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Serous ovarian and primary peritoneal cancers: A comparative analysis of clinico-pathological features, molecular subtypes and treatment outcome

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HIGHLIGHTS

- Primary peritoneal patients were older than patients with ovarian cancer.
- They were more likely treated with neoadjuvant chemotherapy and interval debulking.
- They had better debulking rates but inferior survival after neoadjuvant chemotherapy.
- Most clustered with the C1 subtype, with high stromal response and inferior survival.

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ABSTRACT

Objective. Primary peritoneal cancer is rare and considered equivalent to stage III/IV ovarian cancer, but questions remain concerning its underlying biology, prognosis and optimal management.

Methods. Clinico-pathological and treatment details of primary peritoneal (n = 120) and ovarian cancer (n = 635) were obtained on women recruited to the Australian Ovarian Cancer Study. Log-rank test was used to compare survival and cox proportional hazards models were fitted to obtain hazard ratios and 95% confidence intervals, both unadjusted and adjusted for age, grade, FIGO stage, residual disease and treatment with neoadjuvant chemotherapy. Molecular subtype was determined by gene expression profiling using published data.

Results. Compared with advanced serous ovarian cancer, primary peritoneal cancer patients were older (mean age 65.5 vs. 60.2 years, $p < 0.001$), more often treated with neoadjuvant chemotherapy (38.4% vs. 11.4%, $p < 0.001$). Gene expression profiling classified a substantially higher proportion of primary peritoneal carcinomas as C1 (mesenchymal, reactive stromal infiltration) subtype (70.6% vs. 32.1%, $p = 0.029$), which was associated with lower complete surgical resection rate. Women with primary peritoneal cancer had significantly shorter progression-free (11.6 vs. 13.6 months, $p = 0.007$) and overall survival (31.7 vs. 39.8 months, $p = 0.012$). In multivariate analysis, residual disease and neoadjuvant chemotherapy were both independently associated with increased risk of progression and death.

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Conclusions. Primary peritoneal cancer patients were more frequently treated with neoadjuvant chemotherapy and had inferior survival. Different tumor biology characterized by activated stromal fibrosis in primary peritoneal cancer may underlie the differences in treatment and clinical outcome.

1. Introduction

Primary peritoneal cancer was first reported in 1959 [1]. The diagnosis denotes the diffuse involvement of abdominal peritoneal surfaces by carcinoma that is histologically identical to carcinoma of ovary, in the absence of a demonstrable primary ovarian tumor. Its incidence is considerably lower compared to epithelial ovarian cancer [2] and increased awareness may be responsible for the relative increase in its incidence. Primary peritoneal cancer has been reported not only in women with their ovaries *in situ*, but also in women carrying a germline *BRCA* mutation after prophylactic oophorectomy [3]. In some cases primary peritoneal cancer occurred decades after the procedure. Isolated cases have also been reported in males [4].

At present the origin of primary peritoneal and ovarian cancer is still debated. Increasing evidence suggests that a substantial proportion of ovarian serous cancer cases arise from precursor lesions located in the fallopian tubal epithelium (FTE) [5–7]. This view is supported by the finding of precursor lesions, namely serous tubal intraepithelial carcinoma (STIC), in fallopian tubes of both women with *BRCA* mutations after prophylactic surgery [8,9] and in patients with disseminated high-grade serous carcinoma (HGSC) [5,10]. These putative early lesions share the same morphologic, immunophenotypic features and *TP53* mutation as HGSC [11,12]. Perets *et al.* have successfully developed a genetically engineered mouse model of *de novo* HGSC that originates in fallopian tubal secretory epithelial cells [7]. This model not only recapitulated the key genetic alterations of human invasive ovarian cancer but also offered mechanistic insight into the origin and pathogenesis of HGSC. Intriguingly, removal of the ovary in this mouse model reduced peritoneal spread, suggesting that the ovary provides a permissive environment that facilitates metastasis, potentially via a mechanism involving ovarian hormone action. So while there is increasing evidence that both ovarian and primary peritoneal carcinomas may arise from a common precursor lesion in the fimbrial end of the fallopian tube, it is not clear why some would preferentially metastasize to the peritoneum and whether this represents a differing underlying biology in primary peritoneal carcinomas.

