

Impact of Age and Primary Disease Site on Outcome in Women With Low-Grade Serous Carcinoma of the Ovary or Peritoneum: Results of a Large Single-Institution Registry of a Rare Tumor

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A B S T R A C T

Purpose

Low-grade serous carcinoma of the ovary (LGSOC) or peritoneum (LGSPC) is a rare subtype of ovarian or peritoneal cancer characterized by young age at diagnosis and relative resistance to chemotherapy. The purpose of this study is to report our updated experience with women diagnosed with LGSOC or LGSPC to assess the validity of our original observations.

Patients and Methods

Eligibility criteria for patients from our database were: stage I to IV LGSOC or LGSPC, original diagnosis before January 2012, and adequate clinical information. All patients were included in progression-free survival, overall survival, and multivariable Cox regression analyses. A subset analysis was performed among patients with stage II to IV low-grade serous carcinoma treated with primary surgery followed by platinum-based chemotherapy.

Results

We identified 350 eligible patients. Median progression-free survival was 28.1 months; median overall survival was 101.7 months. In the multivariable analysis, compared with women age \leq 35 years, those diagnosed at age $>$ 35 years had a 43% reduction in likelihood of dying (hazard ratio, 0.53; 95% CI, 0.37 to 0.74; $P < .001$). Having disease present at completion of primary therapy was associated with a 1.78 increased hazard of dying compared with being clinically disease free ($P < .001$). Similar trends were noted in the smaller patient cohort. In this cohort, women with LGSPC had a 41% decreased chance of dying (hazard ratio, 0.59; 95% CI, 0.36 to 0.98; $P = .04$) compared with those with LGSOC.

Conclusion

Women age $<$ 35 years with low-grade serous carcinoma and those with persistent disease at completion of primary therapy have the worst outcomes. Patients with LGSPC seem to have a better prognosis than those with LGSOC.

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INTRODUCTION

Ten years ago, our group first proposed the concept of a binary system for grading ovarian serous carcinoma.¹ Since then, the clinical behavior of low-grade serous carcinoma of the ovary (LGSOC) or peritoneum (LGSPC) has been well characterized, and the two-tier grading system has become widely accepted.²⁻¹² Concomitantly, our understanding of the molecular biology and genetics of low-grade serous carcinoma has greatly expanded.¹³⁻²⁴

In 2006, we reported our clinical experience with women with newly diagnosed stage II to IV

LGSOC.³ The salient features of this cohort included: relatively young age at diagnosis, relative resistance to chemotherapy, and prolonged overall survival (OS). In subsequent publications, we presented our experience with patients with LGSOC who had received neoadjuvant chemotherapy and those with LGSPC.^{5,8} In 2007, we established a longitudinal database to systematically capture demographic and clinical information on all women diagnosed with low-grade serous tumors seen at our institution. The purpose of this study is to present our experience with a larger cohort of women diagnosed with LGSOC or LGSPC to re-evaluate the validity of our original observations.

PATIENTS AND METHODS

An institutional review board–approved longitudinal database—the Low-Grade Serous Tumor Database—was established in 2007, and patients seen at MD Anderson Cancer Center with the following diagnoses are eligible for inclusion in the database: ovarian tumors of low malignant potential, primary peritoneal tumors of low malignant potential, LGSOC, and LGSPC. Data collection is both retrospective and prospective in nature. All patients included in the database have signed informed consent. A consent waiver for those patients who had not been seen for ≥ 1 year from the date of protocol activation was granted by the institutional review board. Eligibility criteria for patients included in this study were: stage I to IV LGSOC or LGSPC, original diagnosis before January 1, 2012, and adequate clinical information. Two distinct groups of patients were analyzed: first, all patients who met these eligibility criteria, and second, a subset of eligible patients who met the same eligibility criteria contained in our initial report (ie, stage II to IV low-grade serous carcinoma and treatment with primary surgery followed by platinum-based chemotherapy).³ The major difference in this report is that we included both LGSOC and LGSPC.

Review of the database identified 597 potentially eligible patients. We excluded 247 patients for the following reasons: diagnosis other than pure de novo low-grade serous carcinoma ($n = 171$), diagnosis after December 31, 2011 ($n = 72$), or limited clinical information ($n = 4$). For the more homogeneous subset analyses, patients were excluded if they: had stage I disease ($n = 7$), did not undergo primary cytoreductive surgery ($n = 33$), did not receive chemotherapy ($n = 11$) or received chemotherapy but no details were available ($n = 8$), or did not receive platinum-based chemotherapy ($n = 4$; Appendix Fig A1, online only).

Pathology slides of all patients were reviewed by MD Anderson gynecologic pathologists and documented as LGSOC or LGSPC. Excluded from this study were patient cases of nonserous histotypes, serous tumors of low malignant potential, low-grade serous carcinoma after a diagnosis of serous tumor of low malignant potential, and high-grade serous carcinoma. Criteria for diagnosis of low-grade serous carcinoma have been previously reported.^{1,8}

Database elements included demographic information, gynecologic history, obstetric history, details of primary and secondary surgical procedures, International Federation of Gynecology and Obstetrics stage, perioperative studies, details of systemic therapies, cancer antigen 125 (CA-125) data, disease status at completion of primary treatment, date of initial disease progression, disease status at date of last contact, and date of last contact or death.

Statistical analyses were performed using SPSS software (version 21; SPSS, Chicago, IL). Progression-free survival (PFS) was calculated from the date of primary surgery (or date of tissue diagnosis) to date of disease progression or recurrence or date of last contact or death resulting from ovarian cancer. OS was calculated from the date of primary surgery (or date of tissue diagnosis) to date of last contact or death resulting from any cause. The cumulative distributions of OS and PFS durations were estimated using the Kaplan-Meier method.²⁵ The log-rank test was used to compare differences between survival curves. Cox proportional hazards regression was used to model the association of important clinical variables and PFS and OS. Variables with P values $< .25$ on univariable analysis were included in the multivariable models. All P values were two sided. P values $< .05$ were considered statistically significant.

