Index

A
Adjuvant systemic therapy
adoptive immunotherapy, 178
antiangiogenic therapy, 180
clinical vignette, 182
cytokines
IFN-α, 176–177
IL-2, 177–178
hormonal agents and chemotherapy, 176
micrometastases treatment, 174
molecular pathway-directed therapy, 174
monoclonal antibody, 180
risk assessment
prognostic system, 175–176
staging, 174–175
second generation adjuvant studies
hormonal therapy, 181
placebo-controlled, randomized trial, 180, 181
TKIs and mTOR inhibitor, 181
VEGF and mTOR pathway, 180
VEGF-R TKIs and mTOR inhibitor, 181–182
vaccines
randomized adjuvant vaccine strategy, 178, 179
tumor-derived lysate vaccine, 178–179
vitespen, 179–180
Adoptive immunotherapy, 178
Adrenal metastases, 129–130
American Joint Committee on Cancer (AJCC), 18, 76, 174
Angiogenesis
CXCR4 and SDF, 35
IL-8, 34
PDGF, 34
thalidomide and lenalidomide, 292–293
thrombospondin-1 agonism, 293
TIE2, 34–35
Tie-2/Ang-1/2 signaling inhibition
AMG-386, 290, 292
mRCC, angiogenic signaling axes, 290, 291
regorafenib antitumor activity and safety, 292
VEGF, 33–34
Angiogenesis inhibitor therapy
clinical vignette, 205
RCC management, 198
tumor-angiogenesis factor, 198
VEGF
axitinib, 203
bevacizumab, 202–203
cediranib, 203–204
gene induction regulation, 198
and HIF pathway, 198, 199
pazopanib, 202
regorafenib, 204
sorafenib, 198–201
sunitinib, 201–202
tivozanib, 204
VEGF-Trap, 204–205
Axitinib, 203, 234–235
B
Bevacizumab
angiogenesis inhibitor
therapy, 202–203
combination therapy, 226–228
everolimus combination, 217
TKIs, 233–235
Biomarkers
application, 47–48
clinical biomarker, 52
clinical vignette, 61
copy number analysis, 56
definition, 47
detection and diagnosis,
RCC, 48–49
gene expression profile, 55
gene biomarker, 52, 55
HIF, 49–50
HIF responsive gene
AKT/mTOR/HIF pathway, 51
CAIX, 50–51
VEGF, 50
histological biomarker, 52
horizon of, 59, 60
hybrid strategy, 55–56
immunotherapy
CAIX, 57
genetic study, 57–58
RCC subtyping, 57
metastatic RCC, 49
mTOR-targeted therapy, 59
Biomarkers (Cont.)
- predictive biomarker (see Predictive biomarker)
- prognostic biomarker, 52–54
- pVHL, 49
- RCC biomarker development, 48
- SNP genotyping, 56
- treatment and advance oncology care, 59
- VEGF-targeted therapy
  - clinical biomarker, 58
  - HIF level, 58
  - VEGF/soluble VEGF receptor level, 58–59
  - VHL mutation, 58
- VHL, 49
- VHL and HIF, 56
- Birt-Hogg-Dubé (BHD) syndrome, 7, 251

Bone metastases
- local therapy, 168
- surgery, 127–128

Brain metastases
- local therapy, 168
- metastasectomy, 128–129

C
- Cardiac toxicity, 275–276
- Cediranib, 203–204
- Charlson Comorbidity Index (CCI), 92–93, 104
- Chronic kidney disease (CKD), 95–96
- Clear cell renal cell carcinoma
  - chicken wire, 18, 19
  - Fuhrman nuclear grade 1, 18, 19
  - PAS histochemical stain, 18, 20
- c-MET signaling, 294–295

Combination therapy
- bevacizumab and erlotinib, 226
- bevacizumab and everolimus, 226
- chemotherapy, targeted agents, 231
- clinical vignette, 236–237
- completed trial, 226–228
- everolimus and sorafenib, 228–229
- immunotherapy, targeted agents
  - bevacizumab and IFN-α, 229–230
  - gefitinib and pegylated IFN-α, 230
  - ROSORC trial, 230–231
  - sorafenib and IFN-α, 230
- INTORACT, 231
- targeted agents, novel drugs, 229
- temsirolimus and bevacizumab, 226, 228
- temsirolimus and sunitinib, 228