Epidemiologic risk factors appear to differ between the two diseases [13–15]. Women with peritoneal cancer have been reported to be significantly older compared to ovarian cancer patients [13,14]. While parity reduced the risk of serous ovarian cancer, it increased the risk of primary peritoneal cancer [13,14] although reports on the association have been conflicting [2,15]. Use of contraception, which also leads to anovulation, has consistently been reported to reduce the risk of both ovarian and primary peritoneal carcinoma [13].

Gene expression profiling of serous and endometrioid ovarian, primary peritoneal and fallopian tube cancer, has revealed six molecular subtypes with distinct differences in survival [16]. Subtypes C3 and C6 were predominantly low-grade/borderline serous tumors and early-stage endometrioid tumors, respectively, while the vast majority of HGSC segregated with four subtypes (C1, C2, C4, C5), first shown by Tothill et al. [16], and robustly identified in multiple independent datasets, with consistent clinical associations [17–19]. The C1 subtype (mesenchymal) is characterized by desmoplasia, extensive myofibroblast infiltration, an epithelial–mesenchymal gene expression signature, and is associated with poor survival. C2 subtype (immunoreactive) tumors are characterized by extensive intratumoral T-cell infiltration and generally have a more favorable prognosis. Patients with a C4 subtype (differentiated) have an intermediate outcome and C5 subtype (proliferative) tumors have low expression of differentiation markers, including CA125, limited inflammatory infiltration, and a similarly poor outcome to C1 subtype [16].

Studies of clinical outcome of ovarian and peritoneal cancer patients have produced conflicting results with survival times being better [20], similar [21–24] or worse compared to patients with advanced ovarian serous carcinoma [25–28]. However most of these studies were small and encompassed a wide spectrum of time periods, imaging technologies, chemotherapeutic regimens and surgical techniques.

To better understand primary peritoneal carcinoma, we conducted a large, multicenter, comparative review of clinico-pathological and treatment data of primary peritoneal and ovarian cancer cases, identified in the prospective population-based Australian Ovarian Cancer Study (AOCS).

2. Methods

2.1. Patient cohort

AOCS is an Australian-wide population-based case-control study. From January 2002 to June 2005, 1859 eligible patients were recruited through an existing network of Gynecologic Oncologists, covering >85% of the Australian population [16]. Cases recorded in the database were identified as potentially primary peritoneal carcinomas based on the initial diagnostic pathology report (n = 208). All histopathology reports were re-reviewed and the Gynecologic Oncology Group (GOG) criteria for primary peritoneal carcinoma were applied as described by Bloss et al. [23]: (i) either ovary must be normal in size (≤4.0 cm) or enlarged by a benign process; (ii) the involvement in the extra-ovarian sites was greater than the involvement on the surface of either ovary and (iii) microscopically, the ovaries were either not involved with tumor or exhibited only serosal or cortical implants <5 mm in depth. According to these criteria, the diagnosis of primary peritoneal carcinoma was confirmed in 127 cases. A complete set of diagnostic H&E stained slides of 97 (76%) cases were available for review by a Gynecological oncology pathologist (LA) and seven additional cases were excluded after the identification of cortical implants ≥5 mm in the ovaries. Of these, 85 cases had sections of fallopian tube available for review to determine the extent of involvement of the fallopian tube and the presence of serous tubal intraepithelial carcinoma (STIC). A total of 120 confirmed primary peritoneal cancer cases were included in the final analysis. Cases of primary ovarian cancer (n = 635) from AOCS, which had undergone centralized pathology review of diagnostic pathology slides by a panel of Gynecological Oncology pathologists at the time of analysis were used for comparison. A planned subset analysis on women with advanced stage (stage III/IV), serous primary peritoneal (n = 112) and ovarian carcinoma (n = 369) was performed to compare clinico-pathological characteristics and clinical outcome.

2.2. Clinical variables

Clinical variables were extracted from medical records and made available from the AOCS database. Histopathological grade was described using a 3-tier system, Grade 1, 2 or 3, corresponding to well, moderately and poorly differentiated tumors [29]. Surgical stage was assessed in accordance with the International Federation of Gynecology and Obstetrics (FIGO) classification. For this analysis, residual disease

after primary surgical debulking was categorized as 'no macroscopic residual disease' and 'macroscopic residual disease of any size'.

