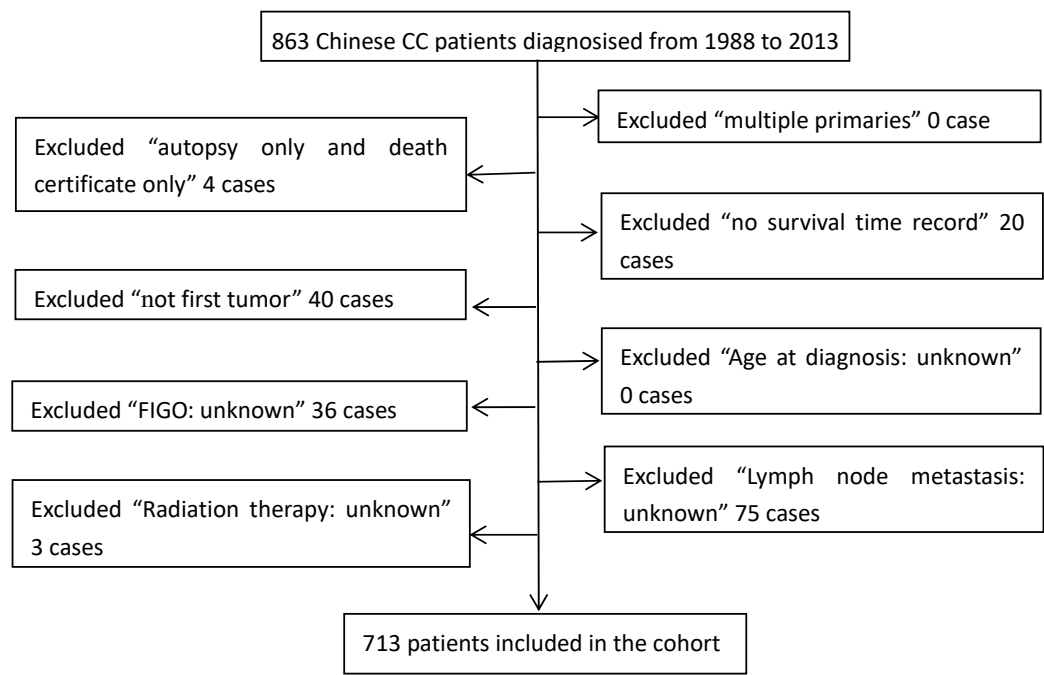


Moving Beyond the Cox Proportional Hazards Model in Survival

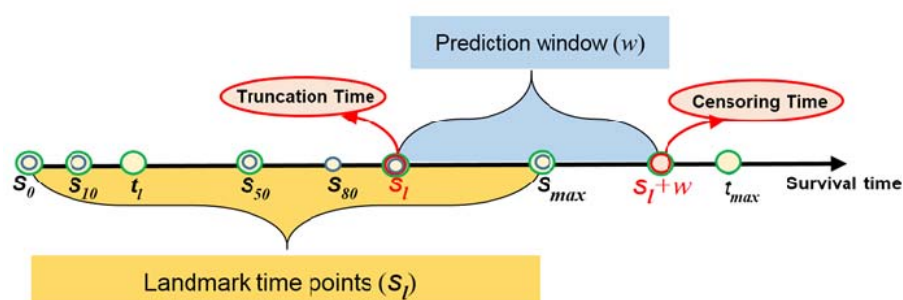
Data Analysis: a Cervical Cancer Study

Supplementary Digital Content



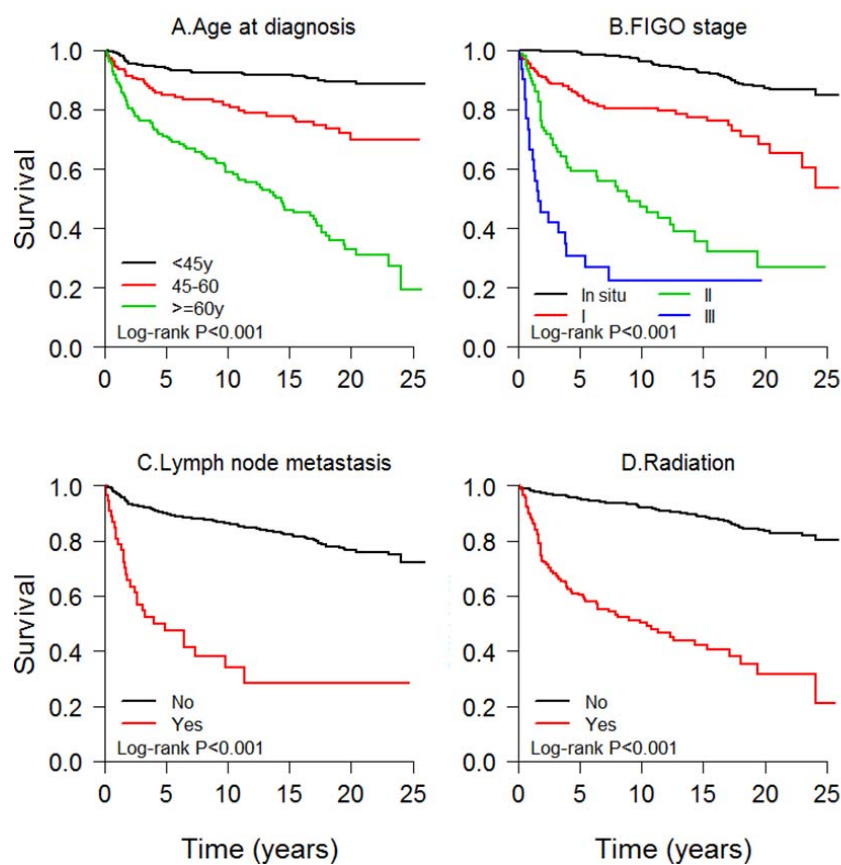
eFigure 1. Inclusion and Exclusion Flowchart.

FIGO: International Federation of Gynecology and Obstetrics.



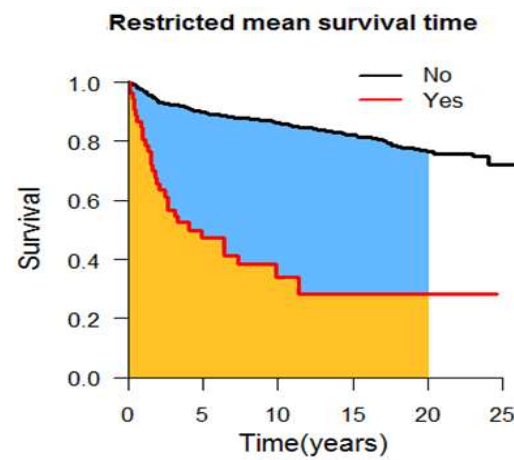
eFigure 2. Landmark time points (s_l) and prediction window (w).

The green circle represents the patients' survival time. The blue circle represents the landmark time points. The red circle represents the two endpoints (Truncation time and Censoring time) of the prediction window. Different types of circles overlapping at the same time indicate that the time points occur at the same time.



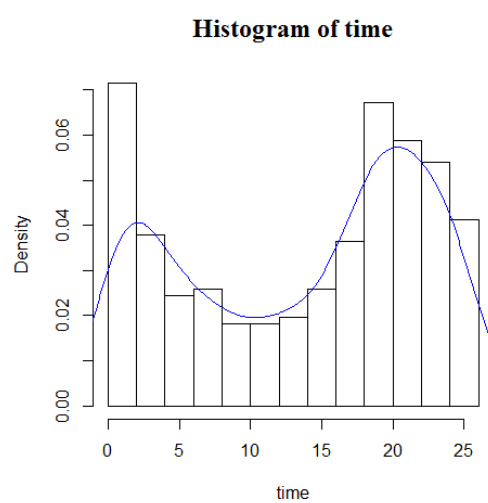
eFigure 3. Survival curves based on Kaplan-Meier estimation.

FIGO: International Federation of Gynecology and Obstetrics.

