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Original Research

Survival after a nationwide adoption of robotic minimally invasive surgery for early-stage cervical cancer – A population-based study

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KEYWORDS
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Abstract ***Aim:*** Lately, the safety of minimally invasive surgery (MIS) in the treatment of cervical cancer (CC) has been questioned. This study aimed to evaluate the risk of recurrence and survival after a nationwide adoption of robotic MIS for the treatment of early-stage CC in Denmark.

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Minimally invasive surgery;
Disease-free survival;
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Overall survival;
Cancer recurrence;
Population-based study

Methods: Population-based data on all Danish women with early-stage CC, who underwent radical hysterectomy January 1st 2005–June 30th 2017 were retrieved from the Danish Gynecologic Cancer Database and enriched with follow-up data on recurrence, death and cause of death. The cohort was divided into two groups according to the year of robotic MIS introduction at each cancer centre. Chi-squared or Fischer test, the Kaplan Meier method and multivariate Cox regression were used for comparison between groups.

Results: One thousand one hundred twenty-five patients with CC were included; 530 underwent surgery before (group 1) and 595 underwent surgery after (group 2) the introduction of robotic MIS. The 5-year rate of recurrence was low: 8.2% and 6.3% (p = 0.55) in group 1 and 2, respectively. In adjusted analyses, this corresponded to a five-year disease-free survival, hazard ratio (HR) 1.23 [95% confidence interval (CI) 0.79-1.93]. No difference in site of recurrence (P = 0.19) was observed. The cumulative cancer-specific survival was 94.1% and 95.9% (P = 0.10) in group 1 and 2, respectively, corresponding to a HR 0.60 [95% CI 0.32–1.11] in adjusted analyses.

Conclusion: In this population-based cohort study, the Danish nationwide adoption of robotic MIS for early-stage CC was not associated with increased risk of recurrence or reduction in survival outcomes.

1. Introduction

During the past decade, minimally invasive surgery (MIS) has been adopted for the surgical treatment of early-stage cervical cancer (CC) [1–6]. Retrospective studies have shown patient and surgeon advantages [7–11]. Recently, the results from an international randomized controlled trial, the LACC (Laparoscopic Approach to Cervical Cancer) study, questioned the safety of using MIS for early-stage CC [12]. Moreover, a multi-institutional retrospective register-based study found that the adoption of MIS for early-stage CC in the US coincided with a significant decline in the 4-year relative survival [13]. In contrast, population-based Swedish data comparing open vs. robotic MIS for early-stage CC did not reveal any difference in survival outcomes [14].

The release of the preliminary results of the LACC trial urged the setup of a Danish national task force group, supported by the Danish Gynaecological Cancer Group. The objective was to evaluate recurrence rate and survival after the nationwide adoption of robotic MIS for the treatment of early-stage CC.

2. Methods

2.1. Surgical treatment of early-stage CC in Denmark

In accordance with the mandate from the executive committee of the Danish Gynecological Cancer group, a working group was settled in 2001 to prepare the first edition of the Danish national guideline for visitation, staging, treatment and follow-up of CC. This first edition was published in 2003, followed by revised editions in 2007, 2011 and 2017. In the guidelines from 2003 to 2007 no specific recommendations were given regarding the radicality of the surgical procedures radical hysterectomy or pelvic lymphadenectomy. However, as part of a research project, centres performing radical hysterectomy in Denmark were asked to describe the procedure they performed according to the Piver classification [15]. Across centres, it was agreed to perform a class II-III radical hysterectomy: the uterine artery was ligated at its origin, complete dissection of the ureter from the pubovesicle ligament to the entry in the bladder with exception of the lateral part and with preservation of the superior vesicle artery, uterosacral ligaments resected midway between the uterus and their sacral attachments, medial half of the cardinal ligaments resected and upper 2–3 cm of the vagina removed [16]. The perspective on quality assurance for radical hysterectomy in CC of the European Organisation of Research and Treatment of Cancer Gynecological Cancer Group was outlined in the revised guideline edition from 2011 [17]. Here, the procedure was adapted to anatomically well-defined structures. In the Danish national guidelines from 2011 to 2017, it was outlined that the radicality of the procedure should be adapted to the presence of risk factors, that is, tumour size, depth of invasion and presence of lymphovascular space invasion. It was recommended that the radicality of the procedure should be described. Nerve-sparing radical hysterectomy was described and illustrated in the guideline according to the publication of Fujii, S *et al.* [18] and recommended for small volume tumours.

