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# Contribution of cervical cytology in the diagnostic work-up of patients with endometrial cancer

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**Introduction:** Abnormal cervical cytology in patients with endometrial cancer (EC) has been associated with poor outcome. The aim of this study was to evaluate whether cervical cytology could contribute to an improved preoperative identification of high-grade EC (serous, clear cell, carcinosarcoma, high-grade endometrioid EC) in final histology.

**Methods:** A retrospective cohort study was performed in five hospitals in the Netherlands. A total of 554 patients with EC that underwent primary surgical treatment between 2002 and 2010 were included. Primary outcome was defined as the contribution of abnormal cervical cytology in the preoperative identification of high-grade EC. As secondary outcome, recurrence-free survival (RFS) and disease-specific survival were determined based on preoperative cervical cytology, and compared to the currently established risk factors: myometrial invasion, high-grade and lymph vascular space invasion.

**Results:** Abnormal cervical cytology was present in 45.1%. For patients with preoperative inconclusive and high-grade histology, the presence of abnormal cervical cytology contributed to an improved identification of high-grade EC in final histology (odds ratio [OR] 6.40 [95% confidence interval {CI}: 1.92-21.26]; OR 2.86 [95% CI: 1.14-7.14]), respectively.

Patients with abnormal cervical cytology had a significant worse 5-year median RFS. Abnormal cervical cytology was independently related to RFS (hazard ratio 1.67 [95% CI: 1.04-2.68]) and disease-specific survival (hazard ratio 3.15 [95% CI: 1.74-5.71]).

**Conclusions:** Abnormal cytology contributes to the preoperative identification of patients with high-grade EC, and is associated with compromised outcome. Future studies are warranted to determine whether cervical cytology could be incorporated into preoperative prediction models for lymph node metastasis.

KEYWORDS
cervical cytology, diagnosis, endometrial neoplasms, Papanicolaou smear, preoperative

  

## 1 | INTRODUCTION

Endometrial cancer (EC) is the most common gynaecological cancer in the developed world, predominantly occurring in postmenopausal women. Since vaginal bleeding is an early symptom, EC is diagnosed at an early stage in the majority of patients, and has a favourable prognosis, with a 5-year overall survival rate of 80%-85% and a cancer-specific survival rate of 90%-95%.[1] Historically, EC is classified into two types.[2,3] Type I tumours (±80%) are endometrioid carcinomas often arising in a background of hyperplasia that are usually low-grade, oestrogen-related and have a favourable outcome. Type II tumours (±20%) are non-endometrioid tumours that arise in endometrial polyps or precancerous lesions in the vicinity of atrophic endometrium. These tumours are high-grade, usually not oestrogen-related, and carry a high mortality rate.[2,3] Recent data of the Cancer Genome Atlas Research network demonstrated that this dualistic model is too simplistic, and proposed to categorize EC based on molecular profile.[4] However, these data have not yet been incorporated in clinical practice.

Surgery is the primary treatment of EC, consisting of at least hysterectomy and bilateral salpingo-oophorectomy.[5,6] Although routine lymphadenectomy is not beneficial in low-grade EC, surgical staging is recommended in patients with high-grade histology such as serous, clear cell, carcinosarcoma, and high-grade endometrioid EC.[7] Other risk factors for extended disease are: deep myometrial invasion, cervical involvement and lymph vascular space invasion (LVSI). However, preoperative assessment of these factors remains a challenge.[8-12] The concordance of preoperative biopsy is relatively good for grade 1 tumours, but only moderate for grade 2 and 3 tumours, 52% and 53%, respectively.[13] As a consequence, some patients are staged unnecessarily and are at increased risk of surgical complications, whereas others need a second surgical procedure. The concordance between pre- and postoperative risk classification might be improved with incorporation of other clinical or molecular markers.[14] In previous studies, the presence of preoperative abnormal cervical cytology has been associated with extrauterine disease, high tumour grade, serous histology and deep myometrial invasion.[15-19]

The aim of the present study was to evaluate whether cervical cytology could contribute to an improved preoperative identification of high-grade EC.

## 2 | MATERIALS AND METHODS

### 2.1 | Setting and patients

A retrospective cohort study was performed in four general hospitals and one university hospital in the south-eastern part of the Netherlands. Data from all patients with EC who underwent primary surgical treatment between 2002 and 2010 were retrieved. Patients for whom a preoperative pathology report was not available were excluded.

