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Received: 16 October 2019 | Revised: 13 January 2020 | Accepted: 14 January 2020

DOI: 10.1111/aogs.13812

ORIGINAL RESEARCH ARTICLE

AOGS Acta Obstetricia et Gynecologica Scandinavica

Short-term surgical complications after radical hysterectomy—A nationwide cohort study

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Abstract

Introduction: Centralization has, among other aspects, been argued to have an impact on quality of care in terms of surgical morbidity. Next, monitoring quality of care is essential in identifying areas of improvement. This nationwide cohort study was conducted to determine the rate of short-term surgical complications and to evaluate its possible predictors in women with early-stage cervical cancer.

Material and methods: Women diagnosed with early-stage cervical cancer, 2009 FIGO stages IB1 and IIA1, between 2015 and 2017 who underwent radical hysterectomy with pelvic lymphadenectomy in 1 of the 9 specialized medical centers in the Netherlands, were identified from the Netherlands Cancer Registry. Women were excluded if primary treatment consisted of hysterectomy without parametrial dissection or radical trachelectomy. Women in whom radical hysterectomy was aborted during the procedure, were also excluded. Occurrence of intraoperative and postoperative complications and type of complications, developing within 30 days after surgery, were prospectively registered. Multivariable logistic regression analysis was used to identify predictors of surgical complications.

Results: A total of 472 women were selected, of whom 166 (35%) developed surgical complications within 30 days after radical hysterectomy. The most frequent

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; OR, odds ratio.

complications were urinary retention with catheterization in 73 women (15%) and excessive perioperative blood loss >1000 mL in 50 women (11%). Open surgery (odds ratio [OR] 3.42; 95% CI 1.73-6.76), chronic pulmonary disease (OR 3.14; 95% CI 1.45-6.79), vascular disease (OR 1.90; 95% CI 1.07-3.38), and medical center (OR 2.83; 95% CI 1.18-6.77) emerged as independent predictors of the occurrence of complications. Body mass index (OR 0.94; 95% CI 0.89-1.00) was found as a negative predictor of urinary retention. Open surgery (OR 36.65; 95% CI 7.10-189.12) and body mass index (OR 1.15; 95% CI 1.08-1.22) were found to be independent predictors of excessive perioperative blood loss.

Conclusions: Short-term surgical complications developed in 35% of the women after radical hysterectomy for early-stage cervical cancer in the Netherlands, a nation with centralized surgical care. Comorbidities predict surgical complications, and open surgery is associated with excessive perioperative blood loss.

KEYWORDS

hemorrhage, hysterectomy, intraoperative complications, postoperative complications, urinary retention, uterine cervical neoplasms

1 | INTRODUCTION

For early-stage cervical cancer with a clinically visible lesion of ≤4 cm in greatest dimension, corresponding to 2009 International Federation of Gynecology and Obstetrics (FIGO) stages IB1 and IIA1, radical hysterectomy with pelvic lymphadenectomy is the standard treatment.

Radical hysterectomy has proven to be highly effective in the treatment of early-stage cervical cancer with excellent survival rates. However, it is associated with surgical complications such as excessive blood loss, bladder dysfunction, abdominal organ injuries, and wound infections.[1] With the introduction of minimally invasive techniques as an alternative to open radical hysterectomy, such as conventional laparoscopic surgery in the early 1990s and robot surgery in the following decade, the prevalence of complications has changed. Benefits of minimally invasive surgery include decreased blood loss, shorter length of hospital stay and fewer postoperative complications,[2-5] but recently reported trial results show laparoscopic surgery to have a negative effect on recurrence and survival.[6]

In the Netherlands, radical hysterectomy for cervical cancer has been centralized to specialized medical centers since the late 1990s, with a minimum of 20 procedures per year since 2012. This presumes high quality of care and a positive impact on the occurrence of short-term surgical complications. To be able to identify areas of improvement, monitoring short-term morbidity is essential.[7] Furthermore, few studies have reported multivariable models on risk factors for short-term intraoperative and postoperative complications.[8] Therefore, the aim of this study was 2-fold: to determine the rate of short-term surgical complications in a nation with centralized surgical treatment for early-stage cervical cancer and to evaluate its possible predictors.

