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Clinicodemographic factors influencing outcomes in patients with low-grade serous ovarian carcinoma

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Abstract

Background—Low-grade serous carcinoma (LGSC) of the ovary is a rare tumor that is distinct from its high-grade counterpart. Our aim was to estimate if patient demographic factors and clinical treatment histories affected survival in a population of women with this disease.

Methods—A review of patients with pathologically-confirmed LGSC of the ovary diagnosed between 1977- 2009 was performed. Abstracted data included medical and social histories, anthropometric measurements, and details about diagnosis, treatment, and follow-up. Statistical analyses included Fisher's exact test, Cox proportional hazards models, and the Kaplan-Meier method.

Results—The study sample included 194 patients with a median follow-up of 60.9 months (range 1-383). By multivariable analyses, smoking was negatively associated with both overall survival (OS) (HR 1.73; 95% CI [1.03-2.92], $p=0.04$) and progression-free survival (PFS) (HR 1.72; 95% CI [1.00-2.96], $p=0.05$). Median OS was shorter in current smokers than former/never smokers (48.0 vs. 79.9 months; $p=.002$). PFS was also predicted by year of diagnosis >1994 (HR 1.74, $p=0.01$). Although not statistically significant, hormone consolidation appeared to be associated with better OS (HR 0.15, $p=.06$) and better PFS (HR 0.44; $p=.07$). A smaller proportion of patients treated with hormone consolidation experienced recurrence compared to those who did not receive hormone consolidation (66.7% vs. 87.6%, $p=0.07$).

Conclusion—Smoking is negatively associated with survival outcomes in women with LGSC of the ovary, while consolidation treatment with hormone antagonists demonstrated a protective associative trend with survival. Both lifestyle modification and innovative treatment plans should be considered in this group of patients.

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Introduction

In 2004, Malpica *et al*¹ described a new two-tier system for grading ovarian serous carcinoma as either high-grade or low-grade based primarily on the degree of nuclear atypia. Since that time, both clinical and molecular evidence has accumulated in support of this distinction. Molecularly, low-grade tumors lack the activated pathways for cellular proliferation and cell-cycle progression seen in high-grade lesions². Whereas mutations in the p53 tumor suppressor gene are common in high-grade serous carcinoma, mutations in the proto-oncogenes BRAF and K-ras are more frequently encountered in its low-grade counterpart^{3,4}. In addition, low-grade serous tumors more highly express both estrogen receptors (ER) and progesterone receptors (PR)⁵, suggesting that hormone-antagonistic agents may be of use in the treatment of this disease.

Clinically, patients with low-grade disease are diagnosed at a much younger age, and have substantially longer overall survival, than patients with high-grade serous carcinoma⁶. Low-grade carcinoma is also relatively chemoresistant, not only to up-front agents, but in the recurrent setting, as well^{7,8}. In 2006, Gershenson *et al*⁶ reported on a cohort of 112 patients with stage II-IV low-grade serous carcinoma from M.D. Anderson Cancer Center, and identified clinical factors affecting outcome. Persistent disease after primary chemotherapy was associated with more than a three-fold increase in risk of death, and a two-fold increase in risk for progression, independent of stage and presence of residual disease after primary surgery⁶. The authors also noted that age older than 45 years at diagnosis was associated with longer progression-free survival⁶.

To date, there has been little research done to investigate patient-specific factors which may contribute to survival outcomes in women with low-grade disease. Possible associations between survival and medical comorbidities, social habits, and body mass index (BMI), for example, have not been studied. Since the life expectancies in these patients are predictably long, identifying factors that affect survival may permit the initiation of lifestyle modifications aimed at optimizing outcomes. Considering these factors in relation to treatment practices is important, as the physician is expected to address all of these factors in developing a plan of care. To this end, our aim was estimate if patient demographic and clinical factors affected both progression-free and overall survival in a historical cohort of women with low-grade serous carcinoma of the ovary.

Materials and Methods

After approval from The University of Texas M. D. Anderson Cancer Center Institutional Review Board, 281 gynecologic oncology patients diagnosed with low-grade serous carcinoma of the ovary between 1977 and 2009 and treated at M. D. Anderson Cancer Center were identified, and their medical records were reviewed. Patients who were diagnosed with FIGO grade 1 or 2 disease prior to the description of low-grade serous carcinoma in 2004 had their pathology reviewed by a group of gynecologic pathologists at our institution to determine if their tumors met low-grade criteria. Patients with serous tumors of low malignant potential, non-serous histology, or non-ovarian primary tumors

(including primary peritoneal) were excluded, as were patients who had never undergone debulking surgery.

