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Original Article

Improved risk assessment by integrating up-regulated GCN5 with clinicopathological features in low-risk endometrial cancer

Qiulin Ge[1], Zhihong Ai[1], Shanyun Wen[2], Li Ma[1], Miao Dai[1], Fei Liu[1], Xiaolu Zhu[1], Wenjing Ding[3], Bingqing Yang[1], Yincheng Teng[1]

[1]Department of Obstetrics and Gynecology, Affiliated Sixth People's Hospital, Shanghai Jiao Tong University, Shanghai, PR China; [2]Department of Obstetrics and Gynecology, Shanghai Songjiang District Central Hospital, Shanghai Jiao Tong University, Shanghai, PR China; [3]Department of Gynecology, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, PR China

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Abstract: Objective: To investigate the clinicopathological relevance of GCN5 protein expression in endometrial cancer (EC). Methods: Immunohistochemical (IHC) analysis by Mann-Whitney *U* test was undertaken on 11 formalin-fixed paraffin-embedded (FFPE) non-tumorous (NT) endometrium tissues and 107 FFPE EC samples collected between 2009 and 2013. The correlations between GCN5 and clinicopathological parameters in EC were analyzed by Fisher's exact test or Chi-square test. Mann-Whitney *U* test was exployed for ranked data and Kaplan-Meier curve with Log-rank test for analyzing the asscociations between OS and categorical variables. Results: The GCN5 IHC expression was significantly up-regulated in EC, where 91% (95/104) and 9% (9/104) of patients with clinical data displayed high GCN5 expression and low GCN5 expression, respectively. Histological staining of GCN5 was stronger in endometrioid adenocarcinoma (EEC) than in non-endometrioid EC (NEEC). Moreover, GCN5 expression was inversely related with lymphatic-metastasis. Patients with high-level GCN5, non-lympho-vascular space invasion (N-LVSI) and early-stage lived significantly longer than those with the opposites; within subsets of grade 1, stage I and non-vascular invasion, high-level GCN5 confers better overall survival. Conclusions: High GCN5 IHC expression is positively associated with endometrioid adenocarcinoma, non-lymphatic metastasis and excellent clinical outcome in EC. Integrating clinicopathological factors with GCN5 results in improved risk assessment in low-risk EC patients.

Keywords: GCN5, histopathological factors, endometrial cancer, clinicopathologic relevance, risk assessment

Introduction

Endometrial cancer (EC) is the most frequent female malignancy in the Western world [1-3]. In spite of less frequency in China, the incidence tends to be increasing recently [4]. The traditional risk assessments of EC based on clinicopathological features such as histological subtype, tumor stage, grade and lympho-vascular space invasion (LVSI) are usually limited for individual treatment. Thus, one hypothesis was made by us that integrating clinicopathological factors with molecular risk elements would contribute more accurate evidence for systemic risk assessments in EC patients.

The imbalance of activities between histone acetylation and deacetylation can lead to cancer development, such as hepatocellular carcinoma, breast cancer and lung cancer [5-7]. Moreover, maintenance in the crucial balance is both dependent on histone deacetylases (HDACs) and histone lysine acetyltransferases (KATs). General control nonderepressible 5 (GCN5), one kind of lysine acetyltransferase, has been reported to be involved in many cellular processes including cell proliferation, DNA damage repair and cell cycle in regards to cancer development [8, 9]. Even in some circumstances of cancer, GCN5 can be a valuable biomarker [9, 10]. However, the particular role of GCN5 in endometrial cancer remains elusive, which therefore become one reason for our current investigation.

To explore the relation of GCN5 with EC, in the current analysis, we evaluated the expression

of GCN5 protein in human EC tissues relative to normal endometrium samples by immunohistochemistry based tissue microarrays (IHC-TMA), and found that GCN5 was strikingly up-regulated in endometrial cancer. Furthermore, by analyzing the correlation between GCN5 protein level and clinicopathological factors of EC patients, we established that GCN5 combined with other clinicopathological features are more constructive to the development of personal management of EC patients (ECs). In particular, Up-regulation of GCN5 positively correlates with clinicopathological features of patients with low-risk endometrial cancer, where the incorporation of GCN5 expression and histopathological factors would reduce over- and under-treatment. Further investigations are needed to illustrate the particular role of GCN5 in EC to provide valuable pathogenesis information for the females, thus advancing the development of molecular subtype-specific study.

