Advances in Predictive, Preventive and Personalised Medicine
Series Editor: Olga Golubnitschaja

Leonard Berliner
Heinz U. Lemke *Editors*

An Information Technology Framework for Predictive, Preventive and Personalised Medicine

A Use-Case with Hepatocellular Carcinoma

EPMA
European Association for Predictive Preventive & Personalised Medicine

Springer

An Information Technology Framework for Predictive, Preventive and Personalised Medicine

Advances in Predictive, Preventive and Personalised Medicine

Volume 8

Series Editor:

Olga Golubnitschaja

Managing Editor:

Kristina Yeghiazaryan

For further volumes:
http://www.springer.com/series/10051

Leonard Berliner • Heinz U. Lemke
Editors

An Information Technology Framework for Predictive, Preventive and Personalised Medicine

A Use-Case with Hepatocellular Carcinoma

Springer

Editors
Leonard Berliner
Weill Cornell Medical College of Cornell
New York
New York
USA

Heinz U. Lemke
Technical University of Berlin
Kuessaberg
Germany

ISSN 2211-3495 ISSN 2211-3509 (electronic)
Advances in Predictive, Preventive and Personalised Medicine
ISBN 978-3-319-12165-9 ISBN 978-3-319-12166-6 (eBook)
DOI 10.1007/978-3-319-12166-6

Library of Congress Control Number: 2014956761

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

What This Book Series is About…

Current Healthcare: What is Behind the issue?

For many acute and chronic disorders, the current healthcare outcomes are considered as being inadequate: global figures cry for preventive measures and personalised treatments. In fact, severe chronic pathologies such as cardiovascular disorders, diabetes and cancer are treated after onset of the disease, frequently at near end-stages. Pessimistic prognosis considers pandemic scenario for type 2 diabetes mellitus, neurodegenerative disorders and some types of cancer over the next 10–20 years followed by the economic disaster of healthcare systems in a global scale.

Advanced Healthcare Tailored to the Person: What is Beyond the Issue?

Advanced healthcare promotes the paradigm change from delayed interventional to predictive medicine tailored to the person, from reactive to preventive medicine and from disease to wellness. The innovative Predictive, Preventive and Personalised Medicine (PPPM) is emerging as the focal point of efforts in healthcare aimed at curbing the prevalence of both communicable and non-communicable diseases such as diabetes, cardiovascular diseases, chronic respiratory diseases, cancer and dental pathologies. The cost-effective management of diseases and the critical role of PPPM in modernisation of healthcare have been acknowledged as priorities by global and regional organizations and health-related institutions such as the Organisation of United Nations, the European Union and the National Institutes of Health.

Why Integrative Medical Approach by PPPM as the Medicine of the Future?

PPPM is the new integrative concept in healthcare sector that enables to predict individual predisposition before onset of the disease, to provide targeted preventive measures and create personalised treatment algorithms tailored to the person. The expected outcomes are conducive to more effective population screening, prevention early in childhood, identification of persons at-risk, stratification of patients for the optimal therapy planning, prediction and reduction of adverse drug-drug or drug-disease interactions relying on emerging technologies, such as pharmacogenetics, pathology-specific molecular patters, sub/cellular imaging, disease modelling, individual patient profiles, etc. Integrative approach by PPPM is considered as the medicine of the future. Being at the forefront of the global efforts, the European Association for Predictive, Preventive and Personalised Medicine (EPMA, http://www.epmanet.eu/) promotes the integrative concept of PPPM among healthcare stakeholders, governmental institutions, educators, funding bodies, patient organisations and in the public domain.

Current Book Series, published by Springer in collaboration with EPMA, overview multidisciplinary aspects of advanced bio/medical approaches and innovative technologies. Integration of individual professional groups into the overall concept of PPPM is a particular advantage of this book series. Expert recommendations focus on the cost-effective management tailored to the person in health and disease. Innovative strategies are considered for standardisation of healthcare services. New guidelines are proposed for medical ethics, treatment of rare diseases, innovative approaches to early and predictive diagnostics, patient stratification and targeted prevention in healthy individuals, persons at-risk, individual patient groups, sub/populations, institutions, healthcare economy and marketing.

Prof. Dr. Olga Golubnitschaja
Book Series Editor

Prof. Dr. Olga Golubnitschaja Department of Radiology, Medical Faculty of the University in Bonn, Germany, has studied journalism, biotechnology and medicine and has been awarded fellowships for biomedical research in Paediatrics and Neurosciences (Medical Centres in Austria, Russia, UK, Germany, the Netherlands, and Switzerland). She is well-cited in the research fields of "gene hunting" and "subtractive hybridisation" applied to predictive prenatal & postnatal diagnostics published as *O.Labudova* in years 1990–2000. Dr. Golubnitschaja is an expert in molecular diagnostics actively publishing in the fields of perinatal diagnostics, Down syndrome, Diabetes mellitus, hyperhomocysteinemia, cardiovascular disease, neurodegenerative pathologies, cancer. She is the *co-founder* of the theory of multi-pathway organ-related blood fingerprinting with specific molecular patterns at epi/genomic, transcriptional and post/translational levels, author of fundamental works in *integrative medicine*. Dr. Golubnitschaja hold appointments, at the rank of Professor, at several European Universities and in International Programmes for Personalised Medicine and author of more than 300 international publications in the field. *Awards:* National & International Fellowship of the Alexander von Humboldt-Foundation; Highest Prize in Medicine and Eiselsberg-Prize in Austria. She is *Secretary-General* of the "European Association for Predictive, Preventive & Personalised Medicine" (EPMA in Brussels, www.epmanet.eu), *Editor-in-Chief* of "The EPMA-Journal" (BioMed Central, London); *Book Editor* of "Predictive Diagnostics & Personalized Treatment: Dream or Reality", Nova Science Publishers, New York 2009; *Book Co-editor* "Personalisierte Medizin", Health Academy, Dresden 2010; *Book Series Editor* "Advances in Predictive, Preventive & Personalised Medicine", Springer 2012; *European Representative* in the EDR-Network at the NIH/NCI, http://edrn.nci.nih.gov/; *Advisor and Evaluator* of projects dedicated to personalised medicine at the EU-Commission in Brussels, NIH/NCI, Washington D.C., USA, Foundations and National Ministries of Health in several countries worldwide.

About The Editor

Dr. Leonard Berliner is Chief of Interventional Radiology at New York Methodist Hospital in Brooklyn, New York and Clinical Assistant Professor of Radiology Weill Cornell Medical College of Cornell University, New York. He received his Medical Degree from Downstate Medical Center /State University of New York (1976) and performed his residency and fellowship training in abdominal imaging and vascular-interventional radiology at New York University Medical Center (1977-1981), serving as Chief Resident in 1980 and 1981.

In addition to full-time clinical practice vascular and interventional radiology, Dr. Berliner has authored/co-authored over 90 articles, book chapters, and conference presentations on aspects of radiology and, most recently, patient modelling and personalised medicine. Current research is related to the role of information and communication technology in predictive, preventive and personalised medicine

Dr. Berliner is a member of the Society of Interventional Radiology. He has served on the editorial board for the EPMA Journal and as a Deputy Editor of the International Journal of Computer Assisted Radiology and Surgery. He is a Fellow of the European Association for Predictive, Preventive and Personalised Medicine. He currently serves as clinical co-chairman of the Workgroup 24: DICOM in Surgery of the DICOM Standards Committee and is a member of the Organising Committee of the Computer Assisted Radiology and Surgery (CARS) meetings (http://www.cars-int.org/).

Heinz U. Lemke is professor of Computer Science and teaches and supervises research on Computer Assisted Medicine at the Technical University of Berlin. He is also Research Professor of Radiology at the University of Southern California, Senior Advisor on research strategies at the Innovation Center Computer Assisted Surgery (ICCAS), University of Leipzig and Visiting Fellow of the Institute of Advanced Studies, Technical University of Munich.

Since 1983 Heinz Lemke is the organiser of the congress series Computer Assisted Radiology and Surgery (CARS), editor-in-chief of the International Journal of CARS and executive director of the International Foundation for CARS. He has been a consultant to many major medical technology companies and health care institutions and was co-founder and board member of professional societies such as ISCAS, EuroPACS (now EuSoMII), CURAC, EPMA and SCAR (now SIIM). During the last 25 years he was Visiting Professor at universities in USA, Japan, China, Egypt and Switzerland.

Heinz Lemke has been actively engaged in mathematical and IT modelling methods for patients and process representations for diagnosis and therapy. This was based on his earlier work on the development of patient-specific modelling, computer assisted radiology and surgery, PACS, computer graphics, medical workstations and model management systems, which have been published in about 170 papers and 50 edited books.

Foreword

So very frustrating as a treating physician to tell Mr. Smith or Ms. Jones that medication (drug) X has a 50–75% chance to be effective, or that our proposed radiofrequency ablation for your liver (or lung or kidney or bone) cancer may be cured with only an 85–90% likelihood. Why can't we be more specific, why can't we help patients to make better informed decisions, why can't we be definitive so that patients, families, and we physicians help guide our patients by clear, data-driven rational reasoning? Through the years, the answer to the above quandaries has been "individual variation", "no two patients are alike", "medicine is an art not just a science", and the vernacular, "everybody's different". All true—but the good news is that it's the dawning of a new day—and that day is Predictive, Preventive, and Personalized Medicine (Personalized Medicine).

Truly, everybody is different, and that's precisely the point; ergo—Personalized Medicine. So what is Personalized Medicine, what's so special about it, and why are there predictions that, "It will change and improve medicine forever"? Personalized Medicine is a medical model based on genomics and molecular analysis that targets each person's gene makeup, thereby allowing customization of individual susceptibility, appropriate disease diagnosis and therapy, and disease follow-up. It's all about taking the guesswork out of medical decision-making, so we can be more specific in effectiveness, avoid unnecessary adverse effects and complications, and utilize resources optimally to tailor health care for our aforementioned Mr. Smith and Ms. Jones.

Mathematical models, genome wide association studies, RNA sequencing, and DNA mutations are watchwords for the methodology of Personalized Medicine. All seek to provide physicians with a structural playbook for their patients—what diseases are their patients more likely to contract, what diagnostic tests are most relevant, what therapies will actually be effective and with fewer adverse reactions. The less the guesswork, the more efficient health care for patients should and will be, the fewer drug-related side effects should occur, and reduced costs can be expected. Almost sounds too good to be true!

Albeit still in its relative infancy, Personalized Medicine already has clinical application for diabetes mellitus type II, breast cancer for receptors (onco-genomics), thrombosis prediction by unwanted antibodies, chronic myelogenous leukemia

managed by 'rational drug design', and colon cancer abnormalities (KRAS protein detection). In this 13 chapter series edited by Drs. Berliner and Lemke, they have focused on primary hepatocellular carcinoma. Their work, and that of their contributing authors, is replete with methods of optimizing information technology, creating targeted patient models, model guided therapy and management, and highlighting evidenced-based medicine. Bayesian network information supports the digital patient model throughout the series. The authors have chosen hepatocellular carcinoma as their disease model, as it is the most common malignant cancer of the liver worldwide, and the fifth most common cancer overall.

Sections of the entire manuscript include those on the aforementioned mathematical models utilized by the authors, as well as specifics related to hepatocellular carcinoma itself—patient assessment, radiologic imaging, PET/CT, personalized chemotherapy, surgery, the spectrum of radiologic ablative methods, radiofrequency ablation therapy, transarterial chemo-embolization, radiation therapy, and information technology systems.

The overall goal of the manuscripts, the Editors tell us, is to integrate the multitude of factors relevant to hepatocellular carcinoma (epidemiology, individual risk factors, biomarkers, environment, diagnostic and therapeutic specifics). This complicated and sometimes disparate information is then compiled into an information technology system that is designed to incorporate and assimilate the evidence-based information for a preventive, predictive, diagnostic, and therapeutic individual model for hepatocellular carcinoma for each individual patient. *Voila*!—Personalized Medicine! Achievement of this integrated information model would be far beyond what is readily available currently.

The Editors and authors are to be commended. Theirs has been an extraordinarily complex task, fraught with innumerable variables—but that is precisely what Personalized Medicine is all about. The sooner Drs. Berliner and Lemke's methods, along with many other workers in the Personalized Medicine field (FDA, the Personalized Medicine Coalition, many medical centers such as Duke University, Personalized Medicine Journal, and genomic companies) implement Personalized Medicine on a grand scale, the better for patients, physicians, cost reduction, and healthcare for America and the world.

Eric van Sonnenberg, MD
Clinical Professor of Radiology, University of Arizona College of Medicine
Visiting Professor of Medicine, David Geffen School of Medicine at UCLA

June 2014

Preface

This book initially was conceived, and gradually has evolved, to seek solutions to issues and tasks relating to Information Technology (IT) and Predictive, Preventive and Personalized Medicine (PPPM) as identified in the 2012 "EPMA White Paper" [Golubnitschaja O, Costigliola V and EPMA. "General Report & Recommendations in Predictive, Preventive and Personalised Medicine 2012: White Paper of the European Association of Predictive, Preventive and Personalised Medicine. EPMA J 2012, 3:14].

Our goal was to define a role and a roadmap for the development of an IT solution to facilitate clinical PPPM. IT is a broad field that already impacts many facets of PPPM, including the design and implementation of databases for biomarkers and genetic research, and the subsequent data-mining made possible by such databases. However, we have chosen to explore another role for IT, and have begun the process of developing an application that pertains to patient modeling—specifically, the creation of a multi-faceted IT System for PPPM (ITS-PM) that will incorporate a Digital Patient Model (DPM) and will introduce Model-Guided Therapy (MGT) into clinical practice. The initial goal for an ITS-PM is to provide the tools that are necessary for the generation of comprehensive, descriptive, computer-based models of specific patients, or DPMs. Subsequent goals involve tasks relating to disease prediction and prevention through enhanced screening, and to personalized health care, through patient-specific decision support. It is proposed that implementation of these IT solutions also may lead to an expansion of evidence-based medicine, derived from MGT, and may be designated as Model-Based Medical Evidence (MBME).

To avoid the pitfalls of developing an IT project in isolation, hepatocellular carcinoma (HCC) was selected as a use-case to ensure medical validity. The fact that HCC is the fifth most common form of cancer worldwide and the second leading cause of cancer death speaks to the virulence of this disease. Despite advances in the understanding, diagnosis, and treatment of HCC in the past several decades, HCC remains an international health problem. This book relies heavily on the enormous contributions relating to the basic science and clinical management of HCC by researchers, hepatologists, diagnostic and interventional radiologists, medical, surgical, and radiation oncologists, and others.

This book defines the general specifications of the IT structures required for patient-specific modeling and MGT, and then, through a review of the clinical aspects of HCC, extracts the patient attributes, or Information Entities (IEs), required for the construction of the requisite databases and DPMs. The concluding chapter provides an outlook for PPPM, based on the ITS-PM and provides expert recommendations relating to clinical applications that may be implemented currently.

We have presented a roadmap for the future, but much work remains to be done. Working examples of the complex IT infrastructure, databases, patient models, and decision support systems need to be created and validated. If this can be achieved, the benefits of a comprehensive ITS-PM can be generalized to virtually any disease or medical condition. It is hoped that through this IT solution, critical medical decisions can be made that are tailored to the specific needs and attributes of each patient, regardless of his or her underlying disease or comorbidities.

Leonard Berliner, MD, Heinz U. Lemke, PhD

New York Methodist Hospital, Brooklyn, NY; Weill Medical College of Cornell University (USA)

Technical University of Berlin; Berlin (D); University of Southern California, Los Angeles (USA)

Contents

Contributors

Hani Ashamalla Weill Medical College of Cornell University, New York, NY, USA

New York Methodist Hospital, Brooklyn, NY, USA

Irene Bargellini Diagnostic and Interventional Radiology, University Hospital Pisa, Pisa, Italy

Carlo Bartolozzi Diagnostic and Interventional Radiology, University Hospital Pisa, Pisa, Italy

Valentina Battaglia Diagnostic and Interventional Radiology, University Hospital Pisa, Pisa, Italy

Leonard Berliner Weill Medical College of Cornell University, New York, USA

New York Methodist Hospital, Brooklyn, NY, USA

Davide Caramella Diagnostic and Interventional Radiology, University Hospital Pisa, Pisa, Italy

David Dosik New York Methodist Hospital, Brooklyn, NY, USA

Weill Medical College of Cornell University, New York, USA

Giuseppe Esposito Georgetown University Medical Center, Washington, DC, USA

Hesham Hazin New York Methodist Hospital, Brooklyn, NY, USA

Heinz U. Lemke Technical University of Berlin, Berlin, Germany

University of Southern California, Los Angeles, USA

Malcolm D. Mattes New York Methodist Hospital, Brooklyn, NY, USA

Smruti Mohanty New York Methodist Hospital, Brooklyn, NY, USA

Weill Medical College of Cornell University, New York, USA

Paul Morrison Brigham and Women's Hospital, Boston, MA, USA

Syed Shah New York Methodist Hospital, Brooklyn, NY, USA

Weill Medical College of Cornell University, New York, USA

Eric vanSonnenberg Kern/UCLA Medical Center, Bakersfield, CA, USA

University of Arizona College of Medicine, Phoenix, USA

Sid Verma New York Methodist Hospital, Brooklyn, NY, USA

List of Abbreviations

AASLD	American Association for the Study of Liver Diseases
AFP	alpha-fetoprotein
BCLC	Barcelona Clinic Liver Cancer
CEUS	contrast enhanced ultrasound
CRYO	cryotherapy
CT	computed tomography
CTP	Child-Turgot-Pugh
DPM	Digital Patient Model
DWI	Diffusion-weighted imaging
EASL	European Association for the Study of the Liver
EMR	Electronic Medical Records
EPMA	European Association for Predictive, Preventive and Personalised Medicine
ETOH	alcohol injection
FDG	fluorodeoxyglucose
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HGDN	high-grade dysplastic nodule
HIFU	high intensity focused ultrasound
IE	Information Entity
ILT	interstitial laser thermotherapy
IRE	irreversible electroporation
IT	Information Technology
ITS-PM	Information Technology System for Predictive, Preventive, and Personalized Medicine
LGDN	Low-grade dysplastic nodule
MAA	macroaggregated albumin
MBME	Model-Based Medical Evidence
MDCT	multi-detector computed tomography

MEBN	Multi-Entity Bayesian Networks
MGT	Model Guided Therapy
MRI	magnetic resonance imaging
MWA	microwave ablation
PSM	Patient-Specific Model
PACS	Picture Archiving and Communications Systems
PDT	photodynamic therapy
PET	positron emission tomography
PET/CT	PET with computed tomography
PPPM	Predictive, Preventive, and Personalized Medicine
RCT	Randomized controlled trial
RFA	radiofrequency ablation
RM-ODP	Reference Model for Open Distributed Processing
SBRT	Stereotactic body radiotherapy
SOA	Service-Oriented Architecture
TACE	Transarterial chemoembolization
TIMMS	Therapy Imaging and Model Management System
US	Ultrasound
Y90	Yttrium-90

Chapter 1
Introduction

Leonard Berliner and Heinz U. Lemke

Abstract This book explores ways in which the requirements and interrelationships between Predictive, Preventive and Personalized Medicine (PPPM), clinical medical practice, and basic medical research could be best served by information technology (IT). To avoid the problems inherent in formulating IT solutions in isolation, a use-case was developed employing hepatocellular carcinoma (HCC). The subject matter was approached from four separate, but interrelated, tasks: (1) review of current understanding and clinical practices relating to HCC; (2) propose an IT system for dealing with the vast amount of information relating to HCC, including clinical decision support and research needs; (3) determine the ways in which a clinical liver cancer center can contribute to this IT approach; and, (4) examine the enhancements and impact that the first three tasks, and therefore PPPM, will have on the management of HCC. An IT System for Predictive, Preventive and Personalized Medicine (ITS-PM) for HCC is presented to provide a comprehensive system to provide unified access to general medical and patient-specific information for medical researchers and health care providers from different disciplines including hepatologists, gastroenterologists, medical and surgical oncologists, liver transplant teams, interventional radiologists, and radiation oncologists.

Keywords Personalized medicine · Hepatocellular carcinoma · Information technology · Information technology system for predictive preventive and personalized medicine (ITS-PM) · Model guided therapy · Therapy imaging and model management system (TIMMS) · Digital patient model · Patient-specific model · Model-based medical evidence · Bayesian network

L. Berliner (✉)
Weill Medical College of Cornell University, New York, USA
e-mail: LeonardB23@AOL.com

New York Methodist Hospital, Brooklyn, NY, USA

H. U. Lemke
Technical University of Berlin, Los Angeles, Berlin, USA
e-mail: hulemke@cars-int.org

University of Southern California, California, USA

L. Berliner, H. U. Lemke (eds.), *An Information Technology Framework for Predictive, Preventive and Personalised Medicine,* Advances in Predictive, Preventive and Personalised Medicine 8, DOI 10.1007/978-3-319-12166-6_1

1.1 Introduction

This book was initially conceived to seek solutions to issues and tasks relating to Information Technology (IT) and Predictive, Preventive and Personalized Medicine (PPPM) as identified in the 2012 European Association for Predictive, Preventive and Personalised Medicine (EPMA) White Paper [1]. As such, this book explores ways in which the requirements and interrelationships between PPPM, clinical medical practice, and basic medical research could be best served by information technology (IT). To avoid the problems inherent in formulating IT solutions in isolation, it was decided to develop a use-case, employing the clinical topic of hepatocellular carcinoma (HCC). The subject matter is therefore approached from the point of view of four separate, but interrelated, tasks: (1) review of current understanding and clinical practices relating to the diagnosis and management of patients with HCC; (2) propose an IT system for dealing with the vast amount of information relating to HCC, including clinical decision support and research needs; (3) determine the ways in which a clinical liver cancer center can utilize and contribute to this IT approach; and, (4) examine the enhancements and impact that the first three tasks, and therefore PPPM, will have on the management of HCC.

The thirteen chapters of this book will describe the initial efforts in designing and implementing a clinical liver cancer program that will be organized in such a way as to allow transition from traditional medical practice toward predictive, preventive, and personalized medicine, as the appropriate and specific information and communication technologies are developed. The combined chapters will address current technical and clinical material regarding assessment, management, and treatment of patients with HCC, within the context of Model-Guided Therapy (MGT), Patient-Specific Modeling (PSM) to create a Digital Patient Model (DPM) and PPPM. It is the intention of the authors to lay the groundwork for a clinical IT solution to assist institutions preparing similar treatment programs (whether they be for liver tumors or any other form of malignancy) while making the transition to MGT and Personalized Medicine. It is also hoped that this IT approach will facilitate the linkage between clinicians and researchers seeking to develop a practical means of identifying clinically useful biomarkers, and incorporating them into clinical applications.

This article has been divided into thirteen chapters, to optimally address the breadth and organization of the subject matter.

1. Introduction
2. The Digital Patient Model and Model Guided Therapy
3. Hepatocellular Carcinoma and Patient Assessment
4. Role of Imaging in Hepatocellular Carcinoma
5. Personalized Chemotherapy for Hepatocellular Carcinoma
6. Surgical Treatment for Hepatocellular Carcinoma
7. Minimally Invasive Therapies for Hepatocellular Cancer
8. Radiation Oncology in the Treatment of Hepatocellular Carcinoma
9. Design of an IT System for Hepatocellular Carcinoma
10. Outlook and Expert Recommendations for Predictive, Preventive and Personalized Medicine and Hepatocellular Carcinoma

The scope of the book will be primarily concerned with issues relating to primary liver cancer (hepatocellular carcinoma) so that the focus on personalized health care can be maintained. (In a comprehensive liver cancer program, the addition of patients with other forms of liver tumors will significantly add to the complexities of patient management.)

1.1.1 Predictive, Preventive and Personalized Medicine

The body of literature relating to PPPM is growing on many fronts and touches on most medical disciplines. PPPM may be thought of as a coalition of a wide variety of disciplines that have a shared goal of meeting the unique needs, desires, and requirements of patients on an individual basis and providing unique predictions and treatments. Information is accumulating in fields as diverse as neurology, ophthalmology, oncology, genetics, epidemiology, etc. and is derived from the core study of these subjects, but reexamined and focused from a **different perspective**. While PPPM intuitively is an admirable goal, it is becoming evident that there are clear-cut practical motivations: scientific, humanitarian, and financial.

From the scientific and humanitarian point of view, the desirability of selecting an appropriate and effective course of treatment requires little explanation. However, the issue of consequences of ineffective treatment needs emphasis. The guiding principle *Primum non nocere (*First, do no harm) must be considered, since there is evidence that current cancer treatments may also have a cancer-promoting effect in patients, in addition to a variety of well-known side effects [2]. It is therefore an important goal of PPPM to be able to detect and understand those individual features of a patient that influence the responses to treatment, both positive and negative.

From the financial point of view, the appropriate use of genetic information can help contain costs by limiting expensive (and potentially harmful) treatments and/or tests to those patients who have the potential to respond, as is the case in certain forms of breast cancer [3].

1.1.2 PPPM and Evidence-Based Medicine

The ***study*** of medical science is based on populations, whereas the ***practice*** of medicine is centered on the individual. This difference in focus between populations and individuals is a fundamentally dichotomous situation. Traditionally, the medical profession has provided care and treatment to patients with malignancy according to protocols and algorithms that have been developed on the basis of observations of tumor responses in large, randomized clinical trials (RCTs). After an appropriate number of patients have been treated in such a clinical trial, the results are collected and analyzed, and then used to predict a generalized prognosis for patients undergoing treatment with the protocol under investigation. Accordingly, when a patient presents for treatment, and after the appropriate diagnostic tests have been

performed and the patient's specific and overall clinical status has been assessed, recommendations for treatment are made on the basis of average *n*-year survival rates. This approach, however, does not produce the kind of information that can be applied directly to provide personalized medical decision making. For example, this situation can arise when a patient poses the following question: "I understand that patients with this tumor who undergo this treatment have a 75 % five-year survival rate, but what are *my* chances?" Current forms of medical evidence do little to help us to answer this question. This problem has recently been emphasized with respect to determining prognosis for individual patients based on evidence obtained from clinical trials; "…in clinical practice, clinicians must extrapolate from population-level estimates to make judgments with or for individual patients. Even if a risk estimate is very precise—say, a 25 % risk of death within 6 months—it is not clear whether the patient is 1 of the 25 out of 100 who will die or 1 of the 75 who will live" [4].

The development of a new approach to medical evidence will be required for PPPM, and ultimately should benefit patients and answer the aforementioned patient's question.

When a patient is in the care of a treating healthcare professional (such as a primary care physician, oncologist, surgeon, radiation oncologist, or interventional radiologist) attention to the individual or personalized needs of the patient is of paramount importance. Physicians hopefully learn to recognize the individual's emotional and spiritual needs and desires, as well as his or her physical strengths and weaknesses. These characteristics influence how that physician will form a treatment plan, based on an assessment and prediction of how that patient will respond within a given therapeutic regimen. Despite the time and effort spent in considering these personalized attributes, due to the lack of organized programs with specific databases to collect and analyze these data, little information is available to the treating physician for use in predicting a single individual's survival rate or treatment outcome when a therapeutic procedure and/or regimen is offered. As a result of this current deficiency in medical knowledge, the ability to pursue PPPM, in which individual responses are the key elements, currently is drastically limited. It is our hypothesis that the issue of individual response in the face of incomplete medical knowledge will be resolved through the development of PPPM.

1.1.3 Personalized Medicine, Biomarkers, and Information Technology

The information required to provide more personalized healthcare has been sought through the investigation of biomarkers that has led to an improved understanding and appreciation of the complex nature of biomarkers. The search for single (or even small clusters of) biomarkers that could provide definitive indication of disease prediction and/or treatment outcome has been frustrating. For example, the concept of finding a single gene for prediction of breast cancer has given way to the

search for a panel of biomarkers [5]. Coalitions of pharmaceutical companies and researchers have sought to study biomarkers and their implications [6].

To further address the issues of medical information management, efforts have been made in the field of medical IT to better understand and redefine the nature and requirements of systems of information management that can be applied to PPPM.

One approach to the management of medical information is based on model theory and seeks to implement a form of MGT that can be used as a decision support system in the treatment of patients with HCC. The IT structures to be utilized in MGT, will be discussed in Chap. 2 of this book and include the Therapy Imaging and Model Management System (TIMMS) and the DPM [7, 8].

The DPM directly relates to PPPM by (1) adopting the broadest definition of biomarker—a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention [5] and (2) allowing any of the component features of the DPM to be an actual or potential biomarker. The DPM can therefore provide a multidimensional and continuous model for individuals working with biomarkers. This may facilitate the collection, analysis, and validation of biomarkers and their integration into a comprehensive, understandable, dynamic, real-time view of the patient. Thus, by utilizing the DPM as a substrate, MGT can provide the framework for injecting biomarkers into clinical practice.

It is our hypothesis that if we can utilize patient-specific modeling techniques to generate valid DPMs (which factor in age, physiologic condition, disease and co-morbidities, genetics, biomarkers, responses to previous treatments) we may be able to develop a statistically valid methodology, on an individual basis, to predict certain diseases or conditions, to predict certain treatment outcomes, to prevent certain diseases or complications, and to develop treatment regimens that are personalized for that particular patient. We are calling this proposed system Model-Based Medical Evidence (MBME) and are engaged in its development. It is further postulated that the Multi-Entity Bayesian Networks (MEBN) used in the construction of the DPM will be utilized in the development of a practical decision support system.

1.1.4 Clinical Liver Tumor Treatment Program as Use-Case

In the course of developing IT solutions for clinical problems, it is essential to make use of clinically valid use-cases to maintain a firm and realistic foundation. A clinical liver cancer center and HCC have been chosen as the basis for the use-case in this paper. Through the review of HCC and its characteristics, diagnosis, and treatment, IT structures such as databases, MEBNs, and DPMs can be designed and populated. Extensive work has been done in this regard by the American Association for the Study of Liver Diseases (AASLD), the Barcelona Clinic Liver Cancer (BCLC), the European Association for the Study of the Liver (EASL), and the European Organisation for Research and Treatment of Cancer (EORTC) [9–11]. The efforts of these organizations have provided guidelines for diagnosis, screening, staging, and

treatment of patients with HCC. These guidelines, when combined with information obtained from research in a wide variety of areas including treatment outcomes, biomarkers, epidemiology, pathology, and molecular physiology, will help provide the framework for the construction of the DPMs required for MGT.

The implementation of the clinical liver cancer center will be designed to facilitate the transition from traditional medical practice toward PPPM. It is our intention to provide a foundation in IT so that institutions preparing similar programs will be able to transition to MGT.

As in any medical treatment program, the results of the initial diagnostic workup and subsequent treatments will be entered into an Electronic Medical Record. In addition, a program for PPPM must also be enabled to record patient attributes, clinical observations, and therapeutic responses in databases specifically developed for these purposes. Comprehensive information, i.e. Information Entities (see Chap. 2), will be necessary for statistical analysis of individual patient characteristics and responses to therapeutic regimens, and to allow validation of personalized healthcare delivery. These Information Entities will also provide the raw data for the development and testing of a comprehensive DPM as well as an IT System for Predictive, Preventive and Personalized Medicine (ITS-PM) for HCC, for evaluation of biomarkers and the development of MBME, which may provide a solid foundation for PPPM. This ITS-PM will be designed to provide unified access to general medical and patient-specific information for medical researchers and health care providers from different disciplines including hepatologists, gastroenterologists, medical and surgical oncologists, liver transplant teams, interventional radiologists, and radiation oncologists.

A decision support system based on these elements may prove to be of tremendous value in the clinical setting, for example, at a hospital's Tumor Board. One drawback of the Tumor Board system is that, at times, decisions relating to treatment regimens may be unduly influenced by the opinions of those who are able to attend, as well as limitations in the technology available at the hospital and the expertise of the treating physicians and surgeons. A decision support system designed for use by a Tumor Board would not dictate treatment choices, but would be a helpful tool in providing an objective means of considering all available treatment options for specific patients, based on the DPM and MBME.

Conclusion

PPPM may have the potential to eventually improve the nature of healthcare delivery. However, the tools required for a practical and comprehensive form of PPPM, that is capable of handling the vast amounts of medical information that is currently available, are currently lacking. This book seeks to provide a rationale for combining and integrating diagnostic and therapeutic management with IT, in a manner that supports patients through their continuum of care from initial presentation through cure, or hospice care, as warranted. It is imperative that any program

devised to explore and develop personalized healthcare delivery must be firmly rooted in clinically confirmed and accepted methodologies and technologies.

It is further understood that the concepts and implementation of MGT, PSM, and PPPM are in their infancy and that our approach may prove to be one of many approaches. The program presented at this time will also, undoubtedly, be modified as the concepts and implementations develop and mature, with subsequent development of new insights and techniques.

References

1. Golubnitschaja O, Costigliola V, EPMA (2012) General report & recommendations in predictive, preventive and personalised medicine 2012: white paper of the European Association for Predictive, Preventive and Personalised Medicine. EPMA J 3:14
2. Characiejus D, Hodzic J, Jacobs JJL (2010) "First do no harm" and the importance of prediction in oncology. EPMA J 1:369–375
3. Armstrong K (2012) Can genomics bend the cost curve? JAMA 307:1031–1032
4. Smith AK, White DB, Arnold RM (2013) Uncertainty—the other side of prognosis. N Engl J Med 368:2448–2450
5. Mallman MR, Staratschek-Jox A, Rudlowski C, Braun M, Gaarz A, Wolfgarten M, Kuhn W, Schultze JL (2010) Prediction and prognosis: impact of gene expression profiling in personalized treatment of breast cancer patients. EPMA J 1:421–437
6. Woodcock J (2011) Biomarkers: physiological & laboratory markers of drug effect. Center for drug evaluation and research. Food and Drug Administration. http://www.cc.nih.gov/training/training/principles/slides/Biomarkers-2010–2011-text.pdf. Accessed 8 April 2012
7. Lemke HU, Berliner L (2010) Personalized medicine and model-guided therapy. In: Niederlag W, Lemke HU, Rienhoff O (ed) Personalisierte Medizin und Informationstechnologie, Bd 15. Health Academy, Dresden, pp 39–48
8. Lemke HU, Berliner L (2010) Personalized medicine and patient-specific modelling. In: Niederlag W, Lemke HU, Golubnitschaja O, Rienhoff O (ed) Personalisierte Medizin, Bd 14. Health Academy, Dresden, pp 155–164
9. Bruix J, Sherman M (2011) AASLD practice guideline. Management of hepatocellular carcinoma: an update. Hepatology 53:1020–1022
10. Bruix J, Sherman M (2010) AASLD Practice Guideline. Management of hepatocellular carcinoma. http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCCUpdate2010.pdf. Accessed 20 Nov 2011
11. European Association for the Study of the Liver. European Organisation for Research and Treatment of Cancer (2012) EASL–EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 56:908–943

Chapter 2
The Digital Patient Model and Model Guided Therapy

Leonard Berliner and Heinz U. Lemke

Abstract One of the goals of this book is to provide a roadmap for the development of information technology (IT) tools to facilitate Predictive, Preventive, and Personalized Medicine (PPPM). Our approach to the management of medical information is based on model theory that has arisen from a conceptual transformation from image-guided patient management to a model-centric world-view or model-guided patient management. This approach seeks to implement a comprehensive form of Model-Guided Therapy (MGT) through the use of a Therapy Imaging and Model Management System (TIMMS), and its application as a decision support system for achieving MGT. It is our hypothesis that if we can utilize patient-specific modeling techniques to generate valid Digital Patient Models (DPMs) we may be able to develop a statistically valid methodology for predicting diseases and treatment outcomes, preventing diseases or complications, and developing personalized treatment regimens. We are calling this proposed system Model-Based Medical Evidence (MBME) and are engaged in its development. It is further postulated that Multi-Entity Bayesian Networks (MEBN) used in the construction of the DPM will be utilized in the development of a practical decision support system.

Keywords Personalized medicine · Hepatocellular carcinoma · Information technology · Model guided therapy · Therapy imaging and model management system (TIMMS) · Digital patient model · Patient-specific model · Model-based medical evidence · Bayesian network

L. Berliner (✉)
New York Methodist Hospital, Brooklyn, NY, USA
e-mail: LeonardB23@AOL.com

Weill Medical College of Cornell University, New York, USA

H. U. Lemke
Technical University of Berlin, Berlin, Germany
e-mail: hulemke@cars-int.org

University of Southern California, Los Angeles, USA

L. Berliner, H. U. Lemke (eds.), *An Information Technology Framework for Predictive, Preventive and Personalised Medicine,* Advances in Predictive, Preventive and Personalised Medicine 8, DOI 10.1007/978-3-319-12166-6_2

2.1 Introduction

As stated in Chap. 1, one of the goals of this book is to provide a roadmap for the development of information technology (IT) tools to facilitate Predictive, Preventive, and Personalized Medicine (PPPM). Our approach to the management of medical information is based on model theory that has arisen from a conceptual transformation from image-guided patient management to a model-centric world-view or model-guided patient management. This approach seeks to implement a comprehensive form of Model-Guided Therapy (MGT) that extends beyond the scope of image guidance and can be used as a decision support system in the treatment of patients. There are three basic domains of discourse that need to be managed by a comprehensive medical and surgical MGT system: data, workflow, and synthesis of information. The two basic functions of such a system are Patient-Specific Modeling (which is involved with data collection, synthesis, and simulation) and Process Modeling (which is related to the execution of a surgical workflow).

2.1.1 Therapy Imaging and Model Management System

A Therapy Imaging and Model Management System (TIMMS) and its application as a surgical assist system for achieving MGT has been described [1]. A TIMMS is a comprehensive medical-surgical communication and assist system (Fig. 2.1) that is composed of interconnected computer hardware and software components such as Engines, Agents, Repositories, and IT infrastructure, and provides the following features and functions throughout the course of medical and surgical treatment:

1. Standardized interfaces for communication and mechatronics (such as robotics), thereby creating a unified environment for the input and output of data (including the representation and display of information and images, as well as the electromechanical control of surgical and navigational devices);
2. Creation and maintenance of a Digital Patient Model (DPM) based on generic Patient-Specific Models (PSMs) modified by the addition of patient-specific data, thereby providing a multi-scalar, comprehensive, precise, personalized representation of the patient;
3. Creation and maintenance of a system for Process Modeling of all aspects of the surgical workflow, to ensure efficiency, learning, and safety throughout operative procedures;
4. Real-time knowledge management and decision support system (Kernel for Workflow and Knowledge and Decision Management) thereby promoting optimized diagnostic, prognostic, and therapeutic decisions throughout the treatment workflow. The key role here is to assist and optimize the practice of medicine in the face of incomplete medical knowledge, which is an inherent part of clinical practice.

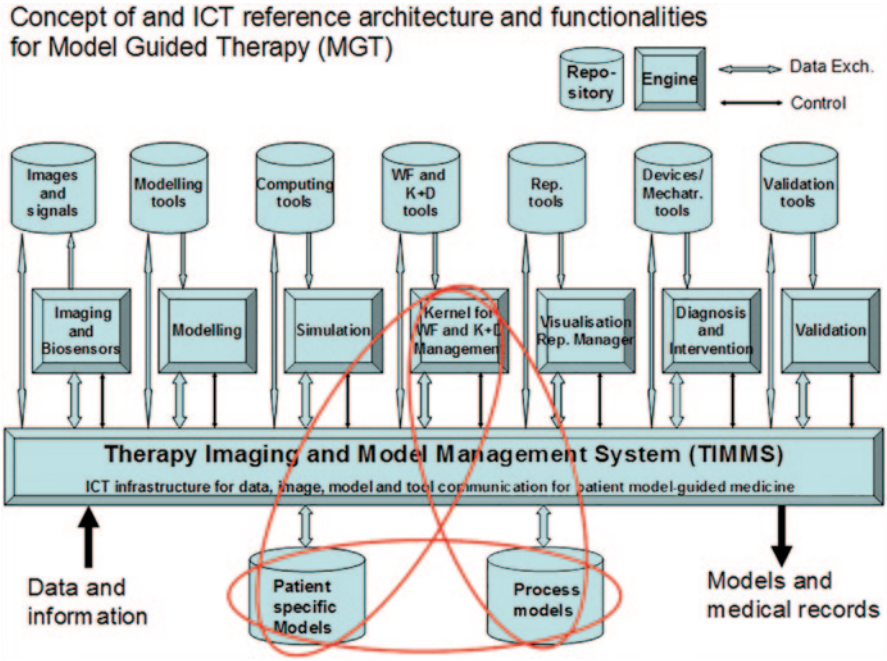

Fig. 2.1 The structure of the therapy imaging and model management system (TIMMS) that may provide much of the IT framework for personalized medicine. The kernel for workflow and knowledge and decision management, the patient specific models repository and the process models repository are the central components for the development of digital patient models through the process of patient-specific modeling (Lemke and Golubnitschaja The EPMA Journal 2014, 5, p. 8). (Legend: *ICT* Information and Communication Technology; *WF* Workflow; *K + D* knowledge and decision; *Rep* Representation; Mechatr Mechatronic)

5. Validation system, thereby providing quality assurance, patient safety, system security, and processing of medical evidence.

