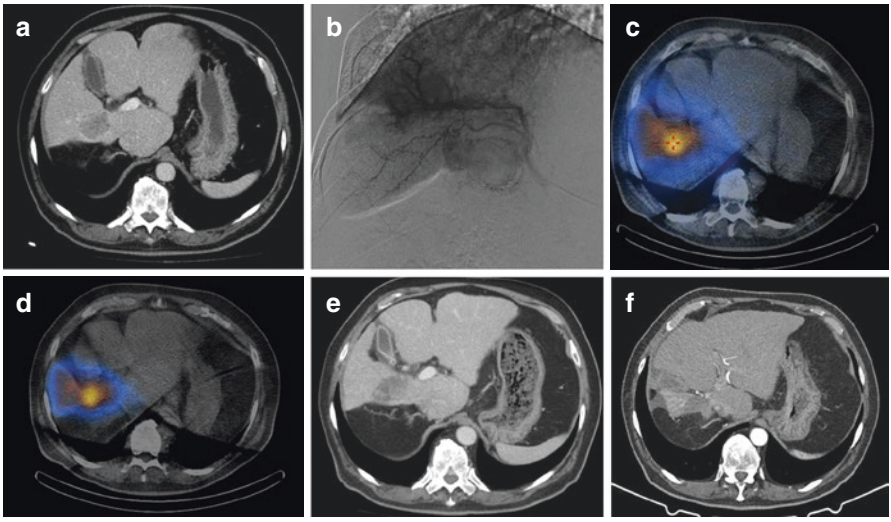

Fig. 9.1 (**a**) Sixty-eight-year-old man with relapse of hepatocellular carcinoma (HCC) at segments 5/7 and previous surgical segmentectomy of segment 6. The patient underwent transarterial radioembolization (TARE) with right lobar delivery of 2.6 GBq of ^{90}Y microspheres (SIR Spheres, SIRTEX) as a bridge to surgery (right lobectomy). (**b**) Pre-TARE planning strategy with angiography mapping and ^{99m}Tc macroaggregated-albumin injection, and (**c**) subsequent SPECT-CT which demonstrated good deposition with respect to the target lesion seen in panel **a**. (**d**) SPECT-CT demonstrating perfect correlation of the deposition of ^{90}Y with pre-treatment imaging: the absorbed dose was 240 Gy. (**e**, **f**) CT scans at 6 and 17 months showing the complete ablation of the HCC and (**f**) hypertrophy of the left lobe with no need for surgery. At 3 years, imaging still shows sustained response, without relapse

9.3.2 Lessons Learned

Careful patient selection has shown to be essential in treating HCC patients with TARE. The expected patient response to TARE correlates with liver function, albumin-bilirubin (ALBI) score, tumor burden, performance status, and the presence of extra-hepatic disease [15]. The ALBI score [16] seems to surpass the Child-Pugh score in selecting patients, albumin acting as a prognostic biomarker. The extent of portal vein thrombosis, when present, can also play a prognostic role [17].

Scintigraphy pre-assessment allows quantification of dosimetry with multi-compartmental or voxel dosimetry. The procedure and the doses need to be accurately tailored to the tumor burden, the vascularization, and the therapeutic purpose.

The selection of centers with multidisciplinary groups, reproducible and standardized techniques, and adequate technology with cone-beam CT are the fundamental factors of good practice.

9.3.3 Indications and Clinical Utility

Historically, TARE has been used in the advanced setting demonstrating good results in particular with portal thrombosis (BCLC stage B/C). The multicentric European analysis ENRY 4 provided robust evidence on tumor responses and high disease control rates with a safe profile all across BCLC stages. However, the three phase III trials, SARAH and SIRveNIB (TARE vs. sorafenib) and SORAMIC (TARE + sorafenib vs. sorafenib), conducted in advanced HCC patients failed to show any benefit in overall survival [18–20]. They also confirmed the non-inferiority of TARE and the clear benefits in terms of reduced toxicity (fewer adverse events) and improved quality of life compared to sorafenib [21]. The limits of these trials have been well analyzed: center selection and skills, patient selection, delay of treatment, and low dosimetry [21]. Consequently, TARE was not included in the 2018 guidelines of the European and American Associations for the Study of the Liver (EASL, AASLD) [22].

In the European Society for Medical Oncology (ESMO) guidelines [2], the indications for TARE moved from the advanced stage on to the early and intermediate stage, but with only a moderate level of evidence. In fact, the concept of ablative setting, radiation segmentectomy or lobectomy, strictly correlated to dosimetry, has emerged more recently with outcomes at 5 years as good as other curative methods, surgery or ablation [23, 24]. The focus on dosimetry of the latest trials DOSISPHERE and LEGACY also clearly showed good results [24, 25].

This has allowed TARE to enter the BCLC stage 0–A, competing with other curative treatments [2].

Despite the fact that there were no more indications in the advanced stage in guidelines, due to the recent development of new systemic therapies, the latest ESMO update of 2021 [2] reintroduced TARE in the advanced setting for patients with liver-confined disease not suitable for TACE and/or systemic therapy.

It should also be underlined the ability of TARE to compete with portal embolization, inducing hypertrophy of the future remnant liver after lobar radioembolization, on a slower timescale than through portal embolization, but with the additional value of local disease control [26] and downstaging for surgery.

9.3.4 Downstaging

The downstaging strategy relies on evidence that a baseline low-risk patient has the same probability of recurrence than a high-risk patient who is reassigned, after locoregional therapy, to low risk [27]. No guidelines exist on the upper limits for downstaging inclusion; however, a general consensus defines the limits as: one lesion >5 cm and ≤8 cm; two to three lesions each ≤5 cm; or four to five lesions each ≤3 cm with total tumor diameter ≤8 cm [28].

In a meta-analysis, Parikh et al. [29] reported a successful downstaging rate of 48% (95% CI 39–58%) without differences between TACE and TARE. Gabr et al. [30] showed that TACE and TARE groups have the same outcome after orthotopic liver transplantation (months to recurrence: 26.6 (95% CI 7.0–49.5) vs. 15.9 months (95% CI 7.8–46.8), respectively; p = 0.48). In addition, in one RCT, Mazzaferro et al. [31], demonstrated that, regardless of downstaging methods (locoregional, surgical or systemic), orthotopic liver transplantation improved event-free survival rate vs. the control group (76.8% [95% CI 60.8–96.9] vs. 18.3% [95% CI 7.1–47.0]). These data seem to suggest that there are no differences between the downstaging strategies. However, several issues must be clarified. First, the choice of which locoregional treatment should be used depends on the patient/disease characteristics, namely BCLC is applied for each patient. For example, TACE patients have on average a lower disease stage compared to TARE patients. Second, the downstaging strategy generally has a multidisciplinary and multimodality approach by including ablation, surgery, trans-catheter, and systemic treatment. However, a RCT comparing the downstaging results of each single modality is unfeasible due to ethical issues.

9.3.5 Bridging

Bridging consists of reducing the drop-out from the active transplant list. The existing 2018 guidelines (AASLD, EASL) [22] suggest bridging to liver transplantation (OLT) within the Milan criteria with the aim of limiting the drop-out and the recurrences post OLT, with low evidence, and with a strong grade of recommendation, particularly if the waiting time on the list is expected to be at least 6 months. Progression after endovascular therapies seems to have a prognostic role, and treatment response is a surrogate biomarker [32]. TACE is the most used technique for bridging, although no trial has demonstrated its superiority over the remaining locoregional strategies [33]. Ettore et al. [34] demonstrated that bridging is achievable in all patients using TARE. Gabr et al. report their experience of 207

transplants after TARE with a bridging success of 75% with survival similar to non-oncologic transplant [35]. Nevertheless, Lee et al. [36] suggest that the impact of the bridging strategy is limited only to the early stage.

9.3.6 Palliation

The palliative indication is reserved for those patients not amenable for curative treatment. Despite a trend in the data [37–39] there are no conclusive trials that demonstrate the superiority of a TARE versus C-TACE or DEB-TACE [40], TACE still being the first treatment option in all guidelines. The TRACE trial (BCLC stage A/B) was interrupted because of the clear superiority of TARE in terms of time to progression (392 vs. 299 days) and overall survival (912 vs. 489 days) [41]. The CIRT registry demonstrated that TARE is a valid tool with an excellent safety profile for palliation [42]. Moreover, Salem et al. published their institutional decision to adopt TARE as the first treatment option in limited HCC, based on 1000 patients in 15 years [43].

9.4 Conclusion

Transarterial treatments (TACE and TARE) are the past, the present and the future of HCC management. TACE has proven its utility in randomized trials and TARE has earned its place in the real world of HCC treatment, entering recently the first stage of BCLC.

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Indications for Surgery in Cirrhotic Patients

10

Felice Giuliante and Francesco Ardito

10.1 Introduction

Liver resection (LR) still remains one of the main curative options for hepatocellular carcinoma (HCC). When HCC is diagnosed in the cirrhotic liver, the indication for LR should be carefully established. The assessment of such patients should not consider only tumor burden, but must also necessarily include an accurate evaluation of the preoperative liver function to reduce the risk of the most feared complication following LR, that is, post-hepatectomy liver failure (PHLF). PHLF represents the most important cause of postoperative 90-day mortality and is the most commonly used measure to assess the early postoperative outcome. The evaluation of liver function includes assessment of functional reserve of the cirrhotic liver, presence of portal hypertension, extent of LR, volume of functional remnant liver (FRLV), patient performance status and comorbidities. Furthermore, LR should be carefully evaluated against liver transplantation, when this can be a chance of cure, and other potentially curative therapies such as ablation.

10.2 Hepatic Functional Reserve Assessment

Several tools are available to evaluate liver function and to stratify the risk of PHLF, but there is no general agreement on the best to be used worldwide.

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10.2.1 Child-Turcotte-Pugh Score

The Child-Turcotte-Pugh score is frequently used because it is a simple system including five easily available variables. In the majority of Western [1, 2] and Eastern guidelines [3] there is a wide consensus that patients with cirrhosis Child-Pugh A are good candidates for LR. However, PHLF may occur also in Child-Pugh A patients [4], because the score does not capture different levels of liver function in the same class of patients. This drawback, defined as the "floor effect" [4], is often associated with the use of the Child-Pugh score, which usually works better in patients with decompensated cirrhosis than in patients with preserved liver function where identifying those with elevated risk of PHLF is crucial.

10.2.2 Model for End-Stage Liver Disease

The model for end-stage liver disease (MELD), developed to predict survival following transjugular intrahepatic portosystemic shunt procedure, is another easily available tool that is effective in predicting PHLF, but once again it has limited capacity for risk stratification in patients not affected by end-stage cirrhosis. Recent evidence has shown that good candidates for LR should have a MELD score $\leq$10 and therefore it was recently included in the European Association for the Study of the Liver (EASL) guidelines, with Child-Pugh score, for treatment allocation [2, 5, 6]. Indeed, above this cut-off the reported morbidity rate reached 50%, with an unacceptable risk of irreversible PHLF (up to 15%) [5, 6].

10.2.3 Indocyanine Green Clearance Test

More accurate liver function evaluation can be obtained with the use of other tests, including the indocyanine green (ICG) clearance test, widely used in Asia. It is a dynamic method for studying liver function. It evaluates the hepatic clearance of indocyanine green 15 min after intravenous administration (ICG-R15) [7, 8]. The safe cut-off ICG retention rate at 15 min, which allows major hepatectomy, is around 10% [9]. A decision algorithm developed by Makuuchi guides the extent of hepatectomy. Three variables are included: ascites, serum total bilirubin level and ICG-R15 [9]. The presence of ascites with serum total bilirubin level $\geq$2 mg/dL is an absolute contraindication for LR. In patients without ascites and normal serum total bilirubin level, the extent of LR is planned according to the ICG-R15 value: major LR should only be performed in patients with ICG-R15 <10–20%, and limited LR when ICG-R15 is <40% [9]. Therefore the ICG-R15 may be useful for guiding the extent of LR and for stratifying the risk of PHLF in Child-Pugh A patients.

10.2.4 Other Liver Function Scoring Systems

Other scoring systems have been proposed to overcome the limitations of the Child-Pugh classification. These are used in different centers, according to different local expertise levels and protocols. These include: the aspartate transaminase-to-platelet ratio index (APRI) score [10], the albumin-bilirubin (ALBI) score [11], the albumin-indocyanine green evaluation (ALICE) score [12] and the bilirubin-cholinesterase (BILCHE) score [13].

10.2.5 Evaluation of Portal Hypertension

According to the EASL guidelines [2], clinical signs of portal hypertension (PH) include the presence of esophageal varices, or splenomegaly (diameter >12 cm) and platelet count <100,000/mm^3. Non-invasive assessment of fibrosis grade by liver stiffness measurement with transient elastography is an additional effective tool for assessing the degree of PH, which has gained more clinical diffusion than invasive measurement of HVGP. The degree of liver stiffness may identify patients at risk of PHLF, with a significant risk of PHLF being predicted by liver stiffness >12–14 kPa [14]. The presence of PH is a significant prognostic factor affecting postoperative outcome [2]. In such patients the risk of PHLF following major LR is >30% with a 90-day postoperative mortality reaching 25%. However, PH in itself should not be considered an absolute contraindication to LR if liver function is preserved. In selected Child-Pugh A patients, with PH and well-compensated cirrhosis, limited LR can be performed with competitive survival outcomes [15–17]. For this reason, the role of PH in evaluating the indication for LR should always be balanced with the extent of resection and liver function tests.

10.2.6 Extent of Liver Resection and Functional Remnant Liver Volume Evaluation

A critical issue is the FRLV following LR. A computed tomography (CT)-based volumetric assessment is generally used to evaluate the FRLV; a value ranging from 40% to 50% may be considered the safe limit for LR in the cirrhotic liver to prevent severe PHLF [18] (Figs. 10.1, 10.2 and 10.3). For this reason, strategies to increase FRLV or reduce the HCC and expand resectability have been developed: portal vein embolization (PVE) (Fig. 10.1); preoperative transarterial chemoembolization (TACE) alone (Fig. 10.2), or followed by PVE [19]; combined hepatic vein embolization and PVE (liver venous deprivation) [20]; radioembolization with yttrium-90 microspheres [21]; portal vein ligation for staged hepatectomy (ALPPS) procedure [22].

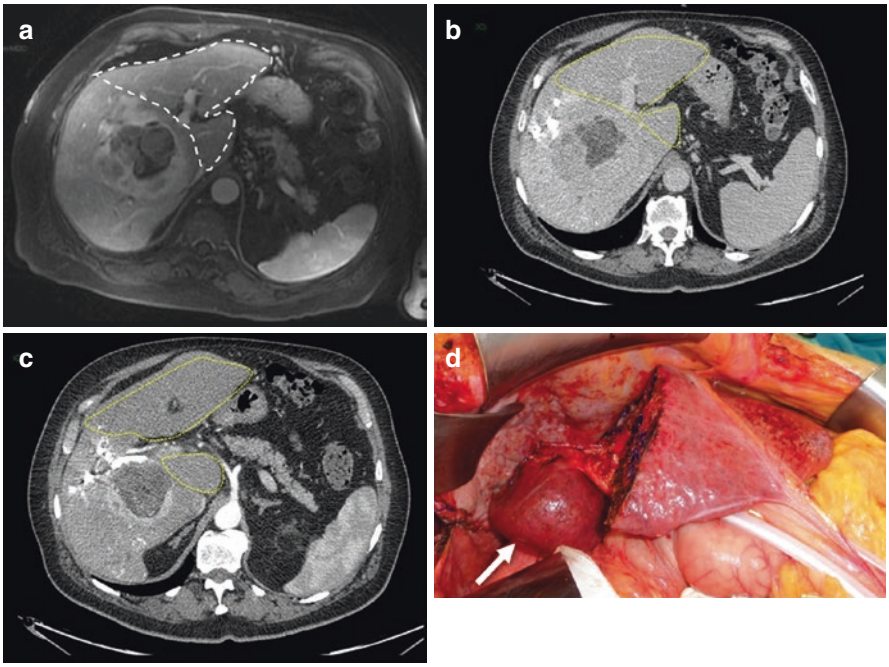

Fig. 10.1 Sixty-six-year-old male. (**a**) CT scan: large hepatocellular carcinoma on non-alcoholic fatty liver disease-related cirrhosis. Indication for right hepatectomy; small functional remnant liver volume (FRLV) (32%). (**b**, **c**) CT scan after right portal vein embolization: FRLV 43%. (**d**) Right hepatectomy. Note the caudate lobe hypertrophy (white arrow)

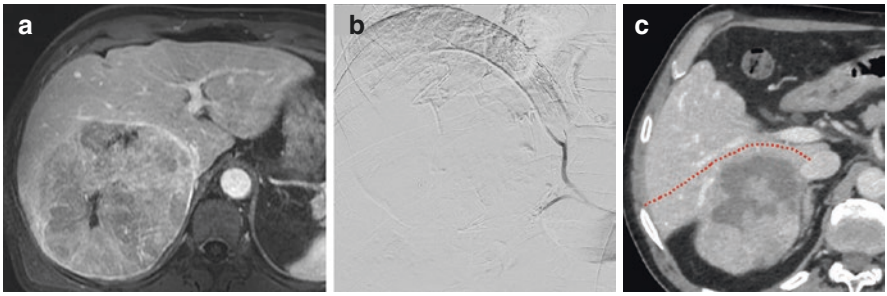

Fig. 10.2 Seventy-year-old male. (**a**) CT scan: large right lobe hepatocellular carcinoma. (**b**) Selective transarterial chemoembolization (TACE). (**c**) CT scan after TACE: tumor shrinkage and partial necrosis. Indication for right posterior sectionectomy (S6–S7)

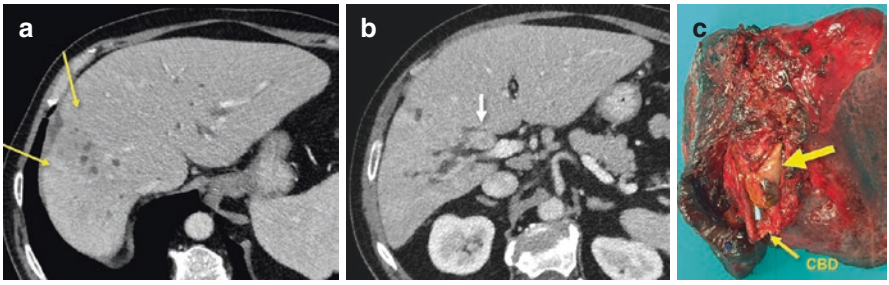

Fig. 10.3 Sixty-two-year-old male. (**a**) CT scan showing a large infiltrative right lobe hepatocellular carcinoma (arrows). (**b**) Biliary thrombosis (white arrow). (**c**) Specimen after right hepatectomy with left hepaticojejunostomy; endobiliary tumor thrombus (thick arrow)

10.3 Indications According to Tumor Stage, Survival Benefit, and Technical Considerations

Accurate tumor staging is crucial to evaluate the indication for LR. The Barcelona Clínic Liver Cancer (BCLC) staging system is one of the most widely used in Western countries [2]. It provides a survival benefit-based treatment algorithm, associated with a prognostic staging system consisting of four variables: tumor burden, degree of liver function, general condition of the patient and treatment efficacy. According to the BCLC system, LR is restricted to a selected group of patients without PH, with very early (single nodule <2 cm) or early (tumors within the Milan criteria: single nodule ≤5 cm or 2–3 nodules ≤3 cm) tumor stage (BCLC stage 0–A). However, this type of treatment algorithm may prove rigid, as it gives only one treatment option for each tumor stage and it is not open to treatment alternatives [23]. This algorithm is not regularly followed in real-life clinical practice throughout the world. In fact, several studies have shown a potential role of surgery also for patients with large multinodular and macrovascular invasive HCC, classified as BCLC stage B/C, or with biliary invasion (Fig. 10.3). A recent multicenter study [24] reported that about 50% of patients with intermediate or advanced stage HCC (BCLC stage B/C) are routinely treated with LR in tertiary referral centers worldwide. Furthermore, the study showed that the 5-year overall survival (OS) of BCLC stage B/C patients following LR was 57% and 38%, respectively.

Based on these observations, with the aim of improving the accuracy of treatment indications for HCC in cirrhotic patients, the concept of "therapeutic hierarchy" strategies has been proposed, which introduces a relative independence between the choice of treatment and the stage of disease [23]. This allows us to tailor the indications to the single patient and avoid the risk of undertreatment with the rigid application of a simple stage-linked treatment algorithm. However, the decision of the first treatment is complex because it requires consideration of several factors that can only be evaluated within a multidisciplinary dedicated team of experts.

As regards the indication for LR, from the technical point of view, one significant improvement was the introduction and wide diffusion of minimally invasive LR for HCC in cirrhotic patients: currently, HCC is the most frequent indication for a laparoscopic LR [25]. The advantages of minimally invasive surgery are particularly significant in cirrhotic patients, with overall better perioperative outcomes than open surgery, and in particular with a lower incidence of PHLF and of postoperative ascites. This has made it possible to consider the extension of surgical indications to selected Child B patients [26]. Furthermore, the significantly reduced surgical risk of laparoscopic LR for HCC in cirrhotic patients, particularly for small HCC, allows reappraisal of the competitive indications between ablation and surgery, in favor of resection. Laparoscopic LR also has a significant role in patients with indications for liver transplantation, as a bridge treatment before transplant, with advantages relating not only to limited postoperative adhesions but also to the possibility of obtaining relevant prognostic information from the surgical specimen before a definitive indication for transplantation.

10.4 Need for a Multidisciplinary Evaluation in High-Volume Centers

It should be highlighted that the indications for LR in cirrhotic patients should be assessed in a multidisciplinary setting in high-volume centers, where the presence of experienced liver and transplant surgeons, hepatologists, anesthesiologists, interventional radiologists and endoscopists, specialized dietitians together with dedicated intensive care unit and high-level nursing care, may all contribute to prevent mortality following LR. Recent advances in surgical technique, patient selection, and perioperative management have contributed to decrease the postoperative mortality rate to <5% in most centers following LR for HCC. However, although reduced by accurate patient selection, the occurrence of postoperative complications, may be unavoidable even in high-volume centers. A new parameter proposed to assess the quality of care during hospitalization is failure to rescue (FTR), defined as the probability of postoperative death among patients with a major complication. FTR reflects the ability to rescue a patient with a major complication from the risk of death. FTR has been shown to decrease significantly with increasing hospital volumes. A recent multicenter Italian study [27] on 1935 patients undergoing resection, showed that the risk of major complications and mortality was related to comorbidities, cirrhosis severity, and complexity of surgery, but these factors were not correlated with FTR. Indeed, the center's volume was the only independent predictor related to severe complications, mortality, and FTR. In other words, the ability to rescue a patient from a major complication was strictly correlated with the center's volume and was significantly lower in high-volume centers. Centralization could be one prerequisite for proper indications and improved outcomes following LR for HCC.

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11 Laparoscopic Approach for the Treatment of Hepatocellular Carcinoma

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11.1 Introduction

Laparoscopic liver resection (LLR) was born in 1991 and gradually expanded during the following thirty years [1]. Even extremely complex procedures are performed in centers with adequate experience [2, 3].

Curative treatments for hepatocellular carcinoma (HCC) include liver resection (LR) and local ablation therapy, which can now be performed using the laparoscopic technique. Moreover, laparoscopy is increasingly being used to expand the indications for surgical treatment for HCC patients, being able to overcome some of the limits or issues linked to traditional open LR.

11.2 Short-Term Outcomes

Many studies have documented the feasibility and safety of LLR and reported advantages with respect to perioperative outcomes. Among the most frequent are the reduction of blood loss, transfusion needs, complications, and length of hospital stay, as well as earlier recovery of physiological functions and patient's autonomy. This is extremely important for HCC, since hepatectomy in cirrhosis is associated with higher complication rates than other conventional settings. In many studies focusing on HCC, the benefits of laparoscopy have been particularly evident and often associated with specific advantages. Of particular interest is the reduction of ascites, a very fearful and frequent complication in the cirrhotic patient, which laparoscopy is able to contain by avoiding large abdominal incisions, thus allowing the surgeon to preserve the parietal circulation and lymphatics and to limit the dispersion of fluids [4, 5]. Also, the incidence of postoperative liver failure was shown to be reduced by many studies

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[6]. These results have been supported by various meta-analyses including a large number of HCC patients. In 2018, Chen et al. performed a systematic review of high-quality case-matched studies: regardless of whether the patients underwent minor or major hepatectomy, ascites was less in LLR than in open LR, and patients undergoing laparoscopy were less likely to suffer liver failure [7].

11.3 Long-Term Outcomes

Most of the studies and meta-analyses showing the short-term advantages of LLR for HCC have also revealed long-term results similar to those of open LR [8]. Few recent publications reported improved survival rates, suggesting a possible long-term advantage on the oncological side. A meta-analysis of 888 HCC patients showed higher 1-, 3- and 5-year overall survival rates and 1-year disease-free survival rate for LLR than for open surgery; moreover, tumor recurrence was also lower [9]. The improved long-term outcomes of LLR are explained by the authors as likely due to decreased blood loss and higher rates of negative surgical margins. In 2021, Sun et al. performed a meta-analysis based on reconstructed time-to-event data of propensity score studies. The results suggested that laparoscopy can improve recurrence-free survival in HCC patients undergoing minor hepatectomy [10].

11.4 Advanced Cirrhosis and Portal Hypertension

Laparoscopy is increasingly used to push the limits for LR to those categories of HCC patients for whom open surgery entails a significant risk of major complications and mortality, i.e., to patients with advanced cirrhosis and portal hypertension.

One study reported that Child A and Child B patients receiving LLR had a similar perioperative course as there was no difference in blood loss, blood transfusions, overall morbidity, postoperative mortality, or liver-specific complications, such as ascites decompensation and liver failure [11]. Moreover, clinically significant portal hypertension was not a risk factor for major morbidity. Some retrospective studies explored the perioperative and long-term effect of LLR on HCC patients with clinically significant portal hypertension, showing comparable overall survival to non-portal hypertension groups [12, 13]. Thus, laparoscopy may offer a protective effect with regard to postoperative liver failure, ascites and major complications even in Child B patients, and its role in extending the candidacy to LR is currently being further investigated on the basis of fresh promising evidence [14].

11.5 Major Hepatectomies

Major LLR were first performed in 1998 but have undergone a slow diffusion due to their technical difficulty and fears of poor bleeding control [15]. Even today, despite their proven safety and feasibility, it is recognized that major LLR must be carried out in the presence of high levels of expertise and experience [16].

In 2019, a multicenter propensity score-based comparative study of 1355 patients reported that major LLR were associated with reduced blood loss, postoperative stay and morbidity than open LR, also in the setting of malignant disease [17].

In the last few years, the results of single-center studies on major LLR have disclosed favorable results for HCC, further confirmed by more than one systematic review. In a meta-analysis of 780 patients, Chen et al. found major LLR to be associated with less intraoperative blood loss and morbidity and shorter postoperative stay despite longer operative times, concluding that it may serve as a promising alternative to open LR [18]. In 2019, Wang et al. considered 1173 HCC patients who underwent laparoscopic and open major hepatectomies, obtaining similar results [19]. Thus, major LLR can be performed safely in patients with HCC, who are often affected by large lesions [20]. Especially in these settings, the anterior approach can be applied to respect the no-touch principles of oncological surgery [21].

11.6 Repeat Surgery

Most HCC arise on a background of chronic liver disease, which can cause intrahepatic recurrence after a first LR and consequently expose patients to the need for repeated hepatectomies. The operative advantage that can derive from a first surgery performed by laparoscopy is the benefit on intra-abdominal adhesions thanks to the limited manipulation of organs [22, 23]. By decreasing the need for adhesiolysis, the surgical time of repeated LR after a first laparoscopic surgery has been shown to be reduced compared to a first open surgery [24]. It should be emphasized that, although repeated LR are complex operations due to the distortion of the parenchyma that follows previous resections and the consequent alteration of the original anatomy, they are nevertheless still associated with perioperative advantages for patients. In 2021, the results of an international multicenter study evaluating the surgical results of repeated LLR for relapsed HCC revealed reduced intraoperative blood loss and complications for the laparoscopic group [25].

11.7 Elderly Patients

The laparoscopic approach has also yielded interesting results for the treatment of patients with advanced age [26]. For HCC, Nomi et al. disclosed the results of a multicenter retrospective propensity-based study on 630 HCC patients aged ≥75 years. As compared to open surgery, intraoperative blood loss, transfusion and morbidity were lower for LLR, including major, cardiovascular and pulmonary complications as well as 180-day mortality for causes other than HCC- or liver-related causes. Moreover, for octogenarians, laparoscopy was associated with decreased major morbidity and length of stay [27]. In 2021, a multicenter propensity-matched study including 184 HCC patients aged >70 years undergoing laparoscopic or open major LR was performed. Laparoscopy was confirmed to be associated with reduced complications and duration of stay with mortality comparable to open

surgery [28]. Hence, age should not be considered a contraindication to LLR for HCC, even for major resections, since the benefits of minimal invasiveness are also confirmed for this category of fragile patients.

11.8 Difficulty Scores

The concept of difficulty is crucial in guiding safely the development of LLR expertise and learning curve. Particular attention has been given to the many factors influencing the complexity of an operation, some related to the topography and nature of the liver injury, others intrinsic to the type of operation, others related to the characteristics of the patient. As a result, various difficulty scoring systems (DSS) to predict surgical difficulty have been produced in recent years. The most popular are the IWATE-DSS, Halls-DSS, Hasegawa-DSS, and Kawaguchi-DSS [29–32].

