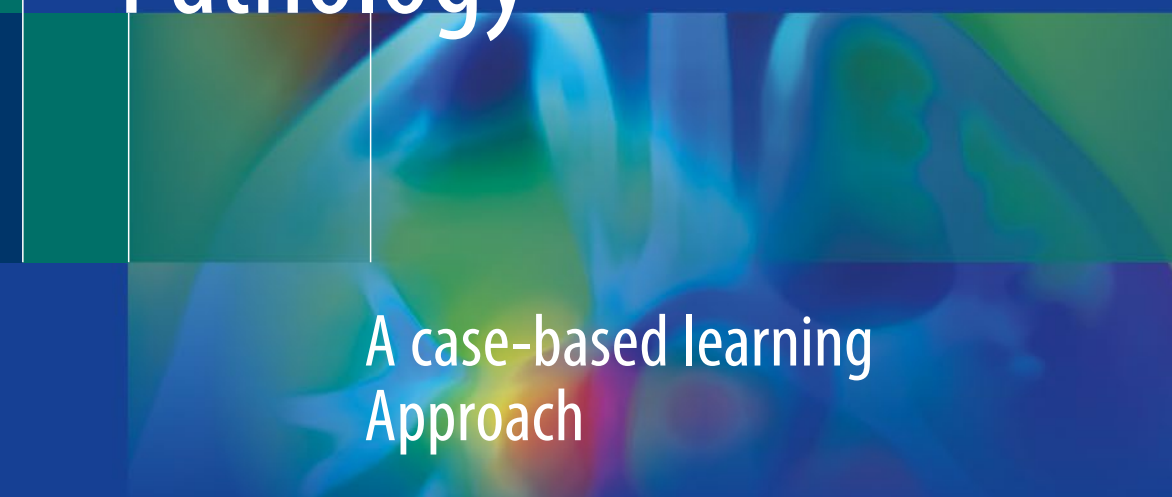
Clinical Genitourinary Pathology



A case-based learning Approach

Andreas C. Lazaris
Editor

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To those colleagues who enjoy their studies and their work

Foreword: Case-Based Learning: An Important Tool for Pathology Education

Pathologists use many sources of information to come to a diagnosis, in the center of which remains the morphology of a process as seen in a tissue slide. To become a reliable pathologist, one has to have a broad knowledge base on disease processes and their features and the ability to integrate the various forms of information into a diagnosis that needs to be communicated to the clinician. Basic knowledge can be found in textbooks and images of processes in atlases. These provide therefore a sound basis that each trainee can use to acquire most of the skills that are needed. But the most important qualities a pathologist needs to have, integration and communication, can only be achieved through experience with real cases/patients. It is often stated that only in routine practice after the traineeship the reliable pathologist is created. It therefore makes sense that case-based learning is used to improve the process by which a person becomes the pathologist who is such an important person for many patients. As an experienced medical oncologist once said to me, I can only be as good as my pathologist. Many experienced pathologists know this quite well (although trainees often think that formal education is more important), which explains why slide seminars and video microscope sessions at congresses are so popular. I am convinced already for many years that only through experiencing many cases one can become an expert.

Therefore, I am so pleased that Prof. Andreas C. Lazaris took up the challenge to create a book fully based on case-based learning. This book is a timely and welcome addition to the possibilities there are to learn pathology. Such a book can only be made by a person who has exceptional teaching qualities, great experience in routine practice, and the stamina to do the work that is needed. I therefore congratulate him with the completion of this work. Not only Prof. A. C. Lazaris should be congratulated, but also the reader and user of the book. He or she will find a wealth of information presented in a way that is different from textbooks and atlases, and using this thoroughly will largely increase the speed by which a young pathologist becomes the reliable partner in the clinic. So, in the end, the patient who will benefit from the increased quality of the pathologist through this book can be congratulated, too.

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Preface

This book aims to present basic clinicopathological insights into common genitourinary diseases, especially those of neoplastic nature, and to introduce experiential learning based on case presentations (case-based learning). One of the tasks that trainees face is converting the extensive amount of data available in classical medical textbooks into medical experience. A beginner pathologist often does not know where to start his/her study under the microscope and what exactly he/she should first assess. By using successive microscopic images within an educational rationale, the book gradually and analytically presents diagnostic procedures for lesions of the genitourinary system (kidney, urinary bladder, prostate gland, and testis). Characteristic real cases from my personal archive of the past 20 years, closely related to day-to-day medical practice, are presented for each organ, each case ending with a clinical commentary and key points/messages. This practical form of presentation helps readers acquire the valuable skill of effective diagnostic thinking, focusing their attention on the essential microscopic findings and disregarding insubstantial findings. A number of images have been deliberately kept showing some artifacts of the respective slides in order to achieve simulation with the daily operating conditions of a pathology laboratory.

Although clinical applications are frequently based on pathologic findings which therefore need to be clearly described and recorded, the importance of this in everyday medical practice is often ignored by medical students and downplayed by clinicians. Demonstrating how knowledge can be practically applied and how pathological-report data determine clinicians' decision-making, this book aims to be a valuable resource mainly for residents in pathology, urology, and oncology but also for medical students with a special interest in histopathology.