Progression-free survival (PFS) was defined as the time interval between the date of first histologic diagnosis and the date of disease recurrence or progression, based on Gynecological Cancer Intergroup (GCIG) criteria, incorporating RECIST 1.1 and serum CA125 measurements [30], global deterioration in health status attributable to the disease, or death, as previously described [31]. Overall survival (OS) was defined as the time interval between the dates of first histologic diagnosis and death from any cause.

2.3. Gene expression profiling

Molecular profiling results of 18 primary peritoneal and 82 ovarian cancers, obtained on the Affymetrix U133 plus2 platform, have been published previously and are available on GEO (GSE9891) [16]. In brief, whole tumor gene expression profiling was conducted on 285 serous and endometrioid tumors of the ovary, peritoneum and fallopian tube. Gene expression data was filtered and clustered using a consensus k-mean method, which identified six molecular subtypes (C1–C6) associated with survival.

2.4. Statistical analysis

Descriptive statistics were used to describe the cohort as a whole and patients with stage III and IV serous carcinoma in a pre-planned subgroup analysis. We calculated median and ranges for continuous variables, and proportions for categorical variables. Crude differences in proportions between groups were assessed by the Chi-square test. Differences in means were assessed by the Student's *t*-test. Time-to-event analyses were conducted in patients with stage III and IV serous carcinoma only. The Kaplan-Meier product limit method was used to estimate and plot progression-free and overall survival probabilities. The log-rank test was used to compare survivals between the groups. Cox proportional hazards models were fitted to obtain hazard ratios (HR) and 95% confidence intervals (95% CI) of the association between disease entity and risk of progression or death, both unadjusted and adjusted for the effects of age as a continuous variable, grade, FIGO stage and residual disease as categorized above and of treatment with neoadjuvant chemotherapy. Statistical tests and *P* values were two tailed and statistical significances were assessed at the conventional level of <0.05. Statistical analyses were done using IBM SPSS (version 23).

2.5. Ethics

AOCS was approved by the Human Research Ethics Committees at the Peter MacCallum Cancer Centre, University of Melbourne, the Queensland Institute of Medical Research, Westmead Hospital, and all other participating hospitals and cancer registries and participants provided written informed consent.

3. Results

We identified 120 women with a diagnosis of primary peritoneal carcinoma from AOCS, following review of anatomical pathology reports and application of GOG criteria as described by Bloss *et al.* [23]. Women with primary peritoneal carcinoma were significantly older than women with ovarian cancer (mean age of 65.4 vs. 60.1, $p < 0.001$). Almost all were diagnosed as serous subtype (n = 115, 96%) and had FIGO stage III/IV disease (n = 117, 98%). By contrast, only 420 (66%) of the ovarian carcinomas from the same population-based cohort were classified as serous, and 464 (75.0% of the cases with known stage) were diagnosed with FIGO stage III/IV disease.

Pathology review of diagnostic H&E stained slides was done on primary peritoneal cases to determine the extent of involvement of the fallopian tube and the presence of serous tubal intraepithelial carcinoma (STIC). The median number of sections of fallopian tubes available for review was 5 per case (ranges 1–29). Most cases reviewed had tumor involvement of the fallopian tubes (57/85, 67.1%), with tumor cells located on the serosal surface (n = 31, 36.4%), in the lumen (n = 46, 54.1%), and in the fallopian tube wall (n = 20, 23.5%). STIC lesions were preferentially seen in sections containing the fimbriae end of fallopian tube and were present in 14 cases (16.5%). There was no statistically significant difference in the number of sections of fallopian tubes available for review and the presence of STIC lesions using independent samples median test ($p = 0.836$).

3.1. Comparative analysis of patients with stage III/IV cancers of serous histology

We compared baseline characteristics, treatment details and survival in the subgroup of patients with stage III/IV cancers of serous histology (Table 1). We found patients with primary peritoneal cancer were significantly older at diagnosis than women with ovarian cancer (mean age 65.5 vs. 60.2, $p < 0.001$). There was no statistically significant difference in the frequency of *BRCA1 or BRCA2* germ-line mutations between primary peritoneal cancer and ovarian cancer (Table 1, *BRCA* mutation data from Alsop et al. [32]).