Lin et al. conducted a single-center study specifically designed to validate these scores in HCC patients [33]. They found significant distributions of applying bleeding control, surgical time, estimated blood loss, postoperative major complications and hospital stay among different groups of each system, and that the IWATE-DSS was also able to predict conversion.

Additionally, in 2020 Goh et al. raised attention regarding the effect of cirrhosis on the difficulty of a LLR, given that none of the four existing DSS included its presence/absence as a determinant factor (only the IWATE-DSS considered Child B cirrhosis as a significant factor, but without distinguishing between patients with Child A liver function and patients with non-cirrhotic livers) [34].

In general, all the DSS show different profiles of utility. As a reasonable approach, we have made the proposal to use the "Kawaguchi-, IWATE-, and Halls-DSS" order for: a first assessment based on the type of operation and exclusion if the learning curve has not yet been overcome; a second stratification within procedures of the same complexity to guide towards progression to the next phase of difficulty; a final evaluation to estimate intraoperative complications and adequately prepare the equipment and team [35].

11.9 Laparoscopic Approach for Local Ablation Therapy

With the accumulation of evidence on its efficacy, ablation has become a viable treatment for HCC and liver malignancies. For HCC, it has moved from palliative to potentially curative treatment in selected patients [36]. The spread of laparoscopy has allowed its adoption for ablations, especially in the presence of limitations due to the percutaneous approach (mainly unfavorable localizations). Furthermore, laparoscopy has the clear advantage of providing real-time monitoring of the ablative process and hemostasis. Some studies have indeed reported a lower complication rate and shorter length of stay for laparoscopic compared with percutaneous ablations [37]. One study also reported comparable local tumor progression rates [38].

However, definitive conclusions on the oncological non-inferiority of laparoscopic ablations are still awaited, as well as validation of their role as a first-choice curative treatment for selected patients.

11.10 Conclusion

LLR has been performed worldwide with oncologic outcomes for HCC comparable to open surgery. The evidence is based on case-control studies, propensity score-matched studies and meta-analyses. Although most of the reports of LLR refer to Child A cirrhotic patients, some studies have demonstrated the feasibility of LLR in selected patients with advanced cirrhosis, for which laparoscopy can extend the indications for surgery. Future studies will need to clarify further which patients with advanced cirrhosis and HCC are most suitable for a minimally invasive approach and elucidate the role of laparoscopy for laparoscopic ablations.

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Robotic Approach for the Treatment of Hepatocellular Carcinoma

12

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12.1 Introduction

Minimally invasive liver surgery has demonstrated several benefits over the classical open approach [1]. In addition to the reduction of morbidity and shorter in-hospital stay compared to the standard open procedure [2], the robot reduces the conversion rate compared to laparoscopy in the setting of high-difficulty procedures, ultimately increasing surgical safety [3]. Therefore, adopting a robotic approach may increase the opportunity for patients to be treated without losing the advantages of minimally invasive surgery, even when a complex procedure is needed [4, 5]. In this chapter we will briefly review some key points for a better understanding of the robotic approach to the liver and its application in the field of hepatocellular carcinoma (HCC).

12.2 Patient Selection and Indications

The indication for surgical resection in a modern hepatobiliary center should be always discussed in a multidisciplinary meeting involving surgeons, radiologists, anestesiologists, hepatologists and oncologists, to ensure the accuracy and appropriateness of the therapeutic strategy [6, 7]. Indocyanine green (ICG) clearance and evaluation of portal hypertension measuring the hepatic venous pressure gradient (HVPG) may help to refine the indication and prevent post-hepatectomy liver failure [8]. Up to now there are no formal contraindications to performing a robotic liver resection, except the general contraindication for pneumoperitoneum. The

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presence of macrovascular tumor infiltration, large exophytic tumors, and the need for major vascular reconstructions can be considered relative contraindications for the robotic approach, and the decision to include those patients relies on the experience of the center. Cirrhotic patients with HVPG >10 mmHg should be evaluated case by case, according to the extension of the resection needed. In the case of repeated resections, minimally invasive approaches and in particular the use of the robot proved to be safe and effective [9, 10].

12.3 Surgical Technique and Learning Curve

12.3.1 Patient Positioning and System Set-Up

Even if other robotic systems are available on the market, most of the evidence produced in the literature so far was obtained using DaVinci robotic platforms (Intuitive Surgical Inc., Sunnyvale, CA, United States), and therefore we are going to discuss details of the most recent model. The DaVinci platform includes a surgeon's console, a patient-side cart and a vision system. Patients are usually positioned supine, 15° to 20° anti-Trendelenburg and can be rotated to the left to allow easier access to right and posterior segments. The position of the trocars varies according to each patient's peculiar conformation and lesion localization, and to the robotic platform in use [11]. Using the Xi platform, the first step, according to the manufacturer, is to determine the target anatomy, which is not the disease location but the area where the midline of the surgical workspace intersects the far edge of the surgical workspace boundary. The initial endoscope port should be placed 10 to 20 cm back from the target anatomy, on the opposite edge of the surgical workspace boundary. The other ports are usually placed on a straight line perpendicular to the target anatomy: for liver procedures two arms are controlled with the right hand (left sided), and one with the left hand (right sided). The trocars should be placed 6 to 10 cm apart according to patient body habitus, and at least 2 cm away from bony structures. Assistant ports can be inserted at least 7 cm from robotic ports, with adequate triangulation to enable the table-side surgeon to reach the desired anatomy and to ensure physical access to the port.

12.3.2 Use of Indocyanine Green-Based Fluorescence

Another novel feature is the integrated Firefly, an indocyanine green (ICG)-based fluorescence imaging system. This technology has several applications to reach the goal of a personalized and tailored surgery. In liver surgery, ICG fluorescence can be used for tumor identification, surface mapping, and real-time cholangiography [12, 13]. Tumor cells can be either hypo-fluorescent or hyper-fluorescent according to their histological features: well-differentiated HCCs show a homogeneous fluorescence pattern, while poorly differentiated HCCs demonstrate an inhomogeneous

or even a rim-type fluorescence pattern [12]. For this kind of visualization an intravenous injection of 0.5 mg/kg bodyweight of ICG is recommended 2–14 days prior to surgery. This recommendation is based on studies and observations in patients that underwent surgery after an ICG clearance test, which explains the dose and the timing. In our experience, a dose of 0.25 mg/kg bodyweight 12 h before surgery is effective for HCC visualization in non-cirrhotic patients (Fig. 12.1). ICG fluorescence can be also used for definition of segmental anatomy as mentioned above, with two different techniques: positive and negative staining. In the negative staining method, the inflow vessels of the hepatic parenchyma to be removed must be temporarily clamped to confirm the demarcation line, followed by systemic injection of 2.5 mg of ICG, resulting in fluorescent enhancement of the hepatic parenchyma to be preserved [14]. The positive staining technique requires direct injection of 2.5 mg ICG diluted in 10 mL of saline solution into the tumor-bearing portal branch through a 16-gauge needle. This way, the segment to be removed becomes

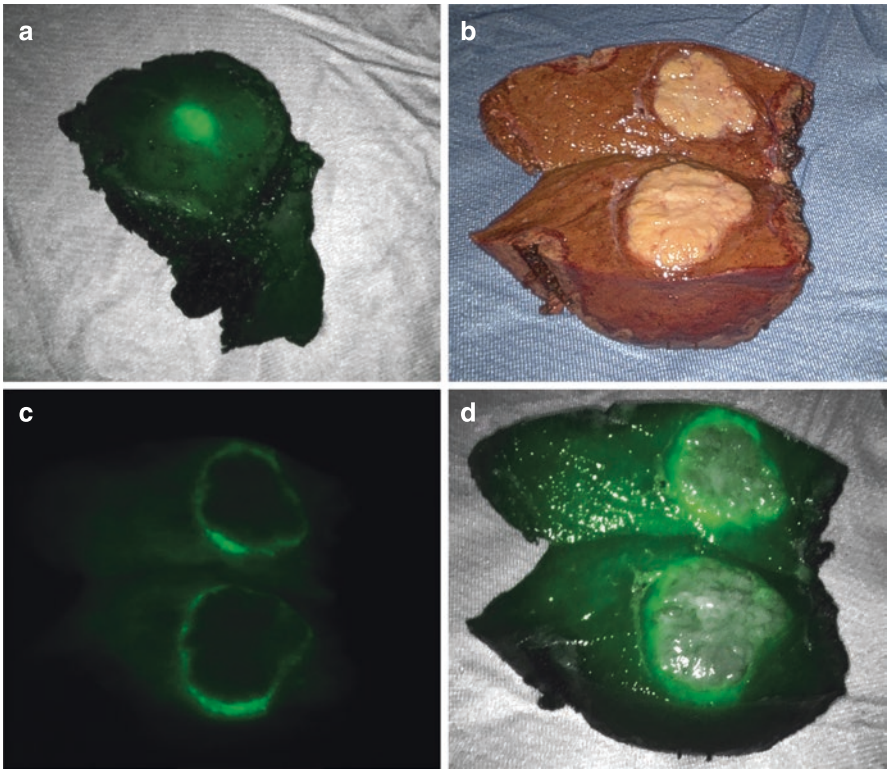

Fig. 12.1 Detail of the use of indocyanine green for tumor mapping. (**a**) Fluorescence pattern on the glissonean surface of a G2 HCC after resection. (**b**) Tumor appearance on surgical specimen. (**c**, **d**) Demonstration of the fluorescence pattern on the specimen with sensitive (**c**) and standard (**d**) Firefly visualization

fluorescence-enhanced on the liver surface and can be marked with monopolar energy to guide the transection between fluorescing and non-fluorescing parenchyma [14].

12.3.3 Parenchymal Transection

For parenchymal transection we adopt a Kelly crush technique with the use of bipolar forceps, combined with monopolar energy and use of the DaVinci Harmonic ACE (Ethicon, Somerville, NJ, USA) for deeper layers (Fig. 12.2). The robotic platform does not support liver-specific devices for parenchyma dissection such as the Cavitron Ultrasonic Surgical Aspirator (CUSA); however, it can be used by the table-side surgeon even though this approach is not comfortable and requires placing the assistant port very high. Moreover, the transection line is determined by the surgeon using the CUSA rather than the console-surgeon. From this perspective, the use of the CUSA from the table-side dispels most of the advantages of the robotic approach and, for those reasons, it does not represent our first choice.

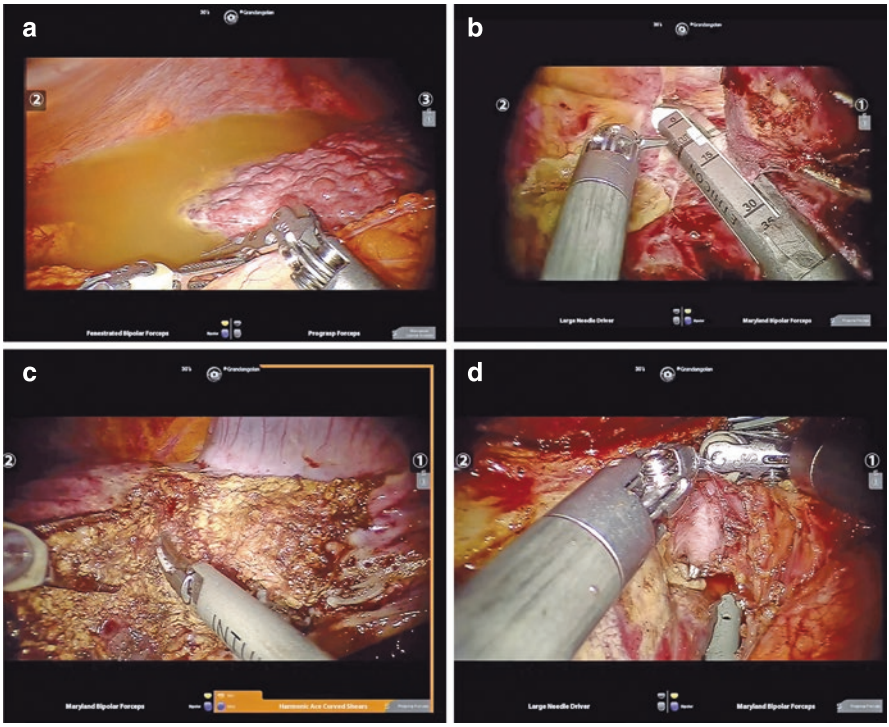

Fig. 12.2 Details of robotic liver resections for HCC. (**a**) Exploratory phase in a Child B patient. (**b**) Division of the right hepatic vein with a 35-mm vascular stapler after complete mobilization of the right lobe. (**c**) Use of DaVinci Harmonic ACE for parenchymal transection. (**d**) Isolation of the right portal vein with the Maryland bipolar forceps

It is well known that non-anatomical liver resections are more difficult to be approached with minimally invasive strategies compared to the straight transection plane of major hepatectomies. Under this perspective, the robot adds several benefits thanks to instrument flexibility and 3-D visualization, which help to reach deep and narrow spaces such as posterior segments, with safe control of vascular structures.

12.4 Postoperative Outcomes

Several studies assessed that robotic surgery is as safe as open and laparoscopic approaches for HCC in terms of operative complications and postoperative morbidity. However, among all the interesting papers published in recent years, few studies focused on the oncological outcomes after robotic liver resection. Choi et al. in their series reported 13 HCC patients all with negative margins and a 92.3% rate of anatomic resection, without recurrences during the 11-month median follow-up [15]. In an Eastern series of 183 patients with HCC treated with robotic liver resection compared to 275 open surgery controls, the robotic group showed longer operation times (343 vs. 220 min), shorter hospital stays (7.5 vs. 10.1 days), and lower dosages of postoperative patient-controlled analgesia (350 vs. 554 ng/kg) [16]. Overall survival (OS) and disease-free survival (DFS) at 3 years after robotic liver resection for HCC are reported to range between 97.7–92.6% and 72.2–71.9%, respectively [17]. The use of the robot proved to be safe and effective also in the field of advanced liver procedures such as associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) for HCC [18, 19].

12.5 Role of Robotics in Transplant Oncology

Given the abovementioned characteristics of the technology, the robot is a valuable tool for bridging and down-staging strategies [20–22] and an alternative to locoregional treatments like percutaneous ablation (PA) [23, 24]. The cumulative incidence of recurrence was found to be decreased in the robotic group versus the PA group in a cohort of very early and early newly diagnosed HCCs [25]. The underlying reason for this different recurrence pattern can be found in the 20% incidence of satellitosis, which is more efficiently treated with a surgical approach. Besides, the robotic approach may ultimately reduce the formation of abdominal adhesions for future liver transplantation [22].

Similarly to the ALPPS, the partition concept of the liver has its basis in the living-donor liver procurement, which today probably represents the highest expression of robotic liver surgery. In an experience from Korea reporting on 52 cases, the authors applied selection criteria at the beginning of the series including less complex cases before approaching advanced vascular variants or larger grafts [26]. The results are outstanding, with low blood loss (109.8 ± 101.5 mL), acceptable operative time (493.6 ± 91.5 min) and short in-hospital stay (9 ± 2.1 days), with a

statistically significant advantage over the open approach. The incidence of postoperative morbidity was 23.1%, with only one case of a complication >3a, according to Clavien-Dindo.

12.6 Conclusions

The robotic approach to the liver is a safe, effective and reproducible strategy for the treatment of HCC, from non-anatomical resections to more advanced procedures, including ALPPS and living-donor hepatectomy. Perioperative and long-term outcomes are at least comparable to the traditional open approach, with additional benefits for cirrhotic patients and those with CSPH, thus reducing the incidence of PHLF and postoperative morbidity, and expanding the indications for surgical resections for HCC.

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Ultrasound-Guided Liver Resection and Parenchymal-Sparing Surgery

13

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13.1 Introduction

Hepatic surgery has had an extraordinary evolution in recent decades, becoming a standardized, routinely performed procedure that has reached near-zero mortality rates and offers a chance of cure to many cancer patients. Anesthesia and technical refinements, together with technological innovations, are some of the factors responsible for the improvements in this field. Regarding surgical technique, two main revolutions have contributed to these developments: the diffusion of parenchymal-sparing surgery (PSS) instead of major/extended hepatectomies and the spread of the minimally invasive (laparoscopic and robotic) rather than the open approach.

PSS aims to preserve as much healthy functional liver parenchyma as possible without compromising the principles of oncological surgery. An independent association of the number of resected segments with postoperative complications and mortality rate is clearly described. As a consequence, PSS is associated with a significant reduction in the rates of postoperative morbidity (e.g., liver failure) and mortality. Finally, some studies have reported better overall survival for patients treated with PSS compared with major resections, due to a higher likelihood of undergoing salvage hepatectomy for recurrence. PSS was initially proposed in patients with colorectal liver metastases (CRLM). Driven by the good results obtained with PSS in CRLM, liver surgeons started thinking they could "spare the liver parenchyma" also in patients with a diagnosis of hepatocellular carcinoma (HCC).

Laparoscopic liver resection (LLR) has gained widespread acceptance after two international and one European consensus conferences. It has been reported as a

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safe procedure with advantages over open surgery in terms of morbidity, blood loss, and postoperative hospital stay [1]. At the same time, the long-term results seem to be at least non inferior to open liver resections in patients with CRLM and HCC. Finally, there is emerging evidence that LLR is associated with better oncological outcomes for HCC when compared to radiofrequency ablation.

In the past, liver surgery for HCC was associated with high rates of mortality and liver failure due to the underlying cirrhosis and poor functional reserve of the liver. Today, the fragility of these patients remains and should not be forgotten, but the combination of PSS and LLR under intraoperative ultrasound (IOUS) guidance has allowed the extension of indications to more complex patients and diseases.

13.2 The Role of Ultrasound in Liver Surgery

While recent technological advances have enhanced the diagnostic performance of computed tomography (CT) and magnetic resonance (MR) imaging, IOUS provides complementary and specific information for intraoperative tumor staging. In addition, IOUS plays a pivotal role at each step of the surgical decision-making process, especially for surgical planning and guidance during open and laparoscopic liver resections. In the next section the aid provided by IOUS in all these phases will be described, with special attention to HCC surgery.

13.2.1 Intraoperative Tumor Staging

The clinical diagnosis and staging of HCC are currently based on CT and MR imaging. Nonetheless, CT and MR imaging have generally low sensitivity for small lesions (<1 cm). Since IOUS scanning is always performed directly on the liver surface, very high-resolution images can be obtained. With current transducer resolutions, lesions as small as 2 mm can be identified with a sensitivity of 90–95%. In cirrhotic livers, IOUS can detect up to 30% more lesions, compared to preoperative imaging. However, more frequently such additional nodules tend to be of a regenerative nature. Therefore, to improve the specificity of basic IOUS in cirrhotic patients and help in the differential diagnosis of small undetermined lesions, new diagnostic tools have been implemented [1], such as contrast-enhanced IOUS (CE-IOUS) and elastography. Moreover, the IOUS patterns of HCC nodules correlate with grading and microvascular invasion, thus providing real-time prognostic data on the risk of tumor recurrence.

13.2.2 Surgical Planning and Resection Guidance

To be considered resectable, a lesion must be removable with a negative margin and allow for the preservation of sufficient functional liver segments with an adequate portal and arterial inflow, venous outflow and biliary drainage. Thus, a precise

understanding of the patient's liver anatomy, tumor localization and topographical relationships are needed for a correct liver resection.

The four-Cs method [2, 3] is an effective and pragmatic four-step technique able to highlight the role of IOUS in both planning (steps 1 and 2) and guiding the resection (steps 3 and 4).

1. *Compose the 3-D mind map* The first step is to perform an in-depth ultrasound study of the relationships between the lesion and the surrounding vessels that are to be correctly identified in order to create a 3-D anatomical mind map.
2. *Create the sketch* The underlying anatomical structures are sketched on the liver surface with cautery (Fig. 13.1a), the goal being to help the surgeon to hold in mind the map of the liver anatomy relative to the lesion. Lines of transection are drawn according to the sketch, thus planning which vessel will be ligated and cut and which will be preserved and exposed on the cut surface.
3. *Check the way* The sketch shows only the glissonean projection of deeper structures, so it is necessary to check the section plane while proceeding with the transection. The resection line is easily visualized as an inhomogeneous hyperechoic linear artefact in the parenchyma, so the surgeon can check the resection plane with respect to relationships with the hepatic veins, portal pedicles, and surgical margin at any time.
4. *Correct the direction* The direction of the section plane is not always initially correct. The correct angle of incidence at which to start the resection may not be obvious; often the direction has to be adjusted to stay clear of the lesion, to reach a pedicle at the correct distance from its origin, or to reach a structure that will be spared and followed up (Fig. 13.2).

13.3 Parenchymal Sparing Surgery for Hepatocellular Carcinoma: Surgical Technique

PSS for HCC encompasses a wide range of liver resections, ranging from minor anatomical resections (AR)—e.g., bi/segmentectomies and subsegmentectomies—to more or less complex non-anatomical resections (non-AR). For all these procedures IOUS has a crucial role both in planning and guiding the liver resection. The main steps of these procedures, with both the open and laparoscopic approach, are described below.

13.3.1 Ultrasound-Guided Minor Anatomical Resections

AR are challenging due to the lack of clear separation of segments in the liver. The fundamental landmarks to determine intersegmental/sectional boundaries are (1) the landmark veins, (2) the feeding glissonean pedicles, and (3) the ischemic demarcation line. IOUS helps surgeons to identify the two main transection planes needed to perform an AR:

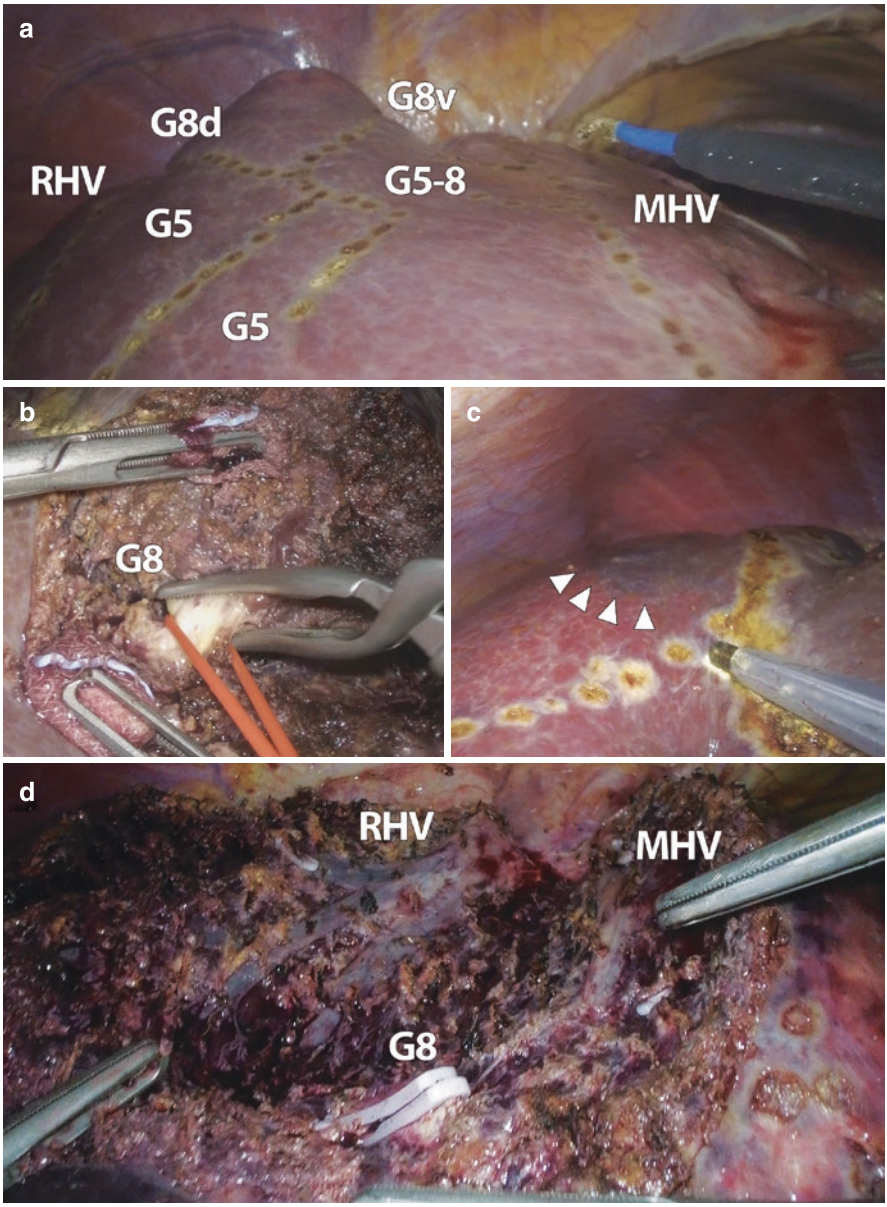

Fig. 13.1 Ultrasound-guided anatomical segment 8 resection. (**a**) The sketch of all the landmarks is completed: middle (*MHV*) and right (*RHV*) hepatic veins, the anterior glissonean pedicle (*G5–8*), Sg8 dorsal (*G8d*) and ventral (*G8v*) glissonean pedicles and segment 5 (*G5*) glissonean pedicles. (**b**) G8 is dissected along the cut surface and clamped. (**c**) Sg8 ischemic demarcation line (arrowheads) is clearly visible. (**d**) Sg8 segmentectomy is completed: MHV, RHV and G8 stump are visible on the cut surface

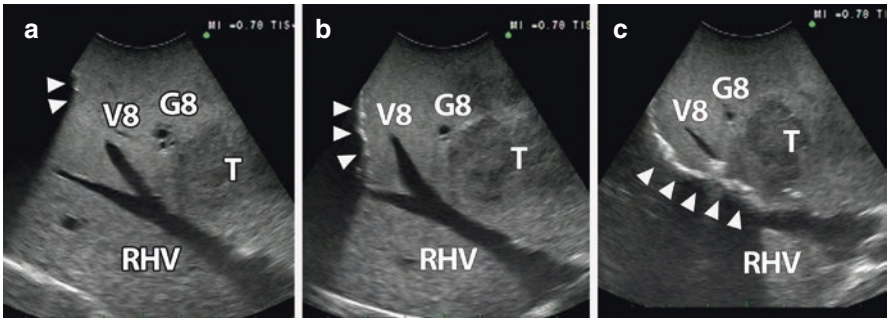

Fig. 13.2 Intraoperative ultrasound guidance to resection. (**a**) The section line (arrowheads) of a laparotomic Sg8 segmentectomy is approaching the right hepatic vein (*RHV*) with too smooth an angle, at the level of a Sg 8 venous branch (*V8*). (**b**) The section line direction has been corrected, now running below V8, then (**c**) reaching the RHV, allowing a safer margin with the tumor (*T*)

- The *longitudinal plane* that runs along one or more hepatic veins: for example, in cases of S8 segmentectomy there are two longitudinal planes, the one of the right hepatic vein (on the lateral part of the cut surface) and the one of the middle hepatic vein (on the medial part). These landmarks are easily identified with IOUS through a sliding movement of the probe on the liver surface with a longitudinal or transversal view.
- The *transverse plane* that runs along the root of tributary glissonean pedicles: in the above example of S8 segmentectomy the transverse plane runs along the anterior portal branch between the pedicles of segment 8 (to be ligated) and segment 5 (to be spared).

During AR, the longitudinal and transverse planes are connected to each other by the surgeons. In this phase IOUS allows the surgeon to check and, if necessary, correct the transection plane in real time. Once reached, the tributary can be managed with different approaches: dye stain portal injection, US-guided pedicle compression or isolation and ligation (Fig. 13.1b). The first two techniques can be difficult to perform in some cases (e.g., posterior segments) and are not reproducible in laparoscopy.

In the laparoscopic US-guided anatomical ventral approach, the glissonean pedicle is reached in an advanced stage of parenchymal transection as opposed to the glissonean pedicle-first approach [4]. This technique (suitable for anatomical segmentectomies and subsegmentectomies of segment 7 and 6 and for Sg6–7 bisegmentectomies) is based on the ultrasonographic identification of the right posterior or segmental pedicle from the dorsal side of the liver after complete mobilization. The pedicle of interest is isolated through mini-hepatotomy and clamped.

Ligation of tributary glissonean pedicle (with ventral or glissonean pedicle-first approach) allows identification of the last AR landmark: the ischemic area on the liver surface (Fig. 13.1c). The use of indocyanine green fluorescence technique

makes the ischemia apparent also inside the liver parenchyma, facilitating parenchymal liver transection.

Thanks to the remarkable advances in radiological imaging and surgical techniques, it is emerging that liver anatomy is definitively more complex than described by Couinaud. Takasaky et al. [5] defined "cone unit" as the smallest anatomical part of the liver, supplied by a tertiary branch and with the base on the hepatic surface and the apex toward the hilum. Majno et al. [6] recently reported that the median number of 2nd-order branches given off by the left and right portal vein was 20 (range: 9–44). In agreement with this new anatomical knowledge, in each segment it is possible to identify many independent anatomical subsegments fed by a tertiary pedicle that can be separately resected.

However, considering the high anatomical variation of the secondary and tertiary branches of the hepatic veins and portal pedicles and the absence of extrahepatic landmarks for these smaller liver units, IOUS has become the only instrument able to identify the "real anatomy" and to plan subsegmentectomy correctly.

