Curr Urol Rep (2015) 16: 1
DOI 10.1007/s11934-014-0473-7

KIDNEY DISEASES (G CIANCIO, SECTION EDITOR)

Renal Cell Carcinoma in Young Patients: a Review of Recent Literature

Michael Daugherty · Gennady Bratslavsky

Published online: 22 January 2015

Abstract Renal cell carcinoma is most common in patients in the seventh decade of life. However, renal cell carcinoma (RCC) patients under the age of 40 represent 3–7 % of all renal tumors. These young patients develop RCC from a variety of mechanisms including genetic syndromes, heritable mutations, and sporadic mutations. This population encompasses a distinct clinical entity that requires early identification and adjustments in standard practices including sometimes-aggressive surgical measures in order to improve oncologic management.

Keywords Renal cancer · Age · Young patients · Hereditary cancer

Introduction

Currently, renal cell carcinoma (RCC) is the third most common genitourinary malignancy, and in 2013, it was estimated to be approximately 65,000 new cases in the USA [1]. The incidence of RCC in recent years has been increasing and is presumed to be due in large part to increased cross-sectional imaging of individuals [2]. Unfortunately, RCC presents as a metastatic disease in about one third of all patients [3, 4].

RCC has a peak age of onset in the seventh decade of life with a median age of presentation of 64 years [5–9]. RCC can develop in patients of all ages, and those younger than 40 years constitute younger patients. These young patients comprise 3–7 % of all RCC cases [5–9]. Often in younger patients, these tumors develop secondary to hereditary syndromes and patients can present with bilateral or multiple tumors [10, 11••]. Others are believed to have developed sporadic tumors, and there are some that likely have undiagnosed mutations predisposing or causing them to develop RCC.

This review will focus on recent literature regarding this young patient population with RCC. For the urologist, these patients can create difficult management strategies as these patients may have recurrent renal tumors and will require lifelong surveillance and management spanning likely several decades.

When patients present with tumors younger in life, there is an increased chance that this disease is due in part to a hereditary predisposition. There are several hereditary RCC syndromes that have been described: von Hippel-Lindau, Birt-Hogg-Dube, tuberous sclerosis, hereditary papillary RCC, hereditary leiomyomatosis and RCC, succinate dehydrogenase kidney cancer, Cowden syndrome, microphthalmia-associated transcription factor, paraganglioma syndromes, familial non-syndromic clear cell RCC, and hyperparathyroidism jaw tumor [12]. These syndromes are associated with various germ line mutations and do not have consistent aggressiveness or histology between syndromes, but these tumor's median age of presentation occurs earlier in life, at an age much younger than sporadic RCC. Often, these syndromes can be difficult to diagnose in patients that do not have a strong family history or an unknown or unclear family history. RCC syndromes can have difficulties with diagnosis as they may have variable penetrance, and multiple tumors can have metachronous presentation leading to a delayed investigation into hereditary causes of disease. Some of these syndromes have known systemic or extra renal manifestations and are predisposed to certain histologies (Table 1).

Recent analysis of the Surveillance, Epidemiology, and End Results (SEER) database and the National Cancer Institute (NCI) hereditary RCC database showed the stark difference in age distribution of these hereditary tumors

This article is part of the Topical Collection on *Kidney Diseases*

M. Daugherty · G. Bratslavsky (✉)
Department of Urology, SUNY Upstate Medical University, Syracuse, NY 13306, USA
e-mail: bratslag@upstate.edu

Table 1 Hereditary RCC syndromes

Syndrome	Gene	Clinical manifestations	Tumor histology
VHL	*VHL*	Hemangioblastoma of retina, brain, and spinal cord; pancreatic neuroendocrine tumors; pancreatic cysts; renal cysts	Clear cell
Birt-Hogg-Dubé	*BHD/FCLN*	Fibrofolliculomas, lung cysts, pneumothorax, colorectal polyps	Clear cell Chromophobe Oncocytoma
SDH	*SDHB* *SDHC* *SDHD*	Head and neck paraganglioma, extra-adrenal paraganglioma, GIST, thyroid carcinoma, pheochromocytoma Head and neck paraganglioma, GIST, pheochromocytoma Head and neck paraganglioma, GIST, pheochromocytoma, extra-adrenal paraganglioma	Clear cell Chromophobe Oncocytoma Clear cell Papillary Clear cell
HLRCC	*FH*	Cutaneous and uterine leiomyoma, leiomyosarcoma	Papillary type 2
HPRC1	*MET 7*	N/A	Papillary type 1
Hyperparathyroidism jaw tumor	*CDC73/HRPT2*	Renal cysts, parathyroid tumors, mandibular and maxillary tumors, renal hamartomas	Papillary Wilms tumor
Tuberous Sclerosis	*TSC1* *TSC2*	Angiomyolipoma, hamartoma, angiofibroma, epilepsy, rhabdomyoma	Clear cell Oncocytoma