The majority of patients received adjuvant chemotherapy and there was no difference in the number of lines of systemic treatments received, including chemotherapy and/or endocrine therapy between the two entities. Women with primary peritoneal cancer were more likely to receive neoadjuvant chemotherapy, followed by interval debulking, compared with ovarian cancer patients (38.4% vs 11.4%, $p < 0.001$) (Table 1). There was no significant difference in complete surgical debulking rate (19.6% vs. 24.1%, nil macroscopic residual disease, $p = 0.276$) (Table 1), but there was a trend of less favorable complete surgical resection in the subgroup of primary peritoneal patients who were treated with upfront surgical debulking (14.5% vs. 23.2%, $p = 0.102$) (Table 2). The complete resection rate for peritoneal cancer

Table 1
Clinico-pathologic characteristics of advanced (stage III or IV), serous, primary peritoneal and ovarian cancer.

	Primary peritoneal cancer	Ovarian cancer	p[a]
	n = 112	n = 369	
Mean age	65.5	60.2	<0.001
Grade[b]			0.796
1	5 (7.2%)	22 (6.7%)	
2	15 (21.7%)	65 (19.9%)	
3	45 (65.2%)	239 (73.1%)	
Unknown	4 (5.8%)	1 (0.3%)	
Stage			0.146
III	92 (82.1%)	323 (87.5%)	
IV	20 (17.9%)	46 (12.5%)	
BRCA germ-line mutation			0.500
Negative	69 (61.6%)	247 (66.9%)	
BRCA1	9 (8.0%)	29 (7.9%)	
BRCA2	8 (7.1%)	17 (4.6%)	
Unknown	26 (23.2%)	76 (20.6%)	
Residual disease			0.276
Nil macroscopic	22 (19.6%)	89 (24.1%)	
Macroscopic, any size	87 (77.7%)	263 (71.3%)	
Unknown	3 (2.7%)	17 (4.6%)	
Chemotherapy			0.068
Yes	106 (94.6%)	363 (98.4%)	
No	6 (5.4%)	6 (1.6%)	
Neoadjuvant chemotherapy			<0.001
Yes	43 (38.4%)	42 (11.4%)	
No	69 (61.6%)	327 (88.6%)	
Lines of systemic therapy			0.247
Mean (range)	3 (1 − 10)	3 (1 – 14)	

[a] *p*-Values are based on Pearson Chi-Square test for significant differences in frequency between groups, excluding unknown cases.
[b] Grade was only included for analysis for tumors removed at primary surgery, neoadjuvant cases were excluded.

Table 2
Complete surgical resection rate (nil macroscopic residual disease) following debulking surgery in women with stage III or IV, serous, primary peritoneal and ovarian cancer treated with adjuvant or neoadjuvant chemotherapy.

	Primary peritoneal cancer n (%)	Ovarian cancer n (%)	*p*
Primary surgery and adjuvant chemotherapy	10/69 (14.5%)	76/327 (23.2%)	0.102[a]
Neoadjuvant chemotherapy and interval debulking surgery	12/43 (27.9%)	13/42 (31.0%)	0.531[a]
p	0.049[b]	0.145[b]	

p-Values are based on Pearson Chi-Square test for significant differences in frequency between groups.
[a] Comparison of complete surgical resection rates between primary peritoneal and ovarian cancer.
[b] Comparison of complete surgical resection rates between adjuvant and neoadjuvant chemotherapy groups.

patients was significantly higher after neoadjuvant chemotherapy (27.9% vs 14.5% $p = 0.049$) and there were higher rates of complete resection in ovarian cancer patients (31.0% vs 23.2%, $p = 0.145$), but this did not reach statistical significance (Table 2).

The distribution of microarray gene expression subtype [16] differed significantly between advanced stage, serous primary peritoneal cancer and primary ovarian cancer ($p = 0.029$). The majority of primary peritoneal carcinoma cases (70.6%, 12/17) segregated with subtype C1 compared with only 32.1% (25/78) of ovarian tumors (Fig. 1). In an exploratory analysis, patients with a C1 tumor subtype, regardless of their classification as primary peritoneal or ovarian cancer, had much lower complete surgical debulking rate (5.4%), compared to 23.1% complete debulking rate in all advanced stage serous cancer patients.

