RESEARCH ARTICLE

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The Impact of Waiting Time-to-Surgery on Survival in Endometrial Cancer Patients

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Abstract

Background: Endometrial cancer (EC) is the most common gynecological cancer in developed countries and a standard treatment of surgery should be performed as expediently as possible. Delay time to surgery and survival was debated. The aim of this investigation was to evaluate the effect of time-interval between diagnosis and surgery (TDS) in EC patients with regards to prognosis and mortality rates. **Methods:** This retrospective study was conducted between January 2009 and May 2021 at Bhumibol Adulyadej Hospital, Thailand. Subjects were EC cases who underwent primary surgery during the study period. Cases with partial treatment were disqualified from the study. Subjects who underwent surgery before and after 6 weeks were classified as early and delayed surgery groups. Baseline and clinical characteristics were collected and analyzed. **Results:** During the study period, 419 EC cases were recruited. The mean age of participants was 56.8 years. Two-thirds (338/491) of subjects were menopausal. Endometrioid histology (406/491) was the most common histology subtype. Five years disease free survival (DFS) of early and delayed surgery groups were comparable at a percentage of 82.5 and 83.0, respectively. Among advanced stage and non-endometrioid EC cases, the delayed surgery group had significantly shorter DFS than the early group. Advanced stage, high grade and positive lympho-vascular space invasion (LVSI) were independent factors for poor DFS. Predictive factors for mortality were advanced stage and tumor recurrence. **Conclusion:** The TDS was not a prognostic factor for disease recurrence or overall mortality. Time to surgery equal to or more than 6 weeks gave worse prognosis for DFS among advanced stage or non-endometrioid histology EC.

Keywords: Waiting time- endometrial cancer- survival

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Introduction

Endometrial cancer (EC) is the most common gynecological cancer in developed nations [1]. Thai women suffered from EC (new cases) at a rate of 5.1% per year. The stage of EC depended on surgical histological findings, so the standard treatment is surgical staging, namely hysterectomy, bilateral salpingo-oophorectomy with lymph node assessment [2]. After undergoing staging surgery, adjuvant treatments such as radiotherapy with or without chemotherapy were prescribed according to final staging by FIGO 2021 [3].

After the EC was diagnosed, the treatment should be delivered as soon as possible. However, the cancer center or referral tertiary hospital in developing or underdeveloped countries are limited, the referred patients may delay receiving the standard treatment, especially patients from rural areas. From previous studies from developed countries, the data showed impact of delay time-to-surgery and survival which reported 6 weeks, or 8 week or 12 weeks of interval predicted the worsen prognosis of survival [4-8]. But Mitric's study reported conflicting outcomes [9].

The purpose of this investigation was to evaluate the prognosis of time-interval between diagnosis and surgery (TDS) in EC patients in the tertiary referral hospital. This data may be beneficial to EC patients in the current practice.

Materials and Methods

Study design and data collection

This retrospective study reviewed the data of patients who were diagnosed with EC between January 2009 and May 2021 at the Department of Obstetrics and Gynecology, Bhumibol Adulyadej Hospital (BAH), Royal Thai Air Force, Thailand. The electronic medical records and pathological reports were reviewed. The inclusion criteria were female patients with age ≥ 18 years old and histologically confirmed EC, underwent primary

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surgery and complete information in electronic OPD card. The exclusion criteria were participants who received neoadjuvant or hormonal treatment before surgery, and who had inadvertent surgery. This study was approved by BAH institutional review board.

All participants received primary surgery at BAH. Participants in this study had been counseled before and after surgery. They signed surgery informed consent after counseling. Baseline characteristics such as age, menopausal status, weight, height, body mass index (BMI), underlying disease, and obstetrics history were obtained. The final diagnosis of EC cases came from the result of histopathology reports. After surgery, adjuvant treatments were reviewed and collected. Moreover, the location of recurrence and time to recurrence were obtained.

The sample size was calculated using the two-proportion formula from Menczer's study [10]. The percentage of survival of early and delayed surgery groups were 0.73 and 0.61, respectively. The 95% confidence level was 0.05. The statistical power of 80% was 0.2. The calculation resulted in the sample size of 480 participants.

