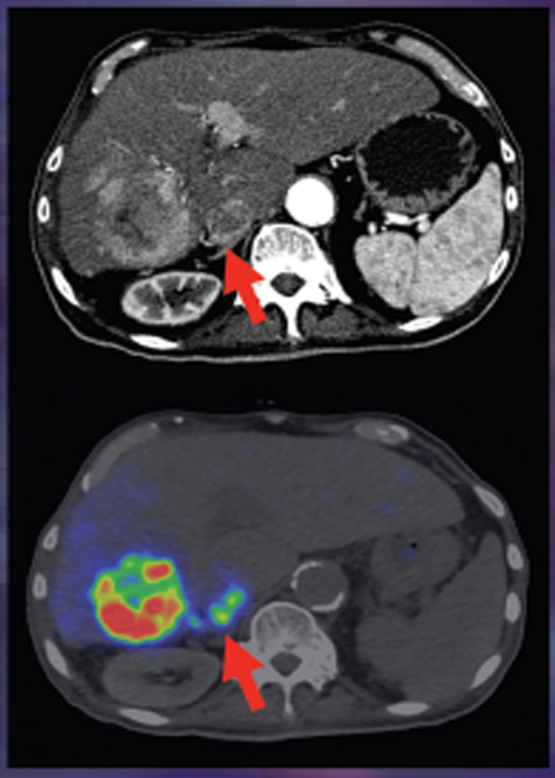
IMAGING IN MEDICAL DIAGNOSIS AND THERAPY

Andrew Karellas and Bruce R. Thomadsen, Series Editors

Handbook of Radioembolization

Physics, Biology, Nuclear Medicine, and Imaging



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Handbook of Radioembolization

Physics, Biology, Nuclear Medicine, and Imaging

Edited by
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Dedication

To Alina…

Contents

Series preface

The advances in the science and technology of medical imaging and radiation therapy are more profound and rapid than ever before since their inception over a century ago. Further, these disciplines are increasingly cross-linked as imaging methods become more widely used to plan, guide, monitor, and assess treatments in radiation therapy. Today, the technologies of medical imaging and radiation therapy are so complex and so computer-driven that it is difficult for the persons (physicians and technologists) responsible for their clinical use to know exactly what is happening at the point of care, when a patient is being examined or treated. The persons best equipped to understand the technologies and their applications are medical physicists, and these individuals are assuming greater responsibilities in the clinical arena to ensure that what is intended for the patient is actually delivered in a safe and effective manner.

The growing responsibilities of medical physicists in the clinical arenas of medical imaging and radiation therapy are not without their challenges, however. Most medical physicists are knowledgeable in either radiation therapy or medical imaging and expert in one or a small number of areas within their discipline. They sustain their expertise in these areas by reading scientific articles and attending scientific talks at meetings. In contrast, their responsibilities increasingly extend beyond their specific areas of expertise. To meet these responsibilities, medical physicists periodically must refresh their knowledge of advances in medical imaging or radiation therapy, and they must be prepared to function at the intersection of these two fields. How to accomplish these objectives is a challenge.

At the 2007 annual meeting of the American Association of Physicists in Medicine in Minneapolis, this challenge was the topic of conversation during a lunch hosted by Taylor & Francis Publishers and involving a group of senior medical physicists (Arthur L. Boyer, Joseph O. Deasy, C.-M. Charlie Ma, Todd A. Pawlicki, Ervin B. Podgorsak, Elke Reitzel, Anthony B. Wolbarst, and Ellen D. Yorke). The conclusion of this discussion was that a book series should be launched under the Taylor & Francis banner, with each volume in the series addressing a rapidly advancing area of medical imaging or radiation therapy of importance to medical physicists. The aim would be for each volume to provide medical physicists with the information needed to understand technologies driving a rapid advance and their applications to safe and effective delivery of patient care.

Each volume in the series is edited by one or more individuals with recognized expertise in the technological area encompassed by the book. The editors are responsible for selecting the authors of individual chapters and ensuring that the chapters are comprehensive and intelligible to someone without such expertise. The enthusiasm of volume editors and chapter authors has been gratifying and reinforces the conclusion of the Minneapolis luncheon that this series of books addresses a major need of medical physicists.

