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Anxiety and quality of life among papillary thyroid cancer patients awaiting final pathology results after surgery

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Abstract

Purpose There is a lack of research on short-term mental health and health-related quality of life (HRQoL) in thyroid cancer patients. This study aimed to assess the short-term anxiety level and HRQoL of patients during the early postoperative period while awaiting pathology results, and to explore the important factors associated with state anxiety.

Methods In this single-center cross-sectional study, 349 patients with papillary thyroid cancer were included. Anxiety and HRQoL were measured using the State-Trait Anxiety Inventory (STAI) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), respectively.

Results In general, papillary thyroid cancer patients reported good quality of life with a mean global quality of life score of 75.69 ± 20.66 (on a scale of 0–100, where 100 means the best). There was no significant difference in HRQoL between the two groups, except regarding social functioning (p = 0.027). The anxiety levels of the two groups were similar; however, the state anxiety score (42.17 ± 12.52) was significantly higher than the trait anxiety score (40.69 ± 11.18) among patients in the non-FNA group (p = 0.023). Dyspnea, insomnia, QL, and trait anxiety were independent factors that affected state anxiety. **Conclusion** Patients with papillary thyroid cancer had good postoperative HRQoL and a significantly higher than usual level of state anxiety while awaiting pathology results. Symptoms of dyspnea and insomnia, global quality of life, and trait anxiety are important factors associated with state anxiety. Preoperative FNA results may moderate the change in anxiety level. These findings may help clinicians provide psychological support.

Keywords Papillary thyroid cancer · Anxiety · Health-related quality of life · STAI · EORTC-QLQ-C30

Introduction

In recent decades, the global incidence of thyroid cancer has shown an annual increase of 3–4% [1–4]. However, there has been no significant change in mortality rates due to the increased detection rate of small papillary thyroid cancer with a favorable prognosis, which accounts for the majority [5]. Many publications have discussed the overdiagnosis of thyroid cancer, and several have suggested that active

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⊠ Xiequn Xu xxq75@163.com surveillance may avoid the risk of surgery and subsequent reduction in quality of life, without increasing the risk of recurrence or death [6–8]. However, it has also been suggested that it is premature to conclude that surgery is overtreatment for small papillary thyroid cancer [9, 10]. Currently, surgery is still the main treatment for papillary thyroid cancer, and considerable research attention has been given to the postoperative mental status and health-related quality of life (HRQoL) of patients.

Several studies have already reported that the long-term HRQoL of thyroid cancer patients is worse than that of patients with other cancers with a worse prognosis, including breast cancer, colorectal cancer, and prostate cancer [11, 12]. Furthermore, there is no significant improvement in HRQoL more than 5 years after surgery for thyroid cancer [13]. Regarding mental burden, thyroid cancer patients are reported to experience more serious anxiety, depression, fatigue, and insomnia than the healthy population, patients with benign thyroid tumors, and patients with other cancers [14–16]. However, the vast



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378 Endocrine (2022) 76:377–384

majority of studies have focused on long-term mental health and HRQoL, and few studies have reported HRQoL at 1 month to 6 months postoperatively [17–19]. There remains a lack of information about anxiety levels and HRQoL during the period when patients are waiting for final pathology results after surgery. Typically, after surgery, patients need to wait for the final pathology reports from the Pathology Department, and the wait time lasts 1–2 weeks. This period is very significant for patients, as they are anxiously waiting to learn whether their thyroid nodules are benign or malignant, as well as worrying about the presence and number of lymph node metastases. Their anxiety levels are worth exploring, as are the factors that affect their anxiety levels.

This cross-sectional study used two validated questionnaires to assess postoperative anxiety and HRQoL in papillary thyroid cancer patients awaiting final pathology reports. Although the final pathology report is the gold standard for diagnosis, ultrasound (US)-guided fine-needle aspiration (FNA), which is generally performed for nodules with suspected malignancy based on clinical characteristics or imaging [20–23], could provide preliminary pathology results, and the diagnosis of thyroid cancer is reported to affect patients' mental status and increase their anxiety [24-26]. In China, the choice of direct surgery or preoperative FNA is recommended to be guided by echographic features in combination with the clinical picture, and some patients with high suspicion of malignancy undergo direct surgical treatment without preoperative FNA. For this reason, we also compared the anxiety levels and HRQoL of patients who underwent preoperative FNA and those who underwent surgery directly.

