GYNECOLOGY

Impact of surgical approach on oncologic outcomes in women undergoing radical hysterectomy for cervical cancer

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BACKGROUND: Recent studies demonstrating shorter survival among cervical cancer patients undergoing minimally invasive versus open radical hysterectomy could not account for surgeon volume and require confirmation in other jurisdictions with larger sample sizes, longer follow-up, and data on disease recurrence.

OBJECTIVE: To determine if surgical approach is associated with oncologic outcomes in cervical cancer patients undergoing minimally invasive or open radical hysterectomy, while accounting for mechanistic factors including surgeon volume.

STUDY DESIGN: We performed a population-based retrospective cohort study of cervical cancer patients undergoing primary radical hysterectomy by a gynecologic oncologist from 2006 to 2017 in Ontario, Canada. A multivariable marginal Cox proportional hazards model and cause-specific hazards model were used to evaluate the association of surgical approach with all-cause death and recurrence respectively, clustering at the surgeon level. We tested for interactions between surgical approach and either pathologic stage or surgeon volume.

RESULTS: We identified 958 patients (minimally invasive 475; open 483) with mean age 45.9 and a median follow-up of 6 years. Of minimally invasive procedures, 89.6% were performed laparoscopically and 10.4% robotically. The unadjusted 5-year cumulative incidences of all-cause death (minimally invasive 12.5%; open 5.4%), cervical cancer death (minimally invasive 9.3%; open 3.3%), and recurrence (minimally invasive 16.2%; open 8.4%) were significantly increased for minimally invasive radical hysterectomy in patients with stage IB disease, but not the cohort overall. After adjusting for patient factors and surgeon volume, minimally invasive radical hysterectomy was associated with increased rates of death (hazard ratio [HR], 2.20; 95% confidence interval [CI], 1.15–4.19) and recurrence (HR, 1.97; 95% CI, 1.10–3.50) compared to open radical hysterectomy in patients with stage IB disease (n = 534), but not IA disease (n = 244; HR, 0.73; 95% CI, 0.13–4.01; HR, 0.34; 95% CI, 0.10–1.10).

CONCLUSION: Minimally invasive radical hysterectomy is associated with increased rates of death and recurrence in patients with stage IB cervical cancer even after controlling for surgeon volume; open radical hysterectomy should be the recommended approach in this population. Although there may be a subset of patients with microscopic early-stage disease for whom minimally invasive radical hysterectomy remains safe, additional studies are required.

Key words: cervical cancer, hysterectomy, laparoscopy, laparotomy, minimally invasive surgical procedures, robotic surgical procedures, uterine cervical neoplasms

Women with early-stage cervical cancer are most frequently treated with radical hysterectomy by an open (OH) or minimally invasive approach (MH).[1,2] Retrospective cohort studies have repeatedly demonstrated reduced perioperative morbidity, shorter hospital stays, and no significant survival differences for patients undergoing MH versus OH.[3–6] Although many such studies were limited by inadequate power and follow-up for survival outcomes or residual confounding,[7–13] strong evidence for the safety of minimally invasive surgery in endometrial cancer[14,15] fueled widespread adoption of MH for cervical cancer over the last decade.[16–18]

Standard practice favoring MH has been questioned following the publication of the Laparoscopic Approach to Cervical Cancer (LACC) trial, which showed that MH was associated with a 4-fold higher rate of recurrence and 6-fold higher rate of all-cause death compared to OH in women with stage IA1–IB1 cervical cancer.[19] Well-designed epidemiologic studies using the Surveillance, Epidemiology, and End Results (SEER) database and National Cancer Database (NCDB) reinforced the association between MH and shorter overall survival.[20]

Because trials in other cancers had previously documented noninferior oncologic outcomes with minimally invasive surgery,[15,21–23] the LACC and NCDB / SEER reports were unexpected and doubted as a result.[24–26] Studies from other jurisdictions, with large sample sizes, longer follow-up, uniform surgical practice, data on recurrence, and the ability to assess possible contributing factors such as surgeon volume, are urgently needed to inform practice. To address these gaps in the literature, we examined the survival and recurrence outcomes of a population-based cohort of early-stage cervical cancer patients undergoing MH versus OH in Ontario, Canada, while accounting for mechanistic factors including surgeon volume.

Methods

Study design and population

We performed a population-based retrospective cohort study using linked

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AJOG at a Glance

Why was this study conducted?

To determine if surgical approach is associated with oncologic outcomes in cervical cancer patients undergoing minimally invasive vs open radical hysterectomy, while accounting for surgeon volume.

Key findings

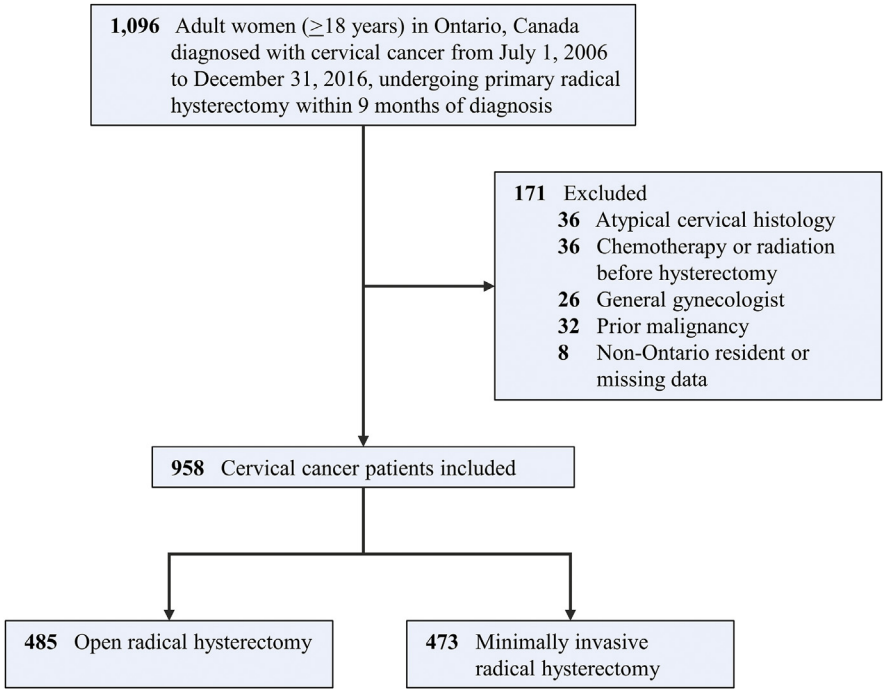
Minimally invasive radical hysterectomy was associated with a 2-fold higher rate of all-cause death and recurrence compared to open radical hysterectomy in patients with stage IB disease, but not IA or II+ disease. This relationship was robust to various methods of controlling for surgeon volume.

What does this add to what is known?

While prior work has been criticized for including surgeons inexperienced in minimally invasive radical hysterectomy, our findings suggest that the harm associated with this approach may be independent of surgeon volume. Given ongoing uncertainty in the field, our population-based study using high-quality databases provides needed real-world confirmation of the Laparoscopic Approach to Cervical Cancer trial.

administrative databases held at ICES, a nonprofit research institute authorized to collect and use health data on all Ontario residents for the purposes of health system evaluation.[27,28] The Research Ethics Board at Sunnybrook Health Sciences Centre confirmed this project was exempt from review under section 45 of Ontario's Personal Health Information Protection Act.

FIGURE 1
Flow diagram of included patients



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The study included all adult women (≥18 years) in Ontario, Canada, diagnosed with cervical cancer from July 1, 2006 to December 31, 2016, who underwent primary radical hysterectomy within 9 months of diagnosis. Patients were identified from the Ontario Cancer Registry (OCR), which contains records for all incident cancers in the province.[29] We excluded patients who (1) were non-Ontario residents; (2) had atypical histology (Appendix: Supplementary Table 1); (3) had radiation/chemotherapy after diagnosis but before hysterectomy; (4) were not treated by a gynecologic oncologist; (5) had a prior malignancy; or (6) had missing data (Supplementary Methods). Patients were followed from the index surgery to March 31, 2018.

Exposure assessment

Patients who underwent MH and OH were identified using procedure codes from the Canadian Institute of Health Information (CIHI) Discharge Abstract Database and Same Day Surgery (SDS) Database (Supplementary Table 2). Both house detailed diagnosis and procedure codes for all inpatient and outpatient hospital visits in Ontario, assigned by trained CIHI medical coders.[28] The procedure code for radical hysterectomy includes resection of the parametrium/uterosacral ligaments, resection of the upper 2−3 cm of the vagina, and pelvic lymphadenectomy. Validation of CIHI hysterectomy codes against chart abstraction has shown 100% agreement on whether hysterectomy was performed and 98% agreement on the approach.[28] We classified abdominal hysterectomies as OH, and laparoscopic/robotic hysterectomies as MH.

