Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplemental Appendix: Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer

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Definitions for inclusion and exclusion criteria

Histology

The histologic categories for cases included in both the patient-level analysis of the National Cancer Database (NCDB) and the interrupted time-series analysis of Surveillance, Epidemiology, and End Results (SEER) data were defined by the following *International Classification of Disease for Oncology, 3rd edition*, codes:

Squamous cell carcinoma: 8070, 8071, 8072, 8073, 8074, 8075, 8076, 8078

Adenocarcinoma: 8140, 8144, 8255, 8384, 8480, 8481, 8482

Adenosquamous carcinoma: 8560, 8570

Radical hysterectomy

For both analyses, we defined radical hysterectomy using the following site-specific surgical codes: 50, 51, 53, and 54.

Lymphadenectomy

For the patient-level analysis, we defined lymphadenectomy using the following NCDB variables:

Patient diagnosed in 2012-2013: RX_SUMM_SCOPE_REG_LN_2012 = 3, 4, 5, 6, or 7

Patient diagnosed in 2010-2011: RX_SUMM_SCOPE_REG_LN = 1-90, 96, 97, or 98

For the interrupted time-series analysis, we defined lymphadenectomy using the following SEER variables:

Patient diagnosed in 2003-2010: SURGSCOF = 3, 4, 5, 6, or 7

Patient diagnosed in 2000-2002: NUMNODES = 1-90, 96, 97, or 98

Neoadjuvant therapy

For the patient-level analysis, we defined neoadjuvant therapy as chemotherapy or radiotherapy initiated before surgery. Radiotherapy and chemotherapy variable were not available in the SEER database.

Stage

For the patient-level analysis, we defined stage using the NCDB American Joint Committee on Cancer (AJCC) clinical stage variable (TNM_CLIN_STAGE_GROUP) when it was known (TNM_CLIN_STAGE_GROUP ≠ OC, 88, or 99). Patients were included when TNM_CLIN_STAGE_GROUP = 1A2 or 1B1. If AJCC clinical stage was unknown but FIGO stage was known (CS_SITESPECIFIC_FACTOR_1 ≠ 888, 987, 988, 999), stage was defined using CS_SITESPECIFIC_FACTOR_1, and patients with CS_SITESPECIFIC_FACTOR_1 = 112 or 121 were included. When both clinical and FIGO stage variables were unknown, stage was defined as TNM_PATH_STAGE_GROUP, and patients were included if TNM_PATH_STAGE_GROUP = 1A2 or 1B1. Stage definition was based on AJCC clinical stage in 81.1% of patients, Collaborative Stage Site-Specific Factor 1 variable in 14.6%, and AJCC pathologic stage in 4.3%.

Clinical stage is not defined in the SEER database, and TNM variables in the SEER database defined on the basis of information from pathology reports whenever such information is available. As such, we could not replicate the clinical stage definition employed in the patient-level analysis of the NCDB in the interrupted time-series analysis of SEER data. Using pathologic data to define stage would exclude patients who often undergo surgical management, such as those with subclinical spread to parametria or lymph nodes, who were of interest in this study. Therefore, to ensure a patient population who were likely to have undergone surgery for clinically early-stage cervical cancer throughout the study period, we included all patients with summary stage 2000 (SUMM2K) values of localized or regional disease who underwent radical hysterectomy. While this population may have

included patients who underwent radical hysterectomy for advanced disease, we believe that this is unlikely to be problematic for three reasons: 1) patients with clinically advanced disease rarely undergo radical hysterectomy, 2) inclusion of such patients is unlikely to bias the time series analysis unless the proportion of patients undergoing radical hysterectomy for advanced stage disease changes over time, and 3) given increased use of preoperative PET during this period, we expect more patients with advanced disease to be detected preoperatively and triaged to treatment with primary radiation, a trend which would tend to demonstrate improved survival over time among patients undergoing surgery.

Detailed methods: patient-level analysis of NCDB

National Cancer Database

The NCDB is a joint quality improvement project of the American College of Surgeons and the American Cancer Society.[1] As of 2016, the NCDB included more than 34 million records of patients with cancer. Data are submitted by institutions' cancer registrars and include patients' clinical and demographic characteristics, histopathologic details, staging data, cancer-directed therapy, perioperative outcomes, and overall survival.