The pathology part of this book was developed by me personally, and it was based on classical genitourinary pathology textbooks which are cited as references. I attempted to record my medical experience in common diagnostic practical issues of genitourinary pathology for the benefit of trainees in pathology, urology, and oncology, interested clinicians, and medical students, in order that learners gain practical insight of the theoretical background they are traditionally taught, recognize basic patterns of tissue injury, and correlate pathologic findings with clinical data. The acquisition of my diagnostic experience in the field of genitourinary pathology was made possible by the fruitful discussions of the presented cases – and many more cases – in the last 20 years, with the following colleague pathologists whom I warmly thank: Prof. Agapitos E, Baliou E, Bobos M, Assoc. Prof. Goutas N, Koniaris E, Liakea A, Liapis G, Masaoutis C, Michaelides C, Assoc. Prof. Nonni A, Prof. Pavlakis K, Perdiki M, Pouloudi D, Sarlanis H, Assist. Prof. Thymara E, Assoc. Prof. Vlachodimitropoulos D, and Xirou P.

The contribution of the graduates of the School of Medicine of the National and Kapodistrian University of Athens Drs. Dimitrios Drekolias and Ilias Nikolakopoulos to the final configuration and clarification of the texts of this book is greatly appreciated.

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Introduction: Implementing Case-Based Learning in Pathology

» There is an intimate and necessary relation between the process of actual experience and education.
John Dewey, 1938

It is indisputable that nowadays one of the hardest and most important tasks in medicine and especially in medical education is the conversion of the extensive amount of available data into medical experience, after a proper analysis and systematization of what constitutes basic knowledge. Medical students are required to learn and retain vast amounts of knowledge on the path to becoming physicians (Yang et al. 2014). It is a common idea that achieving excellence in students once they enter clinical medicine practice poses a challenge in education. In recent years, innovative tools have been developed to supplement traditional materials and are being progressively included into medical education (Kim et al. 2011, Worm and Jensen 2013) due to their teaching potential; the relevant educational methods, in which students are no longer requested to be passive recipients of knowledge (Alur et al. 2002), have been shown to be associated with increased learning outcomes, with regard to various areas of health and medical education (Cook et al. 2010, Lakshmanan et al. 2014).

Pathology represents a major diagnostic field in modern medicine; it is linked with a number of distinct but interrelated medical specialties which diagnose diseases mostly through the analysis of biological samples. Through the analysis of tissue samples, i.e., biopsies and surgical resections, it allows medical doctors to exclude or confirm a suspected clinical diagnosis, such as cancer, and even to identify the presence of unsuspected concurrent diseases. The role that pathologists have in patient care is indeed crucial, since they are responsible for documenting fully the diagnostic evidence tissue samples can provide, in order that a correct final diagnosis is established. For example, the pathologist's interpretation of a tumor specimen is critical to establish the diagnosis of a benign or a malignant tumor, to distinguish between distinct histogenetic types of neoplasia, as well as to estimate the grade and the stage of the malignant neoplastic disease. In everyday working life, pathologists must be able to interpret a biopsy in order to make a final diagnosis, the accuracy of which is crucial for patients. All information provided by pathologists determines patients' prognosis and efficient treatment selection. The pathological examination of specimens under the microscope may be supported by further, tissue-based laboratory tests such as those making use of molecular biology techniques. A high level of competence in recognizing patterns of injury when tissue specimens are approached and in correlating the essential pathological data with other clinical-laboratory information is of vital importance to ensure that the correct diagnosis is made.

In the immense field of modern pathology, an extensive amount of data is available; as many practical skills as possible are requested to be developed by future or present medical professionals. It takes a considerable amount of time and real devotion to acquire professional experience in the field of pathology; actually, it may take over 14 years to become a fully qualified pathologist. Being part of fundamental medical knowledge, pathology is currently taught, firstly on a theoretical basis, from the undergraduate level of medical studies. Medical students are requested to retain an extensive amount of knowledge. Attending lectures and taking advantage of textbooks and atlases, students are supposed to learn how to recognize the state of disease and describe main patterns of tissue injury. In their professional life, pathologists are requested to evaluate microscopic diagnostic features in patients' tissue sections so that a definite diagnosis is set. Too often, trainees/residents in pathology misunderstand the significance of their microscopic findings and cannot distinguish, even after 2 or 3 years of professional experience in the field, the most helpful ones for the correct diagnosis; it takes a considerable amount of time and real devotion to obtain this capacity and become "experienced," though mistakes in the beginning of a pathologist's career can cost time, money, or deterioration of human health.

Teaching is an activity which is helping the student in learning. Teaching and learning are being modified due to innovations in education. Teachers have to understand the modern trends in teaching-learning process and make learning more interesting and interactive, so that students may be motivated to learn and learn better, after having personally experienced the value of a subject (Ambrose et al. 2010, Bass 2012, Boud et al. 1993, Ewert and Sibthorp 2009, Kolb 1984, Lave and Wenger 1991, Linn et al. 2004, Moore 2010, Qualters 2010, Schon 1983, Wurdinger and Carlson 2010). Conventional medical textbooks follow an encyclopedic-type formula citing single diagnostic features of specific diseases. In terms of pathology training, the "encyclopedic" knowledge of pathology is of secondary importance by comparison to the "experiential" one. Today's global educational environment is rapidly changing. The dominant perspective with regard to the future of medical education is experiential learning. Learning authentically implies that learners, simulating their present or future professional practice, gain medical experience in the process of diagnosing human diseases (Herrington and Kervin 2007).

