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Utility of progranulin and serum leukocyte protease inhibitor as diagnostic and prognostic biomarkers in ovarian cancer

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Abstract

Background—Epithelial ovarian cancer (EOC) is the fifth leading cause of cancer death in females and leading gynecologic cause of cancer death. Despite the identification of a number of serum biomarkers, methods to identify early stage disease and predict prognosis remain scarce. We have evaluated two biologically connected serum biomarkers, serum leukocyte protease inhibitor (SLPI) and progranulin (PGRN).

Methods—200 frozen plasma samples were acquired from the Mayo Clinic Biospecimen Repository for Ovarian Cancer Research. Samples were obtained from 50 patients with benign conditions, 50 with AJCC stage I and II EOC, and 100 with AJCC stage III and IV EOC patients. Samples were obtained prior to surgical resection of a mass and were analyzed for absolute levels of SLPI and PGRN using enzyme-linked immunosorbent (ELISA) assays. Receiver-operator characteristic curves were generated for SLPI and PGRN. Median follow-up was 48 months.

Results—Absolute levels of SLPI were significantly elevated in patients with EOC compared to benign disease and predicted the presence of EOC (AUC of 0.812. $P = 0.04$); SLPI remained elevated in the subset of patients with normal CA-125, PGRN levels were not significantly increased in early stage or late stage EOC patients as a whole, but an increase in PGRN levels was associated with decreased overall survival in advanced EOC.

Conclusions—SLPI levels are elevated in epithelial ovarian cancer, and SLPI shows promise as a diagnostic biomarker for patients with both elevated and normal CA-125 levels. An increase in PGRN is associated with decreased overall survival.

Impact—SLPI is elevated in EOC and warrants investigation in a screening study in women at risk for EOC.

Keywords

Ovarian neoplasms; GRN protein, human; SLPI protein, human; Biological Markers; Prognosis

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Conflict of Interest: none

Introduction

Epithelial ovarian cancer (EOC) is the fifth leading cause of cancer death in females and claims over fifteen thousand lives per year in the United States (1), with a five-year survival rate of only 37–45%. The primary reason for the high lethality of EOC is that the majority of patients present with advanced disease at the time of diagnosis (1), and cures for patients with regional or distant metastases are relatively uncommon. Although biomarkers have been used to detect ovarian cancer since the discovery of CA-125 (2, 3), currently available biomarkers have not led to measurable changes in OC-related mortality.

CA-125 is the most widely used biomarker for ovarian cancer. Despite the widespread use of CA-125, this biomarker has poor positive and negative predictive value (4). Besides EOC, CA-125 is also elevated in a variety of other malignant and non-malignant conditions (5, 6), limiting its ability to distinguish benign and malignant adnexal masses. Recently, Human Epididymis Protein 4 (HE4) has received FDA approval for use as a screening biomarker for EOC. Plasma levels of HE4 are increased in epithelial ovarian malignancies (7) and retrospective studies have shown increased specificity when combined with CA-125 (8, 9), compared with use of CA-125 alone. Despite this, a recent prospective study which combined HE4 with CA-125 did not demonstrate increased detection of EOC over CA-125 alone (10).

Progranulin (PGRN) is a heavily glycosylated precursor protein comprised of 7.5 repeats of a 12 cysteinyl motif first identified in inflammatory cell extracts (11). It has been shown to activate phosphatidyl inositol-3 kinase signaling cascades (12) and has been found to upregulate cyclin D1 (13). Recently, PGRN was shown to bind the tumor necrosis factor alpha (TNFα) receptor *in vivo* (14). PGRN is subject to cleavage by serine proteases into granulins (15), and individual granulins have been postulated to be proinflammatory, based on their presence in human inflammatory extracts (11). PGRN has been previously implicated in wound healing (16), tumorigenesis (17, 18), and increased tumor invasion. PGRN levels have been measured in plasma from 23 patients with EOC in remission after completion of initial surgical cytoreduction and chemotherapy. Three months after study enrollment, patients with elevated PGRN levels had a shorter progression-free survival (PFS) and overall survival (OS) than those with normal PGRN levels (19). To our knowledge, PGRN levels have not been measured in presurgical patients with EOC at the time of diagnosis.

