Imaging in Clinical Oncology

Second Edition

Athanasios D. Gouliamos
John A. Andreou
Paris A. Kosmidis
Editors

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This book is dedicated to all cancer patients and their families.
We are grateful to our teachers and thankful to our staff.

Foreword

Biomedical imaging techniques play an essential and ever more increasing role in clinical oncology. Today, imaging is used in all phases of cancer management, including screening, image-guided biopsy, planning and guidance of treatment, assessment of therapy response, detection of recurrence, and even in palliative care patients, for whom minimally invasive interventional radiological techniques provide a valuable alternative to surgery.

During the last decade, the impact of imaging in cancer care has greatly expanded. Clinical oncologists rely increasingly on imaging information to make decisions about a patient. Specialists in oncological imaging have become trusted and highly valued members of the teams involved in tumor board reviews. It is now generally accepted that confrontation of the clinical, radiological, and pathological data is essential to establish a final diagnosis, to develop the management plan of a cancer patient, and to obtain follow-up of such a patient under treatment. The growing impact of imaging has been driven by technological improvements, which have provided new insights into the pathophysiology and behavior of tumors, by combining morphological, functional, and molecular techniques. There is no doubt that imaging constitutes a cornerstone in oncological research and patient management.

Traditionally, the role of imaging in cancer management has been mainly focused on screening and disease management, i.e., diagnosis and staging, treatment monitoring and follow-up. But, as the expression goes, there is much more than meets the eye. The term "*radiomics*" has been coined to describe the process of extracting quantitative features from medical imaging data of tumor phenotypes, by applying advanced data-mining and characterization algorithms. Such methods can potentially disclose tumor characteristics that are not seen, or at least not recognized, by the naked eye. The term "*radiogenomics*" refers to the correlation between imaging features and the underlying gene-expression patterns. Thanks to ongoing technological advances, imaging has gained a foothold in presymptomatic risk assessment (discovering a genetic predisposition to a certain disease through molecular diagnostics). Targeted imaging of receptors on tumor cells and the study of gene therapy expression are being introduced into clinical medicine. A completely different, but no less important, direction in imaging research is the rapid evolution of image-guided and targeted minimally invasive procedures, as an alternative to open surgery. Such imaging-guided therapy holds great promise to reduce complications and collateral effects of cancer treatment and eventually to improve patient outcome.

Screening examinations are performed in asymptomatic individuals for early detection of cancer, at a stage where it is easier to treat and potentially cure the disease. Early diagnosis of cancer through screening, based on imaging, offers the best hope to reduce the human and financial burden of cancer management and is a major contributor to a reduction in mortality for certain cancers. Different imaging techniques can be applied to screen for different types of cancer. Traditional examples of imaging-based screening include detection of breast cancer with mammography or of lung cancer with CT scans of the thorax. *Computer-aided detection/diagnosis* (CAD) has been successfully applied to improve lesion detection, for example in discovering breast cancer in digital mammography examinations. *Artificial intelligence* (AI) methods can extract volumetric and contrast enhancement features from imaging data sets in different types of cancer. There is hope that the development of specific imaging biomarkers to identify the presence of cancer will open the door to molecular diagnostics, thus heralding a new era in screening.

Once a cancer has been detected, the information derived from clinical imaging studies becomes essential to establish a certain *diagnosis*. Though pathology remains the gold standard ("the issue is tissue"), imaging studies are an essential part of the diagnostic work-up of the patient. Moreover, image-guided biopsy offers a good way to obtain tissue samples in a safe and minimally invasive way.

Staging is needed to gain information about how advanced the cancer is. Accurate staging is the cornerstone to determine treatment options and predict the prognosis. Staging involves looking at the primary tumor, the lymph nodes, and distant metastases in other organs. This is the so-called TNM classification system (tumor—nodes—metastasis). Imaging techniques allow us to perform a focused, noninvasive exploration of those organs in the human body where we know that cancer cells will thrive.

In recent years, treatment of cancer has made a giant leap forward. Thus, since more patients survive, it becomes ever more important to *assess the response to treatment*. Imaging can inform us whether there is a change in the tumor burden. The most commonly used imaging response assessment tool for solid tumors is the Response Evaluation Criteria in Solid Tumors (RECIST). RECIST recognizes four categories of response: complete response (i.e., complete disappearance of the target lesions); partial response (i.e., a 30% decrease in the sum of the target lesions); progressive disease (i.e., a 20% increase in the sum of the target lesions); and stable disease (i.e., smaller changes that don't quite meet any of the above criteria). The RECIST guidelines rely on comparison of the baseline scan with the images after treatment (i.e., surgery, radiation, chemotherapy). Unfortunately, the concept of using relatively crude measurements to monitor the tumor (e.g., longest diameter of a mass, or approximate appraisal of the tumor volume) is inadequate; such visual comparisons can only indicate a delayed response to therapy and hold no information about the metabolism, vascularization, cell density, or other parameters of the tumor. This has led researchers to develop *quantitative imaging biomarkers* to accurately monitor changes in tumor volume and structure, angiogenesis and vascularization (perfusion imaging),

biochemical composition (MR spectroscopy), cell proliferation (diffusion weighted imaging), microscopic environment (diffusion tensor imaging), and metabolism (PET, SPECT). The inherent limitations of traditional imaging methods have led to the development of *hybrid imaging* techniques, such as PET-CT or PET-MR, which combine the metabolic sensitivity of nuclear medicine with the spatial and temporal resolution of radiological methods, such as CT or MRI.

Monitoring and *follow-up* refer to the process of following a patient after successful eradication of a tumor. Imaging studies are performed at regular intervals to monitor therapy response and screen the patient for detection of tumor relapse. The great advantage of imaging is that it can provide essential information without tissue destruction, in a noninvasive (or minimally invasive) way, over wide ranges of time. The biggest challenge here is to standardize imaging methodology, so that the technical parameters between baseline and follow-up studies are kept identical, to allow accurate comparisons.

The growing importance of imaging in cancer management has created new opportunities for the radiologist, but also new challenges. In order to function in a multidisciplinary cancer environment, the radiologist must understand and speak the language of the clinicians, and needs to acquire more clinical background knowledge in the field of oncology. At the same time, the imaging specialist should also have a profound understanding of tumor pathophysiology and how different characteristics of a tumor are reflected in morphological, structural, metabolic, and functional imaging studies. Together with oncologists, pathologists, surgeons, radiation therapists, and many other specialists, radiologists and nuclear medicine physicians are an essential part of the tumor board, to assist in the multidisciplinary decision-making on patients with cancer.

On a personal note, I am indebted to the editors of this book, my Greek friends Athanasios D. Gouliamos, John Andreou, and Paris A. Kosmidis, for giving me the opportunity to write this foreword. It is a great honor and a privilege to be invited; I'm very happy to oblige and to write this modest contribution. The editors have pooled their combined experience, wisdom, and skill to create a kaleidoscopic overview of the role of imaging in clinical oncology. They have managed to successfully aggregate an "all-star" team of distinguished authors, to cover a wide range of biomedical imaging techniques, in a variety of tumor types, including all phases of cancer management. The individual chapters in this book are well written and superbly illustrated; this greatly facilitates the task of the reader to comprehend this complex subject matter. Careful attention is given to the concepts that are crucial in understanding modern "multimodality," "multiparametric," and "hybrid" imaging techniques. Integration of different kinds of imaging technology helps the reader to better understand the pathophysiology of tumors and provides complementary information for improved staging and therapy planning. The information in this book is presented in a logical and straightforward manner, thus offering an enjoyable learning experience. I am convinced that *Imaging in Clinical Oncology* will become a standard textbook, useful not only to imaging specialists (including radiologists, nuclear medicine

physicians, and radiation therapists) but also to all clinicians with an interest in oncology. Close multidisciplinary collaboration, within a well-trained and experienced team, is the cornerstone in the management and care of oncological patients; and, as this book eloquently illustrates, imaging holds the key to success in the screening, detection, staging, treatment monitoring, and follow-up of patients with cancer.