After a median follow-up time of 72.9 months, 99 (88.4%) patients with advanced serous primary peritoneal cancer and 313 (84.8%) with advanced serous ovarian cancer had relapsed. The median PFS for patients with primary peritoneal cancer was significantly shorter compared to ovarian cancer patients with 11.6 months (95% CI, 10.2–12.9 months) and 13.6 months (95% CI, 12.6–14.6 months) ($p = 0.007$), respectively (Fig. 2). The median OS in primary peritoneal cancer was 31.7 months (95% CI, 24.2–39.3 months) vs 39.8 months (95% CI, 34.1–45.4 months) ($p = 0.012$) in ovarian cancer patients (Fig. 2). Despite the higher rate of complete resection (Table 2), women in both cohorts had significantly shorter PFS and OS in both cohorts after neoadjuvant chemotherapy (Fig. 3).

In unadjusted Cox regression analysis, women with advanced serous primary peritoneal cancer had increased risk of disease progression (HR = 1.365, 95% CI 1.008–1.712, $p = 0.007$) and death (HR = 1.369, 95% CI 1.073–1.746, $p = 0.012$) compared with women with advanced, serous primary ovarian cancer. In addition, patient age, residual disease after debulking surgery, tumor grade, stage (IV vs III) and treatment with neoadjuvant chemotherapy were significantly associated with increased risk of progression and death (data not shown). In the multivariable Cox regression analysis (Table 3), residual disease after debulking surgery and neoadjuvant chemotherapy remained significantly associated with increased risk of disease progression and death.

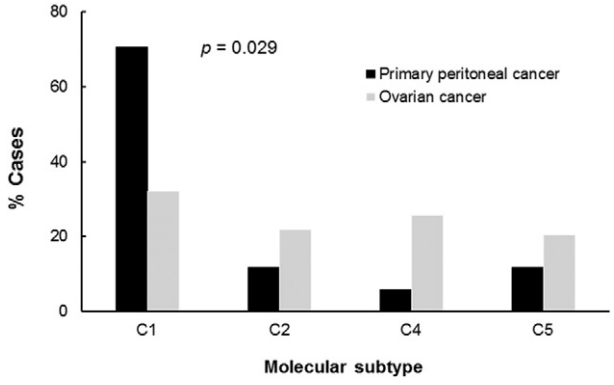

Fig. 1. Distribution of molecular, gene expression array subtypes in advanced stage, serous primary peritoneal cancer and ovarian cancer. Molecular subtype was determined by gene expression array profiling (available on GEO (GSE9891)) and difference in proportions between groups was assessed by using the Chi-square test.

4. Discussion

This study is an analysis of one of the largest prospectively recruited cohort studies of women with primary peritoneal carcinoma reported to date. The diagnosis of primary peritoneal cancer in this study was based on central review of pathological reports and diagnostic slides, and the application of stringent GOG criteria [23]. Compared with ovarian cancer cases from the same study, we confirmed patients with peritoneal cancer to be older at diagnosis, consistent with previous studies [13,14], their tumors more likely to be serous subtype and most presented at advanced stage. Gene expression profiling classified a substantially higher proportion of the advanced serous peritoneal cancers as C1 (mesenchymal) subtype. Patients with peritoneal cancer were more often treated with neoadjuvant chemotherapy and had less favorable complete resection rates and inferior survival.

Review of fallopian tube histopathology in our cohort revealed the presence of STIC lesions in some primary peritoneal cancer cases, suggesting that at least a proportion of cases may arise in the tube. There was preferential involvement of the fimbriae of the fallopian tubes in keeping with previous observations in ovarian cancer [33]. Although the cases with synchronous STIC lesions are likely to be underestimated in our study as the number of fallopian tube sections available for central pathological review was limited in some cases, some primary peritoneal cancer may still arise from peritoneum. Sectioning and extensively examining the fimbriae of the fallopian tube should be considered for all high grade serous adenocarcinoma cases in accordance with the SEE-FIM protocol as originally described by Medeiros *et al.* [9].

