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ORIGINAL ARTICLE

Five New Cases of Primary Renal Carcinoid Tumor: Case Reports and Literature Review

Joel E. Rosenberg[1] · Jacob A. Albersheim[1] · Niranjan J. Sathianathen[1] · Paari Murugan[1] · Christopher J. Weight[1]

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Abstract

Carcinoid tumors, a slow-growing NET, most commonly arise in the gastrointestinal tract (73.7%), followed by the bronchopulmonary system (25.1%), and least commonly in the genitourinary system (<1%). Primary carcinoid tumors of the kidney—with approximately 100 cases reported in the literature since the first described case in 1966—are thought to be so rare because neuroendocrine cells are not typically found in the renal parenchyma. Here we present a series of five cases at our institution with primary carcinoid tumors of the kidney followed by a literature review. In the literature we describe the diagnostic stains used to determine renal carcinoid tumors. We also describe why partial nephrectomies are the gold standard treatment in these cases, while radical nephrectomy can be used in certain circumstances. Limited research on treatment of metastasis of these tumors exists, but we summarize the results of existing treatments. Major prognostic factors and survival of patients with these tumors is described as well as the increased prevalence of this tumors in patients with horseshoe kidneys. This study presents five new cases of primary renal carcinoid tumors and a comprehensive review of the previously published cases. We are able to make limited prognostic predictions from currently published literature, but we will continue to learn from our patients' long-term courses to draw conclusions about biological behavior, treatment outcomes, and recurrence of rare disease.

Keywords Urology · Oncology · Kidney · Renal · Carcinoid · Neuroendocrine · Surgical pathology

Introduction

Neuroendocrine tumors (NETs) are neoplasms that arise from endocrine and nervous system cells, and have traditionally been classified into four categories including typical carcinoid, atypical carcinoid, small cell carcinoma, and large cell neuroendocrine carcinoma.

Carcinoid tumors, a slow-growing NET, most commonly arise in the gastrointestinal tract (73.7%) [1], followed by the bronchopulmonary system (25.1%), and least commonly in the genitourinary system (<1%) [2]. Genitourinary carcinoid tumors have been reported to arise from the kidney, bladder, testes, ovaries and prostate. Testicular and ovarian carcinoid tumors are most prevalent form of genitourinary carcinoid tumors, followed closely by primary renal carcinoid tumors which are equally prevalent in both sexes [3].

✉ Christopher J. Weight
cjweight@umn.edu

[1] Department of Urology, University of Minnesota Medical School, 420 Delaware St. SE MMC 394, Minneapolis, MN 55455, USA

Primary carcinoid tumors of the kidney—with approximately 100 cases reported in the literature since the first described case in 1966—are thought to be so rare because neuroendocrine cells are not typically found in the renal parenchyma [1, 4]. Carcinoid tumors usually spread locally, metastases are rare, but frequency of metastases increases with increasing tumor size [5]. Here we present a series of five cases at our institution with primary carcinoid tumors of the kidney followed by a literature review.

Case Reports

Patient 1: A 51-year-old female with a known horseshoe kidney presenting with flushes and urine 5-HIAA of 3.3 mg/24 h was found to have a right posterior lower interpolar tumor. CT scan revealed a solid, enhancing endophytic 3.5 cm mass that was subsequently biopsied and found to be a low-grade neuroendocrine (carcinoid) tumor. The patient underwent octreotide scan which showed no other site of disease and partial nephrectomy was performed. Macroscopic pathological examination of the resected mass revealed a mass that was 3.4 cm in

diameter. Microscopic examination showed indeterminate lymphovascular invasion, perineural invasion, renal sinus fat invasion and a negative margin of resection. This mass had no necrosis and a mitotic rate of <1/10 *high-power fields* (HPF). Immunohistochemical tests showed diffuse chromogranin and synaptophysin reactivity with a Ki-67 index of <2%. Microscopic and immunohistologic findings complied with a well-differentiated renal neuroendocrine carcinoma. 5-HIAA levels were not assessed post-operatively and follow-up was lost due to care transfer to an outside hospital immediately following her post-operative course.

