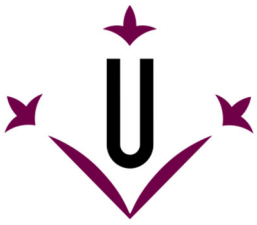

HHS Public Access

Author manuscript

Int J Gynecol Cancer. Author manuscript; available in PMC 2015 April 22.

Published in final edited form as:

Int J Gynecol Cancer. 2013 November ; 23(9): 1620–1628. doi:10.1097/IGC.0b013e3182a5055e.

Redefining Stage I Endometrial Cancer: Incorporating Histology, a Binary Grading System, Myometrial Invasion, and Lymph Node Assessment

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Abstract

Objective—We propose a new staging system for stage I endometrial cancer and compare its performance to the 1988 and 2009 International Federation of Gynecology and Obstetrics (FIGO) systems.

Methods—We analyzed patients with 1988 FIGO stage I endometrial cancer from January 1993 to August 2011. Low-grade carcinoma consisted of endometrioid grade 1 to grade 2 lesions. High-grade carcinoma consisted of endometrioid grade 3 or nonendometrioid carcinomas (serous, clear cell, and carcinosarcoma). The proposed system is as follows:

IA Low-grade carcinoma with less than half myometrial invasion

- **IA1** Negative nodes
- **IA2** No nodes removed

IB High-grade carcinoma with no myometrial invasion

- **IB1** Negative nodes

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The authors declare no conflicts of interest.

IB2 No nodes removed

IC Low-grade carcinoma with half or greater myometrial invasion

IC1 Negative nodes

IC2 No nodes removed

ID High-grade carcinoma with any myometrial invasion

ID1 Negative nodes

ID2 No nodes removed

Results—Data from 1843 patients were analyzed. When patients were restaged with our proposed system, the 5-year overall survival significantly differed ($P < 0.001$): IA1, 96.7%; IA2, 92.2%; IB1, 92.2%; IB2, 76.4%; IC1, 83.9%; IC2, 78.6%; ID1, 81.1%; and ID2, 68.8%. The bootstrap-corrected concordance probability estimate for the proposed system was 0.627 (95% confidence interval, 0.590–0.664) and was superior to the concordance probability estimate of 0.530 (95% confidence interval, 0.516–0.544) for the 2009 FIGO system.

Conclusions—By incorporating histological subtype, grade, myometrial invasion, and whether lymph nodes were removed, our proposed system for stage I endometrial cancer has a superior predictive ability over the 2009 FIGO staging system and provides a novel binary grading system (low-grade including endometrioid grade 1–2 lesions; high-grade carcinoma consisting of endometrioid grade 3 carcinomas and nonendometrioid carcinomas).

Keywords

Endometrial cancer; Stage I; FIGO

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in the United States, with the disease diagnosed in an estimated 47,000 women in 2012. Because most women had their diagnosis at an early stage, only approximately 8000 women died of their disease in 2012.[1] The International Federation of Gynecology and Obstetrics (FIGO) endometrial cancer staging system was changed from a clinical to a surgical staging system in 1988 based on large clinicopathologic studies highlighting the importance of pathologic findings.[2,3] The 1988 FIGO system for stage I endometrial cancer had 3 subgroups: IA, no myometrial invasion; IB, less than half myometrial invasion; and IC, half or greater myometrial invasion. The revised, 2009 FIGO system combined stages IA and IB, resulting in 2 subgroups: IA, no or less than half myometrial invasion; and IB, half or greater myometrial invasion.[4]

Most patients with endometrial cancer have stage I disease at diagnosis, but this is not a homogeneous population. Many of these women will be cured of their disease, but some will recur and may die of their disease. Both the 1988 and 2009 FIGO staging systems for stage I endometrial cancer are based solely on myometrial invasion. A recent publication by The Cancer Genome Atlas Research Network on endometrial carcinoma highlighted the importance of tumortyping in overall survival prognosis.[5] The authors found 4 endometrial

cancer types: DNA polymerase epsilon (POLE) ultramutated, microsatellite instability hypermutated, copy number low, and copy number high. The copy number high group (serous-like), which was composed of mostly serous tumors and grade 3 endometrioid tumors, had the worst prognosis.

This prognostic histologic information can be incorporated into a revisedstaging system. In addition, previous FIGO staging systems for stage I endometrial cancer do not take into account whether or not lymph nodes were removed, which continues to be a controversial area in endometrial cancer surgical staging. Moreover, the grading system remains unchanged, with 3 grade categories.