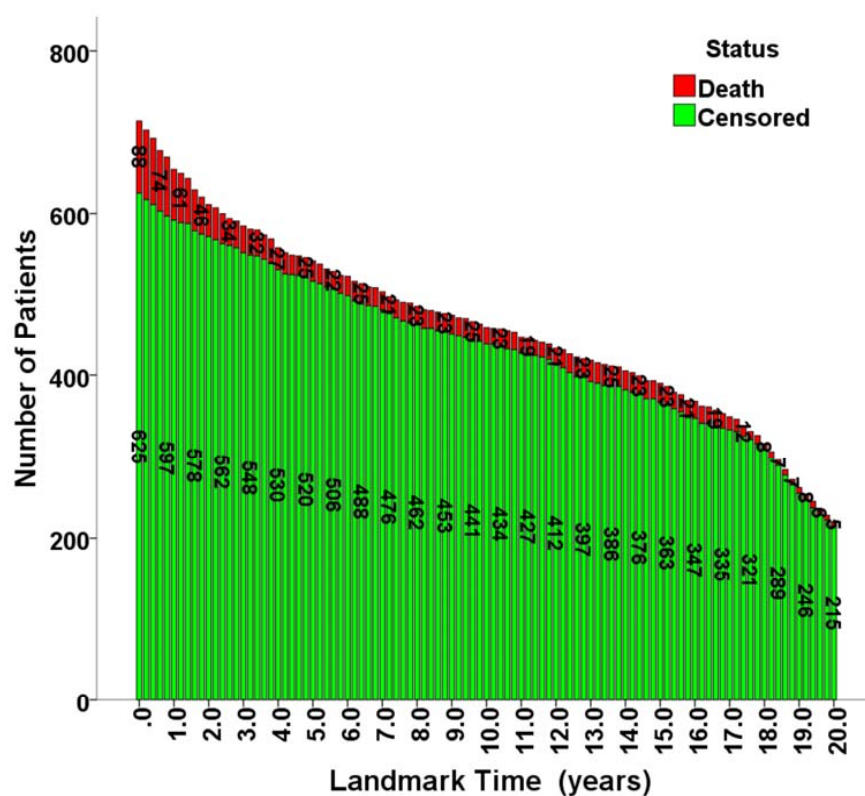


eFigure 4. Restricted mean survival time (RMST) for lymph node metastasis.

The red line represents patients with lymph node metastasis, and the black line represents patients without lymph node metastasis. The orange area represents RMST in patients with lymph node metastasis, and the blue area represents RMST difference between patients with and without lymph node metastasis.

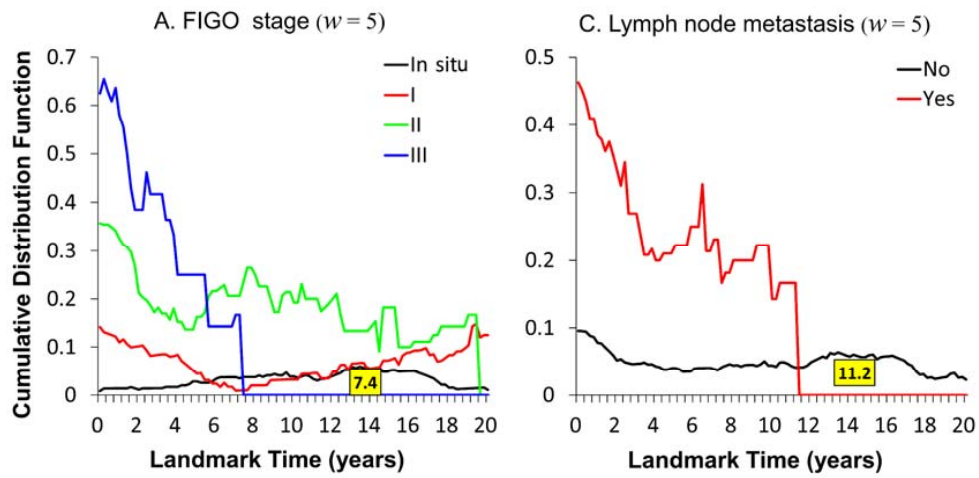


eFigure 5. The distribution of survival time
The blue line represents the empirical distribution function of survival time.