Cryoablaction
- energy ablation technology, 145
- vs. RFA, 101–102, 147

Cytokines
- chemotherapy and biologic agent
  - AVOREN trial, 194
  - CALGB 90206, 194
  - IFN-α and angiogenesis inhibitor, 193–194
  - IFN-α efficacy, 193
- clinical vignette, 194–195
- interferon
- 3-D structure recombinant
  - IFN-α2b, 189
  - IFN-α, 188
  - IFN-α2a vs. vinblastine, 189
  - IFN-β and IFN-g, 188
  - medroxyprogesterone acetate, 189
  - nephrectomy, 189–190
  - interferon and interleukin-2, 192–193
  - interleukin-2
  - lymphokine-activated killer cell, 190
  - SANI score, 192
  - side effects and management, 190–191
  - three-arm study, 191
  - recombinant technology, 188
  - selected immune-based approach, 187–188
  - systemic immunotherapy, 194

Cytoreductive nephrectomy
- action mechanism, 111
- aggressive surgical resection, 115
- CARMENA trial, 118
- clinical vignette, 118
- CULP, Kaplan-Meier analysis, 115
- global ARCC study, 117
- immunotherapy era, 112
- interleukin-2 therapy, 112
- multivariate analysis, 112, 113
- negative preoperative prognostic factor, 115
- non-clear cell histology, 115–116
- prognostic factor, survival, 113, 114
- randomized trial, 111
- RAND/UCLA Appropriateness Method, 113
- refractory symptoms, 110
- strict criteria, 112
- surgical technique
  - lymph node dissection, 116–117
  - nephron sparing, 117
  - survival advantage, 110
  - systemic targeted therapy, 110
  - targeted therapy, 117–118

