The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 15, 2018 VOL. 379 NO. 20

Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer

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ABSTRACT

BACKGROUND

There are limited data from retrospective studies regarding whether survival outcomes after laparoscopic or robot-assisted radical hysterectomy (minimally invasive surgery) are equivalent to those after open abdominal radical hysterectomy (open surgery) among women with early-stage cervical cancer.

METHODS

In this trial involving patients with stage IA1 (lymphovascular invasion), IA2, or IB1 cervical cancer and a histologic subtype of squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma, we randomly assigned patients to undergo minimally invasive surgery or open surgery. The primary outcome was the rate of disease-free survival at 4.5 years, with noninferiority claimed if the lower boundary of the two-sided 95% confidence interval of the between-group difference (minimally invasive surgery minus open surgery) was greater than –7.2 percentage points (i.e., closer to zero).

RESULTS

A total of 319 patients were assigned to minimally invasive surgery and 312 to open surgery. Of the patients who were assigned to and underwent minimally invasive surgery, 84.4% underwent laparoscopy and 15.6% robot-assisted surgery. Overall, the mean age of the patients was 46.0 years. Most patients (91.9%) had stage IB1 disease. The two groups were similar with respect to histologic subtypes, the rate of lymphovascular invasion, rates of parametrial and lymph-node involvement, tumor size, tumor grade, and the rate of use of adjuvant therapy. The rate of disease-free survival at 4.5 years was 86.0% with minimally invasive surgery and 96.5% with open surgery, a difference of –10.6 percentage points (95% confidence interval [CI], –16.4 to –4.7). Minimally invasive surgery was associated with a lower rate of disease-free survival than open surgery (3-year rate, 91.2% vs. 97.1%; hazard ratio for disease recurrence or death from cervical cancer, 3.74; 95% CI, 1.63 to 8.58), a difference that remained after adjustment for age, body-mass index, stage of disease, lymphovascular invasion, and lymph-node involvement; minimally invasive surgery was also associated with a lower rate of overall survival (3-year rate, 93.8% vs. 99.0%; hazard ratio for death from any cause, 6.00; 95% CI, 1.77 to 20.30).

CONCLUSIONS

In this trial, minimally invasive radical hysterectomy was associated with lower rates of disease-free survival and overall survival than open abdominal radical hysterectomy among women with early-stage cervical cancer. (Funded by the University of Texas M.D. Anderson Cancer Center and Medtronic; LACC ClinicalTrials.gov number, NCT00614211.)

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This article was published on October 31, 2018, at NEJM.org.

N Engl J Med 2018;379:1895-904.
DOI: 10.1056/NEJMoa1806395

Radical hysterectomy with pelvic lymphadenectomy remains the standard recommendation for patients with early-stage cervical cancer. Current guidelines from the National Comprehensive Cancer Network and European Society of Gynaecological Oncology indicate that either laparotomy (open surgery) or laparoscopy (minimally invasive surgery performed with either conventional or robotic techniques) is an acceptable approach to radical hysterectomy in patients with early-stage (IA2 to IIA) cervical cancer.[1,2] These recommendations have led to widespread use of a minimally invasive approach for radical hysterectomy, although there is a paucity of adequately powered, prospective, randomized trials evaluating survival outcomes.[3-6]

Retrospective studies involving patients with early-stage cervical cancer have shown that laparoscopic radical hysterectomy is associated with less intraoperative blood loss, a shorter length of hospital stay, and a lower risk of postoperative complications than open abdominal radical hysterectomy.[7-9] Similarly, the minimally invasive approach has not been associated with lower 5-year rates of disease-free survival or overall survival than the open approach.[10-12] A recent meta-analysis showed that robot-assisted radical hysterectomy was associated with better perioperative outcomes than the open approach.[13] In addition, retrospective studies have shown that recurrence rates and survival rates do not differ significantly between the two approaches.[14-16]

We hypothesized that minimally invasive radical hysterectomy was not inferior to open radical hysterectomy in terms of the disease-free survival rate. In the present trial, the Laparoscopic Approach to Cervical Cancer (LACC) Trial, we tested this hypothesis by prospectively assigning patients to minimally invasive (conventional laparoscopic or robotic) or open abdominal radical hysterectomy and comparing the disease-free survival rate, the rate of recurrence, and the overall survival rate between the two groups.

Methods

Trial Design

The trial was a phase 3, multicenter, randomized trial with the primary objective to evaluate the hypothesis that laparoscopic or robot-assisted radical hysterectomy (minimally invasive surgery) was not inferior to open abdominal radical hysterectomy (open surgery) with respect to the percentage of patients who were disease-free at 4.5 years after surgery. Secondary objectives included comparing the two groups with regard to recurrence rates and the overall survival rate. The trial design and characteristics of the patients have been published previously,[17] and the protocol is available with the full text of this article at NEJM.org. The trial was designed by the authors; Medtronic provided financial support for research coordinators. The data were collected and analyzed and the manuscript was written by the authors without input from Medtronic. No one who is not an author contributed to the writing of the manuscript. The authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol. All the patients provided written informed consent.

