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Original Research

Survival after a nationwide introduction of robotic surgery in women with early-stage endometrial cancer: a population-based prospective cohort study

Siv Lykke Jørgensen [a,b,c,*,1], Ole Mogensen [c,d], Chunsen S. Wu [a,c], Malene Korsholm [a,b,c,g], Ken Lund [e,f], Pernille T. Jensen [a,c]

[a] *Department of Gynaecology and Obstetrics, Odense University Hospital, J. B. Winsløws Vej 4, 5000 Odense C, Denmark*
[b] *OPEN, Odense Patient Data Explorative Network, Odense University Hospital, B. Winsløws Vej 9 A, 5000 Odense C, Denmark*
[c] *Department of Clinical Health, Faculty of Health Sciences, Clinical Institute, University of Southern Denmark, J.B. Winsløws Vej 19, 5000 Odense C, Denmark*
[d] *Department of Pelvic Cancer, Karolinska University Hospital and Karolinska Institute, SE-171 77 Stockholm, Sweden*
[e] *Centre for Clinical Epidemiology, Odense University Hospital, Kløvervænget 30, 5000 Odense, Denmark*
[f] *Research Unit of Clinical Epidemiology, Institute of Clinical Research, University of Southern Denmark, Sdr. Boulevard 29, 5000 Odense C, Denmark*
[g] *Danish Centre for Health Economics (DaCHE), Department of Public Health, University of Southern Denmark, J.B. Winsløws Vej 9B, 1st Floor, 5000 Odense C, Denmark*

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Robotic surgical

Abstract ***Purpose:*** The purpose of the study was to evaluate the association between a nationwide introduction of robotic minimally invasive surgery (RMIS) and survival in women with early-stage endometrial cancer.

Materials and methods: Prospective data on consecutive women with early-stage endometrial cancer who underwent surgery during January 2005 to June 2015 in Denmark were identified in the nationwide Danish Gynaecological Cancer Database. Data were linked with national registries regarding comorbidity, education, income and death. The cohort was divided according to the time they underwent surgery: Group 1 before RMIS introduction in their respective region and Group 2 after RMIS introduction. Five-year overall survival was compared by multivariate Cox proportional hazards models stratified by histopathological

* *Corresponding author*. Research Unit of Gynaecology and Obstetrics, University of Southern Denmark, Kloevervaenget 10, 10th Floor, 5000 Odense C, Denmark.

E-mail addresses: siv.lykke.joergensen@rsyd.dk (S.L. Jørgensen), o.mogensen@health.sdu.dk (O. Mogensen), Chunsen.wu@rsyd.dk (C.S. Wu), Malene.korshols@rsyd.dk (M. Korsholm), Ken.lund@rsyd.dk (K. Lund), Pernille.tine.jensen@rsyd.dk (P.T. Jensen).

[1] Present address: Rollosvej 15, 5200 Odense V, Denmark. sivlykke@stofanet.dk

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procedures;
Robotics;
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Proportional hazards
models

risk between Groups 1 and 2 and between surgical modalities within Group 2: total abdominal hysterectomy (TAH), laparoscopic minimally invasive surgery (LMIS) and RMIS.

Results: Women in Group 1 (N = 3091) had significantly lower overall survival compared with those in Group 2 (N = 2563; hazard ratio [HR], 1.22; 95% confidence interval [CI], 1.05–1.42). Age, smoking, socioeconomic status, American Society of Anaesthesiologists (ASA) score, comorbidity and histopathological risk influenced the overall survival. Following RMIS adoption, TAH was associated with higher mortality compared with LMIS and RMIS (HR, 1.42; 95% CI 1.02–1.97 and HR, 1.70; 95% CI 1.31–2.19 for LMIS and RMIS, respectively). There was no significant survival difference between RMIS and LMIS (HR, 1.19; 95% CI 0.85–1.68).

Conclusion: The national introduction of robotic surgery for early-stage endometrial cancer was associated with improved survival irrespective of age, body mass index, ASA score, comorbidity, smoking, socioeconomic status and histopathological risk.

1. Introduction

Any substantial change in the surgical approach to cancer management necessitates evaluation to ensure survival is not compromised. In Denmark, robotic minimally invasive surgery (RMIS) was gradually introduced nationwide in early-stage endometrial cancer treatment during 2008–2013. The proportion of women who underwent minimally invasive surgery (MIS) increased from approximately 10% in 2008 to 95% in 2015 [1]. To our knowledge, only two randomised trials have compared RMIS with total abdominal hysterectomy (TAH) or with conventional laparoscopic MIS (LMIS) in early-stage endometrial cancer, and none of them included survival analyses [2,3]. Randomised trials on LMIS vs. TAH in early-stage endometrial cancer have demonstrated similar survival [4–7]. This has led to a gradual adoption of minimally invasive techniques albeit many women with endometrial cancer worldwide are still undergoing surgery using open techniques.

Emerging data from a randomised controlled trial on MIS vs. open access surgery in cervical cancer treatment (the Laparoscopic Approach to Cervical Cancer) was published recently [8]. The authors demonstrate a significantly increased risk of recurrence after MIS, which translated into decreased disease-free survival compared with open surgery. Hence, internationally, the use of minimally invasive techniques to treat gynaecological cancer is now greatly debated, and several initiatives have been taken to audit national data [9].