Accommodating for the distinctive characteristics of different disease types (histological subtypes) is not novel. International Federation of Gynecology and Obstetrics 2009 recognizes the distinctive characteristics of gynecologic histologic subtypes, providing different staging schemes for uterine carcinoma and carcinosarcoma than for uterine leiomyosarcoma, endometrial stromal sarcoma, and Mullerian adenosarcoma. Our data show that incorporating histological subtype and whether or not lymph nodes were removed ("nodes known" vs "nodes unknown") improves prognostic accuracy for patients with FIGO stage I endometrial carcinoma.

The purpose of this study was to develop a new staging system for stage I endometrial cancer that, in addition to myometrial invasion, takes into consideration disease type (ie, histological subtype), grade (using a binary system instead of a 3-grade system), and whether or not lymph nodes were examined. Such a staging system for stage I endometrial cancers would reflect the current reality of surgical staging of this disease, given the controversy over the role of lymphadenectomy in endometrial cancer staging. We aimed to compare the performance of the new system to the 1988 and 2009 FIGO staging systems.

MATERIALS AND METHODS

With the approval of the institutional review board of Memorial Sloan Kettering Cancer Center, all patients who underwent surgery and had a diagnosis of 1988 FIGO stage I endometrial cancer from January 1993 through August 2011 were analyzed. Sarcomas and undifferentiated carcinomas were excluded. Twelve patients had mixed tumor types, and 14 patients had mucinous histology. After review by our expert gynecologic pathologists, it was decided that these would best be analyzed as part of the endometrioid histologic subtype. Standard demographic, clinical, and pathologic data were extracted. We defined endometrioid grade 1 or 2 cancers as "low grade", and we defined endometrioid grade 3 or nonendometrioid carcinomas (serous, clear cell, and carcinosarcoma) as "high grade". We proposed the following substaging definitions for stage I endometrial cancers:

- **IA** Low-grade carcinoma with less than half myometrial invasion
  - **IA1** Negative nodes
  - **IA2** No nodes removed
- **IB** High-grade carcinoma with no myometrial invasion

IB1 Negative nodes

IB2 No nodes removed

IC Low-grade carcinoma with half or greater myometrial invasion

IC1 Negative nodes

IC2 No nodes removed

ID High-grade carcinoma with any myometrial invasion

ID1 Negative nodes

ID2 No nodes removed

The vital status of each patient was recorded. Overall survival (OS) was calculated from the date of surgery to either date of last follow-up or death. The Kaplan-Meier method was used to estimate OS probabilities. Univariate OS analysis was performed using the log-rank test, and the Cox proportional hazards model was fitted univariately to estimate the hazard ratio for each covariate separately.

We compared the 1988, 2009, and our proposed endometrial cancer stage I system using the concordance probability, which is a measure of predictive accuracy.[6] Analogous to area under the receiver operating curve, concordance probability estimate (CPE) can range from perfect concordance at 1.0 to perfect discordance at 0.0. More specifically, a CPE of 50% implies no predictive accuracy because for 2 randomly selected patients, there is a 50% chance that the patient with the higher predicted probability by the staging system will have longer survival than the other patient, which is no better than a coin flip. To prevent against overfitting the model, the bootstrap-corrected CPE was also reported.[7]

RESULTS

A total of 1843 women met study criteria and were analyzed. Demographic information is summarized in Table 1. More than 80% of the patients were alive without evidence of disease at last follow-up. Among the 1592 survivors, the median follow-up time was 49.7 months. The median age was 61 years, and the median body mass index was 29.9 kg/m^2.

Eighty-seven percent of the women had endometrioid carcinoma; and the remainder had serous carcinoma, carcinosarcoma (malignant mixed Mullerian tumors), or clear cell carcinoma. During the study period, 67.8% of the patients had lymph nodes removed. Among the 1249 patients with lymph nodes excised, the median lymph node count was 16. The median number of pelvic and para-aortic lymph nodes removed was 13 and 3, respectively.