### 2.2 | Data extraction

Population-based data were provided by the Netherlands Cancer Registry (NCR). The NCR, which reached full national coverage in 1989, is based on notification of all newly diagnosed malignancies in the Netherlands by the automated nationwide pathology archive (PALGA).[20] The following data were collected: date of birth, date of diagnosis, results of cervical cytology, findings at physical examination, results of preoperative imaging, preoperative histology, definitive histology, differentiation grade after surgery, evaluation of lymph nodes, recurrence and survival. Data for survival were updated in March 2015. For staging, the 2009 International Federation of Gynecology and Obstetrics (FIGO) surgical classification was used for all patients.[21]

Histology was classified as endometrioid, adenosquamous, serous, clear cell or carcinosarcoma. Low-grade tumours were defined as tumours with histological type endometrioid adeno or adenosquamous endometrial carcinoma grade 1-2. High-grade tumours were defined as tumours with histological type endometrioid grade 3, serous, clear cell, or carcinosarcoma EC. All cases in which preoperative histological type and/or tumour grade were unknown were classified as inconclusive risk. Cervical smears were classified as abnormal if there were atypical glandular or malignant endometrial cells present in the preoperative cervical cytology.

### 2.3 | Primary outcome

Primary outcome was defined as the contribution of abnormal cervical cytology to preoperative histological risk classification, ie, low-grade, high-grade or inconclusive in relation to the risk classification in final pathology.

### 2.4 | Secondary outcome

Secondary outcome was defined as the recurrence-free survival (RFS) and disease-specific survival (DSS) based on preoperative risk classification and cervical cytology, and compared to the established predictors for recurrence and survival: deep myometrial invasion, LVSI, high-grade, non-endometrioid histology and FIGO stage.

### 2.5 | Statistical analysis

Clinicopathological data were compared to cervical cytology using *t* tests for continuous variables and chi-square tests for categorical variables. Associations between pre- and postoperative classification were analysed using logistic regression. The sensitivity, specificity, positive predictive value and negative predictive value were calculated for the prediction of high-grade EC based on preoperative findings of: (1) high-grade histology; (2) high-grade histology and abnormal cervical cytology; and (3) high-grade or inconclusive histology and abnormal cervical cytology. Median and 5-year RFS and DSS were determined by Kaplan-Meier analysis. Cox proportional hazards regression was used to estimate the independent association

of abnormal cervical cytology and other known preoperative findings, such as non-endometrioid histology, and high-grade and postoperative findings such as non-endometrioid histology, high-grade, deep myometrial invasion, LVSI and FIGO stage on recurrence and survival. IBM SPSS (Armonk, NY: IBM Corp.) Statistics version 22 was used. *P*-values were regarded as significant if $P \leq .05$ and tests were two-sided.

## 3 | RESULTS

### 3.1 | Patients

In total, data of 729 patients with EC were extracted from the selected period. In 153 patients (21.0%), cervical cytology was not performed in the diagnostic work-up. There were no significant differences with respect to tumour stage and tumour grade in patients with or without cervical cytology (data not shown). In three patients, tumour grade in final pathology was not documented, and in 19 patients results of preoperative histology were not available, leaving 554 patients for the final analysis with a median follow-up of 60 months (range 1-152 months). In Table 1, baseline characteristics of all patients are shown. Postoperatively, 77.1% (n = 427) were classified as low-grade EC and 22.9% (n = 127) as high-grade EC. Primary treatment consisted of at least a hysterectomy in all cases. Ninety (16.2%) patients underwent a lymphadenectomy. Adjuvant radiotherapy and chemotherapy were given in, respectively, 237 (42.8%) and 22 (4.0%) patients.

Considerable misclassification was observed in the determination of pre- vs postoperative histology. In 12.7% of patients with preoperative low-grade EC, final histology showed high-grade EC, whereas in 28.1% of patients with preoperative high-grade EC, final histology was classified as low grade.

