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Malignant ascites in ovarian cancer is compatible with long-term (10 year) survival with associations to clinicopathological features

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Abstract

Objectives Ovarian cancer can present with malignant ascites at initial diagnosis or disease recurrence. Although indicative of advanced disease, the prognosis of malignant ascites is reported to be favorable for ovarian cancers compared to other malignancies. This study aims to detail the survival, in particular long-term (10 year), and predictive clinicopathological factors.

Methods Cases of malignant ascites confirmed by cytology and radiologic/histologic evidence supportive of ovarian primary, over three-decades, were retrieved. Survival data was obtained, and long-term survivors were identified. Corresponding demographical, clinical, biochemical, hematological, serological, and pathological data at onset of ascites were reviewed for survival analysis.

Results Totally 277 cases were reviewed, with a mean overall survival of 69.3 months, including 27 (9.7%) long survivors. Old age, high-grade histology, low haemoglobin, serum albumin and total protein, long APTT, ECOG score ≥ 3 and prior chemotherapy associated with mortality and shorter overall survival ($p = 0.03$-<0.01), whereas administration of chemotherapy after onset of ascites correlated with better outcome ($p < 0.01$). APTT, ECOG score, total serum protein and prior chemotherapy remained independent predictors on multivariable analysis. Remission was common in long survivors, with only one (3.7%) patient dying of disease. Long survival was more common in patients with younger age, low-grade serous and endometrioid histology, lower platelet count, higher serum albumin and total protein, and patients receiving surgical treatment after ascites ($p < 0.05$).

Conclusion Factors predicting long survival in ovarian carcinoma patients with malignant ascites were age, histology, hematological and biochemical markers, and those with favorable clinicopathological features are compatible with long survival.

Keywords Malignant Ascites, Long survivor, Ovarian cancer

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Synopsis

Nearly 10% of patients achieved 10-year long survival with malignant ascites in ovarian cancer, and is correlated with age, histology, treatment and serological parameters.

What does this study adds to the clinical work

Average overall survival after onset of malignant ascites in ovarian cancer was over 6.5 years with nearly one out of ten surviving more than 10 years. Young age, low-grade histology and debulking surgery, high serum albumin and total protein, and low platelet count also predicted long survival, while patients with malignant ascites as first presentation or recurrence did not differ in outcome.

Introduction

Malignant ascites is a significant complication of ovarian cancer [1]. Patients not uncommonly present with associated symptoms at initial diagnosis [2, 3], or in the event of disease recurrence [4]. The prognosis of malignant ascites is poor but is reported to be more favorable for ovarian cancers than other malignancies such as gastrointestinal and pancreatic carcinomas [5]. However, literature on the specific outcomes of ovarian cancers with malignant ascites is lacking. Either no differentiation was made between different underlying primary cancers, or that tissue diagnosis was not obtained for exclusion other causes of ascites in advanced cancers, such as liver metastasis or organ failure [5–7]. In advanced ovarian cancers, the disease course remains unpredictable up to 5 years follow-up, with the decline of survival stabilizing only at 5 to 10 years after diagnosis [8]. In this study, a retrospective cohort of ovarian cancer patients with cytologically confirmed malignant ascites were reviewed over an extended period, and clinicopathological data, including a broad panel of biochemical, hematological, and serological markers were retrieved, for detailing the long-term (10 year) survival rate, and corresponding predictive factors. As malignant ascites in ovarian cancer appears unique in that may compatible with long-term survival and remission, this study aims to elucidate, the outcome of malignant ascites in ovarian cancers, and to identify factors that are predictive of long-term survival, and thus prognostication and treatment guidance.

Methodology

Consecutive peritoneal fluid cytology reports from the year 1995 to 2022 in the department pathology archives were retrieved. The cytologic diagnosis, and in cases of indeterminate cases, the microscopy and immunocytochemical results, were reviewed. Cases were reclassified into five tiered diagnostic categories [9] of insufficient/inadequate (C1), benign (C2), atypia (C3), suspicious for malignancy (C4) and malignant (C5), and patients with at least one a malignant or suspicious for malignancy cytologic diagnosis were included. Case notes of the corresponding patients were reviewed, and only those with ovarian malignancy, as indicated by the hospital diagnosis code and relevant investigations, were recruited into the study. In addition to the cytologic diagnosis, radiological and/or histological (core biopsy, excisional biopsy, or resection) confirmation of ovarian malignancy was required, and cases without supporting evidence were excluded.