The primary outcome was 5-year disease free survival (5-year DFS). Disease free survival (DFS) was defined as time from the date of surgery until the date of confirmed disease recurrence [11]. The main independent variable was TDS that was defined as the time between the date of diagnosis (date of biopsy by endometrial aspiration or dilatation and curettage) to the date of definite primary surgery. It was categorized into early (less than 6 weeks) and delayed surgery (6 weeks or more) as shown in Figure 1. The other covariates included underlying diseases which were recorded as presented or absent. The common diseases such as diabetes mellitus (DM), hypertension, dyslipidemia, and cardiovascular disease were recorded. Body mass index (BMI) more than 25 kg/m2 was classified as obesity for Asian people [12]. The performance status score was assessed by the criteria issued by the Eastern Cooperative Oncology Group (ECOG). Optimal surgery was residual tumor after surgery less than one cm in size [1].

Statistical analysis

Analysis was performed by using STATA version 17 (Stata Corp, TX, USA.). Descriptive statistics, including frequency, percentage, mean, and standard deviation, were used to summarize the baseline characteristics. The T-test was applied to compare continuous variables, and the χ^2 test or Fisher's exact test was used to compare categorical variables. The Kaplan-Meier survival test and the log-rank test were employed to examine the association between delayed TDS and 5-year survival rates. The Cox-regression analysis was performed to assess the influence of other prognostic factors on the 5-year survival rate. Additionally, multiple logistic regression analyses were used to estimate the odds ratios and 95% confidence intervals of having a mortality rate for each predictor variable. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 419 EC cases who underwent primary surgery were included. The baseline characteristics of participants in early and delayed surgery groups were shown in Table 1. The mean age of participants was 56.8 ± 11.2 years. Sixty-nine percent of participants were of menopausal status. Endometrioid histology was the most common histology subtype. Almost all participants had optimal debulking surgery. Body mass index (BMI), underlying disease, grading and intra-operative blood loss were noticed with significant differences between early and delayed surgery groups (Table 1) while other factors showed no statistical significance.

From Kaplan-Meier analysis, according to TDS (Figure 2a), the 5-year DFS did not show a statistically significant difference between groups. Five-year DFS was 82.5 and 83.0 percent (p = 0.743) in early and delayed surgery, respectively.

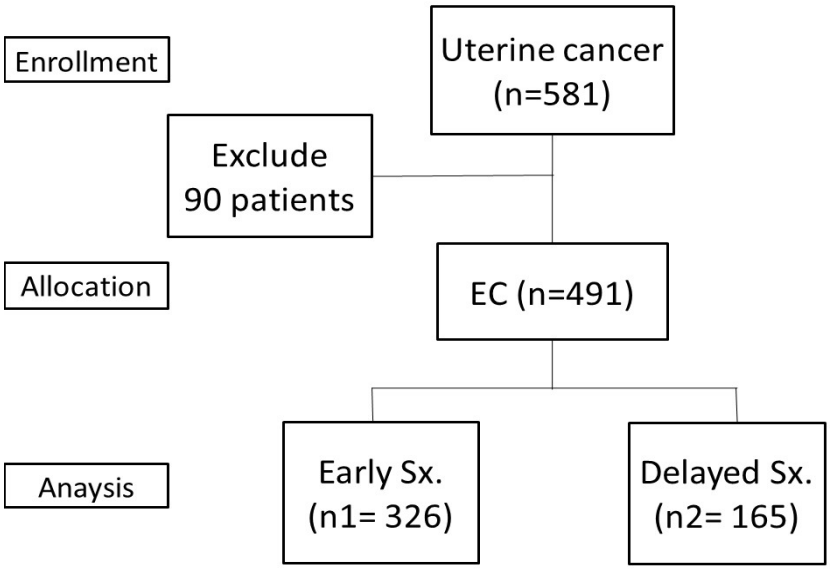

Figure 1. Consort. EC, endometrial cancer; Early Sx, time interval from diagnosis to surgery < 6 weeks; Delayed Sx, time interval from diagnosis to surgery ≥ 6 weeks

Table 1. Baseline Characteristics of Endometrial Cancer Participants According to Time-Interval from Diagnosis to Surgery (n =491)

