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Clinicopathological prognostic parameters in patients with tubo-ovarian carcinoma effusions

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Abstract

Objective: To analyse the predictive and prognostic role of clinicopathological parameters in patients with tubo-ovarian carcinoma and malignant effusion.

Methods: A retrospective series of 700 malignant peritoneal ($n = 610$) and pleural ($n = 90$) effusions from 558 patients was revised for histotype based on the 2014 World Health Organization criteria. The role of clinicopathological parameters in determining outcome was assessed.

Results: The majority of specimens (597 effusions from 473 patients) were high-grade serous carcinomas (HGSC), followed by low-grade serous carcinoma (LGSC; 48 effusions, 37 patients), clear cell carcinoma (CCC; 23 effusions, 19 patients) and carcinosarcoma (CS; 16 effusions, 16 patients). Patients with CCC and CS had the shortest, those with HGSC intermediate, and those with LGSC longest overall and progression-free survival (both $P < 0.001$). For patients with HGSC, older age ($P = 0.002$), more advanced FIGO stage (IV vs III; $P < 0.001$), delayed/no surgery ($P < 0.001$), larger residual disease volume (RD; $P < 0.001$), non-complete response to chemotherapy at diagnosis ($P < 0.001$), and primary platinum resistance ($P < 0.001$) were associated with shorter overall survival. In Cox multivariate analysis, FIGO stage ($P = 0.002$) and primary platinum resistance ($P < 0.001$) were independent prognosticators. Significant association was additionally found for parameters analysed for progression-free survival in HGSC (previous chemotherapy: $P = 0.029$; age: $P = 0.046$; FIGO stage, upfront therapy, RD: $P < 0.001$), of which previous chemotherapy, upfront therapy, and RD were independent prognosticators (all $P < 0.001$).

Conclusions: The vast majority of malignant effusions in patients with tubo-ovarian carcinoma are derived from serous carcinoma or related tumours, such as CS. Histology is a powerful prognostic factor in this patient group, as are established clinical parameters.

KEYWORDS
chemotherapy, high-grade serous carcinoma, malignant effusion, surgery, survival, tubo-ovarian carcinoma

1 | INTRODUCTION

Ovarian cancer is the eighth most common and the eighth most lethal malignancy in women globally, with 313,959 new diagnoses and 207,252 deaths reported in 2020, representing 3.4% of cancer diagnoses and 4.7% of cancer-related deaths in females.[1] The majority (>90%) of ovarian cancers are carcinomas. Based on the 2014 World Health Organization (WHO) classification of tumours of the female genital system,[2] retained in the 2020 edition,[3] the main histological types of ovarian carcinoma are high-grade serous carcinoma (HGSC), low-grade serous carcinoma (LGSC), clear cell carcinoma (CCC), endometrioid carcinoma (EC), and mucinous carcinoma (MC). To these may be added carcinosarcoma (CS), a biphasic tumour originating in high-grade carcinoma, most frequently HGSC. Despite the designation of all adnexal malignancies as ovarian cancer, the majority of HGSC, which constitutes 70% of ovarian carcinomas, originate in the fallopian tube rather than the ovary,[4] making the term tubo-ovarian carcinoma more accurate.

Dissemination of tubo-ovarian carcinoma within the peritoneal, and less frequently the pleural cavity, is a well-documented event that occurs in the majority of patients, particularly with advanced-stage serous carcinoma.[5] The presence of ascites, particularly high-volume ascites, has been shown to be associated with poor clinical outcome in a large number of studies (reviewed by Hoppenot et al.[6] and Wahner Hendrickson et al.[7]). However, the pre-2014 histological classification has been used in the majority of these studies, making it generally difficult to assess the data, and specifically to draw conclusions regarding a given histotype. Many of the more recent clinical studies have retained the designation of "serous," rather than the more specific terms HGSC and LGSC, and continue to include patients with tumours of different histology. Continued use of designations such as "undifferentiated carcinoma," known to be rare using current immunohistochemistry (IHC) panels, or "transitional cell carcinoma," a term removed from the 2014 WHO classification, further confounds data, as is the use of terms such as "others" for non-serous carcinomas or "unknown" for tumours not adequately classified.

In the minority of studies focusing on one histotype, the presence of ascites has been confirmed to be an adverse prognostic factor.[8,9] Nevertheless, the relevance of clinicopathological factors within the group of patients with malignant effusions confirmed by cytology, and classified based on current criteria, remains unknown.

The present study had two objectives: First, to analyse case distribution with respect to the different tubo-ovarian carcinoma histotypes, applying the 2014 WHO criteria to a large case series; and second, to assess the prognostic role of established clinicopathological parameters in this patient group.

2 | MATERIALS AND METHODS

2.1 | Patients and specimens

Effusion specimens (n = 700; 610 peritoneal, 90 pleural) were submitted to the Department of Pathology at the Norwegian Radium Hospital for routine diagnostic purposes during the period 1998–2017. Effusions were centrifuged upon arrival and cell blocks were prepared using the thrombin clot method. Specimens were from 558 patients diagnosed with tubo-ovarian carcinoma. Six effusions were available from two patients, five effusions from one patient, four effusions from three patients, three effusions from 19 patients, two effusions from 81 patients and one effusion from 452 patients.

Effusions were diagnosed based on the 2014 WHO criteria by an experienced pathologist with sub-specialty in cytopathology and gynaecological pathology (BD), based on morphology in Diff-Quik-stained and PAP-stained smears, H&E sections from cell blocks, and IHC. The preoperative biopsy was additionally assessed in all cases with available material, and the surgical specimen was assessed in patients who received upfront surgery.

IHC was applied based on morphology. Antibodies used in all cases included PAX8 for genital origin, WT1 for serous differentiation, and p53 for assessment of tumour grade in serous carcinoma. Markers of CCC, EC, and MC (napsin A, HNF1β, ARID1A, PTEN, CEA) were selectively used in non-serous specimens. Calretinin was used as negative marker to exclude mesothelioma or reactive mesothelial cells.

Informed consent was obtained according to national and institutional guidelines. Study approval was given by the Regional Committee for Medical Research Ethics in Norway (REK # S-04300).

2.2 | Statistical analysis

Statistical analysis was performed applying the SPSS-PC package (Version 28). Analysis was limited to one event/effusion per patient, and to the main four diagnostic groups, ie HGSC, LGSC, CCC, and CS. Probability of <0.05 was considered statistically significant.

The association between histotype and clinicopathological parameters (4-tier analyses comparing HGSC, LGSC, CCC, and CS) was performed using the Kruskal–Wallis H test. For this analysis, clinicopathological parameters were grouped as follows: age—≤60 vs >60 years; effusion site—peritoneal vs pleural; FIGO stage—III vs IV; chemotherapy status—pre- vs post-chemotherapy specimens; residual disease (RD)—0 cm vs ≤1 cm vs >1 cm; response to chemotherapy—complete response vs partial response/stable disease/progressive disease. The association with CA 125 levels at diagnosis was analysed as a continuous variable using the same test.

Survival data were available for all patients, and survival analysis was performed separately for patients with HGSC and LGSC. Progression-free survival (PFS) and overall survival (OS) were calculated from the date of the last chemotherapy treatment/diagnosis to the date of recurrence/death or last follow-up, respectively. Univariate survival analyses of PFS and OS were executed using the Kaplan–Meier method. Multivariate survival analysis was performed using the Cox Regression Model (Enter function). Platinum resistance was defined as PFS ≤ 6 months according to guidelines published by the Gynecologic Oncology Group and progressive disease or recurrence was evaluated by the *Response Evaluation Criteria In Solid Tumours* criteria.