Outcome assessment

The primary outcome was all-cause death; secondary outcomes were cervical cancer−specific death and recurrence. We defined recurrence as health service utilization suggesting treatment of recurrent disease by surgery, radiation, chemotherapy, or palliative care ≥6 months after hysterectomy (to permit administration of adjuvant therapy). Palliative care was included to capture

recurrences without subsequent therapy. While this definition has not been validated in cervical cancer, similar Ontario-specific algorithms have been used to accurately detect recurrence in other abdominopelvic malignancies[30,31] (Supplementary Table 3).

Vital status and cause of death were ascertained from the Registered Persons Database and Ontario Registrar General-Death database, respectively. Recurrence was ascertained through procedure codes in the Discharge Abstract Database, Same Day Surgery Database, and Ontario Health Insurance Plan (OHIP) database (Supplementary Table 3). The OHIP database collects all physician billing claims for health services. Second cancers, which were competing events for recurrence, were obtained from the OCR. Data on all-cause death and recurrence were available to March 31, 2018. However, data on cause of death from the Ontario Registrar General-Death database were available to December 31, 2015 only. Cervical cancer–specific death was therefore examined as a secondary outcome.

Cohort description and covariates

Patient characteristics included age (years), year of surgery (2006–2010, 2011–2017), area of residence (rural/urban), material deprivation (low/high), comorbidities (0–5, 6–9, 10+), and obesity (body mass index >40 kg/m^2). We used Aggregated Diagnosis Groups of the Johns Hopkins ACG System[32] to account for comorbidities identified in the 2 years before the index procedure. Material deprivation is an area-level socioeconomic index derived from Canadian census data and assigned to patients based on their region of residence.[33] Obesity was ascertained with an OHIP code claimed by surgeons/anesthetists.[34]

Tumor characteristics were obtained from the OCR and included stage (IA, IB, II+, unknown) and histology (squamous cell carcinoma, adenocarcinoma, adenosquamous, carcinoma not otherwise specified). Stage in the OCR is derived from surgical pathology reports whenever such information is available, and therefore denotes American Joint Committee on Cancer (AJCC 7th edition) pathologic stage rather than FIGO clinical stage.[35] We assumed all patients in our cohort had FIGO early-stage disease based on practice standards in Ontario[36] irrespective of their AJCC pathologic stage, which was obtained from the OCR as follows: IA (stromal invasion ≤5 mm with horizontal spread ≤7 mm), IB (microscopic >7 mm or clinically visible lesion confined to cervix), II (invades beyond uterus to parametria or vagina), III (regional lymph node metastasis), or IV (para-aortic lymph node metastasis,

TABLE
Baseline characteristics and outcomes of included patients

Characteristic	OH (N=485)	MH (N=473)	Total (N=958)	STD
Patient				
Age (years)				
Mean (SD)	46.5 (11.7)	45.2 (10.6)	45.9 (11.2)	0.12
Median (IQR)	45 (38-54)	43 (38-52)	44 (38-53)	0.11
Age group, n (%)				
18–44	240 (49.5)	268 (56.7)	508 (53.0)	0.14
45–65	207 (42.7)	181 (38.3)	388 (40.5)	0.09
≥66	38 (7.8)	24 (5.1)	62 (6.5)	0.11
Year of surgery, n (%)				
2006–2010	260 (53.6)	147 (31.1)	407 (42.5)	0.47
2011–2017	225 (46.4)	326 (68.9)	551 (57.5)	
Area of residence, n (%)				
Rural	78 (16.1)	36 (7.6)	114 (11.9)	0.26
Urban	407 (83.9)	437 (92.4)	844 (88.1)	
Material deprivation, n (%)				
Low	272 (56.1)	288 (60.9)	560 (58.5)	0.10
High	213 (43.9)	185 (39.1)	398 (41.5)	
Comorbidities, n (%)				
0–5	187 (38.6)	220 (46.5)	407 (42.5)	0.16
6–9	217 (44.7)	193 (40.8)	410 (42.8)	0.08
10+	81 (16.7)	60 (12.7)	141 (14.7)	0.11
Obesity, n (%)				
Yes	30 (6.2)	18 (3.8)	48 (5.0)	0.11
No	455 (93.8)	455 (96.2)	910 (95.0)	
Tumor				
Histology, n (%)				
Squamous cell	272 (56.1)	244 (51.6)	516 (53.9)	0.09
Non–squamous cell	213 (43.9)	229 (48.4)	442 (46.1)	
Stage, n (%)				
IA	109 (22.5)	135 (28.5)	244 (25.5)	0.14
IB	278 (57.3)	256 (54.1)	534 (55.7)	0.06
II+	69 (14.2)	55 (11.6)	124 (12.9)	0.08
Unknown	29 (6.0)	27 (5.7)	56 (5.8)	0.01

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TABLE
Baseline characteristics and outcomes of included patients *(continued)*

Characteristic	OH (N=485)	MH (N=473)	Total (N=958)	STD
Surgeon				
Hysterectomy volume, median (IQR)	70 (53–93)	76 (64–91)	73 (59–91)	0.24
MH volume, median (IQR)	7 (2–18)	31 (19–41)	19 (6–34)	1.49
OH volume, median (IQR)	56 (42–74)	43 (33–54)	49 (37–64)	0.66
Technique-specific volume, n (%)				
High	318 (65.6)	365 (77.2)	683 (71.3)	0.26
Low	167 (34.4)	108 (22.8)	275 (28.7)	
Cervical cancer volume, median (IQR)	10 (6–15)	13 (8–18)	11 (7–17)	0.39
Radical	7 (3–11)	9 (5–13)	8 (4–12)	0.40
Simple	3 (1–5)	3 (2–6)	3 (2–6)	0.25
Cervical cancer volume, n (%)				
High	212 (43.7)	303 (64.1)	515 (53.8)	0.42
Low	273 (56.3)	170 (35.9)	443 (46.2)	
Treatment				
Hospital type, n (%)				
Teaching	434 (89.5)	439 (92.8)	873 (91.1)	0.12
Non-teaching	51 (10.5)	34 (7.2)	85 (8.9)	
Diagnosis to surgery (days), median (IQR)	77 (56–105)	83 (62–113)	79 (57–108)	0.20
Adjuvant radiation, n (%)				
Yes	155 (32.0)	113 (23.9)	268 (28.0)	0.18
No	330 (68.0)	360 (76.1)	690 (72.0)	
Adjuvant chemotherapy, n (%)				
Yes	115 (23.7)	74 (15.6)	189 (19.7)	0.20
No	370 (76.3)	399 (84.4)	769 (80.3)	
Any adjuvant therapy, n (%)				
Yes	161 (33.2)	117 (24.7)	278 (29.0)	0.19
No	324 (66.8)	356 (75.3)	680 (71.0)	
Surgery to adjuvant (days), median (IQR)	51 (40–63)	52 (43–62)	51 (41–63)	0.15
Outcomes				
All-cause death, n (%)				
Yes	46 (9.5)	39 (8.2)	85 (8.9)	0.04
No	439 (90.5)	434 (91.8)	873 (91.1)	
Follow-up for death (years)				
Mean (SD)	6.7 (3.2)	5.3 (2.7)	6.0 (3.0)	0.47
Median (IQR)	7 (4–10)	5 (3–7)	6 (3–8)	0.46

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peritoneal disease). We grouped stages II–IV to represent high-risk features. Intermediate-risk features (eg, tumor size, lymphovascular space invasion, stromal invasion) were not collected by the OCR.

Surgeon characteristics were technique-specific volume (low/high) and cervical cancer volume (low/high), derived from the OHIP database and ICES Physician Database, which holds information on all Ontario physicians. Technique-specific volume was the number of simple and radical hysterectomies performed by the patient's surgeon with the selected approach in the 1 year prior to the index procedure. Cervical cancer volume was the number of hysterectomies of any type (simple and radical) or approach (minimally invasive and open) performed for cervical cancer in the 2 years prior to the index procedure, in order to account for annual fluctuation of a rare disease. Compared to averaging the number of procedures performed over the study years, these definitions ensured that surgeon volume could dynamically change in response to year-to-year variation, as in previous studies.[37–39] For our primary analysis, both technique-specific and cervical cancer volume were dichotomized at the 50th percentile for the cohort across the study period, given a lack of transferrable clinical thresholds from the published literature.[40,41]

Treatment characteristics included adjuvant radiation/chemotherapy, time to adjuvant therapy (days), and hospital teaching status (ICES Institutions Database). We used CIHI/OHIP codes <6 months after radical hysterectomy to determine adjuvant therapy status (Supplementary Table 3).