Materials and methods

Design and patients

This was a cross-sectional study. Participants were recruited from patients who underwent thyroid surgery in the Department of General Surgery at Peking Union Medical College Hospital between August 2014 and January 2021, regardless of whether they underwent preoperative FNA. Eligible participants were patients aged ≥18 years with a postoperative pathology diagnosis of papillary thyroid cancer. Patients with serious comorbidities or other malignant tumors or a history of psychiatric disorders and patients with suspected papillary thyroid cancer found to have benign disease were excluded. At the first postoperative clinic visit after patients were informed of their pathology results, which was usually within 1 month, written informed consent was obtained from the patients, and they were asked to complete an online questionnaire related to anxiety and HRQoL sent through the contact information registered in the electronic medical record system (Online Appendix 1).

The study was approved by the Ethics Committee of Peking Union Medical College Hospital.

Demographic and clinical characteristics

Demographic data, including age, sex, education level, employment status, marital status, and disposable income per year, were obtained from patients. Clinical characteristics, such as a family history of thyroid cancer, tumor size, preoperative FNA, type of surgery, complications after surgery, and length of wait for the final pathology result after surgery, were collected from the hospital's medical record system.

Applied questionnaires

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30): The 30-item EORTC-QLQ-C30 questionnaire is a cancerspecific measure of HROoL [27] that consists of 5 functioning scales (physical, role, emotional, cognitive, and social) and 9 symptom scales (fatigue, nausea/vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties) as well as a global quality of life (QL) scale. Each item is scored on a 4-point Likert scale from 1, "not at all" to 4, "very much", except for the QL scale, which is scored on a 7-point Likert scale from 1, "very poor" to 7, "excellent". The standardized score for each scale was calculated based on the patient's choices, and after linear transformation, all scales and single item measures of the EORTC-QLQ-C30 ranged from 0 to 100. Higher scores on the functioning and QL scales are associated with better HRQoL, and higher scores on the symptom scales are associated with worse HRQoL. The EORTC-QLQ-C30 scale, which is applicable to all types of cancer for the evaluation of HRQoL, has been applied in previous publications to assess the HRQoL of patients with thyroid cancer [12, 13, 21].

State-Trait Anxiety Inventory (STAI): The STAI includes two scales that assess state anxiety at a given time and trait anxiety related to a patient's personality [28]. The 40-item questionnaire consists of 2 subscales scored on a 4-point Likert scale ranging from 1, "almost never" to 4, "almost always", with a minimum score of 20 to a maximum score of 80 for each subscale. Higher scores indicate higher levels of anxiety.

Statistical analysis

Continuous variables are presented as the mean (SD) or median (range), and categorical variables are presented as



Endocrine (2022) 76:377–384 379

rates. Demographic and clinical characteristics and HRQoL and anxiety scores were compared between the FNA group and the non-FNA group by Spearman's correlation analysis, the Mann–Whitney test, the chi-square test, and Fisher's exact test.

A paired sample *t*-test was used to compare the level of state anxiety and trait anxiety. Pearson correlation analysis was used to assess the relationship between continuous variables and state anxiety scores, and the relationship between categorical variables and state anxiety scores was examined using the independent sample *t*-test and one-way ANOVA. Statistically significant variables were included in a multivariable linear regression analysis to identify factors that had an independent impact on state anxiety scores.

All statistical analyses were performed by IBM SPSS version 26.0 (IBM Corp., Armonk, NY), and a two-sided p value of ≤ 0.05 was considered statistically significant.

Results

Baseline characteristics

During the study period, 381 patients who underwent thyroid surgery were approached and they all provided informed consent. Of these, 32 patients were found to have benign thyroid disease via postoperative pathology reports and were excluded. As shown in Table 1, 349 patients with papillary thyroid cancer were finally included in the analysis, 192 of whom underwent preoperative FNA, and 157 of whom underwent surgery without FNA. The majority of patients were female, had an education level higher than college, were employed, were married, had an annual family income of more than RMB 60,000, and had no family history of thyroid cancer. The median ages of the FNA group and the non-FNA group were 39 years (range 20-74 years) and 40 years (range 22-65 years), respectively. There were no significant differences in age, sex, or other demographic variables between the two groups. Most of the patients (92.7% and 94.9% in the FNA and non-FNA groups, respectively) received their final pathology reports within 2 weeks. The distribution of most clinical variables was similar between the two groups, with the exception of the type of surgery and complications. More patients in the FNA group underwent total thyroidectomy (81.8% versus 67.5%, p = 0.002), and more complications (53.1% versus 37.5%, p = 0.001) were reported in patients who underwent preoperative FNA. According to self-reports, the majority of patients who presented complications experienced either transient voice change or brachial plexus nerve injury (31.2%), with a small percentage of patients reporting both (14.9%).

