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Epithelial Ovarian Carcinoma: Analysis of Prognostic Factors

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One hundred and two patients with epithelial ovarian carcinomas treated at Yonsei University College of Medicine from January 1966 through December 1985 were retrospectively reviewed. Stage and tumor grade were found to be highly significant prognostic factors. Other important prognostic factors included residual tumor volume and transcapsular extension. Age and the presence of ascites were prognostic factors of marginal importance. The present study proposes that accurate surgical staging is mandatory at initial surgery and that tumor grading should be included in the FIGO classification of epithelial ovarian cancers. Improved surgical management to reduce the residual tumor volume is important for advanced tumor stage. In early tumor stages, more effective treatment should be reserved for patients with transcapsular extension. Prospective investigation is necessary for further subset analysis.

Key Words: Epithelial ovarian carcinoma, prognostic factor

Ovarian cancer remains the most lethal gynecologic malignancy (Fisher and Young 1977; Silverberg 1983) despite much progress in the treatment of malignant disease in recent years. Its importance amongst gynecological cancers is increasing (Smith and Day 1979). Early diagnosis is hampered by the lack of early and typical signs and symptoms of ovarian carcinoma, and the absence of effective and practicable screening methods to facilitate such diagnosis (Webb *et al.* 1973).

The present study was prompted by the fact that epithelial ovarian carcinoma is the most common histologic type of malignant ovarian tumor (Aure *et al.* 1971; Weiss *et al.* 1977) and evaluation of the prognostic factors should assist in the design of effective therapeutic strategies. Many prognostic factors influencing survival have been identified. These include stage (Long *et al.* 1967; Smith and Day 1979; Schray *et al.* 1983), histological type (Peres *et al.* 1975; Malkasian *et al.* 1975), histological grade (Barber *et al.* 1975; Day *et al.* 1975; Ozol *et al.* 1980), residual disease (Björkholm *et al.* 1982), ascites (Aure *et al.* 1971; Bagley *et al.* 1972), race (Berg and Baylor 1973), age (Smedley and Sikora 1985), and treatment modalities (Bush *et al.* 1977). The purpose of this study was to determine the effects of age, stage, cell type, histological grade, other histological factors, ascites, treatment modalities, and residual tumor size on the survival of patients with epithelial ovarian carcinoma.

MATERIALS AND METHODS

One hundred and two patients with epithelial ovarian carcinoma treated at Yonsei University College of Medicine from January 1966 through December 1985 were retrospectively reviewed. Tumors of boderline malignancy were excluded.

Surgical pathology, operative, and cytology reports were studied to determine histologic tumor type, capsular involvement, bilaterality, presence of ascites, residual tumor size, and stage of tumor. Histologic classification and staging were performed according to the 1978 revised systems adopted by the International Federation of Gynecology and Obstetrics. The microscopic specimens were reexamined when the primary analysis of tumor histology was incomplete or uncertain as to the factors studied when slides or blocks were available for reexamination. Histologic grading was performed according to Woodruff *et al.*

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(1978). All patients were subsequently followed up through medical records and correspondence. Survival curves were calculated from the time of diagnosis by means of the Life-Table method. Differences in survival between groups of patients were examined by the log-rank test using a 0.05 significance level.

RESULTS

Basic data on age and survival are shown in Table 1. The mean patient age was 44 years, with a range of 16 to 69 years. The overall 3-year cumulative survival rate for the complete series was 46%, and the median survival time was 31 months. These survival rates were based on death attributed to epithelial ovarian cancer only.

Distribution of patients by histologic type shows that serous cystadenocarcinoma is predominant (38.2%), mucinous cystadenocarcinoma is next with 34.3%, followed by unclassified adenocarcinoma (13.7%), endometrioid adenocarcinoma (8.8%). The other groups constitute less than 3% each. Tumors of low potential malignancy are not included in this study (Fig. 1). Fig. 2 presents the age distribution of epithelial ovarian cancer. No difference was found in the age distribution of patients with various histologic types.

