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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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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.

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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, 9531 were eligible, evaluable and treated with platinum, of whom 544 (6%) had OCCC, 7054 (74%) had SOC, and 1933 (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.

1. 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.

2. 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

Table 1
Baseline characteristics by cell type – all clear cell and serous patients on platinum-containing regimens treated (N = 7598).

	Histology			p-Value‡
	N	Clear cell n (%)[a]	Serous n (%)[a]	
Total	7598	544 (7%)	7054 (93%)	
Age (y)				
<30	58	2 (0%)	56 (1%)	<0.001
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%)	<0.001
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%)	<0.001
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%)	<0.001
1	3497	229 (42%)	3268 (47%)	
2	593	22 (4%)	571 (8%)	
3	4	1 (0%)	3 (0%)	
Debulking[b]				
[Missing]	2961	355	2606	
Optimal	3413	151 (80%)	3262 (73%)	0.045
Suboptimal	1224	38 (20%)	1186 (27%)	
Grade				
[Missing]	329	296	33	
1	511	5 (2%)	506 (7%)	<0.001
2	2394	30 (12%)	2364 (34%)	
3	4364	213 (86%)	4151 (59%)	

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

[a] Percentages are column percentages except for the total row, which are row percentages. Highlighted arms, excluded from analysis.

[b] 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.

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