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Risk factors for lymph node metastases in women with endometrial cancer: a population-based, nation-wide register study - On behalf of the Swedish gynecological cancer group (SweGCG).

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Research article

Short title: Lymph node metastases in endometrial cancer

Key words: endometrial cancer, lymph node metastases, risk factor, epidemiology

Novelty and impact: This study includes 1165 women with endometrial cancer and verified lymph node status registered in the Swedish Quality Registry of Gynecologic Cancer. The results show a four-fold risk increase of lymph node metastases (LNM) in tumors with deep myometrial invasion, and no significant impact of DNA ploidy. The frequency and localization of LNM are presented. It is one of the largest studies on an unselected population and confirms important results from previous single-center and multi-center studies.

Abbreviations:

EC: endometrial cancer

LNM: lymph node metastases

LA: lymphadenectomy

MI: myometrial invasion

SQRGC: Swedish Quality Registry of Gynecologic Cancer

RR: risk ratio

CI: confidence interval

LVSI: Lymph-vascular space invasion

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Abstract

The role of lymphadenectomy in the management of early endometrial cancer is still controversial. In the recent ESMO-ESGO-ESTRO guidelines, lymphadenectomy is recommended for patients with endometrioid adenocarcinoma grade 3 with deep myometrial invasion, but complete agreement was not achieved. In Sweden, DNA aneuploidy has been included as a high-risk factor. The aim of our study was to evaluate the impact of tumor histology, FIGO grade, DNA ploidy and myometrial invasion (MI) on occurrence of lymph node metastasis (LNM) in patients with endometrial cancer.

The study design is a retrospective cohort study based on prospectively recorded register data. Endometrial cancer patients registered in the Swedish Quality Registry for Gynecologic Cancer 2010-2015 with FIGO stage I-III and verified nodal status were included. Data on DNA ploidy, histology, FIGO grade and MI was included in multivariable logistic regression analyses with LNM as dependent variable.

1,165 cases fulfilled the inclusion criteria. The multivariable analyses revealed increased risk of LNM in patients with tumors with $MI \geq 50\%$ (Risk Ratio [RR]=4.1; 95% CI 3.0-5.6), non-endometrioid compared with endometrioid histology (RR 1.8; CI 1.4-2.4) and FIGO grade 3 compared with grade 1-2 tumors (RR 1.5; CI 1.1-2.0). No statistically significant association between DNA ploidy status and LNM was detected.

This population-based, nation-wide study in women with endometrial cancer confirms a strong association between $MI \geq 50\%$, non-endometrioid histology, and FIGO grade 3, respectively and LNM. DNA ploidy should not be included in the pre-operative decision making of removing nodes or not.

Introduction

Lymph node metastasis (LNM) in endometrial cancer (EC) is a strong prognostic factor for survival^{1,2}. However, there is no convincing evidence of the therapeutic benefit of systematic lymphadenectomy (LA) neither in presumed stage I nor in higher stage disease³. Internationally, the use and the extent of LA in EC are debated and the guidelines for recommendations of surgical treatment vary between countries. The American National Comprehensive Cancer Network's guidelines recommend surgical staging with pelvic and, in patients with high-risk tumors, para-aortic LA, in the primary treatment of early stage EC⁴. In the Swedish National Guidelines for EC pelvic and para-aortic LA is recommended in preoperative high-risk tumors (endometrioid adenocarcinoma FIGO grade 3, non-endometrioid histologic subtypes or DNA non-diploid tumors) whereas LA is not recommended in low risk tumors⁵. Myometrial invasion has until recently not been routinely estimated preoperatively. ESMO-ESGO-ESTRO have in a consensus document from 2016 published common European guidelines on diagnosis, treatment and follow-up of EC⁶ and these are in line with the Swedish guidelines. However, in contrast to most other international guidelines Sweden has a long tradition of using DNA ploidy as a prognostic factor in the pre- and postoperative risk group evaluation⁷.

One of the challenging tasks in EC is to find specific factors predicting metastases of the lymph nodes, hence optimizing the patient group undergoing LA and estimate the need for adjuvant treatment. As the overall prognosis in early endometrial cancer is good, it is important to avoid overtreatment, especially in elderly women who often have increased co-morbidity and an increased risk of complications^{8,9}. Lymphedema is a well-known long-term complication after LA and the incidence might increase over time¹⁰.

