

# Interventional Oncology



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Edited by

Aaron Rohr, Zachary S. Collins,  
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and E. John Madarang

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# CHAPTER 1

## HISTORICAL INTRODUCTION OF INTERVENTIONAL ONCOLOGY

AARON ROHR MD, MS, JOLEY BEELER MD



Dr. Sven-Ivar Seldinger

Interventional radiology (IR) is a relatively new, constantly evolving specialty. The first successful angiography in the human body was performed in 1923, though early angiography was performed by surgeons via direct cutdown. In 1953, Swedish doctor Sven-Ivar Seldinger (Reprinted from Sven-Ivar Seldinger: Biography and Bibliography, American Journal of Roentgenology, January 1984, Volume 142: 4-4. 10.2213/ajr.142.1.4, Copyright© 1984, copyright owner as specified in the American Journal of Roentgenology) introduced his Seldinger technique, which laid down the foundation of interventional radiology. The first angioplasty was performed by Dr. Charles Dotter in 1964, paving the way for therapeutic interventional radiology procedures (1). Since then, the field of interventional radiology

has evolved rapidly from a diagnostic model to a robust clinical specialty with the ability to perform minimally invasive therapies involving nearly every organ system.

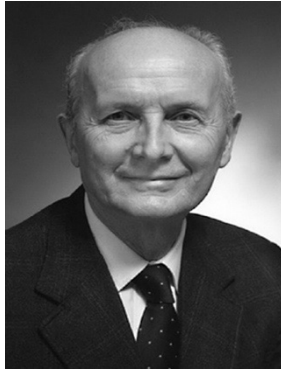
In the mid-1980s, IR continued to garner appreciation as a clinical specialty. As more therapies were discovered, an important subsidiary of IR emerged: interventional oncology.



Dr. Charles Dotter in the angiography suite

Cancer is the second leading cause of death worldwide (2), and there has been a growing demand for faster, safer, and more individualized therapies. Traditional oncologic care, such as surgical resection of tumors, is often not possible due to size/location of tumor burden, and many oncologic patients are not surgical candidates. Interventional oncology, a technology-driven and minimally invasive subspecialty, emerged as a unique solution to these challenges. In addition to oncologic diagnosis via image guided tissue sampling, interventional oncology focuses on treatment and symptom palliation, primarily via transcatheter arterial embolization/therapies and percutaneous ablations. Alongside medical, surgical, and radiation oncology, interventional oncology is now considered the fourth pillar of modern oncology care. Several innovations throughout the second half of the 20<sup>th</sup> century facilitated the advancement of interventional oncology.

## **Transarterial embolization (TAE)**



Dr. Josef Rosch

The groundwork for modern trans-arterial embolization (TAE) of tumors was implemented in the 1960-70s. The first attempt at tumor embolization to induce ischemic tumor necrosis was performed intraoperatively via hepatic artery ligation in 1966 (3), though the effect was transient due to development of collateral vessels. TAE was first attempted by Rosch et al for duodenal bleeding in 1972 (4). In 1974, the first successful TAE for liver tumors was performed (5), and this procedure has been adapted for devascularization of tumors in other organs, including renal cell carcinoma and bone tumors (6, 7).

## **Transarterial chemoembolization (TACE)**

In the late 1970s, intrahepatic arterial injection of chemotherapeutic agents was employed for the treatment of HCC (8, 9). By the early 1980s, the combination of intrahepatic arterial injection of chemotherapy followed by TAE was found to be far more effective than TAE or chemotherapy alone (10), and the foundation for trans-arterial chemoembolization (TACE) was established. This basic approach has continued to undergo advancements to maximize oncologic tumoricidal intervention. More complex chemotherapeutic agents have been employed, individualized to cancer type. In the late 1980s, lipiodol, an iodized oil used as a lymphangiographic dye, was found to remain selectively within the neovascular and extravascular spaces of liver tumors when injected into the hepatic artery (11). Lipiodol began to be used not only as an embolic material but also as a carrier of chemotherapeutic agents. Even more recently, in the early 2000s, TACE has been performed utilizing drug-

eluting beads (DEBs)—non-resorbable PVA-based microspheres that can be loaded with various chemotherapeutic agents (12, 13). In 2002-2003, publication of 2 randomized controlled trials established TACE as standard of care for patients with unresectable HCC (14, 15).

