Journal of Ovarian Research

RESEARCH

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Morphometric analysis of neoplastic cell clusters in high-grade serous ovarian cancer ascites identifies a promising prognostic factor: a retrospective study

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Abstract

High-grade serous carcinoma of the ovary is the most frequent intraperitoneal malignancy in women. It is associated with a poor prognostic outcome owing to the late appearance of clinical signs leading to a delayed diagnosis, and with resistance to platinum-based chemotherapy. One of the clinical signs is the development of ascites. The detection of neoplastic cells in ascites fluid is important as it indicates tumor progression and is associated with shorter survival. Microscopic cytospin analysis of this fluid reveals the cytological and architectural features of the neoplastic cells, allowing the pathologist to identify rapidly the malignancy and the histologic type. In association with immunocytochemistry, this process ensures a definite diagnosis and provides a specific etiology. Our objective was to provide proof-of-principle that the automatized analysis of general cytomorphological criteria, such as carcinomatous cell clustering, in malignant ascites fluid is of prognostic value in high-grade serous carcinoma. We performed a retrospective analysis of the ascites fluid of 24 advanced-stage high-grade serous ovarian cancer patients naïve of treatment. We found that the low number of neoplastic cell clusters in fluid was significantly associated with shorter overall and progression-free survival after adjusting for WHO performance status, Sugarbaker score, age and BMI. These results were independent of the peritoneal implantation of neoplastic cells. We believe this is a promising strategy to improve high-grade serous carcinoma diagnostics using a more informative but simple analysis of ascites tumor cell morphology.

Keywords Ovarian cancer, Ascites, Cell clustering, Peritoneal disease, Prognostic factor, Cytomorphology, Retrospective study

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Introduction

With more than 320,000 new cases in 2022, ovarian cancer is the fourth cancer in women worldwide [1]. High-grade serous ovarian cancer (HGSOC) represents 75% of all epithelial ovarian carcinomas and is the most frequent intraperitoneal malignancy in women [2]. Despite its low incidence, more than 200,000 women die every year from this disease because of a delayed diagnosis [1]. This is due to the late appearance of clinical signs when the cancer is already advanced, either with loco-regional extension (stage III of FIGO classification) or metastatic dissemination (stage IV): 75% of patients are thus diagnosed at stage III or IV and their estimated 5-year survival is around 30% [3]. The spread of neoplastic cells to the peritoneal wall heralds the locoregional advanced stage of HGSOC. In 46% to more than 90% of advanced stage HGSOC patients [4, 5], this spread is associated with the presence of carcinomatous cells in the peritoneal fluid, leading to malignant ascites and local inflammation [6, 7]. Standard care comprises surgery (ablation of the affected ovary and adjacent structures combined with the optimal resection of the affected peritoneum) associated with adjuvant or neoadjuvant platinum-based chemotherapy. Maintenance treatment with Avastin and/or a PARP inhibitor may also be administered [8, 9]. However, most patients relapse (70%) including those treated surgically. Patients who relapse at least six months after their last chemotherapy are defined as 'platinum-sensitive' and have longer survival than 'platinum-resistant' patients, who relapse earlier. Given the limited therapeutic options, the median survival of the latter is between 12 and 16 months [10]. While BRCA mutation is a robust predictive factor of chemosensitivity, there is no equivalent factor for chemoresistance [11, 12]. Improving therapeutic strategies for platinum-resistant patients thus remains a major clinical goal.

Malignant ascites fluid is an easily accessible specimen that is particularly suitable for translational research [13]. So far, however, it has received little attention in clinical practice despite enabling quick and informative molecular assessment of tumor cells in their environment, as shown recently in two seminal studies [14, 15]. Many have focused their attention on soluble factors contained in ascites fluid, showing for example that interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) levels are correlated with shorter progression free survival [16, 17]. Microscopic cytospin analysis of fluid provides a precise analysis of cell shape and architecture, allowing the pathologist to evoke the malignancy and the histologic type. Immunochemistry on cytospin is also a rapid technique, confirms the final diagnosis and provides a specific etiology. Common cytological criteria for the diagnosis of high-grade serous carcinoma in peritoneal fluid have already been reported [18]. However, malignant ascites specimens present heterogeneous cytological and architectural features, including clusters with variable characteristics which to our knowledge have given rise to few publications [18–20] and have never been associated with prognosis. The expression and localization of adhesion-associated membrane proteins such as E-Cadherin and EpCAM, which are known to modify the shape of multicellular cell clusters, provide insights into markers of survival and chemosensitivity in ovarian cancer [21–23].

The aim of our study was to establish easy-to-use cytological and architectural characteristics of ascites fluid to improve the predictive evaluation and prognosis of HGSOC. To fulfill this aim, we carried out a retrospective feasibility study on 24 patients diagnosed with HGSOC and analyzed a panel of morphological criteria focusing on the properties of clusters in relation to patient survival.