The material is unique as it is based on a nation-wide, unselected study population. The aim of the study was to evaluate the impact of tumor histology, grade, DNA ploidy and myometrial

invasion on lymph node metastasis using data from the Swedish Quality Registry for Gynecologic Cancer (SQRGC).

Methods

Data sources

The Swedish Quality Registry for Gynecologic Cancer

All residents of Sweden are allocated a personal identification number facilitating official registries and research. Reporting to the Swedish Cancer Registry, which started 1958, is mandatory for both clinicians and pathologists. The Swedish Cancer Registry has over 95% coverage of all malignant tumors and 99% are morphologically verified ¹¹. However, clinical data including treatments and follow-up are lacking. Hence, the Swedish Quality Registry for Gynecological Cancer (SQRGC) was established in 2008. Reporting to the SQRGC is performed prospectively by all hospitals and clinics in Sweden. The registration is web-based and includes information on patient and tumor characteristics, details on treatments and outcome as well as follow-up data for five years. SQRGC continuously receives date of death from the Population Registry and in addition, cause of death is retrieved from the Cause of Death Registry. The treating doctors in the six medical regions register data in SQRGC and registrars at the Regional Cancer Centers continuously monitor registered data. A register-specific manual with uniform definitions and criteria for each variable in the register is available. Patient consent is obtained for registration. The registration for uterine malignancies in SQRGC started in 2010.

The coverage of reported patients with malignancy of the uterus in the SQRGC compared with the Swedish Cancer Registry shows good to very good agreement (92-100% depending on medical region)¹². The validity of the recorded data in the SQRGC has been assessed, 268 patients were randomly selected and the agreement between the review and the registered data was between 72–98% for 12 core variables with the largest differences for dates. For the

variables analyzed in this study the concordance was for FIGO grade 79.8% (n=243), stage I A/IB 90.3% (n=155), DNA-ploidy 90% (n=243) and LNM 96% (n=83) where n = number of cases analyzed (unpublished data).

The Swedish National Guidelines for Endometrial cancer

According to the Swedish National Guidelines for Endometrial cancer from 2011 ⁵, patients with endometrial cancer with no sign of extrauterine growth is *preoperatively* divided into two categories – those with low and high-risk tumors.

- Low-risk: endometrioid adenocarcinoma, FIGO grade 1-2 with diploid DNA-profile,
- High-risk: non-endometrioid histology (serous or clear cells carcinoma or carcinosarcoma), endometrioid adenocarcinoma FIGO grade 3, or non-diploid tumors

If the preoperative staging shows a high-risk tumor, a LA of the pelvic and para-aortic regions (up to the left renal vein) is recommended in addition to hysterectomy and salpingo-oophorectomy. If there is clinically obvious engagement of the cervix, radical hysterectomy and LA is recommended. In case of non-endometrioid histology an omentectomy is also conducted. Women with preoperative signs of advanced disease (FIGO stage III or IV) are treated individually and the intention of surgery, when applied, is to obtain macroscopic radicality.

Postoperative risk assessment is conducted when the histopathology report from the surgery is available. Patients are then divided into three risk groups:

- Low-risk: women with endometrioid tumor and no extrauterine spread and none of the risk factors: $\geq 50\%$ myometrial invasion (MI), FIGO grade 3, non-diploid tumor.
- Intermediate-risk: women with one of the risk factors above.
- High-risk: women with non-endometrioid histology or endometrioid histology with 2 or more of the risk factors described above or extrauterine spread.

The result of lymph node staging is also considered when adjuvant postoperative treatment is planned. Patients with high-risk histology and negative nodes receive chemotherapy ± brachytherapy and those with positive nodes (or no LA) are offered chemotherapy + external beam radiotherapy. MI \geq 50% is in the present Swedish guidelines considered as a postoperative risk factor referring to the uncertainty of diagnosing invasion pre- and perioperatively. Thus, MI is determined on the hysterectomy specimen and registered postoperatively.

