

Effectiveness of the Gerdq Questionnaire for Diagnosing Gastroesophageal Reflux Disease After Esophagectomy for Esophageal Cancer

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Summary: Background: Gastroesophageal reflux disease (GERD) is a common complication after esophagectomy with gastric tube reconstruction. The GerdQ questionnaire was developed for diagnosing GERD in primary care patients. Its effectiveness in patients after esophagectomy remains unknown. In this study, we evaluated the usefulness of the GerdQ questionnaire for diagnosing GERD after esophagectomy for esophageal cancer.

Materials and Methods: A total of 124 patients with esophageal cancer underwent right transthoracic esophagectomy with gastric tube reconstruction between January 2010 and December 2016. Esophagogastroduodenoscopy and 24-hour esophageal pH-metry were performed at 1 month, 1 year, and 2 years postoperatively. The GerdQ questionnaire was administered at the same postoperative time points. We assessed any correlation between the GerdQ scores and the endoscopy and pH-metry findings.

Results: The incidence rates of GERD at 1 month, 1 year and 2 years post-surgery were 31.6%, 46.9%, and 49.2%, respectively. The GerdQ questionnaire showed 77% sensitivity and 56% specificity for diagnosing GERD at 2 years after esophagectomy when the cutoff point was 7. However, the optimal cutoff points were different at each postoperative time, and the scores showed some imbalance between sensitivity and specificity. Regurgitation may be a useful indicator, as the frequency of regurgitation was significantly higher in patients with GERD than in patients without GERD at 1 year ($P = 0.046$) and 2 years postoperatively ($P = 0.048$).

Conclusion: The GerdQ questionnaire is not a useful diagnostic tool for GERD in patients who have undergone esophagectomy for esophageal cancer.

Keywords gastroesophageal reflux disease, esophageal cancer, esophagectomy, GerdQ questionnaire, reflux symptom

INTRODUCTION

The postoperative prognosis of esophageal cancer has improved due to multidisciplinary treatment methods, and maintaining a good quality of life (QOL) is now becoming important for patients who have undergone radical esophagectomy. Gastroesophageal reflux disease (GERD) is a common complication after es-

ophagectomy with gastric tube reconstruction [1-5]. Reflux symptoms are reported to have a significant impact on QOL in these patients [6,7]. Therefore, effective diagnosis, prevention, and treatment methods of postoperative GERD are important.

Objective tests including esophagogastroduodenoscopy, 24-hour esophageal pH-metry, and esophageal manometry are useful to diagnose GERD [8], but

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Abbreviations: GERD, gastroesophageal reflux disease; PPIs, proton pump inhibitors; SAP, symptom association probabilities

they are invasive and costly. In contrast, GERD questionnaires are effective diagnostic tools as they are low cost and noninvasive and reproducible. Questionnaires are useful tools for diagnosing GERD and for subjectively assessing symptoms in a primary care setting [9]. However, the usefulness of GERD questionnaires in patients after esophagectomy for esophageal cancer has yet to be determined. Patients who have undergone esophagectomy have anatomical changes such as failure of the antireflux mechanism at the esophagogastric junction, gastric tube elevation to the neck, and truncal vagotomy. Therefore, it is necessary to verify whether the GERD questionnaire is useful for patients after esophagectomy. If the questionnaire is useful after esophagectomy, fewer invasive tests will be necessary.

There are various types of GERD questionnaires, including the GerdQ questionnaire, reflux disease questionnaire (RDQ), questionnaire for the diagnosis

of reflux disease (QUEST), and frequency scale for the symptoms of GERD (FSSG) [10-13]. Among them, the GerdQ questionnaire is the simplest and is widely used in primary care [10,14-16]. It is a symptom-based GERD diagnostic tool developed by Jones et al. [10]. It is a self-administered, 6-item questionnaire about heartburn, regurgitation, epigastric pain, nausea, sleep disturbance, and use of over the counter drugs (Table 1). The total GerdQ score is the sum of the score of each item. The GerdQ questionnaire shows 65% sensitivity and 71% specificity for diagnosing GERD when the cutoff point is 8. Its sensitivity and specificity are similar to those achieved by a gastroenterologist [10].