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Preface

This new edition features many exciting changes since the first edition, published in 2013. Four new chapters are included while some of the original chapters have additional contributors. One of the new chapters covers the role of radiogenomics in oncologic imaging. Three new chapters elucidate multiple myeloma. Chapters on lymphomas have been extensively revised by the same authors who participated in the book *PET/CT in Lymphomas: A Case-Based Atlas*, published in 2015.

The new edition of *Imaging in Clinical Oncology* is divided in 20 parts. The first part covers a general approach to molecular imaging in oncology, imaging criteria for treatment response evaluation, imaging in radiation therapy, interventional radiology in oncology, imaging principles in pediatric oncology, and the role of radiogenomics in oncologic imaging. In the following 19 parts, the main types of cancers are addressed in different chapters and organized by organ systems (bone and soft tissue tumors, CNS tumors, head and neck tumors, lung cancer, breast cancer, gynecologic cancer, gastrointestinal cancer, neuroendocrine tumors, urogenital cancer, lymphomas, multiple myeloma, and melanoma).

The aim of this book is to promote the understanding between radiologists and clinical oncologists, presenting all the currently available imaging modalities and covering a broad spectrum of oncologic diseases from most organ systems. In each chapter the clinical oncologist begins with a brief introduction of each type of tumor. All relevant conventional and advanced imaging techniques and technologies of ultrasound, MRI, CT, and PET are then addressed by radiologists and nuclear medicine experts in their respective fields. Finally, the clinical oncologist provides a critical analysis of the treatment implications, usefulness, sequence, and combination of the imaging studies presented. Quantitative imaging data combined with laboratory biomarkers can help the clinical oncologist to recognize at the earliest possible time whether the applied treatment is ineffective so that therapy can be modified.

Incorporation of new data has not changed our initial aim to keep the content of this book as compact as possible. It is hoped that practitioners and

residents in radiology, nuclear medicine, clinical oncology, hematology, radiotherapy, and other specialties involved in cancer management will find this a true companion in their daily practice.

Athens, Greece — Athanasios D. Gouliamos
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We would also like to thank Ioanna Konti for her secretarial assistance.

Contents

Part I

Introductory

1 Molecular Imaging in Oncology: Hybrid Imaging and Personalized Therapy of Cancer

George N. Sfakianakis

(Diagnosis—Staging—Response to Therapy—Restaging of the Tumors).

1.1 Introduction

It has been proposed that the "telomeres" of the chromosomes, their four endpoints, determine our future: Harbingers of mortality, the telomeres at the chromosome tips glow brightly with appropriate color dying; they influence vulnerability, mortality, longevity, and survival. The longer the telomeres, the longer the person lives. If their length decreases, the person dies sooner. However, the utilization of telomeres in clinical practice for patient evaluation is still in the distant future. At the present time, we can report that substantial advances have recently been achieved with the applications of **molecular imaging (MI)** in the evaluation of oncologic patients.

1.1.1 Molecular Imaging: The Principle and Its Historical Development

In searching recent literature, one will find many definitions of molecular imaging (MI).

Sanjiv S. Gambhir, one of the leading experts on this topic, defines MI as follows [1]:

> MI of living subjects is an Emerging Field that aims to study molecular and cellular events in the intact living animal and human. These events can be as simple as location(s) of a specific population of cells or levels of a given protein receptor on the surface of cells (or) more complex events, such as the interaction of two intracellular proteins, cellular metabolic flux, or transcription of a set of genes when a cell type comes into contact with another cell type.

Other definitions stress the point that MI is not just an emerging field but a new field:

> MI is a New Field of Imaging, which includes the following:
>
> - Clinical Multimodality MI with Molecular Probes
> - Laboratory Cellular and Molecular Biology and Research
> - Chemistry/Pharmacology for Molecular Probes
> - Medical Physics for MI
> - New Biomathematics/Bioinformation/Biomechanics [2].

However, based on our knowledge and experience, the correct definition of MI ought to be:

"MI is a New Name for an Old Imaging Field," because in nuclear medicine (NM), we were practicing MI since the beginnings of the NM Specialty.

In his new book, *A Personal History of Nuclear Medicine*, Henry N. Wagner Jr., a NM guru, specifies in the introduction: "…MI had been the hallmark of Nuclear Medicine since its beginning" and later "The tracer principle was invented in 1913 by George Hevesy" [3].

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1.2 General Methods of Molecular Imaging

MI promises significant progress in the clinical practice of oncology. It is usually performed after injecting the patient with a **molecular probe** (the **tracer**, or **biomarker**), a biologic molecule, most of the time labeled with a radioactive atom (e.g., ^{99m}Tc or ^{18}F, etc.). This probe is selected after detailed biological research of the target to be studied (normal cells or abnormal cells, e.g., cancer cells) and helps to study molecular events by participating in the molecular reactions taking place within that target cell. The probe, like a natural molecule, participates in the biological functions of the studied cells, but having been carefully and purposefully chemically altered before injection, it is not fully metabolized, like the physiologic molecules it mimics, but, instead, it finally accumulates within the cells under study and leads finally to MI, when its concentration is high enough, by utilizing the radioactive decay of its radioactive labels.

MI of living organisms is an expanding field, which by using specific harmless biologically active molecular indicators, as explained above, tries to study specific molecular and cellular functions with imaging of normal or abnormal tissues, in living humans or animals, without danger, as well as in cell cultures. Thus, sensitivity and specificity of imaging are substantially improved, and discovery of molecular characteristics of tumors and their sensitivities to drugs is enabled to improve results of diagnosis and eventually therapy of cancers.

1.2.1 External Probes

Most applications of MI are based on the introduction into the body of a living organism (usually intravenously) of a molecular probe (the biologic marker or biomarker), usually a radiolabeled diagnostic molecule of great biologic significance for the case. This probe is specifically selected to react biologically with the target (tumor, etc.), to accumulate within the target cells at higher quantities than in the normal cells and, since it is (radio)-labeled, to allow the MI of the target with the current imaging equipment.

This probe must not have a pharmacologic effect on the living organism, and, of course, it must not be toxic in either the acute or chronic phase.

The external probes, prior to injection, undergo specific chemical modification of their molecules. These specific modifications maintain the useful properties of the probes while altering them in such ways that they are not completely metabolized and they accumulate locally, thus allowing imaging. The external probes are also labeled. There are different methods of labeling these molecules; therefore there are different methods of MI: radioisotopes = nuclear studies, magnetic = MRI, and light = optical.

After their injection, the modified and labeled external probes enter the metabolism/function of the cell and participate to the point the modification allows, with imaging performed at the most appropriate time point for MI techniques.

1.2.2 Internal Probes

These are normal or pathologic molecules in the body that may be imaged in vivo utilizing their magnetic or other properties or properties of the cells that carry them (fMRI, optical, etc.).

The selection and the study of the diagnostic molecular probes currently constitute the most important effort in research for MI and cancer therapy.