Material and methods

Samples and clinical database

This retrospective study included samples of 11 formalin-fixed paraffin-embedded (FFPE) non-tumor (NT) normal endometrium and 107 FFPE endometrial cancer (EC) obtained between May 2009 and March 2013 from Sixth People's Hospital affiliated to Shanghai Jiao Tong University, China, the Changning District Central Hospital of Shanghai, China and the Huai'an First People's Hospital, Jiangsu, China. Those patients who had suffered from other solid tumors, treated with radical surgery, chemotherapy, radiotherapy, or other anticancer managements preoperatively were excluded. Official approval and informed consent were from local ethics authority for sample utilization. For high-qualified data, all FFPE tissues containing more than 80% cancer cells were ensured and evaluated independently by at least two gynaeco-pathologists, blinded for patient clinico-pathologic characteristics. Time-to-event overall survival (OS) was defined as the time range from surgery to endometrial carcinoma death or last follow-up.

Tissue microarray construction

Tissue microarray was constructed by Shanghai Zuoli Biotechnology Co., Ltd (Shanghai, China). Tissue paraffin pieces of EC samples were stained by pathologists with hematoxylin-eosin to make certain diagnoses and marked at fixed positions displaying the most typical histological parameters microscopically. 1.1 mm-diameter cores from each donor piece were diverted into micro-arrayer recipient blocks, cut into sections of four-micron-thick and mounted on glass slides for ultraviolet cross linkage by adhesive tape transfer system.

Immunohistochemistry

The slides from FFPE samples were dewaxxed in dimethylbenzene for 15 min twice and rehydrated by a series of graded alcohol. Antigen retrieval was performed by toasting the slides in microwave oven with different tempreature interruptions (medium fire, cease fire and middle-low fire, for 8 min, respectively). Protein detection was initially accomplished by incubation with primary GCN5 antibody (#ab87966, 1:200, Abcam, Cambrige, UK) overnight at 4°C before subjected to HRP-conjugated anti-mouse secondary antibody incubation for 1 hour at room temperature. The slides were developed under DAB substrate soakage before counterstained by haematine. Finally, ranked analysis of GCN5 (range from 0 to 3) was performed by combination of the proportionality and intensity of positive staining cells. Score 1 was defined as weak-positive (low GCN5 expression), while scores of 2 and 3 were strongly positive (high GCN5 expression). All the rating were completed independently under the supervision of at least two experienced pathologists blinded to clinicopathologic data.

Statistical analysis

Correlations between clinicopathological factors and GCN5 protein alterations were analyzed by Fisher's exact test or Chi-square statistics in case of enumeration data. Mann-Whitney *U* test was exploited for ranked data. Especially, we used Kaplan-Meier curve with Log-rank test to analyze the associations between OS and categorical variables. Statistical analyses were completed by SPSS 13.0 software (Chicago, IL, USA) and GraphPad Prism 5.0 (La Jolla, CA, USA). All demonstrated *P*-values were built on two-tailed tests with *P*-values≤0.05 believed statistically significant. Throughout the test: *P≤0.05, **P≤0.01, ***P≤0.001.

