

Index

A

- Addison self-help group (ADSHG), 529
- Adenomas, 40, 67–68, 73–74, 77–81, 86, 95, 118–119, 128, 138, 145, 165–166, 198, 247, 469–470, 472–473
- lipid-poor, 52–53, 80
 - lipid-rich, 74, 79
 - pituitary, 336
- Adenomatous polyposis coli (APC), 263–264, 266–270, 276, 294, 494, 497
- APC gene, 165, 296, 499
- Adjuvant mitotane, 344, 375–378, 433, 518
- Adjuvant radiotherapy, 344, 427, 432–434, 436
- Adjuvant therapy, 7–8, 375, 377–378, 427, 436–438, 450
- Adjuvant treatment, 7, 344, 377, 518, 525
- Adrenal adenomas, 11, 50–53, 58, 68–69, 74, 77–80, 86–87, 91, 97, 107, 123, 250, 460
- resected, 78
- Adrenal cancers, 9, 24, 489–490, 499
- calretinin immunostaining, 117
 - diffuse pattern, 111
 - fibroses and scar, 113
 - gross findings, 107–109
 - increased and slightly irregular mitochondria, 120
 - intramitochondrial granular bodies, 120
 - invasion of veins, 111
 - irregular nucleus, 119
 - Ki-67 (MiB-1) immunostaining, 116
 - lobated nucleus, 119
 - melan A immunostaining, 117
 - necroses, 112
 - pleomorphic mononuclear cells, 113
 - P53 protein immunostaining, 118
 - synaptophysin immunostaining, 117
 - thrombosis, 112
- Adrenal capsule, 236, 291–293, 295, 298
- Adrenal cortex, 5, 10, 52, 229, 269–270, 311–312, 328, 333, 335–336, 383–384, 386–387, 468, 483
- carcinoma, 50, 70, 75, 524
 - fetal, 291, 295, 297, 470
 - tumors, 523, 525, 527
- Adrenal cortical carcinoma (ACC), 524–527, 530
- Adrenalectomy, 18, 343, 403, 407, 411, 422–423
- Adrenal glands, 5–6, 253–254, 305, 384, 403, 414–415, 420
- adrenal cysts, 50, 72
 - adrenal masses, 23, 36, 38–43, 49–51, 53, 55, 59, 169
 - incidental, 68, 87
 - right, 71, 74–75, 315, 434, 471
 - unilateral, 81–82
 - adrenal steroidogenesis, 383, 387–388
 - adult, 236, 238–239, 243, 270, 291, 293
 - development, 288, 292–294
 - disease, 49, 523, 529
 - enlarged, 245
 - fetal, 237, 254, 305–306
 - insufficiency, 10–11, 14, 143, 293, 374, 445–446, 462
 - left, 326, 405, 407–408, 414
 - lesions, 10, 39–40, 49–50, 52, 54, 86, 89, 93, 96, 166, 169, 272, 414
 - metastases, 42, 54, 70–71, 73, 76, 85–87, 123
 - normal, 68, 73, 93, 95, 118, 388
 - pheochromocytomas, 70
 - right, 96, 404, 406–408, 414
- Adrenal glands, surgical approaches
- anterior transabdominal, 414
 - primary adrenal malignancy, laparoscopic surgery, 420–422
 - resections

- Adrenal glands, surgical approaches (*cont.*)
 aorta and arterial supply, 419
 diaphragm, 420
 liver, 416–417
 vena cava, 418–419
 thoracoabdominal incision, 415–416
- Adrenal hemorrhage, unilateral, 72–73
- Adrenal hyperplasia, 297, 469
- Adrenal hypoplasia congenita (AHC), 229
- Adrenal incidentalomas (AI), 23, 36, 49, 67, 71, 81, 91, 93
 autonomous hormone, epidemiological studies, 54
 hormone excess, 55–58
 biopsy studies, 53–54
 epidemiological studies
 adrenal lesions, 52
 adrenocortical tumors, 50–51
 metastasis, 51
 pheochromocytomas, 51
 imaging studies, 52–53
 pathologic diagnoses, distribution of, 50
 surgery and, 58
 delineating the diagnostic approach, 59
- Adrenal steroid biosynthesis
 adrenal steroidogenesis and dysregulation
 PKA, 388–389
 steroidogenic enzymes
 AKRs, 386–387
 cytochromes P450, 385–386
 HSDs, 385–386
 Rossman fold, 386
 short-chain dehydrogenase/reductases (SDRs), 386
 steroidogenic pathways in adrenal gland
 DOC, 387
 zona fasciculata, 387
- and zonation
 ACTH binding, 383
 adrenal gland and the enzymatic, zones, 384
 catabolic reactions, 385
 cholesterol to pregnenolone, conversion, 384
 DHEAS, 383
 downstream metabolism of pregnenolone, 384–385
 peripheral and target organ metabolism, 385
 redundant pathways and layers, 385
- Adrenal tissue, normal, 73–74, 218, 243, 298, 469–470, 497, 499
- Adrenal tumors, 3–4, 9–10, 32, 36, 39, 49, 51, 55–58, 218, 316–318, 325–328, 334–336, 483, 500, 521–525, 529–530
 gonadectomy-induced, 326–327
 growth, 328, 334–336
 phenotype, 326, 333–334
 primary, 87
- Adrenal vein
 left, 405–406
 right, 405–407
- Adrenocortical adenoma, 73
 CT and MRI studies
 lipid-rich adenoma, 74
- Adrenocortical adenoma (ACA), 52, 73, 77, 81, 89, 91, 107, 128, 164–165, 169, 219, 263, 273, 287, 459, 484, 486, 489
- Adrenocortical carcinoma (ACC), 403–404
 adjuvant management
 current surgical and, 428–431
 adrenal glands, surgical approaches
 anterior transabdominal, 414
 difficult resections, 416–417
 primary adrenal malignancy,
 laparoscopic surgery, 420–422
 thoracoabdominal incision, 415–416
 advanced, 26, 35, 39, 346, 351–354, 357, 359–360, 362–365, 369, 371–372, 378, 476
 age and sex distribution, 24
 aldosterone-producing, 459, 461, 463
 associated malignancies, 27
 case studies for
 adjuvant radiotherapy, 434–436
 liver metastasis, 437–438
 cells, 24, 244, 252, 298, 300, 332, 352–354, 388–389, 469, 493, 500
 in children, 469, 471, 473, 475, 477
 cohort, 450, 484, 486
 CT and MRI studies, 74–75
 cytotoxic chemotherapy,
 effectiveness of, 500
 differential diagnosis
 carcinoma, 81–82
 metastasis, 76–81
 experimental, 158
 human, 141
 imaging and staging
 with FDG-PET, 82
 incidence and prevalence, 23–24
 laboratory evaluation, 445–446
 localization, 26

