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Research Article

Nucleolus Scoring May Increase the Objectivity of Pathological Evaluation of Endometrial Cancers

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Abstract

Aim: Nucleolus has been shown as a prognostic parameter in many cancer types. In this study, we showed that the nucleolus score may provide more objective FIGO grading in endometrial cancers (ECs). We examined the role of nucleolus score in predicting treatment and prognosis in ECs.

Material and Methods: The presence of nucleoli were scored as 1, 2 and 3 in curettage materials. The relationship between this value and clinicopathological parameters was examined.

Results: Nucleolus score was associated with FIGO grade, myometrial invasion and lymphovascular invasion. The nucleolus score, which has the potential for objective evaluation,was found as an independent risk factor for disease-free survival (DFS) as well as there was an association between nucleolus score and DFS.

Conclusion: Nucleolus score was associated with better prognosis in ECs. It can be evaluated objectively with no need of requiring extra cost and time. Thus, adding nucleolus score in FIGO grading can provide more reliable prediction in prognosis and choice of the treatment method.

Keywords: Endometrial carcinoma, nucleolus score, FIGO grade, prognosis

INTRODUCTION

Endometrial carcinoma is the most common gynecological malignancy among women in worldwide (1-3).

Endometrioid type endometrial cancers (ECs) are are grading according to Federation Internationale des Gynaecologistes et Obstetristes (FIGO) grade based on the glandular differentiation (4,5). Assesment of tumor grading together with the depth of tumor invasion and cervical involvement plays an important role in curettage specimens, since the need for a complete surgical procedure including lymph node dissection rely on these. Grade 1 ECs have a better prognosis compared to Grade 3. However, there has not been enough data in the literature for Grade 2 ECs (6) and this group of tumors remain in the gray area. FIGO ternary grading system comprises a combination of two different parameters includingarchitectural and nuclear grading (4,6,7). According to this system, features for architectural grading have been adopted from the well-defined criteria of the Gynecologic Oncology Group (GOG) pathology committee (4,8), Grading is based on the percentage of the solid component within the tumor. If the tumor has solid component less than 5%, 6-50% and more than 50%, it is graded as 1, 2 and 3 respectivelyThe overall grade is increased by one for tumors with nuclear atypia (6,9).

In FIGO grading, quantitative values are used for architecture grading. However, there is no quantitative

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criteria for nuclear atypia. Therefore, the lack of rigorous criteria for evaluating nuclear atypia makes grading subjective (6,10). The absence of a defined criterion causes confusion for pathologists and clinicians (7,8) Nucleolus evaluation in tumor cells can be performed using silver staining of argyrophilic nucleolar organiser regions (AgNOR), and digital techniques (11,12). A morphological nucleolus grading method was firstly defined by Helpap for renal cell cancer (13). In ECs there is no optimal method for nucleolus prominence and only used as a component of nuclear atypia.

In this study, we evaluated the nucleolus of tumor cells in the endometrial curettage samples with the Modified Helpap method, in order to find an objective parameter that can be used in grading. Additionally, we examined the relationship of nucleolus score with prognostic variables and other clinicopathological parameters.

MATERIAL AND METHOD

Patients and Tissue Samples

Our retrospectively planned study included patients with a tissue diagnosis of EC from curettage sample in our hospital, between January 2010-2020. Hematoxylin-eosin (HE) stained slides were retrieved from the pathology archive. Cases whom paraffin-embedded blocks, HE slides or clinical data could not be obtained, as well as patients with a second primary or who died within the first month after surgery were excluded. As a result, a total of 101 patients were included.

Clinical Data

The age, distant organ metastasis, adjuvant treatment status, and survival data were obtained from the hospital database, while tumor size, FIGO grade, nuclear grade, pathological stage, were obtained from pathology reports.

FIGO grade, nuclear grade, and nucleolus prominence were reevaluated from HE stained slides. The patients were classified as EC according to the World Health Organization criteria (14).

Outcomes

Overall survival (OS) and disease-free survival (DFS) were defined as the time from diagnosis to death, and the time from diagnosis to the first recurrence, respectively.

Histopathological Evaluation of Nucleolus Score

In this study, HE-stained slides (N=101) were evaluated by two pathologists (SDO, ÇO). Nucleolus prominence was assessed with a conventional light microscope (Olympus, BX-51, ocular 22mm) with Modified Helpap method (13). We divided the nucleolus scores into three subgroups. Nucleolus that was not evident in any way or were difficult to see at 20x magnification were given 1 point. A nucleolus was scored as three if there was a prominent nucleolus or dysmorphic nucleolus or it was easily visible at 10x magnification and was identified in at least 20% of the tumor. Nucleolus not rated as 1 or 3 was scored as 2 (Figure 1).

