Original Article

Effects of anxiety, depression, and fatigue on quality of life in early esophageal cancer patients following endoscopic submucosal dissection

Yan Wu[1], Yin Zhang[2], Lili Zou[3,4]

[1]Department of Gastroenterology, the People's Hospital of Rugao, Rugao, China; [2]Department of Digestive Diseases, the First People's Hospital of Changzhou, Changzhou, China; [3]Nursing Department, Wujin Hospital Affiliated with Jiangsu University, Changzhou, China; [4]Nursing Department, the Wujin Clinical College of Xuzhou Medical University, Changzhou, China

Contributions: (I) Conception and design: Y Wu, L Zou; (II) Administrative support: L Zou; (III) Provision of study materials and patients: Y Wu; (IV) Collection and assembly of data: Y Wu; (V) Data analysis and interpretation: Y Wu, Y Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Lili Zou. Nursing Department, Wujin Hospital Affiliated with Jiangsu University, Changzhou 213002, China. Email: 778765909@qq.com.

Background: Emotional problems such as anxiety, depression, and fatigue may affect the quality of life (QoL) of cancer patients. However, there are no related studies investigating the effects of emotional problems on the QoL of early esophageal cancer (EC) patients receiving endoscopic submucosal dissection (ESD).

Methods: This is a prospective observational study enrolling 75 early EC patients. Demographic and clinical characteristics of enrolled patients were recorded. QoL was assessed according to the European Organization for Research and Treatment of Cancer QoL (EORTC QLQ-C30). The Beck Anxiety Scale and the Beck Depression Scale were used to measure the severity of anxiety symptoms and depression intensity, respectively. Fatigue was assessed according to the symptom subscale of the EORTC QLQ-C30. Multivariable logistic regression models were constructed to determine the causes of emotional problems and linear regression models were employed to identify the independent risk factors for reduced QoL.

Results: Of the enrolled early EC patients, 21, 15, and seven had symptoms of mild, moderate and severe anxiety, respectively. Also, 15, 19, and two patients had symptoms of mild, moderate, and severe depression, respectively. In total, 27 patients frequently felt fatigue. The multivariable logistic regression model revealed that the financial capacity to pay for treatment had an important effect on the prevalence of anxiety and depression symptoms in enrolled patients (both P values <0.001). Age, gender, education status, and tumor size also played a role in emotional problems. Meanwhile, fatigue was found to be related only to age and gender. The mean score for QoL was 76.9±15.2. After adjusting for confounding factors using the multivariable linear regression model, moderate or severe symptoms of anxiety, depression, and fatigue, older age, and insufficient capacity to pay were identified as independent risk factors for reduced QoL.

Conclusions: Emotional distress is a significant problem for early EC patients receiving ESD treatment as it may affect their QoL.

Keywords: Anxiety; depression; fatigue; quality of life (QoL); endoscopic submucosal dissection (ESD); early esophageal cancer (early EC)

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Introduction

Esophageal cancer (EC) is among the most prevalent cancers of the upper digestive tract and was reported as the sixth most common cause of death due to malignant tumors worldwide (1). In China, EC has the sixth highest incidence rate among cancers, affecting an estimated 17.87 per 100,000 people, and a mortality rate of 13.68 per 100,000 people (2). EC has a poor prognosis, with a five-year survival rate of 20% (at most) (3). Surgical intervention can provide a relatively satisfying prognosis for patients with early or middle stage EC. However, esophagectomy for EC is often associated with a high incidence of complications that worsen the prognosis of patients (4).

The development of endoscopic submucosal dissection (ESD), which is now considered an acceptable treatment for early EC, has several advantages compared to esophagectomy including preservation of esophageal function, minimal invasiveness, less complications, lower cost, and shorter hospital stay (5). In addition, quality of life (QoL) following ESD is also considered as an important outcome for EC patients. Several studies have demonstrated that ESD provided a better postoperative QoL than surgery for early gastric and colorectal cancer patients (6,7). However, many EC patients may suffer from physical and psychosocial problems due to cancer symptoms and side effects of treatment, which may dramatically impact their QoL. Previous studies have mainly focused on the effects of physical problems on QoL in EC patients (8,9). Minimal attention has been given to the repercussions of emotional problems on the QoL of EC patients. Baudry *et al.* revealed that reducing the emotional distress of EC patients could improve their QoL either in the pre- or postoperative stage (10).