Commission on Cancer–accredited hospitals must report on all patients who received some element of their cancer care (treatment or diagnosis) at the facility.[1] These facilities represent 30% of all US hospitals but capture approximately 70% of all patients with newly diagnosed cancer in the US.[2] While there is variation in the case coverage in the NCDB by cancer site, 78% of cervical cancer cases in the US are included in the database.[3] Importantly, NCDB coverage varies by age (less for older patients) and state. Furthermore, Commission on Cancer–accredited hospitals are larger, more frequently urban, and have more cancer-related services, higher surgical volume than hospitals without accreditation.[2]

Assumption of proportional hazards

In the main inverse probability of treatment–weighted Cox model, the proportionality of hazards was investigated by examining correlation between Schoenfeld residuals and time since diagnosis. Linear, log-transformed, and squared functions of time were considered. No evidence of non-zero slope was found ($p>0.05$ for all tests).

Additional sensitivity analyses

To ensure that our main analysis was not sensitive to stage definition, we repeated the analysis, including only patients who had AJCC clinical stage. We found that the estimated hazard ratio (HR) for minimally invasive surgery was similar to that found in the main analysis (HR=1.68; 95% CI=1.22-2.32). In other sensitivity analysis, we excluded patients who underwent conversions from minimally invasive to open surgery. We found that this exclusion did not alter out findings (HR=1.68; 95% CI=1.25-2.26).

Multiple imputations

Because all variables with missing values were categorical, we assigned an "unknown" category to missing variables in the main analysis. However, because using missing data indicators can generate biased results in observational studies, we repeated the main analysis using a multiple imputations strategy.[4] Variables that were unknown in at least one patient included race, insurance, income, education, urban/rural location, grade, and tumor size. We performed multiple imputation using chained equations with M=100 imputations. The discriminant function method was used to impute the categorical variables. Year of diagnosis, age, comorbidity, facility type and location, stage, and histology were used as covariate effects. Then we repeated the inverse probability of treatment–weighted

analysis by refitting the weighted Cox proportional hazards model in each imputed dataset and pooling the results.

Multivariable regression analysis

We used a Cox proportional hazards regression model to examine the effect of surgery type (minimally invasive vs. open) on overall survival. We used data with missing values for categorical variables classified as "Unknown" and performed model selection using the Hosmer-Lemeshow purposeful model selection approach.[5] The final selected model included age, race, insurance type, tumor grade, lymph node status, tumor size, and adjuvant treatment as covariates. After model selection, multiple imputations was undertaken as described above. Next, we fitted a Cox regression model using the imputed data and pooled the results to obtain an estimate of the HR for surgery type. We then re-fitted the selected multivariable Cox model in each imputed data set and pooled the estimates to obtain the HR adjusted for covariates.

Propensity score matching

Propensity score matching was performed for each of M=100 imputed datasets using a one-to-one nearest-neighbor algorithm with a caliper size of 0.5. Covariate balance was evaluated in each matched set using standardized mean. Matched sets were found to have good covariate balance (standardized mean difference <0.10 for all variables). We estimated the relative hazard of minimally invasive surgery in each matched set with a univariable Cox model and pooled these estimates. Additionally, to control for any residual covariate imbalance, we estimated the relative hazard in the propensity score–matched data using the multivariable Cox model that included the covariates from the selected multivariable regression analysis described above.

Detailed methods: interrupted time-series analysis

Cohort selection

In the interrupted time-series analysis, we included women who underwent radical hysterectomy for squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix between 2000 and 2010 in the SEER 18 registry research data file. We excluded patients without histological confirmation and those who did not undergo a lymphadenectomy. Because SEER lacks variables for AJCC clinical and FIGO stage, we could not replicate the stage criteria used in the main patient-level analysis. We included patients categorized as having localized and regional disease by SEER summary stage.

Outcome

We use 4-year relative survival as the primary outcome. We chose relative survival as the primary endpoint to adjust for trends in non-cancer-related mortality. Relative survival measures the effect of cancer on mortality by comparing the overall survival of a cohort of cancer patient with that of a cohort of unaffected individuals of the same age and race. This approach is preferred by some investigators to cancer-specific survival because it does not rely on accurate death attribution. We calculated 4-year relative survival for patients diagnosed in each year, using the default Ederer II method in SEER*Stat 8.3.5 software.[6] Standard errors and 95% confidence intervals for relative survival were calculated using the same software and based on Ederer's modification of Greenwood's method.[7]

