Translational Oncology
www.transonc.com

Volume 5 Number 6 December 2012 pp. 469–474 469

Histologic Parameters Predictive of Disease Outcome in Women with Advanced Stage Ovarian Carcinoma Treated with Neoadjuvant Chemotherapy[1]

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Abstract

The use of neoadjuvant chemotherapy followed by tumor reduction surgery, also called interval debulking surgery (IDS), is considered an alternative therapeutic regimen for selected patients with advanced stage epithelial ovarian cancer (EOC). Although minimal residual disease has been proven to be a prognostic factor in traditional cytoreduction for advanced stage EOC, predictive factors after IDS still remain unexplored. The aim of this study was to determine the prognostic value of post-neoadjuvant histologic changes with clinical outcome. Three pathologists evaluated 67 cases for the following parameters: fibrosis, necrosis, residual tumor, and inflammation. The Cohen's kappa statistic was used to measure agreement among pathologists. Univariate and multivariate Cox proportional hazards models were used to determine the association between histologic parameters and recurrence-free survival (RFS) and overall survival (OS). There was substantial to almost perfect agreement among the three pathologists in all four histologic parameters (k ranged from 0.65 to 0.97). Fibrosis was associated with longer RFS ($P = 0.0257$) with a median of 20 months for tumors with fibrosis (3+) *versus* 12 months for tumors with fibrosis (1+, 2+) and longer OS ($P = 0.0249$) with a median of 51 months for tumors with fibrosis (3+) *versus* 32 months for tumors with fibrosis (1+, 2+). Our results revealed that patients with tumors exhibiting fibrosis (1+, 2+), as well as necrosis (0, 1+), had significant shorter RFS and OS ($P = 0.059$ and $P = 0.0234$, respectively). We suggest that the assessment of fibrosis and necrosis should be implemented in pathologic evaluation and prospectively validated in future studies.

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Introduction

Epithelial ovarian cancer (EOC) is the most common type of ovarian cancer, representing 80% to 90% of all ovarian cancers. It is the leading cause of death in the United States in women diagnosed with gynecologic malignancies with 21,990 new cases and 15,460 women estimated to die of ovarian cancer in 2011 [1]. The high mortality rate is mainly due to advanced stage disease at initial diagnosis. Primary cytoreduction surgery followed by chemotherapy is considered the standard of care for patients with advanced stage surface EOC [2]. There have been several debates about whether neoadjuvant chemotherapy followed by interval debulking surgery (IDS) is superior to primary tumor reductive surgery. In fact, a recent randomized clinical trial has shown that the survival rate after neoadjuvant platinum–based chemotherapy followed by IDS is similar to the survival after the standard approach of primary cytoreduction surgery followed by chemotherapy in women with advanced stage (stage IIIC and stage

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[1]No funding sources to declare. The authors declare that there is no conflict of interest.
Received 1 August 2012; Revised 1 August 2012; Accepted 23 August 2012

 1944-7124/12/$25.00
DOI 10.1593/tlo.12265

IV) EOC [3]. Furthermore, the recent National Comprehensive Cancer Network guidelines for 2012 recommended that physicians should consider neoadjuvant chemotherapy with carboplatin and paclitaxel, rather than immediate surgery, in selected patients. This recommendation was supported by strong clinical data, indicating that using this approach decreases surgical morbidity with equivalent survival times [4].

The morphologic effects on ovarian carcinoma after neoadjuvant chemotherapy have been described and consist of a wide range of changes in both tumor cells and stroma. The changes in tumor cells consist of nuclear and cytoplasmic alterations including nuclear enlargement, hyperchromasia, chromatin clumping and smudging, eosinophilia, and vacuolization and foamy/clear cell changes. The stromal alterations consist of dense fibrosis, inflammation, foamy histiocytes, cholesterol clefts, necrosis, and dystrophic calcifications [5,6]. Similar morphologic effects of neoadjuvant chemotherapy or chemoradiation therapy in other organs such as pancreas, breast, rectum, and esophagus have also been described in the literature [7–13].