Patients enrolled in this study received surgical treatment. To our knowledge, there are no related studies investigating the effects of emotional factors on QoL in early EC patients. Hence, the present study was conducted to preliminarily investigate the QoL of early EC patients following ESD treatment and determine the effects of anxiety, depression, and fatigue on QoL. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1632).

Methods

Patient selection

This was a prospective observational study to assess the QoL of early EC patients. Early EC patients admitted to the People's Hospital of Rugao from December 2017 to January 2019 were enrolled in this study. Patients eligible for inclusion were older than 18 years of age, diagnosed as early EC (cT1aN0M0 or cT1bN0M0) by biopsy or imaging test, had no contraindications of ESD, received no previous surgical resection treatment and signed the written informed consent. Patients who refused to participate in the study or sign the written informed consent were excluded. The study was performed in compliance with the ethical principles outlined in the World Medical Association's Declaration of Helsinki (as revised in 2103) and was approved by the ethics committee of the People's Hospital of Rugao (No. 00201714).

Data collection

Demographic and clinical characteristics of patients were recorded following enrollment in the study. Recorded data included age, gender, education, marital status, employment status, capacity to pay for treatment, number of comorbidities, tumor stage, tumor location, tumor size, circumferential range, complete resection rate, and complications of ESD. All ESD procedures in this study were performed by skilled operators, in order to minimize the impacts of different operators on patients.

Assessment of QoL

QoL was assessed according to the European Organization for Research and Treatment of Cancer QoL (EORTC QLQ-C30) (11) within 3–6 months after the patients were discharged from hospital. EORTC QLQ-C30 is a self-report scale specifically designed for cancer patients, and includes 30 items that can be divided into five functional scales (physical function, role function, emotional function, cognitive function, and social function) and one global health status scale. The total score in each scale ranges from 0 to 100, with a higher score indicating better QoL of patients. In this study, a total score of 75 was set as a cut-off; so a score <75 represented a poor QoL, while a score >75 represented a satisfying QoL.

Assessment of anxiety, depression, and fatigue

The Beck Anxiety Scale (BAS) was used to measure the severity of anxiety symptoms in enrolled patients (12). The BAS is a self-report scale and generally consists of 21 items,

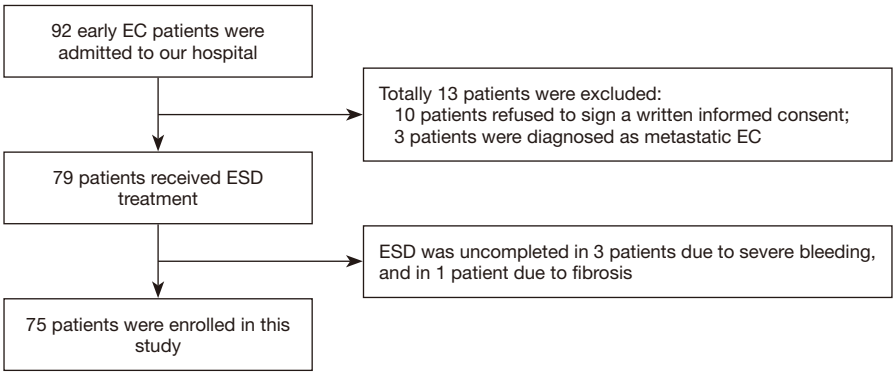

Figure 1 Flow chart showing the process of patient selection.

with each item being scored from 0 to 3. Therefore, the total score of each patient ranges from 0 to 63 scores. In this case, a higher total score indicates more severe anxiety symptoms in patients. Our study defined anxiety symptoms as minimal if the total score was between 0 and 7, mild if between 8 and 15, moderate if between 16 and 25, and as severe if between 26 and 63.

The Beck Depression Scale (BDS) was then employed to assess the intensity of depression (13). Similar to the BAS, the BDS also contains 21 items, with each item being scored from 0 to 3 to obtain a total score ranging from 0 to 63. A total score of 0–9 indicated minimal depression, 10–18 indicated mild depression, 19–29 indicated moderate depression, and 30–63 indicated severe depression.

Fatigue was assessed according to the symptom subscale of the EORTC QLQ-C30. There were three items regarding physical strength in the symptom subscale, and each item could be scored from 0 to 3 scores. The total score of the three items were then transformed on a 0–100 scale. In this study, a total score of >75 represented a poor condition of physical strength.

