Published in final edited form as:

J Surg Oncol. 2018 June ; 117(8): 1716–1720. doi:10.1002/jso.25080.

The Association of Renal Cell Carcinoma with Gastrointestinal Stromal Tumors

Shawn J Mendonca, MD^{1,2}, Alejandro Sanchez, MD¹, Kyle A Blum, MD MSc¹, Mazyar Ghanaat, MD¹, Mahyar Y Kashan, BA¹, Nicole Benfante, BSc¹, Paul Russo, MD¹, Jonathan A. Coleman, MD¹, Aimee M Crago, MD³, and A. Ari Hakimi, MD¹

¹Division of Urology, Sidney Kimmel Center for Prostate and Urologic Cancers, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY

²Lenox Hill Hospital, Northwell Health, New York, NY

³Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY

Abstract

Background and Objectives—Prior small studies have reported a possible association between renal cell carcinoma (RCC) and gastrointestinal stromal tumors (GISTs). In the largest known series, our objective was to describe the prevalence of RCC among patients with GISTs over 26 years at Memorial Sloan Kettering Cancer Center (MSKCC).

Methods—We retrospectively reviewed MSKCC's prospectively maintained sarcoma and RCC databases and identified all patients with both RCC and GIST between 1980 and 2016. Demographic and clinicopathological characteristics were obtained.

Results—9/405 (2.2%) GIST patients were identified with RCC, with a mean follow-up of 9.2 [Range 3.8 – 28.4] years. 5/9 (55.6%) patients had RCC and GIST diagnosis within 6 months of each other. Mean RCC tumor size was 3.0 [Range 1.8 – 8] cm and 8/9 (88.9%) patients were RCC stage 1. 4/9 (44.4%) patients had papillary RCC (pRCC) histology, 5/9 (55.6%) had additional alternative malignancies, and 4/9 (44.4%) had primary small bowel GIST.

Conclusions—Our series suggests a possible association of RCC with GISTs. In addition, we found a high frequency of pRCC histology, alternative malignancies and small bowel GISTs in co-occurring RCC-GIST patients. Further investigation to identify genetic mutations, in this population, would assist in surveillance and treatment.

Keywords

Clinical association; Renal cell carcinoma; Gastrointestinal stromal tumors

Corresponding Author: Shawn James Mendonca, 170 E 77th St, Suite B, New York, NY 10075, Telephone: 919 218 7568, Fax: 212 288 1462, shawn.j.mendonca@gmail.com.

Disclosures: No conflicts of interest.

Introduction

First described in 1983, gastrointestinal stromal tumors (GISTs) are the most common sarcoma of the gastrointestinal tract [1 – 3]. While the majority of these tumors are thought to arise spontaneously, approximately 5% are considered hereditary [4]. There are multiple single institution and population based studies that have shown GIST patients to have an increased risk of developing additional malignancies, including renal cell carcinoma [5 – 9]. Similar to GISTs, a minor proportion (5 – 8%) of RCCs are known to occur due to hereditary etiology and some with an identifiable genetic abnormality [10]. Prior studies, based on smaller case series and individual reports have identified specific genetic mutations in patients diagnosed with both RCC and GIST within a lifetime [11 – 15]. While these studies suggest an association between these two malignancies, limited conclusions can be drawn due to their small sample sizes of 1–3 patients. In an effort to elucidate a true association between RCC and GIST, we report our findings after retrospectively analyzing our 26-year experience of patients diagnosed and surgically treated for both RCC and GIST.

Methods and Materials

This study was conducted using two prospectively maintained oncology databases from the Sarcoma and Urology division within the Department of Surgery at Memorial Sloan Kettering Cancer Center. After obtaining Institutional Review Board approval, the two databases were independently queried for patients who were diagnosed and underwent surgical treatment for both RCC and GIST between January 1980 and June 2016. Confirmation of diagnosis was based on pathologic specimens. The date of diagnosis for each malignancy was defined as the date of surgical resection.

