

# Survival Outcomes for Different Subtypes of Epithelial Ovarian Cancer

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## ABSTRACT

**Background:** The distribution pattern of histological subtypes of epithelial ovarian cancer (EOC) is inconsistent across the countries. Serous carcinoma is not the most common subtype in Thailand and some Asian countries. It may have a different survival outcome. The objective is to compare the survival outcomes among different subtypes. **Method:** A total number of 398 EOC patients who underwent primary cytoreductive surgery from January 2007 to December 2014 were recruited. **Results:** Endometrioid carcinoma was the most frequent subtype (32.4%) followed by serous carcinoma (25.1%), clear cell carcinoma (23.4%), and mucinous carcinoma (19.1%). Stage I was the most common stage except serous carcinoma, which usually presented in an advanced stage with suboptimal surgery. For the entire cohort, 5-year disease-free survival (DFS) and overall survival (OS) were 64.1% and 65.4%, respectively. Patients with mucinous subtype had significantly better 5-year DFS and OS than non-mucinous (86.2% vs. 58% and 87% vs. 59.8%, respectively). Patients with serous EOC had the poorest 5-year DFS (39.9%), and 5-year OS (41.2%). Stage, residual tumor volumes and histological subtypes particularly clear cell carcinoma remained significant factors after multivariate analysis. **Conclusions:** Serous carcinoma was less prevalent in Thai EOC patients, caused different survival outcomes. Stage, residual tumor volumes and clear cell carcinoma were independent prognostic factors.

**Key words:** Histopathology, ovarian cancer, survival

## INTRODUCTION

Ovarian cancer is the second most common gynecologic cancer in women behind cervical cancer and the leading cause of gynecological cancer death in Thailand. The incidence rate in Thai women was 6 per 1,00,000 persons in 2011,<sup>[1]</sup> and this rate is gradually increasing especially in Asian countries.<sup>[2]</sup> It can occur in all ages of women, but it is most common among ages of 55–64 years.<sup>[2]</sup> Majority of ovarian cancer is epithelial ovarian cancers (EOC). They are divided into different histological subtypes: Serous, mucinous, endometrioid, and clear cell. Each subtype represents distinct genetic alteration and unique molecular pathogenesis.<sup>[3]</sup> Therefore, the clinical presentation and survival outcome may be different. In

general, the surgical stage has been reported to be the most significant prognostic factor, 5-year survival rate in stage I is about 90%, but for advanced-stage tumors, the 5-year survival rate is only 18–40%.<sup>[2,4]</sup> However, the histological subtype is also one of the prognostic factors. The distribution of EOC subtypes varies among different countries. Serous carcinoma is the most common subtype worldwide with a 70% incidence rate<sup>[5]</sup> but it is only 20–30% in Thailand.<sup>[6,7]</sup> More non-serous subtypes included endometrioid, clear cell, and mucinous carcinoma have been reported.<sup>[6]</sup> Racial difference may affect the survival outcomes. The previous study showed that Asians who lived in the United States had better 5-year disease-specific survival than Caucasians because Asians were more likely to be younger, presented at an earlier stage and have non-serous histological subtypes.<sup>[8]</sup> The objectives

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of this study were to compare the survival outcomes among different subtypes of EOC in Thai patients and to identify the prognostic factors that affect the survival outcomes.

## METHODS

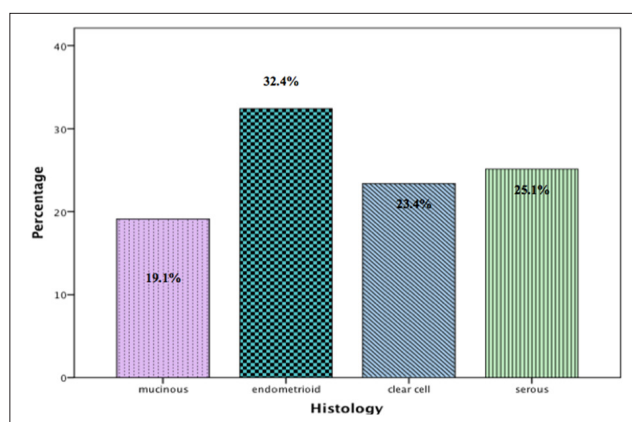
This is a retrospective study that was conducted in patients with EOC included those with fallopian tube cancer and primary peritoneal cancer. All patients had primary cytoreductive surgery at the King Chulalongkorn Memorial Hospital, Bangkok, Thailand, between January 2007 and December 2014. Patients with borderline EOC, unspecified adenocarcinoma, non-EOC, secondary malignant neoplasm of the ovary, and incomplete medical records were excluded. This study was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University.