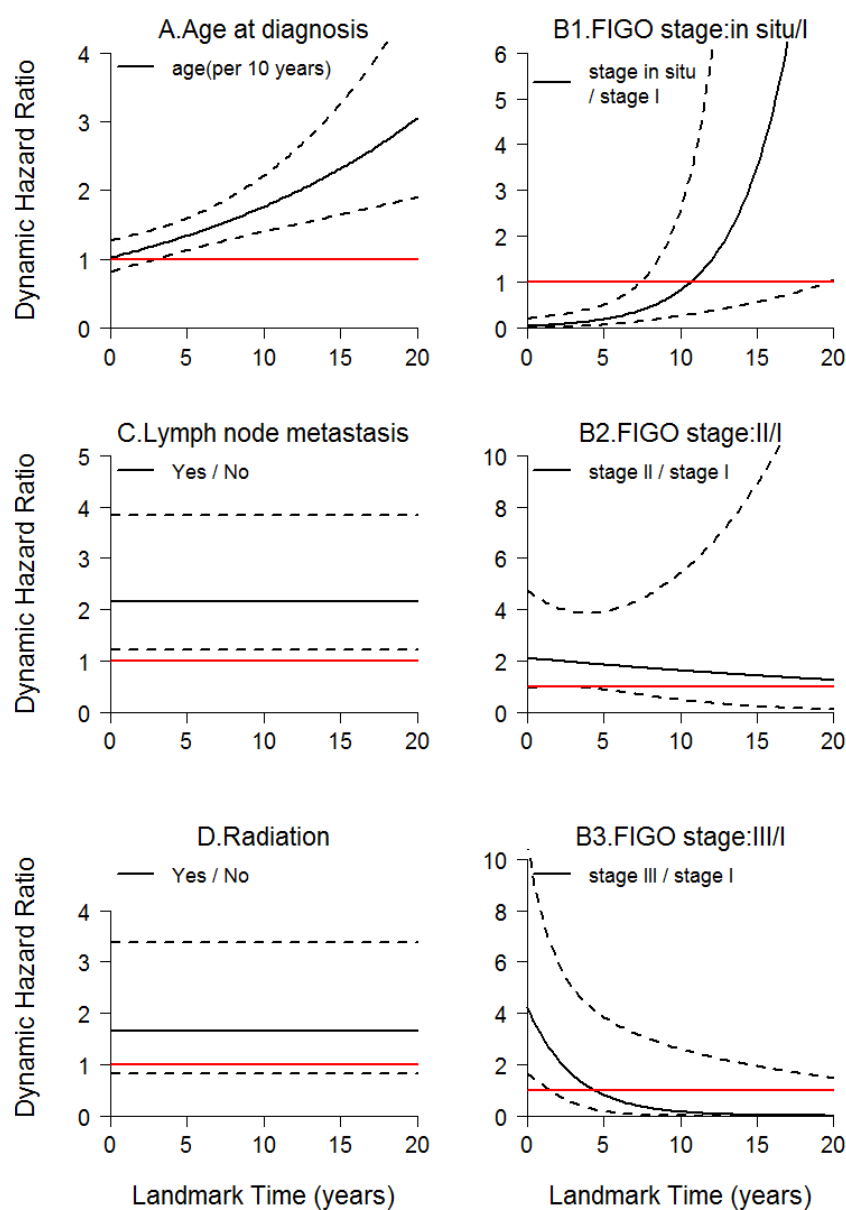
eFigure 6. Stacked bar charts indicate the number of censored patients and the number of deaths in the landmark datasets ($w=5$ years).

The green bar shows the censored patients in each landmark time point, and the red bar shows the deaths in each landmark time point. w : prediction window.



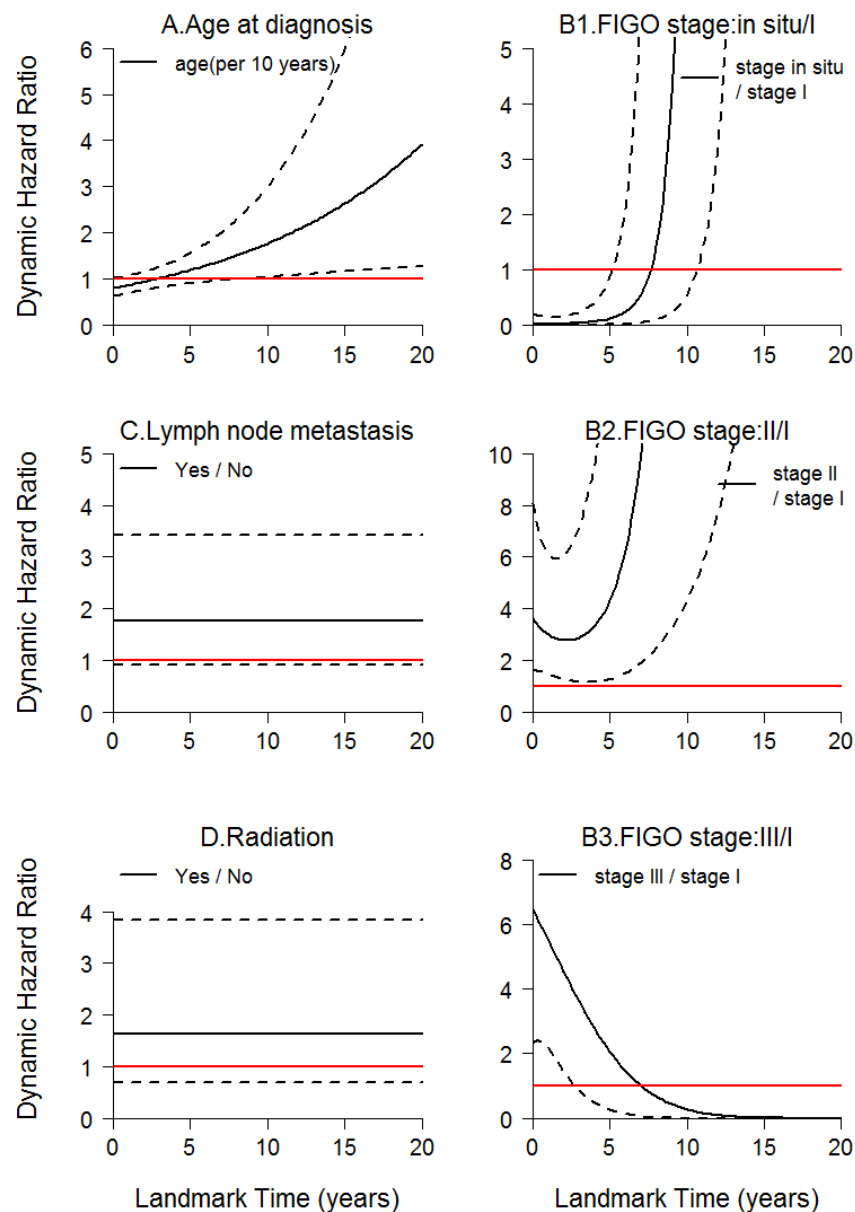
eFigure 7. Cumulative distribution functions in different landmark time points and different width predictions based on the FIGO stage and the lymph node metastasis.