3 | RESULTS

Pathology diagnoses and specimen site are detailed in Table 1. The majority of specimens (597 effusions from 473 patients) were diagnosed as HGSC, followed by LGSC (48 effusions from 37 patients), CCC (23 effusions from 19 patients), and CS (16 effusions from 16 patients). Other histotypes were represented by only a few specimens (Figure 1).

Clinical data for patients with the four most common histotypes are detailed in Table 2. Patients diagnosed with HGSC or CS were significantly older than those diagnosed with LGSC or CCC ($P<0.001$) and had higher CA 125 levels at diagnosis ($P = 0.004$). Debulking to 0 cm was most common in CS and least common in HGSC ($P = 0.013$). No significant differences were observed for FIGO stage and response to first-line chemotherapy (Table 2). The same was true for effusion site ($P = 0.326$) and the presence of primary platinum resistance ($P = 0.17$; data not shown).

The follow-up period for all 545 patients ranged from 1–295 months (mean = 38 months, median = 30 months). PFS ranged from 0–233 months (mean = 13 months, median = 7 months). At the last follow-up, 488 patients were dead of disease, 28 were alive with disease, and 17 were with no evidence of disease. Five patients died of complications, 1 died of unrelated cause, and 6 were lost to follow-up.

In univariate analysis, patients with CCC and CS had the shortest, those with HGSC intermediate, and those with LGSC longest OS and PFS (both $P<0.001$; Figures 2A,B).

The number of patients diagnosed with HGSC, and to a lesser degree LGSC, was deemed sufficient for separate analysis of the clinical role of clinicopathological parameters in these groups.

The follow-up period for the 473 patients with HGSC effusions ranged from 1–295 months (mean = 38 months, median = 30 months). PFS, available for 453 patients, ranged from 0–233 months (mean = 12 months, median = 7 months). At the last follow-up, 430 patients were dead of disease, 23 were alive with disease, and 10 were with no evidence of disease. Four patients died of complications, 1 died of unrelated cause, and 5 were lost to follow-up.

For patients with HGSC, older age ($P = 0.002$; Figure 3A), more advanced FIGO stage (IV vs III; $P<0.001$; Figure 3B), delayed or no surgery—as opposed to primary debulking ($P<0.001$; Figure 3C), larger RD volume ($P<0.001$; Figure 3D), non-complete response to first-line chemotherapy ($P<0.001$; Figure 3E), and primary platinum resistance ($P<0.001$; Figure 3F) were associated with shorter OS. Effusion site ($P = 0.195$), previous exposure to chemotherapy ($P = 0.25$), and CA 125 levels at diagnosis ($P = 0.923$) were not significantly related to OS (data not shown).

All parameters with a *P*-value of <0.2 were entered into the Cox multivariate analysis for OS. In this analysis, FIGO stage ($P = 0.002$) and primary platinum resistance ($P<0.001$) were independent prognosticators (Table 3).

The above-mentioned parameters, with the exception of response to first-line chemotherapy and primary platinum resistance, which define PFS, were additionally assessed for potential association with PFS. Previous exposure to chemotherapy ($P = 0.029$; Figure 3G), older age ($P = 0.046$; Figure 3H), more advanced FIGO stage (IV vs III; $P<0.001$; Figure 3I), delayed or no surgery—as opposed to primary debulking ($P<0.001$; Figure 3J), and larger RD volume ($P<0.001$; Figure 3K) were associated with shorter PFS. Effusion site ($P = 0.108$) and CA 125 levels at diagnosis ($P = 0.869$) were not significantly related to PFS.

All parameters with a *P*-value of <0.2 were entered the Cox multivariate analysis for PFS. In this analysis, previous chemotherapy ($P<0.001$), delayed or no surgery ($P<0.001$), and RD volume ($P<0.001$), were independent prognosticators (Table 3).

The follow-up period for the 37 patients with LGSC effusions ranged from 1–187 months (mean = 55 months, median = 41 months). PFS, available for 35 patients, ranged from 0–116 months (mean = 31 months, median = 11 months). At the last follow-up, 28 patients were dead of disease, 1 was alive with disease, and 7 were with no evidence of disease. One patient was lost to follow-up.

For patients with LGSC, older age ($P = 0.001$; Figure 4A), larger RD ($P = 0.01$; Figure 4B), non-complete response to first-line chemotherapy ($P = 0.009$; Figure 4C), and primary platinum resistance ($P<0.001$; Figure 4D) were associated with shorter OS. Effusion site ($P = 0.509$), previous exposure to chemotherapy ($P = 0.728$), FIGO stage ($P = 0.056$), and CA 125 levels at diagnosis ($P = 0.474$) were not significantly related to OS (data not shown). Delayed or no surgery was not assessed for prognostic relevance since the number of patients was too small (total = 6 patients).

All parameters with *P*-value <0.2 were entered the Cox multivariate analysis for OS. In this analysis, age ($P = 0.019$), FIGO stage ($P = 0.021$), response to first-line chemotherapy ($P = 0.043$), and primary platinum resistance ($P<0.001$) were independent prognosticators (Table 4).

The above-mentioned parameters, with the exception of response to first-line chemotherapy and primary platinum resistance, which define PFS, were additionally assessed for potential association with PFS. Older age ($P = 0.003$; Figure 4E) and larger RD

TABLE 1 Histotype and anatomic site ($n = 700$ effusions)

	Anatomic site		
Histology	**Peritoneum**	**Pleura**	**Total**
HGSC	514	83	597
LGSC	43	5	48
CCC	22	1	23
CS	15	1	16
EC	8	0	8
MC	3	0	3
Mixed type	3	0	3
Undifferentiated	2	0	2
Total	610	90	700

Abbreviations: CCC, clear cell carcinoma; CS, carcinosarcoma; EC, endometrioid carcinoma; HGSC, high-grade serous carcinoma; LGSC, low-grade serous carcinoma; MC, mucinous carcinoma.

