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Time to surgery and its impact on survival in patients with endometrial cancer: A National cancer database study

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HIGHLIGHTS

- Time from diagnosis to surgical treatment of endometrial cancer has increased over the past decade.
- Delay in time to surgery beyond 42 days is associated with worse survival in patients with stage I and II disease.
- Delay in time to surgery is directly influenced by socioeconomic variables.

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ABSTRACT

Objective. To determine patient and facility-specific factors associated with time to surgery (TTS) in patients with endometrial cancer (EC), and define the impact of delay in TTS >6 weeks on overall survival (OS) by tumor histology and stage.

Methods. The National Cancer Database (NCDB) was queried to identify patients with EC who underwent definitive primary surgical treatment between 2004 and 2013. Patients were stratified by EC histology into type I (endometrioid) and type II (non-endometrioid). TTS (number of days from diagnosis to definitive surgery) was calculated and trends in TTS during the study period were analyzed. Poisson regression was used to identify factors associated with TTS for patients with type I and type II EC, respectively. Cox regression was used to assess the impact of delay in TTS > 6 weeks on OS by tumor histology and stage.

Results. Out of 284,499 patients included in the study, 83% had type I EC and 17% had type II EC. Median (interquartile range; IQR) TTS for type I and II EC was 27 days (10–41) and 26 days (13–40), respectively. TTS increased over the study period in both groups. In Type I EC, delay in TTS was associated with worse OS in patients with early stage (I-II) EC only. In type II EC, delay in TTS had no significant impact on OS in stage I-III EC, while a paradoxical relationship between TTS > 6 weeks and improved OS was observed for stage IV EC.

Conclusion. TTS increased over the study period. TTS >6 weeks was negatively associated with OS in early stage type I EC. Interventions to reduce TTS in specific stages and settings for EC are necessary given this impact on mortality.

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1. Introduction

High value is placed on the timely diagnostic workup of patients with cancer, and this has become an important quality metric in cancer care [1–4]. Longer wait times may enable cancer cells to acquire poor prognostic characteristics. Prior studies have shown that longer wait times were associated with reduced survival in breast cancer, colorectal cancer, bladder cancer and melanoma [5]. A recent systematic review of 209 studies found an association between shorter time to diagnosis and favorable outcomes for these cancers [5]. Not only does the length of time a patient must wait to undergo cancer surgery have implications on patient outcomes, quality of life and quality of care, but long wait times can exacerbate anxiety and distress [6].

In general, data on wait times for initial cancer treatment are sparse. The available evidence, however, shows that time to treatment has been increasing for all cancers and appears to be particularly longer in NCI-designated Comprehensive Cancer Centers (CCC) [2]. Other factors shown to be associated with delay in initial therapy include older age, black race, greater comorbidities and stage I disease [2,7].

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In endometrial cancer (EC), patients with early stage and low risk disease (as determined by favorable histology and grade) have a 96% 5-year survival in contrast to 20% for patients with high risk and advanced stage disease. Therefore, it is presumed that prolonged time to treatment, particularly in high risk patients, may negatively impact survival. However, there are currently no recommendations regarding the recommended time to definitive treatment in EC. Studies utilizing large sample populations have confirmed that prolonged time to surgical treatment in EC adversely impacts survival [8,9]. Whether this effect is explained by the predominance of low risk histology in EC is uncertain. Strohl et al. used data from the National Cancer Database (NCDB) to show that surgical wait times >6 weeks from diagnosis of EC had a negative impact on survival in all patients with EC [8]. Shalowitz et al. showed that delay in surgical treatment was an important risk factor for mortality in low-risk cancers only [9]. The authors suggested a target interval between diagnosis and treatment of ≤8 weeks [9]. Given the remarkable impact of tumor histology and stage on EC prognosis, we hereby examine baseline factors associated with time to surgery (TTS) and define the impact of delay in TTS >6 weeks on overall survival (OS) by EC histology and stage.