13.3.2 Ultrasound-Guided Non-anatomical Resections

The role of IOUS for resection guidance is crucial not only in anatomical but also in non-anatomical resection. It can be used during both open and laparoscopic non-AR with different goals:

1. To identify and reach the vascular structures to be ligated and the right level of the ligature. In this way, laparoscopic US can prevent iatrogenic injury of tributaries to non tumor-bearing liver parenchyma while reducing the risk of major bleeding.
2. To identify the hepatic vein root to be followed inside the liver as a landmark boundary between subsegments or segments. According to the tumor position, type of segment and liver morphology, the hepatic vein root can be approached with a cranial or caudal approach.
3. To study venous drainage of the remnant liver (Fig. 13.3). Tumors involving the hepatic veins at the hepatocaval confluence often require major or extended hepatectomies. The use of intraoperative color Doppler US, first described by Sano et al. [7], is most important in the evaluation of liver hemodynamics to assess venous congestion in the remaining liver when the main hepatic veins are clamped. The lack of alternative drainage routes to one or more hepatic veins (e.g., venovenous shunts or accessory veins) in these patients may result in congested and sometimes unperfused liver parenchyma along the cut surface [8]. Unperfused remnant liver parenchyma is to be avoided, not only to reduce the risk of postoperative complications (bile leakage and bleeding) but also not to worsen the long-term results [9]. An imbalance of cytokines leading to a suppressed immunological status eventually promoting tumor growth have been recently shown to affect oncological outcomes in remnant liver ischemia after partial resections for HCC.

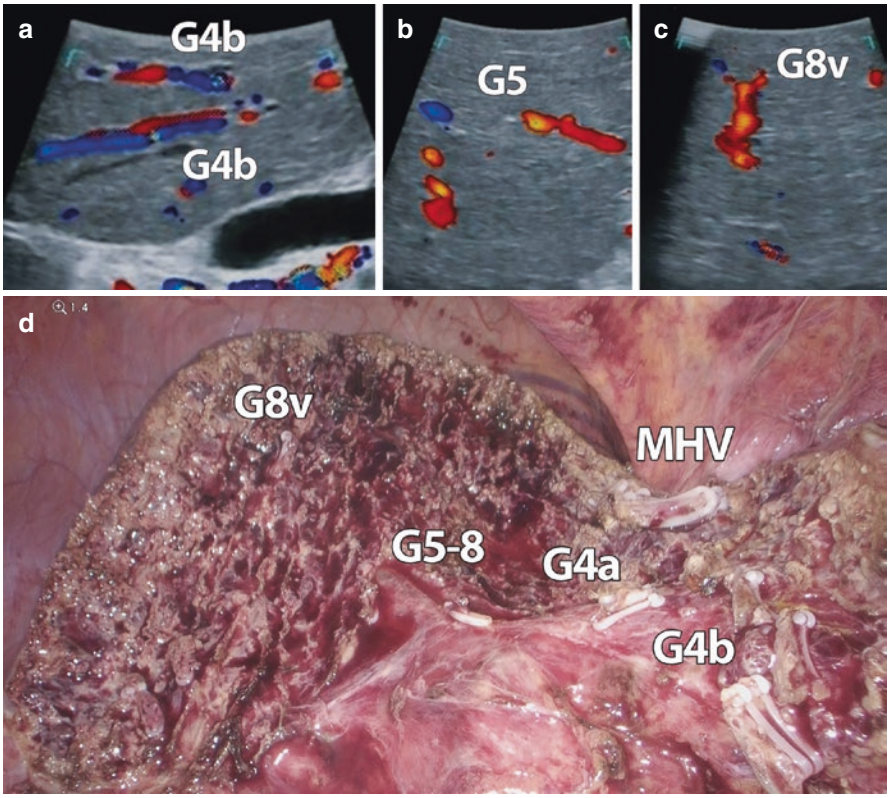

Fig. 13.3 Color Doppler intraoperative ultrasound (CD-IOUS). Patient with an HCC in Sg8v-Sg4a involving the middle hepatic vein (MHV) close to the hepatocaval confluence. The MHV has been clamped to assess the portal flow. (**a**) CD-IOUS check of Sg4b glissonean pedicles (*G4b*). After MHV clamping, the portal flow reverses and becomes hepatofugal, opposite to the arterial hepatopetal (displayed in red) flow. Sg4b has therefore to be resected. Sg5 (**b**, *G5*) and Sg8 ventral (**c**, *G8v*) glissonean branches remain hepatopetal (displayed in red) after MHV clamping and will be spared. (**d**) Based on the CD-IOUS findings, a Sg4 segmentectomy extended to part of Sg8v has been performed. The anterior glissonean pedicle (*G5–8*) is exposed on the cut surface, and the MHV, G4b and G8v stumps are visible

13.4 Conclusion

The ultrasound liver-mapping technique enables planning and real-time guidance during anatomical and non-anatomical liver resections. IOUS allows the surgeon to follow the map inside the parenchyma thanks to the continuous verification and correction of the surgical plane, thus preventing damage to vascular structures that should be spared.

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Surgical Margins for Hepatocellular Carcinoma

14

Giammauro Berardi, Nicola Guglielmo, Germano Mariano, and Giuseppe Maria Ettorre

14.1 Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor and the third leading cause of cancer-related deaths worldwide [1]. Depending on the patients' conditions and tumor status, surgical options such as liver resection or transplantation represent the treatment of choice as they offer long-term survival [2, 3]. Liver transplantation is the best surgical option as it not only allows removal of the whole tumor burden, but it also gives the opportunity to remove the diseased liver, avoiding the carcinogenetic effect of cirrhosis [4]. Unfortunately, given the organ shortage, patients on the waiting list have a 5% to 30% risk of progressing beyond the acceptable oncologic criteria or they decompensate and never receive transplantation [5]. For this reason, liver resection is widely accepted as a valid curative intent treatment offering a 5-year survival ranging between 40% and 70%, depending on oncological-, patient- and liver-related prognostic factors [6, 7].

Liver resection for HCC is widely adopted and standardized in many specialized centers worldwide. Given the unique conditions upon which HCC develops, liver resections in these patients require special considerations. Indeed, HCC frequently occurs in patients with underlying liver disease, negatively affecting the prognosis and increasing the complexity of management [8]. In this setting, margins during hepatectomies for HCC have been debated for many years and strong evidence to support a standardized approach is currently lacking. In this chapter, we will review the pathophysiology of HCC and try to summarize the evidence on this debated topic.

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14.2 Pathophysiology of Hepatocellular Carcinoma

The cytological features of HCC are unique in their form and differ from any other malignancy. Pre-clinical studies have clarified that HCC has a low incidence of lymph node metastasis and is not characterized by lymphatic invasion, which is common among gastrointestinal malignancies. Indeed, the rate of positive lymph nodes in patients undergoing liver resection for HCC has been reported to be less than 2% [9, 10]. Conversely, HCC is associated with a high rate of capsular invasion, vascular invasion, and intrahepatic metastasis in the form of satellite nodules. One of the most important factors associated with capsular and vascular invasion and with the genesis of intrahepatic metastasis is the size of the tumor [9, 10]. Small HCCs initially tend to grow and respect their capsule, while larger HCCs tend to first determine vascular invasion and then seed in the adjacent parenchyma in the form of satellite nodules. Interestingly, experimental studies have previously shown that vascular invasion in HCC does not follow a common pathway. In 1996, Mitsonobu et al. investigated the vascular pattern of 231 HCCs by injecting contrast into the tumor before the hepatectomy [11]. Furthermore, they injected siliconized rubber after the hepatectomy to create a cast of the tumor and the vascular pattern. Besides providing beautiful imaging of the vascular architecture of HCC, they demonstrated that its drainage pattern could be of two types: a portal vein drainage pattern or a portal vein and hepatic vein drainage pattern. The vast majority of HCCs on liver cirrhosis are drained by the portal vein while HCC in healthy liver or in initial stage fibrosis show a combination of portal vein and hepatic vein drainage. One of the explanations for this vascular architecture is that liver cirrhosis creates a mechanical obstacle to the natural drainage of the liver. Indeed, given the thin and easily collapsible wall of sinusoids, the blood drainage is inverted because of the occlusion of the small vessels by the cirrhosis. This could also explain the natural hepatic vein drainage of HCCs in healthy liver. These preclinical studies defined a peculiar cytoarchitecture of HCC that is currently considered valid, despite not having been studied in a prospective manner or in further larger studies (Fig. 14.1). Cells of hepatocellular carcinoma are fed by a peripheral branch of the hepatic artery allowing the tumor to receive nutrients and therefore grow. Conversely, the portal vein acts as the efferent vessel, draining blood from the tumor and sustaining the metastatic process. Within the tumor itself, arterio-portal shunts are invaded by HCC cells through a budding process and eventually enter the portal system and seed in the nearby parenchyma, generating satellite lesions.

14.3 Anatomical Resections for Hepatocellular Carcinoma

Almost 90% of HCCs grow in liver cirrhosis. Because cirrhotic livers are compromised in function and regeneration, the margins during hepatectomies need to be well planned to avoid postoperative decompensation, while maintaining oncological goals [12, 13]. Because of the cytoarchitecture and infiltration pathway, Makuuchi et al. theorized that liver resections for HCC should be anatomical,

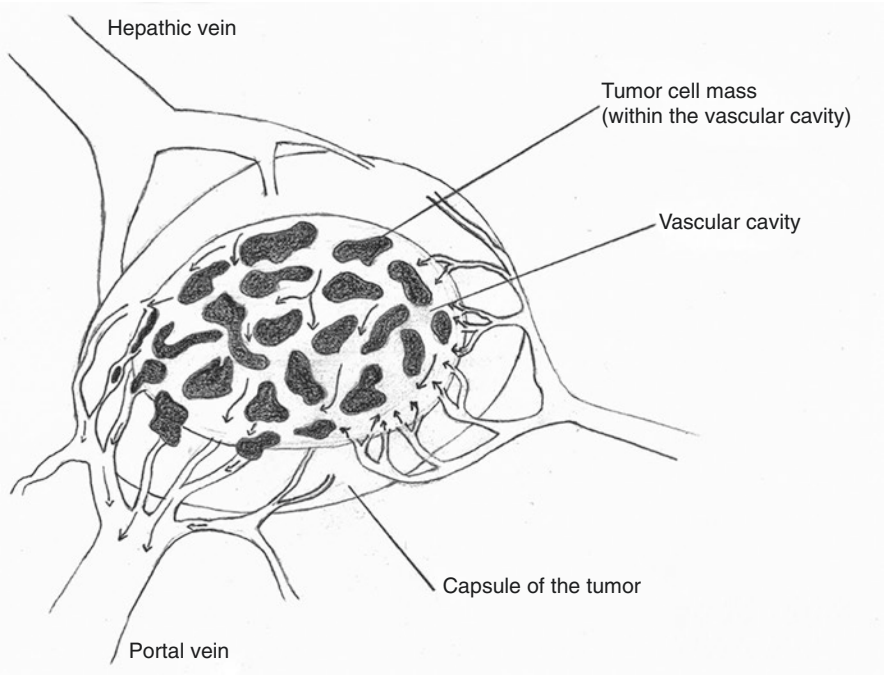

Fig. 14.1 Cytoarchitecture of hepatocellular carcinoma

removing the whole tumor-bearing area vascularized by the serving portal pedicle [14]. Indeed, given the portal venous drainage of HCCs, all the territory fed by the same pedicle vascularizing the tumor could be harboring micrometastatic disease and eventually lead to recurrence if not removed. Following this principle, in Makuuchi's famous technique of anatomical segmentectomies, after intraoperative ultrasound identification of the portal pedicle feeding the tumor, the surgeon injects methylene blue in the portal system. This allows depiction of the area feeding the segment in which the tumor resides and complete removal of the whole parenchyma, therefore respecting anatomical principles. By these means, according to Makuuchi, you completely remove the tumor and the micrometastatic disease, minimizing residual disease, improving R0 resections and decreasing the rates of cancer recurrence.

14.4 Recurrence Following Surgery for Hepatocellular Carcinoma

Studies investigating surgical margins in HCC focus on the outcome of recurrence, analyzing the crude number of patients experiencing recurrence and reporting results among prognostic factors. However, the history of this disease and its recurrence is more complex and necessitates further considerations. HCC recurs in up to

70% of patients following liver resections [7]. Tumor recurrence can be divided into two different entities depending on the timing of occurrence. Previous studies have shown that the natural history of HCC includes a first risk of recurrence within 2 years, called early recurrence, and a second occurrence after 2 years, the late recurrence [9]. These two different patterns seem to be related to different mechanisms: for early recurrence, the primary tumor itself which could have generated micrometastatic disease early in the process; for late recurrence, the cirrhosis which, because of its intrinsic carcinogenetic properties, continues to generate aberrant clones of cells and therefore new tumors. Poon et al. have demonstrated that early recurrence was associated with the tumor's characteristics and with poor prognosis, while late recurrence was associated with better prognosis and with cirrhosis [15]. Further supporting this theory, a study focusing on clonality of recurrence included five HCCs on a background of HBV-related cirrhosis and analyzed the HBV DNA integration in both the primary tumor cells and in the recurrence. Interestingly the authors found that two patients had identical clonality between the primary tumor and the recurrence, while three patients had completely different DNA integrations. This led to the conclusion that HCC recurs with a "true recurrence" pattern and with a "de-novo" pattern [16]. Given the complexity of the disease, studies investigating the oncological outcomes of surgery should break down the recurrence into two time frames ("early" and "late") and two patterns ("true" and "de-novo") to correctly assess oncological efficacy and standardize terminology in the literature.

14.5 Surgical Margins for Hepatocellular Carcinoma

Patients with well-compensated liver function and no significant portal hypertension represent the ideal surgical candidates. While the international guidelines are clear on which patients should and should not undergo resection, there is no clear indication on what type of surgery should be performed and which surgical margins should be respected. The only guideline that is somehow clearer is the European Association for the Study of the Liver (EASL) guideline, which states that anatomical resections should be preferred in patients with HCCs of at least 2 cm [4]. However, the same guideline concludes that this statement should be interpreted with caution since the evidence comes from retrospective studies with a high chance of selection bias. Indeed, most of the studies comparing anatomical (AR) and non-anatomical resections (non-AR) carry the bias of including more advanced patients in terms of liver function in the AR group. Eguchi et al. reviewed the Japanese HCC registry, reporting the outcomes of 5781 patients who underwent resection [17]. A statistically significant association of AR with survival and disease-free survival was shown. However, this association was lost when stratifying patients according to the Liver Damage score. A recent meta-analysis demonstrated more blood loss, longer operative time, and wider margins in ARs compared to non-ARs, and no differences in morbidity and mortality [18]. Furthermore, an association with survival was shown and the authors concluded that anatomical resections should be considered the treatment of choice in patients undergoing resection for HCC. Unfortunately,

this pooled analysis carries significant selection bias, which limits its conclusions. A significantly lower number of cirrhotic patients were operated on in the AR group (53% vs. 66%; $p < 0.001$), with fewer Child-Pugh B patients (4.4% vs. 30.8%) and most of the preoperative variables having an $I2 > 75\%$, including number of lesions, grading and microvascular invasion, indicating a high heterogeneity between groups.

Evidence from randomized controlled trials comes into play in 2007: Shi et al. randomized 173 patients with solitary HCCs on Child-Pugh A liver function to undergo resection with a margin of 1 or 2 cm [19]. The preoperative characteristics of patients were well balanced, and the postoperative outcomes were not different. Five-year overall survival was significantly better in the 2-cm margin group (74% vs. 49%; $p = 0.008$), as was the 5-year disease-free survival (52% vs. 40%; $p = 0.04$). The number of patients developing recurrence was significantly lower in the wide margin group, as was the number of recurrences at the transection margin [19]. The reason for this association with survival might be attributable to the treatment of recurrences, which was potentially aimed at cure (using resection or ablation) in more patients in the wide margin group. Although this study provides the first piece of level 1 evidence, it answers the question of width of margin during resection but not the question on whether resections should be anatomical and respect the portal territory principle (Fig. 14.2). A randomized controlled trial in 2017 tried to answer the question on AR vs. non-AR. The authors randomized 105 patients with single

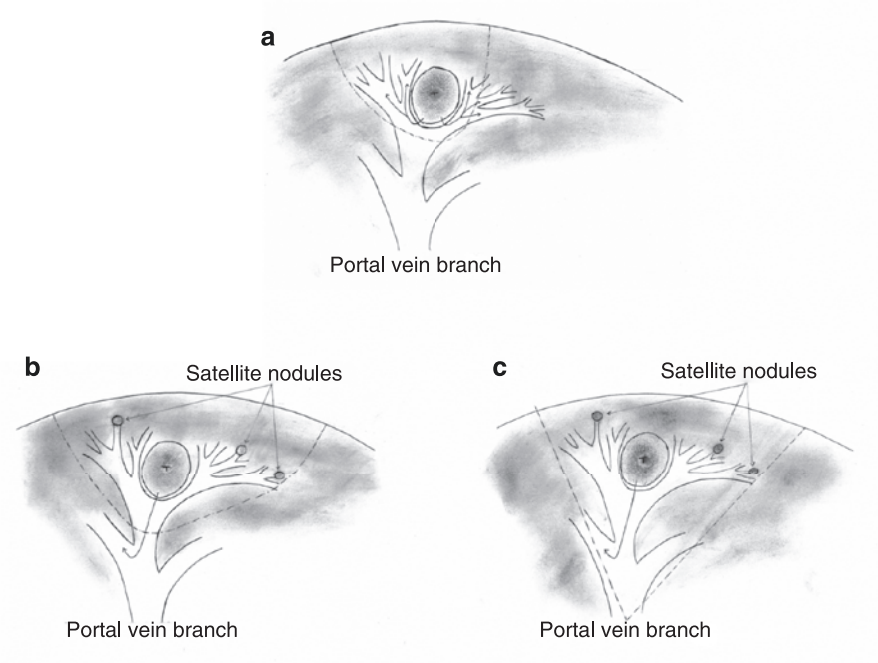

Fig. 14.2 Different margins in hepatocellular carcinoma. Non-anatomical (**a**), wide margin (**b**), and anatomical (**c**) resections

HCCs in Child-Pugh A cirrhosis, indocyanine green dye retention rate <14%, and no moderate or severe portal hypertension, to undergo AR or non-AR [20]. No differences were found in the postoperative outcomes. Furthermore, no differences in the oncological outcomes were found, including overall survival and overall recurrence-free survival. The only difference that was shown in this trial was in the primary outcome. Indeed, AR showed a significantly better local recurrence-free survival ($p = 0.01$) and a lower number of local recurrences within 2 years (30% vs. 59%; $p = 0.001$). Furthermore, overall local recurrence was significantly lower in the AR group (42% vs. 68%; $p = 0.008$) and median time to recurrence was significantly longer (53 vs. 10 months; $p < 0.001$). The results of this trial were later confirmed in a recent meta-analysis of propensity score studies which showed no differences between AR and non-AR in terms of overall survival, a significantly better disease-free survival at 1 and 3 years following surgery in the AR group and a comparable disease-free survival at 5 years [21]. Pooling together the results of the above-mentioned studies and the evidence available so far, in patients with normal liver function, single HCCs and adequate future liver remnant, anatomical resections seem to provide better local control within 2 years from surgery, and comparable long-term overall survival and disease-free survival.

14.6 Conclusions

HCC is a complex disease with peculiar cytoarchitecture and a high chance of recurrence following treatment. Tumor recurrence should be investigated and reported considering both its timing and pattern, to correctly determine the prognosis of patients and manage the disease. There is currently a lack of strong evidence to support narrow, wide, or anatomical margins in patients undergoing surgical resection. Most of the conclusions come from retrospective studies with a high chance of selection bias. The only randomized controlled trials available to date report a benefit in terms of local control within 2 years from surgery for wide anatomical margins in patients with single HCC with preserved liver function. Conversely, long-term overall and disease-free survival are comparable. Future and larger studies are required to test the results of the trials, incorporating advanced techniques addressing the biology of the disease such as circulating tumor cells.

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Major Hepatectomies for Hepatocellular Carcinoma

15

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15.1 Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver tumor and the third leading cause of cancer-related deaths worldwide [1]. When feasible, surgery represents the treatment of choice as it can offer long-term survival [2, 3]. HCC frequently occurs in patients with underlying liver disease, and this negatively affects prognosis and increases the complexity of treatment [4]; liver cirrhosis in fact is an independent prognostic factor for both short- and long-term outcomes, and the assessment of liver function is critical in the management of these patients as treatments may induce liver damage leading to decompensation [5].

Despite the recent advances, a substantial proportion of patients still presents with large and multinodular tumors, or lesions involving major vascular structures. These patients bear a poor prognosis such that international guidelines recommend a systemic approach to avoid the perioperative risks of surgery [6, 7]. Despite this, some authors have shown that radical resections in large or multinodular disease is feasible and is associated with good long-term outcomes [8–10]. These patients often require major hepatectomies to achieve radical resections of their tumor burden [11]. Major hepatectomies for HCC require special consideration as they are associated with increased postoperative risks related to the background liver. In this setting, careful preoperative selection of patients, discussion of treatment options and adequate preparation for surgery are key to avoid postoperative complications and offer long-term survivals. We herein discuss the preoperative management, surgical and oncological outcomes of major hepatectomies for HCC.

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15.2 Preoperative Management

Major hepatectomies for HCC require careful preoperative patient evaluation, especially when compromised liver function is suspected. Specific biochemical and radiological investigations are necessary. Low platelet number, high international normalized ratio (INR) values, a positive history of variceal bleeding, encephalopathy, ascites, as well as radiological findings of an enlarged spleen, cirrhotic liver, and portosystemic shunts, should raise a suspicion of decreased liver function and compromised portosystemic circulation. Liver function impairment in these cases is estimated using well-known scores (i.e., the Model for End-Stage Liver Disease, and the Child-Turcotte-Pugh). Then, the type of hepatectomy and the volume of liver to be removed is balanced with the degree of liver function and the volume of the future liver remnant (FLR), to assess the feasibility of the procedure. Preoperative evaluation of the FLR is crucial to determine whether an extended resection can be safely performed. In cases of cirrhotic liver, an FLR of at least 40% should be maintained [12]. Moreover, liver function is investigated using methods that estimate the regenerative and functional capacity of the FLR, to avoid any potential risk of post-hepatectomy liver failure (PHLF). Indeed, recent studies have demonstrated that liver function is not necessarily related to liver volume and that PHLF could occur even in sufficient liver volume. Increasingly used in experienced hepatobiliary centers, these methods are the indocyanine green dye retention test, the LiMAx test (using 13C-methacin), the monoethylglycinexylidide test, magnetic resonance imaging with liver-specific contrast, and ^{99m}Tc-mebrofenin hepatobiliary scintigraphy. These tests are used as a complementary method and provide useful information on the FLR.

Most of the patients requiring major hepatectomies for HCC will have insufficient or borderline volume and function to safely undergo a major hepatectomy without the risk of PHLF. In this setting, preoperative strategies to induce FLR hypertrophy have been described that aim to increase the number of surgical candidates. Preoperative portal vein embolization (PVE) was introduced more than 30 years ago by Makuuchi et al. as a strategy to expand the indications for major hepatectomies in borderline FLR [13]. By preoperatively shifting the portal blood flow, PVE induces a volume and functional growth in 4–6 weeks, leading to a better postoperative recovery without impairing the long-term results [14, 15]. Furthermore, PVE can be combined with chemotherapy in what is defined as transarterial chemoembolization (TACE): this combination may strengthen the effect of PVE by embolizing the arterioportal shunts in the tumor, simultaneously preventing progression thanks to the chemotherapy [16]. Recently, the associating liver partition and portal vein embolization for staged hepatectomy (ALPPS) procedure has been described as an alternative to PVE for decreasing the risk of drop-out during the interstage, by inducing a more rapid increase in FLR [17]. Limited data are available on ALPPS for HCC and cirrhotic livers: our group has previously reported good and safe perioperative and oncological outcomes [18]. We currently reserve this procedure for cases with large and advanced HCC with macrovascular invasion, when a conventional two-stage approach is not feasible due to portal vein branch invasion, when a

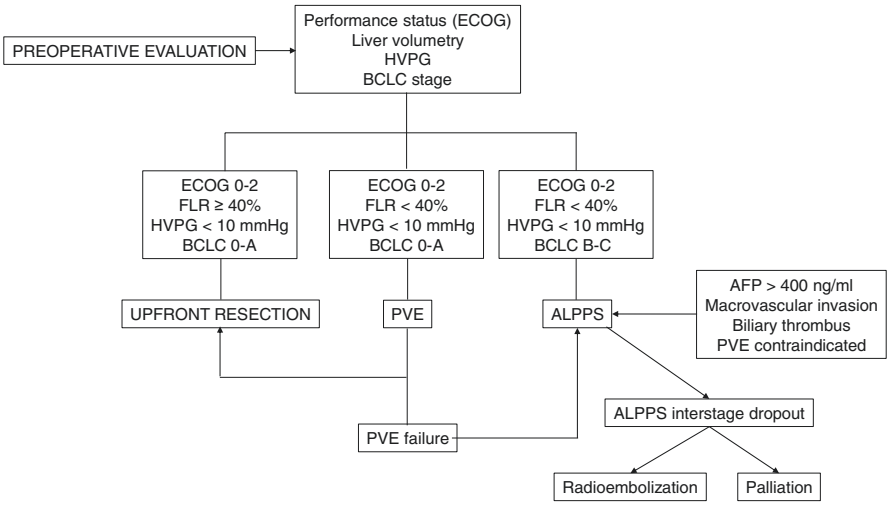

Fig. 15.1 Management of patients with hepatocellular carcinoma requiring major hepatectomies at our institution. *AFP* alpha-fetoprotein; *ALPPS* associating liver partition and portal vein embolization for staged hepatectomy; *BCLC* Barcelona Clinic Liver Center staging system; *ECOG* Eastern Cooperative Oncology Group; *FLR* future liver remnant; *HVPG* hepatic vein portal vein pressure gradient; *PVE* portal vein embolization

previous PVE has failed or in bleeding tumors. An interesting recent approach to large HCCs requiring major hepatectomies in patients with limited FLR is radioembolization with yttrium-90. This technique involves arterial embolization of the affected liver to treat the tumor and induce contralateral hypertrophy. A 42% increase in the size of the non-embolized liver has been reported in cirrhosis [19]. Finally, a developing technique in this field is liver venous deprivation, which allows for a rapid volume increase of the FLR thanks to combined portal and hepatic vein embolization: the results are promising but randomized trials are still ongoing. The current management of patients with HCC requiring a major hepatectomy at our department is summarized in Fig. 15.1.

15.3 Postoperative Outcomes of Major Hepatectomies for Hepatocellular Carcinoma

Major hepatectomies for HCC are associated with significant operative mortality and morbidity, especially when underlying liver cirrhosis is present [20, 21]. PHLF and all the spectrum of associated conditions are the most common scenarios. Indeed, the FLR is frequently not enough to tolerate the changes in pressures following the removal of a major portion of the liver, and the metabolic functions are significantly reduced. As a result, patients have a prolonged postoperative stay, which can lead to liver failure and eventually death. Therefore, postoperative

morbidity following major resections strictly depends on patient selection, preoperative evaluation, and intra- and postoperative management.

Overall, postoperative mortality ranges between 0–9% while morbidity ranges between 10–60% [22]. With the improvement of perioperative care and surgical techniques, zero hospital mortality rates can be achieved in experienced hepatobiliary centers [23, 24]. The risk of complications depends on the severity of the cirrhosis and increases with impaired liver function. In a landmark study, the degree of fibrosis strongly correlated with the development of postoperative complications, especially liver failure, ascites and liver decompensation [20]. Furthermore, while patients with Child-Pugh A liver function well tolerate major hepatectomies, patients with Child-Pugh B disease are at high risk of postoperative events. Recently, we have shown that patients with Child-Pugh B liver function undergoing major hepatectomies had a high mortality (10.3%) and morbidity rate (69.2%), a high rate of major complications (46.1%) and frequently developed ascites (61.5%) and PHLF (10.2%) [25]. Therefore, in the setting of advanced liver cirrhosis and large or multinodular HCCs requiring major hepatectomies, extreme caution is necessary: patients must be carefully selected and potential alternatives evaluated to reduce the chance of postoperative morbidity and mortality.

The technical aspects of major hepatectomies themselves can impact postoperative outcomes. The so-called "anterior approach" is a technical modification during right hepatectomy that was first described by Ozawa in 1990: in this variant, mobilization of the right liver from the diaphragm is left as a last step, after parenchymal transection [26]. In a randomized controlled trial, Liu et al. demonstrated that the anterior approach was associated with less blood loss and fewer patients requiring blood transfusions [21]. In this study, although the difference was not statistically significant, the anterior approach group had lower rates of PHLF (1.7% vs. 10%; $p = 0.114$). This could be attributed to the lack of extensive manipulation maintaining physiological circulation throughout the procedure. In 2001, Belghiti et al. first described a safe approach to right hepatectomies without liver mobilization using the "hanging maneuver": this guides the transection of the parenchyma and reduces intraoperative bleeding [27]. In our institution, right hepatectomies are performed in a standardized fashion using the anterior approach with the hanging maneuver, the intrafascial approach to the hilar structure, ultrasonic transection and bipolar coagulation of the parenchyma, intraparenchymal stapling of the bile duct and right hepatic vein, and liver mobilization at the end of the procedure.