On univariate analysis, age, grade, disease type (ie, histological subtype), and staging using the 1988, the 2009, and the new proposed staging systems were all significantly associated with OS (Table 2). The removal of lymph nodes was not statistically significant ($P = 0.103$). The 5-year OS rates for the 1988 staging system were the following: IA, 95.4%; IB, 88.4%; and IC, 81.1% ($P < 0.001$). The Kaplan-Meier OS curves stratified by the 1988 FIGO stage I system are shown in Figure 1A. The 5-year OS rates for the 2009 staging system were IA,

91.5%; and IB, 81.1% ($P < 0.001$), as illustrated in Figure 1B. When patients were restaged with our proposed system for stage I disease, the 5-year OS rates significantly differed ($P < 0.001$) as follows: IA1, 96.7%; IA2, 92.2%; IB1, 92.2%; IB2, 76.4%; IC1, 83.9%; IC2, 78.6%; ID1, 81.1%; and ID2, 68.8%. The Kaplan-Meier analysis for the proposed new system is presented in Figure 2.

A cross-tabulation of the 1988, the 2009, and the proposed endometrial cancer stage I systems is shown in Table 3. Most patients had no or less than 50% myometrial invasion and had grade 1 or 2 endometrioid adenocarcinoma. Thirteen percent (239/1843) of the patients who would otherwise have been classified as stage IA using the 2009 system were classified as stage ID using the proposed system.

DISCUSSION

The Proposed Staging System Is More Prognostically Powerful Than Existing and Previous Systems

Gynecologic cancer stage definitions are designed to provide relevant clinical information, inform prognosis, and assist in guiding patient management decisions.[8] It has been stated that a good staging system must have 3 basic characteristics: it must be valid, reliable, and practical.[9] It should group patients who experience similar outcomes together, ensure that identical cases are always assigned to the same category, and should reflect clinical practice. Because endometrial cancer often presents with postmenopausal or irregular vaginal bleeding, most women are diagnosed at an early stage. However, patients with early-stage endometrial cancer comprise a heterogeneous population with regard to histologic subtype, tumor grade, and prognosis. A stage I definition that divides this group into 2 groups based solely on myometrial invasion, as with the 2009 FIGO stage I system, is inadequate for providing accurate prognostic information. Additional relevant clinical information should be incorporated to place patients in the appropriate prognostic group and manage them appropriately. We propose a staging system for stage I endometrial cancer that goes beyond myometrial invasion and incorporates disease type (ie, histological subtype), grade (a binary system of low versus high grade), and whether or not lymph nodes were evaluated.

The FIGO staging system for endometrial cancer has undergone several revisions through the years based on emerging information, but these changes have not always improved the performance of the staging system. Specific to stage I disease, our group questioned whether the 1988 FIGO stages IA and IB should have been altered.[10] Using data from more than 1600 women, the OS of women with stage I endometrial cancer was analyzed to evaluate the performance of the 1988 and 2009 FIGO staging systems for stage I endometrial cancer. Both systems provided statistically significant survival differences between substages, but the adjusted concordance probability for the 1988 stage I group was 0.612 compared to 0.536 for the 2009 stage I group. The authors concluded that the revised 2009 system eliminated the most favorable group with no myometrial invasion and did not improve its predictive ability over the 1988 system, emphasizing the importance of individualized risk prediction models.

The landmark article by Creasman et al. describing the surgical pathologic spread patterns of endometrial cancer confirmed previous findings[2,11] and laid the groundwork for the change in endometrial cancer staging from a clinical to a surgical staging system; they reported that the depth of myometrial invasion was an important predictor of extrauterine disease.[3] Myometrial invasion was divided into 4 groups: endometrium only, inner third, middle third, and deep third. Invasion was significantly associated with frequency of nodal metastasis. The 1988 and 2009 FIGO stage I systems are based solely on depth of myometrial invasion, which is an overly simplified division of patients with stage I endometrial cancer.

Grade was another significant risk factor for nodal metastasis in the article by Creasman et al and continues to commonly be referred to in combination with depth of myometrial invasion to describe the frequency of pelvic and para-aortic node metastases.[3] For instance, no patients with tumor limited to the endometrium and grade 1 histology had positive pelvic or para-aortic nodes, whereas patients with deep myometrial invasion and grade 3 histology had a 34% risk of pelvic node metastasis and a 23% risk of para-aortic node metastasis. Clearly, grade and depth of invasion are critical pieces of information in determining prognosis and management, and our proposed stage I endometrial cancer system takes both grade and myometrial invasion into consideration. It further simplifies the grading process into a binary system (low vs high grade).