Statistical analysis

Statistical analyses were performed using SPSS (version 22.0, SPSS Inc., Chicago, IL, USA). Categorical variables were reported as numbers and percentages, and continuous variables were reported as means ± standard deviations. Univariable and multivariable logistic regression models were constructed to determine the causes of three emotional problems, namely anxiety, depression, and fatigue. Furthermore, a linear regression model was employed to explore the impacts of the aforementioned emotional difficulties on the QoL of early EC patients undergoing ESD. Some demographic and clinical characteristics of patients were adjusted in both multivariable regression models to reduce the bias of these data on the results. For all analyses, a P value <0.05 was considered statistically significant.

Results

In total, there were 92 early EC patients admitted to the hospital from December 2017 to January 2019. Of this initial cohort, 13 patients refused to participate in this study. ESD procedures were uncompleted in three patients due to severe bleeding, and in one patient due to fibrosis. Finally, 75 early EC patients were enrolled in this study (as shown in *Figure 1*). Demographic and clinical characteristics of enrolled patients are summarized in *Table 1*. The majority of patients were elderly, with the 60–70 years old cohort accounting for 48% of all included patients. There were 41 male and 34 female patients. Most patients were not well educated and only 12 patients had attended high school or above. Approximately 75% of the patients had a partner and 32 patients were employed at the time. Most importantly, roughly one third of patients had insufficient financial capacity to pay for treatment, and half of the patients suffered from at least two comorbidities.

In terms of cancer characteristics, only early EC patients were enrolled in this study. Of the 75 included patients, 53 were diagnosed as T1aN0M0 and 22 as T1bN0M0. Most tumors (73.3%) were located in the middle of the esophagus. The tumor size was small (<20 mm) in 49 patients and relatively large (≥20 mm) in the remaining 26 patients. Tumors had invaded more than half of the circumference of the esophagus in 63 patients. 74 patients received a complete resection.

Table 1 Demographic and clinical characteristics of enrolled patients (n=75)

Variables	N (%)
Age (years)	
40–50	3 (4.0)
50–60	17 (22.7)
60–70	36 (48.0)
70–80	13 (17.3)
>80	6 (8.0)
Gender	
Male	41 (54.7)
Female	34 (45.3)
Education	
Primary school	33 (44.0)
Middle school	30 (40.0)
High school or above	12 (16.0)
Marital status	
Married	57 (76.0)
Single or widowed	18 (24.0)
Employed	
Yes	32 (42.7)
No	43 (57.3)
Capacity to pay	
Yes	49 (65.3)
No	26 (34.7)
Number of comorbidities	
0	21 (28.0)
1	17 (22.7)
≥2	37 (49.3)
Tumor stage	
T1aN0M0	53 (70.7)
T1bN0M0	22 (29.3)
Tumor location	
Upper	7 (9.3)
Middle	55 (73.3)
Lower	13 (17.3)
Tumor size, mm	
<20	49 (65.3)
≥20	26 (34.7)
Circumferential range	
<1/2	63 (84.0)
≥1/2	12 (16.0)
Complete resection rate	
Yes	74 (98.7)
No	1 (1.3)

Table 2 Prevalence of emotional problems in enrolled EC patients (n=75)

Variables	N (%)
Anxiety	
Minimal	32 (42.7)
Mild	21 (28.0)
Moderate	15 (20.0)
Severe	7 (9.3)
Depression	
Minimal	39 (52.0)
Mild	15 (20.0)
Moderate	19 (25.3)
Severe	2 (2.7)
Fatigue	
Yes	27 (36.0)
No	48 (64.0)

EC, esophageal cancer.

Emotional problems including anxiety, depression, and fatigue were assessed in all enrolled patients (*Table 2*). In general, 32 patients had symptoms of minimal anxiety, 21 patients had symptoms of mild anxiety, 15 patients had symptoms of moderate anxiety, and seven patients had symptoms of severe anxiety. With regards to depression, 39 patients had symptoms of minimal depression, 15

patients had symptoms of mild depression, 19 patients had symptoms of moderate depression, and two patients had symptoms of severe depression. Furthermore, 27 patients frequently felt fatigued.