Inclusion and Exclusion Criteria

Patients were eligible if they had squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix; had a disease stage of IA1 (lymphovascular invasion), IA2 (stromal invasion, 3 to 5 mm in depth and <7 mm in width), or IB1 (tumor size of ≤4 cm in the greatest dimension and no node involvement), according to the staging system of the International Federation of Gynecology and Obstetrics; underwent type II or III radical hysterectomy (Piver classification, described in the Supplementary Appendix, available at NEJM.org)[18]; and had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a 5-point scale, with higher values indicating greater disability). Exclusion criteria included a uterine size larger than 12 cm in length, a history of abdominal or pelvic radiotherapy, or evidence of metastatic disease on positron-emission tomography–computed tomography, magnetic resonance imaging, or computed tomography. Patients were also excluded if they were considered by the investigator to be unable to undergo surgery or unable to withstand lithotomy and steep Trendelenburg position.

Trial Conduct and Oversight

Each participating site required accreditation by the trial management committee to ensure proper surgical technique during minimally invasive surgery. Participating sites submitted perioperative

outcomes from a minimum of any 10 laparoscopic or robot-assisted radical hysterectomies. No sites or individual surgeons performed only the open approach or only the minimally invasive approach. The trial management committee required two unedited videos of laparoscopic or robot-assisted type III radical hysterectomies. The committee members reviewed the patients' outcomes and the videos to ensure the adequacy of the surgeon's technique.

Randomization was performed with a Web-based system. We used the method of minimization with equal assignment to treatment group. Randomization was between open surgery and minimally invasive surgery. There was no randomization between laparoscopy and robot-assisted surgery, and the decision as to which platform to use in the minimally invasive approach was left to the discretion of the surgeon. The technique for the radical hysterectomy is described in the Study Treatment section in the protocol. Adjuvant chemotherapy, radiotherapy, or both were delivered according to the practice of each center.

An independent recurrence adjudication committee reviewed all recurrences to ensure that these were due to disease and to verify the date and location of recurrence. The protocol was approved by the scientific ethics committee at each participating site. An independent data and safety monitoring committee (see the Supplementary Appendix) monitored the progress of the trial.

EARLY CLOSURE TO NEW PATIENT ENROLLMENT

In June 2017, the data and safety monitoring committee recommended that randomization be temporarily suspended and additional follow-up sought owing to an imbalance in deaths between the two groups. At that time, the trial management committee instructed all sites to submit any missing follow-up data. In November 2017, it was determined that, with this additional follow-up information, the previously identified imbalance was confirmed, prompting the data and safety monitoring committee to make a final recommendation that the trial be permanently closed to new patient enrollment and that investigators be made aware that the minimally invasive surgical intervention was associated with higher rates of death. At that time, 631 eligible patients had been enrolled of the initially planned 740 patients.

STATISTICAL ANALYSIS

The sample size was based on an expected disease-free survival rate of 90% in the open-surgery group at 4.5 years and a noninferiority margin of 7.2 percentage points for minimally invasive surgery, which reflected an acceptable difference in the expected survival rate of at most 8 percentage points. In previous studies involving patients with other types of cancer, a noninferiority margin of 6 to 8 percentage points has been considered to be clinically acceptable.[19-21]

A total sample of 740 patients with 4.5 years of follow-up was estimated to provide 87% power to declare minimally invasive surgery noninferior to open surgery, on the basis of a noninferiority margin of –7.2 percentage points for the difference in disease-free survival at 4.5 years (minimally invasive surgery minus open surgery). Disease-free survival rates at 4.5 years were estimated with the use of the Kaplan–Meier method, and confidence intervals for the primary outcome were calculated with the use of Greenwood's formula.[22] Disease-free survival was defined as the time from randomization to disease recurrence or death from cervical cancer, and progression-free survival was defined as the time from randomization to disease recurrence or death from any cause. Data regarding patients with no evidence of recurrence or death were censored at the date of last follow-up.

All analyses were performed on an intention-to-treat basis, except for a sensitivity analysis that was performed according to per-protocol treatment. A statistical analysis plan (available with the protocol) was prepared before the unblinding of the results to the trial management committee (see the Supplementary Appendix). Treatment comparisons of continuous variables were conducted with parametric methods if assumptions of normal distribution were confirmed. Non-normally distributed variables and categorical data (postoperative histopathological characteristics) were compared between treatment groups with the use of nonparametric tests. Survival curves were generated with the use of the Kaplan–Meier method, and proportional-hazards models were used to estimate the hazard ratios and 95% confidence intervals for the effect of treatment on disease-free, progression-free, and overall survival. The assumption of proportional hazards was tested with the approach of Harrell and Lee[23] and assessed for all analyses

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Open Surgery (N=312)	Minimally Invasive Surgery (N=319)
Age — yr	46.0±10.6	46.1±11.0
Body-mass index†	26.2±5.3	27.2±5.6
Histologic subtype — no. (%)		
Squamous-cell carcinoma	210 (67.3)	214 (67.1)
Adenocarcinoma	80 (25.6)	87 (27.3)
Adenosquamous carcinoma	6 (1.9)	9 (2.8)
Not reported	16 (5.1)	9 (2.8)
Stage of disease — no. (%)		
IA1: lymphovascular invasion	5 (1.6)	5 (1.6)
IA2	20 (6.4)	21 (6.6)
IB1	287 (92.0)	293 (91.8)
ECOG performance-status score — no. (%)‡		
0	289 (92.6)	292 (91.5)
1	23 (7.4)	27 (8.5)
Median length of hospital stay (range) — days	5 (0–69)§	3 (0–72)
Treatment received — no. (%)		
Open surgery	274 (87.8)	2 (0.6)
Minimally invasive surgery	8 (2.6)	289 (90.6)
Patient withdrew before surgery	19 (6.1)	12 (3.8)
Surgery was aborted	11 (3.5)	16 (5.0)