### **Transarterial radioembolization (TARE)**

Trans-arterial radioembolization (TARE) has evolved alongside TACE, utilizing similar arterial embolization techniques with the administration of particles loaded with a radionuclide (yttrium-90) to selectively target high levels of ionizing radiation to tumors within the liver. Embolization with yttrium-90 (90Y) microspheres has been investigated for cancer treatment in animal models since the 1960s (16, 17), demonstrating promise in hepatic applications (18). Human trials followed, with TARE demonstrating safety and efficacy in the treatment of liver metastases and unresectable HCC in the 1990s (19-21). The two currently available radioembolization delivery methods, Y90 incorporated into a glass matrix (22) and 90Y-doped resin (23), were approved by the FDA in 1999 and 2002, respectively.

### **Thermal Ablations**

Image-guided percutaneous tumor ablation focally destroys tumors by inducing irreversible cellular injury by the direct application of chemical (i.e., nonenergy) or thermal/nonthermal (i.e., energy-based) therapies (24). Early tumor ablations utilized percutaneous chemical injection to treat hepatic tumors. Ethanol was the first ablation agent used in the 1980s (25, 26), and shortly after acetic acid was utilized with increased efficacy (27). However, chemical ablation therapy is limited by the difficulty in achieving uniform diffusion throughout a larger tumor volume (28).

Energy-based, thermal ablations were then introduced, with the ability to destroy tumors by increasing or decreasing temperatures to induce irreversible cellular injury. There are three main modalities for thermal ablation—radiofrequency ablation, microwave ablation, and cryoablation—with the modality selected based on tumor size, location, and operator preference.

Radiofrequency length sound waves have long been known to heat tissue, first described in 1891 and leading to the creation of the intraoperative electrocautery Bovie knife in 1928 (29). Initial utilization of radiofrequency for percutaneous ablation of hepatic tumor in animal models was described

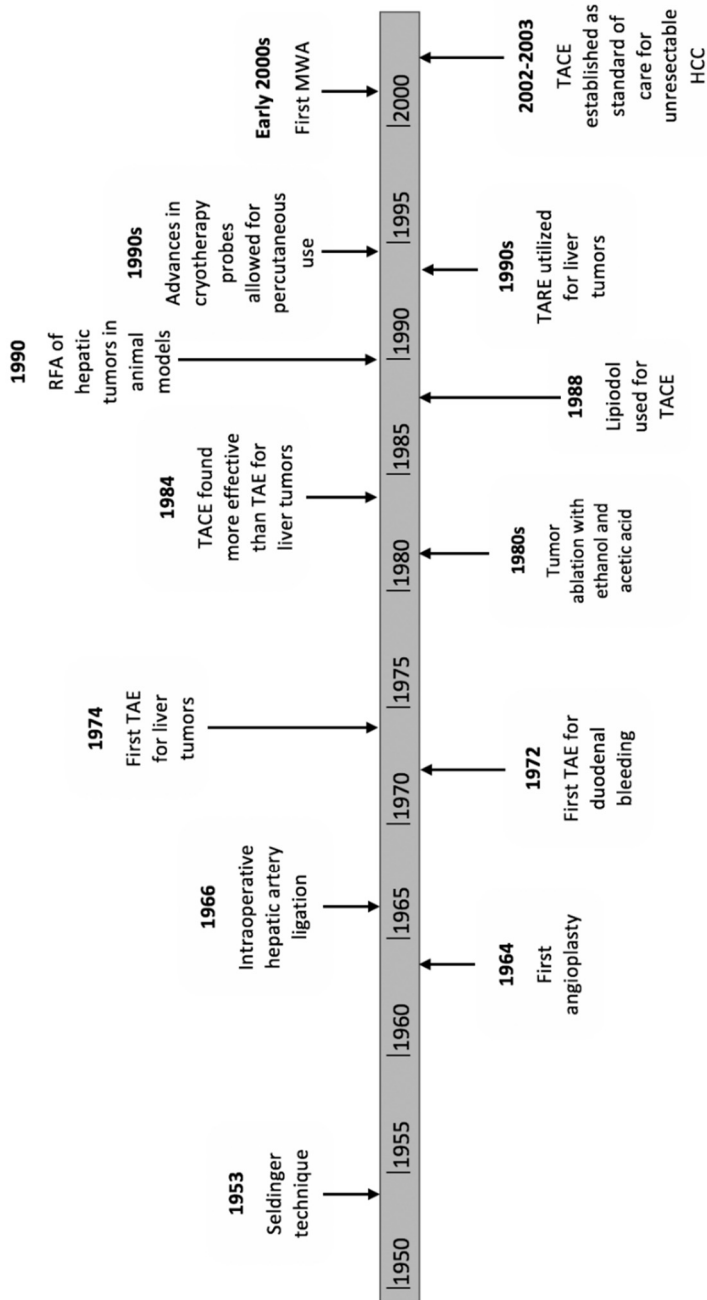
using a modified Bovie knife with an insulated needle in 1990 (30, 31). Radiofrequency ablation (RFA) was trialed in humans in the 1990s and was shown to be superior to chemical ablation with respect to local recurrence and overall survival in hepatocellular carcinoma (32). RFA has been generalized to tumors in other locations such as renal, lung, bone (33-35), and more recently in thyroid tumors (36).