RESULTS

Study Population Analyses

A total study population of 350 patients was identified. Demographic and clinical characteristics are listed in Table 1. As noted, most patients were white, had LGSOC, had stage III disease, and received postoperative chemotherapy.

Median follow-up time for the entire group was 72.4 months. Median PFS was 28.1 months (95% CI, 24.0 to 32.2), and median OS was 101.7 months (95% CI, 91.0 to 112.4). At the time of analysis, 55

Table 1. Characteristics of Patients With Low-Grade Serous Carcinoma of Ovary or Peritoneum (N = 350)

Characteristic	No.	%
Age at diagnosis, years		
Median	46.5	
Mean	46.9	
Range	11.9 to 81.1	
BMI at diagnosis, kg/m ^{2a}		
Median	26.9	
Mean	27.9	
Range	16.8 to 52.8	
Pretreatment CA-125 ^b		
Median	146.3	
Mean	401.1	
Range	6.0 to 10,000.0	
Race		
White	294	84.0
Black	19	5.4
Hispanic	31	8.9
Other	6	1.7
Smoking history ^c		
Never	216	61.7
Former or current	133	38.0
Parity ^d		
Nulliparous	94	26.9
Parous	254	72.6
Site		
Ovary	275	78.6
Peritoneum	75	21.4
Surgery		
None	5	1.4
Primary cytoreductive	317	90.6
Interval cytoreductive	28	8.0
Residual disease at completion of primary cytoreductive surgery ^e		
No gross residual	53	16.7
Gross residual	199	62.8
Residual disease at completion of interval cytoreductive surgery ^f		
No gross residual	6	21.4
Gross residual	18	64.3
FIGO stage ^g		
I	7	2.0
II	8	2.3
III	292	83.4
IV	29	8.3
Primary treatment ^h		
Adjuvant chemotherapy	305	87.4
Neoadjuvant chemotherapy	31	8.9
No chemotherapy	13	3.7
Chemotherapy		
Platinum	324	98.5
Nonplatinum	5	1.5
Disease status at completion of primary treatment ⁱ		
NED	169	57.3
Disease present	126	42.7

Abbreviations: BMI, body mass index; CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; NED, no evidence of disease.

^aNot available for 126 patients.

^bNot available for 145 patients.

^cNot available for one patient.

^dMissing for two patients.

^eNot available for 65 patients.

^fMissing for four patients.

^gNot available for 14 patients.

^hModality of chemotherapy was missing for one patient; 10 of 305 patients who received adjuvant chemotherapy also received concurrent hormonal therapy; one of 13 patients who did not undergo chemotherapy was treated with hormonal agent.

ⁱNot available for 55 patients.

women (15.7%) were alive and disease free, 103 (29.4%) were alive with disease, six (1.7%) were alive with unknown disease status, 177 (50.6%) were dead as a result of disease, and nine were dead as a result of other causes.

Of the 295 patients for whom clinical information was available at completion of primary treatment, 169 (57.3%) were clinically disease free based on the following examinations, tests, or record statements: abdominopelvic computed tomography, serum CA-125, or physical examination. A total of 242 patients received platinum and taxane-based chemotherapy, and 148 patients received maintenance therapy before first recurrence or progression; of this number, 62 patients received hormonal agents, 63 received chemotherapy, and 14 received hormonal therapy and chemotherapy.

Neither progression nor recurrence occurred in 52 women; they were censored. Women with LGSPC had significantly longer PFS and OS compared with women with LGSOC (PFS: 36.2 v 25.4 months; $P = .02$; and OS: 129.0 v 95.2 months; $P = .01$, respectively). Survival outcomes differed by age. Women diagnosed at age > 35 years had a longer median PFS compared with women diagnosed at age ≤ 35 years (32.6 months; 95% CI, 26.8 to 38.5; and 18.8 months; 95% CI, 14.2 to 23.5; $P < .001$, respectively). Detailed outcomes for PFS and OS of the 350 women are listed in in Appendix Table A1 (online only).

Univariable analysis for PFS showed that primary site, stage (II v III or IV), age group (≤ 35 v > 35 years), race (white v nonwhite), parity (nulliparous v parous), and clinical disease status at the end of primary therapy (no evidence of disease v disease present) met the criteria of $P < .25$ for inclusion in the multivariable analysis. Only age and disease status at the end of primary therapy remained significant in the multivariable setting. Compared with women age ≤ 35 years, those age > 35 years at diagnosis had a lower likelihood of progression or recurrence (hazard ratio [HR], 0.55; 95% CI, 0.38 to 0.79; $P ≤ .001$). Women with disease present at the end of primary therapy had a 1.79 greater chance of progression or recurrence compared with those without evidence of disease at the end of primary treatment (95% CI, 1.30 to 2.46; $P < .001$). The results of univariable and multivariable Cox proportional hazards regression for PFS for the overall study population of 350 patients are listed in Appendix Table A2 (online only).

Univariable analysis for OS showed that primary site, age group, maintenance therapy, race, and disease status at the end of primary therapy met the criteria of $P < .25$ for inclusion in the multivariable analysis. After adjusting for these variables in the multivariable analysis, only age group and disease status at the end of primary therapy remained statistically significant. Women who were older than age 35 years at diagnosis had just under half the risk of dying compared with women who were age 35 years or younger at diagnosis (HR, 0.53; 95% CI, 0.37 to 0.74; $P < .001$). Presence of disease at completion of primary therapy was associated with a 1.78 increased hazard of dying compared with no clinical evidence of disease at the end of primary treatment (95% CI, 1.30 to 2.45; $P < .001$). Results of univariable and multivariable Cox proportional hazards regression for OS for the overall study population of 350 patients are available in Appendix Table A3 (online only).

Subgroup Analysis

A subgroup analysis was conducted among 287 eligible patients who were diagnosed with stage II to IV LGOSC or LGPSC and treated with primary cytoreductive surgery followed by platinum-based che-

motherapy. Table 2 lists clinical and demographic information for this group.

