Thai Journal of Obstetrics and Gynaecology
December 2002, Vol. 14, pp. 269-276

GYNAECOLOGY

Impact of Residual Tumor on Survival of Patients with Advanced Stage Common Epithelial Ovarian Cancer at King Chulalongkorn Memorial Hospital from 1995 to 1999

Somjate Manipalviratn MD,
Pongkasem Worasethsin MD,
Surang Triratanachat MD,
Damrong Tresukosol MD.

Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

ABSTRACT

Objective To evaluate the influence of residual tumor on survival of patients with advanced stage common epithelial ovarian cancer. Prognostic factors on survival and progression free period in patients with advanced stage common epithelial ovarian cancer were determined as secondary objective.

Study design Retrospective analytical study.

Setting Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, King Chulalongkorn Memorial Hospital.

Methods A retrospective review of 110 medical records of patients with advanced stage common epithelial ovarian cancer being treated at King Chulalongkorn Memorial Hospital from 1995 to 1999. Data were reviewed to determine variables having significant correlation with survival time and progression free period. Survival time was analysed using Kaplan-Meier survival curves. Prognostic variables were analyzed using the Log rank and Cox regression analysis.

Results One hundred and ten patients were included in this study with age ranging from 27 to 76 years. Survival time could be evaluated in 102 patients ranging from 3 to 88 months with a median of 19 months. Progression free period could be evaluated in 93 patients ranging from 0 to 70 months with a median of 10.5 months. Cox regression analysis revealed that histology of the tumor and compliance to chemotherapeutic protocol influenced both survival time and progression free period ($p<0.05$) while size of residual tumor following primary cytoreduction influenced only progression free period ($p<0.05$).

Conclusion Residual tumor size following primary cytoreductive surgery does not influence patient survival but influences progression free period. Histology of the tumor and compliance to chemotherapeutic protocol appear to be important determinants of both survival time and progression free period in patients with advanced stage common epithelial ovarian cancer.

Key words: common epithelial ovarian cancer, survival, residual tumor

Common epithelial ovarian cancer is the second leading gynecologic cancer in Thailand.[1] Late manifestation is common, and most patients have abdominal metastasis at the time of initial diagnosis. Approximately 50% of ovarian malignant disease, however, are in FIGO stage III by the time of presentation.[2] Nowadays, treatment of advanced common epithelial ovarian cancer is multi-modality including surgery, chemotherapy and radiation.[3] However, surgery continues to be the principal treatment of common epithelial ovarian cancer. Surgical removal of localized abdominal tumor can be curative in early stage disease and has been employed in advanced disease as a major treatment followed by systemic chemotherapy.[4] Advantage of optimal cytoreductive surgery over suboptimal cytoreductive surgery on survival has been extensively studied.[5-9] There is no study in our institute to confirm this though we have performed quite a few surgery on common epithelial ovarian cancer patients. The success of debulking surgery depends on so many factors such as surgical technique, anesthetic technique, post-operative care, patient education, post-operative chemotherapy regimen and so on. The more extensive the surgery is, the more complication is expected to ensue. Given the limited ability of chemotherapy to cure ovarian cancer, and the acceptable morbidity of extended operation, the availability of ideal initial surgical effort for patients with advanced stage disease may be the most important variable in current ovarian cancer care.

Known prognostic factors for this malignancy based on previous research[8-9] include: presence of bulky residual tumor following primary cytoreductive surgery, histologic subtype of tumor, presence of ascites, tumor differentiation, age at diagnosis, and type of chemotherapy given.