Statistical analysis

Datasets were linked using unique encoded identifiers and analyzed at ICES. We compared baseline characteristics between MH and OH with χ^2 tests for categorical variables and *t* tests or Mann-Whitney *U* tests for continuous variables. The index surgery date was

TABLE
Baseline characteristics and outcomes of included patients *(continued)*

Characteristic	OH (N=485)	MH (N=473)	Total (N=958)	STD
Recurrence, n (%)				
Yes	53 (10.9)	57 (12.1)	110 (11.5)	0.04
No	432 (89.1)	416 (87.9)	848 (88.5)	
Follow-up for recurrence (years)				
Mean (SD)	6.2 (3.4)	5.0 (2.9)	5.6 (3.2)	0.37
Median (IQR)	6 (3–9)	5 (2–7)	6 (3–8)	0.35

IQR, interquartile range; *MH*, minimally invasive radical hysterectomy; *OH*, open radical hysterectomy; *SD*, standard deviation; *STD*, standardized difference.

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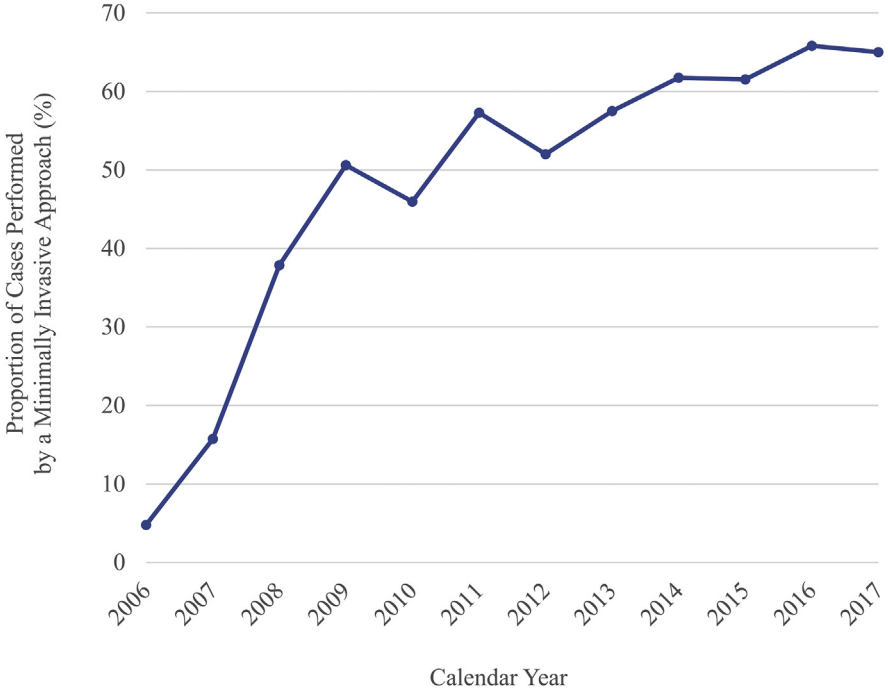
considered time 0. The cumulative incidence of death was compared between groups with the log-rank test. The cumulative incidences of cervical cancer–specific death (taking death due to other causes as a competing event) and recurrence (taking second cancer and death as competing events) were compared between groups with the Gray test.

We used a marginal Cox proportional hazards model to compare the hazards of all-cause death by approach, and censored at loss to follow-up and end of follow-up. We used a marginal cause-specific hazards model to compare the hazards of recurrence by approach, and censored at second cancer, death, loss to follow-up, and end of follow-up. We used a Fine & Gray regression model to also assess the subdistribution hazards of recurrence by approach. Since cause of death was available to 2015 only, we had insufficient events for multivariable modeling of cervical cancer–specific death. All models used robust variance estimators to account for clustering of multiple procedures within the same surgeon, and adjusted for age, year of surgery, material deprivation, comorbidities, stage, technique-specific volume, and cervical cancer volume. Covariates were selected a priori based on clinical reasoning and literature.[19–21]

Because the association between approach and outcomes may vary based on stage and surgeon volume, we tested for interactions between approach and stage, and approach and technique-specific volume. The final models for both all-cause death and recurrence included statistically significant interaction terms only. We present hazard ratios (HR) and 95% confidence intervals (CI) for each level of the interaction and for our covariates. The proportional hazards assumption was confirmed in all models by testing for an interaction between approach and time, which was not significant.

To confirm our findings for recurrence were robust, we re-ran the model excluding patients who had palliative care, had exenteration, or were censored prior to 6 months. To confirm that we had adequately controlled for surgeon volume, we (1) recategorized technique-specific volume into tertiles; (2) dichotomized technique-specific volume at the 50th percentile for each year of the study, to account for temporal trends; and (3) included total hysterectomy volume as a continuous covariate (log-transformed). To ensure any approach-related survival or recurrence differences were not confounded by a differential use of adjuvant therapy, we re-ran both models controlling for receipt of postoperative radiation or chemotherapy (yes/no). Tests were two-sided with $P < .05$ deemed significant. Standardized

FIGURE 2
Annual proportion of radical hysterectomy cases performed by a minimally invasive approach over the study period (2006–2017)



Note: Year of surgery was categorized into 2 periods (2006–2010, 2011–2017) based on changes in the annual proportion of radical hysterectomy cases performed by a minimally invasive approach (rapid increase from 2006 to 2010; gradual increase from 2011 to 2017)

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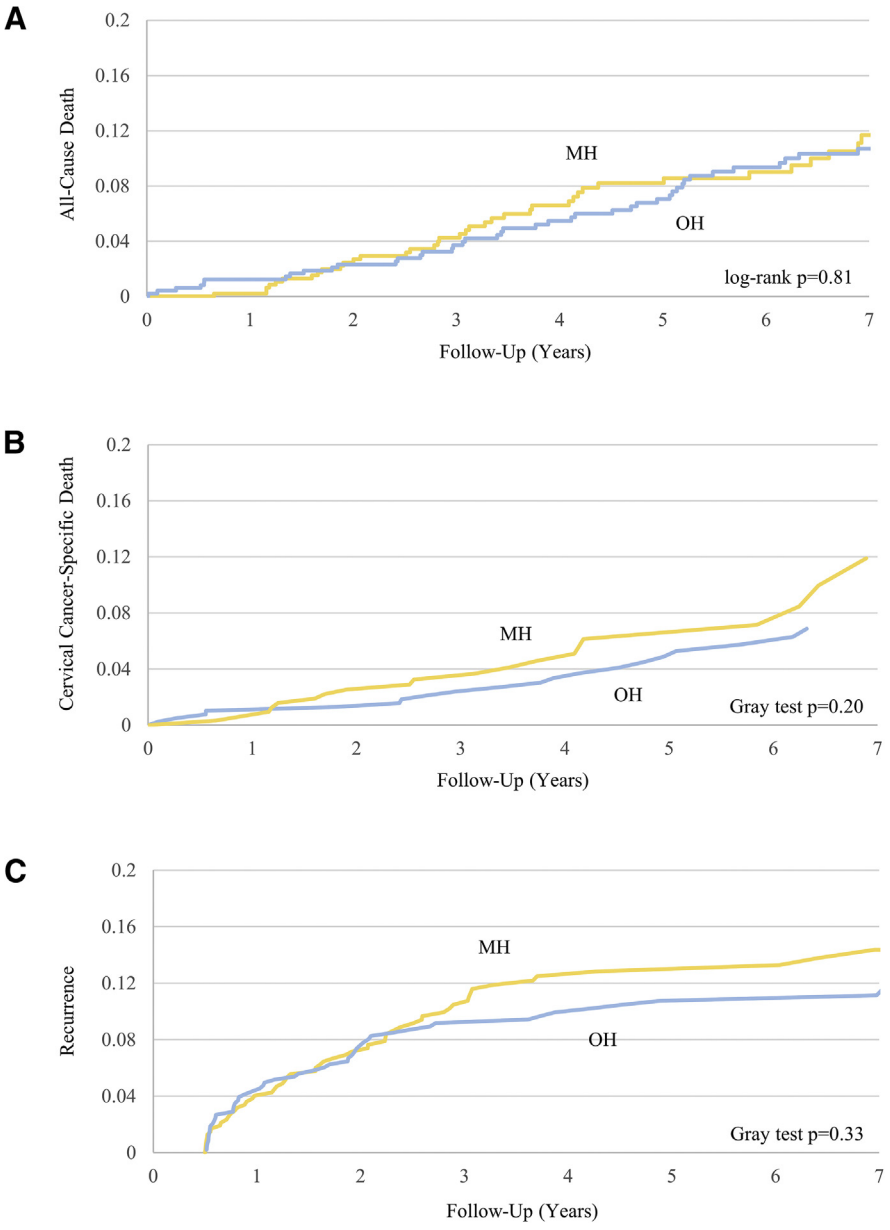
FIGURE 3
Unadjusted cumulative incidence curves for (a) all-cause death, (b) cervical cancer–specific death, and (c) recurrence for the complete cohort



Abbreviations: *MH*, minimally invasive radical hysterectomy; *OH*, open radical hysterectomy.

