GREB1 Protein Expression is Associated with Low Recurrence Risk on Stage I Endometrioid Endometrial Carcinoma

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INTRODUCTION

Endometriod endometrial carcinoma (EEC) is usually diagnosed in early stages and has a favorable prognosis. However, some cases may present unexpected relapse with poor responsiveness to treatment. A previous DNA microarray assessment was performed with stage I EEC tumors, comparing gene expression profile of recurrent and non-recurrent cases. GREB1 (Growth Regulation by Estrogen in Breast Cancer 1) overexpression showed significant association with relapse. This gene is known to mediate proliferation in breast and prostate cancer hormone-dependent lines. Its overexpression is associated with positivity of ER-alpha. Therefore, the purpose of this study was to evaluate GREB1 protein expression on stage I EEC regarding recurrence status.

OBJECTIVE

Assessment of GREB1 protein expression on stage I EEC, comparing cases with and without relapse, by IHC.

METHODS

Stage I EEC → **FFPE Stage I EEC Samples** → **Protein Expression -IHC**


Clinicopathological features of 107 stage I EEC cases were collected, from which 35 presented recurrence and 72 had no relapse. GREB1 protein expression was assessed by immunohistochemistry (IHC) with the primary rabbit polyclonal antibody against GREB1 (N-13) (Santa Cruz Biotechnology, Inc®). The staining score evaluation was performed by two independent pathologists. Protein expression was considered positive when nuclear staining was greater than 10% and its results were compared to relapse status and other clinicopathological data. The chance of recurrence was calculated by Odds Ratio (OR).

RESULTS

IHC revealed that GREB1 expression was found positive on 54 (50.5%) of 107 cases. Regarding non-recurrence group (n=72), it was positive in 42 (58.3%) cases; in 35 cases that presented relapse, it was positive in 12 (34.3%) (p=0.0196) (table 1).

Table 1: GREB1 protein expression detected by IHC according to nuclear staining. Recurrence cases (n=35) and non-recurrence cases (n=72) of stage I EEC.