FIGO: International Federation of Gynecology and Obstetrics; w : prediction window.



eFigure 8. Dynamic *HRs* with 95% confidence intervals in the dynamic prediction PBLS model ($w=5$ years) for all-cancer-specific survival.

The red line represents $HR=1$. The black solid line represents dynamic *HRs*, and the black dashed line represents 95% confidence intervals. FIGO: International Federation of Gynecology and Obstetrics; *HR*: hazard ratio; PBLS: proportional baselines landmark super.



eFigure 9. Dynamic *HRs* with 95% confidence intervals in the dynamic prediction PBLS model ($w=5$ years) for cervical-cancer-specific survival.

The red line represents $HR=1$. The black solid line represents dynamic *HRs*, and the black dashed line represents 95% confidence intervals. FIGO: International Federation of Gynecology and Obstetrics; *HR*: hazard ratio; PBLS: proportional baselines landmark super.

eTable 1. Example patient characteristics

Patient	Variables			
	Age at diagnosis	FIGO stage	Lymph node metastasis	Radiation
According to the Age at diagnosis				
A	30	I	No	No
B	45	I	No	No
C	60	I	No	No
D	75	I	No	No
According to the FIGO stage				
E	45	In situ	No	No
B	45	I	No	No
F	45	II	No	No
G	45	III	No	No
According to the Lymph node metastasis				
B	45	I	No	No
H	45	I	Yes	No
According to the Radiation				
B	45	I	No	No
J	45	I	No	Yes

Abbreviations: FIGO: International Federation of Gynecology and Obstetrics.

eTable 2. Estimates of regression parameters of AFT models

Variable	Weibull		Log-normal		Log-logistic	
	β (SE)	P	β (SE)	P	β (SE)	P
(Intercept)	7.108(0.521)	<0.001	6.268(0.456)	<0.001	6.415(0.465)	<0.001
Age at diagnosis (per 10 years)	-0.539(0.076)	<0.001	-0.480(0.068)	<0.001	-0.501(0.070)	<0.001
FIGO Stage						
In situ	0.647(0.272)	0.017	1.071(0.257)	<0.001	0.744(0.254)	0.003
I(reference)						
II	-0.513(0.286)	0.072	-0.619(0.315)	0.050	-0.653(0.303)	0.031
III	-0.959(0.359)	0.008	-1.221(0.428)	0.044	-1.331(0.401)	0.001
Lymph node metastasis						
No(reference)						
Yes	-1.109(0.267)	<0.001	-1.326(0.330)	<0.001	-1.343(0.329)	<0.001
Radiation						
No(reference)						
Yes	-0.403(0.289)	0.164	-0.402(0.305)	0.188	-0.389(0.295)	0.325

Abbreviations: AFT: accelerated failure time; SE: standard error; FIGO: International Federation of Gynecology and Obstetrics.

