Clinical characteristics and outcomes in those with primary extrahepatic malignancy and malignant ascites

Omar Alshuwaykh1, Amanda Cheung1, Aparna Goel1, Allison Kwong1, Renumathy Dhanasekaran1, T. Tara Ghaziani1, Aijaz Ahmed1, Tami Daugherty1, Deepti Dronamraju1, Radhika Kumari1, Mindie Nguyen1, W. Ray Kim1 and Paul Yien Kwo1,2*

Abstract
Background: Malignancy-related ascites accounts for approximately 10% of causes of ascites. Our AIM was to characterize the ascites fluid and correlate clinical outcomes in those with extrahepatic malignancy and ascites.

Methods: 241 subjects with extrahepatic solid tumors and ascites were reviewed from 1/1/2000 to 12/31/2019, 119 without liver metastasis and 122 with liver metastasis.

Results: Ascites fluid consistent with peritoneal carcinomatosis (PC) was most common, 150/241 (62%), followed by fluid reflecting the presence of portal hypertension (PH), 69/241 (29%). 22/241 (9%) had low SAAG and low ascites fluid total protein, with evidence of PC on cytology and or imaging in 20/22. Lung cancer was the most common malignancy in subjects with ascites due to PC at 36/150 (24%), pancreatic cancer was the most common in subjects with ascites with features of PH at 16/69 (23%). Chemotherapy or immunotherapy alone was the most common management approach. Significantly higher 5-year, 3-year and 1-year mortality rate were noted in subjects with evidence of PC on cytology/imaging versus subjects with no evidence of PC, and in subjects with liver metastasis compared to subjects without liver metastasis. Subjects with pancreatic cancer and evidence of PC on cytology/imaging had higher 1 and 5-year mortality rates compared to subjects without PC.

Conclusions: Ascites in solid tumor malignancy is most commonly due to PC. We also observed ascites fluid with characteristics of PH in 29% of subjects. Higher mortality rates in subjects with peritoneal carcinomatosis and liver metastasis was noted. These findings may help in prognosis and treatment strategies.

Keywords: Malignant ascites, Peritoneal carcinomatosis, Portal hypertension, Serum ascites albumin gradient

Background
Among patients with ascites, 85% have evidence of portal hypertension and cirrhosis [1]. Malignancy is the etiology of ascites in approximately 10% of cases [1, 2]. Ascites in the setting of primary extrahepatic solid tumors may occur due to peritoneal seeding, portal hypertension from massive liver metastasis, obstruction of lymphatics, treatment complications, or infiltration of hepatic sinusoids with malignant cells [3, 4]. Peritoneal carcinomatosis appears to cause ascites by producing proteinaceous fluid from tumor cells lining the peritoneum, and extracellular fluid enters the peritoneal cavity to restore the oncotic equilibrium and was reported to account for 53% of malignancy-related ascites in one series [5]. Extrahepatic malignancy with liver metastases may cause
suggests other causes of ascites such as peritoneal carcinomatosis due to right ascites. Total protein < 2.5 g/dL is highly suggestive of the etiology of ascites, diagnostic paracentesis for analysis of the ascitic fluid to obtain total protein, albumin, triglyceride, cytology, and other laboratory testing and cultures is performed. The serum albumin ascites gradient (SAAG) may be calculated by subtracting the ascitic fluid albumin from the serum albumin in simultaneously obtained samples. A serum albumin ascites gradient ≥ 1.1 g/dL with ascitic total protein < 2.5 g/dL is highly suggestive of the presence of portal hypertension, typically caused by liver disease with an accuracy of approximately 97%. A serum albumin ascites gradient ≥ 1.1 g/dL with ascitic total protein of > 2.5 g/dL is highly suggestive of a post hepatic sinusoid source of ascites such as ascites due to right heart failure. A serum albumin ascites gradient < 1.1 g/dL suggests other causes of ascites such as peritoneal carcinomatosis, tuberculosis, and other clinical conditions. Chylous ascites is defined as ascitic fluid triglyceride values > 200 mg/dL.

