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Just how accurate are the major risk stratification systems for early-stage endometrial cancer?

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Background: To compare the accuracy of five major risk stratification systems (RSS) in classifying the risk of recurrence and nodal metastases in early-stage endometrial cancer (EC).

Methods: Data of 553 patients with early-stage EC were abstracted from a prospective multicentre database between January 2001 and December 2012. The following RSS were identified in a PubMed literature search and included the Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC-1), the Gynecologic Oncology Group (GOG)-99, the Survival effect of para-aortic lymphadenectomy (SEPAL), the ESMO and the ESMO-modified classifications. The accuracy of each RSS was evaluated in terms of recurrence-free survival (RFS) and nodal metastases according to discrimination.

Results: Overall, the ESMO -modified RSS provided the highest discrimination for both RFS and for nodal metastases with a concordance index (C-index) of 0.73 (95% CI, 0.70–0.76) and an area under the curve (AUC) of 0.80 (0.78–0.72), respectively. The other RSS performed as follows: the PORTEC1, GOG-99, SEPAL, ESMO classifications gave a C-index of 0.68 (0.66–0.70), 0.65 (0.63–0.67), 0.66 (0.63–0.69), 0.71 (0.68–0.74), respectively, for RFS and an AUC of 0.69 (0.66–0.72), 0.69 (0.67–0.71), 0.68 (0.66–0.70), 0.70 (0.68–0.72), respectively, for node metastases.

Conclusions: None of the five major RSS showed high accuracy in stratifying the risk of recurrence or nodal metastases in patients with early-stage EC, although the ESMO-modified classification emerged as having the highest power of discrimination for both parameters. Therefore, there is a need to revisit existing RSS using additional tools such as biological markers to better stratify risk for these patients.

Endometrial cancer (EC) is a major cause of mortality for patients worldwide. Although its incidence differs throughout the world, it is estimated to be the most common cancer of the female genital tract and the fourth most common cancer in North America and Europe (Jemal *et al*, 2010; Colombo *et al*, 2013).

Early-stage EC restricted to the uterus represents nearly 80% of all cases (Creasman *et al*, 1987, 2006; Colombo *et al*, 2013). The estimated 5-year overall survival for these patients is 95% but decreases substantially to 67.0% and 15.9% for local and distant disease, respectively (Creutzberg *et al*, 2000a; Randall *et al*, 2006;

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Benedetti Panici *et al*, 2008; ASTEC study group *et al*, 2009). Moreover, the recurrence rate for early-stage EC is widely variable ranging from 2 to 26% (Creutzberg *et al*, 2000a; Benedetti Panici *et al*, 2008; ASTEC study group *et al*, 2009; Nout *et al*, 2010; Todo *et al*, 2010; Nugent *et al*, 2012). In this specific setting, many epidemiological and histological factors such as increasing age, depth of myometrial invasion, histological tumour type and grade, presence of lymphovascular space invasion (LVSI) and the International Federation of Gynecology and Obstetrics (FIGO) classification (Pecorelli, 2009) have been reported to be correlated with a higher risk of recurrence and nodal metastases (Creasman *et al*, 1987; Mariani *et al*, 2002; Keys *et al*, 2004; Nout *et al*, 2010; Todo *et al*, 2010; Nugent *et al*, 2012; Colombo *et al*, 2013).

Over the last decade, these criteria have been aggregated into several risk stratification systems (RSS) that are currently used worldwide to guide decision-making and clinical trial design (Creutzberg *et al*, 2000a; Keys *et al*, 2004; Todo *et al*, 2010; Colombo *et al*, 2013; Bendifallah *et al*, 2014). The assumption is based on defining recurrence risk groups, which can help identify clinical situations where multimodality therapy and/or nodal staging should be proposed for high-risk patients or, conversely, single modality or wait-and-see strategies for low-risk patients. Although the core variables of these RSS are very similar (Creutzberg *et al*, 2000a; Keys *et al*, 2004; Todo *et al*, 2010; Colombo *et al*, 2013; Bendifallah *et al*, 2014), finally, it appears that for major RSS: (i) most have never been externally validated; (ii) accuracy is not reported and (iii) no simultaneous comparisons using the same cohort have been performed.

Hence, the aim of this study was to compare five major RSS (Creutzberg *et al*, 2000a; Keys *et al*, 2004; Todo *et al*, 2010; Colombo *et al*, 2013; Bendifallah *et al*, 2014) in a multicenter cohort of patients with early-stage EC with regard to their discriminative performance in stratifying the risk of recurrence and nodal metastases.

