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Determinants and prognostic implications of malignant ascites in metastatic papillary renal cancer

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Abstract

Objective—To describe the incidence of ascites in metastatic papillary renal cell cancer (pRCC), identify the factors associated with its development and evaluate its prognostic effect on the survival of these patients.

Methods—A retrospective evaluation of the medical records of patients with metastatic pRCC seen at National Cancer Institute (2000–2014) was undertaken. Logistic regression to identify predictors of the development of malignant ascites and Kaplan-Meier analysis to estimate survival was done.

Results—106 consecutive patients with metastatic pRCC were identified; sufficient data was available in 100 patients to enable assessment of ascites. 20% had evidence of malignant ascites. Median age at diagnosis of ascites was 48.0 years (26.1–76.6 years) and median time to development of ascites from initial diagnosis of metastatic disease was 16.0 (0–73.3) months. There was no significant difference in the incidence of ascites between patients with hereditary or sporadic pRCC ($p=0.803$) or among patients with different subtypes of pRCC ($p=0.456$). Elevated platelet-lymphocyte ratio (PLR) predicted development of malignant ascites in our cohort ($p=0.009$). Median overall survival was shorter for patients who developed ascites [25.0(10.2–39.8 months)] compared to patients who did not develop this complication [42.5(30.5–54.4) months, $p=0.041$].

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AS: manuscript writing

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RS: research design

Conclusion—To our knowledge, this is the first systematic evaluation of the incidence, predictors and prognostic impact of ascites in metastatic pRCC. Malignant ascites is a common manifestation of metastatic pRCC and is associated with a shorter overall survival. An elevated PLR predicts a higher risk of developing malignant ascites.

Keywords

Papillary renal cell cancer; malignant ascites; peritoneal carcinomatosis; metastasis; survival; platelet-lymphocyte ratio

Introduction

Malignant ascites results from involvement of the peritoneum by cancer and is a rare but ominous complication of metastatic cancer. It is seen most commonly in advanced or metastatic gastrointestinal, gynecological and primary peritoneal malignancies and leads to further deterioration in quality of life of these patients^{1, 2}. Development of malignant ascites in these cancers portends a poor prognosis, diminishing the survival of affected patients to a few months. While several therapies have been described in the literature to treat malignant ascites, the outcomes reported are suboptimal with limited success in achieving lasting remission or resolution^{2, 3}.

Peritoneal involvement and malignant ascites in metastatic renal cell cancer is exceedingly rare, with an incidence of less than 1%^{4, 5}. However, this low incidence is a reflection of the infrequent occurrence of this complication in clear cell RCC, the most predominant and well-studied variant of RCC. Although papillary renal cell carcinoma (pRCC) constitutes 10–15% of all kidney cancers, the clinical characteristics associated with this entity, including the incidence of malignant ascites, remain inadequately characterized. Here, we evaluate the incidence of ascites in the largest single center cohort of pRCC patients reported to date, attempt to identify factors predisposing to its development and estimate its prognostic effect on the survival of these patients.

Methods

Study Design and Participants

A retrospective evaluation of the medical records of all patients with metastatic RCC treated in the Urologic Oncology Branch of the National Cancer Institute on various institutional review board-approved protocols between 2000 and 2014 was performed. One hundred and six patients with metastatic pRCC were identified in that time period.

Study data

Patient demographics, tumor characteristics, and patient outcomes were reviewed. Based on histologic characteristics, tumors were divided into the following subtypes: Papillary type 1, Papillary type 2 and Papillary not otherwise specified, including patients with mixed histology or cases without specified papillary subtype. Patients were considered metastatic at presentation if there was radiological evidence of lymph node or distant metastases at the time of primary diagnosis or pathologic evidence for metastases was found at the time of

first surgery within 3 months of primary diagnosis. Baseline laboratory data at the time of diagnosis of metastatic disease and before initiation of systemic therapy was recorded. The diagnosis of malignant ascites was made based on cytologic evaluation of ascitic fluid and/or characteristic imaging findings of peritoneal carcinomatosis in the presence of with free peritoneal fluid in the absence of any other evident etiology for ascites (Figure 1). Patients' vital status was determined from medical records and social security death index registry in October 2015.