Microwave ablation (MWA) utilizes electromagnetic energy at specific frequencies to heat tissue. The evolution of MWA in the early 2000s has permitted several advantages over RFA, including more efficient heating, better penetration through tissue with higher impedance, and less susceptibility to the heat sink effect (37, 38).

Cryotherapy induces cell death by disrupting cellular membranes through alternately freezing and thawing, though early cryotherapy systems were large and limited to open operative use (39). Technological advances in the 1990s resulted in smaller cryoprobes and the ability to use cryotherapy percutaneously, which have been demonstrated safe and effective for use in kidney and lung tumors (40, 41).

Energy-based, non-thermal techniques, such as irreversible electroporation and histotripsy, are the newest developments in ablation and will be discussed in the new innovations chapter.

Collectively, these advancements have established interventional oncology as an essential pillar within oncologic care over time (Fig. 1). While the benefits of interventional oncology are many—shorter recovery, treatments on an outpatient basis freeing up hospital beds, intra-arterial chemotherapy increases potency and removes harsh systemic side effects—oncology is a field that relies heavily on data. To that end, mounting evidence and major clinical trials have demonstrated the efficacy of interventional oncology treatment and even incorporated interventional therapies into accepted clinical guidelines. The ensuing chapters are intended to help illuminate, in detail, current therapies provided by IR for oncologic treatment.



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## CHAPTER 2

# OVERVIEW OF PRIMARY HEPATIC MALIGNANCY

ADAM ALLI MD, LARRY MATHIAS MD,  
ADRIEN CAYE MSIV

At the time of writing, the World Health Organization's (WHO) international agency for research on cancer currently lists primary hepatic malignancy as the sixth most common cancer in the world amongst all age groups. However, primary liver cancer is noted to be the third most deadly malignancy behind lung and colorectal cancer.<sup>1</sup> Within the United States (US), primary hepatic malignancy falls off the list of the ten most common malignancies. Despite this it continues to be the sixth most common cause of mortality related to malignancy with death rates increasing significantly for both men and women.<sup>2</sup> While data is not available based on Tumor, Metastases, and Nodal (TMN) staging the American Cancer Society (ACS) estimates the 5-year mortality rate at 20% for all stages of liver cancer.<sup>3</sup>

Traditionally, primary liver cancer was predominantly attributed with either alcoholic or viral hepatitis, with hepatitis B (HBV) and hepatitis C (HCV) as the most likely infectious etiologies. However, the steadily rising rates of morbid obesity and development of effective treatments for viral hepatitis have allowed for a shift in the pendulum with primary liver cancer now more frequently directly attributable to non-alcoholic fatty liver disease (NAFLD). In many developed nations such as the US, the increasing incidence of non-alcoholic steatohepatitis (NASH) is noted to coincide with the rising rates of hepatocellular carcinoma (HCC). There is now direct evidence correlating NASH as the most rapidly growing cause of HCC amongst liver transplant patients.<sup>4</sup> Overall, both increasing rates of primary hepatic carcinoma alongside an overall poor prognosis have made primary hepatic malignancy the fastest growing cause of cancer related death within the US.<sup>4</sup>

While certainly variants of primary hepatic malignancy do exist (e.g., mixed hepatocholangiocarcinoma), the two most common types of primary liver cancer, hepatocellular carcinoma (HCC), and intrahepatic cholangiocarcinoma (ICC) will be the focus of this discussion.

## **Hepatocellular Carcinoma**

Most malignancies are noted to arise in setting of pathologically normal tissues. However, HCC is somewhat novel in that it often arises in the setting of chronic hepatic parenchyma change. Most causes of HCC result in chronic hepatic inflammation, which overtime leads to the development of hepatic fibrosis and cirrhosis. This milieu creates an environment ideal for hepatocarcinogenesis, which is comprised of aberrant hepatocyte regeneration. Often considered the first step in hepatocarcinogenesis, dysplastic foci are microscopic foci of hepatocytes with cytologic changes measuring less than 1.0 mm pathologically.<sup>5,6</sup> As foci begin to accumulate and chronic inflammatory change progresses, the gates begin to open for the development of nodularity, which should be considered as a spectrum rather than a continuum. The spectrum of hepatic nodularity begins with regenerative nodularity, leading to dysplastic nodularity and ultimately culminating in the development of HCC; with shifts in hepatocyte function and blood supply/neovascularity central to this pathway.<sup>6</sup>