Key message

Short-term surgical complications developed in over one-third of the women after radical hysterectomy. Chronic pulmonary disease and vascular disease are its independent predictors. Monitoring quality of care is advised in medical centers with limited experience in open surgery.

2 | MATERIAL AND METHODS

We performed a historical cohort study by analyzing data from the Netherlands Cancer Registry, a population-based registry with coverage of all newly diagnosed malignancies in the Netherlands since 1989. The Netherlands Comprehensive Cancer Organization is an independent institute that registers the data from >95% of the Dutch medical centers. The registration clerks routinely extract patient and complication information from medical records within hospitals. They all undergo the same extensive training, using 1 coding manual specifically developed for cervical cancer, creating uniformity in data interpretation and entry.

All women diagnosed with cervical cancer 2009 FIGO stage IB1 and IIA1 between January 2015 and December 2017 who underwent a radical hysterectomy by a gynecological oncologist, were included. Data on patient, treatment, tumor characteristics, and recurrence were collected. Women were excluded if primary treatment consisted of simple abdominal or vaginal hysterectomy (ie, without parametrial dissection) or radical trachelectomy. Women in whom radical hysterectomy had been aborted during the procedure, for example, because of nodal involvement, were

also excluded. In the Netherlands, gynecologic oncologists from 9 specialized medical centers are authorized to perform a radical hysterectomy for cervical cancer. To guarantee anonymity of center-specific data, medical centers were randomly categorized 1 to 9. Vital status was obtained from the municipal demography registries. Data on recurrence and vital status were available until January 2019.

The set of surgical complications was registered according to national agreements in 2013 by the Working group on Oncological Gynecology of the Dutch Society of Gynecology and Obstetrics. Intraoperative and postoperative surgical adverse events occurring within 30 days after surgery are prospectively registered. Complications were categorized as (a) being present or absent and (b) type of complications, including blood loss, functional disorder, infection, injury, systemic, technical, thrombosis, and wound defect.

The following possible predictors of the occurrence of complications were selected based on literature and availability of data: age at diagnosis, body mass index (continuous), type and number (0, 1, >1) of comorbidities, previous abdominal surgery, medical center, American Society of Anesthesiology classification, operative time, surgical approach (open, conventional laparoscopic, or robot surgery), simultaneously performed bilateral salpingo-oophorectomy, number of removed lymph nodes and positive lymph nodes, timing of radical hysterectomy, clinical tumor and pathological size, histological subtype, differentiation grade, and pathological parametrial invasion.

In literature, delaying radical hysterectomy until 6 weeks after a diagnostic excision was reported to result in fewer surgical complications, impacted by parametrial inflammation.[9] Accordingly, we categorized women who underwent radical hysterectomy after a diagnostic excision (eg, conization or large loop excision of the transformation zone) by timing: those receiving early radical hysterectomy (≤6 weeks) versus delayed radical hysterectomy (>6 weeks).

In the Netherlands Cancer Registry tumors are not classified according to the FIGO staging system. Therefore, TNM stages (UICC TNM Classification of Malignant Tumors, 7th edn) were converted into FIGO stages, with clinical TNM stages T1b1, NX/0/1, M0, and T2a1, NX/0/1, M0 corresponding to FIGO stages IB1 and IIA1, respectively.