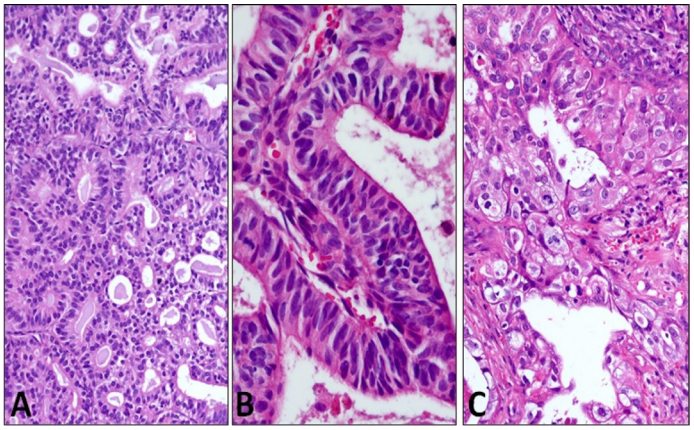

Figure 1: Examples of nucleolus scores 1, 2 and 3 in. Hematoxylin&Eosin x400. (A: score 1 . B: score 2. C: score 3)

Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics, Version 22.0 (SPSS Inc., Chicago, USA). The Chi-square test (Pearson Chi-square) or Fisher's Exact Test, where appropriate was used to compare the association of categorical variables. The possible prognostic factors identified with univariate analyses were further entered into the Cox regression analysis with backward selection to specify independent predictors of overall and disease-free survival, and a hazard ratio (HR) with 95% CI is presented. The Kaplan-Meier method was used for survival analysis and was evaluated with the log-rank test to identify the effect of nucleolus prominence on overall and disease-free survival. For statistical significance, a 5% type-1 error level was used.

Ethical Approval

Ethics committee confirmation for our study was obtained from the ethics committee of University Faculty of Medicine, non-interventional clinical research. The study was managed under the Declaration of Helsinki and the ethical standards of the institutional research committee, and the Reporting recommendations for tumor marker prognostic studies (REMARK) guidelines (15).

RESULTS

Clinical Features

A total of 101 cases with a tissue diagnosis of EC were included. The median age was 59 years (range, 41 to 87 years) for the entire cohort. Tumor diameter was less than 3 cm in 51 (51%) of the cases, and 3 cm or more in 50 (49%) cases. 66 (61%) cases were classified as FIGO Grade 1, while 33 (32%) were FIGO Grade 2, and 6 (6%) were FIGO Grade 3.

The number of cases with nuclear grade 1, 2 and 3 were 26 (26%), 68 (67%), and 7 (7%) respectively. Myometrial invasion was found less than 50% in 81 (80%), while equal to or more than 50% in 20 (20%) cases. The cervical invasion was detected in only 10 (10%) cases. Lymph node dissection was performed in 81 of 101 patients, and lymph node metastasis was observed only in 6 (7%) (Table 1).

Table 1. Clinicopathological data

		n	%
Nucleolus score	1	29	28.7
	2	46	45.5
	3	26	25.7
Tumor size	<3cm	51	50.5
	≥3 cm	50	49.5
FIGO grade	1	62	61.4
	2+3	39	38.6
Nuclear grade	1	26	25.7
	2+3	75	74.3
Pathologic stage	0	76	75.2
	1+2	25	24.8
Myometrial invasion ratio	<50%	81	80.2
	≥50%	20	19.8
Lymph node status	Negative	75	92.6
	Positive	6	7.4
Lymphovascular invasion	Negative	79	78.2
	Positive	22	21.8
Cervical invasion	Negative	91	90.1
	Positive	10	9.9
Paracentesis cytology	Benign	60	92.3
	Malign	5	7.7
Adjuvant chemotherapy	0	86	85.1
	1	15	14.9
Follow-up	0	91	90.1
	1	10	9.9
Distant metastasis	0	91	90.1
	1	10	9.9