Study population

All women with diagnosed cancer of the corpus uteri registered in SQRGC between 2010-01-01 and 2016-01-27 were eligible to the study. Data regarding number of pelvic or para-aortic lymph nodes removed, presence and location of LNM, DNA ploidy status, pathology results of the hysterectomy specimen (histology, FIGO grade and degree of MI) and FIGO stage were collected from SQRGC. Data on preoperative histology is not registered in SQRGC. Table 1 presents the clinical and pathological characteristics of all cases of cancer of the uterus registered in SQRGC and the selected study population. The variable "other histology" mostly consisted of sarcomas. In all 7,150 of 8,315 had one or more of the following exclusion criteria; incomplete or missing registration (n=1,996), LA was not performed or there was missing information if LA was performed (n=4,574), LA was not performed or there was missing information about lymph node pathology (n=4,984), non-carcinomas (n=297), stage IV or missing stage (n=452). We thus selected 1,165 women who had undergone pelvic ± para-aortic LA with information about lymph node pathology, FIGO surgical stage I-III, and an endometrial carcinoma.

DNA analyses

Data on DNA-analyses is not entirely complete due to either DNA-analysis is not performed or not stated in the register and accordingly the percentages following do not reach 100%.

The majority (79%) of DNA-analyses in this study were performed as flow cytometry and 12% on image cytometry. Flow cytometric analysis of DNA ploidy is described by Baldetorp et al.¹³ and Schutte et al.¹⁴ and summarized in guidelines from the Swedish Association of Flow Cytometry¹⁵. In one region of Sweden (Stockholm/Gotland) image cytometry is the standard procedure (further described by Auer et al.¹⁶). In 67% of cases deparaffinized tumor specimen were used and in 12% fresh frozen specimen. The analyses were performed either on preoperative curettage sample (74%) or on postoperative hysterectomy specimen (18%).

Statistics

The study design is a retrospective cohort study based on prospectively recorded register data. Generalized linear model (log-binomial regression) was used to evaluate the association between histology, DNA ploidy status, FIGO-grade, MI, age at diagnosis and number of pelvic nodes removed (provided 10 or more nodes were removed) and the risk of LNM. Estimates of risk ratios (RR) and 95% confidence intervals (95% CIs) were calculated. A p-level of ≤ 0.05 with a two-sided test was considered statistically significant. Non-endometrioid tumors that were not graded were assigned grade 3 (n=153) in the regression analyses. Risk factors with a statistically significant association in the univariable analyses were entered into the multivariable model. An analysis of sensitivity, specificity, positive and negative predictive values for the present (including DNA ploidy status) and the proposed new risk model (including MI) was performed. The STATA Statistical Software release 13 (StataCorp, College Station, TX, USA) was used. The study was approved by the Regional Ethics Committees in Gothenburg (D.nr. 814-15).

Results

The frequencies of positive lymph nodes in the pelvic and para-aortic regions for women with adequate LA (defined in the Swedish Guidelines as 10 or more pelvic nodes and five or more para-aortic nodes removed⁵) in relation to histologic features are presented in Table 2. LNM were most frequently found among clear cell tumors (35%) followed by carcinosarcoma (27%).

In tumors with deep MI (all histologies) the frequency of LNM was 27%. The rate of LNM did not differ between tumors with diploid versus non-diploid DNA-profile (13% in both). The rate of LNM in the para-aortic region only was highest for carcinosarcoma (10%) followed by clear cell carcinoma (4.3%).

The results of the uni- and multivariable models are presented in Table 3. Neither DNA non-diploidy, grade 2, age at diagnosis nor number of pelvic nodes removed had any statistically significant association with an increased risk of LNM in the univariable analysis. In the multivariable analysis, $MI \geq 50\%$ presented the strongest association with LNM (RR=4.1, 95% CI=3.0-5.6) followed in numerically order of the RRs for non-endometrioid and grade 3 tumors. We finally performed predictive analyses presuming a new preoperative risk model based on these results. In the new model preoperative high-risk endometrial cancer would include patients with at least one of the risk factors; non-endometrioid histology, endometrioid grade 3 or $MI \geq 50\%$ whereas low-risk endometrial cancer would include; endometrioid grade 1-2 and $MI < 50\%$. We calculated the sensitivity, specificity and predictive values for the new and the present risk models. The results showed that the new risk model had a better predictive power with a sensitivity of 91%, a specificity of 39%, a negative predictive value of 96% and a positive predictive value of 23% (Table 4).

Discussion

The results of this large population-based, nation-wide study on endometrial cancer demonstrate that $MI \geq 50\%$, non-endometrioid histology, and FIGO grade 3 endometrioid carcinomas are strong independent risk factors for lymph node metastases. The study failed to demonstrate any statistically significant association between DNA ploidy status and positive lymph nodes. There was no significant difference in the risk for LNM between FIGO grade 1 and grade 2 endometrioid carcinomas.