2.1 | Statistical analyses

Descriptive statistics were used to describe the characteristics and occurrence of surgical complications. Qualitative variables were expressed as absolute frequencies and percentages. For quantitative variables means and standard deviations were reported. Associations between complications and qualitative variables were assessed using Pearson's chi-squared test. Quantitative variables were assessed by independent samples t-test. To identify risk factors associated with the occurrence of complications, backward logistic regression analyses were performed. Candidate predictors from univariable analyses were included in the multivariable model if $P < .10$ or if associated with complications, according to literature (ie, delayed radical hysterectomy). Comorbidities were grouped in categories (see Table 2) and included as binary variables (absent/present) in the logistic regression analyses. Converted patients remained in the laparoscopic surgery group for analysis, according to the intention-to-treat principle. The medical center with the median number of women with complications was set as reference category. Kaplan-Meier analysis was used to estimate disease-free and overall survival rates. All analyses were performed using STATA/SE version 14.2 (Stata Corp., College Station, TX, USA). Statistical tests were 2-tailed and independent predictors were considered significant at $P < .05$.

2.2 | Ethical approval

This study was approved by the Privacy Review Board of the Netherlands Cancer Registry (03/12/2018; K18.375).

3 | RESULTS

Of the 2309 women with cervical cancer diagnosed in the Netherlands between 2015 and 2017, 472 were selected for this study (see

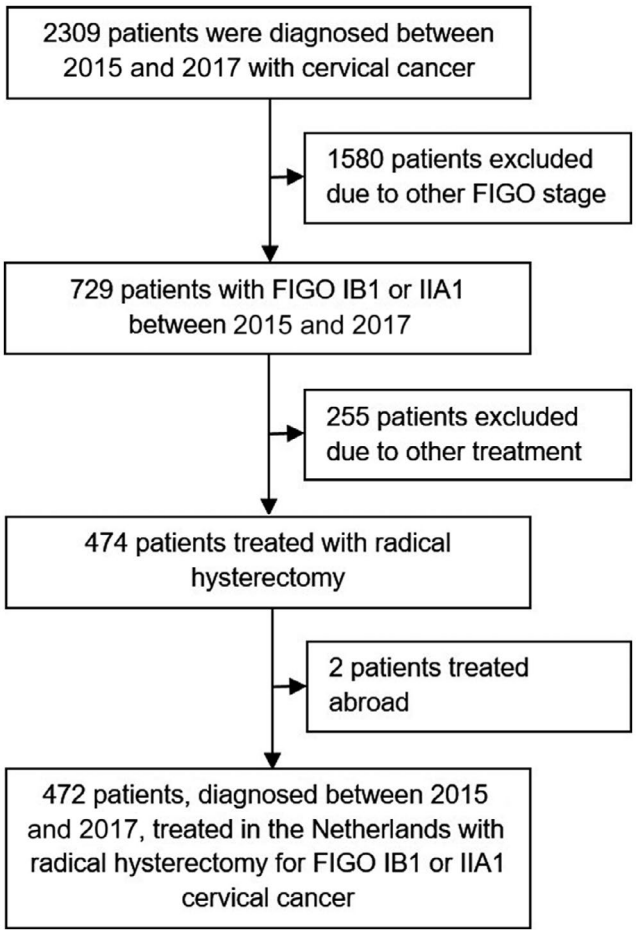

FIGURE 1 Patient selection flowchart

TABLE 1 Characteristics of 472 women with cervical cancer (FIGO stage IB1 and IIA1) treated with radical hysterectomy between 2015 and 2017 in the Netherlands, related to the occurrence of complications

