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Hypoxia inducible factor 1-α expression as a factor predictive of efficacy of taxane/platinum chemotherapy in advanced primary epithelial ovarian cancer

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Abstract

To investigate the impact on survival of HIF 1-α expression on primary advanced epithelial ovarian cancer (EOC), we examined the correlations between prognosis and HIF 1-α expression by Western blot analysis in 52 cases of stage III/IV EOC. HIF 1-α expression was confirmed in 36 cases (69.2%) of EOC, and HIF 1-α-expressing tumors had a significantly higher rate of response ($p < 0.01$) to postoperative paclitaxel/carboplatin combination chemotherapy (TC) than tumors without HIF1-α expression. Moreover, patients with HIF 1-α-expressing tumors with suboptimal resection of stage III/IV tumors indicated for postoperative TC exhibited significantly better survival ($p < 0.01$).

Keywords: HIF 1-α; Epithelial ovarian cancer; Chemotherapy; Prognostic factor

1. Introduction

Hypoxia inducible factor 1-α (HIF 1-α) has been reported to be an important predictor of tumor progression for several types of solid cancers [1–5]. However, although several *in vitro* studies have reported correlations between HIF 1-α expression and cell biological features in ovarian cancer, study of the clinical significance of HIF 1-α still has been limited [6]. To determine the clinical usefulness of HIF 1-α expression in treatment of primary epithelial ovarian cancer (EOC), we examined whether HIF 1-α expression can predict effects of postoperative induction chemotherapy and long-term prognosis in patients with stage III/IV advanced EOC.

2. Materials and methods

The study included 52 cases of stage III/IV EOC. Fourteen patients underwent optimal resection (residual tumor <1 cm), while 38 patients underwent suboptimal resection at primary surgery. Furthermore, all patients with suboptimal resection had measurable disease usable for determining direct effects of TC. The clinicopathological characteristics of patients did not differ significantly between optimal resection and suboptimal resection as summarized in Table 1. All of the patients were indicated for postoperative TC (175–180 mg/m^2 paclitaxel and a dose of carboplatin an area under the concentration curve

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Table 1
Correlations between HIF-1 α expression and clinicopathologic factors

Factors	HIF-1 α[a] positive	HIF-1 α negative
Total number of cases	36	16
Mean ages (range)	57.9 ± 8.2 years (34–84)	57.2 ± 7.3 years (39–73)
FIGO stage (%)[b]		
Stage III	31 (68.9)	14 (31.1)
Stage IV	5 (71.4)	2 (28.6)
Histologic subtype (%)		
Serous	19 (65.5)	10 (34.5)
Endometrioid	7 (77.8)	2 (22.2)
Mucinous	3 (60.0)	2 (40.0)
Clear-cell	7 (77.8)	2 (22.2)
Histologic grade (%)[c]		
Grade 1	13 (68.4)	6 (31.6)
Grade 2	10 (71.4)	4 (28.6)
Grade 3	6 (60.0)	4 (40.0)
Surgical status (%)		
Optimal surgery	9 (64.3)	5 (35.7)
Sub optimal surgery	27 (77.1)	11 (28.9)
Overall response rate of postoperative chemotherapy (%)		
	18 (66.7)	5 (45.5)**
Complete response rate of postoperative chemotherapy (%)		
	13 (48.1)	2 (18.2)**

[a] HIF, hypoxia inducible factor.
[b] FIGO, Federation of International Gynecology and Obstetrics.
[c] Not including clear-cell carcinomas.
** $p < 0.01$.

by Calvert's formula of 5–6). Direct effects of chemotherapy were assessed using the World Health Organization criteria. HIF 1-α expression was determined by Western blot analysis using anti-HIF 1-α (Novus Biologicals, Littleton, CO) for stocked fresh-frozen tissues, and if an independent positive band in the region of 120 kDa was confirmed on quantification using NIH image analysis, it was taken to indicate HIF 1-α expression (Fig. 1). We obtained fully informed written consent from all patients prior to obtaining the specimens. We used the chi-square test and log-rank test for statistical analysis, with p-values less than 0.05 considered significant.

3. Results

HIF 1-α expression was confirmed in 36 (69.2%) of the patients with FIGO stage III/IV tumors, and no significant correlation was observed between frequency of HIF 1-α expression and patient age, histologic subtype, histologic grade, FIGO stage (III or IV), or surgical status (optimal or suboptimal resection). However, HIF 1-α-expressing tumors exhibited significantly higher overall response rate ($p < 0.01$) and complete response rate ($p < 0.01$) to TC than tumors without HIF 1-α expression (Table 1). Moreover, HIF 1-α predicted prognosis for neither the group of all stage III/IV patients nor that with optimal resection. Although no significant differences were noted in clinicopathologic characteristics between patients with optimal and those with suboptimal resection (Table 2), but among patients in stage III/IV who underwent suboptimal resection at primary surgery and were indicated for postoperative TC, those with HIF 1-α-expressing tumors had a significantly better prognosis than those with tumors without HIF 1-α expression (Fig. 2).