2. Methods

The NCDB was queried to identify patients with EC diagnosed between 2004 and 2013. Patients with strictly grade 1–3 endometrioid histology (type I) and non-endometrioid histology (type II) who underwent primary surgical treatment were included in the study. Patients with non-epithelial carcinomas, in-situ disease, inconsistent treatment data, treatment start date >6 months after diagnosis and questionable distance to facility (>3000 miles) were excluded. Those with no histologically proven EC or with myometrial confined disease were also excluded.

TTS was defined as the number of days from diagnosis to definitive surgery and summarized as medians and interquartile ranges (IQR). Median TTS for each year of diagnosis was calculated by histologic subgroup (type I or type II), overall and by stage. Thirteen baseline characteristics were included in the analysis: year of diagnosis, age, race, Charlson-Deyo score, insurance status, residence, household income, education level, type of facility, distance from facility, EC as first cancer diagnosis (i.e., was there a prior cancer), stage, and transitional care. Year of diagnosis was categorized in 2-year intervals. Transitional care is defined as treatment outside of the reporting facility.

2.1. Statistical analysis

Poisson regression with Pearson scaling for overdispersion was used to identify characteristics associated with TTS. All thirteen baseline characteristics were included in a multivariable model. Results are summarized as incident rate ratio (IRR) and 99% confidence interval (CI); the reference group for each variable is noted. IRR > 1 indicates longer TTS relative to the reference group, while IRR < 1 indicates shorter TTS. Descriptive statistics are shown as median (IQR) TTS. OS was measured from the date of surgery. Delay in TTS was defined as TTS > 6 weeks. Cox proportional hazards analysis was used to assess the impact of delay in TTS on OS by stage, separately for type I and II EC. Cox models were stratified by year of diagnosis and adjusted for all baseline characteristics. Results are summarized as hazard ratio (HR) and 99% CI. HR > 1 indicates higher mortality risk relative to the reference group, while HR < 1 indicates lower mortality risk. Descriptive statistics are shown as survival estimates 2 and 5 years after surgery along with the standard error of the estimate (SE) and as median survival; these estimates are from Kaplan-Meier analysis. Analyses were performed with SAS® software, version 9.4 (SAS Institute, Inc., Cary, NC, USA). All statistical tests were two-sided; and $P < 0.01$ was used to indicate statistical significance.

3. Results

Out of 349,303 patients diagnosed with EC from 2004 to 2013, 284,499 were eligible for analysis after exclusion of those with incomplete or inconsistent treatment data. Overall, 83% of patient had type I EC and 17% type II EC. Median TTS for type I and type II EC was 27 days (IQR 10–41) and 26 days (IQR 13–40), respectively. Over the study time period, an increase in TTS was noted for both type I and type II EC: an increase from 23 days (IQR 8–37) during 2004–2005 to 28 days (IQR 13–43) during 2012–2013 in type I tumors, and 22 (IQR 9–36) to 28 (IQR 15–42) in type II tumors (Fig. 1). Increase in TTS was also seen among each disease stage for both type I and II EC. For both types, median TTS increased from 2004 to 2005 to 2012–2013 by 5 days in stage I, 2 days in stage II, 5 days in stage III, and 4 days in stage IV.

On univariable analysis (data not shown), a statistically significant difference in TTS was seen among all baseline characteristics, which is attributed to the large number of patients included in the analysis. Factors found to be predictive of TTS based on multivariable analysis are shown in Tables 1 (type I EC) and 2 (type II EC). For type I EC, all thirteen