Patient characteristics		P[b]
Age, years (SD)	45 (12)	.084
Body mass index, kg/m^2 (SD)	26 (5)	.021
Previous abdominal surgery, n (%)		
Absent	310 (66)	.891
Present	155 (33)	
Unknown	7 (1)	
ASA classification, n (%)		
I	218 (46)	.434
II	199 (42)	
III	18 (4)	
Unknown	37 (8)	
Treatment characteristics		
Operative time, min (SD)	260 (89)	.387
Surgical approach, n (%)		
Open	271 (57)	.002
Conventional laparoscopic	70 (15)	
Robot	131 (28)	
Bilateral salpingo-oophorectomy, n (%)		
Absent	281 (60)	.317
Present	187 (40)	
Unknown	4 (1)	
Pelvic lymph nodes		
Removed, mean (SD)	25 (10)	.220
Positive, n (%)	71 (16)	.419
Timing radical hysterectomy[a], n (%)		
Early (≤6 weeks)	109 (23)	.114
Delayed (>6 weeks)	178 (38)	
No diagnostic excision	186 (39)	
Tumor characteristics		
Clinical tumor size, n (%)		
<20 mm	170 (36)	.469
≥20 mm	224 (47)	
Unknown	79 (17)	
Histological subtype, n (%)		
Squamous cell carcinoma	302 (64)	.306
Adenocarcinoma	141 (30)	
Adenosquamous carcinoma	19 (4)	
Other	10 (2)	
Differentiation grade, n (%)		
1	28 (6)	.166
2	178 (38)	
3	138 (29)	
Unknown	128 (27)	
Pathological parametrial invasion, n (%)		
Absent	407 (86)	.888
Present	22 (5)	
Unknown	43 (9)	
Pathological tumor size, mm (SD)	23 (13)	.988

(Continues)

TABLE 1 (Continued)

Abbreviation: ASA, American Society of Anesthesiology.

[a]After diagnostic conization/large loop excision of the transformation zone.

[b]*t*-test for continuous variables, χ^2-test for categorical variables in univariable analysis; because of rounding, percentages might not sum to 100%.

TABLE 2 Number of comorbidities organized by category, related to the occurrence of complications

Comorbidity category	n (%)	P[a]
Prior malignancy	15 (3)	.880
Cardiac disease	20 (4)	.987
Vascular disease	65 (14)	.011
Diabetes mellitus	15 (3)	.134
Chronic pulmonary disease	34 (7)	.001
Neurological/psychiatric disease	30 (6)	.079
Gastrointestinal and liver disease	39 (8)	.193
Urogenital disease	6 (1)	.444
Thrombosis	9 (2)	.196
Muscle, connective tissue and joint disease	8 (2)	.103
Endocrine	18 (4)	.401
Infectious disease	2 (0)	.660

[a]χ^2-test for univariable analysis.

Figure 1). Patient, tumor, and treatment characteristics are summarized in Table 1. Mean age of the women was 45 ± 12 years and mean body mass index was 26 ± 5 kg/m^2. Vascular disease (14%) was the most prevalent comorbidity (see Table 2). Sixty-three women (13%) had multiple comorbidities. The predominant FIGO stage was IB1 (97%) and women were mainly treated with open surgery (58%). Conversion rate from laparoscopic to open surgery was 1% (n = 2). In 1 woman no pelvic lymphadenectomy was executed, for undocumented reasons.

Recurrence and vital status information was available for 449 women (94%). Median follow-up duration for disease-free survival and overall survival were 22 months and 30 months, respectively. Thirty-seven of the women (8%) had developed a recurrence and 17 (4%) had died at the time of analysis. Disease-free survival and overall survival were 87% and 95%, respectively.

Surgical complications within 30 days after radical hysterectomy were reported in 166 women (35%). In 2015, 73% of the patients were treated by open surgery and 37% experienced a complicated course, whereas in 2017 these values were 43% ($P < .001$) and 33% ($P = .745$), respectively. For definitions of types