Statistical Methods

The primary objective of this retrospective analysis was to evaluate the incidence of ascites in this single center cohort of pRCC. Secondary objectives were to identify factors predisposing to the development of malignant ascites and estimate its prognostic effect on the survival of these patients. Statistical analysis was done using Statistical Package for Social Sciences version 21 (IBM, Chicago, IL, USA) and STATA version 13 (StataCorp LP, College Station, TX USA). Mann–Whitney U test was used to compare means of continuous variables. Fisher's exact and Pearson's Chi-square were used to compare proportions. Univariate and multivariate logistic regression analysis was done to identify predictors of development of ascites. Age at the time of the diagnosis of metastatic disease, gender, race, histologic subtype, hereditary origin and presence of metastasis at presentation along with laboratory data were included in regression analysis. For laboratory data, previously published cut-offs relevant in metastatic kidney cancer survival including hemoglobin below normal (<13.7 g/dL for males and <11.2 g/dL for females), platelet count above 300,000 per microliter, corrected calcium above 10mg/dL, lactate dehydrogenase above upper limit of normal (225mg/dL) were used^{6, 7}. For neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), since no widely accepted cut points have been adopted, we used the medians of distribution (3.3 for NLR and 187.4 for PLR in our cohort) as cut-points for dichotomization. Multivariate model selection was done in backward stepwise fashion using minimum Akaike information criterion. Survival was determined from the date of first diagnosis of metastasis to the date of last follow-up or death. Survival was estimated using Kaplan–Meier survival analysis and log-rank test was used to compare survival between the cohorts with or without ascites. All tests were two sided with statistical significance considered at $p < 0.05$.

Results

A total of 106 consecutive patients with metastatic pRCC were identified. Sufficient clinical and radiological data were available in 100 patients to enable assessment and characterization of ascites. Half the patients (50/100, 50%) included in the study had a hereditary form of papillary cancer, including 46 (46%) with Hereditary Leiomyomatosis and Renal Cell Cancer, 3 (3%) with Hereditary Papillary Renal Cell Carcinoma and 1 (1%) with Birt-Hogg-Dube. Twenty (20%) and 39 (39%) patients had papillary type 1 and papillary type 2 renal cancers respectively; in 41 (41%) patients, tumors were classified as papillary, not otherwise specified. Sixty-nine (69%) patient had only lymph node metastasis (regional or distant), 59 (59%) had visceral metastasis (lung, liver etc.), 32 (32%) had bone metastasis and 27 (27%) had metastasis at other sites (including recurrences in nephrectomy

bed, on psoas muscle and peritoneal carcinomatosis). Patient and tumor characteristics are summarized in table 1.

Twenty patients (20/100, 20%) had evidence of malignant ascites. Median patient age at diagnosis of ascites was 48.0 years (26.1–76.6 years) and median time to development of ascites from initial diagnosis of metastatic disease was 16.0 (0–73.3) months. All patients had characteristic radiographic findings of peritoneal carcinomatosis supporting the diagnosis of malignant ascites. Nine patients (9/20, 45%) had at least one diagnostic and/or therapeutic paracentesis for ascites and 89% (8/9) of those had cytology positive for malignancy. There was no significant difference in the incidence of ascites between patients with hereditary and sporadic pRCC ($p=0.803$) or between patients with different histological subtypes of pRCC ($p=0.456$). Logistic regression was done to identify predictors for development of ascites. Age at the time of the diagnosis of metastatic disease, gender, race, histologic subtype, hereditary origin, evidence of metastasis at presentation, anemia, thrombocytosis, hypercalcemia, elevated lactate dehydrogenase, NLR and PLR were included in the analysis. On univariate analysis, NLR greater than 3.3 ($p=0.021$) and PLR greater than 187.4 ($p=0.021$) were found to be significant predictors (Table 2). NLR and PLR were also significantly correlated in our cohort ($r=0.74$, $p<0.001$). On multivariable model selection, only a high PLR was found to be a significant predictor of ascites (OR 8.75 (95% CI 1.7–45.0, $p=0.009$).

