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Neuroendocrine Tumors of the Kidney: A Single Institution Experience

Purnima Sravanti Teegavarapu¹, Priya Rao², Marc Matrana³, Diana H. Cauley⁴, Christopher G Wood⁵, and Nizar M. Tannir⁶

¹Lymphoma Department, The University of Texas MD Anderson Cancer Center, Houston, TX

²Pathology Department, The University of Texas MD Anderson Cancer Center, Houston, TX

³Hematology/Oncology Fellowship Program, The University of Texas MD Anderson Cancer Center, Houston, TX

⁴Pharmacy Clinical Programs, The University of Texas MD Anderson Cancer Center, Houston, TX

⁵Urology Department, The University of Texas MD Anderson Cancer Center

⁶Genitourinary Medical Oncology Department, The University of Texas MD Anderson Cancer Center, Houston, TX

Abstract

Background—Renal neuroendocrine tumors (NET), comprising carcinoid tumors and small cell carcinomas, are a rare group of neoplasms. The rarity of these tumors poses a diagnostic and therapeutic challenge. Our purpose was to characterize the cases treated at a tertiary cancer center and to evaluate patients' outcomes with the available treatment modalities.

Methods—This is a retrospective study of patients with renal NET seen at The University of Texas MD Anderson Cancer Center between January 1, 2001, and January 1, 2011. Patient and tumor data were analyzed by descriptive statistical methods.

Results—Three cases of carcinoid tumors and six cases of small cell carcinoma were identified. The median age at diagnosis was 53 years for patients with carcinoid and 65 years for patients with small cell carcinoma. The most common presenting symptoms were back pain, flank pain, and hematuria. The morphological appearance of the tumor cells and their immunohistochemical reactivity for neuroendocrine markers and cytokeratin helped establish the diagnosis.

Nephrectomy was the mainstay of treatment for carcinoid tumors, yielding good long-term results, even in the presence of metastases. Surgery and chemotherapy were utilized for small cell

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*Correspondence to: Nizar M. Tannir, MD, FACP, Department of Genitourinary Medical Oncology, Unit 1374, The University of Texas MD Anderson Cancer Center, 1155 Pressler Street, Houston, TX 77030-3721, USA. Tel: 713-563-7265; Fax: 713-745-1625; ntannir@mdanderson.org.

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carcinoma of the kidney. The median overall survival for patients with small cell carcinoma of the kidney was 17.3 months.

Conclusion—Renal carcinoid tumors are indolent and are associated with prolonged survival, while small cell carcinomas of the kidney are aggressive tumors with relatively short overall survival. Although palliative in nature, cytotoxic chemotherapy is the mainstay of therapy and is best given before surgery.

Keywords

carcinoid tumors; small cell carcinomas; kidney tumors; chemotherapy; cytoreductive nephrectomy

Introduction

Neuroendocrine tumors (NET) are a heterogeneous group of neoplasms that differ in biologic behavior, histologic pattern, and response to treatment. They are broadly classified as well-differentiated or poorly-differentiated neoplasms. The well-differentiated NET are indolent in nature, characterized by organoid arrangement of tumor cells and secretion of hormones and vasoactive substances, with diffuse immunoexpression of neuroendocrine markers. The poorly-differentiated NET, on the other hand, display sheet-like or diffuse architecture, less cytoplasmic granularity than the well-differentiated NET, and limited immunoexpression and are aggressive in nature, with extensive metastasis (1).

Well-differentiated NET such as carcinoid tumors most frequently arise from the gastrointestinal tract, pancreas, or lungs. Carcinoids of the genitourinary tract, especially those arising primarily from the kidney, are very rare; approximately 90 cases have been reported. They are frequently associated with horseshoe kidney (2). Poorly-differentiated NET such as small cell carcinomas most often originate in the urinary bladder, prostate, or gastrointestinal tract (3, 4), but these high-grade neoplasms can arise in virtually any organ, either *de novo* or through transformation of a lower grade tumor. Extrapulmonary small cell carcinoma accounts for 2.5-5% of all small cell carcinomas, and approximately 1000 new cases are diagnosed every year in the United States (5). Extrapulmonary small cell carcinoma arising *de novo* from the kidney is extremely rare (6); only 50 cases of primary renal small cell carcinoma have been reported.

Given the rarity of renal NET, information regarding treatment course and outcomes of patients with carcinoid tumor or small cell carcinoma of the kidney is limited, prompting this retrospective study. We present here a case series of renal carcinoid tumors and small cell carcinomas of the kidney treated at our institution, summarizing their clinical characteristics, treatment courses, and outcomes.