Materials and methods

Patient cohort

This was a retrospective, observational non-randomized single-center study carried out at IUCT-Oncopole, Toulouse, France. HGSOC cytology in ascites was analyzed for 24 women diagnosed positively from June 2014 to September 2021 at IUCT-Oncopole. Each patient has provided his informed consent in accordance with the Declaration of Helsinki. Samples were stored in the CRB Cancer des Hôpitaux de Toulouse (CRB Cancer des Hôpitaux de Toulouse, IUCT-O, Toulouse– BB-0033-00014, DC-2008-463, AC-2013-1955) collection. In accordance with French law, the CRB Cancer collection has been declared to the Ministry of Higher Education and Research (DC-2020-4074) and obtained a transfer agreement (AC-2020-14031) after approval by ethical committees. Clinical and biological annotations of the samples were declared to the CNIL, i.e. the French Agency for Data Privacy.

Disease stage was FIGO III or IV and the patients were naive of chemotherapy or radiation. The samples were obtained and processed after ascites puncture for diagnostic purposes in association with a biopsy or during surgery. All clinical data are shown in Supplementary Table 1.

We collected date of birth, age at disease detection, histological type of ovarian cancer, FIGO stage, treatment received, type of chemotherapy received, start and end of chemotherapy, date of relapse, date of death, date of sampling, puncture method (peritoneal or intraoperative), chemotherapy response score (CRS). The latter is a score for histopathologic assessment of response to neoadjuvant chemotherapy that has been validated to evaluate the amount of remaining tumor in the omentum, 1 indicating no or minimal tumor response while 3 indicates

a complete or near-complete response with no residual tumor [24, 25]. Ascites characteristics were reported from cytospin analysis and included the percentage of neoplastic cells, the percentage of clusters and isolated tumor cells, the number of clusters (normalized number per cytospin spot), cluster sizes (number of cells in the largest cluster), the number of white blood cells per µL, the formula of the white blood cells (type, percentage and absolute values in cells per µL of the major white blood cells observed in optic microscopy: macrophages, lymphocytes, neutrophils). BRCA and HRD status were collected when possible. Other parameters such as the Sugarbaker score, aka the peritoneal cancer index, body mass index (BMI), WHO performance status and CA125 concentration at detection (in UI) were also collected.

Cytopathology and immunocytochemistry analysis

After the puncture, the clinical department transferred the ascites fluid to an anticoagulant tube. On arrival in the department of cytopathology, the fluid was observed on a Malassez slide and the mononuclear cells were counted. To ensure adequate analysis, the ascites fluid was diluted to 200 cells /µL. The cytofunnel was filled just after agitation with 200 µL of the dilution and centrifuged (Cytospin 4 Thermo Scientific™) for 8 min at 55 g. The spotted cells were stained with modified May-Grünwald-Giemsa (MGG) (Supplementary Fig. 1). This allowed the detection of HGSOC characterized by three-dimensional clusters and some isolated cells. To further confirm both malignancy and the nature of the cells, we performed immunocytochemistry with BerEP4/EpCAM antibody (Roche Diagnostics, 05435676001) following the manufacturer's recommendations. The number of malignant clusters was counted on the slide with the cellular cytocentrifugated spot stained with MGG.

Statistical analysis

Principal component analysis (PCA) was performed using R Studio 2024.04.2 using the corrr, ggcorrplot, FactoMinerR and factoextra packages. Univariate and multivariate analysis of overall survival (OS) and progression-free survival (PFS) was performed using the Cox proportional hazards regression model, including adjustment variables known to be independently associated with survival (Sugarbaker score, WHO performance status, BMI and age). Stata 15 statistical software (College Station, TX: StataCorp LLC) was used to perform the Cox regression analysis. Pearson and Spearman tests were used for linear and non-linear correlation tests, respectively. Group comparisons were made using Mann-Whitney tests. The level of significance was adjusted for multiple testing using the Bonferroni correction.

Endpoints

The primary endpoint was OS defined as the time (in months) from the start of treatment to death by cancer. The secondary endpoint was PFS defined as the time (in months) from the start of treatment (surgery and/or chemotherapy) to relapse.

Results

Design of retrospective study

We analyzed the ascites fluid of 24 patients with HGSOC stage III or IV collected between June 2014 and September 2021. At the time of sampling, these patients were treatment-naive for their cancer. Our aim was to characterize the morphological criteria of the tumor cells: percentage of tumoral cells, percentage of tumoral clusters and isolated tumoral cells, cluster number and size. We also analyzed immune cell composition (white blood cells, specifically macrophages, lymphocytes and neutrophils) and collected other clinical and biological data such as the patient's age and CA125 concentration at disease detection, body mass index (BMI), WHO performance status and Sugarbaker score (Supplementary Table 1, Fig. 1).