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differences ≥0.1 were deemed meaningful. Analyses were done in SAS v9.4 (SAS Institute Inc, Cary, NC).

Results

Study Population

There were 1096 patients diagnosed with cervical cancer from July 1, 2006 to December 31, 2016, who subsequently underwent radical hysterectomy within 9 months of diagnosis (Figure 1). After exclusions, our cohort included 958 women (Table) with mean age 45.9 years and predominantly stage IB disease (IA 244; IB 543; II+ 124; unknown 56). OH was performed in 50.6% (n = 485) and MH in 49.4% (n = 473). Of MH procedures, 10.4% were robotic (n = 49) and 89.6% were laparoscopic (n = 424). The proportion of cases performed by MH increased from 4.8% in 2006 to 65.0% in 2017 (Figure 2).

Patients receiving MH were younger with fewer comorbidities, less likely to live in rural areas, more likely to have stage IA tumors, less likely to have high-risk features (stage II+), and more likely to have had a high-volume surgeon for both technique and cervical cancer. Patients receiving MH were less likely to have adjuvant therapy (25% vs 33%; Supplementary Table 4).

Cervical cancer–specific death was available on a subcohort of 771 patients (OH 391; MIS 320) with similar baseline characteristics, diagnosed between July 1, 2006 and December 31, 2013, and followed to December 31, 2015 as per Ontario Register General-Death availability (Supplementary Table 5).

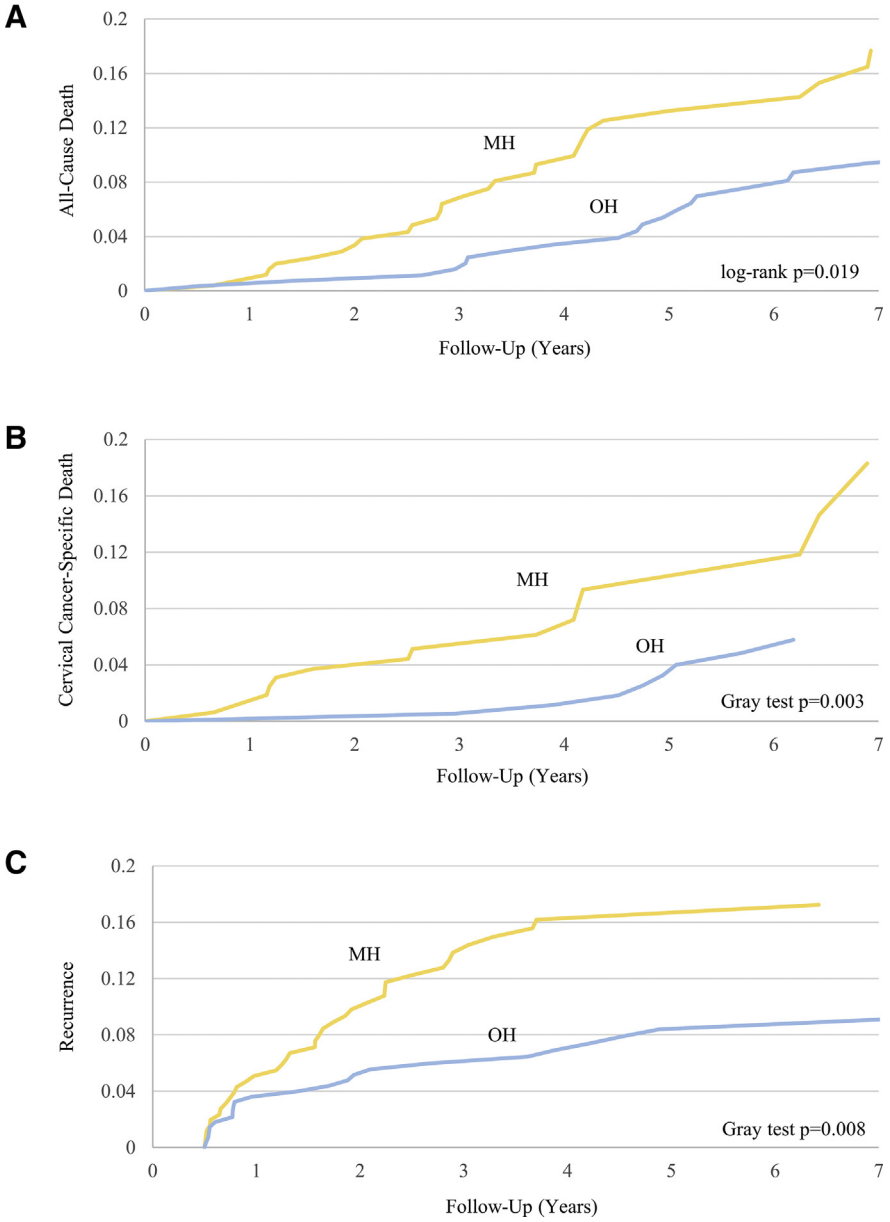
Effect of surgical approach on oncologic outcomes

Median follow-up for all-cause death was 6 years (interquartile range, 3–8 years) overall, 5 years (interquartile range, 3–7 years) for MH patients, and 7 years (interquartile range, 4–10 years) for OH patients. Median follow-up for cervical cancer–specific death and recurrence are outlined in Supplementary Table 5 and the Table. There were 85 deaths and 110 recurrences (Table), and 40 cervical cancer–specific deaths in the subcohort (Supplementary Table 5).

The unadjusted cumulative incidences of all-cause death, cervical cancer–specific death, and recurrence were not statistically different across approaches (Figure 3; Supplementary Table 6). However, stratified by stage, the 5-year cumulative incidences of death (MH 12.5% [95% CI, 8.5–18.3]; OH 5.4% [3.1–9.4]), cervical cancer–specific death (MH 9.3% [4.9–15.4]; OH 3.3% [1.2–7.0]), and recurrence (MH 16.2% [11.6–21.4], OH 8.4% [5.3–12.3]) were significantly higher for MH in those with IB disease (Figure 4).

We detected a statistically significant interaction between approach and stage in the models for all-cause death ($P_{interaction}$ = .03) and recurrence

FIGURE 4
Unadjusted cumulative incidence curves for (a) all-cause death, (b) cervical cancer–specific death, and (c) recurrence for patients with pathologic stage IB disease



Abbreviations: *MH*, minimally invasive radical hysterectomy; *OH*, open radical hysterectomy.

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($P_{interaction}$ = .0.04), but not between approach and technique-specific volume ($P_{interaction}$ = .23 for all-cause death; $P_{interaction}$ = .29 for recurrence). After we adjusted for patient and surgeon factors, MH was associated with increased hazards of all-cause death (HR, 2.20; 95% CI, 1.15–4.19) and recurrence (HR, 1.97; 95% CI, 1.10–3.50) compared to OH in patients with stage IB disease (Figure 5). We did not identify statistically significant associations between surgical approach and outcomes in patients with stage IA disease (death HR, 0.73; 95% CI, 0.13–4.01; recurrence HR, 0.34; 95% CI, 0.10–1.10), stage II+ disease (death HR, 0.92; 95% CI, 0.33–2.53; recurrence HR, 1.07; 95% CI, 0.49–2.37), or unknown stage (death HR, 0.22; 95% CI, 0.04–1.22; recurrence HR, 0.79; 95% CI, 0.21–2.94). A Fine & Gray regression model showed that MH was associated with increased subdistribution hazards of recurrence in stage IB patients only (sHR, 1.99; 95% CI, 1.12–3.53) (Supplementary Table 7).

MH was consistently associated with increased rates of death and recurrence in stage IB patients whether we controlled for volume in tertiles (death HR, 2.46; 95% CI, 1.30–4.67; recurrence HR, 2.10; 95% CI, 1.16–3.80), as a continuous variable (death HR, 2.21; 95% CI, 1.17–4.20; recurrence HR, 1.97; 95% CI, 1.10–3.53) or dichotomized on yearly volume (death HR, 2.22; 95% CI, 1.16–4.25; recurrence HR, 1.95; 95% CI, 1.10–3.46) (Supplementary Table 8). Controlling for adjuvant therapy (death HR, 2.28; 95% CI, 1.17–4.46; recurrence HR, 2.08; 95% CI, 1.17–3.70) (Supplementary Table 9) and excluding patients who were censored or had palliative care/exenteration before 6 months (recurrence HR, 1.93; 95% CI, 1.09–3.40) (Supplementary Table 7) yielded similar findings in stage IB patients.