Patients and Methods

Following Institutional Review Board approval, we conducted a retrospective review of clinical, radiographic, and pathologic records of patients treated for primary renal NET at The University of Texas MD Anderson Cancer Center from January 1, 2001, through

January 1, 2011. Data collected included baseline patient demographic details (age, race, sex); medical history; treatment, including nephrectomy and systemic therapy; initiation and discontinuation dates of therapy; and last available date of follow up at our center or date of death. Overall survival was defined as the period from diagnosis to death.

Results

Nine patients met our inclusion criteria, comprising three cases of renal carcinoid tumor and six cases of small cell carcinoma of the kidney. Median age at diagnosis was 53 years for patients with renal carcinoid tumor and 65 years for patients with small cell carcinoma of the kidney (range, 21-73). The most common presenting symptoms were back pain, flank pain, or hematuria; one case of small cell carcinoma was diagnosed incidentally when the patient was noted to have a renal mass. Although no particular predilection for either kidney has been reported in the literature, all three renal carcinoid tumors arose from the right kidney, and five of the six small cell carcinomas arose in the left kidney. The carcinoid tumors ranged in size from 4 cm to 5.4 cm, while the small cell carcinomas ranged from 2 cm to 9.4 cm.

None of the three patients with renal carcinoid tumor displayed any symptoms of carcinoid syndrome; however, one of these patients had elevated levels of 5-hydroxyindoleacetic acid (5HIAA)/chromogranin and a positive octreotide scan result. The remaining two patients did not undergo an octreotide scan. Carcinoid tumors of the kidney are known to be associated with congenital anomalies, and one of the three patients with a renal carcinoid tumor had a horseshoe kidney and Ehler-Danlos syndrome. The carcinoid tumors demonstrated a trabecular growth pattern, composed of tubules and small nests of cells. The small cell carcinomas were high grade and poorly-differentiated, with cells arranged in sheets with areas of necrosis and high mitotic activity. Immunohistochemical studies for all nine patients demonstrated reactivity with synaptophysin, cytokeratin, neuron-specific enolase (NSE), vimentin, and chromogranin. Stains for thyroid transcription factor 1, CK-20, and renal cell carcinoma antigen were negative. All three renal carcinoid tumors and all six small cell carcinomas of the kidney stained positively for synaptophysin and chromogranin.

Two of the three patients with renal carcinoid tumor underwent biopsy of the renal mass prior to nephrectomy. All three of these patients showed evidence of metastases at the time of presentation. Two of the three patients had liver metastases. However, local control with nephrectomy and resection of metastases achieved excellent response in these patients. The two patients who had metastatic retroperitoneal lymphadenopathy underwent retroperitoneal lymph node dissection and lymphadenectomy. These three patients with carcinoid tumor were monitored for a mean period of 66 months (range, 52-113.9), and all three were alive at last follow up. Table 1A summarizes the demographic characteristics of the patients with carcinoid tumor and the clinical, pathological, and immunohistochemical features of the tumors. Table 1B summarizes the treatment and follow-up data for these three patients.

Only one of the six patients with small cell carcinoma of the kidney underwent pre-operative renal mass biopsy. Three of the six patients had regional lymph node involvement at diagnosis, and all six patients developed distant metastases later on. The most frequent sites

of metastasis were the brain, mediastinum, and retroperitoneum. Surgery and chemotherapy were the two main therapeutic modalities used to treat these patients. Five of the six patients underwent nephrectomy, and one of those also underwent lymphadenectomy. All six received cytotoxic chemotherapy; a platinum-based regimen that included etoposide was most often used. Two of the six patients received whole brain irradiation for brain metastases. The mean follow-up period was all six patients was 28.2 months (range, 11.5-156.7). Four of the six died of their disease, and the median overall survival for all six patients was 17.3 months. Table 2A summarizes the demographic characteristics of the patients with small cell carcinoma and the clinical, pathological, and immunohistochemical features of the tumors. Table 2B summarizes treatment data and outcomes for these patients. Table 3 displays summary and survival statistics.

Discussion

Our study summarizes the clinical characteristics, treatment modalities, and outcomes of three cases of renal carcinoid and six cases of small cell carcinoma of the kidney. Prolonged survival was achieved with nephrectomy alone in patients with renal carcinoid, even in those with metastatic disease. Despite having a worse prognosis than patients with renal carcinoid, patients with small cell carcinoma of the kidney demonstrated improved overall survival using upfront systemic chemotherapy, compared to published reports on this aggressive tumor.

