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ORIGINAL ARTICLE **CME**

Comparison of Risk Stratification Systems for Predicting Clinical Outcomes in Patients with Endometrial Carcinoma

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ABSTRACT

Objectives: *We sought to compare three risk stratification systems (RSSs) in terms of ability in predicting recurrence and survival in endometrial cancer: the joint 2010 International Federation of Gynecology and Obstetrics/American Joint Committee on Cancer (FIGO/AJCC) staging system, the 2013 European Society for Medical Oncology (ESMO) classification system, and the 2016 European Society for Medical Oncology, European Society of Gynaecological Oncology and European Society for Radiotherapy & Oncology (ESMO-ESGO-ESTRO) classification system.*

Methods: *Data of patients with FIGO stage I to III endometrial carcinoma requiring adjuvant oncological treatment from 1 January 2005 to 31 December 2014 in a single institution in Hong Kong were retrospectively reviewed. The three systems were evaluated in terms of accuracy of predicting recurrence, cancer-specific survival, and overall survival using Harrell's concordance index (C-index).*

Results: *Data from 128 patients were analysed. Recurrences occurred in 22 (17%) and cancer-related deaths occurred in 18 (14%). The joint 2010 FIGO/AJCC staging system had the highest C-index of 0.75 (95% confidence interval [CI] = 0.65-0.86) for recurrence and 0.76 for overall survival (95% CI = 0.65-0.88). In terms of predicting cancer-specific survival, the ESMO-ESGO-ESTRO subgroup classification had the highest C-index of 0.80 (95% CI = 0.58-1.00).*

Conclusion: *We demonstrated the discriminative abilities of the joint 2010 FIGO/AJCC staging system, the ESMO classification, and the ESMO-ESGO-ESTRO classification in predicting disease-free survival, cancer-specific survival, and overall survival using Harrell's C-index. The ESMO-ESGO-ESTRO classification has potential in guiding clinical decision making and patients' risk assignment in studies. Integration of molecular classification may represent the way forward in classifying endometrial carcinoma and instituting personalised treatment algorithms.*

Key Words: *Endometrial neoplasms; Recurrence; Risk; Survival*

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中文摘要

比較不同風險分級系統預測子宮內膜癌臨床結果的能力

葉欣怡、彭希文、陳麗君、吳宇光、張天怡、宋崧

目的：對比2010年FIGO/AJCC（國際婦產科聯盟／美國癌症聯合委員會）分期系統、2013年ESMO（歐洲醫學腫瘤學會）分類系統及2016年ESMO-ESGO-ESTRO（歐洲醫學腫瘤學會－歐洲婦科腫瘤學會－歐洲放射腫瘤學會）分類系統的三種不同風險分級系統針對子宮內膜癌復發和存活率的預測能力。

方法：回顧性研究2005年1月至2014年12月期間於香港單一中心接受輔助性抗癌治療的FIGO分期I-III子宮內膜癌患者的臨床資料。利用Harrell的一致性指數(Harrell's C-index)評估上述三種風險分級系統預測預測復發率、腫瘤相關存活率和整體存活率的能力。

結果：128名患者納入分析，當中22名患者（17%）復發，而18名患者（14%）因子宮內膜癌死亡。2010年FIGO／AJCC分期系統針對預測復發和整體存活率得出的C-index分別是 0.75（95%置信區間0.65-0.86）和 0.76（95%置信區間0.65-0.88），均為三種風險分級系統中最高。ESMO-ESGO-ESTRO亞組分類系統針對預測腫瘤相關存活率則為最高，即C-index為0.80（95%置信區間0.58-1.00）。

結論：利用Harrell一致性指數，證實2010年FIGO／AJCC分期系統、ESMO分類系統及ESMO-ESGO-ESTRO分類系統均有能力預測無病存活率、腫瘤相關存活率和整體存活率。ESMO-ESGO-ESTRO分類系統具有指導臨床決策和在研究中對患者風險區分的潛力。結合分子分型是對子宮內膜癌進行分類並建立個性化治療的重要未來發展趨勢。

