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Functional Imaging in Oncology

Biophysical Basis and Technical Approaches

Volume 1

Springer

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ISBN 978-3-642-40411-5 ISBN 978-3-642-40412-2 (eBook)
DOI 10.1007/978-3-642-40412-2
Springer Heidelberg New York Dordrecht London

Library of Congress Control Number: 2013956428

Printed on acid-free paper

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

To my parents for forming me into what I am today
With all my love to my Marias for their patience and support

Antonio

To my wife Cris for her patience and understanding; and to our daughter Cristina, and son Eduard, with love.

Kai

To my parents, Luiz Celso and Leonice, as well as to my wife Simone, for their support and understanding during the process of preparing this work.

Celso

To my friend and mentor Jeremy Erasmus
To my family and my wife Clara

Santiago

Foreword

Molecular and functional imaging can improve the diagnosis, treatment and outcomes in oncologic patients. The ability to non-invasively visualize, characterize and quantify biologic processes at the cellular, molecular and genetic level presents a new era in oncology. This book provides a practical approach to the different imaging techniques used to obtain and understand this functional information. The editors, Drs. Luna, Vilanova, Da Cruz and Rossi are well-renowned radiologists experienced in functional and molecular imaging. They have assembled an international group of acclaimed experts that complement their expertise and have written a two-volume tour de force on state-of-the-art functional imaging useful in the assessment and management of oncologic patients. This comprehensive review was a pleasure to read and will undoubtedly become an indispensable resource for clinicians-in-training as well as practicing radiologists and oncologists. The authors are adept at simplifying complexity and their ambitious effort provides a complete review of diffusion MRI, perfusion CT and MRI, dual-energy CT, spectroscopy, dynamic contrast-enhanced ultrasonography, and positron emission tomography (PET). The text is clearly written and complemented by numerous high-quality illustrations that highlight key features and major teaching points. The first volume explains the biologic basis of the functional imaging modalities and provides meaningful clinical insight and understanding of the techniques used in the imaging of angiogenesis, tumor metabolism and hypoxia. The second volume considers specific malignancies and the use and benefit of the different imaging modalities in the diagnosis, prediction of treatment outcome, and early evaluation of treatment response in oncologic patients. The chapters are concise and comprehensive enough for the reader to obtain a firm foundation in the essential aspects of the topic reviewed. In fact, both volumes 1 and 2 impart knowledge in an easy-to-read, concise, coherent format. It is impossible to over-applaud the clarity and well-written and structured format of these books. In summary, the authors have used their experience to write an excellent textbook and the scope, structure and attention to detail are superb. The topics are well focused and this wide-ranging review is an invaluable guide to functional imaging.

This is a thoughtful and well-developed book that is without doubt an excellent, comprehensive text of the essentials required to understand and use functional imaging.

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Preface

In the last decades, comprehensive cancer care and research have both been critically dependent on imaging. The role of anatomical imaging with ultrasound, CT and MRI has grown progressively in the last decades. In this manner, the application of medical imaging to cancer patients has expanded from diagnosis and staging to screening, guide of treatment, therapeutic monitoring, detection of recurrence and prediction of treatment response. This change in the role of imaging has been due in part to the introduction of functional imaging with PET at the end of the last century, and posteriorly with other techniques such as advanced MRI sequences.

The recent advances in cellular biology, molecular biology and genetics have led to a better understanding of the biological bases of cancer. These advances in oncology biologics and the development of new biological therapies and treatment options have produced a paradigm shift in cancer treatment. In many clinical scenarios, cancer is now considered a chronic disease instead of an untreatable malignancy. Furthermore, the approach to cancer management is moving from treating the disease to personalized therapies. All these major changes need multidisciplinary teams where experts in biomedical imaging are – and will be – an important part of the puzzle. Very wide scales have to be covered by imaging, from the molecular and cellular level to organ to whole organism for clinical staging. In this manner, combined functional and anatomical imaging techniques are necessary to visualize and target different aspects of cancer. At this point, functional and molecular imaging might transform and improve all phases of cancer management.