- new agents with potential, examples, 495–496
- newer modes of therapy
 - adenoassociated virus (AAV), 507–508
 - SCID, 507
- novel strategies
 - metastasis suppression, therapy aimed, 506–507
 - microenvironment, targeting, 503–506
 - tumor vasculature, targeting, 501–503
- patient follow-up
 - history, 444
- perioperative considerations
 - beta-adrenergic blockade, 408
 - CT scan, 409–410
 - glucocorticoid insufficiency, 409
 - high-quality preoperative imaging, 409
 - intraoperative, 410–411
 - postoperative, 411
- physical examination, 444–445
- proapoptotic strategies, 500–501
- prognosis of, 26–27
- radiotherapy for, 427, 431–438
- risk factors, 24–25
- risk modifiers for, 451–452
- and sites for emerging therapies, progression, 494
- stage at presentation, 25–26
- stage IV cortisol-secreting, 413
- surgery
 - complications, hernia formation, 422
 - curative intent, primary therapy, 411–412
 - hormonal control and tumor debulking, palliation, 413
 - management, 14
 - recurrences, 412–413
- surgical adrenal anatomy
 - adjacent structures, 406–407
 - adrenal glands and surrounding retroperitoneal structures, 404
 - arterial supply, 405
 - Gerota's fascia, 408
 - left adrenal gland and overlying pancreas and spleen, anatomic relationship, 408
 - lymphatic drainage, 406
 - right adrenal gland and overlying liver, anatomic relationship, 407
 - venous drainage, 406
- survival of patients with, 4
- suspected, 37, 39–41, 414
- tumor size at primary diagnosis, 25
- 47-year-old female with large left adrenal, 17–18
- 32-year-old female with large right adrenal, 15
- 35-year-old female with nonfunctional, 16
- 40-year-old male 1 year post right adrenalectomy, 16
- Adrenocortical cells, 90, 92, 107, 142, 215, 239–240, 245, 289, 297, 469
 - bovine, 215, 220, 239, 318, 329
 - lines, 305–306
- Adrenocortical growth, 142–143, 235, 290, 293, 295
- Adrenocortical lesions, 141, 166–169, 446
- Adrenocortical stem and progenitor cells
 - adrenal adult stem and progenitor cells
 - DAX1, 293–294
 - IGF2, 295
 - Shh, 294
 - telomerase, 295
 - Wnt/ β -Xatenin, 294
 - adrenocortical carcinoma initiation
 - IGF2, 297
 - maintenance of adrenocortical carcinoma, 299
 - Pod1, 298
 - p53/telomerase, 298
 - Wnt/ β -catenin, 296
 - cancer maintenance, 286
 - normal adrenal adult stem cells
 - adrenal development and structure, 288–289
 - adrenal precursor cells in fetal zone, 291
 - capsular stem cell niche and definitive cortex, 290
 - establishment of stem cell niche, 290
 - histologic organization, 288
 - homeostatic model of adrenocortical growth, 290
 - organogenesis, 289
 - stem/progenitor cells in adrenal capsule, 291–293
 - origins of cancer stem cells
 - adrenocortical tumors, 287
- Adrenocortical steroidogenesis, 305–306, 312, 460
- Adrenocortical tissues, normal, 91, 95, 140, 143, 247
- Adrenocortical tumor
 - growth, 255, 326, 328

- Adrenocortical tumorigenesis, 127, 137, 141–144, 218–219, 240, 247–248, 250, 252, 254–255, 271, 275–276, 299, 326, 333, 470
 human, 221
- Adrenocortical tumors pathogenesis, 249
- Adrenocorticotrophic hormone (ACTH), 90
 ACTH-independent macronodular adrenal hyperplasia (AIMAH), 140–141, 273, 275, 468
 induced steroidogenesis, 237
 responsiveness, 311, 313, 318
- Adriamycin, 352–353
- ADSHG, *see* Addison self-help group (ADSHG)
- Adult ACCs, 143, 164, 193, 198, 243–244, 247, 470, 472
- Advanced adrenocortical carcinoma, 369, 371
- AHC, *see* Adrenal hypoplasia congenita (AHC)
- Aldo-keto reductases (AKR), 386–387
- Aldosterone, 54–56, 165, 310–314, 383, 385, 387–388, 391, 446, 457–458, 460–462, 472
- Aldosterone-producing adenoma (APA), 458, 524
- Aldosterone producing adrenocortical carcinoma (APAC), 34
 epidemiology of, 457–458
 hormonal features
 clinical and, 458–460
 imaging characteristics of, 461
 pathology of, 460–461, 463
 prognosis, 461–462
 treatment, 462–464
- Altered signaling pathways, therapy targeted
 BWS, 494, 496
 EGF receptor, 499
 FGF receptor, 498–499
 IGF2-IGF1R pathway, 497–498
 anti-IGF1R antibodies, 498
 small molecule TKIs, 497–498
 LFS, 494
 multi-kinase inhibition strategies, 499
 signaling targets identification, 493
 gene expression analysis, 497
 genetic syndromes, 494, 496–497
 Wnt signaling pathway, 499–500
 APC, 499–500
- Aminoglutethimide, 12, 92, 346, 392, 395–397, 399
- Anaphase bridges, 207, 213–214
- Anderson's syndrome, 11
- Androgens, 33, 57, 119, 363, 384–385, 388, 390, 392, 395, 397, 445, 459
 excess, 32–33, 37, 383, 389, 396–398
- Aneuploidy, 127, 129–130, 144, 212, 219, 489
- Angiogenesis, 139–140, 176, 195–196, 269, 361–362, 484, 499
 in adrenocortical carcinoma, 139
- Angiopoietin 2 (ANGPT2), 484
- Angiotensin II, 306, 383
- Antagonists, 265, 267, 390, 392, 396
- APA, *see* Aldosterone-producing adenoma (APA)
- APAC, *see* Aldosterone producing adrenocortical carcinoma (APAC)
- APC, *see* Adenomatous polyposis coli (APC)
- Apoptosis, 128, 137, 176–177, 179, 181, 184–185, 194–196, 199, 207, 209, 212–213, 216, 248, 275, 299, 500–501
- ARAR0332 protocol, 477–478
- Arteries, 405, 419
- B**
- Beckwith–Wiedemann syndrome (BWS), 158, 160, 246, 271, 297, 468, 494, 496–497
 BWS Registry, 228, 230–232
 cancer, 231–233
 clinical features, 228–230
 diagnosis, 227–228
 genetics, 230–231
 IGF2 imprinted locus, 231
- Benign adenomas, 37, 39, 51–52, 82, 218, 253, 431
- Benign adrenal adenomas, 52, 89, 91
- Benign adrenal lesions, 39, 86, 91, 160, 167
- Benign adrenal nodules, 86–87
- Benign adrenal tumors, 287, 297
- Benign lesions, 39–40, 53, 74, 81, 86–87, 130, 136, 166, 218–219
- Benign tumors, 42, 51, 71, 87, 140, 144, 249–250, 459, 484, 497, 523
- BFB cycles, *see* Breakage fusion bridge (BFB) cycles
- Biological resource centers (BRC), 525, 529
- Blood pressure, 34, 392, 398, 445, 474
- Bone marrow elements, 71–72
- Bovine adrenocortical cell lines, 318
- BRAF mutations, 137–138
- BRC, *see* Biological resource centers (BRC)
- Breakage fusion bridge (BFB) cycles, 214
- Breast cancer, 144, 174–175, 182, 185, 200, 214, 219, 390, 395, 432–433, 501, 508