In advanced stage EOC treated with standard cytoreduction followed by chemotherapy, the best predictive factor for better disease outcome is still defined by successful tumor reduction (residual disease $\leq$ 1 cm) [14–16]. However, the predictive factors for disease outcome are still lacking for patients treated with the alternative IDS. Therefore, the aims of this study are two-fold: 1) to assess specific, seemingly reproducible morphologic parameters such as percentage of residual tumor (RT), fibrosis, necrosis, and inflammation on hematoxylin-eosin slides from patients with ovarian cancer treated with neoadjuvant chemotherapy for advanced stage EOC and 2) to determine whether each of these morphologic parameters or any of their combinations might be helpful in predicting patient outcome.

Materials and Methods

Patient Population

After institution-specific institutional review board (IRB) approval, patients with advanced stage EOC treated with neoadjuvant therapy between January 2002 and December 2011 were retrospectively identified through the medical and pathology records at the University of Southern California and the Oregon Health and Science University. The initial diagnosis was made by core biopsy or cytology of the ascitic

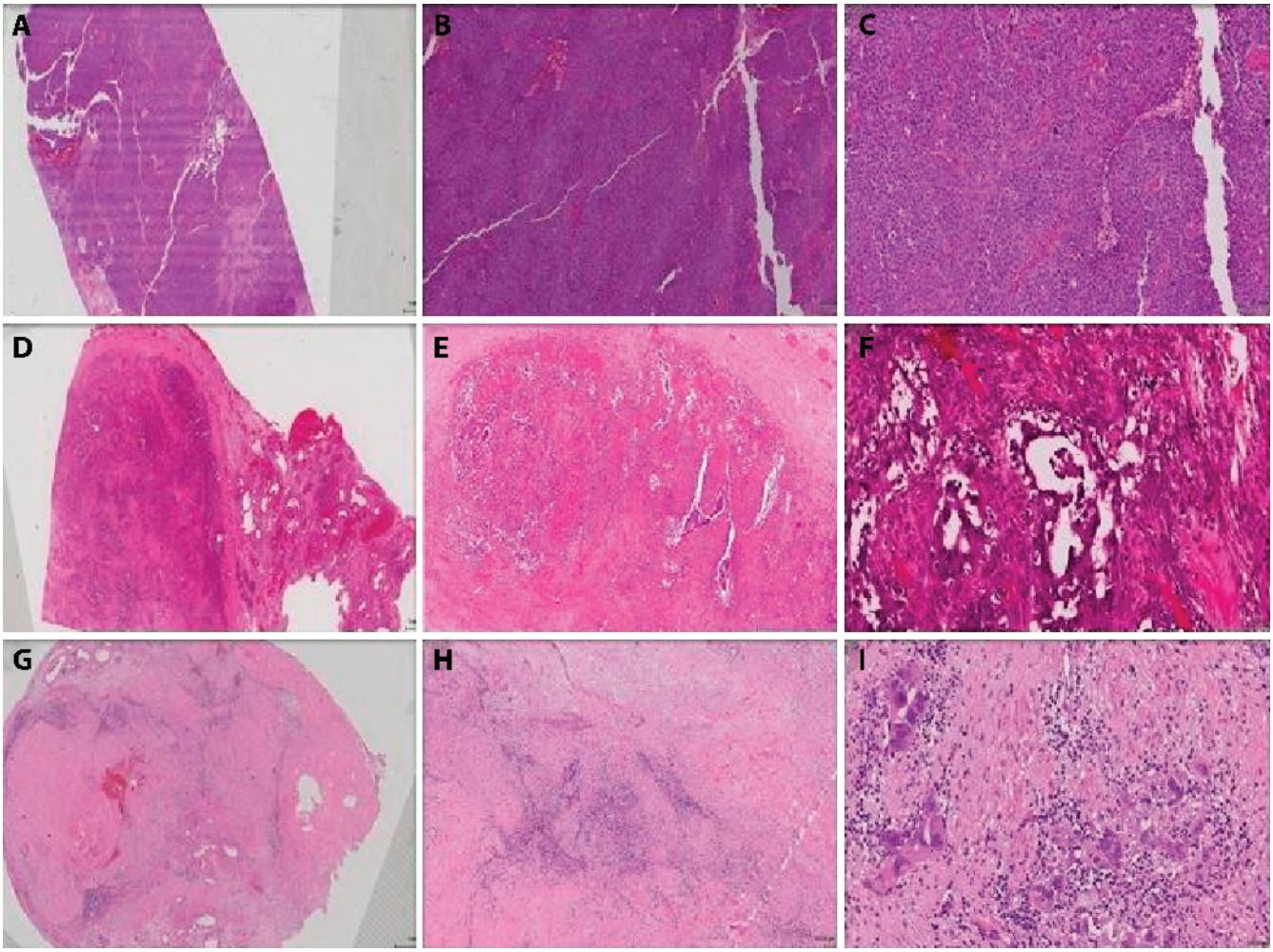

