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Effectiveness of the Risk of Malignancy Index and the Risk of Ovarian Malignancy Algorithm in a Cohort of Women With Ovarian Cancer

Does Histotype and Stage Matter?

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Objective: To examine the performance of the Risk of Malignancy Index (RMI) and Risk of Ovarian Malignancy Algorithm (ROMA) by histologic subtype and stage of disease in a cohort of women with ovarian cancer.

Methods: All patients with confirmed ovarian cancer at the Princess Margaret Hospital between February 2011 and January 2013 were eligible for study inclusion. Preoperative cancer antigen 125, human epididymis protein 4, and ultrasound findings were reviewed, and the sensitivity and false-negative rates of the RMI and ROMA were determined by stage of disease and tumor histology.

Results: A total of 131 patients with ovarian cancer were identified. High-grade serous (HGS) histology was most frequently associated with stage III/IV disease (n = 46 [72% of stage III/IV]) vs stage I (n = 5 [11% of stage I]; $P < 0.0001$). Clear cell (CC) and endometrioid (EC) histology presented most commonly with stage I disease (n = 9 [20%] and n = 13 [29% of stage I cases], respectively). Median cancer antigen 125 and human epididymis protein 4 values were significantly higher for HGS than for EC or CC histology. Risk of Malignancy Index II demonstrated the highest sensitivity of the 3 RMI algorithms. All RMIs and ROMA were significantly more sensitive in predicting malignancy in patients with HGS than EC or CC histology. Risk of Malignancy Index II (n = 38) and ROMA (n = 35) exhibited sensitivities of 68% and 54% and false-negative rates of 32% and 46%, respectively, for patients with stage I disease vs sensitivities of 94% and 93% and false-negative rates of 6% and 7% for patients with stage III/IV disease.

Conclusion: Both RMI and ROMA performed well for the detection of advanced ovarian cancer and HGS histology. These triaging algorithms do not perform well in patients with stage I disease where EC and CC histologies predominate. Clinicians should be cautious

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The authors declare no conflicts of interest.

ISSN: 1048-891X
DOI: 10.1097/IGC.0000000000000442

using RMI or ROMA scoring tools to triage isolated adnexal masses because many patients with stage I malignancies would be missed.

Key Words: Ovarian carcinoma, Risk of Malignancy Index (RMI), Risk of Ovarian Malignancy Algorithm (ROMA), Histology

Received November 24, 2014, and in revised form February 17, 2015.
Accepted for publication February 22, 2015.

(*Int J Gynecol Cancer* 2015;25: 809–814)

Ovarian cancer is the fifth leading cause of cancer-related death in the United States, Canada, and Europe.[1–3] Although the 5-year survival rate for women diagnosed as having International Federation of Gynecology and Obstetrics (FIGO) stage I disease is 83% to 93%, 68% to 85% of women present with advanced stage disease, where the median 5-year survival is 11% to 47%.[4,5] Definitive surgical management by a gynecologic oncologist results in decreased morbidity and improved overall survival when compared with surgery performed by a nononcologist.[6] However, without obvious evidence of extraovarian disease on preoperative imaging, it is difficult to discriminate a benign from a malignant adnexal neoplasm and identify those patients in need of subspecialist referral.

Multiple models have been developed to determine the risk of malignancy of an adnexal mass. The first was the Risk of Malignancy Index (RMI), combining ultrasound (US) findings, menopausal status, and the level of the serum tumor marker cancer antigen 125 (CA-125).[7] The RMI is still the most widely used system in many countries.[8,9] Three versions, RMI I, II, and III, have been derived, yielding cumulative sensitivities for the prediction of ovarian cancer among patients undergoing surgery for an adnexal mass of 78%, 79%, and 74%, respectively, with specificities of 87%, 81%, and 91%, respectively.[7,10,11] All 3 versions are heavily dependent on the CA-125 level. Although CA-125 is elevated in 80% of all patients with epithelial ovarian cancer, only 50% of patients with stage I disease demonstrate an increased value,[12] compared with 90% of patients with stage III/IV disease.[13] This is reflected in the decreased sensitivity of the RMI I (65%) when applied to patients with stage I/II disease.[14]