This study aimed to assess the effectiveness of the GerdQ questionnaire for diagnosing GERD in patients who have undergone esophagectomy for esophageal cancer.

TABLE 1.
The GerdQ questionnaire

Question	Frequency score (points)			
	0 day	1 day	2-3days	4-7days
1. How often did you have a burning feeling behind your breastbone (heartburn)?	0	1	2	3
2. How often did you have stomach contents (liquid or food) moving upwards to your throat or mouth (regurgitation)?	0	1	2	3
3. How often did you have a pain in the center of the upper stomach?	3	2	1	0
4. How often did you have nausea?	3	2	1	0
5. How often did you have difficulty getting a good night's sleep because of your heartburn and/or regurgitation?	0	1	2	3
6. How often did you take additional medication for your heartburn and/or regurgitation, other than what the physician told you to take? (such as Tums, Roloids, Maalox?)	0	1	2	3

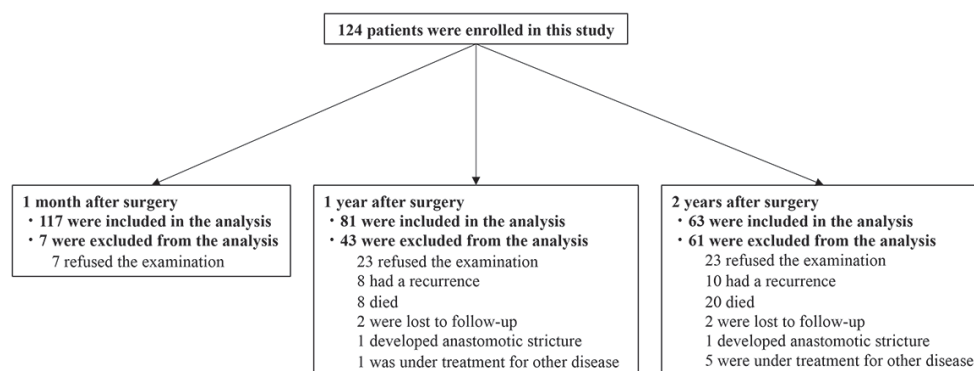


Fig. 1. Study participants selection criteria flow diagram

MATERIALS AND METHODS

Patients

One hundred twenty-four patients who underwent right transthoracic esophagectomy and esophagogastrostomy for esophageal cancer at Kurume University Hospital between January 2010 and December 2016 were enrolled in this study. Exclusion criteria were as follows: examination refusal, recurrence, death, loss to follow-up, and development of anastomotic stricture. The patient population consisted of 112 men and 12 women, with an average age of 66 years (range: 50-75 years). The number of patients with recorded follow-up date at 1 month, 1 year, and 2 years postoperatively were 117, 81, and 63, respectively (Fig. 1). The clinical characteristics of the patients were summarized in Table 2.

Written informed consent was obtained from each patient. This study was approved by the Kurume University Hospital Ethics Board (approval number: 16259).

Surgical procedure

A right transthoracic esophagectomy with two or three-field lymphadenectomy (depending on the location of tumor) was performed. A subtotal gastric tube was constructed using linear staplers, and was pulled up to the neck through one or other of three routes: posterior mediastinal, retrosternal, or subcutaneous. Esophagogastrostomy was performed using a circular stapler. Pyloric digital dilatation was performed.

Study protocols

Each patient underwent esophagogastroduodenoscopy and 24-hour esophageal pH-metry at 1 month, 1 year, and 2 years postoperatively. The GerdQ questionnaire was also administered at those times. Patients taking proton pump inhibitors (PPIs) were instructed to discontinue PPIs at least 3 days prior to these examinations. Reflux esophagitis was evaluated in accordance with the Los Angeles Classification of Gastroesophageal Reflux Disease [17]. Esophageal pH-metry was performed using a DIGITRAPPER pH 400 (Medtronic, Tonsbakken, Skovunde, Denmark) and a four-channel antimony electrode sensor (Medtronic). The pH sensor was introduced transnasally using fluoroscopy. The esophageal pH was measured at 2.5 cm above the esophagogastrostomy. An esophageal pH < 4 was defined as acid exposure, and the percentage of acid exposure time was noted.

