RAPID REVIEW

Dysplasia severity is associated with poor quality of life in patients with Barrett's esophagus referred for endoscopic eradication therapy

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SUMMARY. Limited data exist regarding patient-reported outcomes and quality of life (QOL) experienced by patients with Barrett's esophagus (BE) referred for endoscopic eradication therapy (EET). Specifically, the impact of grade of dysplasia has not been explored. The purpose of this study is to measure patient-reported symptoms and QOL and identify factors associated with poor QOL in BE patients referred for EET. This was a prospective multicenter study conducted from January 2015 to October 2017, which included patients with BE referred for EET. Participants completed a set of validated questionnaires to measure QOL, symptom severity, and psychosocial factors. The primary outcome was poor QOL defined by a PROMIS score >12. Multivariable logistic regression analysis was performed to identify factors associated with poor QOL. In total, 193 patients participated (mean age 64.6 years, BE length 5.5 cm, 82% males, 92% Caucasians) with poor QOL reported in 104 (53.9%) participants. On univariate analysis, patients with poor QOL had lower use of twice daily proton pump inhibitor use (61.5% vs. 86.5%, $P = 0.03$), shorter disease duration (4.9 vs. 5.9 years, $P = 0.04$) and progressive increase in grade of dysplasia (high-grade dysplasia: 68.8% vs. 31.3%, esophageal adenocarcinoma: 75.5% vs. 24.5%, $P < 0.001$). Multivariate analysis demonstrated that high-grade dysplasia was independently associated with poor QOL (OR: 5.57, 95% CI: 1.05, 29.5, $P = 0.04$). In summary, poor QOL is experienced by the majority of patients with BE referred for EET and the degree of dysplasia was independently associated with poor QOL, which emphasizes the need to incorporate patient-centered outcomes when studying treatment of BE-related dysplasia.

KEY WORDS: Barrett's esophagus, esophageal adenocarcinoma, patient preferences, quality of life.

INTRODUCTION

Barrett's esophagus (BE) is the only identifiable precursor lesion to esophageal adenocarcinoma (EAC), a cancer with rapidly rising incidence worldwide.¹ BE develops as a consequence of long-term gastroesophageal reflux disease (GERD) and

follows a stepwise series of pathologic changes from non-dysplastic BE (NDBE) to low-grade dysplasia (LGD), high-grade dysplasia (HGD), and finally invasive EAC.² At present, degree of dysplasia is the best current biomarker to predict the risk of progression to EAC and to determine further management. Recent guidelines have

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endorsed endoscopic eradication therapy (EET) as a first-line treatment option for LGD, HGD, and mucosal EAC with the goal of diminishing risk of progression to invasive EAC and reducing the morbidity and mortality associated with this lethal cancer.^{3,4} The effectiveness and safety of EET in eradicating BE-related neoplasia and maintaining remission have been demonstrated in randomized controlled trials, large observational studies, and population-based studies.^{5,6} The goal of EET is complete eradication of dysplasia (CE-D) and complete eradication of intestinal metaplasia (CE-IM).⁵

In addition to achieving CE-IM, important objectives in the care of patients with BE should be to improve patient-reported outcomes and promote individualized patient-centered care when performing EET. However, knowledge of patient perceptions, preferences, and expectations with regards to EET for BE is deficient. While symptoms of GERD are reportedly associated with psychosocial distress and impaired quality of life (QOL),⁷ many patients with BE do not experience typical GERD symptoms.^{8,9} In the absence of symptoms, it remains difficult to fully assess the effect of BE on patients and indeed, little is known regarding the impact of BE on QOL. Furthermore, there are several patient experiences and considerations unique to BE, such as the emotional distress and QOL impairment related to risk of cancer and treatment adverse events.^{10,11} Recognizing these complex patient experiences, we hypothesized that QOL is impaired in patients with BE and that degree of BE dysplasia is associated with poorer QOL. Thus, in this prospective multicenter observational study we aimed to (1) measure QOL impairment among patients with BE referred for EET and (2) identify factors associated with reduced QOL.