eTable 3. Estimates of regression parameters of transformation models

Variable	β (SE)			
	$r=0$	$r=1$	$r=1.5$	$r=2$
Age at diagnosis (per 10 years)	0.464(0.060)	0.581(0.070)	0.637(0.078)	0.693(0.086)
FIGO Stage				
In situ	-0.587(0.237)	-0.685(0.282)	-0.738(0.306)	-0.794(0.331)
I (reference)				
II	0.451(0.246)	0.629(0.338)	0.721(0.383)	0.815(0.429)
III	0.814(0.311)	1.290(0.467)	1.499(0.541)	1.706(0.617)
Lymph node metastasis				
No(reference)				
Yes	0.924(0.229)	1.237(0.360)	1.397(0.423)	1.558(0.485)
Radiation				
No(reference)				
Yes	0.355(0.250)	0.460(0.333)	0.507(0.373)	0.555(0.414)

Abbreviations: SE: standard error; FIGO: International Federation of Gynecology and Obstetrics.

eTable 4. Two models for all-cancer-specific survival

Variable	Baseline Characteristics No. of Patients (Deaths)	Cox Proportional Hazard Model			RMST Based on Pseudo-values (GLM)		
		Univariable <i>HR</i> (95% CI)	Multivariable <i>HR</i> (95% CI) ¶	<i>P</i> *	Univariable RMST (95% CI) §	Multivariable RMST (95% CI) ¶	<i>P</i> *
Age at diagnosis (per 10 years)	713(99)	- 1.66 (1.47, 1.87)	- 1.24 (1.07, 1.44) ‡	0.003	§ -1.08 (-1.41, -0.75)	19.72 (17.81, 21.63) -0.38 (-0.74, -0.21)	<0.001 0.038
FIGO Stage							
In situ	375 (15)	0.16 (0.08, 0.29) †	0.25 (0.13, 0.49) ‡	<0.001	2.85 (1.93, 3.77)	1.72 (0.75, 2.68)	<0.001
I (reference)	205 (32)						
II	101 (37)	3.26 (2.02, 5.250)	1.74 (0.99, 3.07)	0.055	-4.12 (-6.03, -2.21)	-2.41 (-4.72, -0.10)	0.041
III	32 (15)	6.45 (3.47, 12.01)	2.56 (1.23, 5.33)	0.012	-6.67 (-10.00, -3.34)	-3.79 (-7.32, -0.25)	0.036
Lymph node metastasis							
No(reference)	659 (72)						
Yes	54 (27)	8.71 (5.54, 13.71)	2.67 (1.62, 4.42)	<0.001	-7.98 (-10.47, -5.49)	-4.35 (-7.14, -1.55)	0.002
Radiation							
No(reference)	532 (37)						
Yes	181 (62)	9.59 (6.26, 14.68)	1.62 (0.89, 2.95)	0.114	-5.94 (-7.24, -4.63)	-1.34 (-3.29, 0.62)	0.180

Abbreviations: *HR*: hazard ratio; RMST: restricted mean survival time; CI: confidence interval; FIGO: International Federation of Gynecology and Obstetrics; GLM: generalized linear model.

§ The intercepts for each variable are 22.68, 17.05, 18.27 and 19.17, respectively.

¶ Adjusted for the age at diagnosis, FIGO stage, lymph node metastasis and radiation.

* *P* values were obtained from the Wald test and adjusted for the age at diagnosis, FIGO stage, lymph node metastasis and radiation.

† Grambsch-Therneau proportional hazards test, *P*<0.05 for univariate analysis.

‡ Grambsch-Therneau proportional hazards test, *P*<0.05 adjusted for age at diagnosis, FIGO stage, lymph node metastasis and radiation.

eTable 5. Two models for cervical-cancer-specific survival

Variable	Baseline Characteristics No. of Patients (Deaths)	Cox Proportional Hazard Model			RMST Based on Pseudo-values (GLM)		
		Univariable <i>HR</i> (95% CI)	Multivariable <i>HR</i> (95% CI) ¶	<i>P</i> *	Univariable RMST (95% CI) §	Multivariable RMST (95% CI) ¶	<i>P</i> *
Age at diagnosis (per 10 years)	713(75)	- 1.49 (1.31, 1.71)	- 1.00 (0.84, 1.18)	0.984	§ -0.75 (-1.06, -0.43)	18.41 (16.59, 20.24) -0.02 (-0.35, 0.31)	<0.001 0.911
FIGO Stage							
In situ	375 (4)	0.07 (0.02, 0.20)†	0.09 (0.03, 0.26)‡	<0.001	2.33 (1.49, 3.16)	1.72 (0.82, 2.61)	<0.001
I (reference)	205 (23)						
II	101 (34)	3.82 (2.25, 6.50)†	2.63 (1.38, 4.98)	0.003	-4.27 (-6.16, -2.38)	-3.20 (-5.44, -0.95)	0.005
III	32 (14)	7.37 (3.77, 14.41)	4.32 (1.93, 9.67)	<0.001	-6.67 (-10.01, -3.34)	-4.75 (-8.32, -1.18)	0.009
Lymph node metastasis							
No(reference)	659 (51)						
Yes	54 (24)	9.45 (5.77, 15.47)	2.22 (1.29, 3.81)	0.004	-7.45 (-10.00, -4.90)	-3.82 (-6.69, -0.95)	0.009
Radiation							
No(reference)	532 (21)						
Yes	181 (54)	12.09 (7.23, 20.24)	1.61 (0.82, 3.19)	0.168	-5.37 (-6.66, -4.09)	-0.91 (-2.76, 0.94)	0.336