Functional imaging using biomarkers can assess and quantify the biological characteristics of tumors by a wide range of techniques. In this manner, ultrasound can explore tumor angiogenesis by means of contrast-enhanced acquisitions and tissue elasticity using elastography. New CT approaches such as CT-perfusion and spectral energy CT have broadened the knowledge of tumor angiogenesis and tissue characteristics. Furthermore, MRI is now able to develop multiparametric studies of a tumor in a single study, being possible to analyze tumor cellularity, angiogenesis, hypoxia and metabolism simultaneously using diffusion-weighted, dynamic contrast-enhanced, BOLD and spectroscopic sequences, respectively. PET and multimodality (hybrid) imaging have also expanded their applications with the use of other metabolites different to 18-FDG. Therefore, it is possible to explore different cancer hallmarks, such as angiogenesis, metabolism, apoptosis, proliferation

or hypoxia. In addition, the development of new approaches such as optical imaging and nanocomposites, novel imaging probes for PET and MRI permit to target different molecular and cellular processes. All these developments are directed to the phenotyping of cancer by imaging techniques. The advances in functional and molecular imaging have laid to apply imaging as a cancer biomarker, to help direct cancer treatment in a way that is complementary to plans based on tissue- and blood-based biomarkers. The ability to measure in vivo cancer biology with functional imaging during treatment provides a unique opportunity to identify and select the therapy that is most likely to successfully treat an individual patient's cancer. Furthermore, in a very near future, new methodologies will deal with theranostics, looking for a combined and simultaneous diagnosis and treatment of the disease.

The purpose of this book is to provide a useful manual to be used by the wide range and variety of disciplines involved in the management of oncologic patients, including radiologists, nuclear medicine, oncologists, radiotherapist and the different medical specialists and nonmedical disciplines involved in the oncologic patient's care. We have tried to cover and provide all the extensive information related to the different imaging modalities in clinical use and research from the technical bases to clinical applications. For this purpose, the book is divided in two volumes. The first volume is focused on the biophysical basis and technical approaches of functional imaging techniques. This first volume is divided in four parts. The first part covers a general approach to cancer biology, imaging biomarkers and role of functional imaging in diagnosis and treatment. The three following parts that deal with the role of functional and molecular imaging in the study of cancer hallmark and review their technical basis and applications in clinical practice and research. This part of the book is organized by different imaging techniques in separate chapters to stress the importance of an adequate imaging technique and acquisition to optimize the performance of each technique. The second volume of the book is the largest, where the main types of cancers are addressed in different chapters and organized by system and organ. In each of these chapters, the role of functional imaging in the management of different tumor types is discussed.

This book has been possible due to the generous effort of all contributing authors. All of them, well-known experts in their respective fields, have shared with us their experience in cutting-edge topics. They have make possible to compile lots of new information in a surprisingly short period of time. Furthermore, it has been easy to coordinate such a great team, making editing of this book a learning and enjoyable process.

Finally, we would like to acknowledge the enormous support of Dr. Jeremy J. Erasmus in the first conception of this book and Dr. Roberto Garcia-Figueiras for his help in the organization of the contents.

We hope that this book can be helpful for all interested in cancer imaging, and readers may share some of the learning and enjoyment we had editing this book.

Jaén, Spain — Antonio Luna
Girona, Spain — Joan C. Vilanova
Rio de Janeiro, Brazil — L. Celso Hygino da Cruz Jr.
Buenos Aires, Argentina — Santiago E. Rossi

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Volume 2 Clinical Applications

Part I

Clinical and Therapeutic Approach to Functional Oncological Imaging

Cancer Biology: What's Important for Imaging

1

José L. Vercher-Conejero, Zhenghong Lee, and Pablo R. Ros

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Abbreviations

ABL	Abelson gene
ADC	Apparent diffusion coefficient
AR	Androgen receptor
ATSM	diacetyl-bis(N4-methylthiosemicarbazone)
BLI	Bioluminescence
BOLD	Blood oxygen level dependent
CCD	Charge-coupled device
CEST	Chemical exchange saturation transfer
CML	Chronic myeloid leukemia
CT	Computer tomography imaging
DCE-MRI	Dynamic contrast-enhanced magnetic resonance imaging
DECT	Dual-energy computer tomography
DEN	Diethylnitrosamine
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
DOTA-CTT	DOTA-Cys-Thr-Thr-His-Trp-Gly-Phe-Thr-Leu-Cys
DOTA-STT	DOTA-Ser-Thr-Thr-Gly-His-Phe-Trp-Thr-Leu-Ser

A. Luna et al. (eds.), *Functional Imaging in Oncology*,
DOI 10.1007/978-3-642-40412-2_1, © Springer-Verlag Berlin Heidelberg 2014