- Budd Chiari syndrome, 16
- BWS, *see* Beckwith–Wiedemann syndrome (BWS)
- C**
- Calcifications, 39, 52, 71–73, 75, 81–82, 113, 461, 472
- Cancer
- cell, 128, 216, 286, 325, 356, 498, 500
 - high incidence of, 197, 468–469
 - risk, 160, 175, 201, 227, 231
 - screening, 232
 - stem cells, 286–288, 299–300
- Cancer-associated fibroblasts (CAFs), 504
- Canonical WNT/ β -catenin signaling pathway, 264, 294
- Canrenone, 392
- Carcinogenesis, 127–128, 160, 166, 207, 210, 212–213, 235–236, 254–255, 468
- Cardiovascular disease, 11
- Carney Complex, 468
- β -Catenin, 165, 294, 296–297
- accumulation, 265, 272, 274
 - activation, 165, 263, 266–267, 274–275
 - mutation, 272, 275–276
 - mutation somatic, 266, 275
 - phosphorylation, 266–267
- Cells
- cycle arrest, 176, 185, 195–196, 199, 433, 494
 - growth, 246, 248, 251–252, 307, 309
 - model, cancer stem, 285–286
 - types, 118, 208, 212, 216, 285, 289–290, 315, 494, 500, 502–503
- Chemotherapy, 7, 14, 42, 95, 232, 251, 344, 412–413, 427, 433, 438, 518
- chemotherapeutic agents, 196, 353, 365
 - combination theory, 354–357
 - plus mitotane, 357–360
 - plus target therapy, 361–362
 - prognostic and predictive factors, 363–365
 - single-agent, 352–354
- Childhood adrenocortical carcinoma (ACC), 143, 158, 160, 164, 193, 197, 199, 201, 328, 334, 467, 470–471, 475, 477
- biology of, 468–470
 - clinical characteristics, 470–472
 - collaborative research initiative, 477–478
 - diagnosis, 472–473
 - prognostic factors, 473–475
 - staging, 475
- St. Jude Children’s Research Hospital International Outreach Program, 471
- treatment, 475–477
 - 2-year-old boy with virilization, 471
- Childhood adrenocortical tumors, 200
- Children’s Oncology Group (COG)
- COG ARAR 0332 protocol treatment, 477
- Cisplatin, 345, 351–354, 356–357, 359–360, 362–364, 372, 431, 476, 519
- Classical histopathology and immunohistochemistry, 107, 109, 111, 113, 117, 119, 121, 123
- Clinical presentation of ACC
- hormone excess, 31–33
 - incidentally detected, 36
 - loco-regional manifestations, 34–35
 - metastatic disease, 35
- Collaborative Group for Adrenocortical Cancer (COACT), 362
- Combination chemotherapy, 354, 357
- plus mitotane, 357–360
 - without mitotane, 355–357
- COMETE, *see* Cortico-medullo-tumors endocrines (COMETE)
- Comparative genomic hybridization (CGH), 129–132, 213, 470, 488
- Computed tomography (CT), 67–68
- adrenocortical adenoma, 73
 - bar graph, 79
 - lipid-rich adenoma, 74
 - adrenocortical carcinoma, 74–75
 - clinical utility
 - adrenal adenoma, 69
 - adrenal carcinoma, 69
 - cyst
 - adrenal pseudocyst, 72
 - differential diagnosis, adrenocortical adenoma
 - carcinoma, 81–82
 - metastasis, 76–81
 - hemorrhage, 72
 - adrenal hematoma, 73
 - incidentaloma, 70–71
 - metastasis, 76
 - adrenal cortical carcinoma, 75
 - from renal carcinoma, 76
 - myelolipoma, 71–72
 - pheochromocytoma
 - intravenous contrast, 70
- Congenital adrenal hyperplasia (CAH), 3, 25, 33, 51, 57, 158, 468, 472