Survival criteria are associated with ascites morphological data

To determine which of these data were associated with survival, we performed a PCA (Fig. 2). OS, PFS and time to relapse were strongly associated with ascites morphological data, i.e. number of clusters, number of cells in largest cluster, neoplastic cell percentage, and with immune cell composition.

We first investigated morphological data. In ascites, cells can appear as clusters or as individual cells. We observed that some patients had few clusters, whereas others had many clusters (Supplementary Figure 1). We divided the cohort into two groups, taking the median of the number of clusters as a threshold. The 12 patients with fewer than 24 clusters were named "cluster-poor" and the 12 patients with more than 24 clusters were named "cluster-rich" (Figure 3A, 3B). We then compared the clinical and biological parameters between both groups (Table 1). None of those parameters was found significantly different between cluster-poor and cluster-rich patients (Supplementary Figure 2).

Cluster-poor patients have a significantly poorer overall and progression-free survival compared to cluster-rich patients

Because some parameters, other than the number of clusters, could independently influence the survival of patients, we adjusted the overall survival and progression-free survival with the WHO performance status,

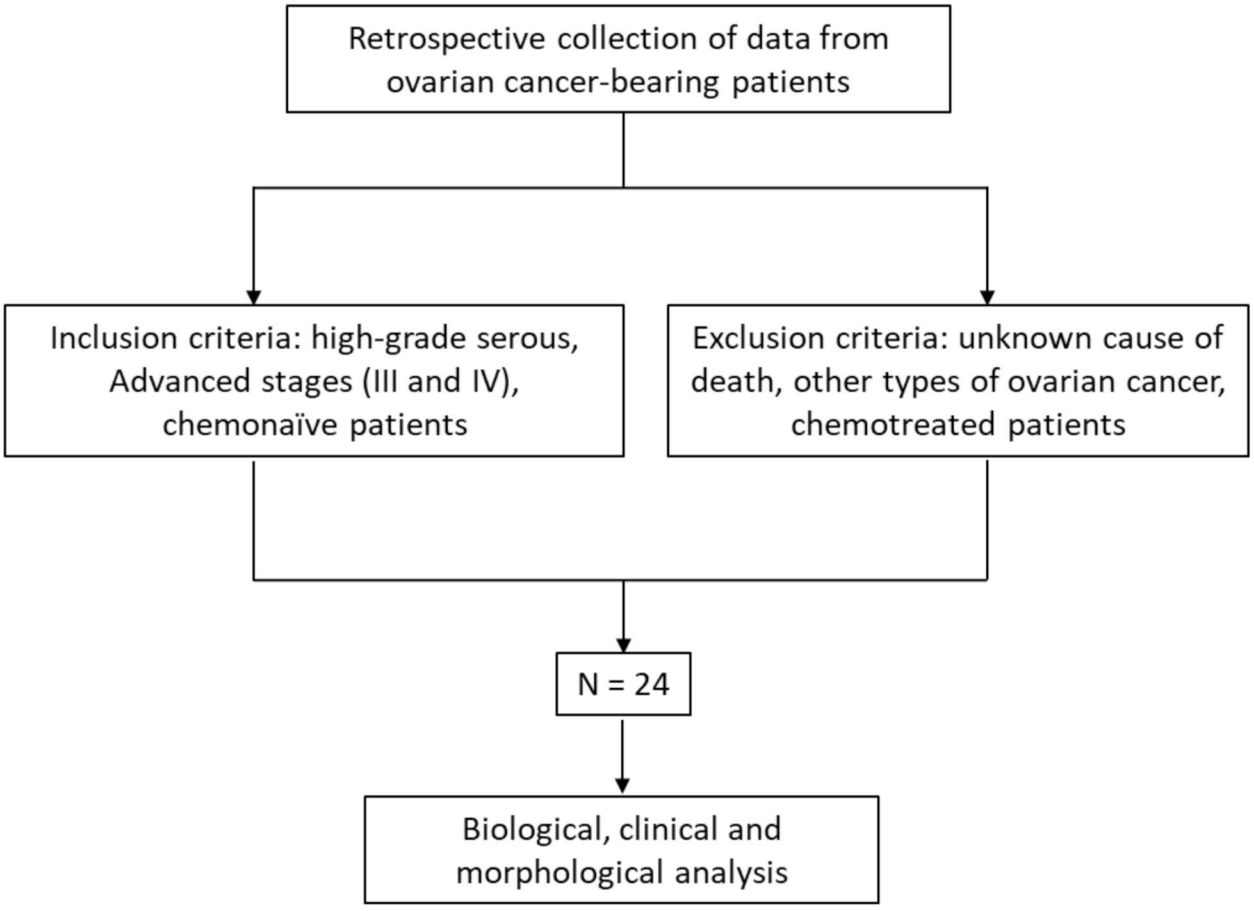

Fig. 1 Detailed criteria and selection of the cohort

Sugarbaker score, age and BMI using cox proportional hazards regression models.

