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# Survival After Minimally Invasive Surgery in Older Women With Endometrial Carcinoma

JOEL CARDENAS-GOICOECHEA[1], YU WANG[2], JI-HYUN LEE[2,3],
MASSOUD SHORAKA[4], SEMIRAMIS L. CARBAJAL-MAMANI[5],
DAVID FISHMAN[6], ANDREA N. RINER[7] and JOSE G. TREVINO[8]

[1]*Department of Gynecology. Division Gynecologic Oncology, Cleveland Clinic Florida, Weston, FL, U.S.A.;*
[2]*Division of Quantitative Science and Biostatistics Shared Resource, University of Florida Health Cancer Center, Gainesville, FL, U.S.A.;*
[3]*Department of Biostatistics, University of Florida College of Medicine, Gainesville, FL, U.S.A.;*
[4]*Department of Obstetrics and Gynecology, University of Florida College of Medicine, Gainesville, FL, U.S.A.;*
[5]*Department of Medicine, University of Florida College of Medicine, Gainesville, FL, U.S.A.;*
[6]*Department of Obstetrics and Gynecology, Weill Cornell Medicine, New York Presbyterian Queens, New York City, NY, U.S.A.;*
[7]*Department of Surgery, University of Florida College of Medicine, Gainesville, FL, U.S.A.;*
[8]*Department of Surgery, Virginia Commonwealth University School of Medicine, Richmond, VI, U.S.A.*

**Abstract.** *Background/Aim: To analyze the impact of minimally invasive surgery for endometrial cancer on overall survival among age >65. Patients and Methods: We examined women who underwent hysterectomy from 2010 to 2015 from the U.S. National Cancer Data Base (NCDB). We evaluated the impact of surgical approach on survival. Results: Of 243,601 endometrial cancer cases, 42,458 met the inclusion criteria. Laparoscopic approach was associated with improved survival by 14% (HR=0.86; 95%CI=0.80-0.92; p<0.001) and robotic approach was associated with improved survival by 12% (HR=0.88; 95%CI=0.83-0.93; p<0.0001), compared to the open approach. Similarly, the weighted adjusted 5-year overall survival was 73.1% (95%CI=72%-74.2%), 76.4% (95%CI=75.1-77.7%), and 75.5% (95%CI=74.7-76.4%) for open, laparoscopic, and robotic approaches, respectively (p<0.001). Conclusion: Minimally invasive surgery improved overall survival in women over 65 years with endometrial cancer.*

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*Correspondence to:* Joel Cardenas-Goicoechea (ORCID: 0000-0002-0589-5785), MD MBA, Cleveland Clinic Florida. Division of Gynecologic Oncology, 2950 Cleveland Clinic Blvd, Weston, Florida, 33331, U.S.A. Tel: +1 9546595559, Fax: +1 9546595560, e-mail: joelcardenas@yahoo.com, cardenj3@ccf.org

*Key Words:* Robotic surgical procedure, laparoscopy, laparotomy, endometrial neoplasm, aged, survival.

Increasing age has long been associated with the diagnosis of uterine cancer. The World Health Organization reported 72 years as the average life expectancy at birth of the global population in 2016 (1). The U.S. Census Bureau projects that the number of people older than 65 is expected to almost double from 2020 to 2060 (2). Endometrial cancer is the most common gynecologic cancer in developed countries. It is estimated that there will be 66,570 new cases and 12,940 deaths due to uterine cancer in the United States in 2021 (3). The expected increase in the elderly population and incidence of endometrial cancer will challenge our healthcare system and may become a significant public health issue.

The cornerstone treatment of early-stage endometrial carcinoma is surgery. Current guidelines recommend total hysterectomy, bilateral salpingo-oophorectomy, and lymph node assessment by any surgical route (4). The surgical approach has been rapidly evolving. Historically, a large skin incision (open surgery) was the standard approach and was associated with significant perioperative adverse events that may prevent older women from undergoing surgery. However, with the introduction and adoption of minimally invasive surgery (laparoscopic and robotic), the paradigm changed over the past 20 years. The short-term advantages of laparoscopy

Table I. *Demographic characteristics of patients ≥65 years old who underwent surgery for endometrial cancer by surgical approaches.*