Cytotoxic chemotherapy
- ixabepilone, 295–296
- S-1, 295

E
- End stage renal disease (ESRD), 23–24
- Energy ablative technique, 151
  - adjunctive technique
    - angioplasty balloon, 151
    - Foley catheter, 150
    - pneumothorax risk, 151
    - probe retraction technique, 150–151
  - clinical vignette, 156
  - complications
    - direct thermal injury, 156
    - hemorrhage, 155–156
    - incidence rate, 155
  - cryoablaction, 145
  - laparoscopic ablation, 148, 150
  - laser ablation, 144–145
  - microwave ablation, 145
mid- and long-term outcome, cryoablation, 152–153
patient selection, 145–146
percutaneous ablation, 150
percutaneous vs. laparoscopic ablation, 151–152
preprocedure planning
cryoablation vs. RFA, 147
imaging modality, 148, 149
patient evaluation, 146
surgical vs. percutaneous approach, 147–148
tumor assessment, 146–147
radiofrequency ablation
coaugulation necrosis, 142
vs. cryoablation, 152
image-guided percutaneous renal tumor, 142
impacts of, 154
mid- and long-term outcome, 152, 153
percutaneous ablation, 142
treatment efficacy, 155
tumor selection, 146
ultrasound ablation, 145
ErbB-directed therapy, 294
European Organization for Research and Treatment
of Cancer (EORTC), 246
Everolimus
and bevacizumab, 217–218
dose-escalation study, 215–216
RECORD-1, 216
safety and efficacy, metastatic RCC, 216
side effects, 217
S6K1 inhibition and antitumor effect, 215
in vitro and animal study, 215
External beam radiotherapy (EBRT), 168
F
Fatigue and asthenia
molecular mechanism, 267–268
prevention, and side effect management, 268–269
sunitinib-related fatigue, 268
Fibroblast growth factor receptor (FGFR), 293–294
H
Hand-foot syndrome (HFS), 271–272
Hematologic toxicity, 274
Hereditary leiomyomatosis and renal cell cancer
(HLRCC), 7
Hereditary paraganglioma (HPG), 8
Hereditary RCC, 6
Hypertension, 5–6, 72, 274–275
I
Inherited renal cancer
BHD syndrome, 7
HLRCC, 7
HPG, 8
HPRC, 6–7
tuberous sclerosis, 7–8
Intensity-modulated radiotherapy (IMRT), 164
Interferon
3-D structure recombinant IFN-α2b, 189
IFN-α, 188
IFN-α2a vs. vinblastine, 189
IFN-β and IFN-g, 188
medroxyprogesterone acetate, 189
nephrectomy, 189–190
Interleukin-2
lymphokine-activated killer cell, 190
SANI score, 192
side effects and management, 190–191
three-arm study, 191
L
Laser ablation, 144–145
Liver metastases, 127
Lymph node dissection (LND), 116–117
Lymph node metastase, 130–131
M
Mammalian target of rapamycin (mTOR)
clinical vignette, 219
everolimus
and bevacizumab, 217–218
dose-escalation study, 215–216
RECORD-1, 216
safety and efficacy, metastatic RCC, 216
side effects, 217
S6K1 inhibition and antitumor effect, 215
in vitro and animal study, 215
mTORC1 activity, 210–211
mTORC2 and homeostatic feedback loops, 211–212
rapamycin action mechanism, 212–213
rapamycin and rapamycin analogs, 212, 213
resistance mechanism, 218
ridaforolimus, 217
signaling pathway, 211
structure, 210
temsinterolimus
and bevacizumab, 217
dosing and safety, 213
IFN, 219
monotherapy and combination regimens efficacy, 214
phase III study, 214–215
and VEGF-targeted therapy, 217
TOR gene, 210
Memorial Sloan Kettering Cancer Center (MSKCC) model, 52, 77, 79–80, 113, 125, 199, 216
Metastasectomy
adrenal metastases, 129–130
biological response modifier, 133
bone metastases, 127–128
brain metastases, 129
clinical vignette, 135–136
evolution, prognostic factor, 125–126
incidence, 124
liver metastases, 127
lymph node metastase, 130–131
MSKCC risk score, 125
multiple synchronous RCC metastases, 132
Metastasectomy (Cont.)
oligometastasis, survival rate, 132
pancreas, 131
prognosis and management, 124–125
pulmonary metastases resection, 126–127
targeted therapy
CT scan, 133, 134
nonrandomized trial, 135
pretreating rationale, 133, 134
sunitinib therapy, 133–135
thyroid gland, 131–132
Microwave ablation, 145
Molecular biology
angiogenesis inhibitors
CXCR4 and SDF, 35
IL-8, 34
PDGF, 34
TIE2, 34–35
VEGF, 33–34
carbonic anhydrase and lactate dehydrogenase, 36
Cdk4/6, 36
clear cell renal carcinoma, 30
CTLA4 and PD1, 36–37
HIF antagonists, 32–33
HIF biology and mTOR inhibitor, 36–37
histone methylases and demethylases, 36
IL6, 36
NFkB, 36
tumor cell receptor tyrosine kinases
c-MET, 35
EGFR, 35
IGFR, 35–36
ROR2, 36
VHL
HIF activity control, 30–31
kidney cancer development, 32
microtubule stabilization, 32
pVHL, 30
pVHL and HIFα interaction, 31
tumor suppressor gene, 30
mTOR. See Mammalian target of rapamycin (mTOR)
Mucinous tubular and spindle cell carcinoma (MTSCC), 21–22

renal medullary carcinoma, 251, 254
sarcomatoid dedifferentiation, 252, 254
survival
CDRCC, RMC, 254
localized PRCC and CHRCC, 253–254
metastatic PRCC and CHRCC, 254
sarcomatoid dedifferentiation, 254–255
temsirolimus and BRYO, 260
variant NCCRCC subtypes, 250, 251
VEGF pathway-targeted therapy
cromophobe RCC, 257–258
collecting duct and medullary, 258
neoadjuvant treatment, 258–259
papillary RCC, 257
sarcomatoid dedifferentiation, 258
Xp11.2 translocation RCC, 258
Xp11.2 Translocation RCC, 251–252
Novel immune strategies
clinical vignette, 296–297
CTLA4 blockade, 289
denileukin diftitox, 289–290
immune effects, targeted agent, 296
programmed death-1 inhibition, 288–289
targeting IL-6, 290
vaccine therapy
IMA901, 287
MGN1601, 288
MUC1-based vaccine, 287–288
selected emerging immune therapy, mRCC, 286, 287
sunitinib and AGS-003, 286–287
Nucleolin, 295