MATERIALS AND METHODS

Study population. The data of 553 patients with apparent early-stage EC, who received primary surgical treatment between January 2001 and December 2012, were abstracted from five institutions with maintained EC databases in France (Tenon University Hospital, Reims University Hospital, Dijon Cancer Center, Creteil hospital and Jeanne de Flandre University Hospital) and from the Senti-Endo trial (Ballester *et al*, 2011). All patients had undergone a preoperative endometrial biopsy. All enrolled patients underwent a preoperative MRI unless contraindicated, in which case a CT scan was performed. Patients with histologically proven EC were staged on the basis of final pathological findings according to the 2009 FIGO classification (Pecorelli, 2009). Clinical and pathologic variables included patient age, surgical procedure, 2009 FIGO stage and final pathological analysis (histological type and grade, depth of myometrial invasion and LVSI status). A tumour was considered LVSI-positive when tumour emboli were found within a space clearly lined by endothelial cells (Tsuruchi *et al*, 1995). The research protocol was approved by the institutional review board of the French college of obstetricians and gynecologists (CEROG 2014-GYN-020).

Treatment and follow-up. We included all women who underwent primary surgical treatment including at least total hysterectomy with bilateral salpingo-oophorectomy, with or without nodal staging (pelvic ± paraaortic lymphadenectomy) according to the current guidelines (Querleu *et al*, 2011; Colombo *et al*, 2013) and to the surgeon's discretion. Sentinel lymph node biopsies (SLNB) were performed by a dual intracervical injection based on the histological validation of SLN by Delpech *et al* (2007). A para-aortic lymphadenectomy was recommended for women with metastatic pelvic SLN on intraoperative histology or after final histology. Systematic pelvic and para-aortic lymphadenectomy was also recommended for patients with type 2 EC (clear-cell, serous EC and carcinosarcoma) and type 1, grade 3 with a depth of myometrial invasion $>50\%$. Adjuvant therapy was administered on an individual basis at the discretion of a multidisciplinary committee according to international guidelines (Colombo *et al*, 2013) and involved vaginal brachytherapy and/or external beam radiotherapy (EBRT) and/or chemotherapy. Clinical follow-up consisted of physical examinations and the use of imaging techniques depending on the findings. Follow-up sessions were conducted every 3 months during the first 2 years, every 6 months during the following 3 years and once a year thereafter.

RSS description. Five major RSS related to the risk stratification of early-stage EC were identified in the medical literature using PubMed: the Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-1 classification (Creutzberg *et al*, 2000a), the Gynecologic Oncology Group (GOG) 99 classification (Keys *et al*, 2004), the Survival effect of para-aortic lymphadenectomy (SEPAL) in EC classification (Todo *et al*, 2010), the ESMO (Colombo *et al*, 2013) and ESMO-modified (Bendifallah *et al*, 2014) classifications. RSS were selected with respect to their acceptance in the literature and clinical applicability. Table 1 describes the criteria for each RSS.

Recurrence events and recurrence-free survival (RFS). The clinical end point was recurrence. Disease recurrence was diagnosed by biopsy or imaging studies and defined as a relapse without differentiating between their local or distant nature. RFS was defined as the time from surgery to the date of recurrence. Estimates were produced using the Kaplan–Meier method.

Statistical analysis

Stratification accuracy. The receiver operating characteristic area under the curve (ROC-AUC) as well as the concordance index (C-index) indicate the discriminatory properties and quantify the stratification accuracy (i.e., whether the relative ranking of individual stratification was in the correct order) (Hanley and McNeil, 1982; Heagerty *et al*, 2000; Heagerty and Zheng, 2005). The AUC requires binary outcomes (presence or absence of the event) and is reserved for binary logistic regression models. The c-index represents an adaptation of the AUC for censored data and is necessary when time-to-event data are used. In the current analysis, the accuracy of each RSS for RFS (censored data) was conducted using the Cox Proportional Hazards Model. Similarly to quantify the discriminatory properties of each RSS with regard to the risk for LNM, a binary logistic regression model was performed. The AUC, as well as the c-index of 0.5, represents no discriminating ability, and a value of 1.0 represents perfect discrimination.

RSS diagnostic accuracy. Sensitivity, specificity, negative predictive values, positive predictive values and the overall diagnostic accuracy (ODA) (i.e., the probability of a patient being correctly classified by the RSS) with 95% CI were calculated to study the diagnostic ability of each RSS to classify patients at low risk and those at high risk of recurrence and nodal metastases.