Serum leukocyte protease inhibitor (SLPI) is a 12 kDa serine protease inhibitor that has been shown to inhibit the protease activity of neutrophil elastase, cathepsin G, and trypsin (20). SLPI protects progranulin from serine proteases and cleavage into individual granulins (15). SLPI has been hypothesized to potentiate the tumorigenic effects of PGRN in ovarian cancer (21). SLPI expression has been shown to increase malignant potential of tumor cells (21–23), and expression of SLPI has been shown to be induced *in vitro* by TNFα in the Lewis lung cell 3LL cells (24). It has been previously studied as a biomarker in ovarian cancer with a small, prospective study demonstrating its ability to differentiate benign cysts from malignant tumors (25).

In this study, we assess the utility of SLPI and progranulin as diagnostic and prognostic biomarkers in a cohort of early (AJCC stages I and II) (26) and advanced (AJCC stages III and IV) ovarian cancer patients compared to patients with benign adnexal masses.

Materials and Methods

Study Population

A cohort of patients undergoing surgery for an adnexal mass was consented to provide plasma specimens prior to undergoing an operation for removal of the mass and diagnosis. Frozen plasma specimens were obtained through the Mayo Clinic Biospecimen Repository for Ovarian Cancer Research (Mayo Clinic IRB #08-005749). Specimens were selected from women who were diagnosed with epithelial ovarian cancer (EOC) (Stage I–IV, Grade 1–4, histology including serous, mucinous, endometrioid, clear cell, and mixed) or who had benign conditions warranting surgery between October 2002 and April 2008. Specimens were excluded if inadequate plasma was available, stage of cancer was unknown, age was greater than 82, or the patient experienced perioperative death (less than 90 days from surgery). Specimens were coded prior to assays and analysis, and all clinical information was provided without release of personal identifiers.

Biochemical Analysis of Serum Biomarkers

Frozen plasma samples were stored at −80 C until the time of use. All biochemical assays required thawed samples, and each sample underwent one freeze-thaw cycle prior to re-aliquoting. Samples were assigned a random location for each assay plate. Plasma levels of progranulin were measured in duplicate using the human progranulin Quantikine® ELISA kit (R&D Systems, Minneapolis, MN). Plasma levels of SLPI were also measured in duplicate using the human SLPI Quantikine® ELISA kit (R&D Systems)

Statistical Analysis

Elevation of PGRN and SLPI in EOC groups was determined using the 95^{th} percentile in the benign group as a cutoff. Wilcoxon rank sum tests were used to compare the continuous distributions of SLPI and PGRN by study group. Both markers were evaluated by a receiving operational characteristic (ROC) curve and area under the ROC curve (AUC). Overall survival (OS) was defined as time from diagnosis until death due to any cause. Event free survival (EFS) was defined as time from diagnosis until disease recurrence, retreatment after completion of initial chemotherapy, or death due to any cause. Patients without an event or living were censored at last known follow-up for EFS and OS, respectively. Cox proportional hazards models and Kaplan-Meier curves were used to assess the association of SLPI and PGRN with OS and EFS in the high-stage EOC group. PGRN and SLPI were assessed as both as a dichotomous (elevated vs. normal) variable and continuous variable using penalized smoothing splines.

Results

Patient characteristics

Study groups consisted of 50 patients with benign adnexal masses, 50 patients with AJCC stage I or II disease, and 100 patients with AJCC stage III or IV disease (Table 1). Median age at diagnosis was 59.5 years (range 35–82). The majority of patients with late stage disease underwent an optimal debulking (88%). The morphology of the tumors varied, with serous being the most common subtype. At a median follow-up of 48 months (range 19–99 months), 35 patients with advanced stage EOC (35%) had died.

