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Original Research

# No survival difference between robotic and open radical hysterectomy for women with early-stage cervical cancer: results from a nationwide population-based cohort study

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**KEYWORDS**
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Radical hysterectomy;
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Surgery;
Survival;
Disease-free survival

**Abstract** ***Purpose:*** The aim of the study was to compare overall survival (OS) and disease-free survival (DFS) after open and robotic radical hysterectomy for early-stage cervical cancer.
***Patients and methods:*** This was a nationwide population-based cohort study on all women with cervical cancer stage IA1-IB of squamous, adenocarcinoma or adenosquamous histological subtypes, from January 2011 to December 2017, for whom radical hysterectomy was performed. The Swedish Quality Register of Gynaecologic Cancer was used for identification. To ensure quality and conformity of data and to disclose patients not yet registered, hospital registries were reviewed and validated. Cox and propensity score regression analysis and univariable and multivariable regression analysis were performed in regard to OS and DFS.
***Results:*** There were 864 women (236 open and 628 robotic) included in the study. The 5-year OS was 92% and 94% and DFS was 84% and 88% for the open and robotic cohorts, respectively. The recurrence pattern was similar in both groups. Using propensity score analysis and

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matched cohorts of 232 women in each surgical group, no significant differences were seen in survival: 5-year OS of 92% in both groups (hazard ratio [HR], 1.00; 95% confidence interval [CI], 0.50–2.01) and DFS of 85% vs 84% in the open and robotic cohort, respectively (HR, 1.08; 95% CI, 0.66–1.78). In univariable and multivariable analysis with OS as the end-point, no significant factors were found, and in regard to DFS, tumour size ($p < 0.001$) and grade 3 ($p = 0.02$) were found as independent significant risk factors.

***Conclusion:*** In a complete nationwide population-based cohort, where radical hysterectomy for early-stage cervical cancer is highly centralised, neither long-term survival nor pattern of recurrence differed significantly between open and robotic surgery.



## 1. Introduction

Radical hysterectomy constitutes the primary treatment of early-stage cervical cancer. The Swedish national guidelines [1] are consistent with the National Comprehensive Cancer Network [2], which recommends that radical hysterectomy can be performed either by laparotomy or by minimally invasive surgery (MIS). In Sweden, radical hysterectomy by conventional laparoscopy has never gained acceptance, whereas there has been a dramatic uptake of robotic surgery in the past decade.

Observational studies suggest that MIS for cervical cancer is associated with shorter hospital stay, fewer complications and reduced blood loss compared with laparotomy [3–7]. Furthermore, retrospective data suggest that the oncological safety is comparable between the two approaches [4,8–12]. However, two studies raise serious concerns regarding the safety of MIS for the treatment of early-stage cervical cancer. In a population-based cohort study based on 2461 women in the US [13], with a median follow-up of 45 months, inferior survival was found after MIS compared with laparotomy (hazard ratio [HR] 1.65, $p = 0.002$). Furthermore, the Laparoscopic Approach to Cervical Cancer (LACC) trial [14], a randomised controlled trial (RCT) enrolling 631 women, showed a disease-free survival (DFS) of 86.0% after 4.5 years in the MIS arm compared with 96.5% in the open arm. The LACC trial mainly included women treated with conventional laparoscopy in the MIS arm. In addition, all recurrences in the MIS arm were concentrated to 14 of 33 participating centres why internal validity may be questioned. The possible bias could be caused by the multicentre and multinational design with different medical health care structures. Furthermore, the challenging MIS technique with, that conventional laparoscopy was used in the majority of the cases in the MIS arm. where the surgeons' experience may have an impact on the outcome, although the study tried to assess the surgeons' skill.

The age-adjusted incidence rate of cervical cancer in Sweden is approximately 8 of 100 000, with 560 new cases annually [15]. The management of cervical cancer is highly centralised to seven university hospitals, and all women treated are registered in a nationwide quality register (Swedish Quality Register of Gynaecologic Cancer [SQRGC]). Robotic surgery for gynaecological cancer was introduced in Sweden in 2005. After a structured implementation, the robotic surgical technique gradually replaced open surgery for cervical cancer at most centres. Robotic radical hysterectomy was introduced in Sweden by 2 tutors, and only a few gynae-oncology surgeons at each university hospital perform radical hysterectomies in close collaboration with each other as per national protocols and guidelines, ensuring conformity. Furthermore, uterine manipulators are not recommended in any gynae-oncology robotic surgeries.

The purpose of this study was to assess the oncological safety of robotic radical hysterectomy compared with that of open radical hysterectomy based on prospectively entered data in the SQRGC, which were validated and complemented by reviews of medical records and follow-up. Our primary and secondary objectives were to assess overall survival (OS) and DFS, respectively.