There are seven TIMMS engines that may be defined as software modules that can be executed on an appropriate computing machine to provide functionalities. These engines relate to imaging and biosensor data acquisition, modeling, simulation, workflow and knowledge and decision management, visualization, intervention, and validation.

The TIMMS engines, repositories, and IT infrastructure initially were designed to facilitate model-guided surgical therapy. Subsequently, the TIMMS structures and functions have been generalized to apply to all forms of model-based medical management (suitable for patients with cancer, diabetes, etc.) and may be abbreviated MIMMS (Medical Imaging and Model Management System).

For the purposes of developing a working TIMMS or MIMMS for PPPM, it is necessary to understand the functions of the central TIMMS engine (Kernel for Workflow and Knowledge and Decision Management; Kernel), the Modeling Engine, and their substrate, the DPM.

The Kernel provides the strategic intelligence for therapeutic planning and workflow execution. Often this module (or parts thereof) is integrated into some of the other engines, as the need demands. This important computing Kernel (or "brain") of the system may use different forms of logic, different database structuring, agents, machine learning, and other forms of artificial intelligence, depending on the specific applications of the procedure or procedures being performed. Agents may be defined as software modules, containing some form of intelligence, which, with some degree of autonomy and adaptability, carry out functions or tasks. A full description of the role of the Kernel is beyond the scope of this book, but attention will be focused on the design, development, and management of the DPM. The use-case, as developed in this book, will focus on the requirements for a DPM to facilitate the management of patients with HCC.

2.1.2 Digital Patient Model

In every day terms, the DPM may be thought of as a representation of the patient, composed of both the static and dynamic features of the human organism, maintained within a multi-layered database structure [2]. Certain features are relatively stable, such as the DNA sequence within the chromosomes, or a radiograph of an extremity, while other features are in a constant state of fluctuation, such as pulse and respiration. In addition, the clinical significance of physiologic fluctuations may vary in different clinical settings. Thus, the DPM must be capable of managing a constellation of interacting static and fluctuating causes and effects of varying degrees of certainty, predictability, and significance. As the database of knowledge underlying the creation and maintenance of DPMs increases, a statistically valid tool that increases in accuracy as more data are added (to be discussed below), will be available for assistance in medical and surgical management in the face of incomplete medical knowledge.

Ideally, the DPM has the capabilities to capture patient specific information in a way that facilitates evaluation and application of that information:

a. The DPM can receive and process information from an unlimited number of sources, and at a rate required for real-time activity.
b. The DPM is comprehensive, yet flexible enough to be extensible at any time.
c. The information contained within the DPM can be extracted by a wide variety of selection parameters, templates, and constellations.
d. Extraction is flexible and controllable by the end-user and researchers.
e. Extraction may take in a variety of formats or representations—charts, tables, lists, images, graphs, and models.
f. The DPM allows and facilitates simulations, prognosis, prediction, and therapy planning. One of the key functions of the DPM is to allow simulated evaluation of hypothetical, alternative therapies to predict and optimize patient outcomes, and to anticipate adverse effects of the proposed therapies.

g. The DPM allows comparisons and compilations with other DPMs to collect Model-Based Medical Evidence, Population-Based Medical Evidence, and Disease-Based Medical Evidence.
h. The DPM facilitates actions with workflows, algorithms, and databases.

Features of the patient that are amenable to graphical representation are maintained as references within the DPM database structure to Picture Archiving and Communications Systems (PACS) and repositories that allow access to the actual images, for example, through functionalities of a suitable IT infrastructure for simulations and interventions. This allows medical images to be loaded into advanced medical workstations for purposes of treatment planning and simulation, as well as allowing real-time interaction with hardware and software for image-guided interventions, such as radiation therapy and minimally invasive therapies.

Those features of the DPM that are measurable and/or have cause-and-effect relationships, and can be quantified may be dealt with in a different manner than non-quantifiable features, such as constitution and appearance. In Bayesian terms, these quantifiable features, or entities, may be thought of as a dynamic set of data elements, i.e. attributes with interconnected and fluctuating probability distributions.

The probability distribution of each attribute or variable reflects and represents the state of uncertainty associated with the knowledge about a particular feature of an individual patient. The existence of relationships among attributes, represented by appropriate links and their binding strength, are also subject to probability distributions. The value of each attribute probability distribution lies within a statistically definable range of normal and abnormal values. The boundaries of the values for each attribute, and the volatility of the changes of these values, vary in health and disease, and at different ages, and may be subject to further alterations based on the body's homeostatic mechanisms, as well as constitutional, genetic and epigenetic, and environmental factors, including prior medical and surgical interventions. It is therefore reasonable to assume that the described situation surrounding the patient is amenable to be represented by a form of Bayesian Network. However, standard Bayesian Networks that have been utilized in previous medical decision support and knowledge management systems are inadequate for this purpose. A Multi-Entity Bayesian Network (MEBN) [3] is available that can overcome the limitations of standard Bayesian Networks.

A MEBN is a logic system that integrates first-order logic with Bayesian probability theory and can provide a descriptive and functional framework for the quantifiable components or entities of the DPM. These entities of the DPM will be stored as attributes within both a PSM Database (to be described below) and the appropriate nodes of the graph created for the MEBN.

The First and Second Order Information Entities (IEs) for the generic PSM may relate to the entities listed in Tables 2.1 and 2.2. The attributes of these IEs may be obtained through links with the appropriate databases, spreadsheets, Electronic Medical Records (EMRs), and repositories, for example by means of the functionalities of a suitable MIMMS. These Primary and Secondary IEs are broken down

Table 2.1 First order information entities

First order information entities	
1	Genome
2	Proteome
3	Cellular
4	Tissue
5	Organ
6	Organism

Table 2.2 Second order information entities

Second order information entities	
1	General health status
2	Central nervous system
3	Sensory organs
4	Cardiovascular
5	Gastrointestinal
6	Respiratory
7	Genitourinary
8	Endocrine
9	Nutritional/metabolic
10	Hematological/lymphatic
11	Musculoskeletal
12	Integument
13	Psychological
14	Genetic/proteomic
15	Prostheses/devices
16	Growth/development
17	Aging
18	Environmental factors

into Third Order IEs and further subdivisions that include the vast, and continually expanding, list of patient-related information.

A finer granularity is developed and refined as more patient and disease specific attributes are enumerated as third and fourth order (and beyond) IEs. A general template for a range of attributes of a generic PSM is presented in Fig. 2.2. The central area of the template represents the current status of the generic PSM, and is divided into three categories: pre-determined factors, anatomic factors, and physiologic/functional factors. Allowances are made for those influences that have a direct role on altering the PSM—processes, such as aging, development, diseases, surgical procedures; extrinsic inputs or interventions; intrinsic mediators. A separate section of the template displays the PSM output that generates the current or working model of the actual patient, or the DPM.

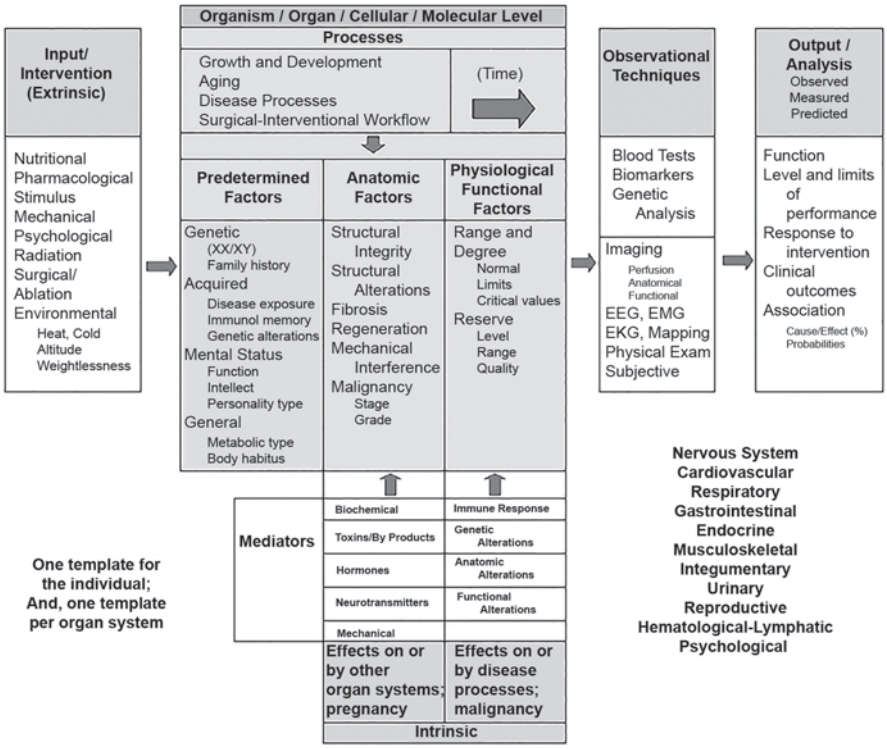

Fig. 2.2 A generic PSM template. The DPM is generated when the specific factors and values are entered into the full set of templates and the output is analyzed and may be used for prediction

It can be surmised that the full collection of templates that includes each of the First and Second Order IEs represents a vast amount of information that would be overwhelming for rapid clinical problem solving, given the capabilities of today's computer systems. It would, however, be possible to store this information in properly designed database systems with the appropriate database architecture. It is also proposed that for management of clinical problems in a feasible manner, a specific selection of PSM attributes (or PSM Constellation) relevant to the clinical problem at hand, can be identified and formed into a limited or working DPM. The attributes of the DPM would be available to the clinician in whatever forms are desired and useful—graphic, tabular, descriptive, and 3-D model. The ability to make queries regarding patient status, diagnosis, treatment plans, and prognosis would be provided. (This approach would not preclude independent, separate, and deeper database queries and data-mining from the complete PSM database [or, databases] to detect as yet unrecognized causes, effects, and outcomes, and for other forms of research.)

The PSM Constellation may be presented as a pictorial representation, as in Fig. 2.3, with only the First-Order IEs being shown. However, the PSM Constellation is multi-scalar and contains, within the computer structure the active entities of

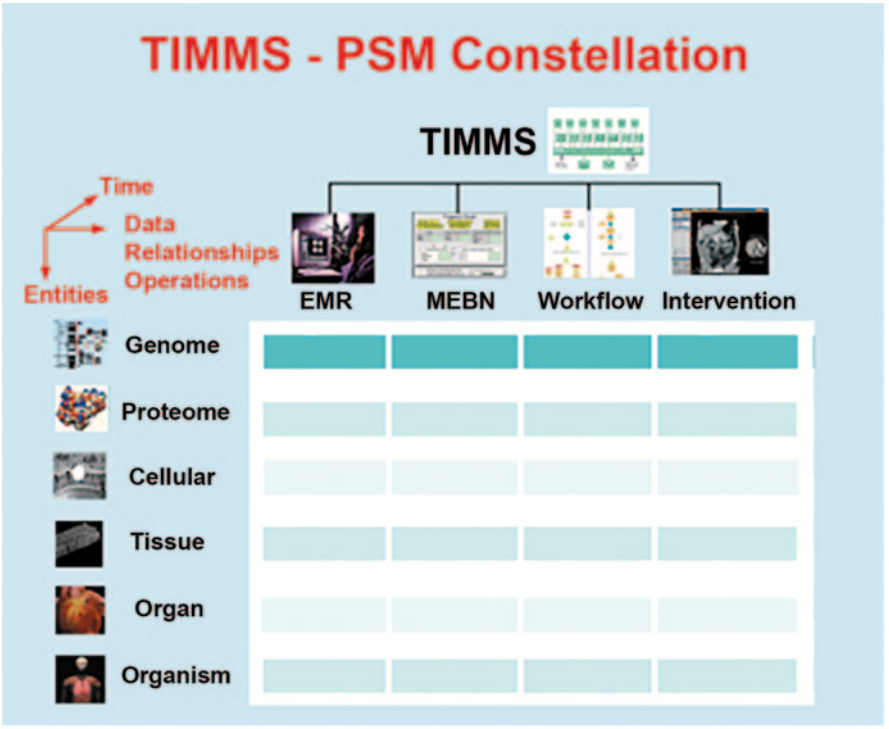

Fig. 2.3 Generic PSM constellation grid showing first order information entities

all orders. Linkages between any entity, of any order, (on the y-axis) and an associated TIMMS Component (on the x-axis) may be displayed as needed.

The attributes defining the DPM will change over time, especially during the course of a medical treatment or surgical intervention. It is one of the roles of the DPM and associated software tools to gather, calculate, record, tabulate, or otherwise organize, maintain, and communicate values for each of these entities, and to predict and record the changes in values brought about through the interactions with the entities. These changes over time would be reflected in changes to the grid along the z-axis.

2.1.3 Multi-Entity Bayesian Network (MEBN)

A MEBN [3] is a logic system that integrates first-order logic with Bayesian probability theory and can provide a descriptive and functional framework for the DPM. It is the nature of a MEBN to increase in overall accuracy as the precision of the data used to generate the various component probabilities increases (see below).

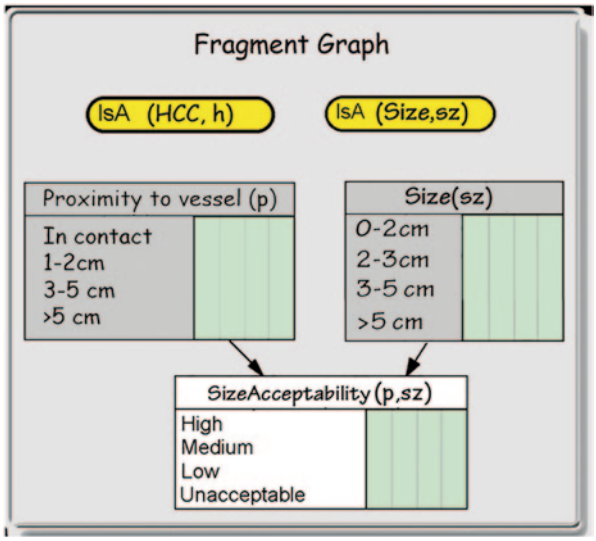

Fig. 2.4 MFrag. This MFrag demonstrates the relationships between the **a** proximity of a discrete HCC lesion. **b** a nearby vessel, and **c** the size of the lesion. (Preliminary draft; under development)

With the addition of sufficient context-appropriate patient-specific data, it is hypothesized that the MEBN will provide a flexible and sufficiently accurate model of a patient, and will also provide the necessary framework for the associated situational awareness and decision support that will be required for the performance of MGT, as well as the generation and validation of Model-Based Medical Evidence (MBME) when generated through MGT.

Structurally, MEBN logic expresses probabilistic knowledge as a collection of MEBN fragments (MFrags) organized into MEBN Theories (MTheories) [3]. An MFrag represents a conditional probability distribution of the instances of its resident random variables, given the values of instances of their parents in the Fragment graphs and given the context constraints. An example of an MFrag that might be used in conjunction with other MFrags to predict the outcome of an ablation treatment of HCC is presented in Fig. 2.4. There is no theoretical limit to the number of MFrags that may be used in an MEBN.

A collection of MFrags represents a joint probability distribution over an unbounded, possibly infinite number of instances of its random variables. The joint distribution is specified by means of the local distributions together with the conditional independence relationships implied by the fragment graphs. Context terms are used to specify constraints under which the local distributions apply [3].

A collection of MFrags that satisfies consistency constraints, ensuring the existence of a unique joint probability distribution over its random variables, is called an MTheory. MTheories can express probability distributions over truth values of arbitrary First Order Logic sequences and can be used to express domain-specific ontologies that capture statistical regularities in a particular domain of application [3].

In addition, MTheories can represent particular facts relevant to a given reasoning problem. Conditioning a prior distribution represented by an MTheory on its findings is the basis of probabilistic inference with MEBN logic [3].

The MFrags may be assembled to form graphs, e.g. Situation Specific Bayesian Networks (SSBN), for evaluating hypothetical conditions [3]. Support for decision constructs in MEBN is provided via Multi-Entity Decision Graphs (MEDG) that are related to MEBN the same way influence diagrams are related to Bayesian Networks [3]. An MEDG can be applied in any application that requires optimizing a set of alternatives (i.e.—an MEDG policy) over the given constraints of a specific situation. MEBN logic also provides a means of learning the structure of a MEBN Theory on the basis of data (i.e. Bayesian learning), while parameter learning can be expressed as inference in MEBN theories that contain parameter random variables. Thus, the MEBN provides comprehensive methodology for DPM description, as well as tools for decision support.

2.1.4 UnBBayes

The design of a MEBN is facilitated through the open source software called UnBBayes [4, 5]. This is a probabilistic network framework with a graphical user interface (GUI) and an application programming interface (API) supporting applications for inference, sampling, learning, evaluation, and other functions.

To create a MEBN in UnBBayes, for a generic PSM relating to HCC, it is important to identify and define the domain of discourse of interest and then to select the relevant IEs for this domain. IEs may be derived from the information accumulated in a clinical cancer center—medical examination, medical imaging, endogenous human characteristics (e.g. age, gender, and genetics), and exogenous factors (e.g. alcohol consumption and pathogens such as hepatitis exposure). Criteria need to be established that enable classification and organization of the identified IEs.

This activity will be accomplished through the extraction of IEs (which will be identified in the following Chapters), and the establishment of adequate probabilities for the criteria and importance ratings (weights) for the IEs (which will be addressed in future work). After this information is accumulated, sets of IEs will be formed that can be regarded to be logically connected. Subsequently, independent IEs will be assigned as Resident Nodes with their own MFrags.

After finalizing an MTheory with a complete set of MFrags, a generalized patient entity will be created. From this generic entity, instances for every real patient may be created. Finally, findings for a specific patient may be assigned to a particular instance and the corresponding MTheory may then be visualized as a graph with the given IEs, probabilities, and findings. It is important to keep in mind that the relationship between IEs (or, random variables) in the MEBN can be updated as more experience and evidence are added to the system, according to Pearl's Bidirectional Belief Updating Algorithm [6, 7]. Therefore, in the initial development of the MFrags and MTheories, close approximations of probabilities as established

by experts, can provide an effective starting point with the knowledge that the overall system will increase in accuracy and validity as more data are added.

A vast number of biomarkers, from any source, can be maintained in the Repositories contained in a TIMMS environment. These biomarkers can therefore be made available for incorporation, as IEs, into new MFrags and into MEBNs as new information becomes available. This too, will promote continued growth and accuracy of the MEBNs and PSMs as research adds new information.

Conclusion

The basic features of an IT system built upon a MEBN and TIMMS have been described in this Chapter. In the following Chapters, the clinical information required for constructing a preliminary MEBN for HCC will be reviewed and presented. Appropriate IEs will be extracted from the data in these Chapters so that in future works the preliminary MEBN, its MFrags, and a generic PSM template for HCC can be developed.

Once the preliminary MEBN and PSM template have been established, the addition of patient records, images, and outcomes in the appropriate TIMMS Repositories will allow the creation of a functioning MEBN. It is our goal to utilize this IT approach to medical management to maximize the use of established medical information, to assist decision making, to advance our understanding of health and disease when there is incomplete medical knowledge, and to facilitate PPPM.

References

1. Lemke HU, Berliner L (2010) Personalized medicine and model-guided therapy. In: Niederlag W, Lemke HU, Rienhoff O (eds) Personalisierte Medizin und Informationstechnologie, vol 15. Health Academy, Dresden, pp 39–48
2. Lemke HU, Berliner L (2010) Personalized medicine and patient-specific modelling. In: Niederlag W, Lemke HU, Golubnitschaja O, Rienhoff O (eds) Personalisierte Medizin, vol 14. Health Academy, Dresden, pp 155–164
3. Laskey KB (2008) MEBN: a language for first-order bayesian knowledge bases. Artif Intell 172(2–3):140–178
4. UnBBayes (2013) http://unbbayes.sourceforge.net/. Accessed 11 Nov 2013
5. Carvalho RN, Laskey KB, Costa PCG, Ladeira M, Santos LL, Matsumoto S (2010) UnBBayes: modeling uncertainty for plausible reasoning in the semantic web. Semantic Web. Gang Wu (Ed.) ISBN: 978-953-7619-54-1, InTech, DOI: 10.5772/7315. Available from: http://www.intechopen.com/books/semantic-web/unbbayes-modelinguncertainty-for-plausible-reasoning-in-the-semantic-web. Accessed 28 March 2011
6. Pearl J (1988) Probabilistic reasoning in intelligent systems: networks of plausible inference. Morgan Kaufmann Publishers, San Mateo
7. Bayesian Networks (2013) http://www.pr-owl.org/basics/bn.php#pearl1988. Accessed 17 Nov 2013

Chapter 3
Hepatocellular Carcinoma and Patient Assessment

Smruti Mohanty, Sid Verma, David Dosik, Hesham Hazin and Leonard Berliner

Abstract Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and the fifth most common cancer worldwide. Due to its aggressive nature and poor survival rate, incidence and mortality rates are almost equivalent, accounting for approximately 500,000 deaths annually. Since HCC is most often seen in patients with chronic liver disease or cirrhosis, the incidence of HCC and the epidemiology of underlying liver diseases are closely linked. This Chapter provides a review of the literature regarding HCC including epidemiology; risk factors; infectious etiologies; pathology, microenvironment, and biomarkers; screening and diagnostic technologies; and treatment modalities. The information accumulated in this review will be used to generate the information entities (IEs) that will be used to populate the patient databases and Multi-Entity Bayesian Networks (MEBNs) required for generating Digital Patient Models (DPMs) to facilitate data mining and decision support. For any given patient with HCC, the DPM will need to be continuously updated to ensure appropriate guidance of the patient throughout the course of their disease.

Keywords Personalized medicine · Hepatocellular carcinoma · Hepatitis B · Hepatitis C · Chronic alcoholism · Cirrhosis · Pathology · Risk factors · Biomarkers · Genomics · Diagnosis · Screening · Imaging · Staging

S. Mohanty (✉) · S. Verma · D. Dosik · H. Hazin · L. Berliner
New York Methodist Hospital, Brooklyn, NY, USA
e-mail: srm9006@nyp.org

S. Mohanty · D. Dosik · L. Berliner
Weill Medical College of Cornell University, New York, USA

S. Verma
e-mail: vermasi@hotmail.com

D. Dosik
e-mail: ddosik@aol.com

H. Hazin
e-mail: heshamhazin@yahoo.com

L. Berliner
e-mail: LeonardB23@AOL.com

L. Berliner, H. U. Lemke (eds.), *An Information Technology Framework for Predictive, Preventive and Personalised Medicine,* Advances in Predictive, Preventive and Personalised Medicine 8, DOI 10.1007/978-3-319-12166-6_3

3.1 Introduction

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and the fifth most common cancer worldwide [1]. Due to its aggressive nature and poor survival rate, incidence and mortality rates are almost equivalent, accounting for approximately 500,000 deaths annually [1]. Since HCC is most often seen in patients with chronic liver disease or cirrhosis, the incidence of HCC and the epidemiology of underlying liver diseases are closely linked. HCC diagnosed after the onset of symptoms portends a poor prognosis with a 5-year survival of 0–10%, highlighting the importance of screening for HCC in high risk patients and early treatment. It is important to note that at the time of diagnosis, 20–60% of small lesions are found to be multifocal and, despite adequate preoperative assessment, up to 30% of tumors in patients with cirrhosis are under-staged [2].

3.1.1 Pathology of Hepatocellular Carcinoma

The development of HCC is currently felt to take place in a sequential process, with transformation from a small monoclonal dysplastic focus (<1 mm) to a low-grade dysplastic nodule (LGDN) (>1 mm), and then to a high-grade dysplastic nodule (HGDN) before it evolves into a true carcinoma [3]. The absence of a true structured basement membrane along the hepatic sinusoids makes it difficult to distinguish an early invasive HCC from a HGDN. One of the distinguishing features of early HCC is stromal invasion into the portal tracts. In addition, early diagnosis of HCC is supported by molecular markers (glypican 3, heat shock protein 70 (Hsp70), and glutamine synthetase). If two of these three markers are positive, a sensitivity of 72% and specificity of 100% is reached for the diagnosis of HCC [3]. Transformation into carcinoma is further accompanied by the recruitment of an arterial blood supply, venous invasion, and, finally, metastasis. Some of these features will be exploited in the early detection of HCC by contrast enhanced CT and MRI (to be discussed below and in Chap. 4).

It is currently felt that conditions affecting hepatic progenitor cells (HPCs) (K19+, K7+, EpCAM+, CD133+), capable of differentiating into hepatocytes (K19−, K7−) or cholangiocytes (K19+, K7+, mucin+), provide a common pathway for the development of liver tumors, and that liver carcinomas are monoclonal, i.e. derived from a single cell [3]. There is evidence that oxidative stress and chronic inflammation form common carcinogenic risk factors in all primary liver cancers. Chronic viral hepatitis B and C, alcoholic and nonalcoholic steatohepatitis, metabolic diseases, and mutagens, such as aflatoxins, are the most important risk factors for the development of HCC. Chronic inflammatory biliary diseases, such as primary sclerosing cholangitis, hepatolithiasis (intraductal gallstones), and liver fluke infestation by Opisthorchis viverrini and Clonorchis sinensis, are known risk factors for the development of cholangiocarcinoma (CC) [3].

A number of genetic markers have been associated with poor prognosis in HCC (more rapid progression, earlier recurrence after surgical resection or trans-

plant) and include primarily Keratin 19 (K19), Keratin 7 (K7), EpCAM, AE1-AE3, alpha-fetoprotein (AFP), MRP1, and vimentin. In addition, high expression of adenosine triphosphate-binding cassette (ABC) transporters, such as MDR1, ABCG2, and ABCC2 renders the cells resistant to chemotherapy, including cisplatin and doxorubicin, which can be reversed with inhibitors or by using an antisense approach [3].

The relationship between HCC and infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), and with cirrhosis is of paramount importance. Up to 80% of HCC is attributable to HBV or HCV worldwide [4, 5]. The risk of HCC is increased 5–15-fold in chronic HBV carriers [6,7] and 11.5–17-fold in HCV-infected patients [7, 8]. Antiviral therapy is effective in preventing HCC in only a small proportion of patients [9, 10] and sustained clearance of HBV or HCV may be difficult to accomplish, particularly among cirrhotic patients. Of all HCCs, 80–90% develops in a cirrhotic liver [11]. After 20–30 years of chronic infection, 20–30% of patients develop liver cirrhosis. HCC develops at an annual rate of 1–7% in HCV-infected cirrhotic patients [6] and 3–8% in HBV-infected cirrhotic patients [12].

3.1.2 Clinical Liver Cancer Center

A heterogeneous population of patients will be encountered in a clinical liver cancer center (CLCC). Ideally, this group of patients will include: first, a population of patients who are at risk for developing HCC and can be triaged into screening protocols; second, patients whose clinical status or diagnostic testing suggests the presence of primary or metastatic liver cancer; and third, patients with a definitive diagnosis and are either under treatment or are in remission and are being monitored.

A community outreach program can be developed as part of a CLCC to identify and educate patients early in the course of their disease, and to maximize the efficacy of treatments and services being offered. This includes a referral hotline; mailings; lectures provided for the community; screening for high risk patients; and access to Social Services.

A basic Triage Algorithm (Fig. 3.1) is provided for the flow of patients, who present from a variety of sources with a possible liver tumor. The patient will first be evaluated by their primary care physician, or in absence of this, be a member of the medical team of the CLCC. At times the patient may be referred directly to the Medical Oncologist, Oncological Surgeon, Interventional Radiologist, or Radiation Oncologist. Presentation at Tumor Board and multi-specialty clinical cancer conferences is of extreme importance since a multi-disciplinary approach is essential for optimal treatment planning for each patient. In all cases, a complete and thorough review of previous medical records, as well as a current work-up for diagnosis and staging is to be completed.

In most cases, the clinical presentation will suggest whether the patient is at risk for primary or metastatic liver cancer. Once it is established that there is sufficient evidence of hepatic tumor, the initial diagnostic work-up of the patient will require adequate and cost-effective tests to confirm the presence of malignancy and the

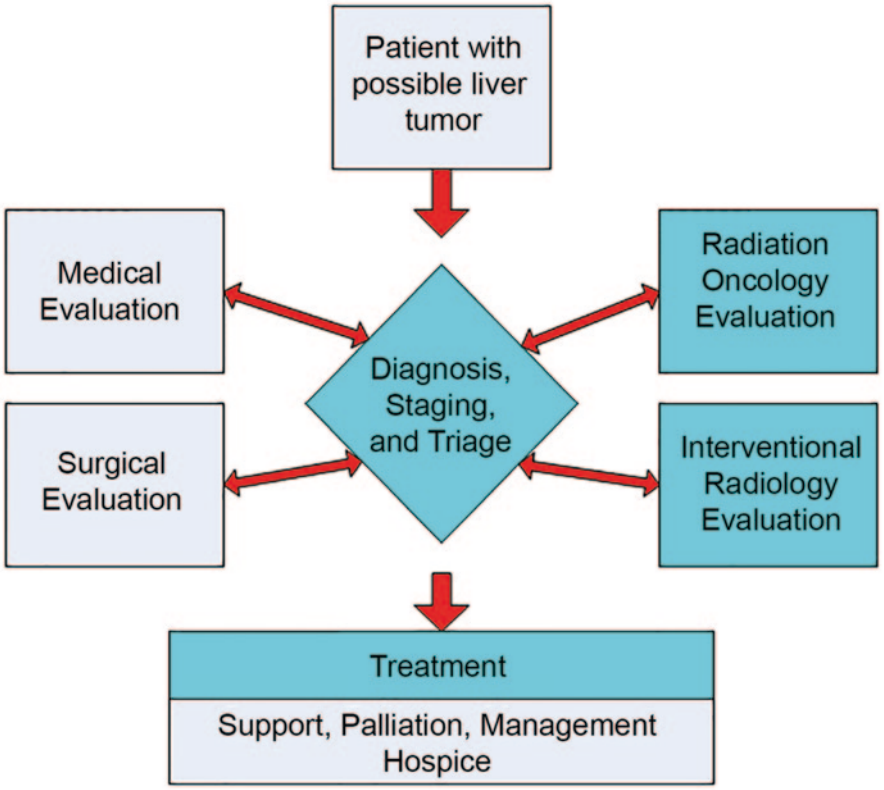

Fig. 3.1 Triage algorithm for patients with suspected hepatocellular carcinoma

cell type, and to provide sufficient information to design and begin a treatment plan based on current guidelines and algorithms. The diagnostic work-up will include complete medical history, social and family history, physical examination, laboratory testing, and, diagnostic imaging. Laboratory testing will include metabolic profile, liver function tests, complete blood count, clotting tests, and tumor markers, such as AFP. Initial diagnostic imaging may include Computed Tomography (CT), Ultrasound (US), Magnetic Resonance Imaging (MRI) including Functional MRI, and, Photon Emission Tomography (PET).

3.1.3 Screening for Hepatocellular Carcinoma

Screening for HCC in high risk individuals is recommended since early identification of small tumors has been reported to lead to improved survival [13, 14]. High risk individuals include hepatitis B carriers and those with cirrhosis caused by HCV, alcoholic liver disease, genetic hemochromatosis, primary biliary cirrhosis, and autoimmune hepatitis [1] (Table 3.1).

Table 3.1 Persons who require screening for HCC. (Adapted from [16])

Hepatitis B carriers (HBsAg positive)	Non hepatitis B carriers with cirrhosis
Anyone with cirrhosis	Hepatitis C
Asian males > 40 years	Primary biliary cirrhosis
Asian females > 50 years	Alcoholic cirrhosis
Africans > 20 years	Genetic Hemochromatosis
Any family history of HCC	Alpha− 1- antitrypsin deficiency (possibly)
Long term HBV carriers who lose HBsAg/ develop anti-HBs	Cirrhosis from any other cause

US has been recommended as a noninvasive imaging modality for screening for HCC; with a > 60 % sensitivity and > 90 % specificity in detecting HCC [15]. However, there may be considerable variations in detection rates based on operator experience, body habitus, the use of contrast agents, the size of liver mass, and the presence of cirrhosis [16]. Diagnostic features of HCC on US include irregular margins and internal echoes; however, smaller lesions can be hypoechoic [17]. Due to its low cost and wide availability, this modality is often used for screening in high risk patients. Screening is generally performed by experienced personnel in these patients at 6 month intervals with an US of liver [18]. Shorter follow-up interval (every 3–4 months) is recommended when a nodule of less than 1 cm has been detected and as a follow-up strategy for patients who have undergone resection or locoregional therapies [18].

AFP is a serologic marker that is elevated in many patients with HCC and is usually diagnostic in patients with at serum levels > 500 mcg/L [19]. However, AFP may also be elevated in pregnancy, those with HCV, cirrhosis without evidence of tumor [20], and in acute and chronic hepatitis [21]. In addition, serum AFP levels may also be normal in patients with a small HCC [22]. With a cutoff value of 25 ng/ml the sensitivity and specificity of AFP in diagnosing HCC has been reported as 69 % and 87 % respectively [23]. Given the limited sensitivity and specificity, AFP should not be used alone as either a screening agent or diagnostic tool [24]; however, AFP may be helpful in making a diagnosis of HCC in conjunction with other imaging modalities. Analysis of recent studies shows that AFP determination lacks adequate sensitivity and specificity for effective surveillance (and for diagnosis) [25, 26].

Another biomarker, des-gamma-carboxy prothrombin (DCP), is a prothrombin protein measured in the serum that is increased in patients with HCC [27]. DCP is thought to be a result of defective post-translational carboxylation that is found in patients with HCC [28]. A recent study in a Western population comparing AFP and DCP showed that DCP was more sensitive and specific in differentiation HCC from benign chronic liver disease [27]. However, in a more recent study, DCP did not offer substantial advantages with respect to AFP [28]. In addition, DCP levels have been associated to portal vein invasion and advanced tumor stage, a fact that prevents the usage of this marker for early detection [18, 29].

3.1.4 Diagnosis of Hepatocellular Carcinoma

Imaging plays an important role in confirming the diagnosis of HCC, and is discussed in greater detail in Chap. 4A. It is essential that diagnostic testing be performed properly according to established protocols so that errors in diagnosis are avoided, and so that the full extent of disease is established. The basic features in diagnostic liver imaging will include: (1) the size and number of hepatic lesions; (2) the location of these lesions with respect to segmental anatomy and relationship to adjacent intrinsic and extrinsic structures, including vasculature, diaphragm, structures of the GI tract; (3) enhancement characteristics on CT and/or MRI; (4) metabolic activity on PET scan and/or functional MRI studies; and, (5) the presence or absence of extra-hepatic disease or portal vein involvement.

Images, and at times 3-D reconstructions, should be available to the treating physicians so that specific anatomical relationships can be fully evaluated when precise treatment plans are being formulated.

Lesion size has a major impact on the evaluation and implication of findings on CT and MRI imaging.

3.1.4.1 Liver Lesions > 2 cm in Diameter

In the setting of a cirrhotic liver, a lesion that measures > 2 cm and has radiographic characteristics of HCC (arterial enhancement and portal phase washout) on a dynamic imaging study such as CT or MRI, liver biopsy is not required [18, 25, 26, 30]. In addition, if serum AFP measurement > 200 ng/ml and the mass seen on CT or MRI scan has features of HCC, a biopsy of liver lesion is also not necessary. Biopsy should be obtained in all lesions > 2 cm without a characteristic vascular enhancement profile or if the lesion occurs in a non-cirrhotic liver [18, 25, 26].

3.1.4.2 Liver Lesions 1–2 cm in Diameter

Lesions measuring 1–2 cm in a cirrhotic liver may be treated as HCC if they exhibit characteristic arterial hypervascularity with washout on two imaging modalities (CT, MRI or contrast US). However, if this pattern is not observed in both imaging studies a biopsy of liver lesions should be considered [18, 25, 26].

3.1.4.3 Liver Lesions < 1 cm in Diameter

Liver nodules measuring < 1 cm should be monitored with US imaging at 3–6 month intervals. If no growth is seen in 2 years, no action is needed and routine US surveillance is recommended [18, 25, 26].

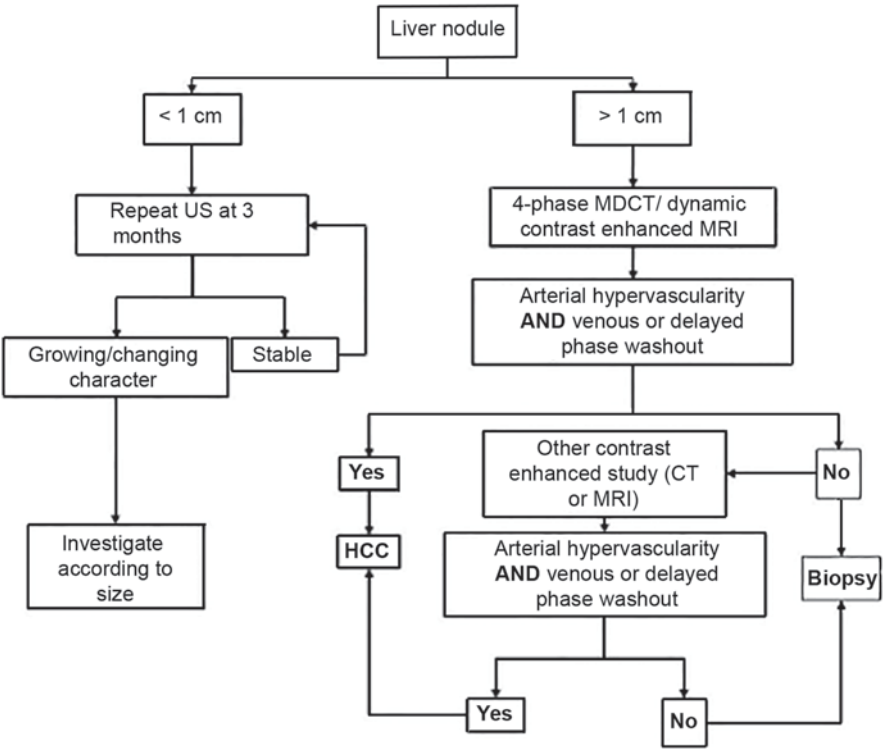

Fig. 3.2 Diagnostic algorithm for suspected HCC [25]

An imaging algorithm for the diagnosis of HCC (Fig. 3.2) has been described by the American Association for the Study of Liver Diseases (AASLD) [25].

Liver biopsy is not recommended routinely for lesions > 2 cm that have imaging characteristics compatible with HCC in patients with cirrhosis and/or a serum a-fetoprotein level > 200 ng/mL. Confirmatory diagnostic testing, such as CT directed biopsy may still be required, especially when evaluation by imaging is inconclusive. However, it is important to note that the interpretation of biopsies and distinction between high-grade dysplastic nodules and HCC is challenging. Expert pathology diagnosis is reinforced by staining for glypican 3, Hsp 70, and glutamine synthetase, because positivity for two of these three stains confirms HCC [18, 25, 26].