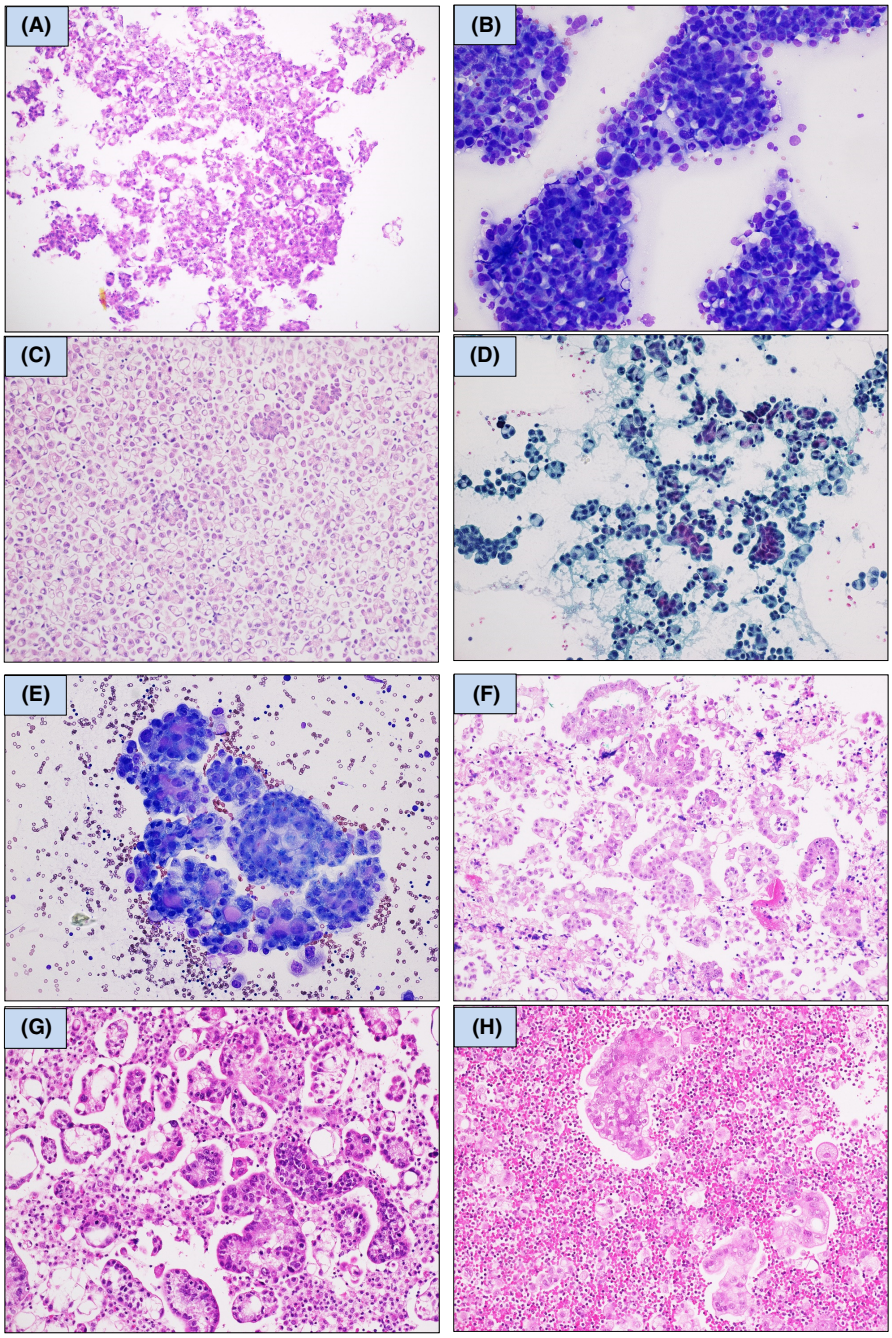


FIGURE 1 Morphology. (A,B) High-grade serous carcinoma (A: H&E; B: Diff-Quik). (C,D) Low-grade serous carcinoma (C: H&E; D: PAP). (E) Clear cell carcinoma (Diff-Quik). (F) Carcinosarcoma (epithelial component; H&E). (G) Endometrioid carcinoma (H&E). (H) Mucinous carcinoma (H&E)

($P = 0.005$; Figure 4F) were associated with shorter PFS. Effusion site ($P = 0.893$), previous exposure to chemotherapy ($P = 0.167$), FIGO stage ($P = 0.064$), and CA 125 levels at diagnosis ($P = 0.969$) were not significantly related to PFS (data not shown).

All parameters with P-value <0.2 were entered the Cox multivariate analysis for PFS. In this analysis, only RD volume was an independent prognosticator ($P = 0.046$; Table 4).

4 | DISCUSSION

The present study constitutes, to the best of our knowledge, the first large-scale clinicopathological analysis of malignant effusion specimens based on the current diagnostic classification of tubo-ovarian carcinoma. Specimens represent the diagnostic spectrum at a teaching cancer hospital certified for the treatment of patients with gynaecological cancer, and have been selected in a non-biased manner, with the sole inclusion criterion being sufficient material for thorough assessment.

In Western countries, HGSC and LGSC constitute approximately 70% and <5%, respectively, of tubo-ovarian carcinomas in surgical specimens, with the majority of remaining tumours diagnosed as CCC (10%), EC (10%) or MC (<5%).[10] This division is not fully reproduced in effusion specimens based on the present study, in which 645/700 (92%) of effusions were from patients diagnosed with HGSC or LGSC. Inclusion of CS, a tumour that often originates from HGSC,

TABLE 2 Clinicopathological parameters for patients with HGSC ($n = 473$), LGSC ($n = 37$), CCC ($n = 19$) and CS ($n = 16$) effusions

Parameter	HGSC	LGSC	CCC	CS	*P*-value
Age (mean)	23–88 years (62)	31–83 years (55)	29–70 years (54)	47–84 years (66)	$P < 0.001$
FIGO stage					
I	4	0	1	0	$P = 0.165$[a]
II	8	3	0	0	
III	283	25	13	12	
IV	175	9	5	4	
NA	3	0	0	0	
Residual disease					
0 cm	74	10	5	8	$P = 0.013$
≤1 cm	154	9	5	6	
>1 cm	155	9	7	2	
NA	90	9	2	0	
CA 125 at diagnosis range (median)[b]	10–62,400 (1239)	82–4613 (500)	56–9800 (538)	38–15,000 (1096)	$P = 0.004$
Chemoresponse after primary treatment					
CR	220	18	6	9	$P = 0.165$
PR	114	5	3	2	
SD	35	3	1	2	
PD	46	2	8	1	
NA[c]	58	9	1	2	

Abbreviations: CCC, clear cell carcinoma; CR, complete response; CS, carcinosarcoma; HGSC, high-grade serous carcinoma; LGSC, low-grade serous carcinoma; NA, not available; PD, progressive disease; PR, partial response; SD, stable disease.

[a]$P = 0.316$ for analysis of FIGO stage III vs IV.

[b]Available for 392 patients with HGSC, 28 patients with LGSC, 15 patients with CCC and 15 patients with CS.

[c]Not available (missing data or disease response after chemotherapy was incorrectly evaluated).

in this group raises this figure to 661/700 (94%). Analysis based on one specimen per patient generates similar results, ie 510/558 (91%) for serous carcinomas alone, 526/558 (94%) with inclusion of CS. EC and MC were represented by only a few cases, as were mixed and undifferentiated carcinoma, entities that have been reduced to isolated cases in recent years. This histotype distribution owes to the overwhelming propensity of both HGSC and LGSC to metastasise within the serosal cavities, as opposed to the very low tendency of EC and MC to do so, with CCC having a moderately higher tendency than the latter two entities. The clinical implication of this finding is that therapeutic strategies designed to interfere with peritoneal (or pleural) metastasis should focus on HGSC and LGSC, with less effort directed at EC or MC. This also stresses the fact that MC found in ascites or pleural effusion is far more likely to originate from the gastrointestinal tract than the ovary.