SLPI and PGRN concentrations in EOC versus control patients

Plasma SLPI levels were increased in patients with advanced EOC (median 29.6 ng/ml, interquartile range—IQR 23.8–41.5 ng/ml) relative to early stage EOC (median 27.6 ng/ml, IQR 21.2–32.1 ng/ml), and between patients with early stage EOC relative to patients with

benign disease (median 19.9 ng/ml, IQR 17.7–23.7) (Figure 1A). There were no significant differences between patient groups for absolute levels of PGRN, although there was a positive trend with increasingly advanced disease (Figure 1B). ROC curves were generated to assess the ability of PGRN and SLPI to distinguish patients with EOC from those with benign disease (Figure 2). SLPI demonstrated good sensitivity and specificity in identifying patients with all stages of EOC (AUC = 0.812), while PGRN was a poor predictor of EOC (AUC = 0.535). In patients with early stage disease, SLPI retained its predictive ability (AUC = 0.752, Supplemental Figure 1A). In patients with advanced disease, the predictive ability of SLPI was increased (AUC = 0.838, Supplemental Figure 1B). Furthermore, SLPI showed utility in distinguishing EOC from benign disease even among patients with normal (< 35 U/ml) CA-125 levels (AUC = 0.760, Figure 2C, Supplemental Figure 2).

PGRN and SLPI and survival in advanced EOC

Both SLPI and PGRN were evaluated as predictors of survival in advanced EOC. Increases in plasma PGRN levels were associated with decreased overall survival (OS, p = 0.042, Figure 3). By contrast, SLPI levels did not correlate with survival (p = 0.39). Since relatively few patients with advanced EOC had PGRN levels that were elevated above the 95th percentile of control patients, PGRN was only a statistically significant predictor of poor survival when analyzed as a continuous (not a dichotomous) variable.

Discussion

Screening strategies for EOC have failed to effectively identify early stage disease (1). CA-125 is currently the most widely used marker in ovarian cancer, but it is a poor screening tool, as approximately one-half of early-stage EOC patients have normal-range CA-125 levels (27). Metastatic progression is postulated to occur early in EOC (28), and one potential explanation for the large number of patients with normal CA-125 in early stage disease is that the cancer has not reached a critical mass to secrete sufficient amounts this marker.

We have found that SLPI has good sensitivity in distinguishing benign conditions from early stage EOC and does so even in patients with normal CA-125 levels, albeit with a slightly lower AUC in patients with normal CA-125 (AUC = 0.760) than in patients with any CA-125 level (AUC = 0.812). A previous study has also found SLPI to elevated in ovarian cancer, but this study was severely limited by low sample size and did not report detection of early stage disease or utility in the setting of normal CA-125 (25). It should be noted that evaluation of SLPI as a true screening marker is limited in this study of patients with preoperative adnexal masses and warrants formal investigation in a screening cohort of women at risk for EOC.

Given the association of SLPI with inflammatory responses, one possible explanation for the elevation of SLPI in early stage EOC is that inflammatory reactions associated with EOC have been noted early in the disease course prior to the development of a mass large enough to secrete sufficient amounts of MUC-16/CA-125. Supporting the hypothesis that systemically detectable inflammation occurs relatively early in the course of EOC, others have found consistently elevated C-reactive protein (CRP) levels in EOC patients prior to diagnosis (29). Chronic inflammation is associated with an increased risk of a variety of malignancies (30, 31), and causes of chronic inflammation such as endometriosis may increase the risk of EOC (32).