After discussing and implementing teaching strategies in pathology and evaluating students' learning, teachers have been developing new-style pathology courses (Marshall et al. 2004). The main characteristics of the modern pathology module consist of pathology images combined with delivery of compact and guided learning courses (Hamilton et al. 2012, Lam et al. 2005). It is indisputable that simulation with everyday practice is a promising pedagogical tool in medicine (Carron et al. 2011). In this context, case-based learning is a newer modality of teaching healthcare. Case-based learning is a teaching tool used in a variety of medical fields using human cases to impart relevance and aid in

connecting theory to practice. The impact of case-based learning can reach from simple knowledge gains to changing patient care outcomes (McLean 2016, Nair et al. 2013). The application of experiential learning principles in the field of pathology aims at the integration of theory and practice in pathology, and this is directly linked with case-based learning (Lazaris et al. 2015, Riccioni et al. 2015). One of the major challenges for the medical student approaching the subject of pathology, the resident in pathology starting his/her diagnostic practice, and the future professional in general is to acquire the *basic knowledge* deriving from the huge amount of available information and be able to transform it to medical experience, essential for daily pathology practice. The introduction of experiential learning based on real, common cases helps the learner notice the connections between basic theory and experience. The prospect to record basic professional experience is intimately associated with the presentation of selected, common case studies; in this way, as many practical skills as possible can be developed by medical professionals. A new teaching approach based on case studies and discussions/commentaries has already been considered successful in medical teaching (Van Dijiken et al. 2008). The motivation *to learn* is greatly improved by the *study of cases* (Dacre and Fox 2000); the latter makes pathology *easier to understand*, and, furthermore, in this way, students can relate knowledge to a *real-world context* and their future profession (Weurlander et al. 2009). Cases should of course be carefully chosen for their learning potential. Through selected educational case studies, the learner is assisted to gain *practical insight* of the theoretical background he is traditionally taught, recognize and consolidate patterns of injury in basic pathologic lesions, and correlate them with clinical data and decisions.

Andreas C. Lazaris

References

Alur P, Fatima K, Joseph R (2002) Medical teaching websites: do they reflect the learning paradigm? Med Teach 24(4):422–424

Ambrose SA, Bridges MW, Di Pietro M, Lovett MC, Norman MK Mayer RE (2010) How learning works: seven research-based principles for smart teaching. Jossey–Bass, Wiley, San Francisco, CA

Bass R (2012) Disrupting ourselves: The problem of learning in higher education. EDUCAUSE Review, 47(2). Available via http://er.educause.edu/articles/2012/3/disrupting-ourselves-the-problem-of-learning-in-higher-education

Boud D, Cohen R, Walker D (eds) (1993) Using experience for learning. Open University Press, McGraw-Hill Education, Bristol

Carron PN, Trueb L, Yersin B (2011) High-fidelity simulation in the nonmedical domain: practices and potential transferable competencies for the medical field. Adv Med Educ Pract 2:149–155

Cook D, Levinson AJ, Garside S, Dupras DM, Erwin PJ, Montori VM (2010) Instructional design variations in internet-based learning for health professions education: a systemic review and meta-analysis. Acad Med 85(5):909–922

Dacre JE, Fox RA (2000) How should we be teaching our undergraduates? Ann Rheum Dis 59(9):662–627

Ewert A, Sibthorp J (2009) Creating outcomes through experiential education. New directions for teaching and experiential education: the challenge of confounding variables. J Exp Educ 31(3):376–389
Hamilton PW, Wang Y, McCullough SJ (2012) Virtual microscopy and digital pathology in training and education. APMIS 120(4):305–315
Herrington J, Kervin L (2007) Authentic learning supported by technology: 10 suggestions and cases of integration in classrooms. EMI Educ Media Int 44(3):219–236
Kim S, Song SM, Yoon YI (2011) Smart learning services based on smart cloud computing. Sensors, Basel, 11(8):7835–7850
Kolb DA (1984) Experiential learning: experience as the source of learning and development, 1st edn. Prentice-Hall, Englewood Cliffs
Lakshmanan A, Leeman KT, Brodsky D et al (2014) Evaluation of a web-based portal to improve resident education by neonatology fellows. Med Educ Online 19:24403
Lam AK, Veitch J, Hays R (2005) Resuscitating the teaching of anatomical pathology in undergraduate medical education: web-based innovative clinicopathological cases. Pathology 37:360–363
Lave J, Wenger E (1991) Situated learning: legitimate peripheral participation. Cambridge University, New York
Lazaris AC, Riccioni O, Solomou M et al (2015) Implementation of Experiential Learning in Pathology: impact of Hipon Project Concept and Attainment. Int Arch Med 8(211):1–7
Linn PL, Howard A, Miller E (eds) (2004) The handbook for research in cooperative education and internships. Lawrence Erlbaum Associates, Mahwah
Marshall R, Cartwright N, Mattick K (2004) Teaching and learning Pathology: a critical review of the English literature. Med Educ 38(3):302–313
McLean SF (2016) Case-based learning and its application in medical and health-care fields: a review of worldwide literature. J Med Educ Curric Dev 3:39–49
Moore DT (2010) Forms and issues in experiential learning. In: Qualters DM (ed) New directions for teaching and learning, Wiley, New York, p 3–13
Nair SP, Shah T, Seth S et al (2013) Case Based Learning: a method for better understanding of biochemistry in medical students. J Clin Diagn Res 7(8):1576–1578
Qualters DM (2010) Bringing the outside in: assessing experiential education. Special Issue 124: Experiential Education: Making the Most of Learning Outside the Classroom, p 55–62
Riccioni O, Vrasidas C, Brcic L et al (2015) Acquiring experience in pathology predominantly from what you see, not from what you read: the HIPON e-learning platform. Adv Med Educ Pract 8(6):439–45
Schon D (1983) The reflective practitioner: how professionals think in action. Basic books, New York
Wurdinger DD, Carlson JA (2010) Teaching for experiential learning: five approaches that work. Rowman & Littlefield Education, Lanham
Van Dijiken PC, Thevoz S, Jucker-Kupper P et al (2008) Evaluation of a case-based interactive approach to teaching pathophysiology. Med Teach 30(5):e131–e136
Weurlander M, Masiello I, Soderberg M et al (2009) Meaningful learning: students' perceptions of a new form of case seminar in pathology. Med Teach 31(6):248–253
Worm BS, Jensen K (2013) Does peer learning or higher levels of e-learning improve learning abilities? A randomized controlled trial. Med Educ Online 18:21877
Yang A, Goel H, Bryan M et al (2014) The Picmonic(®) Learning System: enhancing memory retention of medical sciences, using an audiovisual mnemonic Web-based learning platform. Adv Med Educ Pract 5:125–332