BACKGROUND

Endometrial cancer is the most common gynaecological malignancy in developed countries.[1] In Hong Kong, it represented the fourth most common cancer and was ranked eleventh in causes of mortality in females in 2015, with a median age of 55 at diagnosis. The proportions of patients found to have stage I, II, III, and IV disease were 64.4%, 8.2%, 10.1%, and 7.1%, respectively, while the remaining 10.2% were unstaged.[2,3]

Although the majority of endometrial cancers are diagnosed at an early stage (I and II), the stage does not always accurately predict the prognosis, with 5-year survivals ranging from 75% to 90%.[4] The prognosis is governed by stage, histological subtype, grade, depth of myometrial invasion, and lymphovascular space invasion (LVSI).[5-8] In clinical practice, these factors, in addition to the results of recent studies of external beam radiotherapy and brachytherapy, including GOG-99,[9] PORTEC-1,[10] ASTEC/EN.5,[11] PORTEC-2,[12] as well as chemotherapy (GOG-122,[13] pooled analysis of NSGO-EC-9501/EORTC-55991 and MaNGO ILIADE-III[14]) and chemoradiotherapy (PORTEC-3[15]), strongly influence the choice of single or combined adjuvant therapies.

Against this background, several risk stratification systems (RSSs) have been proposed, with the aim of guiding adjuvant treatment, formulating a prognosis, and determining treatment appropriateness and efficacy in clinical studies. Currently, three widely used RSSs are the joint 2010 International Federation of Gynecology and Obstetrics/American Joint Committee on Cancer (FIGO/AJCC) staging system,[16,17] the European Society for Medical Oncology (ESMO) classification,[18] and the joint European Society for Medical Oncology, European Society of Gynaecological Oncology and European Society for Radiotherapy & Oncology (ESMO-ESGO-ESTRO) classification.[19]

However, there is a lack of literature that examines the external validity or performance of the RSSs. The objective of this study was to evaluate the discriminative ability of the aforementioned three RSSs in predicting recurrence and survival.

METHODS

Study Population

Data from patients with FIGO stage I to III endometrial carcinoma requiring postoperative adjuvant oncological treatment from 1 January 2005 to 31 December 2014 in the Department of Clinical Oncology of Pamela Youde Nethersole Eastern Hospital, Hong Kong were included in this retrospective study. Cases with macroscopic residual disease were excluded. Clinical data were collected retrospectively from medical records. Clinical and pathological characteristics, including tumour and nodal stage, grade, histological subtype, presence or absence of myometrial invasion, LVSI, treatment details, and clinical outcome were recorded.

Treatment and Follow-up

Preoperative workups consisted of magnetic resonance imaging of the pelvis and/or computed tomography (CT) of the abdomen and pelvis, chest X-ray and CT of the thorax or whole-body positron emission tomography–computed tomography. Patients with endometrioid (type 1) adenocarcinoma underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAHBSO) with or without pelvic ± paraaortic lymphadenectomy at the operating surgeons' discretion, while patients with non-endometrioid (type 2) carcinoma, i.e., serous and clear-cell carcinoma, underwent TAHBSO as well as lymphadenectomy, omentectomy, and peritoneal biopsies.

Proposed adjuvant treatment varied depending on stage of disease, tumour pathology, age, performance status, and the time of treatment commencement. Stage IB cases with at least one of the following three risk factors: grade 3, age >60 years or LVSI, and those with stage II and III disease were generally treated with whole pelvic irradiation (WPI) and intravaginal brachytherapy.

With the advent of PORTEC-2,[12] from October 2010, patients were administered brachytherapy alone (in contrast to previous treatment with WPI and brachytherapy combined) if they had the following characteristics: stage IA grade 2 with either age >60 years or LVSI, stage IA grade 3, and stage IB without the aforementioned three risk factors.

Since September 2010, adjuvant chemotherapy was administered to patients with non-endometrioid carcinomas of all stages and stage III endometrioid carcinomas post-radiotherapy, based on the pooled analysis of NSGO-EC-9501/EORTC-55991 and MaNGO ILIADE-III as mentioned above.[14]

Patients were followed up every 3 to 4 months during the first 2 years, every 6 months for the third to fifth year, and annually thereafter.