Abbreviations: *HR*: hazard ratio; RMST: restricted mean survival time; CI: confidence interval; FIGO: International Federation of Gynecology and Obstetrics; GLM: generalized linear model.

§ The intercepts for each variable are 21.50, 17.72, 18.61 and 19.41, respectively.

¶ Adjusted for the age at diagnosis, FIGO stage, lymph node metastasis and radiation.

* *P* values were obtained from the Wald test and adjusted for the age at diagnosis, FIGO stage, lymph node metastasis and radiation.

† Grambsch-Therneau proportional hazards test, *P*<0.05 for univariate analysis.

‡ Grambsch-Therneau proportional hazards test, *P*<0.05 adjusted for age at diagnosis, FIGO stage, lymph node metastasis and radiation.

eTable 6. The dynamic prediction used the PBLs model (*w*=5 years) for all-cancer-specific survival

	Variable	Time function [‡]	Coefficient	SE	<i>P</i>
$\beta_{LM}(s)$	Age at diagnosis (per 10 years)	1	0.03	0.11	0.822
		<i>s</i> /20	1.09	0.29	<0.001
	FIGO Stage				
	In situ	1	-3.07	0.78	<0.001
		<i>s</i> /20	5.78	1.888	0.002
	I (reference)				
	II	1	0.74	0.42	0.073
		<i>s</i> /20	-0.52	1.44	0.717
	III	1	1.44	0.47	0.002
		<i>s</i> /20	-6.56	2.85	0.021
$\theta(s)$	Lymph node metastasis				
	No(reference)				
	Yes	1	0.77	0.29	0.009
	Radiation				
	No(reference)				
	Yes	1	0.51	0.36	0.162
		<i>s</i> /20	-4.83	1.72	0.005
		(<i>s</i> /20) ²	-3.84	1.33	0.004

Abbreviations: PBLs: proportional baselines landmark super; SE: standard error; FIGO: International Federation of Gynecology and Obstetrics.

ϕ : Time function: $\beta_{LM}(s) = \beta_0 + \beta_1(s / 20) + \beta_2(s / 20)^2$

$\theta(s) = \theta_1(s / 20) + \theta_2(s / 20)^2$

eTable 7. The dynamic prediction used the PBLS model ($w=5$ years) for cervical-cancer-specific survival

	Variable	Time function [§]	Coefficient	SE	P
$\beta_{LM}(s)$	Age at diagnosis (per 10 years)	1	-0.22	0.12	0.076
		$s/20$	1.58	0.62	0.011
	FIGO Stage				
	In situ	1	-3.74	1.07	<0.001
		$s/20$	0.25	7.27	0.973
		$(s/20)^2$	24.95	11.63	0.032
	I (reference)				
	II	1	1.29	0.41	0.002
		$s/20$	-4.86	4.33	0.262
		$(s/20)^2$	22.22	9.97	0.026
	III	1	1.86	0.52	<0.001
		$s/20$	-2.78	7.49	0.711
		$(s/20)^2$	-7.17	18.49	0.698
$\theta(s)$	Lymph node metastasis				
	No(reference)				
	Yes	1	0.56	0.34	0.098
	Radiation				
	No(reference)				
	Yes	1	0.50	0.44	0.254
		$s/20$	-1.78	4.73	0.706
		$(s/20)^2$	-27.86	9.40	0.003

Abbreviations: PBLS: proportional baselines landmark super; SE: standard error; FIGO: International Federation of Gynecology and Obstetrics.

ϕ : Time function: $\beta_{LM}(s) = \beta_0 + \beta_1(s/20) + \beta_2(s/20)^2$

$\theta(s) = \theta_1(s/20) + \theta_2(s/20)^2$

eFile 1: Other models when handling non-PHs

In addition to the RMST model mentioned in the text, there are also other models that are commonly used when the PHs assumption fails. We will discuss the complementary roles of these models in fully assessing the results of time-to-event analyses. To focus on ideas, let T denote the survival time of interest with survival function $S(t)$, and let Z denote a covariate vector that does not depend on time.