Figure 1. An example of high-grade serous carcinoma case presenting with ≥50% RT (3+): (A) ×10, (B) ×20, and (C) ×60. A case of ovary with RT of 6% to 50% (2+): (D) ×10, (E) ×20, and (F) ×60. A case of ovary with minimal RT of 0% to 5% (1+): (G) ×10, (H) ×20, and (I) ×60.

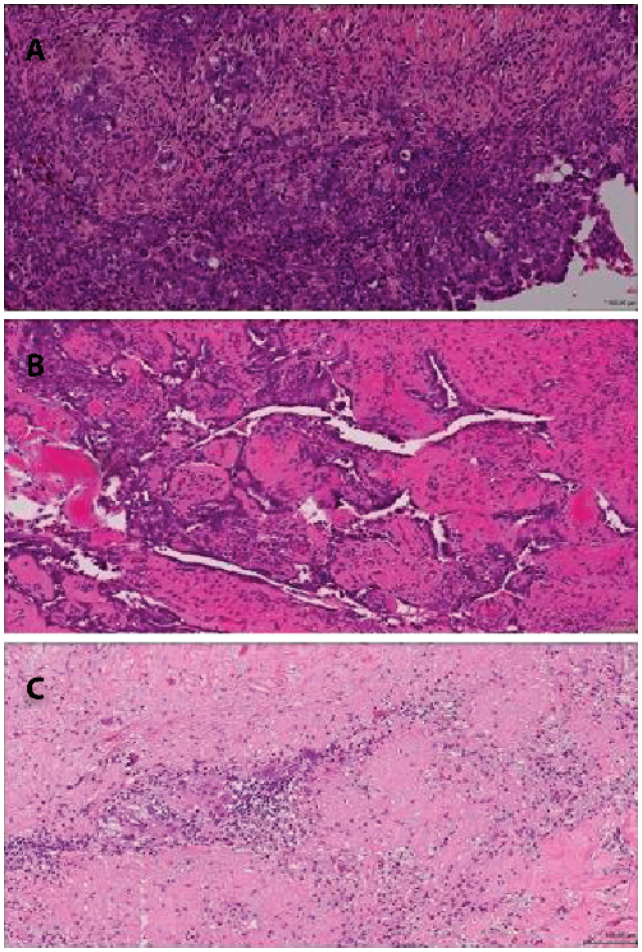

Figure 2. (A) A case of ovarian carcinoma with mild fibrosis (1+) ×40, (B) moderate fibrosis (2+) ×40, and (C) severe fibrosis (3+) ×40.

fluid. All patients had imaging studies and serum cancer antigen-125 levels. After diagnosis, the patient was given carboplatin (AUC 5) and paclitaxel (175 mg/m^2) for three or four cycles. The patients were then reassessed with computerized tomography scanner (CT scan) and sometimes with serum carcinoembryogenic antigen (CEA) levels. If tumor burden was reduced, the patient underwent IDS, and another three or four cycles was administered after surgery depending on the disease burden intraoperatively. Hematoxylin and eosin slides from the debulking surgery were retrieved from the pathology archives, and the clinical and follow-up data were retrieved from medical records. The pathology reports were reviewed to assess tumor sampling; when the ovaries were small and fibrotic, they were submitted entirely. Furthermore, one section for every 1 cm of tumor was submitted for histologic evaluation when tumors were bulky and large.