The human epididymis protein 4 (HE4) has recently emerged as a novel tumor marker overexpressed in ovarian and endometrial cancer. It is reported to be comparable to, or better than, CA-125 in the detection of ovarian cancer.[5,15] In 2010, Moore et al[14] validated the Risk of Ovarian Malignancy Algorithm (ROMA), a biomarker-based algorithm that incorporates CA-125, HE4, and menopausal status. The ROMA has been compared with the RMI in multiple studies with conflicting evidence for their relative performance.[5,14,16] For stage I/II disease, the ROMA was cited as having a sensitivity of 85% and a specificity of 75% for the prediction of epithelial ovarian cancer among patients undergoing surgery for an adnexal mass.[14]

In ovarian cancer, stage at presentation is associated with histologic subtype. Studies have suggested that most ovarian cancers diagnosed at an early stage are of endometrioid (EC) and clear cell (CC) histologic subtypes, whereas those with widespread disease are typically of high-grade serous (HGS) histology.[17–19] Recent evidence supports the hypothesis that many HGS carcinomas may actually arise from the fallopian tube,[20,21] where the potential exists for early dissemination. As such, it is unclear whether it is possible to detect early HGS ovarian cancer with the algorithms currently available. Conversely, it is unclear whether the RMI and ROMA are well suited to detect the histologic subtypes that tend to present with early-stage disease, such as EC and CC ovarian cancers.

In the present study, we sought to determine the performance characteristics of the RMI and ROMA by histologic subtype and stage of disease in a cohort of patients with ovarian cancer managed at a tertiary care referral center. We hypothesized that most patients with early-stage ovarian cancer would consist of nonserous histologic subtypes, for which the RMI and ROMA would perform poorly, and that the scoring system performance for stage I disease would be lower than previously reported for stage I and II diseases combined.

MATERIALS AND METHODS

This study was approved by the University Health Network Research Ethics Board. All patients with confirmed ovarian cancer managed at Princess Margaret Hospital between February 2011 and January 2013 were eligible for study inclusion. Tumor markers were obtained from a blood banking database of gynecologic patients referred to Princess Margaret Hospital with an adnexal mass, BRCA mutation, or ovarian cancer. There is more than 90% participation in this blood banking program. All patients underwent radiologic imaging with pelvic US, computed tomography, and/or magnetic resonance imaging to document the presence and characteristics of pelvic disease and any evidence of metastases; blood was drawn for tumor markers at the time of presentation, before treatment. Patient demographics, preoperative tumor markers and imaging results, dates and details of surgery, and pathologic findings were reviewed. International Federation of Gynecology and Obstetrics staging was applied. For the purposes of this study, complete surgical staging was defined as hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and bilateral pelvic and/or para-aortic lymphadenectomy. Patients with complete and incomplete surgical staging were included in the study. Patients with cancer metastatic to the ovary were excluded.

Risk of Malignancy Calculations

Risk of Malignancy Index scores using RMI I, RMI II, and RMI III were calculated using the 3 specific scoring systems as summarized by Clarke et al.[22] The RMI threshold

TABLE 1. Demographic data

	n	Mean	SD	Range
Age at diagnosis, y	131	58	12	19–84
		n	Frequency	%
Postmenopausal		130	89	68
Premenopausal			41	32
Stage				
IA		130	18	14
IB			3	2
IC			24	18
IIA			9	7
IIB			8	6
IIC			4	3
IIIA			7	5
IIIB			5	4
IIIC			48	37
IV			4	3
Histology				
HGS		131	58	44
EC			23	18
CC			15	11
Low-grade serous			7	5
Sex-cord stromal			7	5
Germ cell			3	2
Mucinous			4	3
Mixed			4	3
MMMT			4	3
Other			6	5

of 200 was used because this is the threshold recommended by the Society of Obstetricians and Gynecologists of Canada guidelines for referral to a gynecologic oncologist.[8]