		Time interval*		p-value
		Early (n=326)	Delayed (n=165)	
Age (year)**	56.9 ± 11.2	56.3 ± 10.6	58.2 ± 12.3	0.076
Menopause	338 (68.8)	222 (65.7)	116 (34.3)	0.618
BMI	27.27 (7.68)	26.08 (5.68)	29.64 (10.20)	
BMI ≥ 25 kg/m^2	272 (55.4)	157 (57.7)	115 (42.3)	< 0.001
U/D	309 (62.9)	187 (60.5)	122 (39.5)	<0.001
ECOG 2/3	4 (0.8)	2 (0.5)	2 (0.5)	0.605
Non-endometrioid	85 (17.3)	61 (71.8)	24 (28.2)	0.249
Grade 3	143 (29.1)	108 (75.5)	35 (24.5)	0.006
Stage III/IV	144 (29.3)	103 (71.5)	41 (28.5)	0.121
Suboptimal	21 (4.3)	15 (71.4)	6 (28.6)	0.618
EBL**	352.4 ± 389.1	311.5 ± 338.7	433.2 ± 463.9	0.001
Adjuvant	321 (65.4)	216 (67.3)	105 (32.7)	0.564
Interval	6.9 ± 11.6	7.3 ± 12.5	6.0 ± 9.6	6.9 ± 11.6

*n (%), **mean ± standard deviation (SD), Early, early surgery; Delayed, delayed surgery; BMI, body mass index; U/D, underlying disease; ECOG, Eastern Cooperative Oncology Group; Grade 3, poorly differentiated histology; EBL, estimated blood loss; Adjuvant, adjuvant treatment after surgery; Interval, time interval from surgery to adjuvant treatment

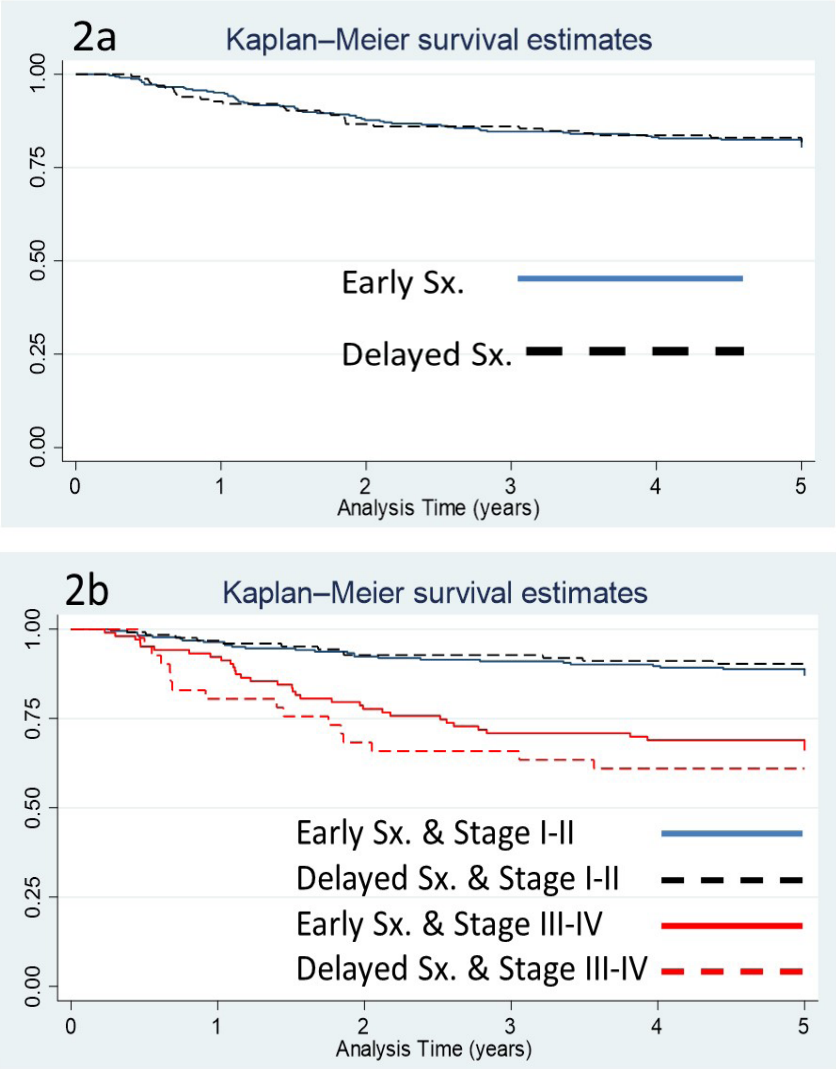

Figure 2. Disease free survival (DFS) according to (2a) time interval from diagnosis to surgery, (2b) surgical stage and time interval from diagnosis to surgery. Early Sx, time interval from diagnosis to surgery < 6 weeks; Delayed Sx, time interval from diagnosis to surgery ≥ 6 weeks; Endo, endometrioid, Non-Endo: non-endometrioid

