The influence of intraoperative tumor rupture on recurrence risk in Stage Ic epithelial ovarian cancer

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Summary

Objective: To characterize the outcomes of patients with Stage Ic epithelial ovarian carcinoma, taking into consideration the criteria that were used to assign staging. We hypothesized that tumor rupture is a less ominous prognosticator in early-stage epithelial ovarian cancer than malignant washings or ovarian surface invasion. *Methods:* A retrospective analysis of patients diagnosed with Stage I epithelial ovarian carcinoma at the University of Minnesota between 1990 and 2005 was carried out. Information was collected about demographics, diagnosis date, stage, grade, adjuvant treatment, last contact date and status at last contact. Statistical analysis was performed using the Kaplan-Meier method and the Cox proportion hazard model. *Results:* One hundred and seventeen patients with Stage I epithelial ovarian cancer were identified and included in this review. Three distinct groups of patients were considered: 1) patients with Stage Ic cancers, so-assigned because of intraoperative tumor rupture only, 2) patients with Stage Ic cancers, so-assigned for any other reason(s) than rupture alone, and 3) patients with Stages Ia and Ib cancers. The recurrence risk of patients in group 1 was not significantly different from that of patients in groups 2 or 3 (p values 0.13 and 0.69, respectively), although a trend toward decreased risk of recurrence was seen in patients from group 1 compared to both other groups. *Conclusions:* In our cohort of patients, the risk of tumor recurrence in patients with Stage Ic epithelial ovarian cancer, so-assigned because of intraoperative rupture alone, is not significantly different from the two other groups of patients with Stage I disease.

Key words: Epithelial ovarian cancer; Intraoperative tumor rupture; Stage Ic ovarian cancer.

Introduction

Ovarian cancer is the second most common gynecologic malignancy in the United States and accounts for more than half of all deaths from gynecologic malignancy [1]. In 2005, 22,220 new cases of ovarian cancer were diagnosed and 16,210 deaths were attributed to the disease [1]. The poor outcomes seen in ovarian cancer patients are largely attributed to the fact that the majority of patients have advanced (Stage III or IV) disease at the time of diagnosis.

Ovarian cancer is a surgically staged disease. The International Federation of Gynecology and Obstetrics (FIGO) guidelines for ovarian cancer staging were most recently modified in 1988 [2]. Prior to these modifications, ovarian cancers confined to one or both ovaries were referred to as Stage Ia and Ib, respectively, and when evidence of ovarian capsule invasion or intraoperative tumor rupture was diagnosed, the stage was referred to as either Iaii or Ibii. Also, under the previous staging criteria, Stage Ic was reserved for early ovarian cancers limited to one or both ovaries in patients that were also found to have malignant ascites. Because both capsule invasion and intraoperative tumor rupture were considered to be poor prognostic signs, similar to malignant ascites, the revised staging in 1988 reclassified Stage Ic to include all tumors confined to one or both ovaries that involved malignant ascites, capsule invasion or intraoperative rupture of the tumor [2]. This change suggested that the prognostic implication of intraoperative rupture was similar to that of malignant cells in peritoneal washings and ovarian surface invasion of the tumor.

Intraoperative tumor rupture of early-stage ovarian cancer has been the subject of many scientific studies and much debate ever since the 1988 FIGO classification came into use. Some authors have questioned whether intraoperative rupture actually has any negative effect on prognosis at all, or if the possible negative effect is as significant as the effect of other known negative prognosticators [3-9]. There have also been studies that have confirmed the negative prognostic impact of intraoperative tumor rupture in early ovarian cancer [10-12]. Most studies, however, have been retrospective [3-6,8-12] and only a few have been carried out in he United States [9,10]. We sought to evaluate the outcomes of early-stage ovarian cancer patients at our institution to help answer the question of whether intraoperative tumor rupture is a negative prognosticator in patients with early-stage epithelial ovarian cancer.

Materials and Methods

The Institutional Review Board at the University of Minnesota approved this retrospective chart review prior to its initiation. Several internal systems were used to identify patients with early-stage ovarian cancer, including paper records identifying patients by name and disease as well as a computerized database that allows searches by any number of characteristics, including disease and stage. A total of 204 patients were

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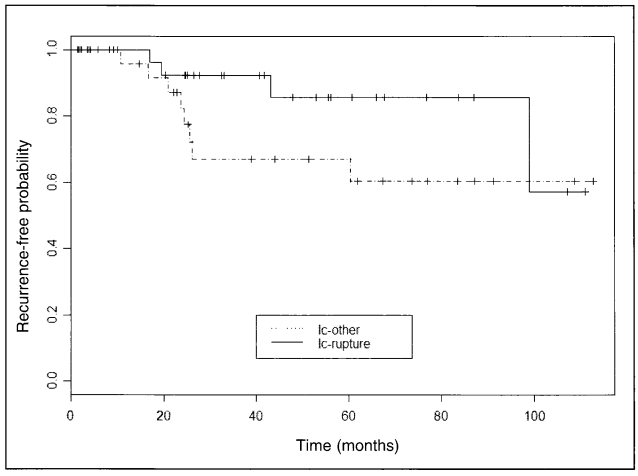

Figure 1. — Kaplan-Meier estimation of recurrence-free probability: Stage Ic-rupture versus Stage Ic-other.