## 2. Materials and methods

All residents in Sweden are allocated a personal identification number. Reporting to the Swedish National Cancer Registry (NCR) is compulsory for clinicians and pathologists [16]. The SQRGC was established in 2008, and cervical cancer was included in 2011. Reporting to the SQRGC is performed prospectively by all clinics. The registration includes information concerning patient and tumour characteristics, details on received surgical and oncological therapies, outcomes and follow-up data. Linkage to the National Death Registry ensures lifelong follow-up and recording the date of death. The coverage relative to the NCR is approximately 95%, and the SQRGC data have been independently validated [17]. The SQRGC was used to identify women according to the defined criteria. Importantly, local hospital registries and patient records were reviewed to identify women not yet entered in the SQRGC. To ensure quality and conformity

of data on follow-up, a chart review using defined criteria for relevant clinical parameters was performed on the complete cohort of women with cervical cancer between January 2011 and December 2017 having a primary radical hysterectomy according to Querleu–Morrow classification type B or C performed in Sweden. The study included all women ≥18 years with FIGO stage IA1-IB1 cervical cancers of squamous, adenocarcinoma or adenosquamous histological subtypes. Selection of the type of surgery was mainly based on the availability of the robotic system at each centre. The exclusion criteria were all other histological subtypes such as neuroendocrine among others, radical hysterectomy in conjunction with a caesarean section and where the radical hysterectomy had been aborted in favour of chemoradiation therapy because of an intraoperative finding. Among commonly defined parameters extracted from the patient's charts were tumour size, nodal count and status together with sites of recurrence. Tumour size was defined as the largest tumour diameter in the cone biopsy or hysterectomy specimen. Adequate margins were defined as at least a 10-mm margin from the tumour to the resected area, according to national guidelines. Expert gynae-oncological pathology reviews were registered, as well as the location of the radical hysterectomy performed, as in one of the seven university hospitals (tertiary centre) or other regional hospitals. Received adjuvant therapy was registered. Patients were followed up until 24th October 2018 or death, whichever came first. The ethical review board at Gothenburg University (Dnr397-18) approved the study.

### 2.1. Statistical methods

Student's t-test was used for comparing continuous variables, whereas categorical variables were evaluated using Pearson's chi-squared test or Fisher's exact test depending on the category size. The Kaplan–Meier [18] estimator was used to estimate the survival function. Using the proportional hazards model, we estimated HRs for each of the variables: age, grade, tumour size, lymph-vascular space invasion (LVSI), lymph node status and primary treatment. We performed propensity score matching [19] to reduce the bias in the estimate of the difference in survival for open and robotic radical hysterectomies for cervical cancer. The propensity score model was made accounting for age, grade, tumour size, LVSI, lymph node status, primary treatment and diagnosis year. To estimate the difference in survival between the two surgical methods, we estimated a proportional hazard model [20] in matched data. A $p$-value less than 0.05 was considered significant. R statistical software version 3.5.1 was used for all statistical analysis. The 'Survival' package version 2.42.3 was used for survival estimation and proportional hazard estimations. The 'MatchIt' package version 3.0.2 was used to match the data based on the propensity score.

## 3. Results

### 3.1. Patient characteristics

In total, 864 patients were identified; their clinical and pathological characteristics are shown in detail in Table 1. Open surgery was performed on 236 (27%) patients, and 628 (73%) had minimal invasive (all robotic) surgery. A flow chart is shown in Fig. 1.

There were no significant differences in FIGO stage or histology between the groups. A difference was seen regarding tumour size ($p < 0.020$) and LVSI ($p < 0.001$). The median number of retrieved lymph nodes was 26 in the open compared with 23 in the robotic group ($p = 0.006$). However, no difference was noted regarding the number of positive lymph nodes. The majority of the surgeries 814 (94.2%) were performed at a tertiary centre with an expert gynae-oncology pathology review in the majority of cases, 623 of 864 (72.1%) with no differences between the groups. A significant difference was seen in primary treatment between the groups ($p < 0.001$), where 32.2% in the open group received adjuvant therapy compared with 20.9% in the robotic group. Altogether, 84 (9.7%) patients had a recurrence, and there was no difference between the groups ($p = 0.119$). Stratifying for the site of recurrence did not show any significant result ($p = 0.269$). The open group had a longer follow-up (55.7 months; range, 6.5–93.2) compared with the robotic group (44.5 months; range, 2.2–93.6) ($p < 0.001$).

### 3.2. Overall survival

The OS in the open and robotic group is shown in Fig. 2A. A total of 18 deaths (8%) were seen in the open group, and 31 (5%), in the robotic group. No difference in the 5-year OS was detected with 92% in the open (95% confidence interval [CI], 88–96) and 94% in the robotic group (95% CI, 91–96). The OS adjusted for tumour size did not reveal any differences regarding tumour size ≤20 mm (open: 95% [95% CI, 91–99], robot: 94% [95% CI, 92–97]), >20 ≤ 40 mm (open: 89% [95% CI, 81–98], robot: 91% [95% CI, 86–97]) and >40 mm (open 71% [95% CI, 48–100], robot 92% [95% CI, 77–100]) between the open and robotic group (Supplementary Figure 2A). Moreover, the OS was stratified according to surgery alone or surgery combined with adjuvant therapy (Supplementary Figure 1A), and no differences were noted with 95% (95% CI, 91–99) in open surgery alone compared with 95% in the robotic group (95% CI, 93–98). The corresponding results for open surgery combined with adjuvant therapy were 86% (95% CI,