| Characteristics | Cohort before inverse probability of treatment weighting | | | | Cohort after inverse probability of treatment weighting | | | |
|---|---|---|---|---|---|---|---|---|
| | Open | Laparoscopic | Robotic | | Open | Laparoscopic | Robotic | |
| | N=12,099 (%) | N=7,898 (%) | N=22,461 (%) | *p*-Value | N=12,052 (%) | N=7,909 (%) | N=22,536 (%) | *p*-Value |
| Age | | | | <0.0001 | | | | 0.7118 |
| Median (range) | 71 (65-90) | 71 (65-90) | 70 (65-90) | | 71 (65, 90) | 71 (65, 90) | 71 (65, 90) | |
| Mean (SD) | 72.6 (6.4) | 72.5 (6.5) | 72 (6.1) | | 72.3 (6.3) | 72.2 (6.2) | 72.3 (6.3) | |
| Race | | | | <0.0001 | | | | 0.9998 |
| White | 10,034 (82.9) | 6,859 (86.8) | 20,017 (89.1) | | 10,467 (86.9) | 6,868 (86.8) | 19,565 (86.8) | |
| Black | 1,569 (13) | 701 (8.9) | 1,639 (7.3) | | 1,124 (9.3) | 737 (9.3) | 2,105 (9.3) | |
| Other | 374 (3.1) | 259 (3.3) | 600 (2.7) | | 344 (2.9) | 225 (2.9) | 653 (2.9) | |
| Missing | 122 (1) | 79 (1) | 205 (0.9) | | 116 (1) | 79 (1) | 213 (0.9) | |
| Year of diagnosis | | | | <0.0001 | | | | 1.0000 |
| 2010 | 2,790 (23.1) | 966 (12.2) | 2,066 (9.2) | | 1,671 (13.9) | 1,103 (13.9) | 3,142 (13.9) | |
| 2011 | 2,287 (18.9) | 1,163 (14.7) | 2,883 (12.8) | | 1,810 (15) | 1,180 (14.9) | 3,364 (14.9) | |
| 2012 | 2,011 (16.6) | 1,218 (15.4) | 3,541 (15.8) | | 1,926 (16) | 1,259 (15.9) | 3,612 (16) | |
| 2013 | 1,841 (15.2) | 1,447 (18.3) | 4,241 (18.9) | | 2,151 (17.8) | 1,416 (17.9) | 3,972 (17.6) | |
| 2014 | 1,641 (13.6) | 1,526 (19.3) | 4,571 (20.4) | | 2,175 (18) | 1,427 (18) | 4,092 (18.2) | |
| 2015 | 1,529 (12.6) | 1,578 (20) | 5,159 (23) | | 2,318 (19.2) | 1,525 (19.3) | 4,353 (19.3) | |
| Charlson/Deyo score | | | | <0.0001 | | | | 0.9999 |
| 0 | 8,252 (68.2) | 5,587 (70.7) | 15,856 (70.6) | | 8,406 (69.8) | 5,507 (69.6) | 15,727 (69.8) | |
| 1 | 2,929 (24.2) | 1,793 (22.7) | 5,207 (23.2) | | 2,833 (23.5) | 1,860 (23.5) | 5,286 (23.5) | |
| 2 | 694 (5.7) | 386 (4.9) | 1,074 (4.8) | | 618 (5.1) | 410 (5.2) | 1,155 (5.1) | |
| ≥3 | 224 (1.9) | 132 (1.7) | 324 (1.4) | | 195 (1.6) | 132 (1.7) | 368 (1.6) | |
| Hospital stay | | | | <0.0001 | | | | <0.0001 |
| Median (Range) | 3 (0-146) | 1 (0-97) | 1 (0-140) | | 3 (0, 146) | 1 (0, 97) | 1 (0, 140) | |
| Mean (SD) | 4.2 (5.2) | 2.1 (3.4) | 1.5 (2.8) | | 3.9 (4.8) | 2.2 (3.5) | 1.6 (2.9) | |
| Facility type | | | | <0.0001 | | | | 0.7294 |
| Academic | 5,448 (45) | 3,084 (39) | 9,728 (43.3) | | 5,134 (42.6) | 3,417 (43.2) | 9,669 (42.9) | |
| Other | 6,651 (55) | 4,814 (61) | 12,733 (56.7) | | 6,917 (57.4) | 4,492 (56.8) | 12,867 (57.1) | |
| Insurance | | | | <0.0001 | | | | 0.9985 |
| Private/Managed Care | 1,654 (13.7) | 1,316 (16.7) | 3,296 (14.7) | | 1,758 (14.6) | 1,158 (14.6) | 3,342 (14.8) | |
| Medicare | 9,894 (81.8) | 6,304 (79.8) | 18,496 (82.3) | | 9,866 (81.9) | 6,476 (81.9) | 18,383 (81.6) | |
| Medicaid | 260 (2.1) | 165 (2.1) | 378 (1.7) | | 232 (1.9) | 150 (1.9) | 432 (1.9) | |
| Not Insured | 79 (0.7) | 51 (0.6) | 90 (0.4) | | 66 (0.5) | 42 (0.5) | 123 (0.5) | |
| Missing | 212 (1.8) | 62 (0.8) | 201 (0.9) | | 130 (1.1) | 82 (1) | 256 (1.1) | |
| Income (2012-2016) | | | | <0.0001 | | | | 0.9982 |
| <$40,227 | 2,365 (19.5) | 1,212 (15.3) | 3,496 (15.6) | | 2,040 (16.9) | 1,317 (16.7) | 3,786 (16.8) | |
| $40,227-50,353 | 2,712 (22.4) | 1,539 (19.5) | 4,851 (21.6) | | 2,606 (21.6) | 1,697 (21.5) | 4,857 (21.6) | |
| $50,354-63,332 | 2,767 (22.9) | 1,792 (22.7) | 5,530 (24.6) | | 2,851 (23.7) | 1,874 (23.7) | 5,349 (23.7) | |
| ≥$63,333 | 4,112 (34) | 3,261 (41.3) | 8,332 (37.1) | | 4,416 (36.6) | 2,930 (37) | 8,282 (36.7) | |
| Missing | 143 (1.2) | 94 (1.2) | 252 (1.1) | | 138 (1.1) | 92 (1.2) | 262 (1.2) | |
| Geographic location | | | | <0.0001 | | | | <0.0001 |
| Midwest | 3,708 (30.6) | 1,704 (21.6) | 6,417 (28.6) | | 3,735 (31) | 1,736 (21.9) | 6,290 (27.9) | |
| Northeast | 2,729 (22.6) | 2,031 (25.7) | 5,000 (22.3) | | 2,751 (22.8) | 2,022 (25.6) | 4,924 (21.9) | |
| South | 4,093 (33.8) | 2,846 (36) | 7,875 (35.1) | | 3,973 (33) | 2,909 (36.8) | 8,151 (36.2) | |
| West | 1,569 (13) | 1,317 (16.7) | 3,169 (14.1) | | 1,593 (13.2) | 1,242 (15.7) | 3,171 (14.1) | |
| Stage | | | | <0.0001 | | | | 0.9900 |
| I | 8,549 (70.7) | 6,664 (84.4) | 19,191 (85.4) | | 9,749 (80.9) | 6,396 (80.9) | 18,201 (80.8) | |
| II | 816 (6.7) | 353 (4.5) | 904 (4) | | 593 (4.9) | 381 (4.8) | 1,115 (4.9) | |
| III | 1,714 (14.2) | 661 (8.4) | 2,059 (9.2) | | 1,265 (10.5) | 836 (10.6) | 2,344 (10.4) | |
| IV | 1,020 (8.4) | 220 (2.8) | 307 (1.4) | | 444 (3.7) | 297 (3.7) | 877 (3.9) | |
| Tumor histology | | | | <0.0001 | | | | 0.9982 |
| Endometrioid | 9,315 (77) | 6,828 (86.5) | 19,854 (88.4) | | 10,197 (84.6) | 6,694 (84.6) | 19,074 (84.6) | |
| Non-endometrioid | 2,784 (23) | 1,070 (13.5) | 2,607 (11.6) | | 1,855 (15.4) | 1,216 (15.4) | 3,462 (15.4) | |

