



Rates over time and regional variation of radical minimally invasive surgery for cervical cancer: A population based study



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HIGHLIGHTS

- Rate of radical MIS for cervical cancer in Ontario increased from 18% in 2002 to 62% in 2015.
- Most of this increase was driven by high volume centres.
- Radical MIS for cervical cancer results in shorter hospital stays and similar readmission rates compared to open surgery.
- Abandonment of MIS for cervical cancer may have a significant impact on surgical training and patient care in the future.

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ABSTRACT

Objective. Determine rates of radical minimally invasive surgery (MIS) for cervix cancer in Ontario, and whether these rates varied over time and by region. Assess whether changes in the use of MIS impacted length of hospital stay and readmissions.

Methods. Retrospective population-based cohort study of women undergoing radical surgery for cervical cancer between 2002 and 2015. Radical MIS versus laparotomy were compared. Trends in rate of MIS over time, length of hospital stay, and readmission within 30 days were determined. Multivariate logistic regression was used to determine factors associated with MIS approach.

Results. 805 women underwent radical abdominal surgery versus 538 radical minimally invasive surgery. Radical MIS increased over the study period, from 17.7% in 2002 to 61.5% in 2015. The most significant predictor of MIS approach was hospital site, with a 14-fold difference in sites with highest and lowest uptake of MIS. Mean length of hospital stay was significantly shorter after radical MIS compared to radical abdominal surgery (1.1 v. 4.2 days). Hospital readmission within 30 days was reduced over the study period for MIS but remained stable following abdominal surgery.

Conclusions. Although rates of radical MIS increased in Ontario over the time period studied, this seems to have been driven by a few high volume centres. Cervical cancer is rare and it takes time to develop the skills to carry out the procedure effectively. Abandonment of minimally invasive radical hysterectomy may have a significant impact on surgical training and subsequent proficiency in the skills unique to this procedure.

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1. Introduction

It is estimated that approximately 1500 Canadian women are diagnosed with cervical cancer annually [1]. Most are diagnosed at an early stage and with appropriate treatment cure rates are high. Cervical cancer tends to affect women at a younger age compared to other

gynecologic malignancies, and therefore treatment related morbidity and recovery time are of particular interest.

The definitive surgical management of early cervical cancer includes radical hysterectomy with pelvic lymph node assessment. Traditionally, surgery is completed through a laparotomy, or open surgery. However, procedures accomplished by minimally invasive surgery (MIS) have been shown to be associated with lower intraoperative blood loss [2–6], less postoperative pain [7], and shorter length of hospital stay [2–6,8]. Also, same day discharge after minimally invasive radical hysterectomy has been shown to be feasible and safe [9].

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Although the perioperative benefits of MIS for cervical cancer have been well described, emerging data has called into question the oncologic safety of this approach [10,11]. Minimally invasive radical hysterectomy is difficult to accomplish and requires advanced surgical expertise. MIS for cervical cancer has been performed for over 10 years, however it is currently unknown what proportion of patients in Ontario are having MIS procedures for the treatment of cervical cancer, and the impact of this approach on patients in the province.

The aim of this study was to evaluate trends over time and regional variation in uptake of radical MIS for early cervical cancer in Ontario and how this translates into perioperative outcomes. A secondary objective was to determine if the differences in the use of MIS have impacted the length of hospital stay and postoperative hospital readmission following radical surgery for cervical cancer. We did not specifically aim to evaluate oncologic outcomes and therefore they are not reported here.