1.3 Clinical Applications of Molecular Imaging

1.3.1 Traditional Clinical Applications of MI

Single Photon and **Positron Imaging** in Oncology (Planar and Tomographic, SPECT and PET)

As mentioned above MI has been applied in oncology since the advent of nuclear medicine, first utilizing **rectilinear scanners** and later **gamma cameras** for planar and tomographic studies and eventually **positron emission tomography (PET)**. Some work had also been done with MRI. For the nuclear studies, the probes are external, for the fMRI usually internal. Characteristic examples are shown in Figs. 1.1, 1.2, and 1.3.

1.3.2 Current Clinical Applications of MI

Multifunctional/Multimodality/Hybrid Imaging in Oncology (PET/CT, SPECT/CT, PET/MRI, SPECT/MRI, fMRI, etc.)

The old in vivo imaging methods (X-rays/US/MRI) are based on imaging differences in water content and differences in tissue densities

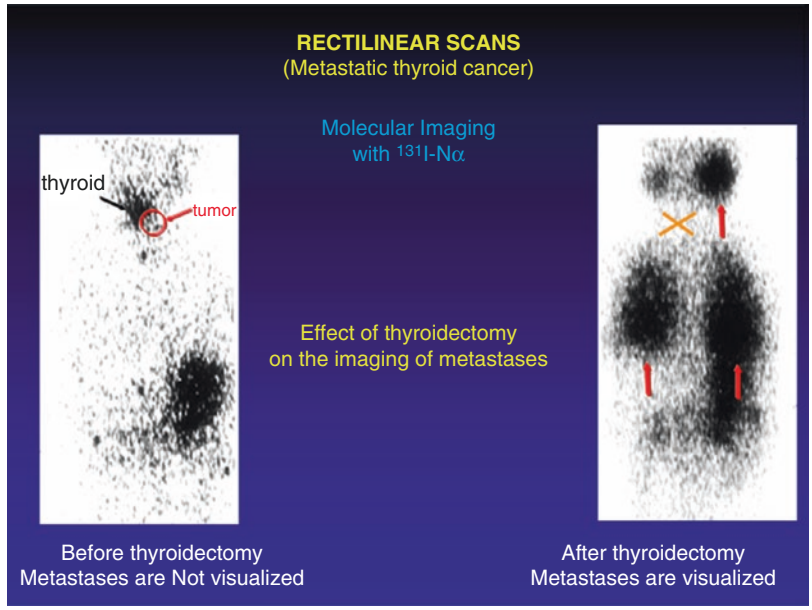

Fig. 1.1 Rectilinear scans for metastatic thyroid cancer with ^{131}I–Na. The studies were performed before and after thyroidectomy to evaluate for metastasis

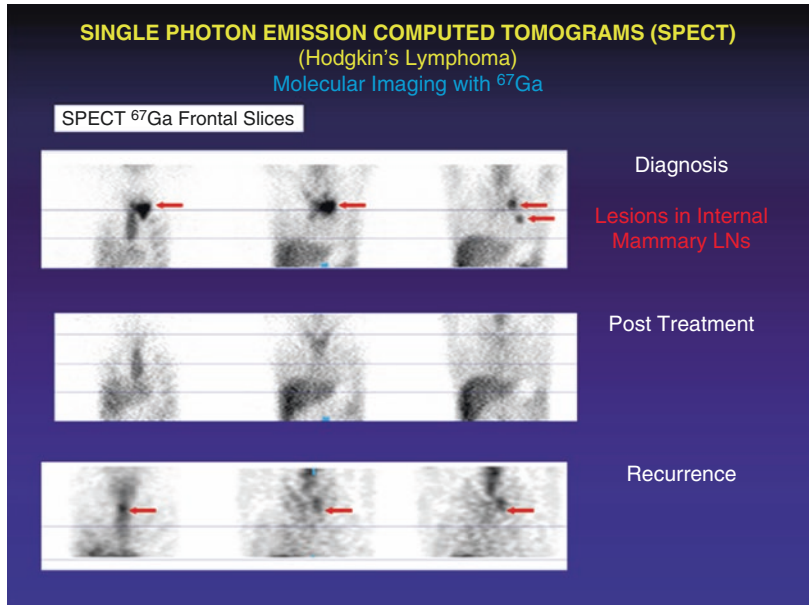

Fig. 1.2 SPECT studies with ^{67}Ga citrate in Hodgkin's lymphoma, coronal views. The studies were performed for diagnosis, for treatment effect, and for recurrence

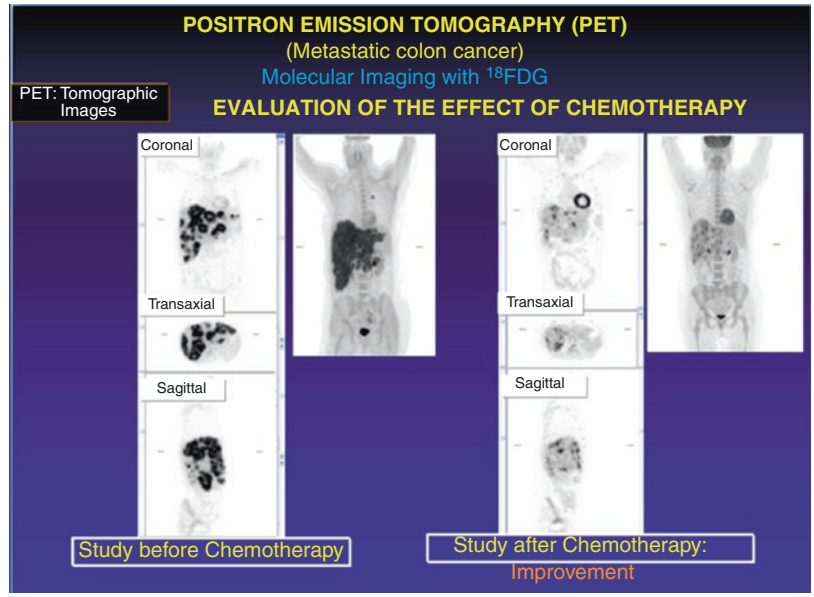

Fig. 1.3 FDG-PET studies in metastatic colon cancer. The studies were performed before and after partially effective therapy of lesions in the liver and lungs

or magnetic properties of body tissues and tumors. They were amplified by contrast enhancement and tomography (CT), and they provide excellent anatomical images of the body and its anomalies and diseases including tumors.

Molecular imaging begins with molecular biology, that is, the study and understanding of the biological problem to be evaluated (e.g., the study of tumors). This is followed by the selection, development, and production of the **probes**, the biologic markers. The new MI utilizes these probes for studies in vitro or in vivo (PET-SPECT-fMRI-Optical).

Despite the fact that clinically MI provides very useful information, on its own it is suboptimal in identifying the anatomic localization of the lesions. This generated the multimodality imaging.

A multimodality (hybrid) imaging perspective, that is, the combination of the old and the new imaging methods by simultaneously or sequentially performing MI and CT or MRI, is currently used to identify the exact location of the accumulation of the molecular probes (PET/CT, SPECT/CT, PET/MRI, etc.). This approach improves the diagnosis, staging, treatment response, and restaging, by providing excellent anatomical localization of the PET findings.

Although molecular and hybrid imaging can be applied to study many benign conditions, their most common clinical application is the study of malignant tumors.

Contemporary Hybrid Imaging of Cancer

1. **Morphologic Characteristics of Tumors**

The old imaging of tumors (X-rays/CT-US-MRI) is based on their size and X-ray attenuation: masses of a specified size, orthotopic or ectopic, and destructive of organs in their vicinity.