We found that cluster-poor patients had a significantly lower overall survival, with a 8.52-fold higher risk of death, compared to cluster-rich patients (Hazard ratio: 8.52; 95% confidence interval: 1.88–38.49; p-value = 0.005)(Fig. 3C). Cluster-poor patients also had significantly lower progression-free survival, with a 4.90-fold higher risk of progression, compared to cluster-rich patients (Hazard ratio: 4.90; 95% confidence interval: 1.38–17.37; p-value = 0.014) (Fig. 3D).

Cluster-poor and cluster-rich patients are not distinguishable on other prognostic clinical and biological parameters

Each group of patients contained the same number of stage III and IV HGSOC (Supplementary Table 1). Most patients received a combination of surgery and chemotherapy. 2 patients in both poor-cluster and rich-cluster groups received chemotherapy only. 3 cluster-poor and rich patients received a carboplatin and taxol/taxotere combination. 7 cluster-poor and 6 cluster-rich patients received carboplatin or carboplatin/taxol associated with avastin. Notably, one of these cluster-rich patients also received gemcitabine as a second-line treatment. One patient of each group received an anti-PARP treatment (olaparib or niraparib) in combination with classical treatment. Finally, one cluster-poor and 2 cluster-rich patients received a treatment with nintedanib, a tyrosine kinase inhibitor, in combination with classical treatment. Even though different treatments were received in this cohort, these were equally distributed between cluster-poor and rich patients (Supplementary Table 1). Unfortunately, data on BRCA and HRD status were too sparse to assess its incidence (Supplementary Table 1). There was no significant difference between the groups regarding the number of white blood cells, macrophages, lymphocytes and neutrophils (Supplementary Fig. 3A-D).

Overall survival is correlated with the number of clusters and with the percentage of neoplastic cells

Cluster-rich patients had a significantly higher percentage of neoplastic cells in their fluid compared to cluster-poor patients (Supplementary Fig. 3E). They also had a higher number of cells in their largest cluster (Supplementary Fig. 3F). When we tested the association