DWI	Diffusion-weighted imaging
ECM	Extracellular matrix
EGFR	Epidermal growth factor receptor gene
ESR	European Society of Radiology
EUS	Endoscopic ultrasound
FDG	Fluorodeoxyglucose
FDHT	Fluorodihydrotestosterone
FLT	Fluorothymidine
FMAU	1-(2′-deoxy-2′-fluoro-beta-D-arabinofuranosyl)thymine
FMISO	Fluoromisonidazole
fMRI	Functional magnetic resonance imaging
Gd	Gadolinium
GIST	Gastrointestinal stromal tumors
GLUT	Glucose transporters
H&E	Hematoxylin and eosin stain
HCR	Hepatocarcinogenesis reporter
Her2	Human epidermal growth factor receptor 2
IGT	Imaging-guided therapy
IVUS	Intravascular ultrasound
MDCT	Multidetector CT
MIP	Maximum intensity projection
ML10	2-(5- Fluoro-pentyl)-2-methyl malonic acid
MMPs	Matrix metalloproteinases
MRI or MR	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
mTor	Mammalian target of rapamycin
NETs	Neuroendocrine tumors
NH3	Ammonia
NIR	Near-infrared region
OCT	Optical coherence tomography
OI	Optical imaging
PARACEST	Paramagnetic chemical exchange saturation transfer
PET	Positron emission tomography
PTSM	Pyruvaldehyde-bis(N4-ethylthiosemicarbazone)
RAS/ERK	Ras-extracellular signal-regulated kinase
Rb	Retinoblastoma protein
RbCl	Rubidium chloride
R-CHOP	Rituximab-cyclophosphamide hydroxydaunorubicin, Oncovin (vincristine), prednisone
RGD	Arginine-glycine-aspartate peptide
SPAIR	Spectral attenuated inversion recovery
SPECT	Single-photon emission tomography
SPIO	Superparamagnetic iron oxide
TK1	Thymidine kinase 1
US	Ultrasound
VEGF	Vascular endothelial growth factor

1.1 Introduction

1.1.1 Cancer Hallmarks and Tumor Microenvironment

In cancer, new pathways and oncogenic features are continuously discovered. Cancer cells show different characteristics among distinct tumor types allowing them to proliferate and metastasize to distant organs. In addition, cancer cells have distinguished characteristics from normal cells such as rapid proliferation, immortality, resistance to apoptosis, metastatic capacity, and resistance to immunologic blitz [1].

The main focus of cancer imaging is often directed to contrast the differences between neoplastic and normal tissues. From a targeting point of view, the phenotypic abnormalities could be grouped into two main categories: those typical of certain cells such as the existence, or not, of a particular malignant biomarker and those related to the tumor microenvironment including angiogenesis, perfusion, and hypoxia [1].

As *Hanahan and Weinberg* summarized in 2000 [2], the hallmarks of cancer could be categorized into six features needed to understand its biology. Recently, they introduced new elements to this complex mechanism as shown in Fig. 1.1 [3].

1.1.1.1 Sustaining Proliferative Signaling

One of the fundamental attributes of cancer cells is their capability to proliferate even with no associated signaling. This is what *Hanahan and Weinberg* called *sustaining proliferative signaling* and can be achieved by increasing the production of growth factors, stimulating normal cells to provide cancer ones with growth factors, activating protein in the downstream

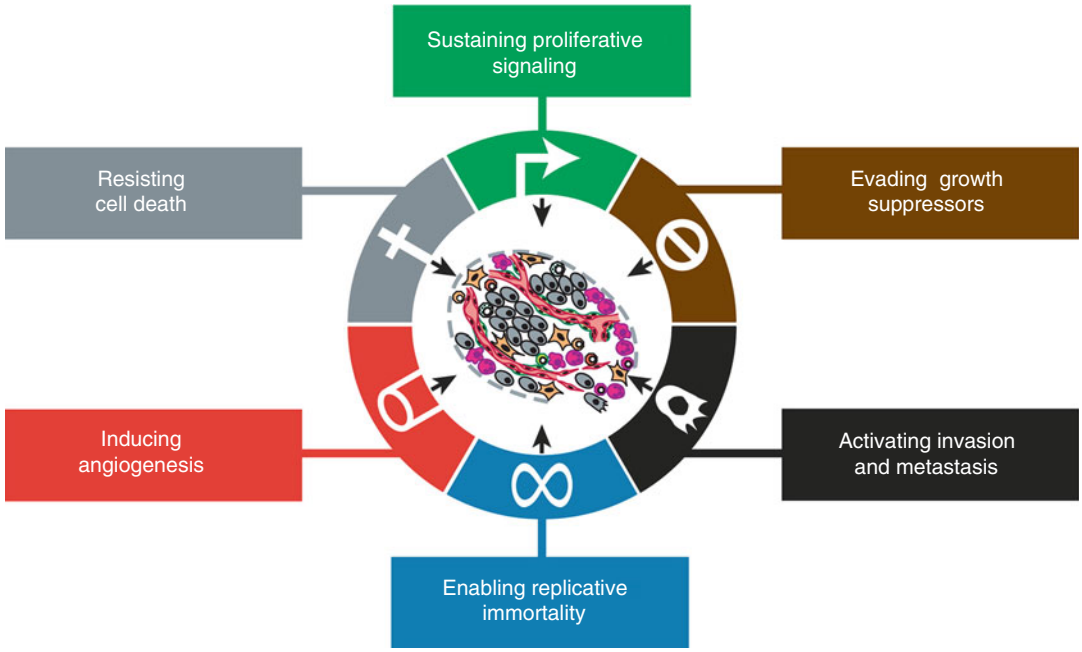


Fig. 1.1 The illustration shows the acquired biologic characteristics of malignant tissues proposed by Hanahan and Weinberg that has helped to understand the fingerprints of cancer cells (From Hanahan and Weinberg [3] with permission)