2. **Molecular Characteristics of Cancer Cells**

MI is based on molecular/biologic characteristics of the tumors as follows:

(a) Blood flow: ^{15}O-water
(b) Metabolism: metabolism of glucose (^{18}FDG-PET) and other metabolic molecules
(c) Proliferation: ^{11}C-thymidine
(d) Hypoxia: ^{18}F-FMISO
(e) Angiogenesis: ^{18}F-Galacto-RGD
(f) Receptor binding: somatostatin, PSA, transporter imaging of cerebral cells (^{18}F-DOPA)

(g) Specific atom or molecule binding iodine ^{131}INa, ^{123}INa, ^{124}INa
(h) Mitochondrial binding ^{201}Thallium/^{99m}Tc-Agents/^{82}Rubidium/^{67}Gallium
(i) Tumor antigen binding in receptors (antibodies)
(j) Senile plaques ^{18}F-FDDNP
(k) Gene expression: ^{18}F-FHBG

In clinical practice PET and SPECT were initially compared with CTs acquired at different times using the "side-by-side" approach (Fig. 1.4). The "multimodality imaging" or "hybrid imaging" emerged later, and it is currently utilized for both PET/CT (Fig. 1.5) and SPECT/CT (Fig. 1.6), and it is advancing for the PET/MRI and SPECT/MRI.

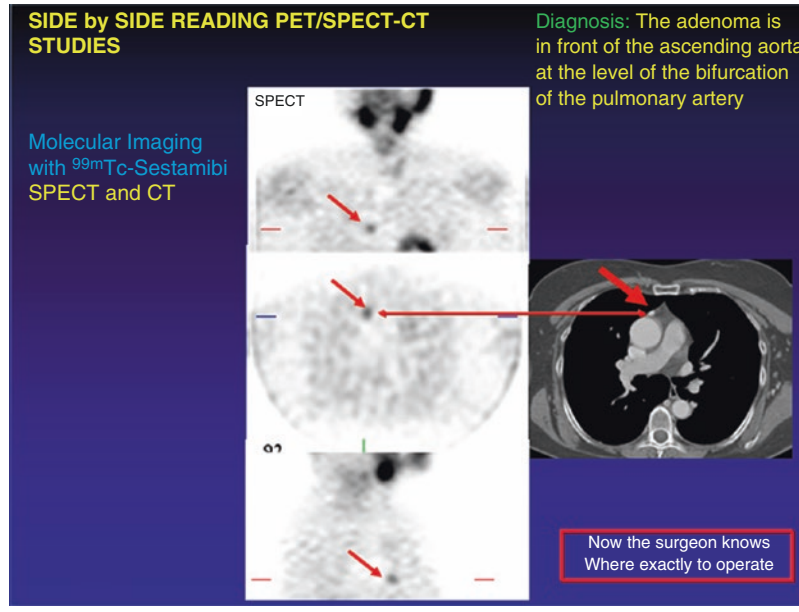

Fig. 1.4 SPECT and CT studies of benign parathyroid ectopic tumor. The studies were acquired separately and interpreted SIDE by SIDE

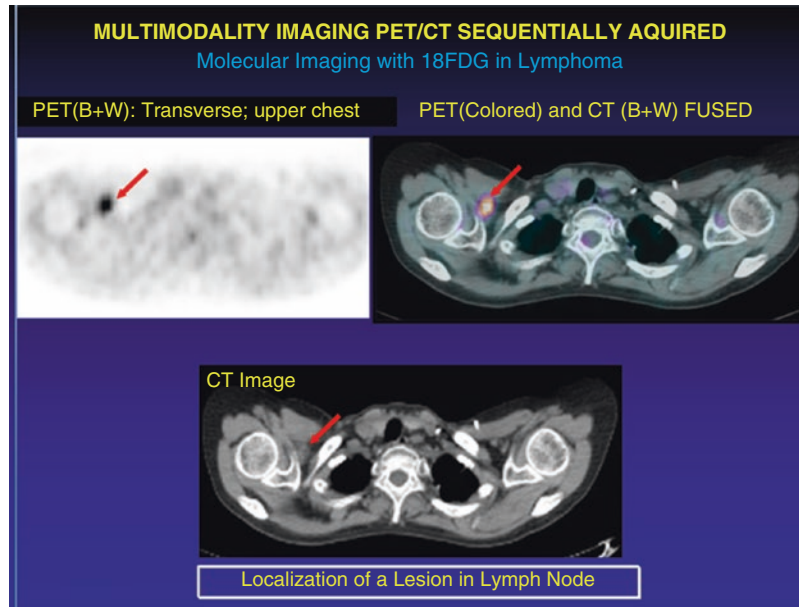

Fig. 1.5 PET/CT studies, multimodality imaging, of malignant tumor (lymphoma). This study enabled the characterization of activity (right axilla) as due to an abnormal, enlarged (lymphomatous) lymph node

The selection of the probe for MI is based on the molecular characteristics of tumor cells.

A more detailed table of probes is in the Seminars in Nuclear Medicine July 2011 [4].

1.3.3 Personalized Therapy of Cancer [5]

Cancer as a Genomic Problem

Cancer is a DNA aberration, a gene mutation, which leads to the genesis of the cancer cell. Same histologic tumors may be the result of different gene mutations. In the same tumor, there may originally be multiple aberrations, and multiple gene mutations, which may lead to genomic differences in primary tumors of the same histology. There can also be tumor genomic changes later in the history of the specific tumor, additional gene mutations, as the tumor increases in size, metastasizes, or is treated. These may lead to:

(a) Differences in tumor cell genomics in extensions of the (same) tumor in the same or other parts of the body
(b) Differences in genomics of metastases of same tumor to different organs
(c) Differences in genomics of tumors as a result of therapy

Differences in cancer genomics lead to therapy issues, such that patients with the same histologic cancer may need different therapy and patients responding to therapy originally may need to change therapy for additional treatments (if there is another medicine now or discovered later).

Current Therapeutic Issues of Cancer

MI in clinical oncology progressed from the simple SPECT, PET, and fMRI to hybrid imaging (SPECT/CT, PET/CT, PET/MR, etc.), which improved substantially sensitivity and specificity of imaging tumors. However, at present oncology faces important therapeutic problems, which demand further advances in MI and the other diagnostic tests. These issues include the following:

(a) Most histologic types of cancer cannot be treated successfully.
(b) The responses of patients with the same histologic cancer to the same therapy differ.
(c) Histology by itself cannot foresee the response of the neoplasms to treatment or retreatment.

Potential solutions for these problems include the following:

(a) Continuing research for new effective therapeutic medications for cancers in general.
(b) The development of cancer genomics and new biomarkers for in vitro/vivo tumor analysis to find explanations for the differences in response to therapy of the same histologic types of tumors in different patients and in the same person/tumor.
(c) This requires the development of **personalized therapy** for same/different cancers.

Personalized Cancer Therapy (PCT)

Personalized therapy was described by Sir William Osler in 1892. The current ideal is "right drug and right dose, for the right patient, the first time of therapy." The understanding of tumor biology and genomics indicates that tumors are heterogeneous: "No one size fits all." Patients with the same histologic diagnosis are not the same, and the same histologic tumors cannot be treated as a single disease. The M.D. Anderson Hospital Research Experience [5] is important, as they created and built a Center for Personalized Cancer Therapy and they try to finance its function, but they foresee many difficulties.

