Prognostic factors for women with Stage 1 ovarian cancer with or without adhesions

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Summary

Objective: To identify those prognostic factors in women with Stage 1 epithelial ovarian cancer that predict survival.

Methods: A population-based cohort study was conducted which included all newly diagnosed ovarian cancer patients treated initially with surgery from 1996-1998 in Ontario, Canada (N = 1,341). We abstracted charts from hospitals and cancer centres and used hospital and billing claims databases. Cox survival analysis was used to model the association between prognostic factors (including patient characteristics, surgical findings, pathologic findings and subsequent treatment) and survival for those with Stage 1 ovarian cancer.

Results: 327 women had Stage 1 or 2 ovarian cancer (where Stage 2 was based on adhesions alone). Prognostic factors that had significant, unadjusted, association with survival were patient age, presence or absence of adhesions, grade, and surface involvement. The multivariable model that best described survival included premenopausal age group (HR 0.32, 95% CI, 0.18-0.55), poor differentiation (HR 2.17, 95% CI, 1.33-3.51), and surface capsule involvement (HR 2.97, 95% CI, 1.59-5.55). A lack of influence of treatment modality stands in contrast to the literature.

Conclusions: Our dataset confirmed that poor grade and surface capsule involvement are poor prognostic factors. Adjuvant therapy did not confer an improved outcome; however, it was likely used in only those patients with poor prognostic indicators and so improved their survival to that of women with good prognostic factors who received surgery alone.

Key words: Stage 1 ovarian cancer; Prognosis.

Introduction

Approximately 15-25% of patients with epithelial ovarian cancers present with disease confined to the ovary. The combined results of the two randomized studies in women with Stage 1 disease (European Organization for research and Treatment of Cancer (EORTC) and International Collaborative Ovarian Neoplasm (ICON) studies) [1, 2] showed a benefit of adjuvant chemotherapy to surgery alone. In those patients with "optimal" surgical staging, similar survival was observed comparing surgery alone with adjuvant chemotherapy although insufficient statistical power was present to confirm equivalence. A larger study with well-staged patients will be required to determine if surgery alone is a viable treatment option. If a patient has poorly conducted staging surgery then adjuvant chemotherapy is clearly the best management. The question remains as to whether, in a patient who has received appropriate staging surgery, there are important factors which predict for a good outcome which would enable this individual to avoid chemotherapy.

Several authors have identified poor prognostic factors in women with Stage 1 ovarian cancer suggesting that these women might benefit from adjuvant therapy. Factors examined include adequacy of surgical staging [3], degree of differentiation [3-15], clear cell histology [11, 12], large volume ascites [6, 16], malignant ascites/washings [17], excresences [6], dense adhesions [16], rupture prior to surgery [9, 12, 17, 18], bilaterality [17], aneuploidy [4], CA125 greater than 65 u/ml [19], mitosis, necrosis, anisocaryosis, Bax negative [20], p53 positive, Ki67 positive, HER2 positive [21, 22], high microvessel density [4], VEGF, EGFR [21], Cox-2 positive [22], and post-surgical treatment [7, 10]. Some of these prognostic factors have significant shortcomings due to their subjectivity, lack of reproducibility and low prognostic power [4].

In 1996-1998, we undertook a population-based cohort study to assess the structure and process factors affecting the outcome of women treated initially with surgery for ovarian cancer in Ontario. In this dataset there was a group of 338 patients with Stage 1 ovarian cancer in whom information on several of these prognostic factors was available. We attempted to assess the impact on survival of these various factors which describe the patient (ie., age), the surgical findings (i.e., ascites), the tumor (ie., grade) and treatment (ie., adjuvant therapy).

Material and Methods

Data sources and elements

This is a population-based cohort study of all women with newly diagnosed ovarian cancer treated initially with abdomi-

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nal surgery in Ontario from January 1, 1996 to December 31, 1998. A master dataset was created by record linkage between the Ontario Cancer Registry (OCR), hospital admissions data, data of the Ontario Health Insurance Plan (OHIP) and chart abstraction. The creation of this dataset is described in detail elsewhere [23].

Stage 1 dataset

The cases that were included in the Stage 1 dataset were all women with newly diagnosed Stage 1 ovarian cancer treated initially with surgery in Ontario from January 1, 1996 to December 31, 1998; and those women who were upstaged to Stage 2 solely because adhesions to the ovaries were not biopsied. Patients were excluded if they had a second operation prior to adjuvant chemotherapy and were upstaged. This resulted in 327 cases for assessment. All operative, pathology and cytology records were reviewed. Where a pathology review was available from a tertiary unit, the results of this review took precident over the initial results from the host hospital.