Regenerative nodules, also called siderotic or iron-laden nodules retain their normal hepatocyte function.<sup>7</sup> However, as dysplasia is allowed to continue within a background of chronic hepatic injury, regenerative nodularity is ultimately allowed to progress to dysplastic nodularity which are the true premalignant lesions. Dysplastic nodules can be further differentiated into low grade or high-grade nodules, with the presence of cytologic atypia as the defining factor of high-grade nodularity.<sup>8</sup> Additionally, high-grade nodules contribute the greatest risk to the development of HCC. Ultimately, the defining point of what separates dysplastic nodularity from true HCC is the presence of stromal invasion pathologically, which when present allows for a confident diagnosis of HCC. It should be noted that while this pathway is thought of as a spectrum, histologically defined steps could be skipped.

The second prong of the hepatocarcinogenic pathway is neovascularity and shift in the physiologically normal hepatocyte blood supply.<sup>5,9</sup> It is widely accepted that normal hepatocyte blood supply predominantly arises from the portal venous system rather than the hepatic arteries.<sup>10</sup> Overall, this can be generalized as portal venous supply accounting for approximately 2/3<sup>rd</sup> of blood supply to the liver, with the hepatic arteries supplying the additional

1/3<sup>rd</sup>. However, as carcinogenesis progresses, atypical hepatocytes induce neovascularity and angiogenesis resulting in a shift from portal venous, to predominantly hepatic arterial supply. Due to the marked increase in neovascular arterial supply related to angiogenesis, early dysplastic nodules actually are theorized to have less overall blood supply related to surrounding hepatic parenchyma. As neovascular blood supply becomes more predominant, the physiologic hepatic arteries are observed to degenerate initially accounting for the overall drop in blood supply. This is then thought to allow for up-regulation of vascular endothelial growth factor (VEGF) which paves the way for even further angiogenesis resulting in the loss of the portal veins. As a reduction of portal venous supply occurs, full-scale neovascularity predominates resulting in dominant inflow to the aberrant hepatocytes to arise from the neovascularized arteries. Thus, overt HCC does not have vascular supply arising from portal veins (paired blood supply), but rather is solely supplied only by abnormal hepatic arteries (unpaired blood supply).<sup>10</sup>

HCC is rare in patients without a history of liver disease with 80-90% of cases arising in patients with a history of hepatic cirrhosis.<sup>11</sup> The most common risk factors for the development of HCC include NASH/NAFLD, viral hepatitis (most commonly HBV and HCV) and alcohol. Exposure to foods containing aflatoxin and exposure to chemical carcinogens also noted to contribute to the risk of HCC development. When taken separately, each risk factor certainly contributes an increased risk for the development of HCC with obesity and NAFLD independently conferring a 2.1 times increased risk for the development of HCC.<sup>12</sup> However, when multiple risk factors are encountered in combination, as is a common occurrence, a synergistic effect can be noted. Take for example the synergistic effect of heavy alcohol intake in patients with untreated HCV, which essentially doubles the risk for the development of HCC.<sup>11</sup>

## **Screening for Hepatocellular Carcinoma**

The prognosis of HCC largely depends upon tumor stage at diagnosis. As previously discussed, if HCC is encountered at a late and/or progressed stage it is commonly associated with a dismal prognosis. Additionally, there is a propensity of patients with HCC to not present with symptoms beyond those associated with chronic or end stage liver disease until it has become incurable. Furthermore, if caught early, life-prolonging and potentially curable treatments may be offered to patients. Given the propensity of HCC to arise in patients with high risk factors, certain actions are commonly both

recommended and implemented in the form of screening for HCC to allow for both early detection and treatment. The recommendation for screening is based largely a study demonstrating mortality reduction of 37% when high risk patients were screened every six months with a combination of alpha-fetoprotein analysis and dedicated liver ultrasound.<sup>11</sup> High-risk groups are currently categorized as: patients with cirrhosis (Child-Pugh Class A and B or awaiting liver transplant in Class C); patients with chronic HCV and advanced hepatic fibrosis; patients with porphyria; non-cirrhotic patients with HBV and High-risk groups are currently categorized as: patients with cirrhosis (Child-Pugh Class A and B or awaiting liver transplant in Class C); patients with chronic HCV and advanced hepatic fibrosis; patients with porphyria; non-cirrhotic patients with HBV and active hepatitis (transaminitis); patients with a family history of HCC; those of African descent, African Americans, and Asian males over 40 and females over 50 years old.<sup>12,13</sup> Interestingly, there is no current recommendation for screening patients with NASH until the progression to cirrhosis. However, the caveat to these recommendations is that surveillance is currently limited to high-risk patients who would be candidates for treatment if cancer were found at an early stage.

