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An evaluation of progression free survival and overall survival of ovarian cancer patients with clear cell carcinoma versus serous carcinoma treated with platinum therapy: An NRG Oncology/ Gynecologic Oncology Group experience

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Abstract

Purpose—We examined disparities in prognosis between patients with ovarian clear cell carcinoma (OCCC) and serous epithelial ovarian cancer (SOC).

Methods—We reviewed data from FIGO stage I–IV epithelial ovarian cancer patients who participated in 12 prospective randomized GOG protocols. Proportional hazards models were used to compare progression-free survival (PFS) and overall survival (OS) by cell type (clear cell versus serous).

Results—There were 10,803 patients enrolled, 9,531 were eligible, evaluable and treated with platinum, of whom 544 (6%) had OCCC, 7,054 (74%) had SOC, and 1,933 (20%) had other histologies and are not included further. In early stage (I–II) patients, PFS was significantly better in OCCC than in SOC patients. For late stage (III, IV) patients, OCCC had worse PFS and OS compared to SOC, OS HR= 1.66 (1.43, 1.91; p<0.001. After adjusting for age and stratifying by protocol and treatment arm, stage, performance status, and race, OCCC had a significantly decreased OS, HR= 1.53 (1.33, 1.76; p<0.001). In early stage cases, there was a significantly decreased treatment effect on PFS for consolidative therapy with weekly Paclitaxel versus observation in OCCC compared to SOC (p=0.048).

Conclusions—This is one of the largest analyses to date of OCCC treated on multiple cooperative group trials. OCCC histology is more common than SOC in early stage disease. When adjusted for prognostic factors, in early stage patients, PFS was better for OCCC than for SOC; however, in late-stage patients, OCCC was significantly associated with decreased OS. Finally, treatment effect was influenced by histology.

Keywords

Ovarian; cancer; clear cell; survival; histology

INTRODUCTION

Ovarian tumors are classified into three categories based on progenitor cell type: surface-epithelial, sex cord-stromal and germ cell neoplasms.[1] Of these, epithelial ovarian cancers (EOCs which may, in fact, often originate from the fallopian tube) comprise the majority of cases, and these are usually diagnosed at an advanced stage with an associated poor prognosis. Serous epithelial ovarian carcinoma (SOC) is the most commonly observed subtype of EOC both in the United States[2] and worldwide.[3,4] In the United States, ovarian clear cell carcinoma (OCCC) accounts for approximately 4–9.5%[2] of ovarian tumors, whereas in Japan, the rate is upwards of 15–25%.[3,5] Meanwhile, Asians, as defined in the SEER registry, in the United States account for a disproportionate share of OCCC cases with a percentage of SOC rate of 11.1% when compared with whites (4.8%).[6]

Controversy exists in the literature regarding the prognostic effect of the clear cell histology, although it has been generally accepted as unfavorable when compared with SOC. In long-term follow-up of two early Gynecologic Oncology Group (GOG) studies, multivariate analysis revealed histology other than clear cell or mucinous to be a statistically significant favorable characteristic for overall survival (OS) in advanced stage disease.[7] Several other retrospective studies have highlighted the relatively poor prognosis conferred by clear cell histology, when compared to other histologic subtypes of epithelial ovarian cancer (EOC).[8–10] However, these observations have been refuted by some retrospective studies[11,12].

We sought to clarify the suggested differences in prognosis between OCCC and SOC by leveraging the robust data obtained during the course of twelve prospective cooperative group studies. The objectives of this analysis were to confirm whether disparity exists with regard to outcome between ovarian cancer patients with OCCC and SOC in prospectively enrolled clinical trials, to identify factors associated with survival, and to identify factors related to response to chemotherapy. Factors considered included age, stage, performance status, clear cell versus serous histology, and race.

METHODS

We reviewed data from International Federation of Gynecology and Obstetrics (FIGO) stage I–IV EOC patients who participated in twelve prospective, randomized GOG chemotherapy protocols (GOG protocol 95, 157 (both early stage), 111, 114, 132, 152, 158, 162, 172, 175, 182, 218 (all late stage) Table 1) conducted between 1992 and 2009, all of which were IRB approved. All patients included in these protocols were diagnosed with primary, histologically-confirmed by central pathology review, epithelial ovarian, tubal or primary peritoneal cancer. All borderline and low malignant potential tumors were excluded. All patients signed institutionally IRB-approved informed consent. All patients included in this analysis received platinum based chemotherapy per specific protocol. Table 1 lists the treatment arms for each of the protocols under evaluation.

Pearson chi-square tests were used to test the hypothesis of independence between histology (clear cell versus serous) and baseline characteristics (age, race, performance status, stage,

and optimal (< 1cm residual disease)/suboptimal debulking (>1cm residual disease)). A proportional hazards regression model adjusted for age and stratified by protocol and treatment arm, stage, performance status, and race was used to compare the hazard of progression free survival (PFS) by histology (clear cell vs serous); the same model was used for overall survival. Patients with missing strata variables were excluded from the model; numbers excluded are noted for the specific analyses (see below). Results of significance test were considered statistically significant if p <0.05 (two-sided). Tests of the proportional hazards assumption were done using interactions of histology (clear cell, serous) and log(*time*). If non-proportional hazards were found, the method of fractional polynomials was used to fit an appropriate function of time.[13] For stage III, the function for PFS was *time*$^{-0.5}$ and for OS was *time*$^{-0.5}$+log(*time*); and for stage IV, log(*time*) was used for both PFS and OS.