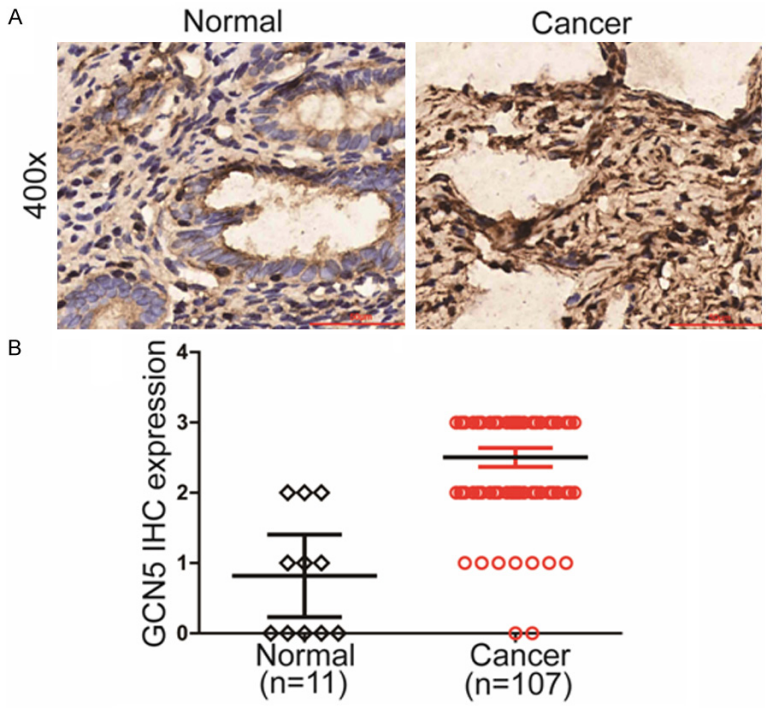

Figure 1. GCN5 protein displayed an upregulation in human endometrial cancer tissues. (A) Immunohistochemical analysis of GCN5 in EC (n=107) versus normal controls (n=11). Original magnification: ×400; scale bars: 50 μm. (B) Quantification of GCN5 IHC as indicated in (A), showing significant elevation of GCN5 protein in EC. Mann-Whitney *U* test, ***P<0.001.

Results

Patient demographic characteristics

In total, 107 cases of EC samples and 11 cases of normal endometrium specimen were available for immunohistochemical analyses of GCN5 protein (**Figure 1**). Of 107 ECs, survival material and demographic characteristics were medically recorded and analyzed for 104 cases. The clinico-pathological characteristics of the reviewed 104 EC patients were summarized in **Table 1**. All patients were staged on the basis of morphological features in accordance with the criterion of the 2009 International Federation of Gynecology and Obstetrics (FIGO) [11]. The main age group is more than 45-year-old. The evaluation of reproduction status revealed that nearly all patients had history of pregnancy (99, 95.2%). Most tumor histology subtype was found to be frequent endometrioid adenocarcinoma (96, 92.3%). Moreover, overwhelming proportion of cases existed in early-stage (stage I, 92.3%; stage II, 4.8%) and low-grade (grade 1, 61.5%; grade 2, 26%), where the proportion of those devoid of vascular invasion and lymphatic metastasis is 92.3% and 97.1%, respectively.

GCN5 protein level presents an up-regulation in EC tissues and inversely correlates with histopathological subtype and lymphatic metastasis

GCN5 expression in 107 FFPE endometrial cancer and 11 FFPE non-tumor normal endometrium tissues was investigated by IHC. IHC results showed that GCN5 expression was dramatically elevated in endometrial cancer samples in comparison with non-tumor normal controls, as indicated in **Figure 1B** (P<0.001), hinting a potential participation of GCN5 in the cancerogenesis of endometrial cancer. Specially, the representative expression profile of series of graded GCN5 protein levels in EC samples were detailly determined in **Figure 2**. In addition, high GCN5 IHC expression considered as scores of 2 and 3 manifested a majority proportion of 91.4%, whereas low GCN5 IHC expression classified as scores of 0 and 1 only presented a minority percentage of 8.6 (**Table 2**).

The relations between GCN5 expression level with available demographic characteristics and histopathologic factors were also examined by Fisher's exact test or χ^2 test. Statistical calculation revealed that the expression level of GCN5 protein appeared to be higher in subgroups with endometrioid adenocarcinoma and without lymphatic metastasis than in the opposites (P=0.05 and P=0.01, respectively), while no variances of GCN5 expression were observed among other parameters (**Table 3**). Noteworthy, however, the mean GCN5 results greatly tended to be higher in populations with low-grade (grade 1-2) compared with those with high-grade (grade 3) (P=0.06).

To be brief, our above foundations certified that the protein level of GCN5 is up-regulated in human endometrial cancer tissues and inverse-

Table 1. Clinico-pathological parameters of endometrial cancer patients (n=104)

Clinicopathological parameters	Number	%
Age (years)		
<45 y	3	2.9
≥45 y	101	97.1
Pregnancy		
No	5	4.8
Yes	99	95.2
Histopathological type		
Adenocarcinoma (type I)	96	92.3
Squamous, papillary serous, and clear cell cancers, etc. (type II)	8	7.7
Stage		
I	96	92.3
II	5	4.8
III and IV	3	2.9
Grade		
G1	64	61.5
G2	27	26
G3	13	12.5
Vascular invasion		
No	96	92.3
Yes	8	7.7
Lymphatic metastasis		
No	101	97.1
Yes	3	2.8

ly associated with pathological subtype and lymphatic metastasis. In view of the established fact that the histological manifestation of type I EC is predominantly endometrioid adenocarcinoma which usually represents a favorable clinical outcome [12, 13], it is speculated that EC patients with high GCN5 expression probably showed superior clinical ends against those with low GCN5 results, prompting us to perform an integrated risk analysis combining clinicopathological factors and GCN5 expression level.