Table 1. Basic data on age and survival of patients in the complete series of epithelial ovarian carcinomas

Age (year)		Total 3-year cumulative survival (%)	Total median survival (mo)
Mean	Range		
44	16-69	46	31

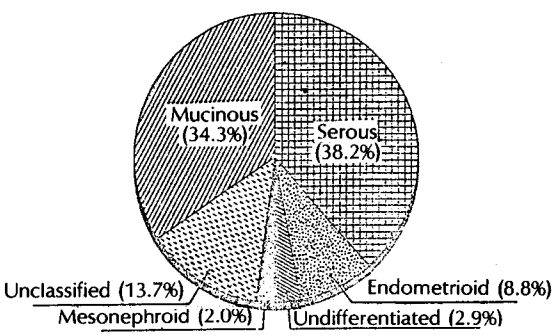

Fig. 1. Distribution of patients by histologic classification.

Tumor stage distribution shows that 43% of the populaton had stage I disease. 16% had stage II, and 41% had stage III or IV (Table 2). The high total survival rates (46%) could be associated with the high proportion of tumors in stage I (43% of the total). Table 3 shows the distribution of stages in relation to tumor types. Definite conclusions cannot be drawn from this table. However, serous cystadenocarcinoma appears

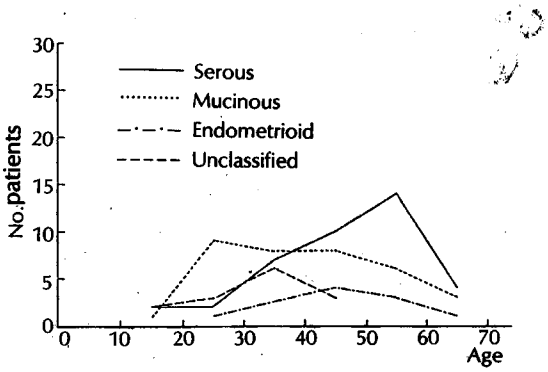

Fig. 2. Age distribution of patients by histologic classification.

Table 2. Distribution of Patients by Stage

Stage	No. of Pafients	Total(No.)	%	Total(%)
Ia	24		23	
Ib	4		4	
Ic	16	44	16	43
IIa	3		3	
IIb	5		5	
IIc	8	16	8	16
III	22		21	
IV	20	42	20	41
Total	102		100	

Table 3. Stage of epithellial ovarian cancer

Types	Stage			
	I	II	III	IV
Serous	15	8	10	6
Mucinous	20	2	7	6
Endometrioid	3	3	2	1
Unclassified	4	2	2	6
Undifferentiated		1	1	1
Mesonephroid	2			

Table 4. Treatment regimens epithelial ovarian carcinoma patients by stage

Method of treatment	Stage I	Stage II	Stage III	Stage IV	Total No (%)
Surgery alone	18	2	6	4	30 (29)
S+R	4	1			5 (5)
S+SC	9	2	2	3	16 (16)
S+CC	4	10	8	5	27 (26)
S+R+C		1	1	3	5 (5)
O+SC	6		2	1	9 (9)
O+CC	3		2	1	6 (6)
Biopsy+C			1	3	4 (4)
Total	44	16	22	20	102 (100)

S: Total abdominal hysterectomy with or without omentectomy, debulk op. if necessary
SC: Single agent chemotherapy
CC: Combination chemotherapy
R: Radiation therapy
O: Unilateral or bilateral oophorectomy
C: Single agent or combination chemotherapy

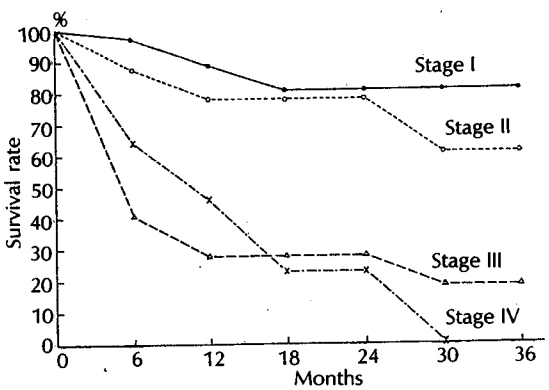

Fig. 3. Cumulative survival rate by stage.

to have a greater tendency to predominate in the higher stages.