The primary aim of the present study was to evaluate the influence of a nationwide introduction of RMIS on the overall survival of women with early-stage endometrial cancer.

2. Methods

Consecutive patients diagnosed with primary endometrial cancer, International Federation of Gynaecology and Obstetrics (FIGO) Stages I–II who underwent surgery during 1st January 2005 to 30th June 2015 in Denmark, were identified through the Danish Gynaecological Cancer Database (DGCD). The DGCD is a national registry of all gynaecological cancer patients. Data are entered prospectively and comprise patient history, clinical and surgical information and preoperative and final pathology [10]. Data entering is mandatory. Annual reports on registered data in the DGCD are audited and published [11]. In Denmark, treatment of endometrial cancer is conducted in public hospitals, free of charge for the individual woman, and surgeons adhere to national guidelines. The national guidelines are evidence-based and updated every third year by a multidisciplinary group.

We identified the date of surgery for each patient. Hereafter, we identified the date of RMIS introduction for each cancer centre using the first date of RMIS performed for early-stage endometrial cancer. For women who were treated outside cancer centres, we used the date of the first RMIS performed in their respective region. The women were then divided into two groups: Group 1 if they underwent surgery before the RMIS introduction in their centre or region, and Group 2 if they underwent surgery after. Furthermore, women in Group 2 were subdivided according to the type of surgical access in TAH, LMIS and RMIS. The introduction of RMIS took place gradually between December 2008 and July 2013 across the Danish regions. This mimics a stepped wedge design although the main division of the data is a multi-institutional before-after design.

Data from the DGCD were unambiguously linked with information from four nationwide registers using the Danish Civil Registration System; all Danish citizens are provided a unique civil registration number at birth or immigration, which is used for all contacts with the authorities and the health care system and further used as an identifying key in multiple registers [12,13]. The Danish National Patient Register was used for extraction of information regarding comorbidity and severe complications as it holds information on all diagnoses and treatments related to hospital admissions and outpatients' visits since 1977 [14,15]. The Cause of Death Register holds nationwide and accurate data on all deaths in Denmark since 1970 and is based on the inquest [16]. Information from the Population Education Register and the Income Statistics Register were combined for information on socioeconomic status [17].

Increasing age is inevitably associated with increasing risk of death, and all models were therefore *a priori* adjusted for age, which was used as a continuous variable. Histopathological risk groups were predefined as low risk (endometrioid adenocarcinoma [EAC] FIGO Stage IA Grades I–II), intermediate low risk (EAC FIGO Stage IB Grades I–II), intermediate high risk (EAC FIGO Stage IA Grade III) and high risk (EAC FIGO Stage IB Grade III, FIGO Stage I with type II histology and FIGO Stage II) [18,19]. Socioeconomic status was categorised by the dispone income the year before surgery and the highest achieved educational level [20,21]. Body mass index (BMI), smoking status, the American Society of Anaesthesiologists score (ASA score) and Charlson Comorbidity Index (CCI) were used as a categorical variable, and lymphadenectomy was dichotomised (yes/no) [15,22,23].

The primary outcome was the postoperative 5-year overall survival. Patients were censored at 5 years after surgery for Cox proportional hazards analyses. The 5-year cut-off was chosen to ensure a sufficient proportion of patients in the exposure groups at the time of comparison while holding a long follow-up.

2.1. Statistical analyses

Demographic and tumour characteristics were compared using chi-squared tests. Age was compared by Wilcoxon rank-sum test between Group 1 and Group 2 and by Kruskal–Wallis test between TAH, LMIS and RMIS in Group 2. Predefined potential confounders were age, BMI, CCI, ASA score, smoking status, histopathological risk (including stage, grade and histological type), socioeconomic status, lymphadenectomy, centralization, adjuvant therapy and surgical year.

The women were followed from the date of surgery to death or end of follow-up, whichever came first; the duration in days from the date of surgery was used as the underlying time scale. The median follow-up including interdecile range was presented for each exposure group, and survival estimates including risk tables were presented by Kaplan–Meier plots.

Crude Cox proportional hazards models quantified the differences between exposure groups by hazard ratio (HR) with a 95% confidence interval (95% CI). To avoid over-adjustment, the multivariate Cox proportional hazards model that compared Group 1 and Group 2 was initially adjusted for the five confounders considered the most important: age, histopathological risk, ASA score, smoking status and socioeconomic status. The proportionality assumptions were evaluated with log-log plots and Schoenfeld residuals. The histopathological risk violated the assumption, and the model was, therefore, stratified by histopathological risk. Collinearity between age and histopathological risk was identified where younger age was associated with low-risk disease and higher age with intermediate-low and high-risk disease. Further adjustment for collinearity was not required due to the stratification. Hereafter, the log-likelihood ratio test was used to check whether the CCI, BMI and lymphadenectomy influenced the model (P value > 0.1). CCI influenced the model significantly, whereas BMI and lymphadenectomy did not. Potential two-way interactions between age, CCI and ASA score were hypothesised and tested with log-likelihood ratio test, and no interactions were identified. Hence, the final multivariate Cox proportional hazards model used to compare Group 1 with Group 2 was adjusted for age, CCI, ASA score, smoking status, socioeconomic status and stratified by histopathological risk. The multivariate Cox proportional hazards model used to compare TAH, LMIS and RMIS within Group 2 was adjusted accordingly.