4. Discussion

HIF 1-α expression in malignant tumors has been reported as a predictive factor for tumor progression and a prognostic factor correlated with angiogenesis. However, HIF 1-α expression in solid cancers exhibits marked variation among primary organs in the English literature [1–5]. Generally, HIF 1-α predicts tumor progression, and HIF 1-α-

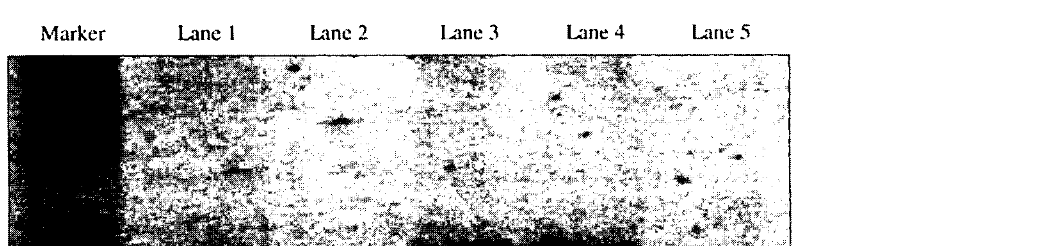

Fig. 1. The expression of HIF 1-α proteins detected by Western blotting. Lane 1: positive control; HCT-116 cell were grown in a chamber containing 1% oxygen, 5% carbon dioxide, and 94% nitrogen at 37 degree for 3 days. Lane 2: negative control; without primary antibody. Lane 3 and 4: HIF 1-α positive cases. Lane 5: HIF 1-α negative case.

Table 2
Clinicopathologic characteristics of all patients

Factors	Optimal	Suboptimal
Total number of cases	14	38
Mean ages (range)	59.6 + 8.3 years (46–84)	57.1 ± 7.6 years (34–74)
FIGO stage (%)[a]		
Stage III	13 (92.8)	32 (84.2)
Stage IV	1 (7.2)	6 (15.8)
Histologic subtype (%)		
Serous	9 (64.3)	20 (52.6)
Endometrioid	2 (14.3)	7 (18.4)
Mucinous	1 (7.1)	4 (10.6)
Clear-cell	2 (14.3)	7 (18.4)
Histologic grade (%)[b]		
Grade 1	6 (50.0)	13 (41.9)
Grade 2	4 (33.3)	10 (32.3)
Grade 3	2 (16.7)	8 (25.8)
Mean treatment courses (range)	5.9 ± 0.3 course (4–6)	5.8 ± 0.9 courses (3–6)
Mean follow up period (range)	58.4 ± 31.4 months (13–135)	48.3 ± 26.3 months (8–110)

[a] FIGO, Federation of International Gynecology and Obstetrics.
[b] Not including clear-cell carcinomas.

expressing cancers tend to have a poor prognosis. However, Nakayama et al. [6] reported finding no relationship between HIF 1-α expression and intratumoral microvessel density, and that vascular endothelial cell growth factor (VEGF) up-regulated HIF 1-α gene, though levels of expression of neither gene affected the survival of patients with EOC. Furthermore, Birner et al. [7] examined HIF 1-α expression in 102 cases of FIGO stage I–IV EOC by immunohistochemical staining, reported that 68.6% of cases of EOC expressed HIF 1-α, and concluded that HIF 1-α protein overexpression also has no impact on prognosis and that response to TC is independent of HIF 1-α expression. However, Escuin et al. [8] recently found that microtubule-targeting drugs, such as taxanes, could be effective in down-regulating HIF 1-α protein via effects on microtubule cytoskeleton that are correlated with HIF 1-α translation activity. For patients with suboptimally resected advanced EOC, survival impact is closely related to effects of postoperative chemotherapy. Therefore, because paclitaxel may exhibit anti-angiogenetic effects through down-regulation of HIF 1-α protein expression, the survival impact of HIF 1-α expression on EOC may be noted only in patients who are stage III/IV, have undergone