The finding of a significant association between MI and LNM in this study is in concordance with previous studies ¹⁷⁻²¹ and emphasizes the importance of a thorough preoperative evaluation of MI. MI has earlier been considered difficult to determine correctly preoperatively with imaging techniques by clinicians and consequently MI has not hitherto been included in the preoperative risk assessment in the Swedish guidelines. Recent research has shown that evaluation of MI with vaginal ultrasound performed by a trained gynecologist has an acceptable quality ²² and the sensitivity and specificity are comparable to that obtained with MRI ²³. In the recent European consensus document, expert ultrasound and/or MRI and/or intra-operative pathological examination should be used to assess MI in clinical stage I endometrial cancer ⁶. The reliability of intraoperative assessment of MI using either intraoperative gross evaluation (IGE) or frozen section (IFS) has been reported and show high sensitivity and specificity for both methods ²⁴. However, a preoperative assessment is to be preferred in order to give the patient adequate information, plan the surgery and if applicable, refer patients to a tertiary referral hospital.

Interestingly we did not show any significant association between DNA ploidy and LNM. A review of papers on the prognostic value of DNA ploidy status reveals that most studies demonstrate a strong association between survival and DNA ploidy status but MI has not always been included as a covariate in these studies ^{25 26}. Likewise did the studies on MI referred to above ¹⁷⁻²¹ not include data on DNA ploidy. In a Norwegian study ⁷ on 568 endometrial cancers DNA non-diploid tumors had a slightly increased risk of LNM (OR=1.94, CI 1.06-3.35) in multivariable analyses including FIGO stage. In a study by Green et al., including 1,140 patients with EC from the south of Sweden, DNA-status did not have an independent prognostic value whereas a S-phase fraction value of >5.5% was associated with worse outcome ²⁷. Their study focused on survival and did not have LNM as an outcome. S-phase fraction has not been included as a preoperative factor in the Swedish guidelines and has not been regularly analyzed or registered. Thus, we have not included it in this study. Further studies are needed to explore

the mechanisms behind the association between DNA ploidy and survival. In our study, DNA ploidy was analyzed either preoperatively or on hysterectomy specimens and with different methods (see Methods). However, the concordance between DNA ploidy on curettage and hysterectomy specimens is considered to be fairly high²⁸. The majority of DNA-analyses were performed by flow cytometry on deparaffinized tumor samples. These methods are widely used and accepted even though image cytometry might be slightly superior^{29,30}. In the PORTEC 1 and 2 studies presence of substantial lymph-vascular space invasion (LVSI) was a strong independent prognostic factor for pelvic regional recurrence, distant metastasis and overall survival³¹. Reporting LVSI is not mandatory in SQRGC and hence not included in the present study.

If risk models are to be used in clinical practice, high negative predictive value and high sensitivity is of great importance otherwise there is a risk to misclassify patients as stage I who actually are stage III and in favor of adjuvant treatment. We demonstrate a higher sensitivity (91%) and negative predictive value (96%) with the new suggested criteria for high-risk tumors (Table 4). However in both models the specificity is low (34% versus 39%), which means that many patients will have lymphadenectomies negative for LNM. We also performed calculations on expected frequency of patients who would be recommended lymphadenectomy with the new risk model (including MI) compared to the present model (including DNA-status). The result shows that approximately 40% of the total population of endometrial cancer patients in this study (n=7840, sarcoma and unclear histology excluded) would have been recommended lymphadenectomy using the new model compared to 34% with the present model.

Pre/perioperative evaluation of MI is not currently registered in the SQRGC, but will now be included. In the future, the significance of assessing MI pre/perioperatively in a non-selected population has to be evaluated further. Tumor size (>2-3 cm) is at some centers suggested as a predictive factor in risk models^{17,32}, but it is neither included in the Swedish guidelines nor in the recent guidelines from ESMO-ESGO-ESTRO⁶.