2. Methods

2.1. Study design and data sources

We conducted a retrospective population-based cohort study by linking various Ontario health administrative databases. These databases contain routinely collected data on health services provided to virtually all of Ontario's 14 million residents through a universal single-payer health insurance plan (OHIP). These datasets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES). ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

We used seven datasets linked at the individual level by an encrypted personal health number. The OHIP Claims Database contains data on all in-patient, out-patient and emergency department services provided since 1991. The Ontario Cancer Registry (OCR) records all newly diagnosed cancers in the province, classified according to the International Classification of Diseases for Oncology, 3rd edition (ICDO-3). The Canadian Institute for Health Information- Canadian Classification of Health Interventions (CIHI-CCI) database contains information on all diagnostic and therapeutic interventions, including surgical procedures. The Discharge Abstract Database (CIHI-DAD) records all admissions to acute care institutions and the National Ambulatory Care Reporting System (NACRS) records all out-patient and emergency department services provided since July 2000. The Registered Persons Database (RPDB) provides demographic information on all Ontario Residents covered under OHIP since 1991 and is updated every two months. The Corporate Provider Database (CPDB) contains information on individual health care providers in the province.

2.2. Eligibility and cohort identification

All female Ontario residents over the age of 18 with valid OHIP coverage during the study period were eligible for inclusion in our cohort. Incident cases of invasive cervical cancer diagnosed between April 1, 2002 and March 31, 2016 were identified through the OCR using ICD-O—3 codes. Those with prior malignancy diagnosed within five years were excluded.

As we were interested only in radical surgical management of early stage cervical cancer, we excluded those who were treated with definitive excisional procedures, as well as those who underwent simple hysterectomy or non-surgical management. In order to account for cases where excisional procedure was followed by radical surgery, in defining our exposure, we included all surgeries 6 months after and including the diagnosis date. We also excluded those with rare cervical cancer

pathologies (e.g. cervical sarcomas, neuroendocrine tumours) where standard management may not be warranted.

Using the datasets outlined above, we identified year of diagnosis and surgical approach for each included case, as well as patient socio-demographic and clinical information. We used Aggregated Diagnosis Groups (ADG) based on in-patient and out-patient ICD code diagnoses within 5 years prior to cervical cancer diagnosis to assess for degree of individual-level comorbidity. This method has been used previously on health administrative data in Ontario and has been shown to accurately predict 1-year mortality among the adult population [12]. Hospital characteristics and provider characteristics for each case were collected. To assess for regional variation in practice in the province, cases were assigned to hospital 'sites' based on centre where the surgery was performed and specialty of provider doing the surgery. This was done to account for clustering, given that the majority of gynecologic oncologists in Ontario work in academic centres. We included five academic cancer centre sites with gynecologic oncologists, as well as community hospitals with gynecologic oncologists, and community hospitals without gynecologic oncologists.

2.3. Study outcomes

The primary outcome of interest was rate of minimally invasive radical surgery versus laparotomy for cervical cancer in Ontario over the study period, and trends in uptake of radical MIS over time. Secondary outcomes included length of hospital stay, and hospital readmission within 30 days of surgery.

2.4. Statistical analysis

Descriptive statistics were used to compare patients with radical abdominal surgery vs. radical MIS for cervix cancer. Crude procedure rates were determined by year and by hospital site. Trends in rates over the study period were determined using Cochran Armitage test. Multivariate logistic regression was used to determine independent factors associated with a minimally invasive approach. Factors included in the model were determined a priori based on clinically important factors that could affect mode of surgery. Mean length of hospital stay was determined by year and by hospital site; trends in length of stay over time were compared using simple regression test. Similarly, rates of hospital readmission within 30 days of surgery were determined by year. Cochran Armitage test was used to determine trends in readmission over time. Logistic regression was used to assess odds of readmission following radical abdominal versus MIS. Statistical analysis was performed using SAS version 9.3.

3. Results

After exclusions, there were 6758 women diagnosed and treated for cervical cancer in Ontario between April 1, 2002 and March 31, 2016 (Fig. 1). Among the 3459 women (51.2%) treated surgically, 1343 (38.8%) had radical surgery, 909 (26.3%) had simple surgery, and 1207 (34.9%) had other procedures, which included excisional procedures, brachytherapy, nephrostomy tube insertion, and other imaging modalities. Among the radical surgery group, 805 (59.9%) had an abdominal approach, and 538 (40.1%) had a minimally invasive approach. This became our cohort of interest for further analyses.