Imaging in Medical Diagnosis and Therapy would not have been possible without the encouragement and support of the series manager, Luna Han, of Taylor & Francis Publishers. The editors and authors, and most of all I, are indebted to her steady guidance of the entire project.

William Hendee
Founding Series Editor
Rochester, Minnesota

Preface

Primary and metastatic liver cancers are the fifth most commonly diagnosed cancer and the second most common cause of cancer-related mortality in men worldwide, with slightly lower rates in women. Environmental factors based on geographic location carry a profound impact in primary liver cancers. In some developing countries, liver cancer is the most common form of cancer with higher rates of incidence secondary to viral hepatitis or exposure to aflatoxin B1. Unfortunately, liver cancer often carries a poor prognosis as surgical options are commonly limited by multifocality combined with other factors, such as underlying liver disease.

External beam radiation therapy (EBRT) is often a preferred treatment modality for many surgically unresectable cancers, especially in concert with chemotherapy. However, for many years, its utility in the treatment of primary and secondary liver cancer has been limited by the high radiosensitivity of normal liver tissue. As is discussed in the chapters of this book, 30–40 Gy represents a maximum tolerable dose to normal liver from EBRT, above which radiation-induced liver disease and liver failure are potentially fatal complications. This fact has completely eliminated the use of conventional whole-liver EBRT as a potential treatment option for liver cancer. Newer advancements in image-guided intensity modulated radiation therapy are greatly improving the prospects of EBRT as a viable treatment modality; however, the high radiosensitivity of normal liver tissue, worsened by underlying liver disease in many patients, remains a challenge.

Despite technological advancements in EBRT, the most common form of radiation therapy for the treatment of primary and metastatic liver cancer is radioembolization, sometimes referred to as selective internal radiation therapy or SIRT. Radioembolization is a brachytherapy treatment delivered as part of a minimally invasive fluoroscopically guided intervention. In this procedure, millions of microscopic embolic spheres containing calibrated activities of either yttrium-90 (^{90}Y) or holmium-166 (^{166}Ho) are infused into the right or left hepatic artery where they embolize both tumor tissue and, to some extent, normal liver tissue. Because the hepatic artery primarily perfuses the tumor, greater concentrations of radioactive microspheres are trapped in the tumor compared to the normal liver. The relative difference in microsphere concentration in tumor compared to normal liver tissue following a successful radioembolization therapy can range anywhere from a factor of 2 to a factor of 15, providing the potential for sparing of healthy liver tissue compared to conventional EBRT. However, there are other advantages. While a 40 Gy absorbed dose to normal liver tissue from EBRT could potentially cause liver failure, it is well below the toxic threshold for a single-session treatment using radioembolization, which is greater than 80 Gy. This unique paradox is due to differences in irradiated tumor volume, dose rate, and other factors, such as the heterogeneous microscopic dose distribution that results from radioembolization. This microscopic absorbed dose heterogeneity, combined with the regenerative propensity of healthy liver tissue, vastly reduces the toxicity of radioembolization and is a hallmark of the technique's utility.

Given the clear inherent benefits of the radioembolization treatment, its use as a treatment option for primary and metastatic liver cancer is advancing extremely rapidly. While the methodology behind radioembolization has been relatively stable over the past 10 years, it is our belief that this treatment is on the cusp of some rapid changes

that will increase both its efficacy and the breadth of its clinical use. Our prediction is based on the following:

- Commercial manufacturers of ^{90}Y radioembolization products are rapidly seeking approval for new hepatic treatment indications both in the United States and worldwide. Over the next several years, on-label indications may match what many leading institutions are currently performing regularly as off-label treatment with radioembolization.
- New techniques in posttreatment quantitative imaging will vastly expand the field's understanding of the dose–response relationships associated with radioembolization. These include the following: ^{90}Y positron emission tomography/computed tomography (PET/CT), quantitative bremsstrahlung single-photon emission computed tomography (SPECT)/CT, and increasing use of directly imageable ^{166}Ho microspheres. Worldwide clinical trials are currently being planned to collect the data necessary to determine these dose–response relationships using advanced imaging techniques.
- Alternatives to ^{90}Y radioembolization, such as ^{166}Ho radioembolization, are currently under clinical use in some parts of the world. Alternative isotopes such as this provide certain advantages over ^{90}Y, including effective imaging with magnetic resonance imaging (MRI) and SPECT, and will undoubtedly lead to expansion of the field of radioembolization in the near future.
- Extrahepatic usage of radioembolization is currently being investigated in clinical trials, including use for treatment of primary renal cell carcinoma.
- Multiple clinical trials are underway to assess the utility of adjuvant ^{90}Y radioembolization with systemic chemotherapy, radio frequency, cryo- and IRE percutaneous ablative techniques with promising preliminary results.