Antibody	Staining	Cases with Recurrence (%)	Cases without Recurrence (%)	p value
GREB1	Negative	23 (65.7)	30 (41.7)	0.0196
	Positive	12 (34.3)	42 (58.3)	
	Total	35	72	
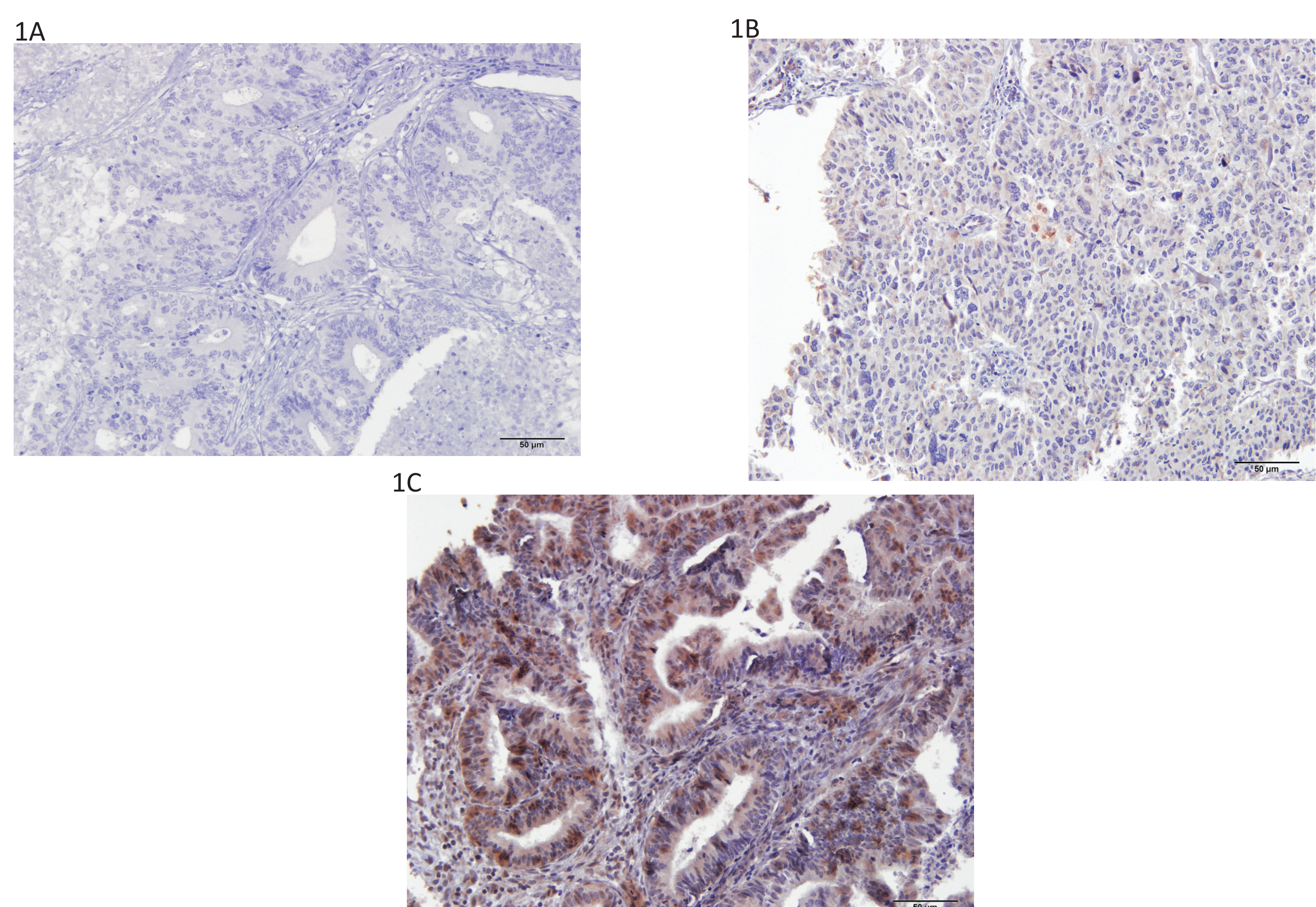
Figures 1A and 1B: negative GREB1 expression (none or less than 10% of nuclear staining); 1C: positive GREB1 expression (more than 10% of nuclear staining)

No variables showed a significant association with GREB1 positive expression. However, women with low grade tumors had a higher chance of 2.7-fold to present positive GREB1 expression (p = 0.044) (table 2).

Table 2: GREB1 protein expression of positive cases (n=54 – 49.1%) and negative cases (n=53 – 48.2%), detected by IHC, according to pathological characteristics of stage I EEC

| Variable	GREB1 Positive (%)	GREB1 Negative (%)	OR	CI 95%	(min/max)	p value
Myometrial Invasion						
< 50%	27 (50.0)	24 (45.3)	1.208	0.565	2.583	0.625
= 50%	27 (50.0)	29 (54.7)	Reference	-	-	
Total	54	53				
Lymphovascular Inv						
Yes	08 (14.8)	07 (14.3)	1.043	0.348	3.126	1.000
No	46 (85.2)	42 (85.7)	Reference	-	-	
Total	54	49				
Grade						
1 e 2	47 (87.0)	37 (71.2)	2.722	1.006	7.364	0.044
3	7 (13.0)	15 (28.8)	Reference	-	-	
Total	54	52				
Tumor size (cm)						
≤ 5,0	27 (55.1)	26 (54.2)	2.889	0.534	15.633	0.321
> 5,0	16 (32.7)	20 (41.7)	Reference	-	-	
Total	49	48				
Death						
Yes	11 (20.4)	14 (26.4)	0.713	0.289	1.754	0.460
No	43 (79.6)	39 (73.6)	Reference	-	-	
Total	54	53				

Crude and adjusted by age OR were calculated and both showed GREB1 positive expression conferred a protection association: positive GREB1 tumors provide 63% lower risk of relapse ocurrence comparing to negative tumors (OR = 0.37; p = 0.021) (table 3).

Table 3: OR for chance of recurrence according to GREB1 protein expression., detected by IHC. Recurrence cases (n=35) and non-recurrence cases (n=72) of stage I EEC.