In our material, the patients with endometrioid grade 1 and 2 tumors had LNM in 7-10 %, which is in line with other papers analyzing LNM in low-risk endometrial cancer patients ³³. Our findings of a low frequency of skip metastases (positive para-aortic nodes only) of 2.1% for endometrioid tumors and up to 10% for non-endometrioid tumors are in accordance with results from previously published single-center studies ³⁴. This may imply that if surgical or patient-related circumstances make high para-aortic dissection difficult, pelvic LA alone might be an acceptable alternative in selected patients, especially those with endometrioid tumors. The introduction of minimal-invasive surgery, especially robot-assisted surgery, has developed rapidly the last ten years in Sweden as well as in other countries and has lead to enhanced recovery for women with endometrial cancer ³⁵. The new techniques have decreased the surgical risks even for elderly women ^{36,37}, which probably will increase the patient population suitable for lymphadenectomy. In the future, the introduction of sentinel node mapping might even further minimize surgical trauma for this patient group. According to the NCCN guidelines sentinel node mapping can be considered for the surgical staging of apparent uterine-confined malignancy ⁴. In the Swedish National Guidelines for Endometrial cancer ⁵ as well as in the ESGO-ESTRO-ESMO guidelines ⁶ it is yet no consensus regarding sentinel node mapping in clinical practice.

The strengths of this study are in particular the size and that it is based on a complete nationwide population. The health care system is quite uniform all over Sweden and free to all citizens living in Sweden, reimbursed by the public social security system. Consequently it is unlikely that the results of this study should be influenced by significant variations or diversity in the treatment in different regions of Sweden. There are some limitations that should be considered. The Swedish guidelines for EC regarding lymphadenectomy was introduced in 2011 but implementation was not introduced immediately in all clinical centers. Women with substantial comorbidity were often not exposed to LA or lymph node sampling at all and women with preoperatively assumed low-risk tumors (DNA-diploid and grade 1 or 2) could be found to have

deep MI or grade 3 postoperatively, hence not all women with high-risk tumors had data on lymph node status.

Another aspect that should be considered is that the estimation of MI is based on postoperative hysterectomy specimen. The transferral to assessing MI preoperatively is a source of uncertainty as factors such as the skills of the examiner ²² and aspects of the tumor ³⁸ can influence the results of a vaginal ultrasound examination. Yet, if MI \geq 50% is diagnosed postoperatively, a staging re-operation might be performed.

This is, to our knowledge, the first nation-wide population-based study that can confirm the predictive significance of myometrial invasion, histology and grade of differentiation previously shown in single and multicenter studies in EC ^{20, 21, 34, 39}.

In conclusion, deep myometrial invasion, non-endometrioid histology or FIGO grade 3 endometrioid adenocarcinoma are strong risk factors for lymph node metastases in EC. Efforts should be done preoperatively to investigate MI in endometrioid adenocarcinomas grade 1 and 2 in order to tailor the surgery concerning use of lymphadenectomy. DNA ploidy status does not seem to have any impact on prediction of LNM.

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Table 1. Clinical and pathological characteristics of all uterine malignancies in SQRGC and the study population.

	All uterine malignancies^a (n=8,315)	Study population^b (n=1,165)
Median age (range)	69 (24-101)	67 (33-88)
Median number of pelvic lymph nodes (range)		19 (1-82)
Median number of para-aortic nodes (range)		11 (0-51)
Endometrioid adenocarcinoma	6,740 (81%)	915 (79%)
Endometrioid grade 1	2,271 (34%)	256 (28%)
Endometrioid grade 2	1,914 (28%)	335 (37%)
Endometrioid grade 3	874 (13%)	274 (30%)
Endometrioid not graded	1,681 (25%)	50 (5.6%)
Morphology		
Serous adenocarcinoma	587 (7.1%)	140 (12%)
Carcinosarcoma	332 (4.0%)	61 (5.2%)
Clear cell cancer	181 (2.2%)	49 (4.2%)
Other morphology	475 (5.7%)	0
Myometrial invasion		
<50%	3,790 (46%)	692 (59%)
≥50%	1,980 (24%)	463 (40%)
Missing	2,545 (31%)	10 (0.86 %)
FIGO stage		
IA	4,010 (48%)	577 (49%)
IB	1,634 (20%)	235 (20%)
II	569 (6.8%)	110 (9.4%)
III	784 (9.4%)	243 (21%)
IV	386 (4.6%)	0
Missing	932 (11%)	0
DNA-ploidy		
Diploid	3,914 (47%)	529 (45%)
Non-diploid	1,559 (19%)	544 (47%)
Missing	2,842 (34%)	92 (7.9%)

^a All patients with malignancies of the uterine corpus registered in SQRGC Jan 2010- Jan 2016

^b All patients with FIGO-stage I-III, registered lymph node sampling/lymphadenectomy, registered pathology of removed lymph nodes, non-carcinoma excluded