Treatment of malignant ascites has been primarily directed toward the primary tumor combined with peritoneal drainage and the use of diuretics. To date, there are limited reports that classify ascites in this setting and assess response to therapy. The aims of this study were to characterize ascites fluid in those with extrahepatic malignancies and correlate with clinical outcomes in patients with primary extrahepatic solid tumors. Based on these findings, we also propose an algorithm for management of those who present with extrahepatic solid tumor malignancy and ascites.

Methods
We performed a single-center, electronic database, retrospective analysis of subjects 18 years and older without chronic liver disease who presented with ascites and primary extrahepatic solid tumors including breast cancer, lung cancer, gastric cancer, pancreatic cancer, ovarian cancer, colon cancer, and renal cell cancer between 1/1/2000 and 12/31/2019. Patients with history of any chronic liver disease and evidence of cirrhosis, liver fibrosis, or hepatocellular carcinoma (HCC) were excluded from this study. Subjects were identified via the Stanford Research Repository (STARR) Tools (aka STRIDE-web) of Stanford University electronic data warehouse. Data was fully anonymized after data extraction. Data abstracted included demographic information (age, sex, race), tumor type, serum ascites albumin gradient (SAAG), ascites total protein (TP) level and cytology, abdominal imaging reports, culture results, and ascites treatment regimen. Causes of ascites were categorized as reflecting portal hypertension (PH, SAAG ≥ 1.1 g/dL), with or without elevated total protein that could reflect sinusoidal portal hypertension (SPH, SAAG ≥ 1.1 g/dL and TP < 2.5 g/dL), peritoneal carcinomatosis (PC, SAAG < 1.1 g/dL and TP > 2.5 g/dL), or chylous ascites (ascites fluid triglyceride > 200 mg/dL).

Evidence of liver metastases, pericardial disease, and pulmonary hypertension were also captured as was exposure to chemotherapeutic agents known to cause non-cirrhotic portal hypertension. We examined outcomes by the presence or absence of liver metastases and by classification of ascites fluid. Statistical analysis was conducted using RStudio version 1.4.63. Shapiro–Wilk test was used to test normality of continuous variables, two-sample t-test was used to compare normally distributed continuous variables, Wilcoxon rank sum test was used to compare continuous variables that were not normally distributed. Categorical variables were compared using Fisher’s exact test. Survival analysis was assessed with Kaplan–Meier method with differences in survival probabilities measured by log-rank testing.

Results
Two hundred forty-one subjects presented from 1/1/2000 to 12/31/2019 with solid tumors and ascites were reviewed with 119 subjects without liver metastasis and 122 subjects with liver metastasis identified. Table 1 describes baseline characteristics in subjects with malignant ascites and differentiates those with or without liver metastasis. Ascites fluid analysis consistent with peritoneal carcinomatosis (low SAAG, high protein) was most common and observed in 150/241 (62%) subjects. Clinical evidence of peritoneal carcinomatosis was observed on cytology in 96/241 (39.8%) of subjects and imaging in 94/241 (39.0%) of subjects. Among the patients with peritoneal carcinomatosis on cytology or imaging, ascites fluid analysis was consistent with presence of portal hypertension in 46/241 (19%) with 9/241 (4%) having SAAG > 1.1 with low total protein (TP < 2.5 g/dL). Out of the 22 subjects who had low SAAG and low total protein ascites, 20/22 demonstrated peritoneal carcinomatosis
on cytology or imaging and the remaining 2/22 had evidence of acute pancreatitis. There was no evidence of nephrotic syndrome, serositis, or tuberculosis in these 22 subjects with low SAAG and low total protein ascites.