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Adult Kidney Neoplastic Pathology

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A pathologic report for renal tubular cancer nephrectomy specimens should include the following information: type of procedure, specimen laterality, tumor site, tumor size (largest tumor, if multiple), tumor focality, macroscopic extent of tumor, histologic subtype, sarcomatoid features, tumor necrosis (any amount), WHO/ISUP nucleolar/nuclear grade, microscopic tumor extension, margins, lymph-vascular invasion (in addition to invasion of renal vein and its segmental branches and inferior vena cava), pathologic staging (pTNM), pathologic findings in nonneoplastic kidney, and other tumors or tumorlike lesions (such as cysts, papillary adenomas).

A pathologic report for renal tubular cancer biopsy specimens should include the following information: type of procedure, specimen laterality, histologic subtype, sarcomatoid features, and WHO/ISUP nucleolar/nuclear grade.

Four major common renal cell tumor subtypes can be distinguished based on morphologic and genetic characteristics [i.e., clear cell renal cell carcinoma (RCC), papillary RCC, chromophobe RCC, and oncocytoma]; WHO/ISUP nucleolar/nuclear grading system is implemented in the first two of the above subtypes.

Based on clinicopathologic findings (such as histologic tumor type, bilateral tumor location, and tumor multifocality), hereditary syndromes (i.e., Birt-Hogg-Dubé, hereditary leiomyomatosis renal cell carcinoma, hereditary papillary renal carcinoma, tuberous sclerosis, and von Hippel-Lindau syndrome) can be suspected and relevant investigation can be proposed. Cytogenetic analysis can confirm the diagnosis of MiTF/TFE family translocation-associated carcinoma.

1.1 Introduction to Adult Kidney Neoplastic Pathology

Dionysia N. Zouki, Eleni A. Karatrasoglou, Vasileios Spapis, and Andreas C. Lazaris

The two bean-shaped kidneys are attached to the posterior abdominal wall, one on each side of the vertebral column. The kidneys have a tough fibrous capsule (irregular dense connective tissue) for protection. The kidney has a granular cortex (outer region) and a medullar inner region which has a more striated appearance. The kidney is organized into many lobes, in a pyramidal structure, where the outer portion is made up of the cortex and the inner portion is made up of the medulla. The kidney contains about one million functional units called nephrons, which are continuous with a system of tubules. The nephron consists of the renal corpuscle and the renal tubule. After leaving the renal corpuscle, the filtrate passes through the renal tubule in the following order: proximal convoluted tubule (found in the renal cortex), loop of Henle (mostly in the medulla), distal convoluted tubule (found in the renal cortex), collecting tubule (in the medulla), and collecting duct (in the medulla).

Renal cell carcinoma (RCC) accounts for about 3% of all adult cancers and approximately 85% of all malignant renal tumors. The incidence of RCC seems to have an upward trend during the last decades (Hock et al. 2002; Levi et al. 2008). It is estimated that about 30% of the patients die of their disease. There is a clear predominance of males over females with a 3:2 male to female ratio. It appears usually between the age of 60 and 70 (Ljungberg 2016). Black men are known to have the highest incidence of RCC, while Asian men the lowest (Miller et al. 2006). Smoking, obesity, hypertension, acetaminophen, and exposure to asbestos and cadmium are other known risk factors. Having a first-degree relative with kidney cancer also increases the risk of RCC (Clague et al. 2009).

RCC can be either sporadic or inherited. Von Hippel-Lindau disease is the best known familial cancer syndrome involving RCC. Patients tend to develop tumors in multiple organs including cerebellar hemangioblastomas, retinal angiomata, and bilateral clear cell RCC. Hereditary papillary renal carcinoma is another familial syndrome characterized by a tendency to develop multiple bilateral renal tumors of the papillary RCC subtype. Acquired cystic disease (ACD) is a well-described entity of multiple bilateral renal cysts. Patients with ACD undergoing dialysis are 30 times more likely to develop RCC (Konety et al. 2013).

About 50% of RCCs are asymptomatic and are diagnosed incidentally. The classic triad of flank pain, palpable mass, and hematuria is now rarely seen (<10%). Symptoms, when they are present, include hematuria, dyspnea, cough, and bone pain; the latter three are typical symptoms secondary to metastases (Konety et al. 2013). Moreover, RCC is associated with a wide number of paraneoplastic syndromes including erythrocytosis, hypercalcemia, hypertension, and Stauffer syndrome (nonmetastatic hepatic dysfunction).

As said before, most renal masses are diagnosed incidentally by abdominal computed tomography (CT) or ultrasound (US) performed for other medical reasons. Traditionally US, CT, and magnetic resonance imaging (MRI) are used for detecting and characterizing renal masses. Most cases are diagnosed accurately by imaging alone (Campbell and Lane 2012). When there is a suspicion that renal function could be impaired, an isotope renogram and total renal function evaluation should be considered to optimize treatment decision-making. The value of positron-emission tomography (PET) in the diagnosis and follow-up of RCC remains to be determined, and PET is not currently recommended (Ljungberg 2016).

