doi:10.4149/neo_2013_071

Clinical significance of ascites in epithelial ovarian cancer

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Received August 30, 2012/ Accepted February 1, 2013

The prognostic significance of ascites in the dissemination of metastases in epithelial ovarian cancer (EOC) is unclear. Our study aimed to investigate the association between clinicopathological factors and the development of ascites, as well as its prognostic significance. Three hundred and thirty three patients with primary EOC were suitable for inclusion. We analyzed the correlation between clinicopathological factors, including the extent of metastases, and ascitic volume. The prognostic significance of ascites was assessed using the Kaplan–Meier method and multivariate Cox's regression analysis. The average ascitic volume was 1,800 ml. Significantly, more patients with advanced FIGO stage disease presented with ascites. The volume of ascites increased significantly when metastatic disease was present in more than three regions ($p<0.05$), and this was the sole factor identified as associated with ascitic volume by multiple linear regression analysis. Median survival was significantly different between those with an ascitic volume less than 1,800 ml (median survival = 58 months), and those with a volume greater than 1,800 ml (median survival = 28.6 months) ($p<0.05$). Subgroup analysis of stage III and IV patients also revealed a poor prognosis in the presence of massive ascites ($p = 0.03$). Multivariate analyses found that massive ascites and poor differentiation were independent poor prognostic factors for stage III and IV EOC patients by Cox regression, using a backward elimination procedure. The volume of ascites increased significantly with the extent of metastastic disease. Massive ascites and poor tumor differentiation were associated with a worse prognosis in patients with advanced stage ovarian cancer.

Key words: ascites, epithelial ovarian cancer, prognosis

Ovarian cancer has the highest mortality rate of all gynecological cancers [1], with diagnosis occurring at an advanced stage is one of the major contributory factors to this poor prognosis. Due to the lack of early symptoms and signs, most patients do not present until abdominal swelling or bloating occurs, and more than 80% of patients present at a late stage [2, 3]. Symptoms are commonly associated with massive ascites and metastases beyond the ovary.

We have observed in our clinical practice that massive ascites is a distinctive and consistent feature in patients with advanced ovarian cancer. With disease progression, disseminated malignant cells spread to the serosal surfaces that cause peritoneal and/or pleural effusions [4]. In addition, the occurrence of the ascites in ovarian cancer is significant higher than with other malignant tumors, such as gastrointestinal tumors [5]. The effusions that accompany disease progression in ovarian cancer are a recognized feature that distinguishes it from other pelvic and abdominal malignant metastastic disease processes.

However, the significance of malignant effusions in the context of metastatic ovarian cancer remains unclear. Limited data exist on the association between ascites and prognosis, as well as with other clinicopathological factors. Some studies suggest that the presence of ascites is associated with a poor prognosis, while others demonstrate that neither the presence of ascites nor the volume, are independent predictors of survival [5-10]

Therefore, we believe that the prognostic significance of effusions in metastatic ovarian cancer needs further exploration. With better understanding of the pathophysiology of malignant ascites, better diagnostic evaluation, and the use of multimodality therapy, both quality of life (QoL) and survival in these patients would improve. In addition, clinical data will help in the further investigation

of mechanisms underlying the formation and development of malignant effusions.

The aim of this study was to investigate the association between clinicopathological factors and the development of ascites in patients with epithelial ovarian cancer (EOC). In addition, the effect of the presence of ascites on prognosis was explored.

Patients and methods

Eligible patients and treatments. Between May 1999 and December 2006, 333 patients with epithelial ovarian cancer, who had undergone primary cytoreductive or comprehensive staging surgery followed by platinum-based chemotherapy, at the Cancer Center of Sun Yat-sen University, were identified. Women with a previous cancer history and those receiving neoadjuvant chemotherapy were excluded.

