Primary epithelial ovarian carcinoma in Taiwanese women

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Summary

Purpose of investigation: Primary epithelial ovarian carcinoma is common in industrial countries but rare in the Orient. In fact, it is still a rare disease in Taiwan. In this article, we report the general data of Taiwanese patients with primary epithelial ovarian carcinoma.

Methods: In this retrospective study we used univariate and multivariate analysis models to analyze the prognosis of patients with surgically confirmed primary epithelial ovarian carcinoma. One hundred and ninety-four patients from 1990 to 1996 were identified and enrolled in this study.

Results: The mean follow-up time was 44.7 months with an interval between 15.1 months and 105.9 months. Univariate analysis showed postmenopausal status, advanced stage, presence of lymph node metastasis, poor differentiation, and suboptimal surgery as risk factors for disease recurrence and subsequent deaths. Multivariate analysis demonstrated stage as the most important factor correlated with recurrent disease (risk ratio: 7.303 and 5.409, respectively), followed by optimal surgery (RR: 2.447), and cellular differentiation (RR: 1.677).

Conclusions: Our data on the Taiwan population were consistent with other reports of different races. Early detection for primary epithelial ovarian cancer is of great importance because stage is still the most important predictor in disease-free survival and disease-related deaths. Application of the most reliable and acceptable methods of screening is our goal in the next century after weighing benefits over costs.

Key words: Epithelial ovarian carcinoma; Multivariate and univariate analyses; Prognosis.

Introduction

Although primary epithelial ovarian carcinoma (PEOC) is not a primary leading cause of Taiwanese mortality, with improving nutrition and increasing age, the disease has been identified in recent years. Many factors have been reported about prognoses in patients with epithelial ovarian carcinoma [1-2]. They include tumor stage, histologic subtype, grade, CA-125 (the antigenic determinant of the monoclonal antibody OC-125), ploidy analysis, image cytometry, genetic factors, biological factors, cytoreductive surgery, and so on. Among these, some factors are still controversial. In this report, we used the easily-available surgico-pathological data as well as clinical data to evaluate their effects on the survival of patients with PEOC. This article is a the report on PEOC which summarizes data from one medical center in Taiwan. These data might provide some information and subsequent guidelines to manage this disease in the future.

Methods

We retrospectively studied 194 patients with PEOC, who were treated at one of the largest medical centers in Taiwan between January 1990 and December 1996. The criteria included (1) Cases of pathologically confirmed primary epithelial ovarian carcinoma (cancer of low malignant potential was not included), (2) Patients who underwent standard surgical treatment with complete cytoreductive surgery (even stage I patients) followed by the same regimen of chemotherapy (to avoid bias data). Patients who were treated before referral and who received taxol-based chemotherapy were excluded from the study. The charts of 194 patients were reviewed using a defined data collection form. All patients with PEOC were confirmed by pathology and reviewed by one of the authors (Dr. Lai). All patients were managed by a standard treatment procedure: washing cytology, total abdominal hysterectomy, bilateral salpingo-oophorectomy, retroperitoneal lymphadenectomy, infracolic omentectomy and excision biopsy of all suspicious lesions, and followed by adjuvant chemotherapy with six courses of CAP (cyclophosphamide 500 mg/m^2, adriamycin 50 mg/m^2, and cisplatin 50 mg/m^2 intravenously, every three weeks). Staging was according to the International Federation of Gynecology and Obstetrics (FIGO) guidelines [3]. The hospital course and clinical follow-up data were obtained from hospital records. The follow-up period was calculated from the date of initial surgery to the date of last follow-up (June 30, 1999) or the time of death. Cross-tabulations, descriptive statistics and recurrence were prepared with the use of SAS software, version 6.03 [4]. Survival curves were estimated by the Kaplan-Meier method and Mantel-Cox statistics [5-7]. This test was also used to select variables to be included in the log-rank analysis. Significance was defined as $p<0.05$.