Disease-free survival (DFS), cancer-specific survival (CSS), and overall survival (OS) were evaluated. DFS was defined as date of diagnosis to date of relapse or death related to endometrial cancer. CSS was defined as date of diagnosis to date of death related to endometrial cancer. OS was defined as date of diagnosis to date of death from any cause.

Risk Stratification Systems Description

The RSSs evaluated in this study included the joint 2010 FIGO/AJCC staging system, the ESMO classification, and the ESMO-ESGO-ESTRO classification. They were selected in view of their recognised clinical applicability. Tables 1 to 3[16-19] describe the categories in each RSS. The performance of the three RSSs, when classified into large risk groups (shown in bold), was evaluated and compared when such risk groups could be further divided into subgroups.

Table 1. Description of the joint 2010 FIGO/AJCC staging system.[16,17]

Stage I	Tumour confined to the corpus uteri
IA	No or <50% myometrial invasion
IB	Invasion ≥50% of myometrium
Stage II	Tumour invades cervical stroma, but does not extend beyond the uterus
Stage III	Local and/or regional spread of tumour
IIIA	Tumour invades the serosa of the corpus uteri and/or adnexae
IIIB	Vaginal and/or parametrial involvement
IIIC1	Positive pelvic lymph nodes
IIIC2	Positive paraaortic lymph nodes with or without positive pelvic lymph nodes

Abbreviation: FIGO/AJCC = International Federation of Gynecology and Obstetrics/American Joint Committee on Cancer.

Table 2. Description of the ESMO classification.[18]

Risk group	Stage	Grade	Histology
Stage I			
Low-risk	IA	1/2	Endometrioid
Intermediate-risk	IA	3	Endometrioid
High-risk	IB	1/2	Endometrioid
	IB	3	Endometrioid
Stage II	II	Any	Any
Stage III	III	Any	Any

Abbreviation: ESMO = European Society for Medical Oncology.

Table 3. Description of the ESMO-ESGO-ESTRO classification.[19]

Risk group	Stage	Grade	Histology	LVSI status*
Low-risk	IA	1/2	Endometrioid	Negative
Intermediate-risk	IB	1/2	Endometrioid	Negative
High-intermediate-risk	IA	3	Endometrioid	±
	IB	1/2	Endometrioid	+
High-risk	IB	3	Endometrioid	±
	II	Any	Endometrioid	±
	III	Any	Endometrioid	±
	I-III	Any	Non-endometrioid	±

Abbreviations: ESMO-ESGO-ESTRO = European Society for Medical Oncology, European Society of Gynaecological Oncology and European SocieTy for Radiotherapy & Oncology; LVSI = lymphovascular space invasion.

* '±' means whether or not LVSI is present would not affect the risk group assignment.

Statistical Analysis

DFS, CSS, and OS were analysed for each RSS by generating Kaplan-Meier plots (Figure) with log-rank significance testing. To assess the discriminative ability of the models, the Harrell's C-index was calculated using the method proposed by Uno et al.[20] It is interpreted as the probability that a randomly selected subject who experienced the outcome will have a higher predicted probability of having the outcome occur compared to a randomly selected subject who did not experience the event. A C-index of 1 indicates that the model can perfectly distinguish between individuals with discordant events, and a C-index of 0.5 means no discriminative ability.[21] Statistical analysis was performed using SPSS (Windows version 22.0; IBM Corp, Armonk [NY], United States) and R (Version 3.3.3; https://www.r-project.org/).

RESULTS

Study Population

Data from a total of 128 cases were included in the analysis. Median follow-up time was 83.5 months (range, 5.5-143.5 months).

In all, 10.9% (n = 14), 67.2% (n = 86) and 13.3% (n = 17) of the cases underwent preoperative pelvic magnetic resonance imaging, CT of the abdomen and pelvis, and a combination of both modalities, respectively, while the remaining 8.6% (n = 11) underwent positron emission tomography–computed tomography.