Clinicopathological variables such as age, parity, marital status, menopausal status, stage, residual tumor volumes, and pathologic reports were collected. The histology of the cancers was classified into four groups: mucinous, endometrioid, clear cell, and serous subtype. Disease-free survival (DFS) was defined as the period from the diagnosis to time of recurrence or last follow-up, if there was no recurrence of the disease. Overall, survival (OS) was defined as the period since the initial diagnosis until cancer-related death or last follow-up.<sup>[9]</sup>

Statistical analysis was performed using SPSS software version 22.0 (IBM Corp., Armonk, N.Y., USA). One-way ANOVA and Pearson's Chi-square test were used to evaluate the difference in continuous and categorical data, respectively. Survival analysis by histology, stage and residual tumor volumes were analyzed using Kaplan–Meier method. Log-rank test was used to compare the differences between these factors. Cox-proportional hazards model was performed to identify independent prognostic factors. These factors were analyzed in the univariate and multivariable analysis. Statistical significance was determined as  $P > 0.05$  and the 95% confidence interval for hazard ratio was calculated.

## RESULTS

A total of 398 patients were diagnosed with EOC, fallopian tube cancer, or primary peritoneal cancer. Demographic data according to different subtypes are shown in Table 1. Endometrioid carcinoma was the most frequent subtype (32.4%) followed by serous carcinoma (25.1%), clear cell carcinoma (23.4%), and mucinous carcinoma (19.1%) [Figure 1]. The mean age of the patients with mucinous subtype was 46.6 years. Patients with mucinous subtype were significantly youngest than those with non-mucinous subtype. Patients with serous subtype were oldest with a mean



**Figure 1:** Distribution of histological subtypes of epithelial ovarian cancer

age was 54.3 years. Stage I was the most common stage for all subtypes except serous subtype. Serous carcinoma usually presented in the advanced stage of disease (Stage 3–4).

The median follow-up time in this study was 48 months (range 1–121 months). DFS and OS for different subtypes were significantly different [Tables 2 and 3]. The mucinous subtype had the best prognosis with mean DFS of 103.1 months compared to other subtypes ( $P < 0.001$ ). The mean DFS for endometrioid, clear cell, and serous was 86.1, 76.8, and 57.6 months, respectively. Overall, 5-year DFS and 5-year OS for all histological subtypes were 64.1% and 65.4%, respectively. Mucinous subtype had significantly better 5-year DFS and OS than non-mucinous (86.2% vs. 58.0% and 87.0% vs. 59.8%, respectively). [Figure 2b and 3b] In non-mucinous subtype, serous subtype had the poorest DFS and OS (39.9% and 41.2%, respectively). On the other hand, endometrioid and clear cell subtype had similar 5-year DFS (66.2% vs. 62.7%) and 5-year OS (66.8% vs. 66.4%). [Figure 2a and 3a]

5-year DFS was highest for those with stage I (90.2%). Stage II, III, and IV had lower 5-year DFS (74.7%, 28.0%, and 27.3%, respectively) [Figure 2c]. 5-year OS for stage I, II, III, and IV was 91.4%, 81.8%, 30.2%, and 30.0%, respectively. [Figure 3c] Residual tumor volumes also influenced the survival outcomes; complete cytoreduction, optimal surgery, and suboptimal surgery had 5-year DFS of 77.6%, 37.7%, and 13.6%, respectively. [Figure 2d] Complete cytoreduction, optimal surgery, and suboptimal surgery had 5-year OS of 79.1%, 39.3%, and 14.7%, respectively. [Figure 3d]

Logistic regression analysis for the factors associated with survival is presented in Table 4. Stage, residual tumor volumes and histological subtypes were significant factors that were associated with OS. However, in the multivariate analysis, the prognostic factors were stage, residual tumor volumes, and only clear cell subtype.