Ascites fluid analysis consistent with the presence of portal hypertension (high SAAG) in 69/241 (29%), with 13/69 having high SAAG, with low total protein. In this group, 21/69 (30%) subjects in this group had received an agent (azathioprine, oxaliplatin, trastuzumab, or emtansine) that has been associated with development of non-cirrhotic portal hypertension. Ascites fluid analysis consistent with chylous ascites was observed in 14/241 (6%) subjects. Ascites reflecting portal hypertension (SAAG > 1.1) and no evidence of peritoneal carcinomatosis on cytology or imaging was significantly greater in subjects without liver metastasis compared to subjects with liver metastasis (16/119;13% vs. 7/122;2%, p = 0.05), with 5 of these 23 subjects receiving either azathioprine, oxaliplatin, trastuzumab, or emtansine. Peritoneal carcinomatosis diagnosis based on cytology or imaging was significantly higher in subjects with liver metastases compared to subjects without liver metastases (105/122;86% vs. 85/119;71%: p < 0.05).

When we examined the 119 individuals without liver metastases, 28 subjects had evidence of pericardial disease (effusion, tamponade, and/or constriction), most of whom had ascites fluid analysis with low SAAG and high total protein (24/28) and the remaining with high SAAG (3/28) or low SAAG and low total protein (1/28).
An additional 14 subjects had underlying pulmonary hypertension with ascites fluid analysis showing low SAAG and high total protein in 12/15 subjects and high SAAG in 3/15.

Table 2 shows the distribution of solid tumors in subjects with ascites due to peritoneal carcinomatosis compared to subjects with ascites due to portal hypertension. Lung cancer was the most common malignancy in subjects with ascites due to peritoneal carcinomatosis (24%), and pancreatic cancer was the most common malignancy in subjects with ascites due to portal hypertension (23%). Ovarian cancer was only found in the group with PC 17/150 (11%). Significantly more subjects with renal cell cancer had ascites with features of portal hypertension 13/69 (19%) compared to 11/150 (7%) in the PC group.

Management of ascites
All subjects received chemotherapy/immunotherapy for the underlying malignancy alongside additional therapies for management of ascites (Tables 1, 3, 4). In subjects with peritoneal carcinomatosis, chemotherapy/immunotherapy alone was the most common management approach 52/150 (35%). The remaining patients received additional therapies including paracentesis.

Table 2 Distribution of solid tumors in subjects with ascites due to peritoneal carcinomatosis and ascites due to portal hypertension based on ascites fluid analysis

| Variable          | Peritoneal carcinomatosis 150 subjects | Portal hypertension 69 subjects | P value |
|-------------------|---------------------------------------|---------------------------------|---------|
| Breast Cancer     | 23/150 (15%)                          | 14/69 (20%)                     | 0.4     |
| Gastric Cancer    | 21/150 (14%)                          | 9/69 (13%)                      | 1       |
| Lung Cancer       | 36/150 (24%)                          | 10/69 (14%)                     | 0.2     |
| Ovarian Cancer    | 17/150 (11%)                          | 0/69 (0%)                       | 0.002   |
| Pancreatic Cancer | 22/150 (15%)                          | 16/69 (23%)                     | 0.1     |
| Renal Cancer      | 11/150 (7%)                           | 13/69 (19%)                     | 0.02    |
| Colon Cancer      | 20/150 (13%)                          | 7/69 (10%)                      | 0.7     |

Table 3 Comparing management in subjects with and without liver metastasis

| Management                      | Without liver metastasis | With liver metastasis | P value |
|---------------------------------|--------------------------|-----------------------|---------|
| Diuretics                       | 15/73 (20.5%)            | 16/77 (21%)           | 1       |
| Paracentesis                    | 11/73 (15%)              | 24/77 (31%)           | 0.02    |
| Peritoneal drain                | 16/73 (22%)              | 15/77 (19%)           | 0.8     |
| Shunt                           | 1/73 (1.4%)              | 0/77 (0%)             | 0.5     |
| Chemotherapy/Immunotherapy*     | 30/73 (41%)              | 22/77 (28.5%)         | 0.1     |