Others analysis. Statistical analysis was based on Student's *t*-test and the Mann–Whitney test for parametric and nonparametric continuous variables, respectively, and the χ^2-test or Fisher's exact test, as appropriate, for categorical variables. Values of $P<0.05$ were considered to denote significant differences. Data were managed with an Excel database (Microsoft, Redmond, WA, USA) and analysed using R 2.15 software, available online.

Table 1. Description of five risk recurrence systems

RSS	Year	Number of patients	Criteria
PORTEC-1 (Creutzberg *et al*, 2000b)	2000	715	Low risk Endometrial adenocarcinoma stage Ia, grade 1 Intermediate risk Endometrial adenocarcinoma Stage I based on uterine factors Grade 1 histology and myometrial invasion of ⩾50% Grade 2 histology with any myometrial invasion Grade 3 histology with myometrial invasion <50% High-intermediate risk Age >60 years with grade 1 or 2 histology and myometrial invasion >50% Age >60 with grade 3 histology and myometrial invasion <50% High-risk Stage III–IV disease Uterine serous carcinoma or clear cell carcinoma of any stage
GOG-99 (Keys *et al*, 2004)	2004	382	Low risk Grade 1 or 2, endometrioid cancers confined to the endometrium stage IA Low-intermediate risk Age ⩽50 years + ⩽2 pathologic risk factors Age 50–69 years + ⩽1 pathologic risk factor Age ⩾70 years + no pathologic risk factors (Risk factors (1) grade 2 or 3 histology; (2) positive lymphovascular space invasion; (3) myometrial invasion to outer 1/3) High-intermediate risk (HIR) Any age + 3 pathologic risk factors Age 50–69 years + ⩾2 pathologic risk factors Age ⩾70 years + ⩾1 pathologic risk factor (Risk factors (1) grade 2 or 3 histology; (2) positive lymphovascular space invasion; (3) myometrial invasion to outer 1/3) High-risk Stage III–IV disease, regardless of histology or grade Uterine serous carcinoma or clear cell carcinoma of any stage
SEPAL (Todo *et al*, 2010)	2010	671	Low risk Stage IA IB, endometrioid type, LVSI negative Intermediate risk Stage IA grade 3 endometrioid adenocarcinoma; any grade of non-endometrioid carcinoma (serous adenocarcinoma, clear cell adenocarcinoma or other type of carcinoma), any LVSI Stage IB, grade 1–2 endometrioid adenocarcinoma, LVSI positive Stage IB, grade 3 endometrioid adenocarcinoma; any grade of non- endometrioid carcinoma (serous adenocarcinoma, clear cell adenocarcinoma or other type of carcinoma), any LVSI Stage IC, stage II, any grade, any LVSI High risk Stage III–IV, any grade, any LVSI
ESMO (Colombo *et al*, 2013)	2013	—	Low risk Stage IA (grade 1 and grade 2) with endometrioid type Intermediate risk Stage IA grade 3 with endometrioid type Stage IB (grade 1 and grade 2) with endometrioid type High risk Stage IB grade 3 with endometrioid type All stages with non-endometrioid type
ESMO modified (Bendifallah *et al*, 2014)	2014	496	Low-risk ESMO/LVSI- Low-risk ESMO/LVSI+ Intermediate-risk ESMO/LVSI- Intermediate-risk ESMO/LVSI+ High-risk ESMO/LVSI- High-risk ESMO/LVSI+

Abbreviations: ESMO = European Society for Medical Oncology; LVSI = lymphovascular space invasion.

RESULTS

Characteristics of the study population. During the study period 553 patients with EC were documented as having received primary surgical treatment according to the following distribution: Dijon Cancer Center ($n=122$; 22%), Creteil Hospital ($n=83$; 15%), Reims University Hospital ($n=87$; 16%), Tenon University Hospital ($n=70$; 13%), Jeanne de Flandre University Hospital ($n=97$; 17%) and Senti-Endo trial ($n=94$; 17%). The demographics and clinicopathological characteristics of the whole cohort are reported in Table 2. The median age of the patients was 65.0 years (range: 31–98 years).

RFS according to each RSS. The median follow-up was 32 (range: 2–165) months and the median time to initial recurrence was 29 (range: 1–165) months. Overall 3-year RFS and 3-year recurrence rates were 83.9% (95% CI, 80.6–87.4) and 16.4%, respectively. Loco-regional, nodal and distant recurrences were observed in 20% (18/91), 24% (22/91) and 56% (51/91) of cases, respectively. The respective 3-year RFS according to each RSS are reported in Figure 1.