With a median follow up of 34.3 (2.4–246.7) months, 17 (85.0%) patients with malignant ascites and 57 (71.3%) patients without ascites had died. Median estimated overall survival from diagnosis of metastatic disease was significantly shorter for patients who developed malignant ascites [25.0 (10.2–39.8) months] compared to patients who did not develop this complication [42.5 (30.5–54.4) months, $p=0.041$, figure 2].

Discussion

Peritoneal carcinomatosis and malignant ascites signify peritoneal spread of cancer and are considered poor prognostic signs. Involvement of peritoneum occurs by hematogenous spread and/or direct invasion and is seen mostly in metastatic ovarian, colorectal, pancreatic and primary peritoneal malignancies^{1, 2}. Malignant ascites ensues as a reaction to cancer cells in the peritoneal cavity, and usually presents unique treatment challenges. The accumulation of malignant ascites occurs through a complex, multifactorial process involving both increased production of peritoneal fluid secondary to increased vascular permeability and decreased absorption due to lymphatic obstruction. In normal circumstances, there is a dynamic balance between the plasma filtered across peritoneal capillaries and peritoneal fluid absorbed by openings of lymphatic vessels called ‘stomata’ in the peritoneum. Cancer cells in the peritoneal cavity cause local production of vascular endothelial growth factor and cytokines, leading to angiogenesis and increased vascular permeability resulting in loss of fluid and proteins into the peritoneal cavity^{1, 8, 9}. Additionally, the lymphatic outflow is obstructed by cancer cells, impairing absorption of increased peritoneal fluid and contributing to malignant ascites accumulation^{10, 11}.

In 1995, Stavropoulos et al proposed a possible mechanism leading to malignant ascites in renal cell cancer¹², suggesting that growth of renal cancer outside the kidney's capsule and Gerota's fascia predisposes to local peritoneal involvement, starting a vicious cycle of ascites formation and more diffuse involvement of the peritoneum. They also described embolic hematogenous metastases involving the omentum, mesentery and peritoneum, initiating the process of development of malignant ascites. Since malignant ascites can occur even with smaller and seemingly localized renal masses, both in our experience and several cases across the world^{4, 13}, the second theory might be a more plausible explanation for this phenomenon.

Although the description of ascites in RCC is restricted to a few case reports, the relative rarity of this complication reflects its incidence in clear cell rather than other variants of RCC^{4, 13}. To date, there has not been a systematic evaluation of the incidence of malignant ascites in papillary renal cancer. Furthermore, little is known about the predictors of this ominous complication. In this study, we have described the incidence of ascites in metastatic papillary renal cancer and have attempted to identify factors that may predispose to its development.

In our cohort, 20% of metastatic papillary cancer patients developed ascites at some point in the course of disease. Our center is a referral center for hereditary renal cancers, and therefore almost half the patients in this cohort had inherited forms of pRCC. We could not identify any difference in the incidence of ascites between sporadic and hereditary papillary renal cancers in this study, with both forms exhibiting a similar propensity for developing this complication. Similarly, no particular histologic subtype of papillary renal cell cancer was more likely to develop ascites than others. In a previous report from our institution, we noted that malignant ascites occurs significantly less frequently in clear cell cancer (0.8%)¹⁴. This disparity might result from a predilection of papillary renal cancers to metastasize to the peritoneum. Further characterization will be needed to better understand this increased propensity of papillary renal cell cancer to cause malignant ascites. Patients who developed ascites in our cohort had a worse outcome compared to patients who did not; additional evaluation is necessary to determine if ascites and its sequelae directly contributed to the inferior survival in patients with this complication or whether ascites was merely a clinical surrogate reflecting aggressive cancer.