**TABLE 1** Baseline characteristics of included patients

| | Total (n = 554) | |
|---|---|---|
| Age | | |
| Mean age (y) | 66.4 | 31.3-95.0 |
| <60 y | 160 | 28.9% |
| ≥60 y | 394 | 71.1% |
| Preoperative grade | | |
| Grade 1 | 215 | 38.8% |
| Grade 2 | 99 | 17.9% |
| Grade 3 | 95 | 17.1% |
| Inconclusive | 145 | 26.2% |
| FIGO stage | | |
| IA | 312 | 56.3% |
| IB | 158 | 28.5% |
| II | 34 | 6.1% |
| IIIA | 18 | 3.2% |
| IIIB | 6 | 1.1% |
| IIIC1 | 15 | 2.7% |
| IIIC2 | 3 | 0.5% |
| IVA | 1 | 0.2% |
| IVB | 7 | 1.3% |
| Histological type | | |
| Endometrioid grade 1-2 | 418 | 75.5% |
| Endometrioid grade 3 | 56 | 10.1% |
| Serous | 48 | 8.7% |
| Clearcell® | 15 | 2.7% |
| Carcinosarcoma | 6 | 1.1% |
| Adenosquamous | 9 | 1.6% |
| Remaining | 2 | 0.4% |
| Tumour grade | | |
| Grade 1 | 251 | 45.3% |
| Grade 2 | 177 | 31.9% |
| Grade 3 | 126 | 22.7% |

FIGO, International Federation of Gynecology and Obstetrics

### 3.2 | Cervical cytology

In 250 out of 554 patients (45.1%), abnormal cervical cytology was present. In Table 2 the actual numbers of preoperative histology and results of cervical cytology are demonstrated in relation to the subsequent final histology, and illustrated in Figure 1. Overall, abnormal cervical cytology was significantly associated with postoperative high-grade EC ($P < .001$). In patients with advanced-stage EC, abnormal cervical cytology was found significantly more often: 62.0% and 43.3% of respectively patients with FIGO stage III-IV and stage I-II ($P = .01$). Also, abnormal cervical cytology was found significantly more often in patients with FIGO stage II (70.6%) vs FIGO stage I (41.5%; $P = .001$).

For patients with preoperative low-grade EC (grade 1-2), abnormal cervical cytology was not associated with postoperative high-grade EC: grade 1; OR 1.40 (95% CI: 0.36-5.36), and grade 2; OR

**TABLE 2** Numbers of preoperative risk classification and cervical cytology in relation to postoperative tumour grade

| | Postoperative tumour grade | |
|---|---|---|
| Preoperative tumour grade cervical cytology | Low grade, n = 427 (77%) | High grade, n = 127 (23%) |
| Grade 1, normal cytology (n = 136) | 131 (96%) | 5 (4%) |
| Grade 1, abnormal cytology (n = 79) | 75 (95%) | 4 (5%) |
| Grade 2, normal cytology (n = 47) | 35 (74%) | 12 (26%) |
| Grade 2, abnormal cytology (n = 52) | 33 (63%) | 19 (37%) |
| Grade 3, normal cytology (n = 36) | 16 (44%) | 20 (56%) |
| Grade 3, abnormal cytology (n = 59) | 12 (20%) | 47 (80%) |
| Grade unknown, normal cytology (n = 85) | 78 (92%) | 7 (8%) |
| Grade unknown, abnormal cytology (n = 60) | 47 (78%) | 13 (22%) |