Table 1: Demographic data

Variables	Total (n=398)	Mucinous (n=76)	Endometrioid (n=129)	Clear cell (n=93)	Serous (n=100)	P value
Mean age ( $\pm$ SD)	51.5 $\pm$ 12.4	46.6 $\pm$ 16.4	52.5 $\pm$ 12.2	50.2 $\pm$ 8.7	54.3 $\pm$ 11.0	<0.05
Parity(%)						
Nulliparity	201 (50.5)	34 (44.7)	70 (54.3)	59 (63.4)	38 (38.0)	0.003
Multiparity	197 (49.5)	42 (55.3)	59 (45.7)	34 (36.6)	62 (62.0)	
Marital status (%)						
Single	164 (41.2)	32 (42.1%)	53 (41.1)	48 (51.6)	31 (31.0)	0.04
Married	234 (58.8)	44 (57.9)	76 (58.9)	45 (48.4)	69 (69.0)	
Contraception (%)						
No	321 (80.7)	57 (75.0)	106 (82.2)	83 (89.2)	75 (75.0)	0.08
Hormonal	24 (6.0)	5 (6.6)	6 (4.7)	6 (6.5)	7 (7.0)	
Nonhormonal	53 (13.3)	14 (18.4)	17 (13.2)	4 (4.3)	18 (18.0)	
Menopause (%)						
No	197 (49.5)	41 (53.9)	63 (48.8)	50 (53.8)	43 (43)	0.40
Yes	201 (50.5)	35 (46.1)	66 (51.2)	43 (46.2)	57 (57)	
Outcome (%)						
Complete cytoreduction	297 (74.6)	67 (88.2)	92 (71.3)	77 (82.8)	61 (61.0)	<0.001
Optimal surgery	38 (9.5)	6 (7.9)	13 (10.1)	7 (7.5)	12 (12.0)	
Suboptimal surgery	63 (15.8)	3 (3.9)	24 (18.6)	9 (9.7)	27 (27.0)	
Stage (%)						
1	187 (47.0)	58 (76.3)	54 (41.9)	59 (63.4)	16 (16.0)	<0.001
2	46 (11.6)	3 (3.9)	21 (16.3)	13 (14.0)	9 (9.0)	
3	132 (33.2)	8 (10.5)	41 (31.8)	20 (21.5)	63 (63.0)	
4	33 (8.3)	7 (9.2)	13 (10.1)	1 (1.1)	12 (12.0)	
Recurrence (%)						
Yes	150 (37.7)	9 (14.1)	47 (36.7)	37 (40.7)	57 (57)	<0.001
No	219 (55.0)	54 (84.4)	76 (59.4)	50 (54.9)	39 (39.0)	
Missing data	15 (3.8)	1 (1.6)	5 (3.9)	4 (4.4)	4 (4.0)	

SD: Standard deviation

## DISCUSSION

Distribution pattern of histological subtypes of EOC is inconsistent across the countries and regions. Serous carcinoma, especially high-grade serous carcinoma, is the most common histological subtype worldwide. The prevalence of serous carcinoma is 50–70%.<sup>[5,10]</sup> On the other hand, this subtype is not common in the Asian population. The prevalence of high-grade serous carcinoma in Thais is only 22%.<sup>[7]</sup> Endometrioid, clear cell and mucinous carcinoma are more frequently found in Asians.<sup>[10]</sup> These findings are consistent with the findings from this study. Our study showed that the incidence of endometrioid, clear cell, and mucinous carcinoma was 32.4%, 23.4%, and 19.1%, respectively, but serous carcinoma was only 25.1%.