Patient 2: A 29-year-old female presenting with flank pain, irregular menstrual bleeding, pelvic cramping, brown urine in the mornings, chronic constipation, and a chromogranin A of 99 ng/ml was found to have a tumor on the right lower/interpolar region. On CT scan of the abdomen/pelvis she was found to have a complex solid endophytic, 8 cm enhancing cystic mass on her right kidney. No evidence of metastatic disease or lymphadenopathy was seen on imaging. Robotic partial nephrectomy with lymphadenectomy of two local retrocaval lymph nodes was subsequently performed. Macroscopic examination of the surgical specimen revealed a unifocal 9.6 cm in diameter mass. Microscopic examination showed lymphovascular invasion, perineural invasion, renal sinus fat invasion and negative margin of resection. This mass had infarction rather than true tumor necrosis and a mitotic rate of <2/10 HPF.

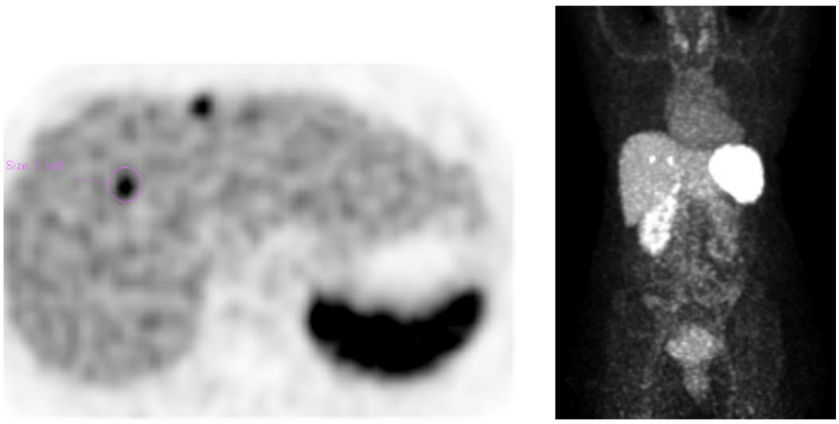
By immunohistochemical tests, the tumor was diffusely positive for CD56, chromogranin, and synaptophysin with a Ki-67 index of 5%. Microscopic and immunohistologic findings complied with a well-differentiated renal neuroendocrine carcinoma with pathological stage pT3aN1. Metastatic neuroendocrine carcinoma was found in two of two dissected retrocaval lymph nodes with one of the lymph nodes measuring 1.5 cm. Chromogranin A levels continued to climb after surgery, up to 287 ng/ml, and continue to be monitored. Yearly CT imaging after surgery shows no sign of recurrence or metastasis in this patient up to 24 months post-partial nephrectomy.

Patient 3: A 47-year-old female presenting with cholecystitis and flank pain was incidentally found to have a ~15 cm partially necrotic and calcified right renal upper pole mass with extensive lymphadenopathy visualized. A coordinated cholecystectomy followed by a combined open right radical nephrectomy and paracaval lymphadenectomy was performed. Macroscopic evaluation showed a 11 cm unifocal upper pole kidney tumor, along with one 9.7 cm paracaval mass demonstrating no appreciable lymph node architecture and one 5 mm positive paracaval lymph node. Microscopic evaluation showed lymphovascular invasion, perineural invasion, and renal sinus fat invasion and negative margin of resection. The mass did not have necrosis and had a mitotic rate of <2/10 HPF.

On immunohistochemical analysis, the tumor was positive for CD56 and synaptophysin while chromogranin was negative. The Ki67 index was 7%. Microscopic and immunohistologic findings were consistent with a well-differentiated renal neuroendocrine carcinoma, pathological stage pT3aN1. Eleven months following surgery, the patient underwent an octreotide scan which revealed radiotracer accumulation both in interaortocaval lymph nodes. She then underwent a robotic assisted retroperitoneal lymph node dissection where 8 of 19 dissected lymph nodes were positive for metastatic neuroendocrine carcinoma with the largest node measuring 2.5 cm. Fifteen months after surgery there is no sign of recurrence or metastasis but is undergoing yearly octreotide scans for appropriate monitoring.

Patient 4: A 51-year-old female presented because she was found to have a left abdominal mass by a massage therapist helping with chronic constipation. An abdominal CT scan showed a 10.8 cm hypoattenuating exophytic mass on the left inferior renal pole containing peripheral calcification and a solid component, as well as 2.7 cm left paraaortic lymphadenopathy. An open left nephrectomy and retroperitoneal lymphadenectomy was performed. Macroscopic evaluation showed a 10.1 cm in diameter mass. Microscopic evaluation showed lymphovascular invasion, perineural invasion, and renal sinus fat invasion with negative margins. The mass had necrosis and a mitotic rate of <6/10 HPF. From immunohistochemical tests, chromogranin and synaptophysin were positive and Ki-67 proliferation index was 10–15% .