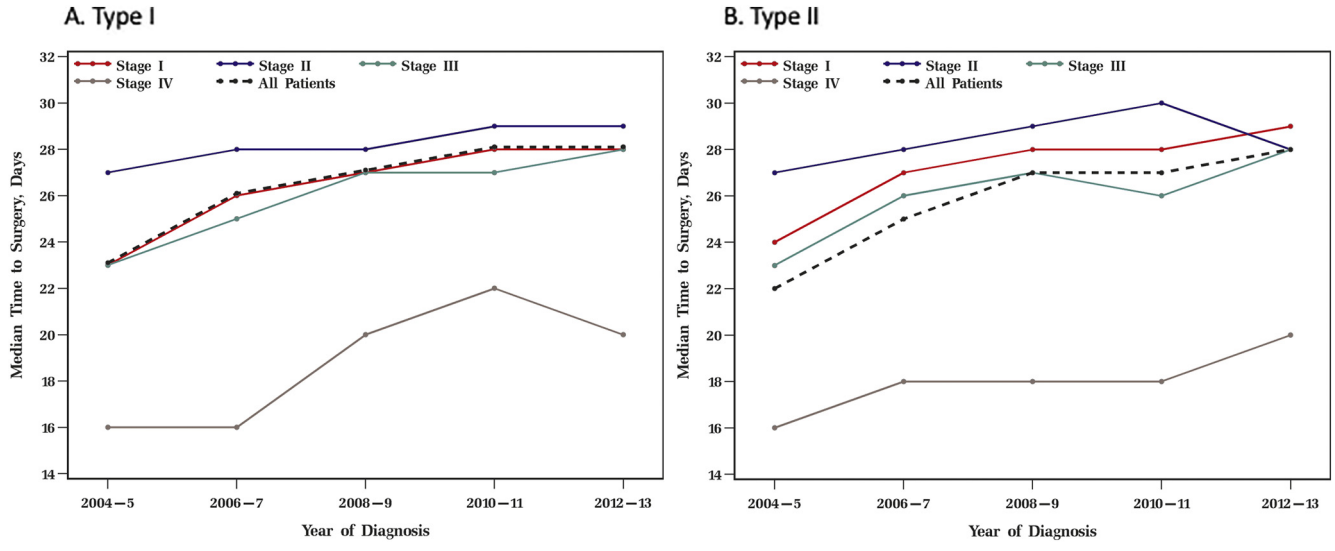

Fig. 1. Median time to surgery by stage and time period in type I EC (a) and type II EC (b).

Table 1
Factors predictive of time to surgery in patients with type I endometrial cancer.

Factor	Days to surgery		Multivariable model	
	Median	IQR	IRR (99% CI)	*P*-value
Year of diagnosis				
2004–2005	23	8–37	Reference	
2006–2007	26	8–40	1.05 (1.03–1.07)	<0.0001
2008–2009	27	10–42	1.11 (1.09–1.13)	<0.0001
2010–2011	28	11–43	1.13 (1.11–1.15)	<0.0001
2012–2013	28	13–43	1.14 (1.12–1.16)	<0.0001
Age				
<50	24	0–41	Reference	
50–59	26	9–41	1.11 (1.09–1.13)	<0.0001
60–69	27	13–42	1.12 (1.09–1.14)	<0.0001
≥70	28	13–42	1.12 (1.10–1.14)	<0.0001
Race				
Caucasian	26	10–41	Reference	
African American	31	12–49	1.13 (1.11–1.15)	<0.0001
Other	27	10–43	1.03 (1.01–1.06)	0.002
Charlson-Deyo Score				
0	26	9–41	Reference	
1	28	13–44	1.09 (1.08–1.11)	<0.0001
2	31	14–49	1.20 (1.17–1.23)	<0.0001
Insurance				
Private	25	8–39	Reference	
Government	28	13–43	1.13 (1.11–1.14)	<0.0001
None	30	8–50	1.21 (1.18–1.24)	<0.0001
Residence				
Large urban	27	9–42	Reference	
Small urban	26	10–41	0.94 (0.93–0.95)	<0.0001
Metropolitan	27	12–41	0.90 (0.88–0.92)	<0.0001
Rural	23	10–37	0.81 (0.78–0.84)	<0.0001
Household income quartiles, dollars				
<38,000	28	11–44	Reference	
38,000–47,999	27	10–42	1.00 (0.99–1.02)	0.61
48,000–62,999	27	10–41	1.00 (0.99–1.02)	0.50
≥63,000	26	9–40	1.00 (0.98–1.02)	0.98
Education level, percent less than high school				
≥21	28	9–46	Reference	
13–20.9	27	10–42	0.95 (0.94–0.97)	<0.0001
7–12.9	27	10–41	0.94 (0.92–0.95)	<0.0001
<7	25	10–39	0.89 (0.87–0.90)	<0.0001
Type of facility				
Academic	29	14–44	Reference	
Community program	24	5–39	0.84 (0.84–0.85)	<0.0001
Network/Other	27	12–41	0.89 (0.88–0.91)	<0.0001
Distance from facility, miles				
<25	26	8–41	Reference	
25–50	28	13–42	1.06 (1.04–1.07)	<0.0001
51–100	28	15–43	1.11 (1.09–1.13)	<0.0001
>100	27	13–42	1.06 (1.04–1.09)	<0.0001
Stage				
I	27	11–42	Reference	
II	28	14–44	1.10 (1.08–1.12)	<0.0001
III	26	12–41	1.00 (0.98–1.01)	0.65
IV	19	1–35	0.79 (0.77–0.82)	<0.0001
First cancer diagnosis				
No	24	0–39	Reference	
Yes	27	11–42	1.11 (1.09–1.12)	<0.0001
Transitional care				
No	27	10–41	Reference	
Yes	26	9–41	1.03 (1.02–1.05)	<0.0001