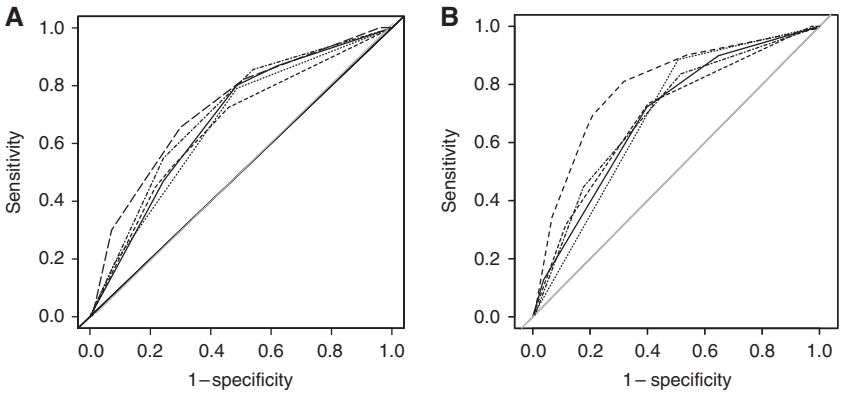
Discrimination and diagnostic accuracy of each RSS system for recurrence. The discrimination of each RSS is reported in Figure 2A. The RSS with the highest discrimination was the ESMO-modified classification (C-index = 0.73 (95% CI,

Table 2. Characteristics of the whole population				
	Overall population $n=553$	No recurrence $n=462$	Recurrence $n=91$	*P*-value[a]
Age-mean (range)	64.9 (31–98)	64.4 (31–98)	67.8 (32–88)	0.0033
Histological grade				
I	48.6% (269)	52.4% (242)	29.7% (27)	
II	27.5% (152)	29.2% (135)	18.7% (17)	
III	23.9% (132)	18.4% (85)	51.6% (47)	<0.0001
Pathological type				
1	86.6% (479)	89.2(412)	73.6% (67)	
2	13.4% (74)	10.8(50)	26.7% (24)	0.0001
Myometrial invasion				
<50%	54.3% (300)	58.4% (270)	32.9% (30)	
⩾50%	45.7% (253)	41.6% (192)	67.1% (61)	<0.0001
Lymphovascular space invasion				
No	66.4% (367)	70.4% (325)	46.1% (42)	
Yes	25.3% (140)	21.2% (98)	46.1% (42)	
NA	8.3% (46)	8.4% (39)	7.8% (7)	<0.0001
FIGO stage				
I	78.1% (432)	81.8% (378)	59.3% (54)	
II	7.6% (42)	6.3% (29)	14.3% (13)	
IIIc	14.3% (79)	11.9% (55)	26.4% (24)	<0.0001
Nodal staging (P/PAL)	86.6% (479/553)	87.1% (402/462)	84.6% (77/91)	0.0001
Nodal metastasis	16.5% (79/479)	13.7% (55/402)	31.2% (24/77)	0.0001
PORTEC-1 (Creutzberg *et al*, 2000a)				
Low risk	32% (175)	35% (163)	13% (12)	
Intermediate risk	19% (106)	21% (97)	10% (9)	
High-intermediate risk	24% (134)	23% (105)	32% (29)	
High risk	25% (138)	21% (97)	45% (41)	—
GOG-99 (Keys *et al*, 2004)				
Low risk	51% (280)	55% (255)	27% (25)	
Low-intermediate risk	2% (13)	2% (10)	3% (3)	
High-intermediate risk	23% (129)	23% (106)	25% (23)	
High risk	24% (131)	20% (91)	44% (40)	—
SEPAL (Todo *et al*, 2010)				
Low risk	43% (238)	48% (221)	19% (17)	
Intermediate risk	43% (236)	40% (186)	55% (50)	—
High risk	14% (79)	12% (55)	26% (24)	
ESMO (Colombo *et al*, 2013)				
Low risk	45.1% (249)	50.4% (233)	17.6% (16)	
Intermediate risk	34.5% (191)	34.0% (157)	37.4% (34)	
High risk	20.4% (113)	15.6% (72)	45.0% (41)	—
ESMO/LVSI (Bendifallah *et al*, 2014)				
Low-risk ESMO/LVSI −	37.6% (208)	41.8% (193)	16.5% (15)	
Low-risk ESMO/LVSI +	2.7% (15)	3.2% (15)	0% (0)	
Intermediate-risk ESMO/LVSI −	18.8% (104)	19.6% (90)	15.4% (14)	
Intermediate-risk ESMO/LVSI +	13.2% (73)	12.1% (56)	18.7% (17)	
High-risk ESMO/LVSI −	9.9% (55)	9.1% (42)	14.3% (13)	
High-risk ESMO/LVSI +	9.4% (52)	5.8% (27)	27.4% (25)	—
NA	8.4% (46)	8.4% (39)	7.7% (7)	
Adjuvant therapy				
No adjuvant therapy	18.1% (100)	20.1% (93)	7.7% (7)	—
EBRT ± brachytherapy	34.7% (192)	30.8% (142)	54.9% (50)	
Brachytherapy	30.1% (166)	34.8% (161)	5.5% (5)	
Chemotherapy	2.3% (13)	0.9% (4)	9.9% (9)	
Multimodal therapy	4.9% (27)	3.5% (16)	12.1% (11)	
NA	9.9% (55)	9.9% (46)	9.9% (9)	