Deaths from causes other than endometrial cancer may influence survival in a complex manner over time, and surgical year serves as a proxy for such influence. Hence, a second model of the comparison of surgical modalities within Group 2 including additional adjustment for the surgical year was tested by the log-likelihood ratio test. Additionally, a subgroup analysis of frail patients was performed. We defined a group of frail women with at least one of the following characteristics; advanced age (80 years or higher), ASA score III or higher, CCI II or higher or women with low/intermediate-low socioeconomic class as these women may be under-represented in randomised trials. Stratified analyses according to frailty were performed. As the distribution of patients with very high CCI and ASA scores could be skewed between exposure groups and thereby explain the significant survival difference between exposure groups among frail women, the analyses were performed using the specific CCI and ASA scores rather than the grouped variable. Furthermore, a sensitivity analysis of the 3-year overall survival was performed to ensure a near complete follow-up of all patients. Survival estimates could become skewed if the proportion of women with less favourable high-risk factors differed widely between exposure groups [24]. Hence, a second sensitivity analysis was performed where the adjusted models were restricted to the population excluding women with non-EACs Stage II, EACs Stage II, and carcinosarcoma Stage I. The entire cohort (all stages and histological types included) were assessed for stage migration. All analyses were conducted using STATA Version 15.0. A P value <0.05 was considered statistically significant.

2.2. Ethics

The study was approved by the Danish Data Protection Agency (13/15219).

3. Results

A total of 5654 women with early-stage endometrial cancer were included; 3091 underwent surgery before (Group 1) and 2563 underwent surgery after (Group 2) RMIS introduction (Fig. 1). The median follow-up was 8.8 years (interdecile range 2.8–12.0) for Group 1 and 4.4 years (interdecile range 2.7–7.2) for Group 2. The use of MIS was 14% and 72% in Groups 1 and 2, respectively. Patient and tumour characteristics of women who underwent surgery before and after RMIS introduction are presented in Table 1. Women who underwent surgery before RMIS introduction were younger, were more often smokers, had lower ASA score, had lower socioeconomic status, had staging lymphadenectomy performed less often and more often underwent surgery at departments outside cancer centres compared with women who underwent surgery after RMIS introduction.

The multivariate Cox proportional hazards model stratified by histopathological risk demonstrated significantly lower 5-year overall survival among women who underwent surgery before RMIS introduction (HR, 1.22; 95% CI, 1.05–1.42) compared with women who underwent surgery after (Table 2). Age, smoking, socioeconomic status, ASA score, CCI and histopathological risk significantly influenced the Cox proportional hazards model. The survival estimates of women who underwent surgery before and after RMIS introduction are presented by Kaplan–Meier plot and Cox proportional hazards adjusted curves in Fig. 2.

After the introduction of RMIS (Group 2), 712 (27.8%) women underwent TAH, 569 (22.2%) underwent LMIS and 1282 (50.0%) underwent RMIS. The median follow-up was 5.5 years (interdecile range,