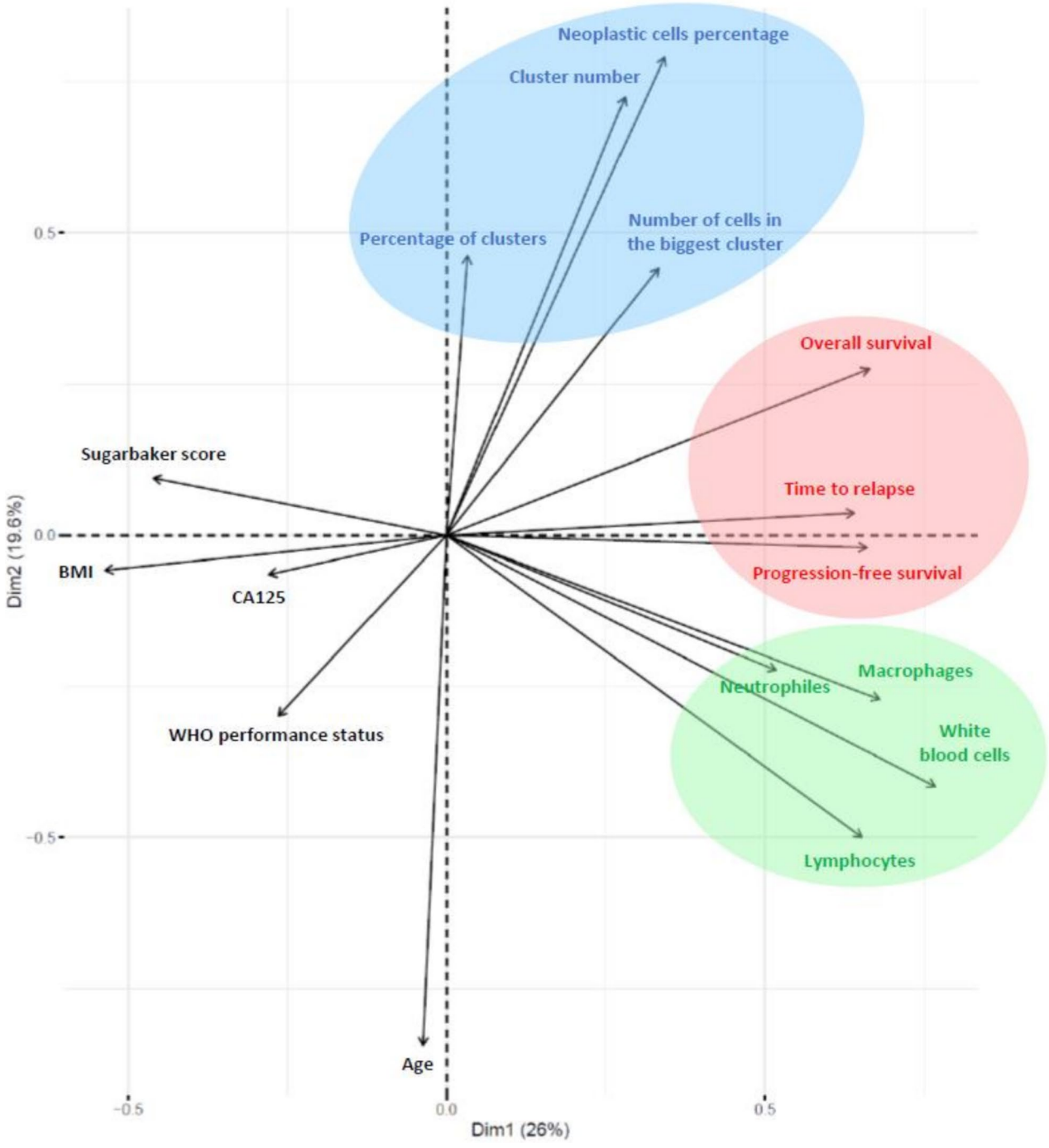

Fig. 2 Principal component analysis (PCA) of morphological, biological and clinical data of patients with an high-grade serous ovarian cancer. A PCA analysis is realized using R software, analyzing morphological data (blue), clinical data (red), immune cells data (green) and other biological data (black) of 24 patients with an high-grade serous ovarian cancer

between the number of clusters and OS, we found a non-linear correlation between OS and the number of clusters in the fluid but not the number of cells in the largest cluster (Fig. 4A and B). There was also a linear correlation between OS and the percentage of neoplastic cells in the fluid (Fig. 4C). We found a non-linear correlation between the number of clusters and the number of cells in the largest cluster (Fig. 4D). Finally, we did not find any correlation between the total number of white blood cells and their major subtypes (macrophages, lymphocytes and neutrophils) and OS (Fig. 4E-H).