GREB1	Recurrence Yes (%)	Recurrence No (%)	OR (crude) OR (CI 95%)	OR (crude) p value	OR (adjusted) * OR (CI 95%)	OR (adjusted) * p value
Positive	12 (34.3)	42 (58.3)	0.37 (0.16-0.87)	0.021	0.37 (0.16-0.86)	0.021
Negative	23 (65.7)	30 (41.7)	Reference		Reference	

*Adjusted by age; GREB1= Growth Regulation by Estrogen in Breast Cancer 1

Univariate analysis showed a significant association between positive protein expression of GREB1 and better prognosis in disease-free survival (p=0.023), but no association with overall survival rates (p=0.505) (figures 2A and 2B).
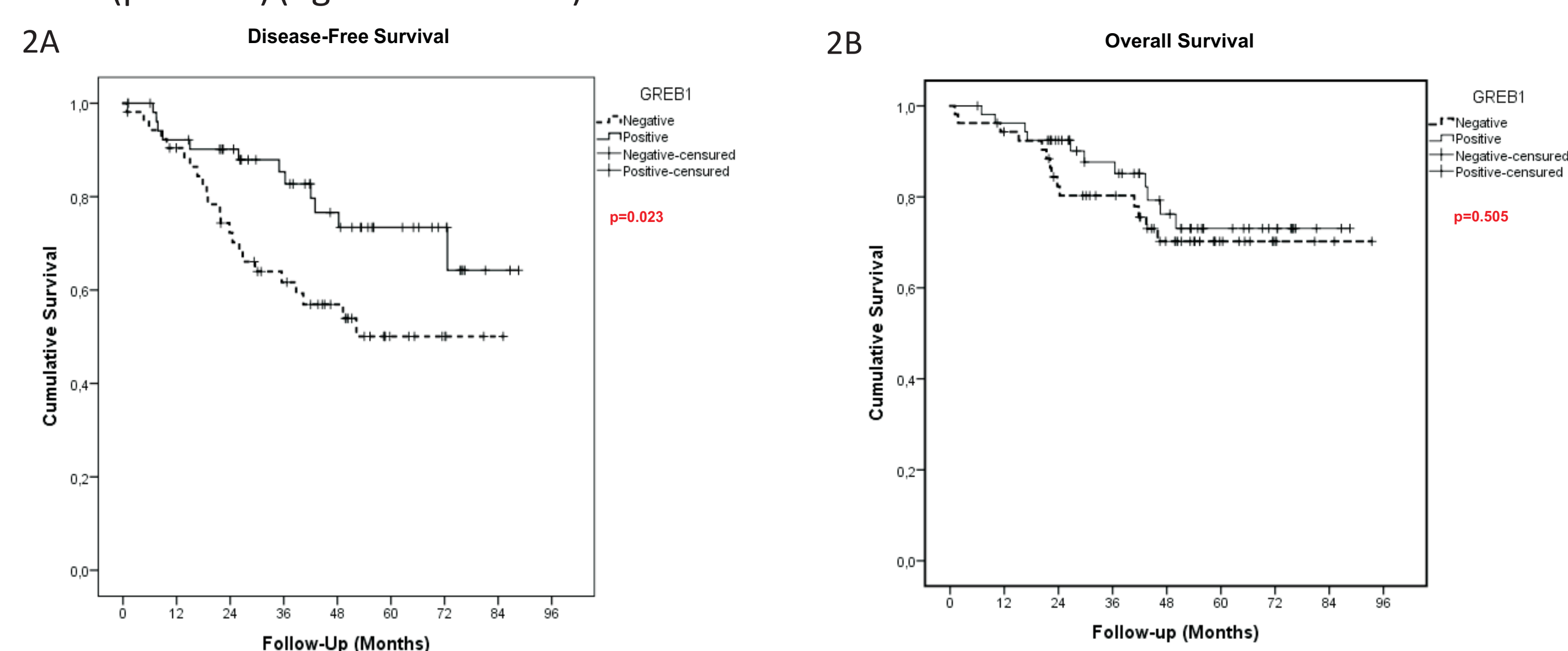
CONCLUSION

Positive GREB1 protein expression is associated with low recurrence risk on stage I EEC.

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