15.4 Oncological Outcomes of Major Hepatectomies for Hepatocellular Carcinoma

According to major international guidelines, resection for HCC is restricted to early-stage disease with preserved liver function [6, 7]. Despite this, studies from different countries have shown that resections for single large and multinodular HCC are associated with low mortality rates and favorable long-term prognosis [8–10]. Furthermore, one randomized controlled trial and one meta-analysis

demonstrated that, despite recurrence remaining an issue, resection is associated with improved long-term outcomes as compared to locoregional therapies [22, 28]. Pooling the results from these studies led to a consensus that surgery should at least be considered a therapeutic option in patients with single large or multinodular disease requiring major hepatectomy.

Overall, the 5-year survival of patients with single large or multinodular hepatocellular carcinoma undergoing resection ranges between 20–70%, while the 5-year disease free survival ranges between 10–50% [22]. The long-term outcomes of major surgeries in these scenarios are promising and resections are currently routine practice in many experienced centers worldwide.

International guidelines recommend locoregional treatments in patients with multinodular or single large HCC. However, the long-term data should be carefully evaluated and compared to available options and the locoregional complications should not be underestimated. In a meta-analysis by Marelli et al., TACE was associated with a 2.4% mortality rate, with other studies demonstrating inferior oncological outcomes as compared to resections [22, 28]. Specifically, a randomized controlled trial involving 173 patients with resectable multiple HCC beyond the Milan criteria revealed that resection was associated with significantly better overall survival than TACE ($p < 0.001$) [28]. Tumor size or number does not influence the patients' long-term survival rates, although more complex surgical techniques are required [29, 30].

It should be mentioned that most studies on long-term outcomes are from Asia where patients mostly present with HCC on the background of hepatitis B-related liver cirrhosis. In Western countries, hepatitis C-related disease and HCCs are more common, followed by alcoholic hepatitis and non-alcoholic fatty liver disease: recurrences and survivals should be investigated in these settings.

15.5 Laparoscopic Major Hepatectomies for Hepatocellular Carcinoma

Despite the initial controversies, laparoscopy is now accepted as an effective alternative in the treatment of liver malignancies, with more than 10,000 cases reported [31]. Laparoscopic liver resections (LLRs) in the treatment of HCC have been widely reported with good short-term results and safe oncological outcomes. LLRs may help reduce the risk of PHLF by respecting the collateral portosystemic shunts, avoiding major liver mobilization, and avoiding electrolyte imbalances [25]. Despite this, most of the series available describe the results of minor hepatectomies in highly selected patients. Major hepatectomies in the setting of liver cirrhosis are challenging procedures that need to be performed in a safe environment, especially if done laparoscopically. In a recent study comparing open and laparoscopic major hepatectomies for HCC, laparoscopy was associated with less blood loss. Furthermore, postoperative morbidity was significantly lower, and hospital stay shorter. R0 resection rates were similar and long-term outcomes were comparable between groups [32]. The only disadvantage reported in most of the studies was that

LLRs were associated with an increase in operative time, which is probably related to a learning curve effect. Nonetheless, there is a non-negligible risk of conversion to open surgery, which is higher than in minor resections and in resections for colorectal cancer liver metastases. The main reasons for conversions are bleeding and oncological. Indeed, the lack of tactile sensation and the challenges in performing ultrasound result in conversion rates of major hepatectomy for HCC ranging between 10–20% [33, 34].

15.6 Conclusions

Major hepatectomies represent a valid therapeutic option for patients with large and multinodular HCCs. Postoperative and oncological results are safe when appropriate evaluation and preparation of patients is carried out. Laparoscopic major hepatectomies are increasingly performed in experienced centers and should be further investigated as a good technical alternative with better postoperative results and comparable oncological outcomes.

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R1-Vascular Surgery for Hepatocellular Carcinoma

16

Matteo Donadon, Bruno Branciforte, Simone Famularo, and Guido Torzilli

16.1 Introduction

Apart from liver transplantation, which remains the standard of care for selected patients, locoregional therapies, such as hepatic resection, percutaneous ablations, and transarterial treatments, are also considered with curative intent for patients affected by hepatocellular carcinoma (HCC) [1, 2]. However, these locoregional therapies are associated with high rates of disease recurrence, up to 60% at 3 years [3, 4], which are usually thought to be counteracted by performing anatomic resection (AR) with negative surgical margins (R0-hepatectomy) [5–7]. However, in the surgical community some confusion exists about these technical concepts, specifically about their definitions, their practical application and, importantly, about their prognostic significance. In this chapter, we review the concepts of tumor exposure, AR, and surgical margins in HCC patients and present objective data and considerations supporting our strategy of minimizing liver sacrifice while maximizing the chance of cure, which led to the introduction and performance of R1-vascular hepatectomy, or vessel-guided liver surgery [8], as a standard of care in liver surgery.

16.2 Anatomic Resection: Forty Years of Studies

Starting in the late 70s, Makuuchi et al. illustrated the surgical technique of anatomical parenchymal-sparing hepatectomy for HCC. The technique was later reported in 1985 and has become a keystone in liver surgery [5]. For the purposes of

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this chapter, some points need to be borne in mind. First, the performance of AR is a technically demanding procedure that requires deep knowledge of liver anatomy; unfortunately, many of the published papers on this topic are flawed because they lack those important surgical technical details that make the message understandable and generalizable. Second, without the use of intraoperative ultrasound (IOUS) the performance of parenchymal-sparing AR is impossible except for major resections, such as right and left hepatectomy. As stated, many of the published papers on this topic lack a description of the surgical technique adopted to perform AR. Third, performance of AR does not depend on the achievement of negative margins. Indeed, complete removal of microsatellites depends on the complete removal of the tumor-containing part, i.e., the entire vascular bed supplying the lesion. However, the removal of an entire hepatic segment does not ensure prevention of tumor exposure. In the case of an HCC located in segment 8 that is in contact with the right and middle hepatic veins at the caval confluence, a full AR of segment 8 will expose the right and middle hepatic veins on the cut surface; the specimen at the level of the detached site of contact between the HCC and the hepatic veins should have exposed the tumoral surface. At that site, the risk of microsatellites is nil, and consequently the risk of local recurrence becomes negligible if an adequate technique is meticulously applied under IOUS guidance [9, 10]. However, sparing of the vessel by means of tumor–vein detachment minimizes the excision of liver parenchyma, which is important since the prognosis of HCC patients depends much more on the residual liver volume than on the width of the surgical margin [11]. Thus, any new lesion occurring in the adjacent segments during the follow-up should not be considered an undetected satellite not removed during surgery, but rather a distant metastasis that would have not been prevented by a wider surgical margin. Fourth, many factors other than margin status play a role in determining local and systemic recurrence of HCC after hepatectomy. Among them are tumor number, tumor size, tumor grading, tumor vascular invasion, as well as factors related to the underlying liver disease that drive the development of new HCCs or at any rate impact survival. Considering these factors, the prognostic significance of true AR might be secondary so that in some cases of advanced tumoral presentations the performance of IOUS-guided non-AR could be also considered adequate.

16.3 To Expose or Not to Expose the Tumor on Cut Surface?

The effect of surgical margin status on the survival of patients with HCC has been studied, but controversies persist among surgeons. In the last two decades several literature reviews have studied the effect of the surgical margin in surgery for HCC, with the specific aim of supporting or not supporting the use of no-margin surgery for HCC patients (see Table 16.1 and online supplementary material). Among 23 studies (years 1999–2021), 6 were in favor of tumor exposure while 10 were explicitly in favor of a large (centimeter) margin. All these studies were retrospective except for a randomized clinical trial by Shi et al. [7] and a prospective trial by Donadon et al. [12]. Shi et al. compared HCC patients with 1-cm margin versus

Table 16.1 Review of the literature of the last two decades on surgical margin in surgery for hepatocellular carcinoma

Author, year	Patients	Study design	Margin	In favor of tumor exposure	In favor of large margin (cm)
Ochiai, 1999	165	Retrospective	<1 cm vs. ≥1 cm	No	Yes
Poon, 2000	288	Retrospective	<1 cm vs. ≥1 cm	No	No
Shi, 2007	169	Randomized	1 cm vs. 2 cm	No	Yes
Matsui, 2007	465	Retrospective	0 mm vs. >0 mm	Yes	No
Nanashima, 2008	113	Retrospective	0 mm vs. >0 mm	Yes	No
Lee KT, 2012	407	Retrospective	1–5 mm vs. 6–10 mm vs. >10 mm	No	No
Nara, 2012	570	Retrospective	≤1 mm vs. >1 mm	Yes	No
Gong, 2015	75	Retrospective	1–9 mm vs. >10 mm	No	Yes
Lee JW, 2016	1022	Retrospective	≤1 mm vs. >1 mm	Yes	No
Field, 2017	130	Retrospective	≤5 mm vs. 5 mm	No	No
Shin, 2018	116	Retrospective	<1 cm vs. ≥1 cm	No	Yes
Donadon, 2019	327	Prospective	1 mm vs. 0 mm	Yes	No
Aoki, 2019	4457 vs. 3507	Retrospective	0 mm vs. >0 mm	No	No
Han, 2019	801	Retrospective	<1 cm vs. ≥1 cm	No	Yes
Yang, 2019	2508	Retrospective	<1 cm vs. ≥1 cm	No	Yes
Tsilimigras, 2020	404	Retrospective	<1 cm vs. ≥1 cm	No	Yes
Wang, 2020	904	Retrospective	2 mm	No	No
Su, 2020	159	Retrospective	<1 cm vs. ≥1 cm	No	Yes
Gruttadauria, 2020	236	Retrospective	≤1 mm vs. >1 mm	No	No
Kobayashi, 2020	454	Retrospective	<1 mm vs. ≥1 mm	Yes	No
Liu, 2021	240	Retrospective	<1 cm vs. ≥1 cm	No	Yes
Zhou, 2021	817	Retrospective	<1 cm vs. ≥1 cm	No	No
Michelakos, 2021	178	Retrospective	≤30 mm vs. 31–10 mm vs. >10 mm	No	Yes

Sources of listed studies alphabetized by author: **Aoki** et al. Br J Surg. 2020;107(1):113–20. **Donadon** et al. Surgery. 2019;165(5):897–904. **Field** et al. Am J Surg. 2017;214(2):273–7. **Gong** et al. J Gastroenterol Hepatol. 2016;31(1):206–12. **Gruttadauria** et al. Updates Surg. 2020;72(1):109–17. **Han** et al. HPB (Oxford). 2019;21(8):962–71. **Kobayashi** et al. Surg Today. 2020;50(11):1471–9. **Lee JW** et al. World J Surg. 2016;40(6):1429–39. **Lee KT** et al. J Formos Med Assoc. 2012;111(3):160–70. **Liu** et al. Front Oncol. 2021;10:610636. **Matsui** et al. Arch Surg. 2007;142(7):596–603. **Michelakos** et al. J Gastrointest Surg. 2021;25(7):1727–35. **Nanashima** et al. Acta Chir Belg. 2008;108(5):532–7. **Nara** et al. Surgery. 2012;151(4):526–36. **Ochiai** et al. Hepatogastroenterology. 1999;46(27):1885–9. **Poon** et al. Ann Surg. 2000;231(4):544–51. **Shi** et al. Ann Surg. 2007;245(1):36–43. **Shin** et al. Ann Hepatobiliary Pancreat Surg. 2018;22(4):326–34. **Su** et al. Surg Oncol. 2021;36:15–22. **Tsilimigras** et al. J Gastrointest Surg. 2020;24(7):1552–60. **Wang** et al. Front Med (Lausanne). 2020;7:139. **Yang** et al. Surgery. 2019;165(4):721–30. **Zhou** et al. J Cancer. 2021;12(15):4455–62

those with 2-cm margin and observed a lower recurrence rate in the wide-margin group and very high rates of local recurrence (29%) in the narrow-margin group. However, such a high rate of local recurrence is inconsistent with other larger series, and the associated unclear description of AR and non-AR remains the major flaw of that study. Conversely, the study from Donadon et al. [12] was in line with the long-standing literature coming from Japan which clearly reports the surgical technical details that are important to make the message understandable and generalizable; moreover, the study endpoint was set exactly on the topic of tumor exposure which, consistent with previous literature, was considered indicated only in cases of detachment from major vascular structures intended to be preserved to preserve the liver parenchyma.

Such controversies in surgical margin for HCC have important practical and clinical implications in terms of patient selection and therapeutic planning. Indeed, as a result of these different publications and their authors' surgical strategies, there are disparate definitions of resectability for HCC, which lead to disparate therapeutic indications and consequently to the flourish of HCC classifications and therapeutic flowcharts [13].

When discussing surgical margin status it is important to define the relationship between the width of the tumor-free margin and the size of the tumor. The risk of satellites increases with tumor size [14], thus a clear margin should be achieved in the case of tumors larger than 2.5 cm. These findings are consistent with the observation that in HCCs smaller than 2 cm similar local control can be achieved using either the ablation technique or hepatic resection [15]. However, this should not act as a confounding finding when attention is focused on 0-mm margins at the site of contact between the tumor and a major vessel, whether a glissonean pedicle or a hepatic vein. In such cases, tumor exposure on the cut surface, even when the HCC is larger than 2.5 cm, should be considered acceptable. Indeed, the possibility of leaving some tumor tissues at that site is negligible as long as the surgery is performed under IOUS guidance [9, 10]. Conversely, sacrificing the vessels could result in major parenchymal removal and increased surgical risk [16, 17] without the counterbalance of improving the long-term outcomes. Indeed, in HCC patients the curability of the tumor should always be balanced against the risk of postoperative liver dysfunction. These concepts are the foundation of our technical protocol that in 2005 we named "radical but conservative surgery" for liver tumors, whose primary model, among the different liver tumors, was precisely HCC [9]. Since then, we developed the concept of tumor detachment from major intrahepatic vascular structures—the so-called R1-vascular hepatectomy—aiming to improve resectability of the tumor and decrease its invasiveness on the liver, which is often diseased. More recently, we were able to report how this technical protocol was associated with good oncological outcomes [12].

Therefore, while a given hepatectomy with anticipated narrow or 0-mm margin should not be denied a priori, the appropriateness of detaching a given HCC from an

intrahepatic vascular structure might be just a reflection of a better tumor biology. Yet, the outcome of a tumor that grows along a major vascular structure may differ depending on whether it has an expansive or invasive growing pattern. However, most HCCs have a typical pseudo-capsule that allows safe separation of the tumor from the underlying liver without affecting long-term survival. Of note, this pseudo-capsule is the result of the host's immune response against tumor cells and represents the natural margin of separation between the tumoral and non-tumoral tissues [18–22]. Moreover, while tumor clearance at the resection margin may be helpful in preventing local recurrence, if we consider that most intrahepatic recurrences originate from either portal venous dissemination [23, 24] or multicentric carcinogenesis [25, 26], it is clear that a wide resection margin may not have a significant impact on the risk of HCC recurrence. These considerations provide a strong background for parenchymal-sparing procedures and conservative treatments of patients with HCC. When a limited functional liver reserve is anticipated, a major or extended liver resection for the sole purpose of achieving large negative margins is not justifiable. Additionally, considering that patients with diseased liver have a high incidence of intrahepatic recurrence in the liver remnant, the strategy of leaving sufficient functional liver parenchyma—both to reduce operative morbidity and mortality and to allow for new locoregional treatments—should be the roadmap in surgery for HCC.

16.4 R1-Vascular Surgery Is the Roadmap for Parenchymal-Sparing Hepatectomy

As stated above, when an HCC is in contact with the veins, it can be removed anatomically, although exposed on the cut surface. In other words, performing an anatomic resection in HCC does not depend on achieving negative margins [27] (Figs. 16.1 and 16.2).

The enormous developments in IOUS over the last two decades are the backbone of modern parenchymal-sparing surgery. Indeed, thanks to IOUS guidance, deeply located tumors may be approached by following complex multiplanar dissection trajectories [27–30], resulting in an opportunity to perform radical surgery while preserving functional non-tumoral parenchyma. These complex approaches are mainly possible by using two techniques. The first consists of detaching the tumors from major intrahepatic vessels whenever IOUS excludes infiltration, that is, R1-vascular hepatectomy. The second involves identifying and using communicating vessels among the main hepatic veins: once detected and preserved, these communicating vessels could guarantee adequate outflow to liver parenchyma even after a main hepatic vein resection [27–30]. The combination of these techniques has led to the possibility of performing several new types of liver resections as an alternative to standard major hepatectomies [31–35].

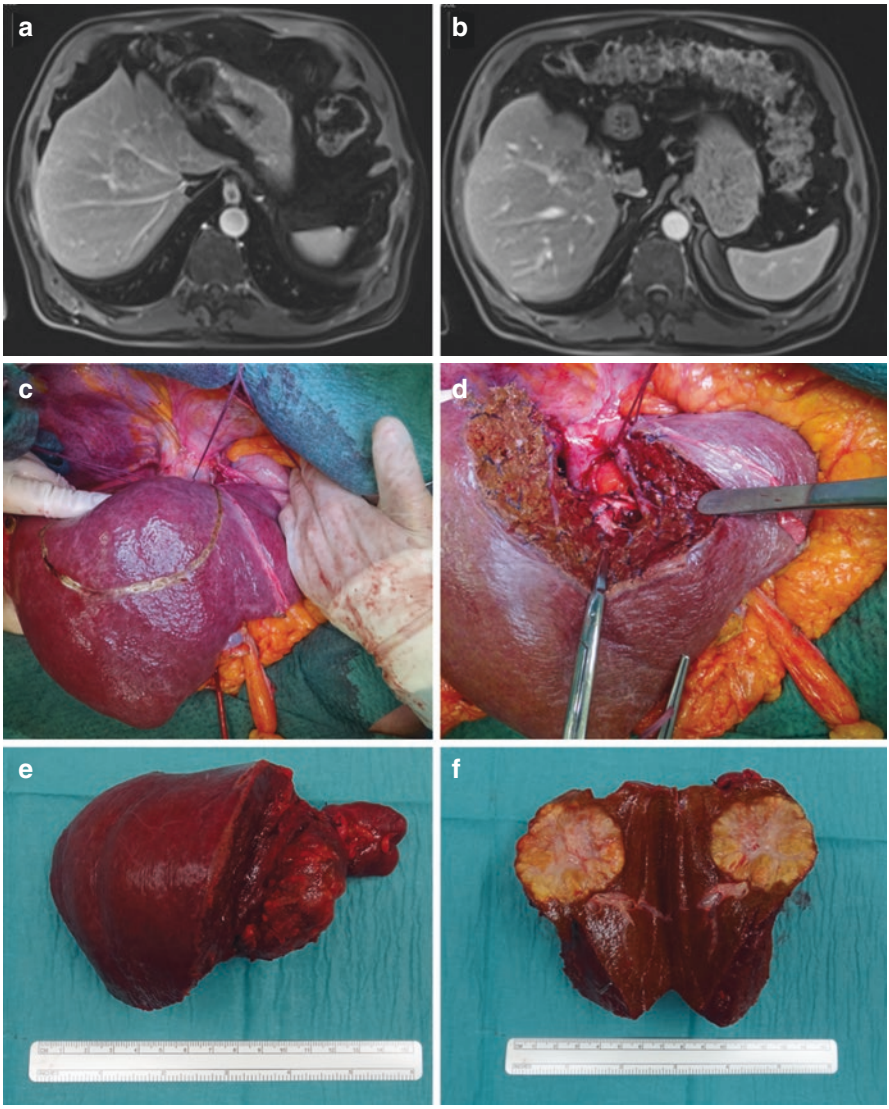

Fig. 16.1 Hepatocellular carcinoma located in segment 1 and 8 (**a**, **b**) in contact with the right and middle hepatic veins that was operated on with intraoperative ultrasound-guided resection of segment 4 s-8-1 en bloc (**c**, **d**). The surgical specimen is also shown (**e**, **f**)

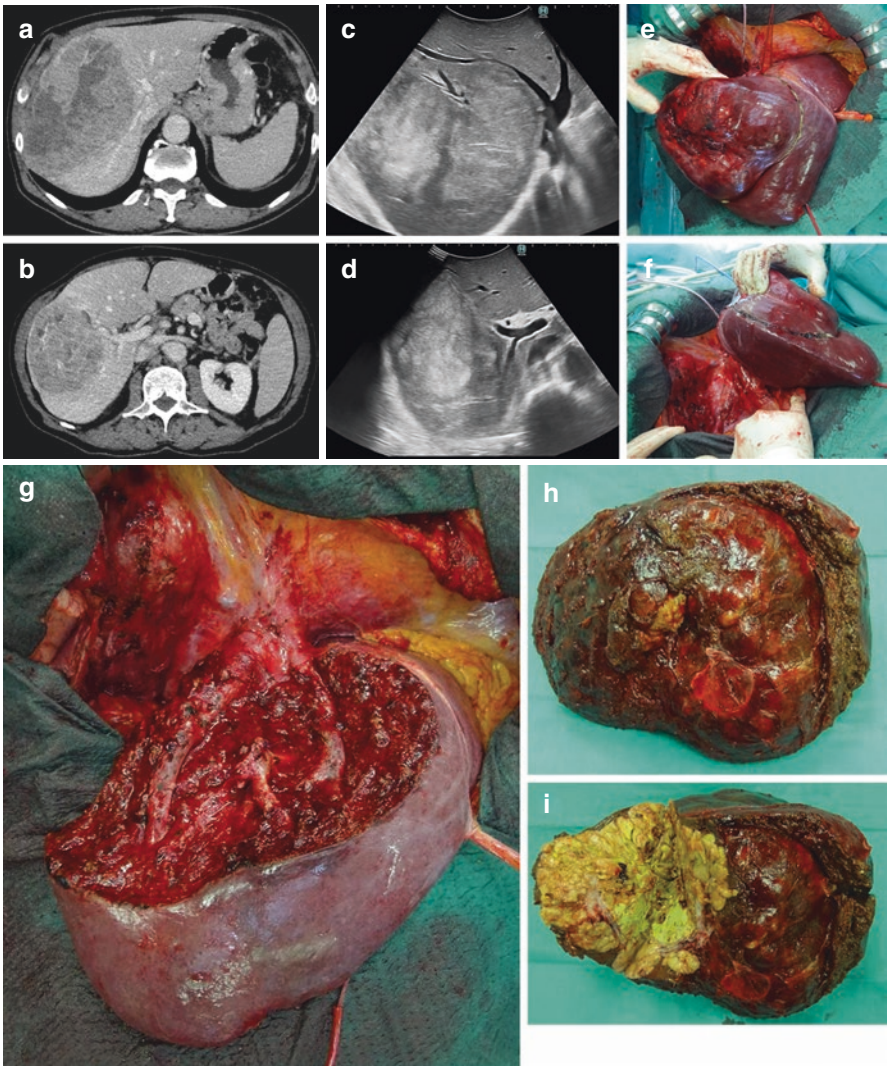

Fig. 16.2 Large hepatocellular carcinoma located in segment 8 (**a**, **b**) that was in contact with the middle and right hepatic vein (**a**–**d**). After preparation and mobilization (**e**, **f**), anatomic resection of segment 8 was performed with full exposure of the right hepatic vein, middle hepatic vein and the stump of G8 (**g**). The surgical specimen is also shown (**h**, **i**)

16.5 Conclusions

In HCC patients, curability of the tumor should be balanced against the risk of postoperative liver dysfunction. Thanks to the use of modern real-time IOUS guidance it is possible to perform complex radical but conservative hepatectomies, for which R1-vascular surgery represents the technical roadmap for parenchymal-sparing hepatectomies.

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17 Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS)

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17.1 Introduction

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is considered one of the main recent innovations in liver cancer surgery. This procedure is a modification of the traditional two-stage hepatectomy which involves in-situ splitting of the liver along the main portal fissure or on the right side of the falciform ligament in association with portal vein ligation to induce rapid hypertrophy of the left future liver remnant (FLR) in patients with non-resectable primary or metastatic liver tumors. The first step is followed by an early (i.e., 7 days) second step in which, after the left FLR has been hypertrophied, resection of the tumor is performed by resection of the contralateral atrophied lobe [1, 2]. The main limiting factor of hepatic resection for hepatocellular carcinoma (HCC) associated with liver cirrhosis is FLR volume. In order to maintain sufficient liver function and avoid small-for-size syndrome or death due to liver failure, it is highly recommended, in cases of underlying liver disease, that the FLR should be 40% of the total liver volume [3, 4]. The gold standard technique to increase the FLR is portal vein occlusion (PVO) with surgical ligation or embolization allowing a hypertrophy rate of 35–70% in 45 days [5, 6]. The drawbacks of PVO are a high rate of interstage dropout for tumoral progression, inability to perform the procedure in the presence of portal vein tumor or hepatic vein thrombosis, and inadequate FLR in cirrhotic liver. It is well known that a liver with an underlying disease has a lower regenerative and

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hypertrophying capacity. Our initial experience shows that the ALLPS procedure is technically feasible and safe even in cirrhotic patients for the treatment of HCC with major liver resections and can induce a significant increase of the FLR in a short period of time [7, 8]. In 2019, Chan et al. reported on 148 patients with HCC who underwent FLR modulation (ALPPS, n = 46; PVO: n = 102). ALPPS still induced a greater FLR hypertrophy than PVO. The percentage of FLR volume gain was more pronounced in chronic hepatitis than in cirrhosis (52.7% vs. 32.5%), but the speed of liver regeneration, as expressed by the daily rate of hypertrophy (24.6 vs. 20.7 mL/day), showed no significant difference [9]. Right portal vein ligation in stage I increases portal pressure and portal flow in the FLR by almost threefold, while the addition of parenchymal transection does not further increase the hemodynamic changes. Indeed, the effect of parenchymal splitting is predominantly the release of liver growth factors rather than a flow issue. At the same time, the hemodynamic changes induced by portal vein ligation enhance the effect of these growth factors, resulting in rapid liver regeneration [10]. Therefore, the ALPPS procedure has been shown to effectively increase the resectability of otherwise inoperable advanced HCC by achieving a rapid and effective hypertrophy of the FLR, also in cirrhotic livers, and overcoming the traditional drawbacks of PVO.

17.2 Indications for ALPPS

The ALPPS procedure is reserved for patients with HCC in cirrhotic liver for the following conditions: (1) conventional PVO is not feasible due to portal branch invasion; (2) a previous PVO has failed to achieve the FLR necessary to safely undergo a major hepatic resection; (3) hepatic vein tumor thrombosis with a risk of rapid progression into the inferior vena cava and atrium; (4) aggressive tumor in which the classical two-step strategy cannot be applied owing to the risk of hepatic tumor progression between the two steps; (5) neoplastic biliary thrombus associated with biliary dilatation and jaundice; (6) emergency resection for large bleeding tumors (Fig. 17.1). These conditions fall within Barcelona Clinic for Liver Cancer (BCLC) stage C (advanced stage) [11]. Tumoral macrovascular invasion (MVI) is common in the natural history of HCC. It affects 10–40% of patients and is defined as infiltration/thrombosis of the supra-hepatic veins (SHVT), inferior vena cava (ICVT), or portal branches (PVTT). Biliary involvement is less common. Several types of MVI are described, but portal vein tumor thrombosis seems to be more frequent than hepatic vein tumor thrombosis [12]. Kokudo et al. recently reported a survival up to 3.95 years for hepatic resection in the case of major vein involvement with inferior vena cava sparing and also for PVTT [13]. The management of HCC with MVI remains quite challenging and patients should be carefully evaluated and selected in order to avoid post-hepatectomy liver failure (PHLF) [14, 15]. In this setting, ALPPS represents a valid surgical alternative for advanced HCC, especially in cases with MVI.