- Conn's adenomas, 34, 74, 95, 457, 459, 522–523
- Cortico-medullo-tumors endocrines (COMETE), 521–522
- Cortisol-secreting adenomas, 166
- CREB-binding protein (CBP), 268–269
- Cushing's disease (CD), 3–4, 18, 32, 34, 36, 67, 69, 88, 95, 167, 395–396, 444–445, 522–523
- ACTH-dependent, adrenal gland
 - appearance, 6
 - clinical remission, 6
 - features, 32
 - management, 11
 - signs and symptoms, 389
- Cyclin D2, 335
- Cyst
 - CT and MRI studies
 - adrenal pseudocyst, 72
- Cytokines, 140, 504–505
- Cytotoxic drugs, 4, 7, 300, 351–352, 361–362, 365
- D**
- Dehydroepiandrosterone sulfate (DHEAS), 445
- 11-Deoxycorticosterone (DOC), 459
- Dexamethasone-suppression test (DST), 55–56
- Differential diagnosis in ACC, 121, 123
 - immunostainings in, 122
- Dilemma, 311, 378–379
- DST, *see* Dexamethasone-suppression test (DST)
- Dutch adrenal network
 - future goals, 519
 - patients registry, 518
 - results of, 518–519
- Dyskeratosis congenita (DC), 217
- E**
- Eastern Cooperative Oncology Group (ECOG)
 - phase II study, 352
- Ectopic GPCR expression, 141
- Endocrine neoplasia type, multiple, 51, 153, 165, 336, 494
- Endocrine work-up, 37–38, 57
- ENS@T, *see* European network for study of @drenal tumors (ENS@T)
- Epithelial membrane antigen (EMA), 116, 123
- Eplerenone, 56, 393
- ESF, *see* European science foundation (ESF)
- Estrogen excess, 57, 389, 398
- Etomidate, 92–93, 96–97, 313, 346, 395, 397
- Etoposide, 345, 353–354, 356, 359, 362–363, 372, 431, 476, 519
- European network for study of adrenal tumors, 379
- European network for study of @drenal tumors (ENS@T)
 - disseminative effects
 - integrational and, 529–530
 - exchange idea
 - harmonization, 524
 - material, 524
 - science, 524–525
 - methodological exchange
 - technical and, 523–524
 - network finance, 528
 - network organization
 - steering committee, 522, 527–529
 - working groups, 527–528
 - patient number, 522–523
 - research advancements, 525–527
 - Website, 528
- European Science Foundation (ESF), 522, 528–529
- F**
- Familial adenomatous polyposis (FAP), 145, 158, 164–167, 169, 263, 267, 276, 296, 357, 494
- FDG-PET, *see* Fluorodeoxyglucose-based positron emission tomography (FDG-PET)
- Fetal adrenocortical cells, 229, 237
- Fibromyxosarcoma, 10
- Fibroses, 108–109, 113, 472
- Fine-needle aspiration (FNA), 476
 - Fine-needle aspiration/cut biopsy, 41–43
- Fine-needle biopsies (FNB), 54, 57
- First International Randomized Trial on locally advanced and metastatic adrenocortical carcinoma treatment (FIRM-ACT), 346, 351, 431, 517–519, 525
 - study, 362
 - trial design, 363
- Fluorodeoxyglucose-based positron emission tomography (FDG-PET), 447–449
- Founder effect, 181
- Front-line therapy, 346
- Functional imaging of adrenocortical carcinoma
 - 18-F FDG PET-CT, 85–87, 89
 - 51-year-old woman with Cushing's syndrome, 88

- molecular imaging, adrenocortical tracers, 89
 - enzyme inhibitors, 92
 - [¹⁸F]-fluoro-etomidate, 96
 - [¹²³I/¹³¹I]-iodo-metomidate, 96–98
 - metomidate (MTO), 92–96
 - norcholesterol scintigraphy, 90–92
 - radiotracer accumulation, mechanisms of, 90
- G**
- Gemcitabine, 354, 357, 361
- Gene mutation carriers, 175
- Gene therapy, 202, 496, 507–508
- Genetic aberrations, 131, 144–145
- Genetically modified mouse models with an adrenal tumor phenotype, 333
- Genetic alterations, 127, 160, 197–198, 201, 246, 253, 263, 270, 272, 276, 468, 470, 489
- Genetic counseling, 167–168, 470
- Genetic syndromes
 - adrenal characteristics, 159
 - associated with adrenocortical cancer diagnostic criteria, 161–163
 - familial adenomatous polyposis, 164–165
 - Li–Fraumeni syndrome, 164
 - multiple endocrine neoplasia type 1, 165–167
 - neurofibromatosis type 1, 167
 - overgrowth syndromes, 160–163
 - germline mutations screening, 167–168
 - hereditary syndromes
 - screening and surveillance, 168–169
 - MEN1 with ACC, statistical significance for, 154
 - overview, 156–157
- Genomic studies
 - gene expression, 483–488
 - hybridization technology, 488–489
 - microRNA (miRNA) profiling, 489
 - molecular profiling
 - diagnosis of, 489–490
 - prediction, 490
 - prognosis of, 490
- German ACC Registry, 36
- German adrenal network improving medical research and education (GANIMED), 521–522, 525–526
- Germline mutations, 27, 155, 167, 176, 178, 180, 263, 272, 276, 433, 467, 469
- Germline *TP53* mutations, 178–182, 194, 201, 467, 469, 476
- Gonadectomy, 333, 335
- Gossypol, 353
- G-Protein-coupled receptors (GPCRs), 139–141, 507
- Grading system, 119
- Gross tumor volume (GTV), 434–435, 437
- Growth factors, 230, 235–237, 247, 251–252, 295, 313, 332–333, 460, 468, 504
- Growth hormone (GH), 240, 251
- GTV, *see* Gross tumor volume (GTV)
- Gynecomastia, 33, 346, 374, 389, 392–393
- H**
- Hemihypertrophy, 228
- Hemorrhage, 72
 - CT and MRI studies
 - adrenal hematoma, 73
- Hepatocyte growth factor (HGF), 504, 506
- Hereditary syndromes, 168–169
 - see also* Genetic syndromes
- HGF, *see* Hepatocyte growth factor (HGF)
- Hierarchical clustering (HC), 484–485
- Hirsutism, 10, 32–33, 389, 396–398, 403, 444, 471
- Histopathology of ACC, 109
 - adrenal cancer
 - diffuse pattern, 111
 - fibroses and scar, 113
 - invasion of veins, 111
 - necroses, 112
 - pleomorphic mononuclear cells, 113
 - thrombosis, 112
 - features of, 110
- Hormonal symptoms, 12, 444
- Hormone excess and AI
 - endocrine functions, 57–58
 - hyperaldosteronism, 56–57
 - hyperandrogenemia, 57
 - hypercortisolism, 56
 - step-wise diagnostic approach, 55
 - pheochromocytoma, 57
- Human adrenal glands, 237–238
- Human adrenocortical carcinoma (HAC), 274, 313–315
- Human adrenocortical cell lines, 239, 330
 - derived cell line
 - ACT-1 human adrenal carcinoma, 314–315
 - RL-251 human adrenal carcinoma, 315
 - SW13 human adrenal carcinoma, 314
 - NCI-H295, NCI-H295R and NCI-H295A cancer therapy tool, 312–313
 - enzyme expression, 312