Microscopic and immunohistologic findings complied with a well-differentiated renal neuroendocrine carcinoma of pathological grade III stage pT2bN1. Metastatic neuroendocrine carcinoma was found in 1/22 dissected retrocaval lymph nodes with one of the lymph nodes measuring 3.5 cm. Flushing was noted on follow-up and MRI scans were recommended every 3 months due probability of recurrence of this tumor. She was found to have 4–5 progressively growing liver lesions (Image 1), concerning for metastasis. Twelve months after surgery a PET DOTA-TATE showed 2 positive uptake liver lesions, consistent with metastatic disease. A liver biopsy was negative, but PET was diagnostic for liver recurrence. Oncology recommended Octreotide therapy which was tolerated well. She is now 16 months post-surgery and is continuing Octreotide therapy treatment with restaging in 6 months.



(a) (b)

Image 1. 2 metastatic lesions detected in patient 4 with positive uptake on PET DOTA-TATE scan 12 months after surgery. These lesions are small measuring 1.2 and 0.7 cm in maximum diameter and are being treated with Octreotide therapy

Patient 5: A 78-year-old male presented with urosepsis and a past medical history of urinary obstruction with gross hematuria. Twenty-three years prior this patient experienced hemoptysis and underwent a transbronchial biopsy. He was found to have carcinoid tumor of the lung and underwent a left lower lobectomy with no signs of metastasis with peri-bronchial node dissections. There have not been signs of bronchial recurrence since this time. Abdominal CT revealed a 3.1 cm solid, exophytic mass on the right lower pole of his kidney posterior to the ureter and subsequent biopsy revealed a well-differentiated neuroendocrine tumor, considered a new primary renal tumor with no signs of metastasis with octreoscan. His chromogranin A was 1204 ng/ml. The decision was made to perform laparoscopic-assisted renal cryoablation due to the solitary nature of the mass and proximity to the ureter. Microscopic evaluation of the surgical specimen showed tumor extending into perirenal soft tissue stroma, and no necrosis or vascular invasion. The mass had a mitotic rate of <2/10 HPF.

From immunohistochemical tests, the tumor was positive for chromogranin and synaptophysin and had a Ki-67 index of 15%. Microscopic and immunohistologic findings complied with a well-differentiated neuroendocrine carcinoma. Six months post-operatively there are no signs of recurrence or metastasis on CT scan and the patient plans to continue yearly follow-up.

Results

Clinical, pathological and immunohistochemical features of the cases are shown in Tables 1, 2, and 3. The average age of detection for our five patients was 52 years, with the youngest age of detection being 30 years and the oldest being 78. 80% of the patients were female and 80% of tumors affected patients' right kidney. Patients presented with varying symptoms of flushing and UTI (1), flank pain (2), constipation (1), and urosepsis (1). The tumor arose from the lower pole of the kidney in 4 of the 5 patients. One patient presented with a horseshoe kidney. Suspicions of renal masses are followed up with CT scans, but it is difficult to differentiate between carcinoid tumor and renal cell carcinoma, so a biopsy must be performed. All of the presented patients had primary renal carcinoid tumors.

Two patients underwent partial nephrectomy, two underwent open radical nephrectomy and one underwent laparoscopic assisted cryoablation. Three of five had metastasis. The average tumor size was 7.44 cm, ranging from 3.1 to 11 cm. Three tumors had a mitotic rate less than 2/10 HPF, and the Ki67 index ranged from less than 2 to 15%. No necrosis was seen in 4 of 5 renal carcinoid tumors and angiolymphatic invasion was seen in 4 of 5 tumors. Perineural invasion was seen in 4 of 5 tumors and renal sinus fat invasion was seen in all 5 tumors.

All tumors stained positive for chromogranin A (except one) and synaptophysin. Two of two stained tumors for CD56 were positive for expression and one of four stained tumors for CK7 were positive for expression. All tumors were classified as low-grade, well-differentiated neuroendocrine carcinomas by surgical pathology.