While this is by no means an exhaustive list, it is still highly suggestive that the field of radioembolization is poised for rapid advancement in the near future. Although generally considered a third- or fourth-line palliative therapy for some forms of metastatic liver cancer, some leading institutions have moved radioembolization to a second-line treatment in combination with chemotherapy by taking advantage of new information and treatment planning techniques.

Many of the recent advancements in radioembolization are related more to radiation biology, nuclear medicine, and the physics of the treatment rather than the vascular aspects. As such, a book focusing on these topics is appropriate, especially in light of the expected near-term growth and advancement of the field. We expect that with the expanded use of radioembolization, many individuals who have little prior experience with the procedure may pick up this book. While they come from different backgrounds—medical physicists, radiation oncologists, nuclear medicine radiologists, interventional radiologists, and health physicists—all have a necessary role to play in the execution of a well-planned radioembolization therapy. We suggest that regardless of background, all individuals begin with Chapter 1, which expertly summarizes all aspects of the procedure in its entirety. The remaining chapters in this book fill in the details of radioembolization treatments as a currently valuable therapeutic method with many clinically relevant examples as well as some ideas that may aid the advancement of the field.

Alexander S. Pasciak, J. Mark McKinney,
and Yong C. Bradley

Editors

Alexander S. Pasciak, PhD, earned a BS in electrical engineering at the University of Washington, MS in health physics and PhD in nuclear engineering at Texas A&M University. In 2010, Dr. Pasciak completed a 2-year diagnostic medical physics residency at the University of Texas MD Anderson Cancer Center after which he worked for 5 years as a diagnostic medical physicist at the University of Tennessee Medical Center in Knoxville, Tennessee. Dr. Pasciak maintains a position as an associate professor of radiology at the University of Tennessee and is concurrently pursuing his MD degree at the Johns Hopkins University School of Medicine in Baltimore, Maryland. Dr. Pasciak is active in multiple research endeavors in the fields of interventional radiology and medical physics, and he has published papers in high impact journals. Dr. Pasciak has published 35 articles in peer-reviewed medical journals, presented 62 research abstracts at national meetings, has written 6 book chapters, and has filed 2 patents. He currently serves as principal investigator on three externally funded research grants involving radioembolization. Dr. Pasciak is certified by the American Board of Radiology (ABR) in diagnostic medical physics and is Mammography Quality Standards Act (MQSA) qualified.

J. Mark McKinney, MD, earned a medical degree at Loma Linda University School of Medicine in California where he completed a diagnostic radiology residency and interventional radiology fellowship. Dr. McKinney joined the Mayo Clinic in 1993. While at Mayo Clinic in Jacksonville, Florida he developed the interventional radiology fellowship, mentored residents, made numerous presentations, and authored more than 60 peer-reviewed articles, abstracts, and book chapters. From 2008 to 2012 Dr. McKinney was Chair of Radiology at the University of Tennessee Medical Center and initiated the University of Tennessee interventional oncology radioembolization program. Dr. McKinney returned to Mayo Clinic in 2012 and is serving as Chair of Radiology. Dr. McKinney is an associate professor of radiology in the Mayo Clinic College of Medicine. Dr. McKinney is a recent past president of the Association of Program Directors in Radiology and is involved in the new interventional radiology residency program.

Yong C. Bradley, MD, is an ABNM and ABR-certified nuclear medicine subspecialist at the University of Tennessee Medical Center in Knoxville, Tennessee. He completed his residency training in radiology at Tripler Army Medical Center in Honolulu, Hawaii, and subsequently completed a 2-year fellowship in nuclear medicine at Brooke Army Medical Center in San Antonio, Texas. Dr. Bradley is a former chief of radiology and nuclear medicine and molecular imaging at the Brooke Army Medical Center, Wilford Hall Medical Center, and San Antonio Military Medical Center. Dr. Bradley has been interested in cancer imaging and therapy for over 20 years. He has been involved in positron emission tomography (PET) and PET/computed tomography (CT) imaging since 1998, when he was first introduced to PET along with radioimmunotherapy. Presently, his interest has been concentrated in liver radioembolization.