They applied successful targeted therapies based on specific genetic aberrations that require targeted therapies: the general current basic concept is that since therapy depends on the exact molecular characteristics of the tumor, or its metastasis, as analyzed above, molecular profiling must be repeatedly performed before each therapy [6]. Tissue availability for biomarker discovery leads to core needle biopsy

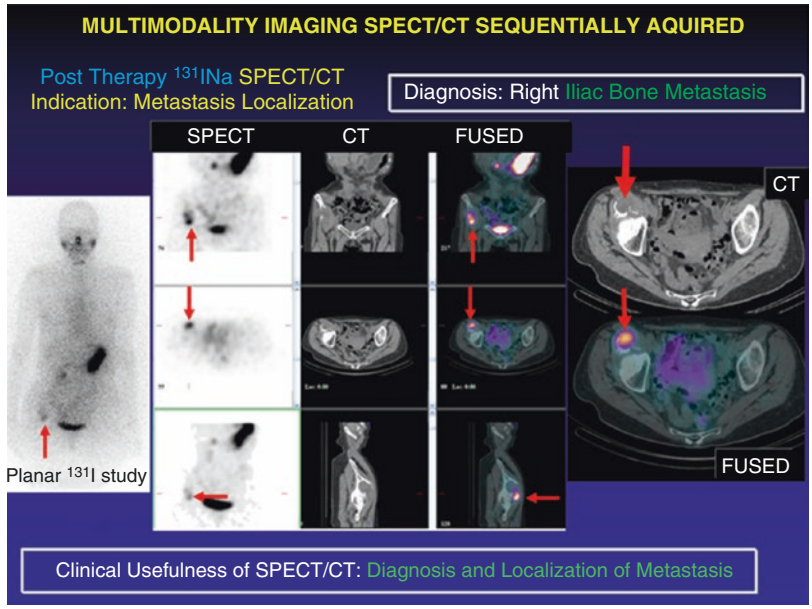

Fig. 1.6 SPECT/CT studies, multimodality imaging of malignant metastatic thyroid tumor. This study enabled the localization of metastasis in the iliac bone

(CNB) of the primary tumor for molecular profiling, before deciding on the type of therapy. CNB is repeated for the metastases and if there is progression of the tumor after the original treatment. Certainly there is a need to verify with biomarkers the uniform existence inside the tumor and its metastasis of the molecular profiling as well as its uniform persistence in vivo. This is usually performed with MI. For this reason it is necessary to develop agents for specific biomarker imaging.

Personalized Cancer Therapy Requirements

Cancer centers should develop and repeatedly offer to their patients the following applications:

(a) The ability to perform and obtain the diagnosis of the genomic characteristics of cancer cells, originally and repeatedly
(b) To be able to verify with biomarkers their uniform existence inside the tumor and their uniform persistence in vivo (MI)

This way personalized therapy of cancers of the same histology will develop, and (due to differences in tumor cell genomics in the same cancer, even in the same patient) repeated treatments of the same histologic cancer may need to be different.

On the basis of the above, the following should be developed:

(a) Establish the clinical necessity for personalized therapy.
(b) Discover biomarkers for in vitro/in vivo MI.
(c) Integrate imaging (PET-SPECT/CT-MRI, other)

Tasks for Molecular and Hybrid Imaging

The effort should commence by identifying the differences in tumor DNA in patients with the same histologic tumor and between the primary and metastatic tumors and tumor posttherapies in each individual patient and by studying the genomics of multiple biopsies of the tumors. Next it should be found how these differences in genomics are expressed as molecular/cellular structural/functional characteristics of the cells of the tumor in each biopsy

(a) Membrane receptor specific characteristics
(b) Nucleus different structure/functions
(c) Protoplasm protein characteristics
(d) Organelle specific activators or suppressors

Probes should be developed to study those differences, first in vitro and later in vivo with MI.

Research should be performed for effective therapies, which can be preselected with the probes and MI, for the primary tumor and for metastases.

Finally, for clinical and financial reasons, it should be proven that these therapies are preferable to traditional cancer treatments.

Current Experience in Applying PCT

The experience in clinical practice regarding PCT is thus far good but not very impressive. Very little progress has been achieved in identifying individual patient tumor genomics, and only a small number of patients have so far benefited from PCT.

However, PCT is promising and needs support and continuing research. It has great potential in the therapy of many types of cancer, yet many promising drugs have produced disappointing results. There are many challenges that must be addressed to advance the field. There are proposals for future trials:

1. Perform clinical trials requiring biopsies to obtain relevant tumor specimens for tumor genomic findings.
2. Adapt novel statistical designs.
3. Develop appropriate biomarkers (BMs, i.e., probes) to help guide the selection of the best treatment for each case with MI or other approach.
4. Go beyond BMs based on single mutations:
   (a) Use BMs based on gene expression or protein expression signatures.
   (b) Use new imaging technologies for new improved BMs.
   (c) Resolve existing challenges impeding the rapid identification and translation of validated BMs with clinically acceptable sensitivity and specificity, from the in vitro laboratory to the clinic (human trials, MI), like limitations of current BM development methodologies and regulatory and reimbursement (funding) policies and practices.

Current Specific Studies in Applying PCT

Clinical research and experience using PET-SPECT/CT-MRI imaging with radiolabeled old and new biomarkers are currently active [7], including the following:

1. Membrane receptor-based imaging
2. Glucose metabolism
3. DNA synthesis
4. Hypoxia
5. Integrins

Future Directions

There are hopes, expectations, and progresses to emerge from these efforts but also new and unforeseen problems.

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2 Imaging Criteria for Tumor Treatment Response Evaluation

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The evaluation of the tumor response to therapy represents a significant and continuously expanding part of the radiological practice, especially in services with oncological departments. The modern imaging modalities are valuable tools for objective quantitative assessment of the result of new antineoplastic therapeutic schemes. The standardization of criteria provides common endpoints for clinical trials, permits comparisons between different studies, facilitates the formation of more effective therapies, and accelerates the procedure of approval of new drugs by the authorized organizations. The most widely used imaging criterion of a successful therapy is the shrinkage of the neoplastic lesions in a certain patient. It represents the typical endpoint in phase II trials, targeted to the preliminary evaluation of the effectiveness of new antineoplastic drugs in order to decide if these have to be further tested in wider clinical studies. Also, the objective criterion of "tumor shrinkage" and the duration of "progression free survival" (PFS) represent the commonest endpoints for phase III clinical trials, aiming to assess the benefit of applying one or more therapeutic schemes in specific patient populations.

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In parallel, the degree of shrinkage of the total tumor burden is widely used in the routine oncological practice in order to assess the therapeutic result in every patient and guide decisions for further clinical management. However, it has to be noted that the most important proof of an effective antineoplastic therapy is the improvement of clinical symptoms and overall survival.

2.1 The Response Evaluation Criteria of the World Health Organization

The first organized attempt for introducing standardized criteria for assessing tumor response, mostly for use in phase II trials, appeared in 1981 through a working group of experts under the auspices of the World Health Organization (WHO). According to the methodology proposed by the "WHO guidelines," in a patient with neoplastic disease, the maximum diameter and the greater diameter perpendicular to the previous had to be measured on each neoplastic lesion, providing a numeric product. The sum of the products of all the neoplastic lesions represents the objective criterion of the measurable tumor burden, and its changes during and at the end of therapy permit the assessment of tumor response [1].

During the following two decades, the WHO criteria were adopted by many research groups

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and pharmaceutical companies and used in numerous phase II and III trials. However, the remarks that arose from their use and the wide application of new imaging modalities imposed the need for modifications, in order to overcome some imperfections and ambiguities of the initial guidelines. An international working group of experts was constituted in 1994, in order to reevaluate and modify the WHO criteria.