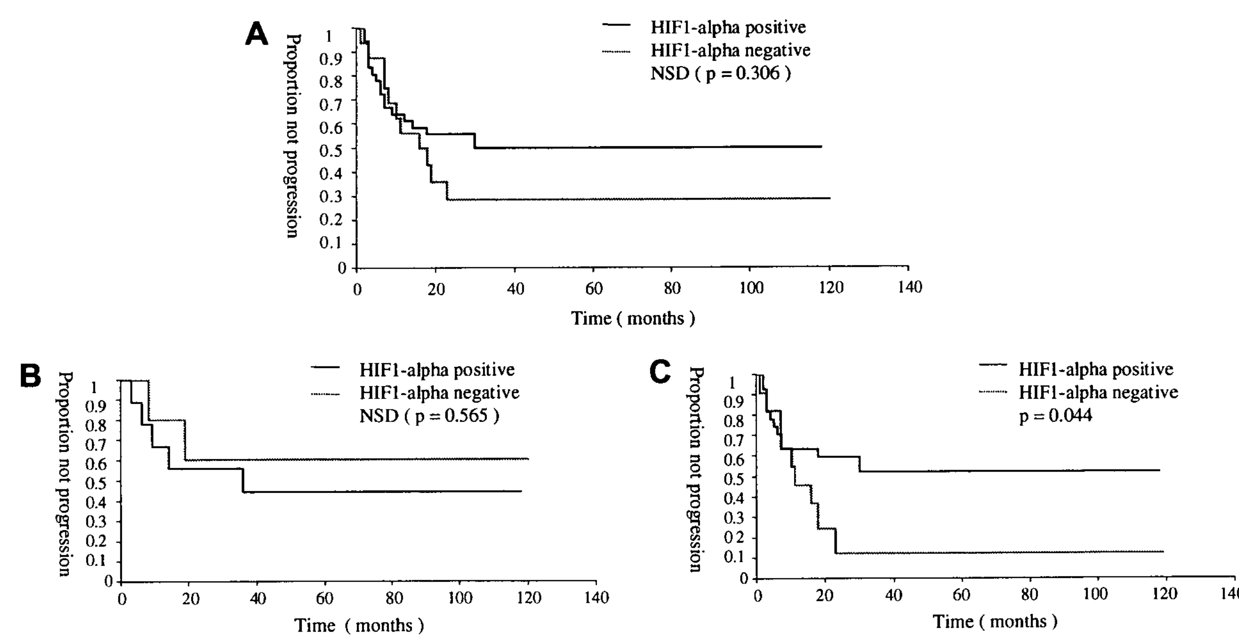

Fig. 2. Correlation between survival and HIF 1-α expression in stage III/IV epithelial ovarian cancer. (A) Progression-free survival in the group of all stage III/IV patients. (B) Progression-free survival of stage III/IV patients who underwent optimal resection at primary surgery and were indicated for postoperative paclitaxel/carboplatin chemotherapy. (C) Progression-free survival of stage III/IV patients who underwent suboptimal resection at primary surgery and were indicated for postoperative paclitaxel/carboplatin chemotherapy. *p*-values were calculated with the log-rank test.

suboptimal resection at primary surgery, and are indicated for postoperative TC. Although TC has been widely used as an effective standard regimen of chemotherapy for primary or recurrent EOC, and TC has achieved a 65–75% overall response rate in several phase 3 clinical trials [9,10], no factors predictive of TC have been found. The present findings suggest that although expression of HIF 1-α is not a factor predictive of survival of patients with early-stage or optimally resected advanced EOC, it does predict the efficacy of chemotherapy using TC. Furthermore, determination of HIF 1-α expression should be useful for devising individualized treatment regimens for advanced EOC. Clinical trials targeting HIF 1-α treatment using taxanes are needed to improve the long-term prognosis of patients with suboptimally resected advanced EOC.

References

[1] G. Gruber, R.H. Greiner, R. Hlushchuk, D.M. Aebersold, H.J. Altermatt, G. Berclaz, V. Djonov, Hypoxia-inducible factor 1 alpha in high-risk breast cancer: an independent prognostic parameter?, Breast Cancer Res 6 (2004) 191–198.

[2] T. Kurokawa, M. Miyamoto, K. Kato, Y. Cho, Y. Kawarada, Y. Hida, T. Shinohara, T. Itoh, S. Okushiba, S. Kondo, H. Katoh, Overexpression of hypoxia-inducible-factor 1 alpha (HIF-1alpha) in oesophageal squamous cell carcinoma correlates with lymph node metastasis and pathologic stage, Br. J. Cancer 89 (2003) 1042–1047.

[3] A. Lidgren, Y. Hedberg, K. Grankvist, T. Rasmuson, J. Vasko, B. Ljungberg, The expression of hypoxia-inducible factor 1 alpha is a favorable independent prognostic factor in renal cell carcinoma, Clin. Cancer Res. 11 (2005) 1129–1135.

[4] D.E. Swinson, J.L. Jones, G. Cox, D. Richardson, A.L. Harris, K.J. O'Byrne, Hypoxia-inducible factor-1 alpha in non small cell lung cancer: relation to growth factor, protease and apoptosis pathway, Int. J. Cancer 111 (2004) 43–50.

[5] T. Fillies, R. Werkmeister, P.J. Van Diest, B. Brandt, U. Joos, H. Buerger, HIF 1-alpha overexpression indicates a good prognosis in early stage squamous cell carcinomas of the oral floor, BMC Cancer 5 (2005) 84.

[6] K. Nakayama, A. Kanzaki, K. Hata, H. Katabuchi, H. Okamura, K. Miyazaki, M. Fukumoto, Y. Takebayashi, Hypoxia-inducible factor 1 alpha (HIF-1 alpha) gene expression in human ovarian carcinoma, Cancer Lett. 176 (2002) 215–223.