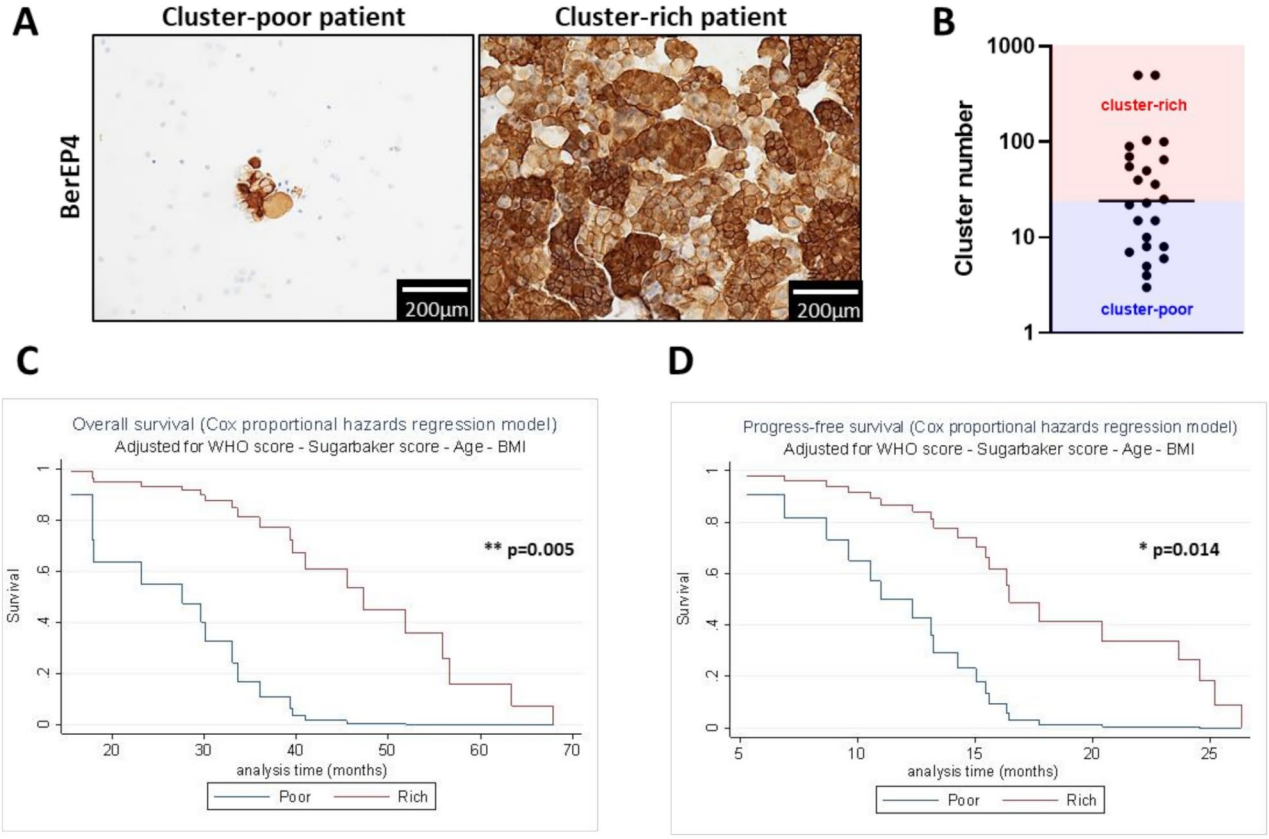

Fig. 3 Cluster-poor patients have a worse prognostic than cluster-rich patients. Cluster-poor and rich patients were compared for morphological and clinical criteria. **(A)** BerEP4 staining (tumor cells) of representative cluster-poor and rich ascites. **(B)** Cluster number distribution in the cohort. Median is represented. **(C)** Overall survival curve and **(D)** progression-free survival curve adjusted for WHO performance score, Sugarbaker score, age and BMI using Cox proportional hazard regression models. * $p < 0.05$, ** $p < 0.01$

Table 1 Characteristics of patients among cluster-poor and cluster-rich groups. Continuous variables represented as mean ± SD. Abbreviations: PCI = peritoneal cancer index, BMI = body mass index, WHO = world health organization, *n* corresponds to the number of patients for which the data was available. Significant differences are in bold (adjusted significance threshold p=0.0055 after Bonferroni correction)

Characteristic	Total cohort (N=24)	Cluster-poor patients (N=12)	Cluster-rich patients (N=12)	p-value	*n*
Age (years)	62.3 ± 11.5	67.3 ± 9	57.4 ± 11.2	0.064	24
White blood cells (cells/µL)	2580 ± 2570	2729 ± 2870	2431 ± 2350	0.954	24
Macrophages (cells/µL)	807 ± 1084	738 ± 1053	876 ± 1157	0.843	24
Lymphocytes (cells/µL)	1005 ± 1083	1132 ± 1215	878 ± 971	0.506	24
Neutrophils (cells/µL)	762 ± 1010	853 ± 959	672 ± 1094	0.843	24
Sugarbaker score/PCI	21 ± 6.3	20.5 ± 6.5	21.6 ± 6.4	1	23
BMI	25.8 ± 6.6	25.6 ± 4.3	26 ± 8.5	0.544	24
WHO performance status	0.5 ± 0.8	0.8 ± 0.9	0.2 ± 0.6	0.022	22
CA125 at detection (UI)	2826 ± 5103	3746 ± 7284	1990 ± 1648	0.605	21

Discussion

Most HGSOC patients present malignant ascites in the advanced stages [4, 5]. Although easy to sample, ascites fluid and its prognostic value have not received the attention it deserves. In this retrospective study, we analyzed the ascites fluid of 24 patients with advanced stage HGSOC naïve of surgery and/or chemotherapy in addition to studying the classical clinical and biological data. Regarding the morphology of their tumor cells, most were organized in clusters whose number was variable between the patients. PCA demonstrated that their morphology was highly associated with clinical data such as OS and PFS (Fig. 2). This allowed us to constitute two groups of patients depending on the number of their malignant clusters: cluster-poor and cluster-rich patients (Fig. 3B, Supplementary Fig. 1).