signaling pathway, and increasing the number of receptors on the cell or either modifying them to ease cancer cell signaling. In cancer cells, the process of intracellular communication may be taken over by specific mutations in otherwise normal genes, resulting in an abnormal gene called oncogene. Oncogenes generate abnormal genes products such as oncoproteins leading to a malignant cell behavior. These mutations may be produced in kinases, including EGFR mutations and c-Kit mutations, among others, that can disturb the signal transmitting function [1]. PI3K-Akt signaling, MAP-kinase pathway, mTOR pathway, cellular senescence, or oncogenes and tumor suppressor genes might contribute in this step [3]. This is key in targeted drug therapy as there is an interaction of membrane receptor-based tyrosine kinase and PI3K-Akt and RAS/ERK pathways and many drugs being used to inhibit signaling in different ways. Molecular-based imaging modalities have been used to image these molecular pathways. For example, some studies have demonstrated the extraordinary effect against gastrointestinal stromal tumors (GIST) of a tyrosine kinase inhibitor imatinib drug (Gleevec). GIST has been related to a transmembrane receptor, the oncogenic protein c-Kit. ^{18}F-fluorodeoxyglucose or ^{18}F-FDG, an analogue of glucose labeled with a positron emitter F-18, has been used in molecular imaging for assessing the therapeutic response of this drug in GIST patients. ^{18}F-FDG has shown the effect of blocking the specific tyrosine kinase activity associated with c-Kit [1]. Depending on the drug being used and its molecular target, a certain type of radiopharmaceutical can be applied to assess treatment response. For example, other tyrosine kinase inhibitor drugs, sunitinib and sorafenib, have been used in a type of kidney cancer. These drugs are targeting a specific angiogenic growth factor called vascular endothelial growth factor or VEGF. Other tracers such as ^{18}F-desatibib, ^{68}Ga-Fab'$_2$ herceptin, and ^{18}F-fluorodihydrotestosterone or ^{18}F-FDHT have been used to image different targets: mutant ABL in resistant chronic myeloid

leukemia (CML), Her2 in breast cancer, and androgen receptor (AR) in prostate cancer, respectively.