Table 1
Clinical and pathological characteristics of the study population before and after propensity score matching.

| Variables | Cohort before propensity score matching | | | | Cohort after propensity score matching | | | |
|---|---|---|---|---|---|---|---|---|
| | Total n = 864 (100%) | Open n = 236 (27%) | Robotic n = 628 (73%) | *p*-value | Total n = 464 (100%) | Open n = 232 (50%) | Robotic n = 232 (50%) | *p*-value |
| Age groups; median (range) years | 43 (22–83) | 46 (24–81) | 42 (22–83) | | 46 (23–83) | 45 (24–81) | 46 (23–83) | |
| 18–37 | 225 (26.0) | 49 (20.8) | 176 (28.0) | 0.001[b] | 104 (22.4) | 49 (21.1) | 55 (23.7) | 0.637[b] |
| 38-43 | 208 (24.1) | 50 (21.2) | 158 (25.2) | | 95 (20.5) | 50 (21.6) | 45 (19.4) | |
| 44-52 | 224 (25.9) | 59 (25.0) | 165 (26.3) | | 122 (26.3) | 57 (24.6) | 65 (28) | |
| 53-83 | 207 (24.0) | 78 (33.1) | 129 (20.5) | | 143 (30.8) | 76 (32.8) | 67 (28.9) | |
| Body Mass Index; median (range) | 25 (16.8 –59.9) | 24.7 (16.8 –47) | 25 (17–59.9) | 0.918[a] | 25 (16.8–53) | 24.7 (16.8 –47) | 25.1 (17–53) | 0.804[a] |
| Data missing n (%) | 40 (4.6) | 17 (7.2) | 23 (3.7) | | | | | |
| FIGO stage n (%) | | | | 0.338[b] | | | | 0.876[b] |
| IA1 | 44 (5.1) | 8 (3.4) | 36 (5.7) | | 16 (3.4) | 8 (3.4) | 8 (3.4) | |
| IA2 | 82 (9.5) | 21 (8.9) | 61 (9.7) | | 37 (8) | 20 (8.6) | 17 (7.3) | |
| IB1 | 738 (85.4) | 207 (87.7) | 531 (84.6) | | 411 (88.6) | 204 (87.9) | 207 (89.2) | |
| Histology n (%) | | | | 0.526[b] | | | | 0.995[b] |
| Squamous | 510 (59) | 145 (61.4) | 365 (58.1) | | 285 (61.4) | 142 (61.2) | 143 (61.6) | |
| Adenocarcinoma | 311 (36) | 78 (33.1) | 233 (37.1) | | 153 (33.0) | 77 (33.2) | 76 (32.8) | |
| Adenosquamous | 43 (5) | 13 (5.5) | 30 (4.8) | | 26 (5.6) | 13 (5.6) | 13 (5.6) | |
| Grade[d] n (%) | | | | <0.001[b] | | | | 0.913[b] |
| G1 | 124 (14.3) | 36 (15.3) | 88 (14) | | 73 (15.7) | 36 (15.5) | 37 (15.9) | |
| G2 | 231 (26.7) | 86 (36.4) | 145 (23) | | 173 (37.3) | 84 (36.2) | 89 (38.4) | |
| G3 | 238 (27.5) | 77 (32.6) | 161 (25.6) | | 149 (32.1) | 75 (32.3) | 74 (31.9) | |
| Not stated | 271 (31.4) | 37 (15.7) | 234 (37.3) | | 69 (14.9) | 37 (15.9) | 32 (13.8) | |
| Tumour size n (%) | | | | 0.020[b] | | | | 0.619[b] |
| ≤20 mm | 610 (70.6) | 150 (63.6) | 460 (73.2) | | 309 (66.6) | 150 (64.7) | 159 (68.5) | |
| >20 ≤ 40 mm | 221 (25.6) | 70 (29.7) | 151 (24) | | 134 (28.9) | 70 (30.2) | 64 (27.6) | |
| >40 mm | 28 (3.2) | 12(5.1) | 16 (2.5) | | 21 (4.5) | 12 (5.2) | 9 (3.9) | |
| Data missing | 5 (0.6) | 4 (1.7) | 1 (0.2) | | 0 (0) | 0 (0) | 0 (0) | |
| Lymph-vascular space invasion (LVSI) n (%) | | | | 0.001[b] | | | | 0.413[b] |
| LVSI - | 369 (42.7) | 83 (35.2) | 286 (45.5) | | 168 (36.2) | 82 (35.3) | 86 (37.0) | |
| LVSI + | 259 (30) | 92 (39) | 167 (26.6) | | 188 (40.5) | 90 (38.8) | 98 (42.2) | |
| Not stated | 236 (27.3) | 61 (25.8) | 175 (27.9) | | 108 (23.3) | 60 (25.9) | 48 (20.7) | |
| Number of lymph nodes retrieved; median (range) | 24 (1–80) | 26 (1–80) | 23 (2–64) | 0.006[a] | 24 (1–80) | 26.5 (1–80) | 23 (4–64) | 0.005[a] |
| Lymph node status n (%) | | | | 0.107[b] | | | | 0.795[b] |
| Negative nodes | 760 (88) | 201 (85.2) | 559 (89) | | 394 (84.9) | 198 (85.3) | 196 (84.5) | |
| Positive nodes | 103 (11.9) | 35 (14.8) | 68 (10.8) | | 70 (15.1) | 34 (14.7) | 36 (15.5) | |
| Data missing | 1 (0.1) | 0 (0) | 1 (0.2) | | 0 (0) | 0 (0) | 0 (0) | |
| Primary treatment; n (%) | | | | <0.001[c] | | | | 0.125[b] |
| Radical hysterectomy alone | 657 (76) | 160 (67.8) | 497 (79.1) | | 319 (68.8) | 158 (68.1) | 161 (69.4) | |
| Radical hysterectomy +adjuvant therapy | 207 (24.0) | 76 (32.2) | 131 (20.9) | | 145 (31.3) | 74 (31.9) | 71 (30.6) | |
| Indication for adjuvant therapy; n (%) | | | | 0.524[c] | | | | 0.797[c] |
| Positive nodes | 103 (49.8) | 35 (46.1) | 68 (51.9) | | 67 (46.2) | 35 (47.3) | 32 (45.1) | |
| Inadequate surgical margins | 94 (45.4) | 36 (47.4) | 58 (44.3) | | 70 (48.3) | 34 (45.9) | 36 (50.7) | |
| Tumour size >40 mm | 10 (4.8) | 5 (6.6) | 5 (3.8) | | 8 (5.5) | 5 (6.8) | 3 (4.2) | |
| Percentage open vs robotic radical hysterectomy and year of diagnosis n (%) | | | | <0.001[b] | | | | 0.296[b] |
| 2011 | 102 (11.8) | 45 (19.1) | 57 (9.1) | | 87 (18.8) | 45 (19.4) | 42 (18.1) | |
| 2012 | 119 (13.8) | 37 (15.7) | 82 (13.1) | | 59 (12.7) | 35 (15.1) | 24 (10.3) | |
| 2013 | 115 (13.3) | 38 (16.1) | 77 (12.3) | | 65 (14.0) | 36 (15.5) | 29 (12.5) | |
| 2014 | 134 (15.5) | 37 (15.7) | 97 (15.4) | | 73 (15.7) | 37 (15.9) | 36 (15.5) | |
| 2015 | 139 (16.1) | 27 (11.4) | 112 (17.8) | | 53 (11.4) | 27 (11.6) | 26 (11.2) | |
| 2016 | 129 (14.9) | 29 (12.3) | 100 (15.9) | | 68 (14.7) | 29 (12.5) | 39 (16.8) | |
| 2017 | 126 (14.6) | 23 (9.7) | 103 (16.4) | | 59 (12.7) | 23 (9.9) | 36 (15.5) | |