* Plus–minus values are means ±SD. Minimally invasive surgery indicates laparoscopic or robot-assisted radical hysterectomy, and open surgery indicates open abdominal radical hysterectomy. There were no significant differences in baseline characteristics between the assigned groups. Percentages may not total 100 because of rounding.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Performance-status scores on the Eastern Cooperative Oncology Group (ECOG) scale range from 0 to 4, with higher values indicating greater disability.

§ A zero length of stay in patients assigned to open surgery indicates patients who either withdrew before surgery or had surgery aborted and were discharged the same day.

that involved hazard ratios. Competing-risks models based on the method of Fine and Gray[24] were used to analyze locoregional recurrence and disease-specific survival. A multivariable analysis of disease-free survival was performed with adjustment for important baseline risk factors. Unless otherwise stated, all analyses were performed with a two-sided significance level of 0.05 and conducted with the use of SAS software, version 9.3 (SAS Institute), and Stata software, version 14.1 (StataCorp). No adjustments were made to account for multiple testing or missing data. Because there was no prespecified plan to adjust for multiple comparisons, the secondary efficacy outcomes are reported with unadjusted 95% confidence intervals, without P values.

RESULTS

CHARACTERISTICS OF THE PATIENTS

A total of 33 centers worldwide recruited patients from June 2008 through June 2017. A total of 631 patients were enrolled; 319 patients were randomly assigned to minimally invasive surgery and 312 to open surgery. The baseline characteristics of the patients are summarized in Table 1. The treatment groups were balanced with respect to baseline characteristics. The mean age of the patients was 46.0 years. Most patients (91.9%) had stage IB1 disease. A total of 68 patients (30 assigned to minimally invasive surgery and 38 assigned to open surgery) did not undergo their randomized surgery: 31 patients withdrew before surgery, 27 patients had their surgery aborted, and 10 patients switched treatment group before surgery (8 to minimally invasive surgery and 2 to open surgery). Of the patients who were assigned to and underwent minimally invasive surgery, 84.4% underwent laparoscopy and 15.6% robot-assisted surgery. A total of 10 of 289 patients (3.5%) had conversion from minimally invasive surgery to laparotomy. All conversions occurred in patients for whom the intended approach was laparoscopy. Reasons included poor visualization (5 patients), intraoperative complications (2 patients), equipment failure (2 patients), and prolonged operative time (1 patient). The median length of hospital stay was 3 days (range, 0 to 72) in the minimally invasive surgery group and 5 days (range, 0 to 69) in the open-surgery group.

There were no significant differences between the two groups with respect to histologic subtype assessed postoperatively, a tumor grade of III (21.0% of the patients in the minimally invasive surgery group and 21.6% of those in the open-surgery group), a tumor size of 2 cm or greater (42.3% and 42.9%), lymphovascular invasion (24.1% and 28.7%), parametrial involvement (6.5% and 3.9%), or lymph-node involvement (12.4% and 13.1%). There was a higher rate of superficially invasive tumors in the minimally invasive surgery group (28.5%, as compared

with 21.6% in the open-surgery group) (Table S1 in the Supplementary Appendix). The rate of any intraoperative complications at the time of the analysis was 11.4% in the minimally invasive surgery group and 10.5% in the open-surgery group, and the rate of early postoperative complications (<6 weeks after surgery) was 25.3% and 25.7% in the respective groups (Table S2 in the Supplementary Appendix).

Rates of postoperative adjuvant therapy (chemotherapy or radiotherapy) were similar in the two groups (28.8% [92 of 319 patients] in the minimally invasive surgery group and 27.6% [86 of 312 patients] in the open-surgery group) (Table 2). There was no significant between-group difference in the rate of the combination of adjuvant chemotherapy and radiation (18.8% in the minimally invasive surgery group and 18.1% in the open-surgery group) or in the time to initiation of any adjuvant therapy, with a median of 41 days (range, 31 to 57) in the minimally invasive surgery group and 46 days (range, 33 to 70) in the open-surgery group (Table S3 in the Supplementary Appendix).

Table 2. Adjuvant Therapy.

Adjuvant Therapy	Open Surgery (N=312)	Minimally Invasive Surgery (N=319)	P Value
	no. (%)		
Chemotherapy or radiotherapy	86 (27.6)	92 (28.8)	0.72
≥1 Cycle of chemotherapy	66 (21.2)	72 (22.6)	0.67
≥1 Dose of radiotherapy	73 (23.4)	81 (25.4)	0.56

SURVIVAL OUTCOMES

At the time of the analysis, the rate of available survival information on the primary outcome at 4.5 years was 59.7%, which provided 84% power for the primary outcome given design assumptions,[25] with a median follow-up time of 2.5 years (range, 0 to 6.3). At the time of the analysis, 34 patients had had a recurrence (27 in the minimally invasive surgery group and 7 in the open-surgery group). Most recurrences occurred in the vaginal vault or pelvis (41% of the recurrences in the minimally invasive surgery group and 43% of those in the open-surgery group). A higher proportion of vault recurrences occurred in the open-surgery group (43%, as compared with 15% in the minimally invasive surgery group), and all non–vaginal vault pelvic recurrences occurred in the minimally invasive surgery group (Tables S4 and S5 in the Supplementary Appendix). The distribution of tumor size among patients who had had a recurrence was similar in the two groups (Table S6 in the Supplementary Appendix). Recurrences occurred in 14 of 33 recruiting centers, with no clear pattern of failure rates across sites. A total of 22 deaths were noted, 19 in the minimally invasive surgery group and 3 in the open-surgery group.