The causes of emotional distress in patients were analyzed using univariable and multivariable logistic regression models (as shown in *Table 3*). The multivariable logistic regression model revealed that older (≥60 years) or female patients were more likely to suffer from moderate or severe anxiety than younger or male patients (P=0.045 and 0.048, respectively). The financial capacity to pay for treatment had a significant impact on the triggering of anxiety symptoms in the enrolled patients (P<0.001). Similarly, age, gender, and capacity to pay also played key roles in depression symptoms. Moreover, higher education level and smaller tumor size may be able to relieve symptoms of depression to some extent (P=0.048 and 0.018, respectively). Fatigue was found to be related only to age

Table 3 Demographic and clinical characteristics were associated with emotional problems in early EC patients according to the logistic regression model

Variables	Anxiety				Depression				Fatigue			
	Minimal or mild	Moderate or severe	P value[a]	P value[b]	Minimal or mild	Moderate or severe	P value[a]	P value[b]	No	Yes	P value[a]	P value[b]
Number	53	22			54	21			48	27		
Age, years												
<60	18 (34.0%)	2 (9.1%)	0.040	0.045	19 (35.2%)	1 (4.8%)	0.025	0.036	17 (35.4%)	3 (11.1%)	0.030	0.042
≥60	35 (66.0%)	20 (90.9%)			35 (64.8%)	20 (95.2%)			31 (64.6%)	24 (88.9%)		
Gender												
Male	33 (62.3%)	8 (36.4%)	0.044	0.048	35 (64.8%)	6 (28.6%)	0.006	0.022	32 (66.7%)	9 (33.3%)	0.007	0.026
Female	20 (27.7%)	14 (63.6%)			19 (35.2%)	15 (71.4%)			16 (33.3%)	18 (66.7%)		
Education												
Primary school	18 (34.0%)	15 (68.2%)	*		17 (31.5%)	16 (76.2%)	*		21 (43.8%)	12 (44.4%)	*	
Middle school	24 (45.3%)	6 (27.3%)	0.044	0.081	26 (48.1%)	4 (19.0%)	0.034	0.048	21 (43.8%)	9 (33.3%)	0.593	
High school or above	11 (20.8%)	1 (4.5%)	0.375	0.496	11 (20.4%)	1 (4.8%)	0.654		6 (12.5%)	6 (22.2%)	0.411	
Marital status												
Married	38 (71.7%)	19 (86.4%)	0.186		38 (70.4%)	19 (90.5%)	0.083		38 (79.2%)	19 (70.4%)	0.394	
Single or widowed	15 (28.3%)	3 (13.6%)			16 (29.6%)	2 (9.5%)			10 (20.8%)	8 (29.6%)		
Employed												
Yes	24 (45.3%)	8 (36.4%)	0.478		22 (40.7%)	10 (47.6%)	0.867		20 (41.7%)	12 (44.4%)	0.815	
No	29 (54.7%)	14 (63.6%)			32 (59.3%)	11 (52.4%)			28 (58.3%)	15 (55.6%)		
Capacity to pay												
Yes	43 (81.1%)	6 (27.3%)	<0.001	<0.001	45 (83.3%)	4 (19.0%)	<0.001	<0.001	28 (58.3%)	21 (77.8%)	0.094	
No	10 (18.9%)	16 (72.7%)			9 (16.7%)	17 (81.0%)			20 (41.7%)	6 (22.2%)		
Number of comorbidities												
0	16 (30.2%)	5 (22.7%)	*		14 (25.9%)	7 (33.3%)	*		13 (27.1%)	8 (29.6%)	*	
1	10 (18.9%)	7 (31.8%)	0.788		12 (22.2%)	5 (23.8%)	0.462		9 (18.8%)	8 (29.6%)	0.578	
≥2	27 (50.9%)	10 (45.5%)	0.302		28 (51.9%)	9 (42.9%)	0.692		26 (54.2%)	11 (40.7%)	0.515	