Cytoreductive or comprehensive surgery was performed via an abdominal midline incision. The surgical procedure included total hysterectomy, bilateral salpingo-oophorectomy, omentectomy and resection of all visible and palpable bulky tumor and lymphadenectomy, according to the NCCN guidelines. Bowel resection, pancreatic resection, splenectomy, diaphragmatic stripping, and partial liver resection were performed if necessary for optimal cytoreduction. Optimal cytoreductive surgery was defined as the presence of residual macroscopic lesions less than 2 cm, according to FIGO guidelines. All surgical procedures were performed by gynecological oncologists. Following debulking, women received between six and eight cycles of two drug combination chemotherapy, which included a platinum agent. The chemotherapy drugs used included paclitaxel (135 – 175 mg/m^2), carboplatin (area under curve [AUC] 5 – 6), doxepaclitaxel (70 mg/m^2), and cisplatin (65 – 75 mg/m^2).

Study design. Following laparotomy, intraperitoneal fluid was aspirated and measured. Where the volume of ascites was more than 100ml, this observation was recorded. Conversely, when the volume was less than 100 ml, this observation was seen as negative and disregarded. Epithelial ovarian tumor tissue was classified histologically as serous, mucinous or other types of epithelial carcinoma which include endometrial, clear cell, and undifferentiated adenocarcinoma. Disease stage was determined according to the FIGO guidelines. The location of metastatic disease included seven sites: the pelvis, the peritoneum and/or pleura, the surface of gastrointestinal tract or mesentery, the omentum, the surface of the diaphragm, the retroperitoneum, and distant areas. The number of regions involved and the diameters of primary and metastastic tumors were recorded.

We divided patients into two groups according to the mean amount of ascitic fluid present, ≤1,800 ml and >1,800 ml, and the prognostic significance of the volume was analyzed. The correlation between clinicopathological factors, such as stage, histology, tumor differentiation, primary tumor size, regions and size of metastases, Ca125 levels, serum albumin levels, and the volume of ascites, was also analyzed.

The student's t-test was used to compare the volume of peritoneal fluid of patients of different ages, FIGO stage, differentiation and histology type. Pearson's analysis and multiple linear regression analysis were used to calculate the association between the volume of the ascites and factors such as serum concentrations of CA125, albumin, body surface area, the size of the primary and metastastic tumors. We analyzed the prognostic significance of the ascitic volume using the Kaplan–Meier method and assessed the association with clinicopathological factors by multivariate Cox's regression. All data was analyzed using SPSS version 16.0 software (SPSS, Chicago, USA). A P-value <0.05 was considered statistically significant.

Results

Demographic characteristics and the incidence of ascites. Three hundred and thirty three cases of EOC were included in the study. The mean age was 47.5 years (range 32 – 78 years). The average ascitic volume was 1,800 ml. There were 184 serous adenocarcinomas, 99 mucinous adenocarcinomas, and 50 other types of epithelial carcinomas. The frequency of both stage III and IV disease was 65%. Overall, 274 cases underwent optimal cytoreductive surgery, and 59 patients were deemed to have had unsatisfactory surgery.

Ascites occurred in 261 (78.4%) of the 333 patients. Significantly more patients at an advanced FIGO stage presented with ascites (P<0.05). The incidence of ascites was 49.4% and 62.5% in stage I and stage II disease, respectively, which increased to 90.1% and 100% in stage III and stage IV patients, respectively (Table 1). No statistical difference in histology or differentiation in those with or without ascites was observed.

Clinicopathological factors related to the volume of ascites. Univariate analysis revealed that the volume of ascites increased significantly as the disease stage advanced. The

Table 1. Demographic characteristics and incidence of ascites.

	N = 333	Incidence of ascites (%)
Age	47.5 (32~78)	78.4%
FIGO stage		
I	81 (24.3%)	50.6%
II	36 (10.8%)	62.5%
III	194 (58.3%)	90.1%
IV	22 (6.6%)	100%
Histology		
Serous adenocarcinoma	184 (55.3%)	84.0%
Mucinous adenocarcinoma	99 (29.7%)	69.1%
Other types of adenocarcinoma	50 (15.0%)	78%
Differentiation		
Well to moderate	203 (61.0%)	75.6%
Poor	130 (39.0%)	82.8%

Table 2. The volume of ascites in patients with different clinicopathological factors.