The rate of disease-free survival at 4.5 years was 86.0% in the minimally invasive surgery group and 96.5% in the open-surgery group (difference, –10.6 percentage points; 95% confidence interval [CI], –16.4 to –4.7; P=0.87 for noninferiority) (Fig. 1A). The lower boundary of the confidence interval included the noninferiority margin of –7.2 percentage points, so noninferiority was not declared. Per-protocol analysis supported these findings (disease-free survival rate at 4.5 years, 87.1% in the minimally invasive surgery group and 97.6% in the open-surgery group; difference, –10.5 percentage points; 95% CI, –16.0 to –5.0; P=0.88 for noninferiority). Results were consistent with those in the 45 patients who underwent robot-assisted surgery (between-group difference, –10.4 percentage points; 95% CI, –24.7 to 3.9) and in the 244 patients who underwent laparoscopic surgery (between-group difference, –10.6 percentage points; 95% CI, –16.4 to –4.7) (Table S7 in the Supplementary Appendix).

Minimally invasive surgery was associated with a lower rate of disease-free survival than open surgery (3-year rate, 91.2% vs. 97.1%; hazard ratio for disease recurrence or death from cervical cancer, 3.74; 95% CI, 1.63 to 8.58) (Fig. 1B), a difference that remained after adjustment for age, body-mass index, stage of disease, lymphovascular invasion, lymph-node involvement, and ECOG performance-status score (Table 3). Minimally invasive surgery was also associated with a lower rate of overall survival than open surgery (3-year rate, 93.8% vs. 99.0%; hazard ratio for death from any cause, 6.00; 95% CI, 1.77 to 20.30) (Fig. 2A), a higher rate of death from cervical cancer (3-year rate, 4.4% vs. 0.6%; hazard ratio, 6.56; 95% CI, 1.48 to 29.00) (Fig. 2B), and a higher rate of locoregional recurrence (3-year rate of locoregional recurrence–free survival,