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PART 1

Introduction

1

Introduction to hepatic radioembolization

ANDOR F. VAN DEN HOVEN, DANIEL Y. SZE, AND MARNIX G.E.H. LAM

1.1 GENERAL INTRODUCTION

1.1.1 WHAT IS RADIOEMBOLIZATION?

Radioembolization is a therapy during which radioactive microspheres are administered through a microcatheter placed in the hepatic arterial vasculature to irradiate liver tumors from within. This therapy is based on the principle that liver tumors are almost exclusively vascularized by the hepatic artery, whereas the healthy liver tissue receives the majority of its blood supply from the portal vein. Therefore, following the administration in the hepatic artery, microspheres will be carried preferentially toward the distal arterioles

in and around tumors. Clusters of microspheres are formed inside and in the periphery of tumors, where they emit high-energy β-radiation to induce cell death, while relatively sparing the healthy liver tissue (Braat et al., 2015). Radioembolization is a minimally invasive, image-guided, locoregional alternative, or adjunct to more conventional therapies such as surgery, systemic chemotherapy, and external beam radiation therapy for patients with liver-dominant malignancy. The advantages of this treatment are the targeted delivery of a very high radiation-absorbed dose to tumors, with limited systemic side effects and hepatotoxicity (Kennedy, 2014).

The efficacy and safety of radioembolization have been proven in patients with primary liver tumors such as hepatocellular carcinoma (HCC) (Hilgard et al., 2010) and intrahepatic cholangiocarcinoma (ICC) (Mouli et al., 2013), as well as in metastatic liver tumors from various primary tumors, with colorectal cancer (CRC) (Kennedy et al., 2015), breast cancer (BrC), neuroendocrine tumors (NET) (Devcic et al., 2014), and uveal melanoma (Xing et al., 2014) being the most common. Typically, radioembolization is performed as a stand-alone treatment in salvage patients with liver-dominant disease, but several clinical trials are currently evaluating its role in earlier lines of treatment and in combination with systemic therapy or other locoregional treatments such as radiofrequency ablation.

"Radioembolization" is used as an umbrella term for the treatment of liver tumors with varying disease extents ranging from a single focal subsegmental liver tumor to extensive disseminated or infiltrative disease, which can be hypo- to hypervascular in nature, situated in livers that are relatively healthy, cirrhotic, partially resected, transplanted, or heavily pretreated with systemic or intra-arterial chemotherapy. These situations pose various challenges and require other approaches with regard to safety precautions, treatment planning and dose calculation, microsphere type usage, and catheter positioning during administration. Furthermore, treatment techniques and strategies are dependent on operator experience and preferences and may differ considerably among practices.

Research continues to provide new insights into how to optimize radioembolization treatment, and new indications continue to arise. Among the latest introductions are radiation segmentectomy as a potentially curative technique to eradicate focal solitary liver tumors (Riaz et al., 2011), downstaging of unresectable disease to enable potentially curative surgical resection or transplantation (Braat et al., 2014), and radiation lobectomy to induce contralateral hypertrophy as an alternative to portal vein embolization in surgical candidates (Gaba et al., 2009; Vouche et al., 2013). Additional information on these techniques is presented in Chapter 6. Applying radioembolization principles to the treatment of solid tumors in organs other than the liver has also been provisionally explored, but falls outside the scope of this book.

1.1.2 A BRIEF HISTORY OF RADIOEMBOLIZATION

Several earlier studies and discoveries have set the backdrop for the clinical development of radioembolization as a technique to treat liver tumors. These investigations showed that large quantities of glass microspheres could be safely administered intra-arterially in animal experiments (Prinzmetal and Ornitz, 1948), that radioactive gold-covered charcoal particles administered intravenously or yttrium oxide particles administered via a pulmonary artery catheter could be used to treat lung cancer patients successfully (Muller and Rossier, 1951), and that liver tumors, even ones that reached the liver via the portal circulation, were preferentially vascularized by the hepatic artery when they exceeded about 50 μm in diameter (Bierman et al., 1951). The first report on radioembolization was published in 1960 by the American surgeon Edgar D. Grady and his colleagues, affiliated with Piedmont Hospital and Georgia Institute of Technology in Atlanta, GA, USA (Grady et al., 1960). Subsequent preclinical and clinical investigations by Kim et al. (1962), Caldarola et al. (1964), Blanchard et al. (1965a), and Ariel (1965) followed shortly thereafter. However, technical aspects such as the method to access the hepatic vasculature, the site of administration, safety precautions, size and material of the particles, and the radioactive isotope and the amount of activity to be infused still needed to be refined in the years to follow.