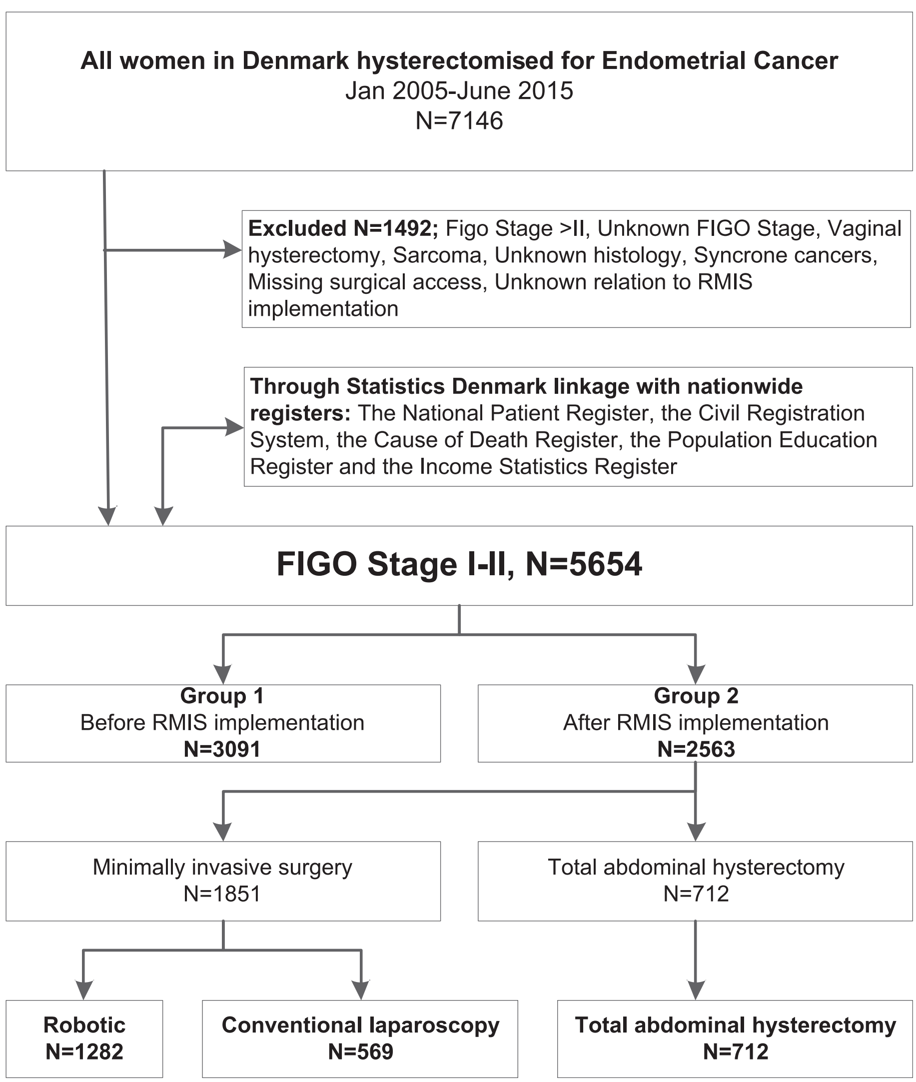

Fig. 1. Flowchart.

2.2–8.1) for TAH, 4.3 years (interdecile range, 2.7–6.3) for LMIS and 4.1 years (interdecile range, 2.7–6.6) for RMIS. Women who underwent TAH in Group 2 had more often high age, low BMI, high ASA score, high CCI, high-risk disease and lymphadenectomy performed than the women who underwent LMIS and RMIS in Group 2 (Table 1). The multivariate Cox proportional hazards model stratified by histopathological risk demonstrated significantly lower survival following TAH compared with LMIS and RMIS (HR, 1.42; 95% CI, 1.02–1.97 and HR, 1.70; 95% CI, 1.31–2.19, respectively), whereas no difference was observed in the LMIS and RMIS groups (adjusted HR, 1.19; 95% CI, 0.85–1.68; Table 2). The Kaplan–Meier survival curve and the Cox proportional hazards adjusted survival curve for women who underwent TAH, LMIS and RMIS are presented in Fig. 3. Additional adjustment of surgical year did not significantly influence the outcome.

The sensitivity analyses regarding the 3-year overall survival and analyses, which excluded women with non-EACs Stage II, EACs Stage II and carcinosarcoma Stage I, did not influence survival estimates significantly. Subgroup analyses of 'frailty' demonstrated no significant difference in overall survival between exposure groups among 'non-frail' women, whereas the overall

Table 1
Demographic and tumour characteristics of women with FIGO Stages I–II endometrial cancer.

Variable	Group 1[a] (N = 3091)	Group 2[b] (N = 2563)	*P*	TAH Group 2[b] (N = 712)	LMIS Group 2[b] (N = 569)	RMIS Group 2[b] (N = 1282)	*P*
Age, median (range)	66 (29–96)	67 (33–98)	0.019	68 (40–98)	67 (37–94)	67 (33–94)	<0.001
BMI (kg/m^2), n (%)							
<25.0	1043 (34.5)	784 (31.9)	0.004	245 (35.3)	178 (33.1)	361 (29.4)	<0.001
25.0–29.9	913 (30.2)	711 (28.9)		217 (31.2)	155 (28.8)	339 (27.7)	
30.0–34.9	579 (19.2)	482 (19.6)		121 (17.4)	117 (21.7)	244 (19.9)	
≥35.0	485 (16.1)	482 (19.6)		112 (16.1)	88 (16.4)	282 (23.0)	
Unknown	71	104		17	31	56	
CCI, n (%)							
0	2062 (66.7)	1662 (64.8)	0.088	442 (62.1)	393 (69.1)	827 (64.5)	0.007
1	488 (15.8)	461 (18.0)		121 (17.0)	91 (16.0)	249 (19.4)	
≥2	541 (17.5)	440 (17.2)		149 (20.9)	85 (14.9)	206 16.1)	
ASA, n (%)							
I	1208 (39.2)	783 (30.9)	<0.001	196 (27.7)	215 (38.5)	372 (29.4)	<0.001
II	1583 (51.3)	1448 (57.2)		407 (57.5)	287 (51.3)	754 (59.6)	
≥III	294 (9.5)	301 (11.9)		105 (14.8)	57 (10.2)	139 (11.0)	
Unknown	6	31		4	10	17	
Smoking status, n (%)							
Never smoker	1677 (65.0)	1507 (66.2)	<0.001	392 (62.7)	365 (69.5)	750 (66.7)	0.177
Former smoker	421 (16.3)	469 (20.6)		140 (22.4)	100 (10.1)	229 (20.3)	
Active smoker	483 (18.7)	299 (13.2)		93 (14.9)	60 (11.4)	146 (13.0)	
Unknown	510	288		87	44	157	
Socioeconomic class, n (%)							
Low	698 (22.6)	455 (17.7)		113 (15.9)	96 (16.9)	246 (19.2)	
Intermediate-low	893 (28.9)	696 (27.2)		202 (28.4)	160 (28.1)	334 (26.1)	
Intermediate	639 (20.7)	568 (22.2)		169 (23.7)	119 (20.9)	280 (21.8)	
Intermediate-high	485 (15.7)	452 (17.6)		129 (18.1)	113 (19.9)	210 (16.4)	
High	376 (12.1)	392 (15.3)	<0.001	99 (13.9)	81 (14.2)	212 (16.5)	0.201
Histopathological risk, n (%)							
Low risk	1642 (54.2)	1445 (57.5)	0.001	319 (45.3)	359 (64.6)	767 (61.3)	<0.001
Intermediate low	614 (20.3)	404 (16.1)		120 (17.0)	107 (19.2)	177 (14.2)	
Intermediate high	102 (3.4)	79 (3.2)		28 (4.0)	17 (3.1)	34 (2.7)	
High risk	670 (22.1)	583 (23.2)		237 (33.7)	73 (13.1)	273 (21.8)	
Unknown	63	52		8	13	31	
Lymphadenectomy, n (%)							
No	2306 (74.8)	1622 (64.6)	<0.001	400 (58.1)	382 (67.5)	840 (66.9)	<0.001
Yes	776 (25.2)	888 (35.4)		289 (41.9)	184 (32.5)	415 (33.1)	
Unknown	9	53		23	3	27	
Treatment at a cancer centre, n (%)							
No	1320 (42.7)	101 (3.9)	<0.001	–	–	–	
Yes	1770 (57.3)	2462 (96.1)		–	–	–	
Unknown	1	0		–	–	–	