IQR, interquartile range; IRR, incidence rate ratio; CI, confidence interval.

variables were significant except for household income. If median TTS differences of at least 5 days are considered clinically relevant, the largest impact on TTS was seen for year of diagnosis, race, Charlson-Deyo score, insurance type, facility type, and stage. Specifically, there was a 5 day increase in median TTS between 2004 and 2005 and 20,012–213 (23 and 28 days), between Caucasians and African Americans (26 and 31 days), Charlson-Deyo score 0 and 2 (26 and 31 days), private insurance and no insurance (25 and 30 days), and community and academic facility (24 and 29 days). There was an 8 day decrease in median TTS between stage I and IV cancers (27 and 19 days). For type II EC, all thirteen variables were significant except for household income and transitional care. The largest impact on TTS was seen for year of diagnosis, Charlson-Deyo score, and stage. There was a 6 day increase in median TTS between 2004 and 2005 and 2012–2013 (22 and 28 days) and between Charlson-Deyo score 0 and 2 (25 and 31 days). There was a 10 day decrease in median TTS between stage I and IV cancers (28 and 18 days). (See Table 2.)

Table 2
Factors predictive of time to surgery in type II endometrial cancer.

Factor	Days to surgery		Multivariable analysis	
	Median	IQR	IRR (99% CI)	*P*-value
Year of diagnosis				
2004–2005	22	9–36	Reference	
2006–2007	25	12–40	1.10 (1.05–1.14)	<0.0001
2008–2009	27	13–41	1.13 (1.09–1.18)	<0.0001
2010–2011	27	14–41	1.13 (1.09–1.17)	<0.0001
2012–2013	28	15–42	1.15 (1.11–1.19)	<0.0001
Age				
<50	23	5–39	Reference	
50–59	26	13–40	1.12 (1.05–1.19)	<0.0001
60–69	27	14–40	1.12 (1.06–1.19)	<0.0001
≥70	27	13–41	1.12 (1.05–1.19)	<0.0001
Race				
Caucasian	26	13–39	Reference	
African American	29	13–46	1.11 (1.08–1.15)	<0.0001
Other	25	12–41	1.05 (0.99–1.11)	0.044
Charlson-Deyo score				
0	25	13–39	Reference	
1	28	14–42	1.09 (1.06–1.12)	<0.0001
2	31	18–48	1.22 (1.17–1.28)	<0.0001
Insurance				
Private	25	13–38	Reference	
Government	27	13–41	1.08 (1.05–1.11)	<0.0001
None	27	9–46	1.14 (1.08–1.21)	<0.0001
Residence				
Large urban	27	13–42	Reference	
Small urban	26	13–39	0.93 (0.91–0.96)	<0.0001
Metropolitan	26	14–40	0.91 (0.87–0.94)	<0.0001
Rural	25	13–39	0.90 (0.83–0.97)	0.0006
Household income quartiles, dollars				
<38,000	28	13–43	Reference	
38,000–47,999	27	14–41	1.00 (0.97–1.03)	0.99
48,000–62,999	26	13–40	0.99 (0.96–1.03)	0.67
≥63,000	25	13–38	0.98 (0.94–1.02)	0.22
Education level, percent less than high school				
≥21	28	13–44	Reference	
13–20.9	27	13–42	0.98 (0.95–1.01)	0.09
7–12.9	26	13–40	0.96 (0.93–0.99)	0.007
<7	25	13–37	0.92 (0.88–0.96)	<0.0001
Type of facility				
Academic	28	15–42	Reference	
Community program	24	11–38	0.89 (0.87–0.91)	<0.0001
Network/Other	27	13–40	0.93 (0.89–0.96)	<0.0001
Distance from facility, miles				
<25	26	12–40	Reference	
25–50	27	14–41	1.04 (1.01–1.07)	0.0019
51–100	27	15–42	1.07 (1.03–1.11)	<0.0001
>100	26	14–42	1.04 (0.98–1.09)	0.08
Stage				
I	28	16–42	Reference	
II	29	15–44	1.07 (1.03–1.11)	<0.0001
III	26	13–41	0.96 (0.94–0.98)	<0.0001
IV	18	4–33	0.74 (0.72–0.77)	<0.0001
First cancer diagnosis				
No	25	10–38	Reference	
Yes	27	13–41	1.06 (1.03–1.09)	<0.0001
Transitional care				
No	27	13–41	Reference	
Yes	25	11–39	0.98 (0.95–1.01)	0.11