Those who had radical MIS were significantly younger (43.3 v. 46.3 years; $p < 0.001$) and more likely to have had their surgery towards the end of our study period (Table 1). Women who underwent radical MIS were more likely to live in urban centres ($p < 0.001$) and be of higher income quintile ($p = 0.045$) than those who underwent open surgery. There was no significant difference in ADG categories (comorbidities) between the groups ($p = 0.677$). Over 90% of radical surgeries were performed by gynecologic oncologists. Median age of the surgeon was significantly younger in the MIS group (46 v. 48 years; $p = 0.01$),

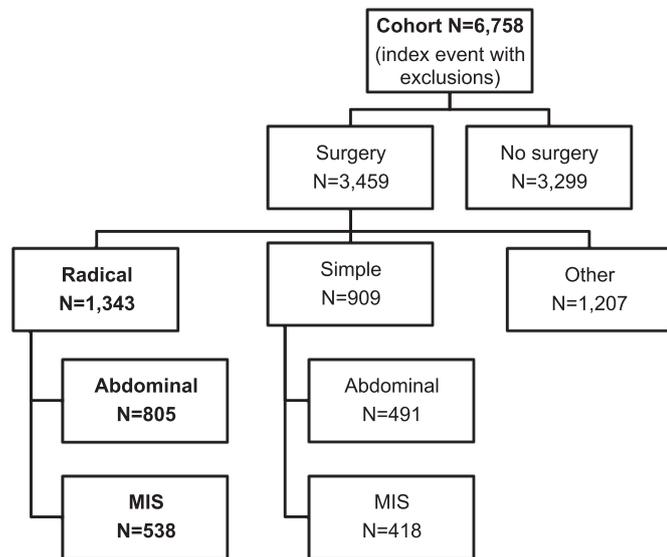


Fig. 1. Treatment for cervical cancer within 6 months following diagnosis in Ontario, 2002–2015.

and the median number of years out of medical school was significantly lower in the MIS group (21 v. 22 years; $p = 0.025$), although these differences are of questionable clinical significance. Rates of radical MIS varied significantly by hospital site, ranging from 0 to 55.9% of total radical procedures for cervical cancer ($p < 0.001$) among centers with gynecologic oncologists ($p < 0.001$).

There was a median of 94 cases per year of radical surgery for early cervical cancer in Ontario between 2002 and 2015 (range 77–122). We did not find a significant trend in annual number of cases over the study period (Fig. S1). Regarding surgical approach, there was a significant increase in rate of radical MIS performed over the study period, from 17.7% in 2002 to 61.5% in 2015 ($p < 0.0001$) (Fig. 2). This increase was seen among all centres with gynecologic oncologists, where over 90% of all radical MIS procedures were performed.

We used multivariate regression to identify factors predictive of a minimally invasive approach (Table 2). Nine patients were excluded for missing data on income quintile or hospital site. After controlling for patient age, year of diagnosis, ADG category (comorbidities), hospital site and income quintile, the most significant predictor of MIS approach was hospital site, with up to a 14-fold difference when compared to the site with the lowest rate of MIS (OR 14.04; 95% CI 7.92–24.89). To a lesser extent, younger patient age (OR 0.97; 95% CI 0.96–0.98) and later year of diagnosis (OR 1.32; 95% CI 1.27–1.37) were also significant predictors of MIS approach. Income quintile and comorbidity score were not significant predictors of radical MIS in our adjusted model.

The mean length of hospital stay was significantly shorter after radical MIS compared to radical abdominal surgery (1.1 v. 4.2 days) (Fig. 3). Mean length of stay was significantly reduced for both surgical approaches over the study period ($p < 0.0001$ for both approaches). In 2002, mean length of stay following abdominal radical surgery was 4.9 days (SD 1.5 days) compared to 2.4 days (SD 1.9 days) for radical MIS. By 2015 length of stay had decreased to 3.4 days (SD 1.0 days) following abdominal surgery compared to 0.9 days (SD 0.6 days) for MIS. Mean length of hospital stay also varied significantly by hospital site ($p < 0.0001$).