Table 2. Frequency and localization of metastatic lymph nodes according to histology of tumor in the subgroup (n=498) with adequate LA defined as ≥ 10 pelvic nodes and ≥ 5 para-aortic nodes removed

	n	LNM	Only pelvic LNM	Only paraortic LNM	Pelvic and paraaortic LNM
Endometrioid	375	47 (13%)	18 (4.8%)	8 (2.1%)	21 (5.6%)
Endometrioid grade 1	86	6 (7.0%)	1 (1.2%)	2 (2.3%)	3 (3.5%)
Endometrioid grade 2	109	11 (10%)	4 (3.7%)	2 (1.8%)	5 (4.6%)
Endometrioid grade 3	148	22 (15%)	10 (6.8%)	2 (1.4%)	10 (6.8%)
Endometrioid not graded	32	8 (25%)	3 (9.4%)	2 (6.3)	3 (9.4%)
Serous	70	10 (14%)	4 (5.7%)	1 (1.4%)	5 (7.1%)
Carcinosarcoma	30	8 (27%)	2 (6.7%)	3 (10%)	3 (10%)
Clear cell	23	8 (35%)	3 (13%)	1 (4.3%)	4 (17%)
Diploid	182	23 (13%)	4 (2.2%)	6 (3.3%)	13 (7.1%)
Non-diploid	277	34 (13%)	18 (6.5%)	5 (1.7%)	11 (3.7%)
MI <50%	298	18 (6.0%)	3 (1.0%)	5 (1.8%)	10 (3.6%)
MI $\geq 50\%$	199	54 (27%)	24 (12%)	7 (3.5%)	23 (12%)

Table 3. Uni- and multivariable analyses of risk factors for lymph node metastases in endometrial carcinomas

Univariable analysis				Multivariable analysis			
	LNM/Total LN ^d	RR (95% CI)	<i>p</i> -value		LNM/Total LN ^d	RR (95% CI)	<i>p</i> -value
Morphology	192/1165			Morphology	176/1,107		
Endometrioid	120/915	Reference		Endometrioid	106/861	Reference	
Non-endometrioid	72/250	2.20 (1.70-2.84)	<0.001	Non-endometrioid	70/246	1.80 (1.36-2.39)	<0.001
DNA-ploidy	157/1073						
Diploid	72/529	Reference					
Non-diploid	85/544	1.15 (0.86-1.53)	0.351				
FIGO-grade^a	179/1115			FIGO-grade^a	176/1,107		
Grade 1	23/267	Reference		Grade 1-2	62/612	Reference	
Grade 2	40/348	1.33 (0.82-2.17)	0.246	Grade 3	114/495	1.49 (1.09-2.04)	0.013
Grade3	116/500	2.69 (1.77-4.11)	<0.001				
Myometrial invasion	189/1155			Myometrial invasion	176/1,107		
<50%	49/692	Reference		<50%	45/663	Reference	
≥50%	140/463	4.27 (3.15-5.78)	<0.001	≥50%	131/444	4.10 (2.99-5.61)	<0.001
Age (continuous)^b	192/1165	1.00 (0.99-1.02)	0.672				
Number of pelvic glands (continuous)^c	125/858	1.00 (0.99-1.02)	0.592				

^a Ungraded non-endometrioid tumors assigned grade 3

^bThe effect of being one year older at diagnosis

^c The effect of removing one additional gland provided 10 or more pelvic glands were removed

^d LNM= number of women with lymph node metastasis/Total LN= number of women who had lymph nodes removed.

Table 4. Prediction of lymph node metastases according to risk classification

	LNM/Total LN^c	Sensitivity, % (95%CI)	Specificity, % (95%CI)	PPV, %(95%CI)	NPV, % (95%CI)
Present model^a	183/1129	79.8 (73.2-85.3)	33.9 (30.9-37.0)	18.9 (16.2-21.9)	89.7 (86.0-92.6)
New model^b	187/1131	91.4 (86.5-95.0)	38.6 (35.4-41.7)	22.8 (19.8-25.9)	95.8 (93.3-97.6)

^a High-risk: DNA non-diploid, FIGO grade 3, non-endometrioid tumors

^b High-risk: MI \geq 50%, FIGO grade 3, non-endometrioid tumors

^c LNM= number of women with lymph node metastasis/Total LN= number of women who had lymph nodes removed.

PPV= positive predictive value.

NPV=negative predictive value.