P
Papillary carcinoma, 18–20, 250, 253
Paraneoplastic syndrome
constitutional symptom, 72
derocrine abnormality, 72
hypercalcemia, 71–72
hypertension, 72
incidence and prognostic significance, 71
nonendocrine paraneoplastic syndrome, 73
nonmetastatic hepatic dysfunction, 72
polycythemia, 72
Pazopanib
angiogenesis inhibitor therapy, 202
therapy, 278–279
treatment refractory mRCC, 234
treatment-related toxicities, 267
PI3K pathway, 218
Pneumonitis, 276, 277
Predictive biomarker
immunotherapy
CAIX, 57
genetic study, 57–58
RCC subtyping, 57
mTOR-targeted therapy, 59
VEGF-targeted therapy
clinical biomarker, 58
HIF level, 58

N
National Cancer Comprehensive Network (NCCN) guidelines, 92, 117
Non-clear cell renal cell carcinoma
chromophobe RCC, 251, 253
clinical vignette, 260
collecting duct RCC, 251, 253
cytokine therapy, 256–257
DNA- and DNA-repair-targeted therapy
CDRCC and RMC, 255–256
CHRCC, 255
PRCC, 255
sarcomatoid dedifferentiation, 256
EGFR pathway, 259
MET pathway, 259–260
mTOR pathway-targeted therapy, 259
papillary carcinoma, 250, 253
<table>
<thead>
<tr>
<th>Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF/ soluble VEGF receptor level</td>
</tr>
<tr>
<td>VHL mutation</td>
</tr>
<tr>
<td>Presurgical therapy</td>
</tr>
<tr>
<td>CARMENA</td>
</tr>
<tr>
<td>clinical vignette</td>
</tr>
<tr>
<td>cytoreductive nephrectomy, 241–242</td>
</tr>
<tr>
<td>downsizing and downstaging</td>
</tr>
<tr>
<td>clinical trial, 242, 243</td>
</tr>
<tr>
<td>evidence, 242, 243</td>
</tr>
<tr>
<td>preoperative bevacizumab</td>
</tr>
<tr>
<td>sorafenib treatment</td>
</tr>
<tr>
<td>sunitinib</td>
</tr>
<tr>
<td>targeted therapy and resection</td>
</tr>
<tr>
<td>EORTC trial</td>
</tr>
<tr>
<td>immunotherapy, pretreatment, 242</td>
</tr>
<tr>
<td>safety</td>
</tr>
<tr>
<td>survival</td>
</tr>
<tr>
<td>therapeutic need</td>
</tr>
<tr>
<td>translational need</td>
</tr>
<tr>
<td>Pulmonary metastases</td>
</tr>
</tbody>
</table>

### R

#### Radiation therapy

- beneficial effects | 163 |
- bone metastases, 168 |
- brain metastases, 168 |
- clinical vignette | 169 |
- IMRT | 164 |
- localized RCC |
  - postoperative, 165–167 |
  - preoperative, 164–165 |
- SBRT | 167 |
- RCC treatment | 164 |
- SRS | 164 |
- survival benefit | 168–169 |
- uses of | 164 |

#### Radiofrequency ablation (RFA)

- coagulation necrosis | 142 |
  - vs. cryoablation | 152 |
  - image-guided percutaneous renal tumor, 142, 143 |
  - impacts of, 154 |
  - mid- and long-term outcome | 152, 153 |
  - percutaneous ablation | 142, 144 |