Crude rate of hospital readmission within 30 days was similar by approach over the entire study period. For radical open surgery, there were 77 readmissions (9.6% crude readmission rate) compared to 49 readmissions (9.1% crude readmission rate) in the radical MIS group ($p = 0.78$). However, rate of readmission after radical MIS was significantly reduced over the study period ($p = 0.016$), from >30%

Table 1
Patient and hospital characteristics.

	Radical abdominal surgery (N = 805)	Radical minimally invasive surgery (N = 538)	P-value
Age at diagnosis			
Mean \pm SD	46.27 \pm 12.08	43.31 \pm 10.92	<0.001
Median (IQR)	44 (37–54)	42 (35–50)	<0.001
Fiscal year of diagnosis			<0.001
2002	65 (82.3%)	14 (17.7%)	
2003	84 (89.4%)	10 (10.6%)	
2004	69 (85.2%)	12 (14.8%)	
2005	67 (87.0%)	10 (13.0%)	
2006	89 (92.7%)	7 (7.3%)	
2007	58 (69.9%)	25 (30.1%)	
2008	57 (61.3%)	36 (38.7%)	
2009	60 (49.6%)	61 (50.4%)	
2010	49 (40.2%)	73 (59.8%)	
2011	57 (49.1%)	59 (50.9%)	
2012	52 (46.0%)	61 (54.0%)	
2013	25 (32.1%)	53 (67.9%)	
2014	36 (38.3%)	58 (61.7%)	
2015	37 (38.5%)	59 (61.5%)	
Location of residence			<0.001
Urban	681 (57.9%)	496 (42.1%)	
Rural	124 (74.7%)	42 (25.3%)	
Income quintile			0.045
missing	^d ≤ 5	0	
Q1	161 (61.0%)	103 (39.0%)	
Q2	169 (65.8%)	88 (34.2%)	
Q3	180 (58.3%)	129 (41.7%)	
Q4	156 (60.2%)	103 (39.8%)	
Q5	^e 131–135	115	
ADG ^a Categories (5 years prior to diagnosis)			0.677
0–5	127 (57.7%)	93 (42.3%)	
6–9	287 (59.5%)	195 (40.5%)	
10+	391 (61.0%)	250 (39.0%)	
Hospital site			<0.001
missing	^d ≤ 5	^d ≤ 5	
Site 1	290 (48.3%)	311 (51.7%)	
Site 2	120 (44.1%)	152 (55.9%)	
Site 3	58 (100.0%)	0 (0.0%)	
Site 4	114 (74.5%)	39 (25.5%)	
Site 5	158 (88.3%)	21 (11.7%)	
Comm hosp gyne onc ^b	43 (82.7%)	9 (17.3%)	
Comm hosp no gyne onc ^c	^e 18–22	^d ≤ 5	

^a Adjusted clinical groups.

^b Community hospital with gynecologic oncologists.

^c Community hospital with no gynecologic oncologists.

^d ICES prohibits reporting of cells ≤ 5 , therefore row percentages have also been omitted to protect from possible re-identification.

^e Actual number suppressed to avoid tabulation of cells ≤ 5 .

readmission rate during the first few years radical MIS was practiced in the province, to under 10% in the last few years of the study period (Fig. 4). Rate of readmission following abdominal surgery remained stable ($p = 0.87$). After adjusting for age, ADG category (comorbidity), and hospital site, odds of readmission after radical abdominal versus MIS were not significantly different (OR 1.01; 95% CI 0.66, 1.52). There were higher rates of readmission in the open group for infectious causes (41.6% of all radical open readmissions versus 28.6% radical MIS readmissions), wound complications (6.5% open versus 2% MIS), and cardiorespiratory causes (5.2% open versus 2% MIS). Conversely, there were higher rates of readmission in the MIS group for GU complications (24.5% MIS readmissions versus 9.1% open readmissions), bleeding (14.3% MIS readmissions versus 9.1% open readmissions), and pain (12.2% MIS versus 6.5% open). Timing of readmission was approximately similar between groups; median 11 days (range 4–30 days) after radical open surgery compared to 10 days (range 2–30 days) after radical MIS. We did not see a significant correlation between volume of radical MIS per site and readmission rates (Spearman correlation 0.31; $p = 0.50$). Given the small number of readmissions over the