Although, noninvasive imaging techniques for the diagnosis of HCC prior to liver transplantation has become accepted it should be kept in mind that in three recent studies there was a false positive rate of 9–30 % with no evidence of tumor in the explanted liver [3, 31, 32, 33]. This approach may have to be reconsidered if it is found that targeted therapy determined by tissue-based histopathological and/or molecular evaluation before treatment is feasible [3].

3.1.5 Staging of Hepatocellular Carcinoma

Staging in HCC differs from other solid tumors where prognosis and treatment are based primarily on tumor size and metastasis. In HCC, underlying liver function has a high prognostic importance and is integrated into many HCC staging systems. Given the complexity in diagnosing and prognosticating HCC, which usually occurs in the setting of poor liver function, many different staging systems including Tumor Node Metastasis (TNM) [34], Okuda staging system [35], Cancer of the Liver Italian Program (CLIP) [36, 37] and Barcelona Clinic Liver Cancer (BCLC) staging system [38] have been proposed that focus on various aspects of this disease. Although there is no consensus on which staging system is preferred, current American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (AESL), and European Organisation for Research and Treatment of Cancer (EORTC) guidelines recommend the use of the BCLC system because it has been validated and integrates tumor stage, liver function, and physical status [18, 25, 26]. The TNM system classifies HCC based on the size of tumor, the number of nodules, and the presence of vascular invasion [39]. Since this staging system originally did not take into account underlying liver function, its use in predicting prognosis and guiding treatment was limited [25, 26]. An alternate version of the TNM staging system has been proposed that incorporates underlying liver histology and may be of greater clinical use. This system has been validated in patients undergoing surgical resection [40] and more recently it has been shown to accurately stratify patients after liver transplantation [41].

Similar to the TNM classification system, the Okuda system accounts for tumor size; however, it differs in that it does not take into account the presence of lymph node involvement and metastasis, and includes liver function parameters such as ascites, bilirubin, and serum albumin to stratify patients [35]. Although, the Okuda system is very useful in identifying patients with end stage HCC, it is limited in accurately differentiating patients with early and intermediate stage disease [25, 26].

The CLIP score is a mathematical score based on tumor morphology, presence or absence of portal vein thrombosis, AFP levels, and Child-Pugh class [37]. This simple scoring system has been shown to predict survival better than the TNM and Okuda systems [36, 42]; however, this system does not adequately stratify patients who may be candidates for resection or transplantation [16].

The BCLC classification system is based on performance status, extent of tumor including presence or absence of vascular invasion, bilirubin level, presence or absence of portal hypertension, and Okuda stage [38] (Fig. 3.3). This system is advantageous in that it classifies patients as very early, early, intermediate, advanced or terminal stages thereby establishing a link between stage of disease and appropriate treatment modalities [18, 25, 26]. Very early stage disease is difficult to diagnose since patients are Child-Pugh class A, have no clinical features of liver disease, and have a single HCC lesion <2 cm. If diagnosis is made at this stage, the treatment of the tumor has a theoretical 5-year survival rate of 100 % [18, 25, 26]. Early stage disease includes patients with up to three nodules, each less than 3 cm, and well preserved liver function (Child-Pugh class A and B).

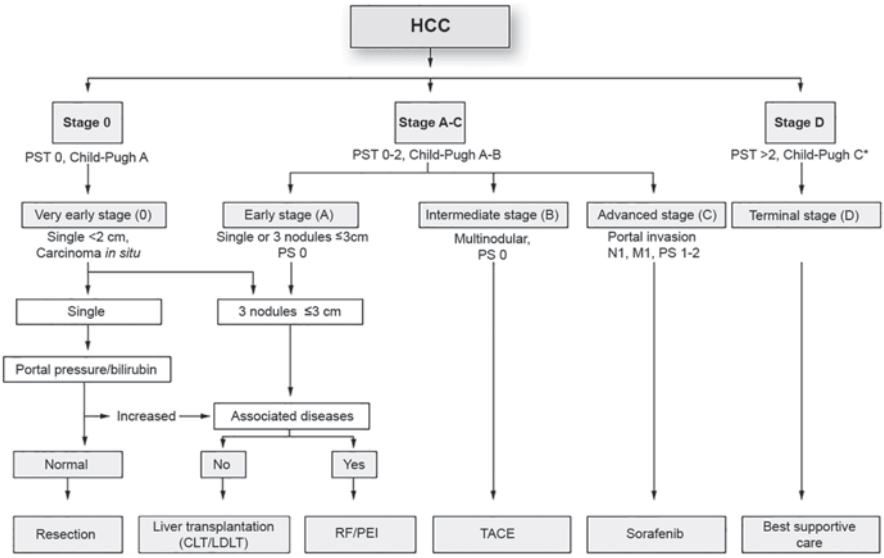

Fig. 3.3 The Barcelona Clinic Liver Cancer (BCLC) staging system for hepatocellular carcinoma—revised 2011 [18]

Appropriate treatment for early stage disease includes resection, liver transplantation or ablation with a 5-year survival rate approaching 75 % [18, 25, 26]. Those with intermediate disease are Child-Pugh class A or B and have large (> 5 cm) or multifocal disease without vascular invasion or intrahepatic spread. Transarterial chemoembolization (TACE) is most appropriate for these patients as a means to prolong survival, but not necessarily as a long term cure [18, 25, 26]. Advanced stage disease includes patients who have cancer related symptoms, vascular invasion or extrahepatic spread of tumor. Although cure is not a realistic goal in most of these patients, treatment with TACE [16] or sorafenib [43], an oral multikinase inhibitor, may prolong life. Finally, patients who have extensive disease (extensive tumor involvement, Child-Pugh class C) are classified as having terminal stage disease and have a < 10 % one year survival [16]. Treatment goals for these patients should be geared towards palliation and management of symptoms.

3.1.6 Functional Assessment

An important component in the determination of the BCLC Staging System is the Eastern Cooperative Oncology Group (ECOG) Performance Status. These scales and criteria are used to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis [44] (Table 3.2).

Table 3.2 Eastern Cooperative Oncology Group (ECOG) performance status*

Eastern Cooperative Oncology Group (ECOG) performance status*	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in [44]

3.1.7 Construction of Database

The results of the initial diagnostic work-up and assessment for each patient will be entered into the Electronic Medical Record (EMR). The categories of data and information stored in the EMR will be organized as Information Entities (IEs) to be utilized in the Multi-Entity Bayesian Network (MEBN) to be developed for HCC (see Chap. 2). The specific patient data entered into the EMR, for each patient, will be used to construct a comprehensive Digital Patient Model (DPM) based on the generic Patient-Specific Model (PSM) as previously described. The DPM can be utilized to understand the health status of that particular patient and will be used to help facilitate decision support in the formulation of optimal treatment regimens and provision of personalized healthcare in an efficient, compassionate, and comprehensive manner.

Conclusion

Once a potential HCC has been detected, patients can be thought of as being within various stages of an HCC continuum: (1) at risk; (2) HCC diagnosed and potentially curable; (3) treated and patient considered cured; (4) HCC treated and in remission; (5) HCC treated with recurrence or progression of disease; (6) patient requiring treatment for complications and/or palliative care; and, (7) advanced HCC requiring end-of-life care. The patient, at various times during the course of their disease and treatment, will be found to progress and/or regress through the various stages of this continuum. For example, the comprehensive management of a patient with a solitary HCC at the time of initial diagnosis will be fundamentally different than the

management of a patient with previous hepatic resection who has recent weight loss and has been found to have developed a new, solitary HCC. Therefore, the DPM will need to be continuously updated throughout the course of the patient's disease by means of ongoing patient assessment to ensure appropriate guidance of patients through each of the stages.

References

1. Aronsohn A, Mohanty SR (2010) Current treatment strategies for hepatocellular carcinoma. Curr Cancer Ther Rev 6:199–206
2. Abrams P, Marsh JW (2010) Current approach to hepatocellular carcinoma. Surg Clin N Am 90:803–816
3. Roskams T (2011) Anatomic pathology of hepatocellular carcinoma: impact on prognosis and response to therapy. Clin Liver Dis 15:245–259
4. Tsai W-L, Chung RT (2010) Viral hepatocarcinogenesis. Oncogene 29:2309–2324
5. Perz JF, Armstrong GL, Farrington LA et al (2006) The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 45:529–538
6. El-Serag HB, Rudolph KL (2007) Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 132:2557–2576
7. Donato F, Boffetta P, Puoti M (1998) A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. Int J Cancer 75:347–354
8. Donato F, Tagger A, Gelatti U et al (2002) Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in men and women. Am J Epidemiol 155:323–331
9. Sorrell MF, Belongia EA, Costa J et al (2009) National Institutes of Health consensus development conference statement: management of hepatitis B. Hepatology 49(5 Suppl):4–12
10. Tai AW, Chung RT (2009) Treatment failure in hepatitis C: mechanisms of non-response. J Hepatol 50:412–420
11. Caldwell S, Park SH (2009) The epidemiology of hepatocellular cancer: from the perspectives of public health problem to tumor biology. J Gastroenterol 44(Suppl XIX):96–101
12. Fattovich G (2003) Natural history and prognosis of hepatitis B. Sem Liver Diseas 23:47–58
13. Wong LL, Limm WM, Severino R et al (2000) Improved survival with screening for hepatocellular carcinoma. Liver Transpl 6:320–325
14. Zhang BH, Yang BH, Tang ZY (2004) Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 130:417–422
15. Bolondi L, Sofia S, Siringo S et al (2001) Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. Gut 48:251–259
16. El-Serag HB, Marrero JA, Rudolph L et al (2008) Diagnosis and treatment of hepatocellular carcinoma. Gastroenterology 134:1752–1763
17. Ishiguchi T, Shimamoto K, Fukatsu H et al (1996) Radiologic diagnosis of hepatocellular carcinoma. Semin Surg Oncol 12:164–169
18. European Association for the Study of the Liver. European Organisation for Research and Treatment of Cancer (2012) EASL–EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 56:908–943
19. Wu JT (1990) Serum alpha-fetoprotein and its lectin reactivity in liver diseases: a review. Ann Clin Lab Sci 20:98–105
20. Di Bisceglie AM, Sterling RK, Chung RT et al (2005) Serum alpha-fetoprotein levels in patients with advanced hepatitis C: results from the HALT-C Trial. J Hepatol 43:434–441

21. Collier J, Sherman M (1998) Screening for hepatocellular carcinoma. Hepatology 27:273–278
22. Chen DS, Sung JL, Sheu JC et al (1984) Serum alpha-fetoprotein in the early stage of human hepatocellular carcinoma. Gastroenterology 86:1404–1409
23. Durazo FA, Blatt LM, Corey WG et al (2008) Des-gammacarboxyprothrombin, alpha-fetoprotein and AFP-L3 in patients with chronic hepatitis, cirrhosis and hepatocellular carcinoma. J Gastroenterol Hepatol 23:1541–1548
24. Sherman M (2001) Alphafetoprotein: an obituary. J Hepatol 34:603–605
25. Sherman M, Bruix J (2011) AASLD practice guideline. Management of hepatocellular carcinoma: an update. Hepatology 53:1020–1022
26. Sherman M, Bruix J (2010) AASLD practice guideline. Management of hepatocellular carcinoma. Hepatology Supplement:1–32
27. Marrero JA, Su GL, Wei W et al (2003) Des-gamma carboxyprothrombin can differentiate hepatocellular carcinoma from nonmalignant chronic liver disease in American patients. Hepatology 37:1114–1121
28. Ono M, Ohta H, Ohhira M et al (1990) Measurement of immunoreactive prothrombin, des-gamma-carboxy prothrombin, and vitamin K in human liver tissues: overproduction of immunoreactive prothrombin in hepatocellular carcinoma. Am J Gastroenterol 85:1149–1154
29. Koike Y, Shiratori Y, Sato S et al (2001) Des-gammacarboxy prothrombin as a useful predisposing factor for the development of portal venous invasion in patients with hepatocellular carcinoma: a prospective analysis of 227 patients. Cancer 91:561–569
30. Torzilli G, Minagawa M, Takayama T et al (1999) Accurate preoperative evaluation of liver mass lesions without fine-needle biopsy. Hepatology 30:889–893
31. Hayashi PH, Trotter JF, Forman L et al (2004) Impact of pretransplant diagnosis of hepatocellular carcinoma on cadaveric liver allocation in the era of MELD. Liver Transpl 10:42–48
32. Wiesner RH, Freeman RB, Mulligan DC (2004) Liver transplantation for hepatocellular cancer: the impact of the MELD allocation policy. Gastroenterology 127:261–267
33. Compagnon P, Grandadam S, Lorho R et al (2008) Liver transplantation for hepatocellular carcinoma without preoperative tumor biopsy. Transplantation 86:1068–1076
34. Cance WG, Stewart AK, Menck HR (2000) The national cancer data base report on treatment patterns for hepatocellular carcinomas: improved survival of surgically resected patients, 1985–1996. Cancer 88:912–920
35. Okuda K, Ohtsuki T, Obata H et al (1985) Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 56: 918–928
36. The Cancer of the Liver Italian Program (CLIP) Investigators (2000) Prospective validation of the CLIP score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. Hepatology 31:840–845
37. The Cancer of the Liver Italian Program (CLIP) investigators (1998) A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. Hepatology 28:751–755
38. Llovet JM, Bru C, Bruix J (1999) Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 19:329–338
39. Fleming ID (2001) AJCC/TNM cancer staging, present and future. J Surg Oncol 77:233–236
40. Vauthey JN, Lauwers GY, Esnaola NF et al (2002) Simplified staging for hepatocellular carcinoma. J Clin Oncol 20:1527–1536
41. Vauthey JN, Ribero D, Abdalla EK et al (2007) Outcomes of liver transplantation in 490 patients with hepatocellular carcinoma: validation of a uniform staging after surgical treatment. J Am Coll Surg 204:1016–1028
42. Farinati F, Rinaldi M, Gianni S et al (2000) How should patients with hepatocellular carcinoma be staged? Validation of a new prognostic system. Cancer 89:2266–2273
43. Llovet JM, Ricci S, Mazzaferro V et al (2008) Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378–390
44. Oken MM, Creech RH, Tormey DC et al (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649–655

Chapter 4
Imaging in Hepatocellular Carcinoma: Radiologic Assessment

Irene Bargellini, Valentina Battaglia, Davide Caramella and Carlo Bartolozzi

Abstract In the context of Predictive, Preventive and Personalized Medicine (PPPM), radiologists play an essential role in patient management throughout the different phases of hepatocellular carcinoma (HCC). This includes diagnosis, staging, treatment planning, and evaluation of response to treatment. This chapter provides an in-depth examination of the fundamental pathophysiologic mechanisms underlying the radiologic diagnosis and assessment of HCC. Observations made in contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI), in conjunction with alpha-fetoprotein (AFP) can allow the diagnosis of HCC to be made with confidence without the need for biopsy, in many cases. Treatment decisions and prognosis are strongly influenced by the tumor extension, the number and size of lesions, tumor location, biliary dilatation, ascites, and the presence of macrovascular invasion and extrahepatic tumor spread. In addition, radiologic assessment of co-morbidities and response to previous treatments must be included in the overall assessment. The patient-specific findings from diagnostic imaging and interventional radiology identified in this chapter will be designated as Information Entities (IEs) in later chapters. These IEs will ultimately be used in the generation of Digital Patient Models (DPMs) to facilitate diagnosis, prognosis, and treatment selection, i.e. Model Guided Therapy (MGT) and PPPM.

Keywords Personalized medicine · Hepatocellular carcinoma · Diagnosis · Screening · Imaging · Staging · Computed tomography · Ultrasound · Contrast-enhanced ultrasound · Magnetic Resonance Imaging · Diffusion-weighted imaging · MR contrast agents · Treatment evaluation

I. Bargellini (✉) · V. Battaglia · D. Caramella · C. Bartolozzi
Diagnostic and Interventional Radiology, University Hospital Pisa, Pisa, Italy
e-mail: irenebargellini@hotmail.com

V. Battaglia
e-mail: novetrequarti@yahoo.it

D. Caramella
e-mail: davide.caramella@med.unipi.it

C. Bartolozzi
e-mail: carlo.bartolozzi@med.unipi.it

L. Berliner, H. U. Lemke (eds.), *An Information Technology Framework for Predictive, Preventive and Personalised Medicine,* Advances in Predictive, Preventive and Personalised Medicine 8, DOI 10.1007/978-3-319-12166-6_4

4.1 Introduction

In the setting of a multidisciplinary clinical liver cancer center, radiologists play an essential role in the different phases of hepatocellular carcinoma (HCC) patients' management, including diagnosis, staging, treatment planning, and evaluation of response to treatment.

According to the Barcelona Clinic for Liver Cancer (BCLC) staging system [1], treatment decisions and prognosis are strongly influenced by the tumor extension, in terms of lesions' number and size, presence of macrovascular invasion, and extrahepatic tumor spread; precise tumor identification is therefore mandatory for proper patient allocation. Moreover, treatment is often determined by other parameters that are not specifically addressed in the BCLC algorithm, such as tumor location, biliary dilatation, ascites, co-morbidities, and radiological response to previous treatments. Therefore, in clinical practice, clinical data need to be fully integrated to an entire spectrum of radiological parameters.

4.1.1 Diagnosis of HCC

The development of a neoplasm in cirrhosis is a long-lasting process. Many cellular changes occur along the pathway from normal hepatocytes to neoplastic cells so that different types of nodules can be detected in a cirrhotic liver, ranging from regenerative nodules to low-grade dysplastic nodules (LGDNs) and high-grade dysplastic nodules (HGDNs), early HCC and, finally, overt HCC.

HGDN nodules and early HCC are considered as premalignant and early malignant nodules. Foci of HCC can be found inside HGDNs, while in early HCC cells degeneration is not usually already associated to all the typical vascular changes found in overt HCC [2, 3]. These vascular alterations include the reduction of portal venous supply and the development of unpaired arteries and arterio-venous shunts [3].

These typical vascular changes account for the pathological background for current non-invasive diagnosis of HCC at dynamic contrast-enhanced imaging, based on the so-called "typical vascular pattern", characterized by wash-in in the arterial phase and wash-out in the portal venous/late phases. This pattern has shown up to 100 % specificity for HCC nodules > 1 cm in size, in the setting of a cirrhotic liver [4–6]. Therefore, according to current guidelines, the detection of the typical vascular pattern at multidetector computer tomography (MDCT) or magnetic resonance (MR) is considered sufficient for the diagnosis of HCC in patients with cirrhosis [7–9]. It should be noted that none of the guidelines reports which cross-sectional imaging modality between MDCT and MR should be performed to evaluate a nodule detected during ultrasound (US) surveillance. In fact, MR and MDCT show similar sensitivity in the detection of the typical vascular pattern, ranging between 44–62 % and between 44–53 %, respectively, although MR has been proven to be superior especially in nodules < 2 cm [10, 11].

Although the typical hallmarks of HCC at dynamic imaging are recognized by all current guidelines, diagnostic algorithms differ in the suggested management of

the detected nodules according to their size. European Society for the Study of the Liver (EASL) guidelines suggest that a single imaging modality is sufficient for HCC diagnosis in nodules > 2 cm, while smaller nodules (between 1–2 cm) should be investigated by two imaging modalities if not performed in centers of excellence with 'high-end radiological equipment' [7]. On the contrary, the American Association for the Study of Liver Diseases (AASLD) guidelines suggest that the detection of the typical enhancement pattern at one single imaging modality in nodules > 1 cm can be considered as sufficient to formulate a diagnosis of neoplasm [8]. Finally, EASL guidelines disregard the dimensions of the nodules, because the diagnosis of malignancy can be assessed even in lesions < 1 cm in the case of a typical enhancement pattern [9].

Only two-thirds of HCCs are reported to show a typical vascular pattern, and diagnosis of atypical HCC nodules remains a controversial issue, with differences in their suggested management according to the available guidelines [12]. While both EASL and AASLD guidelines suggest biopsy for all atypical nodules > 1 cm [7, 8], the Asian Pacific guidelines suggest the use of new diagnostic tools, such as MR using reticulo-endothelial system (RES)- or hepatocyte-specific contrast agents, or contrast enhanced ultrasound (CEUS) using Sonazoid [9], while biopsy should be performed in case of inconclusive findings.

The role of biopsy as a solving problem tool is again controversial. In fact, it should be kept in mind that sampling errors can occur (such as insufficient tissue or samplings not representative of the entire lesions) and that pathological interpretation can be challenging on a specimen obtained from needle biopsy, with inability of evaluating all the criteria suggesting malignancy (especially stromal invasion) [12, 13].

4.1.2 New Diagnostic Tools

Despite being very specific, the diagnosis of HCC based solely on the detection of neoangiogenesis has a low sensitivity. Thus, the role of different diagnostic elements is under evaluation [4]. In this setting, MR seems to provide some advantages compared to MDCT, due to its intrinsic capability of identifying other intracellular components, such as glycogen, hemorrhage, water, and metals, and defining other parameters, such as diffusivity and biliary function [14–16].

4.1.2.1 Diffusion-Weighted Imaging (DWI)

Diffusion-weighted imaging (DWI) is a dedicated MR sequence that allows for the evaluation of the random motion (related to thermal effects) of water molecules ('Brownian motion') within biological tissues. Recently, DWI has been introduced in liver MR protocols, as several studies have reported its usefulness in improving detection and characterization of focal liver lesions, by measuring their apparent diffusion coefficient [17, 18], providing an adjunctive tool in the differential diagnosis between benign and malignant lesions.

4.1.2.2 Hepatospecific Contrast Agents for MR

During carcinogenesis, together with neoangiogenesis, progressive loss of biliary polarization of the hepatocyte and derangement of its microscopic, secretory structure are observed. Recent studies have described modifications of membrane carriers (such as organic anionic transporter protein [OATP] and multidrug-resistance protein [MRP]) that are involved in bilirubin metabolism in neoplastic nodules.

The recent introduction of hepatobiliary contrast agents in MR studies, especially of the highly lipophilic compound Gd-EOB-DTPA, has provided an additional tool for the assessment of the metabolic function of nodules. In fact, due to a competitive binding to bilirubin transporters, these agents provide information regarding the residual performance of cellular membrane proteins and intracellular metabolic activities [19, 20].

Moreover, these agents enable the evaluation of both dynamic vascular and metabolic nodular functions in a single session study since the contrast is taken up within functioning hepatocytes, and then, excreted at the level of the biliary pole at the end of the intravascular phase. This metabolic phase occurs 20–40 min after the injection.

In recent studies, the lack of contrast agent uptake in the hepatobiliary phase has been found in premalignant HGDNs, as well as cases of malignant degeneration (early/overt HCC), even in the absence of the typical vascular pattern [4, 5, 21]. Thus, the use of hepatobiliary contrast agents might increase MR sensitivity in identifying malignant and premalignant lesions. Accordingly, recent studies have demonstrated that the combination of DWI and MR with hepatospecific contrast agents can provide information regarding the risk of premalignant lesions evolving into overt HCC [15, 16].

4.1.3 Therapeutic Algorithm and Treatment Planning

The BCLC staging classification stratifies HCC patients into five major categories (very early, early, intermediate, advanced, and terminal stages) on the basis of tumor extension, liver function, and performance status [1]. For each stage, different prognostic variables are identified, life expectancy is estimated, and the most proper treatment option is suggested.

4.1.3.1 Very Early Stage

The very early stage (stage 0) is composed of patients with single nodule <2 cm in a well-compensated cirrhotic liver without portal hypertension. These patients can benefit from resection with estimated 5-year survival rates exceeding 90%. Livraghi and colleagues have demonstrated that similar clinical outcomes can be obtained also by percutaneous radiofrequency ablation (RFA), with lower costs

and periprocedural risks [22]. Thus, when technically feasible according to lesion location, percutaneous ablation may represent a valid treatment option, although according to the AASLD Practice Guidelines ablation should currently be limited to patients not eligible for surgical resection [8]. Also, lesion location requiring extensive resection could represent a parameter in favor for RFA.

4.1.3.2 Early Stage

The early stage (stage A) is composed of patients in good clinical conditions with a single nodule or less than 3 nodules < 3 cm in size each. These patients can benefit from curative treatments, such as liver transplantation (LT), resection or percutaneous ablation, with estimated 5-year survival rates of approximately 50–75 %.

LT is able to cure both the tumor and the underlying liver disease. Its success is strongly related to the adopted inclusion criteria and to the waiting time. Strict inclusion criteria have been proposed in 1996 by Mazzaferro et al., the Milan criteria, defined as the presence of a single nodule < 5 cm in size, or no more than three nodules each < 3 cm in size [23]; therefore, precise tumor identification is mandatory to set indications for LT. Cautiously expanded criteria have been subsequently proposed [24, 25], with acceptable 5-year survival rates. Some authors have proposed the use of locoregional treatments for tumor down-staging in highly selected patients [26–28], for whom the identification of a radiological complete tumor response after treatment could even represent a marker of favorable biological tumor behavior allowing LT [29, 30]. Locoregional treatments, such transarterial chemoembolization (TACE) and percutaneous ablation, are also extensively used in T2-stage HCC patients waiting for LT and in patients with an expected waiting time > 6 months, to reduce the risks of dropout for tumor progression [31, 32].

There are several clinical factors that contraindicate LT even in patients within Milan criteria such as age, co-morbidities, and alcohol abuse. In this setting, RFA and resection are regarded as treatment options with curative intent.

Exclusion criteria for resection vary from site to site, although several authors agree in excluding patients with portal hypertension. In this scenario, imaging may play a role in identifying signs of portal hypertension such as hepatofugal shunts, varices, and splenomegaly. After resection, residual liver function represents the strongest predictor of survival [1, 33], while pathological findings, such as vascular invasion, satellites, and tumor differentiation, are risk factors for tumor recurrence.

Tumor location, size, and number may limit the indications for percutaneous ablation. In fact, the success of ablation is lower when more than two nodules are treated and in tumors > 3 cm in size [34–36]. For nodules between 3–5 cm in size, the combination of RFA and TACE has proven to be more effective compared to RFA alone [37, 38]. Moreover, technical feasibility and success of ablation are limited in the case of nodules located close to the gallbladder or to large vessels, or in subcaspular locations.

4.1.3.3 Intermediate Stage

The intermediate stage (stage B) of the disease includes a wide variety of patients, who are asymptomatic, with preserved liver function, but with a more extensive liver involvement. In these patients, TACE represents the treatment of choice, being able to improve survival compared to best supportive care [39, 40]. However, tumor relapse after TACE is a major issue, and the combination of TACE and sorafenib is under investigation, in the attempt to reduce tumor recurrence.

The intermediate stage is composed of a very heterogeneous population, ranging from patients with a single large nodule to patients with multifocal extensive bilobar involvement. Therefore, a better stratification of this group of patient is needed [41]. In clinical practice, there is wide variation in the management of these patients. Single large nodules can be treated effectively by surgical resection, downstaging followed by LT (in highly selected patients), or by combining TACE and RFA [42]. Alternatively, patients with extensive tumor involvement might not benefit from TACE and should be considered as advanced-stage HCC patients [43, 44].

4.1.3.4 Advanced Stage

In the advanced stage (stage C) of the disease, performance status is compromised and/or the tumor has spread into the vessels or outside the liver. Two multicenter, phase III, double-blind, placebo-controlled trials [45, 46] have demonstrated that in this stage sorafenib (an oral multikinase inhibitor of the vascular endothelial growth factor, the platelet-derived growth factor receptor and Raf) can prolong survival.

Yttrium-90 (Y90) radioembolization (RE) (also known as selective internal radiation therapy [SIRT]) has been investigated in advanced stage, as well as in intermediate stage, HCC patients who have been excluded from, or have not responded to, TACE. The first phase II clinical study has demonstrated that in this clinical scenario Y90 RE is safe and effective, with promising clinical outcomes, particularly in patients with segmental portal vein thrombosis [47].

In fact, initial reports regarding RE have demonstrated that even in the setting of the advanced stage HCC further efforts are needed for improved patients' stratification. It has been found that long-term survival is different for patients with metastasis compared to patients with HCC confined to the liver, as well for patients with segmental branch portal vein neoplastic thrombosis versus patients with main branch involvement [47–49].

4.1.4 Post-Treatment Evaluation

Response to previous treatment represents a key factor in determining a patient's prognosis and therapeutic management [44]. Traditionally, response is measured

in terms of tumor shrinkage using standard Response Evaluation Criteria in Solid Tumors (RECIST) [50, 51]. However, these criteria can be misleading when applied to molecular-targeted or locoregional therapies in HCC, since tumor necrosis may not always be paralleled by a reduction in tumor size [52]. For instance, a poor correlation was demonstrated between RECIST and clinical outcome of sorafenib treatment in HCC patients [46]. In 2001, EASL recommended measuring change in the area of tumor enhancement on contrast enhanced imaging as the optimal method to assess treatment response [53]. More recently, AASLD has proposed a formal amendment to RECIST that take into account variations in the degree of tumor arterial enhancement: modified RECIST (mRECIST) [54]. mRECIST has been validated in different clinical trials involving both locoregional therapies and systemic targeted agents [55, 56], and a correlation with pathological necrosis evaluated on the explanted liver has been demonstrated [57]. However, while RFA and TACE usually generate well-defined and easily measurable areas of necrosis, the extent of tumor necrosis is usually unpredictable and irregular following treatment with RE and sorafenib; these treatments might reduce tumor vascularization without necessarily creating areas of necrosis [58, 59]. Furthermore, patients with advanced-stage HCC, for whom sorafenib and RE are usually performed, often present with irregular and highly inhomogeneous lesions at baseline due to the infiltrative margins and the irregular perfusion caused by neoplastic portal vein thrombosis and previous locoregional treatments. Thus, mRECIST should be applied with caution when evaluating radiological response to sorafenib and RE.

The uncertainty in evaluating response to sorafenib with mRECIST is further emphasized in recent literature that focuses on the need to find new biological markers that are able to achieve early identification of patients responding to treatment. Some authors have pointed out the usefulness of monitoring AFP levels that might represent a more sensitive prognostic parameter compared to radiological criteria [60–62]. In addition, determination of response, based on changes in tumor density and perfusion parameters, has been proposed, using CEUS, perfusion CT, and/or MR spectral imaging [59, 63–68]. Finally, some authors have underlined the need for volumetric assessment of tumor variations to increase accuracy and reproducibility in assessing tumor response [69–71].

4.1.5 Electronic Medical Records and Radiological Data

As described in Chap. 2, comprehensive Digital Patient Models (DPMs) based on Multi-Entity Bayesian Networks (MEBNs) for patients with HCC may be constructed from electronic databases and repositories. Patient-specific findings of diagnostic imaging and interventional radiology that may be identified as Information Entities (IEs) will need to be integrated as clinical parameters in the MEBNs. Radiological findings that may be used to generate IEs are summarized in Table 4.1.

Table 4.1 Radiological features that may be employed as Information Entities

Clinical Task	Radiological findings
Preprocedural assessment	(a) number and size of HCC nodules; (b) number and size of nodules considered at risk for neoplastic degeneration; (c) presence and extension of portal vein neoplastic thrombosis; (d) presence of extrahepatic tumor spread; (e) radiological signs of cirrhosis (including varices and ascites); (f) biliary dilatations; (g) radiological signs of co-morbidities
Treatment planning	(a) features of nodules such as location, degree of vascularization, and presence of pseudocapsule; (b) vascular mapping; (c) technical details of previous treatments
Evaluation of previous treatment	(a) complications; (b) tolerability and compliance; (c) radiological response

Conclusion

It has been demonstrated that radiological imaging plays a critical role in the diagnosis and management of patients with HCC. The radiological features of HCC lesions provide information that is required to determine staging and prognosis, and to select the optimal treatment protocols.

References

1. Forner A, Reig ME, de Lope CR, Bruix J (2010) Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis 30(1):61–74
2. Theise ND, Park YN, Kojiro M (2002) Dysplastic nodules and hepatocarcinogenesis. Clin Liver Dis 6:497–512
3. International Consensus Group for Hepatocellular Neoplasia (2009) Pathologic diagnosis of early hepatocellular carcinoma: a report of the International Consensus Group for Hepatocellular Neoplasia. Hepatology 49:658–664
4. Bartolozzi C, Battaglia V, Bargellini I et al (2013) Contrast-enhanced magnetic resonance imaging of 102 nodules in cirrhosis: correlation with histological findings on explanted livers. Abdom Imaging 38(2):290–296
5. Forner A, Vilana R, Ayuso C et al (2008) Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. Hepatology 47:97–104
6. Sangiovanni A, Manini MA, Iavarone M et al (2010) The diagnostic and economic impact of contrast imaging techniques in the diagnosis of small hepatocellular carcinoma in cirrhosis. Gut 59(5):638–644
7. European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer (2012) EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 56:908–943
8. Bruix J, Sherman M (2011) American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 53:1020–1022
9. Omata M, Lesmana LA, Tateishi R et al (2010) Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. Hepatol Int 4:439–474

10. Kim K, Kim CS, Han YM et al (2009) Detection of hepatocellular carcinoma: gadoxetic acid-enhanced 3-dimensional magnetic resonance imaging versus multi-detector row computed tomography. J Comput Assist Tomogr 33:844–850
11. Leoni S, Piscaglia F, Golfieri R et al (2010) The impact of vascular and nonvascular findings on the noninvasive diagnosis of small hepatocellular carcinoma based on the EASL and AASLD criteria. Am J Gastroenterol 105(3):599–609
12. Bolondi L, Gaiani S, Celli N et al (2005) Characterization of small nodules in cirrhosis by assessment of vascularity: the problem of hypovascular hepatocellular carcinoma. Hepatology 42:27–34
13. Roskams T (2011) Anatomic pathology of hepatocellular carcinoma: impact on prognosis and response to therapy. Clin Liver Dis 15:245–259
14. Park MJ, Kim YK, Lee MH, Lee JH (2013) Validation of diagnostic criteria using gadoxetic acid-enhanced and diffusion-weighted MR imaging for small hepatocellular carcinoma ($\leq$2.0 cm) in patients with hepatitis-induced liver cirrhosis. Acta Radiol 54(2):127–136
15. Kim YK, Lee WJ, Park MJ et al (2012) Hypovascular hypointense nodules on hepatobiliary phase gadoxetic acid-enhanced MR images in patients with cirrhosis: potential of DW imaging in predicting progression to hypervascular HCC. Radiology 265(1):104–114
16. Park MJ, Kim YK, Lee MW et al (2012) Small hepatocellular carcinomas: improved sensitivity by combining gadoxetic acid-enhanced and diffusion-weighted MR imaging patterns. Radiology 264(3):761–770
17. Ichikawa T, Cederle MP, Grazioli L, Marsh W (2000) Fibrolamellar hepatocellular carcinoma: pre- and posttherapy evaluation with CT and MR imaging. Radiology 217:145–151
18. Gourtsoyianni S, Papanikolaou N, Yarmenitis S et al (2008) Respiratory gated diffusion-weighted imaging of the liver: value of apparent diffusion coefficient measurements in the differentiation between most commonly encountered benign and malignant focal liver lesions. Eur Radiol 18:486–492
19. Narita M, Hatano E, Arizono S et al (2009) Expression of OATP1B3 determines uptake of Gd-EOBDTPA in hepatocellular carcinoma. J Gastroenterol 44:793–798
20. Kitao A, Zen Y, Matsui O et al (2010) Hepatocellular carcinoma: signal intensity at gadoxetic acid-enhanced MR imaging—correlation with molecular transporters and histopathologic features. Radiology 256:817–826
21. Kim SH, Kim SH, Lee J et al (2009) Gadoxetic-acid enhanced MRI versus triple-phase MDCT for the preoperative detection of hepatocellular carcinoma. AJR Am J Roentgenol 192:1675–1681
22. Livraghi T, Meloni F, Di Stasi M et al (2008) Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? Hepatology 47:82–89
23. Mazzaferro V, Regalia E, Doci R et al (1996) Liver transplantation for the treatment of small hepatocellular carcinoma in patients with cirrhosis. N Engl J Med 334:693–699
24. Yao FY, Ferrell L, Bass NM et al (2001) Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 33(6):1394–1403
25. Mazzaferro V, Llovet JM, Miceli R et al (2009) Metroticket Investigator Study Group. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 10(1):35–43
26. Yao FY, Kerlan RK Jr, Hirose R et al (2008) Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. Hepatology 48(3):819–827
27. Ravaioli M, Grazi GL, Piscaglia F et al (2008) Liver transplantation for hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria. Am J Transplant 8(12):2547–2557
28. Lewandowski RJ, Kulik LM, Riaz A et al (2009) A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. Am J Transplant 9(8):1920–1928

29. Otto G, Herber S, Heise M et al (2006) Response to transarterial chemoembolization as a biological selection criterion for liver transplantation in hepatocellular carcinoma. Liver Transpl 12(8):1260–1267
30. Bargellini I, Vignali C, Cioni R et al (2010) Hepatocellular carcinoma: CT for tumor response after transarterial chemoembolization in patients exceeding Milan criteria–selection parameter for liver transplantation. Radiology 255(1):289–300
31. Graziadei IW, Sandmueller H, Waldenberger P et al (2003) Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome. Liver Transpl 9(6):557–563
32. Majno P, Lencioni R, Mornex F et al (2011) Is the treatment of hepatocellular carcinoma on the waiting list necessary? Liver Transpl 17(Suppl 2):98–108
33. Llovet JM, Fuster J, Bruix J (1999) Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 30(6):1434–1440
34. Livraghi T, Giorgio A, Marin G et al (1995) Hepatocellular carcinoma and cirrhosis in 746 patients: long-term results of percutaneous ethanol injection. Radiology 197(1):101–108
35. Sala M, Llovet JM, Vilana R et al (2004) Barcelona Clínic Liver Cancer Group. Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. Hepatology 40(6):1352–1360
36. Lencioni R, Cioni D, Crocetti L et al (2005) Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. Radiology 234(3):961–967
37. Lencioni R, Crocetti L, Petruzzi P et al (2008) Doxorubicin-eluting bead-enhanced radiofrequency ablation of hepatocellular carcinoma: a pilot clinical study. J Hepatol 49(2):217–222
38. Peng ZW, Zhang YJ, Chen MS et al (2013) Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. J Clin Oncol 31(4):426–432
39. Lo CM, Ngan H, Tso WK et al (2002) Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 35:1164–1171
40. Llovet JM, Real MI, Montaña X et al (2002) Barcelona Liver Cancer Group. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 359:1734–1739
41. Bolondi L, Burroughs A, Dufour JF et al (2012) Heterogeneity of patients with intermediate (BCLC B) hepatocellular carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis 32(4):348–359
42. Bargellini I, Florio F, Golfieri R et al (2014) Trends in utilization of transarterial treatments for hepatocellular carcinoma: results of a survey by the Italian Society of Interventional Radiology. Cardiovasc Intervent Radiol 37(2):438–444
43. Dufour JF, Bargellini I, De Maria N et al (2013) Intermediate hepatocellular carcinoma: current treatments and future perspectives. Ann Oncol 24(2):24–29
44. Raoul JL, Sangro B, Forner F et al (2011) Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. Cancer Treat Rev 37(3):212–220
45. Cheng AL, Kang YK, Chen Z et al (2009) Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 10(1):25–34
46. Llovet JM, Ricci S, Mazzaferro V et al (2008) SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359(4):378–390
47. Mazzaferro V, Sposito C, Bhoori S et al (2013) Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. Hepatology 57(5):1826–1837
48. Sangro B, Carpanese L, Cianni R et al (2011) European network on radioembolization with Yttrium-90 resin microspheres (ENRY). Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. Hepatology 54(3):868−8 78

49. Salem R, Lewandowski RJ, Mulcahy MF et al (2010) Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology 138(1):52–64
50. Therasse P, Arbuck S, Eisenhauer E et al (2000) New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205–216
51. Eisenhauer EA, Therasse P, Bogaerts J et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228−247
52. Forner A, Ayuso C, Varela M et al (2009) Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? Cancer 115:616−623
53. Bruix J, Sherman M, Llovet JM et al (2001) EASL panel of experts on HCC European Association for the Study of the Liver. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. J Hepatol 35(3):421–430
54. Lencioni R, Llovet JM (2010) Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 30:52–60
55. Gillmore R, Stuart S, Kirkwood A et al (2011) EASL and mRECIST responses are independent prognostic factors for survival in hepatocellular cancer patients treated with transarterial embolization. J Hepatol 55:1309–1311
56. Shim JH, Lee HC, Kim SO et al (2012) Which response criteria best help predict survival of patients with hepatocellular carcinoma following chemoembolization? A validation study of old and new models. Radiology 262:708−718
57. Bargellini I, Bozzi E, Campani D et al (2013) Modified RECIST to assess tumor response after transarterial chemoembolization of hepatocellular carcinoma: CT-pathologic correlation in 178 liver explants. Eur J Radiol 82(5):e212−218
58. Horger M, Lauer UM, Schraml C et al (2009) Early MRI response monitoring of patients with advanced hepatocellular carcinoma under treatment with the multikinase inhibitor sorafenib. BMC Cancer 9:208
59. Faivre S, Zappa M, Vilgrain V et al (2011) Changes in tumor density in patients with advanced hepatocellular carcinoma treated with sunitinib. Clin Cancer Res 17:4504–4512
60. Personeni N, Bozzarelli S, Pressiani T et al (2012) Usefulness of alpha-fetoprotein response in patients treated with sorafenib for advanced hepatocellular carcinoma. J Hepatol 57(1):101–107
61. Edeline J, Boucher E, Rolland Y et al (2012) Comparison of tumor response by Response Evaluation Criteria in Solid Tumors (RECIST) and modified RECIST in patients treated with sorafenib for hepatocellular carcinoma. Cancer 118(1):147–156
62. Kawaoka T, Aikata H, Murakami E et al (2012) Evaluation of the mRECIST and α-fetoprotein ratio for stratification of the prognosis of advanced-hepatocellular-carcinoma patients treated with sorafenib. Oncology 83(4):192–200
63. Maksimovic O, Schraml C, Hartmann JT et al (2010) Evaluation of response in malignant tumors treated with the multitargeted tyrosine kinase inhibitor sorafenib: a multitechnique imaging assessment. Am J Roentgenol 194(1):5–14
64. Lewin M, Fartoux L, Vignaud A et al (2011) The diffusion-weighted imaging perfusion fraction f is a potential marker of sorafenib treatment in advanced hepatocellular carcinoma: a pilot study. Eur Radiol 21(2):281−290
65. Frampas E, Lassau N, Zappa M et al (2013) Advanced hepatocellular carcinoma: Early evaluation of response to targeted therapy and prognostic value of Perfusion CT and Dynamic Contrast Enhanced-Ultrasound. Preliminary results. Eur J Radiol 82(5):e205−211
66. Sugimoto K, Moriyasu F, Saito K et al (2013) Hepatocellular carcinoma treated with sorafenib: early detection of treatment response and major adverse events by contrast-enhanced US. Liver Int 33(4):605–615
67. Sacco R, Faggioni L, Bargellini I et al (2013) Assessment of response to sorafenib in advanced hepatocellular carcinoma using perfusion computed tomography: Results of a pilot study. Dig Liver Dis 45(9):776–781

68. Dai X, Schlemmer HP, Schmidt B et al (2013) Quantitative therapy response assessment by volumetric iodine-uptake measurement: initial experience in patients with advanced hepatocellular carcinoma treated with sorafenib. Eur J Radiol 82(2):327–334
69. Monsky WL, Garza AS, Kim I et al (2011) Treatment planning and volumetric response assessment for Yttrium-90 radioembolization: semiautomated determination of liver volume and volume of tumor necrosis in patients with hepatic malignancy. Cardiovasc Intervent Radiol 34(2):306–318
70. Lin M, Pellerin O, Bhagat N et al (2012) Quantitative and volumetric European Association for the Study of the Liver and Response Evaluation Criteria in Solid Tumors measurements: feasibility of a semiautomated software method to assess tumor response after transcatheter arterial chemoembolization. J Vasc Interv Radiol 23(12):1629–1637
71. Galizia MS, Töre HG, Chalian H et al (2012) MDCT necrosis quantification in the assessment of hepatocellular carcinoma response to yttrium 90 radioembolization therapy: comparison of two-dimensional and volumetric techniques. Acad Radiol 19(1):48–54

Chapter 5
Imaging in Hepatocellular Carcinoma: PET/CT

Giuseppe Esposito

Abstract In the last two decades, the development of Positron Emission Tomography (PET), and then PET with Computed Tomography (PET/CT) imaging, has had a large impact on the management of a number of cancer types. PET/CT imaging benefits from the possibility of obtaining both structural (CT) and functional (PET) cancer information at the same time. PET obtains images of the biodistribution of radiopharmaceuticals that can be designed to target different biological processes. In current clinical cancer imaging, most PET imaging studies are performed using an analog of glucose, fluorodeoxyglucose (FDG), labeled with the radioactive Fluorine-18. Imaging with FDG is particularly useful because following malignant transformation, various tumors are characterized by increased glucose utilization that is reflected by increased uptake and accumulation of FDG. In oncology, PET imaging with FDG often provides more sensitive and more specific information about the extent of disease than morphologic/anatomic imaging alone. PET also offers an earlier and often better assessment of response to treatment and an overall better accuracy to restage disease after completion of a treatment course. This in turns results in an overall improved prognostic evaluation during and after treatment. Although the role of PET/CT is limited in patients with HCC, the current status of this imaging technology is reviewed.