Table 4 shows the distribution of the clinicopathological characteristics of the study cohort. A total of 114 cases (89.1%) had endometrioid histology. In all, 100%, 78.9% and 16.4% of the cases underwent TAHBSO, pelvic lymphadenectomy and paraaortic lymphadenectomy, respectively. Overall, 11.7% (n = 15) had positive pelvic nodes, whereas only 1.6% (n = 2) had paraaortic nodal disease.

Ten cases received adjuvant brachytherapy alone and 12 received WPI alone. A total of 106 cases received adjuvant radiotherapy in the form of a combination of both modalities. A total of 25 cases received adjuvant chemoradiotherapy.

Survival Analysis

Cancer recurred in 17.2% (n = 22), with first sites of recurrence being local, regional and distant in 9.1% (2/22), 4.5% (1/22) and 86.4% (19/22), respectively. Overall DFS was 82.5% at 5 years and 79.5% at 10 years.

In total, there were 14.1% (n = 18) deaths that were cancer-related. CSS was 88.6% at 5 years and 81.4% at 10 years.

Table 5 and the Figure show the respective DFS and CSS rates and Kaplan-Meier plots according to each RSS.

Performance of Risk Stratification Systems

A comparison of the Harrell's C-index of the RSSs is shown in Table 6. The joint 2010 FIGO/AJCC staging system had the highest C-index of 0.75 (95% confidence interval [CI] = 0.65-0.86) for recurrence and 0.76 for OS (95% CI = 0.65-0.88). In terms of CSS, the ESMO-ESGO-ESTRO subgroup classification had the highest C-index of 0.80 (95% CI = 0.58-1.00).

DISCUSSION

The classification of endometrial carcinoma has evolved over time. It has been staged surgico-pathologically since 1988 according to the FIGO staging system. The revised version in 2009 that resulted from better understanding of tumour biology is currently the most widely adopted RSS, and has been externally validated to improve prediction of prognosis compared to the earlier version.[22] Being practical and reproducible, it allows accurate information exchange among centres. However, its performance is limited by the fact that it does not distinguish patients with non-endometrioid (type II) cancers as a separate subgroup, whose outcome was shown to be inferior, with increased risk of recurrence and distant metastases[23]; moreover, the role of grade and LVSI as independent predictors of recurrence is disregarded.