Abstracted historical data included age at diagnosis, race/ethnicity, anthropometric measurements, past medical history, and social history. Age was recorded categorically in five-year intervals for analysis, resulting in 12 distinct age groups. Patient race was classified as either white or non-white. To account for the potential confounding effect of ascites, body mass index (BMI) was calculated using height and weight measurements obtained within eight weeks after primary surgical intervention. Specific medical comorbidities ascertained included diabetes mellitus, hypertension, history of myocardial infarction, history of cerebrovascular accident, and presence of other preexisting cardiovascular disease (congestive heart failure, coronary artery disease, carotid artery disease, and peripheral vascular disease). Medical comorbidities were classified categorically as either being present or absent. Smoking and alcohol were also classified as categorical variables, and patients were designated as current users, former users, or never users.

Treatment information was collected and included date of diagnosis, surgical procedures performed, stage of disease, and presence of residual disease after debulking (≥ 2 cm vs. < 2 cm). Though by modern convention residual disease greater than 1 cm is associated with poorer overall outcomes, cytoreductive surgeries were considered 'optimal' if there was less than 2 cm of residual tumor for more than a decade during the study interval. To maintain consistency, we utilized this 2 cm cut-off to determine the presence of residual disease. Hormone receptor status (positive or negative), adjuvant chemotherapy and radiation treatments, use of consolidation regimens, recurrences, and dates of last follow-up were also recorded. Patients were classified as either alive or dead at last contact; mortality was not disease-specific. The year of diagnosis was included to account for potential temporal bias associated with changing practice patterns, and patients were classified into one of two groups segregated by the median year of the study interval (1994). This year was selected because it coincided with increased use of taxanes at our institution. Consolidation therapy was defined as receipt of hormone treatment at the completion of adjuvant therapy for patients who were without evidence of disease (negative physical examination and negative radiographic imaging; or, if such data was not available, a negative second-look surgery) at the conclusion of primary therapy. Maintenance therapy was defined as receipt of hormone therapy at the completion of primary chemotherapy for patients who had stable, persistent disease by physical exam and/or imaging but did not demonstrate evidence of disease progression. Overall survival (OS) was measured from the time of diagnosis until date of death or last contact. Progression-free survival (PFS) was measured from the time of diagnosis until clinical recurrence of disease or disease progression through a first-line chemotherapeutic agent, or as the time from diagnosis to last follow-up if the patient did not recur. Date of clinical recurrence/progression was defined as the day on which new findings on physical examination were evident, the date radiographic imaging demonstrated a new or larger lesion, or date a new therapy was initiated.

Statistical analyses were performed using STATA 10.0 (StataCorp, College Station, TX) and SPSS 17.0 (Chicago, IL). Summary statistics were generated to describe the patient

cohort. Student's t-test was used to compare groups of continuous variables. Chi-square testing (or Fisher's exact test when appropriate), was used to analyze associations between categorical variables. Linear regression analyses were performed to estimate associations between continuous variables. The Mann-Whitney test was used for nonparametric comparisons. Univariable and multivariable Cox proportional hazards regression, the log-rank test, and the Kaplan-Meier method were utilized to assess survival outcomes. To avoid inadvertently eliminating potential confounding factors affecting survival, stepwise backwards multivariable regression analyses included covariates with p-values ≥ 0.25 from the univariable models. All tests were two-sided, and p-values <0.05 were considered statistically significant.