2.2 The Response Evaluation Criteria in Solid Tumors

Based on the proposals of the previously mentioned working group, finally the WHO, the National Cancer Institute of the USA and the European Organization for the Research and Therapy of Cancer (EORTC), adopted in 2000 new guidelines, named Response Evaluation Criteria in Solid Tumors (RECIST) [2]. They incorporated the use of new imaging technologies that have appeared, matured, and gained wide clinical application, such as spiral computed tomography (CT) and magnetic resonance imaging (MRI).

With RECIST, the terms of "measurable" and "nonmeasurable" disease were more clearly defined. Also, the procedure for selecting the most representative neoplastic lesions that have to be measured and followed ("target lesions") was better described. Specifically, it was defined that the "target lesions" must be selected among the largest, be representative of all the organs affected by the neoplasia, and should not be more than ten in total and five per organ. The measurement of the size of "target lesions" was simplified, by taking into account only the greater transverse diameter of each lesion and not the product of two perpendicular diameters as with WHO criteria. Additionally, the term of "nontarget lesions" was introduced, and the way of evaluating their changes was described. Finally, the methodology of assessing the "overall response" to therapy was more clearly defined.

The RECIST has been widely adopted by academic institutions, medical research groups, and pharmaceutical companies and was applied in trials where the main endpoints were the "objective response to therapy" or the "time to progression" of the disease. The simplification of the measurement methodology did not seem to influence the reliability of RECIST, compared to WHO criteria. However, together with the wider acceptance and application of RECIST, problems and imperfections were noted regarding their use for evaluation of specific neoplasms, such as pleural mesothelioma and tumors of childhood. Also, the decrease of the number of target lesions, the evaluation of abnormally enlarged lymph nodes, the substitution of unidimensional by three-dimensional (3D) measurement, and the incorporation of newer imaging modalities (providing molecular and "functional" imaging) were proposed.

In order to address all these issues, a new RECIST working group was constituted, including clinical doctors experienced in the development and evaluation of new drugs, representing academic sites, state health organizations, and the pharmaceutical industry, together with imaging specialists and statisticians. The group evaluated the database of EORTC, including more than 6500 patients with more than 18,000 target lesions, and its work resulted in the first revision of RECIST 1.1, published in 2009.

2.3 The Revision 1.1 of RECIST [3]

2.3.1 Aim of Guideline RECIST 1.1

It was defined as the introduction of a new standardized procedure of measuring the extent of solid tumors and a methodology of objective evaluation of its changes, for use in clinical trials concerning neoplasias both of adulthood and childhood. It was, also, stated that it may be applied in trials for brain gliomas, although there are other criteria in wider use [4] (see Sect. III, CNS Tumors). Additionally, it was clarified that this guideline is not proposed for use in trials assessing the response of malignant lymphomas, where other widely accepted guidelines are considered to be more appropriate [5] (see Sect. VIII, Lymphoma).

Although there were proposals of incorporating the use of 3D volumetric measurements of the neoplastic lesions and of functional tech-

niques (such as ^{18}F-FDG-PET, dynamic contrast-enhanced CT, dynamic and functional MRI techniques), it was judged that there is still not efficient standardization nor wide availability of these modalities in order to be adopted into the frame of a general official guideline. However, ^{18}F-FDG-PET has been officially accepted as a complementary method of assessing the extent and progression of some specific neoplasias, in terms of special therapeutic protocols (see Sects. I, IV, VI, IX, and XII).

2.3.2 Assessment of Measurable Tumor Burden

A neoplastic disease affecting a specific patient is defined as "measurable" if it includes at least one "measurable lesion." To consider a lesion as measurable, it must be possible to define with accuracy its greatest diameter, and this should be at least 10 mm on the transverse CT or MRI slices (given that the slice thickness is ≤5 mm) (Fig. 2.1a, b). Although conventional radiographs are nowadays very rarely used for therapy assessment (e.g., in lung tumors), RECIST guideline implies that a measurable lesion on them has to be ≥20 mm. Regarding the lymph nodes (its measurement was first introduced in the RECIST 1.1 edition), in order to be characterized as abnormally enlarged and "measurable," their short-axis diameter must be ≥15 mm on transverse CT slices (given the slice thickness is ≤5 mm). It has to be noted that only the short-axis diameter of the affected lymph nodes has to measured, since it has been shown that it offers more reproducible measurements than the long axis (Fig. 2.1c).

All measurements should be performed using the "metric system," in centimeters (cm) or millimeters (mm), and on the transverse plane, with the exception of some neoplasias where, due to their growth pattern, the measurement is more representative when performed on the sagittal or coronal plane (as in cases of paraspinal tumors). In any case, repeat measurements during follow-up studies should always be performed on the same imaging plane.

As "nonmeasurable" are considered all the remaining lesions, including those with a maximum long-axis transverse diameter <10 mm, enlarged lymph nodes with a short-axis diameter ≥10 mm but <15 mm, and, also, all the tiny and difficult-to-be-measured foci. The latter include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast cancer, carcinomatous lymphangitis of the lung or skin, and abdominal masses which are clinically detectable but not amenable to reproducible measurements with the currently recommended imaging techniques (Fig. 2.1d).

According to the RECIST 1.1 guidelines, secondary deposits to the bones cannot be reliably measured by means of bone scanning, ^{18}F-FDG-PET, or radiographs. However, it is estimated that these imaging modalities can be used to assess the presence or elimination of the bone lesions. It is, also, clarified that secondary deposits to the bones of lytic or mixed type which are accompanied by CT or MRI detectable soft tissue masses may be considered as "measurable" lesions if the accompanying soft tissue mass fulfills the definition described above (Fig. 2.1e). Sclerotic bone lesions are by definition "nonmeasurable."

Neoplastic lesions previously treated (e.g., with radiotherapy) may be considered as measurable, only if the presence of active disease in them was previously established with biopsy or cytology.

2.3.3 Evaluation of Response to Therapy [3, 6–8]

During the first (baseline) examination, which has to be performed within 4 weeks before starting therapy, it is imperative to assess accurately the total tumor burden, in order to have a reference of comparison for the new measurements during follow-up.

After assessing the presence of "measurable disease" (as defined previously) in a certain patient, the next step is to define "target" and "non-target" lesions. According to RECIST 1.1 guidelines, as "target lesions" are selected up to five measurable lesions per patient (while in the