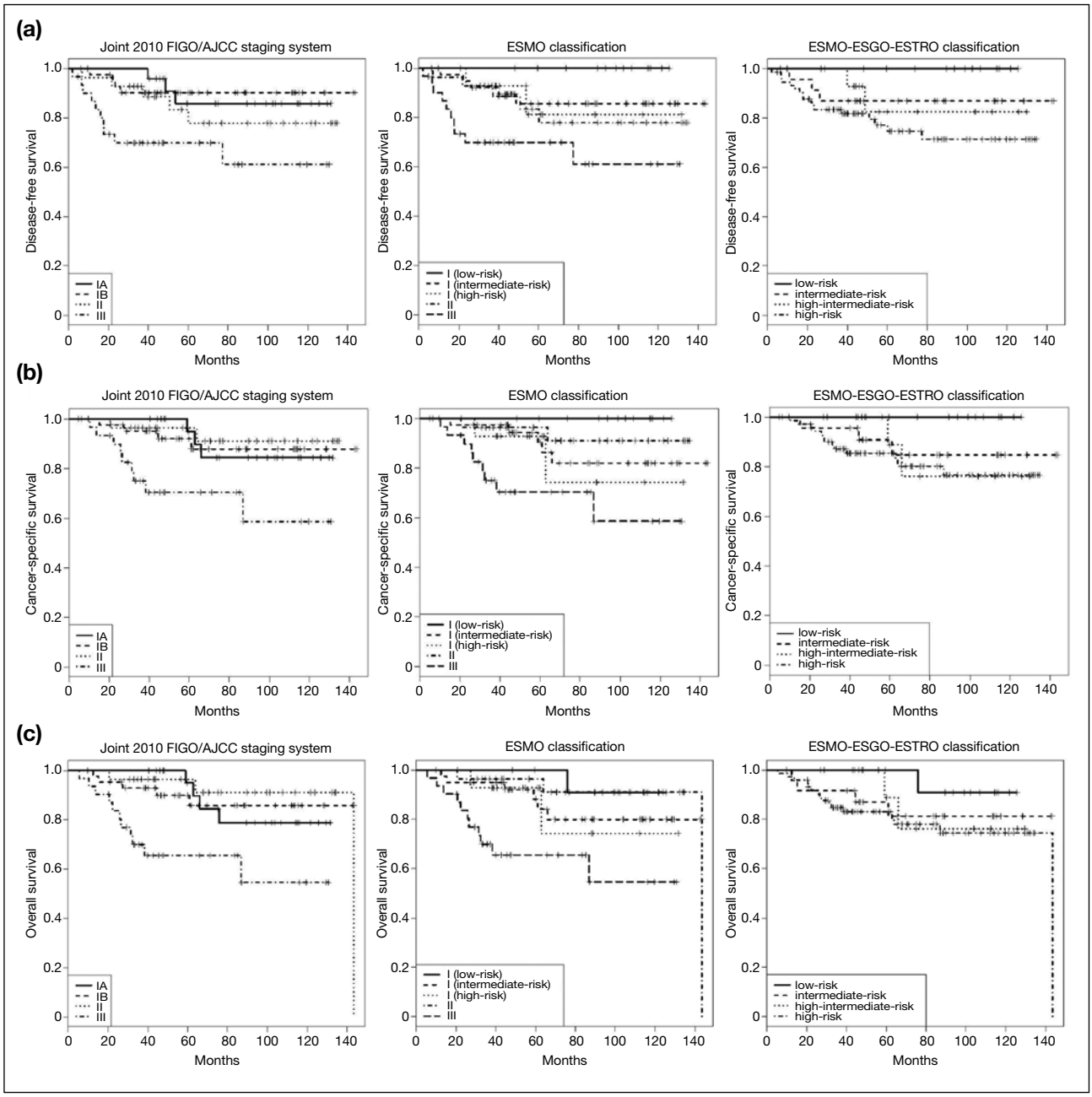

Figure. (a) Disease-free survival, (b) cancer-specific survival, and (c) overall survival curves according to the FIGO/AJCC, ESMO, and ESMO-ESGO-ESTRO risk stratification systems.

Abbreviations: ESMO = European Society for Medical Oncology; ESMO-ESGO-ESTRO = European Society for Medical Oncology, European Society of Gynaecological Oncology and European SocieTy for Radiotherapy & Oncology; FIGO/AJCC = International Federation of Gynecology and Obstetrics/American Joint Committee on Cancer.

Stemming from the perceived inadequacy of FIGO, other risk factors for recurrence were used in the PORTEC and GOG studies to define subgroups of patients that would derive the greatest benefit from adjuvant radiotherapy. Thereafter, ESMO classification and several other RSSs incorporating different combinations of key prognostic parameters were developed, with the goal of dividing early-stage cases into low-, intermediate-, and high-risk groups to improve prognosis prediction and guide treatment. In December 2014, a new classification system was introduced by the multidisciplinary ESMO-ESGO-ESTRO consensus panel,[19] in which a group of high-intermediate-risk patients was defined and the prognostic importance of grade 3 and LVSI was