Table I. *Continued*

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| Characteristics | Cohort before inverse probability of treatment weighting | | | | Cohort after inverse probability of treatment weighting | | | |
|---|---|---|---|---|---|---|---|---|
| | Open | Laparoscopic | Robotic | | Open | Laparoscopic | Robotic | |
| | N=12,099 (%) | N=7,898 (%) | N=22,461 (%) | *p*-Value | N=12,052 (%) | N=7,909 (%) | N=22,536 (%) | *p*-Value |
| Tumor grade | | | | <0.0001 | | | | 0.9990 |
| Well differentiated | 3,419 (28.3) | 3,069 (38.9) | 8,193 (36.5) | | 4,188 (34.8) | 2,716 (34.3) | 7,765 (34.5) | |
| Moderately differentiated | 3,083 (25.5) | 1,919 (24.3) | 5,895 (26.2) | | 3,103 (25.7) | 2,036 (25.7) | 5,780 (25.6) | |
| Poorly differentiated | 3,116 (25.8) | 1,288 (16.3) | 3,384 (15.1) | | 2,243 (18.6) | 1,461 (18.5) | 4,230 (18.8) | |
| Undifferentiated | 516 (4.3) | 243 (3.1) | 571 (2.5) | | 377 (3.1) | 248 (3.1) | 704 (3.1) | |
| Missing | 1,965 (16.2) | 1,379 (17.5) | 4,418 (19.7) | | 2,141 (17.8) | 1,448 (18.3) | 4,058 (18) | |
| Lymphovascular invasion | 2,927 (24.2) | 1,479 (18.7) | 4,106 (18.3) | <0.0001 | 2,398 (19.9) | 1,597 (20.2) | 4,536 (20.1) | 0.8630 |
| Lymph nodes examined | | | | <0.0001 | | | | 0.9690 |
| Yes | 8,361 (69.1) | 5,012 (63.5) | 17,127 (76.3) | | 8,655 (71.8) | 5,691 (72) | 16,146 (71.6) | |
| No | 3,710 (30.7) | 2,868 (36.3) | 5,309 (23.6) | | 3,378 (28) | 2,205 (27.9) | 6,356 (28.2) | |
| Missing | 28 (0.2) | 18 (0.2) | 25 (0.1) | | 18 (0.2) | 14 (0.2) | 34 (0.2) | |
| Adjuvant therapy | | | | <0.0001 | | | | <0.0001 |
| None | 7,563 (62.5) | 5,448 (69) | 15,521 (69.1) | | 8,127 (67.4) | 5,182 (65.5) | 15,216 (67.5) | |
| Radiation | 1,940 (16) | 1,384 (17.5) | 4,007 (17.8) | | 2,066 (17.1) | 1,444 (18.3) | 3,774 (16.7) | |
| Chemotherapy | 1,641 (13.6) | 562 (7.1) | 1346 (6) | | 1,089 (9) | 685 (8.7) | 1,790 (7.9) | |
| Chemotherapy + radiation | 955 (7.9) | 504 (6.4) | 1,587 (7.1) | | 769 (6.4) | 598 (7.6) | 1,756 (7.8) | |

over open surgery have been demonstrated by phase 3 clinical trials. Laparoscopy improved blood loss, hospital stay, and pain with at least similar operative morbidity when compared to open hysterectomy (5-7). Randomized clinical trials showed that laparoscopy was not inferior to laparotomy in terms of recurrence and survival (8, 9). As a result, minimally invasive surgery became the standard of care for patients with early-stage endometrial cancer.

Additionally, older women with cancer have been underrepresented in clinical trials (10, 11). There have been no randomized trials that focus on older patients with endometrial cancer to determine the optimal surgical procedure for aged women. Single and multi-institutional retrospective studies have shown the safety, feasibility, and benefits of minimally invasive surgery in older women (12-17). However, the impact of the surgical approach on survival has yet to be determined. The primary objective of our study was to assess the impact of laparoscopy, robotic, and open surgery on overall survival in women over 65 years of age. A secondary objective was to determine perioperative outcomes associated with surgical approach.

## Patients and Methods

*Data source and patient population*. The data used in the study were derived from the National Cancer Database (NCDB), which is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The NCDB captures approximately 70% of all patients newly diagnosed with cancer. In 2010, the NCDB began capturing surgical approach data (*e.g*., open, laparoscopic, or robotic) (18).

The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator. The University of Florida Institutional Review Board deemed this study to be exempt (IRB202100133).

*Inclusion criteria*. Women 65 years and older with endometrial cancer, who underwent hysterectomy as first line of treatment from 2010 to 2015, were selected. Demographic, clinical-pathological, and treatment variables were extracted from the data set. These variables included age, race (recorded as White, Black, Other, or Missing), Hispanic origin (Spanish or Non-Spanish), insurance status, income, Charlson/Deyo score, tumor grade and histology (endometrioid, serous, clear cell, and carcinosarcoma), regional nodes examined, analytic stage group (stage I, II, III, or IV), lymph-vascular invasion (present or absent), surgical approach (open, laparoscopic, or robotic), unplanned readmission within 30 days of discharge, 30-day and 90-day mortality after surgery, and adjuvant therapy after hysterectomy (none, radiation, chemotherapy, chemotherapy plus radiation). Procedure and histology codes are included in Appendix 1 (available online at: https://www.dropbox.com/s/6l74r4mb8wvb3se/Appendix%201.docx?dl=0).

*Exclusion criteria*. Histologic classification of sarcoma, mucinous, adeno-squamous, adenocarcinoma in situ, squamous cell carcinoma, undifferentiated, leiomyosarcoma, and myxoid leiomyosarcoma were excluded. Disease located in isthmus uteri, myometrium, fundus uteri, overlapping lesion of corpus uteri were excluded. Women who received neo-adjuvant treatment before hysterectomy were excluded to facilitate comparability.

*Outcomes.* The primary outcome of this study was 5-year overall survival, defined as the time from diagnosis until death or last contact. Secondary outcomes were unplanned readmission, 30-day and 90-day mortality rate, as well as hospital length of stay.

*Statistical analysis.* Categorical variables, presented as number of cases and percentages, were compared using the Chi-Squared test. Continuous variables are presented as median, mean, standard deviation, and range. The non-parametric Kruskal–Wallis test was used to compare demographic and clinical characteristics among surgical procedure groups.

Propensity score (ps) approach was used to construct a weighted cohort of women who differed with respect to the surgical approach but were similar with respect to other characteristics. A generalized logistic regression model for surgery type was fitted. Baseline variables that most likely have an impact on survival were selected as covariates (age, race, income, year of diagnosis, histology, tumor grade, stage, lymph-vascular invasion, insurance status, Charlson/Deyo score, facility type and regional lymph node involvement). Restricted cubic spline with five nots was applied on age before entering into the model. The predicted probability of each surgical approach, propensity score (ps), was generated for each patient from the above logistic regression model. Inverse probability of treatment weighting (IPTW) was calculated by 1/ps and 1/(1-ps) for patients who received minimally invasive surgery and for patients who received open surgery, respectively. To avoid extreme weight, stabilized IPTW was used for this study (19). All subsequent survival analyses were weighted in similar manner. Kaplan–Meier methods along with the log-rank test were used to estimate overall survival and to compare the surgical approaches (20). Cox proportional hazard model with robust variance estimator was used to estimate the hazard ratio (HR) and its 95% confidence interval (CI) between surgical approaches. Furthermore, the multivariable Cox proportional hazards model was used as an alternative method to test the surgical approach, while controlling for potential confounding factors and covariates. Statistical analysis was performed with SAS software, version 9.4.