MATERIALS AND METHODS

Study design and setting

We performed a multicenter prospective cohort study from January 2015 to October 2017 at four tertiary academic medical centers (University of Colorado, Washington University in St. Louis, Northwestern University, and University of California, Los Angeles) as part of the Treatment with Resection and Endoscopic Ablation Techniques for Barrett's Esophagus (TREAT-BE) Consortium. The Institutional Review Board at all sites approved the study and participants provided written informed consent.

Study subjects

Patients with NDBE with risk factors for progression (i.e. family history of EAC) or BE-related neoplasia (LGD, HGD, and intramucosal EAC) referred

for EET at any of the four participating academic medical centers were recruited for this study as part of a prospective cohort study examining outcomes related to EET. Adults (≥ 18 years old) with a histologic diagnosis of BE confirmed by expert GI pathologists at any of the four study sites were included. Demographic and endoscopic variables such as age, gender, race, duration of BE (defined as the time from initial diagnosis of BE to date of enrollment), length of BE, and presence of a hiatal hernia were collected. A standardized protocol was followed for EET at all institutions.¹² Briefly, all patients were prescribed twice daily proton pump inhibitor therapy and high-definition endoscopes were used at all participating centers. Endoscopic mucosal resection was performed for all visible lesions followed by ablation of the remaining BE segment with the goal of achieving CE-D and CE-IM. Patients were enrolled in surveillance programs after achieving the endpoint of CE-IM.

Questionnaires and data collection

Enrolled participants completed a set of self-administered validated questionnaires to assess QOL and symptom severity. These questionnaires were given in paper form or sent electronically either at the initial clinic visit prior to EET or in the preoperative area just before endoscopic treatment. Overall QOL was measured via the Patient-Reported Outcomes Measurement Information System (PROMIS) Global 10 survey v1.0, a validated 10-item questionnaire assessing global physical and mental health.¹³ Raw scores (0–40) were converted into T-score values, allowing for a standardized score in reference to a general population, with a higher raw score representing worse quality of life. A score >12 was considered to represent poor quality of life as its converted T-score represented one standard deviation worse than the mean (healthy population).¹⁴ The Gastroesophageal Reflux Disease Questionnaire (GerdQ), a validated 6-item instrument, was used to assess GERD symptoms. Scores ranged from 0 to 18, with a higher score displaying greater symptom severity. A GerdQ score >8 was considered to be abnormal, which a previous study found in 64% of GERD patients with pathologic acid exposure on pH impedance testing on proton pump inhibitor (PPI) therapy.^{7,15} The Discomfort Intolerance Scale, a validated 7-item instrument was utilized to measure tolerance of symptoms.¹⁶ Scores ranged from 0 to 42, with higher scores demonstrating greater intolerance. Lastly, the Brief Symptom Inventory, an 18-item validated questionnaire measured somatization, depression, and anxiety.¹⁷ Scores ranged from 0 to 72, with higher scores representing worse psychosocial distress. Raw scores ranged from 0 to 60, from which mean scores were calculated with

a higher mean score signifying increased symptom severity. Baseline data was also collected regarding demographic information, duration of BE (time since diagnosis), medication use, and baseline endoscopic findings including anatomic landmarks, length of BE, and baseline histology. Study data were collected and managed using the REDCap electronic data capture tools hosted at the University of Colorado.

Study outcomes

The primary outcome of this study was assessment of QOL based on the PROMIS 10 survey. Poor quality of life was defined as a PROMIS score > 12 .¹⁴ The secondary outcome was GERD symptom burden based on the GerdQ questionnaire scores. Abnormal GERD symptom burden was defined as a GerdQ score > 8 .