[7] P. Birner, M. Schindle, A. Obermair, G. Breitenecker, G. Ober huber, Expression of hypoxia-inducible factor 1 alpha in epithelial ovarian tumors: its impact on prognosis and on response to chemotherapy, Clin. Cancer Res. 7 (2001) 1661–1668.

[8] D. Escuin, E.R. Kline, P. Giannakakou, Both microtubule-stabilizing and micro tubule-destabilizing drugs inhibit hypoxia-inducible factor-1alpha accumulation and activity by disrupting microtubule function, Cancer Res. 65 (2005) 9021–9028.

[9] A. du Bios, H.J. Luck, W. Meier, V. Mobus, S. Costa, B. Richter, M. Warm, T. Bauknecht, W. Schroder, S. Olbricht, U. Nitz, C. Jackisch. Carboplatin/paclitaxel versus cisplatin/paclitaxel as first-line chemotherapy in advanced ovarian cancer; an interim analysis of a randomized phase III trial of the Arbeitsgemeinschaft Gynakologische Onkologie, Ovarian Cancer Study Group. Semin Oncol. 24 (1997) S15-44–52.

[10] P.A. Vasey, G.C. Jayson, A. Gordon, H. Gabra, R. Coleman, R. Atkinson, D. Parkin, Paul randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line J, A. Hay, S.B. Kaye. Scottish Gynaecological Cancer Trials Group, Phase III chemotherapy for ovarian carcinoma, J. Natl. Cancer Inst. 96 (2004) 1682–1691.

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ORIGINAL REPORT

PIEPOC: A New Prognostic Index for Advanced Epithelial Ovarian Cancer—Japan Multinational Trial Organization OC01-01

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ABSTRACT

Purpose
The purpose of this study was to construct a simple and powerful prognostic index (PI) of epithelial ovarian cancer, the PIEPOC.

Patients and Methods
In a retrospective review, data from 768 women with stage III or IV epithelial ovarian cancer from 24 institutions in Japan were evaluated for clinical features predictive of overall survival. A PI and risk groups to predict overall survival after initial surgery were developed using the proportional hazards regression model.

Results
Of six factors, the four prognostic factors that remained independently significant in the analysis of a training sample (538 randomly selected patients) were age, performance status (PS), histologic cell type, and residual tumor size. From the regression function, we derived a PI = 1 (if age 70 and above) + 1 (if PS 1 or 2) + 2 (if PS 3 or 4) + 1 (if mucinous or clear-cell) + 2 (if residual size 0.1 cm and above). Patients were classified into three risk groups (PIEPOC): low risk (PI 0-2), intermediate risk (PI 3), and high risk (PI 4-6). The PIEPOC was equally predictive in a validation sample (n = 230), identifying three groups (5-year survival: 0.67 in low, 0.43 in intermediate, 0.17 in high risk).

Conclusion
Our proposed PI, the PIEPOC, was predictive in our patient population and may have utility in clinical practice. Prospective studies would be needed to confirm the prognostic predictive ability of the PIEPOC for patients with advanced epithelial ovarian cancer.

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INTRODUCTION

Ovarian cancer is the leading cause of death among female cancer patients worldwide.[1] Although mortality from ovarian cancer in Japan is relatively low compared with other developed countries, the mortality and incidence of ovarian cancer in the Japanese population have been increasing since the 1970s.[2]

In patients with advanced epithelial ovarian cancer, several studies have identified age, performance status (PS), histologic cell type, stage, histologic grade, residual tumor size, and presence of ascites as independent prognostic factors.[3-6] A Dutch study group identified PS, residual tumor size, stage, histologic grade, and ascites as prognostic factors using data from two clinical trials.[3] On the basis of these prognostic factors, Lund et al compared the prognostic index (PI) of Dutch study and a Danish PI including PS, residual tumor size, age, and weight or body surface area from a clinical trial and proposed a final PI including information on PS and residual tumor size.[7] Those PIs for survival were developed for planning of treatment for individual patients and stratifying patients in further clinical trials.[3,7] Although they proposed a simple two-covariate PI after validating statistical models in two well-defined independent patient populations, the classification method of risk groups according to the PI was not well specified.[7] The identification of different risk groups should have important therapeutic implications. The purpose of this study was to develop a better prognostic-factor model and to construct a simple and powerful PI of epithelial ovarian cancer by using data from a long-term follow-up study.

