

# An exploratory analysis of $\gamma$ -synuclein expression in endometrioid endometrial cancer

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## ABSTRACT

**Objective:** This study aims to investigate the expression of  $\gamma$ -synuclein in endometrioid endometrial carcinoma and assess if the  $\gamma$ -synuclein expression correlates with the aggression of the tumour and its prognostic value in endometrioid endometrial carcinoma.

**Design:** This retrospective study evaluated (60) specimens of the primary untreated endometrioid endometrial carcinoma and (12) normal endometrium tissues, and the expression of  $\gamma$ -synuclein was checked by immunohistochemistry. The correlation between  $\gamma$ -synuclein expression and the clinicopathological features of patients with endometrioid endometrial carcinoma was analysed, and SPSS V.13.0 software was used for statistical analysis.

**Results:** The expression of  $\gamma$ -synuclein was positive in 48.3% (29/60) endometrioid endometrial carcinomas compared with the control group, and the difference was significant ( $p=0.001$ ). The expression level of  $\gamma$ -synuclein in endometrioid endometrial carcinoma was closely associated with FIGO (International Federation of Gynecology and Obstetrics) stages, the depth of myometrial invasion and lymph nodes metastases ( $p<0.05$ ), but not correlated with the histopathological grades, the patient's age and the expression of ER (estrogen receptor) and PR (progesterone receptor) ( $p>0.05$ ). In univariate and multivariate analyses, the  $\gamma$ -synuclein expression was significantly associated with a shorter overall survival (95% CI 1.429 to 101.892,  $p=0.020$ ).

**Conclusions:** This study suggests that the expression of  $\gamma$ -synuclein is expected to be a useful marker for endometrioid endometrial carcinoma invasion, metastasis and prognosis in endometrioid endometrial carcinoma.

## INTRODUCTION

Endometrial carcinoma is one of the most common gynaecological malignancies, and its incidence has recently increased, in the Western countries and in China.<sup>1</sup> Patients with advanced stage endometrial carcinoma frequently exhibits a poor prognosis, even after radical resection combined with radiotherapy or chemotherapy.<sup>2</sup> These poor

## ARTICLE SUMMARY

### Article focus

- The clinical and pathological significances of  $\gamma$ -synuclein expression in endometrioid endometrial carcinoma.
- The relationship between the  $\gamma$ -synuclein expression and the progression of the endometrioid endometrial carcinoma patients.
- The prognostic value of the  $\gamma$ -synuclein expression in the endometrioid endometrial carcinoma.

### Key messages

- The expression of  $\gamma$ -synuclein was positive in 48.3% endometrioid endometrial carcinoma; the expression of  $\gamma$ -synuclein was raised up with the stage of endometrioid endometrial carcinoma; the  $\gamma$ -synuclein expression could predict bad prognosis for the patients with endometrioid endometrial carcinoma.

### Strengths and limitations of this study

- The idea was creative and we have a complete and accurate data of the patients.
- This is a preliminary data study and a bigger number of samples are needed for our study.

outcomes are closely associated with the progression and metastasis of the disease. There are two different pathogenetic types of endometrial carcinoma. And the endometrioid adenocarcinoma, which is known as the first pathogenetic type of endometrial cancer, is the most common tumour among the endometrial carcinomas. Thus, a better understanding of the molecular mechanisms underlying the aggressive behaviour of endometrioid endometrial carcinoma is necessary to identify potential targets for efficient therapy.