When screening is initiated in high-risk patients, at its most basic it is comprised of limited abdominal ultrasound focused at the liver every 6 months. While ultrasound alone is the most basic recommendation (sensitivity in detecting early stage HCC = 78%), there is evidence to support that the addition of alpha-fetoprotein (AFP) to a bi-annual screening regiment which has been shown to increase sensitivity to 97%.<sup>14,15</sup> Additionally, some practices opt to perform CT or MRI every 6 months as a form of screening in patients given the low sensitivity of HCC detection in ultrasound alone.<sup>14</sup> This is even more prevalent in patients whom have a body habitus or fatty hepatic parenchyma consistency, which would prevent adequate visualization of small suspicious lesions by ultrasound. However, current recommendations are that cross sectional imaging, although more sensitive in the detection of early stage HCC should not routinely be pursued. Furthermore contrast enhanced ultrasound as a screening modality remains under investigation; and AFP analysis alone as a method of screening is not recommended as elevated AFP levels may be caused by various factors, including cases of viral hepatitis.<sup>14</sup>

When a hepatic nodule is ultimately detected by screening, the possibility of HCC should always be questioned and further work-up immediately initiated as indicated.<sup>9</sup> In cases when the nodule measures less than 1.0 cm, a repeat ultrasound in 3 months should be obtained to evaluate for interval

growth. If the nodule remains stable, follow up sonography should then be repeated in three months for further assessment. If stability can be demonstrated over two years, regular 6-month follow up screening can then be resumed. However, in a situation where a nodule either enlarges or is initially discovered measuring greater than 1.0 cm, it is considered suspicious for HCC and immediate work-up with a CT or MRI utilizing a liver mass protocol (dynamic phase contrast enhancement) should then ensue.<sup>9</sup>

When a screening test shows signs promising for the diagnosis of HCC, further workup with dynamic contrast enhanced imaging should be pursued.<sup>16, 17</sup> Utilizing extravascular contrast agents, changes in the aforementioned physiologic arterial flow occurring in HCC as opposed to the surrounding physiological normal hepatic parenchyma allows for HCC to be diagnosed based solely upon imaging characteristics. After pre-contrast enhanced thin slice CT or T1-weighted MR images through the abdomen centered upon the liver, post-contrast enhanced T1-weighted images or thin slice CT image acquisition is repeated in conjunction with contrast bolus timing to ensure portal venous phase, and delayed phase images are then obtained. Commonly iodinated contrast is administered at a rate of 4-6 mL/second for CT, whereas gadolinium agents are administered at 2 mL/second for MRI. A saline chaser of the intravenous tubing/line is then performed to ensure residual contrast is cleared. Ultimately, the hallmark features of HCC include hyperenhancement (“wash-in”) on arterial phase imaging, followed by “wash-out” on portal venous or delayed phase images.

## **Imaging of Hepatocellular Carcinoma**

Characteristically, and as would be expected, when utilizing extracellular contrast agents HCC preferentially enhances on arterial phases of image acquisition which is characterized by peak contrast bolus within the anatomic hepatic arteries. Of note, arterial phase can be further divided into early and late hepatic arterial phase, the later of which is characterized by the presence of contrast within both the hepatic arteries and the hepatic veins.<sup>18, 19</sup> Conversely, while the hepatic arteries will be opacified in the early hepatic arterial phase, contrast will not yet have reached the hepatic veins. The importance of this difference becomes apparent when considering in the early hepatic arterial phase, hypervascular HCC may be subtle or missed altogether. Imaging should therefore be performed utilizing contrast bolus tracking given the importance of imaging the liver at late hepatic



arterial phase, with many centers currently omitting the acquisition of early hepatic arterial phase altogether. The physiology of HCC enhancement on arterial phase occurs on imaging due to HCC's unpaired blood supply from aberrant hepatic arteries as previously discussed. Additionally, only further contributing to its apparent arterial enhancement is the dilution of contrast medium within the surrounding hepatic parenchyma due to the preferential vascular supply to hepatic parenchyma by the portal venous supply, which will have a low contrast burden by design. Therefore, by convention, progressed HCC should be observed to hyperenhance on arterial images; whereas both regenerative and dysplastic nodules, as well as early stage HCC may demonstrate a hypo-enhancing or iso-enhancing appearance given the paired hepatic arterial and portal venous blood supply at this stage of disease.