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Anxiety				Depression				Fatigue			
	Minimal or mild	Moderate or severe	P value[a]	P value[b]	Minimal or mild	Moderate or severe	P value[a]	P value[b]	No	Yes	P value[a]	P value[b]
Tumor stage												
T1aN0M0	38 (71.7%)	15 (68.2%)	0.761		39 (72.2%)	14 (66.7%)	0.636		34 (70.8%)	19 (70.4%)	0.884	
T1bN0M0	15 (28.3%)	7 (31.8%)			15 (27.8%)	7 (33.3%)			14 (29.2%)	8 (29.6%)		
Tumor location												
Upper	6 (11.3%)	1 (4.5%)	*		5 (9.3%)	2 (9.5%)	*		5 (10.4%)	2 (7.4%)	*	
Middle	39 (73.6%)	16 (72.7%)	0.421		41 (75.9%)	14 (66.7%)	0.659		37 (77.1%)	18 (66.7%)	0.825	
Lower	8 (15.1%)	5 (22.7%)	0.279		8 (14.8%)	5 (23.8%)	0.351		6 (12.5%)	7 (25.9%)	0.287	
Tumor size												
<20 mm	38 (71.7%)	11 (50.0%)	0.076		41 (75.9%)	8 (38.1%)	0.003	0.018	30 (62.5%)	19 (70.4%)	0.493	
≥20 mm	15 (28.3%)	11 (50.0%)			13 (24.1%)	13 (61.9%)			18 (37.5%)	8 (29.6%)		
Circumferential range												
<1/2	44 (83.0%)	19 (86.4%)	0.720		47 (87.0%)	16 (76.2%)	0.257		42 (87.5%)	21 (77.8%)	0.276	
≥1/2	9 (17.0%)	3 (13.6%)			7 (13.0%)	5 (23.8%)			6 (12.5%)	6 (22.2%)		

[a], the data were analyzed using a univariable logistic regression model; [b], the data were analyzed using a multivariable logistic regression model adjusting for the variables which showed significant difference in univariable analysis; *, reference. EC, esophageal cancer.

Table 4 Summary of EORTC QLQ-C30 in enrolled EC patients

Variables	Mean ± SD
EORTC QLQ-C30	
Physical function	88.1±12.9
Role function	85.5±16.8
Emotional function	77.9±12.5
Cognitive function	93.4±14.7
Social function	91.0±17.2
Global health status	76.9±15.2

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer QoL; EC, esophageal cancer.

and gender.

The QoL of early EC patients was then assessed according to EORTC QLQ-C30. The mean scores of five functional scales and one global health status scale are summarized in *Table 4*. The mean scores in enrolled patients were as follows: physical function was 88.1±12.9, role function was 85.5±16.8, emotional function was 77.9±12.5, cognitive function was 93.4±14.7, and social function was 91.0±17.2. The mean score of global health status was 76.9±15.2. Risk factors for reduced QoL were estimated according to univariable and multivariable linear regression models (shown in *Table 5*). Anxiety, depression, fatigue, age, gender, capacity to pay, and number of comorbidities were initially found to be significantly associated with QoL based on the results of the univariable linear regression analysis. However, after adjusting for confounding factors using a multivariable linear regression model, moderate or severe symptoms of anxiety, depression, and fatigue, older age, and insufficient capacity to pay for treatment were identified as independent risk factors for reduced QoL.

Discussion

To our knowledge, this is the first study to investigate the effects of anxiety, depression, and fatigue on QoL in early EC patients receiving ESD treatment. This study enrolled 75 patients from December 2017 to January 2019, and demonstrated that some demographic characteristics of patients including capacity to pay for treatment, age, gender, education status, and tumor size may cause emotional distress. Additionally, the prevalence of emotional problems,

Table 5 Univariable and multivariable linear regression model estimating independent risk factors for reduced QoL in early EC patients

Variables	Univariable		Multivariable	
	OR	95% CI	OR	95% CI
Anxiety				
Moderate or severe *vs.* minimal or mild	2.040	1.074–3.875	1.977	1.006–3.886
Depression				
Moderate or severe *vs.* minimal or mild	3.881	1.679–8.969	2.406	1.173–4.936
Fatigue				
Yes *vs.* no	1.425	1.312–1.547	1.378	1.242–1.528
Age, years				
≥60 *vs.* <60	1.164	1.095–1.238	1.123	1.035–1.220
Gender				
Male *vs.* female	2.071	1.112–3.858	1.353	0.659–2.777
Education				
Primary school *vs.* middle school or above	0.531	0.116–2.436		
Marital status				
Married *vs.* single or widowed	1.118	0.453–2.761		
Employed				
Yes *vs.* no	1.160	0.507–2.657		
Capacity to pay				
Yes *vs.* no	5.604	1.271–24.612	5.63	1.210–26.170
Number of comorbidities				
0 or 1 *vs.* ≥2	0.487	0.308–0.771	0.595	0.316–1.121
Tumor stage				
T1aN0M0 *vs.* T1bN0M0	0.952	0.542–1.675		
Tumor location				
Upper *vs.* middle or lower	1.617	0.929–2.816		
Tumor size				
<2 *vs.* ≥20 mm	1.290	0.482–3.452		
Circumferential range				
<1/2 *vs.* ≥1/2	3.105	0.880–10.958		

QoL, quality of life; EC, esophageal cancer.

such as anxiety, depression, and fatigue may reduce the QoL of early EC patients following ESD treatment.