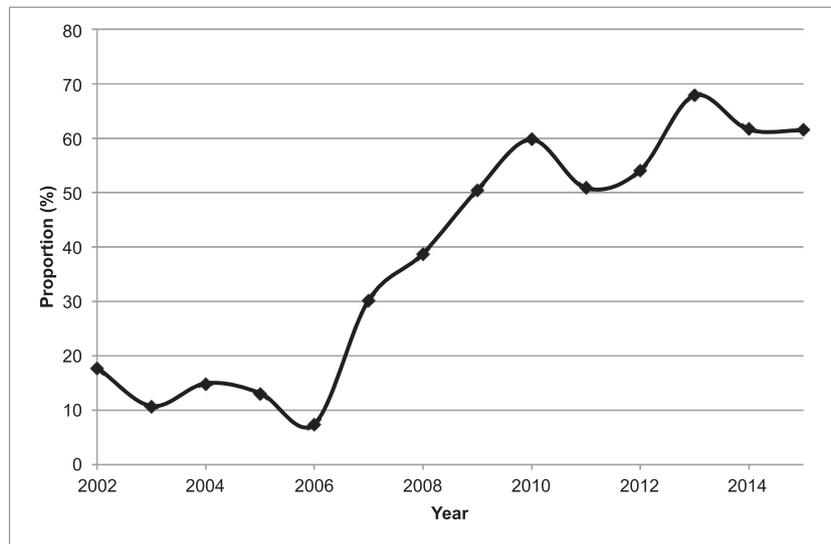


Fig. 2. Crude rate of radical MIS for cervical cancer over time in Ontario.

13 year study period, it was not possible to determine significant trends in readmission by year or by institutional or provider volumes.

4. Discussion

In this population-based cohort study, comparing radical abdominal versus MIS for early cervical cancer, we found a significant trend towards increased rate of MIS over the study period. The steepest uptake appeared around 2008, which corresponds to the introduction of robotic surgery and the performance of the first robotic-assisted radical hysterectomy in the province [13]. Length of post-operative hospital stay was also significantly reduced in the MIS group. Similar results following introduction of MIS for endometrial cancer in Ontario have been described previously [14].

Table 2
Multivariate regression analysis for factors predictive of radical minimally invasive surgical approach ($N = 1334$ observations).

Covariate	Category	Crude odds ratio (95% CI)	Adjusted [§] odds ratio (95% CI)
Age		0.98 (0.97, 0.99)	0.97 (0.96, 0.98)
Diagnosis year		1.26 (1.22, 1.30)	1.32 (1.27, 1.37)
ADG ^a	0–5	Ref	Ref
	6–9	0.93 (0.67, 1.28)	0.85 (0.57, 1.27)
	10+	0.87 (0.64, 1.19)	0.82 (0.55, 1.20)
Income quintile	1 (low)	Ref	Ref
	2	0.81 (0.57, 1.16)	0.95 (0.62, 1.47)
	3	1.12 (0.80, 1.57)	1.17 (0.78, 1.76)
	4	1.03 (0.73, 1.47)	1.28 (0.83, 1.99)
	5 (high)	1.34 (0.94, 1.91)	1.53 (0.99, 2.35)
Hospital site	Site 1	8.07 (4.98, 13.07)	12.95 (7.56, 22.16)
	Site 2	9.53 (5.70, 15.94)	14.04 (7.92, 24.89)
	Site 3	n/a [#]	n/a [#]
	Site 4	2.57 (1.44, 4.61)	4.31 (2.27, 8.19)
	Site 5	Ref	Ref
	Comm hosp gyne onc ^b	1.57 (0.67, 3.69)	1.34 (0.53, 3.36)
	Comm hosp no gyne onc ^c	0.68 (0.15, 3.12)	1.16 (0.24, 5.59)

[§] Adjusted for age, ADG category, hospital site.