VHL von Hippel-Lindau, *SDH* succinate dehydrogenase, *HLRCC* hereditary leiomyomatosis and renal cell carcinoma, *HPRC1* hereditary papillary renal cell carcinoma type 1

compared to the general population [13•]. This study further suggested that any patient less than 46 years old diagnosed with RCC should be recommended to undergo genetic counseling if they do not have a previous hereditary syndrome diagnosis. With the advent of increased genetic testing and the ability to perform large genome analyses, this may increase the ability for clinicians to diagnose those with unknown or subclinical syndromes which would allow for better surveillance strategies and counseling.

A large number of young patients with RCC have small renal masses (SRM) (≤4 cm) at diagnosis. There are various treatment and management options available for patients found to have SRM, although most are treated with extirpation, either radical nephrectomy (RN) or partial nephrectomy (PN). Although the only level 1 evidence currently available comparing RN vs. PN has generated much debate about the appropriateness of partial nephrectomy in light of normal contralateral kidney [14•], in young patients, nephron-sparing surgery is likely to remain the standard of care because of the concern for bilateral metachronous involvement. To further the point of importance of nephron preservation in young patients, recent SEER analysis did find a long-term overall survival benefit of young patients (<45 years) when treated with PN compared to RN [15]. In addition, an analysis of urologic clinics in Germany found that younger patients were more likely to be treated with PN for T1 tumors. Surprisingly, only 32.6 % of patients younger than 66.5 years of age with T1 tumors underwent PN [16].

Minimally invasive management of renal tumors is beneficial in reducing morbidity associated with flank incisions, decreasing hospital stay and shortening recovery times of patients. Although young patients may have an increased desire for postsurgical cosmesis, it would be imperative to ensure that laparoendoscopic single-site (LESS) did not interfere with oncologic or renal outcomes prior to widespread implementation. With the increased availability and utilization of the Da Vinci robotic platform, PN may now be increasingly performed on patients and tumors that previously would have been deemed too difficult to undergo pure laparoscopic nephron sparing. In an attempt to optimally minimize invasiveness, LESS procedures have been implemented for both oncologic and non-oncologic processes. This has also been developed for the robotic platform, and Tiu et al. have analyzed outcomes and feasibility of LESS PN in patients with tumors >4 cm [17]. They compared the LESS PN for patients with T1a and T1b tumors. There was no difference in operative time, conversion rate, or surgical margins. However, it was seen that the larger tumors had a higher nephrometry score, longer length of stay, and longer warm ischemia time. This is a very early study looking at LESS in more complex tumors, but there are no long-term outcomes from this dataset, and it currently raises the question whether single-site surgery is necessary if you are possibly exposing a patient to a longer ischemia time and hospital stay. This may have a further detriment to their long-term renal function, and if hospital stays are prolonged, this starts to defeat the purpose of minimally invasive surgery. There are early data regarding patients undergoing LESS, and it appears that in selected patients, there has been found to be no difference in oncologic or renal outcomes so far [17–20]. However, it has not been established which patients are best suited to undergo LESS.