Methods

After receiving permission from the ethical committee, we conducted a retrospective review of medical records of patients being treated at King Chulalongkorn Memorial Hospital for advanced stage, FIGO stage IIIa to IV, common epithelial ovarian cancer between January 1st ,1995 and December 31st 1999. All patients included in the study had a complete operative note for review of FIGO staging and documented pathologic diagnosis or tissue sections available for pathologic review. Patients in this study included both those who had primary cytoreductive surgery at King Chulalongkorn Memorial Hospital, and those referred to our hospital after primary surgery elsewhere. The age at diagnosis, surgical staging, histologic cell type, date and place of surgery, type of surgery, size of residual tumor following primary cytoreduction, presence or absence of ascitic fluid, date of documented recurrence and compliance to chemotherapy were analyzed. Data sources included outpatient, inpatient medical records and referred medical letters. The date of death for patients who expired was obtained from the population database of the Ministry of Internal Affairs. After receiving a name list of deceased patients, phone calls or letters with return requested were used to contact patients who were not on the list to confirm their survival status. The survival time and progression free period were calculated in terms of month. Our first-line chemotherapy is platinum-based as a single agent or in combination with Cyclophosphamide. For the second-line chemotherapy, there were multiple regimens those were Doxorubicin, Paclitaxel, Etoposide and Gemcitabine as a single agent.

Definitions used in this study included:

Optimal cytoreduction: Residual disease less than 2 centimeters10

Suboptimal cytoreduction: Residual disease 2 centimeters or larger10

Biopsy only: No cytoreduction other than biopsy for tissue diagnosis

Progression free period: The period between the time of surgery with confirmed pathologic result and the time of established recurrence either by clinical examination or laboratory test, regardless of pathologic

result in terms of month

Survival: Determined on April 30th, 2002 as dead or alive

Survival time: From the day of primary cytoreductive surgery to the date of death or being calculated on April 30th, 2002 for surviving patients in terms of month

Compliance to chemotherapy: Complete treatment with chemotherapeutic protocol of death before complete treatment

Non-compliance to chemotherapy: Incomplete treatment with chemotherapeutic protocol

Statistics

The Chi square test was used to compare differences among groups. Kaplan-Meier method was used to construct survival curves. Univariate (Log rank) analysis was used to prove dependent prognostic factors on all listed variables. Multivariate (Cox regression) analysis was used to prove independent variables after univariate analysis was done. All statistical analysis was carried out with SPSS version 10.0 software.

Result

There were 110 patients included in this study with age ranging from 27 to 76 years. The median age of the study group is 51 years. Survival time could be evaluated in 102 patients ranging from 3 to 88 months with a median of 19 months. Progression free period could be evaluated in 93 patients ranging from 0 to 70 months with a median of 10.5 months. (Fig. 1)