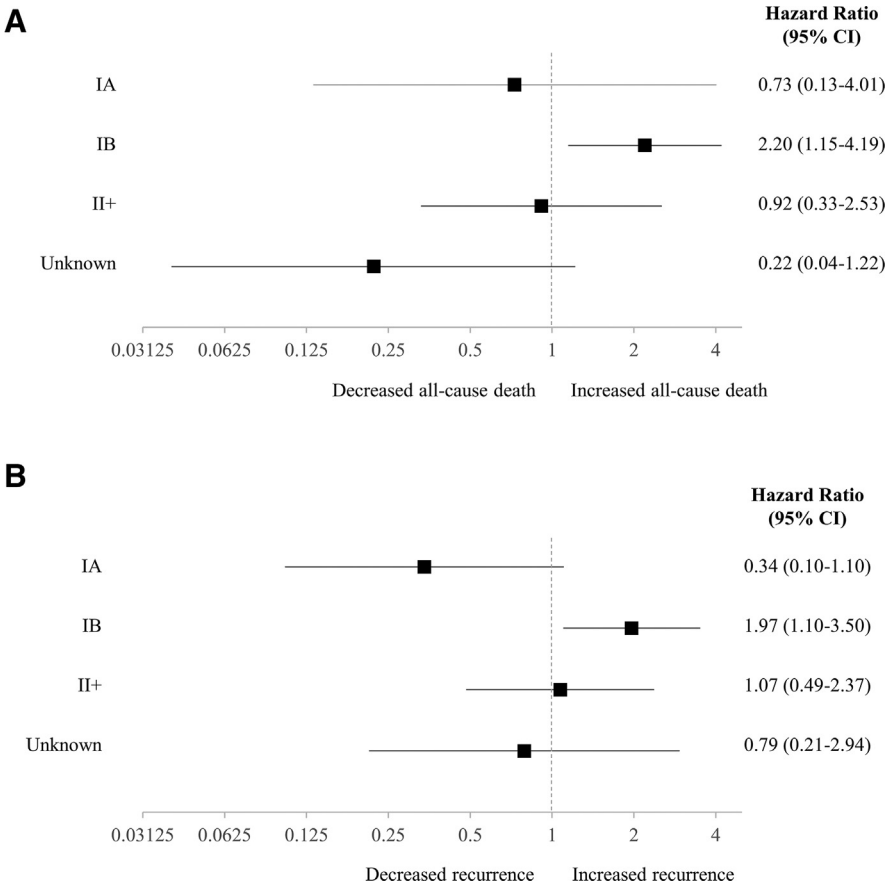
Neither technique-specific volume (death HR, 0.70; 95% CI, 0.45–1.07; recurrence HR, 0.79; 95% CI, 0.49–1.28) nor cervical cancer volume (death HR, 0.88; 95% CI, 0.46–1.68; recurrence HR, 1.17; 95% CI, 0.73–1.87) were significantly associated with oncologic outcomes in our final models (Supplementary Table 10). The hazard ratios for technique-specific volume were similar in all sensitivity analyses except when this variable was categorized in tertiles, revealing a significant association with death (high vs low: HR, 0.50; 95% CI, 0.27–0.92) and a nonsignificant association with recurrence (high vs low: HR, 0.58; 95% CI, 0.30–1.13) (Supplementary Table 8).

Comment

Principal findings

In this population-based cohort study, MH in patients with pathologic stage IB disease was associated with a 2-fold higher rate of death and recurrence

FIGURE 5
Hazard ratios for minimally invasive radical hysterectomy vs open radical hysterectomy by pathologic stage for (a) all-cause death and (b) recurrence



Solid squares represent point estimates and black lines represent 95% confidence intervals for each level of the interaction between surgical approach and pathologic stage. Gray dotted line represents a hazard ratio of 1.

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compared to OH. This relationship was evident in both unadjusted and adjusted analyses, robust to various methods of controlling for surgeon volume, and not observed in patients with stage IA or II+ disease. In contrast to previous studies, this population-based patient-level analysis reflects the real-world impact of minimally invasive radical hysterectomy, as performed by unselected surgeons on unselected early-stage cervical cancer patients.

Results

The direction of the association observed in our study is consistent with that of the LACC trial and retrospective cohort studies that accounted for relevant confounders (Supplementary Table 11). In the largest observational study to date, Melamed et al[20] examined overall survival among 2461 clinical early-stage cervical cancer patients using NCDB data. They found MH was associated with increased rates of death compared to OH (HR, 1.65; 95% CI, 1.22−2.22). Nam et al[8] matched 526 patients (FIGO stage IA2−IIA) undergoing OH and MH on several established risk factors for recurrence. While underpowered with 23 deaths and 31 recurrences, their effect size for death (HR, 1.46; 95% CI, 0.62−3.43) was similar. In the LACC trial, patients randomized to MH had increased hazards of locoregional relapse (HR, 4.26; 95% CI, 1.44−12.60) and death (HR, 6.00; 95% CI, 1.77−20.30) compared to patients randomized to OH.[19]

Neither our study nor the study of Melamed et al reproduce the large hazard ratios observed in the LACC trial. Both observational studies are affected by residual confounding; neither completely accounts for crucial prognostic factors such as tumor size, lymphovascular space invasion, and stromal invasion.[42,43] If surgeons select patients with larger, more aggressive tumors for OH,[12,20] then observational studies may underestimate the effect of MH on oncologic outcomes. However, the LACC trial was also stopped early, had few events (34 recurrences, 22 deaths), and had parameter estimates with wide confidence intervals. Truncated trials, particularly those with a small number of events, are known to overestimate treatment effects; thus with additional follow-up and events, the magnitude of the hazard ratios may decline.[44]

Clinical and research implications

Our study suggests that the effect of surgical approach on cervical cancer outcomes may depend on tumor size; MH was associated with increased hazards of all-cause death and recurrence in patients with pathologic stage IB (microscopic to gross tumors) but not 1A disease (microscopic tumors only). Existing work has considered whether the effect of surgical approach differs for patients with tumors <2 cm and ≥2 cm, but found similar hazards of recurrence[19] and death[20] in both subgroups. We used pathologic stage as a surrogate for tumor size, and could not evaluate this variable directly. However, it is biologically plausible that the impact of surgical approach could vary for microscopic and macroscopic tumors. This hypothesis should be evaluated in future work. There were also small numbers of stage IA and II+ patients, and few events occurred, limiting our power to detect differences.

Our study adds to existing literature by exploring the influence of surgeon volume on the association between surgical approach and cervical cancer outcomes. The LACC and NCDB studies

could not comment on the potential effect of a surgeon learning curve or surgeon volume on their findings.[24–26] We were able to control for surgeon volume in several ways as it changed over the study period, and this did not affect the association between MH and poorer oncologic outcomes. This suggests that the underlying mechanism at play may be independent of surgeon volume. We did not observe statistically significant associations between either cervical cancer volume or technique-specific volume and outcomes in our primary models, but based on sensitivity analyses cannot rule out a possible volume-outcome relationship.

Strengths and limitations

This is the first population-based study directly investigating the association between surgical approach and cervical cancer outcomes at the patient level. We had a large sample size with long follow-up, were able to evaluate recurrence and cervical cancer-specific death as well as all-cause death, and are the first group to account for surgeon procedure and disease volume as covariates. Our findings are generalizable, particularly to other areas in North America and Europe, and complement the LACC trial by reflecting the real-world impact of MH. All the databases and registries employed were of high quality, allowing accurate and complete ascertainment of exposure and outcome.

This study also has limitations. Our recurrence definition based on health service utilization has not been validated in cervical cancer patients specifically, and may introduce outcome ascertainment bias. However, in the absence of pathologic data, such definitions remain the standard approach for identifying cancer recurrence from health administrative databases.[30,45] Our definition was modelled on algorithms for comparably treated abdominopelvic malignancies that had high sensitivity (87–89%) and specificity (87–93%), and employed the same Ontario data sources used in this study.[30,31] Our results for recurrence were also robust to sensitivity analyses, and were further reinforced by parallel findings for all-cause and cervical cancer–specific death.

It is also important to note that we had no data on clinical stage, and could not confirm that all patients were eligible for radical hysterectomy. However, we were able to use pathologic stage as a surrogate. We adopted a relatively crude 50th percentile split for surgeon volume in our primary analysis, but sensitivity analyses operationalizing this variable in different ways showed near-identical results. Finally, despite capturing all cases in Ontario from 2006 to 2017, we were underpowered to detect differences in outcomes among specific patient subgroups and our findings pertain largely to laparoscopic MH, as only 49 patients had robotic MH.

Conclusion

In summary, MH is associated with increased rates of death and recurrence in stage IB cervical cancer patients, even after controlling for surgeon volume; OH should be the recommended approach in this population. While there may be a subgroup with microscopic early-stage disease for whom MH remains safe, further studies with additional patients and granular pathologic data are needed. ■

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Appendix

Supplementary Methods. Description of patients with missing data

We excluded ≤6 patients owing to missing data on material deprivation, 1 of the covariates in our primary analytic model. ICES privacy policy states that small cells <6 must be suppressed. Therefore, we cannot provide further detail on these patients, nor compare the baseline characteristics of these patients with incomplete data to those with complete data.

