

## Part I Technology and Probe Design

<b>Computed Tomography and Magnetic Resonance Imaging</b>	<b>3</b>
1 Imaging Targets in Cancer	4
1.1 Introduction	4
1.2 Physiological Imaging Targets	5
1.3 Molecular Targets	7
1.4 Cellular Targets	8
1.5 Image-Guided Drug Delivery	8
2 Recent Technological Developments in X-ray Computed Tomography of Cancer	9
2.1 Basics of Multi-Slice Spiral Computed Tomography	9
2.2 Multi-Energy Computed Tomography	13
2.3 Preclinical Computed Tomography	14
2.4 Dedicated Imaging Systems and New Developments	15
2.5 Multimodality Imaging	16
3 Recent Technological Developments in Magnetic Resonance Imaging of Cancer	16
3.1 Magnetic Resonance Imaging: Introduction	16
3.2 MRI Signal Formation and Contrast	17
3.3 Magnetic Field Strength and Signal Sensitivity	21
3.4 Imaging Gradients, Signal Encoding, and Signal Reception Chain	21
3.5 MRI Pulse Sequences, Parametric Mapping	23
3.6 Contrast-Enhanced MRI	24
4 Imaging Biomarkers in Cancer	25
4.1 Imaging Biomarkers: X-ray Computed Tomography	25
4.2 Imaging Biomarkers: Magnetic Resonance Imaging	26
5 Magnetic Resonance Imaging Probes in Cancer	33
5.1 Introduction	33
5.2 Non-Targeted Probes	33
5.3 Targeted Probes	43
5.4 Responsive Probes	43
5.5 Reporter Genes	45

6	Future Perspectives .....	53
	References .....	53
	<b>Single Photon Emission Computed Tomography Tracer .....</b>	<b>65</b>
1	Introduction .....	66
2	General Aspects for the Design of SPECT Tracers .....	69
3	Peptide-Receptor Radionuclide Imaging .....	73
	3.1 Somatostatin Analogs .....	74
	3.2 Bombesin Analogs .....	76
	3.3 Neurotensin Analogs .....	79
	3.4 Other Peptides-Based Radiotracers .....	81
4	Antibodies and Antibody Fragments .....	82
	4.1 Targeting Fibronectin Extra-Domain B: Antiangiogenic Antibody Fragment L19 .....	84
5	Vitamin-Based Radiotracers .....	85
	5.1 Folic Acid Conjugates .....	85
	5.2 Vitamin B12 Conjugates .....	87
	5.3 Other Vitamin Targeting Agents .....	89
6	Intracellular Targets .....	90
	6.1 $^{99m}\text{Tc}$ -Carbohydrate Complexes .....	90
	6.2 Radiolabeled Nucleoside Analogs for Targeting Human Thymidine Kinase .....	91
	6.3 Radioiodinated Meta-Iodobenzylguanidine .....	93
7	Optimization of SPECT Tracer Design and Potential Reasons for Failure .....	95
8	Summary and Conclusion .....	96
	References .....	97
	<b>Non-peptidyl <math>^{18}\text{F}</math>-Labelled PET Tracers as Radioindicators for the Noninvasive Detection of Cancer .....</b>	<b>107</b>
1	Introduction .....	108
2	$^{18}\text{F}$ FDG for Imaging Glucose Metabolism .....	109
3	$^{18}\text{F}$ -Labelled Amino Acids (AAs) for Imaging AA Transport and Protein Synthesis .....	111
	3.1 O-(2- $^{18}\text{F}$ Fluoroethyl)-l-tyrosine ( $^{18}\text{F}$ FET) .....	111
	3.2 6- $^{18}\text{F}$ Fluoro-3,4-dihydroxy-l-phenylalanine ( $^{18}\text{F}$ FDOPA) .....	113
4	$^{18}\text{F}$ -Labelled Choline Derivatives for Imaging Membrane Lipid Synthesis .....	115
	4.1 $^{18}\text{F}$ Fluorocholine (Dimethyl- $^{18}\text{F}$ fluoromethyl-2- hydroxyethylammonium, $^{18}\text{F}$ FCH) .....	115
	4.2 $^{18}\text{F}$ Fluoroethylcholine (Dimethyl-2- $^{18}\text{F}$ fluoroethyl-2- hydroxyethylammonium, $^{18}\text{F}$ FECH) .....	117
5	$^{18}\text{F}$ -Labelled Nucleoside Derivatives for Imaging Cell Proliferation .....	118