In the guideline editions from 2011 to 2017, radical pelvic lymphadenectomy was described as a standard procedure with complete resection of all lymphatic tissue along the caudal 2–3 cm of the commune iliac artery, along and behind the external iliac artery and vein to the femoral annulus, between the medial part of the internal iliac artery and the pelvic side wall removing all

lymphatic tissue in the obturator fossa above the level the obturator nerve. Although not described in the earlier editions of the guidelines (2003 and 2007), the mapping of procedures performed in 2003 for radical hysterectomy revealed very similar performance regarding radical pelvic lymphadenectomy across cancer centres.

2.2. Study design

We took advantage of the natural experiment with gradual but complete national adoption of robotic MIS. This mimics a multi-institutional before-after design and allows assessment of the two groups simultaneously. Potential patient selection bias is minimized as exposure to either of the two surgical modalities did not depend on the women's characteristics but rather on the robotic MIS introduction pattern.

2.3. Data source

Clinical and sociodemographic data were retrieved from the Danish Gynecological Cancer Database (DGCD) and unambiguously linked with information from the National Patient Register (NPR) and the Cause of Death Register (CDR) by a unique Civil Personal Registration Number provided to all Danish citizen at birth or immigration to Denmark.

The DGCD is a national registry, established in 2005, that holds prospectively collected clinical, pathological and surgical data on all gynaecological cancer patients in Denmark [19]. The DGCD is maintained by the Danish Clinical Registries and by law required completeness of data of >90%. By legal requirement, data entering is mandatory for all gynaecological cancer surgeons and pathologists at the cancer centres.

Data on oncological treatment derived from the NPR. The National Patient Register holds information on hospital admissions, treatment and discharge diagnoses since 1977 [20]. Based on inquest, the CDR has included data on all deaths in Denmark since 1970 [21]. Data on recurrence were verified through the Danish National Pathology Register, which comprises close to complete data on all cytology and pathology specimens obtained in Denmark [22]. By authorisation from the Danish Health and Medicine Authority, data were enriched with information from the patients' files on recurrence (date, site and vital status) and cause of death if the patients had deceased.

2.4. Cohort selection

We identified all women with early-stage CC treated by radical hysterectomy in Denmark in the period January 1st, 2005–June 30th, 2017. We selected a cohort matching the inclusion criteria in the LACC trial that is, patients with International Federation of Gynecology and Obstetrics (FIGO) 2009 [23] stage IA2 or IB1, squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma who underwent radical hysterectomy and pelvic lymphadenectomy as their primary treatment. For the primary analyses, we excluded women with stage $\geq$ IB2 (N = 76) and those with rare histology (N = 18).

To identify women with recurrent disease, we used an algorithm with linkage of the retrieved data with supplement data sources. We included all deaths, all women who had undergone oncological treatment or who were registered with a histological specimen in the Danish Pathology Data Bank >60 days after the primary treatment. Members of the task force group validated suspected disease recurrences in the individual patient's hospital chart and pathology report.

In the DGCD, we identified the date of surgery and the surgical modality applied to each patient. The cohort was divided into two groups: group 1, women who underwent surgery before and group 2, women who underwent surgery after the first robotic radical hysterectomy was performed at their regional cancer centre. A cut-off of at least four robotic procedures per year for the individual centre was selected to assign the woman to group 2.

2.5. Measures

The primary outcomes were five-year disease-free survival (DFS), cancer-specific survival (CSS) and overall survival (OS). DFS was defined as the time from primary surgery to recurrence. CSS was defined as time from surgery to death due to CC or a complication related to CC treatment. Overall survival was defined as the time from primary surgery to death of any cause. Additional outcomes were rate of recurrence at 12, 36 and 60 months after the date of primary surgery and site of recurrence.

2.6. Ethics

The study was approved by the Danish Data Protection Agency journal nr. VD-2018-111, I-Suite nr.: 6355 and approval of chart review was granted by the Danish Health and Medicine Authority File-No. 3-3013-2524/1.