SUPPLEMENTARY TABLE 1
Codes for histology

Histologic type	Code	Descriptor
Squamous cell carcinoma	80513	Verrucous carcinoma, NOS
	80523	Papillary squamous cell carcinoma
	80703	Squamous cell carcinoma, NOS
	80713	Squamous cell carcinoma, keratinizing, NOS
	80723	Squamous cell carcinoma, large cell, nonkeratinizing, NOS
	80833	Basaloid squamous cell carcinoma
	80943	Basosquamous carcinoma
	83403	Papillary carcinoma, follicular variant
Adenocarcinoma	80983	Adenoid basal carcinoma
	81403	Adenocarcinoma, NOS
	81443	Adenocarcinoma, intestinal type
	82603	Papillary adenocarcinoma, NOS
	82633	Adenocarcinoma in tubulovillous adenoma
	82903	Oxyphilic adenocarcinoma
	83103	Clear cell adenocarcinoma, NOS
	83233	Mixed cell adenocarcinoma
	83803	Endometrioid adenocarcinoma, NOS
	83843	Adenocarcinoma, endocervical type
	84413	Serous cystadenocarcinoma, NOS
	84813	Mucin-producing adenocarcinoma
	84903	Signet ring cell carcinoma
	85703	Adenocarcinoma with squamous metaplasia
Adenosquamous	85603	Adenosquamous carcinoma
Carcinoma NOS	80003	Neoplasm, malignant
	80103	Carcinoma, NOS

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SUPPLEMENTARY TABLE 1
Codes for histology *(continued)*

Histologic type	Code	Descriptor
Atypical histology (excluded)	80043	Malignant tumor, spindle cell type
	80123	Large cell carcinoma, NOS
	80133	Large cell neuroendocrine carcinoma
	80153	Glassy cell carcinoma
	80323	Spindle cell carcinoma, NOS
	80333	Pseudosarcomatous carcinoma
	80413	Small cell carcinoma, NOS
	80423	Oat cell carcinoma
	80453	Combined small cell carcinoma
	80463	Non—small cell carcinoma
	80743	Squamous cell carcinoma, spindle cell
	80823	Lymphoepithelial carcinoma
	80903	Basal cell carcinoma, NOS
	82403	Carcinoid tumor, NOS
	82443	Composite carcinoid
	82463	Neuroendocrine carcinoma, NOS
	85723	Adenocarcinoma with spindle cell metaplasia
	85743	Adenocarcinoma with neuroendocrine differentiation
	87203	Malignant melanoma, NOS
	88003	Sarcoma, NOS
	88043	Epithelioid sarcoma
	88113	Fibromyxosarcoma
	89003	Rhabdomyosarcoma, NOS
	89013	Pleomorphic rhabdomyosarcoma, adult type
	89103	Embryonal rhabdomyosarcoma, NOS
Histologic type	Code	Descriptor

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SUPPLEMENTARY TABLE 1
Codes for histology *(continued)*

Histologic type	Code	Descriptor
Atypical histology (excluded)	89313	Endometrial stromal sarcoma, low grade
	89333	Adenosarcoma
	89353	Stromal sarcoma, NOS
	89503	Mullerian mixed tumor
	89513	Mesodermal mixed tumor
	89803	Carcinosarcoma, NOS
	88903	Mesenchymoma, malignant
	88913	Epithelioid leiomyosarcoma
	89903	Mesenchymoma, malignant
	91003	Choriocarcinoma, NOS
	91103	Mesonephroma, malignant
	92603	Ewing sarcoma
	93643	Peripheral neuroectodermal tumor
	96803	Malignant lymphoma, large B-cell, diffuse, NOS
	96913	Follicular lymphoma, grade 2
	96993	Marginal zone B-cell lymphoma, NOS
	97943	Plasmacytoma, extramedullary (not occurring in bone)
	99303	Myeloid sarcoma

NOS, not otherwise specified.

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SUPPLEMENTARY TABLE 2
Codes for hysterectomy

Hysterectomy	Approach	CCI codes
Radical hysterectomy	Open	1.RM.91.LA
	Laparoscopic	1.RM.91.DA, 1.RM.91.AA, 1.RM.91.CA
	Robotic	1.RM.91.^^ + 7.SF.14.ZX
Simple hysterectomy[a]	Open	1.RM.89.LA
	Laparoscopic	1.RM.89.DA, 1.RM.89.AA
	Robotic	1.RM.89.^^ + 7.SF.14.ZX

CCI, Canadian Classification of Intervention.

[a] Simple hysterectomy codes were used for determination of surgeon technique–specific volume and cervical cancer volume only; patients undergoing simple hysterectomy were not included in our study cohort.

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SUPPLEMENTARY TABLE 3
Codes for adjuvant therapy and recurrence

Therapy	CCI code	OHIP code
Adjuvant therapy: <6 months from index date		
Radiation	—	X310, X311, X312, X313
Chemotherapy	—	G381, G281, G345, G359, G382, G339
Recurrence: ≥6 months from index date		
Radiation	—	X310, X311, X312, X313
Chemotherapy	—	G381, G281, G345, G359, G382, G339
Surgery (in combination with diagnosis of cervical cancer or metastatic cancer)	Vaginectomy: 1.RS.84.^^, 1.RS.87.^^, 1.RS.89.^^ Radical vulvectomy: 1.RW.87.^^, 1.RW.88.^^, 1.RW.91.^^, 1.RW.92.^^ Complete cystectomy with conduit: 1.PM.91.^^, 1.PM.92.^^ Low anterior resection: 1.NQ.87.^^ Abdominoperineal resection: 1.NQ.89.^^ Excision, large intestine (partial, total, radical): 1.NM.87^^, 1.NM.89.^^, 1.NM.91.^^ Pelvic or para-aortic lymphadenectomy: 1.MH.87.^^, 1.MH.89.^^, 2.MH.71.^^, 1.MG.87.^^, 1.MG.89.^^, 2.MG.71.^^ Oophorectomy, salpingectomy, or salpingo-oophorectomy: 1.RB.89.^^, 1.RF.89.^^, 1.RD.89.^^ Excision, abdominal cavity (partial or radical): 1.OT.87.^^, 1.OT.89.^^ Excision partial, soft tissue of chest and abdomen: 1.SZ.87.^^ Excision of cervix (total or radical): 1.RN.89^^, 1.RN.91^^ Excision of lobe of lung (partial or total): 1.GR.87.^^, 1.GR.89.^^, 1.GR.91.^^, 1.GT.87^^, 1.GT.89.^^, 1.GT.91^^ Excision of liver (partial): 1.OA.87.^^	—
Palliative care	—	A945, C882, C945, C982, K023, W872, W882, W972, W982

CCI, Canadian Classification of Intervention; *OHIP*, Ontario Health Insurance Plan.
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SUPPLEMENTARY TABLE 4

Adjuvant treatment characteristics by pathologic stage and surgical approach

Characteristic	OH[a]	MH[a]	Total[a]	STD
Stage IA	N=109	N=135	N=244	
Radiation, n (%)	<6	<6	<6	0.11
Chemotherapy, n (%)	<6	<6	<6	0.05
Any adjuvant, n (%)	<6	<6	<6	0.11
Surgery to adjuvant therapy (days), median (IQR)	96 (96–96)	62 (52–68)	65 (57–82)	NR
Stage IB	N=278	N=256	N=534	
Radiation, n (%)	82 (29.5)	61 (23.8)	143 (26.8)	0.13
Chemotherapy, n (%)	48 (17.3)	29 (11.3)	77 (14.4)	0.17
Any adjuvant, n (%)	84 (30.2)	64 (25.0)	148 (27.7)	0.12
Surgery to adjuvant therapy (days), median (IQR)	51 (40–67)	55 (46–70)	53 (41–69)	0.22
Stage II+	N=69	N=55	N=124	
Radiation, n (%)	58 (84.1)	45 (81.8)	103 (83.1)	0.06
Chemotherapy, n (%)	55 (79.7)	41 (74.5)	96 (77.4)	0.12
Any adjuvant, n (%)	62 (89.9)	46 (83.6)	108 (87.1)	0.18
Surgery to adjuvant therapy (days), median (IQR)	46 (40–55)	49 (40–57)	49 (40–56)	0.06
Stage unknown	N=29	N=27	N=56	
Radiation, n (%)	14 (48.3)	<6	NR	NR
Chemotherapy, n (%)	11 (37.9)	<6	NR	NR
Any adjuvant, n (%)	14 (48.3)	<6	NR	NR
Surgery to adjuvant therapy (days), median (IQR)	53 (45–68)	53 (47–62)	53 (45–68)	0

IQR, interquartile range; *MH*, minimally invasive radical hysterectomy; *NR*, not reportable; *OH*, open radical hysterectomy; *STD*, standardized difference.