RESULTS

The flowchart of patient exclusions is presented in Figure 1. There were 10,803 patients enrolled in the twelve GOG trials. Table 1 provides the treatment arms of each protocol and the number of patients of each histologic subtype prior to exclusions. Of the 10,803 total patients considered, 858 were not eligible or evaluable and 103 were not randomized, leaving 9,842 patients. An additional 311 patients were excluded for absence of platinum in their adjuvant therapy: 98 in GOG 0095 who received intraperitoneal (IP) P32 and 213 in GOG 0132 who received single-agent paclitaxel. The remaining 9,531 patients were randomized to platinum-containing regimens, of which 544 (6%) had OCCC, 7,054 (74%) had SOC, and 1,933 (20%) had other tumor types [data not shown]. Central pathology review was performed on all patients included at the time of original protocol participation, and only the OCCC and SOC patients were considered in this analysis, for a total of 7,598 patients. While the prevalence of clear cell tumors was higher in the Japanese patients (30% [21/71]) than in US patients (6% [515/9216]), the number of Japanese clear cell patients was so small that comparison of US and Japanese OCCC was not feasible [data not shown].

Statistically significant relationships between histology and baseline characteristics were seen for age, race, performance status, stage, optimal/suboptimal debulking, and grade (Table 2). Clear cell patients were significantly younger than serous patients and were more commonly of Asian race. Patients with OCCC more often presented with early stage disease, had better performance status, and more often had optimal cytoreduction when compared to the patients with SOC. Of note, debulking status was assessed only in the 61% (2,961/7,598) of patients who presented with advanced stage (III–IV) disease. Thus, debulking status was more frequently assessed in patients with SOC than in patients with OCCC. All of these factors (except race) point to a potentially better prognosis for clear cell patients than for serous patients.

Prior to any adjustment, clear cell patients had better PFS and OS (Table 3); however, this was due to the preponderance of favorable prognostic factors (stage, age, and performance status) in this cohort. After adjusting for age and stratifying by protocol and treatment arm, stage, performance status, and race, the hazard ratio for PFS was 1.37 (95% CI: 1.20, 1.56; p <0.001) for OCCC versus SOC patients. After adjusting for age and stratified by protocol

and treatment arm, stage, performance status, and race, the hazard ratio for overall survival was 1.58 (95% CI: 1.38, 1.82; p <0.001) for OCCC versus SOC patients. Because grade 1 serous tumors are thought to have different clinical pathology and genetic makeup, we did analyses (across all stages) excluding grade 1 tumors; results were nearly identical to the main results.

There was a statistically significant (p<0.001) interaction between stage and histology for both PFS and OS indicating differing effects of histology across stage (Table 3). In stage I–II patients, PFS was significantly better in OCCC than in SOC, while OS was numerically but not statistically significantly better (Table 3 and Figure 2), tests of nonproportional hazards were not significant for the stage I and II patients. In stage III and IV patients, OCCC patients were at statistically significantly increased risk of progressing or dying (Table 2 and Figures 3 and 4). However, for both stages, tests of nonproportional hazards were statistically significant (p 0.001). For stage III patients, the PFS hazard and OS hazard are dramatically higher for OCCC patients than for SOC patients but this effect lessens and even reverses itself after 2–3 years (Figure 3). In stage IV patients, a similar pattern exists; however, it is not as dramatic as for stage III, and for OS, does not actually reverse directions (Figure 4).

In two protocols (0157 and 0175), there were sufficient numbers of both clear cell and serous patients in order to examine the treatment effect by cell type. GOG 0157 was a randomized phase III trial comparing three cycles of every three weeks carboplatin (AUC 7.5) and paclitaxel ($175mg/m^2$) on day 1 to six courses of the same regimen in stage I and II ovarian carcinomas. GOG 0175 was a randomized phase III trial of carboplatin (AUC 6) and paclitaxel ($175mg/m^2$) every three weeks for 3 cycles followed by weekly paclitaxel ($40mg/m^2$/week) versus observation in patients with early stage ovarian carcinoma. A proportional hazards model adjusted for age, and stratified by performance status, race, and stage comparing 6 cycles of adjuvant q21 day carboplatin/paclitaxel to 3 cycles of the same for GOG 0157 revealed statistically significantly (p=0.048) greater treatment effect on PFS for early stage SOC (HR: 0.42, 95% CI: 0.18, 0.99) when compared with the effect for early stage OCCC (HR: 1.32, 95% CI: 0.62, 2.82) (Table 4). Results for OS in 0157 and for PFS and OS in 0175 were similar to those for PFS in 0157 although the interaction was not statistically significant.