Incorporation of GCN5 protein alterations and clinicopathological factors results in improved risk assessments in low-risk ECs

A univariate analysis employing Kaplan-Meier method generally displayed that the EC risk levels such as FIGO stage, lymphatic metastasis and vascular invasion inversely correlated with the OS, although histological subtype and tumor grade conferred no effects on prognosis (**Figure 3A-E**). Based on the prognostic significance of categorized GCN5 protein level in the whole EC patients (**Figure 3F**, P=0.01), integrated analysis of classified clinicopathological factors (tumor grade, stage, histological subtype and LVSI) with grouped GCN5 was also evaluated by univariate survival model using method of Kaplan-Meier with log-rank test. As a consequence, the OS of GCN5 high-expression group was strikingly better than that of GCN5 low-expression group for all 104 samples defined as low-grade (grade 1), early-stage (stage I) and non-vascular-invasion (**Figure 4B**, **4D** and **4F**). In case of subsets with endometrioid adenocarcinoma and without lymph node metastasis, notably, high GCN5 results also seemed to reflect better OS than low GCN5 expression (P=0.06, **Figure 4A** and **4E**), consistent with the established notion that endometrioid histology and non-LVSI showed beneficial effects on OS [14, 15]. To sum up, we conclude that integrating GCN5 expression level with clinicopathological factors in a risk assessment profile results in more accurate stratification of low-risk EC patients.

Discussion

Endometrial cancer (EC) is the most prevalent gynaecological carcinoma in developed countries. Over half of females with EC present with low-grade, early-stage manifestations, and respond well to surgery treatment [2]. Many clinicopathological features such as histological subtype, tumor grade, stage, and LVSI are usually used for directing surgery and adjuvant therapy recommendations in EC patients [16, 17]. However, these parameters are of limited reliability and sometimes cause considerable

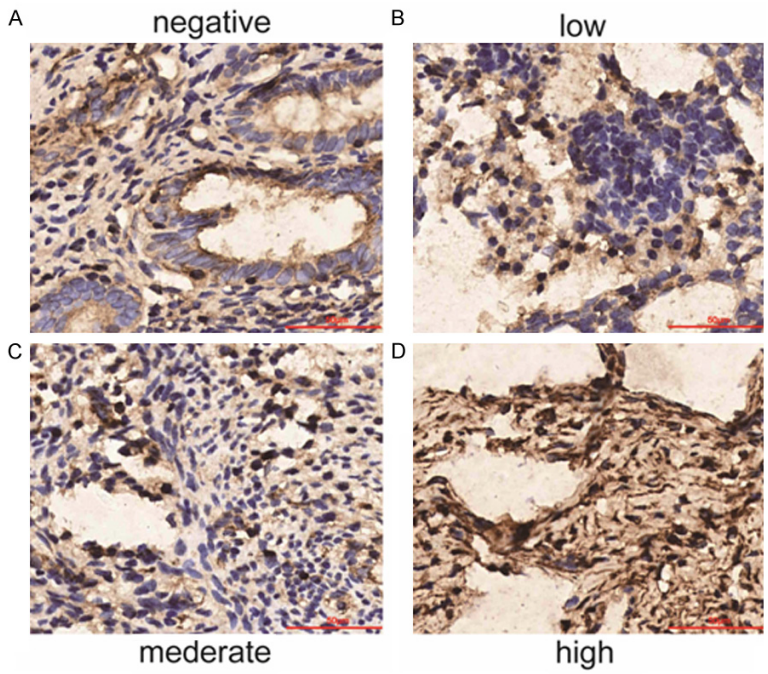

Figure 2. Representative images of GCN5 in endometrial cancer samples are displayed as negative (A), low (B), moderate (C) and high (D), respectively. Original magnification: ×400; scale bars: 50 μm.