[a] Small cells (<6 patients) suppressed as per ICES privacy policy.

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SUPPLEMENTARY TABLE 5
Baseline characteristics for subcohort with cause of death data

Characteristic	OH (N=391)	MH (N=320)	Total (N=711)	STD
Patient				
Age (years)				
Mean (SD)	46.6 (11.9)	44.4 (10.0)	45.6 (11.1)	0.20
Median (IQR)	45 (38–55)	42 (37–49)	43 (38–52)	0.19
Age group, n (%)				
18–44	192 (49.1)	193 (60.3)	385 (54.1)	0.23
45–65	167 (42.7)	113 (35.5)	280 (39.4)	0.15
≥66	32 (8.2)	14 (4.4)	6 (6.5)	0.16
Year of surgery, n (%)				
2006–2010	260 (66.5)	147 (45.9)	407 (57.2)	0.42
2011–2017	131 (33.5)	173 (54.1)	304 (42.8)	0.42
Area of residence, n (%)				
Rural	58 (14.8)	28 (8.8)	86 (12.1)	0.19
Urban	333 (85.2)	292 (91.3)	625 (87.9)	0.19
Material deprivation, n (%)				
Low	216 (55.2)	198 (61.9)	414 (58.2)	0.13
High	175 (44.8)	122 (38.1)	297 (41.8)	0.13
Comorbidities, n (%)				
0–5	143 (36.6)	148 (46.4)	291 (40.9)	0.20
6–9	177 (45.3)	134 (41.9)	311 (43.7)	0.07
10+	71 (18.2)	38 (11.9)	109 (15.3)	0.18
Obesity, n (%)				
Yes	24 (6.1)	2 (3.8)	36 (5.1)	0.11
No	367 (93.9)	308 (96.3)	675 (94.9)	0.11
Tumor				
Histology, n (%)				
Squamous cell	227 (58.1)	166 (51.9)	393 (55.3)	0.12
Non–squamous cell	164 (41.9)	154 (48.1)	318 (44.7)	0.12
Stage, n (%)				
IA	94 (24.0)	105 (32.8)	199 (28.0)	0.20
IB	215 (55.0)	163 (50.9)	378 (53.2)	0.08
II+	55 (14.1)	30 (9.4)	85 (12.0)	0.15
Unknown	27 (6.9)	22 (6.9)	49 (6.9)	0
Surgeon				
Hysterectomy volume, median (IQR)	70 (54–95)	77 (64–95)	73 (59–95)	0.29
MH volume, median (IQR)	7 (2–17)	32 (18–40)	16 (5–34)	1.50
OH volume, median (IQR)	57 (43–76)	47 (37–57)	51 (39–67)	0.55
Technique-specific volume, n (%)				
High	263 (67.3)	237 (74.1)	500 (70.3)	0.15
Low	128 (32.7)	83 (25.9)	211 (29.7)	0.15

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SUPPLEMENTARY TABLE 5
Baseline characteristics for subcohort with cause of death data *(continued)*

Characteristic	OH (N=391)	MH (N=320)	Total (N=711)	STD
Cervical cancer volume, median (IQR)	10 (7–17)	15 (9–22)	12 (7–19)	0.46
Cervical cancer volume, n (%)				
High	183 (46.8)	224 (70.0)	407 (57.2)	0.48
Low	208 (53.2)	96 (30.0)	304 (42.8)	0.48
Treatment				
Hospital type, n (%)				
Teaching	355 (90.8)	307 (95.9)	662 (93.1)	0.21
Non-teaching	36 (9.2)	13 (4.1)	49 (6.9)	0.21
Diagnosis to surgery (days), median (IQR)	77 (55–106)	84 (63–112)	80 (57–108)	0.19
Adjuvant radiation, n (%)				
Yes	122 (31.2)	74 (23.1)	196 (27.6)	0.18
No	269 (68.8)	246 (76.9)	515 (72.4)	0.18
Adjuvant chemotherapy, n (%)				
Yes	92 (23.5)	53 (16.6)	145 (20.4)	0.17
No	299 (76.5)	267 (83.4)	566 (79.6)	0.17
Any adjuvant therapy, n (%)				
Yes	127 (32.5)	78 (24.4)	205 (28.8)	0.18
No	264 (67.5)	242 (75.6)	506 (71.2)	0.18
Surgery to adjuvant (days), median (IQR)	51 (40–61)	52 (41–67)	51 (40–63)	0.17
Outcomes				
All-cause death, n (%)				
Yes	28 (7.2)	21 (6.6)	49 (6.9)	0.02
No	363 (92.8)	299 (93.4)	662 (93.1)	0.02
Cervical cancer death, n (%)				
Yes	20 (5.1)	20 (6.3)	40 (5.6)	0.05
No	371 (94.9)	300 (93.8)	671 (94.4)	0.05
Follow-up for death (years)				
Mean (SD)	5.6 (2.4)	4.6 (2.0)	5.2 (2.2)	0.46
Median (IQR)	6 (4–8)	5 (3–6)	5 (3–7)	0.46

IQR, interquartile range; *MH*, minimally invasive radical hysterectomy; *OH*, open radical hysterectomy; *SD*, standard deviation; *STD*, standardized difference.

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SUPPLEMENTARY TABLE 6

Cumulative incidences of all-cause death, cervical cancer–specific death (taking death due to other causes as a competing event), and recurrence (taking death and second cancer as a competing event) across each year of the study

Year	MH (%)	OH (%)
All-cause death		
1	0.2 (0.0–1.5)	1.2 (0.6–2.7)
2	2.5 (1.4–4.4)	2.3 (1.3–4.1)
3	4.3 (2.7–6.7)	3.7 (2.3–5.9)
4	6.6 (4.5–9.6)	5.5 (3.7–8.1)
5	8.2 (5.8–11.5)	7.1 (5.0–10.0)
6	9.0 (6.4–12.5)	9.3 (6.9–12.7)
7	11.7 (8.5–16.0)	10.7 (8.0–14.3)
Cervical cancer–specific death		
1	0.3 (0.0–1.7)	1.0 (0.3–2.5)
2	2.5 (1.2–4.7)	1.3 (0.5–2.8)
3	3.3 (1.7–5.7)	2.4 (1.2–4.4)
4	4.6 (2.5–7.5)	3.4 (1.8–5.6)
5	6.1 (3.6–9.6)	4.9 (2.9–7.6)
6	7.2 (4.1–11.3)	5.8 (3.5–8.8)
7	11.9 (6.5–19.1)	6.9 (4.2–10.3)
Recurrence		
1	4.0 (2.5–6.1)	4.3 (2.8–6.4)
2	7.2 (5.0–9.8)	7.6 (5.4–10.2)
3	10.5 (7.8–13.6)	9.2 (6.8–12.0)
4	12.5 (9.5–15.9)	9.9 (7.4–12.9)
5	12.8 (9.8–16.3)	10.8 (8.1–13.8)
6	12.8 (9.8–16.3)	10.8 (8.1–13.8)
7	14.4 (11.0–18.2)	11.1 (8.4–14.3)

MH, minimally invasive radical hysterectomy; *OH*, open radical hysterectomy.

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SUPPLEMENTARY TABLE 7

Results of additional analyses for recurrence, including Fine & Gray subdistribution hazards model and cause-specific hazards model excluding patients censored or using palliative care before 6 months

Variable	Fine & Gray Model, HR (95% CI)	Exclusions <6 Months, HR (95% CI)
Approach		
OH	Ref	Ref
MH	—	—
Age (per year)	1.02 (0.99—1.04)	1.02 (0.99—1.04)
Year of surgery		
2006—2010	Ref	Ref
2011—2017	0.97 (0.65—1.46)	0.96 (0.64—1.44)
Material deprivation		
Low	Ref	Ref
High	0.75 (0.51—1.10)	0.75 (0.51—1.11)
Comorbidities		
0—5	Ref	Ref
6—9	0.97 (0.62—1.51)	1.01 (0.64—1.58)
10+	1.62 (0.89—2.94)	1.69 (0.94—3.05)
Stage		
IA	Ref	Ref
IB	—	—
II+	—	—
Unknown	—	—
Technique-specific volume		
Low	Ref	Ref
High	0.80 (0.49—1.32)	0.79 (0.49—1.29)
Cervical cancer volume		
Low	Ref	Ref
High	1.16 (0.73—1.86)	1.17 (0.73—1.87)
Interaction		
MH vs OH at IA	0.33 (0.10—1.09)	0.34 (0.11—1.11)
MH vs OH at IB	1.99 (1.12—3.53)	1.93 (1.09—3.40)
MH vs OH at II+	1.12 (0.51—2.49)	1.17 (0.52—2.67)
MH vs OH at unknown	0.89 (0.24—3.28)	0.75 (0.20—2.90)

CI, confidence interval; *HR*, hazard ratio; *MH*, minimally invasive radical hysterectomy; *OH*, open radical hysterectomy.