EORTC-QLQ-C30 scores

Table 2 presents the HRQoL score of all patients and a comparison of the two groups. The functioning scale scores were generally high, and the scores for the symptom scales were low. The mean QL score was 75.69 (8.33–100.00) for all patients. There was no significant difference in the functioning or symptom scale scores between the two groups, except for the social functioning scale score (p = 0.027). Bivariate analysis showed that patients who underwent preoperative FNA complained more about their physical condition or medical treatment interfering with their family life and social activities, with a score (mean \pm SD) of 79.41 \pm 23.66 compared to 84.64 \pm 19.51 for patients in the FNA group. The QL score among patients who did not undergo preoperative FNA was higher, but the difference was not statistically significant.

STAI scores

Compared to the trait anxiety level, which represented the patients' normal anxiety level as a function of their personalities, the state anxiety level, which represented the anxiety level during the waiting period, was significantly higher than the trait anxiety level among 349 patients (p = 0.003) and among patients who did not undergo preoperative FNA (p = 0.023). The state anxiety level showed a slight but not significant improvement over the trait anxiety level in the FNA group. The state anxiety level and the trait anxiety level of the two groups were similar (Table 3).

Table 4 shows the relationships between different variables and the state anxiety score. Education level, almost all dimensions of the symptom scales except for diarrhea, the QL score, and the trait anxiety score were found to be significantly associated with the state anxiety score. Being undereducated (p = 0.019) and having more symptoms (p < 0.001 for most scales), worse QL (p < 0.001), and a higher trait anxiety level (p < 0.001) were associated with a higher level of state anxiety while waiting for the final pathology report after surgery.

Multivariable linear regression indicated that dyspnea (p=0.017), insomnia (p=0.026), QL (p<0.001), and trait anxiety (p<0.001) were independent factors associated with state anxiety (Table 5).

Discussion

To date, several studies have evaluated long-term mental health and HRQoL and reported serious anxiety and decreased HRQoL in patients with thyroid cancer [11, 12, 14, 15], but no studies have reported on patients' short-term anxiety level or HRQoL while awaiting pathology reports after surgery.



380 Endocrine (2022) 76:377–384

Table 1 Baseline characteristics of papillary thyroid cancer patients

	Total $(n = 349)$	With FNA $(n = 192)$	Without FNA $(n = 157)$	p
Age: median (range)	39 (20–74)	39 (20–74)	40 (22–65)	0.212
Sex				0.502
Male, %	86 (24.6)	50 (26.0)	36 (22.9)	
Female, %	263 (75.4)	142 (74.0)	121 (77.1)	
Education				0.488
≤High school, %	72 (20.6)	37 (19.3)	35 (22.3)	
≥College, %	277 (79.4)	155 (80.7)	122 (77.7)	
Work				0.886
Employed, %	268 (76.8)	148 (77.1)	120 (76.4)	
Not working, %	81 (23.2)	44 (22.9)	37 (23.6)	
Marital				0.370
Married, %	298 (85.4)	161 (83.9)	137 (87.3)	
Single/Divorced/Widowed, %	51 (14.6)	31 (16.1)	20 (12.7)	
Annual family income (RMB) ^a				0.404
<60,000, %	86 (24.6)	43 (22.4)	43 (27.4)	
60,000–150,000, %	124 (35.5)	67 (34.9)	57 (36.3)	
>150,000, %	139 (39.8)	82 (42.7)	57 (36.3)	
Family history				0.590
No, %	271 (77.7)	147 (76.6)	124 (79.0)	
Yes, %	78 (22.3)	45 (23.4)	33 (21.0)	
Tumor size (mm)				0.890
<10, %	175 (50.1)	101 (52.6)	74 (47.1)	
10–19, %	137 (39.3)	71 (37.0)	66 (42.0)	
20–29, %	27 (7.7)	15 (7.8)	12 (7.6)	
30–39, %	8 (2.3)	4 (2.1)	4 (2.5)	
≥40, %	2 (0.6)	1 (0.5)	1 (0.6)	
Surgery				0.002
Unilateral lobectomy	86 (24.6)	35 (18.2)	51 (32.5)	
Total thyroidectomy	263 (75.4)	157 (81.8)	106 (67.5)	
Complications				0.001
None, %	188 (53.9)	90 (46.9)	98 (62.4)	
1, %	109 (31.2)	62 (32.3)	47 (29.9)	
2, %	52 (14.9)	40 (20.8)	12 (7.6)	
Waiting period				0.693
<1 week, %	152 (43.6)	82 (42.7)	70 (44.6)	
1–2 weeks, %	175 (50.1)	96 (50.0)	79 (50.3)	
>2 weeks, %	22 (6.3)	14 (7.3)	8 (5.1)	

