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Ascites as a Predictive Factor in Malignancies in the Last Year of Life–Comparison Between Different Cancer Types

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Abstract

Background: Ascites in malignancies is usually associated with poor prognosis, but the predictive value may vary between different cancer types.
Objectives: The aim was to map the frequency and temporal pattern of paracentesis in patients with malignancies in relation to time to death and to evaluate the occurrence of ascites as a predictive factor in different cancer types, with a limitation to the last year of life.
Design: A retrospective study based on registry data covering all care visits in the Stockholm Region, Sweden, for seven years was performed. All deceased subjects that had at least one registered paracentesis in the last year of life were included.
Results: Of 23,056 subjects dying from cancer, 1863 had undergone paracentesis in the last year of life (8.0%). Ascites requiring paracentesis was most frequently seen in appendiceal cancer (38%), ovarian cancer (35%), cholangiocarcinoma (26%), hepatocellular carcinoma (19%), and pancreatic cancer (17%). The median time for the first paracentesis in all cancer types varied between 248 and 20 days before death. For ovarian cancer, the median time for first paracentesis differed significantly compared with upper gastro-intestinal (GI) cancers, 81 days compared with 30 days ($p < 0.0001$). Ascites in prostate cancer was rare,1.9%, but when present, a pronounced increase in the frequency of paracentesis was observed in the last three months of life.
Conclusion: The occurrence of paracentesis in patients with advanced cancer is generally a sign that death is approaching within the coming months, especially in upper GI cancer. For ovarian and appendiceal cancers, ascites is less useful as a predictive tool.

Keywords: ascites; cancer; epidemiology; malignant ascites; oncology; paracentesis; survival

Key Message

In this cohort study with nearly 2000 patients, we show that in certain cancer types, such as upper GI cancers, increased frequency of paracentesis in the last year of life could be used as a predictive factor that death is approaching.

Introduction

Ascites is defined as increased free fluid in the abdominal cavity, which can be either benign (i.e., due to liver cirrhosis or congestive heart failure) or malignant (e.g., due to peritoneal carcinomatosis).[1–3] The pathophysiology of malignant ascites differs from benign ascites and therefore the medical approach and symptom management also differ somewhat. In benign ascites, common causes are portal hypertension due to liver cirrhosis or due to congestive heart disease. The aim of the treatment is not only symptom relief with the aid of paracentesis but also to affect the underlying condition.

In malignant ascites, however, the mechanisms are different. Although the pathophysiology for malignant ascites is not fully understood, it is often explained as a combination of

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factors including hampered peritoneal filter function due to peritoneal carcinomatosis and the surrounding inflammatory edema, an alteration in ascitic albumin gradient, and obstruction of lymph vessels.[4–6]

To our knowledge, there are no recent epidemiological studies made on malignant ascites. According to data from the 1990s, malignant ascites accounts for 10% of all cases of ascites.[3,4,7,8] However, we believe that the prevalence is higher. Thus, there is a knowledge gap regarding the updated prevalence of ascites in total, and malignant ascites in particular.

Ascites is mostly present in upper gastro-intestinal (GI) malignancies (including cancer in the esophagus, stomach, duodenum, pancreas, liver, and gallbladder) but is also common in ovarian cancer, colon cancer, and breast cancer.[1] In Swedish cancer care, upper GI cancer includes pancreatic cancer, cholangiocarcinoma, gallbladder cancer, and liver cancer. Therefore, these diagnoses are referred to as upper GI malignancies in this study.

Ascites can be troublesome for patients with advanced malignancies, especially in the late stage of the disease. Typical symptoms include bloating, nausea, dyspnea, and loss of appetite. For best symptom relief, paracentesis is performed, either via sporadic paracentesis, via a peritoneal port, or via an indwelling tunneled catheter (i.e., PeritX).[1,4]

The debut of ascites in cancer is usually associated with poor prognosis.[8–12] However, the onset of ascites differs between different cancer types. In ovarian cancer ascites can often be a treatable symptom and in fact, often a primary onset symptom that precedes the diagnosis. Thus, patients with ovarian cancer can sometimes live for several years with recurrent ascites.[12] In other types of cancer, ascites is a symptom that more commonly appears late in the disease trajectory.[13] However, little is known if the increasing volume of malignant ascites, and subsequently increased frequency of paracentesis, in advanced cancer could be a predictive factor to aid health care professionals in distinguishing if the patient is approaching the end stage of life.