Patients from various ethnic groups may have different survival outcomes. Asians with EOC were more likely to be younger, have an earlier stage, non-serous histology, lower grade tumors, and better survival.<sup>[8]</sup> There is a variation in the histological subtypes in different geographic areas, which, may contribute to different survival outcomes of EOC patients. Mucinous carcinoma has been reported to have better prognosis than non-mucinous carcinoma. The current study confirmed this result; 5-year DFS and OS in mucinous subtype were 86.2% and 87.0%, respectively, compared to the non-mucinous type, which had a 5-year DFS and OS of 58.3% and 59.8%, respectively. Mucinous subtype usually presents in younger patients, earlier stage and have more complete cytoreductive surgery. These findings explain why there is a better prognosis in the mucinous subtype. Among non-mucinous subtypes, serous carcinoma had the

**Table 2: Disease free survival**

Variables	Mean survival time (months)	P value
Histology		
Mucinous	103.1±5.1	<0.001
Endometrioid	86.1±4.8	
Clear cell	76.8±5.5	
Serous	57.6±6.2	
Histology		
Mucinous	103.1±5.1	0.001
Nonmucinous	76.7±3.3	
Stage		
I	109.6±2.6	<0.001
II	72.9±5.5	
III	43.4±5.3	
IV	38.8±8.4	
Surgical outcome		
Complete cytoreduction	97.1±2.9	<0.001
Optimal surgery	47.8±8.9	
Suboptimal surgery	19.3±4.8	

worse prognosis because it usually presented in an advanced stage with suboptimal surgery. Endometrioid and clear cell carcinoma commonly presented in stage I and had low residual tumor volumes after cytoreductive surgery.

The proportion of endometrioid and clear cell carcinoma is relatively high in Asians, including Thais. The frequency of endometrioid carcinoma reported worldwide was around 12.6% (1.6–25.5%).<sup>[10]</sup> A previous study from our institute reported the frequency of this subtype to be around 27.6%.<sup>[6]</sup> In this study, the prevalence of endometrioid carcinoma is 32.4%. In western countries, clear cell carcinoma is a rare histological subtype (1–12%), but in Asians, its prevalence is increasing 19–25%, especially among Japanese and Taiwanese people.<sup>[11–13]</sup> This prevalence is consistent with the findings from our study which reported the prevalence was 23.4%. Previous studies reported that these two subtypes are closely related to endometriosis-associated ovarian cancers.<sup>[14,15]</sup> Distinct genetic alteration and pathogenesis of this entity may explain why there are different clinical presentation and survival outcomes. Endometriosis-associated ovarian cancers usually present in younger patients, early stage, and having the low residual disease. As this result, they have better survival rates.<sup>[16]</sup> In this study, the mean age of the patients with clear cell carcinoma, endometrioid carcinoma, and serous carcinoma was 50 years, 52 years, and 54 years, respectively. Patients with clear cell carcinoma tended to be younger than the patients with serous carcinoma. Patients with clear cell carcinoma (63.4%) and patients with endometrioid carcinoma (41.9%) presented in stage I. In contrast, only 16%