Traditionally, radical nephrectomy (RN) was the treatment of choice for all localized renal cancers. The last two decades, however, Nephron Sparing Surgery (NSS) has been the treatment of choice instead, especially for T1-T2a tumors in a favorable position (Ljungberg 2016). NSS offers similar cancer-specific survival and a better quality of life when compared to RN (Poulakis et al. 2003).

Macroscopically, RCCs are usually yellow to orange, unencapsulated masses, even though pseudocapsules made of compressed renal tissue and inflammatory alterations could be present. Histologically, the most common subtypes are the clear cell carcinoma, papillary (types I and II), chromophobe, collecting duct, and unclassified (Campbell and Lane 2012).

Renal cell carcinoma (RCC) in adult patients comprises a heterogeneous group of neoplasms with clinical outcomes that range from indolent to overtly malignant. Soft tissue (perinephric or sinus fat) and vascular spread beyond the kidney are recognized as major adverse prognostic parameters. WHO/ISUP nucleolar/nuclear grading system is prognostically useful in clear cell RCC, the commonest type of renal cancer, and some other cortical carcinomas; its utility remains ambiguous in chromophobe RCC. Established prognostic factors in RCC include primary tumor stage, size (< or = 4 cm, > 4 but < or = 7 cm, > 7 but < or = 10 cm and >10 cm, in greatest dimension), distant/nodal metastases, histologic subtype, nucleolar/nuclear grade, sarcomatoid features, and tumor necrosis (Algaba et al. 2011; Murphy et al. 2004; Zhou and Magi-Galluzzi 2007). Overlapping features among the histologic subtypes of RCCs and benign entities are frequent; so the most characteristic findings of each common (or relatively common) tumor type must be highlighted (Magi-Galluzzi and Zhou 2010; Ross et al. 2012).

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With regard to immunohistochemistry, CD10 and RCC antigen (marker) are sensitive to renal cell neoplasms derived from proximal tubules, including clear cell and papillary RCC, whereas kidney-specific cadherin (Ksp-cadherin), parvalbumin, claudin-7, and claudin-8 are, among others, sensitive markers for renal neoplasms from the distal portions of the nephron including chromophobe RCC and oncocytoma (Algaba 2013; Truong and Shen 2011).

Clear cell RCC shows various architectural patterns and is composed of cells with optically transparent, clear cytoplasm with abundant, fine fibrovascular network, often admixed with cells with eosinophilic (acidophilic)/granular cytoplasm. Clear cytoplasm in clear cell RCC is due to rich cytoplasmic glycogen and lipid contents. Cystic changes may be extensive in clear cell RCC. Carbonic anhydrase IX (CAIX) and CD10 membranous immunoreactivity are consistent with clear cell RCC subtype.

Papillary RCC exhibits a papillary, tubulopapillary or even solid growth, foamy macrophages within fibrovascular cores, psammoma bodies, and possibly mucin. Similar neoplasms measuring 15 mm or less are considered benign and called "papillary adenomas." Based primarily on cytologic features, papillary RCCs have been divided into type 1 and type 2, the latter displaying cells with prominent eosinophilic cytoplasm on papillary cores, nuclear pseudostratification, prominent nucleoli, higher nuclear grade, and a quite variable immunophenotype, which, in contrast to type 1, sometimes includes both CAIX positivity and cytokeratin 7 negativity. An "oncocytic" type of papillary RCC has been described.

Chromophobe RCC is a pseudo-encapsulated tumor characterized by solid sheets of cells separated by long, curvilinear vessels; large cells with voluminous, optically translucent, pale (not clear), reticulated cytoplasm are often mixed with smaller cells with eosinophilic/granular cytoplasm. Cancerous cells of chromophobe RCC display nuclear wrinkling, perinuclear haloes, frequent binucleation, and prominent cell membranes. A diffuse cytoplasmic staining reaction with Hale's iron colloid stain is characteristic.

Oncocytomas are the most common benign renal neoplasms and share similar morphology and immunoprofile with chromophobe RCC, eosinophilic variant. Hybrid tumors do exist (Hes et al. 2013).

In contrast to chromophobe RCC and to oncocytoma, clear cell RCC and papillary RCC are usually immunonegative for KIT (CD117), k-sp cadherin, and parvalbumin. Chromophobe RCC and oncocytoma are usually immunonegative for vimentin, CAIX, and AMACR; oncocytoma is also negative for RCC antigen (marker) (Wang and Mills 2005).

Collecting duct carcinoma, characteristically involving kidney central region, displays various patterns and consists of often highly atypical cells within prominent desmoplastic stroma and associated, adjacent tubular epithelial dysplasia. In order to exclude other subtypes of RCC, we look for lectins PNA and UEA positivity in combination with RCC antigen (marker), CD10, AMACR, and k-sp cadherin immunonegativity. In order to exclude invasive *urothelial carcinoma of the pelvis*, we should consider that the latter displays immunopositivity for thrombomodulin, uroplakin III, GATA3, and S100P (placental), especially when of low to intermediate grade. High-grade urothelial carcinoma must also be distinguished from RCC; the former is typically immunonegative for the common markers for RCC, such as RCC antigen (marker), CD10, and, most importantly, PAX2 and PAX8; the latter two exhibit nuclear immunopositivity in RCC.