Demographical, clinical, biochemical, hematological, serological, and pathological data were reviewed from the electronic patient records under the public hospital, with standardized reporting formats. Biochemical, hematological and serological test results from external laboratories were not included. The date of diagnosis of malignant ascites was defined by that of the first peritoneal fluid cytology specimen with a diagnosis of malignant or suspicious for malignancy. For blood tests, only those collected within one week of diagnosis of malignant ascites were included, with the exception of tumor markers in which tests up to within one month were accepted. Survival data of the patients were reviewed, and long survivors were defined as patients with an overall survival of more than 10 year from the diagnosis of malignant ascites.

Statistical analysis was performed using SPSS (version 26.0) and R. The t-test and Chi-square test were used for comparing clinicopathological parameters between long survivors and non-long survivors as continuous and categorical variables. Survival analysis was performed using the Kaplan Meier curve and hazard ratio. Multivariate analysis was performed using the backward Wald method. This study was approved by The Joint Chinese University of Hong Kong– New Territories East Cluster Clinical Research Ethics Committee (reference number: 2020.289).

Results

A total of 277 cases of metastatic ovarian cancer with malignant ascites were retrieved. The patients had an average age of 56.7 at the time of presentation with malignant ascites, with a mean overall survival of 69.3 months (55.0–83.5) (Fig. 1). The most common histological diagnosis was high-grade serous carcinoma ($n = 42$, 15.2%), followed by clear cell carcinoma ($n = 24$, 8.7%) and endometrioid carcinoma ($n = 13$, 4.7%) (Table 1). There were 143 cases of recurrent disease, including 130 recurrences after surgery, of which 53 also received adjuvant chemotherapy, and 13 recurrent cases after primary chemotherapy.

On univariate analysis, older age ($p < 0.01$), high-grade histology ($p = 0.03$), lower hemoglobin level