Table 4. Characteristics of patients according to T stage (n = 128).*

	T1a (n = 29)	T1b (n = 51)	T2 (n = 31)	T3a (n = 10)	T3b (n = 7)
Nodal staging					
N0	26 (89.7%)	43 (84.3%)	28 (90.3%)	9 (90.0%)	5 (71.4%)
N1	3 (10.3%)	8 (15.7%)	1 (3.2%)	1 (10.0%)	2 (28.6%)
N2	0	0	2 (6.5%)	0	0
Histology					
Endometrioid	25 (86.2%)	47 (92.2%)	27 (87.1%)	9 (90.0%)	6 (85.7%)
Serous	2 (6.9%)	3 (5.9%)	2 (6.5%)	1 (10.0%)	0
Clear cell	0	1 (2.0%)	1 (3.2%)	0	0
Mixed type	2 (6.9%)	0	1 (3.2%)	0	0
Poorly differentiated	0	0	0	0	1 (14.3%)
Grade					
1	4 (13.8%)	19 (37.3%)	12 (38.7%)	2 (20.0%)	0
2	13 (44.8%)	17 (33.3%)	10 (32.3%)	6 (60.0%)	4 (57.1%)
3	12 (41.4%)	15 (29.4%)	9 (29.0%)	2 (20.0%)	3 (42.9%)
Lymphovascular space invasion					
No	26 (89.7%)	33 (64.7%)	22 (71.0%)	4 (40.0%)	5 (71.4%)
Yes	3 (10.3%)	17 (33.3%)	8 (25.8%)	6 (60.0%)	2 (28.6%)
NA	0	1 (2.0%)	1 (3.2%)	0	0
Myometrial invasion					
No	29 (100%)	0	14 (45.2%)	3 (30.0%)	2 (28.6%)
Yes	0	51 (100%)	17 (54.8%)	7 (70.0%)	5 (71.4%)
Pelvic lymphadenectomy					
No	4 (13.8%)	14 (27.5%)	6 (19.4%)	2 (20.0%)	1 (14.3%)
Yes	25 (86.2%)	37 (72.5%)	25 (80.6%)	8 (80.0%)	6 (85.7%)
Paraaortic lymphadenectomy					
No	25 (86.2%)	48 (94.1%)	24 (77.4%)	6 (60.0%)	4 (57.1%)
Yes	4 (13.8%)	3 (5.9%)	7 (22.6%)	4 (40.0%)	3 (42.9%)
Adjuvant radiotherapy					
None	0	0	0	0	0
Brachytherapy alone	7 (24.1%)	2 (3.9%)	1 (3.2%)	0	0
External beam RT alone	11 (37.9%)	1 (2.0%)	0	0	0
External beam RT + brachytherapy	11 (37.9%)	48 (94.1%)	30 (96.8%)	10 (100%)	7 (100%)
Adjuvant chemotherapy					
No	26 (89.7%)	44 (86.3%)	25 (80.6%)	3 (30.0%)	5 (71.4%)
Yes	3 (10.3%)	7 (13.7%)	6 (19.4%)	7 (70.0%)	2 (28.6%)

Abbreviations: NA = not available; RT = radiotherapy.
* Data are shown as No. (%) of patients.

recognised. Additionally, the panel provided evidence-based recommendations on adjuvant treatment strategies tailored for each risk subgroup.

The best definition of risk groups has always been evolving based on the latest evidence. Consequently, the factors entering into the decision to administer adjuvant therapies remain fluid.

Bendifallah et al[24] compared the ESMO risk classification with PORTEC-1, GOG-99, SEPAL, and the ESMO-modified RSS and reported limited diagnostic accuracy in all five RSSs in stratifying patients with regard to the risk of recurrence and nodal involvement in early-stage endometrial cancers. A recent analysis by the FRANCOGYN study group according to the ESMO-ESGO-ESTRO classification showed promise in its ability to reflect outcome, demonstrating a higher incidence of locoregional failure in patients with high- and high-intermediate-risk endometrial cancers, while patients at high risk experienced more distant recurrences compared with other risk groups.[25] To our knowledge, this is the first study to evaluate the ESMO-ESGO-ESTRO risk classification system compared with other RSSs in terms of discriminative ability.

Our data revalidated the high prognostic value and applicability of the joint 2010 FIGO/AJCC staging system, which had a C-index of 0.75 for prediction of recurrence. For each classification system, the discriminative power in terms of C-index was higher when they were further divided into subgroups. In terms of prediction of cancer-specific survival, the ESMO-ESGO-ESTRO subgroup classification had the highest C-index of 0.80.