$\gamma$ -Synuclein, initially identified as a breast cancer-specific gene 1 (BCSG1),<sup>3</sup> maps to chromosome region 10q23 and is composed of five exons and transcribed into a messenger RNA of about 1 kb, coding 127 amino acids.<sup>4</sup> It is a member of synucleins family of small proteins, which is consisting of three known members, synuclein

$\alpha$  (SNCA), synuclein  $\beta$  (SNCB) and synuclein  $\gamma$  (SNCG).<sup>5</sup> While synucleins are highly expressed in neuronal cells, emerging as the central player in the fundamental neural processes and are involved with neurodegenerative diseases.<sup>6</sup>  $\alpha$ -Synuclein and  $\beta$ -synuclein are the major components in the form of pathologically insoluble deposits characteristic of Alzheimer's disease and Parkinson's disease.<sup>7,8</sup> However,  $\gamma$ -synuclein is not clearly involved in neurodegenerative diseases. Instead, it has been implicated in human neoplastic diseases.<sup>3</sup> Several studies have demonstrated that  $\gamma$ -synuclein is abnormally expressed in a high percentage of advanced and metastatic breast and ovarian tumours but not in normal or benign breast tissues.<sup>9</sup> Furthermore,  $\gamma$ -synuclein expression was strongly correlated with disease progression, by that  $\gamma$ -synuclein can stimulate proliferation and induce invasion and metastasis of breast cancer cells.<sup>10</sup> And previous studies of  $\gamma$ -synuclein expression in breast tissues indicated that  $\gamma$ -synuclein increased resistance to certain chemotherapeutic or antimicrotubule agents.<sup>11,12</sup> Besides, it was found that  $\gamma$ -synuclein was also abnormally expressed in a high percentage of tumour tissues of other cancer types including liver, oesophagus, gastric, cervical, colon, prostate, lung, pancreatic ductal adenocarcinoma cancer patients and so on.<sup>13,14</sup> The clinical follow-up studies confirmed that patients with  $\gamma$ -synuclein expression predict poor clinical outcome in breast cancer<sup>9</sup> and in colon cancer.<sup>14</sup> Morgan *et al*<sup>15</sup> demonstrated that  $\gamma$ -synuclein could be a novel biomarker as a prognostic tool and a therapeutic target in uterine papillary serous carcinoma. And Mhaweche-Fauceglia<sup>16</sup> considered that SNCG protein expression is associated with poor outcome in endometrial adenocarcinoma. However, Zhou *et al*<sup>17</sup> had an opposite conclusion in oesophagus cancer, in which  $\gamma$ -synuclein might play a role as a negative regulator in the development of human oesophagus cancer. Therefore, further study in cancer tissues is needed to understand the roles of  $\gamma$ -synuclein in the development of other human neoplastic diseases.

In this study, we examined the expression of  $\gamma$ -synuclein in the 60 specimens of the endometrial carcinoma and 12 normal endometrium. The histological subtype of the endometrial cancer was the endometrioid adenocarcinoma. To better understand the clinical features relevant with the expression of  $\gamma$ -synuclein, the relationship between the expression of  $\gamma$ -synuclein, ER, PR and all clinicopathological features of the patients were explored and analysed.

## MATERIALS AND METHODS

### Clinical specimen

This study was reviewed and approved by The First Affiliated Hospital of Guangxi Medical University. The medical records of 60 endometrial carcinomas and 12 normal endometrium in the First Affiliated Hospital of Guangxi Medical University from 2004 to 2009 were reviewed to have the information of clinical data and detailed follow-up results. Paraffin blocks of 60 tumour

tissues and 12 normal endometrium were obtained from the archives of the Pathology Department. The histological subtype of all the tumour tissues was endometrioid adenocarcinoma. The pathological review confirmed the diagnosis. Clinical stages were diagnosed according to International Federation of the Gynecology and Obstetrics stage system of 1988. None of the patients had received any therapy before surgery. All the primary tumours were treated by comprehensive staging surgery and with specific adjuvant treatments if needed based on FIGO 2003 and NCCN2006.