Median follow-up time was 72.5 months. Median PFS was 25.3 months (95% CI, 21.6 to 29.0), and median OS was 97.8 months (95% CI, 88.6 to 107.1). At the time of analysis, 38 women

Table 2. Characteristics of Patients With Low-Grade Serous Carcinoma of Ovary or Peritoneum Treated With Primary Cytoreductive Surgery Followed by Platinum-Based Chemotherapy (n = 287)

Characteristic	No.	%
Age at diagnosis, years		
Median	46.1	
Mean	46.3	
Range	11.9 to 79.8	
BMI at diagnosis, kg/m ² *		
Median	26.9	
Mean	28.1	
Range	16.8 to 52.8	
Pretreatment CA-125†		
Median	142.1	
Mean	432.8	
Range	6.0 to 10,000.0	
No. of cycles of chemotherapy		
Median	6.0	
Mean	6.5	
Range	1.0 to 16.0	
Race		
White	241	84.0
Black	16	5.6
Hispanic	25	8.7
Other	5	1.7
Smoking history‡		
Never	188	65.5
Former or current	98	34.1
Parity§		
Nulliparous	80	27.9
Parous	205	71.4
Site		
Ovary	227	79.1
Peritoneum	60	20.9
FIGO stage		
II	8	2.8
III	251	87.5
IV	22	7.7
Residual disease at completion of primary cytoreductive surgery¶		
No gross residual	49	17.1
Gross residual	187	65.2
Type of initial systemic therapy		
Adjuvant chemotherapy	278	96.9
Adjuvant chemotherapy plus hormonal therapy	9	3.1
Clinical disease status on completion of primary therapy#		
No evidence of disease	152	53.0
Disease present	102	35.5

Abbreviations: BMI, body mass index; CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics.

*Not available for 112 patients.

†Missing for 103 patients.

‡Not available for one patient.

§Not available for two patients.

||Missing for six patients.

¶Not available for 51 patients.

#Not available for 33 patients.

(13.2%) were alive and disease free, 85 (29.6%) were alive with disease, three (1%) were alive with unknown disease status, 153 (53.3%) were dead as a result of disease, and eight (2.8%) were dead as a result of other causes.

Differences in PFS and OS are listed in Table 3. Neither progression nor recurrence occurred in 33 women; they were censored. Women with LGSPC had significantly longer PFS and OS compared

with women with LGSOC (36.2 v 23.8 months; $P = .007$; 127.0 v 90.0 months; $P = .007$, respectively). Women diagnosed at age > 35 years had longer PFS than younger women (31.2 months; 95% CI, 25.0 to 37.4; and 17.8 months; 95% CI, 15.5 to 21.2; $P < .001$, respectively). Similarly, women in the older age group had longer OS than women diagnosed at age \leq 35 years (102.9 months; 95% CI, 80.7 to 125.2; and 72.8 months; 95% CI, 51.2 to 94.4; $P < .001$, respectively).

Table 3. Median PFS and OS of Patients With Low-Grade Serous Carcinoma of Ovary or Peritoneum Treated With Primary Cytoreductive Surgery Followed by Platinum-Based Chemotherapy (n = 287)

Variable	No. of Patients	PFS ^a			OS		
		Months	95% CI	<i>P</i>	Months	95% CI	<i>P</i>
Age, years							
≤ 35	78	17.8	15.5 to 20.2	< .001	72.8	51.2 to 94.4	< .001
> 35	209	31.2	25.0 to 37.4		102.9	80.7 to 125.2	
Race				.28			.37
White	241	24.5	20.9 to 28.1		93.6	83.3 to 103.8	
Nonwhite	46	31.2	13.7 to 48.7		127.0	85.3 to 168.7	
Parity ^b				.11			.34
Nulliparous	80	20.6	15.0 to 26.2		97.8	78.6 to 117.1	
Parous	205	26.4	22.0 to 30.8		97.5	87.1 to 107.9	
Smoking history ^c				.65			.71
Never	188	24.4	22.0 to 26.8		86.8	43.8 to 129.8	
Ever	98	30.0	23.5 to 36.5		97.5	88.0 to 107.0	
BMI, kg/m ^{2d}				.86			.88
Normal	66	29.7	19.5 to 40.0		103.5	89.5 to 117.5	
Overweight	52	30.0	14.3 to 45.7		102.8	64.1 to 141.5	
Obese	57	34.4	25.3 to 43.4		134.4	84.3 to 184.5	
Pretreatment CA-125 ^e				.01			.52
< 35	28	41.0	21.1 to 60.9		134.4	52.9 to 216.0	
> 35	156	22.0	18.6 to 25.5		91.3	82.6 to 100.00	
FIGO stage ^f				.44			.71
II	8	22.5	0.0 to 57.1		86.8	43.8 to 129.8	
III to IV	273	24.7	21.5 to 27.9		97.5	88.0 to 107.0	
Site				.007			.01
Ovary	241	23.8	20.7 to 26.8		90.0	76.8 to 130.1	
Peritoneal	46	36.2	20.6 to 51.7		127.0	91.0 to 163.0	
Residual disease (primary CRS) ^g				.57			.69
No gross residual	49	23.4	16.9 to 30.0		97.8	72.2 to 123.5	
Gross residual	187	23.9	19.7 to 28.1		93.1	82.2 to 104.0	
Chemotherapy				.25			.35
Adjuvant chemotherapy	278	25.2	21.6 to 28.8		97.5	87.8 to 107.2	
Chemotherapy (any) plus hormonal therapy	9	32.2	9.4 to 55.0		—	—	
Maintenance ^h				.46			.03
None or missing information	159	26.4	20.0 to 32.7		112.9	86.2 to 139.5	
Hormonal therapy	50	25.9	13.4 to 38.3		100.6	80.9 to 120.4	
Chemotherapy	57	23.8	21.5 to 26.1		79.5	71.2 to 87.9	
Chemotherapy (any) plus hormonal therapy	12	19.7	0.0 to 42.9		87.5	30.8 to 144.2	
Disease status at completion of primary treatment ⁱ				< .001			< .001
NED	152	33.4	27.1 to 39.7		112.9	88.1 to 137.6	
Disease present	102	17.2	12.6 to 21.8		74.6	64.8 to 84.5	

Abbreviations: BMI, body mass index; CA-125, cancer antigen 125; CRS, cytoreductive surgery; FIGO, International Federation of Gynecology and Obstetrics; NED, no evidence of disease; OS, overall survival; PFS, progression-free survival.