The ROMA was determined for premenopausal and postmenopausal patients using the algorithms validated by Moore et al,[14] calculating the coefficient of the natural log of serum values of CA-125 and HE4 with integration into a logistic regression formula. The ROMA predicted probability cutoffs for premenopausal and postmenopausal patients, as indicated by Moore et al, were 12.9% and 27.8%, respectively.[14]

Statistical Analysis

Categorical variables were summarized with counts and percentages. Continuous variables were summarized with means, medians, and/or ranges. χ^2 Test or Fisher exact test was used to assess for significant associations between categorical variables of interest. Analysis of variance or Kruskal-Wallis testing was used for continuous variables (eg, CA-125 and HE4) to compare levels of categorical covariates of interest. Two-sided tests were reported, unless there was a hypothesis that was prespecified in advance. Exact McNemar test was used to compare the sensitivity of the RMI I, RMI II, RMI III and ROMA.

RESULTS

Between February 2011 and January 2013, there were 131 patients with confirmed ovarian cancer. Patient demographics and tumor characteristics are summarized in Table 1.

The histologic distribution by FIGO stage is presented in Figure 1. High-grade serous histology was significantly more frequent among patients with stage III/IV disease (n = 46 [72%]) compared with those with stage I disease (n = 5 [11%]; $P < 0.0001$). Clear cell histology was significantly more frequent among patients with stage I disease (n = 9 [20%]) compared with those with stage III/IV disease (n = 2 [3%]; $P = 0.007$). Endometrioid histology was also significantly more frequent among patients with stage I disease (n = 13 [29%]) compared with those with stage III/IV disease (n = 5 [8%]; $P = 0.004$). Cancer antigen 125 values were available for 120 patients, and HE4 values were available for 115 patients. Stage III/IV disease was associated with significantly higher median CA-125 and HE4 scores compared with stage I disease (Table 2). Higher CA-125 and HE4 values were associated with HGS histology compared with CC or EC histology (Table 3).

The RMI and ROMA scores were calculated for each stage of disease. Ultrasound reports were available for 110 patients. Risk of Malignancy Index I, II, and III scores were calculated for 103 patients where menopausal status, CA-125, and US data were available. Risk of Ovarian Malignancy Algorithm scores were calculated for 104 patients where menopausal status, CA-125, and HE4 values were available. The sensitivities and false-negative rates for RMI I, RMI II, RMI III and ROMA are presented by menopausal status and stage of disease (Table 4). For FIGO stage I disease, the RMI II demonstrated superior performance, with a sensitivity of 68%, compared with 51% ($P = 0.02$) and 53% ($P = 0.03$) for RMI I and RMI III, respectively. There was a nonsignificant difference in sensitivity between the RMI II and ROMA for stage I disease (68% vs 54%, $P = 0.23$). The RMI and ROMA scoring systems were significantly more sensitive in the detection of cancer in patients with HGS histology compared with EC histology. For CC histology, a similar trend was observed, with

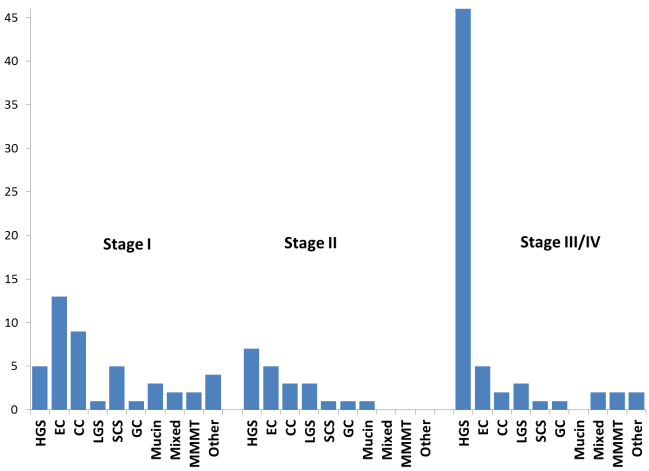

FIGURE 1. Histologic distribution by stage of disease.