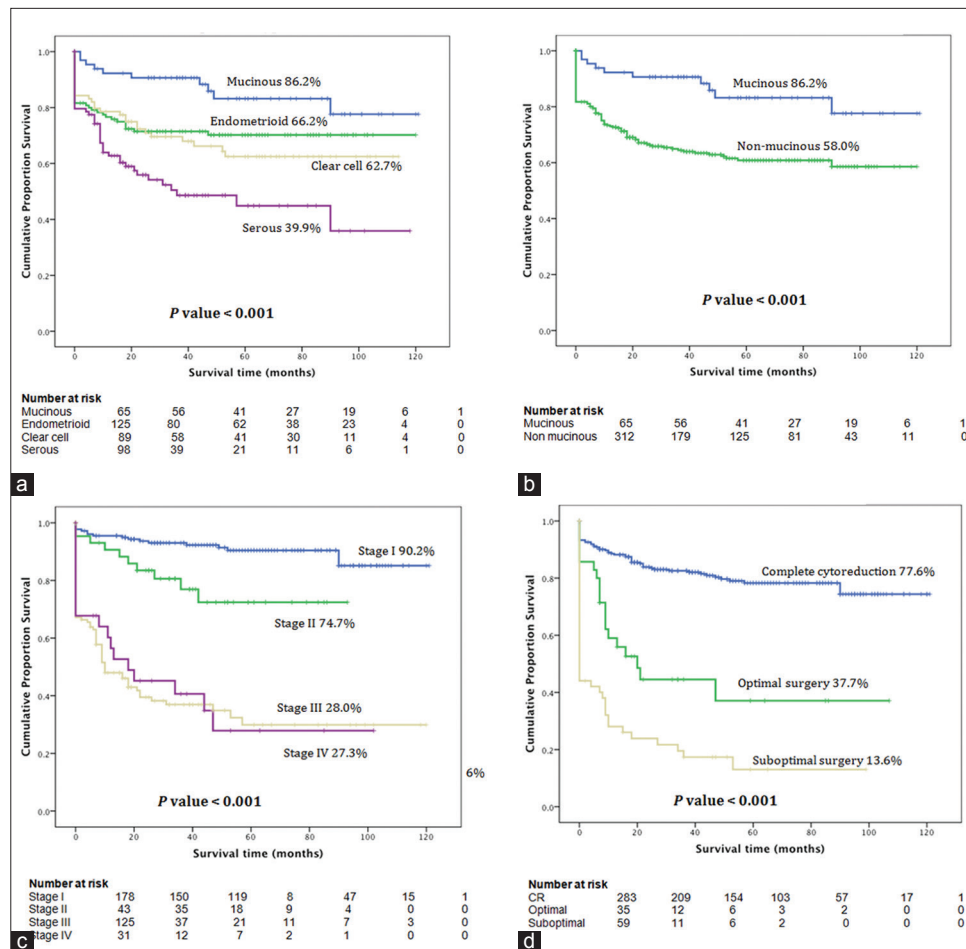
**Table 3: Overall survival**

Variables	Mean survival time (months)	P value
Histology		
Mucinous	103.6±5.0	<0.001
Endometrioid	87.1±4.3	
Clear cell	78.6±5.0	
Serous	61.6±5.0	
Histology		
Mucinous	103.6±5.0	<0.001
Nonmucinous	78.2±3.0	
Stage		
I	109.6±2.5	<0.001
II	74.8±4.7	
III	50.5±4.2	
IV	46.6±6.8	
Residual tumor volumes		
Complete cytoreduction	97.1±2.7	<0.001
Optimal surgery	54.6±7.2	
Suboptimal surgery	31.3±3.8	

of patients with serous carcinoma were presented in stage I. Therefore, the 5-year DFS and OS for patients with clear cell and endometrioid carcinoma were significantly better than serous subtypes.

Significant factors that affected the survival outcomes were stage, residual tumor volumes, and histological subtypes. Advanced stage and suboptimal surgery have been extensively reported as poor prognostic factors.<sup>[17,18]</sup> Serous subtype had the lowest 5-year survival. 5-year DFS and OS for serous subtype in this study were only 39.9% and 41.2%, respectively. This result was consistent with the previous study which reported 5-year DFS in serous histology was as low as 41%.<sup>[8]</sup> Significantly more patients with serous subtype presented in advanced stage had suboptimal surgery. This finding may explain why there is poor survival in the serous subtype. However, stage, residual tumor volumes, and only clear cell subtype remained to be independent prognostic factors in the multivariate analysis. When the other factors were adjusted, clear cell carcinoma was an independent prognostic factor. This subtype had a poorer prognosis than serous subtype particular in those with advanced stage.<sup>[12,13,19]</sup>

Overall, 5-year survival of EOC has been reported worldwide about 30–50%.<sup>[1,4]</sup> The 5-year DFS and 5-year OS in this current study were 64.1 and 65.4%, respectively, which was higher than the previous report. Non-serous subtypes were found more commonly in the Thai patients. Different pattern of histological subtypes was demonstrated in Thai EOC