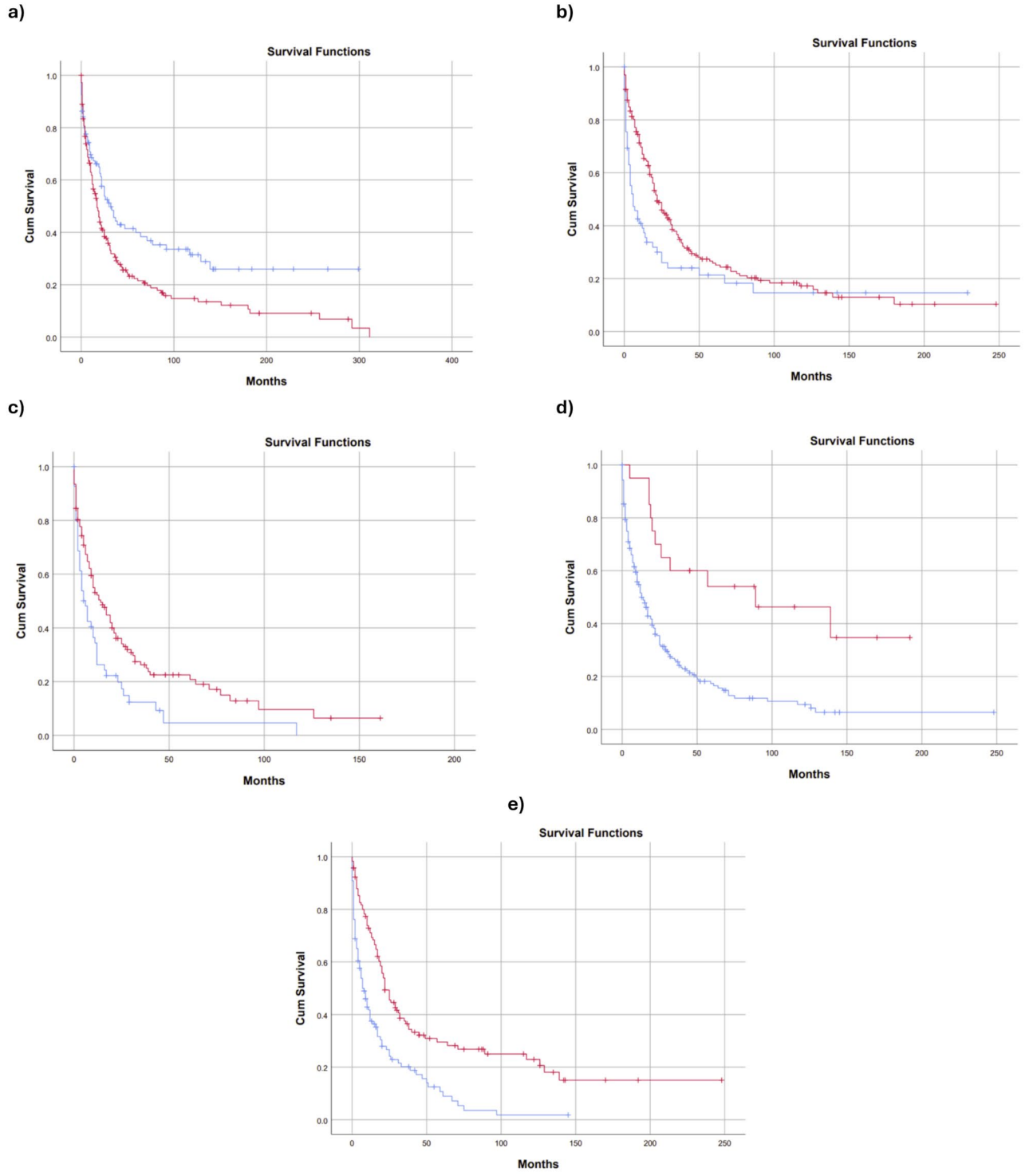

Fig. 1 Significant histological and blood parameters on Kaplan Meier survival analysis. (**a**) Age, red– age > 50 years, blue– age ≤ 50 years, $p < 0.01$. (**b**) Hemoglobin, red– Hemoglobin > 10 g/dL, blue– hemoglobin ≤ 10 g/dL, $p = 0.01$. (**c**) Activated partial thromboplastin time, red– APTT > 30 s, blue– APTT ≤ 30 s, $p < 0.01$. (**d**) Albumin, red– albumin > 40 g/dL, blue– albumin ≤ 40 g/dL; $p < 0.01$. (**e**) Total protein, red– albumin > 40 g/dL, blue– albumin ≤ 40 g/dL, $p < 0.01$

Table 1 Demographics of the cohorts

Number of patients	**277**	
Age (average)	56.7 (10–90)	
Overall survival (months, 95% C.I.)	69.3 (55.0–83.5)	
Histotype		
High grade serous carcinoma	42	(15.2%)
Low grade serous carcinoma	10	(3.6%)
Clear cell carcinoma	24	(8.7%)
Mucinous	10	(3.6%)
Endometrioid	13	(4.7%)
Malignant germ cell tumor	2	(0.7%)
Others*	176	(63.5%)

* Includes those diagnosed as carcinoma, not specified, poorly differentiated carcinoma and radiological lesions without histological confirmation

($p < 0.01$), lower serum albumin ($p < 0.01$) and total protein ($p < 0.01$), shorter activated partial thromboplastin time (APTT) ($p = 0.03$), higher Eastern Cooperative Oncology Group performance status scale score (ECOG score) ($p < 0.01$) and prior chemotherapy treatment ($p < 0.01$) were associated with mortality. Administration of chemotherapy after the diagnosis of malignant ascites ($p < 0.01$) were negatively correlated with mortality (Table 2). Kaplan Meier analysis demonstrated significant cut-offs for age (≤ 50 years, $p < 0.01$), hemoglobin (> 10 g/dL, $p = 0.01$), APTT (≤ 30 s, $p < 0.01$), serum albumin (> 40 g/dL, $p < 0.01$), total protein (> 70 g/L, $p < 0.01$) (Fig. 1) and associations with histologic grade and other clinical parameters similar to univariate analysis (Supplementary Table 1). APTT (HR: 0.93 (0.88–0.98), $p = 0.01$), total serum protein (HR: 0.89 (0.82–0.96), $p < 0.01$),