Renal tumors with high-grade spindle cells include all RCC subtypes with sarcomatoid transformation; these RCC subtypes should be carefully searched with thorough sampling before a diagnosis of a sarcoma is made.

In the handling of small round cell tumors of the kidney, valuable immunomarkers include cytokeratin, leukocyte common antigen, S100, WT1, vimentin, desmin, CD99, CD56, chromogranin, and synaptophysin.

In *angiomyolipoma* (AML), a benign, usually triphasic tumor, the identification of myoid cells, fat tissue, and perivascular tumor cell cuffing is the rule. However, in unusual cases, cellular areas of spindle or polygonal cells predominate (myoid-rich or epithelioid AML, respectively). In epithelioid AML, clear cells frequently show dispersed, irregular, intracytoplasmic, often perinuclear granularity; marked cytologic atypia of cells with abundant eosinophilic cytoplasm may resemble high-grade RCC. Neoplastic cells' desmin, smooth muscle actin, and melanocytic markers' immunopositivity in conjunction with negativity to S100 protein, epithelial markers (i.e., keratins, EMA), CD10, and RCC antigen (marker) confirm the diagnosis of angiomyolipoma, when necessary.

From the *oncologist's view*, RCC patients with metastatic disease divide into three risk categories using International Metastatic Renal Cell Carcinoma Database Consortium criteria (IMDC) (Kantarjian and Wolff 2010). The prognostic criteria are the following (Heng et al. 2009; Heng et al. 2013):

- Karnofsky performance status (PS) <80%
- Hemoglobin <lower limit of normal
- Time from diagnosis to treatment of <1 year
- Corrected calcium above the upper limit of normal
- Platelets greater than the upper limit of normal
- Neutrophils greater than the upper limit of normal

Patients with none of the previously mentioned risk factors have favorable prognosis [first-line median overall survival (OS) 43.2 months and second-line median OS 35.3 months]. One or two risk factors change the prognosis to intermediate with statistically significant decrease in OS [first-line median OS 22.5 months, second-line median OS 16.6 months]. Finally, the prognosis deteriorates and becomes poor, when the total number of risk factors is more than three [maximum 6]. In this case, the first-line median OS is 7.8 months and the second-line median OS is 5.4 months. The International Metastatic Renal Cell Carcinoma Database Consortium prognostic model has an improved prognostic performance and is very useful and applicable in everyday clinical routine.

Management of Local/Locoregional Disease

Currently, there is no evidence from randomized phase III trials that adjuvant therapy is of survival benefit or prolongs disease-free survival (DFS). Several randomized control trials (RCTs) of adjuvant sunitinib, sorafenib, pazopanib, axitinib, and everolimus are ongoing. Data from a large adjuvant trial of sunitinib versus sorafenib versus placebo were reported in 2015 (ASSURE). Results demonstrated no significant differences in DFS or overall survival (OS) between the experimental arms and placebo. As for the neoadjuvant approaches, they are experimental and should not be proposed outside clinical trials. Furthermore, the attempt to downsize venous tumor thrombi with systemic targeted therapy cannot yet be recommended.

Systemic Treatment

Recommendations mainly relate to *clear cell* histology, since most of the pivotal trials have been done in this common histological subtype (Escudier et al. 2016). In addition, recommendations will differ according to risk stratification (see above). The time to

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start systemic therapy is not well defined because some RCCs have a very indolent course; a period of observation before starting treatment should be considered, especially in patients with limited tumor burden and few symptoms. The safety of observation has also been suggested by retrospective and prospective studies.

First-Line Treatment of Patients with Favorable or Intermediate Prognosis

- Three treatments have demonstrated efficacy in pivotal phase III trials: bevacizumab (combined with interferon), sunitinib, and pazopanib (Escudier et al. 2007b; Motzer et al. 2007; Sternberg et al. 2010). All three drugs have been registered based on the improvement of progression-free survival (PFS) over either interferon or placebo. More recently, pazopanib has been shown not to be inferior to sunitinib in a large phase III trial (Motzer et al. 2013). These two tyrosine kinase inhibitors (TKIs) are currently the most commonly used treatments.
- Sorafenib, high-dose interleukin-2, and low-dose interferon combined with bevacizumab are alternative options.
- Single-agent interferon-alpha should no longer be regarded as a standard option.
- Interestingly, very recently, cabozantinib has been reported to be superior to sunitinib in a randomized phase II trial. If these results are confirmed, the role of cabozantinib in the first-line setting will have to be assessed.

First-Line Treatment of Patients with Poor Prognosis

- Temsirolimus is currently the only drug tested in a phase III study, demonstrating evidence of activity in this patient population (Hudes et al. 2007). This pivotal trial demonstrated improvement of OS compared with interferon or the combination of temsirolimus and interferon.
- Sunitinib, sorafenib, as well as pazopanib are other possible alternatives.
- It is clear that, for some poor prognosis patients, best supportive care remains the only suitable treatment option.

Second-Line Treatment

- Recent clinical trials showed that tyrosine kinase inhibitors (TKIs) are active after first-line treatment with cytokines. Sorafenib, pazopanib, and, recently, axitinib can be used (Escudier et al. 2007a; Rini et al. 2011; Sternberg et al. 2010). Sunitinib also has activity in this setting.
- After first-line treatment with VEGF-targeted therapy, both axitinib and everolimus are active (Motzer et al. 2008; Rini et al. 2011). Both drugs have shown significantly improved progression-free survival (PFS). Sorafenib can also be used as an option.
- However, two large trials showed improvement in OS with nivolumab [an anti-programmed death 1(PD-1) inhibitor] and cabozantinib (Choueiri et al. 2015; Choueiri et al. 2016; Motzer et al. 2015) over everolimus (PFS was improved only in the cabozantinib trial). In both trials, patients could be treated after either one or two TKIs.