[#] Site 3 did not perform radical minimally invasive surgery for cervical cancer during the study period.

^a Adjusted clinical groups

^b Community hospital with gynecologic oncologists.

^c Community hospital with no gynecologic oncologists.

Although rates of radical MIS for cervical cancer have increased overall in Ontario, there remains significant regional variability in uptake. Furthermore, this observed increase in MIS in the province seems to be driven by a few high volume centres. Cervical cancer is not a common malignancy and it takes time to develop the appropriate skills to carry out the procedure safely and effectively. A recent study based of the National Inpatient Sample (NIS) in the United States showed a 43.5% overall decline in radical surgical treatment for early cervical cancer between 2012 and 2015 [15]. However, unlike Uppal et al., we did not find a decline in surgically managed cervical cancer over the study period in Ontario. Published studies have suggested a learning curve of 40–50 cases of minimally invasive radical hysterectomy before seeing a significant benefit in perioperative outcomes [16,17]. This number can be reduced with ‘buddy operating’ where two gynecologic oncologists performed all procedures together, thereby doubling exposure. [18] The learning curve can also be reduced when surgeons were exposed to laparoscopic radical hysterectomy during fellowship training. [18,19] We expect that the anticipated reduction in cervical cancer incidence will surely affect this learning curve.

In our study, the rates of readmission after radical MIS were no higher than those seen after radical abdominal surgery, and actually decreased over the study period. We postulate that the higher rate of readmission after radical MIS seen early on in the study period relates to the learning curve observed with the introduction of any new surgical technique. This may reflect both a true initial increase in surgical complications, as well as the comfort level of providers managing women who have undergone this new procedure. A large retrospective cohort of the National Surgical Quality Improvement Project (NSQIP) database showed similar reductions in 30-day post-operative morbidity with concomitant increase in uptake of MIS for endometrial cancer [20]. Although we did not see a significant correlation between volume of radical MIS per site and readmission rates, we note that the lowest rates of readmission were seen at the two highest volume sites, where 87% of radical MIS cases were performed. This highlights the importance of surgical volumes in maintaining procedural competency and, ultimately, optimal patient outcomes.

Retrospective data on oncologic outcomes following radical minimally invasive hysterectomy have been favourable [21–25]. However, the recent publication of the Laparoscopic Approach to Cervical Cancer (LACC) trial has called into question the oncologic safety of minimally invasive radical hysterectomy [10]. This non-inferiority trial was closed to accrual early due to findings of decreased disease free survival (DFS) in the minimally invasive arm compared to the open arm (86% versus

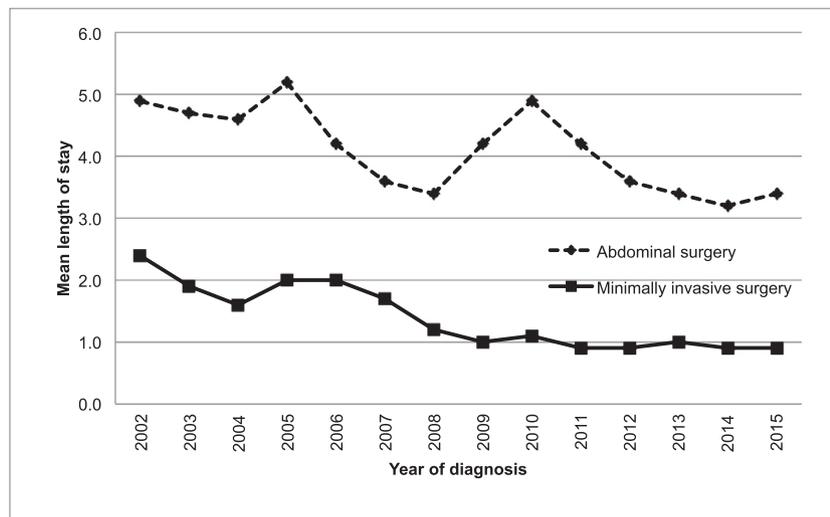


Fig. 3. Length of hospital stay after radical surgery for cervical cancer in Ontario; 2002–2015.