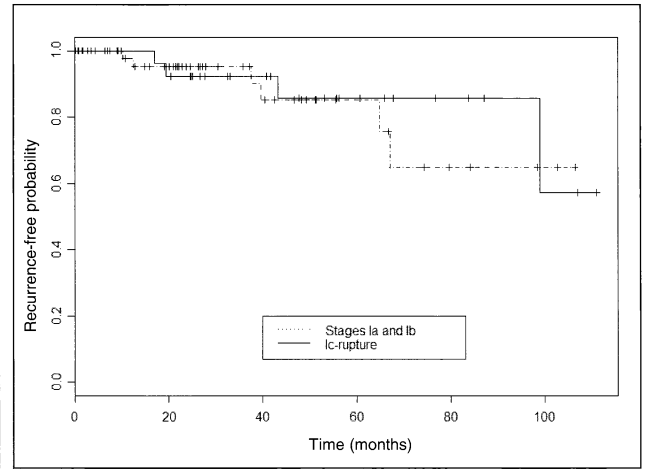

Figure 2. — Kaplan-Meier estimation of recurrence-free probability: Stage Ic-rupture versus Stage Ia and Ib.

identified and their charts were reviewed. All patients with Stage Ia, Ib or Ic epithelial ovarian carcinoma diagnosed at the University of Minnesota between February, 1990 and August, 2005 were included in the review. All patients had undergone complete surgical staging, including hysterectomy, bilateral salpingo-oophorectomy, pelvic and periaortic lymphadenectomy, omentectomy, peritoneal cytology collection and staging biopsies/smears. Patients with germ cell tumors or tumors of low malignant potential were excluded. A total of 117 patients met criteria for inclusion and their charts were abstracted for demographic information, date of diagnosis, stage, grade, histology, adjuvant treatment, date of last contact and status at last contact. Patients with synchronous primary endometrial cancers, identified at the time of initial staging, were included for analysis.

Three distinct groups of patients were considered: 1) patients with Stage Ic cancers, with staging so-assigned because of intraoperative tumor rupture only (Ic-rupture), 2) patients with Stage Ic cancers, with staging so-assigned for reason(s) other than intraoperative tumor rupture alone (Ic-other), and 3) patients with Stages Ia and Ib cancers.

We asked two questions: 1) Is the recurrence-free probability for patients with Stage Ic-rupture cancers different from that of patients with Stage Ic-other cancers? 2) Is the recurrence-free probability for patients with Stage Ic-rupture cancers different from that in patients with Stage Ia or Ib disease?

The recurrence-free probabilities were first estimated using the Kaplan-Meier method. The log-rank test was then applied to test the difference of recurrence-free probabilities among our three patient groups. Next, we applied the Cox proportion hazard model to study the association between covariates and recurrence-free probability. In order to test our two questions, we identified several variables as potential cofounders and accounted for them when performing statistical analysis. These potential cofounders included: age at diagnosis, stage and grade. SAS software (version 9.1) was used for statistical analysis. We defined $p < 0.05$ as the level of statistical significance.

Results

Of the 117 patients with Stage I epithelial ovarian cancer included in our analysis, 48, six and 63 patients had Stage Ia, Ib and Ic disease, respectively. Of the 63 patients with Stage Ic disease, 30 were so-assigned solely because of intraoperative tumor rupture. The other 33 patients with Stage Ic disease were assigned that stage because of positive washings, surface invasion of the tumor, or some combination of the three reasons. Ninety-nine out of 117 patients were recurrence-free at the time of last contact. One hundred and twelve out of 117 patients were alive at the last follow-up. The median follow-up time was 32.6 months (range: 0.1-133.9 months). Basic demographic information is included in Table 1.

Recurrence-free probabilities: Figure 1 shows a Kaplan-Meier estimation of recurrence-free probabilities for patients with Stage Ic-rupture versus Ic-other disease. Two-year recurrence-free probabilities for patients with Stage Ic-rupture disease versus those with Stage Ic-other disease were 92.3% and 77.4%, respectively; 5-year recurrence-free probabilities for these two groups of patients were 85.7% and 60.4%, respectively. Although a trend toward higher recurrence-free probability in the Ic-rupture group is present, results of the log-rank test showed that the probabilities were not significantly different between these two groups (p value = 0.13).