Abbreviations: ASA, American Society of Anaesthesiologists physical status classification system; BMI, body mass index; CCI, Charlson comorbidity index; LMIS, laparoscopic minimally invasive surgery; RMIS, robotic minimally invasive surgery; TAH, total abdominal hysterectomy.
[a] Group 1, women who had surgery before RMIS introduction.
[b] Group 2, women who had surgery after RMIS introduction.

Table 2
Crude and adjusted Cox proportional hazards models comparing groups and surgical modalities within Group 2.

Variables included in the model	Group 1[a] versus Group 2[b]		TAH and LMIS versus RMIS in Group 2[b]	
	Crude	Multivariate[c]	Crude	Multivariate[c]
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Group 1	1.21 (1.06–1.40)	1.22 (1.05–1.42)	–	–
Group 2	1.00	1.00	–	–
TAH in Group 2	–	–	2.08 (1.63–2.65)	1.70 (1.31–2.19)
LMIS in Group 2	–	–	1.03 (0.75–1.42)	1.19 (0.85–1.68)
RMIS in Group 2	–	–	1.00	1.00
Age (years)		1.06 (1.05–1.07)		1.07 (1.05–1.08)
Smoking				
Non-smoker		1.00		1.00
Former smoker		0.96 (0.79–1.16)		1.02 (0.77–1.37)
Active smoker		1.44 (1.18–1.75)		1.29 (0.91–1.82)
Socioeconomic class				
High		0.94 (0.67–1.32)		0.94 (0.56–1.57)
Intermediate-high		0.97 (0.73–1.30)		0.70 (0.44–1.12)
Intermediate		1.00		1.00
Intermediate-low		1.27 (1.03–1.57)		1.26 (0.91–1.73)
Low		1.22 (0.97–1.52)		1.21 (0.85–1.72)
ASA group				
I		0.68 (0.55–0.84)		0.63 (0.44–0.91)
II		1.00		1.00
≥III		1.61 (1.33–1.93)		1.48 (1.11–1.96)
CCI				
0		1.00		1.00
1		1.27 (1.05–1.54)		1.27 (0.94–1.72)
≥2		1.70 (1.42–2.03)		1.69 (1.28–2.24)

Abbreviation: HR, hazard ratio.
[a] Group 1, women who had surgery before RMIS introduction.
[b] Group 2, women who had surgery after RMIS introduction.
[c] Stratified by histopathological risk.