Table 2 Correlation of clinicopathologic parameters with overall survival

Univariate analysis	**Adjusted hazards ratio (95% C.I.)**	***p* value**		**Adjusted hazards ratio (95% C.I.)**	***p* value**
Age	1.02 (1.01, 1.03)	< 0.01	Clotting profile		
			Neutrophil to lymphocyte ratio	1.01 (1,1.03)	0.17
Histotype			Prothrombin time	1.01 (0.96,1.06)	0.68
High grade serous carcinoma	1.03 (0.68, 1.54)	0.90	Activated partial thromboplastin time	0.98 (0.96,1)	0.03
Low grade serous carcinoma	0 (0, ---)	0.99	International normalized ratio	1.03 (1,1.05)	0.08
Clear cell carcinoma	0.80 (0.45, 1.42)	0.45			
Mucinous	1.42 (0.69,2.91)	0.34	Tumor markers		
Endometrioid	0.58 (0.27,1.26)	0.17	Carcinoembryonic antigen	1.03 (0.96,1.09)	0.43
High grade	1.73 (1.05,2.85)	0.03	Cancer antigen 125	1 (1,1)	0.3
Blood count			ECOG performance status scale		
Hemoglobin	0.86 (0.78,0.94)	< 0.01	ECOG ≥ 3	3.98 (2.38,6.66)	< 0.01
White blood cell count	0.99 (0.96,1.01)	0.31			
Platelet count	1 (1,1)	0.19	Treatment received prior to ascites		
Neutrophil	0.98 (0.94,1.03)	0.46	(Adjuvant) chemotherapy*	3.04 (2.22,4.16)	< 0.01
Lymphocyte	0.99 (0.96,1.02)	0.38	Surgery	0.9 (0.67,1.2)	0.46
Liver/renal function			Treatment received after diagnosis		
Creatinine	1.01 (1,1.01)	0.08	Chemotherapy*	0.41 (0.3,0.57)	< 0.01
Serum albumin	0.95 (0.93,0.97)	< 0.01	Radiotherapy	0.7 (0.26,1.89)	0.48
Alkaline phosphatase	1 (1,1)	0.17	Surgery	0.36 (0.24,0.54)	< 0.01
Alanine transaminase	1 (0.99,1.01)	0.7			
Total serum protein	0.95 (0.94,0.97)	< 0.01			
Multivariable regression analysis	Adjusted hazards ratio (95% C.I.)	*p* value			
Age	1.04 (0.99,1.09)	0.09			
High histologic grade	1.58 (0.5,4.97)	0.44			
Haemoglobin	0.91 (0.72,1.16)	0.43			
White blood cell count	1 (0.87,1.16)	0.98			
Activated partial thromboplastin time	0.93 (0.88,0.98)	0.01			
Albumin	0.99 (0.9,1.08)	< 0.01			
Total serum protein	0.89 (0.82,0.96)	< 0.01			
ECOG ≥ 3	10.97 (2.56,47.07))	< 0.01			
Chemotherapy before diagnosis*	6.62 (2.02,21.69)	< 0.01			
Surgery after diagnosis	0.41 (0.12,1.43)	0.16			

* Includes targeted therapy

ECOG score ≥ 3 (HR: 10.97 (2.56–47.07), $p < 0.01$), and prior chemotherapy treatment before diagnosis of malignant ascites (HR: 6.62 (2.02–21.69), $p < 0.01$) were independent predictors on multivariable analysis (Table 2).

There were 27 (9.7%) long survivors identified in the cohort, with a mean survival of 188 months (15.6 years) (Table 3). Ten (37.0%) of the patients were deceased at the end of the follow-up period. The cause of death was documented for 8 patients and only one was attributed to disease, who was a patient with poorly differentiated carcinoma surviving for 139 months with disease (Table 3, Supplementary Table 2). The remaining 17 (63.0%) patients were all alive without disease. The patient with the longest survival was 311 months, with a diagnosis of low-grade serous carcinoma and dying of acute coronary syndrome and without evidence of disease.

The most common type of malignancy with long survival was low-grade serous carcinoma ($n = 5/27$, 18.5%, $p < 0.01$), but high-grade carcinomas including high-grade serous ($n = 3$) and clear cell carcinoma ($n = 3$) were also compatible with long survival. Long survival was correlated with low-grade serous ($p < 0.01$) and endometrioid ($p = 0.04$) histology, younger age ($p = 0.01$), higher serum albumin ($p = 0.01$) and total protein ($p = 0.01$), lower platelet count ($p = 0.02$) and surgical treatment received after ascites ($p < 0.01$), but not ECOG score, clotting profile, serum tumor marker levels and treatment received before ascites ($p > 0.05$) (Table 4).