## Results

*Patient characteristics.* Data selection methodology is presented in Figure 1. A total of 243,601 patients diagnosed with endometrial cancer from 2010 to 2015 were identified in the NCDB. In total, 42,458 women over the age of 65 with single primary endometrial cancer underwent open (n=12,099), laparoscopic (n=7,898), or robotic (n=22,461) hysterectomy. Demographic and clinical variables are presented in Table I. Demographic characteristics were different among the three groups. The open surgery group had more aggressive tumor features than the laparoscopic or robotic cohorts, such as non-endometrioid carcinoma, higher tumor grade, and more adjuvant therapy. The number of Black women was highest in the open group. The median age of diagnosis was 71 years (range=65-90 years).

*Median follow-up was 36 months.* The 90-day mortality rate was two times higher in the open group than in the robotic group (2.3% vs. 1.2%). The 30-day mortality rate was 0.5%, 0.7% and 1.2% for the robotic, laparoscopy, and open group, respectively ($p$<0.0001). The 30-day re-admission rate was 2%, 2.1%, and 3.2% for robotic, laparoscopy, and open group, respectively ($p$<0.0001). The median hospital length of stay was 1 day for robotic and laparoscopic groups, compared to 3 days for the open surgery group.

*Minimally invasive surgery is associated with improved overall survival in elderly women with endometrial cancer.* In the propensity-score-weighted survival analysis, the estimated 5-year survival for open, laparoscopic, and robotic approaches was 73.1% (95%CI=72.0%-74.2%), 76.4% (75.1%-77.7%), and 75.5% (74.7%-76.4%), respectively ($p$<0.0001) (Figure 2). Laparoscopic approach was associated with improved survival by 14% (HR=0.86; 95%CI=0.80-0.92; $p$<0.001) and robotic approach was associated with improved survival by 12% (HR=0.88; 95%CI=0.83-0.93; $p$<0.0001), compared to open surgery. These results are consistent with the multivariable Cox proportional hazard model, which showed that laparoscopic (HR=0.88, 95%CI=0.82-0.95; $p$=0.0009) and robotic (HR=0.85; 95%CI=0.80-0.90; $p$<0.0001) surgical approaches were associated with 12% and 15% longer survival compared to open surgery, respectively (Figure 3).

*Adjuvant therapy and financial wealth contribute to improved survival.* Adjuvant treatment was associated with significantly improved survival, specifically, survival was improved the most by adjuvant chemotherapy plus radiation (HR=0.53; 95%CI=0.47-0.58; $p$<0.0001), followed by adjuvant chemotherapy (HR=0.61; 95%CI=0.56-0.67; $p$<0.0001), and adjuvant radiation (HR=0.80; 95%CI=0.74-0.86; $p$<0.001). Higher median income (≥ $63,333) was also associated with longer survival (HR=0.90; 95%CI=0.84-0.97; $p$=0.0073) (Figure 3).

*Advanced disease, age and Black race confer survival disadvantage.* Factors associated with significantly worse overall survival were increased age (HR=1.06; 95% CI=1.06-1.07; $p$<0.001), Black race (HR=1.33; 95%CI=1.23-1.44; $p$<0.0001), more than 56 days between diagnosis and definitive surgical procedure (HR=1.18; 95%CI=1.09-1.26; $p$<0.0001), Charlson/Deyo score of (score ≥ 3; HR=2.05; 95%CI=1.76-2.40; $p$<0.001), stage II to IV (stage II HR=1.80; 95%CI=1.62-1.99; $p$<0.0001) (stage III HR=2.89; 95%CI=2.67-3.12; $p$<0.0001) (stage IV HR=6.16; 95%CI=5.57-6.81; $p$<0.0001), non-endometrioid histology (HR=1.32; 95%CI=1.23-1.43; $p$<0.0001), higher tumor grade, and presence of lympho-vascular invasion (HR=1.63; 95%CI=1.53-1.73; $p$<0.0001) (Figure 3).

*Transition from open to minimally invasive surgery.* During the study period, endometrial cancer cases increased by 42%, from 5,822 in 2010 to 8,266 in 2015. Concurrently, the