Keywords Personalized medicine · Hepatocellular carcinoma · Liver metastases · Diagnosis · Imaging · Staging · Computed tomography · Positron emission tomography · Fluorodeoxyglucose (FDG) · Treatment evaluation

5.1 Introduction

In the last two decades, the development of Positron Emission Tomography (PET) and then PET with Computed Tomography (PET/CT) imaging has had a large impact on the management of a number of cancer types. PET/CT imaging benefits

G. Esposito (✉)
Georgetown University Medical Center, Washington, DC, USA
e-mail: EXG11@gunet.georgetown.edu

L. Berliner, H. U. Lemke (eds.), *An Information Technology Framework for Predictive, Preventive and Personalised Medicine,* Advances in Predictive, Preventive and Personalised Medicine 8, DOI 10.1007/978-3-319-12166-6_5

from the possibility to obtain both structural (CT) and functional (PET) cancer information at the same time. PET obtains images of the biodistribution of radioactive labeled compounds (radiopharmaceuticals) that can be designed to target different biological processes.

5.1.1 Pharmacology

Several radiopharmaceuticals are available for PET that are able to image various aspects of cancer biology such as cell proliferation and DNA synthesis, tumor hypoxia, tumor angiogenesis, and cell apoptosis. However, in clinical cancer imaging, most of the PET imaging studies are performed using an analog of glucose, fluorodeoxyglucose (FDG), labeled with the radioactive Fluorine-18 (^{18}F). Imaging with FDG is particularly useful because following malignant transformation, various tumors are characterized by an increased glucose utilization that is reflected by an increased uptake and accumulation of FDG. The uptake mechanism and biochemical pathway of FDG has been widely studied both in vitro and in vivo. The transport of the radiotracer through the cell membrane via glucose transport proteins, particularly glucose transporter type 1 (GLUT-1), and subsequent intracellular phosphorylation by hexokinase (HK) have been identified as key steps for subsequent tissue accumulation [1]. Because FDG-6-phosphate is not a suitable substrate for glucose-6-phosphate isomerase, and the enzyme level of glucose-6-phosphatase is generally low in tumors, FDG-6-phosphate accumulates in cells and is visualized by PET.

5.1.2 Role of PET Imaging in Oncology

5.1.2.1 Diagnosis

In oncology, PET imaging with FDG often provides more sensitive and more specific information about the extent of disease than morphologic/anatomic imaging alone. FDG-PET has become a standard imaging procedure for staging and restaging of many types of cancer [2]. The metabolic activity of neoplastic tissue measured by PET offers information about cancer biology and aggressiveness, and has proven to offer, in comparison to other imaging modalities and for most cancer types, an improved ability to differentiate benign from malignant lesions and therefore to identify early truly neoplastic disease. For example, a number of studies and a recent meta-analysis [3] of the available data have found that the addition of PET improves the accuracy of the diagnostic evaluation of single pulmonary nodules, reduces the number of indeterminate readings, and increases the inter- and intraobserver agreement on the presence of malignancy. FDG-PET imaging of cancer offers improved accuracy for the identification of lymph node and distant metastases and therefore provides better initial cancer staging.

5.1.2.2 Response to Treatment

When compared to other imaging modalities, PET offers also an earlier and often better assessment of response to treatment and an overall better accuracy to restage disease after completion of a treatment course. This in turns results in an overall improved prognostic evaluation during and after treatment. There is a large body of evidence on the importance of PET/CT in the assessment of the efficacy of treatment and on the prognostic value of the PET information coming from studies in patients with lymphomas [4]. There is no question that PET and PET/CT imaging has a significant impact on the clinical management of cancer patients. Data obtained from the National Oncologic PET Registry collected by Medicare has demonstrated that because of its greater accuracy, PET imaging significantly changed patient management in approximately 30 % of the cases [5].

There is also no doubt at this point that PET/CT imaging, by means of an overall improved anatomical and functional characterization of cancer, represents an important step towards an individualized, response-adapted treatment of cancer. Information regarding cancer biology, obtained from PET/CT imaging, is used to modify treatment based on the individual degree of response. In the future, the possibility of PET/CT to visualize multiple aspects of tumor biology besides glucose metabolism with FDG offers exciting new possibilities. It may be possible to plan individualized cancer treatments according to different biological cancer characteristics (such as tumor hypoxia for planning radiation treatment, estrogen receptors expression in breast cancer for planning hormonal therapy, and VEGF expression when planning anti-angiogenic treatments).

5.1.3 PET/CT in Guiding Ablation Therapies to the Liver

PET/CT imaging with FDG has been demonstrated to be useful in the clinical evaluation of patients being considered for local ablation therapies of primary and metastatic liver cancers. A number of studies have shown the value of PET/CT for the initial selection of patients being considered for local interventions, for the evaluation of response to local ablation treatment, as well as in the follow-up of these patients.

5.1.3.1 Metastatic Liver Disease

A recent paper on the role of PET/CT imaging in oncology [3] acknowledged that PET/CT has a better overall diagnostic accuracy for the evaluation of colorectal cancer and recommended that PET/CT be used in the initial disease staging, particularly for the evaluation of liver metastases. The same panel of experts recommended that PET/CT be used for the restaging and follow-up of these patients, to evaluate for local recurrence or to detect hepatic and extra-hepatic metastases.

Recently, a Task Force of the National Comprehensive Cancer Network [6] reported on the clinical utility of PET imaging in a variety of tumor types. In this report it was recognized that because liver metastases represent the main cause of mortality from colorectal cancer and because conventional imaging with CT often fails to identify preoperatively those patients whose metastases can be successfully resected, there is the need for better imaging techniques with higher accuracy to detect liver metastases and exclude extra-hepatic disease, to achieve an overall better staging accuracy and avoid futile liver surgeries.

A number of studies have demonstrated that the addition of PET imaging improves the detection of liver metastases. Wiering et al. [7] found that PET imaging was more sensitive and specific than CT for the evaluation of liver metastases. These same authors found that the role of PET/CT was even more important for the evaluation of extra-hepatic disease, with PET having a 91 % vs. 55 % sensitivity when compared to CT. According to a Blue Cross and Blue Shield analysis published in 2000 [8], the better accuracy of PET/CT allowed for a change in patient management in 20 % of the cases: 12 % of the time unnecessary surgical procedures were avoided due to the detection of multiple liver lesions of extra-hepatic disease, and 8 % of the time surgery was initiated because patients initially deemed unresectable were then found to have metastatic disease limited to operable liver lesions after PET/CT evaluation. This same analysis found that PET/CT had very high sensitivity and specificity (96 % and 98 %, respectively) to detect cancer recurrence.

5.1.3.2 Hepatocellular Cancer

FDG-PET imaging seems to have little role in the diagnosis of hepatocellular cancer because this type of cancer has characteristically lower FDG uptake compared to colorectal cancer metastases [9], and an overall lower sensitivity and specificity for the diagnosis of hepatocellular cancer when compared to CT and MRI. However, as with other forms of cancer, the unique contribution of FDG-PET in the clinical evaluation of HCC appears to reside in its ability to measure glucose metabolism, which is in turn an indirect but often reliable index of tumor aggressiveness.

Similar to its performance in other cancers, FDG-PET seems to be more accurate than other imaging modalities to identify lymph node and distant metastases from HCC. It was also pointed out, in the NCCN task force report on PET imaging [6], that PET has high accuracy in the detection of metastatic lesions and may have an increasing role in assessing the impact of liver-directed therapies, which are notoriously difficult to assess by CT alone. Wudel et al. [10] found that FDG-PET added clinically significant information in 26 of 91 patients with HCC (28 %) as a result of metastasis detection and response assessment of local liver treatments.

5.1.3.3 Pre-Operative Evaluation

The role of FDG-PET seems to be potentially very important for the preoperative evaluation of transplant candidates before or after local liver treatments. Lee

et al. [11] retrospectively studied 59 patients with HCC that had undergone liver transplantation; 44 of these patients had undergone different forms of local ablation therapies prior to transplantation. The authors found that the degree of FDG uptake in relation to the normal liver activity was the best predictor of tumor recurrence in a multivariate analysis that also included the presence of vascular invasion, tumor size, tumor stage, and alpha-fetoprotein (AFP) levels. Patient survival over approximately 4 years follow-up was significantly worse in patients whose tumor metabolic activity was more than 1.15 times the activity of the normal liver. Of the 14 patients that had tumor recurrence, 12 had extra-hepatic metastases and 10 had liver metastases (8 had both intra- and extra- hepatic metastases). It is conceivable, as hypothesized by the authors, that tumors with higher metabolic activity and FDG uptake are biologically more aggressive and have greater tendency to recur within and outside the liver. Remarkably, the baseline tumor metabolic activity was a better predictor of tumor recurrence after transplantation than the Milan criteria.

5.1.3.4 Response to Treatment

For patients with unresectable HCC undergoing local liver treatments, FDG-PET may play a role in the early evaluation of treatment response. Higashi et al. [12] found in a study of 67 patients with HCC that PET/CT was accurate and effective in the early detection of the presence of residual viable tumor after locoregional therapy (transarterial chemoembolization [TACE], infusion chemotherapy, and RFA) as well as after systemic treatment. Abnormal FDG in the treated area 1 month after treatment had a 96.4% positive predictive value for residual tumor, and predicted overall worse survival.

FDG-PET has been reported to have high accuracy in predicting the success of local ablation treatments in patients with liver metastases from colorectal cancer. Langenhoff et al. [13] found FDG-PET to be highly accurate in predicting treatment success in 23 patients with a total of 56 metastatic lesions treated with local therapies. PET was able to detect tumor recurrences earlier than CT; all liver recurrences were detected 3–4 months earlier than CT for intra-hepatic recurrences and 1.5 months earlier for extra-hepatic recurrences. In 13 patients with 28 liver metastases treated with RFA, Donckier et al. [14] found that PET was able to detect all 11 tumor recurrences, whereas MRI showed a 2–4 month delay in the detection of the recurrences.

PET/CT offers valuable information in the initial evaluation and following TACE for liver tumors. In 36 patients with HCC treated with TACE, Kim et al. [15] found that PET/CT had better sensitivity, although a lower specificity, than CT alone to detect residual disease. Less well established is the role of PET/CT in the follow-up evaluation of liver cancer treated with selective internal radiation therapy (SIRT) (also known as radioembolization [RE]), with Yttrium-90 labeled microspheres. It appears however that PET/CT could offer a better assessment of tumor response after treatment than CT-based Response Evaluation Criteria in Solid Tumors (RECIST) criteria. In 21 patients with unresectable liver tumors, both HCC and metastatic, Szyszko et al. [16] found a significant decline of FDG uptake after treatment

in 86 % of the patients, whereas CT showed a response in only 13 % of the patients. These results are similar to those of other studies [17], most likely reflecting the limitations of a solely anatomically based method of assessing tumor response. Further evaluation with prospective studies is needed in this area to confirm and better define the role of PET/CT imaging with this form of treatment.

Conclusion

In summary, there is no doubt that the unique information of cancer biology that is offered by PET/CT will play an increasingly important role to direct personalized treatment of liver tumors. Ideally, personalized therapies will be initiated in the initial stages of disease and will be based on the biological characterization of tumor metabolism and aggressiveness. As initial treatment is delivered, subsequent therapies will then be adapted depending on the degree of tumor response as assessed by subsequent anatomical and functional imaging performed during and at the end of treatment cycles, with the goal of maximizing efficacy and minimizing toxicity of treatments.

It can be hypothesized that the performance of PET/CT, in conjunction with CT and MRI, will help improve the initial staging and prognostic evaluation of patients with liver tumors. This will allow improved and individualized evaluation of tumor resectability through the enhanced ability to detect extra-hepatic disease, to determine the exact number of liver lesions, and, to assess tumor aggressiveness. The routine use of PET/CT following treatment will likely improve the accuracy of the assessment and will allow earlier detection of residual or recurrent disease. At the completion of treatment, the higher sensitivity of PET/CT for detecting lymph node and distant metastases will allow greater accuracy in disease restaging.

Although the role of PET/CT appears very promising from the available scientific evidence, there are still unresolved issues that only future studies will help address. Large multicenter prospective trials will be needed to ultimately evaluate the clinical impact of FDG-PET/CT to direct treatment in patients with liver tumors undergoing ablation procedures. Studies are needed to establish PET criteria of response, and how they relate to CT/MRI based criteria. Which of the following response criteria should be used RECIST, World Health Organization (WHO), European Society for the Study of the Liver (EASL), or PET Response Criteria in Solid Tumors (PERCIST), and should these criteria based on hybrid imaging such as PET/CT or maybe even PET/MRI? Finally, as we gather information on the role of PET/CT imaging with FDG, new and very promising PET based biomarkers such as tumor cell proliferation, angiogenesis, hypoxia, apoptosis, are being tested clinically and could offer new perspectives on the evaluation and treatment of liver cancers.

References

1. Brown RS, Wahl RL (1993) Overexpression of glut-1glucose transporter in human breast cancer. An immunohistochemical study. Cancer 72(10):2979–85
2. Rohren EM, Turkington TG, Coleman RE (2004) Clinical applications of PET in oncology. Radiology 231(2):305–32
3. Fletcher JW, Djulbegovic B, Soares HP et al (2008) Recommendations on the use of 18F-FDG PET in oncology. J Nucl Med 49:480–508
4. Gallamini A, Hutchings M, Rigacci L et al (2007) Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's Lymphoma: a report from a joint Italian-Danish study. J Clin Oncol 25:3746–3752
5. Hillner BE, Siegel BA, Liu D et al (2008) Impact of positron emission tomography/computed tomography and positron emission tomography (PET) alone on expected management of patients with cancer: initial results from the National Oncologic PET Registry. J Clin Oncol 26:2155–216
6. Podoloff DA, Ball DW, Ben-Josef et al (2010) NCCN Task Force Report: clinical utility of PET in a variety of tumor types. J Natl Compr Cancer Netw 7(Suppl 2)
7. Wiering B, Krabbe PF, Jager GJ et al (2005) The impact of fluor-18-deoxyglucose-positron emission tomography in the management of colorectal liver metastases. Cancer 104:2658–2670
8. Blue Cross Blue Shield Association (2000) FDG positron emission tomography in colorectal CA. Technology Evaluation Center (TEC) Assessments. Vol. 14
9. Delbeke D, Martin WH, Sandler MP et al (1998) Evaluation of benign vs. malignant hepatic lesions with positron emission tomography. Arch Surg 133:510–516
10. Wudel LJ, Delbeke D, Morris D et al (2003) The role of [18F]fluorodeoxyglucose positron emission tomography imaging in the evaluation of hepatocellular carcinoma. Am Surg 69:117–126
11. Lee JW, Paeng JC, Kang KW et al (2009) Prediction of tumor response by 18F-FDG PET in liver transplantation for hepatocellular carcinoma. J Nucl Med 50:682–687
12. Higashi E, Hatano E, Ikai I et al (2010) FDG PET as a prognostic predictor in the early post-therapeutic evaluation for unresectable hepatocellular carcinoma. Eur J Nucl Med Mol Imaging 37:468–482
13. Langenhoff BS, Oyen WJG, Jager GJ et al (2002) Efficacy of fluorine-18-deoxyglucose positron emission tomography in detecting tumor recurrence after local ablative therapy for liver metastases: a prospective study. J Clin Oncol 20:4453–4458
14. Donckier V, Van Laethem JL, Goldman S et al (2003) [F-18] fluorodeoxyglucose positron emission tomography as a tool for early recognition of incomplete tumor destruction after radiofrequency ablation for liver metastases. J Surg Oncol 84:215–223
15. Kim Ho, Kim JS, Shin YM et al (2010) Evaluation of metabolic characteristics and viability of lipiodolized hepatocellular carcinomas using 18F-FDG PET/CT. J Nucl Med 51:1849–1856
16. Szyszko T, Nahhas AA, Canelo R et al (2007) Assessment of response to treatment of unresectable liver tumours with 90Y microspheres: value of FDG PET versus computed tomography. Nucl Med Commun 28:15–20
17. Popperl G, Helmberger T, Munzing W et al (2005) Selective internal radiation therapy with SIR-spheres in patients with nonresectable liver tumours. Cancer Biother Radiopharm 20:200–208

Chapter 6
Personalized Chemotherapy for Hepatocellular Carcinoma

Hesham Hazin and David Dosik

Abstract Hepatocellular cancer (HCC) is an aggressive tumor that typically occurs in the setting of chronic liver disease and cirrhosis. Although the mainstay of curative therapy for HCC is surgical resection and/or liver transplantation, the majority of patients are not eligible because of underlying liver dysfunction or tumor extent. A personalized approach is useful for conceptualizing the various treatment options that are available for individual patients. This Chapter first explores the underlying molecular and genetic basis of HCC, as well as virology, and other factors that influence the microenvironment of HCC. This is followed by a discussion of the role of systemic chemotherapy for patients with HCC. Among the major risk factors for HCC is infection with hepatitis B virus (HBV) or hepatitis C virus (HCV). These particular hepatic pathogens are involved in a multifaceted process that involves a number of alterations that are genetic and epigenetic such as the activation of cellular oncogenes and the inactivation of tumor suppressor genes. Systemic therapy with single-agent or combination chemotherapy has been studied extensively. However, cytotoxic chemotherapy traditionally has been associated with low response rates and questionable disease control. Thus, systemic chemotherapy has a limited role in HCC. Newer data on the efficacy of molecularly targeted agents have brought sorafenib to the forefront of therapy for advanced HCC. Sorafenib offers the potential for prolonged survival, although objective tumor remissions are scarce. Sorafenib is now the first line treatment in patients with HCC who are not candidates to undergo liver transplant, surgical resection, chemoembolization, or tumor ablation.

H. Hazin (✉) · D. Dosik
New York Methodist Hospital, Brooklyn, NY, USA
e-mail: heshamhazin@yahoo.com

D. Dosik
Weill Medical College of Cornell University, New York, USA
e-mail: ddosik@aol.com

L. Berliner, H. U. Lemke (eds.), *An Information Technology Framework for Predictive, Preventive and Personalised Medicine,* Advances in Predictive, Preventive and Personalised Medicine 8, DOI 10.1007/978-3-319-12166-6_6

6.1 Introduction

Malignancies of the liver are among of the most common tumors in adults, accounting for some of the most ubiquitous cancers in the world, being either metastatic or primary. The majority of liver tumors are comprised of hepatocellular cancer (HCC) and metastatic colorectal cancer (mCRC). HCC ranks as the second leading cause of cancer deaths. In terms of incidence, HCC is the fifth most common type of cancer, of which approximately 630,000 cases are reported per year worldwide [1, 2].

With the advent of the hepatitis B vaccine and education about risk factors of hepatitis C, the incidence of HCC is expected to decline. Given these preventive factors that play a role in HCC, physicians are able to be proactive instead of reactive. By understanding the many conduits involved in HCC, not only on a cellular level, but also on a patient level involving performance status and co-morbidities, one is able to practice powerful, predictive, preventive, and personalized medicine (PPPM).

6.1.1 Preventive Risk Factors in Hepatocellular Carcinoma

The majority of patients that present with, or are diagnosed with, HCC are usually patients with chronic liver impairment or failure. Common risk factors for liver cirrhosis are hepatitis B and C viral infections, which increase the risk of HCC by twenty fold [3]. The prevalence of chronic infections caused by hepatitis B and C is directly related to the incidence of HCC. Other common risk factors include non-alcoholic steatohepatitis (NASH), alcohol abuse, aflatoxins caused by the fungi *Aspergillus*, and hemochromatosis.

6.1.2 Discussion of Molecular/Genetic Etiology of HCC

Among the major risk factors for HCC is infection with hepatitis B virus (HBV) or hepatitis C virus (HCV). These particular hepatic pathogens are involved in a multifaceted process involving a number of alterations that are genetic and epigenetic such as the activation of cellular oncogenes, and the inactivation of tumor suppressor genes. The pathways that are involved include Wnt/β-catenin, p53, pRb, Ras, mitogen-activated protein kinase (MAPK), Janus kinase (JAK)/signal transducer and activator of transcription (STAT), phosphatidylinositol 3 kinase (PI3K)/Akt, Hedgehog and growth factors such as epidermal growth factor (EGFR), and transforming growth factor—beta (TGF-β) [4]. A few of these molecular pathways are involved during the progression of liver injury. At initial insult of the liver, hepatic stellate cells become activated, and convert into fibroblast cells, in that it produces extracellular matrix. Irreversible liver cirrhosis occurs due to this unimpeded

fibrosis caused by these myofibroblastic cells. The aforementioned pathways such as Wnt, Hedgehog, and MAPK are found in these hepatic stellate cells and, in turn, are stimulated to initiate inflammatory cascades causing promotion of possible carcinogenesis.

HBV is a double-stranded DNA virus belonging to the Hepadnavirus family. HBV DNA plays a role as a template for transcription of viral RNA, which is then translated to viral proteins. Numerous HCCs are noted to be have integrated DNA sequences that code for the same HBV proteins, i.e. HBx and pre-S2/S proteins. By integrating into host DNA, the proteins compromise DNA repair, inactivating p53, and transactivates several molecular pathways (JAK, STAT, Wnt, MAPK, Ras, β-catenin) therefore promoting hepatocarcinogenesis [4].

HCV is an RNA virus belonging to the Flaviviridae family. Given that HCV is an RNA virus, it is unable to integrate its genome to the host. Instead, the HCV viral core and envelope proteins initiate a host response that contributes to carcinogenesis. The HCV core protein is believed to be involved in the binding of several tumor suppressor proteins including p53, pRb, and p73. Binding of these particular proteins causes the prevention of dependent cell growth arrest. The chronic inflammation produced by the core proteins shifts the function of the TGF-β pathways from that of tumor suppression to fibrogenesis, accelerating fibrosis and cirrhosis, and increasing the risk of HCC [4].

Nonalcoholic steatohepatitis (NASH) is the most common cause of chronic liver disease in the U.S., attributing 30–40% prevalence, along with a 2–5% increased risk of developing cirrhosis. Even without the presence of cirrhosis, HCC has been shown to develop in patients with NASH. This correlation is quite alarming since the incidence of metabolic syndrome and obesity continues to rise. Some of the risk factors associated with HCC in NASH are obesity, diabetes mellitus, and increased iron stores. Similar to HBV and HCV infections, the development of HCC in NASH involves a multitude of immunologic and genetic events that result in the transformation of hepatocytes to neoplastic cells. Roughly 80% of the time this occurs in the setting of a cirrhotic liver where there is activation of mitotic signaling pathways as well as increased oxidative stress, nuclear factor-kB (NF-kB) activation, and immunologic alterations leading to the formation of dysplastic nodules [5]. The types of genetic alterations include point mutations, hypermethylation of genes, and chromosomal arm gains/losses thereby giving rise to HCC. Inflammation secondary to cytokines (TNF and IL-6) contributes to gene activation of vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), and telomerase reverse-transcriptase (TERT), which, in turn, contribute to cessation of apoptosis, and uncontrolled growth of neoplastic clones.

The pathogenesis of developing HCC in the setting of noncirrhotic NASH is currently being investigated, but likely involves inflammatory cytokines from insulin resistance and metabolic syndrome. It is hoped that by understanding these molecular and genetic pathways it may be possible to predict which patients are at increased risk for developing HCC. These patients may benefit from undergoing intensive screening to prevent HCC or to detect HCC at its earliest stages.

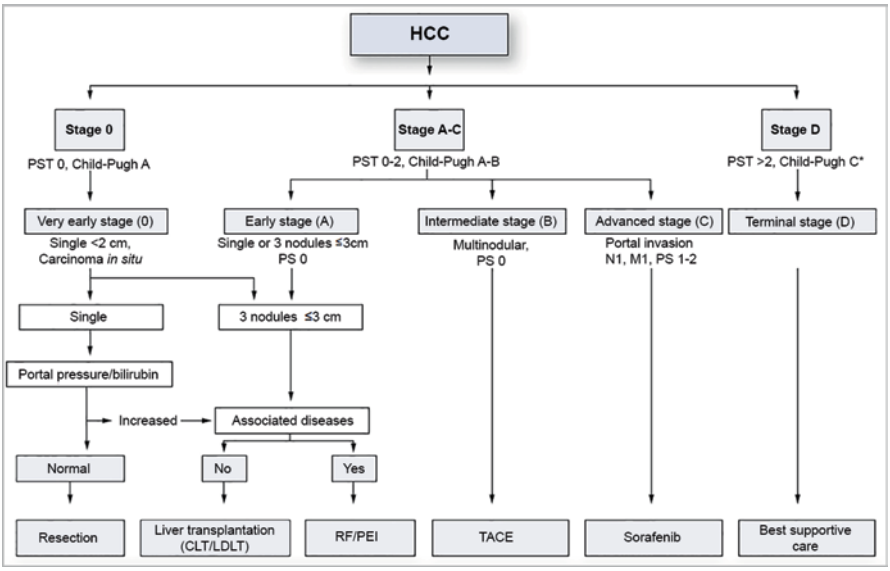

Fig. 6.1 The Barcelona Clinic Liver Cancer (BCLC) staging system for Hepatocellular Carcinoma—revised 2011 [8]

6.1.3 Staging and Personalized Patient Evaluation in Hepatocellular Carcinoma

The diagnosis of HCC involves two standard modalities: radiological liver imaging and measurement of alpha-fetoprotein. Alpha-fetoprotein is known to be elevated in 60–70 % of patients with HCC [6]. By combining these two modalities, one can come to the conclusive diagnosis of HCC. Treatment is dependent on staging, however, the TNM system is no longer feasible in evaluating patients with HCC due to the fact that TNM staging is based on tumor characteristics, not liver function assessment. An integrated staging system that was developed to personalize patients based on prognosis and degree of chronic liver disease is the Barcelona Clinic Liver Cancer (BCLC) staging system. The BCLC staging is a multi-function system that incorporates tumor characteristics, Child-Pugh classification and liver function. This current staging system allows one to assess the patient and based on their characteristics individually, one can direct them to a suitable treatment. The BCLC staging can also predict patient outcomes, by stratifying treatment groups according to the extent of their disease (Fig. 6.1) [7, 8].

The current recommendations based on the BCLC Staging System include:

1. Patients who have a single lesion ≤5 cm, or 2–3 nodules≤3 cm, can be offered surgical resection in the presence of cirrhosis with intact liver function, normal bilirubin, and hepatic vein pressure≤10 mmHg.

2. Liver transplantation is an effective option for patients with HCC who have a single lesion, with elevated bilirubin, and elevated hepatic vein pressure.
3. For patients who are not candidates for liver transplantation due to co-morbid conditions and poor performance status, local ablation is a safe and effective therapy, which can also be used as a bridge to transplantation. In terms of ablation, alcohol injection and radiofrequency ablation (RFA) are equally effective for tumors less than 2 cm, but RFA has a more predictable necrotic effect.
4. Transarterial chemoembolization (TACE) is recommended for patients who have multicentric disease without extrahepatic spread or vascular invasion, lesions > 3 cm, or patients who exhibit portal invasion without extra-hepatic spread/vascular invasion.
5. Systemic chemotherapy has a limited role in HCC.

6.1.4 Targeted and Predictive Treatment in Hepatocellular Carcinoma

Systemic therapy with single-agent or combination chemotherapy has been studied extensively. However, cytotoxic chemotherapy traditionally has been associated with low response rates and questionable disease control.

6.1.4.1 Monotherapy: Doxorubicin

Single agent doxorubicin has been the most studied chemotherapy agent for advanced HCC. Although an early trial in 1975 reported dramatic clinical activity and a 79% response rate [9], subsequent work suggests that the true objective response rate with doxorubicin monotherapy is 20% or less with doses of 75 mg/m^2 [10–15]. Lower doses ($\leq$60 mg/m^2 per cycle) are associated with even lower objective response rates [16, 17]. Despite the modest objective response rate, one controlled trial involving 106 patients suggests that doxorubicin is associated with a small survival advantage compared to best supportive care alone (median survival 10.6 versus 7.5 weeks) [13]. The reason for the disparate survival outcomes in this trial is unclear, but patient selection may have played a role. 5-Fluorouracil (5-FU) has acceptably low toxicity and broad antitumor efficacy. Response rates with 5-FU monotherapy have been low. However, when given in combination with leucovorin, response rates as high as 28% have been reported [18], although lower rates have been noted by others [19].

6.1.4.2 Molecular Targeted Therapy: Sorafenib

Sorafenib is a multi-targeted, orally active, small molecule tyrosine kinase inhibitor (TKI) that inhibits Raf kinase and the VEGFR intracellular kinase pathway [20].

The multi-center European *Sorafenib HCC Assessment Randomized Protocol* (SHARP) trial randomly assigned 602 patients with inoperable HCC and Child-Pugh A cirrhosis to sorafenib (400 mg twice daily) or placebo [21]. Overall survival, the primary endpoint, was significantly longer in the sorafenib-treated patients (10.7 versus 7.9 months), as was time to radiologic progression (5.5 versus 2.8 months). On the other hand, objective response rates were low (7 partial responses [2%]). Treatment was well tolerated with manageable side effects. The only grade 3 or 4 adverse effects that occurred significantly more often in the treated group was diarrhea (8 versus 2%) and hand-foot skin reaction (8 versus < 1%). There were no differences in liver dysfunction or bleeding. The overall incidence of sorafenib-related side effects was low compared to that reported by others [22]. These results established sorafenib monotherapy as the new reference standard systemic treatment for advanced HCC and formed the basis for approval of sorafenib for unresectable HCC in the United States. The efficacy of sorafenib in Asian patients was the subject of a second placebo-controlled phase III trial, in which 226 patients with Child-Pugh A or B cirrhosis and no prior systemic therapy for HCC received sorafenib 400 mg twice daily or placebo [23]. Patients receiving sorafenib had significantly better median overall survival (6.5 versus 4.2 months) and time to progression (TTP) (2.8 versus 1.4 months). Grade 3 or 4 side effects included hand-foot skin reaction (11%), diarrhea (6%), and fatigue (3%). The magnitude of benefit was markedly less in this trial than seen in the SHARP trial. In fact, the treated group in the Asian trial had shorter survival duration than the control group in the SHARP trial (6.5 versus 7.9 months), despite the fact that both trials used the same entry criteria. Nevertheless, patients accrued to the Asian study were more ill at the start of therapy than those in the SHARP trial, with a generally worse performance status and more advanced stage of disease [24].

6.1.5 Personalized Recommendations—Chemotherapy for Hepatocellular Carcinoma

HCC is an aggressive tumor that frequently occurs in the setting of chronic liver disease and cirrhosis. Hepatic reserve, as indicated by Child-Pugh class, often dictates the therapeutic options. Newer data on the efficacy of molecularly targeted agents have brought these agents, particularly sorafenib, to the forefront of therapy for advanced HCC.

Sorafenib offers the potential for prolonged survival, although objective tumor remissions are scarce. This molecular targeted therapy would be the first line treatment in patients with HCC who are not candidates to undergo liver transplant, surgical resection, TACE, or RFA. In terms of liver cirrhosis, the manufacturer recommends no dose adjustment for Child-Pugh class B impairment and makes no recommendation for Child-Pugh C cirrhosis. Nevertheless, the recommendation of an initial dose reduction to 200 mg twice daily in patients with a total bilirubin 1.5–3 times the upper limit of normal and that the drug not be administered to patients

with more severe degrees of hyperbilirubinemia. For other patients with Child-Pugh B cirrhosis, standard dosing from the onset with dose modification as needed is appropriate. Given the poor prognosis of patients with HCC and Child-Pugh C cirrhosis, the associated significantly abnormal liver function and the high risk of treatment-related toxicity, most physicians would not prescribe sorafenib to these patients. The efficacy of cytotoxic chemotherapy is limited in patients with HCC. Even though few randomized trials have been conducted, no single regimen has emerged as superior to any other. Despite objective responses that are occasionally complete, median survival in all of these studies has been short (4.4–11.6 months).

Systemic chemotherapy is an option for patients whose tumors progress while on sorafenib and whose performance status and liver function are sufficient to tolerate it. The best regimen is not established. The side effect profile of each individual regimen must be carefully considered in patients who have advanced liver disease and/or a short life expectancy. Doxorubicin monotherapy is rarely used in the treatment of HCC. Given the cardiotoxic side effects and low response rates, the treatment would be considered for patients who failed molecular targeted therapy and still exhibit a moderate/fair performance status, with fairly intact liver and cardiac function. 5FU/Leucovorin treatment candidates would include the elderly, poor performance status patients, and those who are classified as Child-Pugh Class C.

Conclusion

In conclusion, liver tumors from metastatic colon cancer or primary malignancies of the liver, such as HCC, are aggressive tumors that cause great morbidity and mortality. Although the mainstay of curative therapy in HCC is surgical resection and/or liver transplantation, the majority of patients are not eligible because of underlying liver dysfunction or tumor extent. A personalized approach is useful for conceptualizing the various treatment options that are available for individual patients in both disease states.