	N = 333	Volume X±SD (ml)	P value
Age			
≤47	162	1670±2190	P=0.67
>47	171	1910±2660	
FIGO stage			
I	81	530±1010	P<0.05
II	36	300±540	
III	194	2460±2560	
IV	22	2810±3590	
Histology			
Serous adenocarcinoma	184	1520±2330	P>0.05
Mucinous adenocarcinoma	99	1940±2440	
Other types of carcinoma	50	2500±2830	
Differentiation			
Well to moderate	203	1450±2070	P = 0.133
Poor	130	2320±2860	
Metastatic Regions*			
≤3 Regions	216	700±1040	P<0.05
>3 Regions	117	3,800±2,960	

*The location of metastatic lesions was divided into seven regions: pelvis, peritoneum and/or pleura, surface of the gastrointestinal tract or mesentery, omentum, surface of diaphragm, retroperitoneum, and distant metastasis.

Table 3. Comparison of ascitic volume in FIGO stage III and IV patients with different extents of metastatic disease.

	N = 216	Volume X±S (ml)	P value
Metastatic Regions*			
≤3 Regions	99	990±1150	P<0.05
>3 Regions	117	3,800±2,960	

*The location of metastatic lesions was divided into seven regions: pelvis, peritoneum and/or pleura, surface of the gastrointestinal tract or mesentery, omentum, surface of diaphragm, retroperitoneum, and distant metastasis.

average volumes of ascites in stage I and stage II patients was 300 ml and 530 ml, respectively, which increased to 2,460 ml and 2,810 ml in stage III and stage IV patients, respectively (P<0.05). The volume of ascites in patients with different sites of metastatic disease was also compared, in addition to the FIGO stage. As previously outlined, there were seven regions where metastatic disease was located. The average volume of ascites was 700 ml and 3,800 ml in patients with less than and more than three regions of metastatic disease, respectively (P<0.05) (Table 2).

Even within the same FIGO stage, the volume of ascites increased as the extent of tumor involvement increased. For stage III and IV patients, the volume of ascites was 990 ml and 3,800 ml in patients with less than and more than three regions of metastatic involvement, respectively (P<0.05) (Table 3).

Pearson's correlation analysis showed that the preoperative and postoperative serum albumin concentration had a negative linear correlation with the amount of ascites (P<0.05). There was a significant association between the amount of ascites and the diameter of the metastastic lesion (P = 0.02).

The average ascitic volume in patients with positive retroperitoneal lymph nodes was 2,200 ml, compared with a volume of 1,330 ml in those with negative lymph nodes, a difference that was not statistically significant (P = 0.622). No statistical differences in age, histology, or tumor differentiation between patients with different ascitic volumes were noted. Likewise, Pearson's correlation analysis showed no statistical association between body surface area, the maximum diameter of the primary tumor and CA125 levels, and ascitic volume (Table 4).

Multiple linear regression analysis showed that the number of metastatic regions was the only factor related to the volume of ascites (P = 0.03). The amount of ascites increased significantly with the presence of more than three regions of metastatic disease (Table 5).

Prognostic significance of the volume of ascites. As expected, a survival difference was observed in patients with less than three and more than three metastatic regions (58 months vs. 30 months, P = 0.003). The median survival of patients with ascites greater than 1,800 ml was 28.6 months, versus 58 months for those with a volume less than 1,800 ml (P<0.05) (Fig. 1). In addition, the survival of FIGO stage III and IV patients with different volumes of ascites was compared. A survival difference was observed

Table 4. Correlation between ascitic volume and clinicopathological factors (Pearson's linear analysis).