Among 60 endometrioid endometrial cancer patients, 26 (43.3%) patients were in stage I, 10 (16.7%) patients were in stage II, 23 (38.3%) patients were in stage III and 1 (1.7%) was in stage IV. Patients' age ranged from 30 to 72 years (mean  $\pm$  SD, 51.3  $\pm$  8.8). The median follow-up length was 45.5 months (ranged from 3 to 69.5 months after surgery). Thirty-seven endometrioid endometrial cancer patients received pelvic lymphadenectomy for high-risk factors of lymph node metastasis, according to the pathological grade by preoperative endometrium biopsy and the depth of myometrial invasion by image scan, and 16.2% (6/37) were found to have lymph nodes metastasis. The detailed clinicopathological characteristics of the patients were listed in table 2.

During the follow-up, 26.7% (16/60) of patients died of endometrioid endometrial carcinoma, in which 13.9% (5/36) was in stage I/II and 45.8% (11/24) was in stage III/IV. And 10.0% (6/60) patients developed recurrence after surgery. Overall survival (OS) time was calculated from the date of surgery to death or the last follow-up. Disease-free survival (DFS) time was calculated for patients from the date of surgery to the date of disease progression (local recurrence or distant metastasis).

### Immunohistochemistry

As we previously described,<sup>9</sup> deparaffinised, rehydrated and acid-treated paraffin-embedded slides of endometrium specimens (5  $\mu$ m thick) were treated with 3% H<sub>2</sub>O<sub>2</sub> for 10 min and blocked with 5% goat serum albumin for 10 min. Sections were incubated with the specific mouse monoclonal antibodies against  $\gamma$ -synuclein (sc-65979; Santa Cruz Biotechnology, Santa Cruz, California, USA) diluted 1:100 at 37°C for 60 min, followed by the incubation with the Polymer HRP (Horse Radish Peroxidase) (mouse/rabbit) secondary antibodies (IHC Kit; Maixim's-Bio, Fuzhou, China). After three washes of phosphate-buffered sulphate, the staining was accomplished by using DAB Kit (Zhongshan Goldenbridge Biotechnology, Beijing, China) according to the manufacturers' instructions. Sections were counterstained with haematoxylin, dehydrated and mounted. Positive cases were defined by the presence of intracellular staining with red/brown colour in malignant cells. As seen in positive controls, paraffin sections from breast cancer patients with confirmed strong and  $\gamma$ -synuclein-specific staining in the previous study<sup>9</sup> were used. Negative cases were defined by the absence of

**Table 1** The expression of  $\gamma$ -synuclein endometrial carcinoma and normal tissues

	Case, n	$\gamma$ -Synuclein		$\chi^2$	p Value
		Positive	%		
Normal*	12	0	0		0.001†
Tumour‡	60	29	48.3		

\*Normal tissue of endometrium.  
 †Fischer's exact test.  
 ‡Tissue of endometrial carcinoma.

specific intracellular staining, whereas the primary antibody was omitted for a negative control. The cytoplasmic staining intensity for  $\gamma$ -synuclein and the positive case was regarded as >20% of tumour cells with immunostaining.<sup>9</sup>

Immunohistochemical expression was evaluated under light microscopy independently by two experienced pathologists without the knowledge of the patients' backgrounds and clinicopathological data.