Third-Line Treatment

Beyond second-line treatment, enrolment into clinical trials is recommended where possible. Recent trials showed that nivolumab or cabozantinib are the standard options for these patients. If neither of these drugs is available, everolimus or axitinib can be used. In addition, sorafenib has shown activity in patients previously treated with anti-

VEGF-targeted therapy and an mTOR inhibitor (Motzer et al. 2014b). Finally, another TKI or rechallenge with the same TKI is considered as an option.

Medical Treatment of Metastatic Disease of *Non-clear Cell* Histology

In small prospective trials for this group of patients (Motzer et al. 2014a; Armstrong et al. 2016; Tannir et al. 2016), sunitinib and everolimus have been compared, and in every trial, there is a trend in favor of sunitinib. In addition, patients with non-clear cell histology may benefit from treatment with everolimus, sorafenib, pazopanib, or temsirolimus. However, in most of these studies, only patients with papillary and chromophobe RCCs were enrolled. In the absence of prospective data, genetic considerations may influence treatment decisions: in papillary type 1 tumors, activation of the c-MET pathway has commonly been reported. Novel agents inhibiting the cMET receptor are currently under investigation. However, as the c-MET receptor and VEGF-receptor were shown to cooperate, VEGF-inhibiting agents may be a reasonable choice. Similarly, there is no evidence for the optimal treatment of papillary type 2, which is characterized by inactivation of the fumarate hydratase gene, fumarate accumulation, and HIF upregulation. Again, VEGF inhibitors may be considered in this context. Patients with chromophobe RCC may benefit from mTOR inhibitors since mutation on chromosome 7 was shown to lead to a loss of the folliculin gene with upregulation of mTOR. Finally, collecting duct carcinomas (and also medullary carcinomas) were reported to behave more like aggressive urothelial tumors rather than RCCs and may, therefore, be considered for chemotherapy. None of these "genetic" recommendations can be graded, as data are limited and no clear treatment recommendation can be made for these subgroups with distinct biology (Junker et al. 2012).

Medical Treatment of Renal Cell Carcinoma with Sarcomatoid Features

Approximately 5% of all patients with renal cell carcinoma will demonstrate sarcomatoid transformation/dedifferentiation in their tumors. Presence of sarcomatoid features consists a poor prognostic factor (the median survival for these patients is 9 months). A retrospective analysis of an empirical regimen, which is based on the combination of gemcitabine, capecitabine, and bevacizumab, showed a median PFS of 5.9 months and a median OS of 10.4 months. This observation formed the basis for more studies using this combination of drugs in this group of patients.

1.2 Case 1.1 Clear Cell Renal Cell Carcinoma

Case Study

Data Prior to Microscopy

A 65-year-old obese male smoker is being investigated for hematuria.

A large, solitary, rounded cortical mass of the upper pole of the right kidney, measuring *9 cm* in its maximum diameter and protruding from the cortical surface, is found and surgically resected.

Macroscopically, it is well-circumscribed, bosselated, and lobulated, with a predominant bright, golden-yellow cut surface; focally, the cut surface becomes either brown or tannish gray. Focal cystic change and hemorrhage are noticed.

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1.2.1 Microscopic Evaluation of the Radical Nephrectomy Specimen

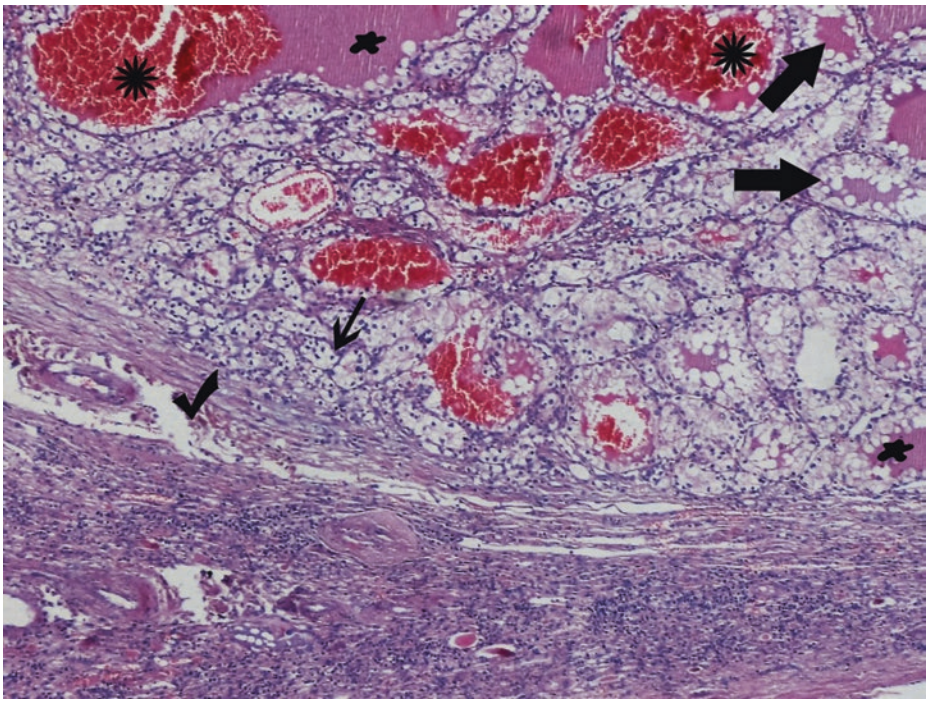

Fig. 1.1 (H-E, ×50) Tumor "pushing" margin – expansile growth. Well- demarcated tumor from adjacent uninvolved kidney with a pseudocapsule (*tick*). *Solid alveolar nests* of clear cells interspersed by a fibrovascular network (*thin arrow*). Fresh hemorrhage (*asterisks*) or eosinophilic amorphous, proteinaceous fluid (*blobs*) into rounded pseudoglandular/microcystic spaces – *acinar arrangement* (*thick arrows*) The solid alveolar and the acinar patterns are the most common patterns of *clear cell renal cell carcinoma (clear cell RCC)*