^a1 RMB is equivalent to 0.16 USD

The bold entries indicate variables with p value less than 0.05

The present study, for the first time, investigated state anxiety and HRQoL among patients with papillary thyroid cancer during the short-term period of waiting for pathology results after surgery, compared anxiety levels and HRQoL according to whether patients had preoperative FNA results, and clarified the factors associated with state anxiety.

The results indicated that the patients had good generally QL with a score of 75.69 ± 20.66 (8.33–100.00)

during the waiting period, except for some complaints about social functioning and physical symptoms. The difference in anxiety levels between the FNA group and the non-FNA group in this study was not significant. However, a significantly higher level of state anxiety than trait anxiety was observed among patients awaiting pathology results after surgery, and symptoms of dyspnea and insomnia, QL, and trait anxiety were found to be potential



Endocrine (2022) 76:377–384 381

Table 2 EORTC-QLQ-C30 scores

	Total	With FNA	Without FNA	p
	Mean (SD)			
Functioning sca	le ^a			
Physical	79.56 (19.80)	80.17 (18.22)	78.81 (21.61)	0.530
Role	75.93 (27.07)	76.13 (26.23)	75.69 (28.15)	0.881
Emotional	66.40 (24.41)	67.49 (22.60)	65.07 (26.47)	0.366
Cognitive	76.93 (23.38)	78.04 (23.06)	75.58 (23.76)	0.330
Social	82.28 (21.60)	84.64 (19.51)	79.41 (23.66)	0.027
Symptom scale ^b	•			
Fatigue	38.20 (25.85)	39.35 (27.02)	36.80 (24.36)	0.360
Nausea/	4.68 (11.39)	5.38 (11.57)	3.82 (11.14)	0.202
vomiting				
Pain	18.14 (20.38)	19.36 (21.10)	16.67(19.43)	0.220
Dyspnea	32.00 (31.40)	34.20 (31.53)	29.30 (28.83)	0.134
Insomnia	32.86 (32.31)	34.55 (32.25)	30.79 (32.37)	0.280
Loss of	15.76 (22.67)	17.19 (24.11)	14.01 (20.72)	0.187
appetite				
Constipation	16.43 (25.10)	16.67 (26.42)	16.14 (23.45)	0.844
Diarrhea	8.98 (18.11)	9.03 (18.98)	8.92 (17.04)	0.955
Financial difficulties	8.98 (19.14)	9.03 (19.28)	8.92 (19.01)	0.957
Global quality of life ^a	75.69 (20.66)	74.57 (20.97)	77.07 (20.25)	0.261

^aA higher score indicates better functioning

The bold entries indicate variables with p value less than 0.05

Table 3 STAI scores

	Total Mean (SD)	With FNA	Without FNA	p ^a
State anxiety	41.78 (11.96)	41.46 (11.51)	42.17 (12.52)	0.580
Trait anxiety	40.51 (10.34)	40.37 (9.63)	40.69 (11.18)	0.775
p^{b}	0.003	0.058	0.023	

^aThe differences between the FNA group and the non-FNA group

factors that affect state anxiety in the short-term postoperative period.