Comparative analysis of the four major histotypes in this series showed that patients diagnosed with LGSC or CCC were significantly younger than those diagnosed with HGSC or CS, well in agreement with current knowledge.[11,12] Significantly higher CA 125 levels were measured in HGSC and the closely related CS compared to patients with LGSC or CCC, in agreement with previous observations.[13] The absence of significant differences between the four groups with respect to FIGO stage may be explained by the fact that the majority of patients with malignant effusions have advanced-stage disease, thereby excluding a substantial group of CCC patients with early-stage disease. Conversely, the differences observed in the extent of debulking, particularly regarding the difference between HGSC and CS, may represent an incidental finding unique to this cohort rather than a real difference, which may be supported by a relative weak *P*-value in this comparison. The same may be true for the lack of difference in response to first-line chemotherapy, as patients with HGSC and CS would be expected to have better response to first-line therapy than those with LGSC or CCC. Finally, OS and PFS were very poor for patients with CCC and CS, reflecting the aggressive nature of these tumours, with intermediate values for HGSC patients and longest survival for patients with LGSC, again in agreement with previous reports.[11,12]

The central part of our statistical analysis focused on a unique cohort of 473 patients with HGSC effusions, part of which has been extensively studied for biological cancer-associated characteristics in the last 23 years (partly reviewed by Davidson et al[5]). The robustness and validity of this cohort was confirmed in the present study by the strong association between established clinical parameters, including age, FIGO stage, RD volume, and chemotherapy response, including the presence of primary platinum resistance, and OS, with

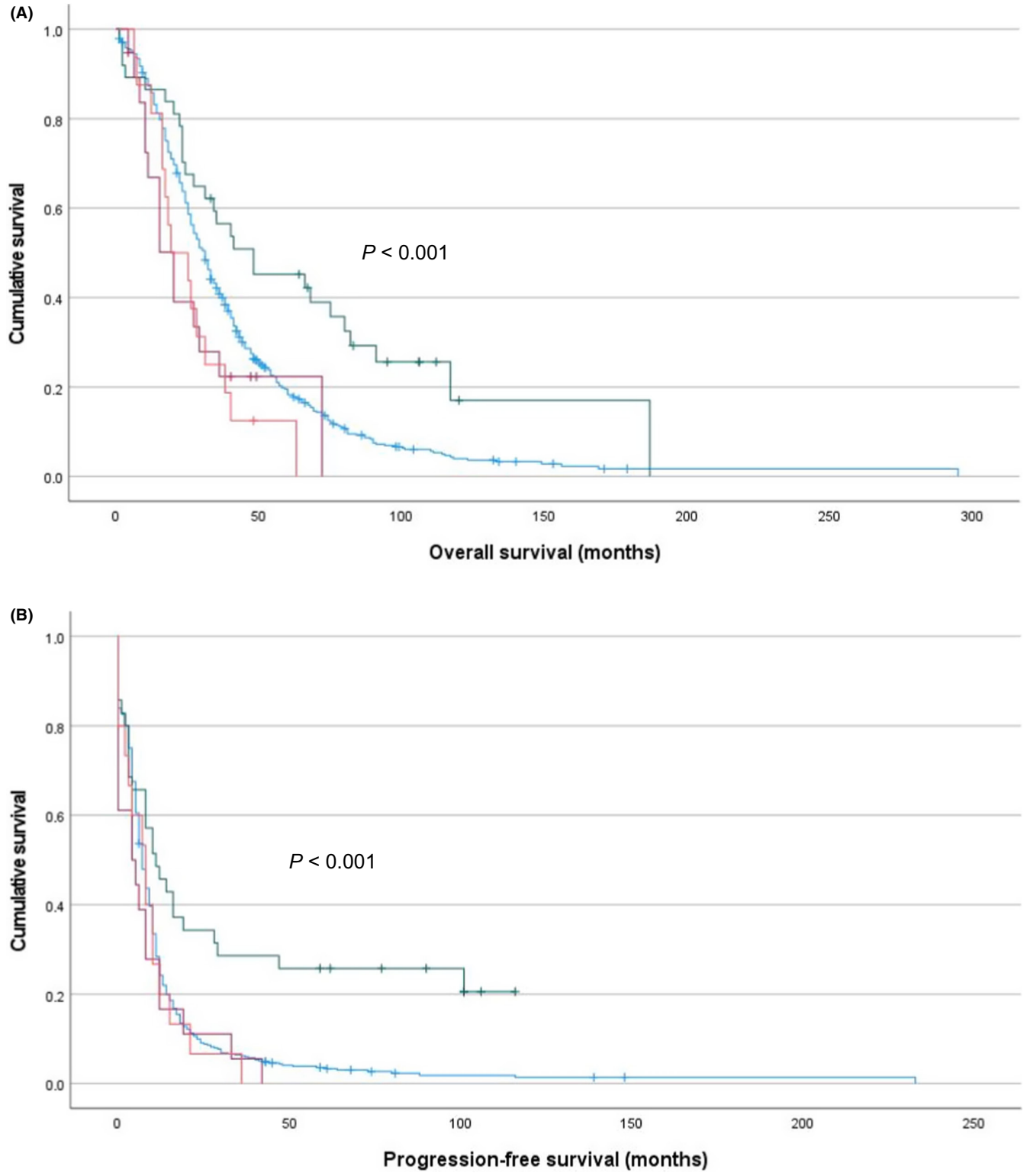


FIGURE 2 Histological type is associated with survival in tubo-ovarian carcinoma effusions. (A) Kaplan–Meier survival curve showing the association between effusion histotype and overall survival (OS; $n = 545$). Patients with carcinosarcoma (CS; $n = 16$; orange line) and clear cell carcinoma (CCC; $n = 19$; red line) had mean OS of 27 and 29 months, respectively, compared to 42 months for patients with high-grade serous carcinoma (HGSC; $n = 473$; blue line) and 70 months for patients with low-grade serous carcinoma (LGSC; $n = 37$; green line) ($P < 0.001$). (B) Kaplan–Meier survival curve showing the association between effusion histotype and progression-free survival (PFS; $n = 521$; 24 patients with no PFS data). Patients with CS ($n = 15$; orange line) and CCC ($n = 18$; red line) had mean PFS of 9 and 8 months, respectively, compared to 14 months for patients with HGSC ($n = 453$; blue line) and 36 months for patients with LGSC ($n = 35$; green line) ($P < 0.001$)