Table 5. Disease-free survival and cancer-specific survival specified for the various risk stratification systems.*

Risk stratification system	Subgroups	Patients	Relapse	Disease-free survival		Cancer-related deaths	Cancer-specific survival	
				5-year (%)	10-year (%)		5-year (%)	10-year (%)
2010 FIGO/AJCC staging system[16,17]	IA	26 (20.3%)	3 (11.5%)	85.9%	85.9%	3 (11.5%)	95.0%	84.4%
	IB	43 (33.6%)	4 (9.3%)	90.3%	90.3%	4 (9.3%)	92.0%	87.9%
	II	28 (21.9%)	5 (17.9%)	83.4%	77.9%	2 (7.1%)	96.4%	91.1%
	IIIA	9 (7.0%)	1 (11.1%)	87.5%	87.5%	1 (11.1%)	80.0%	80.0%
	IIIB	5 (3.9%)	1 (20.0%)	80.0%	80.0%	1 (20.0%)	80.0%	80.0%
	IIIC1	15 (11.7%)	7 (46.7%)	60.0%	40.0%	6 (40.0%)	64.2%	32.1%
	IIIC2	2 (1.6%)	1 (50.0%)	50.0%	50.0%	1 (50.0%)	50.0%	50.0%
ESMO classification[18]	Stage I low-risk	14 (10.9%)	0	100%	100%	0	100%	100%
	Stage I intermediate-risk	40 (31.3%)	5 (12.5%)	85.7%	85.7%	5 (12.5%)	90.5%	82.0%
	Stage I high-risk	15 (11.7%)	2 (13.3%)	81.3%	81.3%	2 (13.3%)	92.9%	74.3%
	Stage II	28 (21.9%)	5 (17.9%)	83.4%	77.9%	2 (7.1%)	96.4%	91.1%
	Stage III	31 (24.2%)	10 (32.3%)	69.9%	61.2%	9 (29.0%)	70.4%	58.6%
ESMO-ESGO-ESTRO classification[19]	Low-risk	14 (10.9%)	0	100%	100%	0	100%	100%
	Intermediate-risk	24 (18.8%)	3 (12.5%)	87.0%	87.0%	3 (12.5%)	90.9%	84.8%
	High-intermediate-risk	16 (12.5%)	2 (12.5%)	82.5%	82.5%	2 (12.5%)	88.9%	76.2%
	High-risk	74 (57.8%)	17 (23.0%)	77.2%	71.5%	13 (17.6%)	85.5%	76.6%
	Stage IB grade 3, endometrioid	10 (7.8%)	0	100%	100%	0	100%	100%
	Stage II, endometrioid	25 (19.5%)	4 (16.0%)	87.2%	80.9%	2 (8.0%)	96.0%	90.0%
	Stage III, endometrioid	25 (19.5%)	4 (16.0%)	87.5%	76.6%	4 (16.0%)	87.1%	72.6%
	Stage I-III, non-endometrioid	14 (10.9%)	9 (64.3%)	33.3%	33.3%	7 (50.0%)	54.2%	43.3%

Abbreviations: ESMO = European Society for Medical Oncology; ESMO-ESGO-ESTRO = European Society for Medical Oncology, European Society of Gynaecological Oncology and European SocieTy for Radiotherapy & Oncology; FIGO/AJCC = International Federation of Gynecology and Obstetrics/American Joint Committee on Cancer.
* Data are shown as No. of patients (%) except where otherwise indicated.

Table 6. Discrimination of the risk stratification systems for recurrence, cancer-specific survival and overall survival.

Risk stratification system	C-index (95% confidence interval)		
	Disease-free survival	Cancer-specific survival	Overall survival
2010 FIGO/AJCC[16,17]			
Combined risk groups	0.735 (0.63-0.84)	0.771 (0.57-0.98)	0.757 (0.57-0.94)
Subgroups	0.753 (0.65-0.86)	0.797 (0.67-0.93)	0.764 (0.65-0.88)
ESMO[18]			
Combined risk groups	0.720 (0.58-0.86)	0.771 (0.61-0.93)	0.748 (0.56-0.94)
Subgroups	0.731 (0.60-0.87)	0.778 (0.59-0.96)	0.757 (0.57-0.94)
ESMO-ESGO-ESTRO[19]			
Combined risk groups	0.618 (0.50-0.74)	0.667 (0.52-0.82)	0.637 (0.52-0.82)
Subgroups	0.738 (0.55-0.92)	0.800 (0.58-1.00)	0.752 (0.55-0.96)

Abbreviations: ESMO = European Society for Medical Oncology; ESMO-ESGO-ESTRO = European Society for Medical Oncology, European Society of Gynaecological Oncology and European SocieTy for Radiotherapy & Oncology; FIGO/AJCC = International Federation of Gynecology and Obstetrics/American Joint Committee on Cancer.