2.7. Statistical analyses

Demographic and clinical characteristics were compared by the chi-squared test or Fisher exact test. Women were followed from the date of primary surgery to death of any cause or censored at the end of follow-up (January 2018), whichever came first. Follow-up was estimated as median with interquartile range in the two groups. The crude incidence of recurrence, recurrence location and death from CC were estimated at 12, 36 and 60 months and compared between groups by the

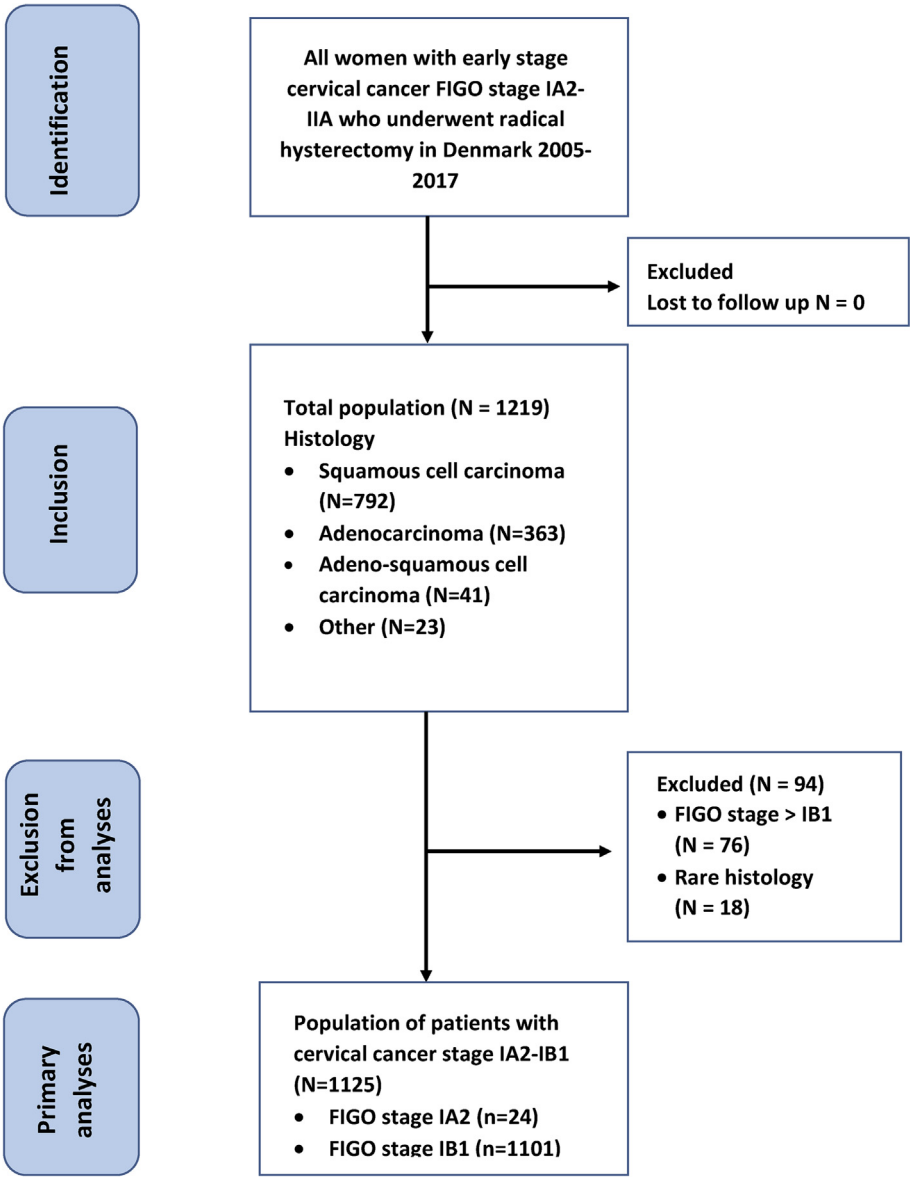

Fig. 1. The CONSORT (Consolidated Standards of Reporting Trials) diagram. All women who underwent radical surgery for early-stage cervical cancer in Denmark during the observation period from January 2005 to June 2017 and included patients for the study.

chi-squared and log-rank test. The 5-year DFS, CSS and OS estimates are presented as Kaplan-Meier plots with risk tables. The crude Cox proportional hazards models quantified the difference between the two groups by hazard ratio (HR) with 95% confidence interval (95% CI). Multivariate Cox proportional hazards regression analyses were performed to compare survival outcomes between the two groups adjusted for age, comorbidity, presence of lymph node metastases, positive margins (parametrial involvement and/or positive margins), lymphovascular space invasion and tumour size (<2 vs ≥ 2 cm) and presented as HR with 95% CI.

Sensitivity analyses on recurrence and survival were performed as sequential analyses according to surgical modality (open access vs robotic MIS and open access vs laparoscopic MIS) and on the full sample (FIGO stage IA2-IIA).

All analyses were conducted using SPSS, version 22.0. A two-sided P-value of <0.05 was considered statistically significant.