Variable definition

Outcome: Mortality was documented in hospitalization data, and vital statistics data linked to public health insurance data and the Ontario Cancer Registry (OCR). Survival time was calculated from pathologically confirmed diagnosis of ovarian cancer (OC) (initial operative date) and date of death from any source. Follow-up ended with latest available health insurance data.

Independent variables that were addressed fall into four categories. Surgical findings included presence or absence of ascites, adhesions involving the ovary, endometriosis, excrescences on the ovary, tumor rupture and timing of the rupture related to the operation. Pathologic findings included malignant versus benign cells in the ascites or washings, tumor size, grade, histology, vascular space or stromal involvement and concurrent uterine cancer. Treatment factors included the degree of surgical staging, surgeon's discipline and use of adjuvant therapy. Demographic variables considered included age at diagnosis.

Statistical analysis

Regression analyses were used to assess associations between surgical findings, disease, aspects of treatment, covariates, and outcomes. Survival analysis used the Cox proportional hazards model. For all models, robust regression models were used to obtain adjusted variance estimates and confidence intervals accounting for the non-independence of patient observations, which shared a surgeon. Analyses were performed using the SAS Genmod procedure (with exchangeable covariance matrix) and comparable procedures in Stata software.

Table 1. — *Characteristics.*

Variable	Category	Number (327)	Percent
Patient characteristcs			
Age	18-59	173	52.9%
	60-69	75	22.9%
	> 70	79	14.2%
Surgical findings			
Ascites	No	233	71.3%
	Yes	94	28.8%
Adhesions	No	185	56.6%
	Yes	142	43.4%
Ruptures	No	208	63.6%
	Yes	119	36.4%
Endometriosis	No	258	78.9%
	Yes	69	21.1%
Pathology findings			
Ascites	Benign	296	90.5%
	Malignant	31	9.5%
Capsule	Smooth	320	94.5%
	Excrescences	18	5.5%
Histology	Serous	93	28.4%
	Mucinous	72	22.0%
	Clear cell		
Grade	1 and 2	185	56.6%
	3 and undifferentiated	84	25.7%
	missing	58	17.7%
Uterine Cancer	No	305	93.3%
	Yes	22	6.7%
VSI	No	317	96.9%
	Yes	10	3.0%
Depth of invasion	No	253	77.4%
	Micro/focal stroma	46	14.1%
	Surface	28	8.6%
Largest ovarian size	No	66	20.2%
	Yes - < 50 yr > 10 cm		
	≥ 50 yr > 5 cm	261	79.8%
Subsequent treatment			
Surgical Staging	No	251	76.7%
	Yes	60	18.4%
	Unknown	16	4.9%
Surgeon	Gyn Onc	105	29.0%
	Ob Gyn	201	61.5%
	Surgeon	25	7.7%
	Other	6	1.8%
Chemotherapy within 6 mos	No	193	59.0%
	Yes	134	41.0%

Results

Three hundred and twenty-seven patients met the inclusion criteria. The median age was 57.5 years (95% CI 55-60). The characteristics of the population are outlined in Table 1. Only 18% had optimal surgical staging as defined by the EORTC and other practice guidelines. Percent survival for this population was 78.2% at five years (95% CI, 73%-82%).

Patient, characteristics, initial surgical findings, tumor and subsequent treatment characteristics that had significant unadjusted associations with survival are presented in Table 2. The factors associated with survival were younger age, presence of adhesions, grade 3 or undifferentiated tumors, and surface capsule involvement. Patient age at diagnosis, findings at the beginning of the surgery and pathologic factors were important in this sample. No treatment factor appeared to influence outcome.

In multivariate models, age, tumor grade and pathologic involvement of the capsule were significantly associated with survival. No other potential prognostic or treatment factor examined was significantly associated with survival after adjustment for patient age.

To determine why adjuvant chemotherapy was not a predictive factor for improved survival, we compared our population cohort to that of the ACTION group [1]. There