Table 4 Comparing management of ascites in subjects with peritoneal carcinomatosis and subjects with portal hypertension

| Management                      | Peritoneal carcinomatosis | Portal hypertension | P value |
|---------------------------------|--------------------------|---------------------|---------|
| Diuretics                       | 31/150 (21%)             | 8/69 (11%)          | 0.13    |
| Paracentesis                    | 35/150 (23%)             | 18/69 (26%)         | 0.73    |
| Peritoneal drain                | 31/150 (21%)             | 20/69 (29%)         | 0.23    |
| Shunt                           | 1/150 (0.7%)             | 0/69 (0%)           | 1       |
| Chemotherapy/Immunotherapy*     | 52/150 (35%)             | 23/69 (33%)         | 0.88    |

*These patients only received chemotherapy or immunotherapy while the others represented in this table received chemotherapy or immunotherapy in addition to the stated therapy
35/150 (23%), diuretics 31/150 (21%), and peritoneal drain 31/150 (21%) and peritoneovenous shunt 1/150 (0.75%) (Table 4). Significantly more subjects with ascites due to peritoneal carcinomatosis and presence of liver metastasis were managed with paracentesis 24/77 (31%) compared to those without liver metastasis 11/73 (15%) (Table 3).

In subjects with portal hypertension, chemotherapy or immunotherapy alone was again the most common management approach of ascites 23/69 (33.3%), with additional therapies including peritoneal drain 20/69 (29%), paracentesis 18/69 (26%), and diuretics 8/69 (11.5%) being added. Significantly more subjects with ascites reflecting portal hypertension were managed with peritoneal drain 18/39 (46%) in those without liver metastasis compared to 2/30 (7%) subjects with evidence of liver metastases (Table 3). Diuretics were administered in subjects with portal hypertension and peritoneal carcinomatosis with no significant difference between the groups regardless of liver metastasis (Table 2).

**Outcomes**

The 5-year mortality rate in subjects with malignant ascites was significantly higher in subjects with liver metastases compared to subjects without liver metastases 75/122 (61%) vs. 53/119 (45%) (p = 0.02) with higher mortality rates noted in those with colon cancer (Table 5, Fig. 1A). Subjects with liver metastasis and ascites reflecting portal hypertension had significantly higher 5-year mortality rate 21/30 (70%) compared to subjects with no liver metastasis and ascites reflecting portal hypertension 14/39 (36%) (Table 5). The 5-year mortality rate in subjects with evidence of peritoneal carcinomatosis on cytology and/or imaging was significantly higher compared to those with no evidence of peritoneal carcinomatosis on cytology or imaging 109/190 (57%) vs. 19/51 (37%), p value 0.009 (Fig. 1B). Subjects with evidence of PC on cytology/imaging were also found to have higher 1-year mortality rate 72/190 (38%) vs 12/51 (23%), p = 0.04 and 3-year mortality rate 102/190 (54%) vs 17/51 (33%), p = 0.009 (Fig. 1C, D). No significant differences were observed in 1 and 3 year mortality rates in subjects with liver metastasis compared to subjects without liver metastasis. In subgroup analysis examining mortality rates by tumor type, subjects with pancreatic cancer and evidence of PC on cytology/imaging had higher 1 and 5-year mortality rates compared to subjects without PC 19/28 (68%) vs. 4/12 (33%), p = 0.04 and 16/28 (57%) vs. 2/12 (17%), p = 0.02 respectively (Table 6, Fig. 1E, F). No significant differences were observed in 1-year, 3-year, and 5-year mortality rates by tumor type in subjects with liver metastases compared to subjects without liver metastases.

We also examined mortality rates over 5-year periods to account for potential advances in systemic therapies, but no period effect was noted (data not shown).