DISCUSSION

This study represents one of the largest analyses in the literature in which patients with OCCC were treated in a uniform manner under cooperative group studies. Early stage OCCC has been generally regarded as grade 3 tumor, however, OCCC often has been shown to display a comparatively chemoresistant phenotype,[5,8,14,15] and the actual effect of adjuvant chemotherapy remains unclear. Clear cell histology has been found to be a significant predictor for impaired chemotherapy response in both univariate and multivariate analysis.[12] Takano et al.[14] performed a retrospective evaluation of 219 patients with stage I OCCC. Multivariate analysis revealed that adjuvant chemotherapy was not a prognostic factor (p = 0.80) for survival.[14] In another retrospective chart review of 158 patients with advanced and recurrent OCCC, the investigators reported a 73% failure rate with adjuvant

and palliative chemotherapies, including platinum-based regimens.[15] In the current study, for early stage SOC, the positive effect on PFS of cytotoxic chemotherapy treatment was statistically significantly greater than in early stage OCCC. These results confirm previous findings that OCCC appears to be chemoresistant as previously believed and this resistance is not limited to taxanes and platinum medications[14]. Another interpretation of the data would say that early stage clear cell is more likely to be controlled with surgery alone and not as likely to have occult metastasis as HGSOC. It also could suggest that early stage OCCC and advanced stage OCCC may have different origins. We realize that including all grades of serous carcinoma could affect analysis given different clinical behavior of low grade serous carcinomas. An analysis omitting grade 1 tumors did not change results.

Recently elucidated molecular and genetic mechanisms distinguishing OCCC from SOC are likely, at least in part, to be responsible for our findings. Yamaguchi et al.[16] highlighted derangements in oxidative stress, hypoxia, mitogen-activated protein kinase activity, and cytokine-related pathways for OCCC. Stany et al.[17] reported whole genomic expression profiling of laser capture micro dissected OCCC specimens, also identifying activation in hypoxic cell growth, angiogenesis, and glucose metabolism pathways involving HIF-1α and enolase. ARID1A has been found to be mutated in over 50% of ovarian clear cell carcinomas (OCCCs)[18]. Somatic mutations of PIK3CA (phosphoinositide-3-kinase) have recently been shown playing an important role in the pathogenesis of ovarian clear cell carcinoma[19]. factor is also a promising therapeutic target for the treatment of clear cell carcinoma of the ovary[20]. The overexpression of certain types of genes in the clear cell histotype can also provide insights into its disproportionately poor prognosis relative to other subtypes of ovarian cancer. Two genes are also implicated in impaired chemotherapy response: overexpression of ANXA4 has been associated with resistance to both paclitaxel[21] and to platinum-based chemotherapy,[22] whereas upregulated UGT1A1 increases clearance of the active metabolite of irinotecan.[23] TFPI2, with its inhibitory effects on the invasion and growth activity of the tumor cells, may serve to maintain OCCC tumors in earlier stages than their SOC counterparts.[24] Increased apoptotic signaling (MAP3K5/ASK1 and GLRX), inhibited cellular proliferation (TFPI2), increased resistance to chemotherapy (ANXA4 and UGT1A1), and insensitivity to hypoxic stress (HIF-1α and HNF-1β) combine to produce early stage, large, indolent, chemotherapy-resistant tumors that may well arise within endometriotic lesions. This disparate hypothesis regarding the origin of OCCC either ovarian or endometriotic could have affected analysis. The histological and genetic alterations in endometriosis seem to explain why endometriosis can be a precursor of some ovarian cancers, especially clear cell and endometrioid carcinomas[25]. This study is subject to weaknesses inherent in retrospective analyses. The patients were not allocated at random to treatments that differed only by total treatment time. As a result you cannot exclude the existence of factors that may have confounded this analysis. The major strength of this work is the high quality of the data, collected prospectively in multi-institutional cooperative group trials in a large number of patients. In fact, this the largest analysis ever conducted on clear cell ovarian cancer patients.Given the relatively rarity of OCCC, compiling data from prospectively accrued patients in cooperative group trials is imperative in order to better investigate variations in the molecular and genetic underpinnings of the clear cell histologic subtype which confer the survival disadvantages described here. As further investigations

better elucidate the molecular and genetic foundations of ovarian carcinogenesis, treatment paradigms can be refined to better address and leverage the differences between various ovarian histologic subtypes. Once such a paradigm is in place, rational drug design can be devoted to the formulation of more diverse and focused targeted therapies. Thus, ovarian cancers can begin to be treated as the heterogeneous group of tumors they represent, an achievement which is paramount to the advancement of truly personalized medicine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Lee, KR., Tavassolli, FA., Prat, J., et al. Surface epithelial stromal tumors. In: Tavassoli, FA., Devilee, P., editors. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Breast and Female Genital Organs. Lyon: IARC Press; 2003. p. 117-145.

2. Kobel M, Kalloger SE, Huntsman DG, et al. Differences in tumor type in low-stage versus high-stage ovarian carcinomas. Int J Gynecol Pathol. 2010; 29:203–211. [PubMed: 20407318]

3. Yahata T, Banzai C, Tanaka K. Histology-specific long-term trends in the incidence of ovarian cancer and borderline tumor in Japanese females: a population-based study from 1983 to 2007 in Niigata. J Obstet Gynaecol Res. 2012; 38:645–650. [PubMed: 22381138]

4. Vasey PA, Jayson GC, Gordon A, et al. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. J Natl Cancer Inst. 2004; 96:1682–1691. [PubMed: 15547181]

5. Sugiyama T, Kamura T, Kigawa J, et al. Clinical characteristics of clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy. Cancer. 2000; 88:2584–2589. [PubMed: 10861437]