Treatment regimens by tumor stages during initial and subsequent treatment are shown in Table 4. Overall, 96% of the patients received surgical treatment. Chemotherapy was administered to 66% of the patients. The proportion of chemotherapy increased as with stage, ranging from 50% in stage I patients to 76% in stage III and IV patients. Radiotherapy was given to 10% of the patients. Because these patients were not randomly submitted to specific treatment

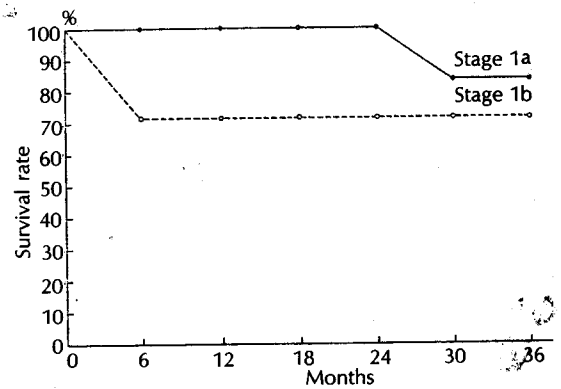

Fig. 4. Comparison of survival rate for stage Ia and Ib.

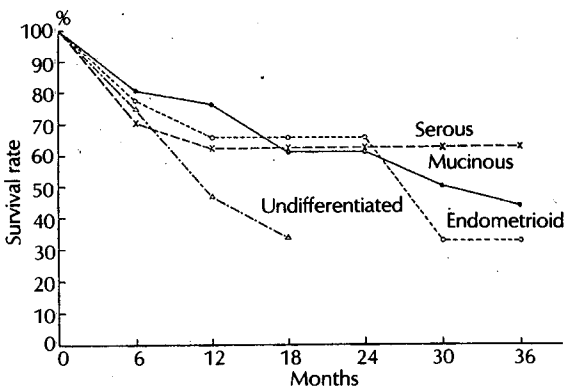

Fig. 5. Cumulative survival rate by histology.

protocols, no conclusions will be drawn regarding treatment efficacy based on comparative treatment regimens.

Life table analysis shows the great prognostic significance of tumor staging. The 3-year cumulative survival rate was 81% in stage I, 61% in stage II, and 18% in stage III patients. In stage IV patients the rate was 0% (Fig. 3). Patient survival differed significantly according to tumor stage ($p<0.005$). Survival rates for stage Ia and Ib are compared (Fig. 4); the difference in 3-year cumulative survival rates between the two groups is significant ($p<0.05$).

The 3-year cumulative survival rates according to tumor type are shown in Fig. 5. No significant differences exist between the histologic tumor types. Tumor grade was significantly correlated with survival. Survival was progressively worse as the grade rose from 1 to 4. The 3-year cumulative survival was 75% for patients with grade 1 and only 16% for those with

grade 4 carcinomas (Fig. 6). Figure 7 shows survival rates for all stages together for patients under 40 years of age and for those 40 years of age or older. The 3-year cumulative survival for the patients under age 40 was 64%, whereas it was 37% for those aged 40 years or older. Table 5 shows the correlation between histologic grading and other histologic features. Cytologic factors such as stratification, nuclear pleomorphism, papillary projection and stromal invasion, appear to be parameters of tumor grade and are related to histologic differentiation.

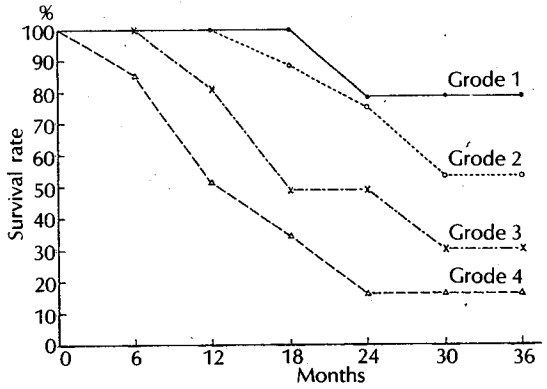

Fig. 6. Cumulative survival rate by grade.