IQR, interquartile range; IRR, incidence rate ratio; CI, confidence interval.

Table 3
Impact of time to surgery on mortality risk by stage in type I endometrial cancer.

Stage/time after surgery	TTS[1]		TTS > 6 versus ≤ 6 weeks[2]		
	≤6 weeks	>6 weeks	HR	99% CI	*P*-value
Stage I					
2 years	96.6 (0.1)	95.6 (0.1)	1.22	1.16–1.29	<0.0001
5 years	90.4 (0.1)	87.6 (0.2)			
Median survival, months	N/O	N/O			
Stage II					
2 years	92.1 (0.3)	89.8 (0.5)	1.18	1.06–1.33	0.0001
5 years	80.6 (0.5)	75.0 (0.9)			
Median survival, months	N/O	N/O			
Stage III					
2 years	81.9 (0.3)	81.1 (0.6)	0.99	0.91–1.08	0.75
5 years	66.3 (0.4)	64.1 (0.9)			
Median survival, months	121.6	100.6			
Stage IV					
2 years	53.4 (0.8)	57.4 (1.6)	0.91	0.80–1.04	0.06
5 years	35.5 (0.8)	36.5 (1.9)			
Median survival, months	28.6	31.7			

TTS, time to surgery; HR, hazard ratio; CI, confidence interval; N/O, not observed.
Kaplan-Meier survival estimates (standard error) at 2 and 5 years after surgery by TTS.
From multivariable Cox analysis stratified by year of diagnosis and adjusted for baseline characteristics.
[1] Values >1 indicate an increase in TTS; values <1 a decrease
[2] 2-year increments

Survival data were not available for patients diagnosed in 2013. Among 206,901 type I patients with survival data, 14.2% died, and 2-year and 5-year survival (±SE) were estimated to be 93.5% ± 0.1% and 85.2% ± 0.1%, respectively. Among 42,577 type II patients with survival data, 40.6% died and 2-year and 5-year survival were estimated to be 72.4% ± 0.2% and 54.2% ± 0.3%, respectively. In multivariable analysis of type I EC, delay in TTS > 6 weeks was associated with higher mortality risk in stage I (HR 1.22, CI 1.16–1.29) and stage II cancers (HR 1.18, CI 1.06–1.33) but not in stage III or IV cancers (Table 3; Fig. 2). This translated to an absolute difference of 2.8% in 5-year survival for stage I cancers (87.6% TTS > 6 weeks versus 90.4% ≤6 weeks) and an absolute difference of 5.6% for stage II cancers (75.0% vs. 80.6%). In multivariable analysis of type II EC, TTS > 6 weeks had no impact on mortality risk in stages I, II, or IV, but it had a modest impact in stage IV (HR 0.89, CI 0.80–0.99), where delay was associated with improved survival (Table 4). This translated into a difference of 1.2 months in median survival, 17.1 months for TTS > 6 weeks and 15.9 months for TTS ≤ 6 weeks.