Model specifications

We considered 2006 to be the year that minimally invasive surgical techniques were first adopted for radical hysterectomy based on published data (Table S2).[8] Because minimally invasive surgery was adopted gradually, we hypothesized that if the practice affected 4-year relative survival, the effect

would also appear gradually. Therefore, we specified an impact model that evaluated whether adoption of minimally invasive surgery resulted in a change in temporal trends. Log-transformed 4-year relative survival was regressed on year of diagnosis, which was modeled as a linear spline with a knot at 2006.[9,10] To account for heteroscedasticity of errors, we fit a weighted least squares model. The model took the following form:

$$\text{Ln}(\textit{Relative Survival}) = \beta_0 + \beta_1(\textit{Year}) + \beta_2(\textit{Year}\text{-}2006)\textit{Year}_{2006}$$

where Ln(*Relative Survival*) is the natural logarithm of the 4-year relative survival in a given year, *Year* is the year of diagnosis, $\textit{Year}_{2006}$ is a dummy variable which is 0 for *Year* ≤ 2006 and 1 for *Year* >2006, β_0 is an intercept term, β_1 is a regression coefficient estimating the annual percentage change in relative survival from 2000-2006, and β_2 is a regression coefficient estimating the difference in annual percent change between 2000-2006 and 2006-2010. Coefficients from this model were used to extrapolate expected relative survival estimates for 2006-2010 based on 2000-2010 trends (Figure 4, main article). We estimated the annual percentage change in 4-year relative survival for 2006-2010 as β_3 in the following alternative parameterization of the same model:

$$\text{Ln(Relative Survival)} = \beta_0 + \beta_1[\text{Year- (Year-2006)Year}_{2006}] + \beta_3(\text{Year-2006})\text{Year}_{2006}$$

To assess for serial autocorrelation, we plotted correlograms and performed the Breusch-Godfrey test for autocorrelation (p=0.21).

Sensitivity analyses

To ensure that use of SEER summary stage was not an important driver of our findings, we repeated the analysis including patients with all stages. We found a change of trend similar to that observed in the main analysis (annual percentage $\text{change}_{2006\text{-}2010}$=0.8%, 95% CI=0.2%-1.4%; $p_{\text{change-of-trend}}$=0.03). We also repeated the interrupted time-series analysis using 4-year cancer-specific survival as the primary

outcome (Table S2). We found that use of this alternative measure of net survival did not change our findings (Figure S1).

Table S1: Characteristics of patients undergoing radical hysterectomy for stage IA2 or IB1 cervical carcinoma by surgical approach, before and after inverse probability of treatment weighting

	Crude cohort					Inverse probability of treatment-weighted cohort				
	Open (N= 1,236)		Minimally invasive (N= 1,225)			Open (N= 1,340)		Minimally invasive (N= 1,334)		
Characteristic	N[*]	(%)	N	(%)	P[†]	N	(%)	N	(%)	P[‡]
Year of diagnosis					<0.001					1.00
2010	408	33.0	211	17.2		338[§]	25.2	336	25.2	
2011	310	25.1	317	25.9		336	25.1	334	25.1	
2012	268	21.7	356	29.1		344	25.7	342	25.6	
2013	250	20.2	341	27.8		323	24.1	322	24.1	
Age, years					0.13					1.00
<40	474	38.3	432	35.3		500	37.3	501	37.6	
40-49	364	29.4	399	32.6		406	30.3	401	30.1	
50-59	243	19.7	220	18.0		255	19.0	250	18.8	
60-69	121	9.8	122	10.0		134	10.0	134	10.0	
70-79	28	2.3	43	3.5		38	2.8	39	2.9	
≥80	*	0.5	*	0.7		*	0.6	*	0.6	
Race/ethnicity					<0.001					1.00
White	789	63.8	853	69.6		899	67.1	896	67.2	
Black	160	12.9	95	7.8		140	10.4	140	10.5	
Hispanic	196	15.9	169	13.8		196	14.6	191	14.3	
Asian	71	5.7	82	6.7		83	6.2	84	6.3	
Other/unknown	20	1.6	26	2.1		23	1.7	23	1.7	
Insurance type					<0.001					1.00
Private	662	53.6	784	64.0		788	58.8	784	58.8	
Medicaid/Other government	311	25.2	226	18.4		287	21.4	282	21.2	
Medicare	137	11.1	122	10.0		143	10.7	142	10.6	
Uninsured	108	8.7	74	6.0		102	7.6	105	7.9	
Unknown	18	1.5	19	1.6		20	1.5	21	1.6	
Income quartile					<0.001					1.00
Lowest	267	21.6	187	15.3		251	18.7	252	18.9	
Second	313	25.3	302	24.7		337	25.1	335	25.1	
Third	337	27.3	341	27.8		370	27.6	363	27.2	
Highest	317	25.6	393	32.1		380	28.4	381	28.6	
Unknown	*	0.2	*	0.2		*	0.1	*	0.1	
Education quartile					<0.001					1.00
Lowest	307	24.8	226	18.4		292	21.8	288	21.6	
Second	341	27.6	316	25.8		363	27.1	364	27.3	
Third	378	30.6	388	31.7		416	31.0	412	30.9	
Highest	209	16.9	294	24.0		268	20.0	268	20.1	
Unknown	*	0.1	*	0.1		*	0.1	*	0.1	
Urban status					0.36					0.99
Metropolitan	1,024	82.8	1,000	81.6		1,099	82.0	1,087	81.5	
Metropolitan-adjacent	119	9.6	109	8.9		128	9.5	132	9.9	
Rural	68	5.5	84	6.9		84	6.2	84	6.3	
Unknown	25	2.0	32	2.6		29	2.2	30	2.3	