**Discussion**

This study evaluated and characterized ascites in subjects with primary extrahepatic solid tumors including breast cancer, lung cancer, gastric cancer, pancreatic cancer, ovarian cancer, colon cancer and renal cell cancer. The most common etiology of ascites was peritoneal carcinomatosis based on fluid analysis (62%) or cytology/imaging (79%). High SAAG with high total protein accounted for 29% of subjects with malignancy and ascites. Among the patients with high SAAG suggesting noncirrhotic portal hypertension based on ascites fluid analysis, 67% had evidence of peritoneal carcinomatosis

| Variable                        | Without liver metastasis | With liver metastasis | P value |
|---------------------------------|--------------------------|-----------------------|---------|
| Total 5-year mortality          | 53/119 (45%)             | 75/122 (61%)          | 0.009   |
| Portal HTN                      | 14/39 (36%)              | 21/30 (70%)           | 0.007   |
| Sinusoidal portal HTN           | 2/4 (50%)                | 7/9 (78%)             | 0.5     |
| Peritoneal carcinomatosis       | 34/73 (46.5%)            | 47/77 (61%)           | 0.1     |
| CA: Breast cancer               | 4/12 (33%)               | 16/29 (55%)           | 0.3     |
| CA: Gastric cancer              | 11/24 (46%)              | 4/9 (44%)             | 1       |
| CA: Lung cancer                 | 15/32 (47%)              | 9/16 (56%)            | 0.8     |
| CA: Ovarian cancer              | 8/15 (53%)               | 5/5 (100%)            | 0.1     |
| CA: Pancreatic cancer           | 6/14 (43%)               | 17/26 (65%)           | 0.2     |
| CA: Renal cancer                | 7/13 (54%)               | 8/13 (62%)            | 1       |
| CA: Colon cancer                | 2/9 (22%)                | 16/24 (67%)           | 0.04    |
on cytology or imaging suggesting that multiple mechanisms are contributing to the development of ascites. Interestingly, 9% had low SAAG and low ascites fluid total protein levels with no evidence of nephrotic syndrome, pancreatic ascites, tuberculous peritonitis, or serositis. The median serum albumin level in this group was low 1.99 g/dl (IQR 1.8–2.03) likely as a reflection of cachexia and other factors and may explain the low SAAG findings.

Liver metastases versus no liver metastases
In those with ascites and no liver metastases, peritoneal carcinomatosis was the most common etiology of ascites in this group at 61%, and lung cancer was the most common malignancy in this group at 27%. Significantly more subjects without liver metastases and no evidence of peritoneal carcinomatosis on cytology or imaging had peritoneal fluid reflecting portal hypertension with high SAAG, 16/119 (13%) compared to subjects with liver metastasis 7/122 (6%). A portion of these individuals (3/16 and 2/7 respectively) received chemotherapies known to be associated with non-cirrhotic portal hypertension which may in part explain these findings. Chemotherapy/immunotherapy administration alone was the most common approach to manage ascites in the no liver metastases subjects with 37% of subjects receiving this type of therapy.

Among subjects with ascites and liver metastases, peritoneal carcinomatosis was again the most common etiology of ascites in this group at 63%, a rate similar to those without liver metastases, though breast cancer was the most common malignancy in this group at 24% (Table 3). In one malignant ascites series, breast cancer was also reported to be the most common extrahepatic tumor associated with ascites [9]. Peritoneal carcinomatosis was commonly present with liver metastases suggesting that the presence of liver metastases reflects a higher overall disease burden. Drainage of peritoneal fluid by paracentesis or indwelling catheter combined with chemotherapy/immunotherapy was the most common method of managing ascites in these subjects at 33% suggesting that fluid accumulation may be more difficult to control.