	Mean	SD	Correlation	P value
BSA*	1.47 m^2	0.10	NA	P = 0.48
Max diameter of primary tumor	17.69 cm	21.41	NA	P = 0.87
Max diameter of metastasis	4.36 cm	5.90	0.28	P = 0.02
CA125	2261.23 U/ml	6198.04	NA	P = 0.66
Albumin pre-surgery	40.36 g/l	4.50	-0.33	P = 0.04
Albumin post-surgery	32.60 g/l	5.36	-0.468	P = 0.02

*Body surface area

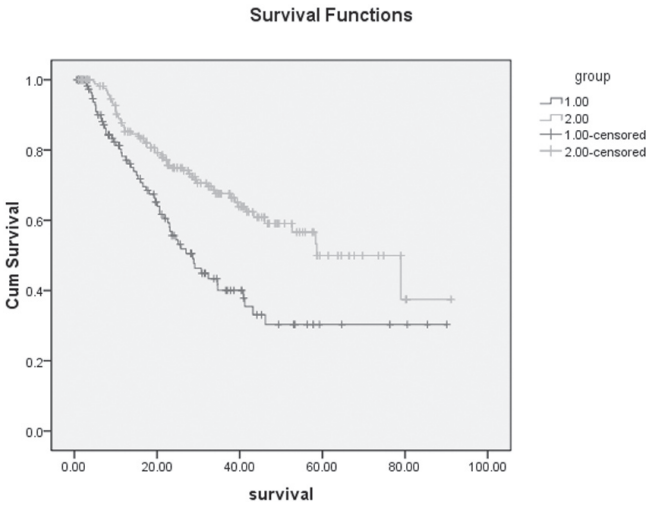

Figure 1. Survival comparison of patients with ascites less than 1,800 ml and greater than 1,800 ml.*
***Median survival was 58 months and 28.6 months for ovarian cancer with ascites less than 1,800 ml and more than 1,800 ml, respectively (p<0.05).**

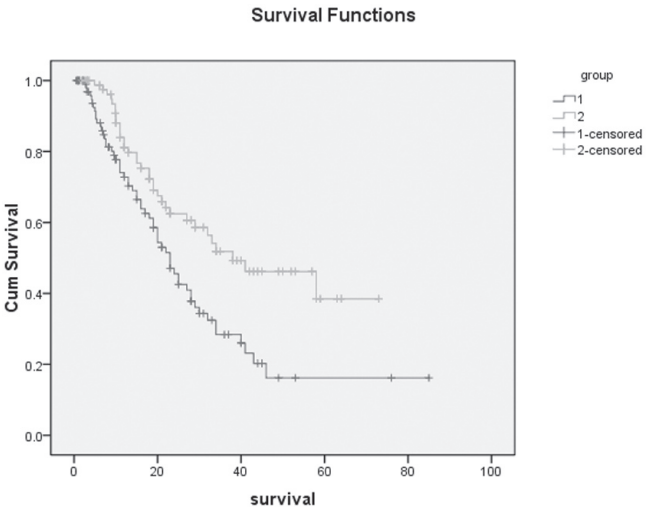

Figure 2. Survival comparison of patients with stage III and IV disease and ascites less than 1,800 ml and greater than 1,800 ml*
***Significant difference was noted at P = 0.003, favoring patients with less ascites. Median survival was 23 months versus 38 months for patients with different ascitic volumes.**

using Kaplan–Meier estimates, and was found to be significant at P = 0.003, favoring those with less ascites. Median survival durations were 23 months versus 38 months for patients with different ascitic volumes (Fig. 2). For patients with stage I or II disease with an average ascites of 450 ml, median survival was 43 months and 59 months for ascites volumes less than 450 ml or more than 450 ml, respectively (P = 0.104).