Sixty-seven patients were available for evaluation. Pathology archives and medical records were searched for the time of initial diagnosis and disease status at last follow-up from initial diagnosis. The end point of recurrence-free survival (RFS) was defined as the time of recurrence. The end point of overall survival (OS) was tumor-related death. The RFS was calculated from the time of diagnosis to the time of recurrence. The OS was calculated from the time of diagnosis to the time of last follow-up.

Study Design

There were two American Board–certified pathologists (P.M.F. and F.O.) and one resident trainee in pathology (D.S.) involved in this study. The first pathologist (P.M.F.) is a general pathologist with 12 years of experience and expertise in gynecologic pathology; the second pathologist (F.O.) is a general pathologist with 3 years of experience, and the third pathologist (D.S.) is a fourth-year pathology resident. Of all the histologic changes seen after neoadjuvant therapy, four parameters were considered for assessment, namely, fibrosis, necrosis, percent RT, and inflammation. Fibrosis was scored as mild (1+), moderate (2+), and severe (3+); necrosis was scored as absent (0), 1% to 50% (1+), and present >50 (2+); RT was scored as <5% (1+), 5% to 50% (2+), and >50% (3+); and inflammation was scored as mild (1+) and extensive (2+) (Figures 1, *A–I*, 2, *A–C*, 3, *A* and *B*, and 4, *A* and *B*). These grading cutoffs were chosen on the basis of previous studies [16–18]. The grading assessment was performed on the hematoxylin-eosin slides of the primary tumor site. The slides were given to one pathologist at a time for scoring. Afterward, using a multiheaded scope, the scores of each of the four parameters on each case was reviewed, and when there was a discrepancy in scoring, a consensus was reached.

Statistical Study

Statistical analyses were performed by R (http://www.r-project.org/). The Cohen kappa statistic was used to measure agreement among the three pathologists for the four histologic parameters studied (fibrosis,

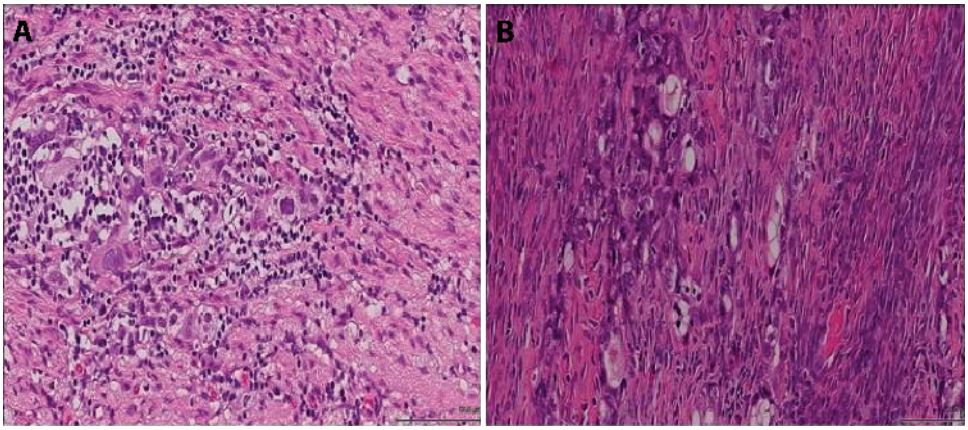

Figure 3. (A) A case of ovarian carcinoma with severe inflammation associated with tumor cells (×60). (B) A case of ovarian carcinoma with mild inflammation association with tumor cells (×60).

