CORRESPONDENCE

Association between hysterectomy wait-time and all-cause mortality for micro-invasive cervical cancer: treatment implications during the coronavirus pandemic

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Dear Editor,

In 2021, a global pandemic caused by a novel coronavirus (COVID-19) continues to be a major health threat. In the United States, nearly 33.5 million people have tested positive for COVID-19 and over 602,400 patients have died from complications related to COVID-19 as of early July 2021 [1]. The pandemic crisis is stressing the healthcare systems creating unprecedented challenges in providing timely oncologic care. Multiple studies have demonstrated that COVID-19 has resulted in delayed cancer care [2, 3].

A recent high-quality meta-analysis concluded that cancer treatment delay is associated with increased mortality in various malignancies, but valid data on cervical cancer remain scant [4]. Given that the majority of women with early-stage cervical cancer are treated surgically with hysterectomy, we examined the association between hysterectomy wait-time and oncologic outcomes for women with micro-invasive cervical cancer.

This retrospective observational study examined women with stage IA squamous, adenocarcinoma, and adenosquamous carcinomas of the uterine cervix diagnosed from 2004 to 2015 in the National Cancer Database. All women underwent primary hysterectomy. Cases with no wait-time were excluded due to the assumption of occult malignancy. Associations between surgical wait-time, defined as time interval from cancer diagnosis to hysterectomy, and oncologic outcomes including surgical-pathological factors (pathological parametrical invasion, nodal metastasis, and lympho-vascular space invasion) and all-cause mortality were examined [5].

A generalized linear regression model was used to assess the association between wait-time and pathologic characteristics. Binary logistic regression and Cox proportional hazards regression models with restricted cubic spline transformation of surgery wait-time were used to assess the non-linear associations between outcome measures, adjusting for other patient and tumor characteristics. The Columbia University Institutional Review Board deemed exempted this study due to the use of publicly available data.

A total of 2732 women were examined. The median age was 43 (IQR 36–52) years. Squamous histology ($n = 1792$, 65.5%) and stage IA1 disease ($n = 1185$, 43.4%) were the most frequent tumor characteristics. The median hysterectomy wait-time was 6 (IQR 4–9) weeks. Non-Hispanic Black and Hispanic patients, and uninsured and Medicaid insurance were independently associated with longer hysterectomy wait-time in multivariable analysis (all, $P < 0.001$; Table 1). Longer hysterectomy wait-time was not associated with increased risks of pathological parametrial involvement, regional lymph node metastasis, or lympho-vascular space invasion (Fig. 1A–C). The median follow-up was 4.5 (IQR 2.2–7.2) years, and 136 (5.0%) deaths occurred. Longer hysterectomy wait-time was not associated with all-cause mortality risk ($P = 0.431$; Fig. 1D).

The observed result with absence of association between hysterectomy wait-time and mortality risk is somehow reassuring. Notably, our results for micro-invasive cervical

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Table 1 Multivariable model for hysterectomy wait-time in micro-invasive cervical cancer