^aEighteen patients were not included in PFS calculations, because exact dates of recurrence were not documented in medical record, or there was interval of time for which no clinical data were available to document patient was diagnosed with recurrent disease.

^bMissing for two patients.

^cNot available for one patient.

^dMissing for 112 patients.

^eMissing for 103 patients.

^fNot available for six patients.

^gMissing for 51 patients.

^hConsidered miscellaneous in nine patients.

ⁱNot available for 33 patients.

Univariable and multivariable Cox proportional hazards regression results for PFS and OS are listed in Tables 4 and 5, respectively. Variables with $P < .25$ on univariable analysis for PFS included primary site of disease, chemotherapy (adjuvant v adjuvant plus hormones), disease status at completion of primary therapy, age group (≤ 35 v > 35 years), parity (nulliparous v parous), and CA-125 at diagnosis (≤ 35 v > 35 U/mL). After adjusting for these in the multivariable setting, only age, primary site, and disease status at end of primary therapy remained signif-

icantly predictive of progression or recurrence. Compared with women age ≤ 35 years, those age > 35 years had a much lower likelihood of progression (HR, 0.55; 95% CI, 0.38 to 0.81; $P = .002$). Women with LGSPC had a lower risk of disease progression compared with women with LGSOC (HR, 0.65; 95% CI, 0.43 to 1.00; $P = .048$). Having disease present at completion of primary therapy was associated with a 1.93-fold chance of disease progression compared with no clinical evidence of disease at the end of primary treatment. When age was included as a

Table 4. Univariable and Multivariable Cox Proportional Hazards for PFS of Patients With Low-Grade Serous Carcinoma of Ovary or Peritoneum Treated With Primary Cytoreductive Surgery Followed by Platinum-Based Chemotherapy (n = 287)^a

Variable	Univariable			Multivariable		
	HR	95% CI	P	HR	95% CI	P
Age, years						
≤ 35 (reference)	—	—		—	—	
> 35	0.51	0.37 to 0.71	< .001	0.55	0.38 to 0.81	.002
Race						
White (reference)	—	—				
Nonwhite	0.82	0.58 to 1.17	.28			
Parity ^b						
Nulliparous (reference)	—	—				
Parous	0.79	0.60 to 1.06	.11			
Smoking history ^c						
Never (reference)	—	—				
Ever	0.97	0.72 to 1.23	.65			
BMI, kg/m ^{2d}						
Normal (reference)	—	—	.86			
Overweight	1.00	0.66 to 1.54	.99			
Obese	0.91	0.61 to 1.36	.63			
Pretreatment CA-125 ^e						
< 35 (reference)	—	—				
> 35	1.86	1.15 to 3.02	.01			
FIGO stage ^f						
II	—	—				
III to IV	1.35	0.63 to 2.87	.44			
Site						
Ovary (reference)	—	—		—	—	
Peritoneal	0.63	0.45 to 0.88	.007	0.65	0.43 to 1.00	.048
Residual disease (primary CRS) ^g						
No gross residual	—	—				
Gross residual	1.11	0.78 to 1.58	.57			
Chemotherapy						
Adjuvant chemotherapy	—	—				
Chemotherapy (any) plus hormonal therapy	0.60	0.25 to 1.45	.25			
Maintenance			.46			
None or missing information	—	—				
Hormonal therapy	0.92	0.64 to 1.32	.66			
Chemotherapy	1.25	0.91 to 1.73	.17			
Chemotherapy plus hormonal therapy	1.10	0.58 to 2.10	.77			
Disease status at completion of primary treatment ^h						
NED (reference)	—	—		—	—	
Disease present	1.92	1.45 to 2.54	< .001	1.93	1.38 to 2.71	< .001

Abbreviations: BMI, body mass index; CA-125, cancer antigen 125; CRS, cytoreductive surgery; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; NED, no evidence of disease; PFS, progression-free survival.

^aEighteen patients were not included in PFS calculations, because exact dates of recurrence were not documented in medical record, or there was interval of time for which no clinical data were available to document patient was diagnosed with recurrent disease.

^bNot available for two patients.

^cMissing for one patient.

^dNot available for 112 patients.

^eMissing for 103 patients.

^fNot available for six patients.

^gMissing for 51 patients.

^hNot available for 33 patients.

Table 5. Univariable and Multivariable Cox Proportional Hazards for OS of Patients With Low-Grade Serous Carcinoma of Ovary or Peritoneum Treated With Primary Cytoreductive Surgery Followed by Platinum-Based Chemotherapy (n = 287)

Variable	Univariable			Multivariable		
	HR	95% CI	P	HR	95% CI	P
Age, years						
≤ 35 (reference)	—	—		—	—	
> 35	0.51	0.37 to 0.71	< .001	0.55	0.39 to 0.79	.001
Race						
White (reference)	—	—		—	—	
Nonwhite	0.83	0.54 to 1.26	.37			
Parity*						
Nulliparous (reference)	—	—		—	—	
Parous	0.85	0.60 to 1.19	.34			
Smoking history†						
Never (reference)	—	—		—	—	
Ever	0.89	0.64 to 1.24	.48			
BMI, kg/m ² ‡						
Normal (reference)	—	—	.88			
Overweight	1.07	0.61 to 1.87	.82			
Obese	0.91	0.53 to 1.59	.75			
Pretreatment CA-125§						
< 35 (reference)	—	—		—	—	
> 35	1.21	0.68 to 2.17	.52			
FIGO stage						
II (reference)	—	—		—	—	
III to IV	1.16	0.53 to 2.52	.71			
Site						
Ovary (reference)	—	—		—	—	
Peritoneal	0.55	0.34 to 0.88	.01	0.59	0.36 to 0.98	.04
Residual disease (primary CRS)						
No gross residual (reference)	—	—		—	—	
Gross residual	1.09	0.72 to 1.66	.69			
Chemotherapy						
Adjuvant chemotherapy (reference)	—	—		—	—	
Chemotherapy (any) plus hormonal therapy	0.52	0.13 to 2.10	.36			
Maintenance						
None or missing information (reference)	—	—	.03	—	—	
Hormonal therapy	1.05	0.64 to 1.73	.86			
Chemotherapy	1.72	1.19 to 2.48	.004			
Chemotherapy plus hormonal therapy	1.38	0.64 to 2.98	.42			
Disease status at completion of primary treatment¶						
NED (reference)	—	—		—	—	
Disease present	2.02	1.44 to 2.85	< .001	1.99	1.41 to 2.81	< .001

Abbreviations: BMI, body mass index; CA-125, cancer antigen 125; CRS, cytoreductive surgery; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; NED, no evidence of disease; OS, overall survival.