Finally, a multivariate analysis of prognostic factors was examined by Cox regression for stage III and IV patients, using a backward elimination procedure. Massive ascites and poor differentiation were independent poor prognostic factors. There was no relationship between prognosis, and age, the amount of ascites, histology, tumor differentiation, surgery satisfaction and CA125 levels (Table 6).

Discussion

Few studies to date have reported on the clinical significance of malignant ascites volume and its relationship with survival. EOC is the most common cause of cancer-related ascites [11-13]. Parsons demonstrated the predominance of ovarian cancer as a cause of ascites. Of the total number of cancer cases, which included ovarian cancer, breast cancer and gastrointestinal cancers, retrospectively analyzed over a two year period in a single institution, the ovarian cancer cohort had the highest proportion of patients with ascites in 38% of female patients [8]. Similar results were reported by Ayantunde, with 36.7% developing ascites in the population studied [5].

However, the reported frequency of ascites varies markedly in the literature. Ayhan et al. retrospectively analyzed 372

Table 5. Multiple linear regression analysis of clinicopathology factors and ascitic volume.*

Model	Unstandardized Coefficients				95% Confidence Interval for B	
	B	Std. Error	t	Sig.	Lower Bound	Upper Bound
1 (Constant)	365.455	404.680	.903	.370	-444.308	1175.219
Metastastic regions	502.139	108.988	4.607	.000	284.054	720.224

*Dependent variable: volume of ascites

Table 6. Prognostic factors assessed by Cox regression for stages III and IV EOC.

Clinical Pathology	B	SE	df	Sig.	Exp (B)	95.0% CI for Exp (B)	
						Lower	Upper
Volume of ascites	-2.142	.847	1	.011	.117	.022	.618
Differentiation	-.071	.035	1	.042	.931	.870	.998

cases of EOC and reported a frequency of ascites of 38.2% [9]. On the other hand, Puls et al. reported the occurrence of ascites in 95 out of 130 FIGO stage III and IV patients (73.1%), and Makar et al. observed ascites in 302 out of 435 FIGO stage III patients (69.4%) [7, 14]. A further study, based in a gynecological oncology unit, reported a rate of 73.1% in 726 suboptimally debulked stage III and IV patients [15]. In our study, 261 of the 333 patients (78.1%) had ascites, a result that is similar to that of Puls et al. The criterion for the presence of ascites in our study was 100 ml, which was similar to that of both Puls et al. and Ahyan et al. Comparing the demographic characteristics of included patients, fewer serous cancers were noted in the study of Ahyan et al. than in that of Puls et al [7]. In some studies, serous tumors were the most frequent histological type observed in patients with ascites, but this has not bee confirmed in other investigations [7, 16]. Further study is needed to determine the correlation between histology and the occurrence of ascites.

Clinical factors related to ascites. The mechanism of ascites development in EOC is complex and unclear. Lymphatic obstruction was originally implicated [17]. More recently, the activation of native mesothelial cells by the malignant metastatic process, and increased vascular permeability driven by the production and secretion of factors such as vascular endothelial growth factor and interleukins 6 and 8, appear to play a more important role [12, 18-20]. The increased vascular permeability and protein leakage may explain the negative linear correlation between the volume of ascites and serum albumin levels. Secretion of tumor seems less important, as there is no association between the size of the primary tumor and the development of ascites.

The limited literature available on the topic suggests that clincopathological factors such as tumor histology, tumor differentiation, lymphatic metastasis, serum CA125 levels, omental and intestinal metastasis, and the diameter of the metastasis, are correlated with the presence of ascites. However, most factors mentioned were included in the univariate analysis and their importance remains discutable. Lymphatic metastasis is also related to the development of ascites. Multivariate analysis has revealed that the mean number of metastatic lymph nodes is significant for the presence of ascites [9]. Furthermore, Plus et al. found that the presence of ascites was correlated with metastases to the omentum and the diaphragm, but the diameter of the primary tumor was not associated with the amount of ascites present [7]. The correlation between differentiation and serum CA125 levels with the presence of obvious ascites has also been controversial [7, 16, 21, 22].