- Human adrenocortical cell lines (*cont.*)
 growth and characterization, 309–310
 hormone receptors and responsiveness, 310–311
 information on, 308–309
 origin and development, 307
 and related clones, 313
 steroidogenesis, 311–312
 pediatric adrenocortical adenoma derived cell line
 growth and steroidogenesis, 314
 origin and development, 314
 tumors, 250, 295, 353
 from viral oncogenes, 315
- Human fetal adrenal gland, 236
- Hyperaldosteronism, 410, 445, 459–460, 522, 527, 530
 primary, 56, 91, 457
- Hyperandrogenemia, 57, 237
- Hypercortisolism, 32, 54–56, 107, 166, 378, 395–396, 422, 471, 522
- Hypernephroma, 9
- Hypertension, 32, 34, 54, 56–58, 73, 346, 389–391, 393–394, 423, 443, 457, 459–461, 472, 522
- Hypoglycemia, neonatal, 227–229
- Hypokalemia, 32, 34, 37–38, 346, 389–390, 392–394, 397, 410, 457, 459–461, 472
- I**
- Idiopathic hyperaldosteronism (IHA), 458
- Imaging for diagnostic work-up
 cross-sectional, 447–448
 CT, 39
 FDG-PET, 40
 functional, 448–449
 MRI, 40
 staging, 40–41
 symptom, 447
 ultrasound, 39
- Immunocytochemistry
 adrenal cancers and immunostaining
 calretinin, 117
 Ki-67 (MiB-1), 116
 melan A, 117
 P53 protein, 118
 synaptophysin, 117
- IMRT, *see* Intensity modulated radiation therapy (IMRT)
- Incidentaloma, CT and MRI studies, 70–71
- INSERM, *see* Institut national de la recherche française (INSERM)
- Institut national de la recherche française (INSERM), 522, 528
- Insulin, 238, 246, 251, 329
- Insulin-like growth factors (IGF)
 alterations in adrenal tumors, 241–242
 binding proteins, 235, 238, 240, 250
 IGF1 and IGF2, 235–239, 244, 247–248, 254
 IGF-binding protein (IGFBP)
 elevated, 250–252, 254
 high-affinity, 238–239
 IGFBP-proteases, 239, 245
 increased, 250–252, 255
 induction of, 239
 inhibitory effect of, 240, 251
 produced, 237, 239, 253
 secretion, 239
 IGF2 overexpression of, 246, 253–255, 468, 497
 IGF receptors, 238, 247
 IGF2/mannose-6-phosphate (IGF2R)-receptor, 249–250
 IGF1R, 247–249
 postulated effects of, 255
 role in adrenocortical tumorigenesis
 IGF1, 240–243
 IGF2, 243–246
 role in normal adult adrenal gland
 IGF-binding proteins, 238–240
 IGF receptors, 238
 insulin-like growth factors, 236–238
- Insulin receptors (IR), 295, 497–498
- Intensity modulated radiation therapy (IMRT), 434–435, 438
- International Pediatric Adrenocortical Tumor Registry (IPACTR), 457, 471–472, 474
- International pediatric adrenocortical tumor registry (IPACTR), 457
- Intervention trials, 331
- Intracellular adrenocortical cell signaling and mechanisms, 306
- Iodometomidate, 53, 96–98
- IPACTR, *see* International Pediatric Adrenocortical Tumor Registry (IPACTR)
- Isolated hemihyperplasia (IH), 229–230, 232
- K**
- Kidney capsule, 215–216, 329, 331
- Kirsten murine sarcoma virus (MSV), 317

L

- Laboratory work-up, 36–39
- Laparoscopic adrenalectomy (LA), 403, 420–422
- Laparoscopy, 420–421, 423
- Lesions
- functional, 165–166
 - patient's liver, 437
 - pre-malignant, 165, 214
- Li–Fraumeni syndrome (LFS), 299, 433, 467
- cancer risk patterns, 175
 - clinical definition, 173
 - family pedigree, 174
 - families, 164, 169, 173, 179, 182, 197, 201
 - germline mutations, relative frequency, 176
 - medical and ethical considerations, 185–187
 - modifier genes in, 179–180
 - mouse models, 182–185
 - role of other genes in, 179
- TP53 and, 178–179
- functional models of germline mutations, 181–182
 - gene inactivation, 177
 - tumor suppressor, 175–177
 - unique Brazilian LFS-TP53 codon mutation phenotype, 180–181
- Liver
- damage, 398
 - metastases, 13, 18, 40, 96–97, 438
- Locally Advanced and Metastatic Adrenocortical Carcinoma Treatment, 362, 431
- Lung cancer, 24, 86, 175, 248, 354, 506
- Lymphatics, regional, 436, 438
- Lymph nodes, positive, 41, 121, 428–429