	No. (%)	Mean (SD)	Estimated parameters (beta) (95% CI)[§]
No. patients	2732 (100.0)		
Age			
< 40	1018 (37.3)	7.2 (4.9)	Referent
40–49	907 (33.2)	7.3 (4.6)	0.29 (−0.84, 1.41)
50–59	458 (16.8)	7.9 (5.1)	0.76 (−0.39, 1.92)
60–69	260 (9.5)	7.9 (5)	0.87 (−0.38, 2.11)
70–79	70 (2.6)	7.2 (4.6)	0.13 (−1.56, 1.83)
≥ 80	19 (0.7)	5.1 (2.8)	−1.74 (−4.17, 0.68)
Race/ethnicity			
Non-Hispanic: White	1803 (66.0)	6.8 (4.5)	Referent
Non-Hispanic: Black	305 (11.2)	8.7 (5.5)	1.21 (0.60, 1.81)**
Hispanic	356 (13.0)	9.2 (5.5)	1.23 (0.64, 1.82)**
Non-Hispanic: Other	109 (4.0)	8.0 (4.7)	0.58 (−0.34, 1.50)
Unknown	159 (5.8)	7.2 (4.9)	0.49 (−0.27, 1.25)
Insurance status			
Not insured	176 (6.4)	9.5 (5.9)	2.09 (1.33, 2.84)**
Private	1656 (60.6)	6.7 (4.3)	Referent
Medicaid	539 (19.7)	8.7 (5.6)	1.49 (1.01, 1.97)**
Medicare	240 (8.8)	7.4 (4.9)	0.52 (-0.28, 1.32)
Other Government	44 (1.6)	7.2 (4.5)	0.53 (-0.86, 1.93)
Unknown	77 (2.8)	8.6 (4.8)	1.58 (0.50, 2.67)*
Neighborhood average household income			
< $40,227	583 (21.3)	8.3 (5.2)	Referent
$40,227—$50,353	640 (23.4)	7.3 (4.6)	−0.47 (−1.03, 0.09)
$50,354—$63,332	636 (23.3)	7.0 (4.7)	−0.65 (−1.26, −0.04)*
≥ $63,333	837 (30.6)	7.1 (4.8)	−0.29 (−0.99, 0.41)
Not available	36 (1.3)	8.9 (5.5)	3.92 (−0.22, 8.05)
Neighborhood education level			
≤ 17.6%	702 (25.7)	8.4 (5.3)	Referent
10.9%–17.5%	753 (27.6)	7.4 (4.8)	−0.12 (−0.65, 0.41)
6.3%–10.8%	708 (25.9)	6.8 (4.5)	−0.48 (−1.10, 0.13)
< 6.3%	538 (19.7)	6.7 (4.5)	−0.66 (−1.38, 0.07)
Not available	31 (1.1)	8.7 (5.4)	−4.20 (−8.67, 0.28)
Urban/Rural			
Metropolitan	2,227 (81.5)	7.5 (4.9)	Referent
Urban	384 (14.1)	6.8 (4.3)	−0.59 (−1.14, −0.05)*
Rural	46 (1.7)	6.3 (4.6)	−0.87 (−2.25, 0.50)
Unknown	75 (2.7)	8.5 (5.6)	0.99 (−0.12, 2.11)
Charlson/Deyo comorbidity			
0	2,397 (87.7)	7.4 (4.8)	Referent
1	285 (10.4)	7.4 (4.8)	−0.37 (−0.95, 0.21)
2	50 (1.8)	8.1 (5.6)	−0.02 (−1.35, 1.31)
Year of diagnosis			
2004	139 (5.1)	7.8 (5.3)	Referent
2005	170 (6.2)	7.8 (5.3)	0.14 (−0.91, 1.18)
2006	177 (6.5)	7.1 (4.6)	−0.52 (-1.56, 0.51)
2007	182 (6.7)	7.5 (4.9)	−0.13 (−1.16, 0.89)
2008	224 (8.2)	7.2 (4.7)	−0.33 (−1.32, 0.65)
2009	284 (10.4)	7.7 (4.7)	0.08 (−0.87, 1.02)
2010	261 (9.6)	7.0 (4.7)	−0.60 (−1.57, 0.37)

Table 1 (continued)