References

1. Jemal A, Bray F, Center MM et al (2011) Global cancer statistics. CA Cancer J Clin 61:69–90
2. Rampone B, Schiavone B, Martino A et al (2009) Current management strategy of hepatocellular carcinoma. World J Gastroenterol 15:3210–3216
3. Donato F, Boffetta P, Puoti M (1998) A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. Int J Cancer 75:347–354
4. Tsai W-L, Chung RT (2010) Viral hepatocarcinogenesis. Oncogene 29:2309–2324
5. Torres DM. Harrison SA (2012) Nonalcoholic steatohepatitis and noncirrhotic hepatocellular carcinoma: fertile soil. Semin Liver Dis 32:30–38
6. Lau WY, Lai EC (2008) Hepatocellular carcinoma: current management and recent advances. Hepatobiliary Pancreat Dis Int 7:237–257

7. Bruix J, Sherman M (2005) Management of hepatocellular carcinoma. Hepatology 42:1208–1236
8. European Association for the Study of the Liver. European Organisation for Research and Treatment of Cancer (2012) EASL–EORTC Clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 56:908–943
9. Olweny CL, Toya T, Katongole-Mbidde E et al (1975) Treatment of hepatocellular carcinoma with adriamycin. Preliminary communication. Cancer 36:1250
10. Chlebowski RT, Brzechwa-Adjukiewicz A, Cowden A et al (1984) Doxorubicin (75 mg/m2) for hepatocellular carcinoma: clinical and pharmacokinetic results. Cancer Treat Rep 68:487.h
11. Ihde DC, Kane RC, Cohen MH et al (1977) Adriamycin therapy in American patients with hepatocellular carcinoma. Cancer Treat Rep 61:1385
12. Nerenstone SR, Ihde DC, Friedman MA (1988) Clinical trials in primary hepatocellular carcinoma: current status and future directions. Cancer Treat Rev 15:1
13. Lai CL, Wu PC, Chan GC et al (1988) Doxorubicin versus no antitumor therapy in inoperable hepatocellular carcinoma. A prospective randomized trial. Cancer 62:479
14. Choi TK, Lee NW, Wong J (1984) Chemotherapy for advanced hepatocellular carcinoma. Adriamycin versus quadruple chemotherapy. Cancer 53:401
15. Yeo W, Mok TS, Zee B et al (2005) A randomized phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. J Natl Cancer Inst 97:1532
16. Sciarrino E, Simonetti RG, Le Moli S, Pagliaro L (1985) Adriamycin treatment for hepatocellular carcinoma. Experience with 109 patients. Cancer 56:2751
17. Gish RG, Porta C, Lazar L et al (2007) Phase III randomized controlled trial comparing the survival of patients with unresectable hepatocellular carcinoma treated with nolatrexed or doxorubicin. J Clin Oncol 25:3069
18. Porta C, Moroni M, Nastasi G, Arcangeli G (1995) 5-Fluorouracil and d, l-leucovorin calcium are active to treat unresectable hepatocellular carcinoma patients: preliminary results of a phase II study. Oncology 52:487
19. Tetef M, Doroshow J, Akman S et al (1995) 5-Fluorouracil and high-dose calcium leucovorin for hepatocellular carcinoma: a phase II trial. Cancer Invest 13:460
20. Liu L, Cao Y, Chen C et al (2006) Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. Cancer Res 66:11851
21. Llovet JM, Ricci S, Mazzaferro V et al (2008) Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378
22. Vincenzi B, Santini D, Russo A et al (2010) Early skin toxicity as a predictive factor for tumor control in hepatocellular carcinoma patients treated with sorafenib. Oncologist 15:85
23. Cheng AL, Kang YK, Chen Z et al (2009) Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 10:25
24. Raoul J, Santoro A, Beaugrand M et al (2008) Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma according to ECOG performance status: a subanalysis from the SHARP trial (abstract). J Clin Oncol 26:234 s. www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=34874/. Accessed 4 May, 2009

Chapter 7
Surgical Treatment for Hepatocellular Carcinoma

Smruti Mohanty, Leonard Berliner and Syed Shah

Abstract The treatment of hepatocellular carcinoma (HCC) has undergone evolution and refinement over the past three decades. Changes in the understanding of HCC with respect to tumor size, number and location, underlying liver function and portal pressure, and hepatic anatomy, in combination with refinement of surgical techniques and technologies, have greatly influenced the approach to surgical management. Surgery is considered the mainstay of curative HCC treatment with resection and transplantation achieving the best outcomes in well-selected candidates (5-year survival of 60–80 %). Surgical resection of HCC, especially within the Milano/Mazzaferro criteria (i.e., solitary tumor $\leq$5 cm or up to three tumors all $\leq$3 cm) in patients with well-preserved liver function (Child-Pugh A and selectively B patients), offers the greatest chances for survival. Liver transplantation is considered the treatment of choice for patients with compromised liver function (Child-Pugh B/C). The clinical parameters identified in this Chapter will be used to generate Digital Patient Models (DPMs) to facilitate diagnosis, prognosis, and treatment selection, i.e. Model Guided Therapy (MGT). The following have been identified as key issues relating to Predictive, Preventive, and Personalized Medicine (PPPM) and surgical treatment for HCC: tumor characterization, such as size, number, and vascular invasion; the patient's clinical status, particularly the presence of cirrhosis, the degree of portal hypertension, and liver functional reserve; pre-operative management, such as patient selection for resection or transplantation, choice of donor, down-staging and bridging therapies; and, surgical techniques, including techniques to minimize blood loss and to ensure an adequate liver remnant.

S. Mohanty (✉) · L. Berliner · S. Shah
New York Methodist Hospital, Brooklyn, NY, USA
e-mail: srm9006@nyp.org

L. Berliner
e-mail: LeonardB23@AOL.com

S. Shah
e-mail: smashah@aol.com

S. Mohanty · L. Berliner · S. Shah
Weill Medical College of Cornell University, New York, USA

L. Berliner, H. U. Lemke (eds.), *An Information Technology Framework for Predictive, Preventive and Personalised Medicine,* Advances in Predictive, Preventive and Personalised Medicine 8, DOI 10.1007/978-3-319-12166-6_7

Keywords Personalized medicine · Hepatocellular carcinoma · Staging · Treatment · Surgery · Hepatectomy · Liver Transplantation · Down-staging · Bridging Therapy

7.1 Introduction

The treatment of hepatocellular carcinoma (HCC) has undergone evolution and refinement over the past three decades. Changes in the understanding of HCC in the context of a wide variety of factors such as tumor size, number and location, underlying liver function and portal pressure, and hepatic anatomy, in combination with refinement of surgical techniques and technologies, have greatly influenced the approach to surgical management. Concerted efforts have been made to review and consolidate the worldwide experience in the management of HCC and recommendations for optimal treatment protocols, based on patient staging, have been made reflecting these findings [1–4].

Surgery is considered the mainstay of curative HCC treatment with resection and transplantation achieving the best outcomes in well-selected candidates (5-year survival of 60–80%) [3]. In general, surgical resection of HCC, especially within the Milano/Mazzaferro criteria for liver transplantation (i.e., solitary tumor ≤5 cm or up to three tumors all ≤3 cm) in patients with well-preserved underlying liver function (Child-Pugh A and selectively B patients), offers the greatest chances for survival, while liver transplantation, in patients with compromised liver function (Child-Pugh B/C), is generally considered the treatment of choice. It is important to note that these recommendations are undergoing constant reassessment and revision. The application of specific techniques, such as radiofrequency ablation (reviewed in Chaps. 8 and 9) and the practice of reclassification of patients with well-compensated liver function, have, in some reports, suggested alternative treatment protocols. These issues relating to surgical management of HCC, and which emphasize the trend toward personalized medicine in HCC, will be discussed in this Chapter.

7.1.1 Surgical Resection

Surgical resection is the optimal treatment for HCC in non-cirrhotic patients (Child-Pugh A) in that it may be curative and because of the high reserve and regenerative capacity of a non-fibrotic liver [5]. Unfortunately, in Western countries only approximately 5% of patients present with HCC without cirrhosis [6]. In Asian countries, approximately 40% of patients will have HCC without cirrhosis due to the high incidence of hepatitis B virus (HBV) infection which predisposes patients to HCC in the absence of cirrhosis [6]. However, with careful patient selection and improved surgical techniques, peri-operative mortality rates in cirrhotic patients

with HCC have been reported to be 2–3% with a 5-year survival rate of approximately 60% and blood transfusion requirements of less than 10% [3]. Selection criteria for surgical resection has previously been based on the Child-Pugh class, however surgical outcomes have been improved when independent criteria, like serum bilirubin levels and presence of portal hypertension, are used to risk stratify operative candidates [7,8]. The Barcelona Clinic Liver Cancer (BCLC) criteria stratify patients for therapy in this fashion [1–3]. Patients with normal bilirubin levels and hepatic-portal vein gradient (HVPG) < 10 mm Hg have been reported to have a 5-year survival rate of < 70%. This is in contrast to patients with hyperbilirubinemia and portal hypertension who have a < 30% 5-year survival rate [7]. Surrogates of portal hypertension include esophageal varices and splenomegaly with platelet count < 100,000/mm^3) [3].

The size and number of tumors, the presence of microsatellites, the presence of vascular invasion, and the width of resection margin have all been shown to have prognostic significance [3, 9–11]. Improved postoperative 5-year survival rates have been shown in patients with tumors < 5 cm in diameter (66% for tumors < 2 cm, compared with 52% for tumors 2–5 cm and 37% for tumors > 5 cm) and with fewer numbers of tumor nodules (73% with one tumor vs. 44% with 3 or more tumors) [11]. The major contraindication to resection of HCC is the presence of extrahepatic disease, as HCC commonly spreads to lymph nodes, lungs, and bone [12].

Vascular invasion has been shown to play a major role in tumor recurrence and it is thought that recurrence often involves spread from the primary resected tumor, rather than metachronous tumor development [4, 13]. Microvascular invasion has been shown to be a significant factor affecting prognosis after surgical resection, especially with identification of invasion of a muscular vessel wall or of invasion more than 1 cm beyond the tumor edge as the two worst risk factors for prognosis [14]. Tumor resection margin also influences recurrence rate in that wider margins (2 cm vs. 1 cm) taken on solitary tumors have been shown to both decrease recurrence and improve survival [15].

Several treatments have been studied as adjuvant therapies to reduce recurrence after resection of HCC. This includes the use of interferon, chemotherapy, preoperative chemoembolization, internal radiation with 131I-labeled lipiodol, immune therapies with activated lymphocytes with interleukin-2 and retinoids, and vitamin K. At this time, the studies have not been sufficiently large or conclusive enough to support their use to improve postoperative survival [3,16].

Pre-operative portal vein embolization (PVE) of the branches supplying the portion of the liver to be resected (with the intention of increasing the residual liver volume if a major resection is envisioned) has been studied [17]. The average increase in the future liver remnant (FLR) following PVE is 9% and 16% in cirrhotic and normal liver, respectively [17] and PVE has been used to increase the volume of the FLR in all patients who undergo trisegmentectomy [12]. PVE has also been employed in those patients with chronic liver disease who are to undergo right hemihepatectomy or when the FLR is less than 40% [12]. However, PVE is associated with a complication rate of 10–20% and the occurrence of severe portal

hypertension in 1% of cirrhotic patients [18]. The overall effectiveness of PVE in the treatment of HCC in cirrhosis has not yet been properly tested in large controlled studies [3].

7.1.2 Surgical Resection Techniques

In addition to selecting patients with preserved liver function reserve, a variety of surgical techniques may be employed to minimize blood loss, which is highly associated with patient outcomes [3]. This includes pre-resection imaging planning, use of ultrasonic dissector, intermittent Pringle maneuver, low central venous pressure maintenance, and immediate post-operative management. These strategies have led to a decrease in blood transfusion from 80 to 90% to less than 10% in two decades [19].

The implementation of anatomic resections according to the Couinaud segments has ensured a surgical approach based on sound oncologic principles, although associated with modest decrease in early recurrence [3]. As described above, anatomic resections of 2 cm margins provide better survival outcome than narrow resection margins < 1 cm. However, it is important to maintain sufficient remnant liver volume to ensure adequate function.

Finally, laparoscopic video-assisted hepatic resection is being investigated as an alternative non-invasive approach aimed at preventing liver deterioration compared to open surgery [3].

7.1.3 Liver Transplantation

Liver transplantation is a curative option for patients with HCC, especially for those with underlying cirrhosis who may be poor candidates for surgical resection. Patients with a single lesion ≤5 cm, or up to 3 lesions each ≤3 cm in diameter, who meet the United Network for Organ Sharing (UNOS) criteria and those meeting extended criteria of University of California San Francisco (UCSF) which allows for a single lesion ≤6.5 cm or up to 4 lesions with none >4.0 cm and a maximum combined tumor bulk of ≤8.0 cm have shown excellent 5-year survival rates of approximately 70% [20–22]. However, the UCSF criteria have not been adopted by UNOS for liver transplantation in patients with HCC.

Priority for transplantation is given to the patients with the earliest predicted mortality which is calculated using the Model for End-Stage Liver Disease (MELD) score [23]. Although MELD is useful prognosticating patients with many forms of chronic liver disease including cirrhosis, the MELD score alone may underestimate disease severity in patients with HCC creating a disadvantage for these patients in obtaining a liver transplant. To make the MELD system more equitable for patients with HCC, exception points are given in an effort to ensure that all patients on the

liver transplant waiting list will be transplanted in an order where patients with the earliest expected mortality are prioritized.

Currently, patients with a single lesion between 2–5 cm, or up to 3 lesions (each lesion < 3 cm), are automatically given a MELD of 22 [24]. If their calculated score is higher than 22, then the calculated score may be used. Patients who receive a MELD upgrade also receive an increase in score by 10 % at each 3 month interval after listing for liver transplantation [20]. Since the MELD system with exceptions for HCC was adopted in 2002, total number of liver transplantations performed in patients with HCC has increased nearly 6 fold. From 1997 to 2002 (pre-MELD exception) 4.6 % of all liver transplants were in patients with HCC compared to 26 % of all liver transplants performed in patients with HCC from 2002 to 2007 [25].

7.1.4 Down-staging and Bridging Therapies

Down-staging of HCC is the use of localized tumor therapy in an effort to reduce tumor size and number of nodules prior to transplantation. In some cases, transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) have been shown to successfully down-stage tumors prior to transplant [26]. Recent data has shown benefit in use of ablative therapy prior to transplantation [27]. Patients with HCC who received ablative therapy prior to transplantation were compared to those who did not receive ablative therapy and were shown to have similar 3 month and 1 year graft and patient survival; however, those who received ablative therapy had improved graft and patient survival three years after transplantation (graft survival 76 % vs 71 %, patient survival 79 % vs 75 %) [27].

One significant problem facing patients with HCC waiting for liver transplant is the risk of dropout due to the progression of disease beyond transplant criteria. By 6 months, 20 % of patients will no longer be eligible for transplant and by 1 year at least 70 % of patients with untreated HCC will have tumor growth, 20 % will develop vascular invasion, and 9 % will develop metastases [28]. Locoregional ablative therapies have served as a bridge to transplantation or as destination therapy in patients who are not originally transplant candidates. These treatments have been used to downsize tumors and prevent lesions from exceeding transplantable criteria while patients await transplantation. In general, for patients within Milan criteria, ablative therapies are used if the expected waiting time until transplantation is greater than 6 months [28].

HCC recurrence following transplantation usually, but not always, manifests within the first 2 years of transplantation and is more likely to occur in patients with more extensive pre-transplant tumor burden [29]. Chemotherapy with agents such as doxorubicin have been evaluated for use pre-operatively, intra-operatively and post-transplantation with limited results. The focus in preventing post-transplant HCC recurrence has shifted to improving down-staging protocols and careful patient selection prior to transplantation [29,30].

7.1.5 Living vs. Deceased Liver Donor

Although liver transplantation is a viable therapeutic option for patients with HCC, there is a shortage of deceased donor livers, and thus, many patients with HCC, die each year waiting for transplantation. Therefore, living donor liver transplantation (LDLT) which does not require a waiting period has emerged as a potential alternative to deceased donor liver transplantation (DDLT). Initial results from a large ongoing multi-center study of LDLT show promising results, especially at high volume centers, with 1-year survival rate of >80% [31]. LDLT has been compared to DDLT in patients with HCC, and although post-transplantation mortality up to 3 years was equal among these groups, patients who underwent LDLT had higher rates of HCC recurrence [32].

There are several explanations for the higher recurrence rates of HCC in patients who undergo LDLT. One possible explanation is that LDLT patients have more advanced disease and which is why they were not eligible for DDLT [32]. Another explanation is that since LDLT patients have very short waiting times to transplant, the biology of the tumor is less known and patients with more aggressive tumors may have been unknowingly selected [32]. Finally, it has been hypothesized that the LDLT surgery itself differs from the DDLT surgery in that it may lead to more tumor manipulation causing tumor embolization [32].

Donor risk is also a concern when considering LDLT. A survey describing 449 living donor transplantations performed in United States reported complications in approximately 14% of donors with one donor death [33]. Complications included bile duct stricture and leak, requirement of blood transfusion, infection, need for rehospitalization, portal vein thrombosis, and pulmonary embolism [32,34]. Worldwide, there have been 9 reported donor deaths and 3 donors have required liver transplantation [34]. The estimated donor mortality risk is 0.2–0.5% [34].

Ethical considerations, donor risk, and recipient outcomes are not yet fully understood in LDLT and should be considered carefully prior to undergoing this modality of therapy for HCC. A recent study analyzed UNOS data regarding outcomes of patients transplanted with HCC. Overall, HCC patients with MELD exceptions had similar survival rates as those who did not have HCC; however, in a subgroup analysis, patients with tumors 3–5 cm had worse survival [25]. This analysis also showed that when adjusting for MELD scores, patients with HCC MELD exceptions had worse post-transplant survival than those with similar MELD scores who did not have HCC [25]. This study has important implications as the transplant community continues to refine the allocation system to create an equitable environment for patients with HCC to compete for transplantable livers.

Conclusion

As described in Chap. 2, in the development of an Information Technology System for Predictive, Preventive and Personalized Medicine (ITS-PM), a wide variety of clinical parameters will be identified and categorized in a Multi-Entity Bayesian Network (MEBN). The MEBN will be used to generate patient-specific Digital Patient Models (DPMs) to facilitate diagnosis, prognosis, and treatment selection, i.e. Model Guided Therapy (MGT). The following have been identified as key issues relating to PPPM and surgical treatment for HCC:

1. Tumor characterization, such as size, number, and vascular invasion;
2. The patient's clinical status, particularly the presence of cirrhosis, the degree of portal hypertension, and liver functional reserve;
3. Pre-operative management, such as patient selection for resection or transplantation, choice of donor, and down-staging and bridging therapies;
4. Surgical techniques, including techniques to minimize blood loss during surgery and to ensure an adequate liver remnant.

References

1. Bruix J, Sherman M (2011) AASLD practice guideline. Management of hepatocellular carcinoma: an update. Hepatology 53:1020–1022
2. Bruix J, Sherman M (2010) AASLD Practice Guideline. Management of hepatocellular carcinoma. Hepatology Supplement:1–32. http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCCUpdate2010.pdf. Accessed 20 Nov 2011
3. European Association for the Study of the Liver. European Organisation for Research and Treatment of Cancer (2012) EASL–EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 56: 908–943
4. Aronsohn A, Mohanty SR (2010) Current treatment strategies for hepatocellular carcinoma. Curr Cancer Ther Rev 6:199–206
5. Bruix J, Sherman M (2005) Management of hepatocellular carcinoma. Hepatology 42:1208–1236
6. El-Serag HB, Marrero JA, Rudolph L et al (2008) Diagnosis and treatment of hepatocellular carcinoma. Gastroenterology 134:1752–1763
7. Llovet JM, Fuster J, Bruix J (1999) Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 30:1434–1440
8. Bruix J, Castells A, Bosch J et al (1996) Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology 111:1018–1022
9. Vauthey JN, Ribero D, Abdalla EK et al (2007) Outcomes of liver transplantation in 490 patients with hepatocellular carcinoma: validation of a uniform staging after surgical treatment. J Am Coll Surg 204:1016–1028
10. Okada S, Shimada K, Yamamoto J et al (1994) Predictive factors for postoperative recurrence of hepatocellular carcinoma. Gastroenterology 106:1618–1624
11. Ikai I, Arii S, Kojiro M et al (2004) Reevaluation of prognostic factors for survival after liver resection in patients with hepatocellular carcinoma in a Japanese nationwide survey. Cancer 101:796–802

12. Earl TM, Chapman WC (2011) Conventional surgical treatment of Hepatocellular Carcinoma. Clin Liver Dis 15:353–370
13. Chen YJ, Yeh SH, Chen JT et al (2000) Chromosomal changes and clonality relationship between primary and recurrent hepatocellular carcinoma. Gastroenterology 119:431–440
14. Roayaie S, Blume IN, Thung SN et al (2009) A system of classifying microvascular invasion to predict outcome after resection in patients with hepatocellular carcinoma. Gastroenterology 137:850–855
15. Shi M, Guo RP, Lin XJ et al (2007) Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. Ann Surg 245:36–43
16. Yamasaki S, Hasegawa H, Kinoshita H et al (1996) A prospective randomized trial of the preventive effect of pre-operative transcatheter arterial embolization against recurrence of hepatocellular carcinoma. Jpn J Cancer Res 87:206–211
17. Farges O, Belghiti J, Kianmanesh R et al (2003) Portal vein embolization before right hepatectomy: prospective clinical trial. Ann Surg 237:208–217
18. Abulkhir A, Limongelli P, Healey AJ et al (2008) Preoperative portal vein embolization for major liver resection: a metaanalysis. Ann Surg 247:49–57
19. Makuuchi M, Sano K (2004) The surgical approach to HCC: our progress and results in Japan. Liver Transpl 10:S46–S52
20. Mazzaferro V, Regalia E, Doci R et al (1996) Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 334:693–699
21. Shetty K, Timmins K, Brensinger C et al (2004) Liver transplantation for hepatocellular carcinoma validation of present selection criteria in predicting outcome. Liver Transpl 10:911–918
22. Yao FY, Ferrell L, Bass NM et al (2001) Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 33:1394–1403
23. Freeman RB Jr, Wiesner RH, Harper A et al (2002) The new liver allocation system: moving toward evidence-based transplantation policy. Liver Transpl 8:851–858
24. Liver transplant candidates with hepatocellular carcinoma. (2008) http://unos.org/PoliciesandBylaws2/policies/pdfs/policy_8.pdf
25. Ioannou GN, Perkins JD, Carithers RL Jr (2008) Liver transplantation for hepatocellular carcinoma: impact of the MELD allocation system and predictors of survival. Gastroenterology 134:1342–1351
26. Yao FY, Hirose R, LaBerge JM et al (2005) A prospective study on downstaging of hepatocellular carcinoma prior to liver transplantation. Liver Transpl 11:1505–1514
27. Freeman RB Jr, Steffick DE, Guidinger MK et al (2008) Liver and intestine transplantation in the United States, 1997–2006. Am J Transplant 8:958–976
28. Masuoka HC, Rosen CB (2011) Liver transplantation for hepatocellular carcinoma: expanding frontiers and building bridges. Clin Liver Dis 15:385–393
29. Schwartz M, Konstadoulakis M, Roayaie S (2005) Recurrence of hepatocellular carcinoma after liver transplantation: is immunosuppression a factor? Liver Transpl 11:494–496
30. Schwartz ME, Sung M, Mor E et al (1995) A multidisciplinary approach to hepatocellular carcinoma in patients with cirrhosis. J Am Coll Surg 180:596–603
31. Olthoff KM, Merion RM, Ghobrial RM et al (2005) Outcomes of 385 adult-to-adult living donor liver transplant recipients: a report from the A2ALL Consortium. Ann Surg 242:314–325
32. Fisher RA, Kulik LM, Freise CE et al (2007) Hepatocellular carcinoma recurrence and death following living and deceased donor liver transplantation. Am J Transplant 7:1601–1608
33. Brown RS, Jr Russo MW, Lai M et al (2003) A survey of liver transplantation from living adult donors in the United States. N Engl J Med 348:818–825
34. Kulkarni S, Malago M, Cronin DC 2nd. (2006) Living donor liver transplantation for pediatric and adult recipients. Nat Clin Pract Gastroenterol Hepatol 3:149–157

Chapter 8
Minimally Invasive Therapies for Hepatocellular Cancer: Ablation Technologies

Paul Morrison and Eric vanSonnenberg

Abstract A wide variety of minimally invasive, or locoregional, therapies are now available for the treatment of hepatocellular carcinoma (HCC) along with surgery, systemic chemotherapy, and, occasionally, radiation therapy. These therapies are highly dependent on the strengths and limitations of the supporting technologies. This Chapter will review thermal ablation techniques including: radiofrequency ablation (RFA), interstitial laser thermotherapy (ILT), microwave ablation (MWA), high intensity focused ultrasound (HIFU), and cryotherapy (CRYO), and non-thermal ablations including: alcohol injection (ETOH), irreversible electroporation (IRE), and photodynamic therapy (PDT). Tumor ablation involves a focal destruction of tissue to achieve a therapeutic effect that may be an attempt at local cure of a tumor, or may be for debulking a tumor for symptomatic (i.e. pain) reasons. At this time, RFA has the largest clinical experience and will serve as the prototype for understanding the principles, mechanisms, and methods that have been developed for the treatment of HCC. Ablation is performed with a minimally invasive approach—the effect is delivered interstitially and intratumorally via a device placed percutaneously. Imaging plays a critical role in the targeting of the lesion, the protection of the surrounding anatomy, and, if possible, in the monitoring and control of the ablation process. The parameters used in the selection of thermal ablation device and the outcomes of their usage will eventually be a factored in generating Digital Patient Models (DPMs) to facilitate diagnosis, prognosis, and treatment selection, i.e. Model Guided Therapy (MGT) and Predictive, Preventive and Personalized Medicine (PPPM).

Paul Morrison is deceased.

E. vanSonnenberg (✉)
Kern/UCLA Medical Center, Bakersfield, CA, USA
e-mail: ericvansonnenberg@yahoo.com

University of Arizona College of Medicine, Phoenix, USA

P. Morrison
Brigham and Women's Hospital, Boston, MA, USA

L. Berliner, H. U. Lemke (eds.), *An Information Technology Framework for Predictive, Preventive and Personalised Medicine,* Advances in Predictive, Preventive and Personalised Medicine 8, DOI 10.1007/978-3-319-12166-6_8

Keywords Personalized medicine · Hepatocellular carcinoma · Locoregional therapy · Treatment · Technology · Radiofrequency ablation (RFA) · Microwave ablation (MWA) · Cryotherapy (CRYO) · Interstitial laser therapy (ILT) · Irreversible electroporation (IRE)

8.1 Introduction

A wide variety of minimally invasive, or locoregional, therapies are now available for the treatment of hepatocellular carcinoma (HCC) along with surgery, systemic chemotherapy, and, occasionally, radiation therapy. These therapies are highly dependent on the strengths and limitations of the supporting technologies. This Chapter will begin with a review of thermal ablation techniques including: radiofrequency ablation (RFA), interstitial laser thermotherapy (ILT), microwave ablation (MWA), high intensity focused ultrasound (HIFU), and cryotherapy (CRYO), and non-thermal ablations including: alcohol injection (ETOH), irreversible electroporation (IRE), and photodynamic therapy (PDT).

The clinical applications that have arisen from these technologies will be reviewed in Chap. 9. At this time, RFA has the largest clinical experience and will serve as the prototype for understanding the principles, mechanisms, and methods that have been developed for the treatment of HCC. The effectiveness of RFA, and of more recent forms of ablation therapy, will be reviewed.

Percutaneous, catheter-directed therapy, or Transarterial Chemoembolization (TACE), will be reviewed in Chap. 10. (Catheter-directed radiation therapy with Yttrium-90 will be discussed in the Chapter on Radiation Therapy, Chap. 11).

8.1.1 Introduction to Tumor Ablation

Tumor ablation involves a focal destruction of tissue to achieve a therapeutic effect. The targeted tissue is focal as well, demonstrable under direct visualization, palpation or via radiologic imaging; multiple foci are individually targeted. The therapeutic effect may be an attempt at local cure of a tumor, or may be for debulking a tumor for symptomatic (i.e. pain) reasons. The term ablation suggests immediacy to the effect, while the results of a tumor ablation may ‘mature’ post-procedurally; the primary direct effects are usually most notable.

Ablation can be practiced in various venues: by a surgeon in the operating room, in an open procedure or under laparoscopy, by an interventional radiologist in a modern hybrid suite or in a simple procedure room. For our purposes here, we discuss image-guided thermal ablation. This suggests an interventional setting in which sonography, computed tomography, fluoroscopy, magnetic resonance imaging, or positron emission tomography could be the imaging modality of choice. In such a setting, the ablation is performed with a minimally invasive approach—the

effect is delivered interstitially and intratumorally via a device placed percutaneously. In a percutaneous procedure, imaging plays a critical role in the targeting of the lesion, the protection of the surrounding anatomy and, if possible, in the monitoring and control of the ablation process.

8.1.2 Forms of Ablation

To provide context for ablation one should note that ablation can be divided into thermal and non-thermal ablations. Thermal ablations are those that involve an energy exchange within tissue. This energy exchange can be one in which energy is added to tissue, or one in which energy is removed from tissue; an exchange in which one cooks or freezes tissue, respectively. Types of thermal ablation include: radiofrequency ablation (RFA), interstitial laser thermotherapy (ILT), microwave ablation (MWA), high intensity focused ultrasound (HIFU), and cryotherapy (CRYO). Examples of non-thermal ablations include: alcohol injection (ETOH), irreversible electroporation (IRE), and photodynamic therapy (PDT).

Thermal ablations take advantage of a number of energy sources including electric current (RFA), electromagnetic radiation (MWA, LASER), and mechanical waves (HIFU). Contemporary cryotherapy uses a closed circuit of high pressure gas to draw heat from tissue. These various thermal agents have each been engineered into various delivery devices. Clinical systems to treat tumors in all parts of the body include the liver, kidney, lung, adrenal, bone, soft tissue, and more.

8.1.3 Radiofrequency Ablation

RFA has long been present in the field of tumor ablation. A RF system is typically comprised of a charged monopolar needle-like electrode. The electrode is electrically insulated along its shaft up to the final distal centimeters from which electrical current flows. A high current density is established immediately adjacent to the electrode and the alternating current oscillates at radio frequencies. This agitates the ions in the tissue and induces frictional heating. Heat then conducts out to establish a volume of tissue coagulation. The flow of current requires a closed circuit; this is established by connecting dispersive electrodes to the patient. Notably, the need for these "grounding pads" is obviated in the Celon RF Ablation System (Olympus Medical Systems) as Celon has engineered both the positive and negative elements of the circuit on the electrode itself. Thus, current flowing between these elements are confined to the tumor region.

The "active" electrodes that are placed in the tumor are either needle-like or array-style. A needle electrode driven at 100–200 W for ablation requires cooling of its tip to prevent tissue char from forming that would impede energy deposition and limit the volume of the ablation. The Covidien Cool-Tip ablation system (Covidien AG) uses a peristaltic pump for cooling its needle electrodes. The array-style

electrodes do not utilize cooling, but still operates in a high power range. These umbrella-like devices are introduced into tissue in a needle-like configuration, and the individual tines of the array are deployed and extend into tissue. This brings the active electrode elements out into the tissue, creating an 'extended source' of energy. Charring is avoided by controlling the power to the array, ramping up gradually for a slow coagulation of the volume subtended by the array. This ramping of the power is typical of the RF 3000 system (Boston Scientific Corporation) and Starburst RF systems (AngioDynamics Corporation).

There are many different device features to these various RF ablation systems. Overall, these features are intended to address the need for greater volumes of ablation to treat larger tumors, and to provide more feedback to the user to assist in efficacy or dosimetry (in a broad sense). A direct way to achieve larger ablation volumes is to make a bigger electrode. All the manufacturers of the various RF systems produce a range of active lengths and/or array diameters. The range can be viewed as extending from the 7 mm active length of the Covidien Cool-Tip needle to the 7 cm diameter array from AngioDynamics. Another direct way to make bigger ablation volumes is to use more electrodes. Celon and Covidien offer systems that can drive up to three active electrodes and is intended for ablations at or above 6 cm in diameter.

Other system features are designed to make a more complete ablation or to provide more feedback to the user to serve as a clinical endpoint for the treatment. The Boston Scientific system is designed to give a slow and thorough cook of the tissue. The system provides added feedback to the user in the form of a display of the impedance (i.e. electrical resistance) in the tissue; when the impedance rises, the tissue has been coagulated. This is intended to provide a more thorough burn, and one with a physical metric associated with the result of the treatment. The AngioDynamics array offers temperature readings to assist in assessing the treatment. Thermal sensors (thermocouples) have been incorporated into every other tine of the array. This provides several discrete readings at the perimeter of the intended ablation volume. These values can be monitored in real-time by the physician, or the device can be set in an automatic mode to target a given ablation temperature as measured by the sensors. The Covidien E-Series generator that can drive from one to three needle-like electrodes, allows for an added needle-like thermocouple to use to monitor tissues adjacent to an ablation site. This can be used to ensure that temperatures reach some minimum planned temperature for coagulation, or used to control a critical region from reaching maximum, so as not to involve the structure in the treated volume.

Additional volumetric thermal feedback can be achieved during ablation by utilizing MR imaging's excellent soft-tissue contrast and its thermal sensitivity. Celon's bipolar electrode and the AngioDynamics array are available in MRI safe versions. The RF generators, however, are not compatible with the MRI environment. Therefore, RFA procedures in the MRI environment require special considerations for integrating the RF system with the MRI environment.

8.1.4 Electromagnetic Radiation

An alternative source of energy for heating tissues is electromagnetic (EM) radiation. For the purpose of tumor ablation, two types of EM radiation have come into practice, laser light and microwaves.

8.1.4.1 Laser Therapy

LASER is an acronym for *light amplification by the stimulated emission of radiation*. Key to the light provided by a laser is that the wavelength of the light, the "color", can be precisely defined. Coupled with the fact that laser light can generally be guided through thin optical fibers allows for useful techniques to deliver light in a medical setting. Laser ablation is often referred to as interstitial laser therapy (ILT) or laser-induced interstitial thermo-therapy (LITT). The wavelength of choice is typically a near infra-red wavelength, invisible to the eye. The near infra-red is chosen because it has generally "deep" penetration into tissue (penetration depth of about 1 cm).

Historically, the Nd:YAG laser at a wavelength of 1064 nm has been the laser of choice for this work. In recent years, smaller but powerful solid state diode lasers at 980 nm (similar penetration depth) have advanced into the field. A characteristic device for this work is the Visualase diode laser at 980 nm (Visualase, Inc.). Light is carried from the laser unit through a thin fiber optic (0.6 mm diameter) to the patient. The light exits the fiber from a diffusing tip fiber from which the light emanates radially over 1–2 cm. The light is absorbed in the tissue and heated. Interestingly, as with RFA, there is concern over forming char within the tissue adjacent to the tip. In this case, black char acts as a ready absorber preventing the light from full penetration and a maximum ablation volume. Contemporary systems cool the tissue at the diffusing tip (to prevent char) by placing the fiber within a water-cooled catheter. Laser ablation has found application primarily in the interventional MRI setting. The fiberoptic is readily compatible with imaging and is MRI safe. MRI can be used to review the soft tissue changes in the coagulated tissues after ILT, or, thermally-sensitive MR imaging can be used to monitor the temperature for on-line control of the heating.

8.1.4.2 Microwave Ablation

Microwave ablation (MWA) is not new in the field of ablation, but it is engaged in fresh growth as both investigators and new manufacturers probe its usefulness. MWA is touted to deliver faster larger ablation volumes than RFA and with less influence of heat sink by blood flow in adjacent vessels, all characteristics of interest to the hepatic ablationist. Indeed, the radiative field of the MW antennae does penetrate centimeters into tissue whereas the high RF current density is limited (i.e.

on the order millimeters). Thus MWA does have a deeper penetration and can overcome a heat sink, whereas RFA might not.

The frequencies currently available and implemented for ablation are 915 MHz and 2450 MHz (aka 2.45 GHz) found in the microwave region of the EM spectrum. Other frequencies are reserved for various industrial, communications, and governmental purposes. As noted, there has been increased interest in MWA as an ablation modality. There are noteworthy features in the various MW systems aside from their operating frequency. Several systems are single-antennae systems; should the user require multiple antennae, multiple generators would be needed. This is in comparison to those that provide power and connections for up to 3 antennae. Overall, the antenna of any microwave system provides radiating waves into tissue. It is possible to get a backward reflection of the forward power from the antenna which can lead to heating of the probe shaft. This generally requires cooling of the shaft in some fashion, typically with cooled water. Thus, while the MW antenna is cooled in a similar fashion to an RF electrode, the cooling here is not to prevent char, but rather to keep the shaft cool for safety of the patient and physician.

The Evident MWA system (Covidien AG) is built around a 60 W single antenna 915 MHz generator. Its relatively thin 18G antenna is water-cooled. A multi-probe treatment requires multiple stacked generators. The AveCure system (MedWaves, Inc.) is centered on 915 MHz as well. Notably, the antenna is not cooled as discussed above; the system is reported to monitor the probe temperature and reflected power and to adjust the microwave power output and frequency in real-time so as to obviate the need for cooling. The system also features a self-regulating mode in which the user can pre-set a target antenna temperature or output power level for the ablation. A third generator operating at 915 MHz is the MicroThermX system (BSD Medical Corporation). It provides an output of up to 180 W total that can be shared by up to three antennae (typically ~ 50 W per probe). Powering three antennae from the one generator allows for the manufacturer to offer a "synchronous mode"' for the device. In this mode, the microwaves from the 3 probes are intended to superimpose so as to eliminate cool spots due to destructive wave interference which this system is said to avoid. The system also provides a thin 18 G external thermocouple that can be used to monitor adjacent structures.

The AMICA system (HS Medical, Inc.) is a 2450 MHz system. It offers up to 140 W to a single water-cooled antenna (with various gauges, 11, 14, 16 g). The system monitors probe temperature and reflected power for safety. It also provides an external thermal sensor for spot monitoring of adjacent tissues. The Acculis system (Microsulis Medical Ltd) is a 180 W 2450 MHz system equipped for a single water-cooled antenna, with typical settings of 120 W for 6 min. It also has an external thermal sensor for added feedback during ablation. A third 2450 MHz MWA ablation system is the Certus (NeuWave Medical Corporation). The current system offers 140 W for a single antenna ablation. The NeuWave antennae are cooled by CO2 gas instead of flowing water. Also, the generator can drive up to 3 antennae simultaneously, each at a maximum of 65 W. Separately, NeuWave also markets an antenna that is "tuned" for specific tissues: liver and lung.

8.1.5 Cryoablation

A thermal alternative to the therapeutic heating of tumors is freezing, cryotherapy instead for pyrotherapy. Contemporary systems are gas-based and utilize the Joule-Thomson effect to generate the low cryoprobe temperatures. This effect can be evoked when certain gases are "throttled", i.e. forced at high pressure through a thin tube and released into a low pressure environment. Argon is most commonly used for current cryoablation systems. It has a positive "J-T coefficient", and when the gas pressure drops on exiting the tube, the temperature of the argon drops as well. Theoretically, it can dip down to approximately −180°C. In a clinical system, this release of gas actually is confined within the cryoprobe. The expansion happens within the tip of the probe which gets cold, and the exhaust gas is directed back out into the room. Argon is non-toxic.

Generally, cryoprobes form an iceball of a diameter of approximately 2.5 cm. Importantly, not all of the iceball is lethal. The lethal isotherm (~− 40°C) is 3–5 mm in from the iceball edge. It is common for cryotherapy procedures to involve 4–8 cryoprobes and for systems to offer multi-probe capability. The Galil cryotherapy system (Galil Medical Corporation) and the Endocare cryotherapy (HealthTronics Corporation) have connections for multiple probes to allow overlapping iceballs that provide adequate coverage of the tumor. Important is that not only are multiple probes available, but that they can be controlled independently. This can help to control the spatial development of the ice to protect adjacent critical structures. Control of iceball growth (and/or at least the monitoring of its system growth) can be achieved with the use of external thermocouples. As noted above for the RF and MW systems, such thin extra thermal sensors can be placed in the ablation field to monitor temperatures. In the Galil system, the value of the temperature reading of any one of up to five thermocouples can actually control the flow of gas to selected probes.

The thermal monitoring of cryoablation can be achieved with virtually any radiologic imaging technique. That said, MRI compatible cryoprobes are available to allow for MRI-guided cryoablation procedures. Notably, cryoablation procedures are relatively long. Current paradigms require a cycle of freezing, thawing, and repeat freezing, the intent of which is to execute a thorough ablation. Thus, after probe placement, the ablation therapy itself can be 25–40 min long. This is often compared to the faster heating of RFA or MWA. The counter to the matter of time, is the visualization of the ice under any imaging modality that can be advantageous in certain critical areas.

8.1.6 Irreversible Electroporation

A relatively new form of ablation technology (NanoKnife; AngioDynamics) is based on the principle of irreversible electroporation (IRE). This technology is not based on the use of thermal energy, but rather subjects the target tissue to a powerful

electrical field using high-voltage direct current (up to 3 kV). This process results in the irreversible creation of holes in the cell membranes inducing cell death. IRE, which is approved for "soft tissue" applications by the FDA, is currently under investigation for the treatment of primary and metastatic tumors of the liver, as well as tumors of the pancreas, kidney, lung, and other organs.

Conclusion

Thermal ablation provides several options for the physician. RFA has its own solid history in the field and offers an approach that has the benefit of documented experience. ILT has its followers, but has yet to receive widespread acceptance, a situation that may be revisited in the years ahead with more MRI interventions. MWA has much to offer and yet users are looking for the proof of time, use, and publication to see that its promise holds. CRYO in recent years has gained its own strong foothold. The parameters used in the selection of thermal ablation device and the outcomes of their usage will eventually be factored in generating Digital Patient Models (DPMs) to facilitate diagnosis, prognosis, and treatment selection, i.e. Model Guided Therapy (MGT) and PPPM.