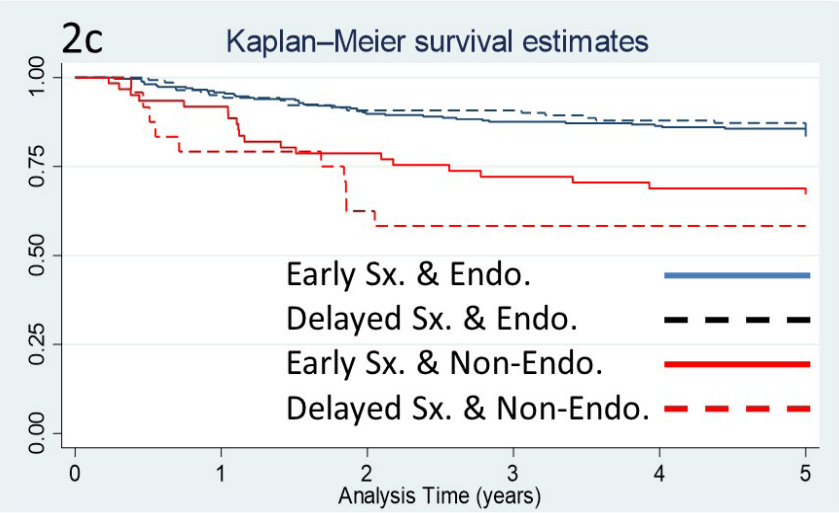

Figure 2 . Disease free survival (DFS) according to (2c) histology and time interval from diagnosis to surgery. Early Sx, time interval from diagnosis to surgery < 6 weeks; Delayed Sx, time interval from diagnosis to surgery ≥ 6 weeks; Endo, endometrioid, Non-Endo: non-endometrioid

Table 2. The Predictive Factors for Tumor Recurrence and Overall Mortality from Univariate and Multivariate Analysis

		Tumor recurrence				Overall mortality			
		Univariate		Multivariate		Univatiate		Multivariate	
		OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Menopause	No	1	-	1	-	1	-	1	-
	Yes	2.0 (1.1-3.6)	0.016	-	-	2.1 (1.3-3.3)	0.002	1.60 (0.90-2.90)	0.09
Parity	No	1	-	1	-	1	-	1	-
	Yes	1.0 (0.8-1.1)	0.551	-	-	1.2 (1.00-1.3)	0.02	-	-
BMI (kg/m2)	<25	1	-	1	-	1	-	1	-
	≥ 25	1.9 (1.2-3.0)	0.008	0.6 (0.4-1.0)	0.054	0.6 (0.4-0.9)	0.015	0.7 (0.4-1.1)	0.152
U/D	No	1	-	1	-	1	-	1	-
	Yes	1.3 (0.8-2.2)	0.267	-	-	1.5 (1.0-23.5)	0.04	1.4 (0.8-2.5)	0.197
ECOG	1	1	-	1	-	1	-	1	-
	2-3	4.9 (0.7-35.1)	0.116	-	-	2.5 (0.3-17.6)	0.372	-	-
Histology	Endo	1	-	1	-	1	-	1	-
	Non	3.2 (1.9-5.5)	<0.001	-	-	2.2 (1.4-3.5)	0.002	-	-
Grade	1-2	1	-	1	-	1	-	1	-
	3	4.5 (2.8-7.4)	<0.001	2.9 (1.7-4.9)	<0.001	1.8 (1.2-2.7)	0.004	-	-
Stage	I-II	1	-	1	-	1	-	1	-
	III/IV	4.5 (2.7-7.3)	<0.001	2.3 (1.3-4.0)	0.004	4.5 (2.9-6.8)	<0.001	2.8 (1.7-4.7)	<0.001
Size (cm.)	< 2	1	-	1	-	1	-	1	-
	≥2	2.1 (0.9-5.0)	0.106	-	-	1.6 (0.8-3.1)	0.154	-	-
LVSI	Negative	1	-	1	-	1	-	1	-
	Positive	4.2 (2.6-6.8)	<0.001	2.2 (1.3-3.9)	0.005	3.5 (2.3-5.3)	<0.001	-	-
PW	Negative	1	-	1	-	1	-	1	-
	Positive	2.6 (1.3-5.4)	0.008	-	-	2.5 (1.3-4.9)	0.006	-	-
Suboptimal	No	1	-	1	-	1	-	1	-
	Yes	4.8 (2.0-11.7)	0.001	-	-	6.7 (2.5-17.6)	<0.001	2.4 (0.7-8.0)	0.145
Surgery	Early	1	-	1	-	1	-	1	-
	Delayed	1.0 (0.6-1.6)	0.887	-	-	1.0 (0.7-1.5)	0.991	-	-
Recurrence	No	1	-	1	-	1	-	1	-
	Yes	-	-	-	-	20.8 (11.7-37.0)	<0.001	16.1 (8.8-29.3)	<0.001