4. Discussion

Increased time to treatment has been shown to be an independent poor prognostic factor of outcome in many solid cancers [2,5]. EC is unique in that the vast majority of patients are diagnosed with stage I disease, and low-grade histology is highly prevalent. Furthermore, low-risk EC is characterized by a protracted growth pattern, and most patients with early stage cancer do not succumb to their disease but in fact die of other lifestyle-related causes. It would thus be expected that delays in time from diagnosis to surgery would have a significant impact on long-term prognosis. Our study ascertained that delay in TTS > 6 weeks was associated with worse OS in Type I EC patients with stage I and II disease after controlling for baseline characteristics. These finding clearly contradict the dogma that delayed treatment of early stage low risk EC is not detrimental to patient outcomes.

We found that socioeconomic factors including race, insurance status, and facility type were the most clinically meaningful variables predictive of delay in TTS. These factors are known barriers to receiving standard of care therapies and are associated with worse cancer-specific outcomes in many cancers including gynecologic cancers [10]. While initiatives to improve access to care such as improvement in medical financing, allocation of resources, cross-cultural education and communication are ongoing, these known disparities persist [11]. A report from the Society of Gynecologic Oncology Healthcare disparities taskforce in 2014 emphasized that lack of access to quality care remains a burden for women with gynecologic cancer despite improvements in treatment and technology [12]. Furthermore, restrictions and delays imposed by insurance companies in approving pretreatment diagnostic testing are increasing in frequency. These delays certainly contribute to prolonging surgical wait times. Other risk factors associated with delay in TTS that are not accounted for in the NCDB may also be important. These include increase in use of preoperative diagnostic testing, individual surgeon case load, lack of surgeon access to robotic surgery platform, or availability of specialist gynecologic oncologists.

An important finding in our study was the trend towards increased TTS over time in patients diagnosed with EC in the United States between 2004 and 2005 and 2012–2013. An increase in median TTS by 5 and 6 days for type I and type II, respectively, raises concern and