Results

Two-hundred eighty-one (281) patients with low-grade serous carcinoma of the ovary were identified during the study interval. Of these, 194 patients met inclusion criteria. Patient demographics are presented in Table 1. Mean age at diagnosis was 44.9 years, and median follow-up time for the overall study group was 60.9 months (range 1-383 months). For patients who were alive at last contact (n=76), median follow-up time was also 64.5 months (mean 78.4; range 2-230 months). The majority of patients were Caucasian, which is consistent with the racial demographics at our institution. Anthropometric data were available for 137 patients. Of these, 25 (18.2%) had a BMI ≥ 30 kg/m². One-fifth of the patients had at least one major medical comorbidity, and more than half had reported no history of smoking or alcohol consumption. Surgical management varied by patient; 164 (84.5%) patients had oophorectomy and 148 (76.3%) underwent hysterectomy. Thirty women (15.5%) had greater than 2 cm of residual disease at the conclusion of primary surgery, and 175 (91.8%) had stage III or IV disease. When immunostaining was performed, tumors were estrogen receptor (ER) positive in 44 of 49 cases (89.8%) and progesterone receptor (PR) positive in 25 of 45 cases (55.6%). The majority of patients (191/194; 98.5%) were treated with platinum and 121 (62.4%) received adjuvant taxane therapy. Thirty-two (16.5%) patients received additional consolidation treatment after adjuvant chemotherapy, and 50 patients (25.7%) received maintenance therapy. Eighty-six percent (86%) of patients eventually experienced recurrent or progressive disease after all primary therapies were completed.

Table 2 summarizes the univariable analysis of factors affecting overall survival. Because the effects of former smoking on outcome were similar to that of nonsmokers, we combined these two groups and designated smoking status as “current smoker yes” versus “current smoker no” for the final analyses. The same approach was taken with the data on alcohol consumption. Current smoking (HR 2.08; 95% CI [1.29-3.34], $p=0.002$), comorbidities (HR 1.56; 95% CI [1.04-2.33], $p=0.03$), and a BMI ≥ 35 kg/m² (HR 2.53; 95% CI [1.19 - 5.38], $p=0.02$) were significantly associated with a greater likelihood of dying. Hormone treatment given after primary chemotherapy was also significantly associated with overall survival ($p=0.017$); specifically, hormonal consolidation was associated with a decreased likelihood of dying (HR 0.13; 95% CI [0.18-0.94], $p=0.04$).

In the multivariable model for overall survival, current smoking (HR 1.73; 95% CI [1.03-2.92], $p=0.04$) remained significantly associated with shorter survival. The median OS was 79.9 versus 48.0 months for never/former smokers and current smokers, respectively ($p=0.002$). A Kaplan-Meier curve for OS by smoking status is depicted in Figure 1. Current smokers were diagnosed with disease at a significantly younger age than never/former smokers (mean 37.0 vs. 45.1 years, $p=0.01$), while a greater proportion of never/former smokers had medical comorbidities (24.0% vs. 4.5%, $p=0.05$). A greater number of current smokers were diagnosed with disease prior to 1994 (50.0% vs. 28.7%, $p=0.04$), while more former/never smokers received treatment with a taxane (68.3% vs. 45.0%, $p=0.04$). The proportion of suboptimal debulking (22% nonsmokers vs. 31% smokers, $p=0.60$) and recurrence (85% nonsmokers vs. 91% smokers, $p=0.52$) did not differ by smoking status. Hormone treatment after primary chemotherapy was also significantly associated with survival (log-rank $p=0.028$). Although not statistically significant in a multivariable setting, compared to women who did not receive any hormone treatment after primary chemotherapy, the data suggest a protective effect for hormone consolidation (HR 0.146; 95% CI [0.02-1.05], $p=0.056$).

Progression-free survival was analyzed using the same group of variables. Several variables demonstrated statistically significant associations with progression-free survival in the univariable analysis, including stage of disease, use of a taxane agent, year of diagnosis, and BMI as a continuous variable. Although not statistically significant, current smoking appeared to suggest shorter progression-free survival (Table 3). In the multivariable model, current smoking (HR 1.72; 95% CI [1.00-2.96], $p=0.049$), and year of diagnosis after 1994 (HR 1.74; 95% CI [1.12-2.69], $p=0.011$), were associated with shorter PFS. Hormone consolidation was associated with longer PFS, but this was not statistically significant (HR 0.44; 95% CI [0.18-1.08], $p=0.07$). Median progression free survival for patients who received hormone consolidation was 76.4 months, 22.93 months for women who received hormone maintenance, and 18.7 months for women who received no hormone treatment after adjuvant chemotherapy (pairwise p -value=0.033 for hormone maintenance vs. consolidation). In addition, the proportion of women who experienced disease recurrence or progression was lower in the hormone consolidation cohort compared with women who did not receive hormone consolidation (66.7% vs. 87.6%, $p=0.07$).