Discussion

Malignant ascites and abdominal/peritoneal involvement are common in ovarian cancers [1] and the majority of patients are with advanced (stage III/IV) disease at the time of diagnosis [10]. Symptoms associated with malignant ascites and abdominal/peritoneal deposits, such as distension, bloating, gastrointestinal disturbance, urinary urgency and pain are the main presenting complaints for ovarian cancer [2, 11]. Similarly, development of these symptoms in patients with treated ovarian cancer heralds disease recurrence [4]. Due to the technical difficulty in obtaining core biopsies from the ovary, the risk of seeding malignant cells and rupturing cystic lesions [12], it is not uncommon for the primary and only tissue diagnosis of ovarian cancer to be peritoneal fluid cytology [13], and diagnosis of malignant ascites is dependent on detection of malignant cells in peritoneal fluid [14].

Table 3 Clinicopathological features of long survivors

Number of patients	27
Age at diagnosis (average, range)	50.4 (19–74)
Overall survival in months (average, range)	188 (120–311)
Deceased during follow-up period	10
Attributable to cancer	1
Not attributable to cancer	7
Cause not documented	2
Histotype	
High grade serous carcinoma	3
Low grade serous carcinoma	5
Clear cell carcinoma	3
Mucinous carcinoma	2
Others	14

The prognosis of malignant ascites is very guarded, as it often equates to non-resectable and widespread abdominal and/or peritoneal tumor deposits [15]. Even with advanced disease, terminal patients with malignant ascites have shorter survival than those without [16]. However, malignant ascites developed as a result of ovarian carcinomas,, compared to types of malignancies, were reported to have better outcomes [11], supported by a reported rate of 18% for long-term (10 year) disease free survival rate of stage III ovarian cancer by Pitiyarachchi et al. [5].

Age, low histologic grade and poor ECOG performance status were associated with shorter survival, in line with established prognostic factors for ovarian cancer irrespective of stage [17]. Whether prior surgical treatment was performed did not affect overall survival (Table 2), suggesting that malignant ascites as an initial presentation does not differ from recurrent disease in terms of prognosis. However, a history of adjuvant chemotherapy was strongly associated with shorter survival, which can be attributed to an increased risk of treatment resistance in recurrence compared to treatment-naïve cases [18, 19]. Patients amenable to chemotherapy, the mainstay being platinum based from the collection period of the cohort (Supplementary Table 2), and debulking surgery after the diagnosis of malignant ascites showed lower mortality, supporting the role of cytoreduction in advanced ovarian cancers [20].

Hematologic and biochemical parameters (lower APTT, higher hemoglobin, serum albumin and total protein) demonstrated correlation with overall survival. Associations between these factors and survival are reported not only in ovarian cancers [21], but also other malignancies such as breast, gastrointestinal, hematological and lung cancers [22–26]. It is postulated that serum proteins (including albumin and clotting factors) and hemoglobin levels are reflective the general nutrition status [27]. Malnutrition impedes wound healing, increases the risks of complications such as bleeding and infection, and negatively affects the response in systemic treatment [25, 28, 29]. In addition, abnormalities in blood counts, clotting profile and liver/renal functions may stem from unrecognized or subclinical medical conditions [30]. APTT, serum albumin and total protein remained strongly associated with overall survival in multivariable regression analysis ($p \leq 0.01$), along with ECOG performance status and a history of adjuvant chemotherapy.