M

- Macfarlane, 12–13, 428
- classification, 41
- Macroglossia, 160, 227–229, 496
- Magnetic resonance imaging
- adrenocortical carcinoma, 67, 73–75
 - clinical utility
 - adrenal adenoma, 69
 - adrenal carcinoma, 69
 - cyst
 - adrenal pseudocyst, 72
 - differential diagnosis, 77–81
 - hemorrhage, 72
 - adrenal hematoma, 73
 - incidentaloma, 70–71
 - lipid-rich adenoma, 74
 - metastasis, 76
 - adrenal cortical carcinoma, 75
 - from renal carcinoma, 76
 - myelolipoma, 71–72
 - pheochromocytoma
 - intravenous contrast, 70
- Malignant adrenal lesions, 40, 86–87
- Malignant adrenal masses, 40
- Malignant adrenal tumors, 10, 287, 431, 497, 523
- Malignant adrenocortical tumors, 114–115, 218, 253, 274–275, 484
- Malignant behavior, 49–51, 115, 473
- Malignant lesions, 39–40, 42, 49, 53, 85, 87, 94–95, 140, 144–145, 215, 218–219, 461, 500
- Malignant neoplasms, 32, 76, 127–128, 131
- Malignant phenotype, 141, 208, 213, 215–216, 243, 246, 251, 253–254, 326, 329–330
- Malignant pheochromocytomas, 53, 123, 420–421
- Malignant transformation, 85, 127, 129, 138, 143, 212, 215–216, 236, 245, 470
- Malignant tumors, 3, 9, 85, 91, 94, 107, 123, 128, 130, 138, 140, 143–144, 252–255, 275, 459–460, 484–485
- MAPK, *see* Mitogen-activated protein kinase (MAPK)
- Markers, polymorphic, 128–129, 131–132
- Matrix-metallo-proteinases (MMPs), 252, 506
- McCune–Albright syndrome, 468
- Medical treatment of adrenocortical carcinoma
- steroidogenic hormone excess, 346
- Metanephrines, 37, 55, 57, 59
- Metastasis, 10–12, 25–26, 50–54, 76–82, 86–87, 107–108, 112, 184, 253–254, 326, 429, 459–462
- brain, 40
 - CT and MRI studies, 75
 - adrenal cortical carcinoma, 75
 - from renal carcinoma, 76
 - suppress, 506–507
 - suspected, 42–43
- Metastatic adrenocortical carcinoma treatment, 346, 525
- Metastatic disease, 4, 6, 12, 16, 26, 31, 35, 42, 51, 76, 81, 89, 244, 428, 476–477
- treatment, 344–346
- Metastatic lesions, 82, 86–87, 89, 94, 98, 286
- Mineralocorticoid excess
- androgen excess, 396
 - drugs for treatment of, 397

- Mineralocorticoid excess (*cont.*)
 inhibitors of, 397
 nonspecific treatment of, 398
 receptor antagonists, 397–398
 drugs for treatment, 391
 estrogen excess, treatment, 398–399
 glucocorticoid excess, 393
 cardiovascular and metabolic consequences, nonspecific treatment, 396
 drugs for treatment of, 394
 inhibitors, 394–396
 receptor antagonists, 396
 inhibitors of, 391–392
 receptor antagonists, 392
 hypertension and hypokalemia, nonspecific treatment, 393
- Missense mutations, 177, 179, 182, 184–185, 199, 249
- Mitogen-activated protein kinase (MAPK), 138–139, 236, 252, 361
- Mitoses, 109, 212–213
 atypical, 107, 112, 461, 473
- Mitotane therapy, 356, 359–360, 379, 427, 434, 443, 446, 518
 ability and metabolic activity, 5
 in adjuvant setting, 375
 European Network for Study of Adrenal Tumors, 379
 recurrence-free survival, 377
 study, advantages of, 377–378
 treatment outcome, 376
 in advanced adrenocortical carcinoma, 371
 Lysodren[®], 372
 treatment outcome, 372–373
 historical background
 atrophic changes, 370
 inhibition by α -tocopherol, 6
 MAVE scheme, 359–360
 pharmacokinetics, 369
 pharmacologic characteristics, 370
 specificity of, 5
 toxicity and dosage, 373–375
 transformation, 5
- Modifier genes, 178–179
- Molecular imaging for adrenocortical tracers, 89
 enzyme inhibitors, 92
 [¹⁸F]-fluoro-etomidate, 96
 [¹²³I/¹³¹I]-iodo-metomidate, 96–98
 68-year-old patient with, 97
 metomidate (MTO), 92–96
 in adrenocortical tumor entities, 94
 patients with ACC, 95
 norcholesterol scintigraphy, 90–92
 radiotracer accumulation, mechanisms of, 90
- Mouse models
 of adrenal tumorigenesis, 325, 327, 329, 331, 333, 335
 with spontaneous/induced adrenal tumor growth, 326–328
 with targeted deletions inducing adrenal tumors, 335–336
 with transgenic expression of oncogene-inducing adrenal tumor, 333–334
 utilizing transplanted adrenal tumor cells, 328–332
- Multiple endocrine neoplasia syndrome type 1 (MEN1), 468
- Murine adrenocortical steroid biosynthetic pathway, 316
- Mutations
 β -catenin-activating, 271
 epigenetic, 228, 230
 hotspot, 184, 195
 oncogenic, 128, 210
- Myelolipomas, 50, 52, 82
 CT and MRI studies, 71–72
- Myeloma, multiple, 498
- N**
- Nab-paclitaxel treatment, 354
- NAPACA, *see* Non-aldosterone-producing adrenocortical adenomas (NAPACA)
- National Cancer Data Base (NCDB), 429, 432
- National Cancer Institute (NCI), 13, 228, 312, 360, 403, 483
- National Italian Study Group on Adrenal Tumors (NISGAT), 521–522, 525–526
- National Mortality Followback Survey, 24
- NCDB, *see* National Cancer Data Base (NCDB)
- Necroses, 39–40, 52, 69–70, 75–76, 80–81, 87, 107–109, 112–113, 434, 461, 463, 472–473
- Necrotic metastases
 CT scan, 77
- Negative predictive value (NPV), 40, 86–88
- Neoplasms, 6, 58, 130, 173, 275, 312, 433, 468, 473, 483
- Nephrectomy, 13–14, 16, 18, 408
- NISGAT, *see* National Italian study group on adrenal tumors (NISGAT)