Both our study and a prior study by Han, et. al. (19) demonstrated an association of PGRN with OS in patients with advanced EOC. While our study only noted an association between PGRN levels and OS, the study by Han, et. al. found that PGRN levels predict both OS and

progression-free survival (PFS). This difference in the reported prognostic utility of PGRN between the two studies can be attributed to differences in study design. The study by Han, et. al. analyzed 23 EOC patients at multiple time points, whereas the present study analyzed samples from 100 advanced EOC patients obtained at a single time point. Whereas Han, et. al. selected for analysis those samples obtained three months after completion of chemotherapy in patients achieving a complete clinical remission, our samples were obtained prior to diagnostic surgery and included patients who did not achieve a complete remission. Moreover, our study design was informed by control patients with benign adnexal masses; since the distribution of PGRN concentrations in both the control and EOC populations was unimodal, and since very few patients with advanced EOC had elevated levels of PGRN relative to control patients, we thought it more appropriate to use PGRN as a continuous variable in our analysis. Thus, while our conclusions differ slightly from those obtained by Han, et. al., we believe our analysis was appropriate and our results are valid.

PGRN is secreted during wound healing (22) and inflammatory responses (33). The role of PGRN in ovarian and other cancers is unclear, despite evidence that higher levels or over-expression lead to enhanced tumor activity and worse outcomes. Mechanistic studies will be needed to determine whether PGRN directly contributes to poor survival in EOC, or whether it serves as a marker of a maladaptive inflammatory reaction.

PGRN and SLPI are two proteins secreted by leukocytes during inflammatory responses. Both are associated with several malignancies, including EOC, but it is not clear whether in the setting of EOC, PGRN and SLPI are secreted by the malignant cells themselves or by tumor-associated leukocytes. Although PGRN and SLPI are biologically related, their role in the pathogenesis and progression of EOC is not yet clear. We have demonstrated that plasma levels of SLPI are elevated in both early and late stage EOC and are increased in patients with both normal and elevated CA-125 levels. By contrast, PGRN levels are not generally elevated in EOC, but higher PGRN plasma concentrations are associated with decreased overall survival in advanced EOC patients. We were surprised to find different biomarker characteristics of these two related proteins. This suggests that while related, SLPI and PGRN concentrations in plasma are not tightly linked, and thus may be regulated by distinct mechanisms. While the utility of PGRN as a biomarker in EOC differs from that of SLPI, both inflammation-associated proteins show significant promise in characterizing EOC patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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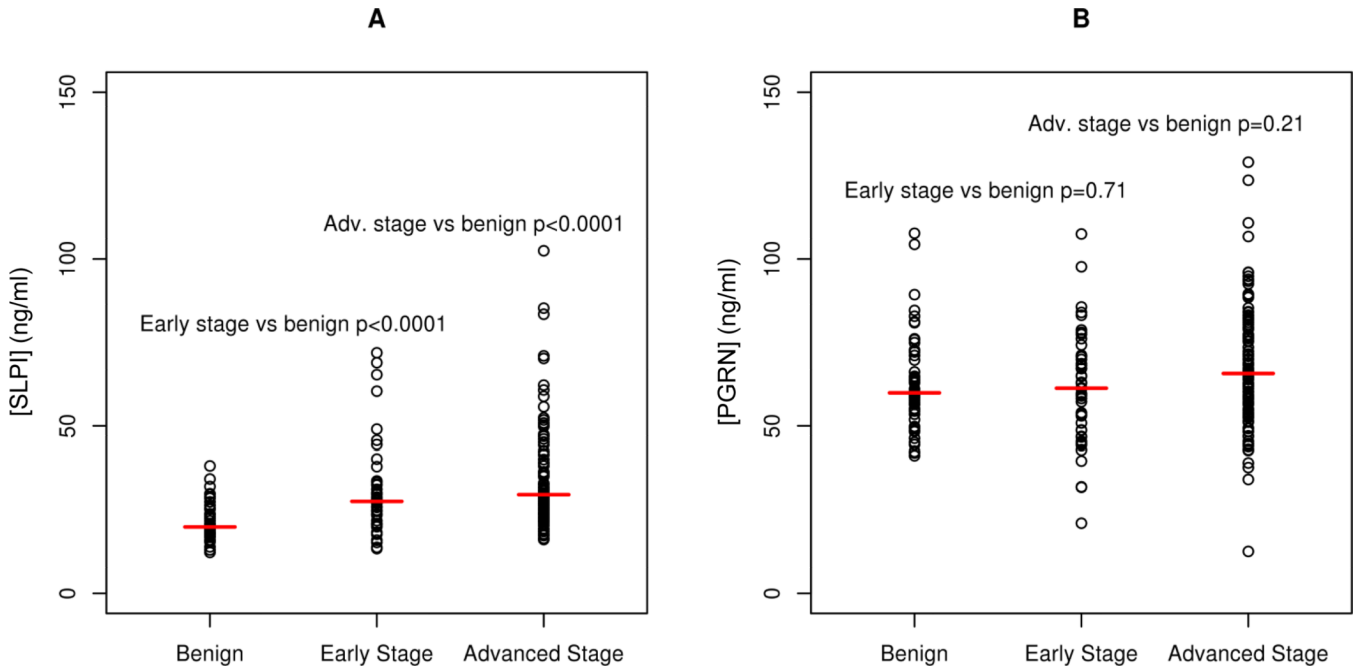