3. Results

The total and the selected population are depicted in the Consolidated Standards of Reporting Trials diagram Fig. 1. We identified 1219 patients who underwent radical hysterectomy for-early stage CC during the inclusion period. Of these, 1125 (92.3%) were selected for the primary analyses (Fig. 1). The majority of the patients had stage IB1 disease (97.9%). Squamous cell

carcinoma or adenocarcinoma (96.6%) was the most common histology.

The nationwide introduction of robotic MIS per cancer centre is illustrated in Fig. 2. Robotic MIS was introduced at different time points during the years 2009–2012 at the initial five cancer centres. In 2013, 65% of the patients were operated with robotic MIS and by 2015 robotic MIS was offered to 98% of Danish women with early-stage CC. In total, 530 (47%) and 595 (53%) patients were operated before (group 1) and after (group 2) the introduction of robotic MIS, respectively. Most of the patients who underwent MIS had robotic MIS (94.9%),whereas 25 patients (5.1%) underwent laparoscopic MIS. The median time to follow-up was 113.0 and 42.4 months in group 1 and 2, respectively.

No difference was observed between the two groups regarding median age, age group, body mass index, stage and histology (Table 1). There was a trend towards worse risk factors in group 1: lymph node metastases (11.0 vs 7.6%, respectively, P=0.05), parametrial involvement (4.2 vs 2.2%, respectively, P = 0.06), positive vaginal margin (2.8 vs 1.3%, respectively, P = 0.06) and lympho-vascular space invasion (36.4 vs 31.1%, respectively, P = 0.07) compared with group 2. Further, in group 1, a higher proportion of women had tumor size ≥ 2 cm compared to group 2 (54.5% vs 45.9%, respectively, P = 0.004). The same proportion of women underwent postoperative chemoradiotherapy in the two groups, 31.9% and 27.9%, respectively, (P = 0.34).

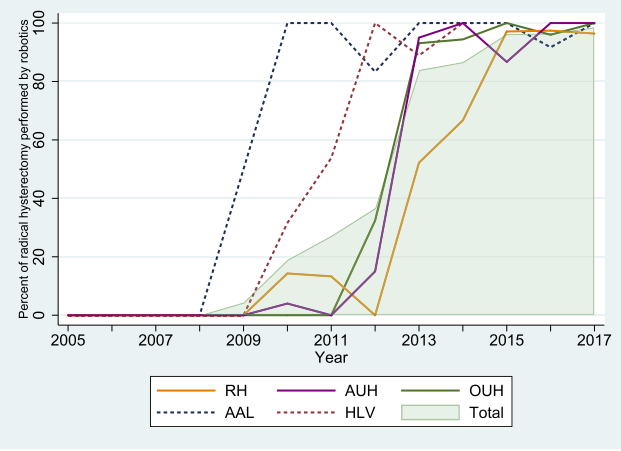

Fig. 2. The introduction of robotic surgery for early-stage cervical cancer in Denmark. The nationwide transition of surgical approach from open access surgery to robotic minimally invasive surgery for the treatment of early-stage cervical cancer in Denmark from January 2005 to June 2017. The surgical treatment and central pathology revision were centralised to five centres from 2004 to 2015 and to four centres since 2015 while the oncological treatment was centralised to four and three centres, respectively, in these time periods. RH, Rigshospitalet (Copenhagen University Hospital); AUH, Aarhus University Hospital; OUH, Odense University Hospital; AAL, Aalborg University Hospital; HLV, Herlev University Hospital.

No significant difference was observed regarding rate of recurrence at 12, 36 and 60 months and site of recurrence between the two groups (Table 2). The five-year rate of recurrence was 8.2% and 6.3% in group 1 and 2, respectively. Kaplan-Meier plots and Cox proportional hazard adjusted curves of DFS, CSS and OS are given in Fig. 3A, B and 3C, respectively. No difference was observed in the five-year DFS between the two groups, 91.8% vs 91.0%, respectively (P = 0.55). This corresponded to a HR of DFS of 1.23 [95% CI 0.79–1.93] in adjusted analyses (Fig. 3A and Table 3). In univariate analyses, the cumulative CSS was 94.1% and 95.9% (P = 0.10) (Table 2) in group 1 and 2, respectively, corresponding to a HR of CSS of 0.60 [95% CI 0.32–1.11] (Fig. 3B and Table 3). Similarly, no difference was observed in the five-year OS between the two groups, 92.3% vs. 94.4% in group 1 and 2, respectively (P = 0.10) corresponding to a HR of OS of 0.62 [95% CI, 0.40–1.09] in the adjusted analyses (Fig. 3C). Positive margins and tumour size ≥2 cm significantly increased the risk of recurrence and death from CC while age ≥50 and lymph node metastases only increased the risk of CC-specific death.