*Missing for two patients.

†Not available for one patient.

‡Not available for 112 patients.

§Not available for 103 patients.

||Missing for 51 patients.

¶Not available for 33 patients.

continuous variable, the results did not change appreciably (primary site: HR, 0.63; 95% CI, 0.41 to 0.96; $P = .03$; and disease status at completion of primary therapy: HR, 2.02; 95% CI, 1.45 to 2.83; $P < .001$).

Variables that resulted in $P < .25$ by univariable Cox proportional hazards regression for OS included primary site, age group, maintenance therapy, and clinical disease status on completion of chemotherapy. On multivariable analysis, maintenance therapy fell out of the model. The final model showed that a diagnosis of LGSPC conferred a decreased chance of dying (HR, 0.59; 95% CI, 0.36 to 0.98; $P = .04$), whereas presence of disease at completion of primary ther-

apy was associated with an almost two-fold chance of dying compared with no clinical evidence of disease at completion of primary therapy (HR, 1.99; 95% CI, 1.41 to 2.81; $P < .001$). Women who were diagnosed at age > 35 years had a lower risk of dying compared with younger patients (HR, 0.55; 95% CI, 0.39 to 0.79; $P < .001$). Figure 1 shows the Kaplan-Meier survival curves by age group (log-rank $P < .001$). When age was included as a continuous variable, only primary site and clinical disease status at completion of primary therapy remained in the model (HR, 0.56; 95% CI, 0.34 to 0.92; $P = .02$; and HR, 2.05; 95% CI, 1.46 to 2.89; $P < .001$, respectively).

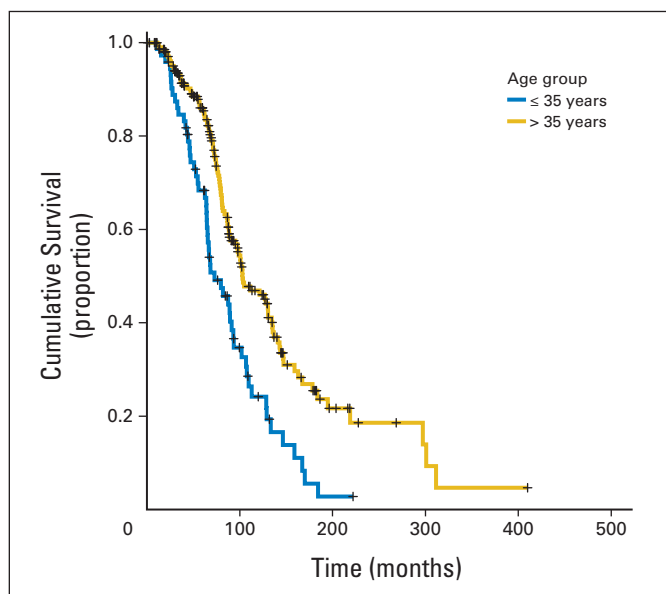


Fig 1. Overall survival by age group at diagnosis of 287 patients with stage II to IV low-grade serous carcinoma of ovary or peritoneum treated with primary cytoreductive surgery followed by platinum-based chemotherapy.

Because of the observation that women with LGSPC had better PFS and OS outcomes than those with LGSOC, we performed an exploratory analysis for the smaller, more homogeneous cohort ($n = 287$) focused on primary site of disease. There were statistically significant differences between patients with LGSOC and LGSPC for serum CA-125 level at time of diagnosis (173.5 v 54.5 U/mL; $P = .007$), body mass index (25.7 v 28.8 kg/m²; $P = .002$), and age (median, 44.3 v 48.0 years; $P = .015$). There were no significant differences in the proportion of patients with LGSOC and LGSPC for serum CA-125 at diagnosis above normal, disease-free status at completion of primary therapy, or age category. There was a statistically significant difference in the proportion of patients with LGSOC versus LGSPC with respect to no gross residual and gross residual disease. A higher percentage of patients with LGSPC had gross residual disease at the end of primary surgery compared with those with LGSOC (91.7% v 76.1% ; $P = .017$). Similar trends were also observed for the entire cohort of 350 patients.

We grouped the entire cohort of 350 patients based on quartiles of OS times for which complete survival data were available: quartile one, 0 to 55.74; quartile two, 55.74 to 78.05; quartile three, 78.05 to 103.13; and quartile four, ≥ 108.13 months. We then compared patient characteristics of deceased patients in the lowest and highest quartiles. Significant differences between the two subgroups were observed for median OS (33.3 v 143.1 months; $P < .001$) and having no disease present at completion of primary therapy (37.2% v 81.1% ; $P < .001$). Age differences between the two quartiles were also significant ($P = .02$). The proportion of patients age ≤ 35 years was significantly higher in the lowest OS quartile (68.8% v 31.2% ; $P = .018$). In addition, when we reviewed the 15 patients in the highest quartile who were still alive and disease free, the only patient characteristics that seemed to reveal a trend were age at diagnosis and disease status at completion of primary therapy. All 15 patients were age ≥ 35 years, and 11 (85%) of 13 for whom disease status at completion of primary therapy was known were disease free.