Figure 1.

Jit-plots showing the range of plasma concentrations of SLPI (A) and PGRN (B). Absolute levels of SLPI were significantly higher in both early stage and advanced stage EOC patients relative to control patients. There was no significant difference in PGRN levels between groups.

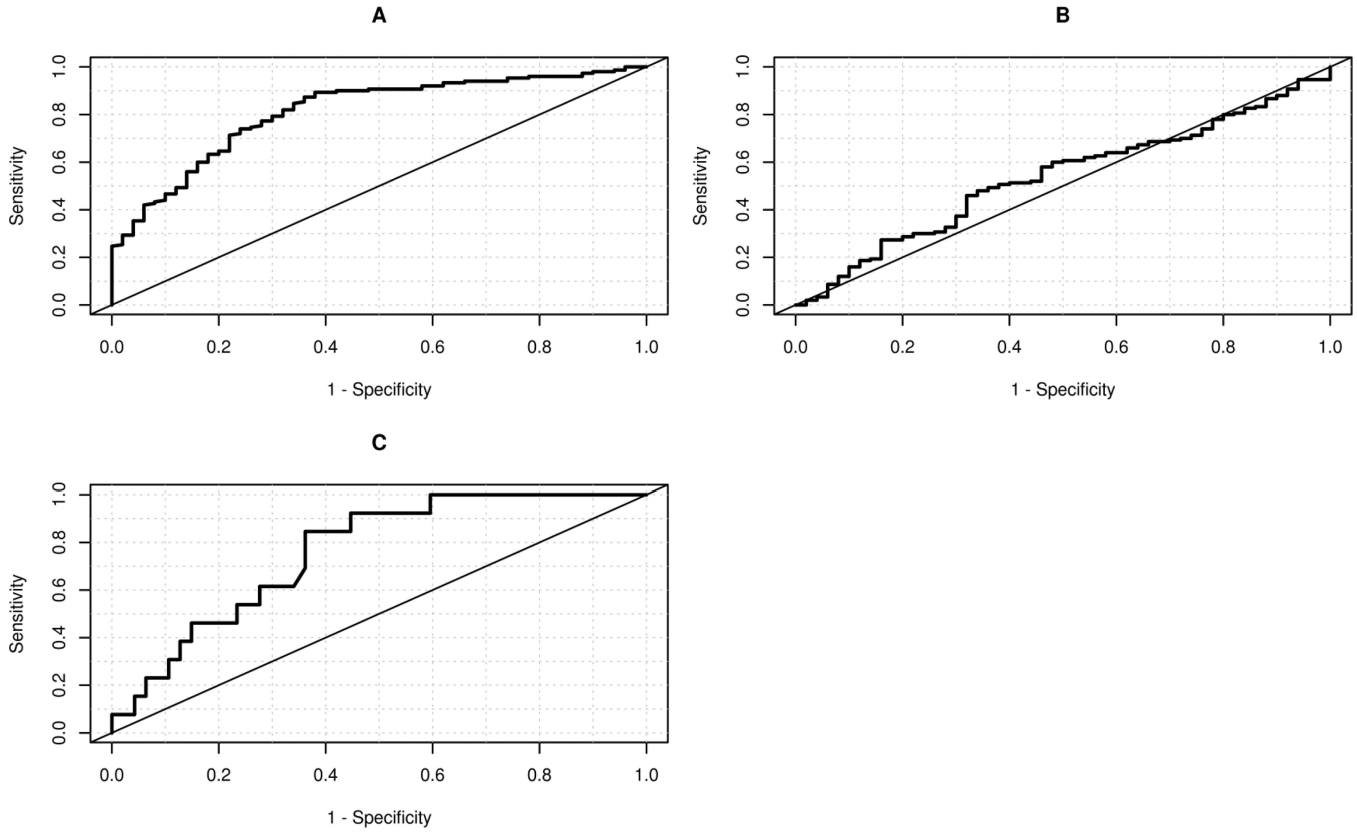

Figure 2.

Receiver-operator curves for both SLPI (A) and PGRN (B). SLPI demonstrated good predictive ability for EOC, with an area under the curve (AUC) of 0.812 for ovarian cancer patients versus controls; PGRN demonstrated poor predictive ability, with an AUC of 0.535. SLPI retained its ability to predict the presence of EOC in patients with normal (< 35 U/ml) CA-125 levels (C), with an AUC of 0.760.