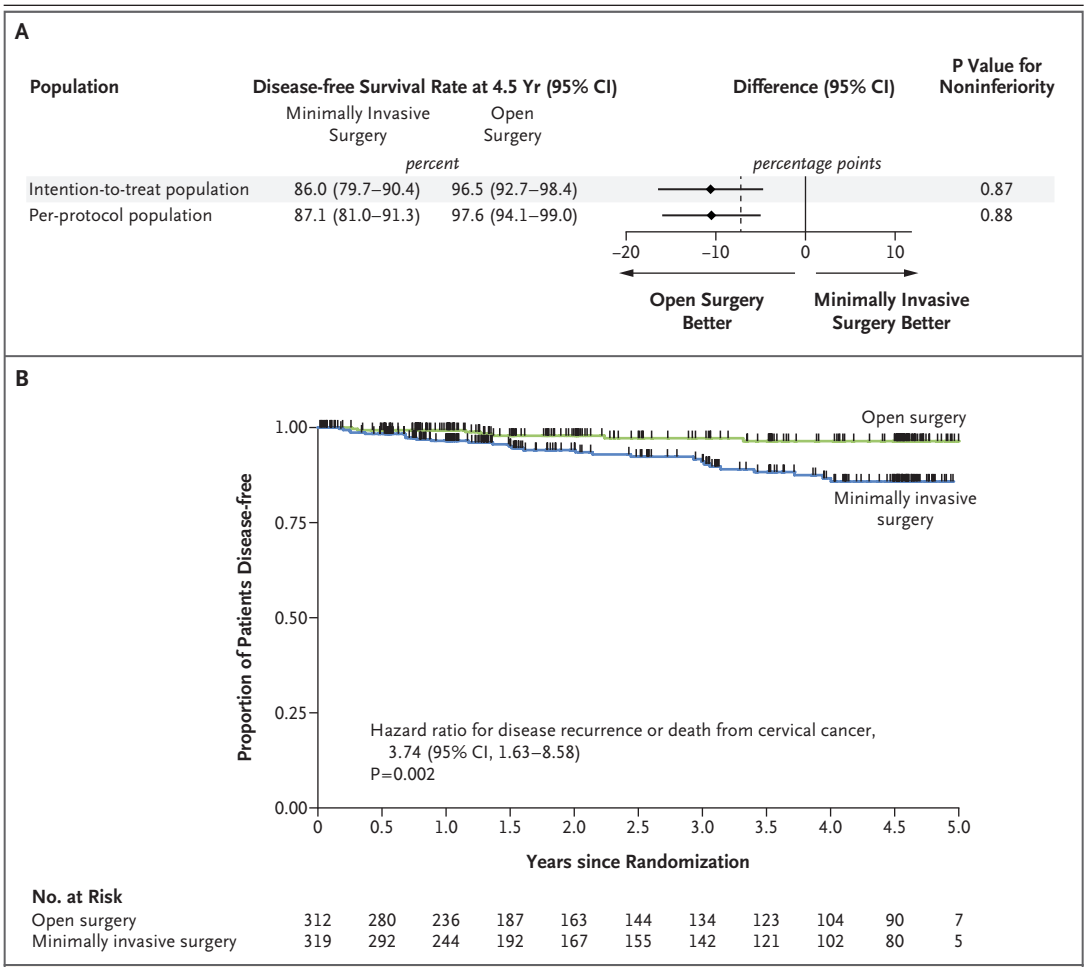

Figure 1. Estimates of Disease-free Survival.

Minimally invasive surgery indicates laparoscopic or robot-assisted radical hysterectomy, and open surgery indicates open abdominal radical hysterectomy. Panel A shows the difference in disease-free survival rates between surgical groups at 4.5 years after surgery for both the intention-to-treat and per-protocol populations. The dashed line denotes the noninferiority margin of –7.2 percentage points. Noninferiority of minimally invasive surgery would be declared if the lower boundary of the two-sided 95% confidence interval were above this margin (i.e., to the right of this line). The P value for noninferiority is two-sided. Panel B shows the Kaplan–Meier disease-free survival curves for the surgical groups. The hazard ratio, 95% confidence interval, and corresponding P value were estimated with the use of Cox proportional-hazards models. Tick marks indicate censored data. Disease recurrence or death from cervical cancer occurred in 27 of 319 patients in the minimally invasive surgery group and 7 of 312 patients in the open-surgery group.

94.3% vs. 98.3%; hazard ratio for locoregional recurrence, 4.26; 95% CI, 1.44 to 12.60) (Fig. 2C).

DISCUSSION

In this prospective, randomized trial, patients who underwent minimally invasive radical hysterectomy for early-stage cervical cancer had lower rates of disease-free survival and overall survival and a higher rate of locoregional recurrence than patients who underwent open abdominal radical hysterectomy. Our results call into question the findings in the literature suggesting that minimally invasive radical hysterectomy is associated with no difference in oncologic outcomes as compared with the open approach.

In a recent meta-analysis, Wang et al.[7] evalu-

Table 3. Proportional-Hazards Models (Tests for Superiority) According to Randomized Treatment.

Outcome	Open Surgery	Minimally Invasive Surgery	Hazard Ratio vs. Open Surgery (95% CI)	P Value
	no. of events/no. of patients			
Disease recurrence or death from cervical cancer				
Unadjusted analysis	7/312	27/319	3.74 (1.63–8.58)	0.002
Adjusted analysis*	7/282	27/295	4.39 (1.88–10.20)	<0.001
Disease recurrence or death from any cause	8/312	32/319	3.88 (1.79–8.41)	
Locoregional recurrence†	4/312	18/319	4.26 (1.44–12.60)	
Death from any cause	3/312	19/319	6.00 (1.77–20.30)	
Death from cervical cancer†	2/312	14/319	6.56 (1.48–29.00)	

* The analysis was adjusted for age, body-mass index, stage of disease, lymphovascular invasion, lymph-node involvement, and ECOG performance-status score.
† The analysis was conducted on a competing-risks basis. Distant relapses and deaths from any cause were considered to be competing risks for locoregional recurrence; deaths not due to cervical cancer were considered to be competing risks for death from cervical cancer.

ated 12 studies comparing laparoscopic radical hysterectomy (754 patients) with open radical hysterectomy (785 patients) for cervical cancer. Their findings revealed no significant differences in the 5-year rate of overall survival (hazard ratio for death, 0.91; 95% CI, 0.48 to 1.71; P=0.76) or 5-year rate of disease-free survival (hazard ratio for disease recurrence or death from cervical cancer, 0.97; 95% CI, 0.56 to 1.68; P=0.91) between the two approaches. However, in that meta-analysis, only four studies[10-12,26] had data on disease-free survival, and two studies[12,26] had data on overall survival. In another meta-analysis of laparoscopic as compared with abdominal radical hysterectomy in cervical cancer, Cao et al.[8] evaluated 22 studies involving 2922 patients (1230 underwent laparoscopic surgery and 1692 underwent open surgery) and found that the disease-free survival rate, the overall survival rate, and the recurrence rate did not differ significantly between the two groups. Both meta-analyses cited a lack of information or short follow-up time as main limitations and noted that long-term oncologic outcomes after laparoscopic radical hysterectomy in patients with cervical cancer remained unknown.

Similarly, robot-assisted radical hysterectomy has been compared with the open approach. Sert et al.[14] found that rates of recurrence and death did not differ significantly between the two approaches. Shah et al.[15] compared robot-assisted with open radical hysterectomy and noted no significant difference in the recurrence rate (10.1% and 10.4%, respectively; P=0.73), concluding that oncologic outcomes were similar with the two approaches. However, in that study, the comparison was with historical controls who had undergone open surgery and who had a higher rate of bulky stage IB2 tumors than patients in the robot-assisted surgery group (11% vs. 4%). Despite having more favorable prognoses, the robot-assisted surgery group still had a recurrence rate of 10%.