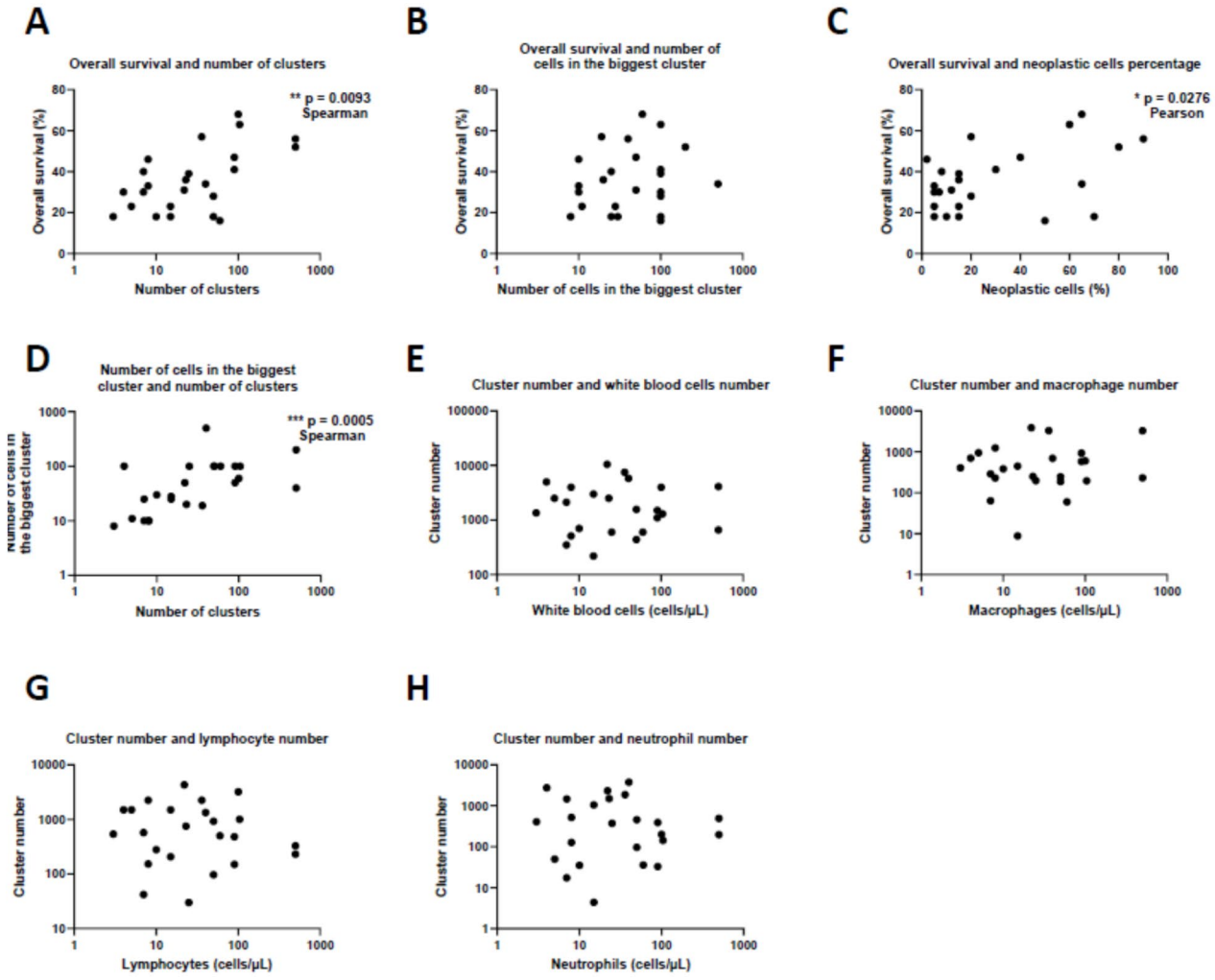

Fig. 4 Overall survival of patients correlates with the number of clusters. Patients characteristics are collected and potential correlations are tested between the following parameters: **(A)** overall survival and number of clusters, **(B)** overall survival and number of cells in the biggest cluster, **(C)** overall survival and neoplastic cells percentage, **(D)** number of cells in the biggest cluster and number of clusters, **(E)** cluster number and white blood cells number, **(F)** cluster number and macrophage number, **(G)** cluster number and lymphocyte number, **(H)** cluster number and neutrophile cluster number

After adjusting for WHO performance status, Sugarbaker score, age and BMI, cluster-poor patients had a poorer prognosis than cluster-rich patients (Fig. 3C and D). In order to verify that other parameters could not influence our conclusions, we also adjusted survival curves for the chemotherapy response score (CRS). This score is an indicator of the residual disease and is associated with OS and PFS. It measures the response to neoadjuvant chemotherapy depending on the number of remaining tumor foci on the omentum [24, 25]. When adjusted for the CRS, cluster-poor patients had a significantly lower overall survival, with a 5.08 fold higher risk of death, compared to cluster-rich patients (Hazard ratio: 5.08; 95% confidence interval: 1.06–24.44; p-value = 0.043) (Supplementary Fig. 4A) but PFS was not significant differently between both groups (Hazard ratio: 2.11; 95% confidence interval: 0.68–6.54; p-value = 0.195) (Supplementary Fig. 4B).

We also found a non-linear correlation between the number of clusters and OS (Fig. 4A). Intriguingly, similar findings were published for early mesothelioma, in which cytology-negative patients had a worse prognosis than those with malignant effusion [26]. We found that as the number of clusters increased, so did their size (Fig. 4D and Supplementary Fig. 3F). This suggests that the tumor cells in the two groups have somewhat different intrinsic properties. We also found that the higher the percentage of neoplastic cells, the better the OS of patients (Fig. 4C and Supplementary Fig. 3E). We wondered whether the higher number of clusters and neoplastic cells in the fluid of cluster-rich patients was the result of an absence of their implantation in the peritoneum. The Sugarbaker score, which is an indicator of tumor implantation, was

equivalent in both groups of patients (Supplementary Fig. 2D), so the poor prognosis of cluster-poor patients could be due to other intrinsic properties of tumor cells, such as their capacity to resist chemotherapy or to maintain a cancer stem-cell pool.