Table 2. Nucleolus score and clinichopathologic criteria

		Nucleolus Score			
		1	2	3	
		n (%)	n (%)	n (%)	p
Tumor size	<3cm	20 (69)	20 (43.5)	11 (42.3)	0.062
	≥3 cm	9 (31)	26 (56.5)	15 (57.7)	
FIGO grade	1	28 (96.6)	29 (63)	5 (19.2)	<0.001
	2+3	1 (3.4)	17 (37)	21 (80.8)	
Nuclear grade	1	15 (51.7)	10 (21.7)	1 (3.8)	<0.001
	2+3	14 (48.3)	36 (78.3)	25 (96.2)	
Pathologic stage	0	25 (86.2)	36 (78.3)	15 (57.7)	0.041
	1+2	4 (13.8)	10 (21.7)	11 (42.3)	
Myometrial invasion ratio	<50%	26 (89.7)	39 (84.8)	16 (61.5)	0.019
	≥50%	3 (10.3)	7 (15.2)	10 (38.5)	
Lymph node status	Negative	18 (94.7)	40 (97.6)	17 (81)	0.056
	Positive	1 (5.3)	1 (2.4)	4 (19)	
Lymphovascular invasion	Negative	27 (93.1)	37 (80.4)	15 (57.7)	0.006
	Positive	2 (6.9)	9 (19.6)	11 (42.3)	
Cervical invasion	Negative	27 (93.1)	42 (91.3)	22 (84.6)	0.537
	Positive	2 (6.9)	4 (8.7)	4 (15.4)	
Paracentesis cytology	Benign	14 (93.3)	30 (96.8)	16 (84.2)	0.266
	Malign	1 (6.7)	1 (3.2)	3 (15.8)	
Adjuvant chemotherapy	0	27 (93.1)	40 (87)	19 (73.1)	0.102
	1	2 (6.9)	6 (13)	7 (26.9)	
Follow-up	0	29 (100)	43 (93.5)	19 (73.1)	0.002
	1	0 (0)	3 (6.5)	7 (26.9)	
Distant metastasis	0	27 (93.1)	45 (97.8)	19 (73.1)	0.003
	1	2 (6.9)	1 (2.2)	7 (26.9)	

Nucleolus Prominence and Clinicopathological Criteria

According to evaluation with a light microscope at 200x magnification, the number of patients with nucleolus score 1, 2 and 3 were 29 (29%), 46 (45%) and 26 (26%) respectively. There was a significant relationship between nucleolus scores and FIGO grade, as well as nuclear grade, myometrial invasion ratio, and lymphovascular invasion (p<0.001, p<0.001, p=0.019, p=0.006, respectively) (Table 2).

The number of cases with nuclear grade 1, 2 and 3 were 26 (26%), 68 (67%) and 7 (7%) respectively. When the nucleolus is evaluated according to the Modified Helpap method, which is known as an optimal method; nucleolus scores were significantly related with nuclear grades (p<0.001).

Relationship Between Nucleolus Score and Prognosis

The median follow up for entire-cohort was 60 months (range, 18 to 120 months). Ten (10%) were died of disease, and 7 (27%) of them had a nucleolus score of 3. The outcome was significantly poor as the nucleolus score increased (p=0.002). Distant organ metastases was observed in 10 (10%) cases . A significant correlation was found between the nucleolus score and disease-free survival (DFS) (Log rank p:0.001) (Figures 2 and 3). In Cox regression analysis, nucleolus score was found to be an independent prognostic factor for DFS (Hazard ratio (HR) 8.045; 95% CI 2.064-31.355; p: 0.003) (Table 3). In Cox regression analysis, nucleolus score, FIGO grade, lymphovascular invasion, and distant metastasis were found as prognostic factors in univariate analysis, but only FIGO grade was an independent variable for OS in multivariate analysis (Table 4).

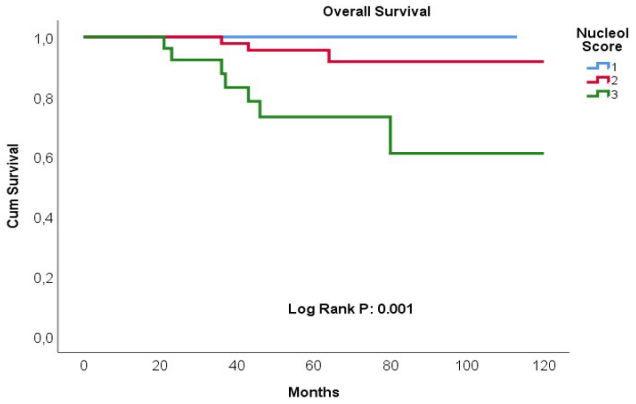

Figure 2. The relationship of nucleolus scores with overall survival by Kaplan Meier analysis