Results

The mean follow-up time was 44.7 months with an interval between 15.1 months and 105.9 months. The

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accumulative 5-year disease-free survival rate of all patients was 56.2%. Univariate analysis showed postmenopausal status, advanced stage, presence of lymph node metastasis, poor differentiation, and suboptimal surgery as risk factors for disease recurrence and subsequent deaths (Table 1). Multivariate analysis demonstrated stage as the most important factor correlated with recurrent disease (RR: 7.303 and 5.409, respectively), followed by optimal surgery (RR: 2.447), and cellular differentiation (RR: 1.677) (Table 2).

Discussion

Primary epithelial ovarian carcinoma presents a special challenge to gynecologic oncologists partly because of aggressive tumor behavior and partly because of relatively limited improvement in survival in recent decades. In addition, many different histological subtypes of the epithelial ovarian carcinomas are classified. Conventionally, many clinical physicians have considered that some histological subtypes contribute to a worse prognosis when compared with other histological subtypes. The histological subtype of clear cell carcinoma might be the worst. DiSaia and Creasman reported that there seems to be limited prognostic significance of histological type of malignant epithelial ovarian carcinoma independent of clinical stage, extent of residual disease, and histological grade [3]. Some physicians have had conflicting data [8-14]. In this study, different cell types did not seem to be an independent prognostic factor. In contrast, most studies have failed to demonstrate a significant correlation between histological grade and survival [1, 2]. The value of grade might only be a particular important prognostic factor in patients with early-stage disease, however, Trope *et al.* found that the degree of differentiation was a powerful prognostic factor of overall survival [15]. In our study multivariate analysis showed that grade was also a significant prognostic factor and it closely followed two other factors: stage and optimal debulking surgery in prognosis without classification of early or advanced stage.

It is a well known that the stage is the most prominent factor for patient survival [3, 8-14]. Patients presenting clinically at an early stage have a markedly better survival rate than those presenting at an advanced stage. That is why the majority of physicians do their best to detect ovarian carcinoma in earlier stages. In addition, it is possible to detect a significant proportion of cases of PEOC at a preclinical stage using screening techniques [16]. Strategies for early detection of patients with epithelial ovarian carcinoma include annual screening with pelvic examinations, CA-125, transvaginal ultrasound and identification of high-risk patients. However, both CA-125 and ultrasound have a significant false-positive rate that precludes their use alone as a one-stage screening of the general population due to excessive morbidity. Immediate physical and psychological morbidity as well as considerable financial implications and risk of long-term surgical/anesthetic complications have been found in a

Table 1. — *Prognostic factors and disease-free survival in 194 patients with epithelial ovarian carcinoma.*

Factors	Number of patients	Number of patients who died of disease (%)	p*
Stage			0.0001
I	49	2 (04.09)	
II	32	8 (25.00)	
III+IV	113	75 (66.38)	
Age			0.0799
<30 y/o	22	5 (22.73)	
Between 20 & 70	158	72 (45.57)	
<70 y/o	14	8 (57.15)	
Menopause			0.0112
Before	103	35 (33.92)	
After	91	50 (54.95)	
Differentiation			0.0001
Well	14	1 (07.15)	
Moderate	135	52 (48.52)	
Poor	45	32 (71.12)	
LN			0.0007
Negative	165	65 (39.40)	
Positive	29	20 (68.97)	
*2nd look ± 2nd operation***			0.7927
No	104	45 (43.27)	
Yes	90	40 (44.45)	
Optimal surgery			0.0001
Yes	125	37 (29.60)	
No	69	48 (69.57)	
Cell Type			0.3871
Mucinous	40	20 (50.00)	
Clear	25	7 (28.00)	
Endometrioid	53	24 (45.29)	
Serous	74	33 (44.59)	
Others	2	1 (50.00)	

*: Kaplan-Meier Analysis; **: 2nd look ± 2nd operation means that patients had been treated with a second-look operation and/or second debulking surgery when the patients had received the complete therapy including surgery and post-operative adjuvant chemotherapy; Others: malignant mixed mesodermal tumors and Brenner tumors; LN: lymph node metastasis.