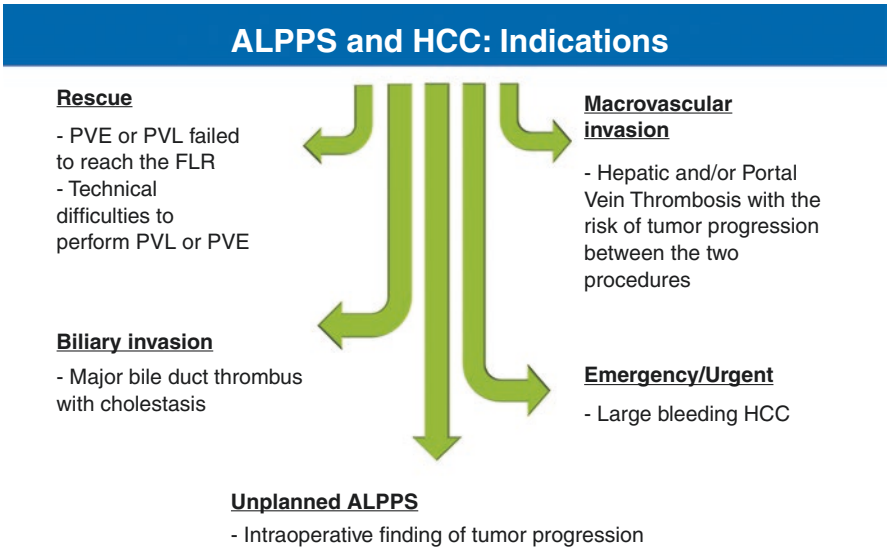

Fig. 17.1 Indications for ALPPS in patients with hepatocellular carcinoma

17.3 Technical Aspects

During step 1, resectability is confirmed by intraoperative ultrasound, checking the tumor's extension in the FLR. The left lobe is fully mobilized. The hepatoduodenal ligament is dissected from the right side and the right portal vein is ligated; the right hepatic artery is encircled with a vessel loop. The arteries, bile ducts and hepatic veins are preserved [16]. To minimize the impact of the first stage and allow for a rapid recovery of the patient, we modified our technique by introducing a partial liver transection (p-ALPPS) and minimal mobilization of the right liver using the hanging maneuver (HM) [17]. Studies have shown that p-ALPPS is comparable to total parenchymal transection up to the inferior vena cava in terms of hypertrophy of the FLR [18]. In our experience, a partial split results in fewer complications related to the transection surface, such as bile leaks and bleeding, as well as reducing surgical time and transfusions. The use of the HM with the anterior approach during ALPPS makes it possible to avoid tumor manipulation, to minimize the right liver mobilization and to facilitate the full transection of the two hemi-livers down the anterior wall of the inferior vena cava during step 2. Furthermore, it might reduce intraoperative blood loss, operative time and potentially reduce postoperative morbidity [19]. In our experience, we avoid using plastic bags and hemostatic agents and we prefer to place a peritoneal patch retrieved from the gallbladder or the whole gallbladder after dissecting it from the liver in order to reduce the adhesions between the two surfaces and ensure easier access to the two hemi-livers during the second step [20, 21]. The tape and the right hepatic artery loop can be externalized

for the second step. During ALPPS step 2, the right hepatic artery, right bile duct and right hepatic vein are ligated and sectioned. The diseased liver is detached from the diaphragm and retroperitoneum and removed from the abdominal cavity using an anterior approach [16]. We avoid using staplers for the transection of the hepatic artery and bile duct because of the high risk of biliary stenosis [22]. Liver function between stages is crucial for the success of this novel and complex procedure. Stage-1 ALPPS might be regarded as a liver function "stress test", with patients who develop liver failure after stage 1 not being suitable candidates to proceed with stage 2 [23]. During the first ALPPS Consensus Meeting held in Hamburg in February 2015, it was stated that step 2 should be completed following the already accepted volumetric standards used for major hepatectomies [1]. Nevertheless, the reported incidence of PHLF in the International Registry ranged from 16% to 31% even when sufficient FLR volumes had been achieved [24]. The rapid volumetric increase during ALPPS may not be paired with functional increase, as recently suggested by histologic hepatocyte immaturity in the FLR parenchyma and volume overestimating function in 60% of patients [25]. Serenari et al. in 2017 investigated the value of interstage SPECT-HBS (hepatobiliary scintigraphy using ^{99m}Tc-mebrofenin with single photon emission computed tomography) in predicting the risk of PHLF after ALPPS step 2, finding a HIBA index of <15% to best predict clinically significant PHLF in patients with an already sufficient FLR volume [26].

17.4 Outcomes

HCC is associated with a 5-year overall survival (OS) ranging from 50% to 70% in the case of early stage disease and when curative treatments such as liver resection, liver transplantation and ablation are feasible. In advanced stages, OS drops to 10–15% [27, 28]. Patients with cancer-related symptoms (bleeding tumor, caval compression, respiratory distress), MVI (either segmental or portal invasion) or extrahepatic disease bear a poor prognosis with expected survival times of 6–8 months and are candidates for systemic treatment according to the guidelines of the European and American associations for the study of liver diseases (EASL and AASLD) [29]. The indications for resection in patients with cirrhosis should be based on liver function and performance status, the presence of portal hypertension, the extent of hepatectomy and the expected volume of the FLR, bearing in mind that the perioperative mortality of liver resection in cirrhotic patients should be less than 3% [30]. Surgery for HCC in cirrhosis represents a challenge: a detailed preoperative evaluation, choosing the appropriate operative approach and surgical maneuver to minimize PHLF and intraoperative bleeding, followed by careful postoperative management, are necessary for a safe liver resection in cirrhotic liver [31]. Up to now, most studies have focused on the indications, the technical aspects, and the feasibility of the procedure, highlighting the high morbidity and mortality rates. The initially reported mortality of 12% triggered an intense debate about the safety of this procedure, limiting its promotion worldwide [2]. Schadde et al. in 2015 showed a complication rate of 59–64% and a postoperative mortality rate ranging between

12% and 16% in a study with 320 ALPPS, 10% of which were HCC [24]. D'Haese et al. in 2015 compared 35 ALPPS for HCC with 225 ALPPS for colorectal liver metastases (CRLM), including all patients registered in the international ALPPS Registry from 2010 to 2015. The 90-day mortality rate was significantly higher for patients with HCC (31%) than for the patients with CRLM (7%), whereas the incidence of severe complications did not differ significantly between the two groups (62.9% and 56.8% for HCC and CRLM, respectively). However, liver failure according to the 50/50 criteria occurred in HCC for twice as many patients compared with CRLM (40% vs. 19%). Finally, the study showed a significantly shorter overall survival for HCC patients after ALPPS. The high perioperative mortality after ALPPS for HCC seems to be the main reason for impaired overall survival [32]. Morbidity and mortality are not the main issue of the ALPPS procedure since it is mostly performed in extreme situations. Increased occurrence of adverse events can be justified by unfavorable conditions such as cirrhosis, bleeding tumors, huge nodules with caval compression, MVI with PVTT, hepatic and caval vein thrombosis, and biliary spread. In these high-risk situations, ALPPS can be considered the only surgical option to obtain a rapid increase of the FLR, allowing a complete resection [33, 34]. Chan et al. showed that ALPPS improved the resection rate in hepatitis-related HCC with a comparable safety profile with PVO and, more importantly, the long-term survival in ALPPS was comparable with that of PVO regardless of tumor stage and without difference in recurrence rate. However, in this study only 45.7% of the ALPPS were performed on cirrhosis and no patients had MVI [9]. In 2018 we reported the outcome of 17 ALPPS for HCC of which 8 with vascular involvement, highlighting a 90-day mortality of 5.8% and a 2-year OS of 38.5% with a median follow-up of 10 months. Recently, we investigated the outcome of 28 patients (85.7% cirrhotic patients) with HCC and MVI undergoing the ALPPS procedure in our center. MVI of the hepatic veins or inferior vena cava was diagnosed in 46.4% of patients while portal vein involvement was present in 64.2% of cases, and four patients (14.2%) were diagnosed with bile duct involvement. No patients died after step 1 while complications occurred in 21.4% of cases. Following step 2, 3 patients (11.5%) died and 20 (69.2%) developed complications. Grade B and C post-hepatectomy liver failure occurred in 57.6% and 11.5% of patients, respectively. After a median follow-up of 18 months (7–35), median survival was 22 months (3–40). Eleven patients (39.3%) recurred. Median disease-free survival was 15 months (5–26) [35]. The prognosis of HCC with vascular invasion is very poor and the guidelines recommend medical treatment with sorafenib, with a median survival of 8–10 months and a poor quality of life. Aggressive surgical treatment in the case of PVTT and SHVT yields an acceptable long-term outcome, which has shown to be better than unresectable HCC treated with sorafenib (47.4 vs. 10.7 months) [36, 37]. Kokudo et al. reported the results of surgery in a cohort of 2000 HCC with MVI of the portal vein showing survival times up to 2.67 years [13]. A French survey reviewed retrospectively 143 HCC with MVI of which 70% with portal thrombosis, showing a 90-day mortality of 16% and an OS similar to that achieved with sorafenib [36]. The ALPPS procedure is an aggressive surgical procedure and not all patients are suitable. Patients should be carefully selected and

can undergo major hepatic surgery only if they are Child-Pugh stage A without portal hypertension. Over the years we have learned that ALPPS should be reserved for extreme situations such as: conventional two-stage hepatectomy not feasible due to portal vein branch invasion; failure of PVO to increase the FLR; SHVT and/or PVTT with a risk of rapid progression into the cava-atrium and main trunk; huge and/or bleeding tumor where the classical two-stage hepatectomy cannot be applied owing to the risk of tumor progression and/or rupture. Serenari et al. compared minimally invasive (MI-ALPPS) with the standard open approach in a study cohort of 66 patients enrolled in the ALPPS Italian Registry. Major morbidity after MI-ALPPS was 8.3% compared with 28.6% reported after open ALPPS, but selection bias was present, such as a low rate of cirrhotic livers in MI-ALPPS (25% vs. 68.9%) [38]. Several studies in patients with HCC treated with sorafenib reported an OS of 15.6–20.1 months for BCLC-B and of 8.4–13.6 months for BCLC-C [39, 40].

17.5 Conclusions

The ALPPS procedure is a feasible approach for advanced HCC in the cirrhotic with small FLR and/or MVI with acceptable OS and disease-free survival, compared with patients treated with medical treatment, as shown by the current guidelines. ALPPS should therefore be included in the management algorithm for FLR modulation in HCC patients.

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"Re-Do" Surgery for Hepatocellular Carcinoma: Indications and Results

18

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18.1 Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related death worldwide. Tumor recurrence mainly accounts for reduced long-term survival. The 5-year recurrence rate following primary resection ranges from 40 to 70%, and up to 95% of recurrences are intrahepatic [1, 2]. Therefore, a strict radiological follow-up is essential to identify early-stage recurrences amenable to a second curative intended treatment. Several treatment options may be considered, which include repeat hepatectomy (RH), salvage liver transplant (SLT), and radiofrequency ablation (RFA). The best treatment option for recurrent HCC is currently debated, and selection criteria may vary between centers. Although there are recognized international guidelines for the management of primary HCC, similar guidelines still need to be implemented for recurrent HCC (Table 18.1) [3–6].

18.2 Types and Mechanisms of Hepatocellular Carcinoma Recurrence

Intrahepatic recurrences are ascribed to two distinct mechanisms. The first is *de novo* carcinogenesis in the remaining liver, which results in multicentric occurrence (MO). However, most recurrences are due to intrahepatic metastases (IM) originating from the same cell lineage of the primary cancer [3]. According to recent research, IM seems to be driven by either local dissemination of the tumor through

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Table 18.1 International guidelines for the management of recurrent hepatocellular carcinoma

Society	Year	Recommendations
Italian Multisocietary Recommendations [3]	2016	A new radical treatment should be planned whenever possible. Resection is the first-choice treatment for late recurrence (>2 years). SLT is recommended in patients eligible for age and comorbidities.
Asian Pacific Association for the Study of the Liver (APASL) [4]	2017	For Child-Pugh class A patients, resectability should be discussed in a multidisciplinary team. SLT may be a second-line treatment.
Korean Liver Cancer Association (KLCA) [5]	2018	RH is recognized as an effective treatment. SLT is one of the most effective treatments compared with RH. Survival rates can be increased if curative therapy is applicable even in patients with recurrence after liver transplantation.
European Society for Medical Oncology (ESMO) [6]	2021	Patients with recurrence following radical therapies may still be candidates for curative therapies.

RH repeat hepatectomy; *SLT* salvage liver transplant

the portal blood flow (local IM) or by systemic dissemination of tumor cells, which may rehome themselves in the liver (systemic IM). The latter mechanism could explain HCC recurrence even after liver transplantation [7]. Patients with MO have shown improved long-term survival following both primary hepatectomy and re-treatment compared to those with IM [8, 9]. Thus, determining the recurrent type could potentially lead to individualized treatment approaches in the future. Evidence exists that time to recurrence could help distinguish between recurrent types. Poon et al. have found that early recurrences arose mainly from IM, while late recurrences were likely to originate from MO [10]. Therefore, a cut-off of 2 years has been adopted to grossly classify early and late recurrences. Liquid biopsy and characterization of genetic differences may help distinguish between the different recurrent types more accurately [9]. However, these methods are not yet part of current clinical practice.

18.3 Repeat Hepatectomy or Salvage Liver Transplant?

In 2000, Majno et al. first reported the use of SLT (i.e., primary resection with curative intent, followed by transplantation in cases of tumor recurrence) with acceptable outcomes [11]. Different studies have subsequently recognized SLT as an effective treatment option, with overall survival (OS) and disease-free survival (DFS) comparable with those after primary liver transplantation (LT) in selected patients. In a recent meta-analysis, Wang et al. have demonstrated that SLT provided comparable OS and 1-year DFS rates to RH, although it was superior in terms of 3- and 5-year DFS [12]. Similar data were reported by another meta-analysis, which confirmed that SLT led to a longer DFS but was burdened by higher postoperative morbidity and comparable mortality to RH [13].

Table 18.2 Advantages and disadvantages of repeat hepatectomy and salvage liver transplant

Advantages	Disadvantages
Repeat hepatectomy	
Immediately available	Does not cure the underlying liver disease
Lower postoperative morbidity	Dependent on liver function
Comparable OS with SLT	
Salvage liver transplant	
Highest radicality (total hepatectomy)	Immunosuppression
Cures the underlying liver disease	Higher postoperative morbidity
Better long-term DFS than RH	Limited by organ shortage

DFS disease-free survival; *OS* overall survival; *RH* repeat hepatectomy; *SLT* salvage liver transplant

If there is no other choice but SLT in cases of HCC recurrence along with deteriorated liver function, the recurrence of resectable HCC in livers with preserved function still leads to a treatment dilemma between RH and SLT (Table 18.2). In this context, RH is the preferable treatment option in the case of late intrahepatic HCC recurrence, with preserved hepatic function [3]. However, Yoon et al. have recently found that SLT is superior to RH even in patients with Child-Pugh class A [14].

Nevertheless, organ shortages and patients' non-suitability due to advanced age and acquired comorbidities impair the widespread use of SLT. Moreover, some tumor recurrences are not compatible with the SLT eligibility criteria [15]. There is, however, a substantial difference in the accessibility to SLT among countries with different resource levels [2]. The short supply of deceased organs in Eastern countries makes this option possible only if a living donor is available. The situation is quite different for Western countries, where allocation systems currently assure a high priority on the transplant waiting list in the case of early recurrence after first-line treatment [3, 16].

18.4 Repeat Hepatectomy Versus Other Treatments

RFA remains an alternative for the radical treatment of HCC recurrence, considering the hepatic functional reserve and percutaneous accessibility of the nodule [3]. A recent analysis of a multicenter Italian registry has shown that RH and RFA were performed in 16.3% and 16.6% of patients with recurrent HCC, respectively [17]. Two recent meta-analyses were not able to demonstrate a clear superiority of either RH or RFA for recurrent HCC in terms of OS and DFS [1, 18]. Nevertheless, in a propensity score-matched analysis, Chua et al. have found that RH, despite a higher morbidity rate, allows a better local disease control and confers a late survival benefit [19]. One possible explanation is that RH is more likely to resect undetectable distant micro-lesions, which are more frequent in recurrent HCC and account for its higher subsequent recurrence rate compared to primary tumors.

Transarterial chemoembolization (TACE) is frequently used to treat HCC recurrence after resection and, in a recent study, it was reported to provide similar results

to RH [1]. However, several other studies have undoubtedly demonstrated that a new radical treatment for recurrent HCC should be assured whenever possible [2, 20].

18.5 Repeated Repeat Hepatectomy

Few studies have reported positive outcomes following more than two hepatectomies. Itamoto et al. showed that the more times an RH was performed, the shorter the recurrence-free interval became [21]. Wu et al. reported that a fourth hepatectomy was not more beneficial than other treatments for third recurrences of HCC [22]. More recently, Yamashita et al. have shown that a third or more hepatectomy could be performed safely in very selected cases with a relatively maintained OS, although 5-year DFS remained significantly lower compared to first and second resection [23]. Nevertheless, the main limitation of this approach remains the low percentage of suitable patients. If approximately 15–30% of patients with recurrent HCC are eligible for a second hepatectomy, even fewer are for a third or more hepatectomy [24].

18.6 Predictors of Recurrence After Repeat Hepatectomy

A 5-year DFS of 10–17% after RH highlights the critical need for proper preoperative risk stratification to avoid futile resections. The main reported predictors of poor survival after RH include time to recurrence of <1 year, tumor number (>1 nodule) and size (>5 cm), micro- and macrovascular invasion, and poor differentiation [24, 25]. As numerous studies have identified the utility of elevated alpha-fetoprotein levels in predicting HCC recurrence after primary resection, other researchers have investigated its prognostic role after RH. However, a high heterogeneity exists between these studies, with variable cut-off values ranging between 20–400 ng/mL [26, 27]. The platelet-to-lymphocyte ratio was more recently found to be an independent risk factor for early recurrence after RH [27].

18.7 The Role of Minimally Invasive Surgery

RH is technically more difficult than primary resection because of adhesions, changes in liver morphology, formation of collateral circulation, and smaller liver remnants. These changes lead to an increased risk of intraoperative bleeding and iatrogenic damage. A history of previous abdominal surgery was traditionally considered a contraindication for laparoscopic surgery. Nevertheless, laparoscopic RH is increasingly adopted worldwide and has proven feasible, safe, and effective [28, 29]. In a recent meta-analysis, laparoscopic RH has shown less blood loss, fewer major complications, and a higher R0 resection rate compared to open RH [30]. These findings are probably attributable to several advantages of minimally invasive

surgery. The magnification and high-resolution view offered by laparoscopy allow a more precise dissection. The pressure of the pneumoperitoneum increases facilitates the separation of the adhesions. Furthermore, the adhesions in non-operating fields could be circumvented by laparoscopic instruments, thus minimizing the section of vascular and lymphatic collaterals, which contributes to the development of postoperative ascites.

However, an appropriate patient selection seems to be necessary. A recent analysis involving 42 high-volume centers around the world has shown that laparoscopic RH was generally reserved for patients with relatively poor performance status and liver function, but favorable tumor characteristics [31]. In this context, Kinoshita et al. have developed a classification of the difficulty of laparoscopic RH [32]. High-difficulty patients have been associated with longer operating times, greater intraoperative bleeding, and more postoperative complications and should therefore be treated by expert teams in high-volume centers.

All these considerations should also encourage the laparoscopic approach from the first-time surgery, which has also been shown to favor SLT in terms of intraoperative bleeding [33].

18.8 Resection of Hepatocellular Carcinoma Recurrence After Liver Transplantation

A few small series report liver resections for recurrent HCC in transplanted livers. Graft resection can be technically challenging due to extensive adhesions and high morbidity rates, which are mainly related to infective complications in immunosuppressed patients [34]. In a large multicenter series, Sapisochin et al. report significant long-term OS (50% at 5 years) in patients amenable to curative-intent treatment, including resection [35]. In a more recent analysis, Bodzin et al. showed that surgical treatment, including graft resection in well-selected patients, was associated with significantly improved OS compared to nonsurgical and supportive therapy [36]. Taken together, these data support pursuing aggressive therapy in highly selected patients. However, mortality predictors, the impact of the treatment procedure, and recurrence characteristics still need more in-depth assessment in large multi-center studies.

18.9 Conclusions

In conclusion, centralization should be the practical solution to the problem of how to treat HCC recurrence. In high-resource countries, treatment modality should not be conditioned by the availability of the treatments that are in place in small non-specialized centers. To ensure equal treatment of these patients, every case should be referred to high-volume specialized centers, where the appropriate treatment options are discussed in a multidisciplinary context and easily available.

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Liver Transplantation for Hepatocellular Carcinoma

19

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19.1 Introduction

From the time of its initial developments in the early 60s, liver transplantation (LT) appeared as the ideal cure for hepatocellular carcinoma (HCC) in liver cirrhosis because it provided the prospect of curing at the same time both the tumor and the underlying liver disease. However, the first experiences were disappointing, with many authors reporting a 5-year survival of less than 40% mainly because of recurrences of the primary tumor. A retrospective review of these discouraging results progressively led to the observation that patient survival was directly related to the stage of HCC at the time of LT. In several studies from the early 90s it was found that the survival of patients with incidental and small size nodules of HCC was increased compared to those who underwent liver resection. Recurrence in incidental/small tumors occurred in less than 15% of cases [1].

19.2 Liver Transplantation for Hepatocellular Carcinoma: The Milan Criteria

These were the basis on which a prospective study was conducted in Milan applying *a priori* restrictive criteria for the selection of HCC candidates for LT (namely a single nodule ≤5 cm or ≤3 nodules ≤3 cm, each with no macrovascular invasion at pre-transplant imaging). The seminal paper published in 1996 demonstrated that by applying such criteria it was possible to obtain long-term results that were better than for any other therapy applied for HCC [2], and similar to the outcomes of LT

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for non-oncologic indications. These so-called Milan criteria (MC) incorporated both single and multiple presentation of HCC and were subsequently validated by many other groups reporting 5-year survival rates of 70% or better, with recurrence rates below 15%, and became the benchmark for selecting patients with HCC for LT. After their implementation, the favorable post-transplant outcomes that were observed in cohort series were so convincing that further validation by randomized controlled trials (RCTs) was prevented. HCC, declared in 1989 a relative contraindication to LT by the US Department of Health, is today the second indication for LT in Europe (26.9% of indications) and it has therefore become one of the major fields of interest in hepatology and liver surgery.

19.3 Expanding Indications and Improving Results of Liver Transplantation for Hepatocellular Carcinoma

HCCs meeting the MC have been confirmed to be a separate prognostic category associated with good outcomes after LT and incorporated into major guidelines. However, in the absence of surveillance programs, only a minority of HCC are diagnosed at an early stage (namely within the MC), and excellent results have been observed in patients who underwent LT with an HCC exceeding the MC. These patients constitute the focus of debate about what is known as "expansion HCC criteria" for LT, either because they are selected as beyond the MC before transplantation or because they are selected as a result of being downstaged to meet the MC after neoadjuvant treatments (Fig. 19.1).

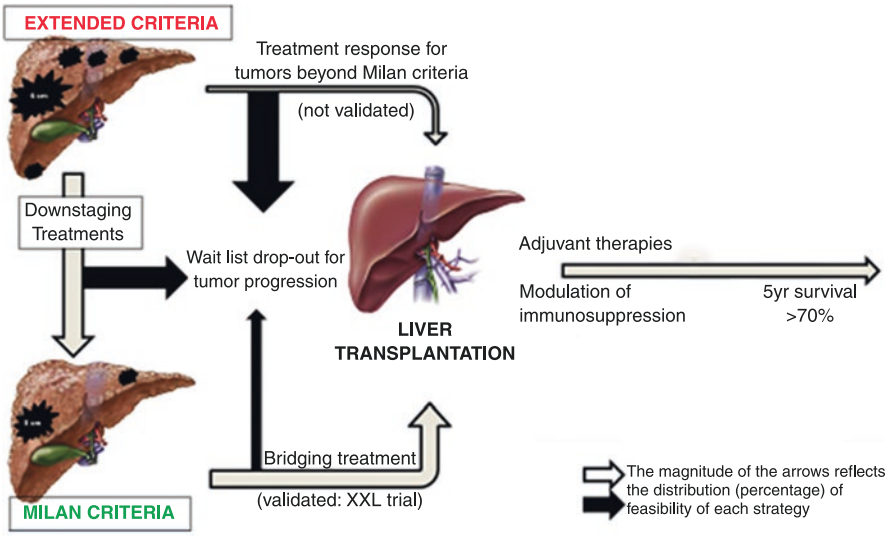

Fig. 19.1 Tumor-related strategies affecting the prognosis of patients undergoing liver transplantation for hepatocellular carcinoma

19.3.1 Role of Neoadjuvant Therapies: Bridging to Liver Transplantation, Salvage, and Pre-emptive Liver Transplantation

The application of conventional therapies for HCC to candidates within MC as a bridge to LT has the primary objective of preventing tumor progression beyond conventional criteria during waiting list time, and consequently preventing dropout. Dropout rates increase with waiting list time, and the risk of dropout for HCC candidates is higher than the risk for candidates with non-malignant diseases after the first three months [3]. The rates of dropout depend on many variables linked to the individual tumor biology and to each transplantation center. For tumors with expected waiting times to LT <6 months, there is no evidence that neoadjuvant treatments are beneficial. For T2 tumors and for longer waiting times, neoadjuvant treatments are usually performed with transarterial chemoembolization, ablation techniques and liver resection in selected cases. Tumor stage and volume, alpha-fetoprotein (AFP) levels, response to treatments, and liver function affect the risk of dropout from the waiting list. These factors, together with vascular invasion and poor tumor differentiation, are major determinants of poor post-LT outcomes [4].

Because of the organ shortage, hepatic resection might serve as primary therapy for HCC, with LT as a salvage procedure in the case of recurrence. Initial experiences reported unfavorable outcomes for primary resection and salvage LT compared to primary LT [5]. Remarkably, secondary LT was associated with significantly higher operative mortality. Further studies, however, reported comparable intention-to-treat outcomes of HCC patients treated with primary LT or primary resection followed by salvage LT in the case of recurrence. In particular, when liver resection is performed with a minimally invasive approach, the risk of delisting, post-transplant patient death and tumor recurrence seem reduced when compared to open surgery [6].

Liver resection with pathological analysis of the specimen allows clinicians to identify those patients at high risk for recurrence (e.g., microvascular invasion, satellite lesions, high grade of differentiation) who might benefit from being listed for LT immediately after resection. The strategy of pre-emptive (or *de principe*) LT was introduced by the Barcelona group [7], and the authors demonstrated excellent long-term outcomes for patients who underwent LT after resection for a high-risk HCC. The feasibility of the pre-emptive LT strategy implies a high availability of liver grafts and a policy of transplanting patients with a high probability of recurrence even though still tumorless: the benefit of preventing an HCC recurrence by means of LT should be carefully balanced with the potential harm caused by the LT itself.

19.3.2 Beyond the Milan Criteria

Several experiences suggested that the restrictive MC may exclude from LT those patients with a more extensive disease but still in the range of a possible cure. The

key aspect of selection criteria is that the definitions used should identify those patients who, despite exceeding the MC, might still do well without an increase in recurrence. At the same time, the definitions should also identify those patients within the MC that will be at high risk of recurrence. This two-end goal is paramount for the equitable use of the available organs.

The proposals for expansion of the MC were initially developed using tumor morphology, namely size and number. These factors have in fact been shown to be surrogate markers of microvascular invasion (MVI) and/or poor tumor differentiation, which are the principal determinants of tumor aggressiveness and consequent risk of post-LT recurrence [8]. Expanded morphological criteria increased the acceptable size and number of HCC nodules with respect to the MC, but the great heterogeneity and different accuracies of liver imaging techniques probably represent the greatest limitation of criteria based only on morphology.

In order to overcome these limits, criteria incorporating serum markers, such as AFP, that surrogate biological tumor characteristics have been proposed (Table 19.1). In particular, by combining the morphological characteristics of the tumor and the AFP values, it was possible to develop selection criteria for LT that definitively exceeded those of Milan without significantly increasing the risk of post-LT recurrence [9, 10]. The calculation of both the size and number of nodules and the AFP serum levels appears simple and available in every context, making these models applicable "dynamically", in addition to the assessment of the HCC response to neoadjuvant treatments. Through multiple predictions made at each interval after tumor treatment, variations of prognosis during the course of disease can be determined.

Table 19.1 Examples of selection criteria for liver transplantation in patients with hepatocellular carcinoma (only externally validated selection criteria are reported)

Criteria	Morphologic limits	Biologic surrogates	Survival
Milan	1 nodule ≤5 cm, ≤3 nodules ≤3 cm each	None	4-year OS: 85%
UCSF	1 nodule ≤6.5 cm, ≤3 nodules ≤4.5 cm each. Total tumor diameter ≤8 cm	None	5-year OS: 72.4%
Shanghai	1 nodule ≤9 cm ≤3 nodules ≤5 cm, Total tumor diameter ≤9 cm	None	3-year OS: 80%
Toronto	No limits in size and number of nodules	AFP ≤400 Histology <G3	4-year OS: 82.9% 4-year RFS: 76.8%
Hangzhou	Total tumor diameter ≤8 cm Total tumor diameter >8 cm with histopathologic G1or G2	If total tumor diameter >8 cm: AFP ≤400 and histology <G3	5-year OS: 70.7%, 5-year DFS: 62.4%
French criteria	Combined score of AFP, size and number	AFP	5-year OS: 69.9%
Metroticket 2.0	Combined score of AFP, size and number	AFP	5-year cancer-specific survival: 75%

AFP alpha-fetoprotein; *G* histology tumor grade; *OS* overall survival; *RFS* recurrence-free survival; *DFS* disease-free survival

Finally, tumor differentiation, MVI, presence of circulating cancer cells and genomic markers have also been suggested as selection criteria for LT, but this assessment requires taking a biopsy that might induce tumor seeding. Furthermore, it is well known that tumors are heterogeneous and show areas of varying degrees of differentiation and genomic features. Hence, such an assessment is not 100% robust and no molecular signature has been properly validated. Nevertheless, it is clear that other parameters beyond tumor size and number will play an increasingly important role in the selection for LT of HCC patients beyond MC.

19.3.3 Downstaging of Hepatocellular Carcinoma Before Liver Transplantation

Downstaging is defined as a treatment given to HCC patients that are not eligible for LT because of tumors beyond conventional criteria, with the objective of reducing tumor burden (in terms of number, size or tumor vitality) to meet pre-established conventional limits (generally Milan or UCSF Criteria) that are considered acceptable for LT. HCC is rarely technically "non-transplantable", and in this case downstaging treatments are performed with the aim of a migration to a stage with better prognosis (the MC). This strategy is treated separately in the following chapter. However, it is worth emphasizing that its effectiveness recently emerged in a RCT (XXL trial) demonstrating with a high level of evidence that, after sustained and successful downstaging of HCC beyond the MC, LT achieves a significant survival benefit with respect to any other non-transplant therapy [11].