Sociodemographic information and recurrence patterns related to surgical modality is given in Appendix A, Table A.1. and Table A.2., respectively. No difference was observed in the rate of recurrence between open access and robotic MIS (P = 0.19), recurrence location (P = 0.15) and survival estimates: HR of DFS 1.35 [95% CI, 0.55 to 2.15], HR of CSS 0.68 [95% CI, 0.36 to 1.29] and HR of OS 0.82 [95% CI, 0.47 to 1.40]. A higher rate of recurrence was noted in the small group (N = 25) of patients undergoing laparoscopic MIS. Survival analyses on the full sample (N = 1219, including women with > stage IB and rare histology) did not change any conclusions regarding survival estimates (data not shown).

4. Discussion

The surprising findings of the LACC trial that MIS significantly compromised the DFS and OS in women with early-stage CC have urged many institutions to abandon or reconsider the use of MIS in CC [24–27]. The present population-based study included prospectively entered and validated data with complete follow-up regarding recurrence and death of all women who underwent radical hysterectomy for early-stage CC during a twelve-year period in Denmark. The fast adoption pattern once the robotic MIS was initiated in the individual institution allowed comparison of the outcome before and after robotic MIS adoption [28,29]. Several sensitivity analyses were performed and historical threats to the internal validity were minimized since

Table 1
Demographic and clinical characteristics of women with early-stage cervical cancer stage 1A2-IB1 who underwent radical hysterectomy in Denmark from January 2005 to June 2017.

Variables	Group 1[a] N = 530	Group 2[b] N = 595	p-value
	N (%)		
Age			
Median age	43.4 (12.4)	43.4 (12.5)	0.35
Age < 50	369 (69.8)	396 (66.6)	0.25
Age ≥ 50	160 (30.2)	199 (33.4)	
BMI			
<25	307 (58.8)	313 (53.1)	0.15
≥25 - <30	132 (25.3)	174 (29.5)	
≥30	83 (15.9)	102 (17.3)	
Smoking status			
Current smoker	145 (27.5)	172 (28.2)	<0.01
Former smoker	88 (16.7)	147 (20.9)	
Never smoker	251 (47.5)	259 (45.4)	
Unknown status	44 (8.3)	17 (5.4)	
Missing	2	0	
CCI			
CCI ≤ 1	517 (97.5)	557 (93.6)	<0.01
CCI ≥ 2	13 (2.5)	38 (6.4)	
Stage			
IA2	10 (1.9)	14 (2.4)	0.59
IB1	520 (98.1)	581 (97.6)	
Histology			
Squamous cell carcinoma	362 (68.3)	382 (64.2)	0.34
Adenocarcinoma	152 (28.7)	191 (32.1)	
Adenosquamous carcinoma	16 (3.0)	22 (3.7)	
Lymph node metastases			
Yes	58 (11.0)	45 (7.6)	0.05
No	471 (89.0)	549 (92.4)	
Parametrial invasion			
Yes	22 (4.2)	13 (2.2)	0.06
No	508 (95.8)	582 (97.8)	
Paracervical positive margin			
Yes	4 (0.8)	3 (0.5)	0.44
No	526 (99.2)	592 (99.5)	
Positive vaginal margin			
Yes	15 (2.8)	8 (1.3)	0.06
No	515 (97.2)	487 (98.7)	
Tumour size			
< 2cm	241 (45.5)	322 (54.1)	0.004
≥ 2cm	289 (54.5)	273 (45.9)	
LVSI			
Yes	193 (36.4)	185 (31.1)	0.07
No	337 (63.6)	410 (68.9)	
Lymph node count			
<20	197 (37.2)	221 (37.1)	0.99
≥ 20	333 (62.8)	374 (62.9)	
Postoperative chemoradiotherapy			
Yes	169 (31.9)	166 (27.9)	0.14
No	361 (68.1)	429 (72.1)	

BMI, body mass index; CCI: Charlson Comorbidity Index; LVSI, lympho-vascular space invasion.
[a] Group 1: Patients who underwent surgery before introduction of robotic minimally invasive surgery (MIS) for early-stage cervical cancer.
[b] Group 2: Patients who underwent surgery after the introduction of robotic MIS for early-stage cervical cancer.