Chapter 9
Minimally Invasive Therapies for Hepatocellular Cancer: Ablation Therapies

Eric vanSonnenberg and Leonard Berliner

Abstract Ablation therapy is proving to be a major tool in the anti-cancer armamentarium. The superb diagnostic capabilities of CT, US, and MRI, along with IR techniques, have combined to allow percutaneous tumor ablation to become fairly widespread in availability at major centers. The fundamental concept of ablation is that the extremes of temperature kill cancer. Thus both heating and freezing methods are effectively tumoricidal. Heating options are via radiofrequency, laser, and microwave. The former is utilized most frequently, laser least, and microwave is in its early clinical experience. Other primary methods of percutaneous tumor ablation include cryotherapy (CRYO) and direct chemical injection. While various agents have been injected for direct percutaneous injection into tumors, alcohol ablation is most effective, and has been utilized most frequently. The efficacy of radiofrequency ablation (RFA) is related to the size of the liver tumor. It is accepted that the lesion should not exceed 2.5–3.0 cm to obtain complete necrosis. It has been reported that certain microwave ablation (MWA) devices may allow successful treatment of lesions as large as 5 cm with an acceptable margin of safety. Notwithstanding, RFA commonly is utilized for lesions greater than 3 cm in diameter, occasionally for palliative debulking rather than cure. Guidelines may assist in the selection and use of the more widely used thermal technologies to provide optimal Predictive, Preventive and Personalized Medicine (PPPM). To achieve maximal effectiveness for cure, basic treatment precepts must be understood and adhered to, including: (1) proper patient selection; (2) treatment of the entire lesion; (3) providing adequate tumor margins.

E. vanSonnenberg (✉)
Kern/UCLA Medical Center, Bakersfield, CA, USA
e-mail: ericvansonnenberg@yahoo.com

University of Arizona College of Medicine, Phoenix, USA

L. Berliner
New York Methodist Hospital, Brooklyn, NY, USA
e-mail: LeonardB23@AOL.com

Weill Medical College of Cornell University, New York, USA

L. Berliner, H. U. Lemke (eds.), *An Information Technology Framework for Predictive, Preventive and Personalised Medicine,* Advances in Predictive, Preventive and Personalised Medicine 8, DOI 10.1007/978-3-319-12166-6_9

Keywords Personalized medicine · Hepatocellular carcinoma · Locoregional therapy · Treatment · Radiofrequency ablation (RFA) · Microwave ablation (MWA) · Cryotherapy (CRYO) · Alcohol ablation

9.1 Introduction

Ablation therapy is proving to be a major tool in the anti-cancer armamentarium. The superb diagnostic capabilities of CT, US, and MRI, along with IR techniques, have combined to allow percutaneous tumor ablation to become fairly widespread in availability. Ablation also may be performed at open surgery or laparoscopically.

The fundamental concept of ablation is that the extremes of temperature kill cancer [1]. Thus both heating and freezing methods are effectively tumoricidal. Heating options are via radiofrequency, laser, and microwave. The former is utilized most frequently, laser least, and microwave is in its early clinical experience.

Other primary methods of percutaneous tumor ablation include cryotherapy (CRYO) and direct chemical injection. The former currently uses argon as the freezing agent and helium for warm-up. While various agents have been injected for direct percutaneous injection into tumors, alcohol ablation, first described by Livraghi [2], is most effective, and has been utilized most frequently.

9.1.1 Mechanisms and Instrumentation for RFA

The mechanisms of tissue destruction differ with the various heating modalities. For radiofrequency ablation (RFA), the mechanism is ionic agitation that causes frictional heating. Tissue death occurs at 60 °C, but in clinical use, the probes generate over 90 °C temperatures. Care must be taken not to overheat, as this can cause charring which is counterproductive to heat therapy, and actually impedes heat propagation and eventual tumor killing. Probes are connected into a generator to disperse the heat effect.

Several type probes and systems exist. Each has features that attempt more complete killing for larger tumors. Thus systems have umbrella type tines, cooling mechanisms to decrease charring, multiple probes (similar to CRYO), different shapes, and variable flexibility to help tailor ablations. Various feedback systems from the different vendors are incorporated into the generators and monitors to guide the operator during the procedures.

9.1.2 Pre-Procedure Requirements

The procedure itself may be performed under US, CT, or MRI guidance. In the United States, CT is utilized most frequently. Contrast enhancement helps depict

active tumor, areas of necrosis, and adjacent structures to be avoided. A pre-procedure biopsy is performed at the same setting (with quick stain pathology analysis) if not obtained previously. Coagulation parameters must be normalized prior to RFA. We use general anesthesia and antibiotics, although both are controversial; some operators prefer conscious sedation, and not all interventionalists prescribe prophylactic antibiotics.

9.1.3 The Procedure

Patients are positioned appropriately with access to the tumor entry site, without arms and metal or other artifacts to compromise the imaging appearances of the tumors. Probes must be placed such that, for cure, the entire tumor and a 1 cm circumferential safety margin of kill in normal liver tissue are obtained. Multiple tumors can be ablated in one or more sessions. Results are best with masses 3 cm or less in diameter, and with 3 tumors or fewer in number. Nonetheless, palliative killing of larger or multiple tumors can be an option as well. In the latter case, combination therapy may include ablation along with chemotherapy, radiation therapy, and/or surgery.

Alcohol may be infused by a percutaneous 22 g needle prior to RFA. A synergistic effect of the two ablation mechanisms has been documented [3]. In addition, alcohol may be used to "clean up" small areas of persistent or recurrent tumor [4]. The RFA is continued until the desired effective coagulation necrosis is achieved. Impedance and temperature are end points, depending on the various vendor algorithms. Typically on removal of the probes, cauterization of the tract is performed. This may diminish the likelihood of bleeding post-ablation.

Once the ablation is complete, general anesthesia is reversed, and the patient is observed in the recovery room. Patients are hospitalized overnight routinely, and discharged the following day if no major complications ensue and once they have recovered well; the vast majority of patients do go home the day after RFA.

9.1.4 Applicability

RFA knows virtually no limits in tumor killing. Thus, the spectrum of tumor cell types is nearly universal to the tumoricidal effects of RFA. Similarly, all varieties of carcinoma, sarcoma, and benign tumors may be treated with RFA. (RFA is not utilized for lymphoma typically, because of the diffuse multisystemic nature of the tumor, and the superiority of other treatment methods.) RFA is applicable in a wide spectrum of organs, as well. Very few sites in the body have not had RFA applied for tumor killing. (Cardiac ablation techniques are anti-arrhythmic, not anti-oncologic.)

A wide variety of liver lesions, histopathologically, has been successfully treated by RFA in our experience, and includes primary and metastatic tumors, vascular and sarcomatous cancers, as well as benign tumors. The latter typically are not treated unless symptoms (such as pain) prompt the need for therapy [5].

RFA can be effective treatment for pain related to tumor masses. Studies have documented the efficacy of RFA to treat pain in bones, soft tissues, and even internal viscera [6].

9.1.5 Complications

In most respects, the complications of RFA are those of biopsy or needle/catheter insertion in general. Thus, bleeding, infection, perforation of the gastrointestinal tract, pneumothorax, and death are potential generic complications that might occur with almost any interventional radiology (IR) procedure.

Several specific complications may result from RFA. An annoying, but non-life threatening complication from RFA is termed, "the Post Ablation Syndrome". Presumably the Syndrome results from ablated necrotic tumors with resultant circulating toxins that cause a flu-like syndrome that may affect muscles, joints, and the overall wellness of the patient. The Syndrome likely correlates with the volume of killed tumor. While treatment is supportive, as with the "flu", prevention may be achieved by performing ablation on large tumors in more than one session so as not to overload the tumoricidal effects on the body. The Syndrome can be more noxious in elderly patients, another caveat for prevention.

A second specific issue with RFA that is preventable is the unwanted effects of heat (similar for cryotherapy) on structures that need to be preserved; most importantly is the gastrointestinal (GI) tract that can be perforated or fistulized by the undesirable properties of the intense heat. Similarly the kidney, gallbladder, and diaphragm may be injured by the heat of RFA. Preventively, the technique of hydrodissection has been developed [7,8]. The goal of hydrodissection is to infuse sterile water or dextrose to displace structures protectively from the tumor being targeted by RFA. Most commonly, various GI structures (e.g. colon, duodenum, stomach) are protected by displacement from the masses. Buffer areas of 1 cm or greater by sterile water or dextrose may be created similarly to protect the gallbladder, pancreas, kidney, and diaphragm. Saline is not used, as it actually further conducts heat.

9.1.6 Follow-Up

Clinical follow-up is of course essential for ablation. How the patient responds, whether or not significant complications occur, overall morbidity and mortality from the procedure, underlying diagnoses, symptom control, recurrent disease, and eventual lifespan all are metrics to assess effectiveness of RFA. In addition, imaging follow-up offers important insights into many factors: prognosis, need for further therapy, complications, recurrent and/or persistent disease.

CT predominantly, along with PET/CT and MRI, provides the bulwark of imaging follow-up information. The hallmark of effective ablation is lack of contrast

enhancement within the tumor, as well as a 1 cm circumferential safety margin around the entire mass. Nodular enhancement, irregular inhomogeneous enhancement, or vessels seen within the mass, indicate persistent or eventual recurrent disease.

9.1.7 Results of RFA and Other Forms of Ablation Therapy

The role of ablation technologies in the management of hepatocellular carcinoma has been well described in the literature, with numerous review articles available [2, 9–12]. However, to date no large randomized clinical trials have been performed that provide the treating clinician, or the patient, precise information in determining the best form of therapy for any given situation. It has been reported that at this time, percutaneous RFA may offer complete tumor kill in patients with lesions up to 3 cm in diameter, and it has comparable survival rates with partial hepatectomy and with fewer complications [10]. It has to be remembered that, in general, cancer control, but not cancer cure, is offered to cirrhotic patients because they have greater than a 10% chance annually of developing new lesions once one tumor occurs. If tumor control is achieved, the outcome is defined by the progression of the liver disease [10].

The efficacy of RFA is related to the size of the liver tumor. It is accepted that the lesion should not exceed 2.5–3.0 cm to obtain complete necrosis [13]. It has been reported that certain microwave ablation (MWA) devices may allow successful treatment of lesions as large as 5 cm with an acceptable margin of safety [13]. Notwithstanding, RFA commonly is utilized for lesions greater than 3 cm in diameter, occasionally for palliative debulking rather than cure.

As stated above, the fundamental concept of ablation is that the extremes of temperature kill cancer. All of the commercially available devices are capable of achieving the required temperatures. The overall success of an ablation device in the clinical setting depends on how well the device can fulfill all of the treatment requirements in a given patient, as well as in a population of patients, with all of their similarities and unique features.

Guidelines may assist in the selection and use of the more widely used thermal technologies: RFA, MWA, and CRYO. To achieve maximal effectiveness for cure, basic treatment precepts analogous to those in surgery, must be understood and adhered to, including: (1) proper patient selection; (2) treatment of the entire lesion; and, (3) providing adequate tumor margins. For ablation therapies, certain additional considerations include: (1) avoidance of anatomic structures that influence effective deposition of energy, such as blood vessels that divert energy from the tumor (“heat sink” or “cold sink”); (2) avoiding tissue alterations that could influence energy deposition, such as too rapid increase in tissue impedance, tissue charring, and creation of microscopic gas bubbles; (3) ensuring complete coverage when overlapping zones of treatment are required so that no gaps of inadequately treated tumor cells remain; and, (4) ensuring an adequate treatment margin when the tumor is in proximity to sensitive or vital structures (e.g. GI tract or myocardium).

It is also important that when we evaluate the results of ablation that we recognize recurrent tumor as treatment failure and distinguish that from the presence of new tumor, especially in patients with hepatitis B and C. It is also important that the efficacy of ablation therapy is best evaluated by the presence or absence of contrast enhancement of viable tumor on contrast-enhanced CT (modified or mRECIST criteria), and that traditional RECIST/WHO criteria rely on decrease in tumor size. It is important to note that post ablation edema, tissue reaction and blood may give the appearance of "enlargement of the tumor" on CT, when it is rather the effect of successful ablation. Methods of combining evaluation techniques are being developed [12].

Conclusion

Ablation therapies are now an integral part of the menu of therapy for HCC. RFA procedures are generally safe and effective, with caveats and guidelines, and are at the time of this writing still considered the gold standard for percutaneous ablation. Alternative technologies, such as MWA, CRYO, interstitial laser thermotherapy (ILT), and percutaneous ethanol ablation are in use, with MWA showing promise for future development.

References

1. Cheung L, vanSonnenberg E, Morrison P et al (2005) Radiofrequency ablation therapy. CDR 28:1–6
2. Livraghi T (2011) Radiofrequency ablation of hepatocellular carcinoma. Surg Oncol Clin N Am 20:281–299
3. Shankar S, vanSonnenberg E, Morrison PR et al (2004) Combined radiofrequency and alcohol injection for percutaneous hepatic tumor ablation. Am J Roentgenol 183:1425–1429
4. Mamlouk MD, vanSonnenberg E, Morrison PR et al (2009, November 29) Indications and uses of alcohol in the RF/Cryo ablation era. Paper presented at RSNA, Chicago
5. Hedayati P, vanSonnenberg E, Shamos R, Gillespie T (2010) Treatment of a symptomatic focal nodular hyperplasia by percutaneous radiofrequency ablation. J Vasc Interv Radiol 21:582–585
6. Nair R, vanSonnenberg E, Shankar S et al (2008) Radiofrequency and alcohol ablation for pain relief in visceral and soft tissue tumors. Radiology 248:1067–1076
7. Goodacre BW, Savage C, Zwischenberger JB et al (2002) Salinoma window technique for mediastinal lymph node biopsy. Ann Thorac Surg 74:276–277
8. Brown S, vanSonnenberg E, Morrison P, Diller L, Shamberger R (2005) CT-guided radiofrequency ablation of pediatric Wilms tumor in a solitary kidney. Pediatr Radiol 35:923–928
9. Abrams P, Marsh JW (2010) Current approach to hepatocellular carcinoma. Surg Clin North Am 90:803–816
10. Guimaraes M, Uflacker R (2011) Locoregional therapy for hepatocellular carcinoma. Clin Liver Dis 15:395–421
11. Aronsohn A, Mohanty SR (2010) Current treatment strategies for hepatocellular carcinoma. Curr Cancer Ther Rev 6:199–206

12. Curley SA, Stuart KE, Schwartz JM, Carithers RL Jr (2012) Up-to-date. http://www.uptodate.com/contents/nonsurgical-therapies-for-localized-hepatocellular-carcinoma-radiofrequency-ablation-percutaneous-ethanol-injection-thermal-ablation-and-cryoablation/. Accessed 10 June 2012
13. Livraghi T, Meloni F, Solbiati L, Zanus G (2012) For the collaborative Italian group using AMICA system complications of microwave ablation for liver tumors: results of a multicenter study. Cardiovasc Intervent Radiol 35:868–874

Chapter 10
Minimally Invasive Therapies for Hepatocellular Cancer: Catheter-Directed Therapies

Leonard Berliner and Smruti Mohanty

Abstract Techniques have been developed for catheter-directed delivery of therapy for hepatocellular carcinoma (HCC) since the 1980s, and are still undergoing evolution. Currently, this involves embolization with particles, as well as delivery of chemotherapeutic agents with a variety of materials, and is referred to as transarterial chemoembolization (TACE). TACE is made both feasible and effective due to the dual blood supply of the liver. Advances in catheter and guide wire technology have been accompanied by the development of techniques for the superselective placement of catheters for the safe and effective delivery of therapeutic agents to hepatic tumors. TACE is recommended for patients with Intermediate Stage, multinodular HCC (Okuda Stage 1–2; Childs-Pugh Stage A-B; Performance Status 0). Combination therapy with RFA and TACE may lead to more extensive tumor necrosis than mono-ablative therapy and may be a more effective treatment for HCC. Further study will be needed to determine the effectiveness of combining RFA and TACE, and in which order. The combination of TACE with antiangiogenic agents, such as sorafenib, is under investigation as well. The use of sorafenib may curtail the post-TACE rise in VEGF-mediated signaling, and simultaneously target tumor foci distant from the site of treatment. Selection parameters and treatment outcomes for locoregional therapies, alone or in combination, such as thermal ablation and TACE, with or without systemic chemotherapy agents will eventually be factored in generating Digital Patient Models (DPMs) to facilitate diagnosis, prognosis, and treatment selection, i.e. Model Guided Therapy (MGT) and Predictive, Preventive and Personalized Medicine (PPPM).

Keywords Personalized medicine · Hepatocellular carcinoma · Locoregional therapy · Treatment · Transarterial chemoembolization (TACE) · Drug-eluting beads · Sorafenib

L. Berliner (✉) · S. Mohanty
New York Methodist Hospital, Brooklyn, NY, USA
e-mail: LeonardB23@AOL.com

Weill Medical College of Cornell University, New York, NY, USA

S. Mohanty
e-mail: srm9006@nyp.org

L. Berliner, H. U. Lemke (eds.), *An Information Technology Framework for Predictive, Preventive and Personalised Medicine,* Advances in Predictive, Preventive and Personalised Medicine 8, DOI 10.1007/978-3-319-12166-6_10

10.1 Introduction

Techniques have been developed for catheter-directed delivery of therapy for hepatocellular carcinoma (HCC) since the 1980s, and are still undergoing evolution [1–4]. This has included bland embolization with particles, as well as delivery of chemotherapeutic agents, with a variety of materials, referred to as transarterial chemoembolization (TACE). (Radioembolization with Yttrium-90 microspheres is discussed in Chap. 11.)

10.1.1 Transarterial Chemoembolization for Hepatocellular Carcinoma

TACE is made both feasible and effective due to the dual blood supply of the liver. HCC derives 95% of its blood supply from the hepatic artery, whereas normal hepatic parenchyma is supplied 75 and 25% by the portal vein and hepatic artery, respectively. (These differences in arterial supply account for the detectability of early HCC on dynamic, contrast-enhanced computed tomography [CT] and magnetic resonance imaging [MRI] as described in Chaps. 3 and 4). Advances in catheter and guide wire technology have been accompanied by the development of techniques for the superselective placement of catheters for the safe and effective delivery of therapeutic agents to hepatic tumors.

As indicated by the Barcelona Clinic Liver Cancer (BCLC) Staging Classification and Treatment Schedule [5, 6] TACE is recommended in patients with Intermediate Stage (Okuda Stage 1–2; Childs-Pugh Stage A–B; Performance Status 0) with multi-nodular HCC. Relative contraindications to TACE, which are evolving as increasing experience is gained, have included: greater than 50% liver involvement (although patients may be consider for staged procedures); LDH > 425; AST > 100; total bilirubin > 2; biliary obstruction; stent; anastomosis; and portal vein invasion or occlusion. Childs-Pugh Class B and C cirrhotic patients, as well as patients with end stage HCC, are at an increased risk of liver failure and death and are not appropriate candidates for TACE [3].

Two different basic methodologies have developed over the years for the transcatheter delivery of chemotherapy to hepatocellular carcinoma.

10.1.1.1 Iodized Poppy Seed Oil

The first method utilizes iodized poppy seed oil, which is injected into the hepatic artery, and remains preferentially localized within the neovascularity of HCC. The oily substance serves as a vehicle for the delivery of cytotoxic agents to tumor sites in the liver. Cytotoxic agents which have been used include doxorubicin (Adriamycin), 5-fluorouracil, cisplatin, and mitomycin. The poppy seed oil, combined with embolic particles, causes ischemia and prolonged contact of the chemotherapeutic

agent with the tumor. The dose of doxorubicin typically ranges from 30 to 75/m^2, to a maximum of 150 mg, which is usually mixed with 5 to 20 mL of lipiodol [7].

10.1.1.2 Drug-Eluting Beads

The second method for transcatheter delivery of chemotherapy to HCC utilizes drug-eluting beads or particles (DEB-TACE) to carry and deliver the chemotherapeutic agent. At the time of this writing, particles in use include 100–300 μm alcohol-sodium acrylate microspheres (QuadraSphere microspheres) and polyvinyl alcohol (PVA) hydrogel that has been modified with sulphonate groups (DC Beads). For patients with single tumor < 5 cm, or multiple tumors (up to three, < 3 cm each), each single treatment should include a planned dose of 50 to 75 mg doxorubicin loaded into one vial containing 2 mL of DC Beads (loading dose, 25 to 37.5 mg doxorubicin/mL of beads). For patients with more advanced disease each single treatment should include a planned dose of up to 150 mg doxorubicin loaded into two vials of DC Beads. In huge or bilobar tumors, treatment typically includes separate sessions approximately 4 weeks apart, in the absence of complications that would require a longer time interval between the two sessions. Obtaining confirmation that the liver enzymes have returned to baseline before performing the second treatment session is recommended [7].

The beads are allowed to remain in a container with the chemotherapeutic agent prior to administration, to allow the agent to be absorbed by the beads. After catheter delivery, the particles remain lodged in the injected hepatic arterial branches, so that the cytotoxic agent is eluted over a prolonged period of time (7–10 days) to tumor sites in the liver. As stated above, at the current time, the cytoxic agent most commonly employed is doxorubicin (Adriamycin). The drug-eluting particles produce tumor ischemia and prolonged contact of the chemotherapeutic agent with the tumor.

Compared with TACE performed with poppy seed oil, TACE performed with drug eluting beads is reported to have a more standardized methodology, to be more reproducible, and to offer improved response and a significantly better safety profile [7, 8]. The improved safety profile is related to the decreased levels of cytotoxic agent found in the system circulation found with drug eluting particles.

10.1.2 Indications for TACE

Current indications for TACE include: (1) primary treatment for those patients with intermediate stage HCC who are not eligible for liver transplantation, patients and cannot receive RFA due to comorbidities or tumor locations; and (2) for downstaging of tumor prior to transplantation [3]. A recent meta-analysis of 7 trials including 545 patients undergoing treatment for unresectable HCC showed a survival benefit at 2 years for those who were treated with TACE compared to controls [9].

In a small trial of 30 patients with tumor burden that exceeded transplantation criteria, 21 (70%) were down-staged to within UCSF transplantation criteria by using TACE [10]. Although data supports TACE as an effective method to down-stage tumors, post-transplant outcomes from patients who have undergone TACE down-staging are largely unknown [3].

TACE is a relatively safe procedure in a carefully selected population. Patients without portal blood flow may be at risk for extensive tumor and nontumor liver necrosis after TACE which can result in liver failure. Therefore, TACE has not been recommended for patients with portal vein invasion by HCC according to the Barcelona Clinic Liver Cancer (BCLC) Staging System [5, 6]. However, more recent studies have shown that TACE is safe and beneficial in patients with both peripheral portal vein invasion, as well as central portal vein invasion, if there is sufficient collateral flow [11].

Adverse events associated with TACE are seen in approximately 10% of patients with a patent portal vein and include hepatic failure, pulmonary embolism, acute renal failure, infection, biliary infarction, and gastrointestinal bleeding [12]. Post-embolization syndrome which consists of fever, abdominal pain, and intestinal obstruction is seen in greater than 50% of patients and usually resolves completely within 48 h.

10.1.3 Combination of RFA and TACE

Combination therapy with RFA and TACE may lead to more extensive tumor necrosis than mono-ablative therapy and may be a more effective treatment for HCC [13]. A randomized controlled trial (RCT) of 291 patients, predominantly with hepatitis B and with >3 cm lesions from a single center in China have shown a mortality benefit from combination therapy with when compared to TACE alone or RFA alone (median survival 37 vs. 24 vs. 22 months respectively) [14]. There was no significant difference in complication rates among the three groups of patients in this study. Further study will be needed to determine the effectiveness of combining RFA and TACE in different patient populations, as well as the order in which these locoregional treatments are to be administered.

10.1.4 Chemoembolization and Portal Vein Embolization Prior to Surgical resection

Portal vein embolization is a catheter-directed technique with an entirely different purpose than TACE. Techniques were developed to embolize the contralateral lobe of the liver, prior to surgical resection of the hepatic lobe harboring the HCC. This was performed to induce compensatory hypertrophy of the embolized, tumor-free lobe, and thereby increase hepatic function, following surgical resection of the diseased lobe.

However, it is currently felt that PVE and pre-operative TACE prior to surgical resection offers no benefit [15–17]. It has also been suggested that malignant hepatocytes may also respond to the proliferative stimulus and this could result in uncontrolled tumor progression. In addition, portal vein obstruction may induce an acute increase in portal pressure and result in variceal bleeding. RCTs are needed to define the benefits and risks of these procedures [18].

10.1.5 Sorafenib and DEB-TACE

A high rate of tumor recurrence has been observed following TACE for HCC. It has been suggested that by interrupting blood flow to the tumor, TACE induces necrosis at the site of disease but may create conditions that permit or even encourage angiogenesis elsewhere in the liver [19]. Surrogate markers of tissue hypoxia have been reported to increase after TACE including hypoxia inducible factor 1α and both plasma and hepatic vascular endothelial growth factor (VEGF). Thus, it has been suggested that the combination of TACE with antiangiogenic agents may curtail the post-TACE rise in VEGF-mediated signaling, and simultaneously target foci distant from the site of treatment [19].

Investigation of this possible synergistic treatment has been studied in a phase 2 randomized double-blind placebo-controlled trial: SPACE study (Sorafenib or Placebo in Combination with DEBTACE for Intermediate-Stage HCC) [20]. The objective of the study was to evaluate the efficacy and safety of sorafenib in combination with DEB-TACE in patients with intermediate stage HCC. The study demonstrated an improved time to progression (TTP) of disease supporting the premise that Sorafenib may reduce the associated angiogenesis, although the results still need to be confirmed with phase 3 trials.

Conclusion

The methods, indications, and results of TACE, alone and in combination with other forms of therapy for HCC, have been reviewed in this Chapter. The selection parameters and treatment outcomes for TACE, as well as other locoregional therapies, alone or in combination, such as thermal ablation, with or without systemic chemotherapy agents will eventually be factored in generating Digital Patient Models (DPMs). It is hoped that diagnosis, prognosis, and treatment selection for patients with HCC will thereby be facilitated by Model Guided Therapy (MGT) and Predictive, Preventive and Personalized Medicine (PPPM).

References

1. Abrams P, Marsh JW (2010) Current approach to hepatocellular carcinoma. Surg Clin North Am 90:803–816
2. Guimaraes M, Uflacker R (2011) Locoregional therapy for hepatocellular carcinoma. Clin Liver Dis 15:395–421
3. Aronsohn A, Mohanty SR (2010) Current treatment strategies for hepatocellular carcinoma. Curr Cancer Ther Rev 6:199–206
4. Curley SA, Stuart KE, Schwartz JM, Carithers RL Jr (2012) Up-To-Date. http://www.uptodate.com/contents/nonsurgical-therapies-for-localized-hepatocellular-carcinoma-radiofrequency-ablation-percutaneous-ethanol-injection-thermal-ablation-and-cryoablation. Accessed 10 June 2012
5. Bruix J, Sherman M (2010) AASLD Practice Guideline. Management of hepatocellular carcinoma. http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCCUpdate2010.pdf. Accessed 20 November 2011
6. Bruix J, Sherman M (2011) AASLD Practice Guideline. Management of hepatocellular carcinoma: an update. Hepatology 53:1020–1022
7. Lencioni R. Petruzzi P. Crocetti L (2013) Chemoembolization of hepatocellular carcinoma. Semin Intervent Radiol 30:3–11
8. Raoul J-L, Sangro B, Forner A et al (2011) Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. Cancer Treat Rev 37:212–220
9. Llovet JM, Bruix J (2003) Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 37:429–442
10. Yao FY, Hirose R, LaBerge JM et al (2005) A prospective study on downstaging of hepatocellular carcinoma prior to liver transplantation. Liver Transpl 11:1505–1514
11. Chung GE, Lee J-H, Kim HY et al (2011) Transarterial chemoembolization can be safely performed in patients with hepatocellular carcinoma invading the main portal vein and may improve the overall survival. Radiology 258:627–634
12. Brown DB, Cardella JF, Sacks D et al (2009) Quality improvement guidelines for transhepatic arterial chemoembolization, embolization, and chemotherapeutic infusion for hepatic malignancy. J Vasc Interv Radiol 20(Suppl 2):S219–S226, S226.e1–S226.e10
13. Bloomston M, Binitie O, Fraiji E et al (2002) Transcatheter arterial chemoembolization with or without radiofrequency ablation in the management of patients with advanced hepatic malignancy. Am Surg 68:827–831
14. Cheng BQ, Jia CQ, Liu CT et al (2008) Chemoembolization combined with radiofrequency ablation for patients with hepatocellular carcinoma larger than 3 cm: a randomized controlled trial. JAMA 299:1669–1677
15. Yamasaki S, Hasegawa H, Kinoshita H et al (1996) A prospective randomized trial of the preventive effect of pre-operative transcatheter arterial embolization against recurrence of hepatocellular carcinoma. Jpn J Cancer Res 87:206–211
16. Farges O, Belghiti J, Kianmanesh R et al (2003) Portal vein embolization before right hepatectomy: prospective clinical trial. Ann Surg 237:208–217
17. Tanaka H, Hirohashi K, Kubo S et al (2000) Preoperative portal vein embolization improves prognosis after right hepatectomy for hepatocellular carcinoma in patients with impaired hepatic function. Br J Surg 87:879–882
18. European Association for the Study of the Liver. European Organisation for Research and Treatment of Cancer (2012) EASL–EORTC Clinical practice guidelines: Management of Hepatocellular Carcinoma. J Hepatol 56:908–943
19. Lencioni R (2012) Management of hepatocellular carcinoma with transarterial chemoembolization in the era of systemic targeted therapy. Crit Rev Oncol Hematol 83(2):216–224
20. Lencioni R, Llovet JM, Han G et al (2012) Sorafenib or placebo in combination with transarterial chemoembolization (TACE) with doxorubicin-eluting beads (DEBDOX) for intermedi-

ate-stage hepatocellular carcinoma (HCC): phase II, randomized, double-blind SPACE trial. [abstract LBA154]. J Clin Oncol 30(Suppl 4):40

Chapter 11
Radiation Oncology in the Treatment of Hepatocellular Carcinoma

Hani Ashamalla and Malcolm D. Mattes

Abstract Optimizing the therapeutic ratio and achieving an adequate safety profile in the treatment of hepatocellular carcinoma (HCC) with radiation therapy (RT) has historically been a challenge. Although HCC is a radiosensitive tumor, it is surrounded by highly radiosensitive organs, including the remainder of the liver and hollow gastrointestinal viscera. As technology has advanced to the point of allowing a highly conformal dose to be delivered to the tumor while sparing the surrounding normal tissues, RT has re-emerged as a viable treatment modality for many patients with HCC, pending randomized controlled trials to confirm its efficacy. Options for RT include stereotactic body radiotherapy (SBRT), external beam radiation therapy (EBRT), and radioembolization. SBRT, which involves the precise delivery of highly conformal, image-guided, ablative doses of external beam radiation, has been shown to be an effective alternative to other ablative procedures in nonsurgical candidates with tumors up to 6 cm in size, including HCC in patients with cirrhosis. Radioembolization involves catheter-based infusion of radioactive particles (such as Yttrium-90-labeled microspheres) targeted at the hepatic artery branches that feed the tumor. Typical prescription doses are in the range of 120–150 Gy, significantly higher than those possible with EBRT. Radioembolization may be used in patients with unresectable primary HCC with liver-dominant tumor burden and life expectancy >3 months. For patients with large HCCs, treatment options include conventionally fractionated EBRT. EBRT is considered safe for all patients with Child-Pugh class A or B.

Keywords Personalized medicine · Hepatocellular carcinoma · Treatment · Locoregional therapy · Radiation therapy · Stereotactic body radiotherapy (SBRT) · External beam radiation therapy (EBRT) · Radioembolization · Yttrium-90 microspheres

H. Ashamalla (✉)
Weill Medical College of Cornell University, New York, NY, USA
e-mail: hashamalla@gmail.com

H. Ashamalla · M. D. Mattes
New York Methodist Hospital, Brooklyn, NY, USA

M. D. Mattes
e-mail: malcolm.mattes@gmail.com

L. Berliner, H. U. Lemke (eds.), *An Information Technology Framework for Predictive, Preventive and Personalised Medicine,* Advances in Predictive, Preventive and Personalised Medicine 8, DOI 10.1007/978-3-319-12166-6_11

11.1 Introduction

Optimizing the therapeutic ratio and achieving an adequate safety profile in the treatment of hepatocellular carcinoma (HCC) with radiation therapy (RT) has historically been a challenge, as although HCC is a radiosensitive tumor, it is surrounded by highly radiosensitive organs, including the remainder of the liver and hollow gastrointestinal viscera. As technology has advanced to the point of allowing a highly conformal dose to be delivered to the tumor while sparing the surrounding normal tissues, radiotherapy has re-emerged as a viable treatment modality for many patients with HCC, pending randomized controlled trials to confirm its efficacy.

11.1.1 External Beam Radiotherapy in the Treatment of Hepatocellular Carcinoma

Some of the earliest trials of irradiation for HCC involved treating the whole liver, though outcomes were generally poor, with 2-year survival rates < 10 %. The advent of computed tomography (CT)-based treatment planning, intensity-modulated radiation therapy (IMRT), and image-guided radiation therapy has allowed for better targeting of the tumor and sparing of surrounding tissue, which in turn has led to a series of trials evaluating whether increasing the dose of radiation improves tumor control and survival. Dawson et al. reported that patients with unresectable tumors who received doses > 70 Gy had a better median survival (> 16.4 mo) than those who received a lesser dose, with a 68 % response rate overall [1]. Mornex et al. showed similar encouraging results in a small Phase II trial, in which tumors < 5 cm were treated to a dose of 66 Gy in 2 Gy fractions, resulting in an 80 % complete response (CR) rate. Grade 4 toxicity was observed in 22 % of patients in this study, though all of them had Child-Pugh class B cirrhosis prior to treatment [2]. Determining dose allocation can be aided with the use of the normal tissue complication probability (NTCP) model for intrahepatic malignancy, which can predict the probability of radiation-induced liver disease (RILD) after treatment to a given dose and volume of liver [3]. Based on this model, patients are to receive a maximum possible dose to the tumor while being subjected to no more than a 10 % risk of RILD. Of note, the NTCP model is limited by the fact that it was not validated for patients with moderate-severe liver disease, which unfortunately represents the majority of patients with HCC. As such, caution should be used when adopting the NTCP model to this group of patients.

The safety and efficacy of conventionally fractionated external beam radiation therapy (EBRT) has also been studied in combination with transarterial chemoembolization (TACE), in an attempt to improve outcomes with a dual modality approach. Seong et al. reported on 158 patients, with a median tumor size of 9 cm, who received 48 Gy either in combination with or after failure of TACE. The objective response rate in this study was 67 %, with a 16 month median survival [4]. Zeng et al. also reviewed 203 patients with unresectable HCC who received TACE with

or without radiation therapy (RT), finding that RT appeared to improve survival in each of the first 3 years after treatment [5]. Finally, Oh et al. reported on prospectively treating 40 unresectable HCC patients who had an incomplete response to 1–2 courses of TACE with 54 Gy, achieving a response rate of 63 % with 2-year overall survival of 46 % [6]. Though none of these studies were randomized, they all support the premise that conventionally fractionated radiotherapy may have some survival benefit in combination with TACE, and is well tolerated overall.

Another potential indication for radiotherapy is in the setting of portal vein tumor thrombosis (PVTT). These patients have a poor prognosis, and in many institutions are not considered candidates for TACE. Tazawa et al. treated 24 patients with PVTT with 50 Gy RT delivered focally to the thrombus, achieving an objective response rate of 58 % and 1-year overall survival of 41 % [7]. A similar approach, using either conventionally fractionated and hypofractionated radiotherapy targeted at the portal vein thrombus, has yielded response rates in the range of 45–83 % in several studies [8–10].

Overall, patients with unresectable, liver-confined HCC treated with conventionally fractionated, conformal radiotherapy can achieve durable tumor responses with an acceptable safety profile, though no RCTs have been carried out to demonstrate a survival benefit. Local control rates range from 40 to 90 % and median survival 10–25 months in various trials [11], depending on several patient and treatment-related factors. Indications for RT may include large unresectable tumors in a patient who is not a candidate (or has failed) other local therapy. Relatively good liver function is necessary for maintaining an adequate safety profile, and the predicted risk of RILD should be kept below 10 % for a given treatment plan. Within these parameters, dose escalation up to a maximum of 90 Gy is associated with the best outcomes.

11.1.2 Stereotactic Body Radiotherapy

Stereotactic body radiotherapy (SBRT), which involves the precise delivery of highly conformal, image-guided, ablative doses of external beam radiation in an abbreviated course of five fractions or less, has been shown to be an effective alternative to other ablative procedures in nonsurgical candidates with tumors up to 6 cm in size. SBRT is also unique from all other therapeutic options in that it is noninvasive. To ensure that enough residual liver is spared from RT, it is important to keep the target volume as small as possible, which has been made feasible through the use of advanced treatment-planning technologies like multi-phasic and multi-modality imaging, breathing motion management, highly conformal plans, and image-guided treatment delivery. The safety and efficacy of SBRT has been shown in several prospective studies of metastatic lesions in noncirrhotic livers [12, 13], and in the past few years data has also emerged from several groups reporting success in treating HCC with SBRT in patients with cirrhosis.

The largest series of patients enrolled in a prospective trial in the United States comes from Indiana University [14, 15], with the Phase I and subsequent Phase II

trials including 60 patients with Child-Pugh score < 7 (though there were nine patients with Child-Pugh score 8–9 included in the Phase 1 trial) who had 1–3 tumors of < 6 cm in cumulative diameter. These were relatively early tumors, as 85 % had a single lesion, the median tumor diameter was 3.1 cm, 60 % were Child-Pugh class A, the median CLIP score was 1, and the median KPS was 90. A stereotactic body frame with abdominal compression was used to immobilize the patient, and margins around the gross tumor were 0.5 cm radial and 1.0 cm superior-inferior. In the Phase II portion of the study, a dose of 48 Gy in 3 fractions (over 5–10 days) was given to patients with Child-Pugh class A, while 40 Gy in 5 fractions (over 3–6 weeks) was given to patients with Child-Pugh class B. Dose-volume constraints were also more rigorous for those patients with Child-Pugh class B (500 cc normal liver was to receive < 12 Gy and one-third of the normal liver was to receive < 18 Gy) than in those patients with Child-Pugh class A (500 cc normal liver was to receive < 7 Gy and one-third of the normal liver was to receive < 10 Gy). At a median follow-up of 26 months, a 70 % complete or partial response rate was observed, with an actuarial 2-year local control (LC) of 90 %. Of note, even though all patients were considered ineligible for transplant at study entry, 40 % of the patients eventually received a liver transplant. Excluding this subgroup from the survival analysis, the median progression-free survival (PFS), overall survival (OS) and time-to-progression (TTP) were 14.1, 20.4, and 36.5 months, respectively. The site of first failure was mostly regional (50 %), meaning elsewhere in the liver. The treatment was well-tolerated overall, with only 12 % of patients with a Child-Pugh score < 7 enduring an increase in hematologic or hepatic dysfunction greater than one grade, and 20 % of patients experiencing an increase in Child-Pugh class within 3 months of treatment. However, the patients from the phase I study with Child-Pugh score 8–9 did have higher rates of toxicity, with 4 of 8 patients developing progressive liver failure (though two of these patients received a higher dose than was later allowed in the phase 2 portion of the trial). Overall, outcomes from this study compare favorably to those of radiofrequency ablation (RFA), TACE, and other locoregional therapies. The median survival to the non-transplant cohort was also comparable to a predicted 22 months for all comers with a CLIP score of 1 [16]. Given these favorable results, the authors report that at their institution, in eligible patients with well-compensated cirrhosis, SBRT is now considered the primary modality for bridging to transplant, and is also strongly considered for first-line definitive therapy in patients who are not transplant candidates.