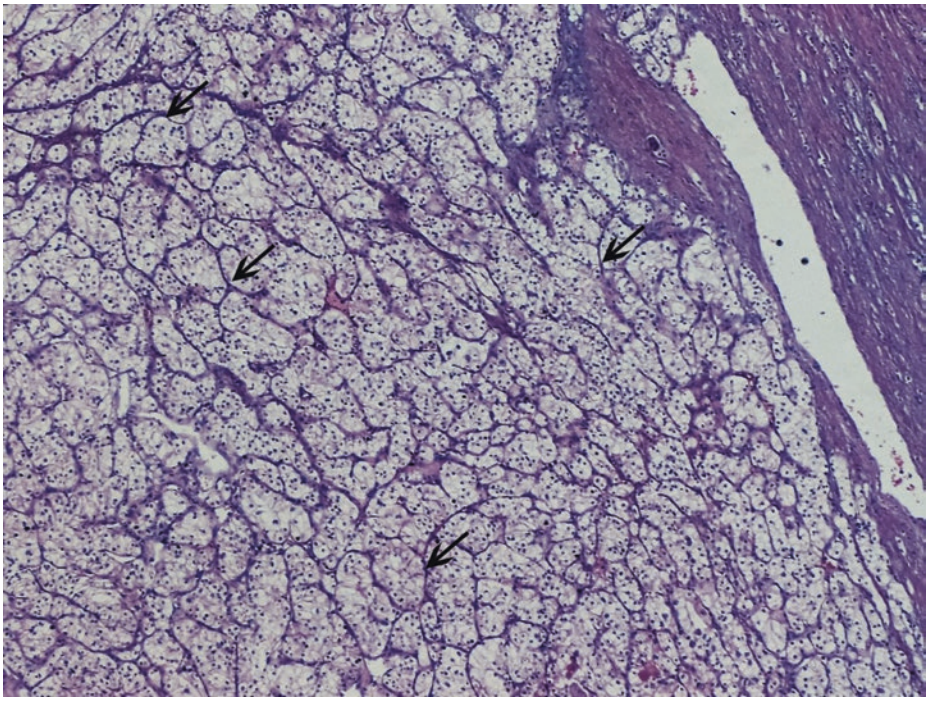

Fig. 1.2 (H-E, ×50) Clear cell RCC. Characteristic regular fibrous network of sinusoidal, small, "chicken wire" vasculature (*arrows*).

Clear cell RCC is the most common histologic variant of RCC, accounting for approximately 70% of the cases

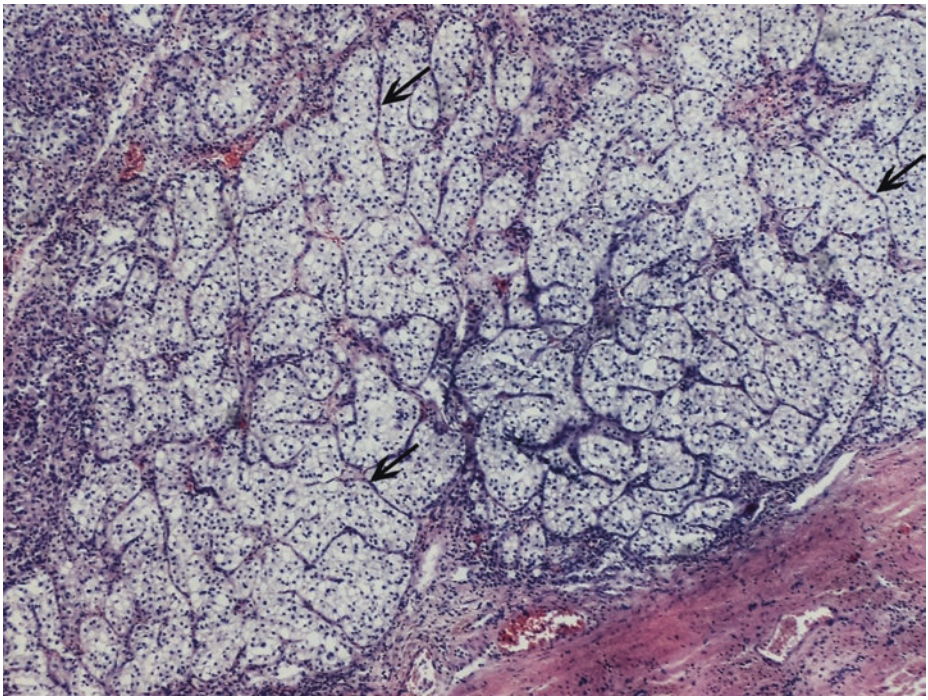

Fig. 1.3 (H-E, ×50) Tumor solid nests surrounded by complete, delicate fibrovascular septa with abundant thin-walled vessels (*arrows*)