All of these patients are still alive. Patient 4, with the 10.8 cm hypoattenuating exophytic mass and paraaortic lymphadenopathy, was the only patient with definitive recurrence and is being managed by oncology and being treated with Octreotide. The patient with recurrence is following up with MRI scans, while the patient with metastasis to the retroperitoneal and right renal hilar lymph nodes is being followed up with by octreotide scans. The two patients without recurrence or lymph node metastasis are followed with yearly CT scans.

Table 1 HSK: horseshoe kidney. PN: partial nephrectomy, RN: Radical nephrectomy

	Gender	Age	Symptoms	Side	Intrarenal location	HSK	Type of surgery
Patient 1	F	54	Flushing and UTI	R	Posterior lower/interpolar	Yes	PN
Patient 2	F	30	Flank pain	R	Lower/interpolar	No	PN
Patient 3	F	47	Flank pain	R	Upper	No	Open RN
Patient 4	F	51	Constipation	L	Lower	No	Open RN
Patient 5	M	78	Urosepsis	R	Lower	No	Laparoscopic assisted cryoablation

Discussion

Primary carcinoid tumors of the kidney have an average age of detection of 49 years with no gender or laterality preponderance [6]. Interestingly, these tumors are incidentally diagnosed in 25–30% of cases. They are also often clinically misdiagnosed as type 1 papillary renal cell carcinoma, urothelial tumors, mesonephric tumors, undifferentiated carcinoma and Wilms tumor [2]. Based on a review of the less than 100 reported cases of renal carcinoid tumor, 12.7% of such patients presented with carcinoid syndrome [1]. Carcinoid syndrome is used to describe the symptoms of flushing, diarrhea, wheezing and potential right-sided valvular heart disease due to the release of serotonin and other vasoactive substances in systematic circulation from a carcinoid tumor [7].

Carcinoid tumors typically grow slowly and are clinically undetected even while growing for many years, due to the unoccupied space of the retroperitoneum. Seventy-five percent of primary renal carcinoid tumors are greater than 4 cm and 45% of tumors invade the perirenal or sinus/hilar fat or invade the renal vein. Synaptophysin (most sensitive) and chromogranin A are the diagnostic stains used to determine renal carcinoid, while the neuroendocrine phenotype is supported by CD56 positivity [3, 8].

Metastases are present in approximately 50% of primary renal carcinoid tumors, with hilar and paraaortic lymph nodes being the most common regions and one study showing 47% of patients having lymph node metastases [9]. Metastases are associated with large size and high mitotic activity (>1/10 HPF), with liver as the most common site of metastasis (34% of metastasized cases) and much less commonly the bone, lung and spleen. Scintigraphy with radiolabeled octreotide is a useful scan for monitoring metastasis and post-treatment recurrence of carcinoid tumors [3]. Octreotide scanning should also be used for patients with elevated levels of metabolites or primary hormones in the plasma or urine [10]. CT and MRI are also useful tools for surveillance, along with chromogranin and 5-HIAA levels [11].

Gold standard treatment for renal carcinoid tumors is partial nephrectomy or cryoablation to spare nephrons depending on location and diameter and since these tumors tend to behave benignly. Radical nephrectomy is a good option when the tumor is too large and cannot be fully removed by partial nephrectomy. Regional lymph node dissection should be performed if there is any evidence of enlarged nodes on scans. No studies have been performed to determine the efficacy of nephrectomy vs. cryoablation therapy. Nephron sparing surgery is yields the benefit of preservation of renal function when the renal mass is small, or when the mass is in close proximity to the ureter or another adjacent structure [12]. Radiation therapy is tolerated well and is found to achieve symptomatic palliative treatment for metastatic malignant carcinoid tumors, and improves symptoms of carcinoid syndrome as well [13]. Octreotide is a long-acting somatostatin analogue used for both detection and as a first line antineoplastic systemic therapy. This is also a good option to decrease symptoms of hormonal excess for patients with positive octreoscan was used for Patient 4 with metastasis to the liver [3, 7]. Cytotoxic chemotherapy has only had limited success in metastatic carcinoid treatment with a low response rate but stabilization of

Table 2 HPF: high-power fields

	Metastatic site	Maximal size, cm	Mitosis (10 HPF)	Ki67 Index	Necrosis	Angiolymphatic invasion	Perineural invasion
Patient 1	None	3.4	<1	<2%	No	Yes	Yes
Patient 2	Retrocaval LN	9.6	<2	5%	No	Yes	Yes
Patient 3	Retroperitoneal LN and right renal hilum	11.0	<2	7%	No	Yes	Yes
Patient 4	Paraaortic LN	10.1	<6	10–15%	Yes	Yes	Yes
Patient 5	None	3.1 (radiographic)	<2	15%	No	No	Yes