DISCUSSION

The principal findings of this study confirm the results of our original publication, indicating that relative to patients with high-grade ovarian or peritoneal cancers, women with low-grade serous carcinoma are younger on average and have prolonged OS.³ In addition, we found that three factors seemed to have a significant influence on patient outcomes: disease status at completion of primary treatment, age, and primary site of disease. The findings related to these variables seemed to be consistent for both cohorts analyzed.

As in our original study, $> 40\%$ of women had persistent disease at completion of primary treatment, and this factor resulted in significantly shorter median PFS and median OS compared with those women who were clinically disease free at completion of primary treatment. In multivariable regression analyses for OS, HR regarding disease persistence was 1.77 for all 350 patients and 1.96 for the cohort of 287 patients. Because most ovarian cancer trials do not report disease status at completion of primary treatment, we cannot directly compare our study population with those in prospective clinical trials. However, it is our clinical impression that persistent disease rates $> 40\%$ may be higher than those observed in patients with metastatic ovarian cancer of all histologic subtypes. Such a high rate of disease persistence may reflect relative resistance to chemotherapy—an observation also supported by reports of chemotherapy in the neoadjuvant and recurrent settings.^{5,6} Although platinum-based chemotherapy remains the standard first-line treatment for these patients, the evidence strongly suggests that randomized clinical trials testing different agents in this setting are warranted.

In this larger long-term follow-up study, two new observations related to age at diagnosis and primary site of disease—ovary versus peritoneum—emerge. Patients age ≤ 35 years old, who comprised $> 25\%$ of the study population, had a significantly worse outcome for both PFS and OS compared with women age > 35 years. Interestingly, breast cancer studies have revealed a similar trend; younger patients with breast cancer have a worse prognosis compared with their older counterparts.^{26,27} In one study of women with invasive breast cancer identified from the British Columbia Cancer Agency Breast Cancer Outcomes Database, age < 40 years predicted inferior relapse-free survival and OS for luminal breast cancer (positive for estrogen and/or progesterone receptor and negative for human epidermal growth factor receptor 2).²⁷ Canello et al²⁸ found that patients with luminal breast cancer age < 35 years had a significantly increased risk of recurrence and death when compared with older patients with similar characteristics. Freedholm et al²⁶ found that among all age groups, the 5-year relative survival ratio was lowest in women age 20 to 34 years. The fact that a high percentage of metastatic low-grade serous carcinomas also have estrogen or progesterone receptor positivity indicates that there may be some relationship between hormonal receptor positivity and poor prognosis in young patients.¹⁰ In addition, it is possible that there may be some estrogenic effects in younger patients compared with older patients regardless of whether fertility-sparing surgery is performed. Such observations clearly warrant further study.

In addition, women with LGSPC had a statistically significantly superior median PFS and median OS compared with patients with LGSOC in both cohorts. This observation was unexpected, and whether it is real or simply chance remains to be elucidated. For ovarian and primary peritoneal cancers of all histologic subtypes,

studies have reported conflicting survival comparisons, with some studies showing equivalent OS times and others indicating worse OS times for primary peritoneal cancer. Two recent, large population-based studies of serous histology revealed a significantly worse prognosis for primary peritoneal cancer compared with primary ovarian cancer.^{29,30}

The limitations of an observational study such as this are well characterized and include incomplete data, a long study period, referral bias, inconsistent therapies, changing detection methods, and other confounding factors. Nevertheless, this report details information of a large cohort of women with a rare ovarian cancer and is hypothesis generating, potentially leading to advances that will make a difference for women with this condition.

In summary, our study not only strengthens the original observations of our group but also provides new insights into the influence of age at diagnosis, disease status at completion of primary treatment, and primary site of disease on patient outcomes. In particular, the finding that the youngest cohort seemed to have a significantly worse prognosis, in the context of a similar phenomenon in women with

luminal breast cancer, raises the issue of hormonal influences and will, it is hoped, encourage additional research in this area.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Impact of Age and Primary Disease Site on Outcome in Women With Low-Grade Serous Carcinoma of the Ovary or Peritoneum: Results of a Large Single-Institution Registry of a Rare Tumor

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Appendix

Table A1. Median PFS and OS of Patients With Low-Grade Serous Carcinoma of Ovary or Peritoneum (N = 350)

Variable	No. of Patients	PFS ^a			OS		
		Months	95% CI	P	Months	95% CI	P
Age, years				< .001			< .001
≤ 35	88	18.8	14.2 to 23.5		79.7	58.2 to 101.3	
> 35	262	32.6	26.8 to 38.5		111.3	91.4 to 131.2	
Race				.11			.06
White	294	26.2	22.4 to 29.9		98.8	88.6 to 108.8	
Nonwhite	56	41.6	23.4 to 59.8		129.0	72.2 to 185.8	
Parity ^b				.03			.28
Nulliparous	94	21.9	16.3 to 27.5		101.5	82.6 to 120.4	
Parous	254	30.6	24.9 to 36.3		101.7	89.5 to 113.9	
Smoking history ^c				.36			.69
Never	216	25.3	21.3 to 29.3		100.6	89.5 to 111.8	
Ever	133	32.2	25.5 to 38.8		107.0	72.8 to 141.2	
BMI, kg/m ^{2d}				.72			.98
Normal	82	31.6	21.7 to 41.5		107.0	74.6 to 139.5	
Overweight	73	36.2	17.2 to 55.2		107.6	74.8 to 140.4	
Obese	69	37.6	26.5 to 48.7		132.4	90.4 to 174.4	
Pretreatment CA-125 ^e				.002			.40
< 35	35	44.1	0.0 to 91.0		134.4	66.0 to 202.7	
> 35	187	23.5	20.7 to 26.3		95.2	84.7 to 105.6	
FIGO stage ^f				.02			.48
I to II	15	66.9	0.0 to 57.1		104.7	46.8 to 162.5	
III to IV	321	25.9	21.5 to 27.9		101.5	90.7 to 112.3	
Site				.02			.01
Ovary	275	25.4	21.4 to 29.3		95.2	84.8 to 105.5	
Peritoneal	75	36.2	21.7 to 50.7		129.0	98.4 to 159.6	
Surgery				.60			.93
None	5	30.5	0.0 to 78.1		132.4	35.9 to 228.9	
Primary cytoreductive	317	26.4	22.4 to 30.4		101.5	90.5 to 112.4	
Interval cytoreductive	28	34.6	11.9 to 57.3		106.5	74.5 to 138.5	
Residual disease (primary CRS) ^g				.44			.77
No gross residual	59	25.4	18.9 to 31.9		98.8	78.6 to 119.1	
Gross residual	217	25.4	19.4 to 31.3		95.2	83.6 to 106.8	
Chemotherapy ^h				.70			.20
Adjuvant	305	26.4	22.2 to 30.5		100.8	89.9 to 111.7	
Neoadjuvant	31	33.6	8.6 to 58.7		88.3	52.8 to 123.8	
None	13	30.5	17.0 to 44.1		135.7	44.2 to 227.1	
Maintenance ⁱ				.26			.03
None or missing information	202	30.0	24.3 to 35.8		113.9	91.7 to 136.1	
Hormonal therapy	62	34.6	16.8 to 52.4		132.4	75.3 to 189.4	
Chemotherapy	63	24.4	22.4 to 26.4		79.7	69.4 to 90.1	
Chemotherapy plus hormonal therapy	14	19.7	0.0 to 44.8		86.5	76.3 to 96.7	
Disease status at completion of primary treatment ^j				< .001			< .001
NED	169	36.2	28.9 to 43.5		114.3	91.7 to 136.9	
Disease present	126	18.7	12.7 to 24.7		80.9	67.3 to 94.4	