Table 4 Clinicopathological parameters associated with long-term survival

	Long survivors	Non-long survivor	*P*-value		Long survivors	Non-long survivor	*P*-value
Histotype				Age	50.41	57.39	0.01
High-grade serous carcinoma							
Yes	3	39		Blood count			
No	21	126	0.22	Hemoglobin	11.43	11.07	0.36
Low-grade serous carcinoma				White blood cell count	8.87	9.93	0.58
Yes	5	5		Platelet count	321.17	378.84	0.02
No	19	160	< 0.01	Neutrophil	8.06	7.45	0.69
Clear cell carcinoma				Lymphocyte	1.23	1.42	0.92
Yes	3	21		Neutrophil to lymphocyte ratio	7.82	10.34	0.51
No	21	144	0.98				
Mucinous carcinoma				Clotting profile			
Yes	2	8		Prothrombin time	11.37	12.08	0.70
No	22	157	0.48	Activated partial thromboplastin time	35.90	31.35	0.38
Endometrioid carcinoma				International normalized ratio	1.08	2.24	0.72
Yes	4	9					
No	20	156	0.04	Liver/renal function			
High grade				Creatinine	66.00	64.59	0.80
Yes	11	72		Serum albumin	37.67	31.89	0.01
No	9	30	0.17	Alkaline phosphatase	82.08	78.57	0.83
				Alanine transaminase	23.83	21.99	0.82
ECOG performance status scale				Total serum protein	76.58	69.53	0.01
ECOG ≥ 3	1	17					
ECOG < 3	14	203	0.88	Tumor markers			
				Carcinoembryonic antigen	2.833	36.380	0.84
Treatment received prior to ascites				Cancer antigen 125	162.33	2232.22	0.39
Chemotherapy*							
Yes	2	64					
No	16	173	0.14				
Surgery							
Yes	11	119					
No	7	118	0.37				
Treatment received after diagnosis							
Chemotherapy*							
Yes	16	176					
No	2	61	0.17				
Radiotherapy							
Yes	1	4					
No	17	233	0.25				
Surgery							
Yes	10	45					
No	18	192	< 0.01				

* Includes targeted therapy

The mean overall survival of the cohort was more than 6.5 years (69.3 months), and nearly 10% of patients in the cohort achieved long-term 10-year survival. These figures are superior to that of gastrointestinal and pancreatic carcinomas [16, 31], the other leading causes of malignant ascites [14]. There was only one patient with active disease in the group of long survivors, which was a case of poorly differentiated carcinoma. The patient presented with advanced disease and received debulking surgery, followed by multiple cycles of chemotherapy without achieving sustained disease remission. It can be concluded that the risk of recurrence after 10 years for patients with malignant ascites is low. Examination of the survival curve also showed mortality plateauing at 9 to 10 years after onset of malignant ascites (Fig. 2). Although late recurrences have been reported in ovarian cancer

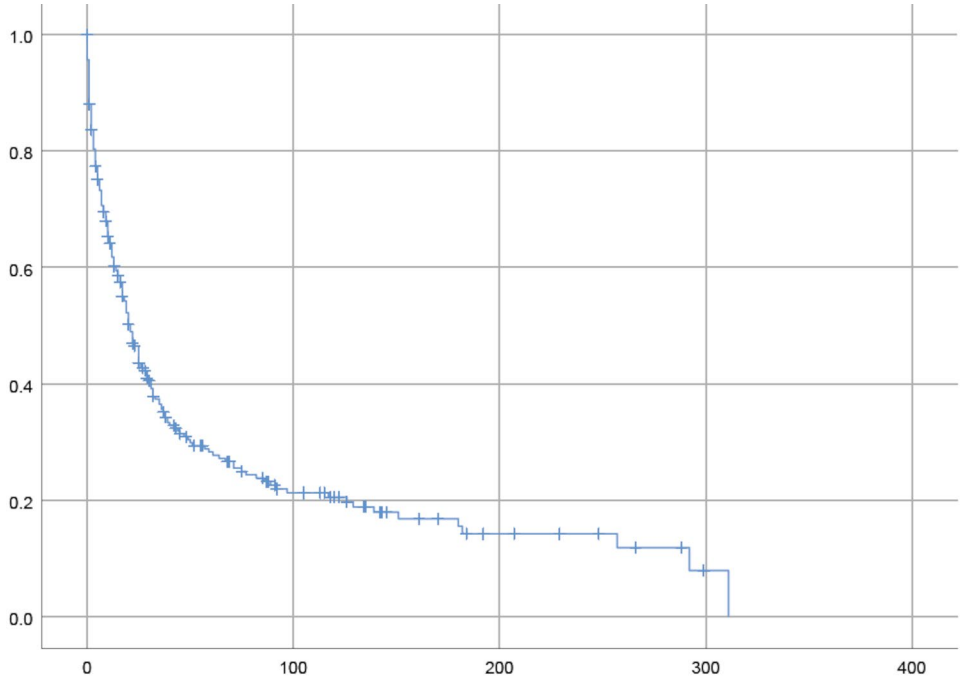

Fig. 2 Survival curve of the cohort (months)

[32], even in status post-hysterectomy, the possibility of a second primary disease arising from endometriosis or residual Mullerian structures cannot be excluded [33]. Notably, concurrent abdominal, peritoneal, nodal, and visceral organ metastasis were present in 40% ($n = 11/27$) long survivors, and complete remission was seen in all but the patient with poorly differentiated carcinoma who died of disease.