CC staging, imaging, pathology revision, oncological treatment and surgery were performed according to nationally adopted guidelines in centralized settings: five cancer centres in 2004 and four centres since 2015. We did not find any difference in recurrence patterns or survival outcomes between patients who underwent surgery before and after robotic MIS adoption. Neither did we find any differences between recurrence and survival outcomes in analyses based on surgical modality. This is reassuring and suggests that in a centralized setting, the adoption of robotic MIS does not seem to compromise survival compared with open surgery.

The register-based study from the National Cancer Database by Mehlamed A *et al.* [13] was supplemented with analyses from the Surveillance, Epidemiology, and End Results (SEER) database to evaluate if MIS adoption for CC affected survival trends. While 85% of the patients undergoing MIS in the LACC trial underwent conventional laparoscopy, 79.8% of the patients who underwent MIS in the SEER series underwent robotic MIS. They found a significantly higher all-cause mortality rate in women who underwent MIS compared with open surgery (HR 1.65) and a significant relative decline in the survival rate after an adoption to MIS. No data on CSS or DFS were available, and they

Table 2
Recurrence, recurrence location and death from cervical cancer in women with early-stage cervical cancer stage 1A2-IB1 who underwent radical hysterectomy in Denmark from January 2005 to June 2017.

Variables	Group 1[a] N = 530	Group 2[b] N = 595	p-value
Median time follow-up; Months (IQR)	113.0 (88.2–134.5)	42.4 (22.3–62.8)	
N (%)			
Recurrence			
12 months	16 (3.0)	15 (2.5)	0.55
CS %	(97.0)	(97.3)	
36 months	32 (6.1)	30 (6.0)	
CS %	(93.9)	(94.0)	
60 months	43 (8.2)	38 (6.3)	
CS %	(91.8)	(91.0)	
Recurrence location			
Vaginal cuff	11 (2.1)	16 (2.7)	0.19
Regional	3 (0.6)	3 (0.5)	
Distant	27 (5.1)	15 (2.5)	
Distant and vaginal	9 (1.7)	7 (1.2)	
Death from cervical cancer			
12 months	8 (1.5)	0 (0.0)	0.10
CS %	(98.5)	(100)	
36 months	24 (4.6)	9 (2.1)	
CS %	(95.4)	(97.9)	
60 months	31 (5.8)	15 (2.7)	
CS %	(94.1)	(95.9)	

IQR, interquartile range; CS, cumulative survival function.
[a] Group 1: Patients who underwent surgery before the introduction of robotic minimally invasive surgery (MIS) for early-stage cervical cancer.
[b] Group 2: Patients who underwent surgery after the introduction of robotic MIS for early-stage cervical cancer.