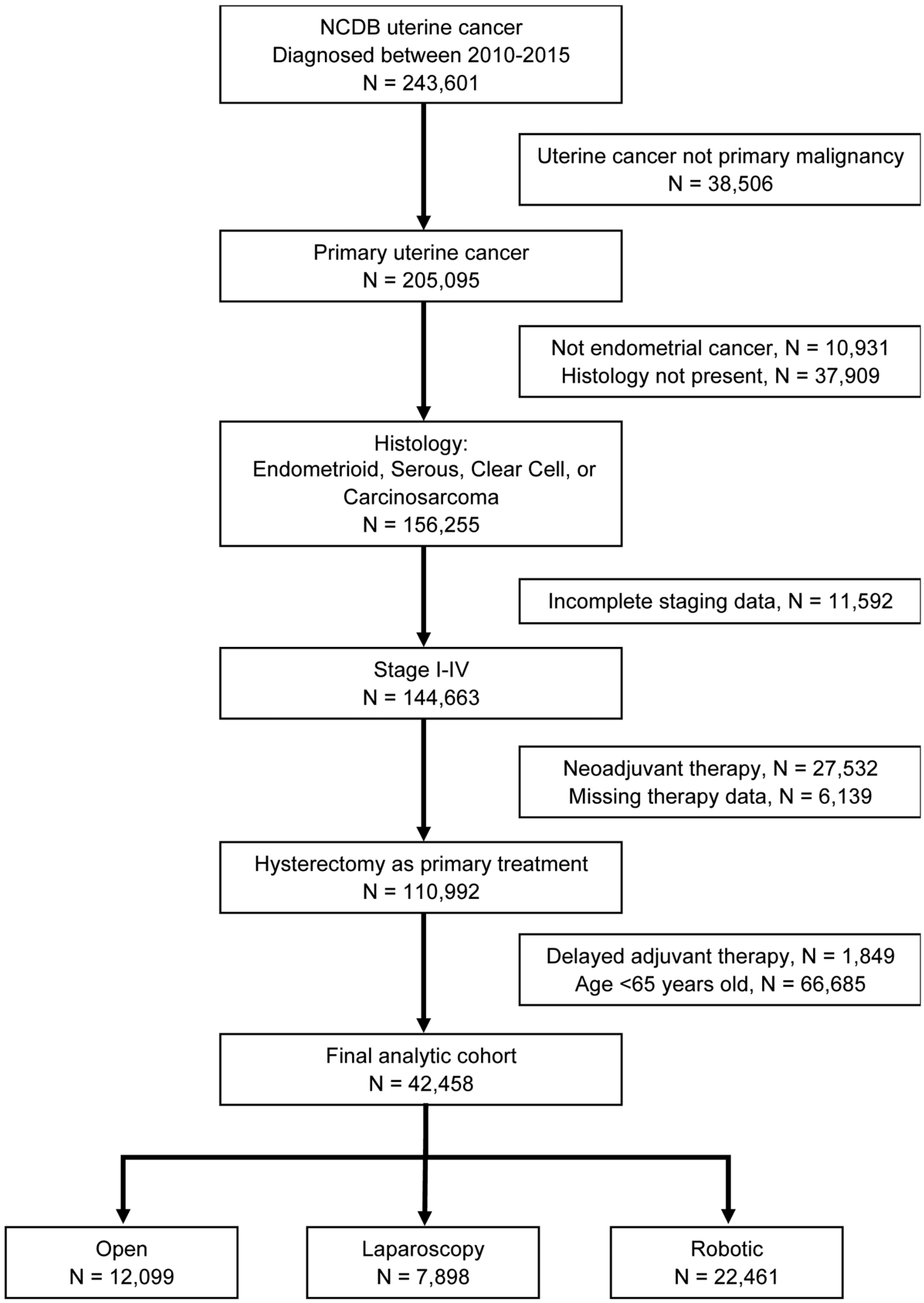


Figure 1. *Patient selection*.

number of minimally invasive procedures increased by 122% (laparoscopic surgery increased by 63% and robotic surgery increased by 150%); meanwhile, open surgery decreased by 45%. Open surgery comprised 48% of total cases in 2010, down to only 18.5% of cases by 2015. Conversely, robotic cases increased from 35.5% of all cases in 2010 to 62% of all cases in 2015 (Figure 4).

*Sensitivity analysis*. For the sensitivity analysis, we excluded conversion to open surgery. The conversion rate was 8.5% and

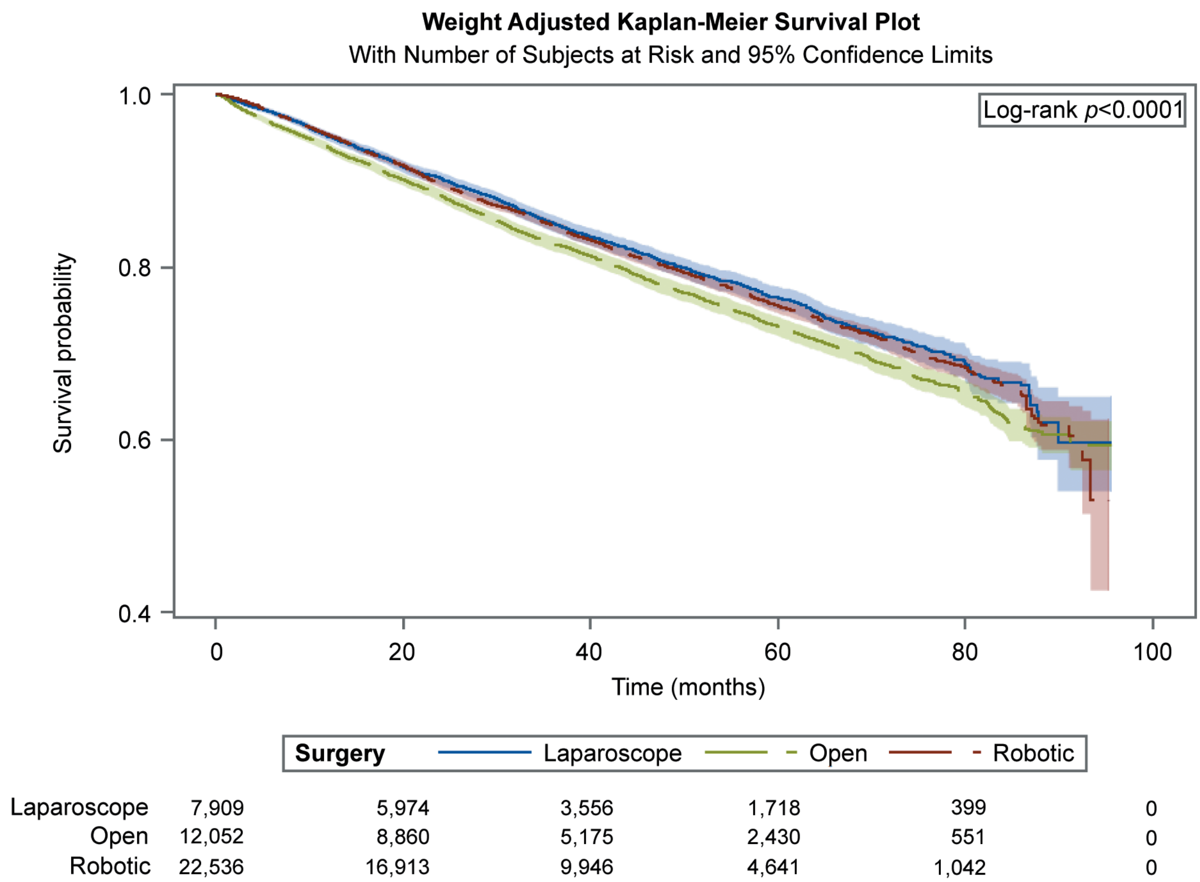


Figure 2. *Weight adjusted Kaplan–Meier curve for endometrial cancer in women age ≥65.*

1.9% for the laparoscopic (672/7,898) and robotic (424/22,461) cohort, respectively. Laparoscopy and robotic surgery improved survival compared to open surgery, after excluding conversion cases to open surgery and adjusting for post-operative adjuvant therapy. In the propensity-score-weighted survival analysis, laparoscopy improved survival by 16% (HR=0.84, 95%CI=0.78-0.90; $p<0.0001$) and robotic improved survival by 12% (HR=0.88, 95%CI=0.83-0.93; $p<0.0001$). Our results are consistent with the results of multivariable Cox proportional hazards modeling; laparoscopy improved survival by 14% (HR=0.86; 95%CI=0.80-0.93, $p=0.0002$), and robotic surgery improved survival by 15% (HR=0.85; 95%CI=0.80-0.90; $p<0.0001$) (Figure 5). After adjusting for post-operative therapy with the IPTW-weighted Cox proportional hazard model, laparoscopy improved survival by 17% (HR=0.83; 95%CI=0.77-0.89; $p<0001$) and the robotic approach improved survival by 13% (HR=0.87; 95%CI=0.83-0.92; $p<0.0001$).