We found that the 5-year mortality rate in subjects with liver metastases was significantly higher at 61% compared to 45% in subjects without liver metastases regardless of ascites characteristics with no differences when examined in 5-year period increments (Fig. 1a). The presence of liver metastases was reported to be an independent predictor for mortality in patients with solid tumors who developed tumor lysis syndrome [10]. Similar to our findings, one prior report has noted that the presence of liver metastasis in subjects with
malignant ascites was an independent prognostic factor associated with poor outcomes [11]

**Ascites reflecting peritoneal carcinomatosis or portal hypertension**

Peritoneal carcinomatosis was the most common etiology of ascites in our cohort with lung cancer being the most common malignancy in subjects with ascites due to PC at 24%. We noted that patients with ovarian cancer had ascites consistent with peritoneal carcinomatosis only. To date, no specific solid tumor has been associated with a higher rate of peritoneal carcinomatosis. In the entire cohort, systemic chemotherapy or immunotherapy alone was the most common management approach of ascites in subjects with peritoneal carcinomatosis 52/150 (35%). The most common approach in those with peritoneal carcinomatosis and no liver metastases (41%) was to administer chemotherapy/immunotherapy alone, whereas the majority of subjects with peritoneal carcinomatosis and liver metastases (31%) required paracentesis in addition chemotherapy/immunotherapy indicating multiple therapies may be required in the setting of malignancy and hepatic metastases to control the ascites. We noted a higher 1 and 3-year in those with ascites due to peritoneal carcinomatosis (Fig. 1B–D). In Subgroup analysis examining mortality rates by tumor type, subjects with pancreatic cancer and evidence of PC on cytology/imaging had higher 5-years and 1-year mortality rates compared to subjects without PC (Fig. 1E, F). A prior study also reported poor prognosis in subjects with pancreatic cancer and peritoneal carcinomatosis [12].

Low SAAG ascites has been reported to be caused by peritoneal carcinomatosis in addition to tuberculous peritonitis, nephrotic syndrome, and pancreatitis [1, 13]. We identified 20/241 (8%) subjects with low SAAG and low total protein, and all had evidence of peritoneal carcinomatosis on cytology and or imaging. Low SAAG ascites has been reported in up to 20% of those with malignant ascites in prior reports and in our cohort, the serum albumin levels were low in our cohort (median 1.99, IQR 1.83–2.13) [14]. In our cohort, the diagnostic accuracy of high ascites fluid total protein in diagnosing PC was 75%, similar to prior studies [15].

Interestingly, evidence of portal hypertension was present in 33% of subjects with no liver metastases and 24% of subjects with liver metastases with pancreatic cancer being the most common malignancy in subjects with ascites due to portal hypertension at 23%. Significantly more subjects with renal cell cancer had high SAAG ascites (13/69; 19%) compared to (11/150; 7%) in the PC group with just 3/13 subjects receiving azathioprine, oxaliplatin, trastuzumab, or emtansine, all therapies associated with non-cirrhotic portal hypertension. In our retrospective series, chemotherapy or immunotherapy alone was the most common management approach for the ascites in subjects with evidence of portal hypertension 23/69 (33.3%). No liver biopsies were performed in the subjects without liver metastases group to determine if sinusoidal infiltration of tumor, nodular regenerative hyperplasia or other etiology was present nor were hepatic venous pressure measurements performed. We noted limited use of diuretic therapies in those with high SAAG ascites fluid total protein in diagnosing PC was 75%, similar to prior studies [15].

In summary, although ascites in solid tumor malignancy is most commonly due to peritoneal carcinomatosis, we observed characteristics of portal hypertension with SAAG > 1.1 in 29% of subjects. We also observed that the presence of liver metastasis was not the sole contributor to the development of ascites.