Because of the improvement in PFS among women receiving hormone consolidation, this subset of patients was further evaluated. Only 9 women had data readily available on length of hormone consolidation treatment, and the characteristics of these women are described in Table 4. The median length of hormone consolidation treatment was 16.8 months (range 4.9-70.8 months). ER/PR staining was positive on the tumors obtained from Patients 1 and 8; no other patients had hormone receptor assessment performed. The majority of women who discontinued hormone consolidation therapy either recurred or self-discontinued for unspecified reasons. Compared to women who were NED and did not get hormone consolidation, PFS was longer in those receiving hormone consolidation (30.1 months vs. 76.4 months, $p=0.29$). Because the median OS was not reached in the hormone consolidation group, comparing the median OS between these women and those who were NED but did not receive hormone consolidation was not possible. However, survival curves suggest that hormone consolidation affords an overall survival advantage (log-rank $p=0.07$).

Discussion

Low-grade serous carcinoma of the ovary is a unique tumor that is distinguished from high-grade serous carcinoma by differences in both its associated molecular changes and natural clinical course. Since the introduction of the two-tier system ¹, low-grade serous carcinoma has been distinctly characterized by younger median age at diagnosis and prolonged overall survival ⁶. In the current study, we report on the adverse effects of smoking and the protective effects of hormone antagonism on survival in a population of patients with this disease.

The association between smoking and ovarian cancer survival has been debated, and there is little consensus regarding its true effects. A large prospective, population-based study noted that neither smoking status at diagnosis nor daily cigarette consumption were associated with survival outcomes in women with epithelial ovarian cancer ⁹. However, there was no distinction made between tumors of differing grades or histologies. Other studies have suggested that current cigarette use at the time of ovarian cancer diagnosis increases the risk of death by as much as 65% ^{10, 11}. While these investigations do adjust for such variables as tumor histology, stage, chemotherapy, and grade, the grading systems do not follow the two-tier system or FIGO grading criteria, thus making these conclusions difficult to interpret.

Interpreting the results of the current investigation emphasizes the question of whether the effect of smoking is tumor-related or not. Given the associations between smoking and both PFS and OS, either one may be true. From a general medical standpoint, smoking has numerous detrimental effects, including impairment of fasting glucose and an increased risk for non-ST elevation myocardial infarction ^{12, 13}. In women, smoking has been associated with up to a 7.7-year reduction in overall life expectancy, with greater proportions of smokers experiencing lung cancer and chronic obstructive pulmonary disease ¹⁴. Therefore, it is reasonable to expect that continued exposure to cigarettes may be a detriment to systems other than those affected by the primary malignancy.

Smoking exposure, however, has been shown to significantly affect the biology of cancer cells. Dasgupta *et al* ¹⁵ reported that after exposure to nicotine, breast and lung cancer cell lines demonstrate down-regulation of E-cadherin and β -catenin with a concomitant up-regulation of vimentin, suggesting that nicotine promotes phenotypic changes consistent with the epithelial-to-mesenchymal transition (EMT). Nicotine specifically has been strongly associated with increased angiogenesis, as well, namely by stimulating increased expression of vascular endothelial growth factor (VEGF) ^{16, 17}. It has also been shown that the human VEGF gene has an estrogen-responsive element ¹⁸, and that in malignancies of the human reproductive tract, VEGF mRNA expression is regulated by estrogen ¹⁹. In a tumor such as low-grade serous carcinoma, where the majority of tumors demonstrate hormone sensitivity, it is possible that the stimulatory effects of estrogen and nicotine may be additive with respect to tumor growth and angiogenesis. If this hypothesis holds true, both anti-angiogenic therapy and hormone antagonists may prove to be effective therapies in this setting.

Treatment with hormone consolidation afforded an extension in progression-free survival in this cohort of patients. The increased disease-free interval observed in women treated with hormone consolidation is important, especially considering that patients with low-grade serous carcinoma are relatively young. Consolidation with agents that have comparatively fewer side effects than cytotoxic therapy may afford patients an interval of time with a high quality of life, during which they can continue to work and maintain their functional and social well-being.