1.1.1.2 Evading Growth Suppressors

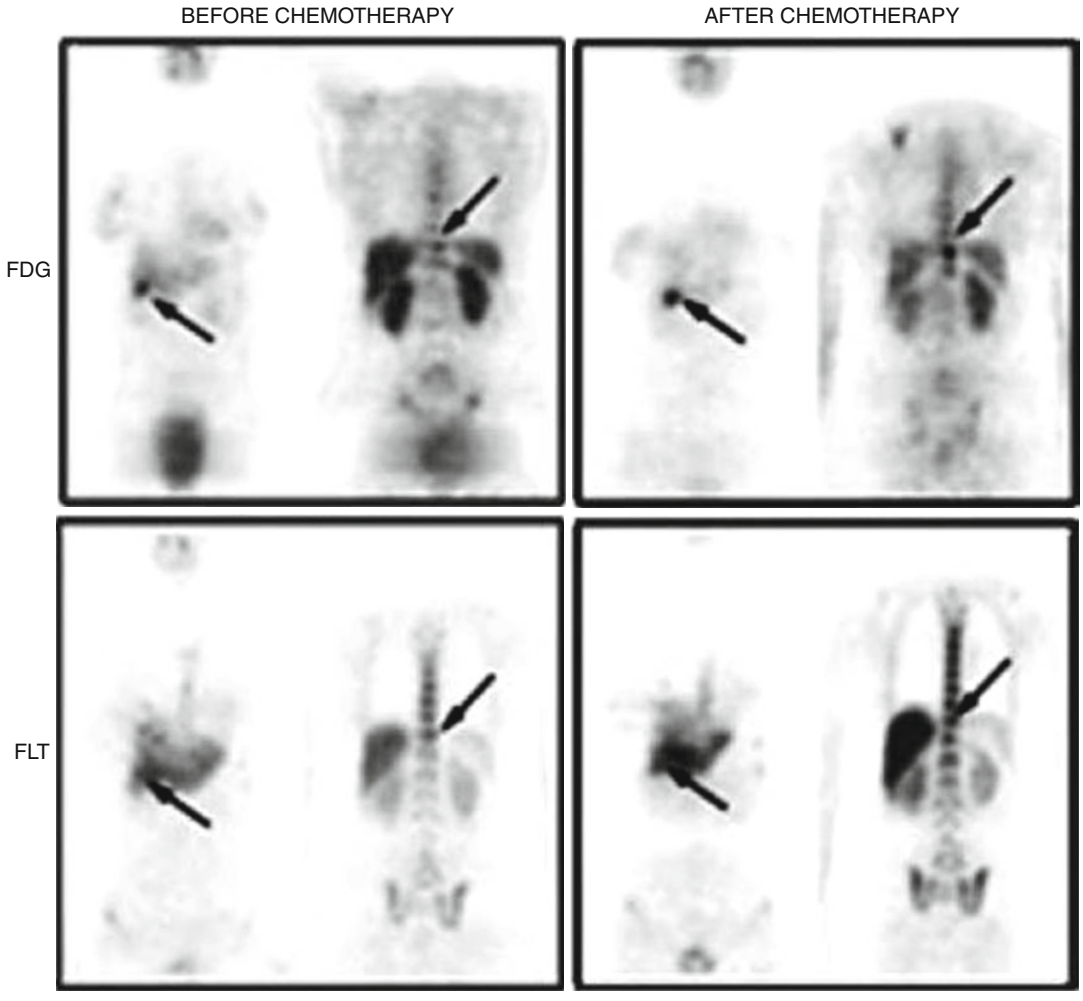
Cell proliferation in normal cells is a controlled process where many signals (pro- and anti-growth) coordinate the cycle phases. For example, the G_1 phase is the most vulnerable cell cycle vital due to the fact that it is at this point where extrinsic mitogenic signals may facilitate more mutations and therefore enable the development of cancer cells [4]. The rapid growth of malignant tissue can be measured by computed tomography imaging (CT) to evaluate changes in volume. Molecular imaging with specific tracers linked to proliferative processes such as the accelerated synthesis of DNA is more suited for this. Many tracers have been tested to image this mechanism. 2-^{18}F-fluorothymidine or ^{18}F-FLT is probably the most interesting and extensively used radiopharmaceutical in this setting. ^{18}F-FLT is a pyrimidine-based tracer taken by the cell via passive diffusion and facilitated transport by Na+-dependent carriers and then phosphorylated by thymidine kinase 1 (TK1) and finally trapped in the cell. In quiescent cells, TK1 activity is virtually absent, but in proliferating cells its activity is increased, particularly in the S phase of the cell cycle. This radiolabeled tracer has shown very promising results in monitoring response to treatment. In one study performed by Pio et al., 14 breast cancer patients were evaluated 2 weeks after the first cycle of treatment. Levels of the cancer antigen 27.29 (CA27.29), which is a soluble form of a mucin-like glycoprotein abundantly expressed on most carcinoma cells, showed very good correlation with ^{18}F-FLT uptake, as shown in Fig. 1.2 [5]. Another study evaluated ^{18}F-FLT in early response evaluation of high-grade non-Hodgkin lymphoma in 22 patients that were treated with combined immunochemotherapy (R-CHOP) or chemotherapy (CHOP) alone showing that a rapid reduction in FLT uptake was shown 7 days after initiation of therapy. However, there was no significant change in FLT uptake following the administration of rituximab alone [6].

The way antiproliferative signals usually work in normal cells is by inducing the G_0 phase or a postmitotic state [4]. However, most cancer cells evade these signals so they can proliferate. This characteristic is known as *evading growth suppressors* [3].

The two most representative tumor suppressors are p53 and the retinoblastoma protein (Rb) which regulate the cell cycle. While the protein p53 operates as a central control of apoptosis when there is a DNA damage, the Rb protein decides whether a cell should go or not through its cell cycle; in other words, it inhibits the pathway through the restriction checkpoint in G_1 [3, 7]. A protein such as p53 has been thought to participate in cancer cells metabolism as a modulator, especially by facilitating oxidative phosphorylation and reducing glycolysis. Therefore, when p53 is inactive due to a mutation, a process of glycolysis is then favored. This process can be studied with ^{18}F-FDG as this is a marker of glucose metabolism as some authors have shown a correlation between p53 and 18F-FDG [8–10]. When any of the tumor suppressors or processes is dysregulated, then the cycle progresses and consequently the cell proliferation is ongoing.