Therefore, the aim of this study was to map the frequency of paracentesis in patients with advanced cancer in relation to time to death and evaluate the occurrence of ascites as a predictive factor in different cancer types. We also wanted to address if the frequency of paracenteses is intensified in the last months of life and whether there are differences between different cancer types. In particular, we wanted to test the hypothesis that malignant ascites in upper GI cancer is associated with shorter survival time than malignant ascites in ovarian cancer, where patients often live longer with malignant ascites.

Patients and methods

The Patients and Methods, Results, and Discussion sections are presented, when applicable, in line with the STROBE criteria (strengthening the reporting of observational studies in epidemiology).[14]

Study design and settings

This was a retrospective cohort study based on registry data from the administrative VAL database of the Stockholm Region's central data warehouse. Each clinic and health care unit in Region Stockholm must report each patient visit to the VAL database, and their financial reimbursement from the Stockholm Region is based on this data. In addition to diagnoses according to International Classification of Diseases 10th Revision (ICD-10), hospital admissions, and Swedish standard codes of classification of healthcare actions (KVÅ), the database also contains other data such as age, sex, and time of death for each subject.

In this study, we extracted data on all deceased patients aged 18 years or older, in Region Stockholm between 2015 and 2021, for their last year of life.

Participants

Subjects that had obtained the classification codes (KVÅ) TJA10, paracentesis, and TJA40, percutaneous local drainage of the abdominal cavity ($n = 3364$) during the last year of life were identified. We separated those with cancer conditions ($n = 1863$) from those with noncancer conditions ($n = 1501$). The patients who had died from cancer and undergone paracentesis in the last year of life comprised the study cohort.

Outcome

With a limitation to the last year of life, the time for the first paracentesis and the last one before death were recorded in the different cancer types. In addition, we mapped the occurrence of paracentesis for each quartile in the last year of life Q1, Q2, Q3, and Q4, where Q4 is the last quartile before death. We then compared the frequency of paracentesis between Q1 and Q4. Moreover, we plotted the time for the first paracentesis for each case in a box and whisker plot divided into different cancer types. We chose to study the most frequent types of cancer in Sweden, i.e., breast (C50), prostate (C61), lung (C34), and colon (C18) cancers and, in addition, the cancer types which we know have a frequent occurrence of ascites; appendiceal cancer (C181), liver cancer (C22.0), ovarian cancer (C56), rectal cancer (C20), pancreatic cancer (C25) with endocrine pancreatic cancer accounted for separately (C25.4), cholangiocarcinoma (C22), and cancer of unknown primary (C80).

Variables

To study other factors that may influence, we extracted data on age, sex, comorbidity, frailty risk score, and sociodemographic facts.

Comorbidities were measured by Charlson Comorbidity Index (CCI),[15] with a modification: as all studied persons had cancer, cancer was excluded from the CCI. A CCI score of 0–1 is assessed as a low degree of comorbidity and 2 or above as a high burden of comorbidities.

The risk of frailty was measured with the Hospital Frailty Risk Score (HFRS) that is based on 109 ICD-10 codes and developed for assessment of "risk for frailty" in register data, a risk assessment that has moderate overlap with other scores such as the Rockwood Frailty Index.[16]

Sociodemographic data was measured with the Mosaic system. The Mosaic system divides a county or city into different groups of socioeconomic areas and is based on information on median income, education, lifestyle, and living arrangements in a specific living area.[17,18] The Stockholm Region is

divided into small areas and each area is classified as Mosaic 1, 2, or 3, where Group 1 corresponds to the most affluent areas. In the current study, we merged the groups Mosaic 1 and 2 (affluent and middle-class areas) and compared them with Mosaic 3, i.e., less affluent areas.

Study size

A total cohort was used and, therefore, no power calculations were performed. The cohort size is dependent on the number of deaths in cancer patients who had undergone paracentesis due to ascites during the last year of life in the Stockholm Region between 2015 and 2021.

Statistical methods

Descriptive statistics are presented as means and standard deviations (SD) in the tables and as median, interquartile range, and range in the box and whisker plot.

Differences between groups were assessed using chi-square test for categorical variables and *t* test for continuous variables and Kruskal-Wallis test followed by Dunns multiple comparison for the data in Figures 2 and 3.

Ethics

This study was approved by the Swedish Ethical Review Authority (Dnr 2024-00125-01). All data were pseudonymized before analysis.