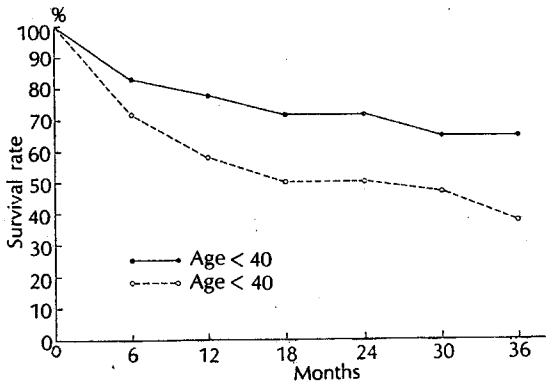

Fig. 7. Cumulative survival rate by age.

The survival rates demonstrated that patients with ascites had a lower rate than those without ($p<0.01$). However, the difference was no longer statistically significant when these groups were adjusted for stage. The presence of bilateral tumor did not seem to adversely affect the prognosis compared with unilateral disease (Table 6).

Factors influencing survival were separately analyz-

Table 6. Prognostic factors by univariate analysis

Factor	No. of patients	% Survival	X^2
Ascites			6.90*
None reported	46	61	
Reported present	56	36	
Involvement of ovaries			4.46
One ovary	66	54	
Both ovaries	36	30	

* $P < 0.01$

Table 7. Early tumor stages (Ia, Ib, Ic and IIa) correlated to prognostic factors and 3-year cumulative survival rate

Factor	No. of patients	% Survival	P
Transcapsular exetension			<0.001*
None reported	38	100	
Reported present	9	48	

* X^2 for trend.

Table 5. Histologic features of epithelial ovarian cancer

Grade	No. patients	Stratification				Nuclear pleomorphism				Papillary projection				Stromal invasion			
		–	+	++	+++	–	+	++	+++	–	+	++	+++	–	+	++	+++
1	31		26	3	2	2	28	1		4	5	16	6	4	17	6	4
2	10		6	4			3	5	2	1	2	2	5		4	3	3
3	16		3	7	6		1	10	5			7	9		4	6	6
4	12		3	5	4		2	5	5		2	6	4		1	4	7

–: None +: Mild ++: Moderate +++: Severe

Table 8. Advanced tumor stages (IIb, IIc, III and IV) correlated to prognostic factors and 3-year cumulative survival rate

Factor	No. of patients	% Survival	P-value
Residual tumor volume			<0.001*
< 2 cm	13	61	
> 2 cm	42	11	

* X^2 for trend.

ed in the early stages Ia to IIa and in the advanced stages IIb to IV. Transcapsular extension of the tumor influenced the survival rate in the early stage. The cumulative 3-year survival rates for those with and without transcapsular extension was 48% and 100%, respectively (Table 7). This difference was statistically significant ($p<0.001$). For advanced tumor stages, survivial was poorer for those with more than 2 cm of residual tumor remaining after surgery. Among the 13 patients in whom the operation left no macroscopic tumor or tumor tissue less than 2 cm, the survival rate was 61%, whereas it was 11% for those with more than 2 cm of residual tumor (Table 8).

DISCUSSION

Tumor stage, grade, and the extent of residual disease have been reported to be important prognostic factors (Björkholm 1982; Dembo and Bush 1982; Schray *et al.* 1983; Einhorn *et al.* 1985). In the present study, stage and tumor grade were found to be highly significant prognostic factors. Other important prognostic factors were residual tumor volume and transcapsular extension. Age and the presence of ascites were prognostic factors of marginal importance.