Because of the rarity of low-grade serous carcinoma, there have been few studies investigating the success of hormones in the overall treatment algorithm. In 1989, Kavanagh *et al*²⁰ reported a prospective trial of 18 patients with refractory or persistent epithelial ovarian cancer who received subcutaneous leuprolide therapy. Six patients had FIGO grade 1 disease. Though the study was performed prior to implementation of the current two-tier system, low-grade and FIGO grade 1 histologies are likely comparable. Of these six patients, three had partial responses, and two had stabilization of disease²⁰. In contrast, only one response was seen among patients with high-grade lesions. The treatment was well-tolerated, with only mild side effects (pedal edema, hot flashes, mild nausea) noted in less than one-third of the patients.

Consideration should be given to why those patients who received consolidation were selected for such therapy, as this may be an inherent selection bias affecting the outcomes between groups. To date, there are no official recommendations for the use of consolidation treatments in patients with epithelial ovarian carcinoma. In fact, randomized Phase III studies have failed to document any significant change in overall survival when cytotoxic consolidation is administered²¹, and in only one study did prolonged treatment with paclitaxel show an improvement in progression-free survival²². In none of these studies was a subset analysis performed to evaluate survival by tumor grade. With no grade-specific criteria to triage patients to consolidation or no further treatment after adjuvant chemotherapy, it is up to the individual physician to determine if the patient should proceed with consolidation. However, if the assumption is made that patients deemed to have the best overall prognosis are those not given consolidation, our finding that patients who received hormone consolidation had longer progression-free survival than those not given consolidation suggests that, regardless of the treating physician's bias about anticipated patient outcome, consolidation with a hormone antagonist may be beneficial.

As a retrospective study, there are expected limitations to our conclusions. The long study interval, incomplete patient information, varying treatments for both primary and recurrent disease, the inability to definitively assess cause of death, and misclassification bias are all factors that may confound interpretation of these data. In addition, the assumption that smoking at the time of diagnosis correlates with continued smoking throughout the disease course, as well as the inability to quantify smoking exposure makes definitive associations difficult. However, because of the rarity of low-grade serous ovarian carcinoma, hypothesis-generating data such as these are important to delineate areas for future study. As more oncologists recognize the unique nature of this disease, the potential for collaborative prospective trials based on retrospective data continues to grow.

Low-grade serous carcinoma of the ovary is a unique tumor that should be considered independent for the purposes of patient counseling and management. Here we demonstrate two significant findings: smoking has a negative impact on both overall and progression-free survival, and consolidation therapy with hormone antagonists may prolong the disease-free interval following adjuvant chemotherapy. These data present the gynecologic oncologist with an opportunity to consider both the molecular aberrations induced by smoking and design patient interventions aimed to reduce the risk of negative health effects associated with tobacco use. In addition, they highlight a potential benefit of modifying current practice algorithms for low-grade serous carcinoma to more regularly utilize non-cytotoxic, anti-hormone medications. Ultimately, a multifaceted approach in women with low-grade serous ovarian carcinoma which addresses both modifiable factors and alternatives to cytotoxic therapies should continue to be studied in order to maximally optimize patient outcomes.

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Figure 1. Overall Survival by Smoking Status

Current smoking at diagnosis was associated with significantly shorter overall survival in patients with low-grade serous ovarian carcinoma (median survival 48.0 vs. 79.9 months, log-rank $p=0.002$; current smokers $n=22$, never/former smokers $n=171$).

Figure 2. Progression-Free Survival by Hormone Treatment After Adjuvant Chemotherapy
 Progression-free survival curves for patients treated with hormone consolidation, hormone maintenance, and no hormone treatment at the completion of adjuvant cytotoxic therapy. Patients who received hormone consolidation (n=9) had significantly longer PFS compared to patients who received hormone maintenance (n=15)(median PFS 76.4 months vs. 22.9 months; log-rank pairwise p-value = 0.03) and longer PFS compared to no hormone treatment (n=170) but this was not statistically significant (median PFS 76.4 vs. 18.7 months; log-rank pairwise p-value = 0.07).