Comorbidities					0.88					0.95
0	1,078	87.2	1,066	87.0		1,162	86.7	1,158	86.8	
≥1	158	12.8	159	13.0		178	13.3	176	13.2	
Facility type					<0.001					0.94
Nonacademic	544	44.0	654	53.4		657	49.0	656	49.2	
Academic	692	56.0	571	46.6		683	51.0	678	50.8	
Region					0.001					1.00
Northeast	183	14.8	223	18.2		215	16.0	214	16.0	
Midwest	322	26.1	241	19.7		313	23.4	315	23.6	
South	476	38.5	490	40.0		528	39.4	526	39.4	
West	255	20.6	271	22.1		284	21.2	279	20.9	
Stage					0.04					0.94
IA2	127	10.3	159	13.0		157	11.7	155	11.6	
IB1	1,109	89.7	1,066	87.0		1,183	88.3	1,179	88.4	
Histologic type					0.01					1.00
Squamous cell	789	63.8	709	57.9		820	61.2	815	61.1	
Adenocarcinoma	381	30.8	452	36.9		450	33.6	450	33.7	
Adenosquamous	66	5.3	64	5.2		70	5.2	69	5.2	
Grade					0.001					1.00
1	155	12.5	219	17.9		200	14.9	201	15.0	
2	582	47.1	554	45.2		623	46.5	621	46.5	
3	391	31.6	338	27.6		396	29.6	394	29.5	
Unknown	108	8.7	114	9.3		121	9.0	118	8.9	
Tumor size, cm					0.005					0.99
<2	459	37.1	534	43.6		543	40.5	541	40.6	
≥2	615	49.8	543	44.3		626	46.7	624	46.8	
Unknown	162	13.1	148	12.1		171	12.8	169	12.6	

[*] Counts of 10 or fewer are suppressed to comply with National Cancer Database privacy requirements.

[†] P values calculated from χ^2 test

[‡] P values calculated from inverse probability of treatment–weighted logistic regression models

[§] Due to rounding error, in the weighted cohort counts may not sum to expected totals, and percentages may not be equal to ratios of counts

Table S2: Frequency of minimally invasive surgery and 4-year relative, and cancer-specific survival among women undergoing radical hysterectomy for localized and regional stage cervical cancer, 2000-2010

Year of diagnosis	N[†]	Percentage with minimally invasive surgery[‡]	Four-year cancer-specific survival, % (95% CI)	Four-year relative survival, % (95% CI)
2000	613	0	91.3 (88.7-93.3)	92.0 (89.2-94.1)
2001	634	0	91.7 (89.3-93.7)	92.3 (89.7-94.3)
2002	579	0	92.2 (89.7-94.2)	92.5 (89.7-94.6)
2003	526	0	92.9 (90.3-94.8)	92.9 (90.0-95.0)
2004	532	0	92.0 (89.2-94.0)	91.6 (88.6-93.9)
2005	546	0	93.7 (91.3-95.5)	94.1 (91.3-95.9)
2006	522	1.8	93.8 (91.3-95.6)	93.7 (90.8-95.6)
2007	535	9.5	93.0 (90.4-94.9)	93.4 (90.6-95.4)
2008	499	18.8	92.0 (89.1-94.1)	90.7 (87.5-93.2)
2009	512	25.9	93.6 (91.0-95.5)	91.6 (88.4-93.9)
2010	493	31.1	90.5 (87.4-92.9)	90.6 (87.2-93.1)

[†]N is for patients in the relative survival analysis. In the cancer-specific survival analysis, 24/5991 patients were excluded for unknown cause of death.