Appropriate stratification of the surgical risks and outcomes has recently been improved using the recently created RENAL (Radius (tumor size as maximal diameter), Exophytic/endophytic properties of the tumor, Nearness of tumor deepest portion to the collecting system or sinus, Anterior (a)/posterior (p) descriptor and Location relative to the polar line) nephrometry scoring system [21••]. It has been developed to aid in assessment or renal masses along with creating a standardized nomenclature to communicate complexity and difficulty of PN for a given mass. This scoring system was developed for RCC and has been shown that higher nephrometry score correlates to higher tumor stage, grade, and more adverse pathology [21••]. This system has been applied to children and adolescents with renal masses as the idea of PN has started to be entertained in patients whose normal standard of care is RN [22]. Interestingly, this study found that adolescents that had a lower nephrometry score and presumed less complex tumor appearance had a higher likelihood of RCC pathology compared to other tumor types. This raises the possibility that RENAL score may play a role in preoperative management and treatment planning of a patient population that can have a variety of renal tumors.

Radiographic assessment of tumors in young patients has made some recent strides. Some studies have looked at using preoperative CT scans and correlating them to final pathology. He et al. found that young patients with a renal lesion that has calcifications with hyperdensity on non-contrast CT with a prolonged enhancement following contrast administration should have an RCC with Xp11.2 translocation considered [23]. Another study looking at multiple tumor types found that papillary, clear cell and oncocytoma have varying enhancement patterns [24]. Papillary tumors had a low peak enhancement with peak HU of 56. These tumors had greatest enhancement in the nephrogenic and delayed phases. Both clear cell and oncocytoma expressed a rapid high attenuation and had a thorough washout in delayed phases. Differences were seen in timing of peak enhancement in that clear cell peaked in the corticomedullary phase, whereas oncocytoma peaked in the nephrogenic phase. In addition, angiomyolipoma and chromophobe RCC both had an intermediate enhancement pattern. These studies add more importance to preoperative imaging in that not only is it needed for diagnosis of a tumor but may also play a role in correlation with final pathology.

As young patients are diagnosed with RCC, they often undergo extirpative surgery. These patients may have genetic predispositions or sporadic tumors, but nevertheless need to undergo lifelong surveillance to evaluate for disease status. With the usage of CT scans as the modality of choice, this can create a difficult situation as patients are subjected to perpetual ionizing radiation, and concern is raised regarding the risk of developing secondary malignancies due to this exposure. Lipsky et al. evaluated the mean annual (13.8 mSv) and mean lifetime (60.1 mSv) radiation exposure from surveillance imaging following surgery for RCC [25•]. They calculated that on average, these patients had a 1.05 and 1.12 relative risk of radiation-induced solid cancer and leukemia, respectively. For this determination of increased relative risk, this number increased with each CT scan conducted. Clinicians should be aware that these young patients with RCC will be likely exposed to far more radiation than in this study and may be at a higher risk of developing secondary malignancies. Of note, there are no guidelines for surveillance strategies of these patients, and without any information on optimal scanning practices, this may result in patients getting overradiated or inappropriately imaged due to radiation concerns. Ultrasonography or MRI can provide a useful alternative in select patients.

It is also known that adult survivors of childhood cancers are at an increased risk of developing other malignancies. The childhood cancer survivor study has found that survivors of childhood cancer are more likely to develop RCC than the general population (standardized incidence ratio [SIR] 8.0, confidence interval [CI] 5.2–11.7) [26]. This effect was even stronger in those survivors of neuroblastoma (SIR 85.8, CI 38.4–175.2). Further analysis of this group found that radiation to the renal unit and cisplatin therapy increased the risk of RCC development (RR 3.8 and 4.1, respectively). The mechanism that causes the subsequent development of RCC is unclear and is likely due to a combination of factors including genetic proclivity, DNA damage from radiation, and possible genetic translocation or injury following alkylating agents.

The literature discussing overall and cancer-specific outcomes of these patients is sparse. Previous studies were single institutional and often compared patients to a representative older cohort [6–9, 27–31]. There had been conflicting data regarding patient disease status at presentation, but it was found in all these studies that young patient did better following surgery than their older counterparts. A recent study of the CORONA database compared young patients to a representative group of patients aged 60–70 and found that young patients had a 2.21 and 3.05 times decreased cancer-specific and all-cause mortality [32]. Cai et al. reviewed all patients undergoing RN for localized RCC at four Chinese institutions and found that patients ≤45 years of age were associated with a higher cancer-specific survival rate on multivariate analysis (hazard ratio [HR] 1.59) along with competing risk regression (HR 3.6) [33]. Even patients with bilateral masses have both excellent oncologic and renal outcomes following surgery. The NCI group analyzed their cohort of patients with bilateral tumors and identified that despite a median number of three interventions, these patients still had an overall and cancer-specific survival of 88 and 97 %, respectively [34•]. Of importance, many of these patients had von Hippel-Lindau (VHL), and most were treated when the largest solid tumor measured 3 cm [35, 36]. This also raises the importance of nephron sparing in such a high-risk patient population because although they may have to undergo multiple subsequent procedures, this allows them to be free of dialysis.