### Statistical analysis

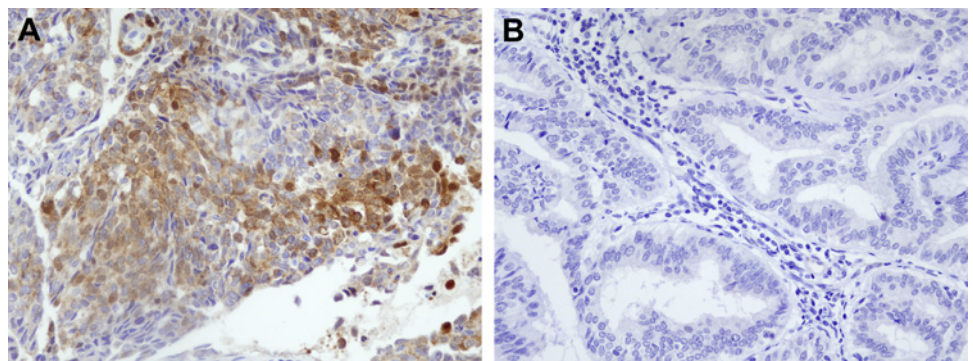
Statistical analyses were performed using SPSS V.13.0 software. Pearson  $\chi^2$  test and Fisher's exact test were used to analyse the differences of  $\gamma$ -synuclein protein expression between cancer and non-cancer tissues, and the correlations between  $\gamma$ -synuclein, ER, PR levels and patient clinicopathological characteristics were assessed. The Kaplan–Meier method was used to estimate DFS and OS rates, and the survival differences were analysed by log-rank test. The Cox proportional hazard model was used for multivariate analysis to investigate the independence of the risk factors identified as significant factors after the univariate analysis. All statistical analyses were two sided, and  $p < 0.05$  was considered statistically significant.

## RESULTS

### The expression of $\gamma$ -synuclein in endometrial carcinoma

As summarised in table 1, 29 of 60 (48.3%) tumour samples displayed clear staining of  $\gamma$ -synuclein protein exclusively in the cytoplasm of malignant cells at different expression levels (figure 1). While no positive staining of  $\gamma$ -synuclein was detected in all 12 normal endometrium tissues ( $p = 0.001$ ).

**Figure 1** (A) Representative immunohistochemical staining for  $\gamma$ -synuclein in the cytoplasm of human endometrial carcinoma and (B) a negative staining of  $\gamma$ -synuclein in endometrial carcinoma (original magnification 400 $\times$ ).



### Correlation with the clinicopathological features

The correlations between  $\gamma$ -synuclein expression and clinicopathological characteristics of all endometrioid endometrial carcinoma patients were analysed and shown in table 2. As it is shown, the  $\gamma$ -synuclein expression in stage I, stage II, stage III and stage IV were 26.9% (7/26), 60.0% (6/10), 65.2% (15/23) and 100.0% (1/1), respectively ( $p = 0.018$ ). The difference between stage I versus stage II and stage III versus stage IV were not significant, so we used the  $\chi^2$  segmentation method, and we found that the difference of  $\gamma$ -synuclein between stage I/II versus III/IV was significant ( $p = 0.020$ ). Similarly, there was a higher percentage of  $\gamma$ -synuclein expression in lymph node-positive tumours compared with the lymph node-negative tumours (6/6 (100%) vs 14/31 (45.2%),  $p = 0.022$ ). And the expression of  $\gamma$ -synuclein was detectable in 31.7% of patients with depth of myometrial invasion  $< 1/2$ , while it raised to 84.2% in patients with myometrial invasion  $\geq 1/2$  ( $p = 0.000$ ). And the expression of  $\gamma$ -synuclein was upraised from grade 1 to grade 3 (from 40.9% to 58.3%), but the difference was not significant ( $p > 0.05$ ). However, there was no significant correlation between  $\gamma$ -synuclein expression and patient age and ER/PR expression ( $p > 0.05$ ).

### Correlations of clinical outcomes of endometrioid endometrial carcinoma patients with $\gamma$ -synuclein expression

To study whether  $\gamma$ -synuclein is a prognostic factor for endometrioid endometrial carcinoma, we correlated  $\gamma$ -synuclein expression in tumours with a median follow-up length of 45.5 months (range from 3 to 69.5 months) after cancer surgery.  $\gamma$ -Synuclein-positive patients showed a significantly poorer prognosis than those with negative  $\gamma$ -synuclein expression in Kaplan–Meier analysis of OS (figure 2,  $\chi^2 = 5.181$ ,  $p = 0.023$ ). Kaplan–Meier analysis did not reveal any significant differences of  $\gamma$ -synuclein expression on DFS (data not shown). During follow-up, 12 (41.4%) patients with  $\gamma$ -synuclein-positive tumour and 4 (12.9%) patients with  $\gamma$ -synuclein-negative tumour died of endometrioid endometrial carcinoma ( $\chi^2 = 6.213$ ,  $p = 0.013$ ).