Results

Participants

In the database, 118,134 deceased adult patients during the study period were identified. Of these, 3364 patients had at least one of the two classification codes for paracentesis in the last year of life, corresponding to 2.85% of the whole population, and total number of paracenteses performed were 8145. Of the 3364 patients who had undergone paracentesis, 1501 did not suffer from cancer and constituted 1.7% of patients with noncancer death.

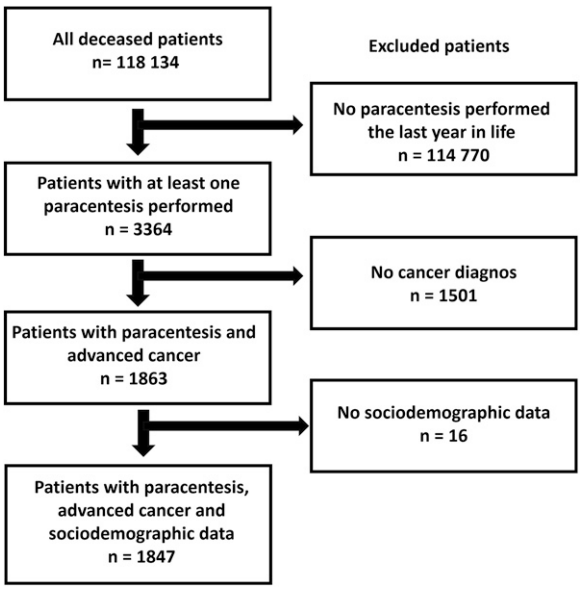

FIG. 1. Flowchart of included and excluded patients in the study cohort.

Of all deceased patients, 23,056 were assessed as having died from cancer. Of these, 1863 had undergone paracentesis at least once during the last time of life, corresponding to 8.0% of all patients dying from cancer. These patients constituted the study cohort. Sociodemographic data (Mosaic) was missing for 16 individuals and those were therefore excluded. Thus, the study cohort comprised 1847 subjects. Included and excluded patients are presented in the flow chart in Figure 1.

The descriptive demographic data of the study cohort is presented in Table 1.

Main outcomes

Of all cancer patients in the study cohort, 25% had their last paracentesis in the last week before death and 58% had their last paracentesis in the last 30 days before death.

In Table 2, the comparison between the number of individuals that had undergone paracentesis for each cancer type compared with all patients suffering from that cancer type is presented. For appendiceal and ovarian cancers, more than one-third of all patients needed paracentesis at least once during the last year before death. In comparison, patients with prostate and lung cancers rarely needed paracentesis, only in less than 2% of the cases.

The comparison of the number of paracenteses during the different quartiles before death (Q1–Q4) in the different cancer types are presented in Table 3. For appendiceal and ovarian cancers, the numbers of paracenteses were rather evenly distributed over the year. In contrast, for breast, lung, pancreatic, and colon cancers, paracentesis was mainly performed in the last three months before death (Q4).

The median time-point for the first registered paracentesis for the different cancer types in the last year of life is shown in Figure 2. It was 248 days in appendiceal cancer and 81 days in ovarian cancer compared with 48–20 days before death in all the other cancer forms. In a separate analysis, the median time-point for paracentesis was compared between ovarian cancer and upper and lower GI cancer types (Fig. 3). As regards time-point, there was a statistically significant difference between ovarian cancer and the GI cancers with 81 days in ovarian cancer, 36 days before death in lower GI cancer (colorectal cancer) and 30 days in upper GI (mainly pancreatic cancer and cholangiocarcinoma), $p < 0.001$.

Appendiceal cancer, although an uncommon diagnosis ($n = 29$), had the highest proportion of paracenteses per patient (38%) (Table 2). Ovarian cancer ($n = 592$) had the second highest proportion of paracenteses (35%). The most common cause of cancer death, lung cancer ($n = 3460$), had the lowest proportion of paracenteses (1.5%) of the different cancer types studied (Table 2).

Pancreatic cancer was the cancer type with the highest amount of paracenteses (events) with 615 in 299 patients, i.e., 2.1 paracenteses per patient.