The overall 3-year cumulative survival rate in the present study is compatible with studies by Sorbe *et al.* (1982) and Swenerton *et al.* (1985). Tumor stage was found to be a prognostic factor of great significance as many other studies had previously reported (Mckay and Sellers 1967; Pomerence and Moltz 1971; Smith and Day 1979; Schray *et al.* 1983; Einhorn *et al.* 1985). The presence of bilateral tumor (Stage Ib) adversely affected the prognosis compared to unilateral tumor (stage Ia). This finding is compatible with the results of van Orden *et al.* (1966) and Aure *et al.* (1971). This study, like others (Munnell and Taylor, 1949; Decker *et al.* 1974; Day *et al.* 1975; Russell, 1979; Sorbe *et al.* 1982) demonstrates the importance of histologic grade for the prognosis. Demopoulos *et al.* (1984) reported that tumor grade remains a useful prognostic indicator even after adjustment for the stage of disease. Swenerton *et al.* (1985) stated tumor grade did not have independent prognostic significance in stage IV patients. This might reflect the overriding effect of the advanced stage or the imprecision of grading systems based on subjective criteria. The report of Friedlander *et al.* (1983) demonstrates that tumor ploidy independently predicts survival in advanced stage disease.

In the present study, histologic grading is correlated with cytologic factors such as stratification, nuclear pleomorphism, papillary projection and stromal invasion. Jacobs *et al.* (1982) reported that mitotic activity and pleomorphism are related to each other and to structural differentiation. Each of these morphologic features is probably an indicator of the same biologic factor which is commonly called differentiation. As stated by Barber *et al.* (1975), improvement of the histologic grading system along with the assessment of stromal infiltration, nuclear grades and stromal reaction will probably make this variable even more valuable as a complementary criterion.

Histologic type has been reported to be a weaker predictor of survival than stage and grade (Dembo and Bush 1982; Schray *et al.* 1983; Swenerton *et al.* 1985). Long *et al.* (1967) showed that there is little difference in survival between the three most common epithelial tumor types (papillary, mucinous and solid adenocarcinomas). Aure *et al.* (1971) reported that endometrioid and mucinous types of ovarian carcinomas have the best prognosis followed by serous, and ultimately by undifferentiated carcinomas. The main impact of histologic type has been reported to be histologic grade (Sorbe *et al.* 1982) and stage of tumors (Einhorn *et al.* 1985). However, van Orden *et al.* (1966) found that histologic grade appeared to be relatively constant throughout a given tumor. In this study, histologic tumor type seemed not to influence prognosis. This might be due to the small number of patients with endometrioid and undifferentiated carcinomas or the orverriding importance of stage in comparison with histologic type.

Patient age seemed to be a prognostic factor of marginal importance. Patients under 40 years of age had a better survival rate than those age 40 or older. This could be caused by better host resistance against the tumor (Barber *et al.* 1975) or the general status of younger patients to withstand aggressive surgery, cytotoxic chemotherapy and radiotherapy better than older patients. Mckay and Sellers (1967), Pomerence

and Moltz (1971), Björkholm *et al.* (1982), Schray *et al.* (1983) and Smedley and Sikora (1985) found that age was a significant independent prognostic factor. However, Swenerton *et al.* (1985) claimed that age could be a significant prognostic factor by univariate, but not multivariate analysis. In this study, age loses its prognostic importance when analyzed in the early (Ia to IIa) and advanced (IIb to IV) stages. From this it could be suggested that age might be related to other significant independent prognostic facors such as stage, histologic grade (Smith *et al.* 1979).

The presence of ascites may adversely affect the prognosis. However, the difference in the survival rates between patients with ascites and those without was not significant when adjusted for early and advanced stages. This finding was compatible with the study of Swenerton *et al.* (1985). However, Aure *et al.* (1971), Björkholm *et al.* (1982) and Richardson *et al.* (1985) reported the presence of ascites to be an independent significant prognostic factor. The difference among these studies might be caused by including some cases in which the ascites are benign. The Oncology Committee of the International Federation of Gynecology and Obstetrics (1985) made changes in the definition of some of the stages of carcinoma of the ovary. One of them is that ascites should contain malignant cells in stage Ic or IIc. The results of the present study supports this change.