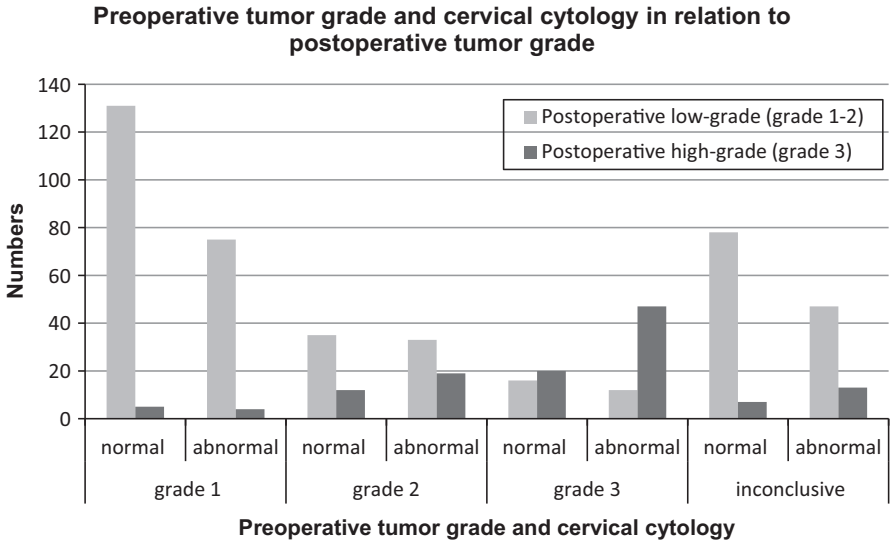


**FIGURE 1** Preoperative risk classification in relation to tumour grade in final pathology

1.68 (95% CI: 0.71-3.99). However, for patients with preoperative inconclusive, or high-grade EC, abnormal cervical cytology was significantly associated with high-grade EC in final histology: inconclusive risk, OR 6.40 (95% CI: 1.92-21.26); and high-grade, OR 2.86 (95% CI: 1.14-7.14). Patients with preoperative high-grade EC and normal cervical cytology, 58.3% (21/36) was diagnosed with high-grade EC in final histology, whereas of those patients with preoperative high-grade EC and abnormal cytology, 80.0% (48/60) were diagnosed with high-grade EC postoperatively. The test characteristics for the prediction of high-grade EC in final histology are demonstrated subsequently as based on preoperative: (1) high-grade EC; (2) high-grade EC and abnormal cervical cytology; and (3) high-grade or inconclusive EC and abnormal cervical cytology. The sensitivity, specificity, positive predictive value and negative predictive value are demonstrated in Table 3.

### 3.3 | RFS and DSS

Overall, patients with preoperative abnormal cervical cytology had significantly worse 5-year median RFS and DSS, when compared to patients with normal cervical cytology, as shown in Figures 2 and 3 ($P = .002$ and $P < .001$, respectively). The hazard ratios for RFS and DSS are calculated for preoperative histology and cytology and compared with the hazard ratios as based on final histology. Results of univariable and multivariable Cox regression are presented in Table 4. Preoperative high tumour grade and abnormal cervical cytology were independent predictors for reduced RFS and DSS.

**TABLE 3** Test characteristics for the prediction of high risk EC in final pathology as based on preoperative risk histology only and with the addition of abnormal cervical cytology

| | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| High grade histology | 54 | 94 | 72 | 87 |
| High grade histology + abnormal cervical cytology | 38 | 97 | 80 | 84 |
| High grade or inconclusive histology + abnormal cervical cytology | 66 | 91 | 75 | 87 |

NPV, negative predictive value; PPV, positive predictive value.

## 4 | DISCUSSION

In the current study, we demonstrated that abnormal cervical cytology was significantly associated with high-grade EC in final pathology. In the subgroup of patients with preoperative high- or inconclusive grade EC, it resulted in improved selection of patients with high-grade EC that needed surgical staging. Interestingly, we demonstrated that abnormal cervical cytology was a predictor of worse outcome, independent of high-grade tumours and non-endometrioid histology.

The overall incidence of abnormal cervical cytology in our study (45.1%) is comparable to numbers reported in the literature (31%-50%).[15-17] In patients with serous endometrial carcinoma, abnormal cervical cytology is reported in up to 65.7%-87.5% of patients, and may even be considered as a prognostic marker for non-endometrioid histology.[22,23] In our cohort, 60.7% of patients with high-grade tumours presented with abnormal cervical cytology. However, in our cohort, high-grade histology included not only serous carcinoma, but also clear cell, carcinosarcoma and grade 3 endometrioid adenocarcinoma histology. In the subset of serous carcinomas, we found an equally high percentage of abnormal cervical cytology of 85.4% (41/48). The association of abnormal cervical cytology with advanced FIGO stage in our study was also demonstrated by Roelofsen et al,[22] who observed a correlation of abnormal cervical cytology with cervical stromal invasion in endometrioid-type endometrial carcinoma, and advanced stage in serous endometrial carcinoma. Also in our series there was a significant relation with abnormal cervical