A number of factors may explain the differences between the results of our prospective, randomized trial and the results of the previously reported retrospective studies. The majority of the retrospective studies were sequential comparisons rather than concurrent analyses. In many of the sequential comparisons, patients in the open-surgery group were treated during an earlier time frame, when indications for radical hysterectomy were broader (including patients with stage IB2 disease), recommendations for radiotherapy may not have been as clearly defined, or the addition of chemotherapy was not standard practice. There are several potential reasons for the inferior oncologic outcomes in the minimally invasive surgery group, among these that the routine use of a uterine manipulator might increase the propensity for tumor spillage. In addition, an effect of the insufflation

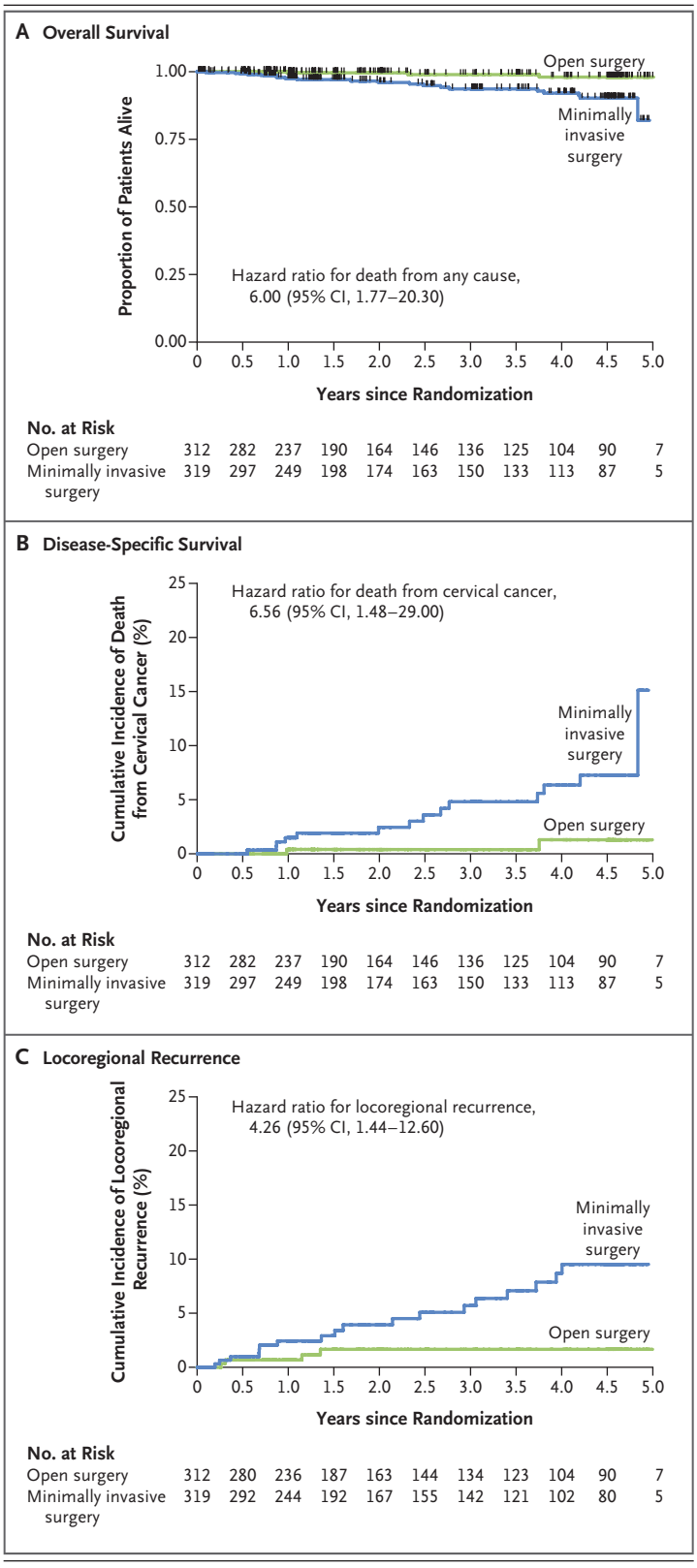

Figure 2. Kaplan–Meier Estimates of Overall Survival, Disease-Specific Survival, and Locoregional Recurrence.

Panel A shows the Kaplan–Meier plot for overall survival, measured from the date of randomization to the date of death or the date that the patient was last known to be alive. A Cox proportional-hazards model was used to determine the hazard ratio and 95% confidence interval. Tick marks indicate censored data. Death occurred in 19 of 319 patients in the minimally invasive surgery group and 3 of 312 patients in the open-surgery group. Panel B shows the cumulative incidence curves for disease-specific survival, measured from the date of randomization to the date of death from cervical cancer. The hazard ratio and 95% confidence interval were estimated with the use of a competing-risks model (based on the method of Fine and Gray[24]) in which death from other causes was considered to be the competing risk. Death from cervical cancer occurred in 14 of 319 patients in the minimally invasive surgery group and 2 of 312 patients in the open-surgery group. Panel C shows the cumulative incidence curves for locoregional recurrence according to randomized treatment. The hazard ratio and 95% confidence interval were estimated with the use of a competing-risks model (based on the method of Fine and Gray). Adjudicated recurrences in the vaginal vault or pelvis were considered to be local recurrences, and all distant or multiple recurrences (with no sites in the vault or pelvis) and deaths from any cause were considered to be competing risks. Locoregional recurrence occurred in 18 of 319 patients in the minimally invasive surgery group and 4 of 312 patients in the open-surgery group.