Univariate analysis showed that several factors were significantly associated with poor OS ( $p < 0.05$ ): deep myometrial invasion (95% CI 1.918 to 15.998,  $p = 0.002$ ), advanced stage (stage III/IV) (95% CI 1.404 to 4.694,

**Table 2** Correlations of  $\gamma$ -synuclein expression with clinic pathological factors of endometrioid endometrial carcinoma

	Case, n	$\gamma$ -Synuclein		$\chi^2$	p Value
		Positive	%		
Age				0.007	0.935
<50	21	10	47.6		
$\geq$ 50	39	19	48.7		
Stage*					0.01†
I	26	7	26.9		
II	10	6	60.0		
III	23	15	65.2		
IV	1	1	100.0		
Grade				0.995	0.608
G1	22	9	40.9		
G2	26	13	50.0		
G3	12	7	58.3		
Lymph node metastasis				0.02†	
Positive	6	6	100.0		
Negative	31	14	45.2		
Depth of endometrial invasion			14.322	0.000	
<1/2	41	13	31.7		
$\geq$ 1/2	19	16	84.2		
ER status				0.537	0.464
Negative	18	10	55.6		
Positive	42	19	45.2		
PR status				1.115	0.291
Negative	15	8	53.3		
Positive	45	21	38.2		

\*The difference between stage I versus stage II and stage III versus stage IV were not significant, so we used the  $\chi^2$  segmentation method and we found that the difference of  $\gamma$ -synuclein between stage I/II versus III/IV was significant (p=0.020).

†Fischer's exact test.

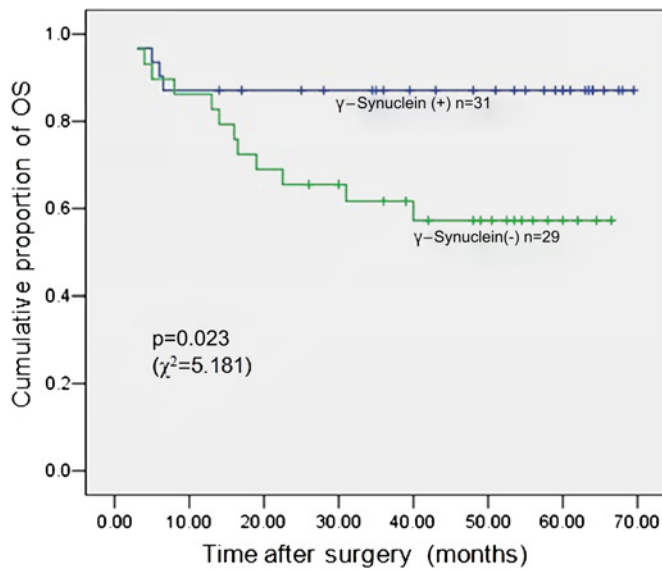
p=0.002) and  $\gamma$ -synuclein expression (95% CI 3.692 to 208.257, p=0.003). When analysed with multivariate analysis,  $\gamma$ -synuclein expression, myometrial invasion and clinical stage were significant independent prognostic factors for OS (table 3). No significant differences were found between  $\gamma$ -synuclein expression and DFS, either analysed with univariate analysis or multivariate analysis (p>0.05) (data not shown).