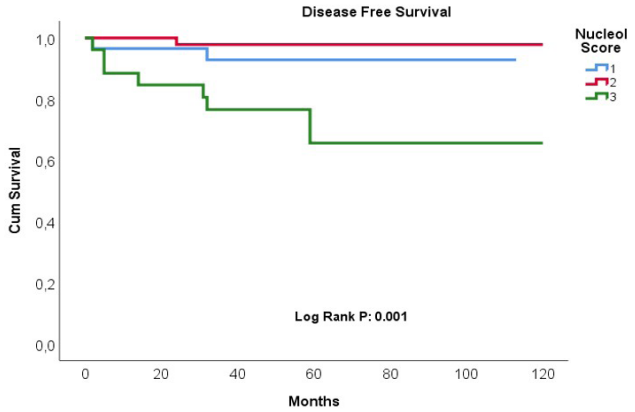

Figure 3: The relationship of nucleolus scores with disease free survival by Kaplan Meier analysis

Table 3. Disease free survival

	p	HR (95% CI)	p	HR (95% CI)
Nucleolus Score	0.003	8.045 (2.064-31.355)	0.003	8.045 (2.064-31.355)
Tumor size	0.216	2.35 (0.607-9.104)		
FIGO grade	0.016	6.668 (1.416-31.407)		
Nuclear grade	0.249	32.865 (0.087-12467.469)		
Pathologic stage	0.080	3.038 (0.877-10.525)		
Myometrial invasion ratio	0.023	4.221 (1.22-14.601)		
Mucin	0.544	0.044 (0-1088.848)		
Lymphovascular invasion	0.032	3.887 (1.124-13.436)		
Necrosis	0.910	1.094 (0.232-5.15)		
Squamous metaplasia	0.070	3.228 (0.91-11.449)		
Cervical invasion	0.318	2.207 (0.467-10.443)		

Nucleolus score, FIGO Grade, lymphovascular invasion, pathologic stage were selected as covariate

Table 4. Overall survival

	p	HR (95% CI)	p	HR (95% CI)
Nucleolus Score				
Tumor size	0.641	1.353 (0.38-4.813)		
FIGO grade	0.010	15.432 (1.951-122.087)	0.024	11.432 (1.380-94.724)
Nuclear grade	0.241	33.956 (0.094-12237.687)		
Pathologic stage	0.358	1.812 (0.51-6.439)		
Myometrial invasion ratio	0.138	2.621 (0.735-9.352)		
Mucin	0.523	0.043 (0-670.927)		
Lymphovascular invasion	0.034	3.829 (1.108-13.235)		
Necrosis	0.479	0.474 (0.06-3.747)		
Squamous metaplasia	0.931	0.934 (0.198-4.416)		
Cervical invasion	0.108	3.054 (0.782-11.921)		
Distant metastasis	0.002	7.362 (2.07-26.188)	0.053	3.593 (0.982-13.149)

Nucleolus score, FIGO Grade, lymphovascular invasion, distant metastasis was selected as covariate

DISCUSSION

The FIGO ternary grading system has been widely used in ECs all over the world (6). While the FIGO grading has significant criteria rely on tumor architecture, it does not have rigorous criteria for nuclear atypia (4). This grading, which is directly related to the prognosis of the patients, also plays a critical role in additional lymph node dissection during the surgical procedure. The lack of distinct criteria for nuclear grading in endometrial curettage specimens is confusing for pathologists, and most tumors are graded as nuclear Grade 2 (4). There has not been enough data in the literature regarding the prognosis of cases evaluated as FIGO Grade 2 (7). Our original proposal was to evaluate the nucleolus more objectively as a part of nuclear atypia, and add it to the FIGO grading system. Although, there are different methods in the literature for nucleolus evaluation, our idea was to evaluate the nucleolus with the Modified Helpap method, since it is a practical method and can be used for grading in endometrial curettages.

In our study, we found that nucleolus prominence was associated with FIGO grade, nuclear grade, myometrial invasion, lymphovascular invasion, OS, and DFS. Adding nucleolus score to FIGO grading, which is directly related to the prognosis, shows that pathologists can grade more easily, practically, and objectively.