Table 1

Demographic and Clinical Characteristics (N=194)

	Entire Cohort N=194	Survivors N=76	Non-survivors N=118
<i>Mean Age in Years (range)</i>	44.9 (14-79)	45.8 (23-78)	44.4 (14-79)
<i>Race (%)</i>			
Caucasian	164 (84.5)	62 (81.6)	102 (86.4)
African American	9 (4.6)	2 (2.6)	7 (5.9)
Non-white Hispanic	16 (8.2)	7 (9.2)	9 (7.7)
Asian/Other	5 (2.6)	5 (6.6)	0 (0)
<i>Year of Diagnosis (%)</i>			
1994	61 (31.4)	11 (14.5)	50 (42.3)
> 1994	133 (68.6)	65 (85.5)	68 (57.7)
<i>Body Mass Index (kg/m²)(%)</i>			
<25	79 (57.7)	33 (43.4)	46 (39.0)
25-<30	33 (24.1)	13 (17.1)	20 (16.9)
30-<35	17 (12.4)	13 (17.1)	4 (3.4)
35	8 (5.8)	1 (1.3)	7 (5.9)
Unknown	57 (41.6)	16 (21.1)	41 (34.8)
<i>Medical Comorbidities (%)</i>			
Hypertension	37 (19.1)	12 (15.7)	25 (21.2)
Diabetes Mellitus	10 (5.2)	3 (3.9)	7 (5.9)
Any major medical problem [§]	42 (21.6)	14 (18.4)	28 (23.7)
<i>Smoking History (at diagnosis) (%)</i>			
Current Smoker	22 (11.3)	3 (3.9)	19 (16.1)
Former Smoker	52 (27.0)	23 (30.3)	29 (24.6)
Never Smoker	119 (61.7)	50 (65.8)	69 (59.3)
<i>Alcohol History (at diagnosis) (%)</i>			
Current alcohol use	80 (41.5)	37 (48.7)	43 (36.4)
Former/Never alcohol use	113 (58.5)	39 (51.3)	74 (63.6)
<i>Stage (%)</i>			
I-II	8 (4.2)	3 (3.9)	5 (4.2)
III-IV	175 (90.2)	67 (88.2)	108 (91.6)
Unstaged	11 (5.6)	6 (7.9)	5 (4.2)
<i>>2 cm Residual Disease after Debulking (%)</i>			
Yes	30 (15.5)	45 (59.2)	59 (50.0)
No	104 (53.1)	10 (13.2)	20 (16.9)
Unknown	60 (31.4)	21 (27.6)	39 (33.1)
<i>Hormone treatment after adjuvant chemotherapy (%)</i>			
None	170 (87.6)	65 (85.5)	105 (89.0)
Consolidation	9 (4.6)	8 (10.5)	1 (0.8)
Maintenance	15 (7.7)	3 (4.0)	12 (10.2)

§ Includes hypertension, diabetes, congestive heart failure, peripheral vascular disease, cardiac valvular disease, coronary artery disease, carotid artery disease, prior myocardial infarction, and prior cerebrovascular accident

Table 2

Cox Univariable Analysis of Factors affecting Overall Survival

Variable	N	Hazard Ratio	95% Confidence Interval	p-value
<i>Stage</i> *				
I/II	8	1.00		
III/IV	179	2.05	0.83-5.09	0.12
<i>Estrogen Receptor</i>				
Negative	5	1.00		
Positive	44	1.08	0.41-2.89	0.88
<i>Progesterone Receptor</i>				
Negative	20	1.00		
Positive	25	0.94	0.45-1.94	0.86
<i>All CV disease/DM</i> *				
No	152	1.00		
Yes	52	1.56	1.04-2.33	0.03
<i>Taxane</i>				
No	64	1.00		
Yes	121	1.17	0.81-1.70	0.40
<i>Current alcohol use</i>				
No	113	1.00		
Yes	80	0.83	0.58-1.20	0.33
<i>Year of Diagnosis</i>				
1994	61	1.00		
> 1994	133	1.17	0.81-1.70	0.40
<i>BMI</i> *				
Continuous	137	1.02	1.0-1.1	0.05
<i>BMI</i> *				0.12
< 25 kg/m ²	79	1.00		
25 to < 30 kg/m ²	33	1.15	0.70-1.89	0.58
30 to < 35 kg/m ²	17	1.02	0.43-2.38	0.97
35 kg/m ²	8	2.53	1.19-5.38	0.02
<i>Current smoker</i> *				
No	171	1.00		
Yes	22	2.00	1.22-3.30	<0.01
<i>Age at diagnosis</i>				
By group	194			0.40
<i>Hormone treatment after adjuvant chemotherapy</i> *				0.017
None	170	1.00		
Consolidation	9	0.13	0.18-0.94	0.04
Maintenance	15	1.83	1.01-3.33	0.05

Variable	N	Hazard Ratio	95% Confidence Interval	p-value
<i>Race</i>				
White	164	1.00		
Nonwhite	30	0.88	0.53-1.47	0.63
<i>Residual disease after primary surgery</i>				
No	104	1.00		
Yes	30	1.29	0.80-2.10	0.29

* Covariates included in multivariate regression model. BMI was included as a continuous variable because of the smaller p-value ($p=0.05$) in the univariable analysis.