Table 3 Chr A: Chromogranin stain, Syn: Synaptophysin stain

	Renal sinus fat invasion	Chr A	Syn	CD56	CK7	CD10	Pax-8	Classification
Patient 1	Yes	+	+	NS	–	–	NS	Low grade well differentiated neuroendocrine carcinoma
Patient 2	Yes	+	+	+	NS	NS	NS	Low grade well differentiated neuroendocrine carcinoma
Patient 3	Yes	+	+	+	+	NS	+	Low grade well differentiated neuroendocrine carcinoma
Patient 4	Yes	+	+	NS	–	NS	NS	Low grade well differentiated neuroendocrine carcinoma
Patient 5	Yes	+	+	NS	–	–	NS	Low grade well differentiated neuroendocrine carcinoma

the disease in 40–60% of cases, while systemic chemotherapy is more beneficial in patients with aggressive carcinoid tumors [10]. Radiation therapy has not been studied extensively, but radiolabeled somatostatin analogues (Octreotide) have shown to shrink tumors and clinically improve patients with metastatic carcinoid tumors [7]. This therapy in advanced disease is linked with a 36–70% response rate [10].

For liver metastasis of carcinoid tumors, Lanreotide or Octreotide injections can be given monthly and are used as first line treatment for small lesions with high proliferation index and immunoreactivity to somatostatin receptors to slow growth and improve symptoms of carcinoid syndrome [14]. However, if the tumor is large enough, hepatic resection is safe and achieves longest lasting symptom control. One study has pleaded for liver resection by showing untreated hepatic neuroendocrine metastases having a 30–40% 5 year survival with a median 2–4 year survival, but with resection having a greater than 60% survival at 5 years with a median survival of 6.5 years [15]. The symptom recurrence was 59% at 5 years, and tumor recurrence of 84% at 5 years suggests a cure for liver metastasis might not be possible, but doubling the expected survival with better symptom control justifies this approach [15].

5-year, 10-year, and 20-year disease-specific survival rates of primary gastrointestinal tract carcinoid tumors are 91.3, 86.1, and 77.1%, respectively [16]. The 5-year survival rate of patients with lung carcinoid tumors stages I–IV respectively are 93, 85, 75, and 57% [17]. Prognosis of renal carcinoid is hard to predict because of their rarity and heterogenous behavior [6]. The stage of the tumor seems to be the most indicative prognostic factor. Patients with primary renal carcinoid tumors with metastases to the bone, liver and contralateral kidney have a poor prognosis with average survival of only a few months [3].

For patients with renal carcinoids there are, however, three major prognostic factors that have been identified. The first is rapid tumor progression and more severe initial presentation in patients above age 40. Second is less tumor metastasis with maximum tumor diameter less than 4 cm or tumors confined to the renal parenchyma. Third, high mitotic rate greater than 2/10 HPF, lymphovascular invasion, atypical cytology, and presence of necrosis is associated with more metastases and thus worse prognosis. However, histological parameters are not worthy of relying on for prognostic value since some tumors that show these characteristics have unpredictable clinical courses [3].

One of our patients was previously found to have a carcinoid tumor in a horseshoe kidney. Of the approximately 100 cases reported with renal carcinoid tumors, 30 were found in patients with horseshoe kidneys. One study calculated a relative risk of 62 for developing a carcinoid tumor in patients with horseshoe kidney compared with those with anatomically normal kidneys [18]. Likewise, patients with horseshoe kidneys have a twofold increase in relative risk of developing Wilms Tumor and three- to four-fold increased relative risk for developing transitional cell carcinoma compared to patients with anatomically normal kidneys [18].

Neuroendocrine cells are not found in normal adult renal parenchyma so the histogenesis of these tumors is uncertain, however they are present in the kidney during embryogenesis. Tumors associated with horseshoe kidney are often more benign and are suggested to arise from preexisting hyperplasia of neuroendocrine cells in the foci of aberrant epithelium in the kidney. This epithelium may represent intestinal metaplasia in the lining of the renal collecting system or a manifestation of teratomatous elements in the kidney [18]. It is thought that there are distinct pathological mechanisms between horseshoe and non-horseshoe carcinoid tumors. Horseshoe kidneys are thought to develop from a teratogenic event resulting in the abnormal migration of posterior nephrogenic cells to form an isthmus. A larger proportion of renal carcinoid tumors originate on, or have involved, this isthmus/interpolar region, including the one presented in our case report [18].