Table 1 (*continued*)

| Variables | Cohort before propensity score matching | | | | Cohort after propensity score matching | | | |
|---|---|---|---|---|---|---|---|---|
| | Total n = 864 (100%) | Open n = 236 (27%) | Robotic n = 628 (73%) | *p*-value | Total n = 464 (100%) | Open n = 232 (50%) | Robotic n = 232 (50%) | *p*-value |
| Follow-up in months; median (range) | | | | <0.001[a] | | | | 0.054[a] |
| Total | 46.5 (2.2–93.6) | 55.7 (6.5–93.2) | 44.5 (2.2–93.6) | | | 55.3 (6.5–93.2) | 49.0 (8.4–93.6) | |
| Data missing | 0 (0) | 0 (0) | 0 (0) | | 0 (0) | 0 (0) | 0 (0) | |
| Recurrences n (% of radical hysterectomy) | | | | 0.119[b] | | | | 0.886[b] |
| No | 780 (90.3) | 207 (87.7) | 573 (91.2) | | 409 (88.1) | 205 (88.4) | 204 (87.9) | |
| Yes | 84 (9.7) | 29 (12.3) | 55 (8.8) | | 55 (11.9) | 27 (11.6) | 28 (12.1) | |
| Vital status | | | | 0.128[b] | | | | 0.714[b] |
| Alive | 815 (94.3) | 218 (92.3) | 597 (95) | | 432 (93.1) | 215 (92.7) | 217 (93.5) | |
| Dead | 49 (5.7) | 18 (7.6) | 31 (5) | | 32 (6.9) | 17 (7.3) | 15 (6.5) | |
| Site of recurrence n (% of the sum of recurrences) | | | | 0.269[c] | | | | 0.134[c] |
| Vaginal | 42 (32.8) | 13 (27.7) | 29 (35.8) | | 21 (26.3) | 12 (26.7) | 15 (35.7) | |
| Laterally in the pelvic cavity | 34 (26.6) | 12 (25.5) | 22 (27.2) | | 24 (30.0) | 12 (26.7) | 9 (21.4) | |
| Port-site metastasis | 7 (5.5) | 0 (0) | 7 (8.6) | | 6 (7.5) | 0 (0) | 6 (14.3) | |
| Ascites/upper abdomen | 12 (9.4) | 6 (12.8) | 6 (7.4) | | 6 (7.5) | 6 (13.3) | 3 (7.1) | |
| Para-aortal/mediastinal | 14 (10.9) | 6 (12.8) | 8 (9.9) | | 10 (12.5) | 6 (13.3) | 5 (11.9) | |
| Distant metastasis | 16 (12.5) | 7 (14.9) | 9 (11.1) | | 10 (12.5) | 6 (13.3) | 4 (9.5) | |
| Data missing | 3 (2.3) | 3 (6.4) | 0 (0) | | 3 (3.8) | 3 (6.7) | 0 (0) | |