More patients with peritoneal cancer had undergone neoadjuvant chemotherapy at the time of surgery, and there is possibility that treatment could impact on the distribution of tumor load with less tumor remaining in the ovaries, potentially leading to an over-diagnosis of peritoneal cancer. However, the proportion of primary peritoneal cases compared with ovarian cancer in our study is similar to that reported in other studies where neoadjuvant cases were excluded [14], suggesting that this was unlikely to be a confounding factor.

The extent of residual disease after debulking surgery has consistently been reported to be the most important prognostic marker in ovarian cancer patients [34], but whether this association is causal or whether unresectable tumors are intrinsically more chemo-resistant and more aggressive is unclear. Tumor volume and pattern of peritoneal spread, with more general involvement of the peritoneal cavity particularly the upper abdomen, may contribute to the difference in treatment and surgical outcome. Compared to ovarian cancer patients, peritoneal cancer patients were more often treated with neoadjuvant chemotherapy. In these patients, this approach led to a higher proportion of cases with complete surgical resection when to compared to upfront surgery. Differences in metastatic spread and resectability may also explain the trend of less favorable surgical outcome after upfront surgery when compared to ovarian cancer. Increased age with associated comorbidity may also contribute to a less aggressive upfront cytoreductive surgical

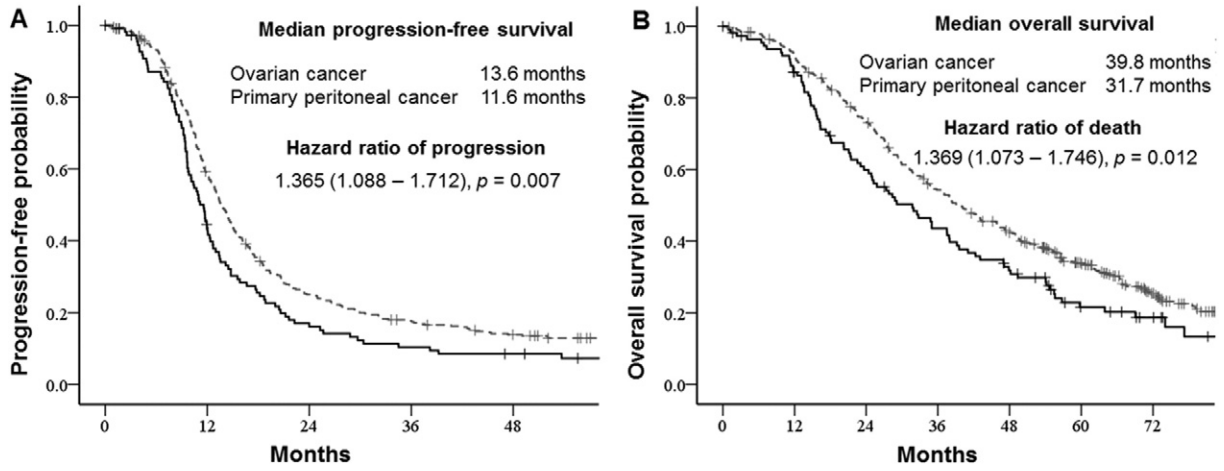

Fig. 2. Kaplan-Meier curves for (A) progression-free survival and (B) overall survival in stage III and IV, serous primary peritoneal (solid line) and ovarian cancer (broken line).

approach, aiming rather for a shorter, less complex procedure after three cycles of neoadjuvant chemotherapy.

Intrinsic tumor biological differences may further hinder optimal surgical resection in primary peritoneal cancer. A recent analysis of three large ovarian cancer gene expression datasets including the AOCS dataset used in our analysis [16] identified a subset of genes to be associated with suboptimal cytoreduction [35]. The gene network termed SCAN (suboptimal cytoreduction associated network) genes, including POSTN, FAP and TIMP3, were particularly expressed in the tumor stroma, and suggested to cause extensive stromal reaction and increased invasiveness and thereby challenging surgical resectability. This gene set was more highly expressed in tumors that cluster in Tothill C1 subtype and the TCGA counterpart termed 'mesenchymal'. This is in line with our finding that the majority of peritoneal cancers segregate to