Table 2. — *Bivariates.*

Variable	Category	HR	95% confidence interval	
Patient characteristics				
Age	18-59	1.00		
	60-69	2.08	1.19	3.63
	> 70	3.70	2.25	6.08
Surgical findings				
Ascites	No	1.00		
	Yes	0.94	0.59	1.51
Adhesions	No	1.00		
	Yes	1.56	1.02	2.37
Ruptures	No	1.00		
	Yes	1.27	0.83	1.95
Endometriosis	No	1.00		
	Yes	0.71	0.40	1.26
Pathology findings				
Ascites	Benign	1.00		
	Malignant	1.45	0.77	2.74
Capsule	Benign	1.00		
	Malignant	1.60	0.74	3.46
Histology	Serous	1.00		
	Mucinous	1.57	0.99	2.49
	Clear cell	1.12	0.65	1.91
Grade	1 and 2	1.00		
	3 and undifferentiated	2.62	1.64	4.20
Uterine cancer	No	1.00		
	Yes	0.78	0.31	1.91
VSI	No	1.00		
	Yes	1.57	0.58	4.29
Depth of invasion	No	1.00		
	Micro/focal	1.10	0.59	2.04
	Surface	2.88	1.63	5.08
Largest ovarian size	No	1.00		
	Yes: < 50 yr > 10 cm ≥ 50 yr > 5 cm	0.94	0.56	1.57
Subsequent treatment				
Surgical Staging	No	1.00		
	Yes	0.95	0.54	1.67
Surgeon	Gyn Onc	1.00		
	Ob Gyn	1.17	0.72	1.90
	Surgeon	0.80	0.30	2.09
	Other	2.36	0.71	7.88
Chemotherapy within 6 mos	No	1.00		
	Yes	1.46	0.96	2.23

was no difference in terms of histology, grade, and depth of invasion (data not shown). Significantly more women were optimally surgically staged in the ACTION group (34%) compared to the Ontario cohort (18.4%). The adjuvant chemotherapy group did not differ from the surgery alone group in terms of optimal staging and surface capsular involvement. In the Ontario dataset, patients were more likely to receive chemotherapy if they had Stage 1C disease but this was not statistically significant ($\chi^2 = 3.48$, $p = 0.06$). Those with grade 3 disease were more likely to receive adjuvant chemotherapy (79%) compared to the surgery only group (51%).

Table 3. — *Regression model simultaneously including five covariates.*

Variable	Category	HR	95% confidence interval	
Age	18-59	1.00		
	60-69	1.91	1.01	3.90
	> 70	3.50	1.95	6.28
Grade	1-2	1.00		
	3-undiff.	2.11	1.29	3.45
Stoma	No	1.00		
	Micro	1.25	0.64	2.45
	Surface	2.52	1.30	4.87
Adhesions	No	1.00		
	Yes	1.09	0.67	1.78
Surgeon	Gyn Onc	1.00		
	Ob Gyn	1.36	0.76	2.43
	Surgeon	0.75	0.22	2.59
	Other	4.83	0.95	24.51

Discussion

For cancer patients, the potential length of survival, or disease free interval, are important factors in making a treatment decision. In the current population-based observational study, we did not find a significant relationship between treatment factors (adjuvant chemotherapy) and survival. This is in contrast to the ACTION/ICON randomized controlled trials [1, 2], where adjuvant chemotherapy did provide a survival benefit. In our population, there was a treatment philosophy for providing adjuvant chemotherapy for those patients with poor prognostic factors (ie., grade 3 disease). It could be hypothesized that this group would have a poor survival and that adjuvant chemotherapy would improve their survival to at least that of surgery alone for those with good prognosis disease. Indeed, survival in our study was no different between those who did and did not receive adjuvant chemotherapy. Our overall survival was juxtaposed between the two arms of the ACTION/ICON trial [1, 2]. In our work, the 5-year survival was 78.2% compared to the surgery alone survival of 74% and the adjuvant chemotherapy arm of 82% of the ACTION/ICON trial. Thus the Ontario system of providing adjuvant chemotherapy only for poor prognostic factors does give an acceptable survival benefit. The opportunity for improving care, comes in that not all patients in Ontario received chemotherapy for grade 3 histology of Stage 1C disease. Our study shows that poor grade and ovarian capsule involvement conferred a poorer prognosis. The latter findings are in keeping with the literature.

The limitations of this work are that although all the data were collected in a standardized fashion from medical records, the data were not entered into the medical records in a standard fashion. Thus rates of endometriosis and adhesions may be under-reported as these depended on the detail with which the surgeon completed the operative notes. The consistency of the adhesions (i.e., filmy versus thick) could not be discerned from the notes and so was not assessed. We accepted the

pathology reports as found in the medical records but there was no pathology review of all the cases according to a predefined protocol. Thus, the presence of vascular space involvement (VSI) may be under-recorded and there may have been the use of different grading systems across centers and pathologists. Whether sample size influences the lack of benefit of adjuvant therapy is not clear.

Conclusion

We present an assessment of prognostic factors for women with early stage ovarian cancer in Ontario. Only one-fifth of the population had optimal surgical staging as defined by the EORTC. Forty percent of patients received adjuvant chemotherapy for poor prognostic factors or incomplete surgical staging. In our dataset, poor grade and capsular involvement predicted poorer survival. Adjuvant chemotherapy in this group enhanced survival to that of the group that had surgery alone for good-prognosis disease.

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