## DISCUSSION

This study used an immunohistochemical method to detect the expression of  $\gamma$ -synuclein in paraffin-embedded tissues from Chinese's patients with endometrioid endometrial carcinomas. We presented the clinical and experimental data to indicate that  $\gamma$ -synuclein played a key role in endometrioid endometrial carcinoma invasion and metastasis. We analysed the relationship between  $\gamma$ -synuclein expression in 60 endometrioid endometrial carcinoma tissues and the clinicopathological characteristics and confirmed that endometrioid endometrial carcinoma tissues exhibited abundant  $\gamma$ -synuclein expression in the cytoplasm of cancer cells, in contrast to normal endometrium tissues, in which no  $\gamma$ -synuclein expression was detectable. Moreover, the frequency of  $\gamma$ -synuclein expression was a stage specific for endometrioid endometrial carcinoma with the positive rate raised up from stage I to stage IV (from 26.9% to 100%). Similar studies also demon-

strated that  $\gamma$ -synuclein expression was stage specific in breast, ovarian, colon cancer and many other different cancer types.<sup>13 18</sup> A previous study<sup>9</sup> demonstrated that the demethylation in a CpG island located in exon 1 of  $\gamma$ -synuclein is a primary reason for the aberrant expression of this protein in a variety of different cancer types. The loss of epigenetic control by demethylation of  $\gamma$ -synuclein gene can be used as a sensitive molecular tool in early detection in morphologically normal tissues before tumours emerge.<sup>13</sup>

Deep myometrial invasion and lymph nodes metastasis are recognised as important features of malignant tumours. A prior study<sup>19</sup> has been demonstrated that expression of  $\gamma$ -synuclein in breast cancer cells leads to a significant increase in motility and a profound augmentation of metastasis. Consistent with the ability to confer metastatic potential to breast cancer cells, studies in colon and ovarian cancer indicated that patients with positive  $\gamma$ -synuclein expression had a statistically higher incidence of metastasis compared with patients with  $\gamma$ -synuclein negative cancer.<sup>14</sup> In this study, we also found that patients with positive  $\gamma$ -synuclein expression in endometrioid endometrial carcinomas had statistically higher incidence for deep myometrial invasion and lymph node metastasis compared with patients with negative  $\gamma$ -synuclein expression (p<0.05). Although the significant correlation was not reached, there was a tendency that  $\gamma$ -synuclein expression increased from grade 1 to grade 3



**Figure 2** Kaplan–Meier estimation of overall survival (OS).

(from 40.9% to 58.3%) in endometrioid endometrial cancers, and we believe that if these results are confirmed in a larger cohort, we would have a conclusion of demographic value. All these results gave evidence that  $\gamma$ -synuclein may indeed function as a key mediator of cancer cell invasion and metastasis. This is in line with the notion that  $\gamma$ -synuclein promotes disease progression.<sup>20</sup>

While, how  $\gamma$ -synuclein induces disease progression in different cancer types remains unclear. Since  $\gamma$ -synuclein gene amplification and mutation were not detected in breast tumours, transcriptional activation could be responsible for its abundant expression in malignant cancer cells.<sup>9</sup> Previous studies have demonstrated that ectopic expression of  $\gamma$ -synuclein increased breast cancer cell growth by inhibiting the mitotic checkpoint control through interaction with BubR1.<sup>21</sup> In previous in vitro studies, retinoblastoma cell lines over-expressing  $\gamma$ -synuclein were shown to have higher MMP9 protein level and activity, which were enhanced in cell motility and invasion, indicating that  $\gamma$ -synuclein increased invasion might be mediated through the activation of matrix metallo proteinases (MMP) proteins.<sup>22</sup> The study by Pan *et al*<sup>18</sup> in breast and ovarian cancer indicated that the small G-protein RHO GTPases and extracellular signal-regulated kinase (ERK) may be involved in  $\gamma$ -synuclein-enhanced cell motility and metastasis. Li *et al*<sup>23</sup> revealed that  $\gamma$ -synuclein induced cell proliferation and migration by physically interacted with Insulin Like Growth Factor I Receptor (IGF-IR) and Insulin Receptor Substrate 2 (IRS-2). It has also been shown that  $\gamma$ -synuclein could replace the function of heat shock protein 90, chaperone ER- $\alpha$  36 activity, stimulate ligand-dependent cell growth and render tamoxifen resistance.<sup>24</sup>