	No. (%)	Mean (SD)	Estimated parameters (beta) (95% CI)[§]
2011	251 (9.2)	7.3 (4.8)	−0.27 (−1.24, 0.71)
2012	238 (8.7)	7.6 (5.2)	−0.16 (−1.14, 0.83)
2013	256 (9.4)	7.3 (4.7)	−0.33 (−1.30, 0.65)
2014	286 (10.5)	7.1 (4.7)	−0.49 (−1.44, 0.47)
2015	264 (9.7)	7.4 (4.9)	−0.11 (−1.08, 0.87)
Histology			
Squamous cell	1,792 (65.6)	7.6 (5)	Referent
Adenocarcinoma	873 (32.0)	6.9 (4.5)	−0.23 (−0.63, 0.18)
Adenosquamous	67 (2.5)	7.0 (5.4)	−0.36 (−1.51, 0.78)
Clinical Stage IA			
IA1	1185 (43.4)	7.4 (4.8)	Referent
IA2	449 (16.4)	7.4 (4.9)	0.16 (−0.35, 0.68)
IA NOS	1098 (40.2)	7.3 (4.9)	0.01 (−0.39, 0.41)
Grade			
Well	595 (21.8)	7.4 (4.8)	Referent
Moderate	822 (30.1)	7.3 (4.7)	−0.44 (−0.94, 0.07)
Poorly	323 (11.8)	7.2 (4.9)	−0.64 (−1.29, 0.01)
Unknown	992 (36.3)	7.6 (5)	−0.20 (−0.68, 0.29)
Facility location			
Eastern	344 (12.6)	7.8 (4.9)	Referent
South	449 (16.4)	7.0 (4.4)	−0.64 (−1.31, 0.04)
Midwest	647 (23.7)	7.1 (4.6)	−0.67 (−1.30, −0.05)*
West	274 (10.0)	8.8 (5.5)	0.75 (−0.01, 1.50)
Unknown	1018 (37.3)	7.2 (4.9)	Non-estimated
Facility type			
Community cancer program	88 (3.2)	7.6 (4.2)	Referent
Comprehensive community cancer program	582 (21.3)	6.7 (4.5)	−0.31 (−1.36, 0.75)
Academic/research program	863 (31.6)	8.2 (5.1)	0.63 (−0.40, 1.65)
Integrated network cancer program	181 (6.6)	6.7 (4.1)	−0.27 (−1.47, 0.93)
Other or unknown	1018 (37.3)	7.2 (4.9)	Non-estimated

No number; *SD*, standard deviation; *CI* confidence interval; and *NOS* not otherwise specified

Mean wait-time (weeks) from cervical cancer diagnosis to hysterectomy is shown

[§]Estimated parameters (beta) from generalized linear regression model. *$P < 0.05$, **$P < 0.001$. Due to the collinearity between age < 40, facility location and type unknown categories, betas were non-estimated for facility location and type unknown categories

cancer differ from data for stage IB tumors in which longer wait times to hysterectomy are associated with increased mortality [5]. Our findings may be due, at least in part, to the favorable prognosis for micro-invasive cervical cancer. Important limitations in this study included missing information on underlying reason of hysterectomy delay, comorbidities, occult cancer diagnosis, and use of excisional biopsy prior to hysterectomy.