Disease Type Should Be Accounted for in an Endometrial Cancer Staging System Authors have argued that the 2009 FIGO staging system for use in uterine serous carcinoma is oversimplified.[16] Seward et al[17] evaluated the prognostic ability of the revised 2009 staging system compared to the 1988 system in uterine serous carcinoma and concluded that the 2009 criteria did not adequately delineate survival for uterine serous carcinoma in early-stage disease. The patients with no myometrial invasion had the most favorable prognosis, which the authors argued warranted a separate substage. Distinguishing serous and low-grade endometrioid carcinomas without myometrial invasion in a staging scheme allows for the discrimination of patients with favorable and potentially highly unfavorable clinical outcomes. Unlike low-grade endometrioid carcinomas without myometrial invasion, serous carcinomas lacking myometrial invasion are frequently metastatic at presentation, and suboptimal staging strategies might fail to recognize patients at highest risk of distant, particularly peritoneal, failure. Once low stage is verified after a comprehensive staging surgery, our proposal allows for the separation of serous carcinomas into 2 groups stratified by the presence of myometrial invasion, thereby preserving the best prognostic group.

Reports that compare clinical outcomes in FIGO grade 3 endometrioid and serous carcinomas do not uniformly conclude that these tumor types are comparable, but there are several noteworthy studies that describe similar clinical outcomes. During a study period using contemporary therapeutic interventions for high-risk endometrial carcinoma, Ayeni et al[18] controlled for disease stage and reported no difference in OS when comparing grade 3 endometrioid, serous, and clear cell carcinomas. Another recent publication by Voss et al similarly found that disease-specific and recurrence-free survivals were similar between grade 3 endometrioid endometrial cancer and serous cancer or clear cell cancer. Previous reports have also demonstrated similar clinical outcomes when comparing patients with grade 3 endometrioid endometrial carcinoma to women with uterine serous or clear cell

histology.[19,20] Our proposed stage I endometrial cancer system recognizes the similar clinical behavior of grade 3 endometrioid endometrial cancer and the type 2 cancers and therefore combines grade 3 endometrioid carcinoma with nonendometrioid carcinoma, which in this study included serous, clear cell, and malignant mixed Mullerian tumors.

Furthermore, recent data from The Cancer Genome Atlas Research Network's study of endometrial carcinoma indicate significant genotypic overlap between FIGO grade 3 endometrioid and serous carcinomas, using historical criteria for diagnosis.[5] This work has also provided outcomes data that emphasize the distinctive and aggressive nature of serous carcinomas and related tumors that mapped to the copy number high cluster. This cluster included 94% of serous tumors, 62% of mixed-histology tumors, and 24% of grade 3 endometrioid tumors. Our staging system provisionally combines grade 3 endometrioid carcinoma with nonendometrioid carcinoma while we await the development of precise, clinically validated histological criteria that separate the most clinically aggressive tumor types (serous carcinoma, carcinosarcoma, and serous-like endometrioid carcinoma) from otherwise intermediate-risk carcinomas, such as prototypical FIGO grade 3 endometrioid carcinoma.

CONCLUSION

By incorporating the well-recognized and important variables of disease type, grade, myometrial invasion, and whether or not lymph nodes were removed (a measure of surgical staging), our proposed staging system for stage I endometrial cancer has a superior predictive ability over the 2009 FIGO staging system and provides additional relevant clinical information over both the 1988 and 2009 systems. In the era of personalized medicine, it logically follows that we should use more of the information available to us to guide and individualize care for the heterogeneous population of women who have early-stage endometrial cancer. Adopting this new staging system would provide more accurate prognostic information and may assist in treatment planning. The new system also more accurately reflects the reality of surgical staging in which patients may not have any nodes pathologically assessed. The proposed staging system is not meant to be comprehensive or definitive but rather emphasizes the continuous need to revise the existing staging system as more is discovered about endometrial carcinoma. The proposed groupings are preliminary and could be reformulated for ease of use. Further work is needed to externally validate the proposed staging system.

Acknowledgments

This work was supported in part by the National Institutes of Health Cancer Center core grant (P30 CA008748). The core grant provides funding to institutional cores, such as Biostatistics and Pathology, which were used in this study.