In our study, the number of regions involved in metastatic spread was the only factor related to the volume of ascites, as shown by multiple linear regression. There was no statistically significant association between age, histology, body surface area, diameter of primary tumor, retroperitoneal lymph node status or CA125 levels, with the volume of ascites. Even within the same FIGO stage, the volume of ascites increased with the extent of tumor involvement in stage III and IV patients. Some recent reports have revealed that certain cytokines or growth factors and cellular contents present in ascitic fluid can cause tumor growth [23]. As intraperitoneal seeding is a known pathway in the spread of EOC, the development of ascites may correlate with tumor spread and growth.

Prognostic effect of ascites. The relevant mechanism of ascites formation in early and advanced stage ovarian cancer may not be exactly identical. As mentioned previously, the mechanism of ascites development in EOC is complex. Lymphatic obstruction was originally implicated, particularly in early stage ovarian cancer. In stage I and II disease with fewer metastases, the volume of ascites does not represent tumor spread and growth (tumor burden). Therefore, no association between the volume of ascites and FIGO stage (stage I and II) existed, as evidenced by no survival difference in our study. Additionally, the relatively good prognosis in early stage of ovarian cancer led to less observed difference in survival durations, which indicated a large number of patients may be needed to identify this difference in future studies.

In stage III and IV ovarian carcinoma, multiple risk factors have been identified that are associated with decreased survival. Advanced stage, a higher grade tumor and significant residual tumor after primary surgery, are all associated with a poor prognosis. The degree of tumor differentiation was shown to be a prognostic factor in our study, a finding that agrees with the conclusions of Vergote et al. [24].

The presence of ascites as a prognostic factor is discutable. We evaluated various factors that may influence survival in patients with malignant ascites, and our findings are in keeping with the few published articles that have addressed this issue. Research suggests that in general, presentation with effusions is associated with a poor prognosis in many malignancies, although some studies have shown no significant decrease in survival [5, 7-9, 11, 12]. As mentioned previously, we have observed in our clinical practice that the increase of ascites volume is always accompanied by a widespread dissemination of the underlying ovarian cancer. In addition, the presence of ascites is associated with a greater extent of tumor involvement, even within the same FIGO stage. Thus, survival analysis based solely on the presence or absence of ascites is not sufficient for the evaluation of the prognostic impact of massive ascites on outcome in ovarian cancer. Based on the average amount of ascites, we divided patients into two groups, those with a volume equal to or less than 1,800 ml and those with a volume greater than 1,800 ml, in order to compare survival. We observed a poorer survival in those with massive ascites. Subgroup analysis for stage III and stage IV patients also revealed a poorer survival with massive ascites ($P = 0.03$), which was similar to the findings of Puls et al. and Ayantunde et al [5, 7]. However, contrary to our findings, Ayhan et al. did not find the amount of ascites to be an independent prognostic factor in multivariate analysis [9]. Further prospective randomized

studies are needed to evaluate the prognostic significance of malignant ascites.

From our results, ascites may correlate tumor spread and advanced stage with poor prognosis. In addition, ascites indirectly adversely affects prognosis. As is generally known, massive ascites causes abdominal distension, nausea, asphyxia, electrolyte disturbances, and a general worsening of the overall condition of those with ovarian cancer. These factors, apart from the primary tumor itself, significantly contribute to mortality in this group of patients. The poor prognosis observed is most likely related to poor nutritional reserve, the association with a low total serum protein and impaired immune function in patients with ovarian cancer [25].

The number of regions with metastatic involvement was independently related to the volume of ascites. Ascitic volume increased significantly as the extent of the disease increased. A poor prognosis in patients with advanced stage ovarian cancer was correlated with a large amount of ascites and poorly differentiated tumors.

Acknowledgments: This work was supported by a grant from the Natural Science Foundation of Guangdong Province, China (No. 7001535).

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