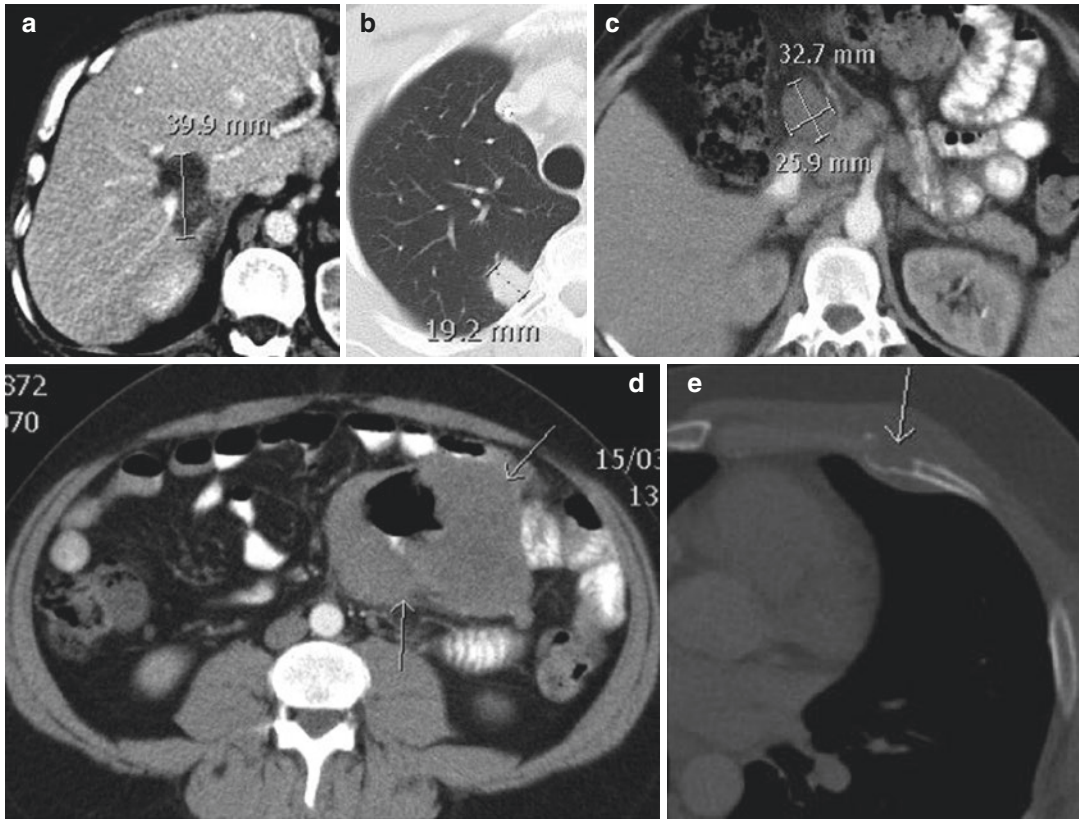

Fig. 2.1 Measurable disease: "target" and "non-target" lesions. Selected images from a CT scan of the thorax and abdomen, performed in terms of the baseline examination of a patient with metastatic melanoma of the skin, before the initiation of chemotherapy. Two secondary deposits at the *right* hepatic lobe (**a**) and *right* upper pulmonary lobe (**b**) are shown, which have a maximum transverse diameter >1 cm, and, hence, they fulfill the criteria to be defined as "measurable lesions" and be selected as "target lesions." The maximum diameters of these two lesions (4 cm and 1.9 cm, respectively) will be incorporated in the "total sum of diameters" of all target lesions. Also, an abnormally enlarged lymph node is depicted in the abdomen (**c**) which has a short-axis transverse diameter of 2.6 cm (>1.5 cm); consequently, it can also be selected as a "target lesion." In the "total sum of diameters" of target lesions, the short-axis diameter of 2.6 cm (not the long-axis diameter of 3.3 cm!) of the lymph node must be encountered. On image (**d**), the largest secondary deposit in this patient is shown, located in the small bowel wall. However, despite its large size, this lesion is not recommended to be selected as "target lesion" since its location on the bowel wall makes its appearance on transverse slices unstable, and, hence, the corresponding measurements of its diameter during the follow-up studies will lack reproducibility. On the image (**e**), a small lytic secondary deposit in the anterior part of a left rib is depicted (*arrow*), with a small accompanying soft tissue mass <1 cm, which is considered as a "nonmeasurable" lesion

initial RECIST guideline, they could be up to ten). These must be selected in order to be representative of all the organs affected by the neoplasia and, generally, should not exceed two lesions per organ (while in the initial RECIST, they could be selected up to five target lesions per organ). The selection criteria of target lesions are their size (the larger lesions in each organ should be chosen) and their suitability for reproducible repetitive measurements (Fig. 2.1a, b, d). It is advised to prefer non-cystic lesions, instead of cystic or necrotic. Also, they have to be representative of all organs affected by the tumor. In each follow-up (CT or MRI) examination, the longest diameter of each target lesion has to be measured on the transverse slice and with the direction that reflects better its size (Fig. 2.1a, b). If a target lesion separates during follow-up into more than

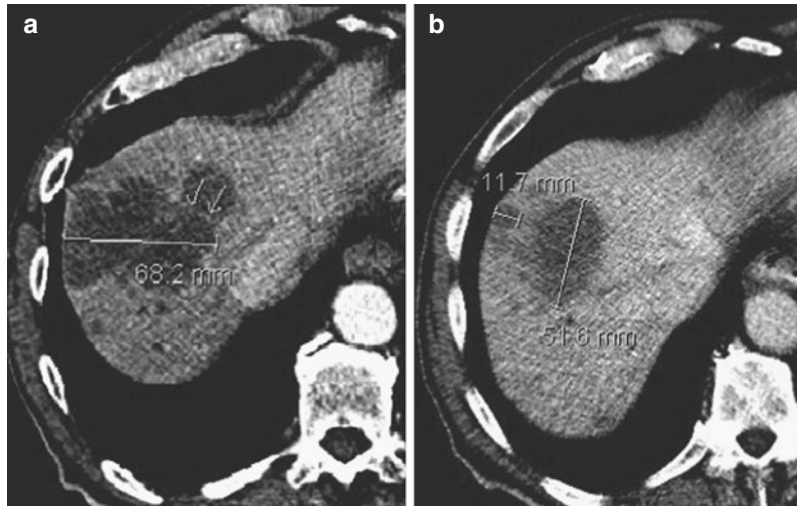

Fig. 2.2 Splitting lesions. On a CT image, (**a**) a metastatic "target" lesion in the liver is shown, with a maximum diameter of 68.2 mm, which is separated from another adjacent lesion by a thin line of normal-appearing liver parenchyma (*arrows*). On follow-up CT (**b**), after effective chemotherapy, the previous lesion has split in two smaller adjacent lesions, clearly separated by normal-appearing liver tissue. Eventually, the longest transverse diameters of the two resulting lesions (51.6 and 11.7 mm) must be added in the sum of diameters of target lesions

one fragments, the sum of the longest diameters of these fragments has to be measured (Fig. 2.2). In the case that two adjacent target lesions coalesce (without leaving a plane of normal tissue between them), then the longest diameter of the new lesion has to be measured (Fig. 2.3). If a target lesion becomes, during follow-up, too small to be measured accurately, its diameter that will be added to the sum is advised to be, by default, 5 mm.

Enlarged lymph nodes with a short-axis diameter ≥15 mm can also be selected as target lesions (Fig. 2.1c). On follow-up studies, if the maximum short-axis diameter of a "target nodal lesion" reduces below 10 mm, this is no longer considered pathologic, but it still has to be measured on future studies in order to assess a possible progression.

After selecting and recording the target lesions, the sum of the largest long-axis diameters of all the non-nodal lesions and the short-axis diameters of the selected lymph nodes has to be calculated. During follow-up, the changes of this "sum of diameters" provide the measure for assessing the objective response of the neoplastic disease to therapy. It is important that the same target lesions (initially selected on the baseline examination) have to be measured on every follow-up examination. For all the remaining measurable lesions, which were not selected as target lesions (including, also, all the enlarged lymph nodes with a short-axis diameter 10–15 mm), there is no need to measure their diameters during follow-up but simply to record on each examination their presence or absence or any "unequivocal increase of their extent." Based on these changes, the response of the "non-target" lesions is assumed. The final judgment concerning the "overall response" must take into account both the "target" and "non-target" lesions and, also, the appearance or not of new lesions during follow-up. It has to be noted that, in order to categorize a patient case as "stable disease" (SD) or "progressive disease" (PD), one must not use as reference the measurements of the baseline examination but, instead, the measurements of the examination where the smallest "sum of diameters" was encountered (occasionally, this examination could be the baseline one).