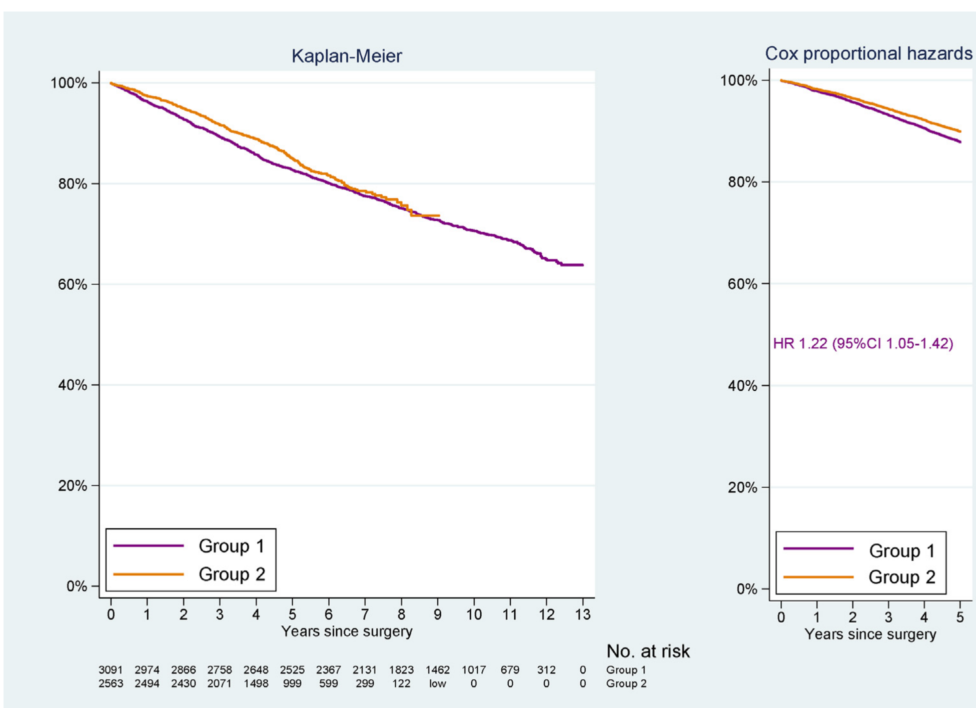

Fig. 2. Survival estimates before (Group 1) and after (Group 2) introduction of robotic minimally invasive surgery. The output of the Cox proportional hazards model on the group comparison remained close to unchanged whether stratified by or adjusted for histopathological risk. For visual simplicity, the multivariate Cox proportional hazards plot was adjusted for histopathological risk (reference low-risk group) rather than presented as a panel of curves for each stratum.

survival was significantly lower in Group 1 compared with Group 2 and following TAH compared with LMIS and RMIS among ‘frail’ women (Table 3).

4. Discussion

To our knowledge, this is the first evaluation of the association between a nationwide introduction of RMIS and survival of women with early-stage endometrial cancer. Introduction of RMIS has been demonstrated to increase the use of MIS [25–27], and MIS is associated with decreased complications [1,2,7,28,29]. Two different analytical approaches were used in the present study to compare survival in patients who underwent surgery before and after RMIS introduction and between groups of patients undergoing surgery by different surgical modalities after the introduction of RMIS. Independent of the analytical approach, the adoption of RMIS was associated with improved survival despite inclusion of the RMIS learning curve for all surgeons and an increased use of MIS among women with high BMI, high ASA score, high-risk histopathology and more lymph node dissection performed. The positive association between minimally invasive techniques and survival was further substantiated by the sensitivity analyses, which indicated that the improved survival was not due to a shorter follow-up in the minimally invasive cohorts or to a selected allocation of women with more favourable risk factors in Group 2.

Our results are in accordance with the study of Safdieh *et al.*, who recently published an American population–based register study deriving from the National Cancer Database of 43,985 women with non-metastatic endometrial cancer [30], approximately encompassing one-third of the women diagnosed with early-stage endometrial cancer in the United States over the study period [31]. The overall survival following RMIS improved significantly compared with TAH when adjusted for age, surgical year, comorbidity, race, lymph-node yield, stage, adjuvant oncological treatment and economic class [30]. The authors did not adjust for BMI or histopathological risk. The obesity pandemic is particularly present in the United States, and severe obesity is associated with low-risk endometrial cancer, which has a good prognosis [32]. In the study of Safdieh *et al.*, the allocation of severely obese women could be skewed towards RMIS as the technique has been demonstrated to be favourable for this group [33–38]. The inclusion of a large proportion of women with low-risk histology may potentially overestimate the survival benefit. The present investigation takes account of the influence of histopathological risk and BMI, thereby further substantiating the positive association between a

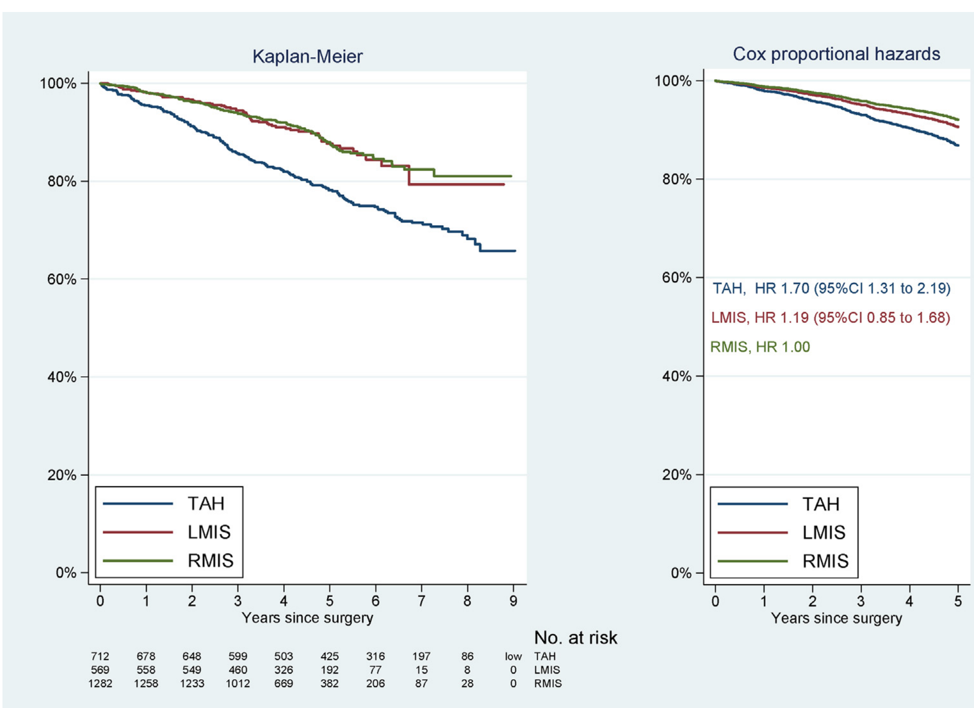

Fig. 3. Survival estimates after introduction of robotic minimally invasive surgery. TAH, total abdominal hysterectomy; LMIS, laparoscopic minimally invasive surgery; RMIS, robotic minimally invasive surgery. The output of the Cox proportional hazards model on the comparison of surgical modalities remained close to unchanged whether stratified by or adjusted for histopathological risk. For visual simplicity, the multivariate Cox proportional hazards plot was adjusted for histopathological risk (reference low-risk group) rather than presented as a panel of curves for each stratum.