6. Chan JK, Teoh D, Hu JM, et al. Do clear cell ovarian carcinomas have poorer prognosis compared to other epithelial cell types? A study of 1411 clear cell ovarian cancers. Gynecol Oncol. 2008; 109:370–376. [PubMed: 18395777]

7. Omura GA, Brady MF, Homesley HD, et al. Long-term follow-up and prognostic factor analysis in advanced ovarian carcinoma: the Gynecologic Oncology Group experience. J Clin Oncol. 1991; 9:1138–1150. [PubMed: 1904477]

8. Goff BA, Sainz de la Cuesta R, Muntz HG, et al. Clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy in stage III disease. Gynecol Oncol. 1996; 60:412–417. [PubMed: 8774649]

9. Winter WE 3rd, Maxwell GL, Tian C, et al. Prognostic factors for stage III epithelial ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol. 2007; 25:3621–3627. [PubMed: 17704411]

10. Duska LR, Garrett L, Henretta M, et al. When 'never-events' occur despite adherence to clinical guidelines: the case of venous thromboembolism in clear cell cancer of the ovary compared with other epithelial histologic subtypes. Gynecol Oncol. 2010; 116:374–377. [PubMed: 19922988]

11. Bamias A, Psaltopoulou T, Sotiropoulou M, et al. Mucinous but not clear cell histology is associated with inferior survival in patients with advanced stage ovarian carcinoma treated with platinum-paclitaxel chemotherapy. Cancer. 2010; 116:1462–1468. [PubMed: 20108307]

12. Pectasides D, Fountzilas G, Aravantinos G, et al. Advanced stage clear-cell epithelial ovarian cancer: the Hellenic Cooperative Oncology Group experience. Gynecol Oncol. 2006; 102:285–291. [PubMed: 16516283]

13. Sauerbrei W, Royston P, Look M. A new proposal for multivariable modelling of time-varying effects in survival data based on fractional polynomial time-transformation. Biom J. 2007; 49:453–473. [PubMed: 17623349]

14. Takano M, Sugiyama T, Yaegashi N, et al. Less impact of adjuvant chemotherapy for stage I clear cell carcinoma of the ovary: a retrospective Japan Clear Cell Carcinoma Study. Int J Gynecol Cancer. 2010; 20:1506–1510. [PubMed: 21119366]

15. Al-Barrak J, Santos JL, Tinker A, et al. Exploring palliative treatment outcomes in women with advanced or recurrent ovarian clear cell carcinoma. Gynecol Oncol. 2011; 122:107–110. [PubMed: 21463887]

16. Yamaguchi K, Mandai M, Oura T, et al. Identification of an ovarian clear cell carcinoma gene signature that reflects inherent disease biology and the carcinogenic processes. Oncogene. 2010; 29:1741–1752. [PubMed: 20062075]

17. Stany MP, Vathipadiekal V, Ozbun L, et al. Identification of novel therapeutic targets in microdissected clear cell ovarian cancers. PLoS One. 2011; 6:e21121. [PubMed: 21754983]

18. Bitler BG, Aird KM, Zhang R. Epigenetic synthetic lethality in ovarian clear cell carcinoma: EZH2 and ARID1A mutations. Mol Cell Oncol. 2016; 3:e1032476. [PubMed: 27308548]

19. Rahman M, Nakayama K, Rahman MT, et al. Clinicopathologic and biological analysis of PIK3CA mutation in ovarian clear cell carcinoma. Hum Pathol. 2012; 43:2197–2206. [PubMed: 22705003]

20. Mabuchi S, Kawase C, Altomare DA, et al. Vascular endothelial growth factor is a promising therapeutic target for the treatment of clear cell carcinoma of the ovary. Mol Cancer Ther. 2010; 9:2411–2422. [PubMed: 20663925]

21. Han EK, Tahir SK, Cherian SP, et al. Modulation of paclitaxel resistance by annexin IV in human cancer cell lines. Br J Cancer. 2000; 83:83–88. [PubMed: 10883672]

22. Choi CH, Sung CO, Kim HJ, et al. Overexpression of annexin A4 is associated with chemoresistance in papillary serous adenocarcinoma of the ovary. Hum Pathol. 2013; 44:1017–1023. [PubMed: 23290009]

23. Schulz C, Boeck S, Heinemann V, et al. UGT1A1 genotyping: a predictor of irinotecan-associated side effects and drug efficacy? Anticancer Drugs. 2009; 20:867–879. [PubMed: 19770637]

24. Arakawa N, Miyagi E, Nomura A, et al. Secretome-based identification of TFPI2, a novel serum biomarker for detection of ovarian clear cell adenocarcinoma. J Proteome Res. 2013; 14:4340–4350.

25. Munksgaard P, Blaakaer J. The association between endometriosis and ovarian cancer: a review of histological, genetic and molecular alterations. Gynecol Oncol. 2012 Jan; 124(1):164–9. [PubMed: 22032835]

HIGHLIGHTS

- In early stage patients, PFS was better for OCCC than for SOC.

- In late-stage patients, OCCC was significantly associated with decreased OS.