Abbreviations: EBRT = External beam radiotherapy; ESMO=European Society for Medical Oncology; FIGO = Federation of Gynecology and Obstetrics; GOG = Gynecologic Oncology Group; LVSI = lymphovascular space invasion; NA = not applicable; P/PAL = pelvic and/or paraaortic lymphadenectomy; PORTEC = Post Operative Radiation Therapy in Endometrial Carcinoma; SEPAL = Survival effect of para-aortic lymphadenectomy.
[a]Univariate logistic regression.

0.70–0.76)). The diagnostic accuracy of each RSS is reported in Table 3. The RSS with the highest ODA to select patients at low risk of recurrence was the PORTEC-1 classification with 56% of patients correctly stratified. The RSS with the highest ODA to select patients at increased risk of recurrence was the ESMO-modified classification with 78% of patients correctly assigned.

Discrimination and diagnostic accuracy of each RSS systems for nodal metastases. Overall, 86.6% (479/553) of the patients



Classification	A	B	Legend
	Recurrence	Lymph node metastasis	
	C-index (95% CI)	AUC (95% CI)	
PORTEC-1 [8]	0.68 (0.66–0.70)	0.69 (0.66–0.72)	
GOG-99 [15]	0.65 (0.63–0.67)	0.69 (0.67–0.71)	
SEPAL [12]	0.66 (0.63–0.69)	0.68 (0.66–0.70)	
ESMO [2]	0.71 (0.68–0.74)	0.70 (0.68–0.72)	
ESMO modified [16]	0.73 (0.70–0.76)	0.80 (0.78–0.72)	

Figure 1. Discrimination of each RSS for recurrence and nodal metastases.