Age divided in quartiles of cohort. Percentages may not total 100 because of rounding.
[a] Student's t-test.
[b] Chi-squared test.
[c] Fisher's exact test.
[d] Grade of differentiation according to World Health Organisation international histological classification of tumours (Silverberg).

78–95) and 88% in the robotic group (95% CI, 82–95) (Supplementary Figure 1A).

### 3.3. Disease-free survival

The 5-year DFS was similar for both groups: 84% in the open (95% CI, 79–90) and 88% in robotic group (95% CI, 85–91) (Fig. 3A). In total, 38 recurrences were registered among the total of 49 deaths. No difference in DFS was noted between the groups when stratifying according to tumour size ≤20 mm (open: 92% [95% CI, 87–97], robot: 91% [95% CI, 88–94]), >20 ≤ 40 mm (open: 75% [95% CI, 64–87], robot: 80% [95% CI, 73–88]) and >40 mm (open: 62% [95% CI, 38–100], robot: 65% [95% CI, 39–100]) (Supplementary Figure 2B). When stratifying the groups for surgery alone or surgery in combination with adjuvant therapy (Supplementary Figure 1B), the DFS was 89% (95% CI, 84–95) and 90% (95% CI, 87–93) in open and robotic surgery alone, respectively. Moreover, in combination with adjuvant chemotherapy, the 5-year DFS was 75% (95% CI, 65–86) for the open and 80% (95% CI, 73–88) for the robotic group (Supplementary Figure 1B).

### 3.4. Propensity score analysis

After propensity score weighting, 232 patients were matched in each surgical group, and there was no difference in any of the patient's characteristics (Table 1). There was no difference seen with a 5-year OS with 92% in both groups (HR, 1.00; 95% CI, 0.50–2.01) (Fig. 2B). In addition, there was no difference found in DFS with a 5-year DFS of 85% in the open and 84% in the robotic cohort (HR, 1.08; 95% CI, 0.66–1.78; $p = 0.756$), as shown in Fig. 3B.

### 3.5. Univariable and multivariable regression analysis

In univariable regression analysis of the complete cohort with OS as the end-point, grade, tumour size, LVSI, lymph node status and adjuvant therapy after surgery were significantly associated with a worse prognosis, but the differences disappeared in the multivariable analysis (Table 2). In the univariate regression analyses with DFS as the end-point, grade, tumour size, LVSI, lymph node status and adjuvant therapy were associated with increased risk of recurrence, whereas in the following multivariable analysis, only tumour size ($p < 0.001$) and grade 3 ($p = 0.02$) were found as independent significant risk factors (Table 2).

## 4. Discussion

In this complete nationwide, population-based cohort study, no significant differences were observed in OS or DFS between women treated with robotic vs open

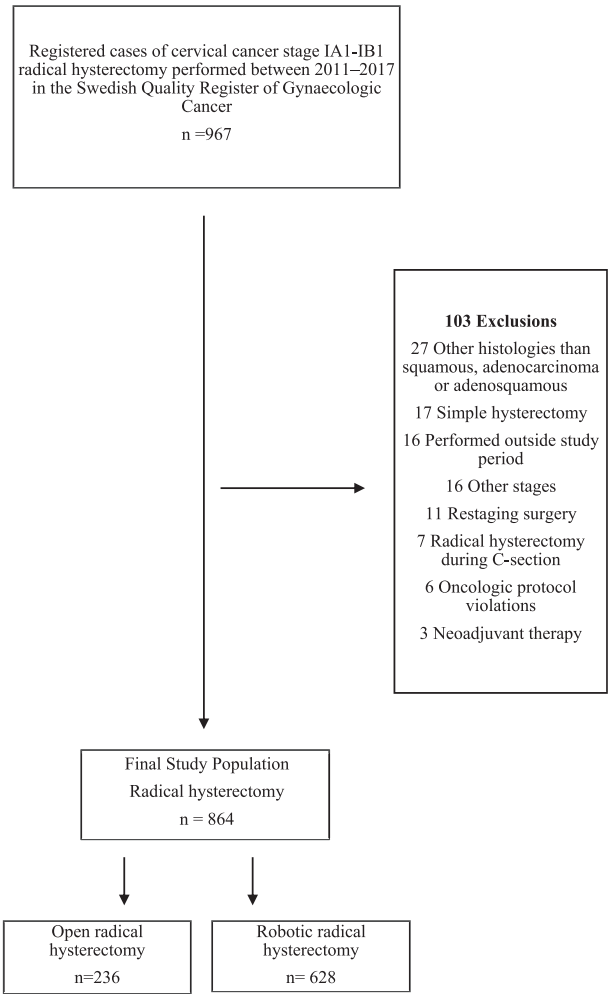


Fig. 1. Flow chart of the study population.

radical hysterectomy for early-stage cervical cancer. Based on these data, it should be considered as safe to continue to use the robot-assisted approach for the surgical management of cervical cancer when performed by high-volume surgeons at tertiary centres.