The estimated 5-year survival for open, laparoscopic, and robotic approaches was 73.3% (95%CI=72.2%-74.3%), 77.3% (75.9%-78.6%), and 75.8% (75%-76.6%), respectively ($p<0.0001$).

## Discussion

The objective of our study was to assess the impact of minimally invasive surgery on survival in women aged 65 years and older who are diagnosed with endometrial cancer. Our findings suggest that minimally invasive surgery (laparoscopy or robotic surgery) is associated with improved overall survival when compared with open surgery. Perioperative outcomes such as hospital length of stay, readmission, and 30-day and 90-day mortality rates also favored the minimally invasive approach. To our knowledge, this is the largest cohort study assessing the impact of surgical approach in women with endometrial cancer who are older than 65 years, demonstrating a survival advantage with minimally invasive surgery.

Aging is accompanied by physiological changes and medical comorbidities that may influence surgery. As a result, older women may be discouraged from surgical intervention for endometrial cancer. However, it has been shown that older patients with cancer desire radical surgery and disease remission as strongly as younger patients (21).

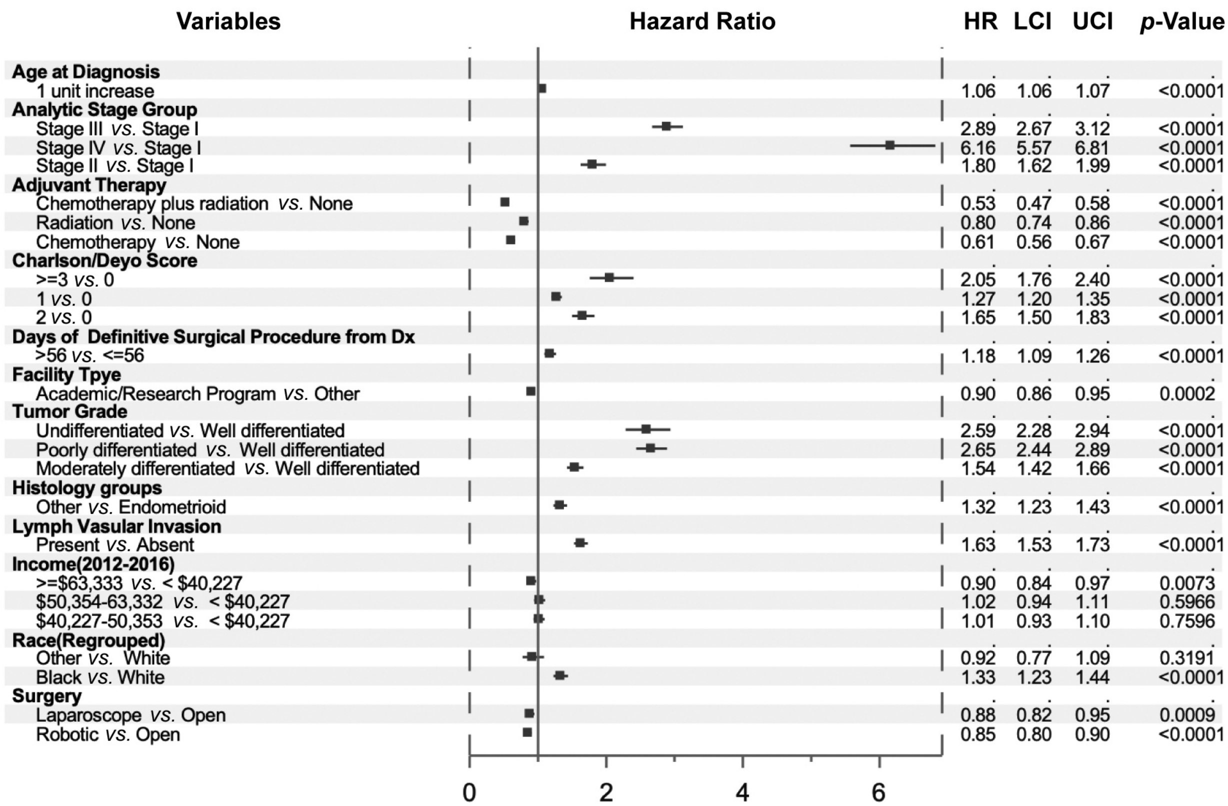


Figure 3. *Forest plot of the hazard ratios of the multivariable cox proportional model. HR: Hazard ratio; LCI: low boundary of the confidence interval; UCI: upper boundary of the confidence interval.*

Most patients with early-stage endometrial cancer who undergo surgical intervention do not experience mortality from their disease, but instead from other comorbid conditions, such as coronary artery disease (22). A geriatric assessment (GA) has been suggested to improve surgical outcomes and to better estimate residual life expectancy and lethality of the cancer in the context of competing comorbidities and other health problems (23). Furthermore, women over the age of 65 years with co-morbid conditions may benefit from minimally invasive surgery through medical optimization for surgery (24).