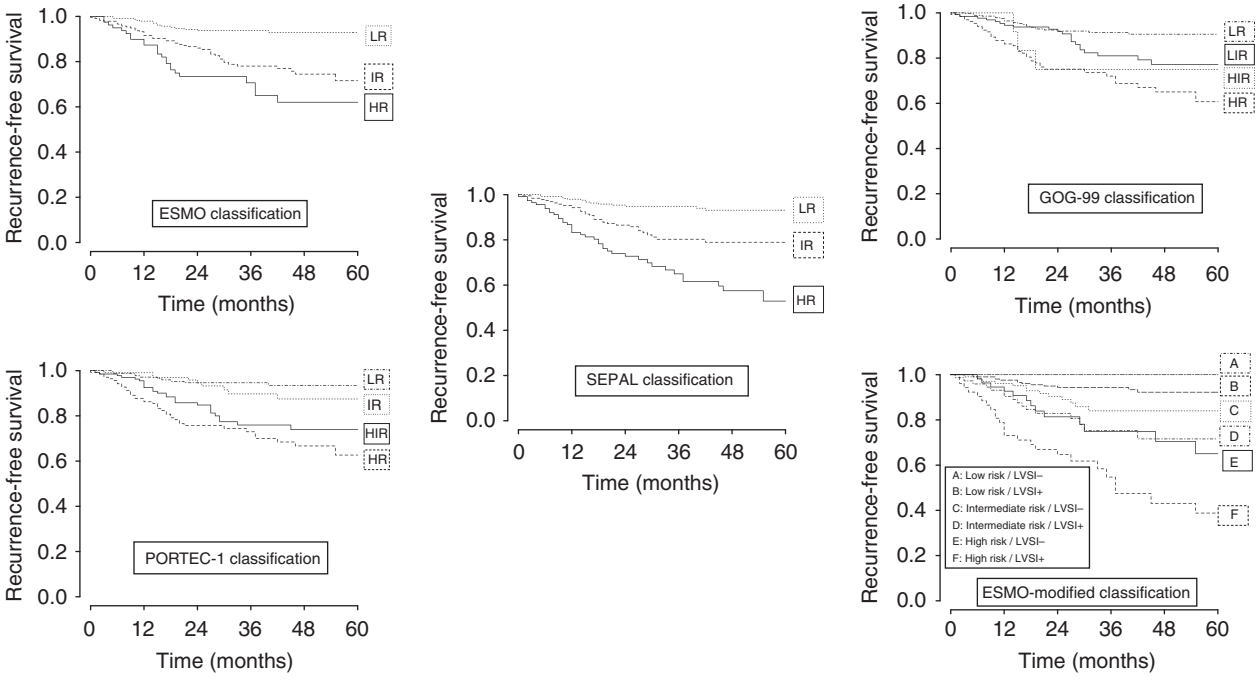


Figure 2. Recurrence-free survival curves according to each risk classification.

underwent systematic nodal staging and 16.5% (79/479) of these had nodal metastases (Table 2). Discrimination of each RSS is reported in Figure 2B. The RSS with the highest discrimination was the ESMO-modified classification (AUC = 0.80 (95% CI, 0.78–0.82)). The diagnostic accuracy of each RSS is reported in Table 3. The RSS with the highest ODA to select patients at low risk of nodal metastases was the PORTEC-1 classification with 56% of patients correctly stratified. The RSS with the highest ODA to select patients at increased risk of metastases was the ESMO-modified system with 77% of patients correctly assigned.

DISCUSSION

To our knowledge, this is the first study to provide a comparison of five major RSS applied to a multicenter population with early-stage EC. The results suggest that these five RSS have a poor-to-moderate discrimination for recurrence and nodal metastases. In addition, the clinical diagnostic accuracy to distinguish subgroups of patients at low- and high-risk of recurrence or nodal metastases appears to be limited and heterogeneous.

Table 3. Diagnostic accuracy for recurrence

		Low risk group (compared with other groups)			High risk group (compared with other groups)		
RSS	Diagnostic accuracy statistics	Value	Low 95% CI	High 95% CI	Value	Low 95% CI	High 95% CI
PORTEC-1 (Creutzberg *et al*, 2000a)	Sensitivity	0.132	0.074	0.216	0.451	0.357	0.545
	Specificity	0.647	0.636	0.664	0.790	0.772	0.809
	PPV	0.069	0.039	0.112	0.297	0.236	0.360
	NPV	0.791	0.777	0.811	0.880	0.859	0.900
	ODA	0.562			0.734		
GOG-99 (Keys *et al*, 2004)	Sensitivity	0.275	0.193	0.371	0.440	0.347	0.534
	Specificity	0.448	0.432	0.467	0.803	0.785	0.822
	PPV	0.089	0.063	0.121	0.305	0.241	0.371
	NPV	0.758	0.731	0.790	0.879	0.859	0.899
	ODA	0.420			0.743		
SEPAL (Todo *et al*, 2010)	Sensitivity	0.187	0.118	0.278	0.264	0.187	0.350
	Specificity	0.522	0.508	0.540	0.881	0.866	0.898
	PPV	0.071	0.045	0.106	0.304	0.215	0.403
	NPV	0.765	0.745	0.791	0.859	0.844	0.875
	ODA	0.457			0.769		
ESMO (Colombo *et al*, 2013)	Sensitivity	0.176	0.109	0.266	0.451	0.359	0.542
	Specificity	0.496	0.482	0.513	0.844	0.826	0.862
	PPV	0.064	0.040	0.097	0.363	0.289	0.437
	NPV	0.753	0.733	0.780	0.886	0.867	0.905
	ODA	0.467			0.773		
ESMO modified[a] (Bendifallah *et al*, 2014)	Sensitivity	0.179	0.109	0.273	0.452	0.357	0.548
	Specificity	0.508	0.494	0.527	0.837	0.818	0.856
	PPV	0.067	0.041	0.103	0.355	0.280	0.430
	NPV	0.757	0.736	0.785	0.885	0.865	0.905
	ODA	0.453			0.776		

Abbreviations: ESMO = European Society for Medical Oncology; GOG = Gynecologic Oncology Group; NPV = negative predictive values; ODA = overall diagnostic accuracy; PORTEC = Post Operative Radiation Therapy in Endometrial Carcinoma; PPV = positive predictive values; SEPAL = Survival effect of para-aortic lymphadenectomy.
[a]Intermediate-risk ESMO/LVSI + and high risk groups compared with intermediate risk ESMO/LVSI- and low risk.