Statistical analysis

Analyses utilized all available data from subjects meeting inclusion criteria. Given the limited published data in this field, there were no formal power calculations for this study and we did not impute missing data. The primary analysis aimed to identify factors associated with QOL using the PROMIS score as a marker of global QOL. An unadjusted univariate analysis compared baseline demographic data, endoscopic data, and symptom questionnaire scores between those with a normal QOL (PROMIS score ≤ 12) and those with a poor QOL (PROMIS score > 12). A student's *t* test was used to compare continuous variables and a chi-square test was used to compare categorical variables. Those variables with differences at a *P* value < 0.20 on univariate analysis were then included in a multivariable logistic regression model to identify factors associated with poor QOL. Dysplasia grades were compared as the absence/presence of each level of dysplasia. The secondary analysis examined factors associated with GerdQ scores (abnormal = GerdQ score > 8) in similar manner to the primary analysis. No corrections were made for multiple comparisons. A *P* value < 0.05 was considered statistically significant. All analyses were conducted using STATA 15.1 (StataCorp, College Station, TX).

RESULTS

Participant characteristics

Out of 225 enrolled subjects, a total of 193 (85.8%) participants completed all questionnaires prior to receiving EET and are included in this analysis. The mean age was 64.6 years (SD 9.9) and the majority of participants were Caucasian males. The mean length of the BE segment was 5.5 cm (SD 4.2) and the majority had a diagnosis of HGD or EAC (66.8%)

Table 1. Baseline characteristics of study population.

Baseline characteristics	N = 193
Age (years)	64.6 (9.9)
Male sex	157 (82.2%)
Caucasian Race	176 (92.1%)
Body mass index (kg/m ²)	28.7 (7.3)
Family history of Barrett's esophagus	7 (3.6%)
Family history of Esophageal adenocarcinoma	12 (6.2%)
Twice daily dosing of PPI	141 (73.1%)
Duration of Barrett's esophagus (years)	6.2 (6.4)
Length of Barrett's esophagus (cm)	5.5 (4.2)
Degree of dysplasia	
Non-dysplastic Barrett's esophagus (NDBE) (n = 15)	15 (7.8%)
Low-grade dysplasia (LGD) (n = 49)	49 (25.4%)
High-grade dysplasia (HGD) (n = 80)	80 (41.5%)
Esophageal adenocarcinoma (EAC) (n = 49)	49 (25.4%)
PROMIS Global Quality of Life	13.6 (8.2)
PROMIS Global Quality of Life > 12	104 (53.9%)
GerdQ	7.2 (2.4)
GerdQ score > 8	63 (32.6%)
Discomfort Intolerance Scale	16.5 (8.3)
Brief Symptom Inventory	5.4 (7.2)

Data expressed as Mean (SD) or *n* (%).

at study inception (Table 1). The mean duration of BE was 6.2 years (SD 6.4) and there was no difference in duration of BE between the varying levels of dysplasia (NDBE: 6.5 years, LGD: 6.6 years, HGD: 6.2 years, EAC: 5.4 years, *P* = 0.94). Poor QOL was reported among 104 (53.9%) participants defined as PROMIS Global QOL score > 12 and abnormal GERD symptom burden (defined as GerdQ score > 8) was noted among 63 (32.6%) participants.

Primary analysis: factors associated with quality of life

In univariate analysis, the duration of BE was significantly lower among participants with a poor QOL compared with those with a normal QOL [5.1 (SD 5.8) vs. 7.6 (SD 6.8) years, respectively, *P* = 0.04] (Table 2). Use of a proton pump inhibitor (PPI) twice daily was also lower among participants with a poor QOL (52.9% vs. 66.4%, *P* = 0.03). In terms of questionnaire scoring, patients with a poor QOL had higher GerdQ scores (7.7 vs. 6.7, *P* = 0.006) and brief symptom inventory scores (7.9 vs. 1.7, *P* = 0.001). The proportion of patients reporting a poor QOL increased as the dysplasia severity of BE progressed from NDBE to EAC with corresponding increases in PROMIS QOL scores (OR: 2.58, 95% CI: 1.90, 3.49, *P* < 0.001 , Fig. 1). The following variables were then included in a multivariable regression model: age, BMI, length of BE, use of PPI twice daily, duration of BE, degree of dysplasia, GerdQ score, Discomfort Intolerance Scale score, and Brief Symptom Inventory score. In this multivariable analysis, HGD (adjusted OR: 5.57, 95% CI: 1.05, 29.5) was associated with a poor QOL with EAC having a slightly higher OR (adjusted OR: 5.87,

Table 2 Factors associated with poor quality of life.