#### RAND/UCLA Appropriateness Method

- 113 |

#### Regorafenib

- 204 |

#### Renal cell carcinoma (RCC)

- acquired cystic disease-associated rcc | 23 |
  - adjuvant systemic therapy (see Adjuvant systemic therapy) |
  - AJCC TNM staging system | 75, 76 |
  - ancillary technique |
    - immunohistochemical stain | 24–25 |
    - molecular biology | 25 |
  - angiogenesis inhibitor therapy |
    - axitinib | 203 |
    - bevacizumab | 202–203 |
    - cediranib | 203–204 |
    - clinical vignette | 205 |
    - gene induction regulation | 198 |
    - and HIF pathway | 198, 199 |
    - pazopanib | 202 |
  - RCC management | 198 |
  - regorafenib | 204 |
  - sorafenib | 198–201 |
  - sunitinib | 201–202 |
  - tivozanib | 204 |
  - tumor-angiogenesis factor, 198 |
  - VEGF-Trap, 204–205 |
  - biomarkers (see also Biomarkers) |
    - carbonic anhydrase IX | 83 |
    - hypoxia-inducible factor | 82–83 |
    - VEGF(R), 82 |
  - VHL Pathway | 81–82 |
  - chromophobe RCC | 20–21 |
  - CKD assessment and implication | 95–96 |
  - clear cell papillary RCC | 23 |
  - clear cell RCC |
    - chicken wire | 18, 19 |
    - Fuhrman nuclear grade 1 | 18, 19 |
    - PAS histochemical stain | 18, 20 |
    - clinical vignette | 10, 27 |
    - collecting duct carcinoma | 21 |
  - competing risks analysis |
    - active surveillance | 93–94 |
    - CCI | 92–93 |
    - risk assessment algorithm | 92, 93 |
    - SEER program | 93 |
  - cryoablation vs. RFA, 101–102 |
  - cytokines (see Cytokines) |
  - demography | 3–4 |
  - diagnostics of | 73 |
  - energy ablative techniques (see Energy ablative technique) |
  - Fuhrman nuclear grading system | 25, 26 |
  - genetic polymorphism | 10 |
  - gold standard | 103–104 |
  - growth rate | 102 |
  - hereditary leiomyomatosis-related RCC | 23 |
  - imaging technique |
    - computed tomography scanning | 74 |
    - FDG- PET | 74–75 |
    - magnetic resonance imaging | 74 |
    - ultrasound | 73 |
  - immunohistochemical profile and cytogenetic | 24 |
  - incidence rate | 4 |
  - incidental vs. symptomatic RCC | 70 |
  - interferon (see Interferon) |
  - lytic bone lesion | 70–71, 84 |
  - metastatic disease |
    - debulking nephrectomy | 80 |
    - MSKCC model | 79–80 |
    - survival probability | 80 |
  - morphologic features | 18, 19 |
  - mucinous tubular and spindle cell carcinoma | 21–22 |
  - NCI study | 70 |
  - neuroblastoma and carcinoma | 22 |
  - nonmetastatic RCC, prognostic factor |
    - anatomical feature | 75 |
    - clinical prognostic feature | 76–77 |
    - histological feature | 75–76 |
  - open and minimally invasive technique |
    - laparoscopic radical nephrectomy | 98–99 |
    - oncologic comparison | 98, 99 |
Renal cell carcinoma (RCC) (Cont.)
RALPN, 99–100
retroperitoneal approach, 100–101
papillary renal cell carcinoma
clinical difference, 20
hemorrhage and necrosis, 18–19
type 1, 19, 20
type 2, 19, 20
paraneoplastic manifestation
constitutional symptom, 72
endocrine abnormality, 72
hypercalcemia, 71–72
hypertension, 72
incidence and prognostic significance, 71
nonendocrine paraneoplastic syndrome, 73
nonmetastatic hepatic dysfunction, 72
polycythemia, 72
pathologic staging, 25–26
percutaneous vs. laparoscopic approach, 102
preoperative evaluation, 92
presurgical therapy
CARMENA, 246
clinical vignette, 247
cytoreductive nephrectomy, 241–242
downsizing and downstaging, 242–244
EORTC trial, 246–247
immunotherapy, pretreatment, 242