In this study, GERD was defined as grade A-D esophagitis on esophagogastroduodenoscopy or an es-

TABLE 2.
Patients' clinical characteristics

	n (%)
Median age, years (range)	66 (50-75)
Gender	
Male	112 (90.3)
Female	12 (9.7)
BMI, kg/m ² (range)	19 (14-27)
Number of study population	
1 month	117 (94.4)
1 year	81 (65.3)
2 years	63 (50.1)
<i>H. pylori</i> infection	
Positive	59 (47.6)
Negative	65 (52.4)
Tumor location	
Upper thoracic	15 (12.1)
Middle thoracic	70 (56.5)
Lower thoracic	39 (31.4)
Pathologic type	
Squamous cell carcinoma	116 (93.6)
Adenocarcinoma	3 (2.4)
Other	5 (4.0)
Pathologic staging	
0	13 (10.5)
I	16 (13.0)
II	38 (30.6)
III	36 (29.0)
IV	21 (16.9)
Route of reconstruction	
Posterior mediastinal	52 (42.0)
Retrosternal	4 (3.2)
Subcutaneous	68 (54.8)
Adjuvant chemotherapy	38 (30.6)
No	86 (69.4)
Chemotherapy	20 (16.1)
Chemoradiation therapy	18 (14.5)
Postoperative laryngeal nerve palsy	35 (28.2)
Recurrence	29 (23.3)

BMI, body mass index; *H. pylori*, *Helicobacter pylori*

ophageal pH < 4 for > 5.5% of a 24-hour period on esophageal pH-metry. The correlation between the GerdQ questionnaire scores and the findings from the objective GERD diagnostic tests was assessed. In addition, the usefulness of each question item was evaluated.

PPIs were administered immediately after surgery to those patients with a history of gastroduodenal ulcer. For other patients, PPIs are prescribed after GERD is diagnosed by these objective tests.

Statistical analysis

The Pearson chi-square test was used to compare the presence of GERD at each postoperative time point. The Wilcoxon rank-sum test was used to examine the relationship between the presence of GERD and the GerdQ score. A 2×2 table was created by dividing the GerdQ score into two groups based on a cutoff point of 6, 7, 8 or 9. Fisher's exact test was used to determine the P value of each 2×2 table. The cutoff point with the smallest P value was selected as the optimal cutoff point for each postoperative time point. Then, the sensitivity and specificity of each optimal cutoff point were calculated.

The question items of the GerdQ questionnaire were dichotomized into presence and absence, and the Pearson chi-square test was applied to test the difference between patients with GERD and those without GERD. A P value was considered statistically significant at a level of < 0.05. The JMP program (version 11; SAS Institute, Cary, NC, USA) was used for all analyses.

RESULTS

The incidence of GERD at 1 month, 1 year, and 2 years postoperatively was 31.6%, 46.9%, and 49.2%, respectively (Table 3). PPIs were used in 5.1% of patients at 1 month, 45.6% of patients at 1 year, and 63.4% of patients at 2 years after surgery (Table 4). The response rate for the GerdQ questionnaire was 100%. The GerdQ score at 1 month and 2 years after surgery was significantly higher in patients with GERD than in patients without GERD ($P = 0.04$ and $P = 0.03$, respectively), but no significant difference was shown at 1 year after surgery ($P = 0.23$) (Fig. 2).

The optimal cutoff points for the GerdQ questionnaire scores at 1 month, 1 year, and 2 years postoperatively were 8, 6, and 7, respectively. The sensitivity and specificity of the GerdQ questionnaire for detecting GERD were 32% and 88% at 1 month after surgery, 95% and 16% at 1 year after surgery, and 77%

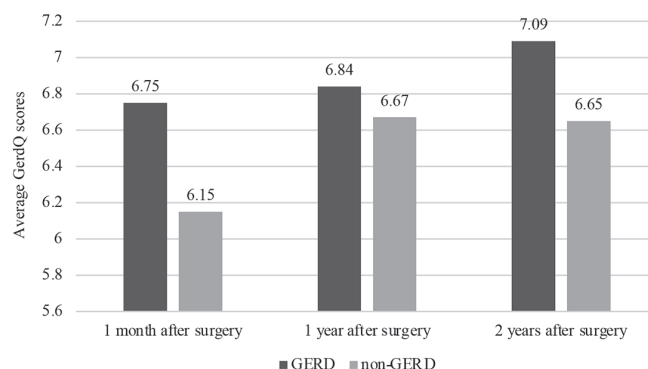


Fig 2. The average GerdQ scores in patients with gastroesophageal reflux disease (GERD) and in those without GERD at each postoperative time point.