PATIENTS AND METHODS

Participants

The study participants were patients with FIGO (International Federation of Gynecology and Obstetrics) stage III or IV epithelial ovarian cancer who were treated with adjuvant chemotherapy after maximal surgical debulking between 1994 and 2000 at 24 institutions in Japan (Japan Multinational Trial Organization OC01-01).[8] In the consecutive series of 880 women, information regarding important patient characteristics was not available for 112 patients (68 for PS, 16 for histologic cell type, and 30 for residual tumor size). Thus, data from 768 women were included in the present study and evaluated for clinical features predictive of overall survival. The patient characteristics evaluated for potential prognostic importance were age, Eastern Cooperative Oncology Group PS, FIGO stage, histologic cell type, histologic grade, and residual tumor size. The presence of ascites was not assessed because the study subjects were patients with surgically confirmed stage III or IV ovarian cancer and we gave greater importance to the surgical findings than to the ascites itself. Overall survival was defined as time from the initial surgery until death resulting from any cause.

Statistical Analysis

A data set was randomly split into training sample for model development and validation sample for model validation for evaluating reproducibility of prognostic-factor model. The survival curves were estimated with the Kaplan-Meier method. The univariate association between potential prognostic factors and overall survival were analyzed with the log-rank test. A PI to predict overall survival was developed using proportional hazards regression model with backward elimination methods. Additivity assumption of the model was verified by the pooled interaction test. We selected the best risk classification in an attempt to separate the prognosis of patients based on the Akaike's information criterion (AIC).[9]

The model performance was assessed with respect to calibration and discrimination. Calibration was examined with graphical expressions (calibration curves) of the relationship between the observed 5-year Kaplan-Meier estimates of overall survival and the predicted probabilities for each group. We used bootstrapping with 200 repetitions to obtain relatively unbiased estimates. Discrimination was evaluated with the concordance index (c index), which is the proportion of all pairs of patients whose survival time can be ordered such that the patient with the lower risk is the one who survived longer.[10] Statistical analyses were done by using SAS version 9.1 (SAS Institute, Cary, NC) and S-Plus version 6J (Mathematical Systems Inc, Tokyo, Japan) with the Design and Hmisc libraries added.

RESULTS

Of 768 patients, 408 patients had died, and the median follow-up times for all patients or 360 surviving patients were 4.1 year or 4.2 years, respectively. The patient characteristics and the 5-year survival probability according to the factors are shown in Table 1. All characteristics except for histologic grade were significantly related to overall survival by the univariate analysis.

We randomly selected 538 patients (70% of all patients) as a training sample in which to identify independent prognostic factors for building a model. Prognostic factors that remained independently significant in the multivariate analysis of the training sample were age, PS, cell type, and size of residual disease. After combining levels of factors that appeared to have a similar effect on survival and checking additivity of effects by pooled interaction tests ($P = .667$), the characteristics and categories that remained independently significant were age (≤ 69 *v* ≥ 70 years), PS (0 or *v* 1 or 2 or *v* 3 or 4), cell type (mucinous or clear-cell *v* others), and residual tumor size (0 *v* ≥ 0.1 cm; Table 2). A linear function based on estimated regression coefficients was as follows: 0.448 (if age 70 years and older) + 0.539 (if PS 1 or 2) + 0.980 (if PS 3 or 4) + 0.488 (if mucinous or clear-cell) + 0.943 (if residual size 0.1 cm and above). From the weight of variables in the

Table 1. Characteristics of 768 Patients and Outcome According to Patient Characteristics

Characteristic	No.	%	Overall Survival: 5-Year Survival (%)	*P*
Age, years				.007
≤ 39	50	7	54	
40-49	181	24	47	
50-59	257	33	45	
60-69	191	25	49	
≥ 70	89	12	31	
Performance status				< .001
0	308	40	61	
1	293	38	39	
2	102	13	34	
3	43	6	21	
4	22	3	17	
FIGO stage				< .001
IIIA	22	3	79	
IIIB	68	9	59	
IIIC	524	68	46	
IV	154	20	31	
Histologic cell type				.022
Serous	505	66	45	
Mucinous	56	7	43	
Endometrioid	101	13	51	
Clear cell	51	7	36	
Mixed epithelial	14	2	50	
Others	41	5	36	
Histologic grade				.144
1	121	24	51	
2	146	29	35	
3	235	47	44	
Unknown	266			
Residual tumor size, cm				< .001
0 (microscopic)	119	16	70	
0.1-0.9	129	17	54	
1.0-1.9	71	9	51	
≥ 2.0	449	58	35	

Table 2. Final Prognostic-Factor Model in the Training Sample (n = 538)

Factors	Hazard Ratio	95% CI	*P*
Age, years			
≤ 69	1.00	—	—
≥ 70	1.57	1.11 to 2.20	.010
Performance status			
0	1.00	—	—
1 or 2	1.71	1.31 to 2.24	< .001
3 or 4	2.67	1.79 to 3.96	< .001
Histologic cell type			
Others	1.00	—	—
Mucinous or clear cell	1.63	1.14 to 2.33	.007
Residual tumor size, cm			
0 (microscopic)	1.00	—	—
≥ 0.1	2.57	1.67 to 3.95	< .001

function, we derived a simplified PI as follows: PI = 1 (if age 70 and above) + 1 (if PS 1 or 2) + 2 (if PS 3 or 4) + 1 (if mucinous or clear-cell) + 2 (if residual size 0.1 cm and above).