5.1	3'-Deoxy-3'-[ <sup>18</sup> F]fluoro-1-thymidine ([ <sup>18</sup> F]FLT) . . . . .	118
5.2	1-(2'-Deoxy-2'-[ <sup>18</sup> F]fluoro-β-d-arabinofuranosyl)-5-methyluracil ([ <sup>18</sup> F]MAU). . . . .	119
6	<sup>18</sup> F-Labelled Nitroimidazole Derivatives for Imaging Tumour Hypoxia . . . . .	120
6.1	[ <sup>18</sup> F]Fluoromisonidazole ([ <sup>18</sup> F]FMISO) . . . . .	120
6.2	1-(5-Deoxy-5-[ <sup>18</sup> F]Fluoro-α-d-arabinofuranosyl)-2-nitroimidazole ([ <sup>18</sup> F]FAZA). . . . .	122
7	[ <sup>18</sup> F]FES for Imaging Estrogen Receptor Status. . . . .	122
8	[ <sup>18</sup> F]Fluoride for Imaging Bone Metabolism . . . . .	124
9	Perspectives . . . . .	124
	References . . . . .	125
	<b>Optical and Opto-Acoustic Imaging . . . . .</b>	<b>133</b>
1	Introduction. . . . .	134
2	Multi-Spectral Optoacoustic Tomography . . . . .	135
2.1	Sensitivity of Biomarker Detection . . . . .	139
2.2	Other Applications of Optoacoustic Imaging . . . . .	142
3	FMT-XCT. . . . .	142
4	Overview of Performance Characteristics . . . . .	145
5	Quantification . . . . .	146
6	Optical Imaging Applications in Oncology . . . . .	148
	References . . . . .	149
	<b>Multifunctional Magnetic Resonance Imaging Probes . . . . .</b>	<b>151</b>
1	The Need for Imaging and Contrast Agents in Oncology . . . . .	152
2	Imaging Techniques and Contrast Agents . . . . .	155
2.1	Magnetic Resonance Imaging of Cancer . . . . .	155
2.2	Multifunctional Imaging Probes . . . . .	159
3	Probing the Tumor Vasculature . . . . .	161
3.1	Dynamic Contrast-Enhanced MRI . . . . .	162
3.2	Macromolecular Dynamic Contrast-Enhanced MRI. . . . .	164
4	Molecular Imaging. . . . .	167
5	Combined Imaging and Therapy . . . . .	175
6	Translations and Future Outlook . . . . .	181
	References . . . . .	183

## Part II Preclinical Studies

<b>Preclinical SPECT and SPECT/CT . . . . .</b>	<b>193</b>
1 Introduction. . . . .	194

2	Part I: Considerations when Evaluating the Potential Role of SPECT/CT Imaging in a Preclinical Oncology Research Application . . . . .	195
2.1	Choice and Implications of Various Small Animal Models of Cancer . . . . .	195
2.2	Framing the Research Question in Imaging Terms . . . . .	198
2.3	Available in vivo Imaging Modalities and Characteristics of Preclinical Oncology Applications Amenable to SPECT . . . . .	198
2.4	SPECT Versus SPECT/CT. . . . .	199
3	Part II: Technical Considerations when Implementing SPECT/CT in Preclinical Oncology Research . . . . .	200
3.1	Anesthesia and Animal Handling . . . . .	200
3.2	Availability of Radiopharmaceuticals and Evaluation of Their Biodistribution Characteristics . . . . .	201
3.3	Injection of the Radiopharmaceutical . . . . .	203
3.4	Injection of CT Contrast Agent . . . . .	203
3.5	Radiation Exposure. . . . .	203
4	Part III: State-of-the-Art Preclinical SPECT/CT Systems . . . . .	205
4.1	SPECT/CT System Design . . . . .	205
4.2	A Sampling of Available Small-Animal SPECT- and SPECT/CT Systems . . . . .	207
4.3	Image Reconstruction Techniques and the Quest for Quantitative SPECT. . . . .	208
5	Part IV: Recent Examples of SPECT/CT as Applied in the Preclinical Oncology Setting . . . . .	210
5.1	Characterizing Tumor Perfusion or Other Inherent Characteristics . . . . .	210
5.2	Imaging the Targeting Abilities of Molecules in the Development of Potential Therapeutics and Molecular Imaging Agents . . . . .	210
5.3	Imaging Cell Trafficking. . . . .	213
5.4	Imaging Gene Transfer and Expression. . . . .	213
5.5	Imaging Biodistributions and Evaluating Dosimetry—Chemotherapeutics and Combined Therapeutic/Imaging Agents . . . . .	215
5.6	Imaging Other Pathologic Processes Associated with Cancer or Cancer Therapies . . . . .	216
6	Conclusion . . . . .	216
	References . . . . .	216
	<b>Optical Imaging . . . . .</b>	<b>221</b>
1	Non-Invasive Optical Imaging Techniques . . . . .	222
2	Imaging Agents for Fluorescence Imaging . . . . .	223
3	Reporter Systems for Bioluminescence Imaging . . . . .	224