Management of women with early-stage EC remains controversial and practice patterns vary widely among gynecologic oncologists (Creutzberg *et al*, 2000a; Keys *et al*, 2004; ASTEC study group *et al*, 2009; Nout *et al*, 2010; Colombo *et al*, 2013; Ko *et al*, 2013). This is mainly because there are several criteria defining risk groups for recurrence, unstandardised protocols for surgical staging and different indications for adjuvant therapies (Creutzberg *et al*, 2000a; Keys *et al*, 2004; ASTEC study group *et al*, 2009; Nout *et al*, 2010; Colombo *et al*, 2013; Ko *et al*, 2013). To overcome these limitations and guide clinicians in their decision-making and in providing patient information, several authors have developed RSS to create a common nomenclature (Creutzberg *et al*, 2000a; Keys *et al*, 2004; Creasman *et al*, 2006; Querleu *et al*, 2011; Colombo *et al*, 2013; Bendifallah *et al*, 2014). Although all of these RSS include similar variables, the combination of variables differs substantially between the United States and European countries leading to widely differing practice patterns for adjuvant therapies and indications for nodal staging (Creutzberg *et al*, 2000a; Keys *et al*, 2004; ASTEC study group *et al*, 2009; Nout *et al*, 2010; Colombo *et al*, 2013; Ko *et al*, 2013). The potential of ROC curves in medical diagnostic testing was recognised as early as 1960 (LUSTED, 1960) as the most relevant statistical tool to describe diagnostic performance (Hanley and McNeil, 1982; DeLong *et al*, 1988). Classically, the predictive accuracy of a classification is based on the assumption that all patients within a given risk group are equal. However, in practice, heterogeneity in both biological parameters and patients' characteristics within each risk subgroup has been reported, especially for women with early-stage EC (Creutzberg *et al*, 2000a; Keys *et al*, 2004; Ballester *et al*, 2011, 2013; Nugent *et al*, 2012), leading to incorrect risk assignment. Our results confirm that the ESMO-modified classification (Bendifallah *et al*, 2014) was the RSS with the highest discrimination according to recurrence with a C-index of 0.72. We also found that the PORTEC-1 classification (Creutzberg *et al*, 2000a) was the most accurate in selecting patients at low risk of recurrence with an ODA of 55% and the ESMO-modified classification (Bendifallah *et al*, 2014) more accurate in selecting patients at increased risk with an ODA of 78%. These results also suggest that these RSS are heterogeneous in terms of classification performance. Moreover, it highlights the high rate of misclassified patients whatever the RSS used and the potential risk of inadequate surgical staging and over- or under-treatment. Finally, these results underline that new biological markers or stratification tools are probably needed to improve discrimination of such classifications, resulting in a more adapted surgical staging and adjuvant treatment.

Despite a reported good overall survival, almost 15% of patients with localised disease experience recurrence during the first 2 years following initial treatment (Creasman *et al*, 2006; Benedetti Panici *et al*, 2008; ASTEC study group *et al*, 2009; Bendifallah *et al*, 2014). It is therefore essential to distinguish patients at increased risk of recurrence who require systematic adjuvant EBRT and/or chemotherapy. A debate exists regarding the optimal adjuvant therapy for patients with early-stage EC. Published trials involve a wide variety of patients with different characteristics, rendering interpretation of the results somewhat difficult (Creutzberg *et al*, 2000a; Keys *et al*, 2004; Nout *et al*, 2010; Ko *et al*, 2013). Moreover, there are several differences in surgical staging from one study to

another; in some trials, lymphadenectomy was systematically performed (Kuoppala *et al*, 2008; Reed *et al*, 2008; Susumu *et al*, 2008), whereas in others it was not required (Creutzberg *et al*, 2000a; Maggi *et al*, 2006; Randall *et al*, 2006; ASTEC/EN.5 Study Group *et al*, 2009; Nout *et al*, 2010) or performed only in case of suspicious lymph nodes (Morrow *et al*, 1990; Sorbe *et al*, 2009, 2012). This gives rise to an important confounding bias. Three randomised trials on adjuvant pelvic radiation versus a wait-and-see approach have shown significantly improved loco-regional control in case of additional EBRT, with no impact on overall survival (Aalders *et al*, 1980; Creutzberg *et al*, 2000a; Keys *et al*, 2004). Indeed, when focusing on the high-risk cohorts, the reported loco-regional recurrence rates vary from 13 to 23% with no adjuvant EBRT (Aalders *et al*, 1980; Creutzberg *et al*, 2000a; Keys *et al*, 2004) versus 5% when adjuvant EBRT is administered systematically (Aalders *et al*, 1980; Creutzberg *et al*, 2000a; Keys *et al*, 2004). This underlines the importance of accurate risk stratification in selecting the most adapted treatment option. Similarly, few data exist on the role of chemotherapy in early-stage EC. In high-risk EC, the Cochrane meta-analysis showed a positive impact of chemotherapy on overall survival, disease-free survival and distant metastasis (Johnson *et al*, 2011). However, these results may be biased by the inclusion of patients with more advanced disease once again rendering interpretation somewhat difficult (Randall *et al*, 2006).