TABLE 3 Short-term surgical complications, organized by category

Surgical complications	n (%)
Hemorrhage	
Perioperative >1000 mL	50 (11)
Postoperative	14 (3)
Functional disorder	
Urinary retention with catheterization	73 (15)
Ileus	5 (1)
Renal/hepatic	2 (0)
Infection	
Local	16 (3)
Organ level	14 (3)
Systemic	11 (2)
Injury	
Nerve	1 (0)
Major blood vessels	2 (0)
Bowel	1 (0)
Bladder	8 (2)
Ureter	10 (2)
Technical	
Corpus alienum	1 (0)
Thrombosis	
Deep vein thrombosis	2 (0)
Pulmonary embolism	2 (0)
Wound defect	
Wound dehiscence	7 (1)
Platzbauch	1 (0)

of complications, see Table 3. The main complication was urinary retention with catheterization (ie, catheter at discharge, reinsertion, or prolonged hospital stay) in 73 women (15%), followed by excessive perioperative blood loss >1000 mL in 50 women (11%). Of all women with complications, 49 (30%) developed multiple complications. The median percentage of women with surgical complications per medical center was 30%.

Results from logistic regression analysis on the occurrence of surgical complications, are reported in Table 4. In univariable analysis, age (P = .085), body mass index (P = .022), >1 comorbidities (P = .004), chronic pulmonary disease (P = .001), neurological/psychiatric disease (P = .083), vascular disease (P = .012), and surgical approach (P = .001) were associated with the occurrence of complications. Timing of radical hysterectomy (early vs delayed) was not significantly related to the occurrence of complications (38% vs 29%, respectively) (P = .115). Finally, in medical center 9 significantly more surgical complications were registered than the median percentage (63% vs 30%, P = .001).

Variables associated with surgical complications were entered into a multivariable logistic regression analysis model. Open surgery compared with robot surgery (odds ratio [OR] 3.42; 95% CI 1.73-6.76; P < .001), chronic pulmonary disease (OR 3.14; 95% CI 1.45-6.79; P = .004), vascular disease (OR 1.90; 95% CI 1.07-3.38; P = .028), and medical center 9 (OR 2.83; 95% CI 1.18-6.77; P = .019) emerged as independent predictors of surgical complications.

Similar analyses were executed for the most prevalent complications urinary retention with catheterization and excessive perioperative blood loss. We found body mass index to be an independent predictor for urinary retention (OR 0.94; 95% CI 0.89-1.00; P = .043). For analysis purposes (blood loss >1000 mL did not occur in women who underwent robot surgery), conventional laparoscopic and robot surgery were combined and compared with open surgery, in examining excessive blood loss. Open surgery (OR 36.65; 95% CI 7.10-189.12]; P < .001) and body mass index (OR 1.15; 95% CI 1.08-1.22; P < .001) were found to be independent predictors of excessive perioperative blood loss.

4 | DISCUSSION

This study shows that intraoperative and postoperative short-term surgical complications occurred in over one-third of the women after radical hysterectomy for early-stage cervical cancer. This indicates that, in terms of morbidity due to surgery, despite centralization of a relatively infrequent operation, there is still room for improvement of quality of care. Looking into possible predictors for the development of surgical complications, we identified surgical approach, chronic pulmonary disease, vascular disease, and medical center as independent predictors of the development of surgical complications.

It has been argued that centralization of surgical care for cervical cancer results in fewer surgical complications.[7] Centralization provides medical centers with more cases to treat, consequently increasing surgical experience and outcome. For example, a study by Trimbos et al reported that blood loss decreased from 1515 mL to 1071 mL and operating time decreased by nearly 90 minutes in open radical hysterectomy over a 13-year period.[10] The study was executed in 1 single institution with the same surgical team and a similar 5-year survival rate to other gynecological cancer centers around the world. The authors conclude that it takes a strikingly long time to achieve surgical experience. In the present study, we found that, in a nation with centralized radical hysterectomy procedures, surgical complications within 30 days after surgery developed in over one-third of the women. In comparison, recently published results from the "Laparoscopic Approach to Cervical Cancer" trial showed 11% of the women to have intraoperative complications and 25% to have early postoperative complications within 6 weeks after surgery.[6]