The EORTC-QLQ-C30, which was used to measure the HRQoL of papillary thyroid cancer patients within 2 weeks after surgery in terms of function, symptoms, and QL, showed that the patients reported generally good QL in the study period, with a mean score of 75.69, which is similar to the results of long-term HRQoL reported by several previous studies based on the same scale [29–31]. In this study, the patients reported high scores regarding physical, role,

Table 4 Bivariate analysis of state anxiety scores

	State anxiety Mean (SD)	p
Sex		0.347
Male	41.20 (11.64)	
Female	41.97 (12.08)	
Education		0.019
≤High school	44.72 (12.15)	
≥College	41.01 (11.82)	
Work		0.799
Employed	41.87 (11.67)	
Not working	41.48 (12.96)	
Marital		0.367
Married	41.54 (11.64)	
Single/divorced/widowed	43.18 (13.76)	
Annual family income (RMB)		0.103
<60,000	43.71 (13.18)	
60,000-150,000	42.13 (12.30)	
>150,000	40.27 (10.69)	
Family history		0.598
No	41.60 (11.56)	
Yes	42.41 (13.31)	
FNA	,	0.580
With	41.46 (11.51)	
Without	40.37 (6.93)	
Tumor size (mm)	,	0.575
<10	41.73 (12.01)	
10–19	41.54 (11.83)	
20–29	44.81 (11.93)	
30–39	37.63 (13.50)	
≥40	38.50 (16.26)	
Surgery	,	0.351
Unilateral lobectomy	40.73 (11.94)	
Total thyroidectomy	42.12 (11.97)	
Complications		0.363
None	40.95 (12.30)	
1	42.94 (11.77)	
2	42.35 (11.05)	
Waiting period		0.166
<1 week	41.42 (12.09)	
1–2 weeks	41.50 (12.07)	
>2 weeks	46.45 (9.49)	
	Correlation coefficients (r)	
Age	0.002	0.971
Functioning scale		
Physical	0.045	0.405
Role	0.037	0.493
Emotional	0.087	0.103
Cognitive	0.038	0.474



^bA higher score indicates more symptoms

^bThe differences between state anxiety scores and trait anxiety scores The bold entries indicate variables with p value less than 0.05

382 Endocrine (2022) 76:377-384

Table 4 (continued)

	State anxiety Mean (SD)	p
Social	0.082	0.128
Symptom scale		
Fatigue	0.368	< 0.001
Nausea/vomiting	0.156	0.003
Pain	0.310	< 0.001
Dyspnea	0.209	< 0.001
Insomnia	0.373	<0.001
Loss of appetite	0.257	< 0.001
Constipation	0.198	< 0.001
Diarrhea	0.075	0.164
Financial difficulties	0.289	< 0.001
Global quality of life	-0.492	< 0.001
Trait anxiety	0.752	< 0.001

The bold entries indicate variables with p value less than 0.05.

Table 5 Multivariable linear regression of state anxiety scores

	β	95% CI	p
Education	-0.567	-2.630 to 1.496	0.541
Symptom scale			
Fatigue	0.023	-0.025 to 0.070	0.348
Nausea/vomiting	-0.019	-0.097 to 0.060	0.643
Pain	0.032	-0.015 to 0.079	0.182
Dyspnea	-0.040	-0.073 to 0.007	0.017
Insomnia	0.034	0.004 to 0.065	0.026
Loss of appetite	0.007	-0.035 to 0.049	0.760
Constipation	-0.006	-0.041 to 0.028	0.717
Financial difficulties	-0.012	-0.059 to 0.035	0.608
Global quality of life	-0.122	-0.167 to 0.076	<0.001
Trait anxiety	0.745	0.657 to 0.834	<0.001

R = 0.794

 $R^2 = 0.631$

turbance in the short-term after surgery [33], and cancerrelated fatigue and postoperative discomfort are the most likely explanations [34].

The bold entries indicate variables with p value less than 0.05 cognitive, and social functioning, with relatively low scores for emotional functioning, reflecting that the patients were experiencing more tension, worry, irritability, and depression [30–32]. The most common symptom was fatigue, which corroborates the findings of previous long-term observations that fatigue is the most dominant HRQoL issue [29, 32, 33]. This may partly be due to hormonal dis-

Although the OL scores were similar between the two groups, there were more complaints of decreased social functioning in the non-FNA group, which indicates that patients' family life and social activities were interfered with while waiting for pathology reports after surgery. This finding has not been previously described, and the interference with family life and social activities may be explained by the decreased ability to take part in routine life and work, as patients were at the early stage of rehabilitation and were anxiously awaiting the final diagnosis.