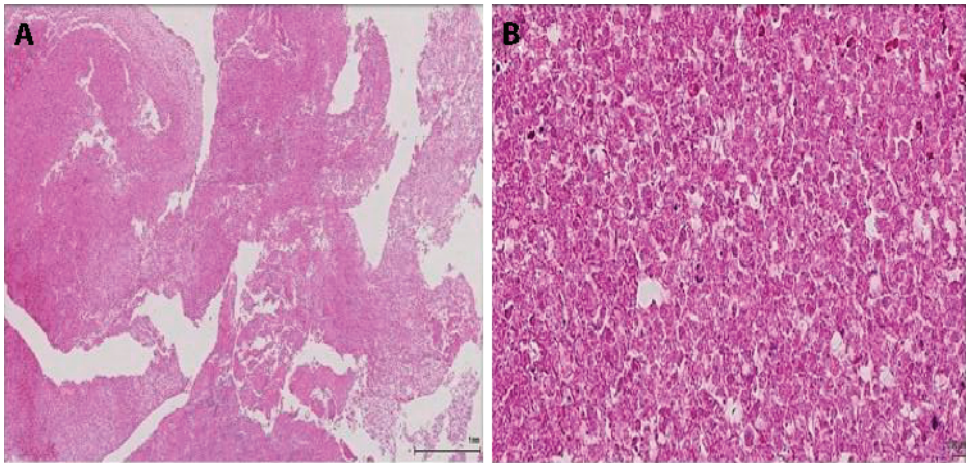

Figure 4. (A) Tumor exhibiting tumoral necrosis ≥ necrosis (2+) (×20). (B) Higher magnification shows ghost cells (×40).

RT, necrosis, and inflammation). Kappa values were interpreted as follows: <0.00 equals no agreement, 0 to 0.20 as slight, 0.21 to 0.40 as fair, 0.41 to 0.60 as moderate, 0.61 to 0.80 as substantial, and 0.81 to 1 as almost perfect agreement. The clinical parameters used for modeling were age, recurrence (yes or no), tumor persistence, death of disease (DOD), time from date of initial diagnosis to time of recurrence, and time from first diagnosis to the time of death. To test the association between the histologic factors and the clinical parameters, we performed Fisher exact test for categorical parameters and used the logistic regression model for continuous ones. To evaluate the association between the histologic factors and the elapsed time, we used univariate and multivariate Cox proportional hazards models to estimate hazard ratios that represented the correlation between relative risk of events among patients and the histologic factors. The Cox model was also used to evaluate the association of the various combinations of grading the four parameters with RFS and OS. All reported *P* values were two-sided. *P* value was considered significant if $P < .05$.

Table 1. Clinical and Pathologic Features of Patients.

Characteristics	
No. of evaluable patients	67
Age, year	
Median	57
Range	32–87
Recurrence	
N	12 (17.91)
Prog	19 (28.36)
Y	36 (53.73)
Progressive disease	
Missing	34 (50.75)
N	3 (4.48)
Y	30 (44.78)
Status	
Alive with evidence of disease	23 (34.33)
Alive with no evidence of disease	17 (25.37)
DOD	27 (40.3)
Fibrosis	
1	24 (35.82)
2	16 (23.88)
3	27 (40.3)
RT	
1	29 (43.28)
2	22 (32.84)
3	16 (23.88)
Necrosis	
0	40 (59.7)
1	19 (28.36)
2	8 (11.94)
Inflammation	
1	36 (53.73)
2	31 (46.27)

Data in parentheses are percentages.