Clinical and Pathological Variables and Outcomes

The primary objective of this study was to describe the prevalence of RCC and GIST co-occurrence. In addition, we aimed to characterize a possible association between these malignancies by evaluating the temporal relationship between their diagnoses and identifying common clinical characteristics in these patients. Baseline demographic and clinicopathologic data, including age, gender, tumor characteristics, chronologic occurrence and survival data, were captured. Data was presented as either continuous variables with a corresponding range or categorical variables. Chronologic co-occurrence of GIST and RCC was defined as either synchronous or metachronous. Synchronous co-occurrence was considered if a patient was diagnosed with GIST and RCC within a 6-month period. Metachronous co-occurrence was considered as RCC being diagnosed greater than 6 months after GIST.

Results

During the study period, the sarcoma database was searched and we identified a total of 405 patients who were surgically treated for GISTs at MKSCC. Of these 405 patients, 9 (2.2%) also had a diagnosis of RCC and were surgically treated at our institution. To validate our results, we independently queried the RCC database, between the same study time period, for patients who had a diagnosis of GIST, which resulted in the same 9 patients. Pathologic

characteristics specific to RCC are presented in Table 1. The diagnosis of RCC was made at the same time as the diagnosis of GISTs in 5/9 (55.6%) patients, prior to GIST diagnosis in 2/9 (22.2%) and after in 2/9 (22.2%). Mean RCC tumor size at diagnosis was 3.0 cm [Range 1.8 – 8.0]. After surgical resection 8/9 (88.9%) patients were found to have stage pT1 RCC on pathologic examination. Histologically, RCC tumors had a high frequency of clear cell (n = 4/9, 44.4%) and papillary RCC (n = 4/9, 44.4%).

Baseline clinical characteristics for all patients and GIST tumor characteristics are displayed in Tables 2 and 3, respectively. Mean earliest age at initial diagnosis of GIST was 58.1 [Range 42.9 – 73.2] years with a mean follow-up of 9.2 [Range 3.8 – 28.4] years. The most common type of GIST originated from the small bowel (4/9 – 44.4%). 5/9 (55.6%) patients had a history of additional malignancies other than RCC and GIST. Other malignancies included prostate, bladder, endometrial, gallbladder, carcinoid, lymphoma and basal cell carcinoma.

At last follow-up, 6/9 (66.7%) patients were alive. Of those alive, 4/9 (44.4%) had no evidence of GIST recurrence and 2/9 (22.2%) had metastatic GIST. 2/9 (22.2%) patients died from GIST and 1/9 (11.1%) died from other causes. None of the patients had evidence of RCC recurrence, metastases, or death at last follow up.

Discussion

Prior small case reports and series have looked at individual patients with co-occurring RCCs and GISTs to hypothesize an association between them. Some studies have shown synchronous GIST and RCC occurrence due to germline mutations in *SDHA*, *SDHC* or a translocation of Xp11 [11 – 13]. In addition, there are case reports and series that identify an association of GIST with papillary RCC over other RCC histologies [14 – 15]. While these studies support RCC and GIST association, there is an absence of large population studies to validate and assess a true relationship between these malignancies. To our knowledge, our study involves searching through the largest cohort of RCC and GIST patients over a lengthy study timeframe of 26 years.

The association between RCC and GIST is supported by common genetic and molecular pathways involving tyrosine kinase, which results in the development of these malignancies. Specific to RCC, the majority of cases is dependent on mutations of the *VHL* gene [16]. Under ideal physiologic conditions, the products of *VHL* bind to transcriptional factor hypoxia-inducible factor (HIF-1 α) rendering it inactive [17]. However when *VHL* is mutated, HIF-1 α becomes perpetually active and binds to a variety of cofactors that ultimately promotes uninhibited transcription of products including VEGFR, which leads to angiogenesis, and EGFR and PDGFR, which leads to cell growth [18]. Tyrosine kinase is an essential mediator in regulating the activity of these proteins. Ultimately, mutations in *VHL* result in a downstream effect of increase in tyrosine kinase mediated proteins that promote RCC tumorigenesis.

The genetic pathogenesis of GIST tumor development shares similar features to that of RCC. Prior studies have shown that a majority of GIST cases (approximately 85%) carry

KIT mutations and 5 – 7% of *KIT*-negative GISTs have activating mutations of *PDGFR- α* [19,20]. Activating *KIT* and *PDGFR- α* mutations are dependent on tyrosine-kinase mediated pathways that are essential for GIST development. Genetic mutations in tyrosine kinase pathways are essential for tumorigenesis of RCC and GIST, and the common origins for these tumors provide support for their clinical association.