[‡]Proportion of patients undergoing minimally invasive surgery obtained from a previous study by Wright et al.[10]

Figure S1

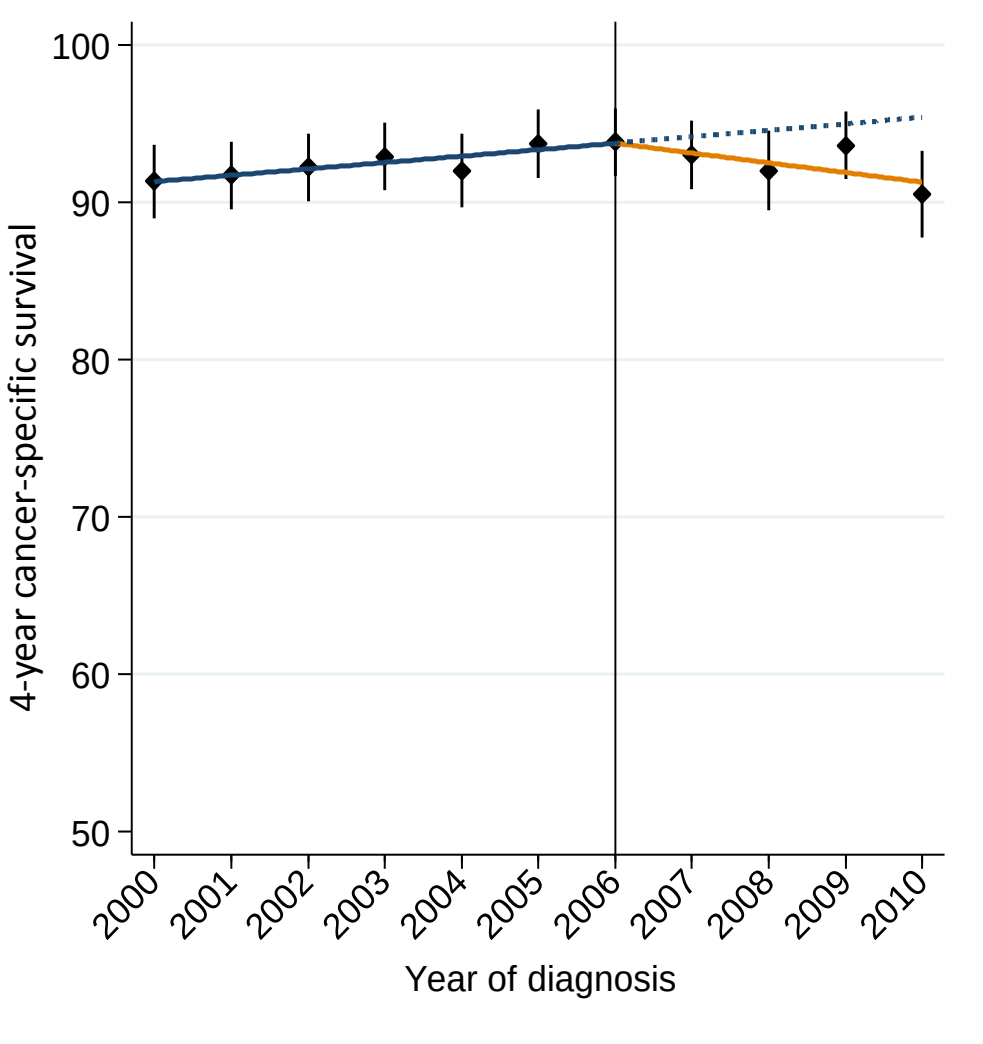

Figure S1. Interrupted time-series evaluating the effect of adoption of minimally invasive radical hysterectomy on 4-year cancer-specific survival. The 4-year cancer-specific survival among women who underwent radical hysterectomy for cervical cancer (diamonds) and 95% confidence intervals (CIs) (whiskers) are plotted against year of diagnosis. Adoption of minimally invasive radical hysterectomy in 2006 was associated with a significant change in the temporal trend (p=0.01) and declining 4-year cancer-specific survival after 2006 (annual percent change, 0.7%; 95% CI; 0.2% to 1.2%).

Author roles and statistical software

This study was designed by Drs. Chen, del Carmen, Keating, Kocherginsky, Margul, Melamed, Rauh-Hain, Seagle, Shahabi, and Wright; the data were acquired by Drs. Melamed, Rauh-Hain, Shahabi, and Wright and analyzed by Drs. Chen, Kocherginsky, Margul, Melamed, and Rauh-Hain and Ms. Yang. All authors contributed to the interpretation of the data, vouch for the data and analysis, contributed to the writing of the manuscript, and agreed to publish this study. Drs. Melamed, Margul, and Rauh-Hain authored first drafts of manuscripts that were combined. Statistical analyses were performed using SAS version 9.4, R version 3.4.2, or STATA version 14.2.

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