An inflammatory microenvironment is the hall mark of cancer and host inflammatory responses play an important role in the development and progression of metastatic cancer. The hematological markers of systemic inflammation have been shown to be of prognostic significance in several malignancies^{15–17}. In metastatic RCC, several studies have demonstrated elevated platelets and neutrophils as poor prognostic factors for progression free and overall survival^{6, 7, 18}. More recently, NLR and PLR has shown to be predictors of overall survival in RCC patients^{19–21}. Zhang et al also demonstrated PLR to be associated with malignant ascites and shorter progression free and overall survival in ovarian cancer patients²². While these markers have been established as important prognostic factors in metastatic RCC, they have not been previously studied in context of malignant ascites in RCC patients. Association of malignant ascites with elevated NLR and PLR was also found in our study, potentially providing insight into the role of the host inflammatory response in

the development of malignant ascites. This association needs to be explored further in future studies to ascertain if measures to control inflammation in these patients might ameliorate development of malignant ascites.

Malignant ascites is a clinically challenging problem and leads to considerable morbidity. Historically, these patients were managed with diuretics and repeated paracentesis with substantial side effects and modest efficacy^{1, 2}. Hyperthermic intraperitoneal chemotherapy with cytoreductive surgery has shown promising results in ovarian and gastrointestinal malignancies and is now being routinely utilized in the management of these malignancies²³. Additionally, reports of targeted pharmaceuticals inhibiting angiogenesis have had early successes. Intraperitoneal bevacizumab (monoclonal antibody against VEGF) and intravenous aflibercept (a fusion protein preventing VEGF receptor binding to its receptor, VEGF Trap) have produced encouraging results, decreasing the need of paracentesis and even resolving malignant ascites in a subset of patients with metastatic ovarian cancer³. Catumaxomab (monoclonal antibody to epithelial cell adhesion molecule) prolonged both paracentesis-free survival and overall survival in a subset of ovarian cancer patients³. Pilanci et al used intraperitoneal catumaxomab in combination with everolimus in a patient with metastatic renal cell cancer with sarcomatoid differentiation and malignant ascites and observed complete resolution of ascites after²⁴. While these agents have shown promising results in patients with metastatic ovarian and gastrointestinal malignancies, there is insufficient data in RCC, and specifically pRCC to establish recommendations for therapy. At the National Cancer Institute, an ongoing phase 2 trial using a combination of bevacizumab (monoclonal antibody against VEGF) and erlotinib (an Epidermal Growth Factor Receptor inhibitor) for metastatic pRCC patients has shown encouraging results in some patients with malignant ascites (NCT01130519, data unpublished). Final results from this study are awaited and will provide more information on efficacy of this combination in inducing clinical response in these patients.

Although this study is the largest of its kind and the first to systematically evaluate ascites in papillary RCC patients, the data represent a retrospective analysis of records from a single institution and are therefore limited by the bias inherent to these analyses. A significant proportion of our patients had hereditary papillary renal cell cancer. However, the incidence of malignant ascites was comparable between the hereditary and sporadic subsets of our cohort, which permits general applicability of our results. Lastly, while we identified elevated PLR as a predictor for malignant ascites, the number of events in our analysis was relatively small; it is possible that a larger series might enhance the power of a multivariate analysis and permit identification of additional predictors. Considering the rarity of this manifestation, a larger analysis based on a multi-institutional cohort will help confirm these findings and further delineate the factors predicting the development of malignant ascites

Conclusion

Malignant ascites is a fairly common manifestation of metastatic pRCC. To our knowledge, this is the largest series evaluating the incidence, predictors and prognostic impact of ascites in metastatic pRCC. Ascites was associated with a worse outcome in metastatic pRCC, with a shorter overall survival observed in patients developing this complication. The association

of PLR with ascites is a promising and readily available measure of the risk of developing ascites in patients with metastatic pRCC.