Table 3
Adjusted and stratified Cox proportional hazards models of 'non-frail' and 'frail' women with early-stage endometrial cancer.

Subgroup	Number of deaths/total[d]	Group 1[a]	Group 2[b]
		HR (95% CI)	HR (95% CI)
'Non-frail' women	125/1887	1.31 (0.90–1.90)	1.00 (reference)
'Frail' women[c]	622/2961	1.23 (1.04–1.45)	1.00 (reference)

Subgroup	Number of deaths/total	TAH Group 2[b]	LMIS Group 2[b]	RMIS Group 2[b]
		HR (95% CI)	HR (95% CI)	HR (95% CI)
'Non-frail' women	44/909	1.58 (0.78–3.20)	1.84 (0.83–4.09)	1.00 (reference)
'Frail' women[c]	254/1362	1.65 (1.25–2.19)	1.10 (0.75–1.60)	1.00 (reference)

Abbreviation: CI, confidence interval.
[a] Patients with missing values are not included.
[b] Group 1, women who had surgery before RMIS introduction.
[c] Group 2, women who had surgery after RMIS introduction.
[d] Frailty is defined by advanced age (≥ 80 years), ASA score III, or higher, low/intermediate-low socioeconomic class, CCI II or higher.

nationwide RMIS introduction and improved survival. Wright *et al.* did a register study of 6304 elderly (65+) middle-class women with early-stage endometrial cancer enrolled in a US national insurance program (Medicare) [39]. They reported a non-significant overall survival in favour of MIS compared with TAH. Social disparities may influence survival [40] and surgical allocation [30,41] in the United States. The present study includes all ages and socioeconomic status and found that RMIS and LMIS were associated with improved survival. Two multinational, randomised controlled trials and a recent meta-analysis have demonstrated that overall survival after LMIS is similar to the overall survival after TAH and that LMIS is associated with reduced surgical morbidity in early-stage endometrial cancer [4,5,7]. Randomised clinical trials have excellent internal validity. However, they do not necessarily describe the influence of a treatment in a complete population as frail subgroups tend to be poorly represented due to strict inclusion criteria [42]. In our study, subanalysis indicated that the positive association between the nationwide adoption of minimally invasive techniques and survival was present among predefined frail patients, whereas similar survival was observed among the more robust women. Population-based studies supplement results from randomised trials by providing insight into the clinical use [42]. Our study group has recently reported that the Danish nationwide introduction of RMIS is associated with reduced risk of severe complications [43]. Hence, a nationwide implementation of MIS for early stage endometrial cancer is therefore not only considered oncologically safe but is likely to provide clear benefits for early-stage endometrial cancer patients in general and in particular for those women considered frail due to comorbidity, age and low socioeconomic status.

During the inclusion period of the present study, the treatment changed at a national level. Pelvic lymphadenectomy increased among women with intermediate risks (2005–2010). This may have contributed to a stage migration from FIGO Stages I to IIIC, which subsequently may have improved the survival in the group with early-stage disease. However, we did not observe any increase of Stage III disease in the latter timeframe (Fig. 4)). In 2009, the Danish Government implemented pre-booked and accelerated cancer patient trajectories called 'cancer packages' that increased the awareness of post-menopausal bleeding among general practitioners and reduced the waiting time. Hence, a potential stage migration towards increased Stage III disease may in the Danish data be counteracted by detection of the disease before it become metastatic due to the introduction of 'cancer packages'. As it appears from Fig. 4 the incidence of endometrial cancer increased over time mainly due to an increase in early stage disease with low-risk and high-risk histology. This could comprise relevant confounders in different directions. However, in our study, the analyses were stratified by histopathological risk, which means that women with, for example, EACs Grades 1–2 Stage IA are compared between exposure groups in their own strata. Hence, neither stage migration following increased performance of lymphadenectomy nor introduction of 'cancer packages' can explain the positive association between improved survival and the introduction of RMIS irrespective of the histopathological strata.