Discussion

In this study, we show that malignant ascites is a recurrent condition in advanced cancer and that at least 8% of all patients dying from cancer in the Region Stockholm need paracentesis in the last year of life. Malignant ascites was most

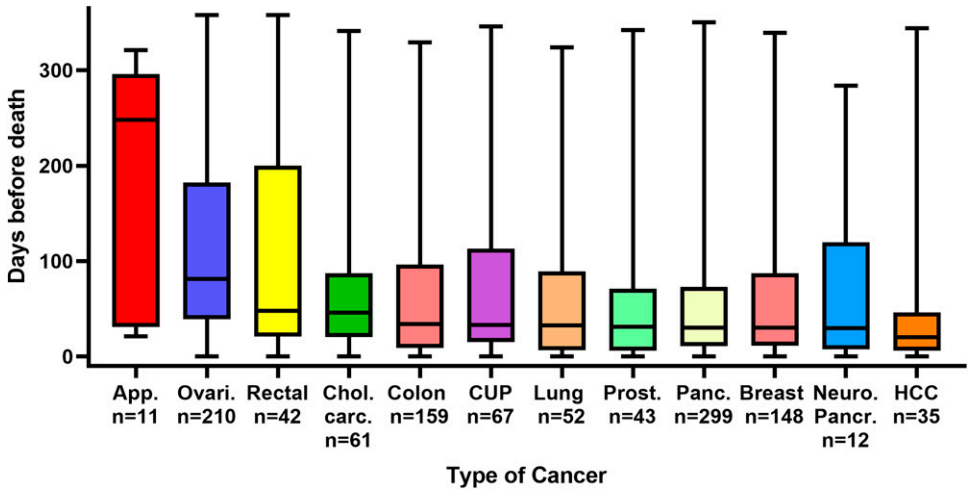

FIG. 2. Box and Whisker plot for time-point for first registered paracentesis in different cancer forms the last year before death. Error bars (whiskers) show range, box shows 25–75 percentile, and the line shows the median. Kruskal-Wallis test showed that there was a significant difference in median time between the different cancer types ($p < 0.0001$) where ovarian and appendiceal cancers (App.) had significantly higher values. CUP, cancer of unknown primary; HCC, hepatocellular cancer.

frequently seen in appendiceal cancer, ovarian cancer, cholangiocarcinoma, hepatocellular cancer (HCC), and pancreatic cancer, where 17%–38% of all patients suffered from ascites. The median time gap between the first paracentesis and death varied between 248 and 20 days. Particularly in upper GI cancer, the occurrence of ascites was a sign of approaching death, with a median survival time of one month from the first paracentesis. Paracentesis was also performed very close to death; 25% of all patients had their last paracentesis during their last week of life.

Malignant ascites occurred earlier in the disease trajectory in appendiceal and ovarian cancers (median 248 and 81 days before death) compared with GI cancer. Appendiceal cancer is a rare slow-growing cancer type with only 29 cases in our study of which 11 had malignant ascites. However, the symptom presentation in appendiceal cancer often includes ascites at the time of diagnosis and in addition, the lack of peritoneal carcinomatosis in appendiceal cancer (due to its pathophysiology), the frequency of paracenteses did not increase.[2]

Primary ovarian cancer often presents with ascites, due to the anatomical localization with proximity to the peritoneum and the relationship between ovarian and peritoneal cells. Since palliative oncologic treatment for ovarian cancer often is successful with a prolonged survival time, the median time from first paracentesis to death was quite long in our cohort (81 days). However, previous studies have shown even longer survival times for patients with ovarian cancer and ascites, and the median time from the occurrence of ascites and death varied between 7 and 24 months in different studies,[12,19] data that we were not able to verify, as our database only included data for the last year of life.

Our results on upper GI cancer, comprising mainly pancreatic cancer and cholangiocarcinoma, are in line with a recent study showing that the mean time from occurrence of malignant ascites to death in pancreatic cancer was 27 days.[13]

For the other cancer types investigated in this study, the median time from first paracentesis to death was 48–20 days, with the poorest prognosis for HCC. Previous studies show that the time from the first occurrence of malignant ascites to death varies between one and six months in different cancer types, i.e., somewhat longer before death than in our cohort.[8,13,20,21] Ascites as a strong predictive factor for short survival time in HCC has been shown previously.[22]

The cancer types with the most frequently performed paracenteses (events) were ovarian cancer and pancreatic cancer with 452 and 615, respectively. This is in good agreement with previous studies.[6,8,19] In cholangiocarcinoma and pancreatic cancer, the high increase of paracentesis frequency over time (Q4/Q1: 40 and 29, respectively) is considered as an effect of both high proportion of peritoneal carcinomatosis as well as elevated presence of liver metastases in these malignancies.