The PI of patients in the training sample was distributed between 0 and 5 (0, n = 46; 1, n = 31; 2, n = 143; 3, n = 223; 4, n = 88; 5, n = 7). We selected best classification among all possible classification in an attempt to separate the prognosis of patients with respect to the AIC. The total number of examined classification was 15, including five for two categories and 10 for three categories. As a result, patients were classified into three risk groups, named PIEPOC (PI of Epithelial Ovarian Cancer): low-risk group (PI 0 to 2), intermediate-risk group (PI 3), and high-risk group (PI 4 to 6). The PIEPOC was equally predictive in a randomly selected validation sample (n = 230), identifying three groups (5-year survival probability: 0.67 in low-risk group, 0.43 in intermediate-risk group, 0.17 in high-risk group; Fig 1). If a reference category was the low-risk group, the hazard ratio was 2.29 (95% CI, 1.44 to 3.65) in the intermediate-risk group and 4.87 (95% CI, 2.97 to 7.98) in the high-risk group. This predictability was reproducible in all patients (Fig 2A) and stage IIIc or IV patients (Fig 2B).

The PIEPOC was well calibrated to predict 5-year survival in the all patients, although overestimation (3.0% in the low-risk group) and underestimation (0.8% in the intermediate-risk group and 1.3% in the high-risk group) were observed (Fig 3). The calibration curve was similar to that both in the training sample and the validation sample. The estimated c index in the training sample, the validation sample, and all patients were 0.63, 0.67, and 0.64, respectively. The c index for the PI (0 to 6; seven groups) was 0.65 in all patient; thus, the difference of c index between the PI and the PIEPOC (three groups) was only 0.01.

DISCUSSION

We developed a PI to differentiate risk groups among advanced epithelial ovarian cancer on the basis of demographic, clinical and pathologic characteristics of patients. Accuracy of the simple risk group model was statistically evaluated with respect to discrimination and calibration and reproducibility of the model was accessed by data-splitting method.[10] Analyses for prognostic factors in advanced epithelial ovarian cancer have been carried out since the late 1980s. The Gynecologic Oncology Group in the United States performed a prognostic factor analysis using data from six clinical trials (n = 2,123) and identified age, PS, and residual tumor size as independent significant factors for predicting survival.[5] A Dutch study group identified PS, residual tumor size, FIGO stage, histologic grade by Broders' classification, and ascites as prognostic factors using data from two clinical trials (n = 268).[3] On the basis of the analysis by the Dutch study group, Lund et al compared the PI of Dutch study and a Danish PI including PS, residual tumor size, age, and weight or body-surface area from a clinical trial (n = 301) and proposed a final simple PI including

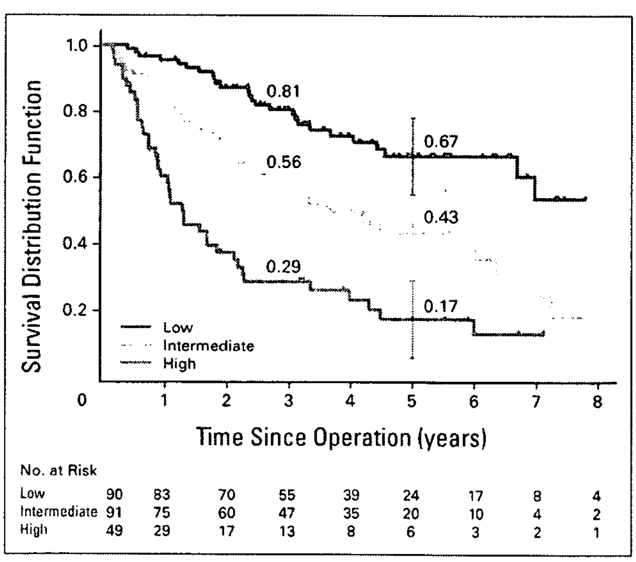

Fig 1. Survival curves according to risk group based on PIEPOC, a new prognostic index of epithelial ovarian cancer, in the validation sample. Bars indicate 95% CIs.