19.3.4 Role of Adjuvant Treatments

Despite strict selection criteria, tumor recurrence after LT for HCC occurs in up to 20% of the cases [12] and is associated with a poor prognosis. The main strategies to prevent HCC recurrence involve adjuvant treatments and modulation of immunosuppression. Systemic therapy with several drugs (e.g., cisplatin or 5-fluorouracil) have failed to provide any benefit. Sorafenib, an oral multikinase inhibitor that improves survival of patients with advanced HCC, has been tested in some studies to prevent or treat HCC recurrence after liver transplantation. No solid evidence emerged from these studies and, even though its safety was confirmed, the potential for effective HCC treatment using sorafenib after transplant is doubtful [13].

Immunosuppression is a risk factor for tumor growth: the calcineurin inhibitors (CNI) cyclosporin and tacrolimus currently form the main components of immunosuppression after LT, although their potential tumor-promoting action is well known [14]. Several studies reported a higher risk of tumor recurrence for patients treated with high doses of CNIs, especially in the first month after LT [15]. Thus, an adequate balance between low immunosuppression and the risk of rejection should be encouraged. Because of their immunosuppressive and antiproliferative effects, the mTOR inhibitors sirolimus and everolimus have been suggested for

immunosuppression of HCC patients. Several retrospective analyses and meta-analyses have reported a protective effect of sirolimus on the risk of post-LT HCC recurrence. All these data have been challenged by the negative results of a prospective phase III, international multicenter RCT that randomized patients to sirolimus and sirolimus-free immunosuppression regimens, reporting no difference in 5-year disease-free survival [16]. Thus, the use of mTOR inhibitors to reduce tumor recurrence cannot currently be recommended.

19.4 Organ Allocation in Patients with Hepatocellular Carcinoma

In most Western countries, liver allocation follows the principle of *urgency*, allocating the available organ to the sickest first. The MELD score, originally developed by the United Network for Organ Sharing Priority (UNOS), is used to prioritize patients with the highest short-term mortality risk. As it solely consists of biochemical variables (i.e., bilirubin, creatinine, INR), it would fail to assess the risk of disease progression and dropout in patients with malignant disease and compensated liver function. Thus, most allocation systems will give exception points to patients with HCC, with pre-fixed increases over time, in order to equalize the risk of death or dropout in both populations. However, a system that guarantees fixed points at baseline and fixed increases does not allow an equitable graft allocation between patients with and without cancer or a correct prioritization amongst patients with HCC at different stages and risk of dropout. To solve this issue, it has been recently suggested that priority be stratified for patients with HCC according to stage, response to therapy and evolution after therapy [17]. This kind of model does not require pre-determined entry criteria, and eligibility to transplant and priority is defined at the end of the therapeutic neoadjuvant process, namely after the best available therapy has been completed. Thus, preliminary tumor response to treatments could become the most flexible and defined criteria for expanding the indication to LT in HCC beyond the MC, without compromising the post-transplant outcome and therefore fully justifying the use of donated organs for cancer patients. This concept, which is a blend between urgency and utility principles also considering other variables related to local scenarios and resource distributions, has been adopted in Italy since 2016 and may improve the transparency and the efficacy of the allocation systems in place for HCC patients [18].

19.5 Future of Liver Transplantation for Hepatocellular Carcinoma

The number of patients diagnosed with HCC in several areas around the world is increasing. At the same time, the introduction of direct-acting antiviral agents has dramatically improved the outcome of patients infected with hepatitis C virus and will result in a reduced number of patients in need of LT because of end-stage liver

disease. As a consequence, in the near future, it is expected that more organs will be available for patients with liver cancer, potentially justifying a careful expansion of the selection criteria.

The increase of non-alcoholic steatohepatitis (NASH) in the Western world has increased the rate of this disease as an indication for LT as well as an etiopathological factor for HCC. To date, conflicting evidence exists on the outcomes after LT for patients with NASH-related HCC compared to patients with HCC of different etiologies. Some studies have suggested a better oncological outcome when treating patients with HCC and NASH but, on the other hand, the post-LT outcomes of patients with NASH might be significantly affected by the associated comorbidities (obesity, diabetes, hypertension).

Current research targets clinical and molecular predictors of the risk of post-transplant recurrence, with the objective of overcoming the limits of current selection criteria based on morphology and serum tumor markers. Overall, this will hopefully result in a wider and more individualized access to the waiting lists. Identifying adjuvant strategies to reduce the risk of recurrence represents an unmet need, as does defining the most cost-effective approach for detecting and treating tumor recurrence after transplantation.

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Downstaging Strategies Prior to Liver Transplantation

20

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20.1 Introduction

Hepatocellular carcinoma (HCC) is the most common liver cancer with rising incidence over the past two decades. HCC is a leading indication for liver transplantation (LT), which can remove the tumor and the cirrhotic liver. The Milan Criteria (MC), proposed by Mazzaferro et al. [1] in 1996, have stood the test of time and have remained the benchmark for the selection of candidates for LT. They consider HCC with a single lesion ≤5 cm or ≤3 lesions ≤3 cm and account for 2-year and 5-year post-transplant survival rates of 75–95% and 70–80%, respectively. MC have been endorsed by both the European Association for the Study of the Liver (EASL) [2] and the American Association for the Study of Liver Diseases (AASLD) [3]. Subsequently, they have been incorporated in the Barcelona Clinic Liver Cancer (BCLC) classification and in the American Joint Committee on Cancer (AJCC) TNM classification. However, it has been proven that a modest expansion of the MC can achieve similar post-LT survival.

The term "downstaging" (DS) refers to the application of locoregional therapy (LRT) to tumors outside the accepted transplant criteria, commonly MC, with the aim of reducing tumor burden and selecting appropriate candidates for LT. DS provides a viable alternative approach to expand the limits of the MC.

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Conversely, the term "bridging" refers to the application of LRT to those HCC patients on the waiting list to reduce the risk of dropout when the expected transplant waiting time is >6 months.

20.2 Indications

There are no universally accepted upper limits, no inclusion/exclusion criteria for DS protocols, nor is there a standard definition of successful DS. Until a few years ago, DS protocols were mainly based on the assessment of tumor burden and tumor response to LRT according to radiological criteria, such as the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria [4]. Modern DS protocols also tend to consider the response in terms of biomarkers. Additionally, even patients with more advanced oncological disease, such as HCC with portal vein tumor thrombosis (PVTT), can be considered for LT.

20.2.1 Morphological Criteria

The latest EASL [2] and AASLD [3] guidelines suggest that patients beyond the MC or T3 stage should be considered for LT after successful DS to meet the MC. In 2005 Yao et al. [5] proposed the University of California San Francisco (UCSF) DS protocol. In brief, the eligibility criteria for enrolment into this DS protocol included a single lesion ≤8 cm and total tumor diameter ≤8 cm. Patients with HCC successfully downstaged presented a 5-year post-LT [78% vs. 81%, p = 0.66) and intention-to-treat survival rate [56% vs. 63.3%, p = 0.29) comparable to the control group of patients with T2 HCC [6].

20.2.2 Combining the Morphological with the Biological Criteria

Alpha-fetoprotein (AFP) levels have shown to be highly predictive of patient survival [7, 8], and several cut-offs have been proposed for incorporation into transplant criteria, ranging from 100–500 ng/mL; however, no consensus has been reached on how to combine them with HCC morphological features. Duvoux et al. [8] observed that patients exceeding the MC with AFP <100 ng/mL presented with a lower 5-year risk of recurrence in comparison with patients with AFP >1000 ng/mL.

In an effort to standardize the DS criteria for HCC in 2017, UNOS (United Network for Organ Sharing) adopted the UCSF/Region 5 DS protocol (UNOS-DS) as a new national policy in the United States (Table 20.1) [9, 10]. This protocol emphasizes two important novel concepts:

(a) patients with elevated AFP, even >1000 ng/mL, could still be considered for inclusion provided that there was a significant drop in AFP to <500 ng/mL;
(b) the stability of the disease after DS for a period of 6 months.

Table 20.1 Summary of UNOS Criteria for DS (UNOS-DS)

Inclusion criteria
(a) Single lesion 5.1–8 cm
(b) 2–3 lesions each ≤5 cm with the sum of the maximal tumor diameters ≤8 cm
(c) 4–5 lesions each ≤3 cm with the sum of the maximal tumor diameters ≤8 cm
(d) Absence of vascular invasion or extrahepatic disease
Criteria for successful DS
Residual tumor size and diameter within MC (1 lesion ≤5 cm, 2–3 lesions ≤3 cm)
Criteria for DS failure
(a) Progression of tumor(s)
(b) Tumor invasion of a major hepatic vessel based on cross-sectional imaging
(c) Lymph node involvement by tumor or extrahepatic spread of tumor
(d) Infiltrative tumor growth pattern
(e) Decrease of AFP to <500 ng/mL if before DS AFP ≥1000 ng/mL
Timing of LT in relation to DS
(a) Minimum observation period of 3 months of disease stability from successful DS to LT
(b) Patient must remain within MC for 6 months after successful DS

AFP alpha-fetoprotein; *DS* downstaging; *HCC* hepatocellular carcinoma; *LT* liver transplantation; *MC* Milan Criteria; *UNOS* United Network for Organ Sharing

A recent study by Metha et al. [7] evaluated the results of the UNOS-DS protocol, comparing three groups of patients: those always within the MC (n = 3276), those within the UNOS-DS criteria and successful downstaged (n = 422), and "all-comers" (AC) with an initial tumor burden beyond the UNOS-DS criteria (n = 121). They demonstrated comparable 3-year post-LT survival between patients meeting UNOS-DS criteria, successfully downstaged (79%), and those within MC (83%). Nevertheless, the 3-year post-LT survival in the AC cohort was significantly lower than the other two groups, at 71%.

Therefore, it can be concluded that:

- Data available so far support favorable outcomes of DS followed by LT for those HCC patients beyond the MC
- Important factors to consider when assessing the response to DS are:
  - The morphological response, usually assessed by the mRECIST criteria
  - The biological response, usually assessed by the drop in AFP
  - The stability of disease over time after LRT.

20.2.3 The Issue of Portal Vein Thrombosis

Another controversial issue is whether patients with HCC and neoplastic PVTT should be considered for LT after successful DS. Additionally, transarterial chemoembolization (TACE) has been contraindicated in HCC patients with PVTT. However, as shown by Ettorre at al. [11, 12], patients treated with transarterial radioembolization (TARE) with a complete response for the thrombosis associated with biochemical response can achieve a favorable oncological outcome (Fig. 20.1).

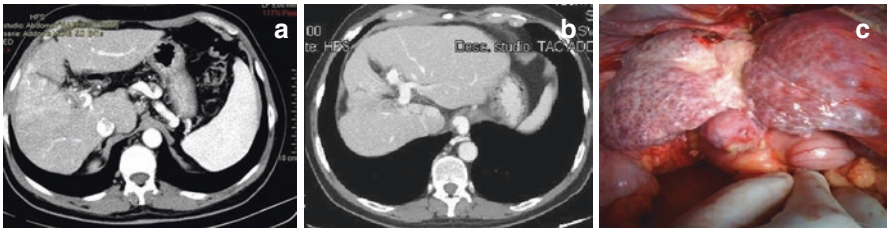

Fig. 20.1 (**a**) Hepatocellular carcinoma (HCC) with right portal vein tumor thrombosis. (**b**) HCC after transarterial radioembolization showing tumor response and disappearance of right portal vein tumor thrombosis. (**c**) Macroscopic appearance of HCC after liver transplantation

Therefore, PVTT should no longer be regarded as an absolute contraindication to LT: very selected patients responding to TARE could be considered for LT. Nevertheless, solid prospective data validating these findings are still needed.

20.3 When

Depending on the timing of DS, two main scenarios can be identified:

- *DS an HCC otherwise unsuitable for transplantation before listing*. It refers to patients with HCC beyond the MC and selected for DS therapies before LT. This strategy has a double rationale: meeting morphological and biological inclusion criteria for LT and selecting HCC patients with favorable biological features. The concept of a "wait and see strategy" after LRT and before LT is of paramount importance [9].
- *Rescue patient with HCC with progression while on the waiting list.* In these cases, DS therapies should still be considered, and in case of regression, the patient could be re-listed for LT.

20.4 How

20.4.1 Transarterial Chemoembolization

TACE is the most common DS approach. It is based on the concept that HCC is highly dependent on arterial supply. TACE is performed by the administration of chemotherapeutics (i.e., doxorubicin or cisplatin) mixed with an oil-base vehicle (lipiodol), followed by embolization with gelfoam of the artery supplying the tumor. Thus, the chemotherapeutic effect is intensified by ischemia. Complications following TACE can occur in up to 25–45% of cases, with the majority being post-embolization syndrome characterized by a reversible elevation of transaminases and bilirubin, fever, abdominal pain and nausea. Other possible complications are liver or renal failure, liver or splenic abscess, hepatic artery damage, upper

gastrointestinal bleeding and gastroduodenal ulcer. When there is risk of decompensation, superselective TACE should be recommended to reduce toxicity. Additionally, in order to decrease the risk of arterial complications after TACE in patients listed for LT, drug-eluting bead TACE (DEB-TACE) has been developed. This approach is based on the administration of microspheres that, with their reduced size, minimize the angiogenetic effect on the main arterial branches. However, the potential benefit of DEB-TACE has never been confirmed: the Precision Italian Trial [13] comparing DEB-TACE with conventional TACE did not show significant differences between the two approaches.

Contraindications of TACE include Child-Turcotte-Pugh class C disease, main portal vein thrombosis, active peptic ulcer, serum bilirubin >3 mg/dL, renal insufficiency, ascites, elevated prothrombin time and low platelet count [2, 3].

The literature reports successful rates in DS ranging from 24–70%. Even though TACE is the most used method, there have been no large prospective trials comparing TACE with other DS approaches before LT. Therefore, although the available data seem encouraging, there is still a lack of strong evidence-based recommendations on its role in comparison to other DS approaches.

20.4.2 Transarterial Radioembolization

TARE has recently gained interest. It is based on the utilization of yttrium-90 (Y-90) carried by glass or resin microspheres. Y-90 is a 100% beta emitter injected into the branches of the hepatic artery feeding the HCC. Y-90 half-time is 2.67 days, which means that almost the entire amount of radiation is delivered into the HCC within 2 weeks of the injection. The procedure aims to achieve tumor necrosis by radiation instead of interrupting the arterial supply as with TACE. Thanks to a mean tissue penetration of 2.5 mm, it does not damage the surrounding liver.

In comparison with TACE, TARE has two main advantages: the highly concentrated radioactive substance administrated into the HCC does not harm the remaining liver parenchyma, and it preserves the arterial blood supply, so that it can be used in patients with portal vein thrombosis. The most common side effect of TARE is post radioembolization syndrome with an incidence between 20 and 70%. This consists of fatigue, nausea, abdominal pain and loss of appetite, peaking within the first 2 weeks post-TARE administration. Other relatively unusual toxic effects are radioembolization-induced liver disease, gastroduodenal ulcer/bleeding, biliary toxicity and radiation pneumonitis. Before administering the microspheres, a mandatory mesenteric angiography with technetium-99-labeled leukocytes is needed 2 weeks before the TARE to detect and quantify the presence of shunts to the gastrointestinal tract or lung. If shunts are ≥20% of the hepatic artery blood flow, or if a radiation dose >30 Gy is absorbed by the lungs, there is a high risk of gastroduodenal ulcer and radiation pneumonitis, and therefore TARE should not be performed.

The effectiveness of TARE in downsizing tumors prior to surgery is variable. Ettorre et al. showed successful DS in 78.9% of cases in 22 patients who received TARE prior to LT [12]. A recent systematic review [14] described a successful DS

rate between 8 and 100%. There have been few prospective studies comparing TACE with TARE in the setting of DS patients before LT; the PREMIERE trial [15], a pilot trial comparing TARE vs. TACE in unresectable HCC, suggested that TARE appeared to be as safe and tolerated as multiple sessions of TACE. Additionally, TARE is the preferred DS option in patients with HCC and PVTT [16].

20.4.3 Ablative Therapies

Several ablative procedures have been proposed:

- *Radiofrequency ablation*: the most common ablation technique employed for its advantages in terms of efficacy, cost-effectiveness and tolerability. The limitations of radiofrequency ablation include lesion size, proximity of the lesion to blood vessels due to a "heat-sink effect", where heat is lost due to the nearby flow of blood, proximity to bile ducts due to the risk of stenosis, and proximity to vital structures or the diaphragm.
- *Microwave ablation*: with similar indications and contraindications to those of radiofrequency ablation but producing a wider and more homogeneous ablation zone, ablating larger volumes with less "heat-sink effect". The procedural time is shorter.
- *Ethanol injection*: nowadays, only used when other techniques are not available, due to the lower rate of local tumor response.
- *Cryoablation*: now replaced by more modern LRT, as it has been associated with severe post-procedure morbidity and high local recurrence rates
- *Irreversible electroporation*: there is a paucity of data on its use and it is applied less often, as it is more expensive and requires general anesthesia.
- *Stereotactic body radiotherapy*: there is still paucity of data on its use as a DS.

20.4.4 Surgery

Liver resection has been traditionally used as a form of primary treatment for HCC; however, several reports have confirmed its potential as a bridging or DS strategy for HCC before LT [17]. The rationale of this strategy is based on the following clinical observations:

– a proportion of patients may survive without recurrence for 5–10 years without the need for LT;
– a "rescue" LT, in the case of HCC recurrence, will have similar short- and long-term outcomes as primary LT.

It could be argued that an operated abdomen could make LT technically more difficult and demanding. However, the recent diffusion of laparoscopic liver resection (LLR) plays an important role in this field, as it has been associated with reduced

post-operative adhesions. LLR could be considered the best surgical option for peripheral tumors, especially if located in the left lobe or in anterior segments (S4b–S5) [18]. Laurent et al. [19] published the first series reporting LT after LLR for HCC showing that LLR prior to LT is a safe procedure with no mortality in 24 consecutive patients and associated with a potential technical advantage for the subsequent LT. More recently, robotic liver surgery before LT has shown encouraging results as well. Data from an Italian multicenter study confirmed that salvage LT after minimally invasive liver surgery seems safer than those LT performed after open liver resection [20].

20.4.5 Combination Methods

In order to achieve a successful DS, it is frequent in clinical practice to combine DS therapies either in a simultaneous or sequential fashion. For example, in the case of unsuccessful TACE, patients with persistent disease can be subjected to TARE. Similarly, HCC recurrence after LLR can be managed with LRT. Every possible effort should be made in order to successfully downstage HCC patients included within accepted DS protocols.

20.5 Conclusions

The goal of DS is to allow the opportunity of LT to a larger portion of HCC patients without affecting the survival benefit. Robust data emphasize that the sole reliance on radiologic tumor size and number is a relatively crude method to measure the complexity of HCC cases. The modern approach has shifted from a morphological to a combined morphological plus biochemical approach. AFP, novel biomarkers and response to DS protocol should be utilized as predictors of post-LT outcomes. Additionally, PVTT does not represent an absolute contraindication for DS protocols.

TACE represents the most used DS approach while TARE has shown some benefit in DS patients with larger tumors and with PVTT. Ablative therapies, usually used as primary treatment for HCC in unfit patients with small lesions, have shown encouraging results even as LRT. Liver resections by minimally invasive approaches are emerging as possible alternatives for DS. Given the complexity of this disease, it is difficult to determine a specific DS method that is more successful than the others. In general, careful patient selection combined with aggressive LRT appears to have the best outcomes in the long term.

In conclusion, prospective multicenter, well-designed studies are necessary to identify and validate reliable selection parameters and protocols. Regional disparities in LT waiting times and program-specific practices should dictate patient eligibility for DS and individualized treatment decisions must be taken within multidisciplinary teams involving radiologists, hepatologists, surgeons, pathologists and oncologists.

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Hepatocellular Carcinoma Medical Therapy

21

Carlo Garufi and Andrea Mancuso

21.1 Introduction

The identification of single pathways responsible for carcinogenesis is inconclusive. Different genetic, epigenetic and microenvironment alterations affecting intracellular signaling cascades are involved. The development of hepatocellular carcinoma (HCC) is the result of the underlying disease, cirrhosis in most of the cases, liver immune status and microenvironment. Moreover, the different etiology of hepatic infection, hepatitis B virus (HBV) or hepatitis C virus (HCV), the role of alcohol, the increasing evidence of non-alcoholic steatohepatitis (NASH) associated with metabolic syndrome or diabetes, make possible different backgrounds for the development of HCC [1–3].

Different pathways have been implicated in the pathogenesis and progression of HCC. Among them, telomerase activation via TERT promoter mutations, evading cell senescence, Wnt/β-catenin signaling, by mutations or inactivation, and the AKT-mTOR and MAPK pathways seem to be the most interesting.

The liver is an immune-tolerant organ, a condition enabling it to cope with the large number of immunogenic signals coming from the gut. On the other hand, a failure to clear harmful stimuli, as viral or metabolic stress, may lead to chronic inflammation with characteristic hepatic stigmata [4]. There is no evidence for the detection of programmed death-1 (PD-1)/PD-ligand (PD-L1) PDL-1 expression as a prognostic/predictive factor for immune checkpoint inhibitors (ICI) activity. This complex network is made more complicated by vascular endothelial growth factor (VEGF) production by tumor cells and the surrounding stroma. Besides promoting tumor angiogenesis, VEGF inhibits the antigen-presenting functions and T cell stimulatory ability of dendritic cells (DCs), and generates myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tsreg) [5]. Inhibition of VEGF by

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bevacizumab and an anti-PDL-1 agent such as atezolizumab represents a synergistic way to overcome VEGF inhibition as shown in the IMbrave trial.

Different prognostic systems have been proposed for HCC. Among them, the Italian CLIP (Cancer for Liver Cancer) score and the BCLC (Barcelona Clinic Liver Cancer) algorithm have been mostly used in Western countries. The CLIP score is calculated on the Child-Pugh classification of cirrhosis, tumor volume, portal thrombosis and alpha-fetoprotein (AFP) value. The CLIP score is prognostic, with survival decreasing from 41.5 months (score 0) to only 3.4 months (scores 4–6) [6].

The BCLC algorithm introduces the ECOG (Eastern Cooperative Oncology Group) performance status among the prognostic factors and, more relevant, indicates when a local treatment or a systemic treatment represents the best option. Moreover, it is largely used in clinical trials. Recent modifications in study designs include the separation of extrahepatic spread and portal vein invasion, the importance of elevated AFP levels, and the incorporation of mRECIST (modified Response Evaluation Criteria in Solid Tumors) assessments [7].

The natural history of advanced-stage HCC patients involves a median overall survival (OS) of about 8 months, a progression-free-survival (PFS) of less than 6 months, with rare objective responses (OR) and frequent complications due to the underlying disease.

Currently six systemic therapies have been approved based on phase III trials (atezolizumab plus bevacizumab, sorafenib, lenvatinib, regorafenib, cabozantinib, and ramucirumab) and three additional therapies have obtained accelerated FDA approval owing to evidence of efficacy. New trials are evaluating combination therapies, including ICI and tyrosine kinase inhibitors (TKI) or anti-VEGF therapies, or even immunotherapy combinations.

21.2 First-Line Therapy

21.2.1 Single Agents

TKI are the most studied single agents in HCC. Two drugs are now approved in the first-line setting, sorafenib and lenvatinib. More than 15 years ago sorafenib showed an increase in OS when compared to placebo in the SHARP trail (10.7 months versus 7.9 months) and in a parallel Asian trial. Efficacy of sorafenib was confirmed in a meta-analysis in patients with HCV-associated HCC and liver-only disease, who showed greater benefit than those with HCC from non-HCV causes or with extrahepatic disease [8, 9].

Lenvatinib is a recent TKI agent, initially studied in thyroid cancer, with a more potent inhibition against VEGF receptors. In the non-inferiority phase III REFLECT trial head-to-head against sorafenib, lenvatinib improved median OS from the 12.3 months of sorafenib to 13.6 months. It seems relevant that the arm with sorafenib performed better than the original arm in the SHARP trial. The study excluded patients with extrahepatic main portal vein invasion or in whom >50% of the liver was involved. Lenvatinib also significantly improved PFS (7.4 versus

3.7 months; HR 0.66, 95% 95% CI 0.57–0.77; $p < 0.001$). For the first time, a clinical activity in terms of objective response rate (ORR) was found (24.1% versus 9.2%; 95% CI 2.15–4.56; $p < 0.0001$) according to mRECIST, with hypertension being the prevalent side effect of lenvatinib. Lenvatinib is a new standard first-line of treatment in advanced HCC [10].

21.2.2 Combination Therapies

Given that angiogenesis promotes the formation of an immunosuppressive environment, the combination of atezolizumab (anti-PDL-1 antibody) and bevacizumab (anti-VEGF antibody) was studied for synergistic antitumor effects.

The IMbrave150 trial was an open-label prospective randomized phase III study in unresectable untreated hepatocellular carcinoma; 336 patients were treated with the combination of atezolizumab and bevacizumab and 165 with sorafenib. OS at 12 months with the combination was 67.2% (95% CI 61.3–73.1) versus 54.6% (95% CI, 45.2–64.0) with sorafenib. Median PFS was 6.8 months (95% CI, 5.7–8.3) and 4.3 months (95% CI, 4.0–5.6). Grade 3–4 adverse events were not different (56.5% with combination versus 55.1% with sorafenib). Hypertension grade 3–4 affected 15.2% of patients treated with bevacizumab. All patients had been previously studied with gastroscopy for detection of gastric varices. This combination now represents the new standard treatment for advanced HCC patients who have no contraindications to bevacizumab or atezolizumab. Patient-reported outcomes were also better for the combination arm, with the median time to deterioration of quality of life being 11.2 months compared with 3.6 months for sorafenib. Cost-effectiveness analyses indicate a threshold of $ 150,000 for a 35% incremental quality-adjusted life-year, suggesting the need for predictive factors for this combination [11].

Cabozantinib is a multi-kinase inhibitor with activity against VEGF receptor 2, AXL and MET. The COSMIC-312 trial, recently presented at ESMO 2021, is a phase III trial, comparing cabozantinib plus atezolizumab (432 patients) versus sorafenib (217 patients) as first-line treatment for advanced HCC. Patients were stratified by etiology, geographic region, presence of extra-hepatic disease and/or macrovascular invasion. The dual primary endpoint was PFS and OS. The PFS end point was met, with 6.8 months for cabozantinib plus atezolizumab vs. 4.2 months for sorafenib (HR 0.63; 95% CI 0.44–0.91; $p = 0.001$). The interim analysis for OS did not show a statistically significant benefit for the combination. Grade 3/4 adverse events occurred in 54% of patients with cabozantinib plus atezolizumab vs. 32% with sorafenib, with hypertension and increased transaminase levels being most frequent. Final analysis for survival is ongoing [12].

These two phase III trials reinforce the role of combining TKI and ICI versus sorafenib. At this time no direct comparison of ICI + TKI combinations versus lenvatinib has been completed, nor is there a clear selection of patients who could benefit from one of the two options. In the absence of head-to-head trials or established biomarkers, treatment decisions must rely upon the magnitude of benefits, drug toxicity profiles and drug availability. A note of caution comes from

experimental data reporting a lack of response to ICI in patients with NASH-induced HCC. A meta-analysis of three randomized trials in 1600 patients treated with ICI revealed that ICI did not improve survival in this important subgroup of patients [13].

Trials stratified by etiology of HCC need to be run in order to clarify this question.

21.3 Second-Line Therapies

21.3.1 Single Agents

Three drugs (regorafenib, cabozantinib and ramucirumab) were approved for the treatment of HCC patients after progression on sorafenib. In addition, three additional ICI alternatives, namely nivolumab, pembrolizumab and nivolumab plus ipilimumab, have been approved by the FDA after a first-line treatment with sorafenib.

Regorafenib, a multi-kinase inhibitor targeting VEGF receptors 1–3 and other kinases, demonstrated a survival advantage over placebo after sorafenib. The median OS with regorafenib was 10.6 months versus 7.8 months with placebo (HR 0.63, 95% CI 0.50–0.79; $p < 0.0001$). The median PFS was 3.1 months versus 1.5 months (HR 0.46, 95% CI 0.37–0.56; $p < 0.0001$) and the ORR was 11% and 4% for regorafenib and placebo, respectively [14].

The CELESTIAL trial demonstrated an improvement in the median OS for cabozantinib (10.2 months) compared with placebo (8 months; HR 0.76, 95% CI 0.63–0.92; $p = 0.0049$) and in median PFS (5.2 months with cabozantinib versus 1.9 months with placebo; HR 0.44, 95% CI 0.36–0.52; $p < 0.001$) [15].

Ramucirumab is the only biomarker-guided therapy for HCC in patients with baseline AFP levels of ≥400 ng/dL. In the REACH-2 trial ramucirumab demonstrated an improvement in OS (8.5 months versus 7.3 months in the placebo group; 95% CI 0.531–0.949; $p = 0.0199$). PFS was increased with ramucirumab (2.8 months versus 1.6 months; 95% CI 0.339–0.603; $p < 0.0001$) with no difference in response rate [16].