1.1.1.3 Activating Invasion and Metastasis

Another important cancer hallmark is *activating invasion and metastasis*, responsible for the spreading of neoplastic cells from the primary site into surrounding tissues and distant organs. It is believed, though not clear, that this process involves modifications in the cells so they can be attached to other cells and to the extracellular matrix (ECM) [3]. This may include different stages: local tissue invasion, intravasation, transition via blood and lymphatics, and colonization of foreign tissue [3]. Matrix metalloproteinases (MMPs) consist of a family if zinc-dependent endopeptidases for degrading ECM constituents, playing an important role in



	FDG (avg. SUV)	FLT (avg. SUV)	CA 27.29 (U/mL)
Before Chemo.	2.6	4.9	40
After Chemo.	3.6	6.1	78
Difference	+1.0	+1.2	+38
%Change	+41.2%	+23.5%	+95%

Fig. 1.2 PET studies of a 43-year-old female with known metastatic breast carcinoma. ^{18}F-FDG-PET and ^{18}F-FLT-PET were performed before and after Aromasin treatment (an aromatase inhibitor). Both FDG and FLT studies show an increase of radiotracer uptake in the right kidney between the pre- and posttreatment scans. In addition, levels of tumoral biomarker CA27.29 also increased (From Pio et al. [5] with permission)

tumor invasion and metastases. The overproduction and uncontrolled function of MMPs have been correlated to many different tumors (brain, colon, melanoma, breast, etc.) [11]. Cross talk between cancer cells and cells of neoplastic stroma introduces the idea that metastatic process requires input from the surrounding tissue, so they do not originate from a cell-autonomous model [3, 12]. Imaging MMP expression with noninvasive imaging techniques such as PET, single-photon emission tomography (SPECT), and optical imaging may offer important information to predict metastatic potential of a tumor. Some synthetic sulfonamide-based MMP inhibitors including ^{64}Cu-DOTA-CTT, ^{64}Cu-DOTA-STT, and ^{123}I-CGS 27023A, among others, have been used as radiotracers to image overexpression of MMPs in tumors [11, 13].

1.1.1.4 Inducing Angiogenesis

The formation of new blood vessels, also called angiogenesis, is an essential process of tumor growth and metastatic dissemination [14]. Generally, angiogenesis is strongly controlled by a balance between stimulatory and inhibitory signaling molecules. However, when this balance is disrupted, a rapid proliferation of new vessels can happen, for instance, when a primary tumor releases angiogenic growth factors. The tumor-associated neovasculature is a multistep mechanism including signaling input from multiple angiogenic growth factors like VEGF, known as "angiogenic switch," and also the integrin signaling pathway [3]. Integrins are a group of cell adhesion molecules that are present on both neoplastic cells and newly formed vessels. Among the different integrin molecules already known, $\alpha_v\beta_3$ is the most studied in angiogenesis. Angiogenesis is therefore essential to the survival and growth of neoplastic tumors. *Inducing angiogenesis* eases tumor expansion mainly by delivering of oxygen and nutrients and production of growth factors for the cancer cell [14]. Angiogenesis has attracted some attention in therapy as a target for chemotherapeutic drugs. In fact, the first anti-angiogenic drug proven in humans was bevacizumab, a humanized monoclonal antibody which targets VEGF [15].

These processes can be imaged with radiolabeled tracers such as ^{64}Cu(DOTA)-VEGF$_{121}$ (targeting VEGF) or ^{18}F-galato-RGD (targeting integrin $\alpha_v\beta_3$) for PET imaging [16, 17]; ^{125}I-VEGF and ^{111}In-perfluorocarbon for SPECT imaging [18]; NP-RGD for SPECT imaging; RDG-Gd^{3+} for magnetic resonance imaging (MRI); RGD MBs and anti-VEGFR-2-Ab-microbubbles for ultrasound (US) or RGD-QD705; and QD-VEGF(DEE) for optical imaging (OI) [19].

1.1.1.5 Perfusion

The perfusion of tumors and their surrounding tissues is considered an essential physiological characteristic of tumor microenvironment as it is meant to be very important for planning and monitoring treatment response. Many imaging modalities including CT, MRI, and radionuclide techniques have shown their utility in understanding perfusion not only in oncology but also in heart pathologies (myocardium viability) and neurodegenerative disorders (dementia). Several tracers have been used to study blood flow, hypoxia, and neovascularization in primary tumors to investigate tumor perfusion. For example, ^{15}O-H_2O has turned out to be one of the most promising tracers to explain tumor perfusion in breast, kidney, colon, or lung cancer [20–22]; ^{62}Cu^{II}PTSM or other more commonly used PET perfusion imaging agents such as ^{82}Rb-RbCl, ^{13}N-NH_3, and ^{64}Ga-citrate have shown potential in brain, myocardium, and kidney, although with limitations [1]. Different CT techniques and novel MRI sequences are being used to learn more and quantify perfusion in neoplastic tissues and will be detailed in Sect. 1.2.