Since there was no significant difference in BMI, WHO performance status, CA125 concentration, cancer stage, treatment schedule and type between the groups (Table 1, Supplementary Table 1), we assessed the degree of resistance to chemotherapy, especially platinum salts. Classically, HGSOC patients are defined as "sensitive" when the disease does not relapse or relapses after 6 months after the end of the treatment, "resistant" when the disease relapses less than 6 months after the end of the treatment and "refractory" if the disease relapses before the end of the treatment [2]. There were 1 refractory, 4 resistant and 7 sensitive patients in the cluster-poor group and 2 resistant and 10 sensitive patients in the cluster-rich group (Supplementary Table 1). Cluster-rich patients might therefore be more sensitive to chemotherapy than cluster-poor patients, so their OS might be impacted.

We did not find any difference in white blood cell count and composition (macrophages, lymphocytes and neutrophils) between the groups (Table 1 and Supplementary Fig. 3). This is in agreement with the literature indicating that the OS of HGSOC patients is not correlated with the percentage of dendritic cells and T lymphocyte subtypes [27].

This study was designed as a proof-of-concept of the simple morphological analysis of tumoral cells in ascites fluid when ovarian cancer is diagnosed. Other authors analyzed the impact of cell aggregation on metastatic spread and as a prognostic factor [22, 28]. They also explored the role of the extracellular matrix (ECM) on cell aggregation. In ascites, the tumor cells float with limited ECM, so other mechanisms are likely involved and should be explored, such as the potential interaction with other cells from the microenvironment such as mesothelial cells which could affect the growth of tumor cells [29] or the morphogenetic programs implicated in cell aggregation. Indeed, the spontaneous 3D organization of tumor cells could alter the mechanical stresses that each tumor cell undergoes. These changes are reflected in intracellular signaling in a process called mechanotransduction. For example, the mechanosensitive YAP pathway is activated in response to increased tensile stress in 3D-organised gastrointestinal ascites tumor cells [30]. These mechanical stresses could be considered as emerging oncogenic signals promoting the progression of HGSOC. They act on tumor cells, modulating oncogenic cell signaling and the response to therapy. We and others recently highlighted the PI3K pathway, and in particular the PI3Kβ isoform, as a mechanosensitive pathway poorly explored to date but necessary for the oncogenic action of the YAP pathway [31, 32].

Our study has some limitations. First, there is its retrospective nature. Since the patients were included between 2014 and 2021, BRCA and HRD status could not be determined in most of them. Nowadays these biomolecular factors are necessary to determine treatments such as PARP inhibitors. Our next step is to conduct a prospective study to validate these findings in a larger cohort of patients. The results would allow us to identify early those patients who will recur rapidly, the platinum-resistant patients, and to offer them combination therapies with adjuvant chemotherapy to improve their recurrence-free survival and thus their survival.

In conclusion, the status of tumor cell clusters in the ascites fluid of HGSOC patients should be investigated as a prognostic factor for the efficacy of chemotherapy and to establish whether their treatment regimen should be modified. Prospective studies with a higher number of patients and a standardized method to collect and analyze fluid are needed to improve their diagnosis thanks to an easy-to-use but highly informative analysis of ascites tumor cell morphology.

Abbreviations

BMI	Body mass index
ECM	Extracellular matrix
HGSOC	High-grade serous ovarian cancer
IL	Interleukin
MGG	May-Grünwald-Giemsa
PCI	Peritoneal cancer index
VEGF	Vascular endothelial growth factor
WHO	World health organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13048-025-01653-y.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Acknowledgements

We are grateful to SigDYN members, past and present, including C. Lenaoures, for their technical support, sample banks, common tools, and fruitful discussions. We thank Prof. Anne Brouchet-Gomez and the IUCT clinicians and patients who provided samples to the CRB biobank. We thank Samira Icher, project manager and Philippe Schapiro, cytotechnologist for their participation to the pathological analysis of the cases. We thank the Imag'IN platform of CHU Toulouse (https://www.imagin-labs.net/imagin_v2/) for providing access to whole slide scanning and image analysis facilities.

Author contributions

BT: conceptualization; data curation; formal analysis; investigation; methodology; supervision, validation; visualization; writing– review & editing. RD: investigation; methodology; writing– original draft. SR: data curation; formal analysis, methodology; visualization. MWK: formal analysis;

methodology; writing– review & editing. GB: data curation; formal analysis; methodology; writing– review & editing. CB: data curation; formal analysis; funding acquisition; investigation; methodology; resources; visualization; writing– original draft; writing– review & editing. JGG: conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; supervision; validation; visualization; writing– original draft; writing– review & editing.

Funding
JGG's laboratory is part of Toucan, Laboratoire d'Excellence, ANR, an integrated research program on Signal-targeted Drug Resistance. JGG's laboratory for this topic was funded by Toucan ANR Laboratory of Excellence, Fondation Claudius Regaud– IUCT-O, Translational Research@IUCT-O.

Data availability
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest
The authors have no conflict of interest to declare.

Clinical trial number
Not applicable.

Received: 27 November 2024 / Accepted: 22 March 2025
Published online: 08 April 2025

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