Many questions still remain regarding the biological mechanisms and long-term outcomes of primary renal carcinoid tumors, but key prognostic factors and treatment options are becoming well established. Progressive treatment of metastasis is demonstrated in this paper, but long-term outcomes of metastatic treatment options is not well-established yet. Patients with a horseshoe kidney should be monitored for renal tumors and are more likely to develop primary renal carcinoid tumors compared to the rest of the population.

Conclusion

This study presents five new cases of primary renal carcinoid tumors and a comprehensive review of the previously published cases. We are able to make limited prognostic predictions from currently published literature, but we will continue to learn from our patients' long-term courses to draw conclusions about biological behavior, treatment outcomes, and recurrence of rare disease.

References

1. Sun K, You Q, Zhao M, Yao H, Xiang H, Wang L (2013) Concurrent primary carcinoid tumor arising within mature teratoma and clear cell renal cell carcinoma in the horseshoe kidney: report of a rare case and review of the literature. Int J Clin Exp Pathol 6(11):2578–2584
2. Seker KG, Sam E, Sahin S et al (2017) Partial nephrectomy in horseshoe kidney: primary carcinoid tumor. Arch Ital Urol Androl 89(4):316–318
3. Korkmaz T, Seber S, Yavuzer D, Gumus M, Turhal NS (2013) Primary renal carcinoid: treatment and prognosis. Crit Rev Oncol Hematol 87(3):256–264
4. Resnick ME, Unterberger H, McLoughlin PT (1966) Renal carcinoid producing the carcinoid syndrome. Med Times 94(8):895–896
5. Litwinowicz R, Szpor J, Januś G, Worek M, Okoń K (2011) Primary carcinoid tumour in horseshoe kidney. Pol J Pathol 62(1): 72–74
6. Omiyale AO, Venyo AK (2013) Primary carcinoid tumour of the kidney: a review of the literature. Adv Urol 2013:579396
7. Kulke MH, Mayer RJ (1999) Carcinoid tumors. N Engl J Med 340(11):858–868
8. Xiang L, Kong B (2013) PAX8 is a novel marker for differentiating between various types of tumor, particularly ovarian epithelial carcinomas. Oncol Lett 5(3):735–738
9. Romero FR, Rais-Bahrami S, Permpongkosol S, Fine SW, Kohanim S, Jarrett TW (2006) Primary carcinoid tumors of the kidney. J Urol 176(6 Pt 1):2359–2366
10. Singh PP, Malhotra AS, Kashyap V (2009) Carcinoid tumor of the kidney: an unusual renal tumor. Indian J Urol 25(4):537–538
11. Gedaly R, Jeon H, Johnston TD, McHugh PP, Rowland RG, Ranjan D (2008) Surgical treatment of a rare primary renal carcinoid tumor with liver metastasis. World J Surg Oncol 6:41
12. Ismail M, Nielsen TK, Lagerveld B et al (2018) Renal cryoablation: multidisciplinary, collaborative and perspective approach. Cryobiology 83:90-94
13. Chakravarthy A, Abrams RA (1995) Radiation therapy in the management of patients with malignant carcinoid tumors. Cancer 75(6): 1386–1390
14. Bondanelli M, Ambrosio MR, Zatelli MC, Cavazzini L, Al Jandalirifa'y L, degli Uberti EC (2005) Regression of liver metastases of occult carcinoid tumor with slow release lanreotide therapy. World J Gastroenterol 11(13):2041–2044
15. Sarmiento JM, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, Que FG (2003) Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg 197(1):29–37
16. Mocellin S, Nitti D (2013) Gastrointestinal carcinoid: epidemiological and survival evidence from a large population-based study (n = 25 531). Ann Oncol 24(12):3040–3044
17. Society TAC (2016) Survival rates for lung carcinoid tumors. https://www.cancer.org/cancer/lung-carcinoid-tumor/detection-diagnosis-staging/survival-rates.html#written_by. Accessed 5 May 2018
18. Krishnan B, Truong LD, Saleh G, Sirbasku DM, Slawin KM (1997) Horseshoe kidney is associated with an increased relative risk of primary renal carcinoid tumor. J Urol 157(6):2059–2066