Although classification based on FIGO staging remains robust and widely used, it is insufficient to rely solely upon it to determine the optimal adjuvant treatment in clinical practice. FIGO staging cannot guide adjuvant therapy precisely with the current treatment algorithms. Patients of the same FIGO stage may have indications for different adjuvant therapies in clinical practice depending upon different prognostic factors that are disregarded, e.g. LVSI, tumour grade, and histological subtypes. Compared with FIGO, the ESMO-ESGO-ESTRO classification is more exacting by taking into account the aforementioned prognostic factors in the risk

grouping. Thus, the same stage I patients in FIGO can be stratified into the four risk groups (low, intermediate, high-intermediate, high) by LVSI, tumour grade and histologic subtypes. The choice of adjuvant therapy is suggested for each risk group by the level of evidence.

Risk stratification for endometrial carcinoma is continually evolving to help clinicians to assign the appropriate treatments to different risk groups. At present, there are still unresolved questions on the choice of adjuvant treatment. For instance, the benefit of combining radiotherapy and chemotherapy in high-risk groups is controversial.[14,19] In addition to providing prognostic value and guiding treatment, a good risk stratification system also allows the identification of patients for studies in developing new treatment strategies to improve the outcomes of high-risk cases while minimising overtreatment of low-risk groups.

The strength of this study is that the present cohort had a relatively high proportion of cases that underwent pelvic lymphadenectomy (78.9%), compared with other large studies evaluating FIGO staging.[22,26] However, there are some limitations, including the relatively small sample size and a low number of events, as well as the potential selection bias inherent in its retrospective design. Moreover, during the relatively long study period, there had been modifications in surgical and adjuvant treatment. Cases that did not receive adjuvant oncological treatment were excluded from the study. This was due to concern about inaccurate assessment of long-term outcome resulting from early loss to follow-up of this group of cases, as they might not have been referred to our unit postoperatively, or in cases where they were referred to us, they would receive subsequent follow-up at their mother units only. However, this also means that our results might not have been the same if all cases of endometrial cancer had been included.

Moving forward, a major obstacle in improving care for patients with endometrial carcinomas is the presence of interobserver variation among pathologists in evaluating key pathological variables that current RSSs heavily rely on,[27,28] implying risk group misassignment thus over- and under-treatment. This inspired the search for complementary tools such as immunohistochemical markers (p53, oestrogen receptors, etc.) and mutational profiles for more precise risk quantification. Data from The Cancer Genome Atlas studies support classification of endometrial carcinomas into four prognostically distinct subgroups based on genomic architecture, but this genomic approach is not in routine clinical use due to cost, logistics and lack of applicability to biopsies and curettings, implying that patients can only be stratified after surgical staging.[29] Talhouk et al[30] presented a clinically practical method for molecular classification of endometrial cancers using formalin-fixed paraffin-embedded samples, which could replicate the Cancer Genome Atlas' genomic-based classification without the need for labour-intensive and cost-prohibitive genomic methodology; additionally, it can be applied to biopsy specimens, enabling earlier planning of the optimal course of treatment and consideration of fertility-sparing options in selected cases. When integrated with clinicopathological factors or risk group classifications, the molecular classifier provided the highest level of discrimination of survival outcomes. Another future direction for personalised medicine is the development of risk scoring models. For example, AlHilli et al[31,32] created nomograms for individualised prediction of lymphatic dissemination and OS. Further clinical validation is certainly needed to determine the best way of incorporating these molecular classifiers and risk scoring models into clinical care and evaluating their impact on outcome.

CONCLUSION

We demonstrated the discriminative abilities of the joint 2010 FIGO/AJCC staging system, the ESMO classification, and the ESMO-ESGO-ESTRO classification in predicting DFS, CSS, and OS using Harrell's C-index. The ESMO-ESGO-ESTRO classification has potential in guiding clinical decision making and patients' risk assignment in studies. Integration of molecular classification may represent the way forward in classifying endometrial carcinoma and instituting personalised treatment algorithms.

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