96.5%, respectively). As a result several centres around the world have stopped performing the procedure. However, we note that as a non-inferiority trial, LACC was inconclusive with respect to the primary endpoint as the confidence interval for the 4.5 year DFS in the minimally invasive group included the lower bound of non-inferiority [26]. As described in the LACC trial, this non-inferiority boundary was determined a priori based on accepted differences in oncologic outcomes, while considering perioperative benefits, following minimally invasive versus open surgery in other disease sites. While we recognize the importance of the LACC trial with respect to oncologic outcomes, several questions remain as to the underlying reasons for the findings in LACC, including surgical volumes at each participating centre and the adjuvant treatments and outcomes specifically at the 14 centres where recurrences were clustered. In the absence of significant differences in these institutional variables, it remains unclear as to the mechanism of poorer outcomes in the MIS group; hypotheses include use of a uterine manipulator and the exposure of the cervix to the peritoneal cavity after colpotomy with MIS approach [27,28], both of which can be modified with appropriate surgical education.

While randomized trials are heralded as the gold standard by which medical practice should be defined, they often employ inclusion criteria and protocols that are not mirrored in the real-world setting. That being said, a recently published SEER retrospective propensity-score

weighted time-series analysis also showed shorter overall survival following MIS radical hysterectomy among women with early stage cervical cancer [11]. More recently, a retrospective review by Kim et al. [29] also found significantly poorer progression free survival among 158 patients undergoing radical MIS compared to 435 patients undergoing radical open surgery for early stage disease. However, this difference in progression free survival by approach did not hold true for patients with stage 1B1 tumours ≤ 2 cm on preoperative MRI. In light of these important randomized and retrospective findings, individual centres have been encouraged to critically appraise their own data on oncologic outcomes following radical surgery for cervical cancer.

The purpose of this study was to evaluate trends in MIS over time and how this translates into perioperative outcomes. We did not specifically aim to evaluate oncologic outcomes and therefore they are not reported here. However, trends in uptake and surgical volumes are intrinsically related to both oncologic and perioperative outcomes. Although in our findings the rate of radical MIS increased in the province over the study period, this was driven by a few high volume centers, whereas some sites performed no radical MIS. We postulate that this high variability in uptake would impact learning curve, maintenance of competency, and ultimately perioperative and oncologic outcomes. Our study demonstrating variable rates of uptake of radical MIS for cervical cancer within a centralized healthcare system highlight this