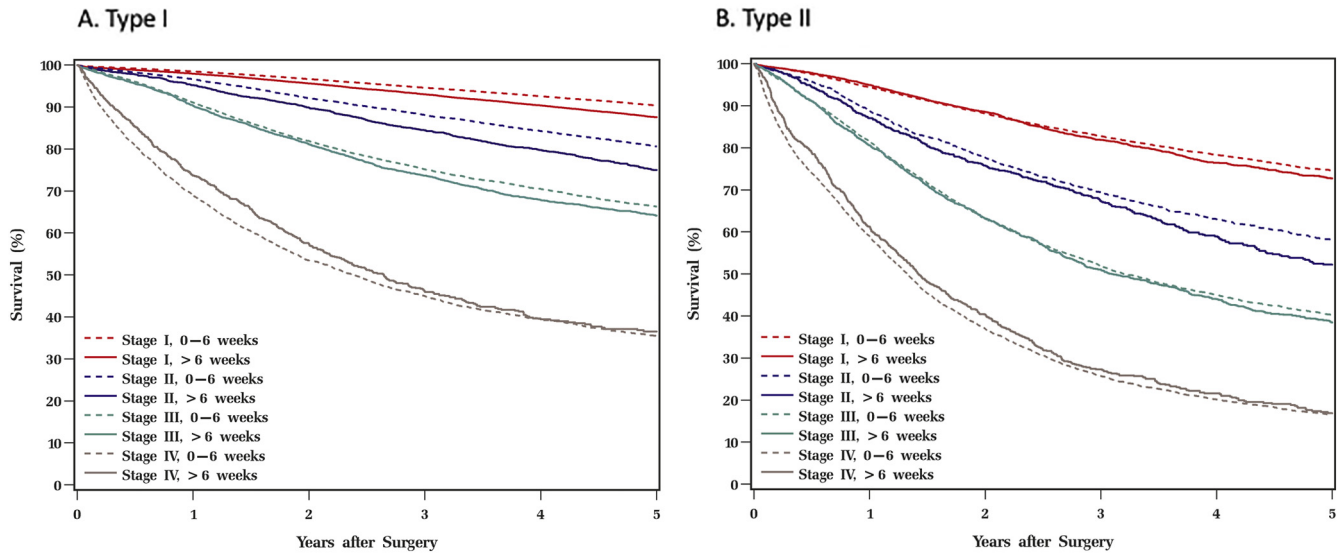

Fig. 2. Overall survival by stage and time to surgery >6 weeks vs. ≤6 weeks in type I EC (a) and type II EC (b).

Table 4
Impact of time to surgery on mortality risk by stage in type II endometrial cancer.

Stage/time after surgery	TTS[1]		TTS > 6 versus ≤ 6 weeks[2]		
	≤6 weeks	>6 weeks	HR	99% CI	*P*-value
Stage I					
2 years	88.2 (0.3)	88.5 (0.5)	1.07	0.97–1.18	0.08
5 years	74.6 (0.4)	72.7 (0.9)			
Median survival, months	N/O	121.4			
Stage II					
2 years	77.6 (0.9)	75.8 (1.5)	1.11	0.94–1.31	0.10
5 years	58.0 (1.1)	52.2 (2.0)			
Median survival, months	85.6	67.2			
Stage III					
2 years	63.3 (0.6)	63.1 (1.1)	0.96	0.88–1.06	0.31
5 years	40.2 (0.7)	38.4 (1.3)			
Median survival, months	38.3	37.1			
Stage IV					
2 years	36.9 (0.7)	40.3 (1.7)	0.89	0.80–0.99	0.007
5 years	16.6 (0.6)	16.9 (1.5)			
Median survival, months	15.9	17.1			

TTS, time to surgery; HR, hazard ratio; CI, confidence interval; N/O, not observed.
Kaplan-Meier survival estimates (standard error) at 2 and 5 years after surgery by TTS.
From multivariable Cox analysis stratified by year of diagnosis and adjusted for baseline characteristics.
[1] Values >1 indicate an increase in TTS; values <1 a decrease
[2] 2-year increments

compels us to explore underlying causes. Traditionally, general gynecologists commonly performed surgery for apparent early stage EC patients. Data has since emerged showing that outcomes are improved when patients with EC are treated by gynecologic oncologists [13,14,15]. In 2005, the American College of Obstetrics and Gynecology issued a statement recommending that all women with endometrial cancer be referred to a gynecologic oncologist. This was reaffirmed in 2015 [16]. In a subsequent study that evaluated the patterns of referral to gynecologic oncologists between 2014 and 2015, 90.9% of hysterectomies were performed by gynecologic oncologists [17].The increase in TTS over time from 2004 to 2013 can possibly be attributed to increase in subspecialty referrals and increase in transitions of care. Although referral to gynecologic oncologists is considered to be an important quality metric in EC care, this should not be viewed as a negative finding. In fact, a reasonable delay between diagnosis and surgery of up to 6 weeks allows flexibility in scheduling with gynecologic oncologists and proper preoperative evaluation and staging which overall lead to improvement in improved quality of care. As shown in our study, patients with type II disease were less sensitive to delays in TTS which emphasizes the importance of appropriate referral in these patients.