Table 2. IHC scores of GCN5 in 104 cases of EC

Score	GCN5	%
0	2	1.9
1	7	6.7
2	33	3.17
3	62	88.23
Total	104	100

over- and under-treatment. Therefore, it is hypothesized by us that integration of molecular biomarkers and clinicopathological factors could more accurately predict individual tumor behavior, thus contributing to the improvement in personal management. It has been reported that lysine acetyltransferases exert complicated roles in cancer development [18-21]. In particular, increasing evidence has evinced that GCN5 is implicated in diverse malignant processes such as cell cycle and apoptosis, and even has some certain prognostic value [5, 7, 9, 22, 23]. Nevertheless, the biological function of GCN5 and its prognostification significance in EC have been unexplored.

In the present study, we revealed that GCN5 protein presented an elevated expression in endometrial cancer tissues in comparison with non-tumor normal endometrium samples, indicating that GCN5 may account for EC development. We also explored the correlation between GCN5 and clinicopathological characteristics of EC patients. As a result, we found that GCN5 expression was significantly higher in patients with endometrioid adenocarcinoma and without lymphatic metastasis than in those with the opposites. Moreover, there was a distinct trend towards enhanced GCN5 protein within the low-grade EC samples. Therefore, we conclude that high-level GCN5 dramatically make for low-risk EC patients presenting with EEC subtype, low-grade and non-lymphatic metastasis, implying that GCN5 mainly operate an oncogenic role at the onset stage of EC. This conclusion can be supported by the following observations. It has been proposed that the mRNA level of GCN5 is obviously reduced in the secretory phase of normal endometrium metabolism when compared with that in proliferative phase. Furthermore, this is corroborated by the foundation that GCN5 expression is enhanced when endometrial epithelial cells was supplemented with estradiol [24]. It has been established that estradiol mainly facilitates the proliferation of endometrium that is one essential stage of initial neoplasia of low-risk EC [25]. In addition, it is demonstrated that GCN5 expression is up-regulated in varieties of human cancers including breast cancer, colon cancer and lung cancer [9, 26]. Moreover, reconstruction of GCN5 can rescue the GCN5-deletion induced growth inhibition of human colon carcinoma cell lines. And multiple histone acetyltransferase inhibitors, such as CBP and p300, have been shown to bring about growth inhibition and apoptosis induction in many types of human malignancies in vitro as well as in vivo [27, 28]. Taken together, this study is the first exploration of GCN5 expression in human primary endometrial cancer, indicating that the potential GCN5 oncogene is a possible thera-

Table 3. The clinico-pathological parameters in relative response to the GCN5 expression profile of endometrial cancer patients

Clinicopathological parameters	GCN5				*P* value
	Low (n)	%	High (n)	%	
Age (years)					0.91
<45 y	0	0	3	2.9	
≥45 y	9	8.7	92	88.5	
Pregnancy					0.45
No	0	0	5	4.8	
Yes	9	8.7	90	86.5	
Histopathological type					0.05*
Adenocarcinoma (type I)	9	8.7	87	83.7	
Squamous, papillary serous, and clear cell cancers, etc. (type II)	0	0	8	7.7	
Stage					0.30
I	7	6.7	89	85.6	
II	2	1.9	3	2.9	
III and IV	0	0	3	2.9	
Grade					0.06
G1	5	4.8	59	56.7	
G2	1	0.96	26	25	
G3	3	2.9	10	9.6	
Vascular invasion					0.85
No	9	8.7	87	83.7	
Yes	0	0	8	7.7	
Lymphatic metastasis					0.01**
No	8	7.7	93	89.4	
Yes	1	0.96	2	1.92	

Fisher's exact test or Chi-square statistics was performed; P≤0.05 are believed statistically significant: *P≤0.05, **P≤0.01.

peutic target for human endometrial cancer early intervention.