- Treatment effect was influenced by histology.
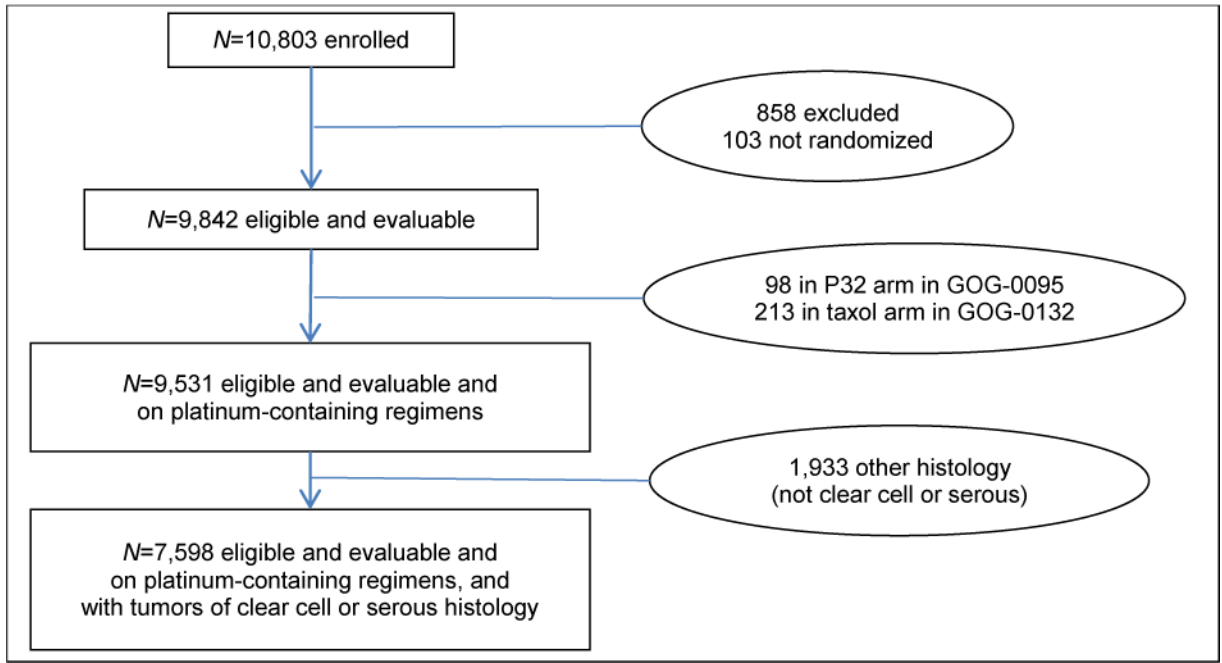
Figure 1.
Flowchart of Patient Exclusions
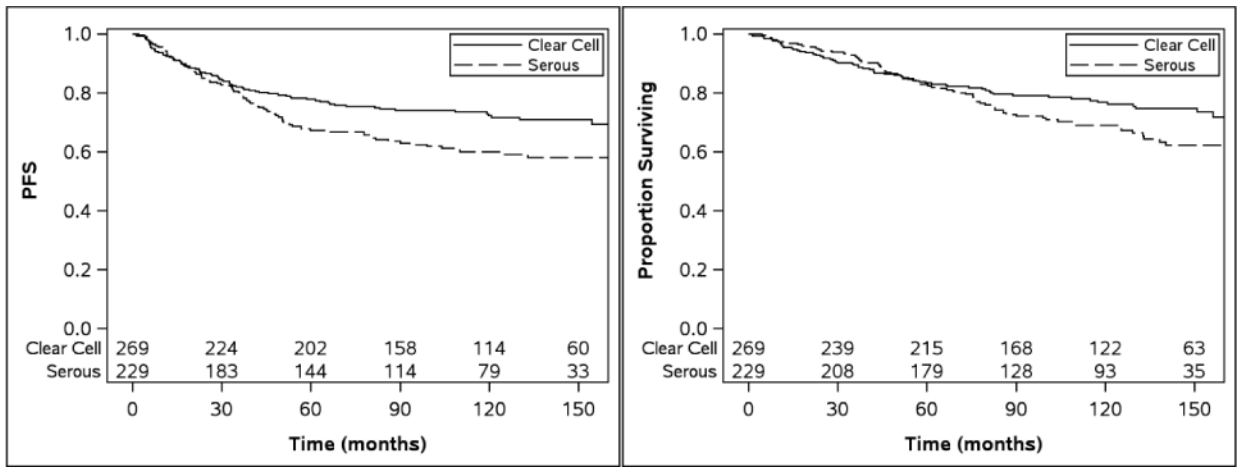
Figure 2.