	Normal quality of life (<i>n</i> = 89)	Poor quality of life (<i>n</i> = 104)	Unadjusted <i>P</i> value	Adjusted OR (95% CI)	Adjusted <i>P</i> -value
Age (years)	63.9 (10.9)	65.3 (8.9)	0.3	1.02 (0.91, 1.12)	0.72
Male sex	73 (82.0%)	84 (82.4%)	0.95		
Caucasian race	85 (93.4%)	91 (87.5%)	0.4		
BMI (kg/m ²)	29.4 (7.9)	28.1 (6.6)	0.21	1.12 (0.92, 1.36)	0.27
PPI twice daily	77 (86.5%)	64 (61.5%)	0.03	0.39 (0.1, 1.2)	0.1
Duration of BE (years)	7.6 (6.8)	5.1 (5.8)	0.04	0.86 (0.71, 1.04)	0.12
Family History of BE	2 (2.3%)	5 (4.8%)	0.35		
Length of BE (cm)	4.9 (4.2)	5.9 (4.1)	0.25		
Degree of dysplasia					
LGD (<i>n</i> = 49)	22 (44.9%)	27 (55.1%)	0.84	2.5 (0.5, 12.9)	0.28
HGD (<i>n</i> = 80)	25 (31.3%)	55 (68.8%)	<0.001	5.57 (1.05, 29.5)	0.04
EAC (<i>n</i> = 49)	12 (24.5%)	37 (75.5%)	<0.001	5.87 (0.97, 35.5)	0.05
GerdQ score	6.7 (1.9)	7.7 (2.6)	0.006	1.73 (0.87, 3.46)	0.12
Discomfort Intolerance Scale	53.3 (33.5)	58.3 (23.4)	0.18	0.96 (0.89, 1.03)	0.07
Brief symptom inventory	1.7 (2.8)	7.9 (8.1)	<0.001	1.34 (1.13, 1.58)	0.04

Data expressed as mean (SD) or *n* (%).

BE, Barrett's esophagus; BMI, body mass index; EAC, esophageal adenocarcinoma; LGD, low-grade dysplasia; HGD, high-grade dysplasia; PPI, proton pump inhibitor; NDBE, non-dysplastic Barrett's esophagus.

Fig. 1 Proportion of patients with poor quality of life by degree of dysplasia. EAC, esophageal adenocarcinoma; LGD, low-grade dysplasia; HGD, high-grade dysplasia; NDBE, nondysplastic Barrett's esophagus; *P* = 0.003.

95% CI: 0.97, 35.5). In addition, the Brief Symptom Inventory score remained significantly associated with poor QOL (adjusted OR: 1.34, 95% CI: 1.13, 1.58).

Secondary analysis: factors associated with GERD symptoms (GerdQ)

A total of 63 (32.6%) patients reported abnormal GerdQ scores. The univariate analysis of factors associated with GerdQ scores is displayed in Table 3. On univariate analysis, the Discomfort Intolerance Scale score was significantly lower in the abnormal GerdQ group (11.3 (SD 9.9) vs. 17.4 (SD 7.7), *P* < 0.001) than the normal GerdQ group. Longer lengths of BE were seen among patients with an abnormal GerdQ compared to those with a normal GerdQ score [6.8 (SD 4.8) cm vs. 5 (SD 3.9) cm, respectively, *P* = 0.08]. Multivariate analysis showed that only the Discomfort Intolerance Scale score was independently associated with abnormal GerdQ scores (adjusted OR: 0.92, 95% CI: 0.86, 0.98, *P* = 0.01).