There have been studies evaluating effects of gender on RCC, in both outcomes and pathologic features [32, 37, 38]. It appears that gender plays a role in tumor histology and that younger females have a higher propensity for developing chromophobe RCC than other non-clear cell subtypes [32]. May et al. in their analysis of the CORONA database found that the female gender independently influenced cancer-specific and overall survival (HR 0.75 and 0.80, respectively). This difference however was not present on multivariable analysis. It is not clear where this difference in gender on survival is stemming from, but could be related to, tumor stage and grade at presentation as men had higher Fuhrman grade and T stage in this study.

It is known that RCC has a higher risk of development in patients with chronic kidney disease (CKD). Hofmann et al. performed a population-based case-control study of blacks and whites and found that RCC risk increased in relation to chronic renal failure [39]. In addition, the association was stronger in black patients than in whites (odds ratio [OR] 8.7 and 2.0, respectively). They also determined that the risk of RCC in this population was higher among those patients that did not have concurrent diabetes (OR 8.3 and 1.9). In addition, they found that these associations were stronger in patients under the age of 65; it is possible that young patients with CKD may benefit from scheduled surveillance of their native renal units for the development of RCC; however, these guidelines have not yet been determined.

Kidney cancer has recently been described as a metabolic disease with a series of genres that are known to cause renal cancer: VHL, fumarate hydratase, succinate dehydrogenase, MET, TSC1, FLCN, TSC2, TFE3, TFEB, MITF, and PTEN [10, 11••]. All of these genes play an inherent role in cell regulation, specifically sensing of oxygen and respiration. For hereditary renal cancers, these genes are affected by changes in the genome, whether they are inherited mutations, sporadic mutations, or other issues. Regardless, the affected gene predisposes the patient to develop various types and aggressiveness of RCC dependent on the gene that is affected. The majority of hereditary renal cancers in patients present at a younger age and have a higher likelihood of bilateral or multiple tumors [13•].

RCC with an Xp11.2 translocation was initially recognized as a separate entity in the 2004 WHO classification of kidney tumors. This tumor develops with the translocation of the Xp11.2 band with various gene locations that involve transcription factor E3 (TFE3). Unlike some of the other genetic RCC types, this translocation RCC has been shown to have genomic heterogeneity along with crossover in various pathways of other more common types of RCC [40]. Translocation RCC can have pathologic features similar to clear cell and papillary RCC, and this may be due in part to similar pathways of disease progression [41]. In addition, genetic differences also have been found to be different among translocation RCC in pediatric patients and young adults with the disease [40]. Given this variability in genetics of translocation RCC, the use of immunochemistry has been evaluated as a screening tool to possibly identify patients with TFE3 fusion genes in a tumor, regardless of knowing the location of the translocation [42]. This would then need further molecular testing to confirm the suspected diagnosis but might allow for a less intensive initial evaluation of tumors that might be suspected to be Xp11.2 translocation RCC.

In a variety of cancers, accumulations of single nucleotide polymorphisms (SNPs) in the displacement loop of mitochondrial DNA have been described, and it is possible that there is an association with risk of cancer development and disease progression. There have been two SNPs identified from separate studies that have been shown to have correlations with RCC outcome and age of onset [43, 44]. Bai et al. found that a SNP of allele 262C/T was associated with a decreased overall survival in patients with 262T, whereas Xu et al. found that a SNP at allele 16293A/G was related to age of onset of RCC development and that those with 16293G had an earlier age of onset. Although these are both preliminary studies, they do offer another avenue for further investigation that may play a role in screening of patients or identifying those with high-risk disease that may benefit from closer surveillance.