PFS and OS in Patients with Stage I–II Tumors
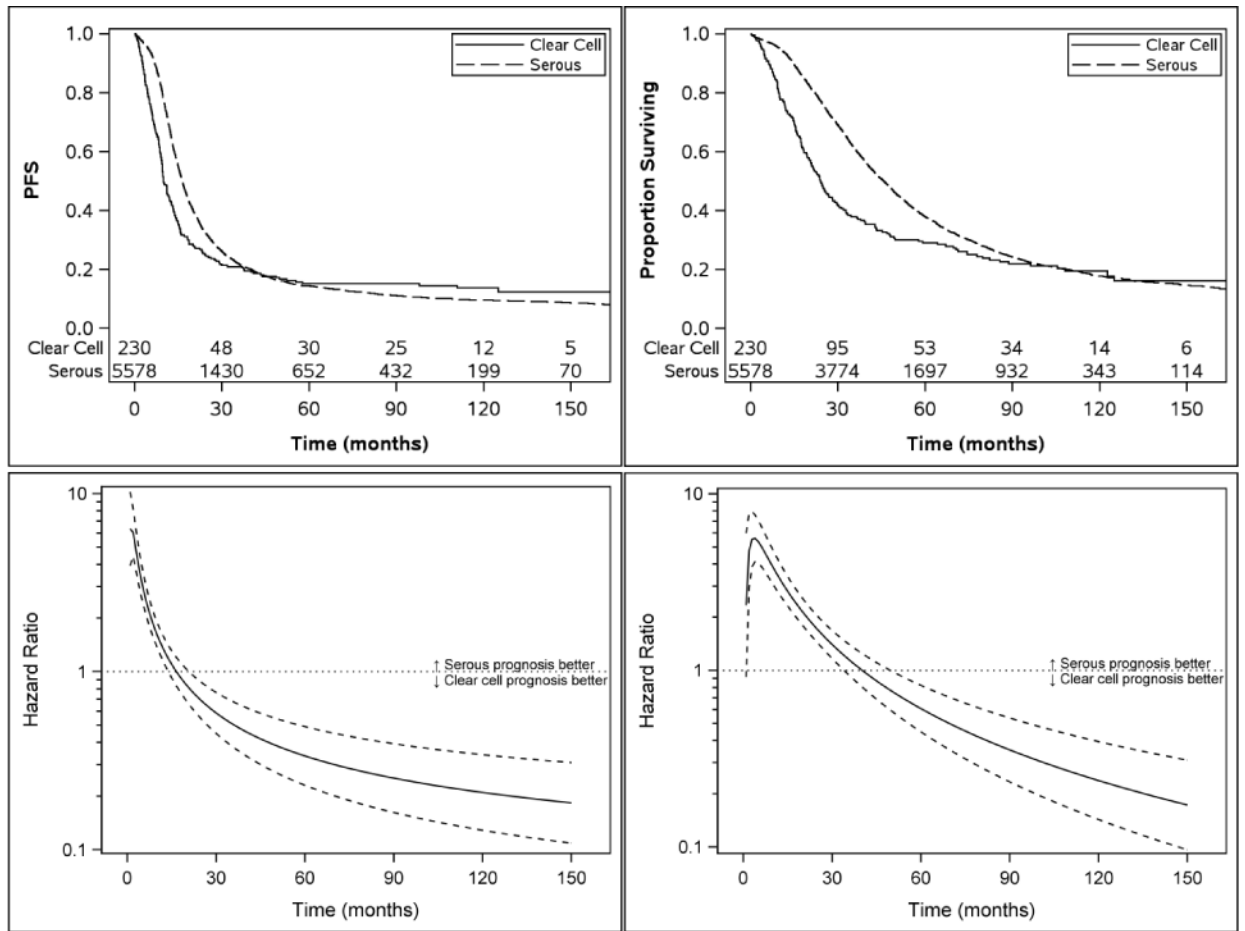
Figure 3.
PFS and OS for Time-varying Hazards Ratios in Patients with Stage III Tumors