Results

The clinical and pathological features of the 67 cases are summarized in Table 1. The patient age ranged from 32 to 87 years old (median, 57 years). No recurrence was seen in 12 of 67 (17.91%) patients, 36 of 67 (53.73%) had recurrence, and 19 (28.36%) patients had persistent disease. As for disease status at last follow-up, 23 of 67 (34.33%) were alive with evidence of disease, 17 of 67 (25.37%) were alive with no evidence of disease, and 27 of 67 (40.3%) were DOD. For the assessment of histologic parameters, 27 of 67 (40.3%) cases showed severe fibrosis (3+), 16 of 67 (23.88%) cases had >50% residual disease, 8 of 67 (11.94%) cases had >50% necrosis, and 31 of 67 (46.27%) cases showed severe inflammation. The intraobserver agreement is illustrated in Table 2. There was substantial agreement for assessment of "fibrosis" with a *k* value of 0.756, 0.713, and 0.669 for reviewers 1, 2, and 3, respectively ($P < .001$). There was a substantial to almost perfect agreement for "RT" assessment with a *k* value of 0.867, 0.646, and 0.736 for reviewers 1, 2, and 3, respectively ($P < .001$). There was almost a perfect agreement for "necrosis" assessment with a *k* value of above 0.83 for all three pathologists ($P < .001$), and finally,

Table 2. Interobserver Agreement for Each of the Four Histologic Parameters.

	Pathologist	Agreement	*k*	95% CI for *k*		*P* Value
Fibrosis	rev1	84.1%	0.756	0.623	0.888	<.001
	rev2	81.2%	0.713	0.572	0.854	<.001
	rev3	78.3%	0.669	0.521	0.817	<.001
RT	rev1	91.3%	0.867	0.766	0.969	<.001
	rev2	76.8%	0.646	0.495	0.798	<.001
	rev3	82.6%	0.736	0.601	0.872	<.001
Necrosis	rev1	98.6%	0.973	0.920	1.026	<.001
	rev2	91.3%	0.831	0.702	0.960	<.001
	rev3	92.8%	0.859	0.740	0.978	<.001
Inflammation	rev1	91.3%	0.828	0.696	0.959	<.001
	rev2	84.1%	0.674	0.497	0.851	<.001
	rev3	85.5%	0.713	0.548	0.877	<.001

Table 3. Association of the Histologic Parameters to RFS and OS.

	RFS *P* Value	HR	CI	OS *P* Value	HR	CI
Fibrosis (3 *vs* 1 and 2)	.0257	0.4581	0.2245–0.9345	.0249	0.3806	0.1531–0.9461
Necrosis (2 *vs* 0 and 1)	.847	1.111	0.3877–3.183	.168	0.5237	0.1968–1.393
RT (3 *vs* 1 and 2)	.535	0.7814	0.3525–1.732	.721	0.8689	0.4027–1.875
Inflammation (2 *vs* 1)	.804	1.089	0.5569–2.128	.385	1.4103	0.6504–3.058

there was a substantial to almost perfect agreement in "inflammation" assessment with a *k* value of 0.828, 0.674, and 0.713 for reviewers 1, 2, and 3, respectively ($P < .001$).

The association of the four histologic parameters to RFS and OS is shown in Table 3. Calculating from initial diagnosis, the median of RFS was 20 months for tumors with fibrosis 3+ *versus* 12 months for tumors with fibrosis 1+ and 2+ ($P = .0257$) (Figure 5). The median OS from the time of diagnosis to last follow-up was 51 months for tumors with severe fibrosis *versus* 32 months for tumors with mild to moderate fibrosis ($P = .0249$; Figure 6). When we evaluated the association of various combinations of the four parameters with disease outcome, we found that tumors exhibiting (1+, 2+) fibrosis as well as (0, 1+) necrosis seemed to have shorter RFS with $P = .059$ (hazard ratio [HR] = 1.921–95%, confidence interval [CI] = 0.9572–3.857) and shorter OS with $P = .0234$ (HR = 2.645–95%, CI = 1.064–6.576). However, RT failed to be a significant predictive factor by itself or in any combination with the other three parameters.