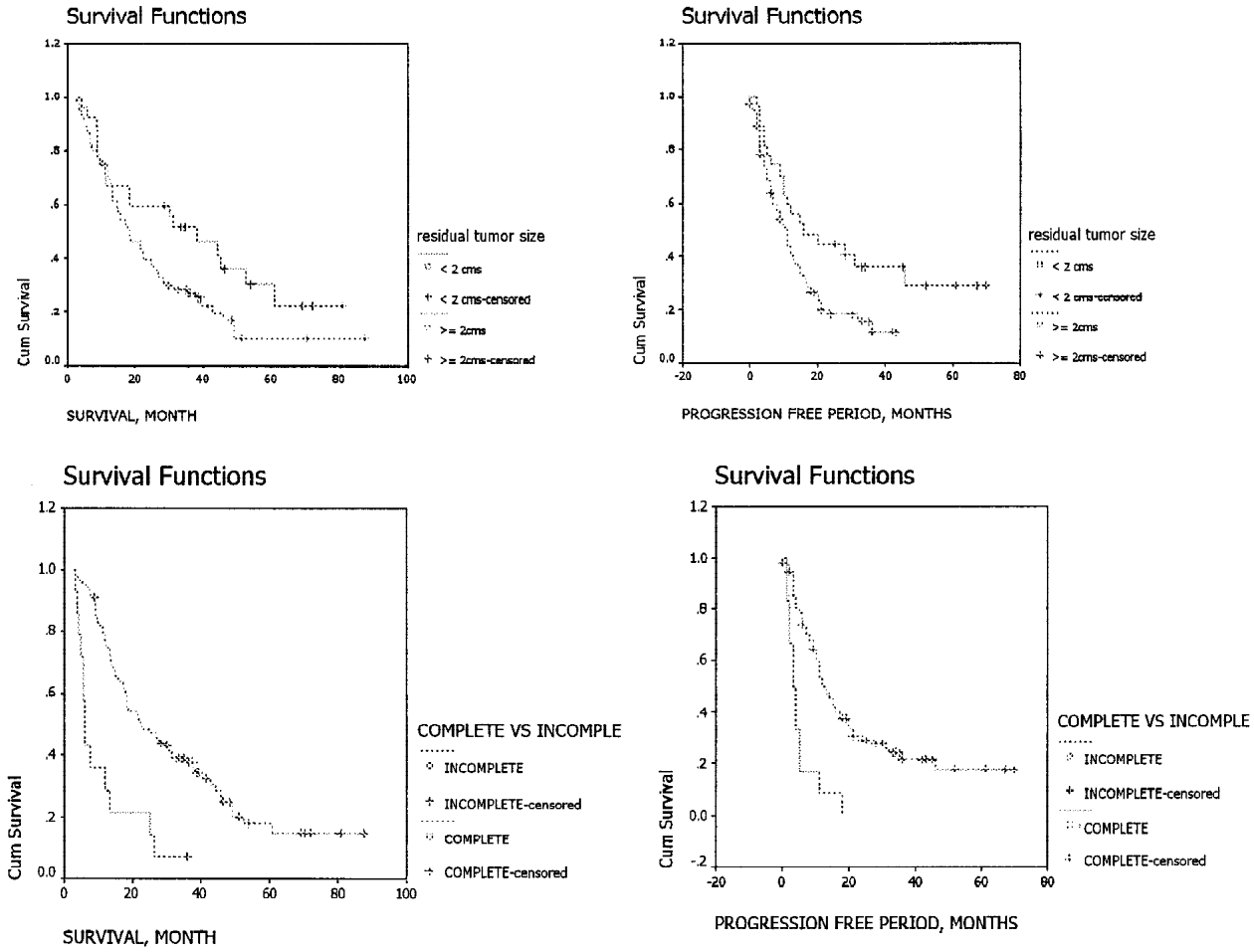

Fig. 1. Survival curve.

Seventy-nine patients (71.8%) underwent 111primary surgery at King Chulalongkorn Memorial Hospital. The other 31 patients (28.2%) were referred cases after primary surgery elsewhere. Twenty-seven patients (24.5%) achieved optimal surgery leaving residual tumor less than 2 centimeters while 61 (55.5%) and 19 (17.3%) patients achieved suboptimal and biopsy only surgery respectively leaving residual tumor 2 centimeters or larger. Eighty-four patients (76.4%) had ascites at the time of surgery while the other 20 patients (18.2%) did not. Histologic cell types include serous cystadenocarcinoma, mucinous cystadenocarcinoma, endometrioid carcinoma, clear cell carcinoma, mixed malignant epithelial tumor and adenocarcinoma accounted for 50(45.5%), 9(8.2%), 27(24.5%), 13(11.8%), 4(3.6%) and 7(6.4%) patients, respectively. Ninety-six patients (87.3%) complied with chemotherapeutic protocol while fourteen (12.7%) patients did not. (Table 1)

Table 1. Patient characteristics

Characteristic	Number	Percent
Age		
< 55 years	68	61.8
≥ 55 years	42	38.2
Histologic type		
Serous cystadenocarcinoma	50	45.5
Endometrioid carcinoma	27	24.5
Clear cell carcinoma	13	11.8
Mucinous cystadenocarcinoma	9	8.2
Adenocarcinoma	7	6.4
Mixed malignant epithelial tumor	4	3.6
Type of surgery		
Biopsy only	19	17.3
Suboptimal cytoreduction	61	55.5
Optimal cytoreduction	27	24.5
No data	3	2.7
Institute of primary cytoreduction		
Chula	79	71.8
Referred	31	28.2
Compliance to chemotherapy		
Compliance	96	87.3
Non-compliance	14	12.7
Ascites at time of surgery		
Present	84	76.4
Absent	20	18.2
No data	2	1.8
Residual tumor		
Less than 2 centimeters	27	24.5
2 centimeters or larger	80	72.7
No data	3	2.7