Figure 4.
PFS and OS for Time-varying Hazards Ratios in Patients with Stage IV Tumors

Table 1

Protocol Treatment Arms by Cell Type All – Non-Excluded Patients (N=9,842)

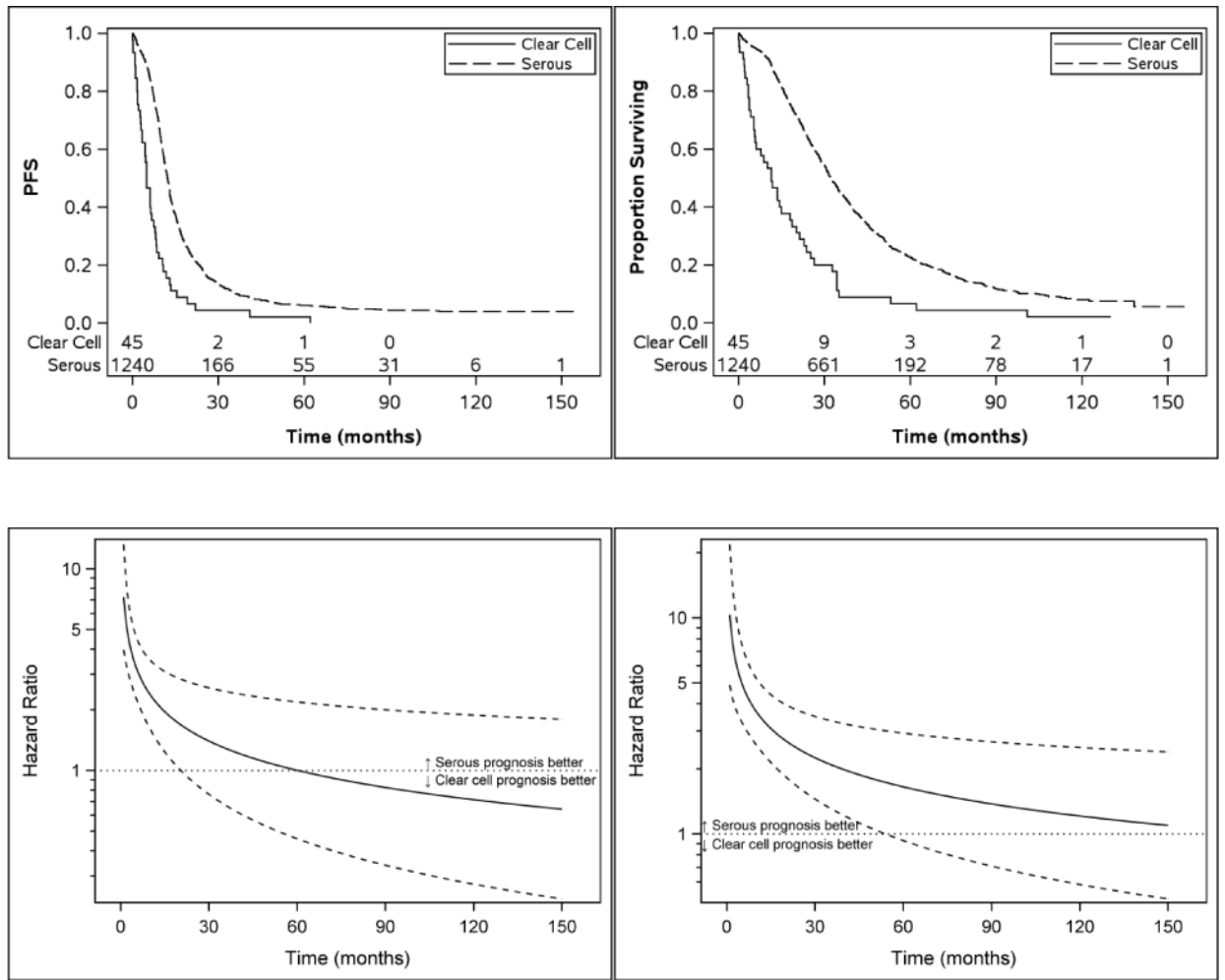| GOG Protocol/Treatment		Clear Cell, Serous, or Other					
		Clear Cell		Serous		Other	
		n	(%)	n	(%)	n	(%)
All		573	(6)	7233	(73)	2036	21
95	IP P32[†]	25	(26)	22	(22)	51	(52)
	Cyclophosphamide + Cisplatin	22	(21)	19	(18)	66	(62)
111	Cyclophosphamide + Cisplatin	5	(2)	131	(65)	66	(33)
	Paclitaxel + Cisplatin	3	(2)	141	(77)	40	(22)
114	Cyclophosphamide + Cisplatin	2	(4)	34	(62)	19	(35)
	Paclitaxel + Cisplatin	7	(3)	158	(70)	61	(27)
	Carboplatin, then Cisplatin + paclitaxel	8	(3)	150	(64)	78	(33)
132	Cisplatin	1	(1)	142	(71)	57	(29)
	Paclitaxel[†]	4	(2)	157	(74)	52	(24)
	Paclitaxel + Cisplatin	8	(4)	131	(65)	62	(31)
152	Cisplatin + Paclitaxel, 2nd surgery	4	(2)	163	(77)	46	(22)
	Cisplatin + Paclitaxel	3	(1)	159	(76)	47	(22)
157	Carboplatin + Paclitaxel × 3	52	(33)	34	(22)	70	(45)
	Carboplatin + Paclitaxel × 6	38	(26)	33	(23)	75	(51)
158	Cisplatin + Paclitaxel (24 hr)	10	(3)	281	(70)	109	(27)
	Carboplatin + Paclitaxel (3 hr)	21	(5)	290	(74)	81	(21)
162	Cisplatin + Paclitaxel (24 hr)	5	(4)	103	(74)	32	(23)
	Cisplatin + Paclitaxel (96 hr)	6	(4)	108	(77)	26	(19)
172	IV Paclitaxel + Cisplatin	9	(4)	170	(81)	31	(15)
	IV Paclitaxel + IP Cisplatin + IP Paclitaxel	11	(5)	157	(77)	36	(18)
175	Paclitaxel + Carboplatin followed by weekly Paclitaxel	80	(31)	69	(27)	105	(41)
	Paclitaxel + Carboplatin followed by observation	77	(31)	74	(29)	100	(40)
182	Paclitaxel + Carboplatin	19	(3)	614	(83)	105	(14)

	GOG Protocol/Treatment	Clear Cell, Serous, or Other					
		Clear Cell		Serous		Other	
		n	(%)	n	(%)	n	(%)
	Paclitaxel + Carboplatin + Gem	27	(4)	618	(84)	89	(12)
	Paclitaxel + PLD + Carboplatin	26	(4)	604	(81)	112	(15)
	Carboplatin + Topotecan followed by Paclitaxel + Carboplatin	23	(3)	600	(81)	114	(15)
	Carboplatin + Gemcitabine followed by Paclitaxel + Carboplatin	26	(4)	594	(81)	116	(16)
218	Carboplatin + Paclitaxel + Placebo, then Placebo	11	(2)	510	(88)	60	(10)
	Carboplatin + Paclitaxel + Bevacizumab, then Placebo	21	(4)	479	(84)	69	(12)
	Carboplatin + Paclitaxel + Bevacizumab, then Bevacizumab	19	(3)	488	(86)	61	(11)

Protocols 95, 157, and 175 include only early stage (I–II) cancers. All other protocols include only late stage (III–IV) cancers.