Succinate dehydrogenase (SDH) RCC has recently been identified and recognized as an inheritable form of kidney cancer associated with the Krebs cycle [45–49]. These tumors have been found to be highly aggressive and are due to the Warburg hypothesis on renal tumors. As these tumor cells have disruption in the Krebs cycle and subsequent trouble with oxidative phosphorylation, these cells are obligated to undergo increased glycolysis [50]. Unfortunately, tumor cells that have a high glycolytic rate exhibit increased aggressiveness and the ability to metastasize at a small primary tumor size, sometimes <1 cm. A recent study from Ricketts et al. recommended close surveillance of patients with a known risk of SDH RCC and to undergo wide excision of these renal tumors for the optimal oncologic outcome [50].

Conclusion

Young patients diagnosed with RCC represent a distinct patient group that has a large variety of tumor histologies, patient characteristics, genetic causes, and sporadic mutations that make the clinical management of these patients difficult. This younger group is significantly different compared to the majority of patients diagnosed with RCC. Care should be taken when evaluating young patients with the renal mass

with further investigation into genetic predispositions, search for known hereditary syndromes, and tailoring of management and surveillance strategies to optimize long-term outcomes.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Michael Daugherty and Dr. Gennady Bratslavsky each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63(1):11–30.
2. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin. 2011;61(4):212–36.
3. Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma. N Engl J Med. 1996;335(12):865–75.
4. Tosco L, Van Poppel H, Frea B, Gregoraci G, Joniau S. Survival and impact of clinical prognostic factors in surgically treated metastatic renal cell carcinoma. Eur Urol. 2013;63(4):646–52.
5. Abou El Fettouh HI, Cherullo EE, El-Jack M, Al Maslamani Y, Novick AC. Sporadic renal cell carcinoma in young adults: presentation, treatment, and outcome. Urology. 2002;60(5):806–10.
6. Cao Y, Paner GP, Perry KT, Flanigan RC, Campbell SC, Picken MM. Renal neoplasms in younger adults: analysis of 112 tumors from a single institution according to the new 2004 World Health Organization classification and 2002 American Joint Committee on Cancer Staging System. Arch Pathol Lab Med. 2005;129(4):487–91.
7. Gillett MD, Cheville JC, Karnes RJ, et al. Comparison of presentation and outcome for patients 18 to 40 and 60 to 70 years old with solid renal masses. J Urol. 2005;173(6):1893–6.
8. Goetzl MA, Desai M, Mansukhani M, et al. Natural history and clinical outcome of sporadic renal cortical tumors diagnosed in the young adult. Urology. 2004;63(1):41–5.
9. Sanchez-Ortiz RF, Rosser CJ, Madsen LT, Swanson DA, Wood CG. Young age is an independent prognostic factor for survival of sporadic renal cell carcinoma. J Urol. 2004;171(6 Pt 1):2160–5.
10. Linehan WM, Rathmell WK. Kidney cancer. Urol Oncol. 2012;30(6):948–51.
11.•• Linehan WM, Srinivasan R, Schmidt LS. The genetic basis of kidney cancer: a metabolic disease. Nature reviews. Urology. 2010;7(5):277–85. *This article describes the metabolic pathways that are predominant in kidney cancer. It delineates how various hereditary cancers develop due to specific changes in normal metabolism.*
12. Bausch B, Jilg C, Glasker S, et al. Renal cancer in von Hippel-Lindau disease and related syndromes. Nat Rev Nephrol. 2013;9(9):529–38.