As mentioned earlier, radical hysterectomy for cervical cancer is centralized to 9 specialized medical centers in the Netherlands. Two of these centers only perform open surgery, whereas some gynecological oncologists from other centers are mainly trained in minimally invasive procedures. The trial by Ramirez et al reopened the

TABLE 4 Univariable and multivariable logistic regression analysis of risk factors for the occurrence of short-term surgical complications

	Group with complications n = 166	Group without complications n = 306	Univariable *P*	Multivariable[a]		
				OR	95% CI	*P*
Age, years (SD)	47 (12)	45 (11)	.085			
Body mass index, kg/m^2 (SD)	26 (5)	25 (5)	.022			
Number of comorbidities, n (%)						
0	94 (57)	205 (67)	Reference			
1	40 (24)	70 (23)	.347			
>1	32 (19)	31 (10)	.004			
Type of comorbidities, n (%)						
Chronic pulmonary disease	21 (13)	13 (4)	.01	3.14	1.45-6.79	.004
Neurological/psychiatric disease	15 (9)	15 (5)	.083			
Vascular disease	32 (19)	33 (11)	.012	1.90	1.07-3.38	.028
Medical center, n (%)						
1	14 (8)	27 (9)	.701			
2	13 (8)	30 (10)	Reference			
3	8 (5)	29 (9)	.385			
4	25 (15)	43 (14)	.480			
5	11 (7)	30 (10)	.730			
6	9 (5)	27 (9)	.606			
7	23 (14)	51 (17)	.924			
8	17 (10)	42 (14)	.877			
9	46 (28)	27 (9)	.001	2.83	1.18-6.77	.019
Surgical approach, n (%)						
Robot	31 (19)	100 (33)	Reference			
Laparoscopic	23 (14)	47 (15)	.163			
Open	112 (67)	159 (52)	.001	3.42	1.73-6.76	<.001
Timing radical hysterectomy, n (%)						
Early	41 (25)	68 (22)	Reference			
Delayed	51 (31)	127 (42)	.115			

[a]Nonsignificant results omitted for clarity; OR, odds ratio; CI, confidence interval; because of rounding, percentages might not sum to 100%.

debate on surgical approach in early-stage cervical cancer, arguing that open radical hysterectomy is superior over laparoscopy regarding recurrence rates and disease-free survival.[6] In the aftermath of this trial, a shift can be expected towards open surgery. However, advocating open surgery as treatment of choice poses challenges to countries where surgery for cervical cancer is organized similarly to the Netherlands. For those with limited experience in open surgery, altering surgical approach means facing a new learning curve. Such changes possibly affect the quality of surgical care, making it essential to monitor outcome parameters.

We identified surgical approach as an independent predictor for surgical complications. Open surgery as predictive factor of overall complications was primarily accounted for by excessive perioperative blood loss, with 98% of the cases registered in those treated with open surgery ($P < .001$). As stated previously, this is in accordance with multiple reviews on radical hysterectomy, which report higher blood loss in women who undergo open surgery versus conventional laparoscopic or robot surgery.[3,11] However, in the studies under review, blood loss was measured as average number of millilitres, whereas in our study excessive blood loss is defined using a cutoff of 1000 mL. In a review by Zhao et al,[11] mean blood loss was approximately 180 mL higher in women treated by open surgery. In open surgery studies, means ranged from 145 to 836 mL, whereas mean blood loss in laparoscopic surgery ranged from 65 to 449 mL. This offers a possible explanation for the near absence of excessive blood loss in our laparoscopic surgery sample.

Next, body mass index emerged as independent predictor of excessive perioperative blood loss ($P < .001$). The relation between obesity and surgical complications has been reported previously. Specifically, blood loss has been associated with obesity in several studies on radical hysterectomy for cervical cancer.[12-15] In part, this may be attributed to surgery in obese women being technically more difficult.

Chronic pulmonary disease and vascular disease also emerged as predictors of complications ($P = .004$ and $P = .028$, respectively).