Selecting patients who might benefit from systematic nodal staging is a major issue to guide postoperative treatment in patients with early-stage EC (Benedetti Panici *et al*, 2008; ASTEC study group *et al*, 2009; Ballester *et al*, 2011; Nugent *et al*, 2012). In this setting, a meta-analysis of two randomised trials on the impact of systematic lymphadenectomy in early-stage EC showed no benefit on overall and recurrence-free survival (Benedetti Panici *et al*, 2008; ASTEC study group *et al*, 2009). In contrast, in the SEPAL study Todo *et al* (2010) reported a survival benefit for systematic pelvic and para-aortic lymphadenectomy especially in patients with intermediate- and high-risk EC. These results highlight that the intermediate-risk group, as currently defined by the major classifications, is a heterogeneous group of patients in terms of nodal metastases rendering indications for complete surgical staging and adjuvant therapies somewhat blurred. Moreover, in a retrospective study on the rate of nodal metastases in clinical stage 1 type 1 EC according to the PORTEC 1 (Creutzberg *et al*, 2000a) and GOG-99 criteria (Keys *et al*, 2004) for high-intermediate risk patients Nugent *et al* (2012) reported that patients have substantial risk of nodal involvement and recurrence, suggesting that complete nodal staging is crucial for this subgroup. Our results confirm that the ESMO-modified classification has the highest discrimination for nodal metastases. Moreover, we found that the PORTEC-1 RSS (Creutzberg *et al*, 2000a) was the most accurate to select patients at low risk with an ODA of 56%, whereas the ESMO-modified RSS (Bendifallah *et al*, 2014) was the most accurate to select patients at high-risk with an ODA of 77%. These results underline the need in the future for precise quantification of the risk of nodal metastases using a complementary approach based on individualized prediction models such as nomograms (Bendifallah *et al*, 2012; AlHilli *et al*, 2013). In this specific setting, AlHilli *et al* (2013) developed two nomograms in patients with surgically treated stage I–IV endometrioid EC to predict the probability of lymph node metastases. However, the definition of an optimal threshold to decide whether to perform secondary lymphadenectomy is lacking. Finally, the authors did not focus on women with early-stage disease, which is the subgroup with the most discrepancies in terms of nodal metastases.

Some limitations of the present study deserve to be mentioned. First, it included patients treated for early-stage EC over a relatively long period. During the data collection period, modifications in staging modalities (FIGO classification (Pecorelli, 2009)) and surgical techniques (LN staging) were introduced. For example, SLNB was introduced and shown to be a possible first-line treatment for patients with early-stage EC. Indeed, Raimond *et al* (2014) recently demonstrated that SLN mapping and ultrastaging improved staging and made it possible to adapt adjuvant therapy to the risk of recurrence. Second, our cohort included patients from several centers and discrepancies in patient management might have affected our results in part. However, all included centers were regional referral centers applying the current French guidelines. Third, although the ESMO-modified classification seems to be associated to higher stratification accuracy, an external and independent validation study of the current results is needed. Fourth, although the multicentre nature of this study provides an overview of clinical practice during a long period, the overall survival analysis could not be performed. Finally, central pathology review was not available. However, dedicated pathologists from tertiary referral centers assessed all biopsies and specimens.

In conclusion, we demonstrate here that none of five major RSS shows high accuracy to stratify recurrence risk and nodal metastases in women with early-stage EC. Therefore, there is a need to revisit existing RSS using additional tools such as biological markers to better stratify patient risk in this setting. Moreover, several promising prognostic *in situ* biomarkers such as DNA ploidy, expression of P53, oestrogen and progesterone receptors have been identified (Ballester *et al*, 2013; Murali *et al*, 2014). These biomarkers could be used in clinical practice for a more individualised management in EC. At last, the therapeutic challenge for early-stage EC lies in promoting a personalized therapeutic strategy to avoid over- or under-treatment.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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