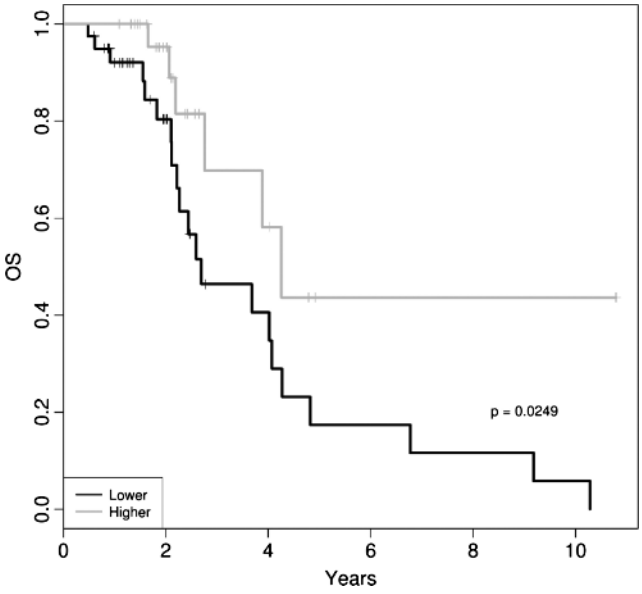

Figure 6. Kaplan-Meier survival analysis revealed the association of fibrosis with OS. The median OS from the time of diagnosis to last follow-up was 51 months for tumors with severe fibrosis (3+) *versus* 32 months for tumors with mild to moderate fibrosis (1+ and 2+; $P = .0249$).

Discussion

Optimal cytoreduction (RT < 1 cm) is considered a reliable prognostic factor in patients with advanced stage EOC treated with primary debulking surgery followed by chemotherapy [14–16]. However, predictive factors of disease outcome in patients treated with neoadjuvant therapy are still lacking, and therefore, defining them will be of great value for patient care. The morphologic alterations after neoadjuvant chemotherapy have been uniformly seen in all tumors regardless of types and sites. There are few data evaluating the histologic prognostic factors of patients with EOC treated with IDS. In one study of just 18 patients, the authors were not able to find an association of morphologic features including mitotic activity, volume percentage of epithelium, mean nuclear area, and clinical response to chemotherapy as reflected by CEA levels [6]. However, in that study, no clinical follow-up was recorded and parameters such as fibrosis, necrosis, RT, and inflammation were not considered. Our study is the largest and the first to address this issue.

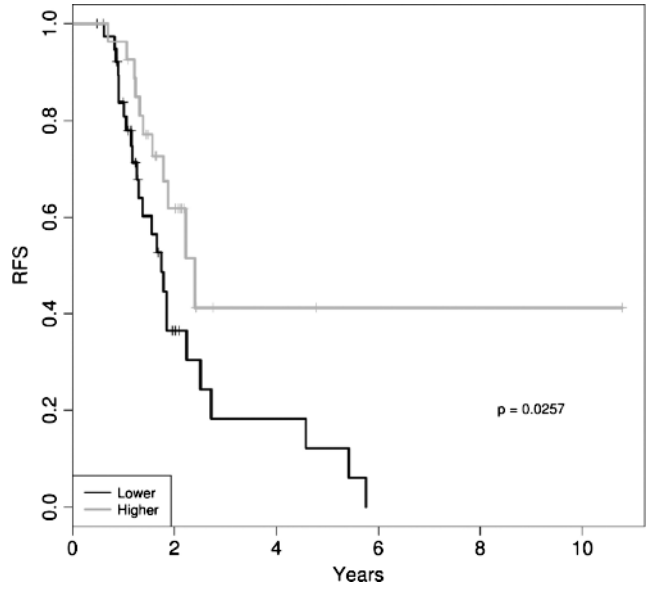

Figure 5. Kaplan-Meier survival analysis revealed the association of fibrosis with RFS. The median of RFS was 20 months for tumors with severe fibrosis (3+) *versus* 12 months for tumors with mild and moderate fibrosis (1+ and 2+; $P = .0257$).