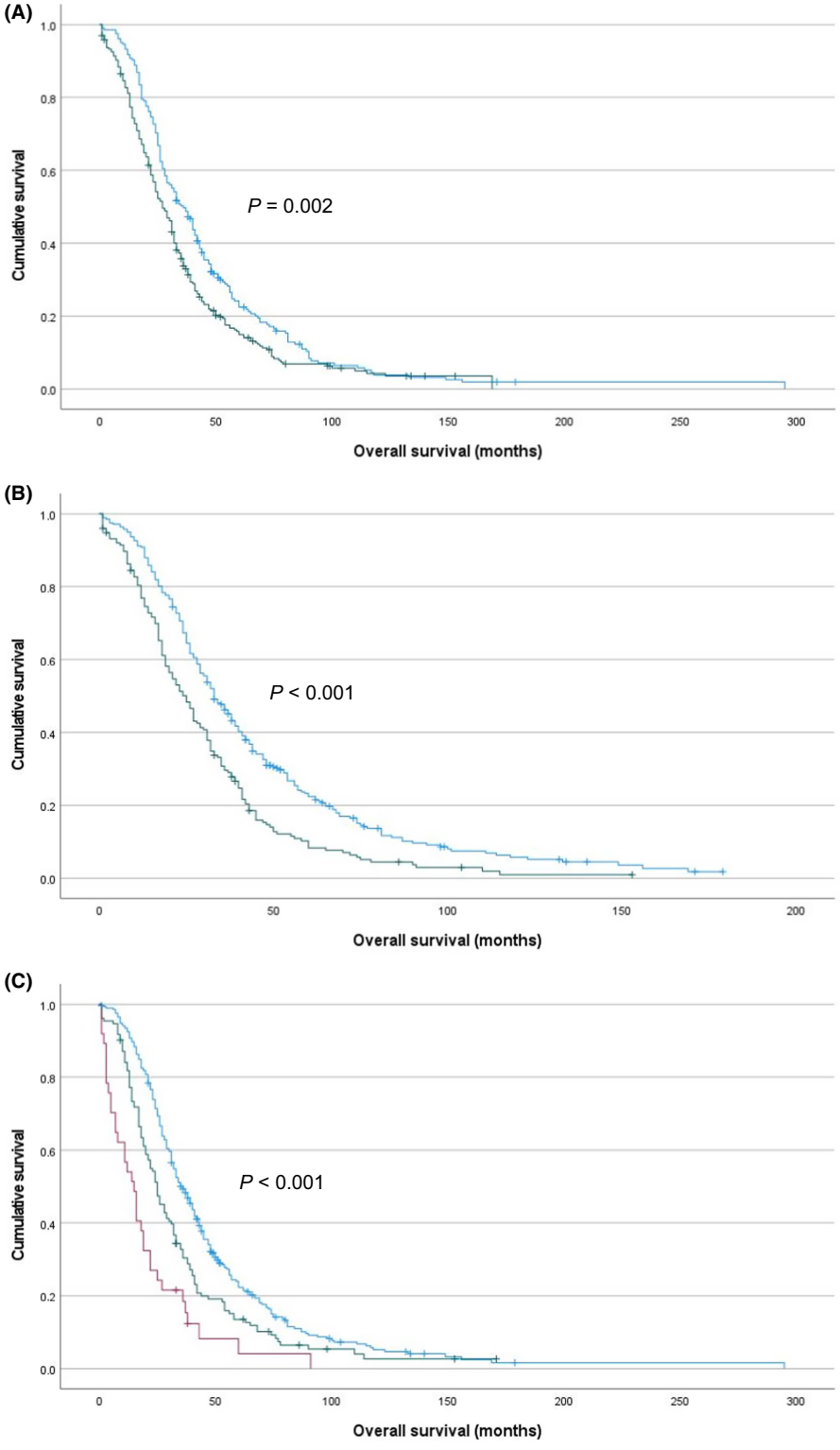
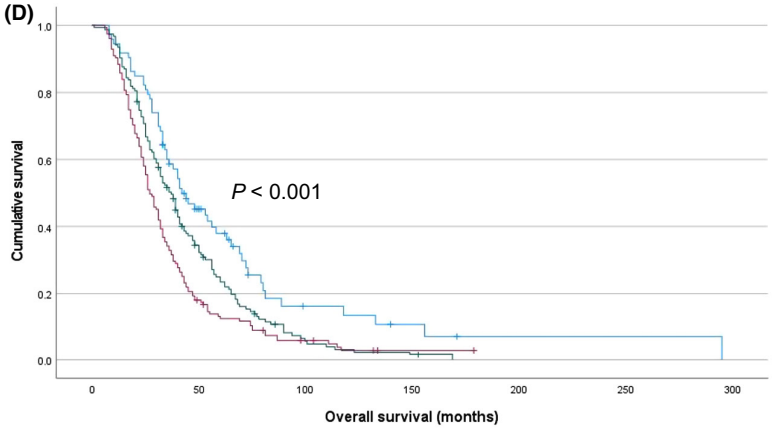
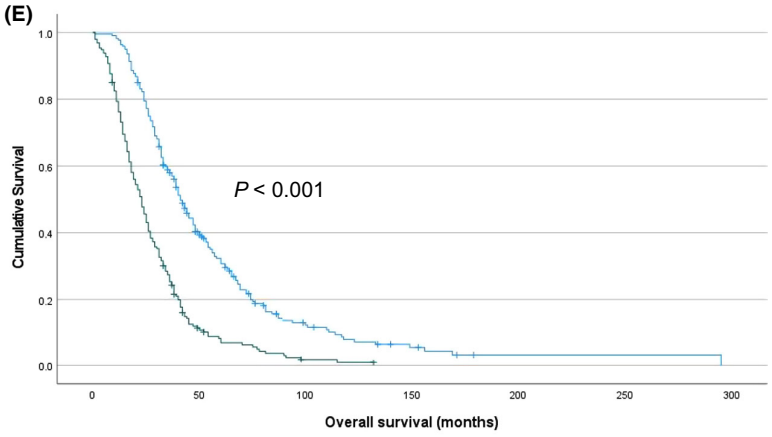


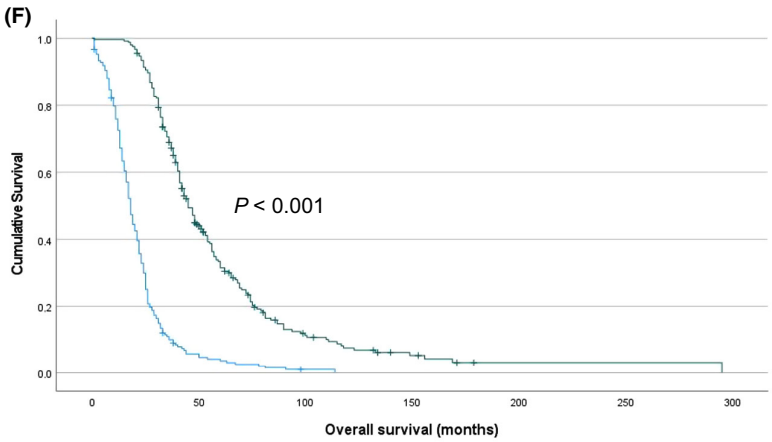
FIGURE 3 (Continued)

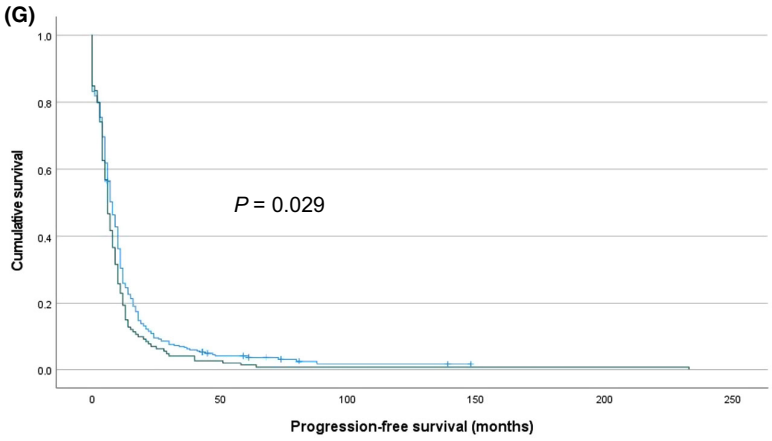
FIGO stage and primary platinum resistance emerging as independent prognosticators in multivariate analysis. Age, FIGO stage, and RD volume were also significantly related to PFS, with the latter retaining its significance in multivariate analysis.