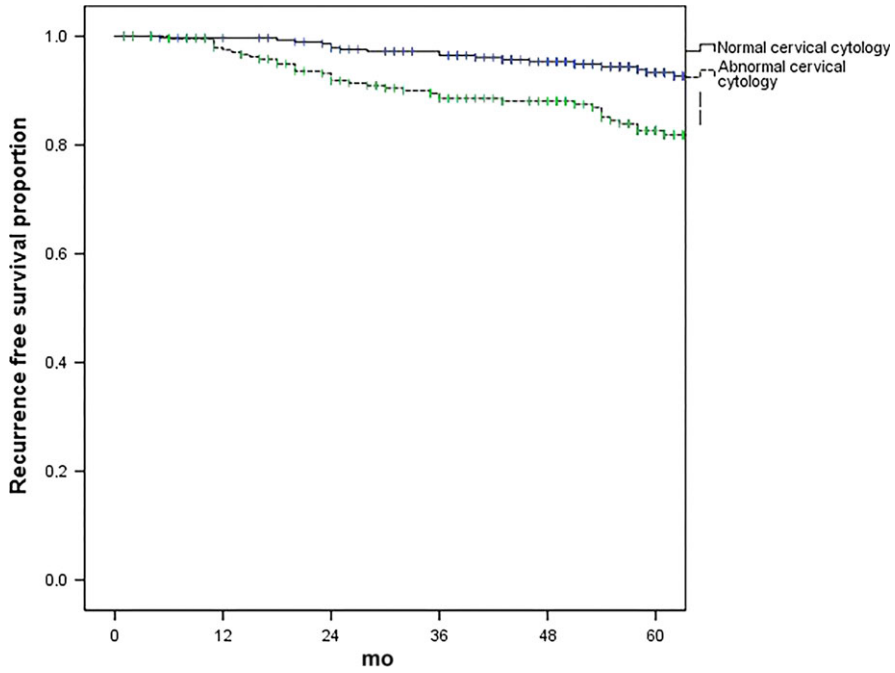


**FIGURE 2** Kaplan-Meier analysis of recurrence free survival of patients with endometrial cancer for normal and abnormal cervical cytology. Vertical lines represent censored individuals

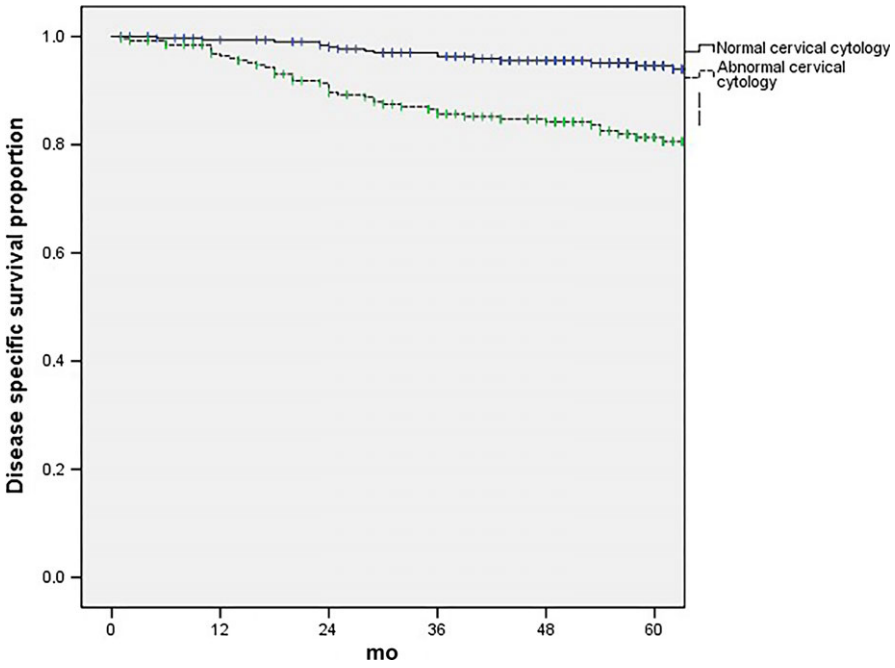


**FIGURE 3** Kaplan-Meier analysis of disease specific survival of patients with endometrial cancer for normal and abnormal cervical cytology. Vertical lines represent censored individuals

cytology and cervical stromal involvement. However, in contrast to Roelofsen et al,[22] we also found a correlation of abnormal cervical cytology with both disease-specific and overall survival.[22,24] This might be explained by the differences in study cohorts, since in our cohort all histological types were included, whereas Roelofsen et al[22] only included patients with endometrioid and serous-type endometrial carcinoma. Moreover, there was a difference in the criteria for abnormal cytology. We defined abnormal cytology more strictly as the presence of atypical glandular cells or EC cells, whereas Roelofsen et al[22] included the presence of endometrial cells into *abnormal cervical cytology*. Categorization of the presence of endometrial cells into *normal cervical cytology* is supported by recent data of Izadi-Mood et al,[25] who demonstrated in a series of 199 cases that the presence of endometrial cells in cervical cytology tests of women older than 40 years was not associated with significant endometrial lesions.[25,26]

The correlation of abnormal cervical cytology with poor outcome was reported in 2005 by Brown et al[18] In this study, a recurrence rate of 12% was reported in patients with abnormal cervical cytology, vs 4% in patients with normal cervical cytology. We observed higher recurrence rates for both patients with abnormal and normal cervical cytology, 16.8% and 9.9% respectively. This might be