As there are few data to describe the survival effect of delay in hysterectomy in cervical cancer [4, 6], our analysis of stage IA tumors provides valuable information in the management of women with early-stage cervical cancer and suggests that recommendations by recent expert panels to postpone hysterectomy for 6–8 weeks among patients with early-stage cervical cancer in centers or regions with a high burden of COVID-19 disease are reasonable for stage IA disease and do not adversely impact survival [7].
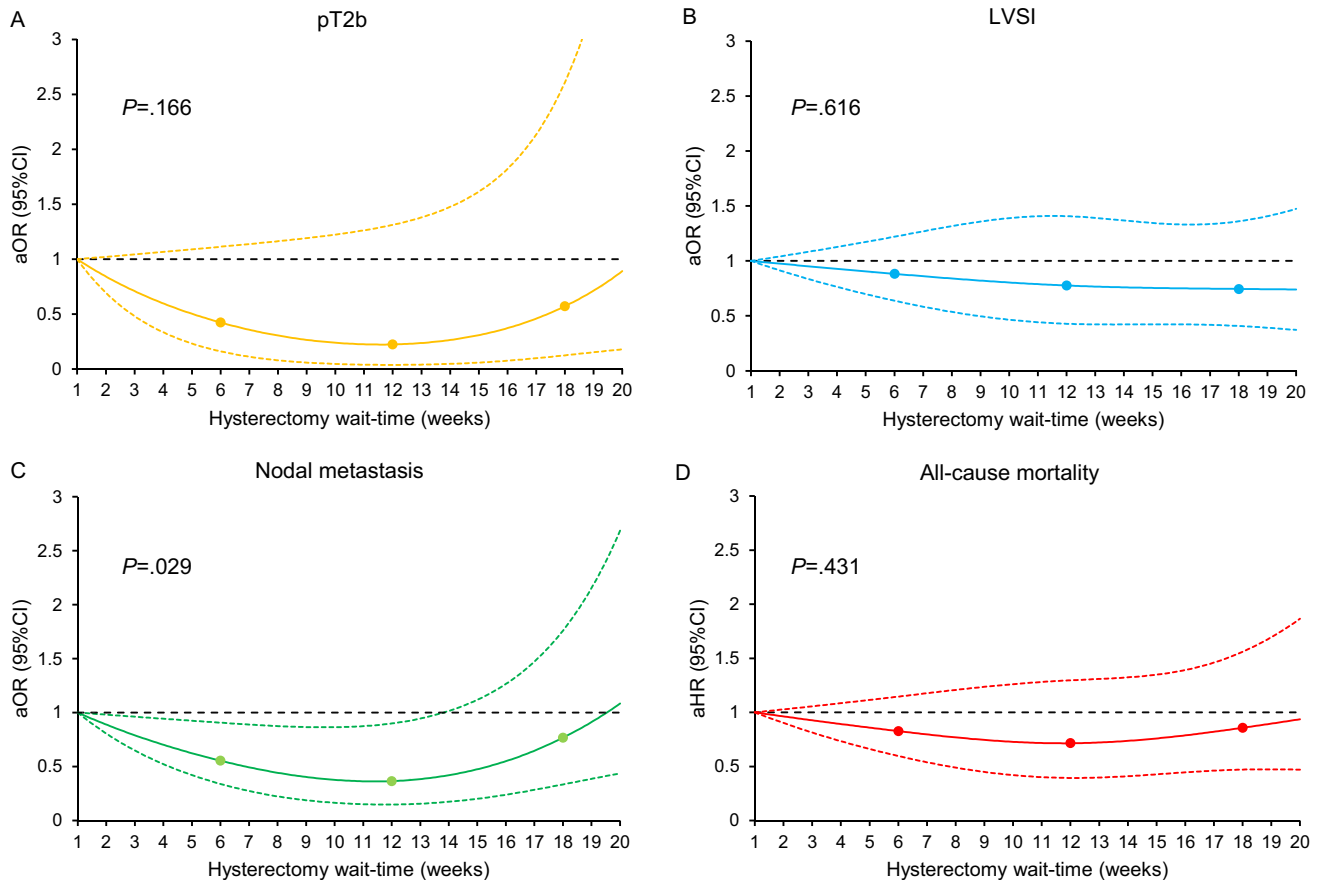
Fig. 1 Associations between hysterectomy wait-time and oncologic outcomes and all-cause mortality (adjusted model). A total of 2,732 women with clinical stage IA cervical cancer who had primary hysterectomy were examined. Adjusted-odds ratio for pathological stage T2b (**A**), LVSI (**B**), and nodal metastasis (**C**), and adjusted-hazard ratio for all-cause mortality (**D**) are shown by week of hysterectomy wait-time. Waiting time was coded using restricted cubic spline transformation with clinically relevant cut-points at 6, 12, and 18 weeks. The Y-axis represents the effect size (adjusted-odds ratio or adjusted-hazard ratio). The X-axis represents the wait-time (week) from cervical cancer diagnosis to surgical treatment with hysterectomy. Week 1 is set as the reference. The solid line represents the esti-mate as adjusted-effect size. The dashed lines are corresponding 95% confidence interval. Three dots represent the knots. *P* values indicate the overall associations. For the surgical-pathological factors, adjusting factors were age, year, race/ethnicity, insurance status, average neighborhood household income, average neighborhood education level, year of diagnosis, comorbidity score, urban/rural type, histology type, tumor differentiation, stage, and hospital factors (location and setting). For all-cause mortality, lympho-vascular space invasion, pathological parametrial tumor involvement, and lymph node metastasis were additionally included as covariates in the multivariable Cox proportional hazard regression model

Declarations

Transparency The manuscript's corresponding author (J.D.W.) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. National Cancer Database is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The program is the source of the de-identified data used; and the program has not verified and is not responsible for the statistical validity of the data analysis or the conclusions derived by the study team.

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