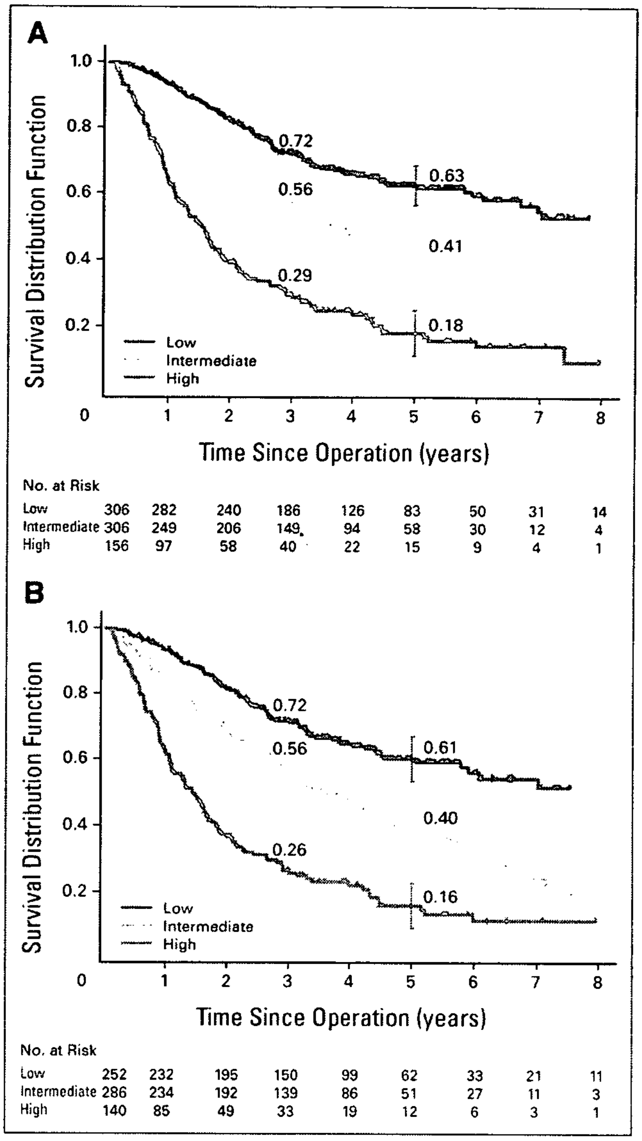

Fig 2. Survival curves according to risk group in (A) all patients and (B) stage IIIC or IV patients. Bars indicate 95% CIs.

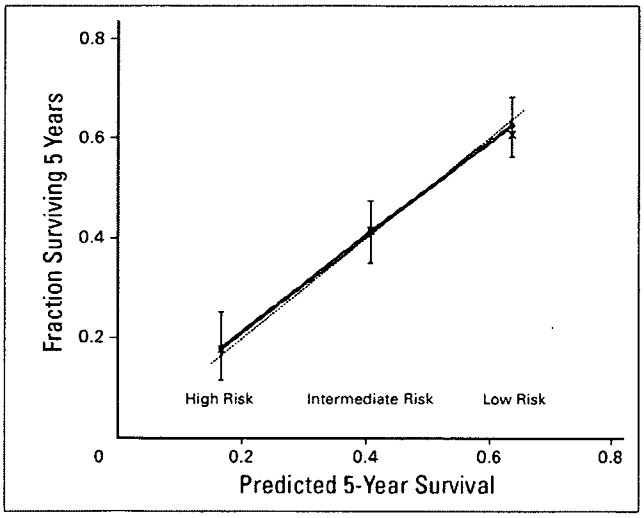

Fig 3. Calibration curve for 5-year survival in all patients. x, bias-corrected calibration.

information on PS and residual tumor size.[7] However, they have not proposed the classification method of risk groups according to the PI. Our proposed PI includes the major prognostic factors (age, PS, and size of residual disease) and histologic cell type, and we could develop the PIEPOC based on the three risk groups from the PI without loss of discrimination ability (difference in c index, 0.01). Because many unknown values might affect the statistical power for detecting the prognostic significance of histologic grade, that was not a significant prognostic factor in the univariate analysis (Table 1). FIGO stage was not a significant independent factor in the multivariate analysis (Table 2) because the factor was highly correlated with PS and residual tumor size. As a result, those two factors were not included in the PIEPOC model. It seems that PS is the strongest prognostic factor and has similar discrimination ability to that of the PIEPOC itself. The c index for PS (0, 1 or 2, 3 or 4) was 0.61 in all patients, and thus the difference on the c index was 0.03 between the PIEPOC and the PI including only PS.

The standard treatment of primary ovarian cancer is internationally considered maximum surgical cytoreduction followed by platinum-based chemotherapy.[11] In our cohort, the patients were treated with paclitaxel + cisplatin/carboplatin (30%), cyclophosphamide + doxorubicin + cisplatin (26%), cyclophosphamide + cisplatin/carboplatin (11%), cisplatin + carboplatin (4%), cisplatin + irinotecan (2%), docetaxel + carboplatin (2%), or other regimens including single agent or other combinations (25%). Although a variety of treatment regimens have been used in the study period and the heterogeneity of treatments is a limitation of this type of study, most regimens may be considered standard chemotherapy in advanced ovarian cancer during the study period. Additionally, the 5-year survival probabilities in patients with the platinum-based regimens (n = 332) were 0.60 in the low-risk group, 0.41 in the intermediate-risk group, 0.22 in the high-risk group. If a reference was the low-risk group, the hazard ratios were 1.83 (95% CI, 1.32 to 2.54) in the intermediate-risk group and 4.38 (95% CI, 2.92 to 6.57) in the high-risk group. The 5-year survival probabilities in patients with the paclitaxel-platinum combination regimens (n = 229) were 0.79 in the low-risk group, 0.37 in the intermediate-risk group, 0.08 in the high-risk group. If a reference was the low-risk group, the hazard ratios were 3.27 (95% CI, 1.82 to 5.88) in the intermediate-risk group and 9.32 (95% CI, 5.04 to 17.2) in the high-risk group. As a result, the PIEPOC would also have predictive ability in the both treatment groups.