gas (CO_2) on tumor-cell growth or spread has been suggested in previous studies.[27,28] Kong et al.[29] evaluated 128 patients with cervical cancer who underwent minimally invasive radical hysterectomy and compared recurrence between patients who underwent vaginal colpotomy (79 patients) and those who underwent intracorporeal colpotomy (49 patients). The rate of disease recurrence was higher in the intracorporeal colpotomy group than in the vaginal colpotomy group (16% vs. 5%), and among patients with recurrence in the intracorporeal group, 62% had intraperitoneal spread or carcinomatosis. The authors concluded that exposure of cervical cancer to circulating CO_2 may result in tumor spillage into the peritoneal cavity. Our trial was not designed to answer questions about the cause of the inferior outcomes with minimally invasive surgery; thus, further investigation is warranted.

Some might argue that the inability to de-

clare noninferiority of minimally invasive surgery in our trial is due to a high rate of disease-free survival in the open-surgery group. However, others[10-12] have found 5-year rates of disease-free survival among patients who underwent open radical hysterectomy that range from 93.3 to 94.4%. These rates are consistent with the 4.5-year rate of disease-free survival of 96.5% reported in our prospective trial. Peters et al.[30] found a 4-year rate of progression-free survival of only 80% among patients undergoing chemotherapy and radiation after open radical hysterectomy. However, in that study, patients were required to have positive pelvic nodes, positive margins, or positive parametrial involvement to be enrolled. Rotman et al.[31] evaluated the recurrence-free interval and overall survival among patients with stage IB cervical cancer with negative lymph nodes but with two or more of the following features: deep stromal invasion, lymphovascular invasion, and a tumor size of 4 cm or more. In that study, the recurrence rate among patients receiving radiation therapy after open radical hysterectomy was 17.5%. However, none underwent the established standard treatment of chemotherapy and radiation therapy.

The strengths of our trial include the fact that it is a prospective, randomized trial evaluating oncologic outcomes of minimally invasive radical hysterectomy. It included a large number of centers throughout the world, and all centers were required to demonstrate proficiency in minimally invasive surgery. We also performed a per-protocol analysis of the primary outcome that included only the patients who underwent the treatment to which they were originally assigned, and we noted that results for the primary outcome of the disease-free survival rate were consistent with those in the intention-to-treat analysis.

Our trial has several limitations in that it did not reach its final intended enrollment, owing to the safety alert raised by the data and safety monitoring committee on the basis of the higher rates of recurrence and death in the minimally invasive surgery group than in the open-surgery group. The initial power was based on the assumption that there would have been a 4.5-year follow-up period for all the patients. However, at the time of analysis, 59.7% of the patients had reached the 4.5-year time point (median follow-up, 2.5 years). Even so, the trial did reach 84% power to declare noninferiority for our primary outcome. Finally, the results of this trial cannot be generalized to patients with "low-risk" cervical cancer (tumor size, <2 cm; no lymphovascular invasion; depth of invasion, <10 mm; and no lymph-node involvement), because the trial was not powered to evaluate the oncologic outcomes of the two surgical approaches in that context.

In conclusion, minimally invasive radical hysterectomy in patients with cervical cancer was associated with a higher rate of recurrence and a lower rate of disease-free survival than the open approach. In addition, the rate of overall survival was lower among patients undergoing minimally invasive surgery.

Supported by a departmental research fund in the Department of Gynecologic Oncology and Reproductive Medicine, University of Texas M.D. Anderson Cancer Center, and by a grant from Medtronic.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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REFERENCES