Only 1.9% of all patients with prostate cancer developed malignant ascites in our cohort, but when present, the median time for the first paracentesis was only 31 days before death. This is in line with previous studies showing that malignant

Table 1. Descriptive Demographic Data of 1847 Patients with Cancer who had Undergone Paracentesis in the Stockholm Region (2015–2021) the Last Year Before Death

	Total n = 1847	Men n = 710	Women n = 1137
Age (mean + SD)	67 (+12)	67 (+11)	67 (+13)
Age groups			
18–64	672 (36%)	257 (36%)	415 (36%)
65–74	643 (35%)	263 (37%)	380 (33%)
75+	532 (29%)	190 (27%)	342 (30%)
Comorbidity (CCI)			
Low CCI: 0–1,	978 (53%)	297 (42%)	681 (60%)
High CCI: >1,	869 (47%)	413 (58%)	456 (40%)
Sociodemographic area			
Mosaic 1–2	1281 (70%)	474 (67%)	807 (71%)
Mosaic 3	566 (30%)	236 (33%)	330 (29%)
HFRS frailty risk groups			
Not frail (1)	1218 (66%)	460 (65%)	758 (67%)
Frail (2 + 3)	629 (34%)	250 (35%)	379 (33%)

Values show amount (n) and % within parenthesis or mean and standard deviation (SD).

Mosaic 3 = less affluent area.

CCI, Charlson Comorbidity Index; HFRS, Hospital Frailty Risk Score.

Table 2. Comparison Between Number of Individuals who had Undergone Paracentesis in the Last Year Before Death for Each Cancer Type Compared with All Patients Suffering from That Cancer Type in the Study Population

Type of cancers	No. of paracenteses/ no. of deaths (%)
Appendiceal cancer ($n = 29$)	11/29 (38%)
Ovarian cancer ($n = 592$)	210/592 (35%)
Cholangiocarcinoma ($n = 233$)	61/233 (26%)
Neuroendocrine pancreatic cancer ($n = 49$)	12/49 (24%)
Pancreatic cancer ($n = 1787$)	299/1787 (17%)
Hepatocellular cancer ($n = 183$)	35/183 (19%)
Cancer of unknown origin ($n = 544$)	67/544 (12%)
Breast cancer ($n = 1252$)	148/1252 (12%)
Colon cancer ($n = 1408$)	159/1408 (11%)
Rectal cancer ($n = 576$)	42/576 (7.2%)
Prostate cancer ($n = 2214$)	43/2214 (1.9%)
Lung cancer ($n = 3460$)	52/3460 (1.5%)

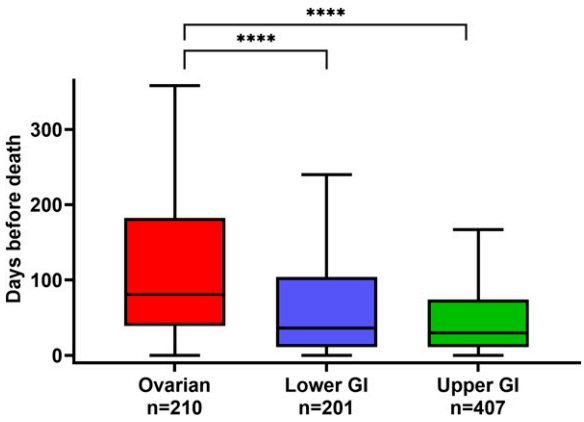

FIG. 3. Comparison of time-point for first paracentesis in the last year before death in ovarian cancer compared with upper GI cancer (including cholangiocarcinoma, pancreatic cancer, hepatocellular cancer, and neuroendocrine pancreatic cancer) and lower GI cancer (colon and rectal cancers). Error bars (whiskers) show range, box shows 25–75 percentile, and line shows median ($p < 0.0001$).

ascites is associated with poor prognosis in prostate cancer with a median survival time of one to four months.[23,24] Interestingly, prostate cancer had the highest increase in paracentesis frequency in the last quartile (Q3/Q4), indicating that when patients with prostate cancer need more frequent paracenteses, death is approaching.

The cancer types with the second highest elevation in frequency Q3/Q4 were HCC and pancreatic cancer, which was more as expected.

To our surprise, as many as 25% of the patients in this study underwent paracentesis during their last week before death. Although paracentesis usually gives valuable symptom relief also at a late stage,[25] it is questionable if these patients really could benefit from paracentesis that close to death. On the other hand, it is often difficult to predict how close to death a patient is.