A meta-analysis reported that the median survival time ranged from 12 months to 62 months and that the mean weighted median survival time was 29 months among patients with stage III or IV ovarian carcinoma.[12] On the other hand, the survival time in our Japanese cohort was relatively longer than that in the Western population (median, 49 months; 95% CI, 40 to 55 months). One of the reasons there was a difference in survival time is that the year of the study period was relatively old in the meta-analysis (publication year 1989 to 1998) in comparison with the present study (operation year: 1994 to 2000). Thus, we may say that the Japanese population in our study is comparable to the Western population in terms of the similarity of administered treatments and long-term prognosis as well as identified prognostic factors.

The definitions of accuracy and generalizability with regard to assessment of a prognostic system have been discussed.[13] Accuracy (calibration and discrimination) is the degree to which predictions match observed outcomes. In the present study, although the errors in calibration were relatively small (0.8% to 3.0%; Fig 3) for 5-year survival probabilities, the discrimination based on c index was not very gratifying (0.64 in all patients). Although discrimination ability tends to be improved on more complex risk group models, we selected the simple risk group model because of making much account of generalizability. Generalizability (reproducibility and transportability) is the ability of a prognostic system to provide accurate predictions in a new sample of patients. Reproducibility requires the system to replicate its accuracy in patients who were not included in development of the system but who are from the same underlying population.[13] We evaluated the reproducibility by using data-splitting method because we had relatively large data sets. It might be reasonable to suppose that our classification is simple and reproducible without loss of discrimination ability because the best c index for a PI based on a six-covariate full model was 0.68 in all patients and the gain of discrimination ability was relatively small. Transportability requires the system to produce accurate predictions in a sample drawn from a different but plausibly related population or in data collected by using slightly different methods from those used in the development sample.[13] The PIEPOC needs to be prospectively studied for transportability in other study populations.

In conclusion, by using data from a long-term follow-up study, we developed a prognostic-factor model which was a simple and powerful PI of epithelial ovarian cancer, the PIEPOC. In two separate samples, the PIEPOC was effective in discriminating the risk of recurrence by categorizing patients into three risk groups: high, low, and intermediate risk. The PIEPOC may be a useful tool for the selection of appropriate treatment options for patients at risk of recurrent disease.

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1. Pisani P, Parkin DM, Bray F, et al: Estimates of the worldwide mortality from 25 cancers in 1990. Int J Cancer 83:18-29, 1999
2. Ioka A, Tsukuma H, Ajiki W, et al: Ovarian cancer incidence and survival by histologic type in Osaka, Japan. Cancer Sci 94:292-296, 2003
3. van Houwelingen JC, ten Bokkel Huinink WW, van der Burg MEL, et al: Predictability of the survival of patients with advanced ovarian cancer. J Clin Oncol 7:769-773, 1989
4. Omura GA, Brady MF, Homesley HD, et al: Long-term follow-up and prognostic factor analysis in advanced ovarian carcinoma: The Gynecologic Oncology Group experience. J Clin Oncol 9:1138-1150, 1991
5. Thigpen T, Brady MF, Omura GA, et al: Age as a prognostic factor in ovarian carcinoma. Cancer 71:606-614, 1993 (suppl)
6. Holschneider CH, Berek JS: Ovarian cancer: Epidemiology, biology, and prognostic factors. Semin Surg Oncol 19:3-10, 2000
7. Lund B, Williamson P, van Houwelingen HC, et al: Comparison of the predictive power of different prognostic indices for overall survival in patients with advanced ovarian carcinoma. Cancer Res 50: 4626-4629, 1990
8. Ochiai K, Kuramoto Y, Yamashita K, et al: The impact of therapeutic modalities on the outcome of advanced epithelial ovarian cancer patients treated in Japan: A JMTO study. J Clin Oncol 22:471, 2004 (suppl; abstr 5097)
9. Akaike H: Information theory and an extension of the maximum principle. Proc 2nd Int Symp Information Theory, 267-281, 1973
10. Harrell FE, Lee KL, Mark DB: Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 15:361-387, 1996
11. Deppe G, Baumann P: Advances in ovarian cancer chemotherapy. Curr Opin Oncol 12:481-491, 2000
12. Bristow RE, Tomacruz RS, Armstrong DK, et al: Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: A meta-analysis. J Clin Oncol 20:1248-1259, 2002
13. Justice AC, Covinsky KE, Berlin JA: Assessing the generalizability of prognostic information. Ann Intern Med 130:515-524, 1999

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).