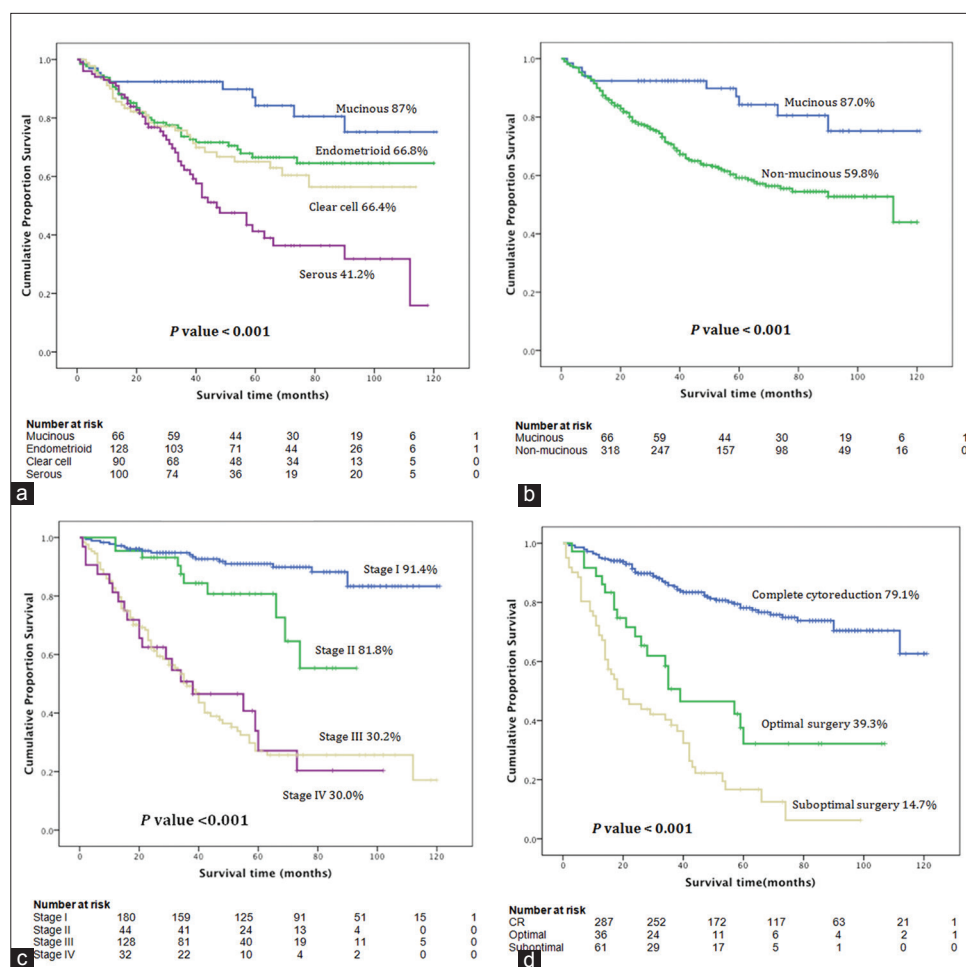
**Figure 2:** 5-year disease free survival. (a) histological subtypes, (b) mucinous and non-mucinous subtype, (c) surgical stage, (d) residual tumor volumes

**Table 4:** Factors affected the overall survival rate (univariate and multivariate analysis)

Factors	Crude HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Stage				
I	1		1	
II	2.69 (1.24-5.85)	0.012	2.25 (1.02-4.95)	0.04
III	10.41 (6.21-17.44)	<0.001	9.04 (4.89-16.73)	<0.001
IV	10.37 (5.46-10.69)	<0.001	11.30 (5.42-23.65)	<0.001
Residual tumor volumes				
Complete cytoreduction	1		1	
Optimal surgery	3.76 (2.26-6.27)	<0.001	1.51 (0.88-2.61)	0.14
Suboptimal surgery	7.43 (5.03-10.97)	<0.001	3.12 (2.03-4.80)	<0.001
Histology				
Mucinous	1		1	
Endometrioid	2.31 (1.15-4.63)	0.018	1.01 (0.49-2.10)	0.98
Clear cell	2.71 (1.33-5.53)	0.006	3.02 (1.42-6.46)	0.004
Serous	4.48 (2.26-8.87)	<0.001	1.18 (0.57-2.46)	0.65

HR: Hazard ratio, CI: Confidence interval





**Figure 3:** 5-year overall survival. (a) Histological subtypes, (b) mucinous and non-mucinous subtype, (c) surgical stage, (d) residual tumor volumes

patients. Serous carcinoma was less prevalent. As this result, the survival outcome in this study was better than the previous studies. This finding confirmed different survival outcomes among different countries and ethnicities. However, stage, residual tumor volumes, and clear cell carcinoma were independent prognostic factors.

## Disclosure statement

The authors have no conflicts of interest to declare.

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