1.1.1.6 Resisting Cell Death

The programmed cell death (apoptosis) is a key process in cancer development and progression. In normal cells when an event such as an irreparable DNA damage is produced, they tend to switch on apoptosis. The ability of cancer cells to avoid apoptosis and continue with their proliferation is one of the fundamental features of cancer and is a major target of cancer therapy development [2, 3]. A signaling dysregulation in cancer cells promotes the overexpression of antiapoptotic

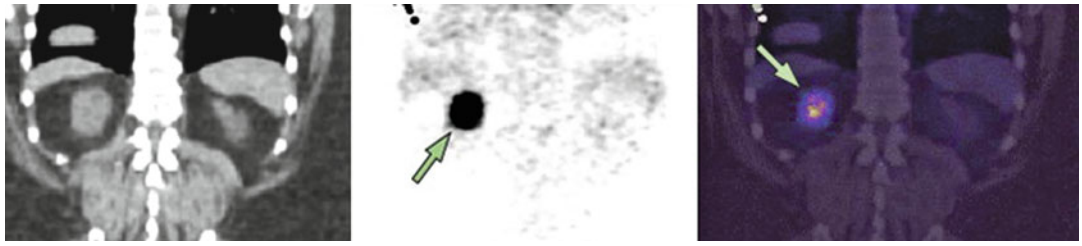


Fig. 1.3 Patient with a clear cell carcinoma scanned with ^{124}I-cG250 PET/CT (coronal CT, PET, and fused image) showing a focus of abnormal uptake (*arrow*) in the posterior portion of the right kidney (From Divgi et al. [37] with permission)

proteins and mutes the production of proapoptotic proteins [23]. Moreover, by altering the necrosis and normal cellular autophagy, cancer cells may *resist cell death* [3]. A radiolabeled molecule to image apoptosis called ^{18}F-ML10 has shown promising results in brain metastasis from non-small cell lung cancer patients treated with radiation therapy with promising results [24].

1.1.1.7 Hypoxia

Related to apoptosis, angiogenesis, tumor invasion, and metastasis, hypoxia is another very interesting feature that has impact on tumor environment. Hypoxia is a pathological condition defined as a reduction of tissue oxygenation and may lead to an insufficient supply of oxygen and nutrients to cells. In oncology, its severity will be dependent on the phenotype of cancer. For instance, cervical cancers are known to be highly hypoxic [1]. It has been exhibited in many studies that hypoxic neoplasias have worse prognosis for disease-free survival after treatment with chemotherapy as cytotoxicity aimed to be produced with certain anticancer drugs decreases in hypoxic tissues [25, 26]. Furthermore, hypoxic cells show significantly more resistance to radiotherapy treatment so affecting the radiation sensitivity [27–30]. Several hypoxia-selective PET tracers have been used with different results, but it is worth highlighting ^{18}F-fluoromisonidazole (^{18}F-MISO) and ^{64}Cu^{II}-ATSM which are being tested in many studies with interesting outcomes [31, 32]. ^{18}F-MISO has affinity for hypoxic cells with functional nitroreductase enzymes; therefore, it accumulates in activated cells but not in necrotic cells [33]. Many studies have shown excellent correlation between ^{18}F-MISO uptake and the oxygenation status of non-small cell lung neoplasms, head and neck cancer, gliomas, and cervical cancer [34].

Another interesting radiopharmaceutical is ^{124}I-cG250, an iodine-based radiolabeled tracer, which has shown the potential in evaluating hypoxia in certain tumors. cG250 is an antibody reacting against carbonic anhydrase-IX, which is overexpressed in hypoxic conditions, especially in clear cell renal carcinomas, the most common and aggressive renal tumor [35, 36]. *Divgi* et al. studied 26 patients with renal masses who were scheduled to undergo surgical resection. They concluded that PET with 124I-cG250 could identify accurately clear cell renal carcinoma; therefore, a negative PET scan would be highly predictive of a less aggressive phenotype helping surgical planning (Fig. 1.3) [37].

Dynamic contrast-enhanced and diffusion-weighted MRI sequences are also contributing in assessing hypoxia in tumor cells and the response of chemotherapy in these neoplasias [38–41].

1.1.1.8 Deregulating Cellular Energetics and Avoiding Immune Destruction

In addition to all those oncologic features, two new hallmarks have been recently introduced in oncology: *deregulating cellular energetics* and *avoiding immune destruction*, together with some enabling characteristics such as the *genome instability and mutation* generating random mutations and the *tumor-promoting inflammation* that favors tumor progression through various ways (Fig. 1.4) [3].