Moreover, the clinical efficacy of Sunitinib, a tyrosine kinase inhibitor utilized in the treatment of both metastatic RCC and GIST, further supports the theory of a common etiology. Based on Sunitinib treatment response studies, both metastatic RCC and GIST patients showed significant improved rates of progression free survival when compared to placebo or other treatments [21 – 25]. Tyrosine kinase pathways are implicated in the pathogenesis of RCC and GIST, and favorable clinical outcomes of both tumors by the inhibition of a common pathway suggests a common relationship.

While our results support a possible association between RCC and GIST, further research is required to identify a specific genetic mutations or a hereditary syndrome for these co-occurring malignancies. Prior studies have identified specific genetic mutations in individual case reports, however, no genetic testing has been performed in a larger series of co-occurring RCC and GIST [11 – 13]. The patients in our series did not undergo genetic testing, however multiple unique clinical findings, aside from the co-occurrence of RCC and GIST, suggest the possibility of a familial syndrome. A majority of patients (55.6%) had other malignancies in addition to RCC and GIST. Furthermore, our results also identified a high occurrence of pRCC (44%) with GIST, which is consistent with findings in prior case reports [14 – 15]. The frequency of pRCC in our data is additionally higher than the expected relative frequency (12 – 14%) in the overall RCC population [26]. pRCC can occur as a recurrent familial tumor involving mutations in the receptor tyrosine kinase molecule c-MET [27]. Finally, our results found a disproportionately higher frequency of GIST originating from the small bowel (44%), relative to the expected frequency in the overall population (31.8%) [28]. While further genetic testing and investigation is required to establish genetic mutations and familial syndromes, the increased frequency of additional malignancies, pRCC and GISTs originating from the small bowel suggest its possibility.

Given the retrospective nature of the study, and the increased use of serial imaging on patients with GISTs during follow up, there is a potential bias for over-detecting RCC within the study population. Once a patient is diagnosed and treated for GIST, serial imaging is an integral component of follow-up care to evaluate for tumor recurrence, or progression to metastatic disease. Evidence in our series supports a potential over-detection bias by noting that RCC was diagnosed at the same time or after the diagnosis of GIST in a majority 77.8% of cases. In addition, renal masses that underwent surgical resection presented at an early pT1 stage (88.9%). Despite the limitations of our study, our reported results are consistent with smaller series and case reports currently available in the literature. Moreover, as the largest study investigating the concomitant occurrence of GIST and RCC, we feel that our findings support the association of RCC with GIST.

Conclusions

Our results complement prior small clinical reports and series of supporting a possible association between RCC and GIST. Moreover, our results demonstrate an increased frequency of additional malignancies, pRCC histology and GISTs originating from the small bowel in patients with co-occurring RCC and GISTs. While larger studies are required to provide more support of an association between these malignancies, results from this study warrant further genetic testing to help identify specific mutations. This would aid clinicians in surveillance and treatment of both these malignancies.

Acknowledgments

Funding Sources: This study is funded in part by the Sidney Kimmel Center for Prostate and Urologic Cancers and the National Cancer Institute Training Grant (T32 CA082088). Patients treated at Memorial Sloan Kettering Cancer Center were supported in part by Memorial Sloan Kettering Cancer Center Support Grant/Core Grant (P30 CA008748).