While hyper-enhancement is characteristic of HCC, other entities may demonstrate a similar appearance. These include small benign flash-filling hemangiomas, focal nodular hyperplasia, atypical cases of focal or confluent fibrosis, and areas of atypical regenerative or dysplastic nodularity.<sup>16,17</sup> Alterations in enhancement characteristics visible only during arterial phase images caused by the duality of hepatic blood supply can also be encountered, with transient hepatic attenuation differences (THAD) and transient hepatic intensity differences (THID) commonly encountered in CT and MRI respectively.<sup>18,19</sup> While these entities may be seen in patients without underlying hepatic dysfunction, these findings may also be noted in patients with cirrhosis or chronic hepatitis where a large majority of wedge shaped and sub-capsular foci of enhancement measuring less than 2.0 cm are typically non-neoplastic. Additionally, non-hepatocellular neoplasms such as hypervascular metastases and small ICCs can also demonstrate a similar appearance of brisk arterial enhancement.<sup>19</sup> Due to the ability of different hepatic lesions to demonstrate similar appearance, care should be taken to compare any encountered suspicious lesion seen on an arterial phase sequence to their delayed contrast enhanced counterparts.

Following the evaluation of arterial phase imaging, attention should then be turned to portal venous phase which is characterized by peak contrast bolus within the portal veins, and commonly occurs at 60-70 seconds status post initial bolus administration; whereas delayed phase images are obtained arbitrarily at 3-5 minutes.<sup>16, 17</sup> These two phases are critical to evaluate in order to detect key features diagnostic of HCC. The first and most likely encountered imaging feature is loss of mass attenuation on CT, or signal intensity on MRI, when compared with the surrounding normal hepatic

parenchyma. This finding is colloquially referred to as “wash-out” and is defined as reduction in enhancement relative to surrounding hepatic parenchyma from an arterial to portal venous/delayed phase. The mechanism of this finding is poorly understood, with several currently suggested etiologies including increased early venous drainage of contrast from the tumor (coined true wash-out), progressive enhancement of background hepatic parenchyma, reduced portal venous vascular supply, lesion hypercellularity with corresponding reduction in extracellular volume, and intrinsic hypoattenuation/hypointensity. This “washout” may be more conspicuous in the delayed compared with the portal venous phase, and in some lesions, “washout” may be depicted only in the delayed phase.<sup>23, 24</sup> The rate at which the tumor appears to washout may also be important as certain studies suggest the presence of washout on portal venous phase imaging likely predicts a higher grade of HCC and higher grade of microvascular invasion than washout only encountered on delayed phase images.<sup>25-27</sup>

Similar to the finding of arterial phase hyperenhancement, the presence of washout alone is not specific for HCC as this appearance may also be encountered within cirrhotic and dysplastic nodularity.<sup>16,17</sup> Furthermore, washout may also be encountered in areas of hepatic parenchymal distortion and enhancing fibrosis thus contributing to the perception of washout.<sup>28</sup> Therefore, given the possible appearance of washout within entities other than HCC, it has been suggested that washout alone should not be utilized in the diagnosis of HCC unless additional findings are present.

Another imaging feature of HCC is the presence of an enhancing capsule surrounding the hepatic mass on portal, and delayed phase images. This appears as a smooth rim of peripheral hyperenhancement with the degree of enhancement continuously increasing after the administration of contrast.<sup>16, 17</sup> This finding may be more likely to be encountered on delayed phase images rather than portal venous phase. The cause for this progressive enhancement has been attributed to slow flow within the vessels supplying the capsule, as well as contrast retention within the extravascular tissues of the capsule itself.<sup>17, 22</sup> The significance of this finding is realized when considering that capsules are not present in regenerative or dysplastic nodules, or even early stage HCC; rather, when a capsule is present it is highly suggestive of an advanced HCC. However, while the presence of an enhancing capsule on imaging certainly correlates with the presence of a capsule on pathologic analysis, there is evidence to suggest that only one out of four nodules with capsules detected on imaging will possess a true capsule at pathologic analysis and in some instances the radiographic

capsule actually corresponds with a pseudocapsule. Regardless, because precursor lesions (cirrhotic and dysplastic nodules) do not demonstrate progressive peripheral enhancement, the presence of a progressively enhancing capsule on imaging has been shown to be a strong predictor of, and hallmark for the presence of HCC. Some investigators have discovered that the presence of a progressively enhancing capsule on imaging is incredibly valuable in that it permits the diagnosis of HCC in the absence of contrast washout.<sup>22</sup>