safety, 244–245
survival, 245–246
therapeutic need, 246
translational need, 246
prevalence, 9–10
prognostic nomogram
Kaplan-Meier survival analysis, 78
localized clear cell RCC, 77
prediction model, 77
RCC-specific survival, 79
UISS categorization, 78
UISS risk category, 78–79
progression rate, 103
pulmonary metastasis, 70–71
radial and partial nephrectomy
EORTC trial, 98
NSS, oncologic outcome, 96, 97
renal medullary carcinoma, 21
risk factor
cigarette smoking, 5
dietary factors and beverages, 9
genetics, 6–8
hormone and reproductive factor, 8
hypertension, 5–6
obesity, 5
occupational and environmental exposure, 8–9
role of radiation therapy (see Radiation therapy)
sarcomatoid dedifferentiation, 22, 23
SEER database, 103
SRM management, 103
staging, 75
symptoms, 70
systemic therapy, 84
toxicity management (see Toxicity management)
tubulocystic RCC, 23
unclassified RCC, 22
WHO classification, 18
Xp11 translocation carcinoma, 21, 22
Renal medullary carcinoma (RMC), 251, 254
R.E.N.A.L. nephrometry scoring system, 94–95
S
Sequential targeted therapy
biomarkers, 236
cytokines, 231–232
sequencing trials, 235, 236
tolerance and quality of life, 236
VEGF inhibitors
axitinib vs. sorafenib, 234–235
pazopanib, treatment refractory mRCC, 234
sorafenib and sunitinib, 232–234
VEGFi and mTORi, 235
Sorafenib, 198–201
angiogenesis inhibitor therapy, 198–201
vs. axitinib, 234–235
downsizing and downstaging, 242
and everolimus, 228–229
and IFN-α, 230
Sporadic RCC, 6
Stauffer’s syndrome, 72
Stereotactic body radiotherapy (SBRT), 167
Stereotactic radiosurgery (SRS), 164
Sunitinib
angiogenesis inhibitor therapy, 201–202
downsizing and downstaging, 243–244
fatigue and asthenia, 268
metastasectomy, 133–135
and temsirolimus, 228
vaccine therapy, 286–287
Survival after Nephrectomy and Immunotherapy (SANI) score, 192
T
Temsirolimus
and bevacizumab, 217
dosing and safety, 213
IFN, 219
monotherapy and combination regimens efficacy, 214
phase III study, 214–215
and VEGF-targeted therapy, 217
Tivozanib, 204
Toxicity management
acute side effect, 266
bleeding, 277–278
cardiac toxicity, 275–276
clinical vignette, 279–280
diarrhea, 273
drug exposure and efficacy, 266
fatigue and asthenia
molecular mechanism, 267–268
prevention, and side effect management, 268–269
sunitinib-related fatigue, 268
hematologic toxicity, 274
hypertension, 274–275
hypothyroidism, 269–270
liver and renal toxicity, 278–279
mTOR inhibitors, 266, 268
oral toxicity, 272–273
pharmacogenomics impact, 279
pneumonitis, 276, 277
side effect, patient education, 279
skin toxicity
  HFS, management strategy, 271, 272
  schedule adjustment, 271
  TKIs and mTOR inhibitor, 270
  topical therapy, 272
targeted therapy, 265–266
TKIs, selected toxicity, 266, 267
Tumor cell receptor tyrosine kinase
c-MET, 35
EGFR, 35
IGFR, 35–36
ROR2, 36

U
Ultrasound ablation, 145
Union Internationale Contre le Cancer (UICC), 18, 75, 174

V
Vascular endothelial growth factor (VEGF) and HIF pathway, 198, 199
inhibition of
  axitinib, 203
  bevacizumab, 202–203
  cediranib, 203–204
gene induction regulation, 198
  pazopanib, 202
  regorafenib, 204
  sorafenib, 198–201
  sunitinib, 201–202
tivozanib, 204
VEGF-Trap, 204–205
Vitespen, 179–180
von Hippel-Lindau (VHL) tumor
  HIF activity control, 30–31
  kidney cancer development, 32
  microtubule stabilization, 32
  pVHL, 30
  pVHL and HIFα interaction, 31
tumor suppressor gene, 30
  VHL syndrome, 6

W
World Health Organization (WHO), 18