Accelerated failure time (AFT) model

This model simply assumes that

$$\log(T) = -Z^T \beta + \varepsilon$$

where β is a set of regression parameters and ε is a residual term with un-specified distribution. There are several types of AFT models; we used the Weibull model, log-normal model, and log-logistic model for the baseline hazard function. The results are shown in eTable 2. The log-logistic model was selected as the final model because it produced the smallest AIC value (1369.838).

The results showed that radiation only did not have a significant effect on survival. The regression parameter β can be used to estimate time ratios (e^β) associated with the covariate. For example, a time ratio of 2.104($=e^{0.744}$) would signify that the time until an event occurs is 2.104 times longer in the FIGO stage in situ group than in the FIGO stage I group with everything else being equal.

However, note that the distribution of survival time must be specified in advance. Due to the special distribution of the survival time in this study (eFigure 5), the results may not be accurate.

Transformation model

Because the PHs assumption may be violated in practice, non-PHs models need to be considered. Under the proportional odds model¹, rather than staying constant, the HR between two subjects with different covariate values within same stratum converges to unity as time increases. Both the Cox PHs and proportional odds models

belong to the class of linear transformation models², which relate an unknown transformation of T linearly to Z :

$$H(T) = -Z^T \beta + \varepsilon$$

where the $H(\cdot)$ is an unspecified monotone function and ε is a known error distribution. The hazard function for error term ε is defined as follows: $h(x) = \exp(x)/(1+r \times \exp(x))$, where the parameter r must be a non-negative value and can be changed for different models.

We chose a set of r values ($r=0, 1, 1.5$, and 2) and the results are shown in eTable 3. Special cases are the Cox PHs model when $r=0$ (ε has an extreme value distribution with distribution function $F(t) = \exp(-\exp(t))$) and the proportional odds model when $r=1$ (ε is a standard logistic distribution). However, for other choices of r the β is more difficult to interpret because it refers to the scale given by the unknown h^3 .

1. Bennett S. Analysis of survival data by the proportional odds model. *Stat Med* 1983; 2(2):273–277. doi: 10.1002/sim.4780020223.
2. Klein JP, van Houwelingen HC, Ibrahim JG, Scheike TH. Handbook of Survival Analysis, chapter 4. Transformation Models. Boca Raton: Chapman & Hall/CRC Press; 2014, p.77-92.
3. Martinussen T, Scheike TH. Dynamic Regression Models for Survival Data, chapter 8. Accelerated failure time and transformation models. Springer, New York; 2006, p.293-311.

eFile 2: Cause-specific analysis

The primary endpoint in the present study was all-cause mortality (i.e., death was considered an event regardless of its cause). However, since there may also be an interest in cervical cancer outcomes per se, in this study, the cause-specific analysis was performed to model cervical cancer mortality by treating deaths from cause of cervical cancer as events and other causes of death as censored. However, note that if the cancer metastasizes, there are instances where the death certificate incorrectly lists the underlying cause of death as the metastatic site. In this case, we considered two definitions for cause-specific analysis: one is by using all cancers as the endpoint; the another is a more sophisticated algorithms for defining endpoints based on common sites of metastases for cervical cancer. When we wish to distinguish between these two definitions, we call the former all-cancer-specific analysis and the latter cervical-cancer-specific analysis.

Similarly, the univariable and multivariable Cox PHs models were used to estimate the *HRs* and 95% confidence intervals (CIs) of the covariates. Compared to all-cause and all-cancer-specific mortality, age at diagnosis was not significantly related to the cervical-cancer-specific mortality (eTable 5, $P=0.984$). According to the Grambsch-Therneau test, we found that the FIGO stage also violated the PHs assumption. Therefore, RMST ($\tau = 20$) was used as another appropriate outcome measure in our analysis and the PBLs model was used to obtain the 5-year DDR after an arbitrary time point s during follow-up.

Although the results of the RMST regression model were consistent with those of the Cox model (eTables 4-5), the RMST regression model does not depend on the PHs assumption and has intuitive clinical interpretation as the difference between areas under the survival curves. In contrast, the PBLs model showed that the age of diagnosis and FIGO stage exhibited changing effects on the $HR^5(s)$ with each successive prediction time point (s), while the radiation was not statistically significant (eTables 6-7, eFigures 8-9).