Univariate (Log rank) analysis revealed size of residual tumor following primary cytoreduction, histology and compliance to chemotherapeutic protocol to influence survival time ($p<0.05$). For histology analysis, serous cystadenocarcinoma was used as the reference group. After obtaining all variables influenced survival on the Log rank analysis, all significant variables were analysed again using Cox regression analysis. Using Cox regression analysis, only histology and compliance to chemotherapeutic protocol appeared to be significant independent variables ($p<0.05$). Serous cystadenocarcinoma was also used as the reference group in multivariate analysis. From Cox regression analysis, clear cell carcinoma and mucinous cystadenocarcinoma were poor prognostic factors with the hazard ratios of 3.004 and 3.828, respectively ($p<0.05$). (Table 2)

Table 2. Survival according to prognostic indicators in univariate analysis

Variable	N	Median[1]	P value[2]
Age			
< 55 years	66	22	0.7416
≥ 55 years	36	18	
Histologic type			
Serous cystadenocarcinoma	44	22	0.001[3]
Endometrioid carcinoma	26	31	
Clear cell carcinoma	13	10	
Mucinous cystadenocarcinoma	9	9	
Adenocarcinoma	6	16	
Mixed malignant epithelial tumor	4	17	
Institute of primary cytoreduction			
Chula	75	22	0.0787
Referred	27	13	
Compliance to chemotherapy			
Compliance	88	22	0.0000
Non-compliance	14	6	
Ascites at time of surgery			
Present	82	18	0.0816
Absent	17	30	
Residual tumor			
Less than 2 centimeters	27	38	0.0402
2 centimeters or larger	75	18	

[1] Median survival in terms of month

[2] Using Log rank test

[3] Using serous cystadenocarcinoma as the reference group

Univariate (Log rank) analysis revealed that size of residual tumor following primary cytoreduction, histology and compliance to chemotherapeutic protocol influenced progression free period. After Cox regression analysis was performed, all these factors were still significant independent variables ($p<0.05$). Serous cystadenocarcinoma was used as the reference group in both univariate and multivariate analysis. (Table 3)

Table 3. Progression free period according to prognostic indicators in univariate analysis

Variable	N	Median[1]	P value[2]
Age			
< 55 years	64	11	0.1727
≥ 55 years	37	9	
Histologic type			
Serous cystadenocarcinoma	43	12	0.0007[3]
Endometrioid carcinoma	25	13	
Clear cell carcinoma	13	3	
Mucinous cystadenocarcinoma	9	5	
Adenocarcinoma	7	15	
Mixed malignant epithelial tumor	4	11	
Institute of primary cytoreduction			
Chula	74	11	0.1611
Referred	27	7	
Compliance to chemotherapy			
Compliance	89	11	0.0000
Non-compliance	12	3	
Ascites at time of surgery			
Present	81	10	0.0868
Absent	18	10	
Residual tumor			
Less than 2 centimeters	27	16	0.0013
2 centimeters or larger	74	9	

[1] Median progression free period in terms of month

[2] Using Log rank test

[3] Using serous cystadenocarcinoma as the reference group

Age at diagnosis, presence of ascitic fluid and place of primary surgery did not affect either survival time or progression free period ($p>0.05$).

The median survival time of the population was 19 months while that of the group of residual tumor less than 2 centimeters was 38 months and that of the group of residual tumor 2 centimeters or larger was 18 months. Median survival according to histologic cell types were 9, 10, 16, 17, 22 and 31 months for mucinous cystadenocarcinoma, clear cell carcinoma, adenocarcinoma, mixed malignant epithelial tumor, serous cystadenocarcinoma and endometrioid carcinoma, respectively. The median survival for compliance and non-compliance to chemotherapeutic

protocol was 22 and 6 months, respectively.

Analyzing the effect of type of surgery on survival between biopsy only and suboptimal surgery using univariate analysis, we found no statistically significant differences on survival time between these two groups (p= 0.2367).

The percentage of patients receiving primary optimal cytoreduction at our institute versus those cases referred after primary cytoreduction elsewhere was 31.6 and 6.45 percent, respectively. Using Chi-Square test, the results showed that primary surgery at King Chulalongkorn Memorial Hospital was associated with residual tumor less than 2 centimeters (p=0.022).