Experiments with New Zealand rabbits demonstrated that injection of radioactive microspheres via the hepatic artery established preferential tumor

targeting, whereas injection via the portal vein did not (Blanchard et al., 1965a), which echoed early clinical results in humans (Grady, 1979). However, it proved challenging to catheterize the hepatic artery in both animals and humans. Access methods included antegrade catheterization of the celiac artery via brachial artery access, retrograde catheterization through femoral arteriotomy with the use of a balloon below the level of the celiac artery, and catheterization of the hepatic artery by accessing the gastroepiploic artery during laparotomy.

After trial and error it was learned that additional safety precautions were required, since extrahepatic deposition of radioactive microspheres (in the gastrointestinal tract or lungs) as well as too much radiation exposure of the healthy liver tissue could result in life-threatening complications (Blanchard et al., 1965b). Therefore, routine "skeletonization" (a surgical term used to describe isolation of the main vascular trunk by ligating all side branches) of the hepatic artery, as well as injection and imaging of radiolabelled albumin particles before treatment to simulate the therapeutic microsphere distribution, was advocated and eventually became standard of practice (Grady, 1979; Ariel and Padula, 1982).

Initially, glass microspheres of 50–100 μm diameter were used. Soon, however, it was recognized that smaller resin microspheres (15–30 μm) were easier to keep in suspension and would still not pass through the capillaries. After several years of experimentation with other isotopes such as Phosphorus-32 (^{32}P) (Caldarola et al., 1964; Grady et al., 1975), Yttrium-90 (^{90}Y) established its dominance. Reported benefits of ^{90}Y included a pure high-energy yield of tumoricidal β-radiation (max energy of 2.28 MeV), a short soft-tissue penetration (max 11 mm), and a 64-h half-life, which limited potential safety hazards for persons in close proximity to a treated patient. Early reports did, however, acknowledge the importance of imaging the posttreatment microsphere distribution and the limited possibilities inherent to the use of ^{90}Y (Grady et al., 1963; Ariel, 1965). The secondary bremsstrahlung γ-ray produced by β-activity could be detected with a Geiger–Muller survey meter or a scintillation crystal probe. Ariel even added Ytterbium-169 (^{169}Yb; γ-ray 52–310 keV; $T_{1/2}$ 32 days) to the microspheres as a radiation source for imaging with a γ-camera (Ariel, 1965).

Determining the optimal treatment activity (pretreatment dosimetry) has been a challenge from the start (Blanchard et al., 1965b). It was already recognized that the intrahepatic microsphere distribution is highly heterogeneous after treatment, but imaging methods available at that time precluded the assessment of the tissue mass exposed to radiation. Therefore, treatment activity could not be adapted to effective tumor-absorbed dose and safe healthy liver-absorbed dose values. Instead, the required treatment activity was calculated based on a target whole liver-absorbed dose of 5000 rad (50 Gy), which had been demonstrated as a safe dose in animal experiments. Doses were prescribed based on the formula that per gram of liver tissue 1 mCi (37 MBq) would be required to deliver an absorbed dose of 182 rad (1.82 Gy) (Grady, 1979).

The first efficacy reports were case series reporting posttreatment survival and the clinical condition of patients with primary or metastatic liver cancer. These results were generally promising, and some cases showed unprecedented disease control, but these reports were written prior to the availability of computed tomography, magnetic resonance imaging, and quantitative ultrasonography. Patients with inoperable disease had no good alternatives at that time, since the effectiveness of systemic chemotherapy and external beam radiation therapy remained disappointing. In 1989, Gray et al. published the first prospective trial results on radioembolization demonstrating an objective treatment response, defined as a decline of carcinoembryonic antigen (CEA) levels after treatment in 9/10 treated patients with colorectal cancer liver metastases (Gray et al., 1989). In the next two decades, only a few prospective studies followed patients with primary liver cancer and colorectal liver metastases (Lau et al., 1994; Rosler et al., 1994; Gray et al., 2001). Among these studies was the first randomized controlled trial, which demonstrated that the addition of radioembolization to regional hepatic arterial chemotherapy (floxuridine) in salvage patients with colorectal cancer liver metastases resulted in significantly improved tumor response.