Abbreviations: BMI, body mass index; CA-125, cancer antigen 125; CRS, cytoreductive surgery; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; NED, no evidence of disease; OS, overall survival; PFS, progression-free survival.

^aTwenty-seven patients were not included in PFS calculations because exact dates of recurrence were not documented in medical record, or there was interval of time for which no clinical data were available to document patient was diagnosed with recurrent disease.

^bMissing for two patients.

^cNot available for one patient.

^dMissing for 126 patients.

^eMissing for 128 patients.

^fNot available for 14 patients.

^gMissing for 74 patients.

^hMedical record of one patient who received chemotherapy did not include detailed information.

ⁱConsidered miscellaneous in nine patients; these patients were excluded.

^jNot available for 55 patients.

Impact of Age and Site on Outcome in Women With Low-Grade Serous Carcinoma

Table A2. Univariable and Multivariable Cox Proportional Hazards for PFS of Patients With Low-Grade Serous Carcinoma of Ovary or Peritoneum (N = 350)

Variable	Univariable			Multivariable ^a		
	HR	95% CI	P	HR	95% CI	P
Age, years						
≤ 35	—	—		—	—	
> 35	0.49	0.38 to 0.66	< .001	0.55	0.38 to 0.79	.001
Race						
White (reference)	—	—				
Nonwhite	0.76	0.55 to 1.06	.11			
Parity ^b						
Nulliparous (reference)	—	—				
Parous	0.74	0.57 to 0.97	.03			
Smoking history ^c						
Never (reference)	—	—				
Ever	0.89	0.70 to 1.14	.36			
BMI, kg/m ^{2d}			.72			
Normal (reference)	—	—				
Overweight	0.94	0.64 to 1.37	.73			
Obese	0.86	0.58 to 1.25	.42			
Pretreatment CA-125 ^e						
< 35 (reference)	—	—		—	—	
> 35	2.07	1.31 to 3.29	.002	1.46	0.91 to 2.34	.11
FIGO stage						
II (reference)	—	—				
III to IV	2.20	1.13 to 4.29	.02			
Site						
Ovary (reference)	—	—				
Peritoneal	0.70	0.51 to 0.95	.02			
Surgery			.60			
None	—	—				
Primary cytoreductive	0.75	0.28 to 2.00	.56			
Interval cytoreductive	0.61	0.21 to 1.82	.38			
Residual disease ^f						
No gross residual (any; reference)	—	—				
Gross residual	1.14	0.82 to 1.59	.45			
Chemotherapy type ^g			.48			
Adjuvant (reference)	—	—				
Neoadjuvant	0.85	0.54 to 1.34	.48			
Chemotherapy (any) plus hormonal therapy	0.66	0.29 to 1.48	.31			
Maintenance			.27			
None or missing information (reference)	—	—				
Hormonal treatment	0.84	0.60 to 1.17	.30			
Chemotherapy	1.21	0.89 to 1.64	.23			
Chemotherapy plus hormonal therapy	1.27	0.71 to 2.29	.43			
Disease status at completion of primary treatment ^h						
NED (reference)	—	—		—	—	
Disease present	1.78	1.38 to 2.31	< .001	1.79	1.30 to 2.46	< .001

Abbreviations: BMI, body mass index; CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; NED, no evidence of disease; PFS, progression-free survival.

^aWhen age was analyzed as continuous variable, presence of disease at completion of primary therapy was associated with significantly increased risk of progression (HR, 1.84; 95% CI, 1.41 to 2.40; $P < .001$), as was stage III to IV disease (HR, 2.13; 95% CI, 1.09 to 4.17; $P = .03$). Having low-grade serous carcinoma of peritoneum conferred decreased risk of progression (HR, 0.66; 95% CI, 0.47 to 0.95; $P = .02$), as did having children (HR, 0.75; 95% CI, 0.56 to 0.99; $P = .045$).

^bMissing for two patients.

^cMissing for one patient.

^dNot available for 126 patients.

^eMissing for 128 patients.

^fNot available for 69 patients.

^gMissing for one patient.

^hNot available for 43 patients.