Discussion

Our results are in contrary to those of previous studies[5-10] which supported the idea of residual tumor as a significant prognostic factor on survival. This study showed that leaving residual tumor smaller than 2 centimeters or leaving the tumor larger than or equal to 2 centimeters did not have any difference in terms of survival. However, there was a report[4] which also showed that extent of primary operation was a significant predictor on survival in univariate analysis but lost the significance in multivariate analysis. These data indicated that reduction of tumor mass to 2 centimeters may be inadequate to improve survival. Other studies have found that surgical tumor reduction to less than 2 centimeters did not offer a significantly different median survival from patients with bulky residual disease,[11-12] and it has been suggested that residual tumor should not exceed 0.5 centimeter in order to optimize the effect of chemotherapy.[13] This may also be explained in part by the unresponsiveness of the remaining tumor regardless of size to chemotherapy. The difference on survival between group of patient having residual tumor and those with no residual tumor will be studied in the future. In our practice, pelvic examination and tumor markers, not imaging, were used as indicators of tumor recurrence so detection of recurrence may be delayed and cause the tumor less responsive to second line chemotherapy which could affect the survival. Earlier detection of recurrence and earlier administration of second line chemotherapy may increase survival. Along with reducing the size of residual tumor, we have to find a better chemotherapeutic protocol to attack the remaining tumor to prolong survival.

Those with residual tumor 2 centimeters or larger, suboptimal and biopsy only surgery, did not show any difference on survival time between these two groups which corresponded with the study of Hoskins, et al.[5] which stated that patients with suboptimal epithelial ovarian cancer those who have residual disease of less than 2 centimeters tended to survive longer than those who have larger residual disease but those with larger residual disease, size did not affect prognosis. If optimal resection is not feasible on exploring the abdomen, the main aim should be to limit morbidity.[7] Anyhow, successful removal of the tumor in patients with advanced ovarian cancer will have dramatic effects on the patients' comfort and will reduce the adverse metabolic effect of the tumor as well as improving the patients' ability to maintain her nutritional status.[14]

In our study, only 24.5% of patients underwent optimal surgery leaving residual tumor less than 2 centimeters while 72.8% of patients obtained suboptimal or biopsy only surgery leaving residual tumor 2 centimeters or larger which was in contrast to the results from other studies reporting more than 60% of patients achieving optimal cytoreductive surgery.[6,7] Delgado stated that only 28% of cases of stage III ovarian cancer could achieve optimal tumor reduction.[15] However, our study showed that primary cytoreduction at our institute offered more optimal cytoreduction than those of referred cases after initial primary cytoreductive surgery elsewhere. Hacker et al. reported that among fourteen patients considered inoperable at laparotomy before referral to UCLA, ten patients (71%) had the tumor optimally resected in their center.[7] Cytoreductive surgery for ovarian cancer requires considerable surgical experience and these patients should be referred to oncology center to undergo optimal cytoreductive surgery.

The most common histologic type in our study

was serous cystadenocarcinoma which corresponded with the results from many studies.[3, 4,8,10,16-19] The second leading histologic characteristic in our study was endometrioid carcinoma which differed from other studies.[10,15-18] Patients with endometrioid carcinoma had the longest median survival while those with mucinous cystadenocarcinoma had the shortest median survival.

Patients receiving complete platinum-based chemotherapy had better survival, however, quality of life in these patients was not evaluated in this study. Roughly, we can assume that most of our patients can tolerate the side effects from our chemotherapeutic protocol because 87.3% of them attached to the prescribed protocol.

A previous study from EORTC[20] showed that interval debulking surgery was beneficial in patients who had initial suboptimal surgery in terms of reduction of death. This also supports a novel approach in ovarian cancer patients, neoadjuvant chemotherapy for advanced stage cancer followed by interval debulking surgery. This approach may be implemented in the future, as similar survival rates are achieved with less surgical morbidity. The efficacy of primary cytoreductive surgery versus neoadjuvant chemotherpy followed by interval debulking surgery will be studied in a randomized fashion in our center in the future.