[†] Highlighted arms, excluded from analysis

Table 2

Baseline Characteristics by Cell Type – All Clear Cell and Serous Patients on Platinum-Containing Regimens Treated (N=7,598)

	N	Histology		p-value
		Clear Cell n (%)†	Serous n (%)†	
Total	7598	544 (7%)	7054 (93%)	
Age (y)				
<30	58	2 (0%)	56 (1%)	<.001
30–39	282	35 (6%)	247 (4%)	
40–49	1374	140 (26%)	1234 (17%)	
50–59	2347	196 (36%)	2151 (30%)	
60–69	2280	121 (22%)	2159 (31%)	
>=70	1257	50 (9%)	1207 (17%)	
Race				
Asian	240	43 (8%)	197 (3%)	<.001
Black	351	7 (1%)	344 (5%)	
Other	202	16 (3%)	186 (3%)	
White	6805	478 (88%)	6327 (90%)	
Stage				
[missing]	7	0	7	
I	355	226 (42%)	129 (2%)	<.001
II	143	43 (8%)	100 (1%)	
III	5808	230 (42%)	5578 (79%)	
IV	1285	45 (8%)	1240 (18%)	
Performance Status				
[missing]	62	2	60	
0	3442	290 (54%)	3152 (45%)	<.001
1	3497	229 (42%)	3268 (47%)	
2	593	22 (4%)	571 (8%)	
3	4	1 (0%)	3 (0%)	
Debulking§				
[missing]	2961	355	2606	
Optimal	3413	151 (80%)	3262 (73%)	0.045
Suboptim al	1224	38 (20%)	1186 (27%)	
Grade				
[missing]	329	296	33	
1	511	5 (2%)	506 (7%)	<.001
2	2394	30 (12%)	2364 (34%)	
3	4364	213 (86%)	4151 (59%)	

†Percentages are column percentages except for the total row, which are row percentages.

‡p-value is from Pearson chi-square test and excludes missing values.

§Debulking was assessed in advanced stage (III–IV) patients not early stage (I–II) patients and thus in only protocols 0111, 0132, 0158, 0172, and 0182.

Table 3

Hazard Ratios for Clear Cell vs. Serous – Overall and by Stage

Stage	m/n	HR (95% CI) for Clear Cell vs. Serous[†]		Non-PH p[‡¶]
		Unadjusted	Adjusted[‡]	
PFS				
All	6,842/7,598	0.47 (0.42, 0.52)	1.37 (1.20, 1.56)	—
I–II	164/498	0.69 (0.51, 0.94)	0.69 (0.50, 0.96)	0.145
III	5,102/5,808	1.26 (1.09, 1.45)	1.35 (1.16, 1.57)	<0.001
IV	1,209/1,285	2.79 (2.07, 3.76)	3.27 (2.39, 4.48)	0.001
Interaction	p[§]	<0.001	<0.001	
Overall Survival				
All	5,482/7,598	0.56 (0.49, 0.63)	1.58 (1.38, 1.82)	—
I–II	137/498	0.75 (0.54, 1.05)	0.76 (0.53, 1.09)	0.140
III	4,286/5,808	1.47 (1.23, 1.66)	1.54 (1.32, 1.80)	<0.001
IV	1,053/1,285	2.68 (1.98, 3.62)	3.41 (2.47, 4.70)	0.001
Interaction	p[§]	<0.001	<0.001	
Excluding Patients with Grade 1 Tumors				
PFS	5,482/7,598	0.56 (0.49, 0.63)	1.58 (1.38, 1.82)	—
OS	5,156/7,087	0.54 (0.48, 0.61)	1.54 (1.34, 1.77)	—

m = number of events. n = sample size (7 patients had missing stage).

[†] Reference group is serous

[‡] Adjusted for age and stratified by protocol and treatment arm, performance staus, and race

[¶] p-value for test of non-proportional hazards (PH): interaction of histology and log(time)

[§] Stage × Histology interaction p-values

Table 4

Treatment Effect in Clear Cell and Serous Patients – Protocols 0157 and 0175

Comparison (latter group is referent)	Cell Type	Stage 1/2 (%)	HR (95% CI)	Interaction *p*
PFS				
0157: Taxol carbo followed by: Weekly Taxol vs. Observation[†]	Clear Cell Serous	81/19 47/53	1.32 (0.62, 2.82) 0.42 (0.18, 0.99)	0.048
0175: Carbo + Taxol × 6 vs. Carbo + Taxol × 3[¶]	Clear Cell Serous	82/18 61/39	1.00 (0.52, 1.91) 0.56 (0.31, 1.00)	0.20
Survival				
0157: Taxol carbo followed by: Weekly Taxol vs. Observation[†]	Clear Cell Serous	89/11 54/46	1.10 (0.50, 2.43) 0.54 (0.22, 1.31)	0.236
0175: Carbo + Taxol × 6 vs. Carbo + Taxol × 3[¶]	Clear Cell Serous	86/14 64/36	1.37 (0.67, 2.80) 0.57 (0.28, 1.14)	0.086

Proportional hazards model adjusted for age, and stratified by performance status, race, and stage.

[†] *n*=2 observations deleted due to missing strata values.

[¶] *n*=2 observations deleted due to missing strata values.