The adjuvant oncological treatment for patients with intermediate-high and high-risk histopathology changed in 2009 from postoperative pelvic external beam radiation to per-protocol adjuvant chemotherapy or observation (ENGOT-EN2-DGCG/EORTC 55102) [43]. Results of the ENGOT-EN2-DGCG/EORTC 55102 are still pending, and interpretation of any potential influence is therefore not possible. External beam radiation therapy is associated with a decreased risk of local recurrence but has not been demonstrated to improve the overall survival in women with early-stage endometrial cancer [44]. The influence of adjuvant chemotherapy in patients with high-risk disease is debated, and the effect has been questioned in several studies [30,44,45]. However, in our national cohort of patients with FIGO Stages

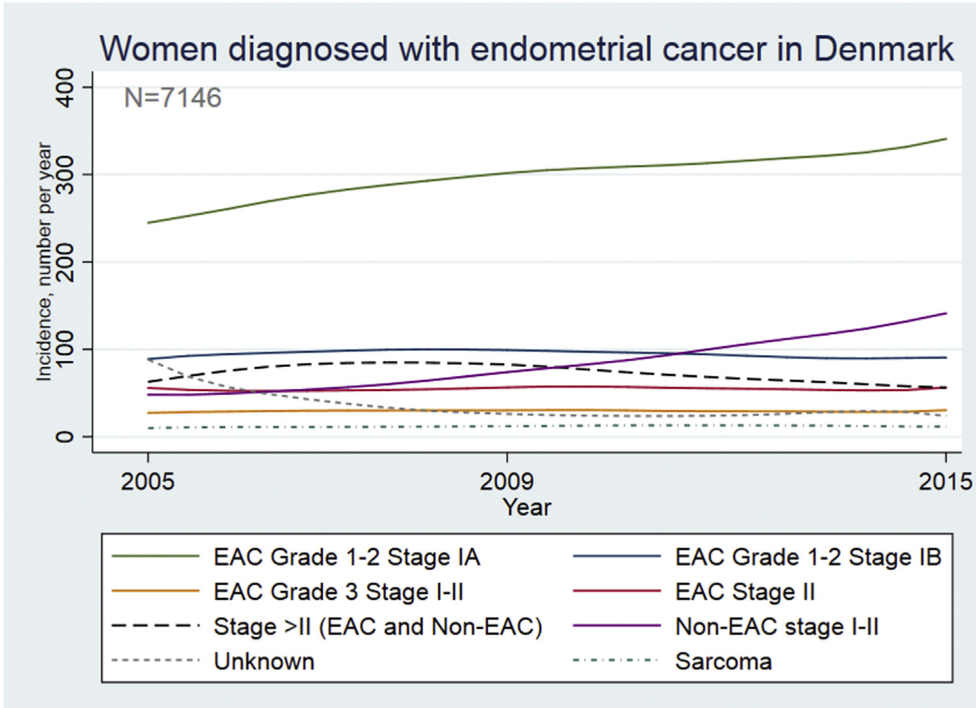

Fig. 4. Danish women diagnosed with endometrial cancer presented by risk groups. EAC, endometrioid adenocarcinoma; Non-EAC, non-endometrioid adenocarcinoma.

I–II only, improved survival following MIS was present irrespective of the histopathological strata, and adjuvant treatment is therefore not likely to have influenced the results significantly.

The surgical treatment was gradually centralised to six cancer centres during the study period and was fully accomplished in 2012 [11,46]. The potential influence on survival of the expertise of high-volume centres is a potential confounder [47]. Centralised treatment may decrease complications due to higher expertise and a higher likelihood of MIS [41]. However, higher expertise may also prompt more comprehensive surgery, for example, including pelvic and/or para-aortic lymphadenectomy for women with high age or severe comorbidity. After the introduction of RMIS, only 101 women, of whom 84% had intermediate-low and low-risk histopathology, underwent surgery outside the cancer centres, and adjustment for centralisation was therefore not possible. However, the positive influence of MIS on survival was still present after centralisation was accomplished (Group 2). It could be questioned whether changes in staging and societal changes during the 10-year period constitutes relevant confounders. In our study, the histopathological risk is based on myometrial invasion, histological grade and type. The stage of those women operated before 2009 were transformed to the FIGO 2009 classification. Hence, changes in the FIGO staging do not influence our analyses. Societal changes may improve overall survival over a decade as it could be influenced by a general focus on healthy living and improved socioeconomic status. However, the Danish background population is, in general, stable, and the overall survival among women in the age group represented in the included population of early-stage endometrial cancer has not changed substantially within the past decade.

4.1. Strengths and limitations

The main strength of the present study is the inclusion of a population-based cohort with prospectively obtained and validated clinical data with a long follow-up. The unique personal identification number provided comprehensive information on in- and out-patient visits in all hospitals, immigration and accurate knowledge of the vital status. In this study, we were unable to control for adjuvant oncological treatment and did not have information on disease recurrence. The latter prevented evaluation of the cancer-specific survival. Adjusted analyses were used to comply with the potential bias, but we cannot rule out that unmeasured covariates may influence the result. Finally, register studies depend on the data entry quality. The registers included in the study from which the exposures, covariates and outcome derive are national and validated, thus minimizing potential information bias. However, the CCI score derived from hospital coding and may underestimate those comorbidities treated by the general practitioner. The underestimation is, however, presumed equally distributed between the surgical modalities.

5. Conclusion

The overall survival among women with early-stage endometrial cancer improved after a Danish national introduction of RMIS. Furthermore, open surgery was associated with a higher mortality compared with its minimally invasive counterparts. It is suggested that MIS should be the preferred surgical access in early-stage endometrial cancer irrespective of age, BMI, ASA score, comorbidity, smoking, socioeconomic status and histopathological risk.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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