Table A3. Univariable and Multivariable Cox Proportional Hazards for OS of Patients With Low-Grade Serous Carcinoma of Ovary or Peritoneum (N = 350)

Variable	Univariable			Multivariable ^a		
	HR	95% CI	P	HR	95% CI	P
Age, years						
≤ 35 (reference)	—	—		—	—	
> 35	0.49	0.36 to 0.67	< .001	0.53	0.37 to 0.74	< .001
Race						
White (reference)	—	—				
Nonwhite	0.67	0.44 to 1.01	.06			
Parity ^b						
Nulliparous (reference)	—	—				
Parous	0.84	0.61 to 1.15	.28			
Smoking history ^c						
Never (reference)	—	—				
Ever	0.97	0.70 to 1.27	.69			
BMI, kg/m ^{2d}			.98			
Normal (reference)	—	—				
Overweight	1.05	0.63 to 1.74	.86			
Obese	1.00	0.60 to 1.68	.99			
Pretreatment CA-125 ^e						
< 35 (reference)	—	—				
> 35	1.27	0.73 to 2.23	.40			
FIGO stage						
II (reference)	—	—				
III to IV	1.29	0.63 to 2.66	.48			
Site						
Ovary (reference)	—	—		—	—	
Peritoneal	0.59	0.39 to 0.89	.01	0.65	0.41 to 1.01	.06
Surgery			.93			
None	—	—				
Primary cytoreductive	0.85	0.27 to 2.66	.78			
Interval cytoreductive	0.91	0.26 to 3.18	.89			
Residual disease ^f						
No gross residual (any; reference)	—	—				
Gross residual	1.06	0.72 to 1.56	.77			
Chemotherapy type ^g			.71			
Adjuvant (reference)	—	—				
Neoadjuvant	1.07	0.63 to 1.81	.81			
Chemotherapy (any) plus hormonal therapy	0.63	0.20 to 1.98	.43			
Maintenance			.03			
None or missing information (reference)	—	—				
Hormonal therapy	1.06	0.68 to 1.66	.80			
Chemotherapy	1.63	1.15 to 2.32	.006			
Chemotherapy plus hormonal therapy	1.62	0.82 to 3.22	.17			
Disease status at completion of primary treatment ^h						
NED (reference)	—	—		—	—	
Disease present	1.80	1.31 to 2.47	< .001	1.78	1.30 to 2.45	< .001

Abbreviations: BMI, body mass index; CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; NED, no evidence of disease; OS, overall survival.

^aWhen age was analyzed as continuous variable, presence of disease at completion of primary therapy was associated with significantly increased risk of dying (HR, 1.83; 95% CI, 1.33 to 2.52; $P < .001$), whereas having primary peritoneal as primary site conferred decreased risk of dying (HR, 0.63; 95% CI, 0.41 to 0.99; $P = .046$).

^bMissing for two patients.

^cMissing for one patient.

^dNot available for 126 patients.

^eMissing for 128 patients.

^fMissing for 69 patients.

^gNot available for one patient.

^hNot available for 43 patients.

Impact of Age and Site on Outcome in Women With Low-Grade Serous Carcinoma

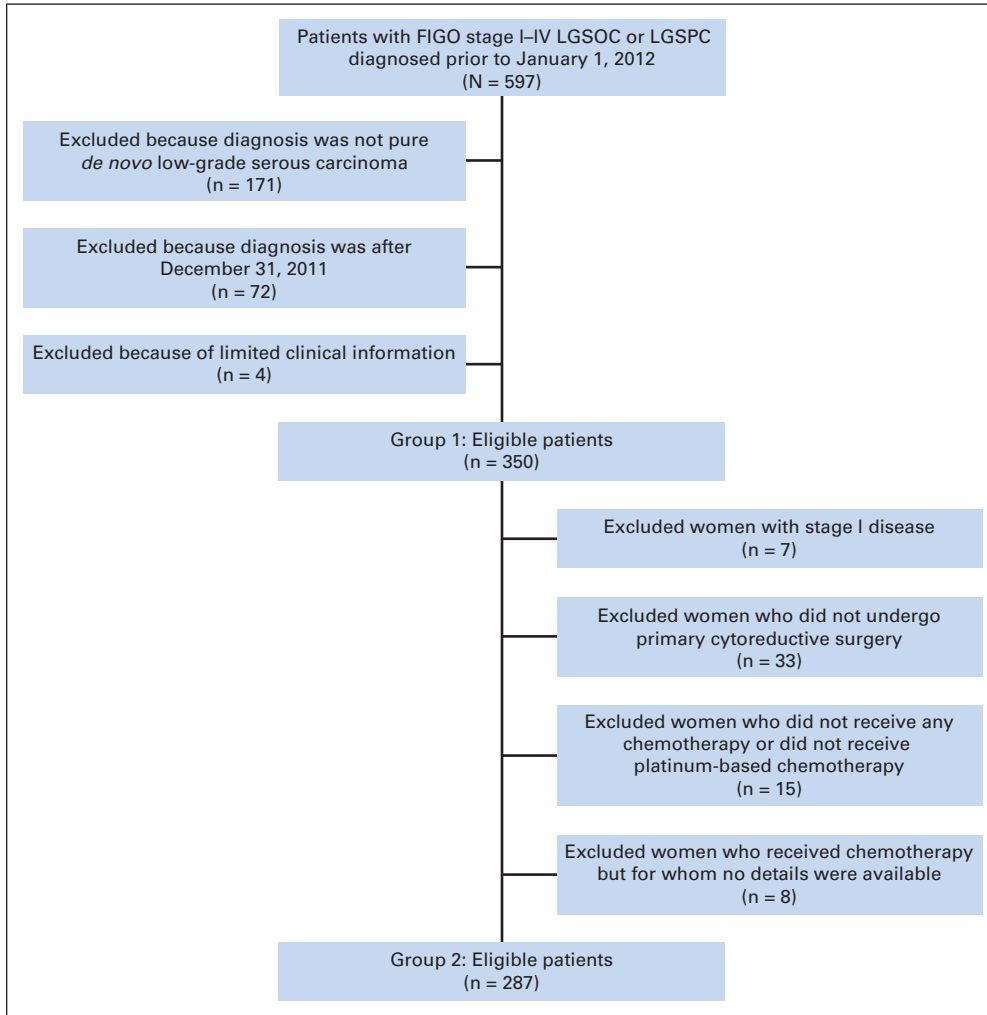


Fig A1. Flowchart of study population. FIGO, International Federation of Gynecology and Obstetrics; LGSOC, low-grade serous carcinoma of ovary; LGSPC, low-grade serous carcinoma of peritoneum.