Similar findings were also reported in a Korean study [17], in which 42 patients (90 % of which were Child-Pugh class A with median tumor size of 15.4 cm^3) underwent 30–39 Gy SBRT in 3 fractions. Of note, unlike in the American series, most of the HCC in this study was HBV-induced, which may have implications in tumor biology or response to radiotherapy. Despite the lower radiation dose, the in-field response rate was 85 %, in-field 3-year PFS was 68 %, median PFS was 15.4 months, and 3-year overall survival was 59 %. Most recurrences were again regional (within the liver but outside the radiation field). One patient had late liver failure, though < 10 % had significant hematologic/hepatic toxicity. In the largest

Table 11.1 SBRT absolute contraindications

Child-Pugh score > 10
< 800 cc of uninvolved liver
Tumor < 0.5 cm from a hollow viscous
Radiation tolerance parameters for uninvolved liver cannot be achieved
Child-Pugh A: 500 cc of normal liver < 7 Gy, $^{1}/_{3}$ of normal liver < 10 Gy
Child-Pugh B: 500 cc of normal liver < 12 Gy, $^{1}/_{3}$ of normal liver < 18 Gy

series, Sanuki et al. reported on the Japanese experience of 185 patients with tumors < 5 cm who were treated in five fractions to a total dose of 40 Gy (for Child-Pugh class A) or 35 Gy (for Child-Pugh class B), with dose reductions as necessary to keep the percentage of liver receiving 20 Gy below 20 % [18]. Outcomes were again excellent, with three year LC 91 % and OS 70 %, both of which were independent of the dose level used. Ten percent of patients had worsening Child-Pugh score by at least two points, though this was reversible in all but 3 patients (two of which with Child-Pugh class B died of liver failure).

Finally, hypofractionated radiation therapy has also been shown to be feasible in patients with larger tumors and more advanced disease, as has been reported in a large Canadian series of 102 patients [19]. In this study, the median tumor volume was 173 cm^3, 55 % of patients had a vascular tumor thrombus, and 61 % had multifocal disease. The dose prescribed was determined according to the estimated risk of RILD, with median dose 36 Gy (range 24–54 Gy) in 6 fractions over 2 weeks. Given the more advanced tumors in this study, along with the fact that the larger tumors received lesser doses due to a higher risk of RILD with larger treatment volumes, it is not surprising that the median PFS was only 5.4 months, considerably lower than the other SBRT studies. However, LC at 1 year was 87 %, and median survival was 17 months, both of which are better than expected for this group of patients. The most frequent site of progression was again outside the treatment volume. Of note, there were 7 deaths that may have been treatment related, and Child-Pugh score progression was observed in 30 % of patients within 3 months of RT, some of which was reversible. The higher toxicity can again probably be accounted for by the large volumes treated, but tumor progression certainly also contributed.

The absolute and relative contraindications of SBRT are shown in Tables 11.1 and 11.2, respectively. Child-Pugh class is an important predictor of morbidity, and while there is sufficient safety data in class A, SBRT should be used with caution (or not at all) in classes B and C. The presence of portal vein thrombosis does not impact the safety or efficacy of SBRT. Other procedural considerations to prevent toxicity, which are not contraindications per se, include keeping an interval of 14 days between SBRT and chemotherapy, and 6 months between SBRT and any local embolization procedure. There may also be some situations in which SBRT is technically feasible, but systemic therapy or best supportive care is more appropriate than any local therapy, including patients with life expectancy < 12 weeks, or patients with progressive or untreated gross extrahepatic disease.

Table 11.2 SBRT relative contraindications

Child-Pugh Score 8–9 (especially if not on the liver transplant list)
ECOG > 2 or KPS < 70
> 3 lesions, or total size of lesions > 6 cm
History of right upper abdomen radiation therapy
Active hepatitis (viral or nonviral)
Significant ascites
Renal insufficiency (Cr > 1.8 or CrCl < 50)
Liver function abnormalities:
Bilirubin > 3 mg/dL
Albumin < 2.5
AST/ALT > 3 × upper limit of normal
PT/PTT > 1.5 × upper limit of normal (and not correctable with Vitamin K)
CBC Abnormalities:
ANC < 1000
Platelets < 50,000
Hemoglobin < 9

In summary, SBRT appears most applicable to relatively small, inoperable tumors, though it could be considered for larger lesions if there is at least 800 cm^3 of uninvolved liver and the liver radiation tolerance is respected. Child-Pugh class is an important predictor of morbidity, and while there is sufficient safety data in Child-Pugh class A, SBRT should be used with caution (or not at all) in Child-Pugh class B and C. Although there is no randomized data comparing SBRT to RFA or TACE, Phase I/II trials suggest comparable, if not superior outcomes with SBRT. At this time, we suggest that the decision for the most appropriate modality be as individualized as possible to the patient, making use of a multidisciplinary tumor board or clinic whenever feasible. With a lack of randomized data to support one modality over another, much of the decision-making at this time will be institution specific.

11.1.3 Radioembolization

The technique of radioembolization is similar in many ways to any other embolization procedure (e.g. TACE), in that it involves catheter-based infusion of particles targeted at the arterial branch of the hepatic artery feeding the portion of the liver where the tumor is located. However, unlike chemoembolization, in which the mechanism of action of tumor necrosis is ischemia secondary to reduced blood flow, the mechanism of action in radioembolization is primarily due to radiation induced necrosis. Since radioembolization has minimal embolic effect, and won't

obstruct the blood supply to the functional liver, it is often considered the safer alternative to TACE for tumors with portal vein thrombosis.

There are two different radioisotopes used for radioembolization worldwide, Iodine-131[I-131]-labeled Lipiodol and Yttrium-90[Y90]-labeled microspheres. The former is not used in the USA due to lack of availability. The latter is available either as the glass Theraspheres or resin SIR-Spheres, with Theraspheres being the more common alternative in North America. Y90 is a β-emitter, with a half-life of 64 h, and maximum penetration of 11 mm in tissue. Typical prescription doses are in the range of 120–150 Gy, significantly higher than those possible with EBRT. According to the Radioembolization Brachytherapy Oncology Consortium Consensus Guidelines, Therasphere may be used in patients with unresectable primary HCC with liver-dominant tumor burden and life expectancy >3 months [20]. Prior to treating a patient, it is important to do a 99^{m}-Tc macroaggregated albumin (MAA) scan to demonstrate that there is no shunting of blood flow to the lung or gastrointestinal tract that cannot be corrected by catheter techniques. The potential for ≥30 Gy radiation exposure to the lung is considered an absolute contraindication to radioembolization. Relative contraindications include a limited hepatic reserve, irreversibly elevated bilirubin and prior RT involving the liver.

The largest prospective trial evaluating Therasphere comes from Northwestern University [21]. 291 patients with HCC were treated, with response rates of 42% using WHO criteria and 57% using EASL criteria. The median TTP was 7.9 months for the entire cohort, and outcomes were strongly correlated with Child-Pugh score and the presence or absence of portal vein tumor thrombosis (PVTT). While Child-Pugh class A patients without PVTT could expect a median TTP of 15.5 months, Child-Pugh class B patients without PVTT had a median TTP of only 13 months. Median TTP was only 5.6–5.9 months for all patients with PVTT, regardless of Child-Pugh score. Complications of treatment most commonly involved a mild postembolization syndrome of fatigue, constitutional symptoms, and abdominal pain (20–55%). Grade 3 or 4 elevation in bilirubin was seen in 19% of patients, while the 30-day mortality was 3% of patients.

Given the significant overlap in patient eligibility for radioembolization and chemoembolization, a randomized trial comparing the two was carried out in France, in which 142 patients with unresectable HCC were randomized to I-131-labeled Lipiodol or TACE [22]. In this study, the response rate and survival were similar in both arms at 1 and 3 years follow-up, however, there was significantly less toxicity in the radioembolization arm, with only 3 patients having severe side effects (as compared to 29 patients after chemoembolization). There are no randomized trials to date involving Therasphere, however, a recent comparative analysis published again by the group at Northwestern by Salem et al. suggests that radioembolization results in a better median TTP than TACE (13 vs. 8 months, respectively), again with less toxicity. There was no difference in median survival in the two groups [23]. It is important to note that in these studies, the chemoembolization groups were treated with the lipiodol technique (70 mg cisplatinum diluted in 140 mL of saline solution and 10 mL Lipiodol [22] and 30 mg mitomycin, 30 mg adriamycin and 100 mg

cisplatin mixed with lipiodol [23]). The more recently introduced technique with drug-eluting beads has been shown to have lower toxicity, as discussed in Chap. 7c.

In summary, radioembolization is an emerging technology in the USA that may be better tolerated than TACE, with similar (if not somewhat improved) efficacy. It is also thought to be a safer alternative than TACE in patients with PVTT, but given the short median survival of these patients, it is unclear if they would benefit more from it than they would from systemic therapy alone. The expense of radioembolization also remains an issue, though may become less so if randomized data were to further clarify the optimal indications for, and benefit from its use. With respect to toxicity, trials comparing radioembolization with TACE with drug-eluting beads will be helpful.

Conclusion

Considering the various forms of treatment for HCC, including radiotherapy, it is necessary to consider patient-specific factors in selecting the optimal treatment. Personalized management of HCC requires the selection of individual and/or combined treatment modalities, provided by different clinicians. For example, there are several types of local therapy for HCC that may be applicable either as a bridging therapy in those patients awaiting transplant, or as a means of attempting to downstage a tumor in a patient with liver-confined disease. While the choice of a therapeutic regimen relies heavily upon the local expertise at a given institution, there are several patient- and tumor-specific characteristics that can guide management.

The indications for SBRT and RFA are somewhat overlapping, in the sense that the optimal candidate for both procedures is a patient with up to 3 lesions, with a total size (of the lesions combined) <6 cm. There is some data to suggest that SBRT can be done for any size lesion assuming that a patient has >800 cc of uninvolved liver and radiation tolerance limits for that normal liver are respected, however, this data comes from a single institution only, and should be further studied to confirm its safety. Although there are no RCTs comparing SBRT to RFA, prospective data suggests that SBRT has approximately equivalent local control rates to RFA for lesions <3 cm, and better local control than RFA for lesions >3 cm. SBRT may be favored for lesions located on the liver capsule due to the risk of tumor rupture and seeding with RFA. SBRT may also be favored for lesions close to major blood vessels, as RFA may be less effective in this situation due to the heat sink phenomenon. Conversely, RFA should be favored, with caution, when the tumor is in close proximity (<0.5 cm) to a hollow viscous (duodenum, stomach, colon) due to the risk of perforation after SBRT.

For patients with larger lesions, options for local therapy include TACE, radioembolization, and conventionally fractionated EBRT. Retrospective data suggests that radioembolization is better tolerated than TACE (with lipiodol techniques), with similar (if not somewhat improved) efficacy. Whereas portal vein thrombosis is a relative contraindication to TACE, it is not a concern for patients receiving

radioembolization or EBRT. Absolute and relative contraindications for radioembolization and EBRT are similar to those for SBRT, though with some variation in radiation dose constraints to the liver and other organs at risk. Prior to radioembolization, a ^{99m}Tc macroaggregated albumin (MAA) scan must be obtained, and if there is a potential for ≥ 30 Gy radiation exposure to the lung (via a "lung shunt"), or if there is flow to the GI tract that cannot be corrected by catheter techniques, radioembolization is contraindicated. EBRT requires sparing of at least 20% of the total liver volume ($V_{effective} < 0.8$), and that strict dose-volume constrains be used for the uninvolved liver to keep the risk of radiation-induced liver disease < 10%. Given the low dose per fraction used in EBRT, the proximity of a tumor to a hollow viscous is of no concern for toxicity. Assuming that the above criteria are met, radioembolization or EBRT are considered safe for all patients with Child-Pugh class A or B (though not class C). Though clinically useful in patients with larger tumors, neither of these therapies would be used for smaller tumors amenable to SBRT.

References

1. Dawson LA, McGinn CJ, Normolle D et al (2000) Escalated focal liver radiation and concurrent hepatic artery fluorodeoxyuridine for unresectable intrahepatic malignancies. J Clin Oncol 18:2210–2218
2. Mornex F, Girard N, Beziat C, et al (2006) Feasibility and efficacy of high-dose three-dimensional-conformal radiotherapy in cirrhotic patients with small-size hepatocellular carcinoma non-eligible for curative therapies–mature results of the French Phase II RTF-1 trial. Int J Radiat Oncol Biol Phys 66:1152
3. Dawson LA, Normolle D, Balter JM et al (2002) Analysis of radiation-induced liver disease using the Lyman NTCP model. Int J Radiat Oncol Biol Phys 53(4):810–821
4. Seong J, Park HC, Han KH, Chon CY (2003) Clinical results and prognostic factors in radiotherapy for unresectable hepatocellular carcinoma: a retrospective study of 158 patients. Int J Radiat Oncol Biol Phys 55:329
5. Zeng ZC, Tang ZY, Fan J et al (2004) A comparison of chemoembolization combination with and without radiotherapy for unresectable hepatocellular carcinoma. Cancer J 10(5):307–316
6. Oh D, Lim do H, Park HC et al (2010) Early three-dimensional conformal radiotherapy for patients with unresectable hepatocellular carcinoma after incomplete transcatheter arterial chemoembolization: a prospective evaluation of efficacy and toxicity. Am J Clin Oncol 33:370
7. Tazawa J, Maeda M, Sakai Y et al (2001) Radiation therapy in combination with transcatheter arterial chemoembolization for hepatocellular carcinoma with extensive portal vein involvement. J Gastroenterol Hepatol 16:660–665
8. Nakagawa K, Yamashita H, Shiraishi K et al (2005) Radiation therapy for portal venous invasion by hepatocellular carcinoma. World J Gastroenterol 11:7237–7241
9. Choi BO, Choi IB, Jang HS et al (2008) Stereotactic body radiation therapy with or without transarterial chemoembolization for patients with primary hepatocellular carcinoma: preliminary analysis. BMC Cancer 8:351
10. Kim JY, Chung SM, Choi BO, Kay CS (2011) Hepatocellular carcinoma with portal vein tumor thrombosis: improved treatment outcomes with external beam radiation therapy. Hepatol Res 41:813–24. doi:10.1111/j.1872-034X.2011.00826.x
11. Hawkins MA, Dawson LA (2006) Radiation therapy for hepatocellular carcinoma: from palliation to cure. Cancer 106:1653–1663

12. Rusthoven KE, Kavanagh BD, Cardenes H et al (2009) Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. J Clin Oncol 27:1572–1578
13. Herfarth KK, Debus J, Lohr F et al (2001) Stereotactic single-dose radiation therapy of liver tumors: results of a phase I/II trial. J Clin Oncol 19:164–170
14. Cárdenes HR, Price TR, Perkins SM et al (2010) Phase I feasibility trial of stereotactic body radiation therapy for primary hepatocellular carcinoma. Clin Transl Oncol 12: 218–225
15. Andolino DL, Johnson CS, Maluccio M et al (2011) Stereotactic body radiotherapy for primary hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 81:e447–453
16. Llovet JM, Bruix J (2000) Prospective validation of the Cancer of the Liver Italian Program (CLIP) score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. Hepatology 32:679–680
17. Kwon JH, Bae SH, Kim JY et al (2010) Long-term effect of stereotactic body radiation therapy for primary hepatocellular carcinoma ineligible for local ablation therapy or surgical resection. Stereotactic radiotherapy for liver cancer. BMC Cancer 10:475
18. Sanuki N, Takeda A, Oku Y et al (2013) Stereotactic body radiotherapy for small hepatocellular carcinoma: a retrospective outcome analysis in 185 patients. Acta Oncol 53:399–404
19. Bujold A, Massey CA, Kim JJ et al (2013) Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol 31:1631–1639
20. Kennedy A, Nag S, Salem R et al (2007) Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phys 68:13
21. Salem R, Lewandowski RJ, Mulcahy MF et al (2010) Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology 138:52–64
22. Raoul JL, Guyader D, Bretagne JF et al (1997) Prospective randomized trial of chemoembolization versus intra-arterial injection of 131I-labeled-iodized oil in the treatment of hepatocellular carcinoma. Hepatology 26:1156–1161
23. Salem R, Lewandowski RJ, Kulik L et al (2011) Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 140:497–507.e2

Chapter 12
Design of an IT System for Hepatocellular Carcinoma

Leonard Berliner and Heinz U. Lemke

Abstract During the development of an Information Technology System for Predictive, Preventive and Personalized Medicine (ITS-PM) for hepatocellular cancer (HCC) a wide number of variables or Information Entities (IEs) will be identified, and their relative value will be determined. These include factors reflecting: (1) clinical assessment of the patient including functional status, liver function, degree of cirrhosis, and comorbidities; (2) tumor biology, at a molecular, genetic, and anatomic level; (3) tumor burden and individual patient response; and, (4) medical and operative treatments and their outcomes. Beyond the development of database systems, our goals include the development of a realistic, plausible approach to the development of Digital Patient Models (DPMs) and Model Guided Therapy (MGT). These will be based on a complex of database and knowledge management systems capable of data storage, data mining, data analysis, and decision support. In this Chapter we have outlined the required structure and function of an ITS-PM that would be suitable for these tasks. The database structure, composed of three layers, has been described and sample entity-relationship diagrams populated from the clinical material described in Chaps. 3–11 have been presented. Methodologies are proposed that include Multi-Entity Bayesian Networks (MEBN), Reference Model for Open Distributed Processing (RM-ODP), and Service-Oriented Architecture (SOA), which can be considered a subset of RM-ODP. These can provide the comprehensive techniques and structures to be employed to successfully meet the requirements for an ITS-PM.

Keywords Personalized medicine · Hepatocellular carcinoma · Information technology · Model guided therapy · Information technology system for predictive,

L. Berliner (✉)
Weill Medical College of Cornell University, New York, USA
e-mail: LeonardB23@AOL.com

New York Methodist Hospital, Brooklyn, NY, USA

H. U. Lemke
Technical University of Berlin, Berlin, Germany
e-mail: hulemke@cars-int.org

University of Southern California, Los Angeles, USA

L. Berliner, H. U. Lemke (eds.), *An Information Technology Framework for Predictive, Preventive and Personalised Medicine,* Advances in Predictive, Preventive and Personalised Medicine 8, DOI 10.1007/978-3-319-12166-6_12

preventive and personalized medicine (ITS-PM) · Digital patient model · Patient-specific model · Model-based medical evidence · Bayesian network · Reference model for open distributed processing (RM-ODP) · Service-oriented architecture (SOA)

12.1 Introduction

In the preceding Chapters we have defined the current state of knowledge, as well as the limits of our knowledge, with respect to hepatocellular carcinoma (HCC). To advance Predictive, Preventive and Personalized Medicine (PPPM), we will be examining HCC in the final two chapters from a more integrated point of view, combining epidemiology, risk factors, infectious etiologies, pathology, microenvironment, biomarkers, screening and diagnostic technologies, and treatment modalities (single, combined, and/or sequential). In this Chapter we will be exploring the ways in which Information Technology (IT) may optimize our ability to manage patients with HCC in a multidisciplinary setting along with Model-Guided Therapy (MGT) as outlined in Chaps. 1 and 2. This will require the development of systems to provide unified access to general medical and patient-specific information for medical researchers and health care providers from different disciplines including hepatologists, gastroenterologists, medical and surgical oncologists, liver transplant teams, interventional radiologists, and radiation oncologists.

It is our assumption that the development of improved IT will promote an approach based on a global understanding of disease and treatment outcomes, rather than reliance primarily upon local availability and expertise. To this end, we need technologies and information systems to optimize the vast amount of information in various repositories by these health care providers and investigators from random controlled trials (RCTs), as well as other data sources.

With this in mind, we will begin to explore the daunting task of defining the IT specifications that would fulfill the requirements for an Information Technology System for Predictive, Preventive and Personalized Medicine (ITS-PM), using a model of HCC as a use-case. Ultimately, to handle the vast amount of available information, we will need to define and develop new types of database solutions and end-user applications. The database solutions should include certain features—easily accessible links to data sources and repositories, functionality that is well organized and easily expandable, the facility for queries that will promote probabilistic and statistically valid investigations, and, features to facilitate decision support and research.

Beyond the selection and development of database systems, the larger task is to find a way of using IT to pool, integrate, and correlate the following: (1) the clinical information relating to diagnosis and treatment of HCC; (2) the research data relating to epidemiology, virology, and pathology at the anatomic, molecular, and genetic levels; and, (3) the role of MGT and Patient-Specific Modeling. One of our goals is to propose a realistic, plausible approach to the development of Digital

Patient Models (DPMs), based on a complex of database and knowledge management systems capable of data storage, data mining, data analysis, and decision support. At this time, there is no system or collection of systems on the market that can accomplish these tasks. In this Chapter we will undertake a systematic approach to identify, analyze, and organize a combination of actual and/or potential software entities that could be assembled with the appropriate architecture to achieve these goals. At this time, the tools that are available to us include database management systems, physiologic models, web services, other mid-layer services, and a variety of tools to create appropriate end-user software and graphics applications. These components would be combined to form a subset of a much larger and more comprehensive Therapy and Imaging Model Management Systems (TIMMS) system as described in Chap. 2.

HCC has been selected as a "use-case" for the development of an ITS-PM. A tentative IT framework, composed of a variety of components, will be described that has the capability to integrate the following: the Patient-Specific Model (PSM) itself (that includes the complete medical description of any number of patients), and the various sources of medical information that may be local or remotely accessed through the Internet. It should be possible to view and access the proposed ITS-PM from multiple points of view, to extract different kinds of information and perform different kinds of tasks by medical practitioners, researchers, and epidemiologists. For example, user interface requirements for the medical oncologist versus the geneticist evaluating DNA sequences will be quite different. This not only reflects the different tasks, and therefore the different needs of the end-users, but also reflects that each end-user will have a somewhat different view of the DPM, itself. The complete collection of DPM databases can provide a view or representation of the patient as required for a variety of specific tasks, whether they are related to achieving improved treatment outcomes, enhanced patient safety, and/or for engaging in basic medical research (Fig. 12.1).

A *Precision Surgery View* may be utilized to enhance surgical guidance for improved safety and efficiency; a *Surgical Workflow View* may be employed in the Operating Room to optimize the surgical process; a *Physiological View* would optimize the process of patient monitoring; a *Decision Support View* would provide assistance in the selection of best treatments; a *Biomarkers and Imaging View* could be employed to help gain a deeper understanding of disease fundamentals, e.g. oncology; and, a *Disease/Epidemiology View* may be utilized to pool large numbers of DPMs to gain insight into patient populations and epidemiology (Model-based Medical Evidence [MBME]).

A few points, from the Chaps. 3 through 11, will serve as reminders of the complexity of creating an ITS-PM for HCC: (1) the treatment spectrum for HCC extends from one extreme to the other, i.e. from transplantation of the entire liver to targeted therapy with Sorafenib at the molecular level; (2) HCC is often treated without tissue diagnosis, i.e. with radiologic and biochemical confirmation; (3) the understanding of the hepatic microenvironment and its relationship to HCC is evolving; and, (4) there are limitations in the RCTs comparing different minimally invasive treatments and/or their roles in down-staging of advanced cases. The science behind

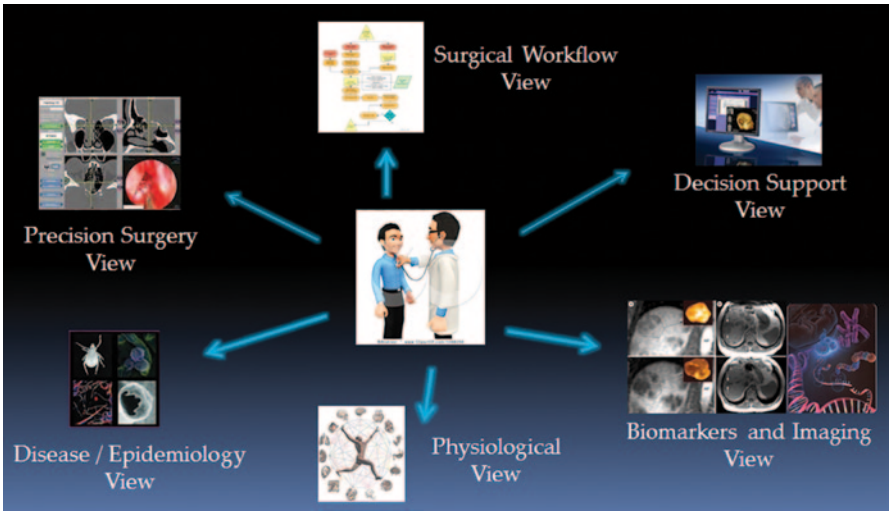

Fig. 12.1 The complete digital patient model provides a variety of views, or representations, of the patient depending on the specific tasks, requirements or areas of interest of the end-user

our treatment choices can be thought of as being in a state of evolution. There are differences of opinion, as well as newly emerging evidence, concerning many facets of HCC and its treatment. Therefore, the ITS-PM system under development must be sufficiently broad, sensitive, and flexible enough to help organize and make sense out of the widespread and disparate information available. It is hoped that the ITS-PM will help fill the gaps of our knowledge by incorporating and integrating new information into the existing fund of medical knowledge and help us make the best decisions for our patients, even when medical knowledge is incomplete. As in any medical decision support system, it is important to emphasize that the role of the ITS-PM is not to replace the physician in decision making, but rather to assist the decision making process, such as at a hospital's Tumor Board.

In summary, the development of the ITS-PM for HCC will provide a comprehensive system to identify and then determine the relative value of the wide number of variables: (1) factors reflecting clinical assessment of the patient including functional status, liver function, degree of cirrhosis, and comorbidities; (2) factors reflecting tumor biology at a molecular, genetic, and anatomic level; (3) factors reflecting tumor burden and individual patient response; and (4) factors reflecting medical and operative treatments and their outcomes. If this project is successful, it can serve as a prototype for IT solutions to assist in the diagnosis, research, and management of other cancers as well as non-malignant diseases.

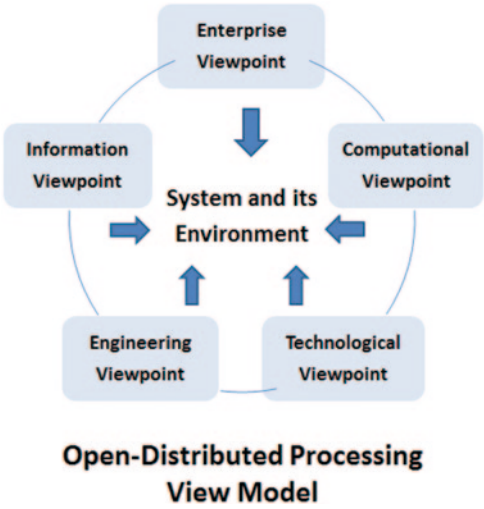

Fig. 12.2 A graphic representation of the points of view utilized in the reference model for open-distributed processes. (Adapted from [1])

12.1.1 ITS-PM: Organization and Architecture

12.1.1.1 Requirements for an ITS-PM

The first task is to consider and define the requirements for an IT approach for PPPM with respect to HCC. It is probably best if we divide this task into broad categories, each of which will have its own focus, data types, tasks, and solutions.

Reference Model for Open Distributed Processes and Service-Oriented Architecture

It is imperative that comprehensive and cohesive hardware and software architecture is provided for the ITS-PM to allow each section to function independently, while synchronized and in communication with each other section. Reference Model for Open Distributed Processing (RM-ODP) and Service-Oriented Architecture (SOA) (which may be considered a related subset of RM-ODP and is perhaps more widely known) are standards, methodologies, or approaches to enterprise system development that could help fulfill the necessary requirements.

RM-ODP is an International Organization for Standardization (ISO) standard that gives a solid basis for describing and building widely distributed systems and applications in a systematic way. Emphasis is placed on the need to build such systems with evolution in mind by identifying the concerns of major stakeholders and then expressing the design as a series of linked viewpoints representing these concerns. Each stakeholder can then develop an appropriate view of the system with a minimum of interference from the others [1] (Fig. 12.2) (Table 12.1).

Table 12.1 Viewpoints utilized in the reference model for open-distributed processes. (Adapted from [1])

Viewpoints for reference model for open-distributed processes
The *enterprise viewpoint* focuses on the organizational situation in which the design activity is to take place. It concentrates on the objectives, business rules, and operational policies that need to be supported by the system being designed.
The *information viewpoint* concentrates on the modeling of the shared information manipulated within the enterprise of interest. By providing a common model that can be referenced from throughout a complete piece of design, we can ensure that the same interpretation of information is applied at all points.
The *computational viewpoint* is concerned with the development of the high-level design of the processes and applications supporting the enterprise activities. It uses the familiar tools for object-oriented software design, expressing its models in terms of objects with strong encapsulation boundaries, interacting at typed interfaces by performing a sequence of operations (or passing continuous streams of information).
The *engineering viewpoint* tackles the problem of diversity in infrastructure provision; it gives the prescriptions for supporting the necessary abstract computational interactions in a range of different situations. It thereby offers a way to avoid lock-in to specific platforms or infrastructure mechanisms.
The *technology viewpoint* is concerned with managing real-world constraints, such as restrictions on the hardware available to implement the system within budget, or the existing application platforms on which the applications must run.

Once the requirements and the approach to fulfill these requirements have been developed, reviewed, and approved by the overall team, the wide variety enterprise software components need to be created and assembled. SOA provides the infrastructure and organization required for both connectivity and interaction between a wide variety of programs and functions (services) that may be written in different software languages to provide proper and secure transactions. SOA does not imply a specific technology or creation of a single all-encompassing program. Rather, SOA is an architectural paradigm and discipline that may be used to build infrastructures enabling those with needs (consumers) and those with capabilities (providers) to interact via services across disparate domains of technology and ownership [2].

Implementation of a SOA will provide for user interfaces, messaging between users, storage of data, access to data and services, establishment of workflow processes, and system security. When properly conceived, SOA is sufficiently flexible to allow incremental development and implementation of the functionality required by the organization. While SOA is often associated with Web Services, it is important to understand that the services provided by SOA need not be web based. SOA is often associated with the streamlining of business practices; however, the organization, interchangeability, and flexibility of SOA can provide advantages for the scientific and medical community as well, that faces similar obstacles created by the wide variety of software and IT tools that are currently difficult to integrate. For the purposes of this article, the importance of SOA resides in its ability for the scientific and medical community to find a realistic methodology for creating a useable and secure system, composed of complex and disparate entities, including Electronic

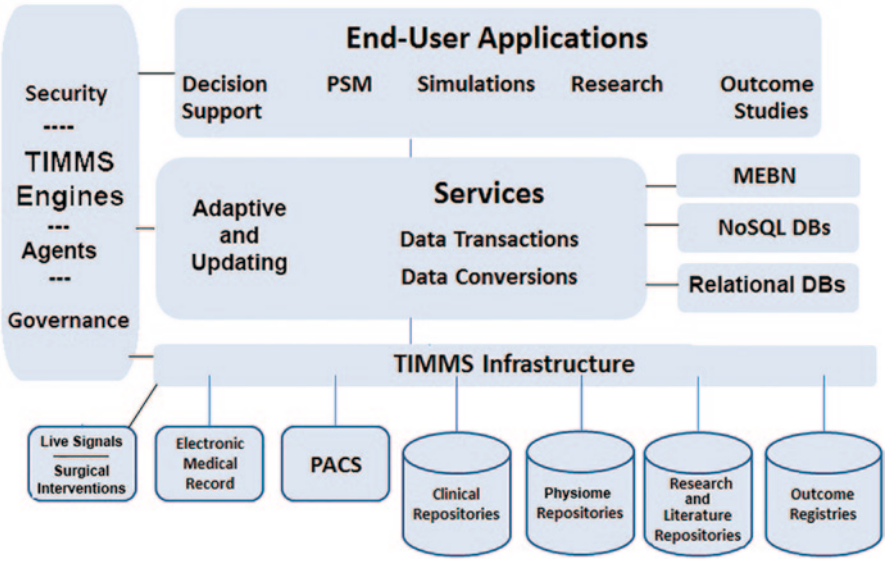

Fig. 12.3 A schematic for organization of an ITS-PHC. This diagram reorganizes many of the TIMMS components in a structure that will enable the secure interchange of information between data sources, database management systems, data analysis systems, and end-user applications. (Legend: *PSM* patient specific model; *TIMMS* therapy and imaging model management system; *PACS* picture archiving and communications system; *MEBN* multi-entity Bayesian network; *NoSQL* not only structured query language; *DBs* databases)

Medical Records, Hospital and Radiology Information Systems, research databases and repositories, as well as the database systems that will form the core of an ITS-PM.

It is beyond the scope of this article to provide a complete RM-ODP enterprise proposal with detailed SOA schema. However, we will try to explore and define the overall objectives and processes (enterprise viewpoint), the requirements relating to data types and data exchange (information viewpoint), and the software categories (computational viewpoint). (In some cases, specific software components, categories or products may be mentioned. However, at this stage of development this is done for illustrative purposes only to indicate the feasibility of a required technology or process. Architectural detail, as well as specific hardware and software selection and development, would be determined much later in the project.) A simplified schematic for the organization of an ITS-PM is presented in Fig. 12.3.

Data Exchange

Provision needs to be made for the exchange of data and interchange of data types between the various forms of databases that will be accessed, processed, and analyzed by the proposed ITS-PM. The vast amounts of data that are available may reside within Electronic Medical Records, Hospital and Radiology Information

Systems, research databases and repositories, in the form of relational databases, multi-dimensional databases, or newer NoSQL databases that may be of several types. The data types utilized within the ITS-PM may include strings, numbers, Boolean functions, images, text files, and XML documents. Much of this information is already in a format that can be utilized for data analysis. However, many entries into the medical record are not in a format that can be readily assimilated and analyzed in an automated IT system. Efforts have been made to create structured reports in Radiology, such as Digital Imaging and Communications in Medicine Structured Report (DICOM SR) [3] and RadLex [4], in which data is stored in retrievable format, such as XML and JSON. It ultimately may be required that full implementation of the ITS-PM may require extensive use of Structured Reports, in an as yet to be defined format.

Database Systems

A wide variety of database systems are currently available and in widespread use. They may be found in hospital information systems, throughout business and internet enterprises, government organizations, and personal computer programs. The most commonly employed databases today, relational databases (RDBs), are based on relational database management systems (RDBMS), in which data are stored in tables that are linked by designated relationships. Data are most commonly extracted from these databases by Structured Query Language (SQL) queries.

A new class of database systems recently has been developed and is known as NoSQL ("Not only SQL"). These systems do not rely primarily on tables, and therefore generally do not use SQL for data manipulation. These databases differ from RDBs in the great speed with which they can handle and sort through large volumes of information and relationships, thereby enabling systems such as Google and Facebook. NoSQL databases may be designed to store records (e.g. key-value stores), to store documents (e.g. XML documents), and/or to store data, whose relations are well depicted and utilized with graphs and graph theory.

The proposed ITS-PM will most likely need to be able to make use of several types of database management systems, in both core programs and data repositories. Thus, the ITS-PM will be well-equipped for different functionalities.

Model Creation

The content and the organization of the ITS-PM should be flexible enough to allow manipulation of the information required for constructing a variety of models to support MGT. This may include, but would not be limited to, models of the patient, i.e. the DPM. It could also include the ability to create models of disease processes, models of patient populations, as well as models of genetic, physiologic, and molecular processes.

The design and structure of the DPM will be discussed in greater detail below.

Clinical Decision Support

The ITS-PM should provide a variety of functions, including data-mining and data-analysis to detect correlations, and ultimately, to reveal and elucidate causal relationships between the patient, the disease processes, and exogenous factors. Through these functions, it is proposed that the ITS-PM will assist in: (1) the understanding of diseases in individuals and populations; (2) basic medical research; and, (3) clinical decision support.

It is important that safeguards be established to ensure that objectivity and strict statistical methodology be employed to prevent erroneous conclusions to be drawn from rapidly accumulating data (e.g. "correlation does not imply causation"). This is especially true in medicine, in which decisions often are made with the best available information (i.e. incomplete knowledge).

12.1.2 Clinical and Research Components

12.1.2.1 Defining the Requirements of the ITS-PM

In this Chapter, the objectives of the ITS-PM will be explored with an emphasis on defining the major processes that will be required, as well as their categories and components (enterprise viewpoint). As these processes are brought into focus, the specific required data types and the requirements relating to data exchange will be enumerated (information viewpoint). The major mid-level software functions and end-user applications will be discussed (computational viewpoint). At this stage of development the following will be considered: (1) the DPM (relational and NoSQL database management systems); (2) clinical decision support including predictive and simulation functions with a Multi-entity Bayesian Network (MEBN) [5, 6]; (3) access to medical research databases; and, (4) modules for outcomes studies for the development of disease models, relating to individuals and populations, as well as for the evaluation of treatment protocols and technologies.

The DPM: Information Entities, PSM Template and MEBN

It is essential that the DPM should have the capacity to contain and organize information of any type that may be medically relevant. It will be required that these attributes will ultimately be organized into structures that can be utilized in a MEBN. At this time, for a DPM to achieve the wide range of functions that have been described, it would appear that the database structure be divided into three functional components or layers. These layers, which are more descriptive than physical, would include: (1) an Attribute Layer for data storage that would be best served with RDBs; (2) a Probabilistic Layer for data analysis and decision support that may be best served with MEBNs and graph theory; and, (3) an Action Layer that

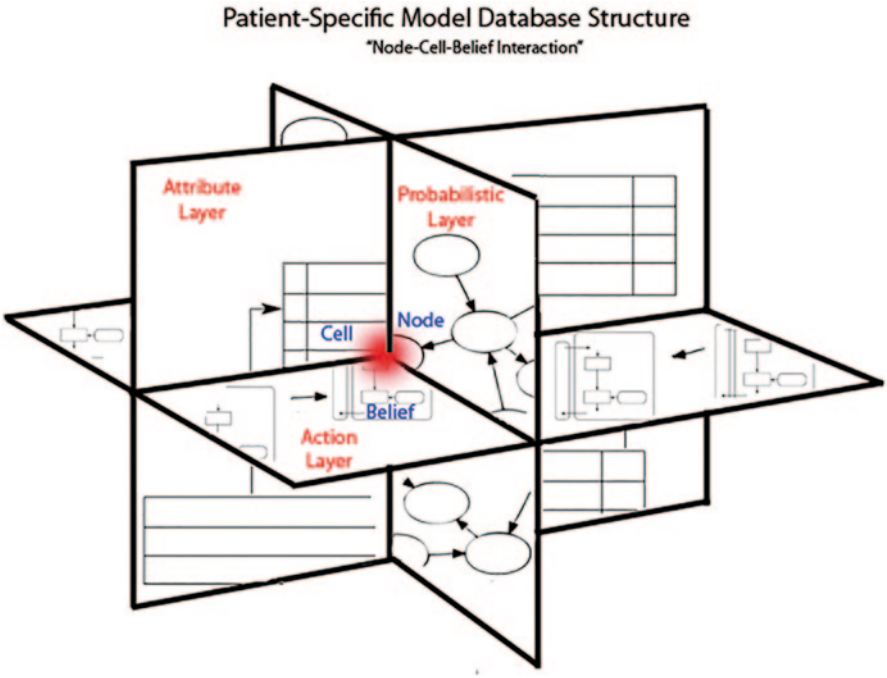

Fig. 12.4 The database structure of the generic PSM may be defined as three converging layers that allow the generic PSM to perform the many tasks assigned to it. Any given data point may contain the value of a patient attribute or Information entity that is associated with a certain probability distribution with respect to a clinical inquiry, and may be acted upon in decision support processes

would actively update databases and perform statistical analyses at specified times. (Fig. 12.4) Therefore, the database structure of a generic PSM may be defined as three converging layers that allow the PSM to perform the many tasks assigned to it. Any given data point may contain the value of a patient attribute or Information Entity (IE) that is associated with a certain probability distribution with respect to a clinical inquiry, and may be acted upon in decision support processes.