The integrity of a capsule associated with HCC should be carefully inspected when encountered, as findings of capsule disruption are highly suggestive of tumor infiltration.<sup>17</sup> This finding may imply the presence of microinvasion into the surrounding hepatic parenchyma, or possibly even macroinvasion. While microinvasion may only be diagnosed pathologically, imaging features specific for the presence of macroinvasion include direct extension of tumor into adjacent vessel. This is common occurrence and imaging feature of HCC and portends a poor prognosis. This manifests as expansile thrombus within an occluded hepatic or portal vein immediately adjacent HCC, which many times can be visualized as a tangle of enhancing neovessels within the vein. Expansion of a thrombosed main portal vein to 23 mm or more is also highly suggestive of intraluminal thrombus, however this finding should be used with caution as bland thrombus may also result in portal venous expansion.<sup>17</sup>

One of the unique features of HCC is its ability to be diagnosed with a degree of certainty by imaging alone. While each aforementioned unique feature may be associated with other entities (other than the presence of a progressive enhancing capsule) and thus may not be suggestive of HCC in isolation; when collectively encountered are diagnostic of HCC with near 100% specificity.<sup>17</sup> When a lesion is visualized demonstrating brisk enhancement on arterial phase, “wash-out” on either portal venous or delayed phase and is associated with a progressively enhancing capsule; the diagnosis of HCC can be confidently made. However, while these imaging findings together are highly specific for the presence of HCC, they have relatively low sensitivity given that they are often only seen together in large advanced HCC and not in early stage HCC, progressed HCC small in size and infiltrative HCC. Therefore ancillary features present on MRI and CT to a lesser extent, are visualized alongside hallmark feature can help to increase the certainty of and can further assist in the characterization of nodules. These can be further divided into features supportive of the diagnosis of HCC, versus supportive of the presence of malignancy. Imaging features suggestive of HCC include the presence of intralesional

fat, corona enhancement (transient zone or rim, “corona” of enhancement around a hypervascular HCC when then fades into background becoming isointense on subsequent phases), nodule-in-nodule appearance (the presence of a nodule within a larger mass) and mosaic architecture (mass of randomly distributed internal nodules or compartments differing in enhancement). Conversely, the presence of mild to moderately increased signal intensity of T2 weighted images, and restricted diffusion are suggestive of the presence of malignancy, but not specific for HCC. Despite low specificity, these sequences may be utilized to increase the conspicuity of intrahepatic lesions and thus contribute to the increased sensitivity in the diagnosis of HCC<sup>17</sup>.

While the discussion to this point has been geared towards extracellular contrast agents in both CT and MRI, contrast geared towards the evaluation of tumor vascularity and hepatocyte function in the form of hepatobiliary is also available which targets organo anion transporters (OATP).<sup>17</sup> Two agents currently predominate the market, Multihance (Bracco Diagnostics, Princeton, NJ) and Primovist/Eovist (Bayer Healthcare, Princeton, NJ); and while the exact cause of contrast accumulation is incompletely understood, the predominant interaction depends upon the degree of OATP expression.<sup>29</sup> When OATP expression is normal, hepatobiliary contrast agents are taken up allowing normal hepatocytes to appear isointense or hyperintense on hepatobiliary phase of imaging.<sup>30,31</sup> As hepatocarcinogenesis progresses, OATP expression decreases which in turn results in a decline in hepatobiliary contrast accumulation and expression. As hepatocarcinogenesis progresses, suspicious liver lesions or nodules demonstrating hypointensity on hepatobiliary phase should be considered suspicious due to the underexpression of OATP. Conversely, most cirrhotic nodules, low grade dysplastic nodules, and some high-grade dysplastic nodules are iso- to hyperintense due to preserved expression of OATP. Another benefit of hepatobiliary contrast agents is to further delineate vascular lesions, which demonstrate strong hyperenhancement on arterial phase images, but are not associated with any significant washout on delayed images. In these lesions there should be preservation of signal intensity on hepatobiliary phase given the preservation of OATP in these lesions thus helping to further differentiate these “pseudolesions” from true arterially enhancing HCC.<sup>32,33</sup> Understanding the interplay between lesion intensity on hepatobiliary phase related to OATP expression allows one to exploit this interaction for diagnostic benefit and further diagnose high-risk premalignant nodules and HCC with confidence.