BMI, body mass index; U/D, underlying disease; ECOG score, Eastern Cooperative Oncology Group score; Endo, endometrioid; Non, non-endometrioid; Grade 3, poorly differentiated histology; LVSI, Lympho-vascular space invasion; PW, Peritoneal washing; Early, time interval from diagnosis to surgery < 6 weeks; Delayed, time interval from diagnosis to surgery ≥ 6 weeks

Table 3. Comparison of Recurrence and Mortality of the Current to the Previous Studies

	This study		Haley		Wutitammasuk	
Year	2023		2017		2020	
Country	Thailand		USA.		Thailand	
Cases (n)	491		594		400	
Mean Age (year)	56		68		58.5	
Mean BMI (kg/m2)	27.3		32.5		25.4	
ECOG 2/3*	4 (0.8)		-		38 (9.5)	
Non-endometioid*	85 (17.3)		0 (0)		154 (38.5)	
Advanced stage (III/IV)*	144 (29.3)		0 (0)		400 (100)	
Positive PW*	39 (7.9)		8 (1.5)		73 (18.2)	
	Recurrence (OR)	Mortality (OR)	Recurrence (HR)	Mortality (HR)	Recurrence (HR)	Mortality (HR)
Menopause	NS	NS	NS	1.1	2.2	2.6
ECOG 2-3	NS	NS	-	-	1.3	5.3
Non-endometrioid	NS	NS	-	-	1.5-21.2	1.5-10.1
Grade						
1-2			0.4	0.6		
3	2.9	NS			8.4	6.1
Stage III/IV	2.3	2.8		-	2.6	6.5
Positive LVSI	2.2	NS	4.2	0.5	1.2	2.2
Positive PW	NS	NS	-	-	NS	1.8
Recurrence	-	16.1	-	-		-

* n (%), BMI, body mass index; ECOG score, Eastern Cooperative Oncology Group score; Non, non-endometrioid histology; Grade 3, poorly differentiated histology; LVSI, Lympho-vascular space invasion; PW, Peritoneal washing; NS, non statistical significance

According to the stage of disease, advanced stage participants (stage III-IV) had significantly poor 5-year DFS. Participants who had delayed surgery showed significantly worse prognosis as shown in Figure 2b. The 5-year DFS of early stage (stage I-II) EC among early and delayed surgery groups were 88.8 and 90.3 percent, respectively (p=0.645). The 5-year DFS of advanced stage EC among early and delayed surgery were 68.8 and 61.0 percent, respectively with statistical significance.

When subgroup analysis by histology was subjected to in the Kaplan-Meier analysis, endometrioid histology showed significant favorable prognosis compared to non-endometrioid histology, regardless of the TDS. The worst 5-year DFS was non-endometrioid histology with delayed surgery. For non-endometrioid histology, the 5-year DFS of participants among early and delayed surgery were 68.8 and 58.3 percent, respectively with statistical significance as shown in Figure 2c. For endometrioid histology, the 5-year DFS of participants among early and delayed surgery were 85.7 and 87.2 percent, respectively (p=0.545).

In univariate analysis, the significant factors associated with overall mortality of EC included menopausal status, parity, BMI, underlying diseases, histology, grading, surgical stage, lympho-vascular space invasion (LVSI), peritoneal washing cytology, and suboptimal debulking surgery. Same variables were associated with tumor recurrence, except parity and underlying diseases. In the multivariate analysis, the independent risk factors associated with overall mortality of EC were advanced stage (III-IV), and recurrence. Then the predictors of disease recurrence were high grade (G3), advanced stage (III-IV) and LVSI (Table 2).

We also used 4 weeks as the cutoff point of TDS, but it was not statistically significantly associated with survival (time interval ≥ 4 weeks OR = 1.06, 95%CI: 0.72-1.57, p-value = 0.770).