We evaluated the most objective and reproducible morphologic alterations (necrosis, fibrosis, inflammation, and RT) in a relatively large series of 67 patients. In fact, when assessing intraobserver agreement to define the reproducibility of our criteria among three pathologists, we found a substantial to almost perfect agreement among all three pathologists in evaluating each of the four set histologic parameters (*k* ranged from 0.65 to 0.97). Furthermore, the assessment of these four parameters did not vary with the pathologist's level of experience making the evaluation of these morphologic changes very reproducible. We found that stromal fibrosis was the most significant factor in predicting disease outcome in patients diagnosed with EOC after IDS. Patients with severe fibrosis had longer RFS (median, 20 months) *versus* those with mild to moderate fibrosis (median, 12 months). In addition, they had longer OS with median OS of 51 months for tumors with severe fibrosis *versus* 32 months for tumors with mild to moderate fibrosis. Even more, patients with tumors exhibiting both mild to moderate fibrosis and necrosis <50% seemed to have shorter RFS and OS than those with severe fibrosis and >50% necrosis.

Numerous studies have looked at the association of the morphologic changes after neoadjuvant therapy and disease outcome in various cancer sites, including colon, esophagus, gastric, pancreas, lung, soft tissue, and breast [7–13,19]. Therapy-induced tumor necrosis was found to be an independent predictive factor for lower local recurrence rate and improved OS in patients with soft tissue sarcoma [20]. However, these findings were not confirmed by another study [21]. In lung

cancer, RT < 10% was regarded as a good predictive factor for longer term outcomes [10]. In breast cancer, histologic evidence of cytotoxicity, such as increased mitosis and cytoplasmic vacuolization, was not associated with disease outcome after neoadjuvant therapy [22]. In rectal tumors, stromal fibrosis with minimal inflammatory infiltrates was associated with reduced RFS [13,23]. Despite the controversial data, tumor regression grading in response to preoperative adjuvant treatment in cancers such as colorectal, exocrine pancreatic, and breast cancers has gained acceptance by the College of American Pathologists (CAP), which subsequently published guidelines on the matter.

Even more, and also on the basis of the CAP guidelines [24], the recent American Joint Committee on Cancer (AJCC) staging manual recommended the recording of tumor regression in the synoptic report for staging colorectal and breast cancers [25]. In colorectal cancer, tumor regression is graded in four tiers as follows: no viable tumors (G0) as complete response, single or small groups of cells (G1) or moderate response, residual cancer outgrowth by fibrosis (G2) as minimal response, and extensive RT (G3) as poor response. In breast cancer, the AJCC recommends defining the tumor regression as complete response, partial response, and no response depending on the absence of tumor, decrease in either or both T and N categories, and no apparent changes in either T or N after chemotherapy, respectively [24,25]. Even though the data of RT are still not definitive, the AJCC and the CAP speculated that complete eradication of the tumor might be associated with a better prognosis and failure to eradicate the tumor might appear as an adverse prognostic factor, and therefore, tumor response is worth mentioning. Thus, RT as a predictive factor for tumor response in patients with EOC after IDS would be highly expected. However, in our present study, RT failed to show any significant value in disease outcome either by itself or in combination with other parameters. This negative result might be due to the fact that our assessment of the RT was conducted in the site of origin, the ovaries, and not in the entire cytoreduction specimen. In addition, advanced stage ovarian cancers are extensive and bulky tumors, making the assessment of tumor regression a very difficult task. Lastly, we did not evaluate tumor grade and subtypes for their prognostic value because of the simple reason that the former can change and the latter could become unrecognizable after chemotherapy, making the evaluation impossible as already demonstrated by many other investigators [5,6].

In summary, our study is the first to find that fibrosis alone and fibrosis in combination with necrosis in ovarian cancer after neoadjuvant therapy has impact on disease outcome. If evaluation of fibrosis and necrosis is to be implemented in pathologic reports, it is clear that a standardized method of assessing tumor response is required. Until then, we propose to include histologic parameters, namely, the grade of fibrosis and necrosis, in the final histologic report, as it could provide an extra tool for clinicians to optimize patient management and care.

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