The introduction of MIS has changed gynaecologic oncology with dramatic effects on training and health care organisations. MIS confers less surgical trauma, and several studies, including a Cochrane review, have demonstrated no significant difference in OS or DFS between MIS and open surgery for women with endometrial cancer [21–23].These outcomes are consistent with data from several retrospective studies of MIS for cervical cancer, most of them derived from high-volume institutions [4,8,10,11,24].

The results from the LACC trial question the safety of MIS for cervical cancer [14]. In the trial, women randomised to MIS were almost four times more likely to have a recurrence compared with women having open surgery. The biggest challenge in RCTs for procedural interventions is controlling for operator proficiency. Although quality assessment was performed in the LACC trial, this issue may be of particular interest because the vast majorities of MIS procedures were conducted by conventional laparoscopy (84.4%). Laparoscopic radical hysterectomy is widely recognised as one of the most challenging MIS procedures in gynaecologic oncology, and the fact that all MIS recurrences in the LACC trial were concentrated to 14 of 33 participating sites may indicate inadequate surgical proficiency. Laparoscopic radical hysterectomy has never gained acceptance in Sweden. In contrast, robotic radical hysterectomy quickly replaced open surgery in most high-volume centres, most likely due to a shorter learning curve. Most robotic surgeries are centralised to either of seven university hospitals and are performed by a limited number of subspecialised gynae-oncology surgeons. The principles for patient selection for both

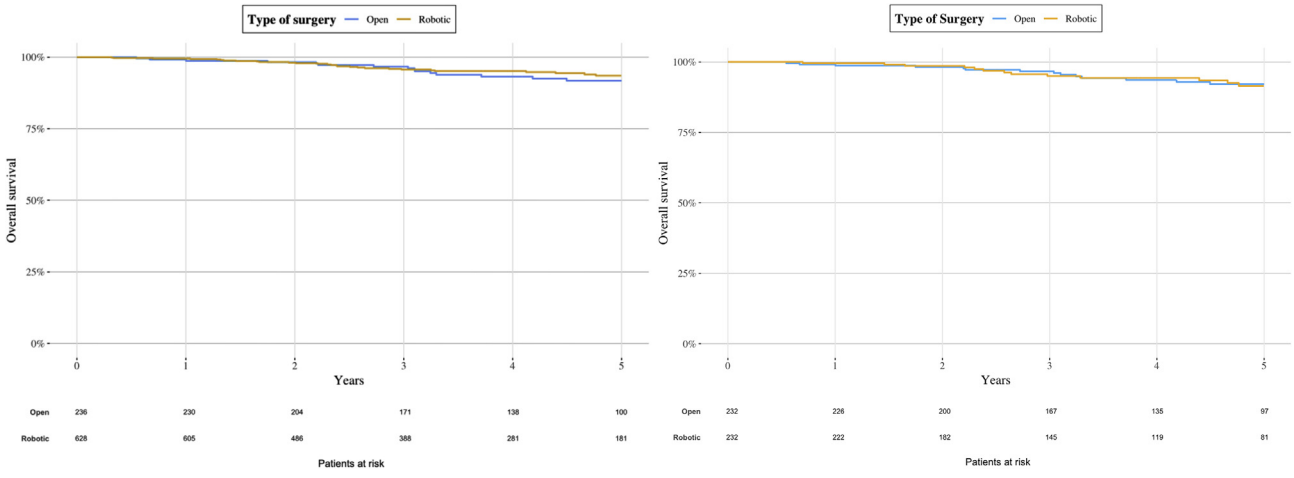


Fig. 2. (A) Overall survival (OS) for women treated for early cervical cancer by radical hysterectomy with an estimated 5-year OS of 92% (95% CI, 88–96) in the open vs 94% (95% CI, 91–96) in the robot-assisted surgical cohort. No statistical differences found. (B) OS after propensity score matching with an estimated 5-year OS of 92% for both the open and robot-assisted surgical cohort with a hazard ratio of 1.003 (95% CI, 0.50–2.01; $p = 0.99$). CI, confidence interval.