Table 2. — *Multivariate analysis of factors and 5-year accumulative survival for patients with epithelial ovarian carcinoma.*

Variable	Standard Error	p	Risk Ratio	95% CI
Optimal surgery* (No/Yes)	0.24044	0.0002	2.447	1.527-3.920
Presence of malignant cells in Cytology** (Yes/No)	0.65606	0.3697	1.801	0.498-6.517
Differentiation (PD/WD+MD)	0.25846	0.0454	1.677	1.011-2.784
Stage				
II/I	0.59291	0.0147	5.409	1.692-17.290
III/I	0.54311	0.0001	7.303	2.519-21.175
Age				
Postmenopause/ premenopause	0.23576	0.2930	0.780	0.492-1.239
Cell Type				
(CI/Other+Ser)	0.46641	0.9022	0.944	0.379-2.356
(CI+Ser/Others)	0.50280	0.5163	1.386	0.517-3.713

*: Optimal surgery means that the biggest residual tumor was less than 1.0 cm.; CI: confidence interval; PD: poorly differentiated; WD: well differentiated; MD: moderately differentiated; CI: clear cell carcinoma; Ser: serous cell carcinoma; Others: mucinous cell carcinoma and endometrioid cell carcinoma; Cox's: proportional hazards analysis.

small proportion of cases [14]. In a recent large study with a sequential combination of CA-125 and ultrasound, 340 of 22,000 postmenopausal volunteers screened had elevated CA-125 levels and underwent transabdominal ultrasound which was acceptable in a general population screening of a postmenopausal population [16]. The overall specificity of this screening strategy was 99.9% and the positive predictive value was 26.8% [16]. However, for women's exams in Taiwan, serum CA-125 testing costs similar to ultrasound. In addition, serum CA-125 testing was not popular in the general hospital. The sequential strategy (serum CA-125 as an initial screening tool and ultrasound as a back-up tool while elevated serum CA-125 was noted) might not be an appropriate application in Taiwan. Although detection abnormality of ovary might be better using transvaginal ultrasound compared with using transabdominal ultrasound [16], the unnecessary exploratory laparotomy would be increased significantly based on low detection rate in positive ultrasound examinations with exploratory laparotomy. Due to this unproved benefit versus risk, the recommendation of PEOC screening of the normal population might be conducted in a clinical research setting. Detecting high-risk patients with PEOC and using prophylactic surgery seems reasonable. Among the frequent gene mutations relating to ovarian cancer, BRCA1 mutation is of paramount importance. Eisen et al concluded that prophylactic oophorectomy seems to be associated with considerable reduction in the risk of ovarian cancer, albeit incomplete [17]. In addition, the surgical morbidity of prophylactic oophorectomy is low, but the complications of premature menopause may be significant. However, in our recent study on BRCA1 mutation in Taiwanese women with PEOC, BRCA1 mutation is still a very rare event [18]; thus the application of screening for all women in Taiwan needs further evaluation.

Optimal debulking surgery is an independent prognostic factor for patient survival. It becomes a most common concept when we deal with patients with PEOC [2, 3, 9-14, 19-28]. Griffiths has demonstrated the theoretical basis for cytoreductive surgery [22, 23]. Removing bulky tumor masses in patients with advanced ovarian carcinoma may improve the patient's comfort, reduce the adverse metabolic consequences of the tumor, and enhance the patient's ability to maintain their nutritional status. Such effects are likely to increase the patient's ability to tolerate the aggressive chemotherapy [23]. Perhaps the most important factor is that removal of large tumor masses may enhance the response of the remaining tumor to chemotherapy [29]. It has been axiomatic among many gynecologic oncologists to be judicious in excising as much tumor as possible when PEOC is encountered at the time of primary surgery. Considering this report, we have provided solid evidence that the maximal surgical effort for complete debulking directly improves survival. In our institute, we routinely use extra techniques such as an ultrasound surgical aspirator to improve the success of cytoreduction. This finding has recently been found by others [30].