4	Biological Processes . . . . .	224
4.1	Activity of Matrix Degrading Enzymes . . . . .	224
4.2	Glucose Metabolism . . . . .	225
4.3	Hypoxia . . . . .	228
4.4	Proliferation . . . . .	230
4.5	Angiogenesis . . . . .	231
4.6	Cell Death . . . . .	233
4.7	Blood Flow . . . . .	235
5	Clinical Perspective . . . . .	237
6	Outlook/A Critical View . . . . .	240
	References . . . . .	241
	<b>Applications of Small Animal PET . . . . .</b>	<b>247</b>
1	Introduction . . . . .	248
2	Small Animal PET . . . . .	249
2.1	General Aspects . . . . .	249
2.2	Small Animal PET . . . . .	251
2.3	Small Animal CT and Small Animal PET . . . . .	252
3	Conclusion . . . . .	254
	References . . . . .	254
	<b>Preclinical Molecular Imaging Using PET and MRI . . . . .</b>	<b>257</b>
1	Introduction . . . . .	258
2	Experimental Models of Cancer . . . . .	259
3	Small Animal Molecular Imaging . . . . .	261
4	Positron Emission Tomography . . . . .	262
5	Magnetic Resonance Imaging and Spectroscopy . . . . .	264
5.1	Contrast Agents . . . . .	266
5.2	Dynamic Contrast-Enhanced MRI . . . . .	268
5.3	Steady-State Susceptibility-Contrast MRI . . . . .	269
5.4	Diffusion-Weighted MRI . . . . .	270
5.5	Arterial Spin Labeling . . . . .	274
5.6	Blood Oxygen Level Dependent MRI . . . . .	274
6	Multimodality Imaging . . . . .	275
7	Applications . . . . .	276
7.1	Metabolism . . . . .	276
7.2	Hypoxia . . . . .	279
7.3	Reporter Gene . . . . .	283
7.4	Angiogenesis . . . . .	285
7.5	Apoptosis . . . . .	288
7.6	Cellular Imaging . . . . .	289
8	Animal Welfare and its Impact on Imaging . . . . .	293
9	Summary and Outlook . . . . .	296
	References . . . . .	297

## Part III Clinical Applications

<b>Quantitative SPECT/CT</b> .....	313
1 Introduction .....	314
2 Technical Aspects .....	314
2.1 SPECT/CT Instrumentation .....	314
2.2 Registration of Multimodal Images .....	315
2.3 Attenuation Correction of SPECT .....	316
2.4 Quantitatively Accurate SPECT/CT .....	318
3 Clinical Aspects .....	326
4 Summary and Outlook .....	327
References .....	327

## **Optical Imaging of Breast Tumors and of Gastrointestinal Cancer by Laser-Induced Fluorescence** .....

1 Introduction .....	332
2 Fluorescence Imaging of Breast Cancer .....	333
2.1 The PTB Fluorescence Mammograph .....	334
2.2 Examination Protocol .....	336
2.3 Results on Malignant and Benign Tumors .....	337
2.4 Advances of Permeability Sensitive Fluorescence Imaging with ICG .....	340
3 Cancer and Early Malignancies of the GI .....	343
3.1 Protoporphyrin IX as Tumor Marker .....	343
3.2 Time-Gated Fluorescence Imaging .....	343
3.3 Clinical Studies .....	346
4 Outlook .....	347
References .....	348

<b>FDG PET and PET/CT</b> .....	351
1 Introduction .....	352
2 Clinical Applications of FDG PET and PET/CT in Oncology .....	353
2.1 Non-Small Cell Lung Cancer .....	353
2.2 Oesophageal Cancer .....	355
2.3 Gastric Cancer .....	355
2.4 Colorectal Cancer .....	356
2.5 Gastrointestinal Stromal Tumors .....	356
2.6 Head and Neck Cancer .....	357
2.7 Melanoma .....	357
2.8 Lymphoma .....	358
2.9 Breast Cancer .....	359
2.10 Ovarian Cancer .....	360
2.11 Sarcomas .....	361
2.12 Pancreatic Cancer .....	362

2.13	Thyroid Cancer . . . . .	363
2.14	Cancer of Unknown Primary . . . . .	364
2.15	Testicular Cancer . . . . .	365
2.16	Prostate Cancer . . . . .	366
3	Therapy Response Assessment with FDG PET and PET/CT . . . . .	366
	References . . . . .	367

<b>Molecular Imaging in Oncology . . . . .</b>		<b>371</b>
1	Introduction to Non-FDG PET Tracers . . . . .	372
2	Clinical Applications of $^{11}\text{C}$ -Choline . . . . .	373
3	Clinical Applications of $^{18}\text{F}$ -DOPA . . . . .	375
4	Clinical Applications of $^{11}\text{C}$ -Methionine . . . . .	379
5	$^{11}\text{C}$ -Acetate . . . . .	382
6	Clinical Applications of $^{18}\text{F}$ -FLT . . . . .	384
7	$^{18}\text{F}$ -FET . . . . .	385
8	$^{18}\text{F}$ -Fluoride . . . . .	386
9	Clinical Applications of PET Tracers for Hypoxia . . . . .	387
10	Clinical Applications of PET Tracers for Angiogenesis . . . . .	388
	References . . . . .	389

## Part IV Future Challenges

<b>Future Challenges of Multimodality Imaging . . . . .</b>		<b>403</b>
1	Introduction. . . . .	404
2	Technology and Probe Design . . . . .	404
2.1	SPECT/CT. . . . .	405
2.2	PET/CT. . . . .	405
2.3	SPECT/MRI and PET/MRI . . . . .	406
3	Tracers . . . . .	407
4	Optical Imaging. . . . .	411
5	Future and Conclusions . . . . .	412
	References . . . . .	413