Disseminated neuroendocrine cells giving rise to a tumor are most often found in the gastrointestinal tract and lungs. Carcinoid tumors arising from the genitourinary tract constitute less than 1% of all carcinoid tumors and have been reported to occur in testis, ovary, kidney, and prostate.⁷ Similarly, poorly-differentiated small cell carcinomas arising primarily from the kidney account for less than 1% of all the epithelial tumors of the genitourinary tract.⁸ The pathogenesis of renal carcinoid tumors remains unclear and is believed to be from entrapped neural crest cells in the kidney. Likewise, the origin of extrapulmonary small cell carcinomas has been debated, and a multipotent stem cell giving rise to neuroendocrine and sometimes exocrine differentiation has been postulated as the possible mechanism for the development of these carcinomas (9).

In the largest series of renal carcinoid tumors reported, Hansel et al. examined 21 cases obtained from archives of five major institutions (10). In that series, renal carcinoid tumors affected relatively younger patients than renal cell carcinoma, affected males and females equally, and were morphologically consistent with carcinoid tumors present at other anatomic sites. Our study showed similar findings, although all three of the patients with renal carcinoid tumor were female. By comparison, five of the six patients with small cell carcinoma in our series were male, which contrasts with the female preponderance reported in the literature. Symptoms of flushing, diarrhea, edema, and elevated 5-HIAA level associated with carcinoid syndrome occur in less than 10% of patients with a renal carcinoid tumor (11), but none of the patients in our small cohort experienced any of the symptoms of carcinoid syndrome, and only one had elevated 5HIAA/chromogranin levels. The presenting symptoms of flank pain and hematuria in our series of patients were similar to those reported

previously, and none of our patients had any evidence of endocrine or paraneoplastic features.

While renal carcinoid tumors show no distinctive pattern on computed tomographic or magnetic resonance imaging, and can present as well-circumscribed, non-enhancing or slightly enhancing masses, a large tumor in a predominantly medullary location with lack of central necrosis should raise suspicion for extrapulmonary small cell carcinoma of the kidney (12). Small cell carcinoma of the kidney has been reported to occur in conjunction with urothelial carcinoma (13), but none of the six patients in our review had any evidence of urothelial carcinoma.

Octreotide scans can be useful for diagnosis and staging of carcinoid tumors as well as for detection of recurrence and metastasis (14). Octreotide imaging was utilized for post-treatment surveillance in one of the three patients with renal carcinoid tumor.

Immunohistochemistry plays an important role in the diagnosis of NET, which exhibit positive reactivity to synaptophysin, cytokeratin, and NSE. The presence of these neuroendocrine markers, along with absence of renal transcription factors such as PAX-2 and PAX-8 (15) and absence of loss of heterozygosity on chromosome 3p21,¹⁶ have been advocated as molecular and morphological features unique to neuroendocrine carcinoid tumors, but these tests were not performed in our patients. Similarly, expression of NSE was noted more consistently than expression of chromogranin in small cell carcinomas of the urinary tract.¹⁷ A high grade of chromosomal instability and loss of the *p53* gene have been demonstrated in poorly-differentiated NET independent of the site of origin¹⁸ and are also applicable to renal small cell carcinoma, as was reported by La Rosa *et al.*¹⁹

Metastasis occurs in as many as 50% of cases of renal carcinoid tumor,²⁰ although primary carcinoid tumors arising within mature teratomas of the kidney are not usually associated with metastasis.²¹ In our small series, all three patients with carcinoid tumor had metastases, a fact that may represent referral bias to a tertiary care center and thus may not be indicative of the general population. Despite metastasis, all three patients with carcinoid tumor were alive at the time of analysis four to nine years from initiation of treatment which is consistent with published reports of prolonged survival in patients with this tumor, even in the presence of metastases.¹⁰ Local control with nephrectomy remains the standard treatment of renal carcinoid tumors, and all our three patients underwent this surgery. One of the three patients also underwent wedge resection of hepatic metastases, and another patient underwent lymph node dissection and surgical debulking. Chiang *et al.* reported a case of renal carcinoid with extensive hepatic metastases, in which tumor resection with para-aortic lymph node dissection was followed a year later by transarterial embolization of hepatic metastases, and noted a good outcome.²² The use of octreotide for the treatment of functional and nonfunctional NET prolonged time to progression in the PROMID study,²³ although there are few publications about the experience with octreotide in renal carcinoid tumors. Korkamaz *et al.* reported progression-free survival of approximately 7 months in patients with renal carcinoid tumor treated with sandostatin.²⁴