|  | PC | No PC | P value |
|---|---|---|---|
| 5-Years | | | |
| Breast | 16/31 (52%) | 4/10 (40%) | 0.63 |
| Gastric | 13/30 (43%) | 2/3 (67%) | 0.4 |
| Lung | 20/34 (59%) | 4/14 (29%) | 0.1 |
| Ovarian | 12/19 (63%) | 1/1 (100%) | 0.78 |
| Pancreatic | 19/28 (68%) | 4/12 (33%) | 0.04* |
| Renal | 7/20 (35%) | 2/6 (33%) | 0.12 |
| Colon | 16/28 (57%) | 2/5 (40%) | 0.44 |
| 3-Years | | | |
| Breast | 15/31 (48%) | 3/10 (30%) | 0.43 |
| Gastric | 12/30 (40%) | 2/3 (67%) | 0.33 |
| Lung | 20/34 (59%) | 4/14 (29%) | 0.1 |
| Ovarian | 11/19 (58%) | 1/1 (100%) | 0.78 |
| Pancreatic | 17/28 (61%) | 4/14 (29%) | 0.08 |
| Renal | 11/20 (55%) | 1/6 (17%) | 0.09 |
| Colon | 16/28 (57%) | 2/5 (40%) | 0.44 |
| 1-Year | | | |
| Breast | 6/31 (19%) | 3/10 (30%) | 0.56 |
| Gastric | 10/30 (33%) | 2/3 (67%) | 0.24 |
| Lung | 12/34 (35%) | 4/14 (29%) | 0.68 |
| Ovarian | 10/19 (53%) | 0/1 (0%) | 0.36 |
| Pancreatic | 16/28 (57%) | 2/12 (17%) | 0.02* |
| Renal | 8/20 (40%) | 0/6 (0%) | 0.08 |
| Colon | 10/28 (36%) | 1/5 (20%) | 0.47 |
with features of portal hypertension which could be related to prior chemotherapies or other factors. With ascites fluid analysis, we believe that ascites in the setting of extrahepatic malignancy can be managed with a combination of therapies directed toward the tumor, especially in the era of increasing targeted therapies, and if present portal hypertension [17]. We also noted that despite advances in targeted chemo/immune-oncology therapies and the decreased mortality rates in cancer patients, patients with evidence of PC continues to have high mortality rates. Based on our results, we propose for the management of ascites in subjects with primary extrahepatic solid tumors, we propose that these subjects undergo diagnostic paracentesis to obtain cytology, albumin, and total protein. If the SAAG is $\geq 1.1$ with/without TP $< 2.5$, then treatment of underlying tumor and initiation of diuretic therapy (furosemide/spironolactone at standard doses) is warranted. If these measures fail to control the ascites, then initiation of serial paracenteses should be the next step while adjusting the therapy of the underlying malignancy. If ascites still remains problematic, placement of peritoneal drain/shunt, should be considered along with a discussion of goals of care. If the SAAG $\geq 1.1$ with TP $> 2.5$, then treatment of underlying tumor and initiation of paracentesis should be the initial management steps. If these measures fail to control the ascites, then placement of a peritoneal drain/shunt, adjustment of therapy toward the primary extrahepatic malignancy if required, again with a discussion of goals of care should be considered. Finally, we noted multiple presentations that predicted higher mortality including those with liver metastasis or peritoneal carcinomatosis on cytology and or imaging.

**Conclusions**

Ascites in solid tumor malignancy is most commonly due to peritoneal carcinomatosis. We also observed ascites fluid with characteristics of portal hypertension in 29% of subjects. We observed higher mortality rates in subjects with peritoneal carcinomatosis and liver metastasis. These findings may help inform prognosis and treatment strategies.

**Abbreviations**

SAAG: Serum albumin ascites gradient; PC: Peritoneal carcinomatosis; HCC: Hepatocellular carcinoma; TP: Total protein; PH: Portal hypertension; SPH: Sinusoidal portal hypertension.

**Acknowledgements**

None.

**Author contributions**

OA and PK designed the study analyzed the data and drafted the manuscript. AC, AG, RD, TTG, AA, TD, DD, RK, AK, MN, WRK participated in analysis of data and provided critical revisions to manuscript. All have approved the submitted manuscript and agree to be personally accountable for the integrity of the manuscript. All authors read and approved the final manuscript.

**Funding**

There was no funding for this study.