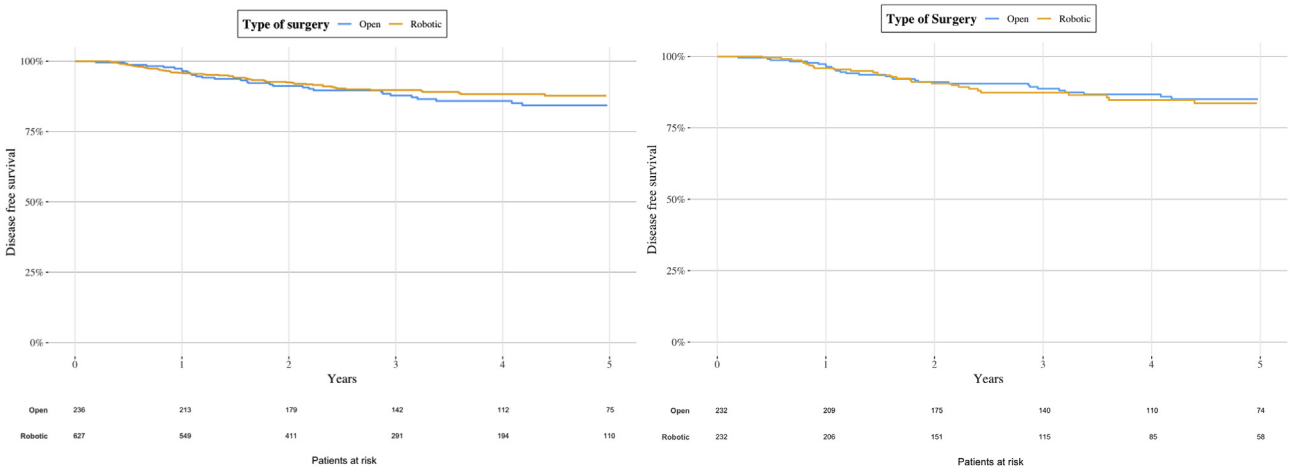


Fig. 3. (A) Disease-free survival (DFS) for women treated for early cervical cancer by radical hysterectomy with an estimated 5-year DFS of 84% (95% CI, 79–90) in the open vs 88% (95% CI, 85–91) in the robot-assisted surgical cohort. No statistical differences found. (B) DFS after propensity score matching with an estimated 5-year DFS of 85% in the open and 84% in the robot-assisted surgical cohort with a hazard ratio of 1.082 (95% CI, 0.66–1.78; $p = 0.756$). CI, confidence interval.

Table 2
Univariable and multivariable regression analysis of the complete cohort (n = 864) with overall survival and disease-free survival as the end-points.

| Variables | Overall survival univariate regression analysis | | Overall survival multivariable regression analysis | | Disease-free survival univariate regression analysis | | Disease-free survival multivariable regression analysis | |
|---|---|---|---|---|---|---|---|---|
| | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value |
| Surgical method | | | | | | | | |
| Open | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| Robot | 0.78 (0.44–1.40) | 0.4078 | 1.03 (0.55–1.94) | 0.9222 | 0.80 (0.52–1.22) | 0.2945 | 1.12 (0.71–1.75) | 0.6309 |
| Age[a] | | | | | | | | |
| 18–37 | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| 38-43 | 1.17 (0.48–2.88) | 0.73 | 1.67 (0.65–4.29) | 0.287 | 0.82 (0.45–1.52) | 0.5296 | 1.01 (0.54–1.88) | 0.9817 |
| 44-52 | 1.54 (0.66–3.60) | 0.3212 | 1.92 (0.77–4.78) | 0.1619 | 0.89 (0.50–1.60) | 0.7001 | 1.02 (0.55–1.87) | 0.9618 |
| 53-83 | 2.12 (0.95–4.76) | 0.0684 | 2.02 (0.85–4.83) | 0.1135 | 1.44 (0.85–2.45) | 0.1773 | 1.14 (0.65–2.00) | 0.645 |
| Grade | | | | | | | | |
| Grade 1 | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| Grade 2 | 1.24 (0.39–3.89) | 0.7155 | 0.95 (0.30–3.05) | 0.9349 | 2.57 (1.07–6.18) | 0.0343[b] | 2.23 (0.92–5.43) | 0.0772 |
| Grade 3 | 3.28 (1.15–9.41) | 0.0269[b] | 2.15 (0.72–6.42) | 0.1705 | 4 (1.70–9.40) | 0.0015[b] | 2.82 (1.17–6.80) | 0.021[b] |
| Tumour size | | | | | | | | |
| ≤20 mm | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| >20 ≤ 40 mm | 1.95 (1.06–3.58) | 0.0307[b] | 1.42 (0.74–2.71) | 0.2938 | 2.76 (1.80–4.22) | <0.001[b] | 2.13 (1.35–3.36) | 0.0011[b] |
| >40 mm | 4.29 (1.49–12.33) | 0.007[b] | 2.97 (0.99–8.96) | 0.0528 | 4.00 (1.80–8.88) | <0.001[b] | 2.88 (1.25–6.64) | 0.0132[b] |
| LVSI | | | | | | | | |
| LVSI negative | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| LVSI positive | 1.93 (1.06–3.51) | 0.0311[b] | 1.09 (0.52–2.28) | 0.8144 | 1.96 (1.26–3.05) | 0.0027[b] | 1.31 (0.78–2.20) | 0.3071 |
| LVSI unknown | 0.38 (0.14–1.02) | 0.0549 | 0.41 (0.15–1.14) | 0.0873 | 0.61 (0.33–1.13) | 0.1144 | 0.74 (0.39–1.41) | 0.3626 |
| Lymph node status | | | | | | | | |
| Negative nodes | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| Positive nodes | 2.79 (1.50–5.18) | 0.0012[b] | 1.47 (0.61–3.53) | 0.3934 | 2.45 (1.54–3.90) | <0.001[b] | 1.31 (0.69–2.48) | 0.4046 |
| Primary treatment | | | | | | | | |
| Radical hysterectomy alone | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| Radical hysterectomy + adjuvant therapy | 2.82 (1.61–4.94) | <0.001[b] | 1.33 (0.57–3.10) | 0.5139 | 2.56 (1.70–3.84) | <0.001[b] | 1.16 (0.63–2.11) | 0.6351 |