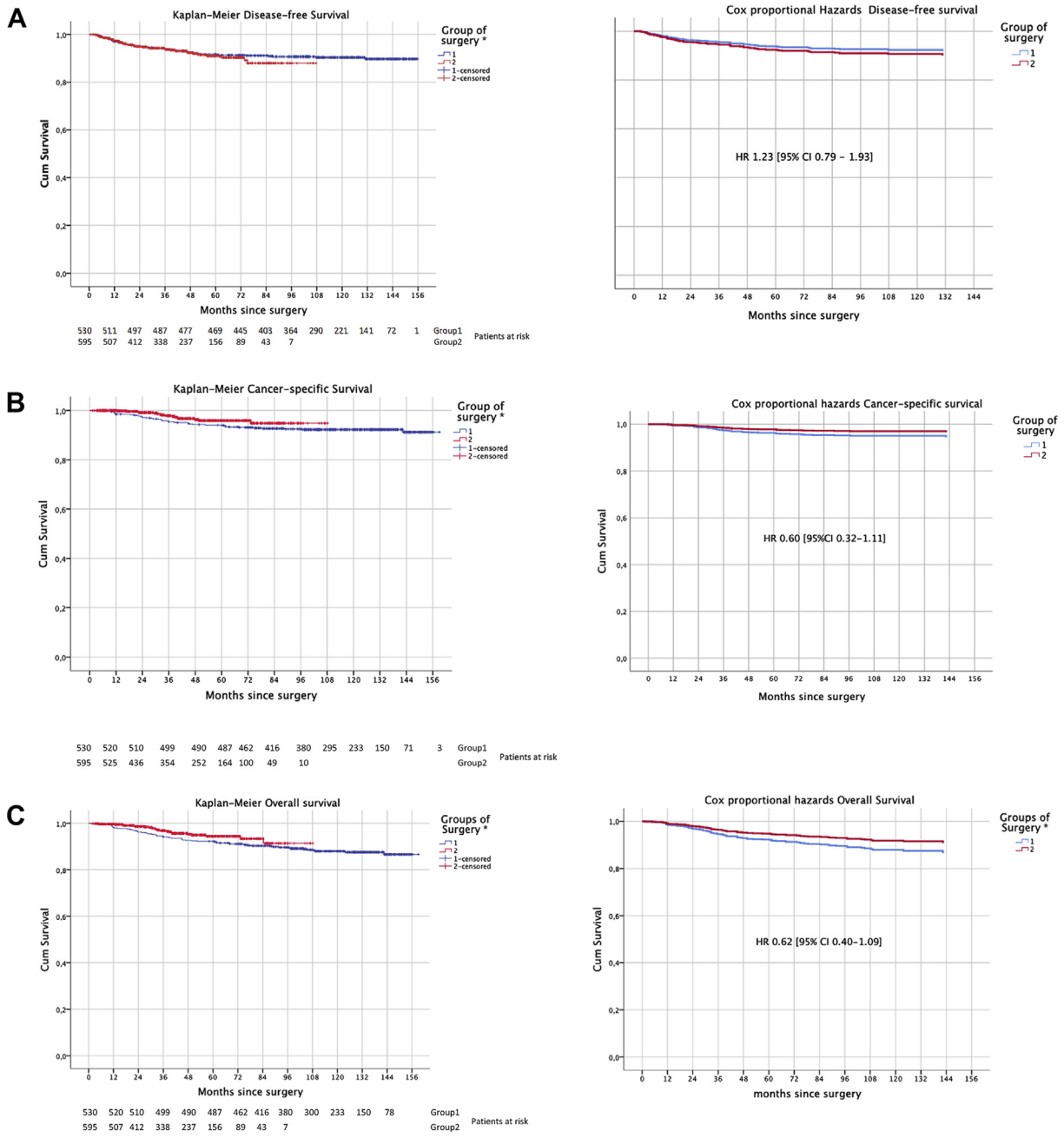

Fig. 3. A. Kaplan-Meier survival estimates and Cox proportional hazards adjusted disease-free survival (DFS) before (group 1) and after (group 2) the adoption of robotic surgery for the treatment of early stage cervical cancer. The Multivariate Cox proportional hazards regression analyses were adjusted for age, comorbidity, presense of lymphnode metastases, positive margins (parametrial involvement and/or postive margins), lymphovascular space invasion, and tumour size (< 2 cm vs >= 2 cm). B. Kaplan-Meier survival estimates and Cox proportional hazards adjusted cancer-specific survival (CSS) before (group 1) and after (group 2) the adoption of robotic surgery for the treatment of early stage cervical cancer. C. Kaplan-Meier survival estimates and Cox proportional hazards adjusted overall survival (OS) before (group 1) and after (group 2) the adoption of robotic surgery for the treatment of early stage cervical cancer.
*Groups of surgery: group 1, women who underwent surgery *before* the introduction of robotic-assisted laparoscopic radical hysterectomy at their regional cancer centre. Group 2, women who underwent surgery *after* the introduction of robotic-assisted laparoscopic radical hysterectomy at their regional cancer centre.

were unable to confirm accuracy of clinical, pathological and follow-up data, which seems crucial in studies with rare events. It appears that the adoption of MIS was very slow and never reached a higher proportion than 31%. This may imply that the surgeons who performed robotic MIS had not reached the peak of their learning curve which is considered steep for radical hysterectomy

[5]. Further, a substantial patient selection bias related to MIS cannot be precluded.

Before the LACC publication, cancer centres worldwide relied on extrapolation of survival and safety data obtained in randomized controlled trials of MIS versus open access in endometrial cancer [30–32]. Today, gynaecological cancer surgeons are searching for explanations to understand the findings of the LACC trial [14,24,33,34]. It has been noted that as many as 34 centres have contributed with patient inclusion over a ten-year time period and that some centres only included a few patients [12,35]. Issues related to surgeon's experience in conventional laparoscopy have been raised because recurrences seem to be concentrated in comparatively few centres. Further, concerns are raised as to the completeness of follow-up data (59.7% of survival data available) because recurrence and survival data in the open arm seem more favourable than ever published in retrospective series [4,14,34,36–38]. Most researchers are looking for a biological explanation for the poorer outcome in the MIS arm. Uterine manipulation and tumour spillage during abdominal colpotomy in combination with CO_2 inflation have been proposed and debated [39]. In our population-based sample, all robotic MIS cases had abdominal colpotomy performed but no uterine manipulation was used. A vaginal probe was used in all cases and our recurrence rate is low and equal in both groups. Finally, in the LACC trial, limited information on the chemoradiation schedule is available and pathology information is missing for a comparatively large proportion of the sample that is, depth of invasion is not reported for one third of the patients [40]. Hence, it is acknowledged that the LACC trial provides level 1 evidence as to the preference of open access surgery in CC. However, several concerns about the quality of the study can be raised and this requires further investigation.