Comorbidities have long been linked to the development of surgical complications. Moreover, chronic pulmonary disease and vascular disease have been reported as predictors of perioperative and postoperative complications in gynecological cancer.[16-22]

Timing of radical hysterectomy after a previous diagnostic procedure was reported to be a predictor of developing complications.[9] Receiving early (ie ≤6 weeks after diagnostic excision) radical hysterectomy was associated with more complications, because of a hypothesized impact of parametrial inflammation, than receiving delayed radical hysterectomy. With our data, comparing surgical approach, no significant associations were found between timing of radical hysterectomy and complications. Therefore, we cannot conclude that timing of radical hysterectomy is a predictor of short-term surgical complications. An explanation for the discrepancy may lie in the different types of complications that were investigated in both studies.

The strength of our study is that by using data from the Netherlands Cancer Registry, a nationally representative sample of the Dutch population was investigated. It provides data from real-world clinical practice instead of a controlled trial environment. By integrating data from multiple gynecological centers, it avoids the weakness of single center studies. Furthermore, monitoring quality of surgical care by an independent institute increases the ability to identify areas of improvement,[7] avoiding possible underrepresentation on the outcome of interest. In the Netherlands Cancer Registry, gynecological data are registered shortly after primary treatment is completed to be able to provide physicians with up-to-date feedback. This registration of short-term data inevitably results in the absence of long-term complications in our database. Consequently, the focus of this study was only on short-term complications.

A limitation of observational research is that it depends on the quality of data in the medical record. For example, if 1 hospital is less accurate in the registration of complications, this underrepresentation might result in a misclassification bias. In the present study, 1 hospital used their own registration clerks, which might have induced bias. However, excluding their data from the analysis did not alter the results. One major limitation is the absence of information on severity in the registration of complications. In surgically treated gynecological tumors, situations deviating from the normal are registered as surgical complications, although they are not graded as in, for example, the Clavien-Dindo classification.[23] For example, the bladder catheter placed during surgery is not classified as a complication. Whereas, in the case of catheter reinsertion, hospital discharge with catheter and readmission because of urinary retention it is classified as a complication. Another limitation is the registration of comorbidities. Although comorbidities are registered in the Netherlands Cancer Registry, their severity is not. Selection may have affected our results as women with severe comorbid disease have possibly been excluded from surgery and assigned to primary radiotherapy, instead. Vascular disease (14%) and chronic pulmonary disease (7%) are relatively common in our cohort. However, this is probably caused by the inclusion of hypertension in the definition of vascular disease and asthma in the definition of chronic pulmonary disease. Furthermore, in our study no differentiation was made in the extent of radicality and nerve sparing. As morbidity of the radical hysterectomy is proportional to the extent of resection, its influence on the development of complications could not be examined. Finally, in medical centers performing both open and laparoscopic procedures, high-risk patients might have been selected for open surgery more often. Although our analysis adjusted for age, body mass index,, and comorbidities, there might have been other predictors that we have not corrected for.

5 | CONCLUSION

Short-term surgical complications develop in 35% of women after radical hysterectomy for early-stage cervical cancer in the Netherlands, a nation with centralized surgical care. We found open surgery to be associated with more frequent excessive perioperative blood loss, whereas chronic pulmonary disease and vascular disease are independent predictors of the occurrence of surgical complications in general. Accordingly, we suggest that women are informed during the treatment decision-making process about the possible consequences of surgical approach and comorbidities.

CONFLICTS OF INTEREST

HN—Grant Dutch Cancer Society; Stock owner SME Vicinivax; Grant Aduro. RZ—Proctor Intuitive Surgical. Other authors: none declared.

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How to cite this article: Wenzel HHB, Kruitwagen RFPM, Nijman HW, et al. Short-term surgical complications after radical hysterectomy—A nationwide cohort study. *Acta Obstet Gynecol Scand*. 2020;99:925–932. https://doi.org/10.1111/aogs.13812