References

1. Sombooncharoen S, Sontipong S. Cancer registration in Thailand. Southeast Asian J Trop Med Public Health 1985;16:598-601.
2. Young R. The staging and treatment of epithelial ovarian cancer. Can Med Assoc J 1978;119:249-56.
3. Berek JS, Fu YS, Hacker NF. Ovarian cancer. In : Berek JS, Adashi EY, Hillard PJA, editors. Novak's gynecology. 12th ed. Baltimore : Williams & Wilkins, 1996:1155-230.
4. Krag KJ, Canellos GP, Griffiths CT, Knapp RC, Parker LM, Welch WR, et al. Predictive factors for long-term survival in patients with advanced ovarian cancer. Gynecol Oncol 1989;34:88-93.
5. Hoskins WJ, McGuire WP, Brady MF, Homesley HD, Creasman WT, Berman M, et al. The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. Am J Obstet Gynecol 1994;170:974-80.
6. Eisenkop SM, Friedman RL, Wang HJ. Complete cytoreductive surgery is feasible and maximizes survival in patients with advanced epithelial ovarian cancer. Gynecol Oncol 1998;69:103-8.
7. Hacker NF, Berek JS, Lagasse LD, Nieberg RK, Elashoff RM. Primary cytoreductive surgery for epithelial ovarian cancer. Obstet Gynecol 1983;61:413-20.
8. Clark TG, Stewart ME, Altman DG, Gabra H, Smyth JF. A prognostic model for ovarian cancer. Br J Cancer 2001;85: 944-52.
9. Redman JR, Petroni GR, Saigo PE, Geller NL, Hakes TB. Prognostic factors in advanced ovarian carcinoma. J Clin Oncol 1986;4:515-23.
10. DiSaia PJ, Creasman WT. Clinical gynecologic oncology. 6th ed. St. Louis : Mosby, 2002: 289-350.
11. Belinson JL, McClure M, Ashikaga T, Krakoff IH. Treatment of advanced and recurrent ovarian carcinoma with cyclophosphamide, doxorubicin, and cisplatin. Cancer 1984;54:1983-90.
12. Gynaecological Group, Clinical Oncological Society of Australia, and the Sydney branch, Ludwig Institute for Cancer Research. Chemotherapy of advanced ovarian adenocarcinoma: a randomized comparison of combination versus sequential therapy using chlorambucil and cisplatin. Gynecol Oncol 1986;23:1-13.
13. Cohen CJ, Goldberg JD, Holland JF, Bruckner HW, Deppe G, Gusberg SB. Improved therapy with cisplatin regimens for patients with ovarian carcinoma (FIGO stages III and IV) as measured by surgical end-staging (second-look operation). Am J Obstet Gynecol 1983;145:955-67.
14. Hoskins WJ, Rubin SC. Surgery in the treatment of patients with advanced ovarian cancer. Semin Oncol 1991;18:213-21.
15. Delgado G, Oram DH, Petrilli ES. Stage III epithelial ovarian cancer : the role of maximal surgical reduction. Gynecol Oncol 1984;18:293-8.
16. Makar AP, Baekelandt M, Trope CG, Kristensen GB. The prognostic significance of residual disease, FIGO substage, tumor histology, and grade in patients with FIGO stage III ovarian cancer. Gynecol Oncol 1995;56:175-80.
17. Unzelman RF. Advanced epithelial ovarian carcinoma: long-term survival experience at the community hospital. Am J Obstet Gynecol 1992;166:1663-72.
18. Omura GA, Brady MF, Homesley HD, Yordan E, Major FJ, Buchsbaum HJ, et al. Long-term follow-up and prognostic factor analysis in advanced ovarian carcinoma: the Gynecologic Oncology Group experience. J Clin Oncol 1991;9:1138-50.
19. Brun JL, Feyler A, Chene G, Saurel J, Brun G, Hocke C. Long-term results and prognostic factors in patients with epithelial ovarian cancer. Gynecol Oncol 2000;78:21-7.
20. Van der Burg MEL, Van Lent M, Buyse M, Kobierska A, Colombo N, Favalli G, et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. N Engl J Med 1995;332:629-34.