13.• Shuch B, Vourganti S, Ricketts CJ, et al. Defining early-onset kidney cancer: implications for germline and somatic mutation testing and clinical management. J Clin Oncol Off J Am Soc Clin Oncol. 2014;32(5):431–7. *This study provides a recommendation for a patient that may benefit from genetic screening for hereditary renal cancer. This is based on SEER analysis and the NCI database of patient's with hereditary RCC.*
14.• Van Poppel H, Da Pozzo L, Albrecht W, et al. A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. Eur Urol. 2011;59(4):543–52. *This study is the only level I evidence analyzing outcomes of nephron-sparing surgery.*
15. Daugherty M, Bratslavsky G. Compared with radical nephrectomy, nephron-sparing surgery offers a long-term survival advantage in patients between the ages of 20 and 44 years with renal cell carcinomas (≤4 cm): an analysis of the SEER database. Urol Oncol. 2014;32(5):549–54.
16. von Klot C, Herrmann TR, Wegener G, et al. Age distribution for partial and radical nephrectomy: whose nephrons are being spared? Adv Ther. 2013;30(10):924–32.
17. Tiu A, Kim KH, Shin TY, Han WK, Han SW, Rha KH. Feasibility of robotic laparoendoscopic single-site partial nephrectomy for renal tumors >4 cm. Eur Urol. 2013;63(5):941–6.
18. Fan X, Lin T, Xu K, et al. Laparoendoscopic single-site nephrectomy compared with conventional laparoscopic nephrectomy: a systematic review and meta-analysis of comparative studies. Eur Urol. 2012;62(4):601–12.
19. Rais-Bahrami S, George AK, Montag S, Okhunov Z, Richstone L. Laparoendoscopic single-site (LESS) partial nephrectomy short-term outcomes. BJU Int. 2013;111(2):264–70.
20. Springer C, Veneziano D, Wimpissinger F, Inferrera A, Fornara P, Greco F. Clampless laparoendoscopic single-site partial nephrectomy for renal cancer with low PADUA score: technique and surgical outcomes. BJU Int. 2013;111(7):1091–8.
21.•• Kutikov A, Smaldone MC, Egleston BL, et al. Anatomic features of enhancing renal masses predict malignant and high-grade pathology: a preoperative nomogram using the RENAL Nephrometry score. Eur Urol. 2011;60(2):241–8. *This study created a reproducible nomogram for analyzing renal tumors. This has further been applied to characterize the difficulty of performing nephron-sparing on said tumors.*
22. Cost NG, Defoor WR, Jr., Crotty EJ, Geller JI. The initial experience with RENAL nephrometry in children, adolescents, and young adults with renal tumors. Pediatr Blood Cancer. 2014.
23. He J, Huan Y, Qiao Q, Zhang J, Zhang JS. Renal carcinomas associated with Xp11.2 translocations: are CT findings suggestive of the diagnosis? Clin Radiol. 2014;69(1):45–51.
24. Pierorazio PM, Hyams ES, Tsai S, et al. Multiphasic enhancement patterns of small renal masses (≤4 cm) on preoperative computed tomography: utility for distinguishing subtypes of renal cell carcinoma, angiomyolipoma, and oncocytoma. Urology. 2013;81(6):1265–71.
25.• Lipsky MJ, Shapiro EY, Hruby GW, McKiernan JM. Diagnostic radiation exposure during surveillance in patients with pT1a renal cell carcinoma. Urology. 2013;81(6):1190–5. *This study quantified radiation exposure that occurs during cancer surveillance. This is of importance in young patients that are subjected to life long surveillance with cross sectional imaging.*
26. Wilson CL, Ness KK, Neglia JP, et al. Renal carcinoma after childhood cancer: a report from the childhood cancer survivor study. J Natl Cancer Inst. 2013;105(7):504–8.
27. Denzinger S, Otto W, Burger M, et al. Sporadic renal cell carcinoma in young and elderly patients: are there different clinicopathological features and disease specific survival rates? World J Surg Oncol. 2007;5:16.