The first task in constructing a generic PSM is to organize the patient-specific information according to a generalized hierarchy of attributes or IEs, extending from most general to specific, as outlined in Chap. 2. From these IEs, an Entity-Relationship Diagram (ERD) may be designed, (Figs. 12.5a and b) from which a RDB may be constructed, as part of the Attribute Layer of the generic PSM. This RDB that will be populated with data from the many sources previously illustrated in Fig. 12.3 (the schematic for organization of an ITS-PM) in accordance with the organization described in the generic PSM template (also defined in Chap. 2), will serve as the reservoir of clinical data, biomarkers, images, and physiologic signals that will be utilized by the PSM. Information is accessed from RDBs by means of SQL queries.

Clinical Decision Support

Clinical decision support functions will reside predominantly within the Probabilistic Layer of the generic PSM. These functions will be available for evaluation and reorganization within categories of risk, diagnosis, prognosis, and treatment response for the purposes of clinical decision support. As envisioned in the proposed ITS-PM, the IEs stored within the RDB (including patient attributes, biomarkers, clinical data, and imaging data) will have greatly enhanced value in decision support systems when incorporated into MEBN and graph database systems.

As discussed in Chap. 2, in medicine, we must be able to reason in the presence of incomplete data and knowledge. There may be uncertainty regarding the existence of relationships among pieces of medical information, the strength of those relationships, and, constraints governing those relationships, such as, cause and effect. Bayesian inference and probability are logically coherent and provide tools and methodology to combine expert knowledge with statistical data, to represent cause-and-effect relationships, to learn from observations, to prevent over-fitting, and, to provide clear and understandable semantics. The ITS-PM will be able to make use of the Bayesian Belief Network or Model that is a probabilistic graphical model (a type of statistical model) that represents a set of random variables and their conditional dependencies via a directed acyclic graph (DAG) (Fig. 12.6). In a DAG,

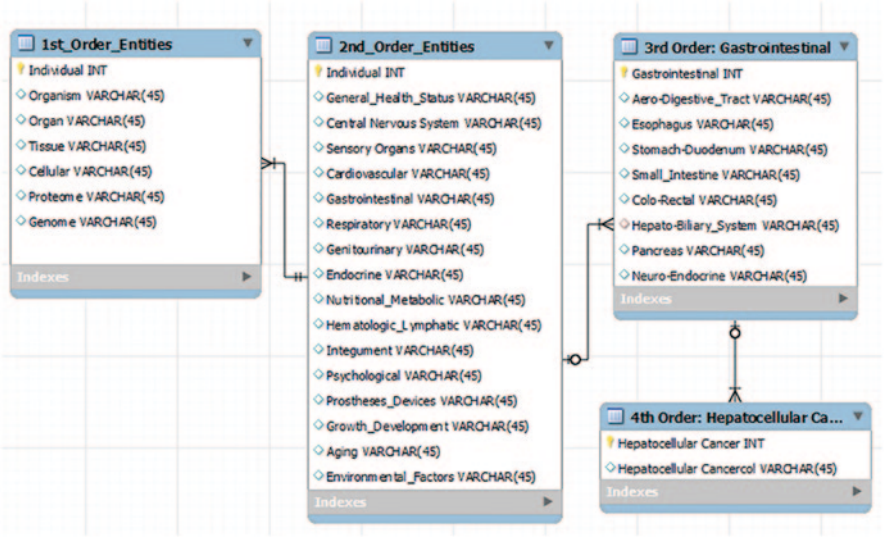

Fig. 12.5 a A portion of a simplified entity-relationship diagram for a relational database is shown displaying the 1st, 2nd, and 3rd order information entities (as defined in Chap. 2) of a generic patient-specific model, and a 4th order entity: Hepatocellular Carcinoma. (Legend: *INT* integer; *VARCHAR* includes text [characters, numbers, punctuation])**. b** A portion of a simplified entity-relationship diagram for a relational database is shown displaying the 5th order information entities relating to Hepatocellular Carcinoma

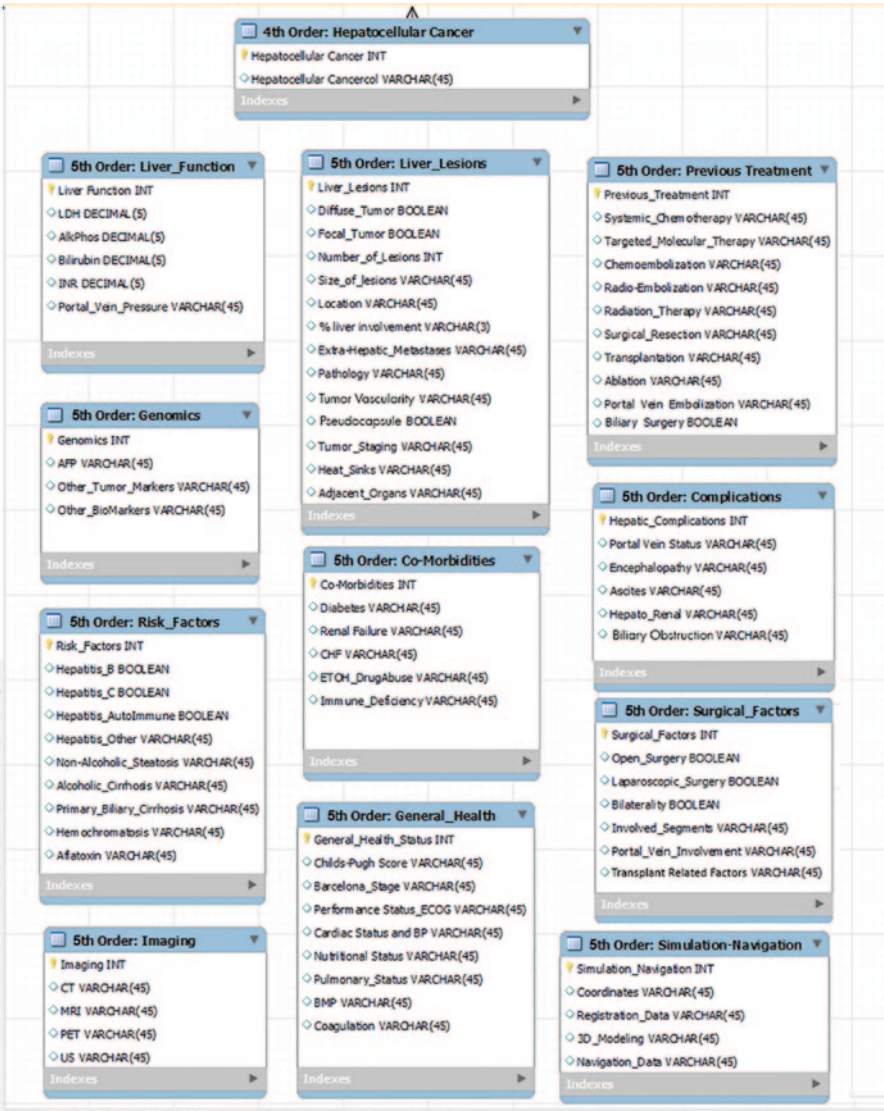

Fig. 12.5 (continued)

each node (numbered circle) presents the attributes of each random variable or IE, while each edge (arrow) indicates the conditional dependency.

Bayesian networks are used for evidential reasoning or explanation. For example, a Bayesian network can be used to represent the probabilistic relationships between diseases and symptoms. Given symptoms, the network can be used to compute the probabilities of the presence of various diseases.

As described in Chap. 2, building on the basic Bayesian Network, a MEBN is a logic system that integrates first-order logic with Bayesian probability theory [7]. A

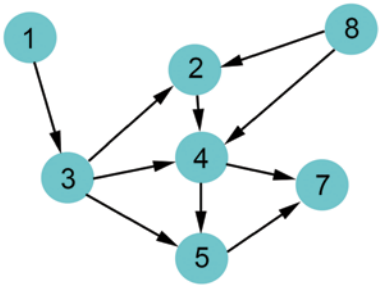

Fig. 12.6 Directed acyclic graph (DAG). Each node (*numbered circle*) presents the attributes of each random variable or information entity, while each edge (*arrow*) indicates the conditional dependency. For a multi-entity Bayesian network, the edges of the DAG also provide validated probability distributions, beyond conditional dependencies

MEBN can provide a descriptive and functional framework for quantifiable medical IEs. The nodes of the DAG in a MEBN contain the attributes of each random variable or IE, as supplied by the relational database systems, while the edges provide validated probability distributions, beyond conditional dependencies (Fig. 12.6). Thus, the MEBN can mathematically provide predictive capabilities and the ability to determine cause and effect relationships, over and above the descriptive, expandable, and correlational capabilities of a simple Bayesian network. Accordingly, the value of any given entity within the RDB systems can be enhanced by determining a relative value (probability distribution) for each factor within the appropriate contexts.

To create an effective clinical decision support system for HCC, utilizing a MEBN, the IEs identified as 5th order relating to HCC, will need to be assembled into MFrags and MTheories as outlined in Chap. 2. Initially, conditional relationships between IEs and their probability distributions will be determined by medical experts utilizing the best available evidence-based medicine. One critically important factor must be understood—it is the nature of Bayesian Networks to increase in accuracy as the system is tested and more information is added, according to Pearl's Bi-directional Belief Updating Algorithm [7]. The MFrags will be assembled to form graphs, e.g. Situation Specific Bayesian Networks (SSBN) to evaluate hypothetical conditions. Support for decision constructs in MEBN will be provided via Multi-Entity Decision Graphs (MEDG). As in any decision support system, the MEBN system will require ongoing updating and validation.

While the MEBN will provide a complex system for answering specific questions relating to the management of patients with HCC, there are other tools available for the Probabilistic Layer of the PSM database system. In recent years, high-performance NoSQL databases have been used to find relationships between entities in very large networks, often with billions of objects. These database systems have been utilized for seeking information (e.g. Google), with vast social networks (e.g. Facebook), and to catalogue and find relationships in genetics research. These systems are known for their rapid answering time for complex queries, i.e.—traversals.

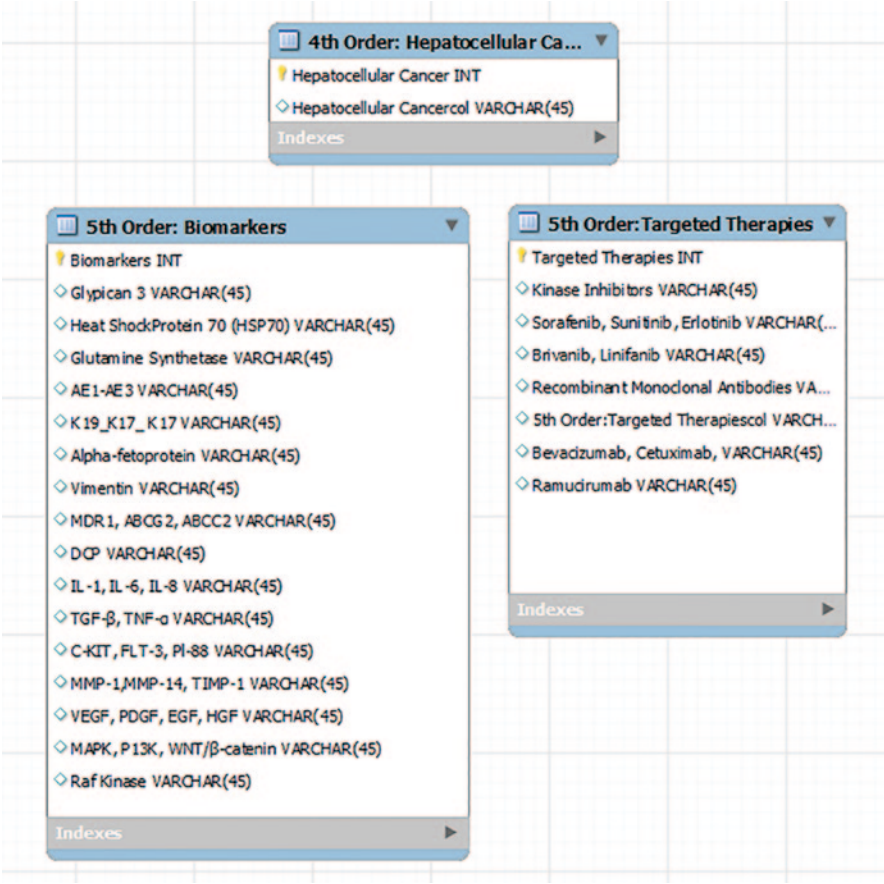

Fig. 12.7 A portion of a simplified entity-relationship diagram for a relational database that may be linked to a graph database for research in biomarker and targeted therapies is shown displaying the 5th order information entities relating to biomarkers and targeted therapies for HCC

One form of NoSQL database, the Graph Databases, may be especially useful by incorporating the IEs of the PSM template. Graph Databases can provide persistent storage for large volumes of data (nodes), to display relationships between entities implicit in the model (edges), to allow a unified view for multiple sources, and, are sufficiently flexible to manage unknown or dynamic schemas. Most importantly, Graph Databases can facilitate analysis of the connected information in network-like structures.

The ability of Graph Databases to find relationships within vast amounts of data will help provide a link between the domain of genetics and biomarkers research with the PSM. Figure 12.7 shows a portion of a simplified Entity-Relationship Diagram for a relational database that may be linked to a Graph database for research in biomarker and targeted therapies. Fifth order IEs relating to biomarkers and targeted therapies for HCC are displayed.

Action Layer

The third layer of the generic PSM database structure can be considered an Action Layer that will be designed to perform many of the tasks that will be required to update the PSM databases. The tasks performed as part of this action layer include data processing that will be required to ensure the increasing accuracy of the MEBN as indicated in Pearl's Theorem or Algorithm. These tasks may be accomplished by means of triggered sub-programs, and may include updating lab values in a graph database, recalculating probabilities in MEBNs, extracting data from structured reports such as imaging studies, and extracting data from the wide variety of local and remote repositories (e.g. genetic data). The system could be used locally at a clinical liver cancer center to monitor patient assessments, treatments, and outcomes.

This process will be facilitated when links can be established to provide access to medical research databases, as well as to established treatment registries through the TIMMS infrastructure as shown in Fig. 2.1, Chap. 2.

Conclusion

In this Chapter we have outlined the required structure and function of an ITS-PM that would be suitable to establish a use-case utilizing HCC within the context of the PSM and MGT. The database structure, composed of three layers, has been described and sample entity-relationship diagrams populated from the clinical material described in Chaps. 3–11 have been presented.

RM-ODP and SOA can provide the comprehensive methodologies to be employed to successfully meet the requirements for such an elaborate system.

In the concluding Chapter, the proposed benefits of this ITS-PM will be presented in the form of expert recommendations and outlook for PPPM and HCC.

References

1. Linington PF, Milosevic Z, Tanaka A, Vallecillo A (2012) Building enterprise systems with ODP: an introduction to open distributed processing. CRC Press, USA
2. Nickul D, Reitman L, Ward J, Wilber J (2007) Service Oriented Architecture (SOA) and Specialized Messaging Patterns. http://www.adobe.com/enterprise/pdfs/Services_Oriented_Architecture_from_Adobe.pdf. Accessed 6 Jan 2009
3. Hussein R, Engelmann U, Schroeter A, Meinzer H-P (2004) DICOM structured reporting: Part 1. Overview and characteristics. Radiographics 24:891–896
4. Radiological Society of North America: RadLex (2012) http://rsna.org/RadLex.aspx. Accessed 9 Dec 2012
5. Lemke HU, Berliner L (2010) Personalized medicine and model-guided therapy. In: Niederlag W, Lemke HU, Rienhoff O (eds) Personalisierte Medizin und Informationstechnologie, vol 15. Health Academy, Dresden pp 39–48
6. Lemke HU, Berliner L (2010) Personalized medicine and patient-specific modelling. In: Niederlag W, Lemke HU, Golubnitschaja O, Rienhoff O (eds) Personalisierte Medizin, vol 14. Health Academy, Dresden pp 155–164
7. Laskey KB (2008) MEBN: a language for first-order bayesian knowledge bases. Artif Intell 172(2–3):140–178

Chapter 13
Outlook and Expert Recommendations for Predictive, Preventive and Personalized Medicine and Hepatocellular Carcinoma

Leonard Berliner, Heinz U. Lemke, Hani Ashamalla and Smruti Mohanty

Abstract In the concluding Chapter, the proposed benefits of an Information Technology System for Predictive, Preventive and Personalized Medicine (ITS-PM) will be presented in the form of expert recommendations and outlook for Predictive, Preventive and Personalized Medicine (PPPM) and hepatocellular carcinoma (HCC). To advance PPPM, the subject of HCC will be presented from a more integrated point of view, combining epidemiology, risk factors, infectious etiologies, pathology, microenvironment and biomarkers, screening and diagnostic technologies, and treatment modalities (single, combined, and/or sequential). It is hoped that by means of an ITS-PM for HCC, greater emphasis may be given to individual patient characteristics than is currently achievable. It is also hoped that through extensions to current screening, staging, and treatment algorithms that we can improve the understanding, prevention, and treatment of HCC. Through the development of an ITS-PM, it may be possible to provide and validate a new methodology for Evidence-Based Medicine utilizing model theory, i.e. Model-Based Medical Evidence (MBME). The information processed in the development of this book was used to reinforce and expand a well-established treatment algorithm, i.e. the Barcelona Clinic Liver Cancer (BCLC) staging system, and, to add extensions that include enhanced screening and greater specifics regarding treatment selections. Finally, new algorithms are presented that relate to alternatives in palliative

L. Berliner (✉) · H. Ashamalla · S. Mohanty
Weill Medical College of Cornell University, New York, USA
e-mail: LeonardB23@AOL.com

L. Berliner · H. Ashamalla · S. Mohanty
New York Methodist Hospital, Brooklyn, NY, USA

H. U. Lemke
Technical University of Berlin, Berlin, Germany
e-mail: hulemke@cars-int.org

University of Southern California, Los Angeles, USA

H. Ashamalla
e-mail: hashamalla@gmail.com

S. Mohanty
e-mail: srm9006@nyp.org

L. Berliner, H. U. Lemke (eds.), *An Information Technology Framework for Predictive, Preventive and Personalised Medicine,* Advances in Predictive, Preventive and Personalised Medicine 8, DOI 10.1007/978-3-319-12166-6_13

treatments, down staging, and dealing with progression of disease. Treatments for HCC included in these algorithms include surgical resection, liver transplantation, percutaneous ablation, transarterial chemoembolization (TACE), local radiotherapy with Yttrium-90 microspheres, stereotactic body radiation therapy (SBRT), and systemic targeted therapy with the oral multikinase inhibitor, sorafenib.

Keywords Personalized medicine · Hepatocellular carcinoma · Algorithms · Screening · Staging · Information technology · Information technology system for predictive, preventive and personalized medicine (ITS-PM) · Model guided therapy · Digital patient model · Patient-specific model · Model-based medical evidence

13.1 Introduction

In this concluding Chapter, the proposed benefits of an Information Technology System for Predictive, Preventive and Personalized Medicine (ITS-PM) will be presented. As we review the current state of knowledge regarding hepatocellular carcinoma (HCC) and current recommendations regarding patient management, undoubtedly there is a role for Predictive, Preventive, and Personalized Medicine (PPPM) to assist in providing care according to best practices. Furthermore, when an ITS-PM has been created, the accompanying database structures and functions may provide tools for PPPM to advance the understanding and treatment of HCC beyond its current limits. This would include a Therapy Imaging and Model Management System (TIMMS), Patient-Specific Modeling and Model Guided Therapy (MGT) as described in previous Chapters.

To restate our position from Chap. 1, it is our hypothesis that if valid patient-specific models (PSMs) (that factor in age, physiologic condition, disease and comorbidities, genetics, biomarkers, and responses to previous treatments) can be generated, it may be possible to develop a statistically valid methodology, for each individual to predict certain diseases or conditions, to predict treatment outcomes, to prevent specific diseases or complications, and to develop treatment regimens that are personalized for each particular patient. This proposed system, currently under development, has been designated as Model-Based Medical Evidence (MBME). It is postulated to be able to make a major contribution to Evidence Based Medicine through the analysis of a large number of patients, with the assistance of Information Technology (IT). It is further postulated that the Multi-Entity Bayesian Networks (MEBN), used in the construction of the Digital Patient Model (DPM), will be utilized in the development of a practical decision support system.

Many studies are being conducted at clinical research centers to determine the most effective forms of treatment for HCC. However, the role of large random controlled clinical trials comparing a restricted number of variables may be of limited value considering the many treatment devices and regimens that are currently available, especially as new techniques and tools are introduced. In the current

environment, where there are so many old and new competing treatment options, it would appear that there are difficulties in applying the usual forms of Evidence Based Medicine. It may be that, in practice, treatment choices often depend on a combination of factors. These may include local expertise; the availability of treatment devices (which, in part, may depend on financial considerations); personal referral patterns; the presence of clinical research protocols involving a particular device; the collective opinions of local tumor boards; and patient preferences that may in part be based on recommendations of friends or opinions expressed on web sites and blogs. In this environment, with so many available treatment options and with so many gaps in medical information, it may be problematic to be able to determine and provide the most ideal form of therapy for each patient based on personal health characteristics.

As originally stated in Chaps. 1 and 2, it is our goal to utilize an IT approach to medical management to maximize the use of established medical information and to assist decision making and advance our understanding when there is incomplete medical knowledge. The approach we are offering, MBME, offers an alternative to evaluate the effectiveness of different treatment modalities, as well as the influence of individual patient responses. Each complete DPM developed through recruitment of patients in the clinical cancer center may be considered a comprehensive study subject. As the number of DPMs increase, the pooling of information will be utilized through the inference system to generate statistically valid medical information, or, MBME. The Bayesian approach we have selected that utilizes MEBNs, with first-order logic, provides a solid backbone of statistical validity. What will remain to be determined is how many individual patient models will have to be accumulated to achieve statistical validity.

Another feature of this approach that enhances PPPM is that rather than selecting a sufficiently large number of patients to minimize the impact of individual patient variation on the outcome, all relevant information regarding the unique features of each patient is preserved. Thus, when the number of patients included in the database reaches a critical level, it may be possible to not only predict the outcome of therapy by treatment modality (specific forms and combinations of ablation, radiation, chemotherapy, radiation therapy, and surgery) but it may be possible to determine the role of individual components of the patient's make-up that have contributed to the success or failure of the treatment.

13.2 Building on the Barcelona Clinic Liver Cancer Staging System

If we examine the Barcelona Clinic Liver Cancer (BCLC) Staging System for HCC [1, 2] (Fig. 13.1) that serves as the basis for the management of many patients with HCC worldwide, we observe a very well thought out and evidence-based approach to patient management. Clear recommendations have been made for the initial management of patients with HCC, according to a variety of factors: performance

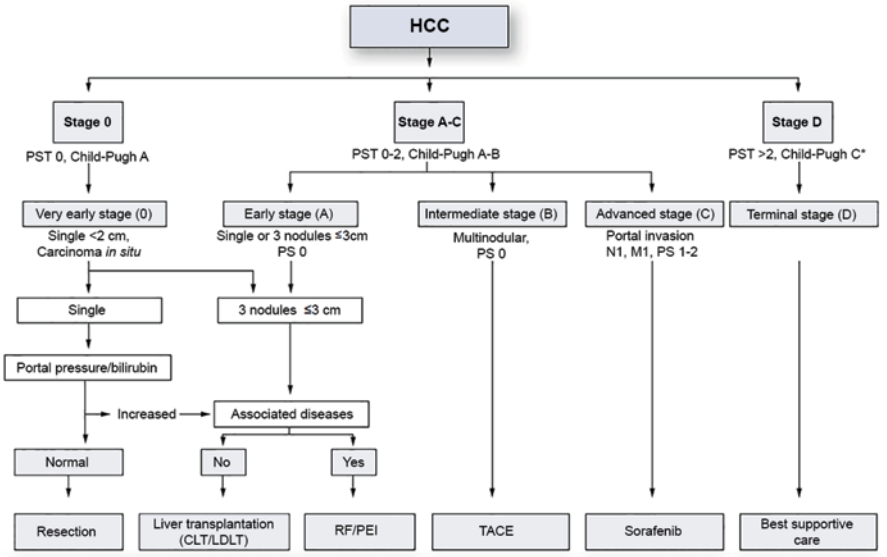

Fig. 13.1 The Barcelona Clinic Liver Cancer (BCLC) staging system algorithm for Hepatocellular Carcinoma—Revised 2011 [3]

status, Child-Pugh classification, lesion size and number, portal vein pressures, and the presence of tumor invasion, comorbidities, and extensive disease.

The BCLC Staging System Algorithm provides a flow chart that was designed for the staging of patients with HCC to determine the most appropriate form of therapy. In addition, we have found that the BCLC Algorithm provides an excellent platform for the development and investigation of extended treatment pathways. Ablation technologies that are currently available include radiofrequency ablation (RFA), microwave ablation (MW), cryoablation (CRYO), interstitial laser thermotherapy (ILT), and irreversible electroporation (IRE). Transarterial embolotherapy includes techniques that employ either oil-based materials or drug-eluting particles to deliver the chemotherapeutic agents (transarterial chemoembolization; TACE), as well as techniques for the catheter delivery of radiopharmaceuticles (Yttrium-90). Several different forms of radiation therapy are available as well. In addition to individual therapies, combinations of these techniques are also under investigation to control advanced disease and/or to down-stage more advanced disease so that the patient hopefully may become a candidate for a curative treatment.

The IEs identified in Chap. 12 may be used to expand and reinforce the BCLC Algorithm in several ways. Extensions may be added to the BCLC Algorithm (Fig. 13.2) that: (1) facilitate enhanced screening for HCC; (2) explore ways in which targeted therapies may be used to improve outcomes; and (3) provide statistically validated evidence regarding the selection of the best treatment from the many options available for palliative, down-staging and bridging therapies.

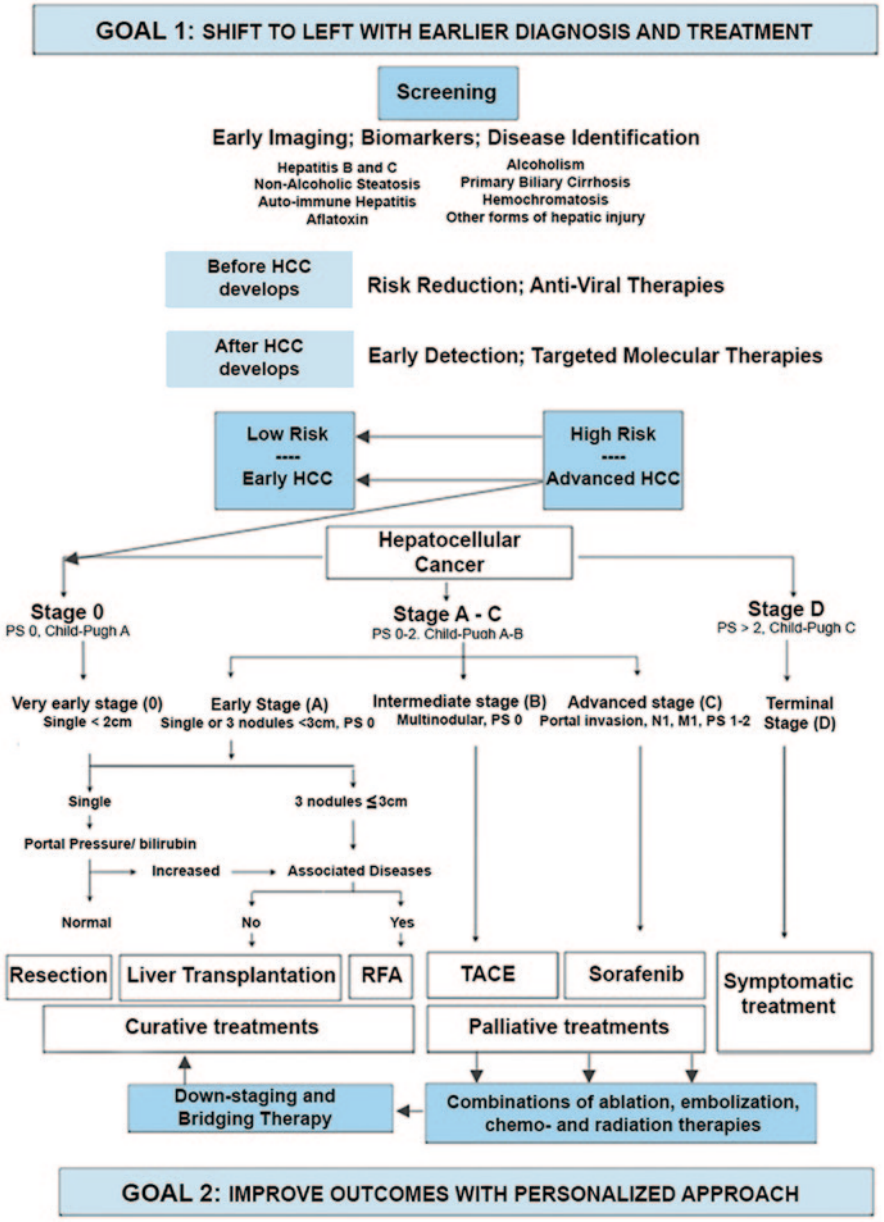

Fig. 13.2 It may be possible to build on the BLCL staging system algorithm with an IT system for predictive, preventive and personalized medicine (ITS-PM). The first goal will be, through enhanced screening, to have patients seek medical attention earlier in the course of their disease, so that they may enter the algorithm at a more favorable stage; i.e.—a "shift to the left". The second goal will be to improve outcomes through a better understanding of treatment subcategories, combined treatments, and the effects of down-staging. (Modified from [2])

13.2.1 Enhanced Screening and "Shift to the Left"

It may be possible to positively influence where in the BCLC Staging System a patient enters the algorithm. It would be desirable to achieve a "shift to the left" with a greater number of patients seeking medical attention at a stage of the disease when there is a greater chance of cure. As more data are accumulated it may become possible to evaluate current screening techniques and criteria, and to improve them in light of accumulated information, with the establishment of more comprehensive programs for earlier and more effective screening.

13.2.2 Possible Expanded Role of Targeted Therapies

Currently, targeted therapies for HCC are finding applications in patients with advanced disease. However, it may also be possible to expand the role of targeted therapies in the future to influence the development or progression of disease in earlier stages. It may even become possible to shift high risk patients into low risk categories, thereby averting the development of HCC altogether.

13.2.3 Improved Outcomes with Further Personalized Approach

The BCLC Staging System Algorithm is concerned primarily with the initial treatment choices for patients with HCC. While several treatment options are indicated for patients with intermediate and advanced disease, the complexities relating to these treatment options have not yet been developed within the context of the Algorithm (although these issues are discussed with elsewhere [1–3]). The ITS-PM may be employed to generate MBME to obtain a better understanding of role of locoregional treatment options, combined treatments, and the effectiveness of down-staging and/or bridging therapies to achieve improved outcomes. The Algorithm may be expanded to include, in greater detail, the currently available treatments for HCC, individually or in combination.

13.3 New Algorithms

New algorithms are presented here that address issues and patient selection relating to alternatives in palliative treatments and efforts to achieve down-staging. Currently available treatments for HCC included in these algorithms are surgical resection, liver transplantation, percutaneous ablation, TACE, radioembolization with Yttrium-90 [Y90] microspheres, stereotactic body radiation therapy (SBRT), and systemic targeted therapy with the oral multikinase inhibitor, sorafenib. In

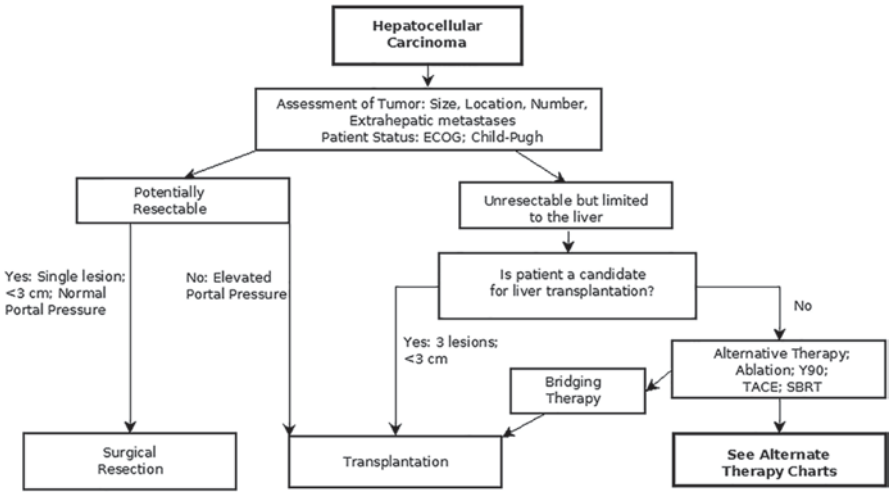

Fig. 13.3 A wider and more flexible assortment of alternative therapies and bridging therapies are introduced in this algorithm. This algorithm continues in Figs. 13.4 and 13.5 (Alternative therapy charts: single and multiple lesions)

accordance with the BCLC Staging System, the efficacy and safety of each treatment modality depends on the stage of liver disease, performance status of the patient, and severity of underlying liver disease.

Treatment algorithms are presented here (Figs. 13.3–13.5) that represent extensions to the BCLC Staging System algorithm by providing a flexible approach to alternative therapies and by introducing the possibility of down-staging and bridging therapy.

These algorithms present treatment pathways based on the current literature, and provide a framework for the accumulation of data regarding specific treatment protocols. The outcomes of these varied treatments can be linked to extensive data collected for each patient (according to the categories itemized in Figs. 12.5a, b, and 12.7 in Chap. 12) within the ITS-PM.

Conclusion

It is the goal of PPPM to identify the best diagnostic tests and treatment modalities objectively, given the patient's actual clinical status. We have presented an approach to advancing the care of patients with HCC, building on the well-established BCLC Staging System, by proposing extensions to include enhanced screening and a means to evaluate more specific treatment regimens. This approach will require the development of a comprehensive ITS-PM that will utilize a computing system for patient modeling and decision support.

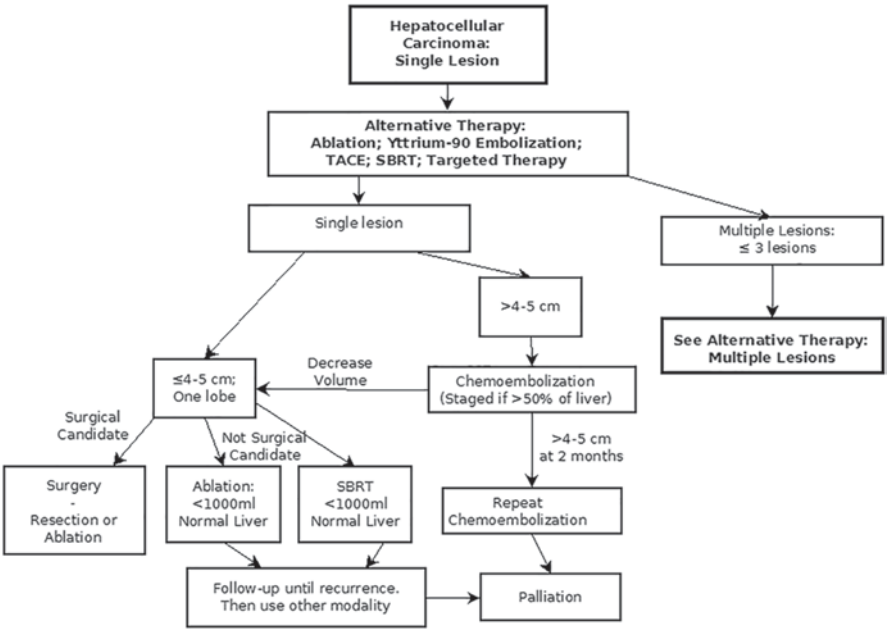

Fig. 13.4 Alternative therapy chart: single lesions

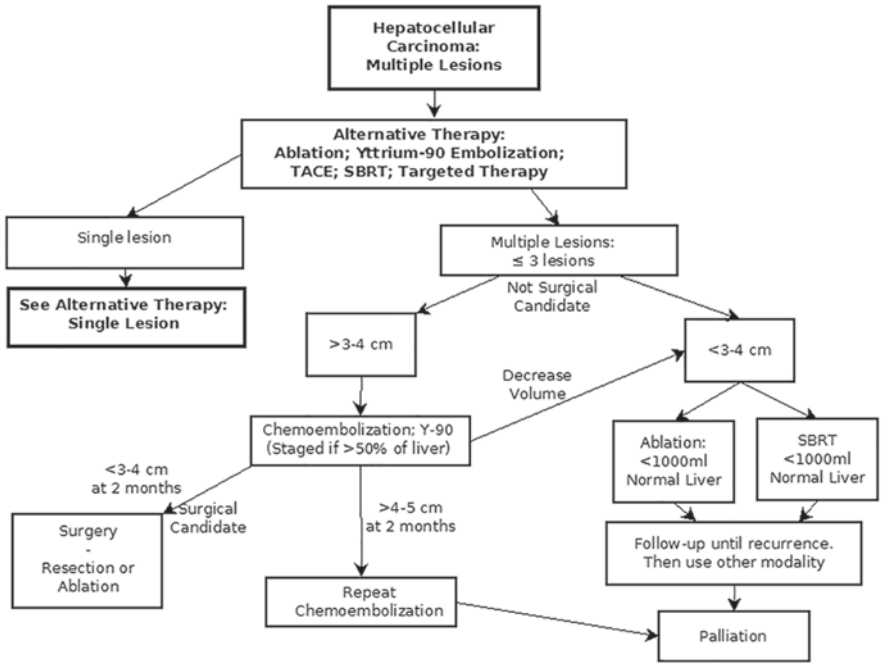

Fig. 13.5 Alternative therapy chart: multiple lesions

The ITS-PM system presented here is in its earliest stages of development, as is the DPM, which is the basic unit for this system. It is the goal of this project to develop a system of Bayesian inference built on large databases of individual patients that will provide a way of giving greater emphasis to individual patient characteristics in expanded patient screening programs and treatment algorithms.

The algorithms presented here, representing extensions to the BCLC Staging System, are based on literature review and current practices. They need to be validated through appropriate prospective clinical studies. In addition, if sufficient individual data regarding each patient are collected it may be possible to generate knowledge that is necessary for a more complete understanding of the pathophysiology, prevention, and treatment of HCC. This may be accomplished through the use of enhanced IT with modeling and inference techniques, thus creating a new methodology for Evidence-Based Medicine utilizing model theory, i.e. Model-Based Medical Evidence.

In addition, as more information is gathered and validated through the ITS-PM, target benchmarks for the effective treatment of hepatocellular carcinoma can be established. Comparative studies of the costs of different treatment protocols may be evaluated with respect to successes and failures in treatment outcomes, and with respect to overall quality of care and the patient's quality of life.

The tasks that lay before us in the immediate future include the development of the databases that incorporate patient-specific Information Entities (as described in Chap. 2 and itemized in Figs. 12.5a, b and 12.7 in Chap. 12) and the development of the MEBN and the associated decision support structures (as described in Chaps. 2 and 12). As these are populated with data from a growing number of patient records, DPMs will be developed. It will then become possible to begin the study and validation of Predictive, Preventive and Personalized Medicine through Model-Based Medical Evidence.

References

1. Bruix J, Sherman M (2010) AASLD Practice Guideline. Management of hepatocellular carcinoma. http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCCUpdate2010.pdf. Accessed 20 Nov 2011
2. Sherman M, Bruix J (2011) AASLD Practice Guideline. Management of hepatocellular carcinoma: an update. Hepatology 53:1020–1022
3. European Association for the Study of the Liver. European Organisation for Research and Treatment of Cancer (2012) EASL–EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 56:908–943

Index

L. Berliner, H. U. Lemke (eds.), *An Information Technology Framework for Predictive, Preventive and Personalised Medicine,* Advances in Predictive, Preventive and Personalised Medicine 8, DOI 10.1007/978-3-319-12166-6