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Abbreviations

pRCC	papillary Renal cell carcinoma
RCC	Renal cell carcinoma
PLR	platelet-lymphocyte ratio
NLR	neutrophil-lymphocyte ratio

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Highlights

- Malignant ascites is a clinically challenging problem and leads to considerable morbidity.
- On account of its rare occurrence in more common forms of kidney cancer, there has not been a systematic evaluation of its incidence in papillary renal cell cancer (pRCC).
- We found that this manifestation is fairly common in metastatic pRCC.
- Moreover, malignant ascites significantly worsens the survival of these patients.
- Elevated platelet-lymphocyte ratio predicts the development of malignant ascites and can be a readily available measure of the risk of developing ascites in patients with metastatic pRCC.

Figure 1. Computed tomographic image depicting peritoneal carcinomatosis and malignant ascites in a patient with metastatic papillary cancer (thin arrow- peritoneal tumor nodules, wide arrow-ascites).

Figure 2.
Kaplan Meier Curves depicting overall survival of metastatic papillary renal cancer patients with or without malignant ascites.

Table 1

Patient and tumor characteristics of metastatic papillary renal cancer patients who developed ascites compared to patients who did not (IQR- Interquartile range)

	Patients with Ascites (n=20)	Patients without Ascites (n=80)	P value
Median age (in years) at the time of diagnosis of metastatic disease (IQR)	47.1 (16.6)	51.6(22.1)	0.548
Gender			0.595
Male (%)	15 (75.0)	53 (66.3)	
Race			0.473
Caucasian (%)	14 (70.0)	68 (85.0)	
African American (%)	3 (15.0)	6 (7.5)	
Other (%)	1 (5.0)	3 (3.8)	
Missing (%)	2 (10.0)	3 (3.8)	
Papillary Histology			0.456
Type 1 (%)	6 (30.0)	14 (17.5)	
Type 2 (%)	7 (35.0)	32 (40.0)	
Unclassified/NOS (%)	7 (35.0)	34 (42.5)	
Hereditary origin (%)	9 (45.0)	41 (51.3)	0.803
Metastases at the time of primary diagnosis			0.609
Regional nodal metastases (%)	5 (25.0)	29 (36.7)	
Distant metastases (%)	6 (30.0)	19 (24.1)	
No metastatic disease (%)	9 (45.0)	31 (39.2)	
First kidney surgery			0.409
Partial Nephrectomy (%)	2 (10.0)	12 (15.0)	
Radical Nephrectomy (%)	18 (90.0)	63 (78.8.0)	
Biopsy only (%)	0 (0.0)	5 (6.3)	
Laterality of first surgery			0.075
Left	8 (40.0)	51 (36.3)	
Right	12 (60.0)	29 (63.8)	
Median follow up (in months) from diagnosis of metastasis (IQR)	24.2 (29.8)	35.1 (38.6)	0.153

Table 2

Univariate logistic regression analysis to identify predictors for development of ascites (CI-confidence interval)

	Odds Ratio (95% CI)	P value
Age at the time of diagnosis of metastatic disease	0.99 (0.96–1.03)	0.677
Gender (male)	1.52 (0.50–4.65)	0.455
Race		
African American (%)	ref	
Caucasian (%)	0.41 (0.09–1.85)	0.246
Other (%)	0.67(0.04–9.47)	0.765
Papillary Histology		
Unclassified/NOS	ref	
Type 1	2.08 (0.59–7.31)	0.252
Type 2	1.06 (0.34–3.37)	0.918
Hereditary origin (%)	0.78 (0.29–2.08)	0.618
Metastases at the time of primary diagnosis		
No metastasis	ref	
Regional nodal metastases (%)	0.59 (0.18–1.98)	0.397
Distant metastases (%)	1.08 (0.33–3.54)	0.889
Anemia (<13.7 g/dL for males and <11.2 g/dL for females)	2.72(0.76–9.75)	0.123
Elevated corrected Calcium (>10 mg/dL)	0.85 (0.09–7.96)	0.887
Elevated LDH (>225mg/dL)	1.33(0.29–5.96)	0.706
Elevated platelets count (>300,000 per microliter)	1.90 (0.56–6.48)	0.302
Elevated NLR (>3.3)	6.66 (1.34–33.28)	0.021
Elevated PLR (>187.4)	6.66 (1.34–33.28)	0.021