- Nonadenomas, 79, 81
- Non-aldosterone-producing adrenocortical adenomas (NAPACA), 524, 527
- Nonsteroidal anti-androgen, 398
- Normal cortex (NC), 484, 486
- Novel strategies for ACC
- metastasis suppression, therapy aimed, 506–507
 - microenvironment, targeting, 503
 - fibroblasts of, 504–505
 - immune cells, 505
 - proteolytic enzymes in, 505–506
 - tumor vasculature, targeting, 501–503
- O**
- OAR, *see* Organs-at-risk (OAR)
- Oncogene, 128, 135, 193, 195, 236, 247, 255, 315, 317, 333, 506, 508
- Oncogenesis, 3, 128, 317, 506
- Organogenesis, 289–290
- Organs-at-risk (OAR), 438
- Overgrowth syndromes, 160, 168
- P**
- Paclitaxel, 313, 353–354
- PAL, *see* Primary aldosteronism (PAL)
- Palpable malignant adrenal tumors, 10
- Paragangliomas, 41, 522, 527, 530
- Patient with ACC
- adrenal steroid excess, clinical manifestations, 389
 - Cushing's Syndrome
 - signs and symptoms, 389
 - therapeutic strategies, 391
 - glucocorticoid receptor antagonists, 390
 - tamoxifen, 390
- PCA, *see* Principal component analysis (PCA)
- PCNA, *see* Proliferating cell nuclear antigen (PCNA)
- Pediatric adrenocortical carcinoma, 471
- see also* Childhood adrenocortical carcinoma (ACC)
- Peritoneal cavity, 407, 412, 414, 449, 452
- P-Glycoprotein, 352, 500
- PHA, *see* Primary hyperaldosteronism (PHA)
- Phaeochromocytoma, 38, 43
- Pharmacokinetics, 518
- Pharmacotherapy for hormone excess in
- adrenocortical carcinoma, 383, 385, 387, 389, 391, 393, 395, 397, 399
- Pheochromocytoma/paraganglioma (PHE/PGL), 524, 526–528
- Pheochromocytomas, 36–37, 50–55, 57, 70, 86, 123, 160, 166–167, 169, 219, 248, 522, 527, 530
- CT and MRI studies
 - human, 248
 - and paragangliomas, 523
- Planning target volume (PTV), 434–435, 437
- Polycystic ovary syndrome, 33
- Positive predictive value (PPV), 40, 86–87
- Post-surgical use of mitotane, 6
- PPNAD, *see* Primary pigmented nodular adrenocortical disease (PPNAD)
- Pregnenolone, 370, 384–385, 387
- Pre-implantation genetic diagnosis (PIGD), 186
- Primary adrenocortical carcinoma, 198
- Primary aldosteronism (PAL), 54–55, 527
- Primary hyperaldosteronism (PHA), 457–460, 464
- Primary pigmented nodular adrenocortical disease (PPNAD), 252, 271–272, 275, 468
- Primary tumor, 7, 27, 40, 42–43, 58, 93, 123, 199, 363, 472, 475–476, 503, 506
- Principal component analysis (PCA), 484, 486
- Progesterone, 317, 387, 392
- Proliferating cell nuclear antigen (PCNA), 460
- Protein
- conformation, 177
 - level, 247–248, 250
- Protein-kinase (PKA), 141, 252, 272, 388
- PTV, *see* Planning target volume (PTV)
- Pulmonary metastases, 437–438
- R**
- Radiation dose distributions, 434, 438
- Radiation therapy, 174, 251–252, 346, 361, 443
- for adrenocortical carcinoma, 429, 431, 433, 437
- Radical surgery of residual disease, 359–360, 363
- Radiotherapy, 14, 344, 427, 431–434, 436–438, 476
- Ras oncogenes, 137–138, 318
- Receptors, 96, 140, 235–236, 243, 247, 249, 251, 254, 265, 295, 310, 326, 331, 383, 499, 504–506
- Renal disease, 230
- Replacement, reduction, refinement (3Rs), 524
- Research network program (RNP), 528–529
- Resected adrenal adenomas
- histologic specimens, 78
 - plot of unenhanced CT, 78

- Residual disease, 344, 351, 359–360, 363, 365, 429
- Risk-based ACC
 high-risk disease, 450
 low-risk localized disease, 450
 unresectable localized disease, 451
- RNP, *see* Research network program (RNP)
- Rodent adrenocortical cell lines
 experimentally induced rodent adrenal cell lines, 317–318
 Y1 adrenal cell line, 315–316
- Rossmann fold, 386
- S**
- SCID, *see* Severe combined immunodeficiency (SCID)
- Scoring systems, 112–113, 115
 system of Hough, 114
 system of van Slooten, 115
 system of Weiss, 114–115
 thresholds for malignancy by Aubert, 115
- Sedation, 395
- SEER, *see* Surveillance, epidemiology and end results (SEER) database
- Senescence, 128, 137–138, 176, 196, 207–208, 212–213, 216, 295, 299, 305, 315
- Severe combined immunodeficiency (SCID), 507
- Simian virus 40 (SV40) T-antigen, 315
- Single-agent chemotherapy, 352–354
- South West Oncology Group (SWOG), 357, 359
- Spironolactone, 56, 392–394, 397–398, 459, 462, 464
- Sporadic adrenocortical tumors, 166, 240, 271, 296
- Stage IV disease, 121, 433, 474, 518
- Staging system, 40–41, 120, 428, 474
 TNM classification, 121
- Steroidogenesis, 34, 140–142, 243, 307, 311, 314, 344, 370, 383–384, 387–388, 390
- Steroids
 biosynthesis, 383, 385
 pathway, 311
 hormones, 142, 311, 314, 458–459
- Streptozotocin, 351, 357, 359, 362–364, 431, 519
 plus mitotane, 359
- Stress, oxidative, 248, 252
- Sunitinib, 499, 502, 505
- Suprarenal cortical syndrome, 10
- Suramin, 312, 352–353
- Surgery
 adrenal, 11
 for adrenocortical carcinoma, 403, 405, 407, 409, 411, 413, 415, 417, 419, 421, 423
 complete, 526
 perspective, 9, 11, 13, 15, 17
 radical, 359, 377
- Surveillance, epidemiology and end results (SEER) database, 428, 432
- SWOG, *see* South West Oncology Group (SWOG)
- Syndromes, 9–11, 153, 158, 160, 164–168, 183, 217, 227, 229, 335, 445, 457, 468, 497
See also specific syndromes
- T**
- Tamoxifen, 291–293, 390, 399
- Tarividar, 360, 500
- Telomerase, 295, 299
 activity, 209–210, 212, 214–216, 218, 295, 460
 and adrenocortical carcinoma, 218
 in experimental adrenocortical carcinoma, 215–217
- Telomere maintenance mechanisms (TMMs), 207–208, 210, 212, 214–219
- Telomeres, 295, 298
 in adrenocortical carcinoma, 218
 associated proteins, 211
 based model of carcinogenesis, 213–215
 end-replication problem and telomerase, 208–210
 focused model of tumorigenesis, 216
 human syndromes and defects in physiology, 217
 maintenance mechanisms, 219
 model of genomic shuffling by BFB cycles, 214
 shortening and telomerase activity model, 209
 and telomerase, 207, 209, 213, 215, 217, 219, 221
 telomere cap complex/shelterin complex, 210
 tumorigenicity by hTERT, 220
 dysfunction, 128, 212–214, 218–219, 221, 335
 human, 218
 length, 209–210, 217, 298
 physiology, 217, 219