**TABLE 4** Univariable and multivariable Cox regression

| | Univariable HR (95% CI) | Multivariable HR (95% CI) |
|---|---|---|
| RFS | | |
| Preoperative | | |
| Abnormal cervical cytology | **1.88 (1.18-3.01)** | **1.67 (1.04-2.68)** |
| Grade 3 | **3.09 (1.90-5.02)** | **2.96 (1.74-5.03)** |
| NEEC | 1.35 (0.83-2.21) | - |
| Postoperative | | |
| MI > 50% | **2.17 (1.36-3.46)** | 1.34 (0.80-2.25) |
| LVSI | **3.76 (2.22-6.36)** | **1.85 (1.03-3.32)** |
| Grade 3 | **3.79 (2.38-6.02)** | **2.44 (1.29-4.62)** |
| NEEC | **2.97 (1.79-4.95)** | 0.98 (0.49-1.94) |
| FIGO 3/4 | **5.36 (3.19-8.99)** | **3.08 (1.68-5.64)** |
| DSS | | |
| Preoperative | | |
| Abnormal cervical cytology | **3.89 (2.16-7.00)** | **3.15 (1.74-5.71)** |
| Grade 3 | **5.14 (3.06-8.62)** | **3.80 (2.15-6.72)** |
| NEEC | **2.35 (1.40-3.94)** | 1.31 (0.75-2.31) |
| Postoperative | | |
| MI > 50% | **3.25 (1.89-5.58)** | 1.63 (0.88-3.00) |
| LVSI | **5.15 (2.97-8.93)** | 1.64 (0.90-2.99) |
| Grade 3 | **9.19 (5.29-15.98)** | **5.48 (2.69-11.16)** |
| NEEC | **5.43 (3.22-9.15)** | 0.95 (0.48-1.86) |
| FIGO 3/4 | **9.30 (5.51-15.72)** | **4.14 (2.24-7.69)** |

HR, hazard ratio; CI, confidence interval; RFS, recurrence-free survival; DSS, disease-specific survival; NEEC, Xxx; MI, Xxx; LVSI, lymph vascular space invasion; FIGO, International Federation of Gynecology and Obstetrics; NEEC, Non-endometrioid endometrial cancer; MI, myometrial invasion.
The significant numbers are all in bold.

explained by the fact that Brown et al[18] considered the presence of normal endometrial cells in cervical cytology as abnormal, which was different in our classification.

To our knowledge this is one of the few studies to analyse the contributive value of cervical cytology in preoperative risk classification of EC, and the impact on patient outcomes. Currently, the primary surgical approach is based on preoperative tumour classification, clinical stage, and the presence of extended disease such as lymph node metastasis or extrauterine involvement based on imaging. It is known from literature that, especially in high-grade EC, there is only moderate concordance with pre- and postoperative histology.[13] The results of cervical cytology might therefore be incorporated in the primary surgical approach.

The strength of this study is the large cohort, including 554 evaluable patients with EC. However, our study is limited by the fact that only 35.1% (n = 47) of the patients with high-grade EC in final histology underwent a lymph node dissection as part of the surgical staging procedure, which might clarify the relatively low percentage of FIGO IIIC1-2 (3.2%). This is explained by the fact that 35.8% (n = 48) of the patients were not preoperatively identified as high-grade EC. But staging was also not performed in 29.1% (n = 39) of the patients with preoperative high-grade EC. It is unclear whether the limited lymphadenectomy occurrence has altered the outcome, since abnormal cervical cytology was predictive of a compromised outcome in both low and high-grade patients. Colombo et al[27] concluded that lymphadenectomy is not recommended but can be considered in patients with grade 3 tumour and superficial myometrial invasion (less than 50%) because lymphadenectomy shows no survival benefit. However, numbers of high-grade patients are still low, and due to the retrospective character of the study, results should be interpreted with caution.

The high percentage of patients with abnormal cervical cytology in serous EC might be explained by the easy detachment and exfoliation of the papillary growing cells of serous cancer in accordance with serous ovarian cancer.[24,28,29] However, for more solid growing tumours such as high-grade endometrioid and carcinosarcoma, this is not completely understood. In a recently published study, DNA extracted from cervical smears was studied to detect genetic EC disorders. Although this was a small series of only 24 cases, the mutation profile in the cervical smear was comparable to the primary tumour in all patients with EC.[30] These results demonstrated that EC cells were frequently found in cervical cytology, even with normal Papanicolaou smear results. Whether this might be useful for future EC screening needs to be determined. However, the fact that in the current study the presence of atypical cells in patients diagnosed with EC can improve the preoperative identification of high-grade EC, it can easily be used in clinical practice. The fact that patients with preoperative low-grade EC and abnormal cervical cytology had a worse outcome when compared to normal cytology, might be explained by the increased number of unidentified high-grade EC. In summary, patients with preoperative normal cervical cytology and low-grade EC had the lowest probability of high-grade EC in final pathology, whereas patients with preoperative abnormal cervical cytology and high-grade EC had the highest probability of high-grade EC with subsequent compromised outcome. This is in line with the data of Werner et al,[31] who demonstrated that discordant risk classification based on histology, between preoperative biopsy and the hysterectomy specimen, identifies a separate group when compared to those with concordant low- and concordant high-grade pathology with respect to disease spread and prognosis. Discordancy in both pre- and postoperative pathology as well as discordancy with respect to cervical cytology and preoperative histology might give additional information of tumour behaviour.