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SUPPLEMENTARY TABLE 8

Results of sensitivity analyses for volume: (1) technique-specific volume as tertiles, (2) total hysterectomy volume as a log-transformed continuous variable, and (3) technique-specific volume dichotomized at 50th percentile each year

Variable	Tertiles (HR, 95% CI)	Continuous (HR, 95% CI)	Dichotomous (HR, 95% CI)
All-cause death			
Technique-specific volume	Low: Ref	0.71 (0.49–1.04)	Low: Ref
	Med: 0.44 (0.25–0.79)		High: 0.70 (0.44–1.13)
	High: 0.50 (0.27–0.92)		
MH vs OH at IA	0.82 (0.14–4.64)	0.74 (0.13–4.06)	0.74 (0.14–4.06)
MH vs OH at IB	2.46 (1.3–4.67)	2.21 (1.17–4.20)	2.22 (1.16–4.25)
MH vs OH at II+	1.00 (0.35–2.87)	0.91 (0.34–2.46)	0.94 (0.33–2.67)
MH vs OH at unknown	0.26 (0.05–1.47)	0.22 (0.04–1.23)	0.22 (0.04–1.24)
Recurrence			
Technique-specific volume	Low: Ref	0.70 (0.44–1.11)	Low: Ref
	Med: 0.57 (0.32–1.02)		High: 0.80 (0.49–1.31)
	High: 0.58 (0.30–1.13)		
MH vs OH at IA	0.36 (0.11–1.18)	0.34 (0.10–1.11)	0.34 (0.11–1.11)
MH vs OH at IB	2.10 (1.16–3.80)	1.97 (1.10–3.53)	1.95 (1.10–3.46)
MH vs OH at II+	1.16 (0.52–2.61)	1.07 (0.49–2.37)	1.08 (0.48–2.42)
MH vs OH at unknown	0.88 (0.24–3.26)	0.78 (0.21–2.93)	0.80 (0.22–3.01)

CI, confidence interval; *HR*, hazard ratio; *MH*, minimally invasive radical hysterectomy; *OH*, open radical hysterectomy.

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SUPPLEMENTARY TABLE 9
Results of sensitivity analyses adjusting for adjuvant therapy

Variable	All-cause death HR (95% CI)	Recurrence HR (95% CI)
Approach		
OH	Ref	Ref
MH	—	—
Age (per year)	1.03 (1.01—1.05)	1.02 (0.99—1.04)
Year of surgery		
2006—2010	Ref	Ref
2011—2017	0.89 (0.59—1.34)	0.99 (0.66—1.49)
Material deprivation		
Low	Ref	Ref
High	0.91 (0.65—1.28)	0.78 (0.52—1.16)
Comorbidities		
0—5	Ref	Ref
6—9	0.95 (0.50—1.79)	0.99 (0.63—1.55)
10+	1.28 (0.65—2.56)	1.68 (0.88—3.19
Stage		
IA	Ref	Ref
IB	—	—
II+	—	—
Unknown	—	—
Technique-specific volume		
Low	Ref	Ref
High	0.74 (0.49—1.11)	0.86 (0.53—1.39)
Cervical cancer volume		
Low	Ref	Ref
High	0.86 (0.46—1.61)	1.10 (0.70—1.73)
Adjuvant therapy		
No	Ref	Ref
Yes	1.76 (1.08—2.87)	2.36 (1.42—3.94)
Interaction		
MH vs OH at IA	0.72 (0.13—3.95)	0.33 (0.10—1.07)
MH vs OH at IB	2.28 (1.17—4.46)	2.08 (1.17—3.70)
MH vs OH at II+	0.96 (0.34—2.72)	1.16 (0.53—2.53)
MH vs OH at unknown	0.29 (0.05—1.77)	1.20 (0.34—4.22)

CI, confidence interval; *HR*, hazard ratio; *MH*, minimally invasive radical hysterectomy; *OH*, open radical hysterectomy.
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SUPPLEMENTARY TABLE 10
Final multivariable survival models for all-cause death and recurrence

Variable	Parameter estimate	Standard error	*P* value	HR (95% CI)[a]
All-cause death				
Approach				
OH				Ref
MH	-0.32	0.87	.72	—
Age (per year)	0.03	0.01	<.001	1.03 (1.02—1.05)
Year of surgery				
2006—2010				Ref
2011—2017	-0.14	0.21	.49	0.87 (0.57—1.31)
Material deprivation				
Low				Ref
High	-0.11	0.16	.50	0.89 (0.65—1.24)
Comorbidities				
0—5				Ref
6—9	-0.09	0.33	.79	0.92 (0.48—1.74)
10+	0.22	0.34	.51	1.25 (0.64—2.42)
Stage				
IA				Ref
IB	1.18	0.62	.058	—
II+	2.36	0.59	<.001	—
Unknown	2.15	0.77	.005	—
Technique-specific volume				
Low				Ref
High	-0.36	0.22	.10	0.70 (0.45—1.07)
Cervical cancer volume				
Low				Ref
High	-0.13	0.33	.69	0.88 (0.46—1.68)
Interaction				
MH vs OH at IA				0.73 (0.13—4.01)
MH vs OH at IB				2.20 (1.15—4.19)
MH vs OH at II+				0.92 (0.33—2.53)
MH vs OH at unknown				0.22 (0.04—1.22)
Recurrence				
Approach				
OH				Ref
MH	-1.08	0.60	0.072	—
Age (per year)	0.02	0.01	0.079	1.02 (0.99—1.04)
Year of surgery				
2006—2010				
2011—2017	-0.04	0.21	0.83	0.96 (0.64—1.43)

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(continued)

SUPPLEMENTARY TABLE 10
Final multivariable survival models for all-cause death and recurrence *(continued)*

Variable	Parameter estimate	Standard error	*P* value	HR (95% CI)[a]
Material deprivation				
Low				Ref
High	-0.28	0.20	0.15	0.75 (0.51–1.12)
Comorbidities				
0–5				Ref
6–9	-0.04	0.23	0.86	0.96 (0.61–1.51)
10+	0.47	0.31	0.13	1.59 (0.88–2.90)
Variable	**Parameter estimate**	**Standard error**	***P* value**	**HR (95% CI)[a]**
Stage				
IA				Ref
IB	0.27	0.36	.49	–
II+	1.45	0.43	<.001	–
Unknown	1.11	0.51	.029	–
Technique-specific volume				
Low				Ref
High	-0.24	0.25	.33	0.79 (0.49–1.28)
Cervical cancer volume				
Low				Ref
High	0.16	0.24	0.52	1.17 (0.73–1.87)
Interaction				
MH vs OH at IA				0.34 (0.10–1.10)
MH vs OH at IB				1.97 (1.10–3.50)
MH vs OH at II+				1.07 (0.49–2.37)
MH vs OH at unknown				0.79 (0.21–2.94)

CI, confidence interval; *HR*, hazard ratio; *MH*, minimally invasive radical hysterectomy; *OH*, open radical hysterectomy.

[a] Hazard ratios for variables involved in interaction are also presented in Figure 5.

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SUPPLEMENTARY TABLE 11

Major studies (sample size >300) of cervical cancer patients undergoing minimally invasive vs open radical hysterectomy that employ some form of confounder control

Study	Country	Size	FIGO stage	Death (HR, 95% CI)	Recurrence (HR, 95% CI)
Observational studies					
Nam, 2012	Korea	OH 263 MH 263	IA2-IIA	1.45 (0.62–3.43)	1.28 (0.62–2.64)
Wang, 2016	China	OH 203 MH 203	IA2-IIA2	NR	NR
Melamed, 2018	USA	OH 1236 MH 1225	IA2-IB1	1.65 (1.22–2.22)	NR
Kim, 2019	Korea	OH 435 MH 158	IB1-IIA	NR	2.88 (1.7–4.86)
Cusimano, 2019	Canada	OH 485 MH 473	NR	2.20 (1.15–4.19)[a]	1.97 (1.10–3.50)[a]
Randomized controlled trials					
Ramirez, 2018	Multiple	OH 312 MH 319	1A1-1B1	6.00 (1.77–20.30)	4.26 (1.44–12.60)

CI, confidence interval; *FIGO*, International Federation of Gynecology and Obstetrics; *HR*, hazard ratio; *MH*, minimally invasive radical hysterectomy; *NR*, not reported; *OH*, open radical hysterectomy.

[a] Hazards only noted in patients with pathologic stage IB disease.

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