The GerdQ score at 1 month and 2 years after surgery was significantly higher in the patients with GERD than in the patients without GERD ($P = 0.04$ and $P = 0.03$, respectively), but no significant difference was shown at 1 year after surgery ($P = 0.23$).

and 56% at 2 years after surgery, respectively (Table 5).

The frequency of regurgitation reported by patients via the GerdQ questionnaire was significantly higher in the patients with GERD than in the patients without GERD at 1 year and at 2 years postoperatively ($P = 0.046$ and $P = 0.048$, respectively). Furthermore, the same tendency was observed at 1 month after surgery, but the difference between the two groups was not significant ($P = 0.06$). Responses to other items on the questionnaire including heartburn, epigastric pain, nausea, sleep disturbance, and use of over the counter medication did not differ significantly between the two groups at any time point (Table 6).

DISCUSSION

We analyzed the relationship between the GerdQ score and the findings from endoscopy and pH-metry to evaluate the usefulness of the GerdQ questionnaire for diagnosing GERD in patients who have undergone esophagectomy. The GerdQ questionnaire showed 77% sensitivity and 56% specificity for diagnosing GERD in patients at 2 years after esophagectomy when the cutoff point was 7. These values are similar to the sensitivity and specificity of the GerdQ questionnaire reported in previous studies of primary care patients [10,14]. However, in our study, the optimal cutoff points were different at each follow-up time point, and the sensitivity and specificity were imbalanced at 1 month and 1 year postoperatively. These results indicate that the GerdQ questionnaire is not useful for the diagnosis of GERD in patients who have

TABLE 3.
The incidence of gastroesophageal reflux disease

	Time after surgery			<i>P</i> value
	1 month (n=117)	1 year (n=81)	2 years (n=63)	
GERD, n (%)	37 (31.6)	38 (46.9)	31 (49.2)	0.028
Reflux esophagitis, n (%)	5 (4.3)	23 (28.4)	17 (27.0)	
Acid reflux, n (%)	35 (29.9)	28 (34.6)	23 (36.5)	

GERD, gastroesophageal reflux disease

TABLE 4.
Use of proton pump inhibitors

	Time after surgery			<i>P</i> value
	1 month (n=117)	1 year (n=81)	2 years (n=63)	
Use of PPIs, n (%)	6 (5.1)	37 (45.6)	40 (63.4)	<0.001

PPIs, proton pump inhibitors

TABLE 5.
The optimal cutoff points for the GerdQ score

	Cutoff point	Sensitivity	Specificity
1 month after surgery	8	32%	88%
1 year after surgery	6	95%	16%
2 years after surgery	7	77%	56%

TABLE 6.
Correlation between each question item in the GerdQ questionnaire and the incidence of gastroesophageal reflux disease

	1 month (n=117)			1 year (n=81)			2 years (n=63)		
	GERD (n=37)	non-GERD (n=80)	<i>P</i> value	GERD (n=38)	non-GERD (n=43)	<i>P</i> value	GERD (n=31)	non-GERD (n=32)	<i>P</i> value
Heartburn (+ / -)	10/27	11/69	0.08	7/31	9/34	0.86	10/21	9/23	0.72
Regurgitation (+ / -)	15/22	19/61	0.06	26/12	20/23	0.046	23/8	16/16	0.048
Epigastric pain (+ / -)	36/1	79/1	0.86	38/0	42/1	0.80	30/1	31/1	0.72
Nausea (+ / -)	36/1	77/3	0.80	37/1	42/1	0.98	30/1	31/1	0.54
Sleep disturbance (+ / -)	11/26	16/64	0.21	12/26	16/27	0.71	12/19	6/26	0.08
Use of OTC medications (+ / -)	0/37	0/80	—	0/38	0/43	—	2/29	1/31	0.56

GERD, gastroesophageal reflux disease; OTC, over-the-counter

undergone esophagectomy.