The prevalence of anxiety (57.3%) and depression (48.0%) among the enrolled patients in the study were similar to previous studies involving cancer patients (10,14). We further investigated the causes of emotional problems. Several previous studies have reported that age and gender may be associated with the incidence of emotional distress in cancer patients (15,16). Mols *et al.* reported that older and male colorectal cancer patients had considerably fewer symptoms of anxiety, yet exhibited more symptoms of depression (15). Moreover, Weiss Wiesel *et al.* found that

anxiety decreased with age in older cancer patients receiving chemotherapy, while depression remained constant with age (17). However, our study found that the severity of both anxiety and depression symptoms decreased in older and male patients, which might be explained by cultural differences between diverse countries. In addition, early EC posed a relatively low psychological burden on patients compared with colorectal cancer.

It is understandable that an inability to pay the cost of treatment acted as a key cause of emotional distress. Several studies have also highlighted the important role of financial difficulties in the development of emotional problems in cancer patients (18,19). Thus, measurements in the present study were taken to ensure that the rate of underdiagnosed psychiatric morbidities was reduced, especially for patients that are financially-burdened.

The most important finding of our study was the independent risk factors for reduced QoL in early EC patients. Depression was the major risk factor impacting QoL, especially functional status. Previous studies have shown that patients with depression typically experience a worse QoL compared with patients that do not suffer from depression (20,21). Our study obtained a similar result, indicating that the prevalence of depression significantly reduced the QoL score in early EC patients. Furthermore, we found that anxiety played a similar role to depression. The QoL of lung cancer patients was reported to be associated with both anxiety and depression (22). Bellali *et al.* proposed that early assessment of anxiety and depression may provide information and insight regarding vulnerable patients and guide the implementation of targeted treatment strategies (23). Fatigue is a common symptom in cancer patients and accounted for 36.0% in our study. Also, it itself was part of scale for assessing QoL. It has been shown that fatigue is associated with the presence of inflammation, as well as poor quality of sleep and QoL in patients with advanced cancer (24). The combination of multiple factors can induce fatigue in cancer patients. Our study demonstrated that fatigue was only related to age and gender considering the relatively low burden of cancer in the enrolled early EC patients.

Interestingly, the characteristics of the tumor had no significant relation to either emotional problems or QoL in early EC patients. In practice, most early EC patients do not require further chemotherapy after ESD treatment, and thus, ESD does not significantly increase the burden on patients. So, the reduced QoL in patients primarily resulted from emotional distress and financial difficulties.

Some limitations of this study should be noted. Firstly, only 75 early EC patients were enrolled in the study. This small sample size, coupled with the short study duration and single center study design hindered further analysis. Secondly, the majority of patients enrolled in this study were not well educated, which made it difficult to analyze the impact of education status on emotional problems and QoL. Thirdly, the incidence of esophageal stenosis after ESD may also be the main factor affecting the recovery and quality of life of patients. However, we didn't record the degree of stenosis in enrolled patients during the period of follow up.

In conclusion, ESD is considered an acceptable treatment for early EC and can provide better QoL outcomes than surgical procedures. Our prospective study verified the incidence of anxiety, depression, and fatigue in early EC patients following ESD treatment, which could reduce the QoL of EC patients. This finding emphasizes the importance of psychosocial health in patients receiving ESD treatment and highlights the need to strengthen psychological counseling in clinical practice.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-1632

Data Sharing Statement: Available at http://dx.doi.org/10.21037/apm-20-1632

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-1632). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was performed in compliance with the ethical principles outlined in the World Medical Association's Declaration of Helsinki (as revised in 2013) and was approved by the

ethics committee of the People's Hospital of Rugao (No. 00201714). Informed consent was taken from all the patients.

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