1. Cibula D, Pötter R, Planchamp F, et al. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer. Int J Gynecol Cancer 2018;28:641-55.
2. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: cervical cancer (version I.2018). 2017 (http://oncolife.com.ua/doc/nccn/Cervical_Cancer.pdf).
3. Conrad LB, Ramirez PT, Burke W, et al. Role of minimally invasive surgery in gynecologic oncology: an updated survey of members of the Society of Gynecologic Oncology. Int J Gynecol Cancer 2015;25:1121-7.
4. Zhao Y, Hang B, Xiong GW, Zhang XW. Laparoscopic radical hysterectomy in early stage cervical cancer: a systematic review and meta-analysis. J Laparoendosc Adv Surg Tech A 2017;27:1132-44.
5. Diver E, Hinchcliff E, Gockley A, et al. Minimally invasive radical hysterectomy for cervical cancer is associated with reduced morbidity and similar survival outcomes compared with laparotomy. J Minim Invasive Gynecol 2017;24:402-6.
6. Park DA, Yun JE, Kim SW, Lee SH. Surgical and clinical safety and effectiveness of robot-assisted laparoscopic hysterectomy compared to conventional laparoscopy and laparotomy for cervical cancer: a systematic review and meta-analysis. Eur J Surg Oncol 2017;43:994-1002.
7. Wang YZ, Deng L, Xu HC, Zhang Y, Liang ZQ. Laparoscopy versus laparotomy for the management of early stage cervical cancer. BMC Cancer 2015;15:928.
8. Cao T, Feng Y, Huang Q, Wan T, Liu J. Prognostic and safety roles in laparoscopic versus abdominal radical hysterectomy in cervical cancer: a meta-analysis. J Laparoendosc Adv Surg Tech A 2015;25:990-8.
9. Frumovitz M, dos Reis R, Sun CC, et al. Comparison of total laparoscopic and abdominal radical hysterectomy for patients with early-stage cervical cancer. Obstet Gynecol 2007;110:96-102.
10. Lee EJ, Kang H, Kim DH. A comparative study of laparoscopic radical hysterectomy with radical abdominal hysterectomy for early-stage cervical cancer: a long-term follow-up study. Eur J Obstet Gynecol Reprod Biol 2011;156:83-6.
11. Malzoni M, Tinelli R, Cosentino F, Fusco A, Malzoni C. Total laparoscopic radical hysterectomy versus abdominal radical hysterectomy with lymphadenectomy in patients with early cervical cancer: our experience. Ann Surg Oncol 2009;16:1316-23.
12. Nam J-H, Park J-Y, Kim D-Y, Kim J-H, Kim Y-M, Kim Y-T. Laparoscopic versus open radical hysterectomy in early-stage cervical cancer: long-term survival outcomes in a matched cohort study. Ann Oncol 2012;23:903-11.
13. Shazly SAM, Murad MH, Dowdy SC, Gostout BS, Famuyide AO. Robotic radical hysterectomy in early stage cervical cancer: a systematic review and meta-analysis. Gynecol Oncol 2015;138:457-71.
14. Sert BM, Boggess JF, Ahmad S, et al. Robot-assisted versus open radical hysterectomy: a multi-institutional experience for early-stage cervical cancer. Eur J Surg Oncol 2016;42:513-22.
15. Shah CA, Beck T, Liao JB, Giannakopoulos NV, Veljovich D, Paley P. Surgical and oncologic outcomes after robotic radical hysterectomy as compared to open radical hysterectomy in the treatment of early cervical cancer. J Gynecol Oncol 2017;28(6):e82.
16. Soliman PT, Frumovitz M, Sun CC, et al. Radical hysterectomy: a comparison of surgical approaches after adoption of robotic surgery in gynecologic oncology. Gynecol Oncol 2011;123:333-6.
17. Obermair A, Gebski V, Frumovitz M, et al. A phase III randomized clinical trial comparing laparoscopic or robotic radical hysterectomy with abdominal radical hysterectomy in patients with early stage cervical cancer. J Minim Invasive Gynecol 2008;15:584-8.
18. Piver MS, Rutledge F, Smith JP. Five classes of extended hysterectomy for women with cervical cancer. Obstet Gynecol 1974;44:265-72.
19. Fleshman J, Branda M, Sargent DJ, et al. Effect of laparoscopic-assisted resection vs open resection of stage II or III rectal cancer on pathologic outcomes: the ACOSOG Z6051 randomized clinical trial. JAMA 2015;314:1346-55.
20. Stevenson ARL, Solomon MJ, Lumley JW, et al. Effect of laparoscopic-assisted resection vs open resection on pathological outcomes in rectal cancer: the ALaCaRT randomized clinical trial. JAMA 2015;314:1356-63.
21. Janda M, Gebski V, Davies LC, et al. Effect of total laparoscopic hysterectomy vs total abdominal hysterectomy on disease-free survival among women with stage I endometrial cancer: a randomized clinical trial. JAMA 2017;317:1224-33.
22. Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. New York: Springer, 2003:92.
23. Harrell FE, Lee KL. Verifying assumptions of the Cox proportional hazards model. In: SUGI 11: Proceedings of the eleventh annual SAS Users Group International Conference, February 9–12, 1986. Cary, NC: SAS Institute, 1986:823-8.
24. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496-509.
25. Gebski V, Garès V, Gibbs E, Byth K. Data maturity and follow-up in time-to-event analyses. Int J Epidemiol 2018 February 12 (Epub ahead of print).
26. Bogani G, Cromi A, Uccella S, et al. Laparoscopic versus open abdominal management of cervical cancer: long-term results from a propensity-matched analysis. J Minim Invasive Gynecol 2014;21:857-62.
27. Lin F, Pan L, Li L, Li D, Mo L. Effects of a simulated CO2 pneumoperitoneum environment on the proliferation, apoptosis, and metastasis of cervical cancer cells in vitro. Med Sci Monit 2014;20:2497-503.
28. Volz J, Köster S, Spacek Z, Paweletz N. The influence of pneumoperitoneum used in laparoscopic surgery on an intraabdominal tumor growth. Cancer 1999;86:770-4.
29. Kong TW, Chang SJ, Piao X, et al. Patterns of recurrence and survival after abdominal versus laparoscopic/robotic radical hysterectomy in patients with early cervical cancer. J Obstet Gynaecol Res 2016;42:77-86.
30. Peters WA III, Liu PY, Barrett RJ II, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000;18:1606-13.
31. Rotman M, Sedlis A, Piedmonte MR, et al. A phase III randomized trial of postoperative pelvic irradiation in Stage IB cervical carcinoma with poor prognostic features: follow-up of a Gynecologic Oncology Group study. Int J Radiat Oncol Biol Phys 2006;65:169-76.