**Table 3** Cox univariate and multivariate analyses of overall survival

Variable	Overall survival	
	HR (95% CI)	p Value
<b>Univariate analysis</b>		
Age		
<50 vs $\geq$ 50	0.805 (0.292 to 2.217)	0.675
Stage		
III/IV vs I/II	2.567 (1.404 to 4.694)	0.002
Grade		
G3 vs G2 vs G1	1.914 (0.981 to 3.733)	0.057
Depth of endometrial invasion		
>1/2 vs $\leq$ 1/2	5.539 (1.918 to 15.998)	0.002
Lymph node invasion		
Positive versus negative	0.556 (0.261 to 1.183)	0.127
ER status		
Positive versus negative	1.939 (0.552 to 6.807)	0.301
PR status		
Positive versus negative	0.987 (0.315 to 3.035)	0.970
$\gamma$ -Synuclein		
Positive versus negative	27.729 (3.692 to 208.257)	0.003
<b>Multivariate analysis</b>		
Stage		
III/IV vs I/II	2.903 (1.010 to 8.340)	0.048
Depth of invasion		
>1/2 vs $\leq$ 1/2	2.831 (1.033 to 7.757)	0.031
$\gamma$ -Synuclein		
Positive versus negative		
>1/2 vs $\leq$ 1/2	12.331 (1.429 to 101.892)	0.020

Multivariable analysis was performed using stepwise Cox proportional hazards regression with forward selection. Candidate exploratory variables included clinical age, grade, stage, depth of invasion, lymph node invasion, ER status, PR status and  $\gamma$ -synuclein.

In our study, we confirmed that  $\gamma$ -synuclein was a predictor of OS along with stage, depth of myometrial invasion with Kaplan–Meier analysis and univariate analyses, similar to some reports that  $\gamma$ -synuclein expression is linked to lower survival rates in different kinds of tumours.<sup>14–19</sup> And multivariable analyses showed that  $\gamma$ -synuclein was correlated with OS of the patients, which is the same as previous observations of an association between  $\gamma$ -synuclein expression and OS in uterine papillary serous carcinoma<sup>15</sup> and is the same with Mhawech-Fauceglia,<sup>16</sup> who considered that  $\gamma$ -synuclein protein expression is associated with poor outcome in endometrial adenocarcinoma and  $\gamma$ -synuclein expression as an independent prognostic factor in endometrial adenocarcinoma. Probably, due to the small number of the patients who got a recurrence (only 6 of 60 patients formed disease recurrence), when analysed the impact of  $\gamma$ -synuclein expression and clinicopathological features to the prognosis of DFS, no significant difference was found (data not shown), in contrast to previous studies.<sup>9–14</sup> Therefore, more specimens will be required for statistically meaningful comparisons.

In summary, we have shown that the expression of  $\gamma$ -synuclein in endometrioid endometrial carcinoma tissues was stage specific and tightly correlated with the depth of myometrial invasion, lymph node metastasis.  $\gamma$ -Synuclein is likely to play an important role in the invasion and metastasis of endometrioid endometrial carcinoma, and it may play an important role in the prediction for prognosis in endometrioid endometrial carcinoma. Additional functional studies will be necessary to further clarify the role that  $\gamma$ -synuclein may play in tumourigenesis and distant metastasis and in  $\gamma$ -synuclein targeting biotherapy.

**Contributors** JZ did experiments and writes the article, works as the first author. YF did the editing and revisions, works as the second author and corresponding author. YM did the data acquisition, works as the third author. HX did the editing and revisions, works as the fourth author. JF did the editing and revisions, works as the fifth author.

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**Patient consent** Obtained.

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**Data sharing statement** There is no additional data available.

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