Eventually, ^{90}Y-microspheres received Conformité Européenne (CE) mark in the European Union and U.S. Food and Drug Administration (FDA) approval in the United States for the treatment of HCC and metastatic colorectal cancer, which in turn led to a

broader availability of radioembolization to patients and a renewed scientific interest.

The past two decades have been characterized by an enormous growth in the widespread use of radioembolization to treat salvage patients, with either primary or metastatic liver cancer. It is increasingly acknowledged that, as long as the liver disease is the survival-limiting factor in the patients' prognosis, radioembolization treatment is expected to be beneficial in patients with all kinds of liver-dominant tumor types. Patient selection, workup, treatment technique, and analyses of treatment toxicity and response have all been vastly improved. Modern imaging techniques including multidetector contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), and C-arm cone beam CT now allow for a detailed assessment of tumor location, tumor characteristics, and individual hepatic arterial anatomy before treatment. This enables the operator to set a feasible individualized treatment strategy with the aim to achieve adequate tumor targeting, while minimizing the chance of treatment-related complications. The advent of nuclear medicine imaging techniques such as single photon emission computed tomography (SPECT)/computed tomography (CT) and positron emission tomography (PET)/CT, as well as the development of non-^{90}Y microspheres such as Holmium-166 (^{166}Ho) microspheres, has enabled imaging of the particle distribution and quantification of radiation-absorbed doses. It is now possible to identify an unfavorable particle distribution early on when the treatment plan can still be modified. Tumor response assessment is also becoming less observer dependent with all the possibilities that functional MRI and 18-fluoro-2-deoxyglucose positron emission tomography (^{18}F-FDG-PET) imaging have to offer.

The challenges for the near future will be to clarify which patients will benefit most from radioembolization, to improve methods for treatment activity calculations, to maximize treatment efficacy, to reduce treatment-related toxicity, to standardize treatment technique, to enhance our understanding of relevant particle-fluid dynamics, radiobiology, and systemic treatment effects, to explore combination therapies, and to strengthen scientific evidence by proving superiority over conventional and emerging therapies in large-scale phase III randomized controlled trials. These topics will be discussed in more detail in Chapter 15.

1.1.3 INDICATIONS FOR RADIOEMBOLIZATION

At this moment, the indication for radioembolization as a stand-alone therapy for patients with liver metastases is primarily based on unresectable, liver-dominant metastases refractory to standard systemic therapy. The standard for systemic therapy differs per primary tumor type and per geographical location, and may include cytotoxic chemotherapeutic agents as well as targeted small molecules, monoclonal antibodies, and immunomodulators. The prevailing principle is that no other therapy should be available with more convincing scientific evidence of effectiveness. Patients with contraindications to or unacceptable toxicity from systemic therapy are also eligible. Since large randomized controlled studies are currently investigating the role of radioembolization combined with systemic therapy in the first- and second-line treatment of colorectal cancer liver metastases, radioembolization may potentially be performed earlier in the treatment cycle in the future.

In patients with HCC, radioembolization is generally reserved for patients with intermediate and early advanced disease stages (Braat et al., 2015). These are patients with large multinodular tumors (>3, ≥3 cm), with or without macrovascular invasion, sufficient liver function (Child–Pugh A–B), and an acceptable clinical condition [World Health Organization (WHO) performance status score 0–2], corresponding to Barcelona Clinic Liver Cancer staging system stages B–C (Forner et al., 2014). Some patients may have already failed chemoembolization and/or systemic treatment with sorafenib, but radioembolization is offered as an alternative to chemoembolization in some practices, even for earlier stage disease.

Treatment with radioembolization should be considered relatively aggressive, and must be technically feasible and clinically tolerable. Additional important criteria for patient selection are summarized in Table 1.1. It should be noted that indications and contraindications are subject to change over time as clinical experience, both positive and negative, accumulate over the years.