Based on phase Ib/II data, nivolumab and pembrolizumab (anti-PD-1 inhibitors) were approved as single agents in the USA. The CheckMate 040 trial assessed nivolumab as monotherapy in 262 patients mostly as second-line treatment, demonstrating an ORR of 14% with a median duration of response of 17 months (95% CI 6–24). The median OS was 15.6 months and the treatment was generally well tolerated [17]. Similarly, the KEYNOTE-224 trial showed an ORR of 17% with pembrolizumab with a median PFS of 4.9 months and a median OS of 12.9 months. The pembrolizumab-associated profile was tolerable [18]. These data were not confirmed in phase 3 trials in first-line therapy in the CheckMate 459 trial exploring nivolumab versus sorafenib in the first-line setting [19] and in the KEYNOTE-240 trial comparing pembrolizumab versus placebo [20].

21.3.2 Emerging Combination Therapies

There at least two other very interesting combinations already active in other tumor types, namely pembrolizumab plus lenvatinib, which is a standard first-line treatment in renal cancer [21], and nivolumab plus ipilimumab, an anti-cytotoxic T-lymphocyte antigen-4 (CTL-4) drug used in melanoma [22].

In the KEYNOTE-524 trial 100 patients were treated with the combination of pembrolizumab plus lenvatinib as first-line treatment of advanced HCC and the data were presented at ASCO 2020: the OR was 46%, median PFS was 9.3 months (CI 95% 5.6–9.7) and median survival 22.2 months (95% CI 20.4–NE) [23].

These results prompted the ongoing phase III trial LEAP-002 comparing lenvatinib plus pembrolizumab with single agent lenvatinib in 750 untreated patients with Child-Pugh A, BCLC stage C or B HCC not amenable to locoregional therapy, and ECOG PS 0–1; the primary endpoints are PFS and OS [24].

The combination of nivolumab plus ipilimumab was first tested in pretreated patients in the phase I/II CheckMate 040 trial in sorafenib-pretreated patients, obtaining an OR of 32% (CI 95% 20–47) with a median OS of 22.8 months (95% CI 9.4–NE) [25]. Nivolumab plus ipilimumab is currently being tested in the CheckMate 9DW trial in 1084 patients randomized against sorafenib or lenvatinib as first-line treatment [26].

At ASCO-GI 2022, final data of the HIMALAYA study with only one dose of an anti-CTLA-4 drug, tremelimumab, followed by an anti-PDL-1, durvalumab (the STRIDE regimen) were compared with sorafenib or durvalumab alone in 1171 patients with untreated unresectable HCC. The primary end point of the study was met, with a median OS of 16.4 months (14.2–19.6) for STRIDE and 13.8 (12.3–16.1) months for sorafenib (HR 0.78, $p = 0.0035$). The OS for durvalumab alone was not inferior to sorafenib, with a favorable tolerability profile. Even the STRIDE regimen may represent a new treatment option as first-line therapy [27].

21.4 Conclusion

The landscape of HCC has changed profoundly in recent years moving from a single drug, sorafenib, to different active agents, lenvatinib among others, and some promising combinations. The development of atezolizumab with bevacizumab or cabozantinib seems to indicate a new avenue for the use of ICI + TKI. The concurrent use of ICI doublets, nivolumab plus ipilimumab or tremelimumab plus durvalumab, leave the opportunity to use TKI as second-line treatment. Still to be defined is the patient profile of those who will benefit best from TKI alone or from doublets in terms of biological fingerprint, tolerability and efficacy. The role of sequential treatment, the need to integrate these new opportunities with local treatments such as surgery or chemo-radioembolization are still new and promising challenges.

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Part IV

Special Considerations and Recommendations

Surveillance for Patients at Risk of Developing Hepatocellular Carcinoma

22

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22.1 Introduction

The goal of screening is to detect subclinical disease, and when screening is performed at regular intervals, it is called surveillance. Almost all adult patients with cirrhosis and some patients with non-alcoholic steatohepatitis (NASH) or chronic hepatitis B virus (HBV) infection are at sufficiently high risk for developing hepatocellular carcinoma (HCC) [1]. Imaging surveillance of at-risk patients results in detection of HCC at an earlier stage, and the development of simple imaging techniques and effective treatments has provided the rationale for surveillance in high-risk populations. In this context, surveillance has a favorable effect on outcomes and has been demonstrated to be cost-effective [2].

Recommendations on specific screening, obtained from the current guidelines produced by the European (EASL) [3], American (AASLD) [4, 5] and Asian Pacific (APASL) [6] associations for the study of the liver are presented and discussed. This chapter will also review the approach to surveillance for HCC in high-risk patients, with established and proposed surveillance tools.

22.2 Effect of Surveillance on Outcomes

The aim of surveillance is to obtain a reduction in disease-related mortality. This is usually achieved through a diagnosis of the disease at the early stage that, in turn, enhances the applicability and improves the cost-effectiveness of therapies [7]. Ultrasound (US) is the non-invasive method of choice and is applied beyond HCC

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surveillance to monitor the development of portal hypertension, ascites or portal vein thrombosis.

A single randomized controlled trial (RCT) of surveillance vs. no surveillance has only once been published [8]. It included more than 18,000 Chinese patients with HBV infection and showed a 37% reduction in mortality following a strategy based on surveillance with alpha-fetoprotein (AFP) test and US examination every 6 months. Several systematic reviews of the literature on surveillance were performed and aimed to guide the recommendations of the scientific societies [9]. The latest guideline from the AASLD analyzed 38 observational cohort studies involving cirrhotic patients on HCC surveillance compared with patients without. The pooled 3-year survival rate was 50.8% among those who underwent surveillance and 27.9% among those without. The survival benefit was mainly due to higher early-stage detection and higher curative treatment rates.

22.2.1 Surveillance Application

Surveillance application in the real word is considered low. According to a population-based retrospective study in Washington State, out of 1137 patients with cirrhosis, 2% underwent consistent surveillance, 33% had inconsistent surveillance, and 65% received no surveillance during follow-up [10]. Racial and socioeconomic disparities accounted for lower rates of surveillance. Also in Europe, only 22% of HCC cases were diagnosed by surveillance, and in one-third of cases surveillance was indicated but missed [11]. Non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease were associated with deficient surveillance, both in America and in Europe.

22.3 High Risk Groups

For some high-risk groups of patients HCC surveillance is recommended by current protocols, while the need for surveillance for other groups is still debated (Table 22.1).

22.3.1 Patient with Cirrhosis

Patients with liver cirrhosis are a high-risk group. The HCC incidence rate among patients with cirrhosis has been shown to be 2–4% per year, independently from etiology [12, 14]. All the guidelines strongly recommend that patients with Child-Pugh A and B stage cirrhosis should be entered into surveillance programs [3–6].

According to the general principles of surveillance, it must be considered that the HCC incidence increases with liver disease evolution, but also that the probability of receiving eradicative therapies becomes lower, because of lower applicability of surgery, tumor ablation or radioembolization. The presence of advanced liver failure

Table 22.1 Groups for which hepatocellular carcinoma (HCC) surveillance is recommended and groups with unproven benefits

Recommended surveillance		
Cirrhosis etiology	HCC risk (per year)	Threshold incidence for surveillance efficacy
HBV	3–5%	0.2–1.5%
HCV	2–7%	1.5%
NASH	2–4%	1.5%
Alcohol-related	1%	1.5%
Primary biliary cholangitis	3–5%	1.5%
Autoimmune hepatitis, α1 antitrypsin deficiency, genetic hemochromatosis and other etiologies	Unknown, but probably >1.5%	1.5%
Need for surveillance still debated		
Chronic non-cirrhotic HBsAg positive carriers	HCC risk (per year)	Threshold incidence for surveillance efficacy
Asian females >50 years and males >40 years	0.3–0.6%	0.2%
Africans aged >20	NA	0.2%
History of HCC in the family	NA	0.2%
HCV with stage 3 fibrosis	<1.5%	1.5%
Non-cirrhotic NAFLD/NASH	<1.5%	1.5%

Sources: [2, 6, 12, 13]
HBV hepatitis B virus; *HCV* hepatitis C virus; *NASH* non-alcoholic steatohepatitis; *NAFLD* non-alcoholic fatty liver disease

(Child-Pugh stage C) prevents effective HCC therapies from being employed, and thus surveillance should only be performed when liver transplantation is indicated, as HCC onset may modify both priority on the list and transplantability [3, 5, 6].

22.3.2 Patient with Hepatitis B Virus Infection Without Cirrhosis

Patients with HBV infection are at risk of HCC development even in the absence of cirrhosis, but the exact degree of risk is ill defined and appears to be influenced by geographical region (higher in Asia and Africa), higher levels of HBV replication, age, and gender [15]. These patients are at higher risk than the general population, and are more suitable for surgical treatments. Thus, the latest European guideline adopts a different scoring system to stratify HBV-infected patients in relation to their risk of developing HCC based on mixed demographic and laboratory parameters (PAGE-B) [16]. Subjects with high or intermediate risk were recommended for surveillance.

22.3.3 Patients with Hepatitis C Virus Infection and Advanced Fibrosis

In 2009, Lok and et al. showed that HCC can occur in non-cirrhotic patients with chronic hepatitis C virus (HCV) infection who suffer from advanced fibrosis [17].

The current availability of simple and new non-invasive methods to assess significant (Metavir F3) fibrosis, such as transient elastography, further simplified the inclusion of these patients in surveillance programs [18]. However, the incidence of HCC in these subjects is lower than 1.5% and their inclusion in surveillance programs is still debated [6] and currently only recommended in the EASL guidelines.

22.3.4 Patients with Non-alcoholic Steatohepatitis or Non-alcoholic Fatty Liver Disease

The estimated prevalence of NASH in the general population ranges from 2 to 3% [19]. Data has revealed that up to 44% of cases of NAFLD can progress to NASH even in the absence of inflammation at baseline [20] and approximately 23% of cases of NASH progress to cirrhosis over the following 10–15 years. The incidence of HCC in patients with NASH cirrhosis has been reported to be 2.3–4.0% per year [21].

Patients with NASH cirrhosis should be considered for HCC screening according to the guidelines of the American Hepatology and Gastroenterology Societies based on a systematic review of NAFLD/NASH cirrhotic patients [22]. However, it is estimated that half of the cases of NASH-induced HCC arise in non-cirrhotic patients [23] and there is a clear need to define which high-risk patients should undergo surveillance. Thus, no recommendation can currently be made on the timing of surveillance or its cost-effectiveness in non-cirrhotic patients with NASH or NAFLD [3, 24].

22.3.5 Patients Successfully Treated for Hepatitis C or B Virus Infection

The arrival of new direct-acting antiviral HCV therapy allowed for the achievement of sustained virological response (SVR) in over 95% of treated patients, irrespective of liver fibrosis stage [25]. Older age, low platelet count, and/or presence of cirrhosis despite SVR are associated with a higher risk for HCC development and warrant surveillance [26]. There is general consensus in guidelines that patients with cirrhosis should continue surveillance after direct-acting antiviral-induced SVR. However, patients, providers and healthcare systems also desperately need guidance as to whether HCC surveillance can ever be safely discontinued after HCV eradication [27].

Currently, the EASL and APASL guidelines recommend maintaining surveillance for SVR patients with advanced liver fibrosis, whereas the AASLD does not [28].

Caucasian patients with HBV-related cirrhosis at the time of initiating nucleos(t)ide analog (NUC) therapy benefit from a decrease in HCC yearly incidence between the first 5 and second 5 years of treatment, specifically from 3.22% to 1.57% [29].

Therefore, these data confirm that surveillance is to be maintained in patients who have reached the stage of cirrhosis, regardless of receiving effective antiviral treatment.

22.4 Approach to Surveillance

22.4.1 Ultrasound in Combination with Serum Alpha-Fetoprotein

In the latest published guidelines, serum AFP in combination with US has become the standard reference for HCC surveillance in high-risk populations.

The American guidelines based their statements on the data emerging from a systematic review of surveillance. The use of US plus AFP improved detection of early-stage HCC compared with no surveillance. Both US alone and US plus AFP led to similar rates of curative treatment [30]. Although several biases may have influenced these data, the combined 6-month interval US plus AFP was recommended by the AASLD in the HCC surveillance setting.

The European guideline, although adopting the US plus AFP protocol as a reference, states that the combination with AFP is not recommended in patients with active liver inflammation, as the 6–8% gain in the detection rate does not counterbalance the increase in false-positive results [31].

22.4.1.1 Cut-Off Value of Serum Alpha-Fetoprotein Applied to Surveillance

The optimal cut-off value of AFP for HCC surveillance should be determined on the premise that it is examined simultaneously with US. In a meta-analysis, AFP with a cut-off value of 200 ng/mL showed a better combined positive likelihood ratio than that with a value of 20 ng/mL [32]. AFP levels decrease according to decreased hepatitis activity in patients with chronic HBV on antiviral treatment or HCV patients after SVR. Thus, the APASL guidelines suggest that the cut-off value of AFP can be set lower (down to 12–20 ng/mL) in a virologically suppressed or eradicated population.

22.4.1.2 The Six-Month Interval

The ideal interval of surveillance for HCC should be dictated by two main features: rate of tumor growth up to the limit of its detectability, and tumor incidence in the target population. The median tumor doubling time in HCC is demonstrated to be 80–117 days [6]. An increased risk of developing HCC does not mean a faster tumor progression, and thus cirrhotic patients at high risk do not require screening at shorter time intervals.

A meta-analysis has demonstrated that the sensitivity of a 6- versus 12-month surveillance strategy increases from 50 to 70% [31]. In a RCT that enrolled patients with compensated cirrhosis, no significant difference was documented in the rate of HCC detection by using an US-based surveillance strategy every 3 or 6 months [33]. Thus, biannual US with AFP-based surveillance is currently recommended.

22.4.2 Proposed Imaging Techniques and Serology Markers for Surveillance

Despite its high diagnostic performance compared with US, magnetic resonance imaging (MRI) has not been recommended for HCC surveillance because of prohibitive costs when widely adopted for screening patients with cirrhosis. Non-contrast MRI also exhibits a high sensitivity for detecting focal liver lesions when performed with sufficient sequences to preserve superior tissue contrast [34], and is potentially a good alternative surveillance tool for HCC. Non-contrast MRI has the significant advantage of eliminating the potential risks of contrast media, reducing costs, and improving efficiency. A multicenter clinical trial is currently ongoing in Korea, which is comparing both annual non-contrast liver MRI and biannual US as surveillance tools for HCC in patients with liver cirrhosis [35].

Contrast-enhanced US (CEUS) is useful for characterization of US-detected liver nodules and is as sensitive as dynamic computed tomography (CT) or dynamic MRI in the diagnosis of HCC [36]. In addition, CEUS has several advantages, and has the possibility of being performed immediately when a suspect nodule is discovered during US surveillance [37]. However, although CEUS may be used in HCC surveillance, the lack of evidence, especially with regard to cost-effectiveness, has led to CEUS not being considered in the current guidelines.

Other tumor markers such as lectin-bound AFP (AFP-L3) or des-γ-carboxyprothrombin (also known as PIVKA II) have been proposed to be more efficacious than AFP. Neither test alone, nor the combination of the two, was adequate for HCC surveillance because the sensitivity of both markers was very low when evaluating efficacy and cost-effectiveness in detecting HCC at an early stage [38]. Thus, at present, the use of these markers is not recommended as part of a surveillance strategy in guidelines.

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Hepatocellular Carcinoma Recurrence: How to Manage

23

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23.1 Introduction

Liver resection (LR) and transplantation (LT) are curative surgical options for patients with hepatocellular carcinoma (HCC). The latter, in particular, is the best treatment option for selected patients with early-stage disease. HCC is the fifth most common cancer type and the third most common cause of cancer-related death worldwide [1, 2]. LT could provide a long-term survival for HCC patients fulfilling the Milan criteria, similar to the LT outcomes in patients without cancer. Despite the restrictive selection policy, the recurrence rate of this tumor drastically affects patient survival in up to 25% of cases [3]. It is well known that the timing of recurrence after LT can represent a key predictor of survival, and that a recurrence occurring within 24 months (early intra- and/or extra-hepatic HCC recurrence) is frequently associated with a worse prognosis [4].

Early recurrence is defined as recurrence within 2 years after resection of HCC. From a pathophysiological perspective, this clinical entity might result from

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circulating HCC cell clones engrafting and growing in a target organ after LT or from non-detectable extra-hepatic metastases being present before LT.

Late recurrence (beyond 2 years after surgery) is more a result of new malignant clones and is related to underlying liver conditions (e.g., liver cirrhosis) [5]. The natural history of HCC is quite heterogeneous and it is possible to distinguish two models of tumor progression, depending on whether the disease develops in a cirrhotic or a non-cirrhotic liver [6].

23.2 Clinical Setting and Risk Factors

The *primum movens* in HCC development is an insult by pathogenic noxious agents (e.g., viruses, alcohol, aflatoxins, etc.) which damage the liver parenchyma. Immediate elimination of the insult can result in restoration of the normal hepatic tissue structure; if instead the causative agent cannot be completely removed, an inflammatory process ensues with fibrotic evolution of the liver and hepatic cell regeneration with nodular arrangement of the cells, and consequent formation of cirrhotic pseudonodules. This leads to subversion of the normal hepatic architecture which will inevitably result in a functional alteration of the liver. Subsequently, a series of genetic mutations involving genes involved in cell apoptosis and proliferation will follow, which will cause the bypass of the physiological mechanism of hepatic senescence. These events will give rise to altered cell lines, with the ability to invade vascular structures and produce distant metastases, and therefore to the onset of permanent lesions that over time can evolve into neoplasia. Specifically, the regenerative pseudonodules will become dysplastic and then neoplastic [7].

Despite much evidence supporting the recommendations of scientific societies around the world, the clinical manifestations of HCC are often late, with a diagnosis that is generally made in the advanced stage of the disease, thus significantly limiting treatment options. Based on genomic profiling and next-generation sequencing, two distinct subgroups of HCC (proliferative and non-proliferative) have been identified, each with "core" genomic alterations and/or oncogenic pathways and distinct histopathologic features and clinical outcomes. Proliferative HCC is an aggressive phenotype with moderate to poor cellular differentiation, high alpha-fetoprotein (AFP) levels, frequent vascular invasion, high tumor recurrence, and poor outcomes. Non-proliferative HCC is a less aggressive phenotype with well- to moderately differentiated tumor at histologic examination, lower AFP levels, and better outcomes [8].

However, translation of this knowledge into clinical practice and therapeutic decision-making has been challenging given the substantial intra- and inter-tumor genetic heterogeneity with some mutations present only in specific regions within the tumor, such that a single biopsy specimen is likely to be insufficient in accurate molecular stratification. To calculate the risk of post-LT HCC recurrence, comprehensive machine-learning algorithms, based on serial imaging, AFP, locoregional therapies, treatment response, and post-transplant outcomes, were recently

proposed that demonstrated higher levels of accuracy than other risk scores for optimizing the allocation of donor organs [9].

23.3 Diagnostic Tools and Oncologic Monitoring

HCC is a neoplasm for which an adequate and careful surveillance program is essential, to diagnose the tumor at an early stage and be able to use a greater number of therapeutic strategies, thus improving patient outcomes [10]. Patients at high risk for developing HCC are those with chronic HBV or HCV infections or even cirrhotic patients. Surveillance should be carried out in cirrhotic patients who have eradicated HCV infection following antiviral therapy; in all cirrhotic patients, regardless of etiology, in Child-Pugh class A and B, and in those in class C awaiting transplant, while no increase in survival was observed for the other class C patients. HBV-positive non-cirrhotic patients, in whom the annual incidence of HCC is greater than 0.2% per year, should also be included in a surveillance program. Similarly, surveillance is recommended in patients with chronic HCV infection and bridging fibrosis in the absence of cirrhosis [11]. Liver ultrasound (US) is the most appropriate means of surveillance available to us, with acceptable diagnostic accuracy when used as a surveillance test (sensitivity between 58% and 89%; specificity >90%). US is less effective in detecting HCC in the early stage, with a sensitivity of only 63% when used for diagnostic purposes. The widespread use of US screening is also due to good patient compliance, low cost, non-invasiveness and the absence of risks. On the other hand, this method is highly dependent on the skill of the operator and the characteristics of the patient (body mass index ≥33, presence of ascites or bloating). With regard to serological markers, the AFP assay is certainly the most widely used in HCC. Persistently high values represent a risk factor for HCC development and can be used to define high-risk populations [12]. However, several studies have confirmed the importance of AFP in diagnosis but not in surveillance, since increased AFP levels in cirrhotic patients could be associated not only with HCC development, but also with a possible exacerbation of the underlying disease or reactivation of HBV or HCV infection; moreover, only a small proportion of early-stage tumors (10–20%) have high serum AFP values, a fact recently associated with a particularly aggressive subclass of HCC. As part of the surveillance, it was found that the combined use of AFP and US leads to an increase in sensitivity by about 6–8% compared to US alone, causing, however, an increase in false positives and costs. The diagnostic accuracy for HCC of this serological test was confirmed by retrospective case-control studies which considered the cut-off of 10–20 ng/mL to be more efficient for diagnosis, with sensitivity around 60% and specificity 80%.

Other tumor markers such as des-gamma-carboxy prothrombin (DCP) also known as vitamin K absence-induced prothrombin, the glycosylated AFP fraction (L3 fraction) on total AFP, alpha-fucosidase, and glypican [13] were evaluated, alone or in combination, more for diagnosis and prognosis than for surveillance. In

particular, DCP levels have been associated with portal venous invasion and an advanced tumor stage, similarly to the levels of the AFP-L3 fraction. At present, none of these serological tests can be recommended for the surveillance of patients at risk of developing de novo HCC. The ideal recommended surveillance interval is six months, since a quarterly interval does not translate into any clinical benefit and vice versa an annual interval, while reducing costs, is associated with fewer diagnoses of HCC at an early stage and lower survival [14].

Recurrence is generally established by radiologic evidence of new tumor on computed tomography (CT) or magnetic resonance imaging (MRI), and systemic treatments are warranted when it presents as or becomes systemically spread [2]. In the last decade, many HCCs have been diagnosed based on imaging features alone in patients at high risk by using the typical radiologic features at dynamic imaging, without histopathologic evaluation. For this reason, correlation of imaging findings with specific molecular traits of HCC has gained substantial interest in recent years [15].

Diagnostic imaging (CT and MRI) is crucial for obtaining the standard of care for HCC evaluation, and they have a role in the preoperative assessment to predict HCC recurrence after LT and or liver resection. Very recently, the role of gadoxetate-enhanced MRI in differentiating proliferative from non-proliferative HCCs was analyzed, demonstrating that the majority of proliferative HCCs showed rim arterial enhancement, defined as irregularly shaped rim-like peripheral enhancement, and a large hypo-enhancing central component (50% or more area) may correlate with larger necrotic areas. Therefore, rim arterial enhancement was shown to predict a proliferative HCC, with reduced overall survival and an increased rate of intra- and extra-hepatic metastases [15].

23.4 Clinical Decision-Making and Surgical Management

The following preoperative CT and MRI findings are specific independent risk factors for postoperative early HCC recurrence as indicators of microvascular invasion [2]:

- tumor size;
- multifocality;
- hypointensity on T1-weighted MRI sequences;
- corona enhancement, hypointensity on hepatobiliary phase MRI;
- peritumoral hypointensity on hepatobiliary phase;
- non-smooth tumor margin;
- incomplete tumor capsule;
- satellite nodule;
- mosaic architecture;
- absence of fat in the mass;
- macro-vascular invasion.

The size and number of tumors, which together represent tumor burden, are important prognostic factors for HCC: as tumor size increases, HCCs tend to have a higher frequency of vascular invasion, extrahepatic metastases and a decrease in patient survival. Multifocal tumors can represent multiple independent HCCs occurring simultaneously (multifocal HCC) or intrahepatic metastases from a primary HCC. The availability and success of curative treatment options, such as liver resection or transplantation, are highly dependent on the size and number of HCCs. Indeed, liver resection for HCC <3 cm improves long-term patient survival [2]. Intrahepatic metastases develop through two different routes. Small satellite nodules around the primary tumor form when cancer cells enter portal venules that drain from the primary tumor and spread into the surrounding parenchyma. Metastatic nodules outside the drainage area, including other segments or the contralateral lobe, develop through the systemic circulation of cancer cells. Multifocal tumors can have variable histological grades and other features, while all metastatic tumors of a single HCC are considered to have advanced lesions with advanced tumor grade. The prognosis of patients with intrahepatic HCC metastases tends to be worse than those with multifocal HCC.

Poorly differentiated HCCs tend to show lower signal intensity on hepatobiliary phase MRI than well-differentiated or moderately differentiated HCC [15]. Vascular invasion is more common in larger or higher histological grade HCCs. Cancer cells involve the portal venous system more frequently than the hepatic veins. Macrovascular invasion is related to poor prognosis because it provides tumor cells with the pathway to access the portal or systemic circulation, which can result in intrahepatic or systemic metastases. Thus, vascular invasive HCCs have frequent multifocality and a higher relapse rate after LR, ablation therapy, or LT [16] (Fig. 23.1).

Surgical resection is regarded as the first-line treatment option for HCC patients with well-preserved liver function. Nevertheless, almost 70% of HCC patients

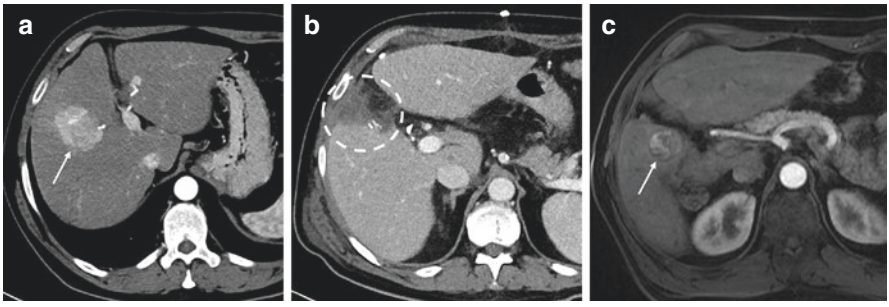

Fig. 23.1 (**a**) Patient with typical hypervascular hepatocellular carcinoma (HCC) in the right hepatic lobe (arrow) on axial arterial phase contrast-enhanced computed tomography (CT) image. (**b**) The same patient underwent hepatic resection (circle), as shown on the axial portal venous phase contrast-enhanced CT image performed some weeks after surgery. (**c**) Six months later, axial contrast-enhanced magnetic resonance imaging in the arterial phase showed recurrent HCC along the hepatic resection margins (arrow)

develop tumor recurrence within 5 years after surgery [5]. Currently, the therapeutic options of HCC recurrence include LR, particularly for isolated hepatic and extrahepatic metastases, and the following range of therapies:

– transarterial chemoembolization or embolization (TACE or TAE);
– radiofrequency and microwave thermal ablation (RFTA and MWTA);
– multi-target tyrosine kinases inhibitor (sorafenib).

Limited but unresectable HCC recurrence in selected patients can be treated with locoregional therapy, which may include TACE, TAE, MWTA, and RFTA, with potential survival improvement, considering their repeatability or potential combination in a multimodality approach [17].

23.5 Conclusion

Managing recurrent HCC is a challenging area, as reflected by the highly heterogeneous conditions and treatment strategies. Since molecular classification and data from molecular analytics are not yet incorporated into the clinical practice guidelines for HCC management or prediction of recurrence, the evaluation of patients with HCC should include preoperative CT or MRI, which can be used to effectively predict early recurrence and preoperatively stratify these patients. Machine learning techniques with deep learning approaches to extract hidden qualitative and quantitative data from clinical images (including texture analysis) are increasingly being studied in oncology. However, they are challenged by repeatability and reproducibility, and they need a large volume data for adequate stratification.

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Liver Biopsy: How and When

24

Gian Luca Grazi and Andrea Scarinci

24.1 Introduction

Hepatocellular carcinoma (HCC) accounts for approximately 90% of primary liver cancers, and its incidence is increasing. It represents the fifth cancer worldwide and is the third major cause of cancer death [1]. The world incidence of HCC is about 15%, with geographic differences [2]. The literature indicates that 70–97% of patients with HCC have underlying liver cirrhosis at the time of diagnosis [3].

HCC is diagnosed by non-invasive procedures, such as imaging studies and tumor markers, and by invasive techniques, such as liver biopsy (LB). LB involves the retrieval of a quantity of tissue from the liver by means of a dedicated needle, and is usually performed percutaneously under local anesthetic. This allows microscopic examination of the obtained tissue. LB can furnish data about diagnosis, prognosis and, in certain circumstances, it guides treatment decisions in HCC. The specificity and sensitivity of LB diagnosis for HCC have been reported to be 100% and around 90%, respectively, depending on location, differentiation, and size of the lesion, as well as on the expertise of the physician performing the biopsy and of the pathologist [4]. The role of LB in the management of HCC is controversial as a result of the good performance of imaging techniques [5]. Needle-tract seeding, sampling errors and risk of morbidity are the limits of LB and, together with imaging refinements, have changed the role of histological examination in HCC.

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24.2 Indications and Technique

LB indications continue to evolve and, although percutaneous LB of a mass is usually possible, biopsy is not always indicated. LB is justified when its result would influence patient management. These indications include establishing a diagnosis before surgery, patients who are not surgical candidates, and assessing hepatic dysfunction.

Although mainly performed percutaneously, LB can also be done through a transjugular/transvenous, endoscopic or laparoscopic access.