It has been displayed that integration of established clinicopathological factors with prognostic molecular alterations results in improved risk assessment. Molecular analysis methods for risk assessment have been clinically applicable and proved feasible in most of low-risk EC patients [29]. Thus, we also analyzed the correlation between GCN5 protein level and OS on the basis of clinicopathological factors. As a result, the OS of EC patients was more favorable within the low-risk populations that present with early-stage and non-LVSI. Furthermore, patients with higher GCN5 expression had significantly better clinical outcome, especially exemplified by the subgroups within grade 1, stage I and non-vascular invasion. Besides, high-level GCN5 greatly tended to confer preferable prognostic effects on those patients with endometrioid adenocarcinoma and non-lymphatic metastasis. Paradoxically, it seemed that our research results contradicted with others [26, 30], indicating the different roles of GCN5 in EC initiation and progression. Presumably, the discrepancy of the prognostic impact of GCN5 between this study and others, by human gastrointestinal tract neoplasms as an example, could be attributed to the different cancer arising sites, i.e. endometrium versus stomach and colon. Thereupon, the influence of GCN5 expressions on dissimilar clinical prognosis are tissue-and-context dependent. However, our integrated analysis results strongly showed that incorporation of GCN5 and clinicopathological characteristics more accurately predicts individual behaviors of ECs with low-grade, early-stage and EEC subtype.

Aside from GCN5 discussed here, the combined approach analysis performed by Smit, et al. reported that an improved risk assessment can be resulted in, where histopathological fac-

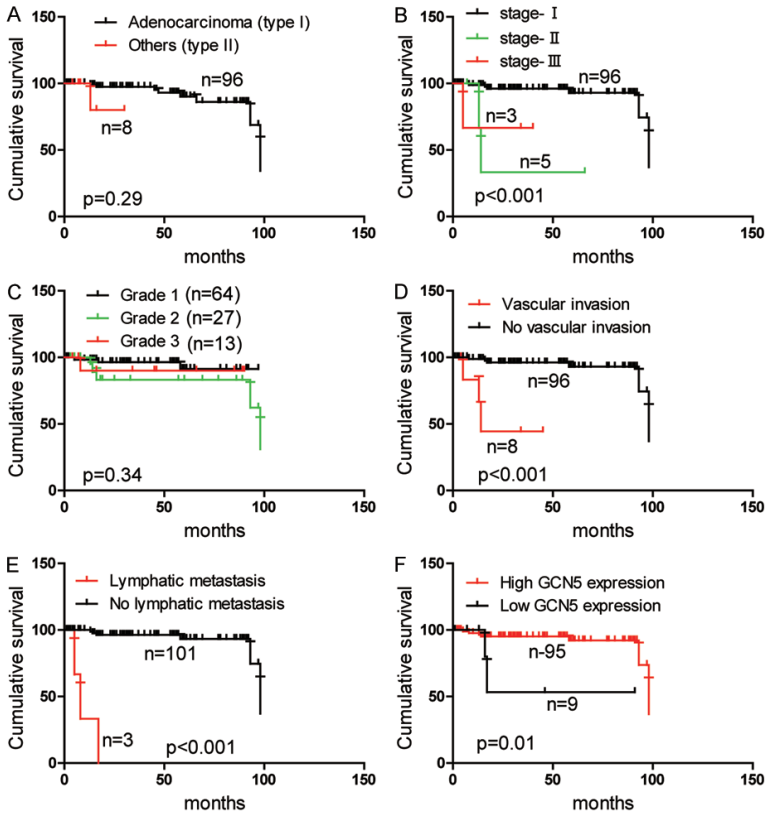

Figure 3. Univariate analyses of variables in relation with overall survival (OS) in EC patients by Kaplan-Meier method and log-rank test. A. Histological type; B. FIGO stage; C. Tumor grade; D. Vascular invasion; E. Lymphatic metastasis; F. Grouped GCN5 expression. P≤0.05 are believed statistically significant.

tors were united with CTNNB1, POLE, L1CAM and MSI in early-stage EC patients [29]. Therefore, our study offers some enlightenment that the combination of GCN5 expression with other molecules may display more accurate risk assessment for low-risk EC. Further exploration based on the combination and association of these different molecular factors can potently help explain multiple profound studies focusing on more indolent and less aggressive EC.