Time to treatment in EC has been reported in prior studies with conflicting results [18,19–22]. A study from Israel found that survival in EC patients was not affected by delay in treatment of four months [23]. In a report by Strohl et al., which assessed surgical wait times in type I and II EC combined in the NCDB, increased wait times were associated with decreased survival [8]. As would be expected the vast majority of patients (76%) had stage I disease and most patients had type I tumors (83%). An overall increase in risk of death of 15% was seen with increase in TTS >6 weeks. The net effect of this is that the results reported by Strohl et al. were heavily influenced by patients with stage I and type II EC. The present study dissects these results by examining type I and II EC separately and examining outcome within each tumor type by stage. Our results reaffirm the cut off of 6 weeks as an important target TTS and suggest that the negative impact of wait times on OS may be limited primarily to stage I and II type I EC.

Similar to our study, Shalowitz et al. evaluated the impact of delay in TTS in EC classified into high risk and low-risk groups [9]. These groups were distinct from our study group in that grade 3 endometrioid adenocarcinomas were included among the high risk cohort in addition to non-endometrioid histologies. Delay in TTS was found to be associated with worse survival in low-risk patients of which ~77% were stage I or II ECs, which correlates with our findings in type I EC patients. Similarly, high risk EC patients with delay up to 3 weeks from surgery did not have a negative impact on survival. As similarly shown in our study, patients with type II EC were less sensitive to delays in TTS. This study also evaluated 30-day postoperative mortality and this was found to be higher for patients who had surgery in the first or second week after diagnosis, similar to other studies [19].

While OS in patients with type I EC and stage III disease in our study did not appear to be affected by TTS, stage IV patients had an improvement in OS with TTS > 6 weeks in type II EC. This intriguing finding suggests that factors that are more complex than clinical and socioeconomic issues that are not captured in the database likely explain the improved survival in stage IV patients. This paradoxical relationship has been demonstrated in other cancers such as lung cancer and is attributed to the negative impact or urgent treatment on prognosis due to high symptoms burden [24]. For instance, patients with non-small cell lung cancer with distant disease and estimated survival <1 year, shorter time to treatment was associated with reduced survival [24]. Elit et al. showed in a large population-based cohort that women with EC who underwent surgery less than two weeks from diagnosis had worse outcomes than those who had wait times between 2 and 12 weeks [19].Therefore, it can be concluded that for patients where disease can be cured surgically, improving TTS can enhance survival. Patients with stage IV EC have a dismal prognosis. In our study, these patients had a 5-year OS of 36% for type I EC and 17% for type II EC. As such, patients with fatal disease where surgery is not curative, expeditious surgery is likely a surrogate for worse disease severity and prognosis. This highlights the importance of tumor biology in determining patient outcomes despite a prolonged time to treatment as seen in type II EC patients in this study.

Limitation of our study includes those inherent to large retrospective tumor registry databases. Selection bias, the possibility of incomplete data or coding errors, and lack of availability of data on cause of death as well as recurrence limit the interpretation of results. Other known treatment benchmarks may also impact survival which were not analyzed as part of this study such as time to administration of adjuvant radiation therapy and adherence to national evidence-based guidelines for treatment [10,25]. The value of other unmeasured variables associated with delivery of timely care for cancer patients such as reduction in psychological distress, impact of treatment on quality of life measures, time to return to physical activity and work on quality of care is highly underreported [3]. As we move towards measuring patient-related outcomes in cancer care, these factors should be taken into account to maintain healthcare value.

In summary, we reaffirm the impact of delay in TTS on overall prognosis in patients with EC. We found that a 6-week window from time of diagnosis to surgery is an optimal cut-off for patients with EC. We further note that patients that appear to derive the most benefit from expeditious surgery are those with early stage type I disease. Addressing disparities in healthcare delivery while ensuring that access to subspecialty care is not hindered is of prime importance in the effort to improve overall patient outcomes and value of care. Enhancing resources directed towards improving TTS such as use of patient navigators, access expansion programs and multidisciplinary clinics may play a vital role in reducing delays in TTS. Policy changes that begin at an institution level are likely to translate into an overall improvement in outcomes on a global scale. More importantly, careful scrutiny and continuous evaluation of time to treatment within institutions is likely to have far-reaching effects.

The authors have no conflicts of interest.

Author contribution

Writing and editing: MMH, LR, AK, PGR.
Concept development: MMH, AK, PE, PGR.
Statistical Analysis: PE, LR.

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