24.2.1 Contraindications and Risk Factors

The approach depends on abdominal wall thickness (the percutaneous route may be problematic in obese patients) but the presence of underlying liver disease or cirrhosis can hamper the maneuver. Cirrhosis with impaired coagulation parameters, ascites, severe portal hypertension, low platelet count and hard liver could contraindicate the performance of a LB. A platelet count <50,000/μL is a risk factor for bleeding for the percutaneous route, and a transjugular approach is advised in this setting [6]. Technical factors could add difficulties: a deep and posterior location of the nodule can be an insurmountable obstacle. LB should not be performed when the obtainable results would not alter patient's prognosis and treatment options.

24.2.2 Percutaneous Liver Biopsy

Percutaneous LB is the most widespread approach. Before the procedure, anesthetic is injected into the skin. The procedure is carried out through a thin needle across the skin into the liver, removing some tissue for pathology. Percutaneous LB is performed under ultrasound (US) or computed tomography (CT) guidance, for better accuracy and safety. As with any invasive technique, there are risks associated with percutaneous LB that should be assessed in advanced. The main reason for limiting LB is the risk of complications that could have an impact on the diagnostic and/or therapeutic pathway.

24.2.3 Transvenous/Transjugular Liver Biopsy

Indications for transvenous/transjugular LB are usually different from those for percutaneous biopsy, thus comparison of morbidity and mortality between these approaches may be misleading. Transvenous/transjugular LB is carried out on patients with: (1) ascites; (2) known or suspected clotting disorders with the risk of bleeding; (3) a hard cirrhotic liver; (4) morbid obesity resulting in difficulty identifying a flank site; (5) a need for preoperative hepatic vein pressure measurement.

A flexible catheter is inserted into the jugular vein, the contrast agent is injected into the tube and images are acquired. This allows visualization of the hepatic vein. A biopsy needle is threaded through the tube and samples are retrieved. Reported minor and major complication rates were 6% and 0.5%, respectively, whereas mortality was 0.09% (hemorrhage 0.06%; ventricular arrhythmia 0.03%) [7, 8].

24.2.4 Endoscopic Ultrasound-Guided Liver Biopsy

Endoscopic ultrasound-guided liver biopsy (EUS-LB) may be a safe and effective alternative that is performed by endoscopic US in the duodenum. Several series have reported its use in performing both targeted and non-targeted LBs, with a sensitivity of 82–94%, specificity of 90–100% and a low complication rate (2.3%). EUS-LB is accurate and versatile but highly operator-dependent. It can offer higher resolution imaging detecting smaller lesions than CT or US. It is useful for small and deep-seated left lobe lesions below CT or magnetic resonance imaging (MRI) resolution or not easily accessible percutaneously. Evidence suggests the superiority of EUS-LB for focal lesions, with less sampling variability in heterogeneous parenchymal disease [9].

24.2.5 Laparoscopic Liver Biopsy

LB can be performed through a laparoscope during surgery under general anesthesia. Biopsy is performed either with typical needle devices or by wedge resection. It is used for lesions discovered accidentally at routine surgery or because the liver is noted to be abnormal prior to planned surgery. This procedure is used for patients with abnormal clotting indexes and/or coagulopathy, when histology is mandatory for treatment. The technique allows adequate tissue sampling with direct control of bleeding. Complications in laparoscopic LB include those of the laparoscopy itself, such as delayed bleeding from the LB site or abdominal wall and intestinal perforation, which occur in 1.0% of cases. Expense and requirements for special expertise limit its use [10].

24.2.6 Risk of Complications

LB is a safe procedure, but there are risks that need to be carefully weighed against the advantages and the results provided. Complications are uncommon (5.9%) and risks include bleeding, organ perforation, sepsis and death. Bleeding occurs in about 10% of cases, and major bleeding accounts for less than 2%. In a small number of cases, there is some minor bleeding, especially in patients with cirrhosis who are at a higher risk of this complication. The mortality associated with LB is <0.001% [6].

24.2.7 Risk of Tumoral Seeding

The possibility of tumor dissemination into adjacent liver tissue after performing LB has been reappraised. Details of the prevalence of tumor cell seeding along the needle tract, which could significantly worsen the patient's prognosis, have yet to be established [11]. The reported incidence of seeding is 0.005%, probably underestimated because most of the reports include single cases. The interval from LB to confirmed implantation varies from 3 months to 4 years. The treatment of implantation has not been clearly established. Surgical resection is reported in many cases; other treatment modalities included local radiotherapy and radiofrequency ablation. Removal of the seeding by surgical resection was shown to be easily performed: it does not affect the outcomes of oncological treatment or the long-term outcomes. Some series reported an overall survival, after surgical excision of seeding, ranging from 3 to 5 years [12].

24.3 Biopsy for Diagnosis of Hepatocellular Carcinoma

Multiphasic contrast-enhanced imaging studies (CT and MRI) are employed to effectively diagnose focal liver nodules based on their vascular and biliary physiological features, in relation to the timing of images obtained after contrast agent administration. Thus, LB is now rarely required to differentiate benign from malignant lesions. The evaluation of nodules having features of HCC is influenced by their size and location, the state of non-neoplastic liver, the patient's clinical condition, the imaging patterns and expertise of the diagnostic physicians. Non-invasive diagnosis of HCC, in the setting of liver cirrhosis, is based on typical patterns on diagnostic imaging performed using specific contrast agents, as shown in the diagnostic algorithm (Fig. 24.1) [4].

A reliable diagnosis of a liver lesion identified by US represents a major clinical issue and it proves almost impossible for nodules <1 cm using the current imaging modalities. On the other hand, the diagnosis of HCC can be confirmed using imaging techniques if a nodule larger than 1 cm displays specific imaging features. Typical patterns of HCC on contrast-enhanced CT and MRI are intense contrast uptake during the arterial phase followed by decreased enhancement and washout during the portal phases, based on the theory of neo-arterial supply feeding the HCC. A single contrast-enhanced imaging study is sufficient for the diagnosis of HCC.

The high specificity and positive predictive value of this pattern in larger lesions have been prospectively validated for HCC only in cirrhotic livers. Because of their higher sensitivity and ability to analyze the whole liver, CT or MRI should be used first. LB should be considered in patients with nodules that are not typical at contrast-enhanced imaging, especially for findings classed as "nodules with features likely for HCC" or "nodules with features highly suggestive or even diagnostic of malignancy, but not specific for HCC" [13]. The specificity of the imaging

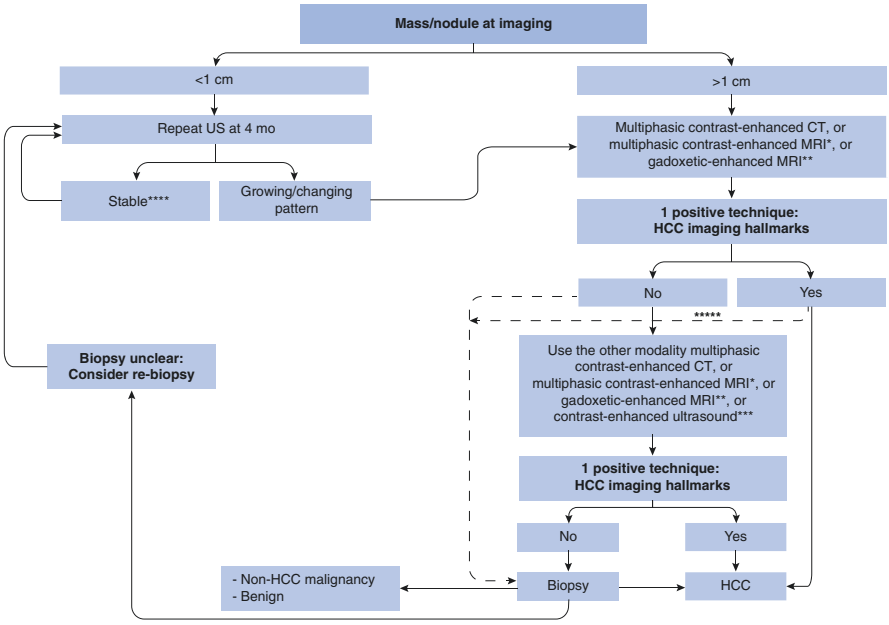

Fig. 24.1 Diagnostic algorithm for a suspicious nodule in cirrhotic patients. The role of liver biopsy in the case of a mass detected in a cirrhotic liver is limited to those nodules without typical features at imaging or at first liver biopsy. * Using extracellular MR contrast agents or gadobenate dimeglumine. ** Using the following diagnostic criteria: arterial phase hyperenhancement (APHE) and washout on the portal venous phase. *** Using the following diagnostic criteria: arterial phase hyperenhancement (APHE) and mild washout after 60 s. **** Lesion <1 cm stable for 12 months (three controls after 4 months) can be shifted back to regular 6 months surveillance. ***** Optional for center-based programs. Reproduced with permission from [4]

hallmarks for HCC is lower in the non-cirrhotic liver, since alternative diagnoses are seen more commonly (e.g., hepatocellular adenoma and liver metastases).

Histological confirmation is suggested when the imaging-based diagnosis remains inconclusive, especially in small tumors (<2 cm), where the features of contrast-enhanced imaging are not specific. Considering a 5–10% level of uncertainty with imaging-based HCC diagnosis, even when the classical diagnostic parameters are satisfied, LB can be considered whenever a higher level of certainty is required.

Despite moderate evidence, the European Association for the Study of the Liver (EASL) recommends that the diagnosis of HCC in non-cirrhotic livers should be confirmed using LB [4]. In non-cirrhotic patients, the specificity of the imaging hallmarks is lower than in cirrhosis, as alternative diagnoses (such as hepatocellular adenoma or hypervascular metastases) are more common. For this reason, imaging studies are not adequate in non-cirrhotic livers and LB is mandatory to confirm HCC.

The diagnosis of liver cirrhosis might be difficult in some cases. When the diagnosis of HCC in patients with cirrhosis is uncertain, LB should be carried out as in non-cirrhotic patients. LB has the additional advantage of providing information regarding the non-neoplastic liver. The American Association for the Study of Liver Diseases (AASLD) does not recommend biopsy for lesions larger than 1 cm if two different imaging studies yield concordant findings [14]. LB is done with varying degrees of sensitivity (66–93%, based on tumor size, operator experience, and needle size) and 100% specificity and positive predictive value [15].

An LB may be needed in patients who are not candidates for curative resection, to establish a diagnosis for the purpose of systemic therapy or liver transplantation (LT).

24.4 Biologic Information Obtainable from Biopsy

One role of LB is the enrollment in trials for new anticancer drugs or innovative interventional therapies. Biopsy of cancers could determine the appropriate therapy for patients affected by diseases with similar characteristics, a possibility that has opened the door to "precision medicine". LB has some role in the diagnosis of HCC, but its role remains under debate. We know that HCC biopsy can accurately predict tumor grading in patients with nodules <5 cm subjected to liver resection [16]; for larger tumors this correlation is weaker.

There are no data on the possibility to diagnose microscopic vascular invasion, which is a prognostic factor of HCC associated with advanced tumor stage, distant metastases and adverse outcome [1].

Attempts made to identify indications for surgery on the basis of biomolecular characteristics of HCC [17] have never led to modifications of the indications for treatment, which remains based on morphological criteria, namely tumor number and size, and the recently added serum tumor markers such as alpha-fetoprotein. There are still no biological or mutational factors able to identify types of cancer with different prognosis, for which different therapies can be indicated. Thus, the usefulness of LB in terms of determining the prognosis of the individual patient is still substantially nil.

24.5 Role of Biopsy for Surgical Resection of Hepatocellular Carcinoma

Liver resection represents the first option in patients with very early and early HCC with a preserved liver function. It has been reported that the accuracy of liver nodule differentiation without biopsy was adequate at least for lesions larger than 2 cm. Biopsy findings are only occasionally not confirmed at surgery. LB has limits in its diagnostic power and this fact may delay proper patient management. An appropriate indication for surgery is achievable without biopsy in 97.9% of patients [18].

24.6 Role of Biopsy for Liver Transplantation in Hepatocellular Carcinoma

The role of LB in the setting of LT is more intriguing. It has been well stated that LT is the best treatment for HCC, as it treats the cancer and the underlying liver disease simultaneously. Nevertheless, we live in an era of persistent scarcity of organs for LT, and we still have to manage the single patient as well as the LT waiting list as a whole.

The most important issues in this respect are the criteria for inclusion on the waiting list, reduction of the dropout rate, the possibility of performing effective bridge treatments, and prioritization of the patients when organs become available.

Biological factors related to the nature of the HCC itself would be of great help in those difficult decisions. There have been several attempts in this direction. In a single-center experience, when poorly differentiated HCC cases at pre-LT biopsy were excluded from LT, 38% of patients did not meet the Milan criteria and 42% were TNM stages III and IV. The 5-year actuarial survival rate was 75% and recurrence-free survival was 92%. HCC recurred in only three patients (6%). The conclusion was that routine pre-LT tumor grading may represent a tool in the selection of HCC patients for LT [19]. In this series, the timing of diagnosis, the Milan criteria, and the TNM stage revealed no statistically significant impact on overall and recurrence-free survival rates. This experience did not have any follow-up, and the indications for LT are still based on the morphology of the tumor. Attempts have been published to refine these criteria by including the response to therapy carried out while waiting for the LT [20] or surrogates of biological factors, such as tumor markers [21]. Performing a LB for the presence of an HCC plays a small role, being limited to nodules that appear of uncertain nature at radiology. The aim is always to define the morphological stage of the tumor and therefore to classify it in relation to the criteria for inclusion in the LT-waiting list.

24.7 Conclusions

Percutaneous LP is an established and safe diagnostic tool for the diagnosis of suspicious nodules that do not exhibit typical features on CT and/or MRI scans. The complications of LB are rare and easily manageable. The declining interest for biopsy is related to several issues, including morbidity due to the most frequent complications (pain and bleeding), especially in cirrhotic patients. Seeding is an issue that should be taken into consideration, particularly in patients who would benefit from LT. There are two drawbacks of the limited use of LB for HCC diagnosis. The systematic avoidance of biopsy for the diagnosis of HCC may have slowed progress in understanding the biologic features of these tumors and in developing targeted therapies. The decision to obtain a biopsy should be taken after discussion in a multidisciplinary tumor board including radiologists, surgeons, oncologists, pathologists and hepatologists. Broader availability of LB in HCC has the potential to provide greater access to clinical trials, expand the treatment options and support research measures expected to improve the therapy of liver cancers.

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Anesthesiologic Management During Surgery for Hepatocellular Carcinoma

25

Micaela Maritti and Luigi Tritapepe

25.1 Introduction

Liver resection is considered a major abdominal surgery. Chronic hepatitis C is still the leading cause of chronic liver disease (CLD) and is implicated in the increase in cases of hepatocellular carcinoma (HCC). Today, non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease represent the second leading etiology for liver disease. Primary NAFLD is associated with insulin resistance and metabolic syndrome: obesity, type II diabetes, arterial hypertension, and hypertriglyceridemia [1].

In the 1970s, perioperative mortality for hepatic resection was about 20%, mostly because of uncontrollable bleeding and postoperative liver failure. Moreover, patients with liver disease such as cirrhosis have higher rates of complications and mortality. In referral centers, the mortality associated with liver resections has decreased to less than 2%, but postoperative adverse events are still high (20–50%) [2].

The Enhanced Recovery After Surgery (ERAS) Society has recently published guidelines for fast-track management of patients undergoing liver resection [3]. Although improvements in surgical and anesthetic techniques have allowed perioperative mortality to be reduced, patients with liver disease have significantly higher complication and mortality rates. The collaboration between the surgeon and anesthesiologist is key for a successful outcome.

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25.2 Preoperative Evaluation and Assessment of Liver Disease Severity

25.2.1 Risk Scores

The liver is fundamental in many physiologic functions and in drug metabolism; furthermore, it synthetizes coagulation factors and plasma proteins. It plays a central role in elimination of endogenous and exogenous substances and in maintaining perioperative homeostasis.

Several studies have investigated the risk of surgery in patients with cirrhosis [4, 5]. These patients with CLD need particular consideration during the preoperative evaluation, because different systems can be affected.

The ESA (European Society of Anesthesiology) and ESC (European Society of Cardiology) classify liver resection and biliary duct surgery as having a high risk for perioperative cardiac events, with an estimated 30-day cardiac event rate of more than 5% [6]. Cardiac evaluation should assess the ability of the system to respond to hemodynamic changes, intraoperative fluid restriction adopted to achieve a low central venous pressure (CVP), vasopressor infusion, and vascular exclusion during liver resection. In the past medical history, it is important to evaluate a previous neoadjuvant chemotherapy, which can reduce functional cardiac reserve, and may be a cause of elevation of CVP; moreover it induces damage to sinusoidal integrity (sinusoidal obstruction syndrome) that eventually increases the risk of intraoperative bleeding [7]. Thus, the cardiologic preoperative evaluation should include a resting echocardiography examination, although exercise or stress echocardiography may be useful to determine the contractile reserve.

The ASA score (American Society of Anesthesiology physical status classification system) is a simple tool adopted for the preoperative evaluation of surgical patients, but it does not consider specific issues of liver surgery and CLD (Table 25.1).

The presence or absence of cirrhosis is the key to understanding and predicting outcomes in liver resections, and this stratification depends on the degree of hepatocellular dysfunction [8]. The Child-Turcotte-Pugh (CTP) and Model of End-stage Liver Disease (MELD) scores are extensively used to stratify liver disease severity. The CTP score emphasizes the sequela of portal hypertension [9]. In particular, the CTP score can be used to predict postoperative mortality: 10% in Child A, 17–30% in Child B, and 60–80% in Child C (Table 25.1).

When a patient with CLD is evaluated for surgery, the MELD score is also widely used [10]; MELD quantifies the degree of liver damage, the degree of portal hypertension and the renal impairment [11], and it is an independent predictor of mortality. When the MELD score is higher than 8, for each additional point there is a 14% increase in mortality in 30–90 days [12] (Table 25.1).

25.2.2 Portal Hypertension

The type and anatomic site of the surgical procedure are important in risk stratification; if the anatomic resection involves three or more segments, as in major

Table 25.1 Scores used to calculate surgical risk in patients with liver disease

Predictive score	Parameters
ASA classification	Class 1: normal healthy person Class 2: mild systemic disease Class 3: severe systemic disease that is not life threatening Class 4: severe systemic disease that is a constant threat to life Class 5: moribund and not expected to survive without the operation Class 6: brain dead patient
CTP score Class A = 5–6 Class B = 7–9 Class C = 10–15	Encephalopathy grade: none, stage 1–2, stage 3–4 (West Haven classification) Ascites level: absent, slight, moderate or severe Total bilirubin mg/dL: <2, 2–3, >3 INR: <1.7, 1.7–2.3, >3
MELD score	Equation: 3.78 × ln (bilirubin mg/dL) + 11.2 × ln (INR) + 9.57 × ln (creatine mg/dL) + 6.43 Patients with renal replacement therapy are assigned a serum creatinine of 4.0 mg/dL

ASA American Society of Anesthesiology; *CTP* Child-Turcotte-Pugh; *MELD* Model of End-stage Liver Disease

hepatectomy, the assessment of perioperative risk and the anesthesiologic approach and support are crucial. Yet, bleeding remains a major complication, and the hepatic veins are a significant source of bleeding.

Hepatic resection for HCC is typically considered in patients without portal hypertension; a hepatic venous pressure gradient (HVPG) <10 mmHg, no venous collaterals on abdominal computed tomography, and no esophageal varices can confirm the absence of portal hypertension. A surrogate marker for the absence of portal hypertension is a platelet count >100,000/μL [13]. A platelet count ≤120,000/μL, creatinine level ≥2 mg/dL, and INR ≥1.1 have been identified as a relevant risk factor.

25.3 General Anesthesia

Anesthesiologic procedures in liver surgery are the same as those for other major operations and the patient's preparation is crucial. The surgical position of the patient plays a fundamental role in the case of laparoscopic or robotic approaches, for the extremely unphysiological position that may be adopted and for accessibility to the surgical field.

Maintenance of the patient's homeothermy during major surgical intervention is necessary and is associated with ERAS, especially in the case of major hepatectomies; hypothermia plays a fundamental role in the coagulation process, which may be further impaired by major liver resection or bleeding. In major liver surgery, intraoperative active warming measures are mandatory, including the application of forced-air convection systems, the adoption of circulating-water mattresses connected to a warming unit and infusion fluid heating systems [3].

Another important aspect is the recruitment and accessibility of venous accesses that must be adequate for the procedure as well as easily manageable and reachable.

A central venous access must be placed to ensure catecholamine infusion, as well as to maintain CVP monitoring.

General anesthesia is mandatory, and the choice of short-acting drugs is preferred.

The decreased functional mass of hepatocytes after liver resection and Pringle maneuver can lead to a reduction in metabolism and hepatic clearance of the drugs. Factors that affect hepatic clearance include blood flow to the liver, the fraction of the drug unbound to plasma proteins, and intrinsic clearance. Moreover, the increase in the free fraction of a drug leads to enhanced effects.

The metabolism of benzodiazepines may be significantly altered, and their effect can be prolonged, so it is questioned if their routine use for preoperative anxiolysis is useful.

General anesthesia can be maintained with volatile anesthetics (isoflurane, sevoflurane or desflurane), intravenous anesthetics (propofol, ketamine, remifentanil), alone or in combination. No significant advantages have been demonstrated when comparing intravenous versus inhaled anesthesia. It is generally suggested to use a low dose of opioids with longer dosing intervals. Cisatracurium as a muscle blockade is often preferred owing to its Hofman elimination. Careful monitoring of the degree of neuromuscular blockade is mandatory.

25.3.1 Vascular and Bleeding Control and Hemodynamic Monitoring

The liver receives around 25% of the cardiac output (CO); 70% is supplied by the portal vein, while the remaining 30% comes from the hepatic artery. This dual perfusion is fundamental for the liver's function and provides a constant oxygen supply. Several surgical techniques can be adopted to reduce blood loss. The Pringle maneuver, consisting of intermittent clamping of the hepatic hilum has been shown to provide protection from damage due to the ischemia-reperfusion injury. The Pringle maneuver is chosen as the main option; during hepatic hilum clamping the afterload increases by 20–30% so the CO could fall up to 10%.

Total vascular exclusion is the most effective vascular control, but this technique induces hemodynamic instability as it is associated with a sharp decrease in venous return and high vascular resistance, requiring aggressive hemodynamic management. Cross-clamping of the inferior vena cava and portal vein result in a 40–60% reduction of venous return and CO, with a compensatory increase in vascular resistances (80%) and heart rate (50%) [14]. In particular conditions, when total vascular exclusion is necessary for the resection of tumor involving the vena cava, a venovenous bypass (usually caval-portal-jugular) must be performed. This technique achieves stable hemodynamics and optimal venous drainage of both kidneys, and it reduces both splanchnic congestion and bleeding. Nowadays, percutaneous cannulation of the femoral vein and internal jugular vein will be performed [15].

Given the above, it is very important to use hemodynamic monitoring for this operation, and a peculiar issue regards monitoring of the CVP [16, 17].

ERAS protocols recommend CVP monitoring for fluid management. A low CVP can be obtained by a limitation of fluid input and nitrate infusion to reach the target, when necessary. A mechanical ventilation strategy with 4–6 mL/kg and PEEP <5 cmH_2O can help to achieve a low CVP. Also important is the invasive and continuous monitoring of the patient's blood pressure; goal-directed therapy allows one to maintain a better organ perfusion and O_2 delivery; goal-directed therapy can also direct and individualize intraoperative fluid management and catecholamine use. CO, stroke volume (SV) and stroke volume variation (SVV) can be used to assess fluid responsiveness and to guide vasopressor administration. SVV is based on heart-lung interactions during mechanical ventilation; respiratory-induced changes in the left ventricular preload and result in cyclic changes in the left ventricular SV and arterial pressure. Today, routine monitoring of CO is available with a non-calibrated pulse contour system (FloTrac, Vigileo) and calibrated pulse contour methods (PICCO2, PULSION Medical Systems, EV1000, LiDCO Rapid, CardioQ-ODM+). Some situations can limit the interpretation of pulse pressure variation and SVV: cardiac arrhythmias, decreased lung compliance and right or left ventricular failure. Further studies are mandatory to establish the impact of laparoscopic surgery, especially the effect of prone positioning and pneumoperitoneum on thoracic compliance. The pulmonary catheter, which remains the gold standard for invasive hemodynamic monitoring in liver transplantation, as it ensures continuous assessment of pulmonary pressure and wedge pressure, does not, under normal circumstances, appear necessary for major liver surgery. The normal range of SVV under controlled ventilation is less than 10–13%. During the resection phase, a SVV of 10–15% can be accepted, while a SVV ≤10% after liver resection represents the target [18, 19].

25.3.2 Acid-Base Issues

During liver resections, some factors can contribute to a metabolic derangement, in particular to lactic acidosis. Serum lactate, a metabolic index of tissue perfusion, is a marker of lower oxygen delivery and is cleared by the hepatocytes. Serum lactate concentration and its clearance seems to be a strong predictor of outcomes following liver resection. Tissue perfusion and hemodynamic optimization must be the target to facilitate lactate restoration. Sodium bicarbonate is not recommended, but it is useful in cases of severe acidosis, renal failure and liver impairment [20].

25.3.3 Coagulation and Blood Products

The liver is the primary synthetic site of coagulation; procoagulant, anticoagulant, fibrinolytic and antifibrinolytic factors are elaborated. Cirrhotic patients are in a particular coagulation balance; deficits in procoagulant factors are contrasted by deficits in anticoagulant proteins synthesized by the liver; when protein C is progressively reduced, this deficiency leads to a thrombophilic state. These patients are

not necessarily predisposed to severe bleeding. The INR is not predictive of bleeding complications, and prophylactic preoperative fresh frozen plasma is not recommended [21].

Thrombocytopenia in cirrhotic patients is due to splenic entrapment, and it indicates the degree of portal hypertension. Moreover, the liver synthetizes thrombopoietin, a function that is impaired in cirrhotic livers. Generally, a platelet count higher than 50,000/μL is adequate to allow clot formation. Prophylactic platelet transfusion is unlikely to be beneficial. Protocol transfusion strategies based on preoperative platelet count and INR are generally ineffective in reducing perioperative bleeding. Moreover, they expose the patient to transfusion-related complications, volume overload, and unexpected thrombosis [21]. Viscoelastic testing (thromboelastography and thromboelastometry) is useful to guide intraoperative transfusions and has been shown to decrease the need for red blood cell and plasma transfusion, especially in cirrhotic patients.

A restrictive strategy of red blood transfusion has been associated with a better outcome: Makuuchi et al. suggested that the cut-off value of hematocrit to start blood transfusion should be 30% intraoperatively and 20% postoperatively [22].

25.4 Pain Control

The complexity, potential adverse events and the derangement of liver function during the first postoperative days, as well as pain control following liver resection, require careful consideration.

Opiates must be used at lower than standard doses; tramadol can be used. Acetaminophen is recommended at a dose not exceeding 2 g daily, even if it is generally contraindicated in cirrhotic patients. Non-steroidal anti-inflammatory drugs can impair renal blood flow in cirrhotic patients and can compromise coagulation.

Thoracic epidural analgesia is controversial in major liver surgery, because of possible derangement in postoperative coagulation and hypotension that may require fluid infusion. As advised in the ERAS guidelines, a multimodal approach is preferred. Postoperative pain control can be ensured by intravenous patient-controlled analgesia [3, 24].

In a multimodal approach, a transversus abdominis plane block and erector spine block can be considered, although a hematoma is likely to form [3, 23].

25.5 Postoperative Course

Major liver resection can be affected by significant complications.

Normally the increasing blood supply to the regenerating liver is associated with increased splanchnic blood flow and CO. If ascites develops in the first 2 days, a hypovolemic state can arise.

A persistent elevation in serum transaminase and phosphatase levels needs attention because it can suggest hepatic ischemia. Another important issue is the urea

level: a low urea level reveals a liver dysfunction. According to the ERAS guidelines, postoperative nutrition and early oral intake are advisable, and supplemental nutrition is indicated in malnourished patients or in prolonged postoperative fasting. Particular attention should be paid to hyperglycemia after major hepatic surgery; it can result from a transient insulin resistance and from a compromised peripheral glucose uptake. There is a close relationship between postoperative insulin sensitivity and intraoperative insulin therapy; moreover, during surgery and the Pringle maneuver there is a rapid change in glucose concentration relating to hepatocyte hypoxia. Furthermore, a high level of lactate during the early postoperative phase can be related to a mix of insulin resistance and ischemia-reperfusion syndrome. On the other hand, in high-risk patients and in large resections, hypoglycemia is possible and requires glucose infusion and periodic control [3].

Renal function can be impaired in postoperative liver resections. Secondary hyperaldosteronism resulting in sodium and water retention with consequent edema can occur. Volume expansion can be obtained, if necessary, with albumin 20% solution. Peptic ulcer prophylaxis with a proton pump inhibitor is recommended [3]. Measurement of blood ammonia can be helpful in cases of encephalopathy and when the diagnosis is unclear.

25.6 Conclusion

A skilled medical team with experience in treating cirrhotic patients is necessary to ensure the best treatment in such a complex surgery. The current total morbidity in hepatic resection remains approximately 15–20%, with a mortality rate of 3–5%. When the size and health of the remnant liver is not enough, post-hepatectomy liver failure may occur. Only a meticulous preoperative evaluation, the right surgical indication, and intraoperative optimization with careful postoperative care can reduce morbidity in this surgical procedure.

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