In conclusion, a better prognosis of Taiwanese patients with PEOC could be expected in early stage with good and moderate differentiation and complete an optimal debulking surgery. This result does not show differences when compared with reports from western countries.

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References

[1] Ozols R. F., Rubin S. C., Thomas G. M., Robboy S. J.: "Epithelial ovarian cancer". In: Hoskins W. J., Perez C. A., Young R. C., eds. "Principle and Practice of Gynecologic Oncology". 2nd ed. Philadelphia: Lippincott-Raven Press, 1997, 919.

[2] Friedlander M. L.: "Prognostic factors in ovarian cancer." *Semin. Oncol.*, 1998, *25*, 305.

[3] DiSaia P. J., Creasman W. T.: "Epithelial ovarian cancer." In: DiSaia P. J., Creasman W. T., eds. "Clinical Gynecologic Oncology", 5th ed. St. Louis: Mosby-Year Book Inc., 1997, 282.

[4] SAS/STAT user's guide, release 6.03 edition. Cary (NC), SAS Institute, 1988.

[5] Kaplan E. L., Meier P.: "Non-parametric estimation from incomplete observation." *J. Am. Stat. Assoc.*, 1986, *4*, 57.

[6] Mantel N.: "Evaluation of survival data and two rank-order statistics arising in its consideration". *Cancer Chemother. Rep.*, 1966, *50*, 163.

[7] Cox D. R.: "Regression models and life tables". *J. Roy. Stat. Soc. B.*, 1972, *34*, 187.

[8] Young R. C., Walton L. A., Ellenberg S. S., Homesley H. D., Wilbanks G. D., Decke D. G., *et al.*: "Adjuvant therapy in stage I and II epithelial ovarian cancer: results of two prospective randomized trials". *N. Engl. J. Med.*, 1990, *322*, 1021.

[9] Krag K. J., Canellos G. P., Griffiths C. T., Knapp R. C., Parker L. M., Welch W. R. *et al.*: "Predictive factors for long term survival in patients with advanced ovarian cancer". *Gynecol. Oncol.*, 1989, *34*, 88.

[10] Tempfer C., Obermair A., Hefler L., Haeusler G., Gitsch G., Kainz C.: "Vascular endothelial growth factor serum concentrations in ovarian cancer". *Obstet. Gynecol.*, 1998, *92*, 360.

[11] Reles A. E., Gee C., Schellschmidt I., Schmider A., Unger M., Friedmann W. *et al.*: "Prognostic significance of DNA content and S-phase fraction in epithelial ovarian carcinomas analyzed by image cytometry". *Gynecol. Oncol.*, 1998, *71*, 3.

[12] Curling M., Stenning S., Hudson C. N., Watson J. V.: "Multivariate analyses of DNA index, p62c-myc, and clinicopathological status of patients with ovarian cancer." *J. Clin. Pathol.*, 1998, *51*, 455.

[13] Tsumura N., Sakuragi N., Hareyama H., Satoh C., Oikawa M., Yamada H. *et al.*: "Distribution pattern and risk factors of pelvic and para-aortic lymph node metastasis in epithelial ovarian carcinoma". *Int. J. Cancer*, 1998, *79*, 526.

[14] Zwart J., Geisler J. P., Geisler H. E.: "Five-year survival in patients with endometrioid carcinoma of the ovary versus those with serous carcinoma". *Eur. J. Gynecol. Oncol.*, 1998, *19*, 225.

[15] Trope C. G., Vergote J. K. I.: "Prognostic factors in platinum-resistant ovarian carcinoma treated with ifosfamide-etoposide". *Eur. J. Gynecol. Oncol.*, 2000, *21*, 255.