Discussion

This retrospective study aimed to determine prognosis of TDS to survival in EC women and factors associated with 5-year DFS. From the current study, TDS was not significantly associated with 5-year DFS, regardless of the cut-off of duration.

There was variation of appropriate cut-off of TDS. We stratified the cut-off at a 6-week interval because 6-week was the best proper interval to cut-off from the ROC curve analysis. Moreover, in real clinical practice, there was waiting time for a pathological report. The duration between getting the endometrial tissue to pathological report was usually about 7-14 days. It might be longer in the primary care hospitals. The referral time from primary care to the tertiary care or cancer center should be considered. From previous studies, Pergialiotis [7] reported that the most common cut-off was 6 weeks. Strohl, Al Hilli and Nica's studies [4, 6, 8] reported waiting times less than 6 weeks gave a more favorable prognosis than 6 weeks or more. Shalowitz's study reported the proper cut-off range at 2 and 8 weeks [5]. Unfortunately, TDS was not a prognostic factor for 5-year DFS in this current and Mitric's studies [9]. According to

subgroup analysis from Kaplan-Meier curve, 5-year DFS of stage III-IV or non-endometrioid histology resulted in significantly worsened survival outcomes, especially in participants with delayed surgery.

From multivariate analysis of this study, high grade (G3), advanced stage (III-IV), positive lympho-vascular space invasion (LVSI) were significantly associated with poor DFS. Furthermore, advanced stage and recurrence status were associated with overall mortality.

In the current study, advanced stage EC was a strong prognosis factor for poor overall mortality and tumor recurrence which was similar to Berek's work [1]. Higher stages offered higher risk of disease recurrence which yielded poor survival in case of recurrence. Recurrence status showed a 16-fold increase for overall mortality risk in our study. High grade and positive LVSI resulted in significantly higher disease recurrence risk similar to Haley's study [13]. Menopause status was not associated with poor prognosis for mortality in the current study unlike other studies [13, 11]. Compared to Haley's study, the mean age of the current study was younger than those of Haley's. Haley reported that age 70 years or older significantly impacted the mortality rate among EC cases [13]. Suboptimal surgery was the essential prognosis factor in Berek's work [1]. From the current and Haley's study, non-endometrioid histology, poor ECOG (2/3) and positive peritoneal washing were not significantly associated with recurrence and mortality [14]. However, Wutitammasuk's work [11] reported that non-endometrioid histology, poor ECOG (2/3) and positive peritoneal washing were associated with recurrence and mortality. Haley's work [13] recruited only from early-stage EC, while Wutitammasak's work [11] recruited only advanced-stage EC in their study. But the participants in the current study included all stages of EC, 70.7 (347/491) percent in early stages and 29.3 (144/491) percent in advanced stages. Positive peritoneal washing was inconclusive to change the early stage to advanced stage. Peritoneal washing during surgical staging was still recommended to perform according to NCCN guidelines [2]. The character of the Haley and present study were rather comparable. The current study supports Haley's report [13]. The characteristics of participants from Wutitammasuk's study [11] were rather different from the current study. This was the reason why the prognostic factor of the current study was not in lieu of Wutitammasuk et al. [11] However, suboptimal surgery was not a prognostic factor of recurrence and mortality from multivariate analysis of the present study. This might be the efficacy of early adjuvant treatment [1]. More than half of participants in the current study received adjuvant treatment within 6 weeks after surgery. The comparison of results from the current study to the previous literature were summarized and presented in Table 3.

Long DFS and early adjuvant treatment among subjects who received sub-optimal surgery were the strength of this study. The 5 years overall survival could not be determined; that was a limitation of study. This work offered an appropriate cut-off of TDS to help the clinician decide to properly manage their patients.

In conclusion, the TDS was not a prognostic factor for disease recurrence or overall mortality among early stage EC. Time to surgery equal to or more than 6 weeks made for worse prognosis for DFS among advanced stage or non-endometrioid histology EC. Advanced stage, high grade of tumor and positive of LVSI were independent factors for poor DFS. Predictive factors for mortality were advanced stage and tumor recurrence.

Author Contribution Statement

All authors contributed equally in this study.

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Ethical confirmation

This study was approved by Bhumibol Adulyadej hospital institutional review board (IRB No.115/64).

Conflict of interest

The authors declare no conflict of interests.

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