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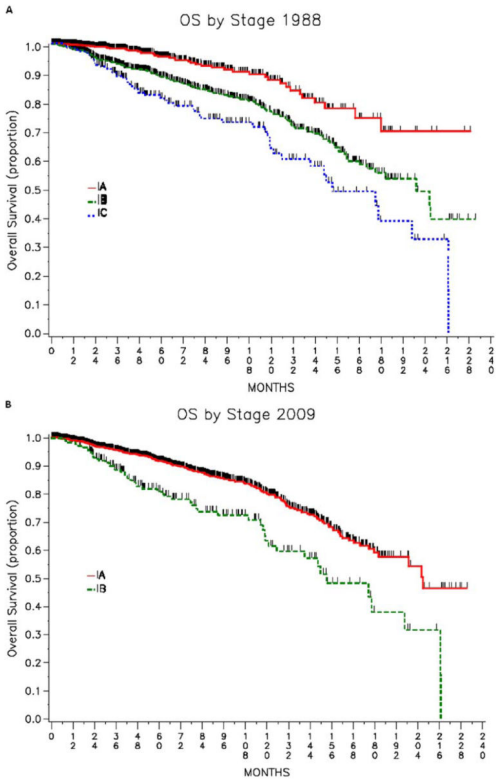

FIGURE 1.

A, Kaplan-Meier OS analysis stratified by the 1988 FIGO stage 1 system ($P < 0.001$). B, Kaplan-Meier OS analysis stratified by the 2009 FIGO stage 1 system ($P < 0.001$).

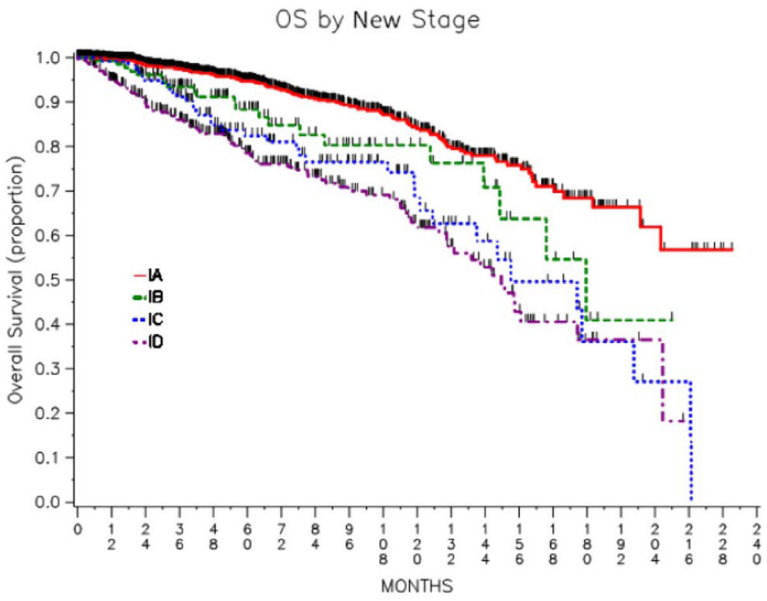

FIGURE 2.

Kaplan-Meier OS analysis using the newly proposed staging system for stage I endometrial cancer without subgroups ($P < 0.001$).

Table 1

Patients' Demographics.

Variable	No. Patients	Percent
All patients	1843	
Vital status		
NED	1547	83.9
AWD	45	2.4
DOD	98	5.3
DOO	114	6.2
DUN	39	2.1
Age at diagnosis		
Median (mean)	61 (61.3)	
Range	25–96	
Weight at diagnosis (71 missing)		
Median (mean)	76.2 (81.1)	
Range	37.0–208.6	
Height at diagnosis (117 missing)		
Median (mean)	160 (160.0)	
Range	102.5–186.0	
BMI (131 missing)		
Median (mean)	29.9 (31.6)	
Range	13.7–84.1	
Uterine weight (579 missing)		
Median (mean)	115 (155.8)	
Range	15–1960	
Final grade		
G1	981	53.2
G2	448	24.3
G3	414	22.5
Myometrial invasion		
None	819	44.4
<50%	833	45.2
≥50%	191	10.4
Lymphovascular invasion		
No	1177	63.9
Yes	231	12.5
Missing	435	23.6
Histologic subtype		
Endometrioid	1602	86.9
MMMT	72	3.9
Clear cell	38	2.1
Serous	131	7.1

Variable	No. Patients	Percent
1988 stage		
IA	849	46.1
IB	804	43.6
IC	190	10.3
2009 stage		
IA	1653	89.7
IB	190	10.3
New stage		
IA1	795	43.1
IA2	473	25.7
IB1	117	6.4
IB2	29	1.6
IC1	95	5.2
IC2	31	1.7
ID1	242	13.1
ID2	61	3.3
Washings		
Negative	1284	69.7
Positive	4	0.2
Suspicious	15	0.8
Missing	540	29.3
Node taken		
None	594	32.2
Yes	1249	67.8
Among the 1249 patients with nodes taken		
Total lymph nodes		
Median (mean)	16 (17.8)	
Range	1–71	
Total pelvic lymph nodes		
Median (mean)	13 (14.1)	
Range	0–53	
Total aortic lymph nodes		
Median (mean)	3 (3.8)	
Range	0–26	

AWD, Alive with disease; BMI, body mass index; DOD, dead of disease; DOO, dead of other; DUN, dead of unknown reason; MMMT, malignant mixed Mullerian tumor; NED, no evidence of disease.