The high incidence of metastasis and initial relative sensitivity of small cell carcinoma to chemotherapy has made cytotoxic chemotherapy the mainstay of treatment for renal small

cell carcinoma. A 72% rate of response to chemotherapy in 22 patients with extrapulmonary small cell carcinoma was reported,²⁵ although the median duration of survival was only 8.5 months. A recent review that included 45 patients with small cell carcinoma of the kidney reported a median survival of 9.9 months.²⁶ A review of the literature by Majhail *et al.* indicated a median survival of 8 months.²⁷ The use of a platinum compound–based chemotherapy regimen has demonstrated favorable outcomes in nonrenal genitourinary and extrapulmonary small cell carcinoma,²⁸ as well as in renal small cell carcinoma, where chemotherapy alone has yielded better survival than surgery alone or combined surgery and chemotherapy (27). Early detection of this aggressive cancer, along with use of platinum-based chemotherapy and careful follow up for detection of local recurrence or metastasis within 6 months after primary treatment, are factors that can play a role in improving the overall survival of patients with primary small cell carcinoma of the kidney (26). Novel, biologically driven therapeutic trials are clearly needed to alter the bleak prognosis of this aggressive malignancy.

Conclusion

NET of the kidney, consisting of carcinoid tumors and small cell carcinomas, are a rare group of neoplasms. Although small cell carcinomas of the kidney and renal carcinoid tumors both demonstrate reactivity with neuroendocrine markers, they are histologically distinct: the poorly-differentiated, higher grade nature of small cell carcinomas contrasts with the more well-differentiated histology of renal carcinoid tumors. Patients with the indolent renal carcinoid tumor tend to have prolonged survival even in the presence of metastases, while patients with the aggressive small cell carcinoma of the kidney have a relatively short overall survival. Patients with small cell carcinoma of the kidney, who were predominantly treated with platinum-based chemotherapy, had a median overall survival of 17.3 months in our series of six cases, exceeding that of most other small series in the literature. The discrepancy in survival outcomes between our series and other published series may be explainable by our preference for treating patients with small cell carcinoma of the kidney with upfront chemotherapy rather than immediate nephrectomy. This study adds to the small number of series in this rare cancer and highlights the importance of upfront chemotherapy, rather than immediate nephrectomy, in the management of small cell carcinoma of the kidney. Prospective, randomized trials incorporating novel therapies are needed to determine the most appropriate treatment strategies in small cell carcinomas of the kidney.

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Clinical practice points

- Renal neuroendocrine tumors, including well-differentiated carcinoid tumors and poorly-
- Differentiated small cell carcinomas of the kidney, represent a very rare group of neoplasms.=
- Most common presenting symptoms of neuroendocrine tumors of the kidney are back pain, flank pain and hematuria.
- Morphological appearance and immunohistochemistry aid in the diagnosis of renal neuroendocrine tumors.
- Nephrectomy was the mainstay treatment of renal carcinoid and was associated with prolonged survival even in patients with metastatic disease.
- Platinum-based chemotherapy regimens were used for small cell carcinomas of the kidney, with median overall survival of 17.3 months.

Table 1A
Clinical, Pathological, and Immunohistochemical Features of Renal Carcinoid Tumors

Case	Age	Sex	Presenting symptoms	5HIAA /chromogranin	Radiographic findings	Octreotide scan	Pathologic findings	Immunohistochemistry	Horseshoe kidney
1	53	Female	flank pain	N/A	R upper pole, 4cm	N/A	well differentiated, no lymphovascular invasion	Syn/Cyto/Chrom+	-
2	43	Female	RUQ pain	N/A	R lower kidney, 5cm	N/A	well differentiated	NSE/Keratin+	-
3	56	Female	Flank pain, gross hematuria	+	R kidney, 5.4cm	R kidney, L paraaortic, aortocaval LN	well differentiated	Syn/Chrom/Vim+	+

5HIAA, 5-hydroxyindoleacetic acid; RUQ, right upper quadrant; R, right; Syn, synaptophysin; Chrom, chromogranin; Cyto, cytokeratin; NSE, neuron-specific enolase; L, left; LN, lymph nodes; Vim, vimentin; +, present; -, absent.

Table 1B. Treatment and Follow-up Data for Renal Carcinoid Tumors

Case	Renal mass Bx	Nephrectomy	Metastases at presentation	Systemic therapy	Time between diagnosis and last follow-up/death (months)	Progression	Death	NED at last follow-up
1	-	+	1 (paracaval LN)	-	113.9	+ (liver metastases)	-	-
2	+	+	2 (retroperitoneum, liver)	-	66	+ (liver metastases)	-	-
3	+	+	1 (retroperitoneum)	-	52	-	-	+

Bx, biopsy; LN, lymph node; FNAC, fine-needle aspiration cytology; NED, no evidence of disease; +, present; -, absent.