It should be commented that response to first-line chemotherapy and primary platinum resistance are parameters that overlap to some extent, but not fully, in the present study, as reflected in different *P*-values in the statistical analysis. The reason for this difference is the fact that in analysis of response to first-line chemotherapy, patients were divided into those who had complete response vs all others. Thus, patients with partial response or stable disease and without primary platinum resistance would end up in the less favourable group









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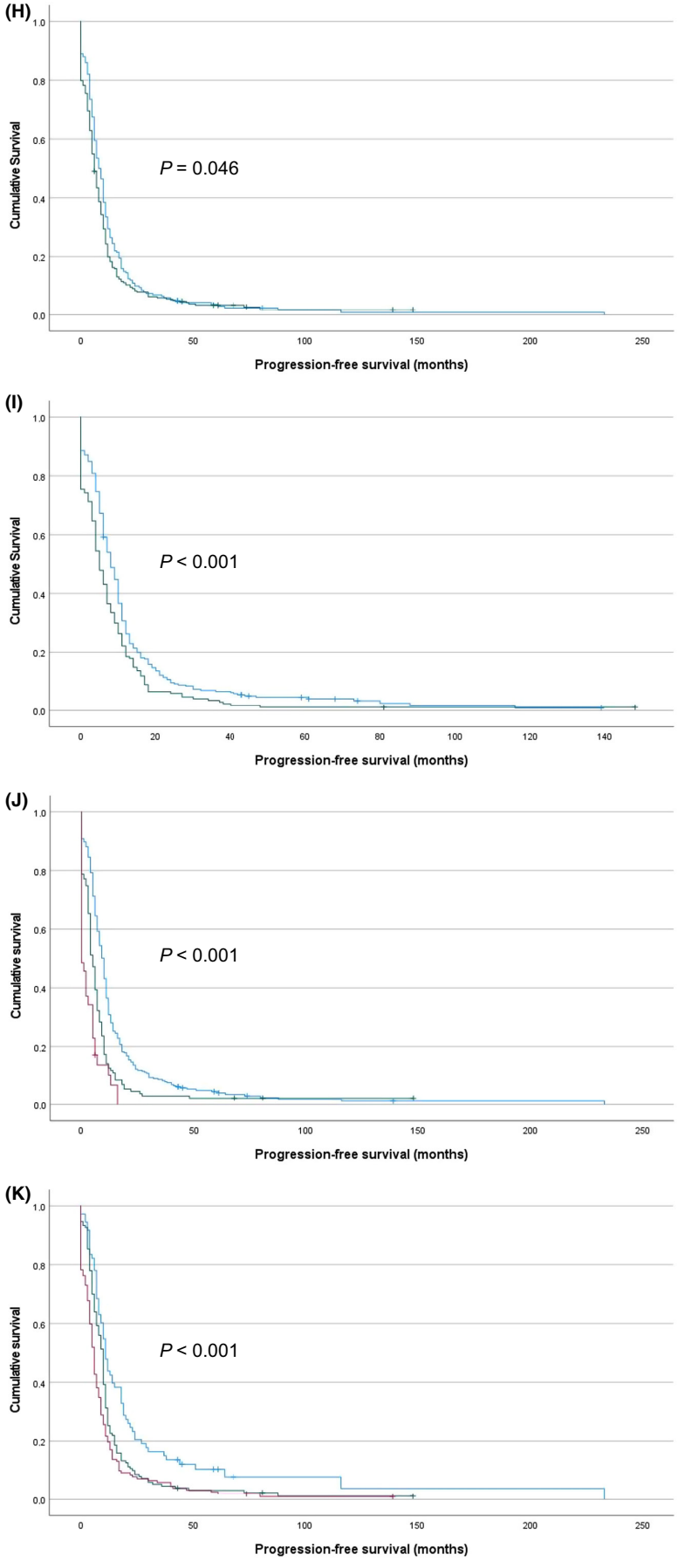

FIGURE 3 Legend on next page

FIGURE 3 Clinicopathological parameters associated with survival in the high-grade serous carcinomas (HGSC) effusion cohort ($n = 473$). (A) Kaplan–Meier survival curve showing the association between patient age and overall survival (OS). Patients aged >60 years at diagnosis ($n = 268$; green line) had mean OS of 37 months compared to 48 months for patients aged ≤60 years at diagnosis ($n = 205$, blue line; $P = 0.002$). (B) Kaplan–Meier survival curve showing the association between FIGO stage and OS. Patients with FIGO stage IV disease ($n = 175$; green line) had mean OS of 30 months compared to 45 months for patients with FIGO stage III disease ($n = 283$, blue line; $P < 0.001$). Fifteen patients with stage I-II disease or no data with respect to FIGO stage were excluded. (C) Kaplan–Meier survival curve showing the association between upfront treatment and OS. Patients who received upfront surgery ($n = 293$; blue line) had mean OS of 48 months compared to 34 months for patients who received neoadjuvant chemotherapy and were subsequently operated ($n = 132$, green line) and 20 months for patients who only received chemotherapy ($n = 37$; red line; $P < 0.001$). Eleven patients with missing data with respect to upfront therapy were excluded. (D) Kaplan–Meier survival curve showing the association between residual disease (RD) volume and OS for 383 patients with RD data. Patients debulked to no macroscopic disease ($n = 74$; blue line) had mean OS of 70 months compared to 45 and 37 months for patients debulked to ≤1 cm ($n = 154$; green line) or >1 cm ($n = 155$, red line; $P < 0.001$). (E) Kaplan–Meier survival curve showing the association between chemotherapy response and OS. Patients who had complete response at diagnosis ($n = 221$; blue line) had mean OS of 58 months compared to 28 months for patients with non-complete response ($n = 194$; green line; $P < 0.001$). Fifty-eight patients with no data were excluded. (F) Kaplan–Meier survival curve showing the association between primary platinum resistance and OS. Patients with primary platinum resistance ($n = 210$; blue line) had mean OS of 21 months compared to 62 months for patients with chemosensitive tumours ($n = 243$; green line; $P < 0.001$). Twenty patients with no data were excluded. (G) Kaplan–Meier survival curve showing the association between previous exposure to chemotherapy and progression-free survival (PFS; $n = 449$ patients; 4 patients with unknown chemotherapy history). Patients with chemo-naïve effusions ($n = 310$; blue line) had mean PFS of 13 months compared to 10 months for patients with post-chemotherapy effusions ($n = 139$, green line; $P = 0.029$). (H) Kaplan–Meier survival curve showing the association between patient age and PFS ($n = 453$ patients). Patients aged >60 years at diagnosis ($n = 253$; green line) had mean PFS of 12 months compared to 14 months for patients aged ≤60 years at diagnosis ($n = 200$, blue line; $P = 0.046$). (I) Kaplan–Meier survival curve showing the association between FIGO stage and PFS ($n = 439$ patients with stage III-IV disease). Patients with FIGO IV disease ($n = 167$; green line) had mean PFS of 9 months compared to 14 months for patients with FIGO III disease ($n = 272$, blue line; $P < 0.001$). (J) Kaplan–Meier survival curve showing the association between upfront treatment and PFS ($n = 447$ patients with available data). Patients who received upfront surgery ($n = 285$; blue line) had mean PFS of 16 months compared to 10 months for patients who received neoadjuvant chemotherapy and were subsequently operated ($n = 127$, green line) and 3 months for patients who only received chemotherapy ($n = 35$; red line; $P < 0.001$). (K) Kaplan–Meier survival curve showing the association between RD volume and PFS for 375 patients with available data. Patients debulked to no macroscopic disease ($n = 73$; blue line) had mean PFS of 27 months compared to 13 and 10 months for patients debulked to ≤1 cm ($n = 150$; green line) or >1 cm ($n = 152$, red line; $P < 0.001$)

TABLE 3 Univariate and multivariate survival analysis for patients with high-grade serous carcinomas (HGSC)

	Overall survival		Progression-free survival	
Parameter	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**
Effusion site	$P = 0.195$	$P = 0.674$	$P = 0.108$	$P = 0.716$
Previous chemotherapy	$P = 0.25$	NP	**$P = 0.029$**	**$P < 0.001$**
CA 125 at diagnosis	$P = 0.923$	NP	$P = 0.869$	NP
Age	**$P = 0.002$**	$P = 0.869$	**$P = 0.046$**	$P = 0.906$
FIGO stage	**$P < 0.001$**	**$P = 0.002$**	**$P < 0.001$**	$P = 0.164$
Upfront surgery	**$P < 0.001$**	$P = 0.870$	**$P < 0.001$**	**$P < 0.001$**
Residual disease	**$P < 0.001$**	$P = 0.274$	**$P < 0.001$**	**$P < 0.001$**
Chemotherapy response	**$P < 0.001$**	$P = 0.453$	NP	NP
Primary platinum resistance	**$P < 0.001$**	**$P < 0.001$**	NP	NP

Note: Clinicopathological parameters were grouped as follows: age—≤60 vs. >60 years; effusion site—peritoneal vs. pleural; FIGO stage—III vs. IV; chemotherapy status—pre- vs. post-chemotherapy specimens; residual disease (RD)—0 cm vs. ≤1 cm vs. >1 cm; response to chemotherapy—complete response vs. partial response/stable disease/progressive disease.