References

1. Mazur MT, Clark HB. Gastric stromal tumors. Reappraisal of histogenesis. *Am J Surg Pathol*. 1983; 7(6):507–19. [PubMed: 6625048]
2. Ducimetière F, Lurkin A, Ranchère-Vince D, Decouvelaere A, et al. Incidence of sarcoma histotypes and molecular subtypes in a prospective epidemiological study with central pathology review and molecular testing. *PLoS One*. 2011; 6:e20294. [PubMed: 21826194]
3. Mazzola P, Spitale A, Banfi S, Mazzucchelli L, et al. Epidemiology and molecular biology of gastrointestinal stromal tumors (GISTs): a population-based study in the South of Switzerland, 1999–2005. *Histol Histopathol*. 2008; 23:1379–1386. [PubMed: 18785120]
4. Nilsson B, Bummig P, Meis-Kindblom JM, Odén A, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era—a population-based study in western Sweden. *Cancer*. 2005; 103:821–829. [PubMed: 15648083]
5. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg*. 2000; 231:51–58. [PubMed: 10636102]
6. Agaimy A, Wünsch PH, Sobin LH, Lasota J, et al. Occurrence of other malignancies in patients with gastrointestinal stromal tumors. *Semin Diagn Pathol*. 2006; 23:120–129. [PubMed: 17193825]
7. Murphy JD, Ma GL, Baumgartner JM, Madlensky L, et al. Increased risk of additional cancers among patients with gastrointestinal stromal tumors: A population-based study. *Cancer*. 2015 Sep 1; 121(17):2960–7. [PubMed: 25930983]
8. Vassos N, Agaimy A, Hohenberger W, Croner RS. Coexistence of gastrointestinal stromal tumours (GIST) and malignant neoplasms of different origin: Prognostic implications. *International Journal of Surgery*. 2014 May 31; 12(5):371–7. [PubMed: 24632413]
9. Sevinc A, Seker M, Bilici A, Ozdemir NY, et al. Co-existence of gastrointestinal stromal tumors with other primary neoplasms. *Hepatogastroenterology*. 2011 May 1; 58:824–30. [PubMed: 21830398]
10. Linehan WM, Srinivasan R, Schmidt LS. The genetic basis of kidney cancer: A metabolic disease. *Nat Rev Urol*. 2010; 7:277–285. [PubMed: 20448661]
11. Jiang Q, Zhang Y, Zhou YH, Hou YY, et al. A novel germline mutation in SDHA identified in a rare case of gastrointestinal stromal tumor complicated with renal cell carcinoma. *International journal of clinical and experimental pathology*. 2015; 8(10):12188. [PubMed: 26722403]
12. Gill AJ, Lipton L, Taylor J, Benn DE, et al. Germline SDHC mutation presenting as recurrent SDH deficient GIST and renal carcinoma. *Pathology*. 2013 Dec 1; 45(7):689–91. [PubMed: 24150194]

13. Torous VF, Su A, Lu DY, Dry SM. Adult Patient with Synchronous Gastrointestinal Stromal Tumor and Xp11 Translocation-Associated Renal Cell Carcinoma: A Unique Case Presentation with Discussion and Review of Literature. *Case reports in urology*. 2015 Jul 13. 2015.
14. Dasanu CA, Jethava A, Ali S, Codreanu I. Gastrointestinal stromal tumor of small intestine and synchronous bilateral papillary renal cell carcinoma. *Connecticut medicine*. 2013 Aug; 77(7):405–7. [PubMed: 24195178]
15. Au WY, Ho KM, Shek TW. Papillary renal cell carcinoma and gastrointestinal stromal tumor: a unique association. *Annals of oncology*. 2004 May 1; 15(5):843–4. [PubMed: 15111359]
16. Latif F, Tory K, Gnarr J, Yao M, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science*. 1993; 260:1317–20. [PubMed: 8493574]
17. Kamura T, Sato S, Iwai K, Czyzyk-Krzeska M, et al. Activation of HIF1 α ubiquitination by a reconstituted von Hippel-Lindau (VHL) tumor suppressor complex. *Proceedings of the National Academy of Sciences*. 2000 Sep 12; 97(19):10430–5.
18. Bárdos JI, Ashcroft M. Hypoxia-inducible factor-1 and oncogenic signaling. *Bioessays*. 2004 Mar 1; 26(3):262–9. [PubMed: 14988927]
19. Heinrich MC, Corless CL, Demetri GD, Blanke CD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *Journal of clinical oncology*. 2003 Dec 1; 21(23):4342–9. [PubMed: 14645423]
20. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. *Journal of Clinical Oncology*. 22.18(2004):3813–3825.
21. Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *The Lancet*. 2006 Oct 20; 368(9544):1329–38.
22. Motzer RJ, Rini BI, Bukowski RM, Curti BD, et al. Sunitinib in patients with metastatic renal cell carcinoma. *Jama*. 2006 Jun 7; 295(21):2516–24. [PubMed: 16757724]
23. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *New England Journal of Medicine*. 2007 Jan 11; 356(2):115–24. [PubMed: 17215529]
24. Motzer RJ, Michaelson MD, Redman BG, Hudes GR, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *Journal of Clinical Oncology*. 2006 Jan 1; 24(1): 16–24. [PubMed: 16330672]
25. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *Journal of clinical oncology*. 2009 Jun 1; 27(22):3584–90. [PubMed: 19487381]
26. Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma. *New England Journal of Medicine*. 1996 Sep 19; 335(12):865–75. [PubMed: 8778606]
27. Schmidt L, Duh FM, Chen F, Kishida T, Glenn G, et al. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. *Nature genetics*. 1997 May 1; 16(1):68–73. [PubMed: 9140397]
28. Søreide K, Sandvik OM, Søreide JA, Giljaca V, et al. Global epidemiology of gastrointestinal stromal tumours (GIST): A systematic review of population-based cohort studies. *Cancer epidemiology*. 2016 Feb 1.40:39–46. [PubMed: 26618334]