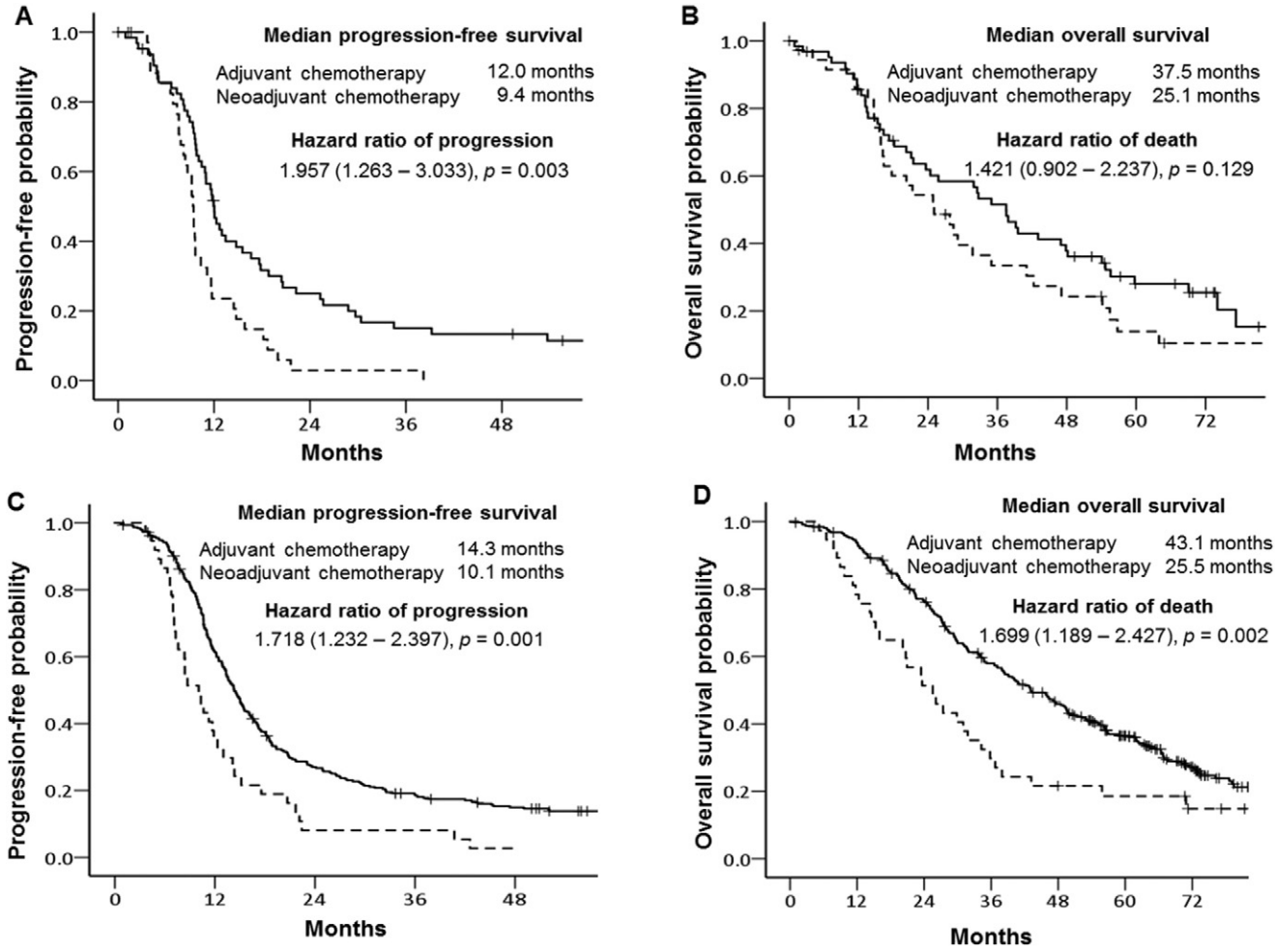

Fig. 3. Kaplan-Meier curves for (A & C) progression-free survival and (B & D) overall survival in stage III and IV, serous, primary peritoneal cancer (A & B) and ovarian cancer (C & D) comparing treatment with adjuvant (solid line) and neoadjuvant (broken line) chemotherapy.