The incidence rate of GERD after esophagectomy with gastric tube reconstruction is high. Reflux esophagitis has been reported to occur in 37-71.6% of patients who undergo esophagectomy, and acid reflux into the residual esophagus occurs in 28-32.1% of these patients [1-5]. The incidence rate of GERD in our study is 31.6-49.2%, which increased as the postoperative course progressed (Table 3). The use of PPIs also increased as the incidence of GERD increased (Table 4). Kim *et al.* reported that gastric acidity increases over time after esophagectomy, and that the duration of esophageal acid exposure is correlated with intragastric pH [5]. Furthermore, Gutschow *et al.* reported that 97.6% of patients who have undergone esophagectomy have normal gastric pH after 3 years [18]. The incidence rate of GERD is expected to increase as the postoperative course progresses.

Reflux is the most prevalent symptom after esophagectomy, and it is associated with a lower QOL [6,7]. However, the results of this study suggest that GERD after esophagectomy is poorly associated with reported symptoms. Truncal vagotomy during esophagectomy influenced the reported symptoms. Esophageal mucosa stimuli are conveyed to the brain via spinal nerves or vagal nerves [19]. In the past, a vagotomy was performed to relieve pain due to digestive system malignancies, which considerably reduced visceral sensation [20]. Chen *et al.* reported that neuronal activities in the medulla oblongata, which is the termination of the vagus nerve, decreased after a vagotomy [21]. This suggests that vagotomy during esophagectomy may lead to decreased sensation of the residual esophagus and the gastric tube.

The GerdQ questionnaire was developed for primary care patients, and most of its question items are influenced by surgery. In the analysis for each question item of GerdQ in this study, only regurgitation was considered useful for diagnosing GERD after esophagectomy. These findings indicate that the pharyngeal and oral sensations are not lost after esophagectomy. However, response to the other questions on the GerdQ questionnaire were not useful. Shibuya *et al.* reported that perception of the cervical esophagus is lost after esophagectomy, and there is no significant relationship between cervical heartburn and reflux esophagitis [1]. In our study, the most reported symptoms are epigastric pain and nausea, which are negative predictors of GERD. However, these are not significantly correlated to GERD in our study. After esophagectomy, these dyspeptic symptoms tend to appear and are not useful for the diagnosis of GERD.

Use of over the counter medication, another GerdQ questionnaire item, was very low in this study. We believe that this is because patients are under the care of a primary care physician who can prescribe medications as needed.

In order to develop a questionnaire that is useful for the diagnosis of GERD in patients who have undergone esophagectomy, it is necessary to include symptoms that are not affected by surgery, such as regurgitation, in the question items. We estimate that extraesophageal symptoms of GERD including pharyngeal discomfort and chronic cough are also less influenced by surgery, as these are not digestive symptoms. Further research is needed to specify the question items that could be useful in a questionnaire developed for diagnosing GERD after esophagectomy.

Our study has some limitations. First, the number of patients decreased over time, and the number of patients that were observed for the full 2-year follow-up period was small. Second, symptom association probabilities (SAP) were not calculated. In previous reports that assess the diagnostic validity of the GerdQ questionnaire, SAP > 95% was one of the diagnostic criteria for GERD [10,14]. Thus, the number of patients with GERD may have been under detected. Third, we discontinued PPI administration for at least 3 days before examinations. Therefore, PPI had no effect on the pH-metry, but may have affected the endoscopy and questionnaire results.

CONCLUSION

The GerdQ questionnaire is not useful for diagnosing GERD in patients who have undergone esophagectomy for esophageal cancer. The diagnosis of GERD after esophagectomy continues to require conventional objective examination methods. More studies are needed to determine if other questionnaires are able to successfully diagnose GERD in this patient population.

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CONFLICT OF INTEREST: The authors declare that they have no conflict of interests.

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