Synopsis

In our series, 2.2% of patients treated for gastrointestinal stromal tumors were found to have renal cell carcinoma. In patients with co-occurring RCC and GIST, a higher than expected frequency of papillary RCC histology (44.4%), alternative malignancies other than RCC and GIST (55.6%) and GIST primarily originating from the small bowel (44.4%) were observed.

Table 1

RCC Tumor Characteristics of Patients with Co-occurring RCC and GIST

	RCC (Total N=9)
Mean RCC size (cm, range)	3.0 [1.8 – 8.0]
RCC chronologic occurrence (n, %)	
Prior to GIST	2 (22.2%)
Synchronous	5 (55.6%)
Metachronous	2 (22.2%)
RCC Treatment (n, %)	
Partial Nephrectomy	7 (77.8%)
Radical Nephrectomy	2 (22.2%)
Laterality (n, %)	
Right	7 (77.8%)
Left	2 (22.2%)
RCC pathologic stage (n, %)	
pT1	8 (88.9%)
pT2	1 (11.1%)
pT3	0
Histology (n, %)	
Conventional clear cell	4 (44.4%)
Papillary	4 (44.4%)
Unclassified	0
Chromophobe	1 (11.1%)
Collecting duct	0
Translocation	0

Table 2

Clinicopathologic and Survival Outcomes among Patients with Renal Cell Carcinoma (RCC) and Gastrointestinal Stromal Tumors (GIST)

	RCC + GIST (Total N=9)
Gender (n, %)	
Male	8 (88.9%)
Female	1 (11.1%)
Age at Initial diagnosis of GIST (n, Range)	58.1 [42.9 – 73.2]
Smoking Status (n, %)	
Never	5 (55.6%)
Prior Smoker	4 (44.4%)
Additional Malignancies? (n, %)	
Yes	5 (55.6%)
No	4 (44.4%)
Additional Malignancies (n)	
Bladder Cancer	3
Prostate Cancer	1
Gallbladder Cancer	1
Carcinoid Tumor	1
Lymphoma	1
Basal cell Carcinoma	1
GIST Survival Status (n, %)	
No Evidence of Disease	4 (44.4%)
Alive with Metastatic GIST	2 (22.2%)
Death from GIST	2 (22.2%)
Death from Alternative Causes	1 (11.1%)

Table 3

GIST Tumor Characteristics of Patients with Co-occurring RCC and GIST

	GIST (Total N=9)
GIST Site (n, %)	
Small bowel	4 (44.4%)
Stomach	3 (33.3%)
Multi-organ	2 (22.2%)
Mean GIST size (cm, range)	7.6 [2 – 27.5]
GIST Variant (n, %)	
Spindle	4 (44.4%)
Mixed Spindle and Epithelioid	3 (33.3%)
Epithelioid	1 (11.1%)
Unknown	1 (11.1%)
Metastatic GIST (n, %)	
Yes	4 (44.4%)
No	5 (55.6%)