Table 3
Associations between clinico-pathologic characteristics and survival in women with stage III or IV, serous, primary peritoneal or ovarian cancer.

	Progression-free survival			Overall survival		
	HR	95% CI	*p*	HR	95% CI	*p*
Group						
Ovarian cancer	1.000			1.000		
Primary peritoneal cancer	1.138	0.885–1.463	0.315	1.069	0.812–1.407	0.634
Grade						
1	1.000			1.000		
2	1.097	0.755–1.595	0.627	1.270	0.833–1.936	0.267
3	1.335	0.892–1.997	0.16	1.367	0.873–2.140	0.172
Stage						
III	1.000			1.000		
IV	1.199	0.899–1.598	0.216	1.122	0.826–1.525	0.460
Residual disease						
Nil macroscopic	1.000			1.000		
macroscopic disease, any size	1.579	1.245–2.003	<0.001	1.610	1.236–1.525	<0.001
Age	1.007	0.996–1.017	0.214	1.013	1.001–1.025	0.028
Neoadjuvant chemotherapy						
No	1.000			1.000		
Yes	1.771	1.349–2.325	<0.001	1.615	1.200–2.172	0.002

subtype C1, characterized by a gene expression signature containing markers of activated myofibroblasts as well as enrichment of pathways and gene ontology groups defining extracellular matrix production and remodeling, and associated with desmoplasia, a fibrotic reaction involving abundant collagen deposition [16]. It is further supported by our observation that C1 tumors, irrespective of being primary peritoneal or ovarian cancer, have an extremely low complete surgical resection rate in this study, although the interpretation of these data is limited by the small numbers of patients with available molecular profiling results.

Peritoneal cancer patients were more likely to be treated with neoadjuvant chemotherapy. Two randomized trials have reported equivalent outcomes of neoadjuvant chemotherapy compared to upfront debulking in patients with advanced ovarian cancer [36,37], however the survival outcomes in the trials were lower than might be expected following surgery by specialist gynae-oncologists and the results have been heavily debated. A recent Cochrane review confirmed the uncertainty of a benefit of this approach. Both primary peritoneal and ovarian cancer patients treated with neoadjuvant chemotherapy in our study had significantly poorer survival despite the higher complete surgical debulking rate after neoadjuvant chemotherapy in peritoneal cancer patients. Although one of the largest series to date, the number of peritoneal cancer cases in the cohort precluded further subgroup analysis, such as a comparison of survival among patients receiving the same treatment modality. The design of this cohort study is not suitable to derive conclusion regarding the role of neoadjuvant chemotherapy as there may be strong patient selection bias for primary debulking or interval debulking. Recent studies have suggested that neoadjuvant chemotherapy followed by interval debulking may increase the risk of platinum resistance to subsequent chemotherapy [38]. One explanation is the theoretical risk of platinum resistance when chemotherapy is used to treat large-volume disease before surgery versus chemotherapy for small or microscopic residual disease after primary debulking. There is also increasing evidence that the biological features which preclude optimal cytoreduction may also be responsible for chemotherapy resistance [39]. Fibrotic stromal reactions that are prominent in tumors in the C1 molecular subtype have been associated with poor drug uptake and primary chemo-resistance in other solid cancers such as pancreatic cancer [40].

In summary, our study suggests that at least a proportion of primary peritoneal cancers derive from the same precursor lesion in the fallopian tube as described in ovarian cancer. The mechanisms inducing a permissive environment for tumor formation within the ovary may be absent in older women, favoring the peritoneal spread of malignant cells from the tube. The mesenchymal phenotype associated with the majority of peritoneal cancers may also contribute to the metastatic pattern. Further in vivo studies are warranted to elucidate the key mechanisms in peritoneal cancer development. Most importantly, this crucial biological feature renders peritoneal cancers less surgical resectable and more chemotherapy resistant, leading to inferior survival. Neoadjuvant chemotherapy followed by interval debulking may be a pragmatic approach in some cases, but it may not necessarily improve survival. The development of new agents or treatment strategies targeting tumor stroma or pathways associated with stromal activation may increase the efficacy of cytoreductive surgery and chemotherapy in patients with primary peritoneal cancer.

Conflict of interest

All author declared no conflict of interest.

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