- shortening, 207–210, 216–217, 315
 - Testosterone, 38, 385, 387–389, 396–397, 445–446, 460
 - Therapies
 - anti-angiogenic, 501, 503
 - cytotoxic, 352, 357, 362, 451
 - Topoisomerase-1 inhibitor (CPT-11), 353
 - TP53 Proteins, 247, 496
 - activity, 135, 194–196, 199
 - constitutional, 197–198, 470
 - functions, 176–178, 183, 193–195, 201–202, 494
 - molecular genetics
 - acquired and inherited TP53 mutations, 197
 - genetic modifiers, 200–202
 - low-penetrance mutant alleles, 198–200
 - mutations in childhood and adult adrenocortical tumors, 197–198
 - pre-eminent tumor suppressor, 193–194
 - schematics of, 194
 - signaling pathway, 195–196
 - transcription, 194–195
 - tumor suppressor signaling pathway, 196
 - TP53* gene, 132, 164, 175, 181, 276, 468–469
 - Transcription factors, 138–139, 176, 193, 265–266, 268, 270, 289, 297, 312, 328, 336, 388
 - Trilostane, 392, 395
 - Tumorigenesis, 127, 136, 141–142, 183, 185, 193, 195, 197, 200–201, 208, 214, 216, 235, 248, 273, 468–469
 - Tumors
 - age of, 174, 180
 - angiogenesis, 361, 501
 - bed, 433–434, 436, 438
 - brain, 173–174, 179, 194
 - capsule, 14, 41, 54, 412, 450–451
 - cells, 14, 41, 109, 215, 217, 252, 254, 285–286, 311, 314, 316, 332, 494, 503, 505
 - characteristic, 174
 - entities, 107, 143–144, 218–219, 327, 335
 - growth, 31, 140, 216, 235–236, 254, 315, 332, 351, 361, 365, 383, 398, 437–438, 443
 - invasion, 34–35, 129, 141, 343, 409
 - lesions, 93–95, 98
 - medullary, 107, 116, 121, 123
 - models, 251, 332, 334
 - recurrence, 82, 412, 422, 443–446, 472
 - spillage, 343–344, 474–475
 - stroma, 505, 508
 - suppression, 199
 - suppressor, 176, 193–194, 202, 236, 238, 249, 255, 496
 - genes, 128, 135, 183, 197, 245–247, 267–269, 299, 335–336
 - thrombus, 16, 18, 412, 418, 472, 474
 - vasculature, 501–503
 - weight, 107–109, 113, 473–474
 - Tyrosine kinase inhibitors (TKIs), 497–499, 504
- U**
- UK adrenal cortical tumors (UKACT), 522
 - Ultrastructural studies, 118
 - adrenal cancer
 - increased and slightly irregular mitochondria, 120
 - intramitochondrial granular bodies, 120
 - irregular nucleus, 119
 - lobated nucleus, 119
 - Uranyl acetate, 119–120
 - Urinary free cortisol (UFC), 55–56, 410, 446
- V**
- Vascular endothelial growth factor (VEGF), 140, 269, 501–502, 505–506
 - VEGFR, 362, 498, 501–502
 - Virilization, 9, 12–13, 32–34, 57, 75, 166–167, 314, 346
 - syndrome, 471
- W**
- Weiss system, 123
 - Wilms tumor, 160, 173, 227, 229–232, 249–250, 264, 268
 - WNT/ β -catenin signaling pathway, 497, 499, 523
 - adenomatous polyposis coli, 267
 - adrenal cortex and adrenocortical tumors
 - ACTH-independent macronodular hyperplasia, 273–274
 - adrenal cortex development, 269–270
 - adrenocortical adenoma, 273
 - adrenocortical diseases, 270–276
 - β -catenin immunohistochemistry, 272–274
 - CTNNB1* mutations, 271
 - digestive cancers, somatic frequency, 270
 - adrenocortical carcinoma
 - APC, 276
 - β -catenin mutations, activation, 274

- WNT/ β -catenin signaling pathway (*cont.*)
- CTNNB1 mutation, alternatives to, 275–276
 - role, 274–275
 - WTX, AXIN1, AXIN2, or GSK3 β , 276
 - axin, 267
 - β -catenin protein, 266–267
 - canonical, 264
 - casein kinase and glycogen synthetase, 267
 - components
 - cytoplasm events, 266–268
 - initiation at cell membrane, 265
 - nuclear components, 267–269
 - T-cell factor, lymphoid enhancer factor, family transcription factors, 268
 - cytoplasmic components, 267
 - dishevelled, 266
 - familial adenomatous polyposis coli, 269
 - molecular mechanisms, 264–265
 - potential target for cancer treatment, 276
 - target genes, 269
 - Wilms tumor gene, 267
- Wnt ligands, 264–265, 294
- Wnt signaling, 139, 264, 270, 293, 296, 499–500
- Working group (WG), designed for tumors, 527