Table 3

Cox Univariable Analysis of Factors affecting Progression-Free Survival

Variable	N	Hazard Ratio	95% Confidence Interval	p-value
<i>Stage</i> *				
I/II	8	1.00		
III/IV	179	2.64	1.08-6.46	.03
<i>Estrogen Receptor</i>				
Negative	5	1.00		
Positive	44	1.79	0.63-5.08	0.28
<i>Progesterone Receptor</i>				
Negative	20	1.00		
Positive	25	0.87	0.47-1.60	0.64
<i>All CV disease/DM</i>				
No	152	1.00		
Yes	52	1.12	0.78-1.62	0.53
<i>Taxane</i> *				
No	64	1.00		
Yes	121	1.47	1.05-2.04	0.02
<i>Current alcohol use</i> *				
No	113	1.00		
Yes	80	0.82	0.60-1.12	0.21
<i>Year of Diagnosis</i> *				
1994	61	1.00		
< 1994	133	1.50	1.07-2.08	0.02
<i>BMI</i> *				
Continuous	137	1.03	1.00-1.06	0.05
<i>BMI</i> *				.20
< 25 kg/m ²	79	1.24	0.80-1.92	.30
25 to < 30 kg/m ²	33	.94	0.51-1.74	.85
30 to < 35 kg/m ²	17	2.38	1.14-4.97	.02
35 kg/m ²	8	1.14	0.80-1.62	.48
<i>Current smoker</i> *				
No	171	1.00		
Yes	22	1.57	0.99-2.48	0.06
<i>Age at diagnosis</i> *				
By group	194			0.12
<i>Hormone treatment after adjuvant chemotherapy</i> *				0.18
None	170	1.00		
Consolidation	9	0.46	0.20-1.05	0.07

Variable	N	Hazard Ratio	95% Confidence Interval	p-value
Maintenance	15	0.99	0.57-1.72	0.98
<i>Race</i>				
Nonwhite	164	0.94		
White	30	1.00	0.63-1.42	0.78
<i>Residual disease after primary surgery</i>				
No	104	1.00		
Yes	30	1.20	0.77-1.85	0.41

* Covariates included in multivariate regression model. BMI was included as a continuous variable because of the smaller p-value ($p=0.05$) in the univariable analysis

Table 4

Characteristics of women receiving hormone consolidation

Pt	Hormonal Agent	Residual Disease	Length of consolidation (months)	Reason for stopping	ER	PR	PFS	OS	Recur	Status at last contact
1	Tamoxifen	Unknown	70.8	Recurrence	+	+	76.4	113.2	Yes	Alive
2	Tamoxifen	no	44.1	Self-discontinued (reason not specified)			81.1	167.6	Yes	Alive
3	Lupron	yes	unknown	Not specified			60.6	60.6 [*]	No	Alive
4	Lupron	Unknown	16.3	Recurrence			24.9	53.2	Yes	Alive
5	Tamoxifen	Unknown	4.93	Self-discontinued b/c of job			11.2	60.0		Alive
6	Tamoxifen/Lupron	yes	5.2	Not specified			103.8	192.7	Yes	Alive
7	Lupron	no	22.2	Recurrence			32.4	77.9	Yes	Dead
8	Letrozole [†]	no	9.8	Patient still on treatment	+	+	15.6	15.6 [*]	No	Alive
9	Letrozole	Unknown	17.27	Patient still on treatment			23.8	23.8 [*]	No	Alive

[†] PFS calculated from date of diagnosis to date of first recurrence/progression or death (whichever occurred first) or date of last contact if no recurrence detected.

^{*} OS survival calculated from diagnosis to last contact for patients who were still alive.

[†] Letrozole given with adjuvant carboplatin/paclitaxel; consolidation with letrozole and docetaxel; patient still on consolidation as of present time