**Availability of data and materials**

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the Stanford Institutional Review Board #55064. The need for consent was waived by the Institutional Review Board.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**Author details**

1 Division of Gastroenterology and Hepatology, Stanford University Medical Center, Stanford, CA, USA. 2 Stanford University School of Medicine, 430 Broadway, Pavilion C, 3rd Floor, Redwood City, CA 94063, USA.

**Received: 6 October 2021 Accepted: 21 August 2022**

**Published online: 05 September 2022**

**References**

1. Runyon BA, Montano AA, Akriviadis EA, et al. The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. Ann Intern Med. 1992;117:215.
2. Runyon BA. Care of patients with ascites. N Engl J Med. 1994;330:337.
3. Alexopoulos A, Koskinaha J, Deutsch M, Delladetsima J, Kountouras D, Dourakis SP. Acute liver failure as the initial manifestation of hepatic infiltration by a solid tumor: report of 5 cases and review of the literature. Tumori. 2006;92:354–7.
4. Millard T, Gupta A, Brenin C, Marshall P, Dillon P. Radiographically occult carcinomatous spread of breast cancer to the liver: a challenging case. Case Rep Oncol Med. Article ID 4935615. 2019.
5. Runyon BA, Hoeffs JC, Morgan TR. Ascitic fluid analysis in malignancy-related ascites. Hepatology. 1988;8:1104.
6. Dhanasekaran R, Kwo PY. The liver in oncology. Clin Liver Dis. 2017;21(4):697–707.
7. Bignis SW, Angell P, Garcia-Tsao G, Ginés P, Ling SC, Nadim MK, Wong F, Kim WR. Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021;74(2):1014–48. https://doi.org/10.1002/hep.31884 (PMID: 33942342).
8. Press OW, Press NO, Kaufman SD. Evaluation and management of chylous ascites. Ann Intern Med. 1982;96(3):358–64. https://doi.org/10.7326/0003-4819-96-3-358.
9. Bami S, Cabiddu M, Ghilardi M, Petrelli F. A novel perspective for an orphan problem: old and new drugs for the medical management of malignant ascites. Crit Rev Oncol Hematol. 2011;79(2):144–53.
10. Harmon J, Allen S, Cassaday J, Ruvinov K, Stoyanova D, Tadipatri R, Ross M, Raj J, Wang J. Liver metastasis as an independent predictor for mortality in patients who developed tumor lysis syndrome: analysis of 132 patients with solid tumors. Journal of Clinical Oncology 2018; 36(15_suppl):e18766–e18766
11. Ayantunde AA, Parsons SL. Pattern and prognostic factors in patients with malignant ascites: a retrospective study. Ann Oncol. 2007;18:945–9.

12. Thomassen I, Lemmens VE, Nienhuijs SW, Luyer MD, Klafer YL, de Hingh IH. Incidence, prognosis, and possible treatment strategies of peritoneal carcinomatosis of pancreatic origin: a population-based study. Pancreas. 2013;42(1):72–5.

13. Hernaez R, Hamilton J. Unexplained ascites Clin Liver Disease. 2016;7(3):53–6.

14. Alexandrakis MG, Moschandrea JA, Kouloukeri SA, Kouroumalis E, Eliopoulos GD. Discrimination between malignant and nonmalignant ascites using serum and ascitic fluid proteins in a multivariate analysis model. Dig Dis Sci. 2000;45(3):500–8. https://doi.org/10.1023/a:1005437005811.

15. Prieto M, José Gómez-Lechón M, Hoyos M, Castell JV, Carrasco D, Berenguer J. Diagnosis of malignant ascites: comparison of ascitic fibronectin, cholesterol, and serum-ascites albumin difference. Dig Dis Sci. 1988;33:833–8.

16. Pockros PJ, Essason KT, Nguyen C, et al. Mobilization of malignant ascites with diuretics is dependent on ascitic fluid characteristics. Gastroenterology. 1992;103:1302.

17. Smolle E, Taucher V, Haybaeck J. Malignant ascites in ovarian cancer and the role of targeted therapeutics. Anticancer Res. 2014;34(4):1553–61.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.