However, this study has some certain limitations in spite of the straightforward analysis. In view of the retrospective analysis, the prospective decision-making process that fits in terminally unhealthy patients may not be adequately captured [31]. Moreover, we failed to cover multi-racial herds because of the circumscribed embrace of ethnic Han Chinese, who are genetically dissimilar to other cultural groups. Multivariate analysis and AUC model could not be carried out due to the lack of the abundance of valuable records. In addition, we can not rule out the probability that other clinical related alterations may have been left out. Finally, automatically standardized staining procedures are the preferable method in the light of non-automatic immunohistochemical protocols used in our study. Inclusion of extensive prospective exploration and a greater number of investigated subjects should be administrated to optimize the research results and figure out issues that were untouched in this study. Obviously, quantitative data of GCN5 expression rather than only ranked information in the original source would undoubtedly advance our work development.

Despite these limitations, our study does provide that integration GCN5 protein level with histopathological factors in low-risk EC results in enhanced risk assessment profile with possible clinical utility. Therefore, our findings provide valuable guides for gynecologic oncologists with individual management so as to make a reduction on over- and under-treatment.

Conclusion

Some clinical studies have contributed evidence that EC patients with low-intermediate risk factors can be free of adjuvant radiotherapy. However, the recommendations of adjuvant therapy are often based on the risk assessment by clinicopathological factors, where substantial over- and under-treatment remains. Our findings reported that the combination of GCN5 protein alterations with established clinicopathological elements results in improved risk assessment for low-risk EC patients. Assessment of this integrated risk schema should be further evaluated in new and broader

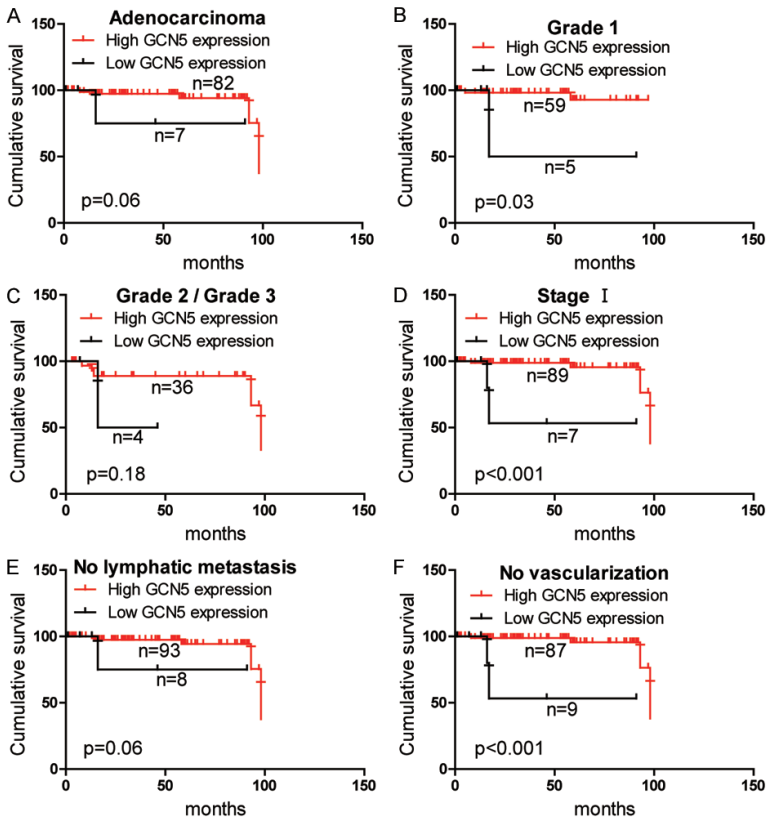

Figure 4. Integrated risk assessment by combination of GCN5 protein level and histopathological factors in ECs. (A) Comparisons of OS between low-level GCN5 expression and high-level GCN5 expression subgroups with adenocarcinoma. (B and C) Comparisons of OS between GCN5 low expression and GCN5 high expression groups in cohorts of grade 1 (B) and grade 2, 3 (C), respectively. (D-F) Comparisons of OS between GCN5 low expression and GCN5 high expression groups within FIGO stage I (D), non-lymphatic metastasis (E) and non-vascular invasion (F), separately. Statistical analyses: Kaplan-Meier method with log-rank test; P≤0.05 are believed statistically significant.

prospective researches to reduce the chances of over- and under-treatment of patients with low-risk.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yincheng Teng, Department of Obstetrics and Gynecology, The Sixth People's Hospital, Shanghai Jiao Tong University, 600 Yishan Road, Shanghai 200233, PR China. Fax: 8621-64701361; E-mail: teng_yc@126.com

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