28. Komai Y, Fujii Y, Iimura Y, et al. Young age as favorable prognostic factor for cancer-specific survival in localized renal cell carcinoma. Urology. 2011;77(4):842–7.
29. Taccoen X, Valeri A, Descotes JL, et al. Renal cell carcinoma in adults 40 years old or less: young age is an independent prognostic factor for cancer-specific survival. Eur Urol. 2007;51(4):980–7.
30. Thompson RH, Ordonez MA, Iasonos A, et al. Renal cell carcinoma in young and old patients—is there a difference? J Urol. 2008;180(4):1262–6. *discussion 1266*.
31. Verhoest G, Veillard D, Guille F, et al. Relationship between age at diagnosis and clinicopathologic features of renal cell carcinoma. Eur Urol. 2007;51(5):1298–304. *discussion 1304–1295*.
32. Aziz A, May M, Zigeuner R, et al. Do young patients with renal cell carcinoma feature a distinct outcome after surgery? A comparative analysis of patient age based on the multinational CORONA database. J Urol. 2014;191(2):310–5.
33. Cai M, Wei J, Zhang Z, et al. Impact of age on the cancer-specific survival of patients with localized renal cell carcinoma: martingale residual and competing risks analysis. PLoS One. 2012;7(10): e48489.
34.• Singer EA, Vourganti S, Lin KY, et al. Outcomes of patients with surgically treated bilateral renal masses and a minimum of 10 years of followup. J Urol. 2012;188(6):2084–8. *This study provides long-term follow up of patient's undergoing bilateral renal surgery and shows long-term outcomes that it is feasible to perform nephron sparing in these hereditary bilateral tumors*.
35. Duffey BG, Choyke PL, Glenn G, et al. The relationship between renal tumor size and metastases in patients with von Hippel-Lindau disease. J Urol. 2004;172(1):63–5.
36. Walther MM, Choyke PL, Glenn G, et al. Renal cancer in families with hereditary renal cancer: prospective analysis of a tumor size threshold for renal parenchymal sparing surgery. J Urol. 1999;161(5):1475–9.
37. May M, Aziz A, Zigeuner R, et al. Gender differences in clinicopathological features and survival in surgically treated patients with renal cell carcinoma: an analysis of the multicenter CORONA database. World J Urol. 2013;31(5):1073–80.
38. Pai A, Brunson A, Brown M, Pan CX, Lara Jr PN. Evolving epidemiologic trends in nonclear cell renal cell cancer: an analysis of the California Cancer Registry. Urology. 2013;82(4):840–5.
39. Hofmann JN, Schwartz K, Chow WH, et al. The association between chronic renal failure and renal cell carcinoma may differ between black and white Americans. Cancer Causes Control CCC. 2013;24(1):167–74.
40. Malouf GG, Monzon FA, Couturier J, et al. Genomic heterogeneity of translocation renal cell carcinoma. Clin Cancer Res Off J Am Assoc Cancer Res. 2013;19(17):4673–84.
41. Ahluwalia P, Nair B, Kumar G. Renal cell carcinoma associated with Xp11.2 translocation/TFE3 gene fusion: a rare case report with review of the literature. Case Rep Urol. 2013;2013:810590.
42. Gaillot-Durand L, Chevallier M, Colombel M, et al. Diagnosis of Xp11 translocation renal cell carcinomas in adult patients under 50 years: interest and pitfalls of automated immunohistochemical detection of TFE3 protein. Pathol Res Pract. 2013;209(2):83–9.
43. Bai Y, Guo Z, Xu J, et al. Single nucleotide polymorphisms in the D-loop region of mitochondrial DNA is associated with renal cell carcinoma outcome. Mitochondrial DNA. 2013.
44. Xu J, Guo Z, Zhang J, Cui L, Zhang S, Bai Y. Single nucleotide polymorphisms in the mitochondrial displacement loop and age-at-onset of renal cell carcinoma. Sci Rep. 2013;3:2408.
45. Baysal BE, Ferrell RE, Willett-Brozick JE, et al. Mutations in SDHD, a mitochondrial complex II gene, in hereditary paraganglioma. Science (New York, NY). 2000;287(5454):848–51.
46. Gill AJ, Pachter NS, Chou A, et al. Renal tumors associated with germline SDHB mutation show distinctive morphology. Am J Surg Pathol. 2011;35(10):1578–85.
47. Gill AJ, Pachter NS, Clarkson A, et al. Renal tumors and hereditary pheochromocytoma-paraganglioma syndrome type 4. N Engl J Med. 2011;364(9):885–6.
48. Ricketts C, Woodward ER, Killick P, et al. Germline SDHB mutations and familial renal cell carcinoma. J Natl Cancer Inst. 2008;100(17):1260–2.
49. Vanharanta S, Buchta M, McWhinney SR, et al. Early-onset renal cell carcinoma as a novel extraparaganglial component of SDHB-associated heritable paraganglioma. Am J Hum Genet. 2004;74(1): 153–9.
50. Ricketts CJ, Shuch B, Vocke CD, et al. Succinate dehydrogenase kidney cancer: an aggressive example of the Warburg effect in cancer. J Urol. 2012;188(6):2063–71.