In the current study, we showed that if surgical staging had been determined on preoperative high-grade histology, 72% of patients were correctly diagnosed and thus 28% would have been unnecessarily subjected to lymph node dissection. With the incorporation of cervical cytology results, we observed a reduced percentage of high-grade pathology (58%) in cases of normal cytology, compared to an increased likelihood of high-grade pathology with abnormal cytology (80%). These risk estimations can be taken into account when

counselling the patient about the risks and benefits of staging at the primary surgical approach.

Several groups of clinicians have developed prediction models for the presence of lymph node metastasis, in order to select those patients that are most likely to benefit from lymphadenectomy.[32-36] However, the best prediction models so far are based on final pathology, which is a shortcoming for the implementation in clinical practice for proper selection of patients preoperatively. So far, the contribution of cervical cytology has not been studied in any of the models. Based on our findings, the presence of abnormal cervical cytology could be added as a marker for high-grade EC, in addition to preoperative histology, age of the patient, serum CA-125, MRI findings of myometrial invasion and abnormal lymph nodes. This should be validated in a larger series with current criteria for abnormal cervical cytology in order to determine the contributive value more specifically.

## 5 | CONCLUSION

Abnormal cervical cytology contributes to the preoperative selection of patients with high-grade endometrial carcinoma, and is associated with compromised outcome. Future studies are warranted to determine whether cervical cytology could be incorporated in preoperative prediction models for lymph node metastasis.

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## CONFLICT OF INTEREST

The authors have no conflicts of interest.

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## REFERENCES

1. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer*. 2010;46:765-781.
2. Prat J. Prognostic parameters of endometrial carcinoma. *Hum Pathol*. 2004;35:649-662.
3. Bokhman JV. Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol*. 1983;15:10-17.
4. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, et al. Integrated genomic characterization of endometrial carcinoma. *Nature*. 2013;497:67-73.
5. Keller D, Kempson RL, Levine G, McLennan C. Management of the patient with early endometrial carcinoma. *Cancer*. 1974;33:1108-1116.
6. Malkasian GD, Annegers JF, Fountain KS. Cancer of the endometrium: stage I. *Am J Obstet Gynecol*. 1980;136:872-888.
7. ASTEC Study Group, Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet*. 2009;373:125-136.
8. Alobaid A, Bruchim I, Verkooijen H, Gauthier P, Petignat P. Adjuvant therapy for patients with stage I papillary serous endometrial cancer. *Eur J Surg Oncol*. 2006;32:358-362.
9. Boruta DM, Gehrig PA, Fader AN, Olawaiye AB. Management of women with uterine papillary serous cancer: a Society of Gynecologic Oncology (SGO) review. *Gynecol Oncol*. 2009;115:142-153.
10. Olawaiye AB, Boruta DM. Management of women with clear cell endometrial cancer: a Society of Gynecologic Oncology (SGO) review. *Gynecol Oncol*. 2009;113:277-283.
11. Look K. Stage I-II endometrial adenocarcinoma evolution of therapeutic paradigms: the role of surgery and adjuvant radiation. *Int J Gynecol Cancer*. 2002;12:237-249.
12. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer: a Gynecologic Oncology Group Study. *Cancer*. 1987;60:2035-2041.
13. Francis JA, Weir MM, Ettler HC, Qiu F, Kwon JS. Should preoperative pathology be used to select patients for surgical staging in endometrial cancer? *Int J Gynecol Cancer*. 2009;19:380-384.
14. MoMaTEC Study Group, Trovik J, Wik E, et al. Hormone receptor loss in endometrial carcinoma curettage predicts lymph node metastasis and poor outcome in prospective multicentre trial. *Eur J Cancer*. 2013;49:3431-3441.
15. DuBeshter B, Warshal DP, Angel C, Dvoretsky PM, Lin JY, Raubertas RF. Endometrial carcinoma: the relevance of cervical cytology. *Obstet Gynecol*. 1991;77:458-462.
16. Fukuda K, Mori M, Uchiyama M, et al. Preoperative cervical cytology in endometrial carcinoma and its clinicopathologic relevance. *Gynecol Oncol*. 1999;72:273-277.
17. Larson DM, Johnson KK, Reyes CN Jr, Broste SK. Prognostic significance of malignant cervical cytology in patients with endometrial cancer. *Obstet Gynecol*. 1994;84:399-403.
18. Brown AK, Gillis S, Deuel C, Angel C, Glantz C, Dubeshter B. Abnormal cervical cytology: a risk factor for endometrial cancer recurrence. *Int J Gynecol Cancer*. 2005;15:517-522.
19. Helpman L, Kupets R, Covens A, et al. Assessment of endometrial sampling as a predictor of final surgical pathology in endometrial cancer. *Br J Cancer*. 2014;110:609-615.
20. Casparie M, Tiebosch AT, Burger G, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. *Cell Oncol*. 2007;29:19-24.
21. Creasman W. Revised FIGO staging for carcinoma of the endometrium. *Int J Gynaecol Obstet*. 2009;105:109.
22. Roelofsen T, Geels YP, Pijnenborg JMA, et al. Cervical cytology in serous and endometrioid endometrial cancer. *Int J Gynecol Pathol*. 2013;32:390-398.
23. Skaznik-Wikiel ME, Ueda SM, Frasure HE, et al. Abnormal cervical cytology in the diagnosis of uterine papillary serous carcinoma: earlier detection of a poor prognostic cancer subtype? *Acta Cytol*. 2011;55:255-260.
24. Gu M, Shi W, Barakat RR, Thaler HT, Saigo PE. Pap smears in women with endometrial carcinoma. *Acta Cytol*. 2001;45:555-560.
25. Izadi-Mood N, Sarmadi S, Sanii S, Sadidi H. Normal-appearing endometrial cells in Pap tests of women aged forty years or older and cytohistological correlates. *Acta Cytol*. 2015;59:175-179.