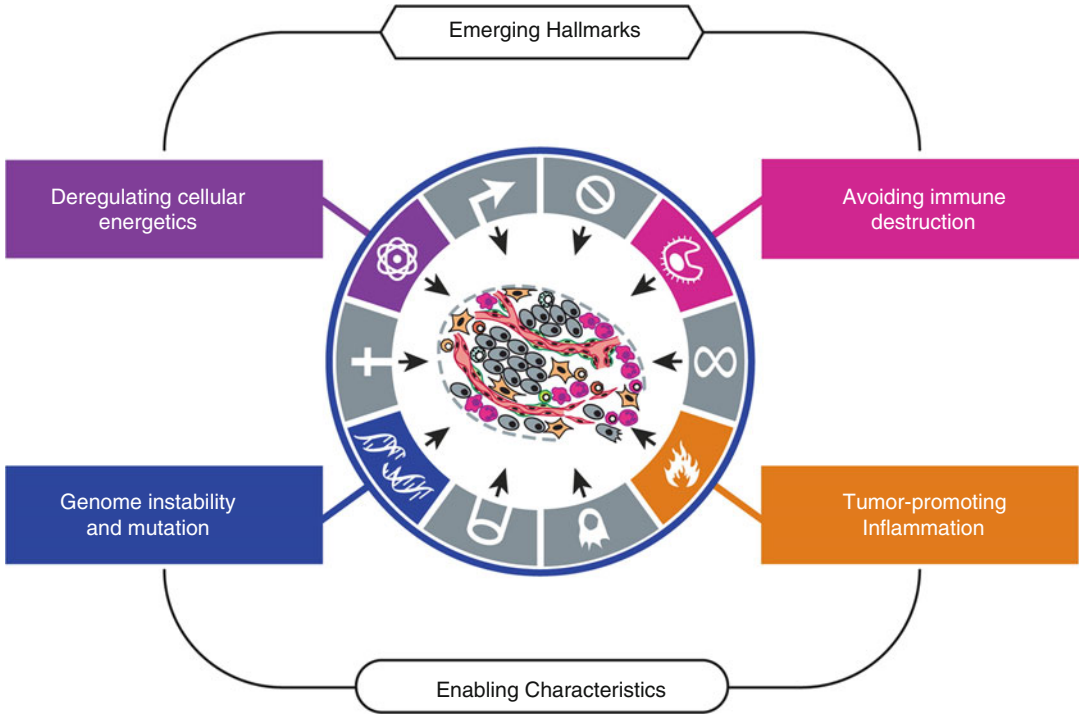


Fig. 1.4 The figure presents new proposed additional hallmarks that are thought to be involved in the pathogenesis of most cancers: one could have the ability to modify cellular metabolism by reprogramming or modifying it, while the other hallmark would be based on the capability of avoiding immunological destruction by cancer cells. In addition, the authors introduced two characteristics of neoplastic cells that could facilitate the acquisition of core and those emerging features: genomic instability and mutation, and inflammation, both of them enabling tumor progression (From Hanahan and Weinberg [3] with permission)

Cancer cells must make adjustments in their energy production in order to maintain the uncontrolled proliferation. Many mechanisms including using alternative metabolic pathways, adapting their glucose metabolism, and upregulating glucose transporters (GLUT) translate into an increase glucose uptake and utilization shown in many neoplasms, easily corroborated by molecular imaging, particularly by ^{18}F-FDG-PET [3, 42]. ^{18}F-FDG, as an analogue of glucose, is transported into cells by glucose transporter proteins and then phosphorylated by hexokinase to form FDG-6-phospate. However, it cannot be degraded via the glycolysis pathway nor dephosphorylated by glucose-6-phosphatase like glucose is. Therefore, FDG-6-phosphate gets trapped within the cell, and in this sense the more FDG there is in the cells, the greater the uptake in the tumor.

Many studies have suggested that a continuously active immune system recognizes and eliminates the majority of cancer cells before settling to form a tumor mass [3, 43, 44]. So the immune system is considered a fundamental process preventing tumor formation.

However, this is an unresolved issue because the role of the immune system is not yet clear. *Hanahan and Weinberg* and other authors introduced the concept of an elimination phase where the immune system recognizes and eliminates cancer cells. Then, the immune system is able to control the cancer cell growth but is not able to eliminate other cancer cells being in an equilibrium phase. Finally, tumor cells or clones not detected or destroyed by the immune system keep on growing [3, 45].

Each of the alterations that are produced in cancer cells of these hallmarks and tumor