Minimally invasive surgery in aged women has been previously investigated. Wright *et al*. assessed the effectiveness of minimally invasive surgery in older women with endometrial cancer from the SEER-Medicare database who underwent hysterectomy. A total of 4,139 (65.7%) women underwent open hysterectomy and 2,165 (34.3%) underwent minimally invasive hysterectomy (25). The study found no significant association with the use of minimally invasive hysterectomy on either overall or cancer-specific mortality. The authors acknowledged that the survival was favorable for early-stage endometrial cancer, but their analysis was not powered to detect small differences in survival between the groups (25). Our study builds on these results by including a sample size that is six times larger and includes patients with private insurance and Medicaid. Two large database studies found a superior survival rate for minimally invasive surgery in the general population (older and non-older) when compared to open surgery (26, 27). Jorgensen, *et al*. evaluated the impact on survival when robotic surgery was introduced in Denmark. The study included 5,654 patients with endometrial cancer and showed that minimally invasive surgery was associated with improved survival compared to open surgery, but did not demonstrate a difference between robotic and laparoscopic approaches (26). This study included patients with a wide range of ages (33-94 for robotic surgery, 37-94 for laparoscopic surgery, and 40-98 for open surgery), leaving a paucity of data on outcomes specific to older patients. Safdieh *et al*. found similar results with regard to survival after robotic surgery compared to open surgery (27). Again, the median patient age was 61 years (interquartile range=55-68 years), with lack of data on elderly patients. In addition, the robotic approach appears to be safe for use with older

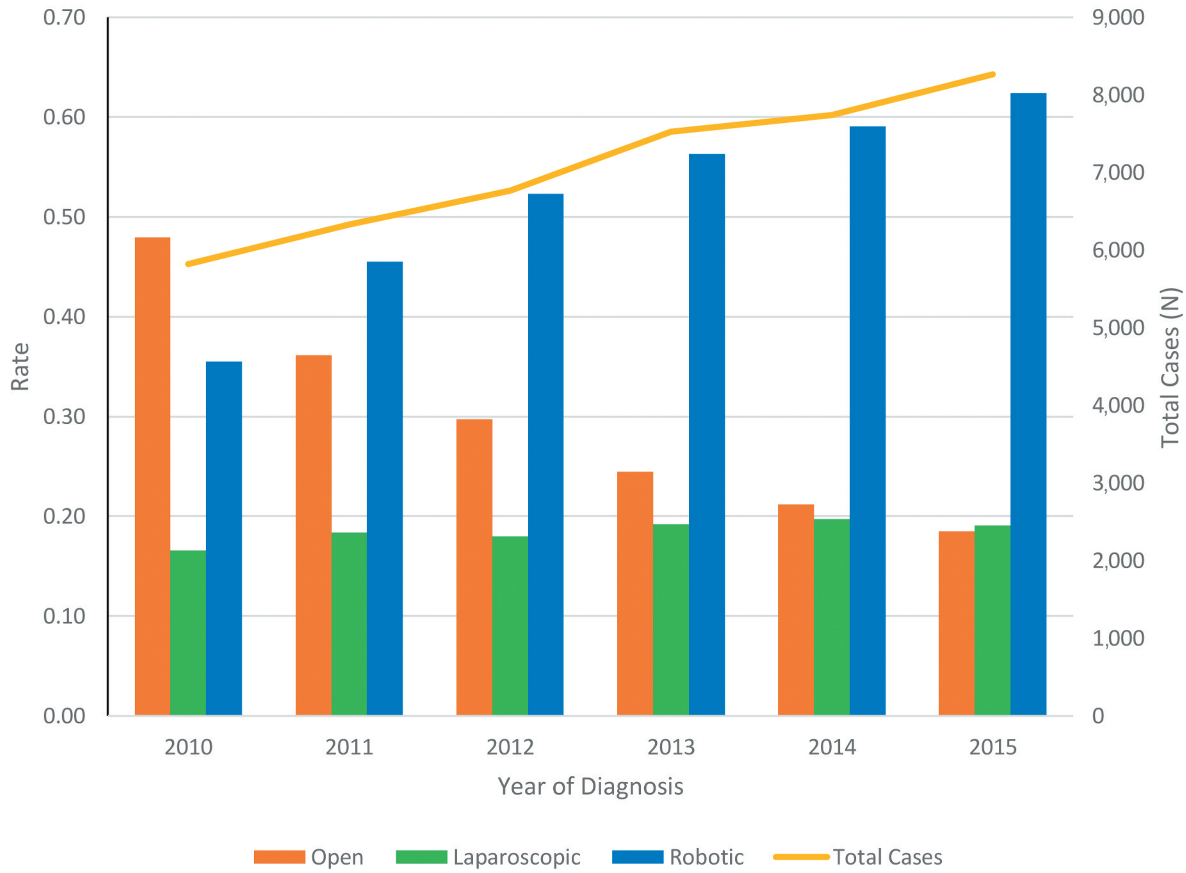


Figure 4. *Trends in rate of surgical approaches per year (bars) and total number of endometrial cancers per year (line) among elderly patients with endometrial cancer.*

patients. When compared with open surgery, the robotic approach was associated with lower rates of perioperative surgical and medical complications, mortality, shorter length of stay, and a higher rate of discharge home.

Our data suggest that the 30-day and 90-day perioperative mortality rate favors minimally invasive surgery over open surgery. Our mortality findings are consistent with two large studies in the elderly population. Wright *et al*. reported a perioperative mortality rate of 0.6% with minimally invasive surgery, while mortality for open surgery was 1% in elderly patients (25). Guy *et al*. compared the outcomes in older and younger patients undergoing open or robotic surgery from the Health Care Cost and Utilization Project National Inpatient Sample database from 2008 to 2010 (13). Mortality rates were 0.0% and 0.8% in the robotic and open groups, respectively ($p$<0.01) (13).

Hospital length of stay and unplanned readmission rate findings also favored minimally invasive surgery compared to open surgery and are similar to previous studies. The comparative readmission rate has been reported as 2% versus 3.6% for minimally invasive and open surgery, respectively ($p$<0.0001) (27, 28). The NCDB does not provide perioperative surgical or medical complication data, but readmission data can be used as a surrogate for complications. Our 30-day unplanned readmission rate was lower in the robotic and laparoscopy group than in the open group.

Among the surgical approaches in our study, there emerged a disparity in the use of adjuvant chemotherapy. Patients who underwent minimally invasive surgery received less chemotherapy than those who underwent open surgery. This may be reasonably attributed to the biology of the disease as we identified an association between more aggressive disease and open surgery. Patients who underwent open surgery had more aggressive disease, such as more non-endometrioid histology, less differentiated tumor, higher rates of lymph-vascular invasion, and higher stages than laparoscopy or robotic surgery (Table I). However, more patients underwent lymph node exploration in the robotic group (76.3%) than in the open group (69.1%). In the multivariable analysis, stage, tumor histology, grade, and lymph-vascular invasion were