HR, hazard ratio; CI, confidence interval; LVSI, lymph-vascular space invasion.
[a] Age divided in quartiles of cohort.
[b] Statistically significant.

surgery and adjuvant radiochemotherapy are based on national guidelines [1]. However, improved preoperative imaging has resulted in a time trend favouring primary radiotherapy during the study period. This trend coincides with the increased use of robotic surgery, resulting in a discrepancy between groups in the proportion of patients with a higher risk of recurrence (larger stage 1B1/clinically understaged patients and the proportion of node positivity). Therefore, detailed data on these subgroups are reported and adjusted for by separate survival curves, multiple regression and propensity score analyses. Still, no significant difference was observed in DFS between the open and robotic groups, and importantly, no differences in the pattern of recurrences were observed.

In the present study, the OS and DFS for robotic and open surgery are comparable with the results from previous studies, both single-centre cohort studies [8–10] and multicentre studies [4,24] showing no significant difference in oncological outcomes between the two surgical methods. Although we report similar oncological outcomes between the groups, both DFS and OS were lower than those in the open arm in the LACC trial. This may be attributed to a longer follow-up, few patients lost to follow-up and a mandatory referral to either of the university hospitals for all suspects or verified recurrences. The low DFS reported from the LACC trial stands out in comparison with other retrospective data and reports [25,26]. However, data maturity from the LACC trial may be questioned, and long-term follow-up is necessary.

The difference in surgical techniques between open surgery and MIS, including robotic radical hysterectomies, when performed according to the Querleu–Morrow classification [27] may also be discussed. One may speculate that the use of a uterine manipulator in MIS may have an impact on the oncological outcomes. Considerations should be made in a constructive manner to limit the use of an invasive uterine manipulator and the time interval of opening the vagina in an attempt to restrain possible cancer cells to shred into the abdomen. Nevertheless, our results with no survival or recurrence differences between the groups indicate otherwise, and future randomised trials are needed to verify our results. Furthermore, one may speculate whether post-conization with no residual tumour at the time of radical hysterectomy could have a positive effect on the oncological outcome. In the present study, we did not plan or perform this analysis evaluating if no residual tumour at the time of surgery was associated with a better survival. Altogether, there is a need for future well-conducted prospective studies with structural criteria for radical hysterectomy surgery, indications, surgeons' skills, uterine manipulators, visible tumour at surgery and other variables that may impact the oncological outcomes.

The strengths of our study include the complete nationwide, population-based design and quality-assured data. Close to 100% of robotic surgeries were performed in tertiary centres, adhering to national treatment guidelines. Furthermore, few women were lost to follow-up, and accurate data were available for relevant confounders. The study is limited by the time-trend bias caused by changes in preoperative imaging occurring during the study period. In addition, selection bias caused by limited access to the robotic system(s) in some centres may have contributed to the uneven distribution of risk factors between the groups. It may be argued that patients in the robotic group with an aborted radical hysterectomy due to metastatic sentinel lymph nodes or patients abstaining from recommended adjuvant treatment should have been included on an intention-to-treat basis. As we wanted to evaluate the impact of the surgical techniques as such, we chose to exclude these patients.

The results from this population-based study do not call for immediate concern regarding the safety of robotic surgery performed by high-volume surgeons in a public health care system, where primary care of cervical cancer is highly centralised. We postulate that the proposed risks associated with robotic surgery are of minor importance when performed by high-volume surgeons at tertiary centres and that the robotic approach facilitates complex surgery in comparison with traditional laparoscopy. Given the results from this study, new randomised controlled trials may be justified to establish the safety of robotic surgery for cervical cancer.

## 5. Conclusion

In a complete nationwide population cohort, no significant difference in OS or DFS was found between open radical hysterectomy and robotic radical hysterectomy for women with early cervical cancer when performed at tertiary centres.

## Conflict of interest statement

Henrik Falconer and Jan Persson are proctors for Intuitive Surgical Ltd robotic surgery. The authors have stated explicitly that otherwise there are no conflicts of interest in connection with this article.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.05.016.

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