The set-up of a national task force group followed the first announcement of the results of the LACC trial in spring 2018. The task force group was given the mandate to evaluate complete national data and from these, in collaboration with the Danish Gynecological Cancer Group, to decide whether robotic surgery should be abandoned for CC in Denmark. Preliminary and final analyses suggest that in the present Danish setting, a continuous use of robotic surgery for CC is safe. A statement outlining the results of the LACC trial and the preliminary Danish national results comparing open versus robotic MIS in early-stage CC was published on the website of the Danish Gynecological Cancer Group in August 2019. It was decided that future patients should be informed about the results of the two studies and that this should be documented in the patient's file along with the patient's response. The three Danish

Table 3
Multivariate Cox proportional hazards model for disease-free and cancer-specific survival in women with FIGO stage IA2-IB1 cervical cancer undergoing surgery from January 2005 to June 2017 in Denmark.

Variables included in the model	Disease-free survival			Cancer-specific survival		
	Group 1[a] versus Group 2[b]			Group 1[a] versus Group 2[b]		
	Crude	Multivariate	*p*-value	Crude	Multivariate	*p*-value
	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	
Surgical group						
Group 1	1	1	0.36	1	1	0.10
Group 2	1.14 (0.74–1.75)	1.23 (0.79–1.93)	0.61 (0.34–1.11)	0.60 (0.32–1.11)		
Age						
<50		1	0.07		1	<0.001
≥50		1.51 (0.97–2.36)		2.80 (1.59–4.93)		
CCI						
1		1	0.57		1	0.71
≥2		0.74 (0.27–2.06)		1.22 (0.43–3.46)		
Lymph node metastases						
No		1	0.20		1	0.01
Yes		1.47 (0.81–2.66)		2.43 (1.27–4.64)		
Margin involvement[c]						
No		1	0.02		1	0.02
Yes		2.16 (1.15–4.06)		2.25 (1.13–4.51)		
LVSI						
No		1	0.09		1	0.32
Yes		1.50 (0.94–2.41)		1.37 (0.74–2.55)		
Tumour size						
<2 cm		1	0.02		1	0.02
≥2 cm		1.83 (1.10–3.05)		2.41 (1.16–5.00)		

HR, hazard ratio; CI, confidence interval; LVSI, lymphovascular space invasion; CCI: Charlson Comorbidity Index.
[a] Group 1: Patients who underwent surgery before the introduction of robotic minimally invasive surgery (MIS) for early-stage cervical cancer.
[b] Group 2: Patients who underwent surgery after the introduction of robotic MIS for early-stage cervical cancer.
[c] Margin involvement: Parametrial involvement OR positive paracervical margin OR positive vaginal margin.

cancer centres which perform surgical treatment for early-stage CC today have decided to continue offering robotic surgery to Danish patients although the patient is also given the opportunity to undergo open access surgery. Considering the results of the present complete national results and the unexpected and somehow controversial results of the LACC trial, it seems ethically plausible to consider further investigation of the safety and patient-related benefits of robotic surgery in early-stage CC.

The strength of our study is the use of high-quality register data. One of the major threats to the internal validity in non-experimental trials is selection bias with systematic differences in patient allocation to one or the other treatment modality. However, from the data of institutional robotic MIS adoption, each cancer centre in Denmark rapidly offered robotic MIS to all patients with CC once they started their robotic program. Hence, selection bias seems neglectable. Historical events, for example, systematic changes, in oncological treatment are potential confounders that may have an interactive effect. However, the criteria for offering postoperative chemoradiation remained unchanged during the observation time [40]. Owing to the study design, analyses are sequential with different follow-up time in the two cohorts. Thus, late recurrences in the group with the shortest follow-up could be undetected.

5. Conclusion

The Danish national adoption of robotic MIS completely transitioned the surgical approach for early-stage CC. In this population-based study, we conclude that in the present setting, robotic MIS in CC is oncologically safe. Prior studies have identified significant patient-related benefits with robotic MIS. The abandonment of the procedure, based on a single randomized controlled trial, may be premature. However, we recognize that the area needs further investigation.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.12.020.

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