Table 2A
Clinical, Pathological, and Immunohistochemical Features of Small Cell Carcinomas of the Kidney

Case	Age	Sex	History of smoking	Presenting symptoms	Radiographic findings	Pathologic findings	Immunohistochemistry
1	73	Female	+	Incidental mass	R lower pole, 1.8cm	High-grade features, extends to parenchymal margin	Syn/Chrom/Cyto+
2	57	Male	-	hematuria	L, 6cm	high grade with lymphovascular invasion	Syn/Cyto/Vim+
3	67	Male	+	abdominal mass	L, 9cm	poorly differentiated, extensive necrosis, invading perinephric space	Syn/Chrom/Cyto+
4	62	Male	+	LUQ/back pain	L midpole, 6cm	poorly differentiated, multifocal tumor necrosis	Syn/Chrom+
5	71	Male	+	hematuria	L inter-lower pole, 3cm	undifferentiated, necrosis, lymphovascular invasion	Syn/Chrom+
6	21	Male	-	flank pain, hematuria	L, 9.4cm	poorly differentiated	Syn/Chrom/Cyto+

R, right; Syn, synaptophysin; Chrom, chromogranin; Cyto, cytokeratin; L, left; LUQ, left upper quadrant; Vim-vimentin; +, present; -, absent.

Table 2B. Treatment and Follow-up Data for Small Cell Carcinomas of the Kidney

Case	Renal Bx	Nephrectomy	Metastases at presentation	Systemic therapy	Time between diagnosis and last follow-up/death (months)	Progression	Dead	NED at last follow-up
1	-	+	(partial)	None	1 Carbo (AUC 5)/Pac (150 mg/m ²) × 6 cycles 2 WBRT 3 SRS	34.9	+	-
2	-	+	1 (retroperitoneum)	1 Cis 50 mg/Etop 100 mg; weekly 2 Cis 50 mg/Etop 100 mg/Pac 100 mg; weekly 3 Dox /Ifos daily × 3 days every 21 days	13	+	+	-
3	-	+	3 (retroperitoneum, supraclavicular, psoas)	1 Carbo 550 mg on day 1/Etop 130 mg daily × 3 days; × 3 cycles 2 Cis 100 mg on day 1/Irin 100 mg weekly × 3 weeks × 5 cycles 3 Topo 2.5 mg daily × 5 days; × 2 cycles 4 Carbo 500 mg/Pac 330 mg	11.5	+	+	-

Table 2B. Treatment and Follow-up Data for Small Cell Carcinomas of the Kidney

Case	Renal Bx	Nephrectomy	Metastases at presentation	Systemic therapy	Time between diagnosis and last follow-up/death (months)	Progression	Dead	NED at last follow-up
4	+	-	1 (retroperitoneum)	1 Carbo (AUC 5) on day 1/Etop 80-100 mg/m ² daily × 3 days; × 6 cycles	75	-	-	+
5	-	+	None	1 Carbo 375 mg on day 1/Etop 180 mg (100 mg/m ²) daily days 1-3; × 6 cycles 2 WBRT	21.5	+ (brain, thoracic, abdominal mets)	+	-
6	-	+	None	1 Etop (120 mg/m ²) daily × 3 days/Cis (35 mg/m ²) daily × 3 days/Dox (45 mg/m ²) daily × 2 days; × 4 cycles	156.7	-	-	+

Carbo, carboplatin; Cis, cisplatin; Dox, doxorubicin; Etop, etoposide; Ifos, ifosfamide; Irin, irinotecan; Pac, paclitaxel; Topo, topotecan
Bx, biopsy; LN, lymph node; + = present, - = absent; Mets, metastases; SRS, stereotactic surgery; WBRT, whole brain radiotherapy

Summary

Table 3

	Carcinoid	Small cell
Number of patients	3	6
Median age at diagnosis, years (range)	53 (43-56)	65 (21-73)
Male	0	5
Nephrectomy	3	5
Median no. of systemic therapies (range)	0 (0-2)	1 (1-4)
Median total time on systemic therapy, months (range)	0 (0-10)	4 (0-11)
Median time between diagnosis and last follow up, months (range)	66 (52-113.9)	28.2 (11.5-156.7)
Median OS, months (95% CI)	Undefined	17.3
Alive at time of analysis	3 (100%)	None

OS, overall survival; CI, confidence interval.