Table 3. Comparison of the Number of *Paracenteses* (Events) in the Different Quartiles (Q) in the Last Year Before Death in the Different Cancer Types Studied where Q4 is the Last Quartile Before Death (i.e., the Last Three Months)

Number of paracenteses, events, in the last year of life in different quartiles (n = number of patients with paracentesis)	*Q1*	*Q2*	*Q3*	*Q4*	*Q4/Q3*	*Q4/Q1*
Appendiceal cancer ($n = 11$)	6	7	5	4	0, 80	0, 67
Ovarian cancer ($n = 210$)	48	37	78	289	3, 71	6, 02
Cholangiocarcinoma ($n = 61$)	3	12	16	120	7, 50	40, 00
Neuroendocrine pancreatic cancer ($n = 12$)	3	—	2	13	6, 50	4, 33
Pancreatic cancer ($n = 299$)	18	22	55	520	9, 45	28, 89
Hepatocellular cancer ($n = 35$)	3	—	5	47	9, 40	15, 67
Cancer of unknown origin ($n = 67$)	4	10	23	88	3, 83	22, 00
Breast cancer ($n = 148$)	10	22	46	241	5, 24	24, 10
Colon cancer ($n = 159$)	7	23	32	185	5, 78	26, 43
Rectal cancer ($n = 42$)	10	19	14	115	8, 21	11, 50
Prostate cancer ($n = 43$)	4	4	3	39	13, 00	9, 75
Lung cancer ($n = 52$)	4	4	7	58	8, 29	14, 50

Strengths and limitations

This study has several limitations that need to be addressed. The first limitation is that not all paracenteses are registered in the VAL database. In Swedish hospital care, all cases (inpatient care) regarding medical interventions are registered with classification codes. However, in outpatient settings (e.g., palliative home care units) and in hospice care (inpatient palliative care), the classification codes are not mandatory in all cases and therefore to an extent, missing in our cohort. Thus, this could be a selection bias since a significant number of deaths in advanced cancer occur in palliative home care or in palliative wards and will therefore be missed in our cohort.

Moreover, once a patient has received an indwelling subcutaneous drainage catheter (i.e., PeritX), the number of paracenteses might not always be recorded with the classification codes. Patients with long expected survival times will probably more often have an indwelling permanent drainage catheter earlier in the disease trajectory and thus, the subsequent paracenteses are not recorded. This might explain why we have shorter survival times in our study for ovarian cancer compared with other studies. It should also be noted that the decision to perform paracentesis could be influenced by several factors, for example, the wish of the patient, the accessibility of having the paracentesis performed, and comorbidities. Above all, the assessed prognosis in itself might influence if paracentesis is performed or not.

Moreover, all patients included had cancer as their main diagnosis, but there might be a few cases that had both liver failure and advanced cancer and an additional diagnosis of liver failure simultaneously. Thus, the paracenteses might have been performed due to liver failure and not due to the cancer disease. However, according to our experience, this is very rare.

As death certificates are not included in the VAL databases, we do not have the exact causes of death. However, as all the

included patients had advanced cancer as their main diagnosis during the last three months of life, it is probable that they died of cancer or cancer-associated causes such as cachexia or terminal pneumonia.

Furthermore, the natural progress of the patients' cancer diseases could obviously affect the length of life, with or without the presence of ascites. However, in this descriptive study, we only address the correlation between paracenteses in the last year of life and time to death in different cancer types. Finally, this study is limited to data for the last year of life before death. Thus, for patients who have ascites more than one year before death, the median survival time will not be correctly assessed. This also implies that we do not have accurate data on what proportion of patients who had their first paracentesis ever in the last week of life since we do not know if they have had a previous paracentesis one year before death.

Despite these limitations, we think that this study brings new valuable knowledge since it comprises a very large cohort of consecutive data comprising a great amount of different cancer types. Previous studies have presented study samples of only 144 to 1040 patients.[7,9,19,22,26] The results presented here could be used for generating new hypotheses and optimizing the design of future, prospective studies on malignant ascites. For the cancer types in which ascites occurs late in the disease trajectory, we think the data are more accurate, while in those with longer survival time, the data should be interpreted with more caution.

Conclusion

In conclusion, the occurrence of paracentesis in patients with advanced cancer is generally a sign that death is approaching within the coming months, especially in the case of upper GI cancer. However, for ovarian and appendiceal cancers, ascites is less useful as a predictive tool.

Data Sharing

The raw data is available from the corresponding author upon request.

Author Disclosure Statement

The authors declare that they have no competing interests.

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