Although the importance of the nucleolus in cancer cells has been konwn , its importance has begun to be realized again. In the literature, prominent nucleolus in cancer cells have been associated with poor prognosis (16,17). For example, the nucleolus, which can be evaluated morphologically, predict metastasis and recurrence in prostate cancer. In addition, prominent nucleolus are associated with poor clinical outcomes in breast cancer in different studies (12,17).

Recently, there have been studies showing that nucleolus can also be used as a target in cancer therapy (18-20). Helpap used nucleolus grading first in renal cell carcinoma and subsequently in prostate cancer (13,21). He showed that nucleolus status can be used in grading and predicting prognosis in renal cell carcinomas (13). Elshrawy, KA et al. evaluated nucleolus in invasive breast carcinomas using the Modified Helpap method, and found nucleolar prominence was associated with prognosis (12). Similarly, in this study, we evaluated the nucleolus using the Modified Helpap method in grading of ECs.

Qianhan Lin et al. showed that heterogeneous nucleolin staining is a potential prognostic marker in endometrial cancers. Besides, in the same study, they argued that the nucleolin immunohistochemistry staining, which was defined for the content of the nucleus, would be used as a therapeutic target (2).

The importance of nucleol in FIGO grading was emphasised in different studies For example, Zaino et al. and Takeshima et al. reported that FIGO grade should be increased in tumors with high nuclear grade (8,22). Later, in the study of Ayhan et al., triple grading was used for nuclear grading, and the architectural grade was increased by one in tumors with high nuclear grade (23). Although grading in this way was important in terms of prognosis, no quantitative value was presented for nuclear grading. In our study, we tried to provide quantitative criteria in grading of ECsby using the nucleolus Modified Helpap method, which is an important indicator of nuclear atypia.

To the best of our knowledge, our study is the first morphological study showing that the nucleolus may be useful in grading of ECs grading. We believe that nucleolus prominence can be evaluated more objectively than nuclear atypia. Thus, tumor grading can be done more objectively.

In the surgical treatment of ECs, it is still controversial whether lymph node dissection should be added to surgery (24,25). Although it is routinely performed in some centers, it has been shown hat performing lymphadenectomy in low-risk ECs does not contribute to survival (26-28). In addition, routine lymphadenectomy has several complication after surgery (26,29). By adding nucleolus score to FIGO grading, the surgical procedure may be directed more accurately. There may be no need to add unnecessary lymph node dissection to the surgical procedure and the morbidity of the complications may decrease. In our study, the nucleolus score increased as lymphovascular invasion increased. However,no relationship was found between nucleolus score and lymph node metastasis. This may be due to the small number of cases. Nucleolus prominence in curettage materials, the only material belonging to pre-surgery patients, can be used as a parameter before adding lymph node dissection to surgical treatment.

In addition, there are many controversial aspects of treatment, including patient selection for adjuvant radiation and chemotherapy. In our study, we observed that more patients receive adjuvant treatment in cases with high nucleolus score. Rebecca A. Brooks et al. argue that there have been recent significant advances in understanding EC biology (30). In their research, they stated that pembrolizumab, one of the current recommendations in endometrial cancer, can be used in immunotherapy with FDA approval in microsatellite unstable and metastatic cases (30). Qianhan Lin et al. suggested the nucleolin immunohistochemistry stain showing nuclear properties for target therapy in EC (2). We think that the nucleolus grading, which is an important component of the nucleus, can also be used as a parameter in choice of treatment method.

Digital pathology is gaining importance day by day. However, this method is not cost effective. In the current study, the nucleolus was evaluated microscopically, not digitally, Therefore, it is practical and low-cost for pathologists. Nucleolus evaluation in larger patient groups in different studies can also be done in combination with digital measurements or histochemical stains.

In our pioneering study, evaluation of the nucleolus prominence in curettage specimens morphologically; a high nucleolus score significantly predicted poor survival. Nucleolus scoring using the Modified Helpap method can be used in FIGO grading alongside architectural and nuclear grades. The current study is a pioneering study in terms of both prognosis and treatment approach in ECs patients. Integrating the nucleolus grading system into FIGO grading can make a significant difference in the clinical approach and prognosis of the cases.

CONCLUSION

Nucleolus score was associated with better prognosis in ECs. It can be evaluated objectively with no need of requiring extra cost and time. Thus, adding nucleolus score in FIGO grading can provide more reliable prediction in prognosis and choice of the treatment method.

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Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *Ethics committee confirmation for our study was obtained from the ethics committee of Recep Tayyip Erdoğan University Faculty of Medicine, non-interventional clinical research (E-40465587-050.01.04-573).*

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