Abbreviation: NP, not performed.

Bold values are statistically significant(<0.05).

in the former analysis, but not in the latter. Similarly, the minority of patients with complete response to first-line chemotherapy and progression within 6 months would end up in opposite groups, ie favourable in first-line chemotherapy response, but platinum resistant.

As in previous studies using part of this cohort, effusion site, ie peritoneal vs pleural, and CA 125 levels at diagnosis were unrelated to OS or PFS. The former finding may appear to be discrepant from the association between FIGO stage and outcome, but is in fact unrelated to it, as some of the patients tapped for ascites were diagnosed with stage IV disease. Less conclusive was the difference between the patient group with chemo-naïve effusions and patients with post-chemotherapy effusions, the majority

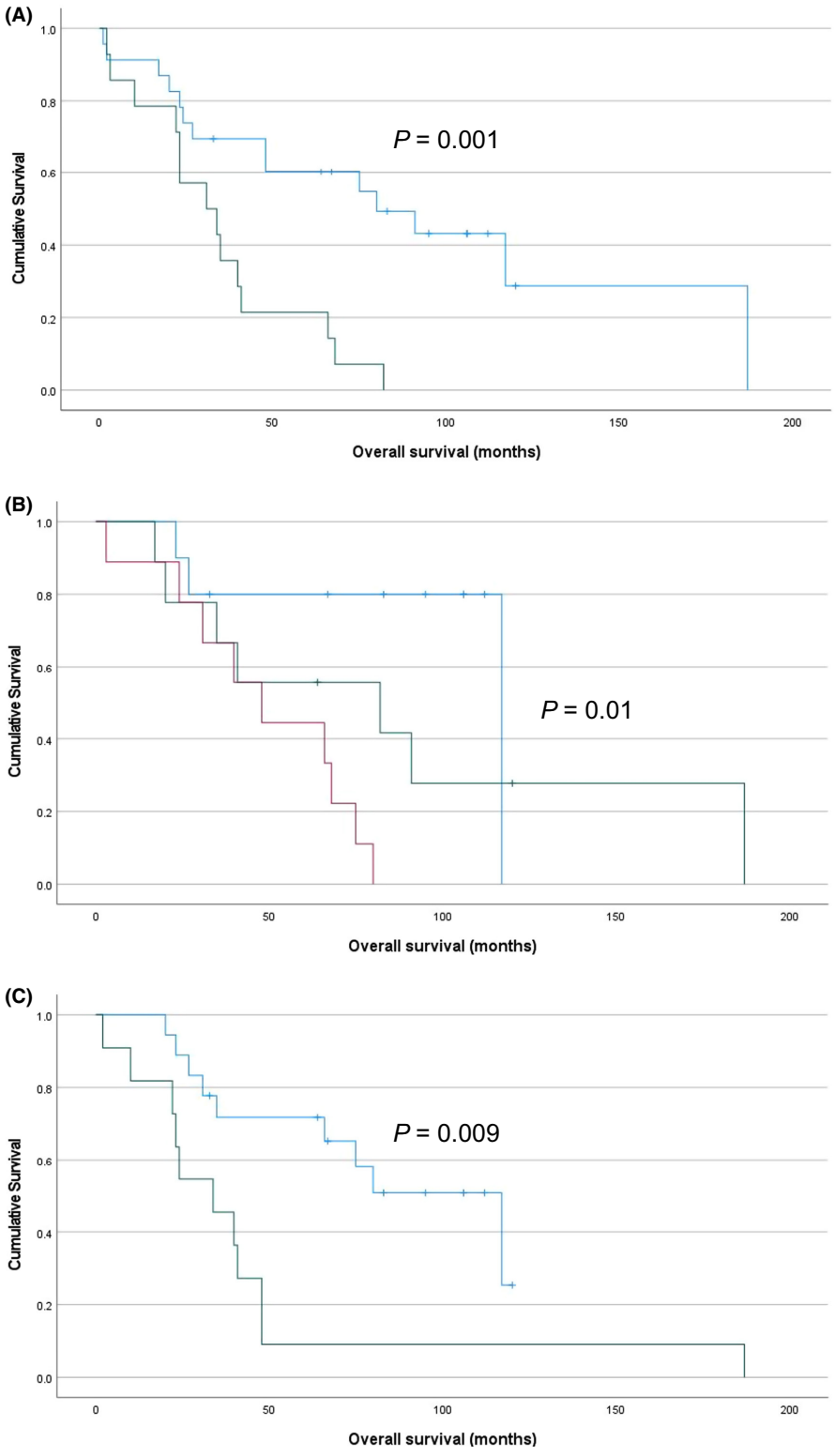

FIGURE 4 (Continued)

of the latter being disease recurrence specimens. Previous chemotherapy was unrelated to OS, but was associated with shorter PFS, including in multivariate Cox analysis. One may speculate that this difference may owe to the fact that some patients with post-chemotherapy effusions have progression under first-line chemotherapy, and may consequently represent a patient group with PFS = 0 months, measured from the completion of first-line chemotherapy.

Finally, a somewhat unexpected finding was the strong association between upfront surgery and longer OS and PFS in the HGSC cohort, which was an independent prognosticator for the latter in multivariate analysis. The benefit of primary debulking surgery