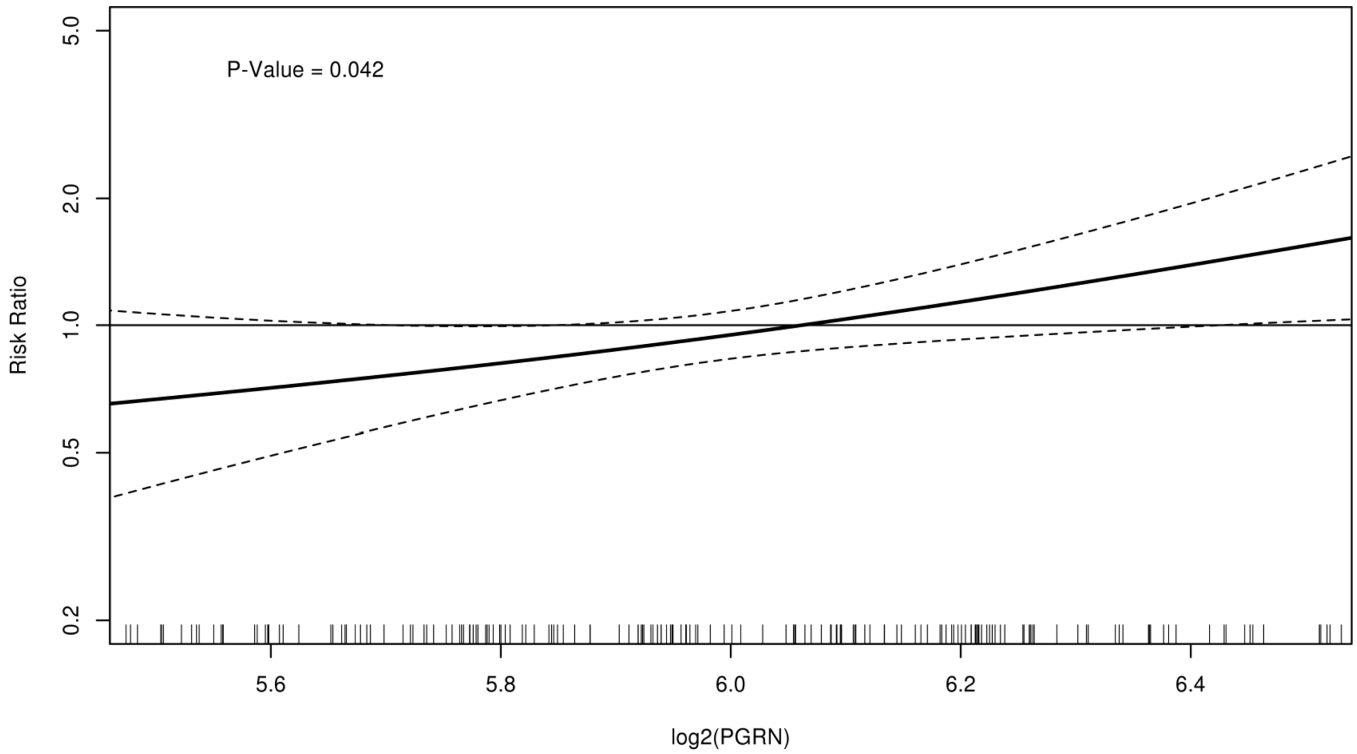

Figure 3.
Smoothing spline showing the nature of association between serum concentration and overall survival across the range of observed values for PGRN.

Table 1

Patient Characteristics Table

	Benign (N=50)	Early Stage (N=50)	Advanced Stage (N=100)	Total (N=200)
Age at Diagnosis				
Median	60.5	54.5	63.0	60.0
Q1, Q3	49.0, 69.0	50.0, 69.0	54.0, 69.5	50.5, 69.0
Range	(38.0–82.0)	(35.0–82.0)	(36.0–81.0)	(35.0–82.0)
CA-125				
Median	10.4	160.1	1043.9	219.8
Q1, Q3	8.0, 17.1	43.8, 735.8	354.2, 3220.8	22.1, 1552.5
Range	(5.1–552.7)	(7.9–7264.8)	(16.3–19131.6)	(5.1–19131.6)
Histology				
Serous	0 (0.0%)	14 (28.0%)	81 (81.0%)	95 (47.5%)
Mucinous	0 (0.0%)	6 (12.0%)	0 (0.0%)	6 (3.0%)