[16] Jacobs I., van Nagell J. R. Jr., DePriest P. D.: "Screening for epithelial ovarian cancer". In: Gershenson D. M., McGuire W. P., eds. "Ovarian Cancer: Controversies in Management". New York, Churchill Livingstone, 1998, 1.

[17] Eisen A., Rebbeck T. R., Wood W. C., Weber B. L.: "Prophylactic surgery in women with a hereditary predisposition to breast and ovarian cancer". *J. Clin. Oncol.*, 2000, *18*, 1980.

[18] Wang P. H., Shyong W. Y., Li Y. F., Lee H. H., Tsai W. Y., Chao H. T., Wu C. Y. *et al.*: "BRCA1 mutations in Taiwanese with epithelial ovarian carcinoma and sporadic primary serous peritoneal carcinoma". *Jap. J. Clin. Oncol.*, 2000, *30*, 343.
[19] Wang P. H., Yuan C. C., Shong W. Y., Chiang S. C., Chao J. Y., Yen M. S., Ng H. T.: "Optimal debulking surgery seems to be an independent prognostic factor in patients with FIGO IIIC primary epithelial ovarian carcinoma". *Chin. Med. J.* (Taipei), 2000, *63*, 220.
[20] Hoskins W. J., McGuire W. P., Brady M. F., Homesley H. D., Creasman W. T., Berman M. *et al.*: "The effect of diameter of the largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma". *Am. J. Obstet. Gynecol.*, 1994, *170*, 974.
[21] Eisenkop S. M., Nalick R. H., Wang H. J., Teng N. N.: "Peritoneal implant elimination during cytoreductive surgery for ovarian cancer: impact on survival". *Gynecol. Oncol.* 1993, *51*, 224.
[22] Griffiths C. T.: "Surgical resection of the tumor bulk in the primary treatment of ovarian carcinoma". *Natl. Cancer. Inst. Monogr.*, 1975, *42*, 101.
[23] Griffiths C. T.: "Surgery at the time of diagnosis in ovarian cancer". In: Blackledge G., Chan K. K., eds. "Management of Ovarian Cancer", London, Butterworths, 1986, 60.
[24] Morton D. L.: "Changing concepts in cancer surgery: surgery as immunotherapy". *Am. J. Surg.*, 1978, *135*, 767.
[25] Brinkhuis M., Meijer G. A., Baak J. P.: "An evaluation of prognostic factors in advanced ovarian cancer". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 1995, *63*, 115.
[26] Hoskins W. J., Bundy B. N., Thigpen J. T., Omura G. A.: "The influence of cytoreductive surgery on recurrence-free interval and survival in small-volume stage III epithelial ovarian cancer: a Gynecologic Oncology Group study". *Gynecol. Oncol.*, 1992, *47*, 159.
[27] Krag K. J., Canellos G. P., Griffiths C. T., Knapp R. C., Parker L. M., Welch W. R. *et al.*: "Predictive factors for long term survival in patients with advanced ovarian cancer". *Gynecol. Oncol.*, 1989, *34*, 88.
[28] Berek J. S.: "Epithelial ovarian cancer". In: Berek J. S., Hacker N. F., eds. "Practical Gynecologic Oncology", 2nd ed. Baltimore, Williams & Wilkins Co., 1994, 327.
[29] Wang P. H., Yang T. Z., Lee W. L., Chang S. P., Chao H. T., Yuan C. C.: "Treatment of infertile women with adenomyosis with a conservative microsurgical technique and a gonadotropin-releasing hormone agonist". *Fertil. Steril.*, 2000, *73*, 1061.
[30] Sert M. B., Abbas F. M., Currie J. L., Zahyrak M. L., Rosenshein N. B.: "Use of the ultrasound surgical aspirator in ovarian cancer: a case-control study". *Eur. J. Gynecol. Oncol.*, 2000, *21*, 24.

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