TABLE 2. Median CA-125 and HE4 values for stage I and II disease compared with stage III/IV disease

Tumor Marker	Stage III/IV		Stage I			Stage II		
	n	Median (Range)	n	Median (Range)	*P*	n	Median (Range)	*P*
CA-125	62	268 (14–21782)	40	42 (3–9305)	<0.0001	18	172 (20–2043)	0.3418
HE4	57	349 (45–1500)	40	70 (32–2680)	<0.0001	17	128 (29–2916)	0.0034

TABLE 3. Median CA-125 and HE4 values for CC and EC histology compared with HGS

Tumor Marker	HGS		CC			EC		
	n	Median (Range)	n	Median (Range)	*P*	n	Median (Range)	*P*
CA-125	54	278 (9–21782)	13	52 (13–1258)	0.0082	23	55 (3–9305)	0.0347*
HE4	51	349 (32–1500)	12	96 (29–982)	0.0026	20	190 (33–2195)	0.1513

*One-sided test.

statistical significance demonstrated for RMI I and III scoring systems (Table 5).

DISCUSSION

The evaluation of strategies for the early detection of ovarian cancer has not previously been considered by histologic subtype. Models used have focused on US findings and biochemical markers such as CA-125 and HE4, which, as highlighted in the present study, are markers more selectively associated with HGS histology. Such a strategy would be justified if the distribution of histologic subtypes was even across all stages of ovarian cancer. This has not proven to be the case, however, with true cases of stage I HGS ovarian cancer an uncommon entity (11% in our cohort).

Scoring systems for the triage of adnexal masses include the RMI, ROMA, OVA1, and US-based logistic regression models, among others.[7,13,23,24] The RMI, the algorithm recommended in the Society of Obstetricians and Gynecologists of Canada, RCOG, and Cancer Australia guidelines,[8,9,25] is heavily dependent on the CA-125 value. As demonstrated in this report, CA-125 is a poor marker in cases of nonserous histology. Most early-stage ovarian cancers are of nonserous histology, with a resultant inferior performance of the RMI in this subgroup. In the present study, RMI II was the most sensitive in the detection of ovarian cancer overall compared with RMI I, RMI III, and ROMA. Risk of Malignancy Index II provides more weight to the US findings than RMI I and RMI III, which likely explains its improved sensitivity. All 3 scoring systems use CA-125 levels, leading to poor performance of the scoring systems in early-stage disease. Applying the RMI II in patients with stage I disease yields a false-negative rate of 32%, which is unacceptably high.

In an attempt to improve tumor-marker risk models, HE4 was identified as a serum biomarker of ovarian cancer in

TABLE 4. Sensitivity and false-negative rates of RMI I, RMI III, and ROMA compared with RMI II

		RMI II		RMI I			RMI III			ROMA			
	n (%)	Sens (%)	FN (%)	Sens (%)	FN (%)	*P**	Sens (%)	FN (%)	*P**	n, (%)	Sens (%)	FN (%)	*P**
All	103 (100)	84.5	15.5	75.5	24.5	<0.01	76.7	23.3	<0.01	104 (100)	78.9	21.1	0.18
Menopausal status													
Pre	30 (29.1)	73.3	26.7	75.9	24.1	1	73.3	26.7	1	30 (28.9)	73.3	26.7	1
Post	73 (70.8)	89.0	11.0	75.3	24.7	<0.01	78.0	22.0	<0.01	74 (71.1)	81.1	18.9	0.07
Stage													
I	38 (36.9)	68.4	31.6	51.4	48.6	0.016	52.6	47.4	0.03	35 (33.7)	54.3	45.7	0.23
II	13 (12.6)	92.3	7.7	84.6	15.4	1	84.6	15.4	1	15 (14.4)	86.7	13.3	1
III/IV	52 (50.5)	94.2	5.8	90.4	9.6	0.5	92.3	7.7	1	54 (51.9)	92.6	7.4	1