26. Chummun K, Fitzpatrick M, Lenehan P, Boylan P, Mooney E, Flannelly G. Diagnostic and therapeutic dilemma associated with atypical glandular cells on liquid-based cervical cytology. *Cytopathology*. 2012;23:378-382.
27. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. *Ann Oncol* 2016;27:16-41.
28. Suzuki M, Suzuki T, Matsuura M, et al. Prediction of histologic type and lymph node metastasis for advanced ovarian cancer on uterine cervical and endometrial cytology. *Acta Cytol*. 2010;54:575-581.
29. Hosford S, Elliott J, Ma ZW, Majeste R, DuBeshter B. CD44 expression in papillary serous endometrial carcinoma. *Int J Gynecol Cancer*. 2003;13:480-484.
30. Kinde I, Bettegowda C, Wang Y, et al. Evaluation of DNA from the Papanicolaou test to detect ovarian and endometrial cancers. *Sci Transl Med* 2013;5:167ra4.
31. Werner HM, Trovik J, Marcickiewicz J, et al. A discordant histological risk classification in preoperative and operative biopsy in endometrial cancer is reflected in metastatic risk and prognosis. *Eur J Cancer*. 2013;49:625-632.
32. Tuomi T, Pasanen A, Luomaranta A, Leminen A, Bützow R, Loukovaara M. Risk-stratification of endometrial carcinomas revisited: a combined preoperative and intraoperative scoring system for a reliable prediction of an advanced disease. *Gynecol Oncol*. 2015;137:23-27.
33. AlHilli MM, Podratz KC, Dowdy SC, et al. Risk-scoring system for the individualized prediction of lymphatic dissemination in patients with endometrioid endometrial cancer. *Gynecol Oncol*. 2013;131:103-108.
34. Akbayir O, Corbacioglu A, Goksedef BP, et al. The ovel criteria for predicting pelvic lymph node metastasis in endometrioid adenocarcinoma of endometrium. *Gynecol Oncol*. 2012;125:400-403.
35. Kang S, Kang WD, Chung HH, et al. Preoperative identification of a low-risk group for lymph node metastasis in endometrial cancer: a Korean gynecologic oncology group study. *J Clin Oncol*. 2012;30:1329-1334.
36. Son JH, Kong TW, Kim SH, et al. Prediction of lymph node metastasis in patients with apparent early endometrial cancer. *Obstet Gynecol Sci*. 2015;58:385-390.

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