Table 1. — *Demographics.*

		Group 1: Stage Ic-rupture and Ib	Group 2: Stage Ic-other	Group 3: Stages Ia	p-value
n		30	33	54	
Mean age (STD) at diagnosis in years		53.44 (10.47)	52.88 (12.73)	52.15 (13.74)	0.90
Tumor grade	1	8 (26.7%)	8 (24.2%)	26 (48.2%)	0.13
	2	12 (40%)	11 (33.3%)	14 (25.9%)	
	3	10 (33.3%)	14 (42.4%)	14 (25.9%)	
Number with recurrence (%)		4 (13.33%)	8 (24.24%)	6 (11.11%)	0.24
Median follow-up (months)		41.27	35.47	26.52	0.15

Figure 2 provides the Kaplan-Meier estimation of recurrence-free probabilities for patients with Stage Ic-rupture compared to patients with Stage Ia or Ib disease. Two-year probabilities were 92.3% and 95.1% for these two groups, respectively; 5-year recurrence-free probabilities for these two groups of patients were 85.7% and 85.1%, respectively. Again, the log-rank test suggested that there was no significant difference in recurrence-free probability between these two groups (p value = 0.69).

Hazard Ratios:

The Cox proportion hazard model was applied to calculate the hazard ratios between groups after adjusting for age at diagnosis and grade. Our data supports the assumption of proportion hazard since time-dependent terms (interaction between all covariates and duration of time) were insignificant. The hazard ratio for risk of recurrence between Ic-rupture patients and those with Ic-other disease was 0.44 (95% confidence interval, CI: (0.13, 1.46)) after adjusting for age at diagnosis and grade; this difference was insignificant (p value 0.18). When comparing Ic-rupture patients to patients with Stage Ia or Ib disease, the estimated hazard of recurrence was 0.76 (95% CI (0.21, 2.84)) after adjusting for age at diagnosis and grade; this difference was also insignificant (p value is 0.69).

Discussion and Conclusions

Adjuvant treatment recommendations for patients with ovarian cancer are based largely on the assigned surgical stage and, in some early-stage cancers, grade of the disease. Based on evidence from large randomized, controlled trials, all patients with high-risk, early-stage ovarian cancer (Stage Ia, grade 2-3; Stage Ib, grade 2-3; all Stage Ic; all clear cell histology types) are offered adjuvant chemotherapy [13-18]. Outcomes are good in patients with early-stage ovarian cancer who have received complete surgical staging, whether they receive adjuvant chemotherapy or not [13]. Subgroup analyses have shown, though, that the benefit of adjuvant chemotherapy may be related to treatment of occult advanced-stage disease in patients who were not optimally surgically staged initially. This suggests that there may be a subgroup of patients that would not benefit from adjuvant chemotherapy if they had been first treated with optimal surgical staging. Also, some studies have suggested that intraoperative rupture alone is not a negative prognosticator [3-9]. It may be, then, that patients who are assigned a Stage of Ic on the basis of intraoperative tumor rupture alone, especially those that have grade 1 tumors, represent a subgroup of early-stage ovarian cancer patients that have a better survival and recurrence risk profile than that of patients who are assigned a Stage of Ic based on other factors. If this were the case, we would expect a recurrence-free survival benefit to exist for patients with Stage Ic disease because of intraoperative rupture alone compared to patients with Stage Ic disease, so-assigned for other reasons. Moreover, if intraoperative tumor rupture were a less-important negative prognosticator than malignant ascites and ovarian surface tumor invasion, one would expect the Stage Ic-intraoperative rupture group to be more similar, in recurrence profile, to patients with Stage Ia and Ib disease than to patients with Stage Ic disease for other reasons. While this retrospective review of cases did show a trend toward benefit for patients whose Ic stage was assigned because of intraoperative rupture alone versus for other reasons, this difference was not significant. Unfortunately, we had a small number of patients in our study.

At our institution, in response to the studies mentioned previously, all patients with high-risk, early-stage ovarian cancer are currently offered adjuvant treatment with platinum-based chemotherapy. There is no evidence, based on this retrospective review, to suggest that this practice should be altered. Further investigation into the possibility that recurrence and/or survival profiles differ for patients with Stage Ic epithelial ovarian carcinoma, so-assigned for different reasons (intraoperative tumor rupture alone versus other reasons) would require much larger scale studies. Because the majority of patients with early-stage ovarian cancer do well and do not die from their disease, large numbers and long follow-up intervals are required to detect survival differences among the various subgroups. Similarly, while the rate of recurrence in patients with early-stage ovarian cancer is more common than death, it is still an infrequent event and larger studies would be necessary to detect the difference we had hypothesized might be present in our population.

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