Table 2

Univariate OS Analysis.

Variable	No. Patients	No. Events	5-Year OS rate (95% CI)	Hazard Ratio (95% CI)	P^*
All patients	1843	251	90.2% (88.4%–91.8%)		
Age at diagnosis				1.09 (1.07–1.1)	<0.001
BMI (131 missing)				0.99 (0.97–1.01)	0.236
Nodes taken					
None	594	135	88% (84.8%–90.6%)	1	0.103
Yes	1249	116	91.5% (89.1%–93.3%)	0.81 (0.62–1.04)	
Final grade					
G1	981	83	94.7% (92.5%–96.2%)	1	<0.001
G2	448	69	91.1% (87.5%–93.7%)	1.61 (1.17–2.22)	
G3	414	99	80.1% (75.1%–84.2%)	3 (2.24–4.02)	
Histologic subtype					
Endometrioid	1602	195	91.8% (90%–93.3%)	1	<0.001
MMMT	72	27	64.8% (50%–76.2%)	3.77 (2.52–5.64)	
Clear cell	38	10	85.7% (65.6%–94.5%)	2.12 (1.12–4.01)	
Serous	131	19	86.6% (77.5%–92.2%)	1.53 (0.95–2.45)	
1988 stage					
IA	849	43	95.4% (92.9%–97%)	1	<0.001
IB	804	155	88.4% (85.6%–90.6%)	2.27 (1.62–3.19)	
IC	190	53	81.1% (73.8%–86.5%)	3.64 (2.43–5.45)	
2009 stage					
IA	1653	198	91.5% (89.7%–93%)	1	<0.001
IB	190	53	81.1 (73.8%–86.5%)	2.04 (1.51–2.77)	
New stage					
IA1	795	36	96.7% (94.3%–98.1%)	1	<0.001
IA2	473	72	92.2% (89%–94.5%)	1.56 (1.04–2.34)	
IB1	117	11	92.2% (82.8%–96.5%)	1.8 (0.92–3.54)	
IB2	29	10	76.4% (54.4%–88.8%)	3.61 (1.78–7.3)	
IC1	95	18	83.9% (73.1%–90.6%)	2.81 (1.59–4.95)	

Variable	No. Patients	No. Events	5-Year OS rate (95% CI)	Hazard Ratio (95% CI)	P*
IC2	31	17	78.6% (58.2%–89.8%)	4.62 (2.57–8.3)	
ID1	242	51	81.1% (74.4%–86.2%)	3.49 (2.28–5.36)	
ID2	61	36	68.8% (55%–79.1%)	6.1 (3.82–9.76)	
New stage†					
IA	1268	108	94.7% (92.9%–96.1%)	1	<0.001
IB	146	21	88.4% (80.1%–93.3%)	1.81 (1.14–2.9)	
IC	126	35	82.4% (73.4%–88.6%)	2.63 (1.8–3.85)	
ID	303	87	78.5% (72.7%–83.3%)	3.24 (2.44–4.3)	

*P values for age and BMI were obtained by the Cox proportional hazards model: the other P values were obtained by the log-rank test.

†An additional analysis for the new staging system by combining subgroups.

Int J Gynecol Cancer. Author manuscript; available in PMC 2015 April 22.

Table 3

Cross table for 1988, 2009, and new proposed staging systems

		New: IA1	New: IA2	New: IB1	New: IB2	New: IC1	New: IC2	New: ID1	New: ID2
1988: IA	2009: IA	445	253	116	29	0	0	4	2
1988: IB	2009: IA	350	220	1	0	0	0	182	51
1988: IC	2009: IB	0	0	0	0	95	31	56	8

Table 4

Concordance probability estimate (CPE) values

	Bootstrap-Corrected CPE	95% Confidence Interval
1988 stage I	0.615	0.582–0.648
2009 stage I	0.530	0.516–0.544
New stage I*	0.627	0.590–0.664

*The reported CPE for the new staging system is using all 8 categories of stage I.