Endometrioid	0 (0.0%)	13 (26.0%)	9 (9.0%)	22 (11.0%)
Clear cell	0 (0.0%)	9 (18.0%)	4 (4.0%)	13 (6.5%)
Mixed Epithelial	0 (0.0%)	8 (16.0%)	6 (6.0%)	14 (7.0%)
Benign	50 (100.0%)	0 (0.0%)	0 (0.0%)	50 (25.0%)
Ascites				
Yes	NA	12 (24.0%)	59 (59.0%)	71 (47.3%)
No	NA	34 (68.0%)	23 (23.0%)	57 (38.0%)
Unknown	NA	4 (8.0%)	18 (18.0%)	22 (14.7%)
Debulking				
Optimal	NA	49 (98.0%)	88 (88.0%)	137 (91.3%)
Sub-optimal	NA	0 (0.0%)	9 (9.0%)	9 (6.0%)
Unknown	NA	1 (2.0%)	3 (3.0%)	4 (2.7%)
Stage				
I	NA	36 (72.0%)	0 (0.0%)	36 (24.0%)
II	NA	14 (28.0%)	0 (0.0%)	14 (9.3%)
III	NA	0 (0.0%)	83 (83.0%)	83 (55.3%)
IV	NA	0 (0.0%)	17 (17.0%)	17 (11.3%)
Grade				
Missing	NA	1	3	4
Low	NA	16 (32.7%)	7 (7.2%)	23 (15.8%)
High	NA	33 (67.4%)	90 (92.8%)	123 (84.2%)