The present study demonstrates that transcapsular extension of tumor influenced the survival rate in the early tumor stage. This finding was compatible with the result of Einhorn *et al.* (1985). These findings point out that transcapsular extension is an important factor in survival for stage I or II disease and that stage I or II with transcapsular extension should be regarded as stage Ic or IIc. The changes in the stages of ovarian carcinoma made at the Oncology Committee of the FIGO (1985) reflect this result in the present study as a stage I or II with tumor on the surface of one or both ovaries or with ruptured capsule is classified as stage Ic or IIc. Demopoulos *et al.* (1984) reported that transcapsular spread did not significantly affect survival rates in patients with stage I serous cystadenocarcinoma of the ovary. Although these studies are not strictly comparable, transcapsular extension of tumor may not have the same significance in the serous carcinoma it has for the mucinous and endometrioid carcinomas. The relatively small number of patients in our study prevented the evaluation of survival for this stage- and histologic type- specific subset analysis.

The successes of primary surgery and of the initial debulking procedure have been claimed to be of major importance for the prognosis in ovarian cancer (Munnell 1968; Griffiths 1975; Surwit and Day 1979; Hacker *et al.* 1983). In the present study, the prognosis was better if the macroscopic remnants of tumor tissue were less than 2 cm. This result was compatible with the study of Wharton *et al.* (1980) and Einhorn *et al.* (1985). Griffiths *et al.* (1979) reported that survival was uniformly poor if the diameter of the largest residual tumor mass exceeded 1.5 cm. Vogl *et al.* (1980) viewed that prognosis worsens with increasing mass in a graded manner, with the best survival associated with masses less than 0.5 cm in diameter. From these studies it could be suggested that prognosis is inversely proportional to the amount of residual tumor mass remaining after surgery. The results in the present study point out that advanced stage tumor needs to be subdivided according to the residual tumor diameter, that is $\leq$ 2 cm versus $>$ 2 cm, in operable cases. The Oncology Committee of the FIGO (1985) subdivided stage III into stages IIIa, IIIb and IIIc based on the size of abdominal implants, that is, microscopic seeding, $\leq$ 2 cm and $>$ 2 cm in diameter.

Evaluating the effect of treatment of epithelial ovarian cancer on survival is difficult because of great variability in the natural history of the disease and its prognostic factors. All 102 patients with epithelial ovarian carcinoma in this study underwent a laparotomy as the initial treatment; sixty-seven patients recieved chemotherapy; 10 patients received radiation therapy; and 30 received no postoperative treatment. Five patients were treated with both chemotherapy and radiation therapy postoperatively. Treatment regimen has changed a little during the study period. Multimodality treatment policies have had a prominent role. A random study comparing chemotherapy and radiation therapy in ovarian cancers showed that patients treated with melphalan had a slightly improved survival rate over those treated with irradiation to the whole abdomen by the moving-strip technic followed by additional radiation to the pelvis (Smith *et al.* 1975). Einhorn *et al.* (1985) reported that multimodality therapy, including surgery, chemotherapy, radiotherapy, gave higher survival rate than surgery or chemotherapy alone in ovarian cancer patients with stages IIb and IIc. In this study, we failed to analyze the influence of postsurgical treatment on survival, either chemotherapy or radiotherapy, because only a few patients received postoperative radiation therapy.

It is possible that an indivisualized therapeutic plan providing a better outcome for patients with epithelial ovarian carcinomas can be selected through an

understanding of the complexity of multiple prognostic factors. As with other studies (Sorbe *et al.* 1982; Swenerton *et al.* 1985) suggest, our study supports the finding that accurate surgical staging is mandatory at the initial surgery and that tumor grading should be included in the FIGO classification of epithelial ovarian cancers. Aggressive surgical bulk reduction to reduce the residual tumor volume is important for advanced tumor stages. In early tumor stages, more effective treatment should be considered for patients with transcapsular extension than those without. Prospective investigation is necessary for further subset analysis.

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