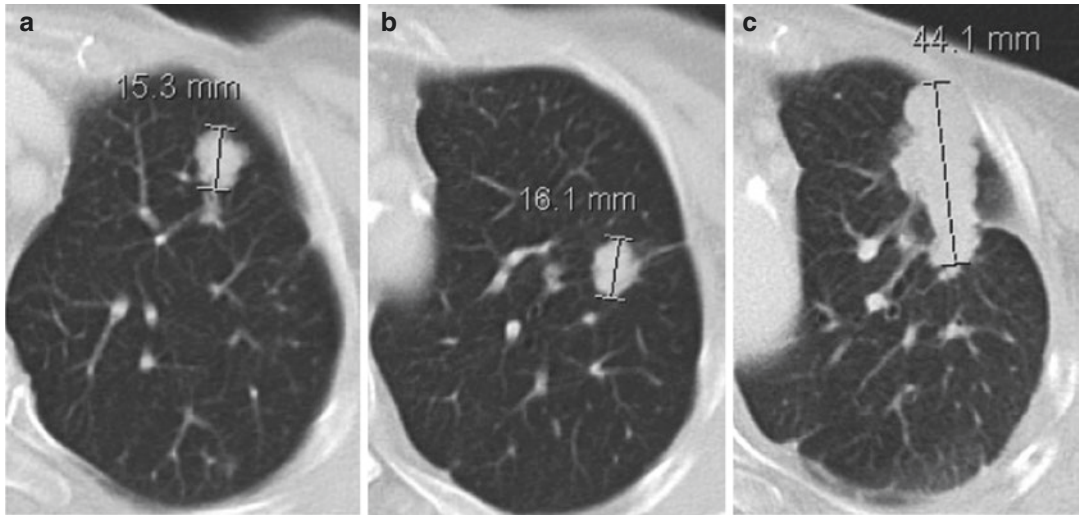

Fig. 2.3 Coalescent lesions. Two secondary deposits, selected as target lesions, in the *left upper* pulmonary lobe (**a**, **b**) have increased in size on the follow-up CT (**c**) and merged in a larger lesion. The largest transverse diameter of the latter must now be added in the sum of diameters of target lesions

There are not strict guidelines regarding the frequency of follow-up examinations. However, it is generally recommended to perform follow-up studies at the end of each chemotherapy cycle (usually every 6–8 weeks), at least in terms of phase II trials where the benefit of the therapy is unknown. The assessment of the "overall response to therapy" is performed on the results of the final examination at the end of therapy.

2.3.4 Evaluation of the Response of "Target Lesions"

According to RECIST 1.1, the definitions on which the response evaluation is based are as follows:

Complete response (CR): disappearance of all target lesions. Additionally, every previously enlarged lymph node must have a decreased short-axis diameter not exceeding 10 mm.

Partial response (PR): decrease of the baseline "sum of diameters" of the target lesions ≥30%.

Progressive disease (PD): increase of the "sum of diameters" of the target lesions of at least 20% in comparison to the smallest value of this sum that was encountered during the whole period of the study (including the baseline sum). Additionally, the "sum of diameters of target lesions" must have shown an absolute increase of at least 5 mm (this criterion was not included in the first RECIST guideline).

Stable disease (SD): changes of the "sum of diameters of target lesions" which do not fulfill the criteria for PR or PD (Fig. 2.4).

It must be noted that RECIST 1.1 includes detailed instructions concerning the methodology of measurement of target lesions, on the baseline and the follow-up imaging studies.

2.3.5 Evaluation of the Response of "Non-target" Lesions

Non-target lesions must be evaluated only qualitatively (present, absent, or unequivocally larger), even if their diameters seem to be measurable. The corresponding criteria and definitions for response evaluation are as follows:

Complete response (CR): disappearance of all the non-target lesions. All lymph nodes must have a short-axis diameter <10 mm. Additionally, tumor marker levels must be within normal limits.

Progressive disease (PD): unequivocal increase of the size/extent of preexisting non-target lesions (Fig. 2.5).

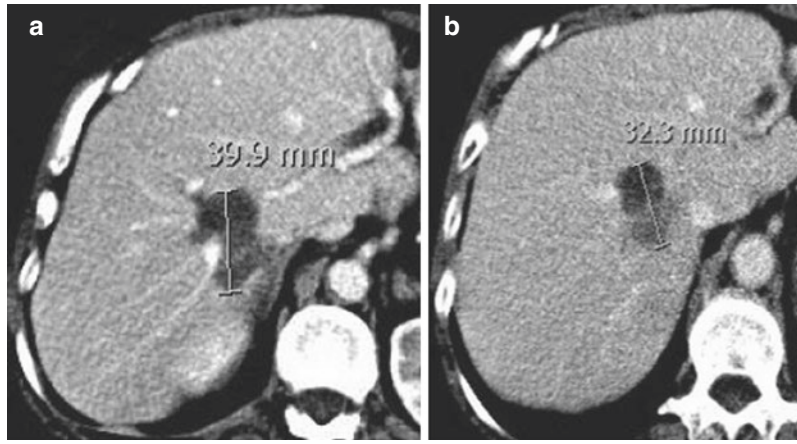

Fig. 2.4 Stable disease. Secondary deposit to the liver, from skin melanoma. On a transverse image from a baseline contrast-enhanced CT, performed before chemotherapy, the maximum diameter of the hepatic lesion is measured 4 cm (**a**). On the corresponding image of the follow-up CT study, performed after one cycle of chemotherapy (**b**), the maximum diameter of this "target lesion" is measured 3.2 cm. The 20% decrease of the maximum diameter of the lesion does not accomplish the definition of partial response (it should be at least 30%). Consequently, the status of this specific lesion has to be assessed as "stable disease"

Non-CR/non-PD: residual one or more non-target lesions and/or tumor markers measured above the normal levels.

The RECIST 1.1 includes clarifications concerning the "unequivocal progression" of non-target lesions and guidelines for the methodology of evaluating response in patients with only "nonmeasurable" disease, since such patients may be included in the population of phase III clinical trials. In cases where non-target lesions show unequivocal increase (PD), while target lesions show PR or SD, the overall response is assessed as PD only if the progression of non-target lesions seems to increase substantially the overall tumor burden. A mild to moderate increase of only few non-target lesions, while the other lesions (target and non-target) show SD or PR, is not considered sufficient to change the overall response assessment to PD.

2.3.6 Evaluation of New Lesions

The appearance of new malignant lesions indicates PD, given that these are unequivocal, meaning not depended on the imaging modality and its technique, and do not represent a false diagnosis. All the previous are very important, especially when the lesions (target and non-target) of baseline examination show PR or CR.

A lesion detected during follow-up at an anatomic area that was not included in the baseline study has to be considered by definition as "new lesion" indicating PD. For that reason, the protocol of each trial must provide to include in the baseline study all the anatomic areas that may be potentially affected by the specific neoplasia. If it is not certain that a new lesion represents neoplasia, its nature must be clarified during the follow-up.

Although ^{18}F-FDG-PET is not included in the basic imaging modalities proposed by RECIST 1.1, it could be used in selected cases as an additional method to confirm new lesions and verify cases of PD. According to the algorithm defined by this guideline, if a ^{18}F-FDG-PET scan performed during follow-up becomes positive while a baseline ^{18}F-FDG-PET was negative, this represents PD. If there is no available baseline ^{18}F-FDG-PET scan, but such a study performed during follow-up is positive for new sites of the disease, this situation is determined as PD only in the case that the new lesions are detectable by CT either at the same time point (but not at baseline CT) or later during the following imaging studies [3, 7].