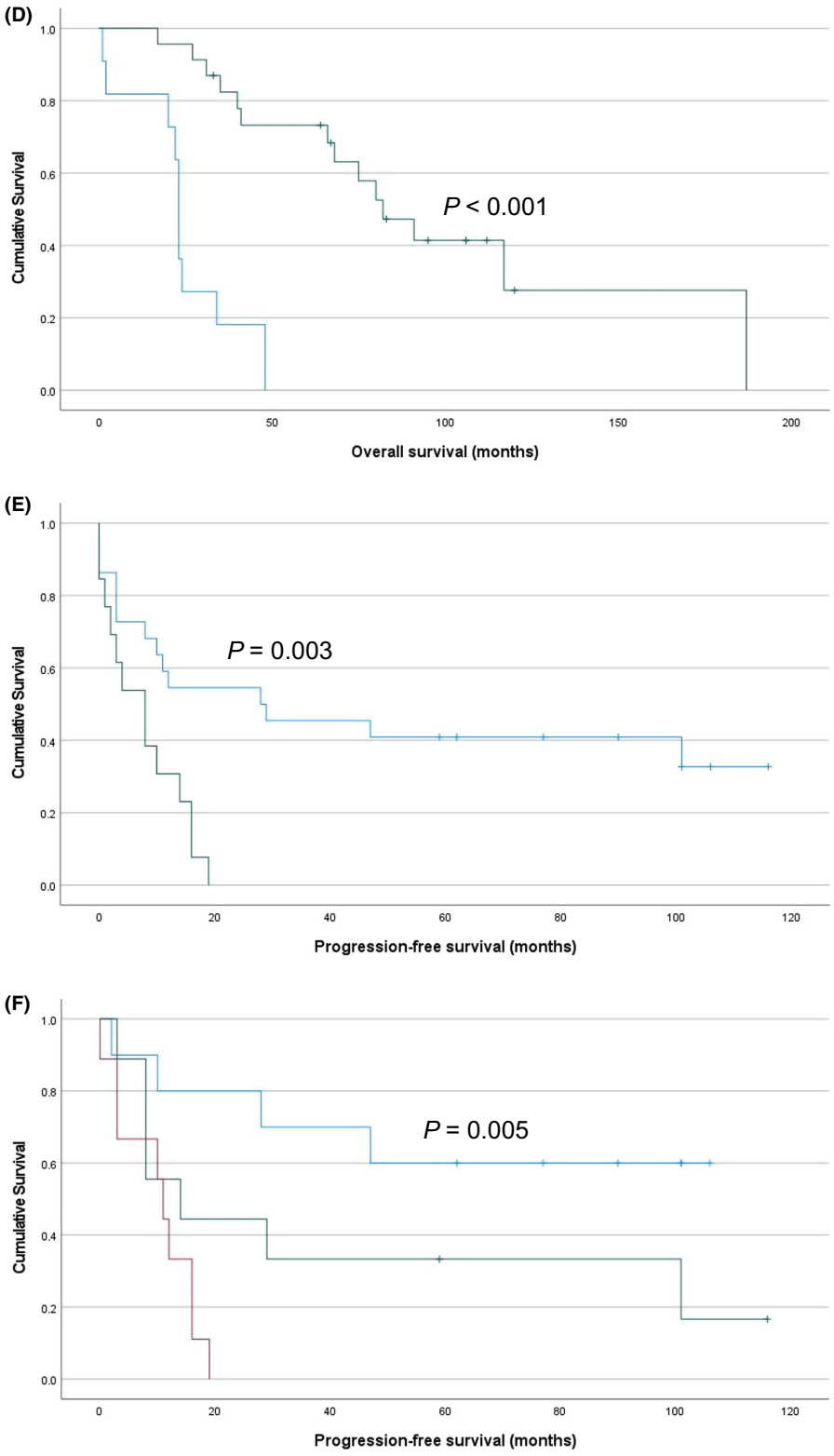

FIGURE 4 Legend on next page

(PDS) vs neoadjuvant chemotherapy (NACT) has long been debated, with evidence suggesting both approaches are valid.[14] In a recent Cochrane database review, survival results for PDS and NACT were comparable,[15] although difficulties in comparing studies from institutions in different countries were emphasised in another paper, among other reasons, due to the different extent of debulking in various centers.[16] As discussed above, the majority of studies in this area have included patients with tumours of different histotype, whereas our analysis focused exclusively on HGSC. It is possible that PDS is critical in this patient group more than it is in

FIGURE 4 Clinicopathological parameters associated with survival in the LGSC effusion cohort ($n = 37$). (A) Kaplan–Meier survival curve showing the association between patient age and overall survival (OS). Patients aged >60 years at diagnosis ($n = 14$; green line) had mean OS of 34 months compared to 94 months for patients aged ≤60 years at diagnosis ($n = 23$, blue line; $P = 0.001$). (B) Kaplan–Meier survival curve showing the association between residual disease (RD) volume and OS. Patients debulked to no macroscopic disease ($n = 10$; blue line) had mean OS of 99 months compared to 86 and 48 months for patients debulked to ≤1 cm ($n = 9$; green line) or >1 cm ($n = 9$, red line; $P < 0.001$). (C) Kaplan–Meier survival curve showing the association between chemotherapy response and OS for 29 patients with available data. Patients who had complete response at diagnosis ($n = 18$; blue line) had mean OS of 83 months compared to 44 months for patients with non-complete response ($n = 11$; green line; $P = 0.009$). (D) Kaplan–Meier survival curve showing the association between primary platinum resistance and OS for 34 patients with available data. Patients with primary platinum resistance ($n = 11$; blue line) had mean OS of 24 months compared to 101 months for patients with chemosensitive tumours ($n = 23$; green line; $P < 0.001$). (E) Kaplan–Meier survival curve showing the association between patient age and PFS ($n = 35$ patients). Patients aged >60 years at diagnosis ($n = 13$; green line) had mean PFS of 8 months compared to 53 months for patients aged ≤60 years at diagnosis ($n = 22$, blue line; $P = 0.003$). (F) Kaplan–Meier survival curve showing the association between RD volume and PFS for 28 patients with available data. Patients debulked to no macroscopic disease ($n = 10$; blue line) had mean PFS of 72 months compared to 44 and 10 months for patients debulked to ≤1 cm ($n = 9$; green line) or >1 cm ($n = 9$, red line; $P = 0.005$)

TABLE 4 Univariate and multivariate survival analysis for patients with LGSC

	Overall survival		Progression-free survival	
Parameter	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**
Effusion site	$P = 0.509$	NP	$P = 0.893$	NP
Previous chemotherapy	$P = 0.728$	NP	$P = 0.167$	$P = 0.456$
CA 125 at diagnosis	$P = 0.474$	NP	$P = 0.969$	NP
Age	**$P = 0.001$**	**$P = 0.019$**	**$P = 0.003$**	$P = 0.341$
FIGO stage	$P = 0.056$	**$P = 0.021$**	$P = 0.064$	$P = 0.075$
Residual disease	**$P = 0.01$**	$P = 0.099$	**$P = 0.005$**	**$P = 0.046$**
Chemotherapy response	**$P = 0.009$**	**$P = 0.043$**	NP	NP
Primary platinum resistance	**$P < 0.001$**	**$P < 0.001$**	NP	NP

Note: Clinicopathological parameters were grouped as follows: age—≤60 vs. >60 years; effusion site—peritoneal vs. pleural; FIGO stage—III vs. IV; chemotherapy status—pre- vs. post-chemotherapy specimens; residual disease (RD)—0 cm vs. ≤1 cm vs. >1 cm; response to chemotherapy—complete response vs. partial response/stable disease/progressive disease.
Abbreviation: NP, not performed.

slower-growing tumours, such as LGSC, in which debulking to no macroscopic disease may be less decisive, though excluding other causes, eg the better general condition of patients undergoing PDS, cannot be excluded.

The number of patients diagnosed with LGSC in our cohort was substantially lower than those diagnosed with HGSC. Nevertheless, series size, at 37 patients, was deemed sufficient for statistical analysis, more so in view of the dearth of data regarding patients with LGSC effusions. Notably, results were by and large similar to those observed for HGSC.

As in HGSC, age, RD volume, and response to first-line chemotherapy were significantly related to OS in LGSC patients, with age and response to first-line chemotherapy emerging as independent prognosticators in multivariate analysis. Although the association with FIGO stage was marginal in univariate analysis, possibly due to the smaller number of cases, this parameter became significant in multivariate analysis. Effusion site, previous chemotherapy, and CA 125 levels at diagnosis were again unrelated to OS. Older age and larger RD were additionally associated with shorter PFS, the latter being an independent prognosticator in Cox multivariate analysis.

In conclusion, analysis of a large cohort of patients with tubo-ovarian carcinoma and malignant effusion showed a predominance of serous carcinomas, particularly HGSC, and an almost uniformly fatal outcome, in this patient group, with shortest survival for patients with CCC and CS. Established clinical parameters informative of outcome are valid in the HGSC and LGSC groups, with PDS being superior to NACT.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

BD: Designed the study, performed the statistical analysis and wrote the manuscript. MBE: Provided the clinical data, critically read the manuscript.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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