* Values are calculated for the sensitivities compared with the sensitivities of RMI II.
Sens, sensitivity; FN, false-negative rate; Pre, premenopausal; Post, postmenopausal.

TABLE 5. Sensitivity of RMI I, RMI II, RMI III, and ROMA for the detection of cancer in patients with EC and CC compared with HGS histology

	HGS	EC		CC	
	Sensitivity	Sensitivity	*P*	Sensitivity	*P*
RMI I	89.1	55.6	<0.01	54.6	0.017
RMI II	93.5	66.7	0.012	72.7	0.079
RMI III	89.1	55.6	<0.01	54.6	0.017
ROMA	93.5	65.0	<0.01	70.0	0.063

2003.[26] A recent meta-analysis of its performance characteristics identified a pooled sensitivity of 83% and a specificity of 91%.[27] Compared with CA-125, HE4 is less frequently elevated in benign disease.[15] It has been found to be more accurate with HGS histology compared with other histologies. Moore et al[14] combined HE4 with CA-125 in the ROMA and demonstrated that in stage I/II disease, the ROMA outperformed the RMI I with a sensitivity of 85% at a specificity of 75%, compared with a sensitivity of 65% at a set specificity of 75% for the RMI I. However, performance for stage I disease was not specifically examined. In our study, ROMA offered no benefit over RMI II for the prediction of stage I disease. We have demonstrated that ROMA scoring has a sensitivity of 54% in the detection of stage I ovarian cancer compared with 68% for RMI II. These values suggest that HE4, like CA-125, is preferentially elevated in cases of HGS histology, which is rare in stage I disease. As expected, both ROMA and RMI I had lower sensitivities for the detection of stage I disease than what has been previously reported for stage I/II disease.[14]

One limitation of this study is that only 24 (53%) of 45 patients with apparent stage I disease at the time of surgery underwent complete surgical staging, as defined above. The reasons documented for the omission of lymphadenectomy were as follows: (*a*) not warranted based on frozen section (31%), (*b*) unlikely to change management (13%), (*c*) technically unsafe (6%), and (*d*) not stated (50%). Because a lack of complete surgical staging in the stage 1 cohort could overestimate the number of true cases of stage 1 disease, the RMI and ROMA calculations were repeated for the 24 patients who underwent a complete systematic staging procedure at the time of their original procedure. The repeated analysis revealed similar results, with sensitivity values of 50%, 73%, 55%, and 60% for RMI I, RMI II, RMI III, and ROMA, respectively.

The correct preoperative discrimination of an isolated pelvic mass remains a diagnostic dilemma. Strategies using algorithms such as the RMI and ROMA have improved detection of ovarian cancer cases with high specificity. However, the algorithms are most reliable in cases of advanced HGS ovarian cancer. Although this has merit, the next challenge is the management of a negative test result in the presence of an apparent isolated adnexal mass.

Reliance on current algorithms may risk missing an unacceptably large proportion of patients with early-stage cancers for whom improved outcomes may be possible with referral to a gynecologic oncologist. New strategies for discriminating solitary adnexal masses using biochemical markers that detect nonserous histologic subtypes are essential. Until that time, clinicians should exercise caution in relying exclusively on an RMI or ROMA risk score to guide referral to a gynecologic oncologist.

ACKNOWLEDGMENTS

The authors recognize Mathew J.C. Smith for his contributions to the statistical analysis in this study. They thank Abbott Diagnostics for providing HE4 reagents for this study.

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