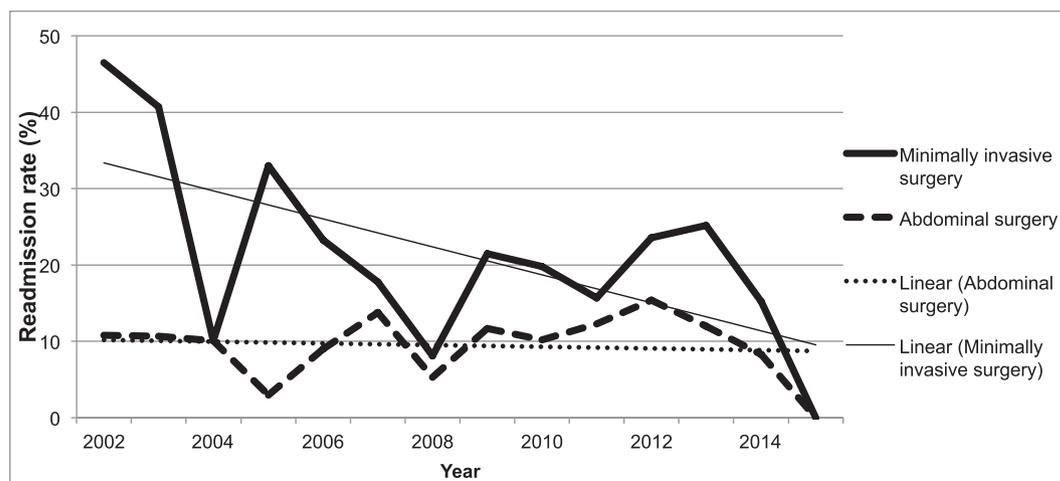


Fig. 4. Crude rate of hospital readmission within 30 days of surgery, by year.

possible discrepancy in care. This may be further compounded by a future decline in cervical cancer incidence, due to increased vaccine uptake and advances in cervical screening. There is legitimate concern that complete abandonment of minimally invasive radical hysterectomy may have a significant impact on surgical training and subsequent proficiency in the skills unique to this procedure. If a specific patient population is ever identified in which there is no survival difference by approach, and in which the advantages of MIS are sustained, this could result in a generation of gynecologic oncologists who are no longer comfortable in performing or teaching these skills. Given the perioperative benefits of MIS discussed here, this could have a detrimental effect on patients in the future.

A major strength of this study is the robustness of the population-based datasets used. These datasets have been used extensively for health research in the province and their quality has been demonstrated previously [30]. Also, we included all consecutive cases of cervical cancer in our analyses. We feel that our results reflect the real-world setting in Ontario. However, we also acknowledge the limitations of our study. Our datasets lack information on adjuvant therapy and cost-effectiveness. At present, FIGO clinical stage is not recorded for the entire timeframe of this cohort in the Ontario Cancer Registry, and the pathologic data of tumor size, depth of stromal invasion, and LVSI are not available. Also, we do not have specific data on obesity in our study population, which may affect surgical approach. However, unlike endometrial cancer, obesity is not a known risk factor for cervical cancer and is not highly prevalent in this population. Furthermore, readmission within 30 days of surgery may not be a precise marker of postoperative morbidity. However, we were reassured when after adjustment for age and comorbidities, the rates of readmission did not differ based on surgical approach. Finally, we acknowledge that our data does not make a distinction between laparoscopic and robotic radical minimally invasive hysterectomy.

5. Conclusion

This study identifies an increase in uptake of radical MIS for cervical cancer in Ontario over time and demonstrates the perioperative benefits of MIS in terms of shortened hospital stay with no observed increase in post-operative readmission. There remains significant regional variation in uptake of radical MIS in the province, which we hypothesize relates to the learning curve for the procedure. This is one of the largest population-based studies to assess trends in uptake and perioperative outcomes following radical MIS for cervical cancer using high quality health administrative databases and reflects real-world practice in a centralized healthcare system. With emerging data to suggest higher recurrence rate following radical MIS, we are in the process of exploring the oncologic outcomes in the cohort presented here. In the meantime, we remain aware that the complete abandonment of radical MIS could significantly impact surgical training, and subsequently, perioperative outcomes of women diagnosed with cervical cancer.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ygyno.2019.05.019>.

Declaration of Competing Interest

None of the other authors have any conflicts of interest that could affect the design, analysis or interpretation of results for this project.

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Author contributions

LTG designed the study and supervised the analysis. RK, DV and AC contributed to the conception and design of the study and to the interpretation of the data. KW contributed to the interpretation of the data. LTG and CD had full access to all of the data in the study, analyzed the data, and take responsibility for the integrity of the data and the accuracy of the data analysis. KW drafted the manuscript. All authors critically revised the manuscript for intellectual content and approved the final draft for submission.

Transparency declaration

The senior author and the manuscript's guarantor (LTG) 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 have been explained.

Data sharing

The analysis dataset for this study can be directly requested from the data custodians (ICES, Toronto, Canada).

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