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

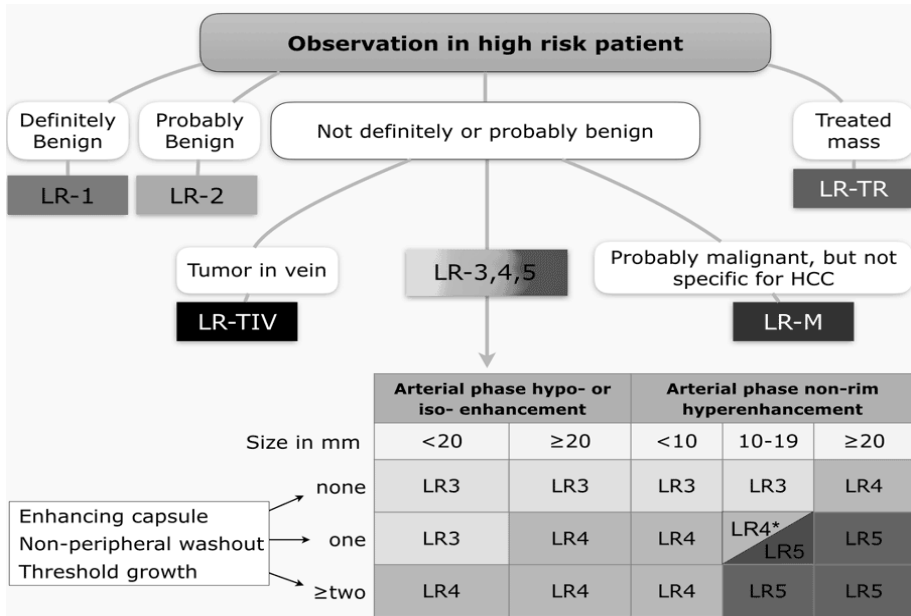


Figure 1.

As discussed, a wide spectrum of liver lesions (observation per LI-RADS terminology) may be encountered, all of which can demonstrate a breadth of findings on imaging. Given the variability of both imaging findings and style of reporting and interpretation amongst radiologists, the American College of Radiology (ACR) in conjunction with the American Association for the Study of Liver Disease (AASLD) developed LI-RADS (Figure 1).<sup>42</sup> While the first iteration was 2006, it has subsequently undergone multiple revisions and at the time of writing is in its 5<sup>th</sup> version with the 2018 adaption as the most recent publication. While the purpose of this chapter is not to delve into the depths of the LI-RADS manual, touching upon the algorithm is of the utmost importance given its propensity to guide both diagnosis and treatment of suspicious liver lesions in high-risk patients.

The LI-RADS reporting system grades liver lesions in high-risk patients on a scale from 1-5, with LI-RADS 1 encompassing benign lesions and category 5 being characterized as HCC. The two categories of most importance within this spectrum in regards to the treatment of HCC are categories 4 and

5; with approximately 80% of LI-RADS 4 observations being HCC, and 98% of LI-RADS 5 observations being HCC. Of important note, all LI-RADS 5 lesions are HCC; however, not all HCC can be categorized as LI-RADS 5 due to the variability of HCC on imaging. The goal is for LI-RADS 5 to have a strong positive predictive value in the diagnosis of HCC and therefore only observations meeting strict criteria to be labeled as such. This strong positive predictive value allows healthcare professionals to often forego biopsy and proceed straight to treatment in the case of LI-RADS 5 lesions, and LI-RADS 4 lesions to a lesser extent after multidisciplinary discussion. While multidisciplinary discussion is recommended for LI-RADS 5 observations as well, this is for the purpose of guiding treatment. Finally, while a LI-RADS 5 observation does not require biopsy prior to treatment, it may often times be performed for the purpose of molecular characterization or for clinical trial requirement.<sup>121</sup>

Additional LI-RADS categories worth mentioning include LI-RADS TIV (tumor in vein), and LI-RADS M (probably or definitely malignant, not HCC specific). LI-RADS M is defined as high probability or 100% certainty of the presence of malignancy, but in the absence of features of HCC. Imaging features consistent with LI-RADS M include: the presence of a targetoid mass with dynamic enhancement, restricted diffusion or increased signal intensity on post-arterial phase sequences; or the presence of a non-targetoid mass without tumor expansion into a vein (indicative of LI-RADS LIV - discussed below), and associated with an infiltrative appearance, restricted diffusion, necrosis or ischemia, or other features suggestive of malignancy. LI-RADS TIV should only be reported when there is 100% certainty that macroinvasion of HCC has occurred and enhancing soft tissue is present within vein, regardless of visualization of a parenchymal mass. When this finding is present LI-RADS TIV can be reported with certainty. However, if there are only findings suggestive of tumor in vein such as an occluded vein next to a parenchymal mass, ill-defined venous walls, presence of intravenous restricted diffusion, or heterogeneous enhancement not related to artifact; caution should be utilized to not over diagnose LI-RADS TIV.<sup>121</sup>

If there ever exists any uncertainty about the presence of HCC (LI-RADS 5), malignancy (LI-RADS M) or tumor in vein (LI-RADS LIV); than the LI-RADS category should be downgraded to preserve the high positive predictive value. Take into consideration a hepatic observation meeting many, but not all of the criteria necessary to diagnose a LI-RADS 5 observation. If uncertainty regarding the presence of HCC is present or additional differential considerations are possible, the LI-RADS 4