In terms of anxiety level, of the 349 patients who underwent surgery, state anxiety levels during the waiting period were significantly higher than trait anxiety levels, indicating that the patients had higher than usual levels of anxiety while awaiting their pathology results. This result was not reported in previous studies, which only indicated that anxiety was a problem for most patients in the long term [30, 35]. However, it is in line with our expectations regarding anxiety levels during the short term. During the special period after surgery, the patient is awaiting the final pathology report, which determined the nature of the thyroid nodule as well as the future course of treatment. This may be a major component of anxiety during this short period. Another possible alternative explanation of the high state anxiety level may be the high incidence of postoperative complications (approximately 46%), which could be due to the short time window after surgery for the recovery of reversible adverse events; this could, in itself, influence responses to psychometric tests.

The current study showed that higher levels of state anxiety during this period were manifested in patients with lower education levels, more symptoms, lower QL scores, and higher trait anxiety levels. Education level has previously been reported to be associated with long-term anxiety [36]. More educated individuals were more knowledgeable about their condition [25], which may lead to lower anxiety levels. Our study also showed that symptoms including fatigue, nausea and vomiting, pain, dyspnea, insomnia, loss of appetite, and constipation were significantly associated with short-term postoperative anxiety, which may be explained by short-term postoperative surgery-related discomfort. Due to worse social functioning and a lack of ability to get a job, financial difficulties have been reported to be significantly associated with postoperative anxiety [37], which was confirmed in bivariate analysis of state anxiety in this study.

In the multivariable linear regression analysis, patients with symptoms of dyspnea and insomnia and lower QL scores reported higher state anxiety scores during the waiting period. Another significant finding is that trait anxiety level was an independent factor positively related to state anxiety. A recent study on patients' views on management options for papillary thyroid microcarcinoma reported that state anxiety seemed to be mostly related to an



Endocrine (2022) 76:377–384 383

individual's trait rather than management [38], and it remains a long-term outcome. Our study proved that trait anxiety was an independent influential factor of state anxiety even during a short period after surgery among thyroid cancer patients. Patients with a higher level of trait anxiety were likely to present a higher level of state anxiety during this period.

It is worth noting that there was a statistically significant difference between state anxiety and trait anxiety in patients who did not undergo preoperative FNA, indicating that the anxiety level during the waiting period was higher than that during usual life. This interesting result was not observed in patients who underwent FNA before surgery. Since preoperative FNA provides patients with a preliminary pathology result and subsequently with a psychological expectation regarding the nature of their thyroid nodules, it may lead to smaller fluctuations in their anxiety levels during that particular period relative to their trait anxiety in normal times. Since preoperative FNA is not routinely performed in every patient with suspected thyroid cancer in China, more consideration should be given to the individualized profile of the patient, including his or her usual personality.

Despite these encouraging findings, this study has several limitations. First, this was a cross-sectional study, and the causality between state anxiety and the variables examined herein needs to be further validated with prospective studies in the future. Second, the questionnaire we used is a translated Chinese version, and although its quality has been validated, it may differ slightly from the original in terms of the details conveyed. Additionally, the symptoms of anxiety were assessed through self-report questionnaires, and the impact of personality aspects on psychological symptoms may need to be evaluated by psychiatrists in future studies.

In conclusion, patients with papillary thyroid cancer reported a higher than usual level of state anxiety independently related to symptoms of dyspnea and insomnia, QL, and the level of trait anxiety. Preoperative FNA did not significantly improve postoperative HRQoL, but it may be useful to alleviate patients' perioperative fluctuations in anxiety levels. Postoperative anxiety in patients with malignant tumors may cause a great impact on physical recovery and psychological health, which seriously affects normal life and work. In the present study, it was possible to identify risk factors and methods for assessing the level of short-term anxiety among patients after surgery. Thus, psychological guidance and intervention should be provided, and psychological support and assistance should be provided.

Data availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are

available from the corresponding author on reasonable request.

Author contributions S.Y.: data analysis, data interpretation, original manuscript drafting; X.X.: study concept and design, data collection, data interpretation, original manuscript drafting and editing.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Consent to participate All individual participants consented to participate in the study.

Consent for publication All individual participants consented to have their data published.

Ethical approval The study was approved by the Ethics Committee of Peking Union Medical College Hospital (JS-2555).

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384 Endocrine (2022) 76:377–384

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