Young age, endometrioid and low-grade serous histology favored long survival, but aggressive histotypes (clear cell, high-grade serous and poorly differentiated carcinomas) are still occasionally compatible with long survival. However, in contrast with overall survival, ECOG score and treatment received before and after onset of malignant ascites were not different in the long survivor group, except for debulking surgery after development of malignant ascites. As ovarian cancers affect a younger demographic, a considerable proportion of patients have low ECOG scores and are fit for treatment [34], and differences may not be observable for comparison in the relatively small subgroup of long survivors without a greater number of cases. Higher serum albumin and total protein, and lower platelet count were seen in long survivors. It is unknown whether optimization of serum protein levels benefits survival or that it is merely a prognostic indicator. Current indications for albumin infusion in cancer patients are largely limited to the correction of hypoalbuminemia [35], but not supported for the improvement of general nutrition status [36]. Association between elevated platelet count and poor survival in cancers, including ovarian cancers, have been reported [37, 38], and is postulated to be an effect of pro-inflammatory cytokines stimulating platelet production [37].

However, the associations between overall survival and platelet, neutrophil and lymphocyte counts were not demonstrable in the current cohort. There is modest evidence that elevated neutrophil and/or platelet counts are prognostically significant, not only in ovarian cancers [39, 40] but also other solid human cancers [41]. The difference may be that only metastatic ovarian cancers were included in the cohort. Neutrophil and platelet are an indicator systemic inflammatory response and can be an indicator of disease dissemination [41].

The study was limited by a retrospective design. Periodical imaging was not performed, as such, disease remission cannot be confidently determined in cases without extended clinical follow-up, thus disease-free survival and recurrence was only analysed in long survivors. The prognostic value of biochemical, hematological, serological markers may not be limited to only at the time of diagnosis, but also in terms of serial changes in regard to treatment and recurrence. Interval monitoring particularly pertains to tumor markers, as carcinoembryonic antigen, and cancer antigen 125 levels at the time of diagnosis failed to demonstrate correlation with mortality nor long survival. Tumor markers are useful in initial diagnosis, monitoring of disease progression/recurrence and treatment response [42, 43], but the true prognostic value of tumor markers lies the decrease in serum level

and/or a low nadir level indicating a reduction in tumor burden or even remission [44, 45].

Conclusion

The mean overall survival after onset of malignant ascites due to ovarian cancer was over 6.5 years (69.3 months), with nearly 10% of patients achieving long survival (10 year). Significant factors correlating long survival were young age, low-grade serous or endometrioid histology, surgery after onset of malignant ascites, higher serum albumin and total protein, and lower platelet count. Whether surgery was performed prior to the onset of malignant ascites was not predictive of survival, suggesting similar outcomes between patients with malignant ascites as first presentation and recurrence. Findings of the study confirm that age, histology, hematological and biochemical markers are useful in predicting outcomes in patients with ovarian cancer developing malignant ascites, and that long survival is compatible with advanced ovarian cancers.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13048-025-01657-8.

Supplementary Material 1

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Clinical trial number: not applicable.

Author contributions
LHC, AMYN and JJXL conceptualized the study. LHC, AMYN, CYT, JJXL collected and interpreted the data. CYT, ALHL and JJXL analyzed the data. JHSL, ALHL and PPCI validated the findings. LHC and JJXL prepared the figures and tables. LHC prepared the original draft and JJXL and PPCI critically revised the manuscript. All authors have read and approve of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Ethical approval was granted by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (reference number 2020.089) with waiver of written informed consent. The research has been performed in accordance with the Declaration of Helsinki.

Conflict of interest
The authors declare that there is no conflict of interest regarding the publication of this paper.

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