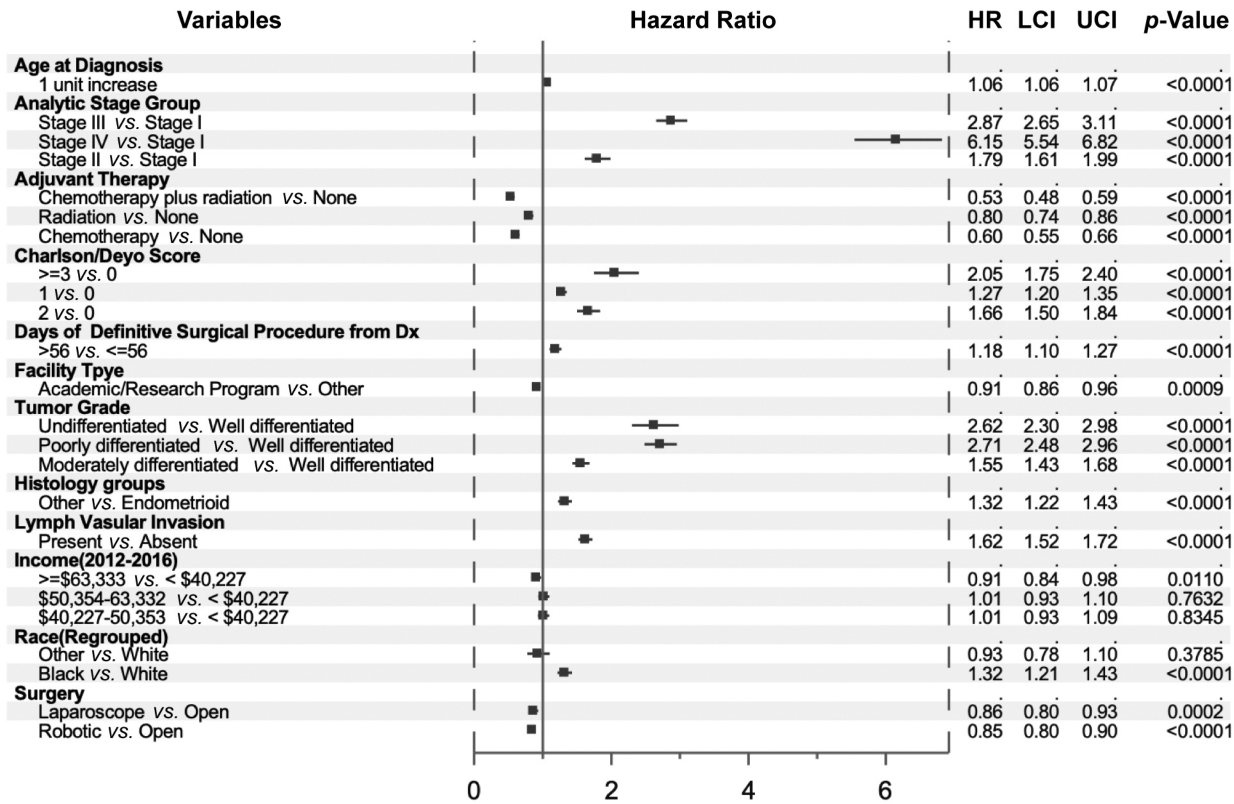


Figure 5. *Forest plot of the hazard ratios of the multivariable cox proportional model of overall survival after excluding conversion. HR: Hazard ratio; LCI: low boundary of the confidence interval; UCI: upper boundary of the confidence interval.*

independent prognostic factors of survival. Patients who received adjuvant treatment (radiation, chemotherapy, and chemotherapy plus radiation) had improved overall survival (Figure 5), indicating that systemic treatment in addition to surgical resection improves survival.

There are many possible explanations for low overall survival in elderly patients with cancer. Deficits in geriatric domains may potentially be explained by several factors (*e.g.*, increased risk of death resulting from causes other than cancer, increased risk of death resulting from cancer due to less aggressive treatment, or death related to complications of cancer treatment). Therefore, we advocated for disease-specific survival and overall survival being reported in clinical trials and tumor registries. In addition, Charlson/Deyo score derived from hospital coding may underestimate an older patient's performance status. Implementation of GA in prospective studies may provide better evaluation of surgical outcomes (23).

Minimally invasive surgery may mitigate some of the poor prognostic factors associated with elderly patients. Consistent with our findings, its adoption among gynecologic oncologists has increased over time, most notably using robotics between 2006 and 2012 (Figure 4) (25, 29). Age alone should not be the only factor in surgical decision making as other factors should be considered, including multidisciplinary care, optimizing pre- and post-op recovery with a full geriatric evaluation, and implementing Enhanced Recovery after Surgery guidelines. In older patients, prolonged hospitalization is related to an increased risk of cognitive dysfunction, poor outcomes, and risk of death. Delirium and frailty contribute to mortality in hospitalized patients (30). Minimally invasive surgery may reduce these risks as it is associated with a reduction in hospital length of stay to one third of that of open surgery.

Our study's strengths include a large sample size that includes a range of socioeconomic statuses, endometrioid and non-endometrioid histology, and represents a real-world population across the nation.

The limitations of our study are inherent to its retrospective design, which includes possible selection bias, incomplete data, or coding errors. Moreover, complications other than readmission and death within 30 or 90 days of surgery are not captured in the NCBD. However, hospital length of stay (a surrogate for complications) was available.

Readmissions may also be underestimated because the NCDB only captures readmissions to the reporting facility, which potentially excludes readmissions to other facilities that did not perform the initial surgery. Chemotherapy data included only the start date, leaving gaps regarding information on completion of therapy or number of cycles. Pattern of recurrence, progression-free survival, quality of life data, and cause of patient's death were not available, thus cancer-specific survival (CSS) cannot be calculated (18). Further studies are needed to assess CSS in elderly patients who are beyond current life expectancy.

## Conclusion

Minimally invasive surgery is associated with improved perioperative outcomes and survival compared to open surgery in patients over the age of 65 with endometrial cancer. The benefits of minimally invasive surgery may encourage patients and healthcare providers to partake in this approach.

## Conflicts of Interest

The Authors report no conflicts of interest in relation to this study.

## Authors' Contributions

Joel Cardenas-Goicoechea: Conceptualization, formal analysis, writing – original draft, writing – review and editing, supervision, project administration; Ji-Hyun Lee: Conceptualization, formal analysis, writing – review and editing, supervision, project administration; Yu Wang: Conceptualization, formal analysis, writing – review and editing, project administration; Massoud Shoraka: Conceptualization, writing – original draft, writing – review and editing, visualization, project administration; David Fishman: Formal analysis, writing – review and editing, supervision; Andrea Riner: Conceptualization, writing – review and editing; Bernie Amaro: Writing – original draft, writing – review and editing, visualization; Semiramis Carbajal-Mamani: Conceptualization, writing – original draft, writing – review and editing, project administration; Jose Trevino: Conceptualization, formal analysis, writing – review and editing, supervision, project administration.

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