DISCUSSION

Endoscopic eradication therapy for BE has transformed the management of BE related neoplasia and

Table 3 Factors associated with abnormal reflux symptoms (GerdQ > 8)

	Normal GERDQ (<i>n</i> = 130)	Abnormal GERDQ (<i>n</i> = 63)	Unadjusted <i>P</i> value	Adjusted OR	Adjusted <i>P</i> -value
Age (years)	65.2 (10)	63.5 (9.7)	0.28		
Male sex	103 (79.2%)	54 (85.7%)	0.22		
Caucasian Race	119 (91.5%)	57 (90.5%)	0.35		
Length of BE	5 (3.9)	6.8 (4.8)	0.08	1.12 (0.99, 1.26)	0.05
PPI twice daily	83 (63.8%)	58 (92.1%)	0.17	0.68 (0.24, 1.89)	0.46
Degree of dysplasia			0.84		
NDBE	10 (7.7%)	6 (9.5%)			
LGD	33 (25.4%)	15 (23.8%)			
HGD	56 (43.1%)	23 (36.5%)			
EAC	31 (23.8%)	19 (30.2%)			
PROMIS global quality of life	13.2 (7.9)	14.2 (8.6)	0.37		
Discomfort intolerance Scale	17.4 (7.7)	11.3 (9.9)	<0.001	0.92 (0.86, 0.98)	0.01
Brief symptom inventory	4.8 (6.8)	4.9 (6.9)	0.95		

EAC, esophageal adenocarcinoma; LGD, low-grade dysplasia; HGD, high-grade dysplasia; NDBE: nondysplastic Barrett's esophagus.

has the potential to halt the progression to invasive EAC while avoiding the morbidity and mortality associated with esophagectomy.⁵ In an era of patient-centered health care, measurement of the effect of EET in BE should include not only objective histologic endpoints (CE-D and CE-IM), but should also encapsulate patient perceptions, preferences, expectations, and symptoms. In this prospective multicenter study, we examined the burden of QOL impairment among patients with BE-related neoplasia referred for EET, and examined factors associated with impaired QOL. Greater than half of the patients reported a poor QOL. The proportion of patients with poor QOL increased as the severity of dysplasia increased. Multivariable regression analysis found that HGD in particular was associated with a poor quality of life (OR: 5.57).

Health-related QOL encompasses a number of domains, including physical, social, and emotional well-being that are directly affected by a particular disease. Poor health-related QOL can negatively impact patients not only in terms of their general well-being, but in other aspects of their life such as adherence to treatment, motivation, functional status, and ultimately even mortality.¹⁸ For these reasons, understanding the specific effects of BE on QOL is critical in delivering better care to this group of patients. This study highlights that the majority of patients with BE experience a poor QOL. This is consistent with a previous cohort study by Chang *et al.*, which found that patients with BE overall have a worse QOL compared to the general population.¹⁹ A second prospective cohort study by Kulig *et al.* described that the impairment in QOL among patients with BE to be similar to that of patients with GERD.²⁰ While chronic GERD is an important factor in the development of BE, patients with BE represent a unique subset of GERD patients. The formation of intestinal metaplasia has been associated with reduced acid sensitivity and symptomatic response to acid and reflux symptoms have been found to be a poor predictor for BE.^{21,22} The findings in our study are consistent with this phenomenon as only 32.6% of patients reported an abnormal GerdQ burden (GerdQ score >8), albeit on medical therapy. The secondary analysis compared patients with abnormal GerdQ scores and normal GerdQ scores to identify risk factors for abnormal reflux symptoms in a BE population. Only the Discomfort Intolerance Scale was found to be associated with abnormal GerdQ scores, which may reflect a lower tolerance for discomfort in patients with worse reflux symptoms. In addition to differing symptom experiences, the health status of patients with BE is influenced by a host of social, psychological, and physical health factors that the general GERD population is not subject to. In a prospective study of 42 patients with BE, Rosmolen *et al.* described the

fear of cancer recurrence as a predominant concern of patients receiving EET.²³ Chang *et al.* found in a prospective study comparing 84 patients with BE to 168 healthy controls that poor sleep and rest, and high dependence on medications reduced QOL in patients with BE.¹⁹ Thus, BE represents a unique clinical condition, which requires specific health status understanding with regards to patient centered care and outcomes.

In this study, two factors were independently associated with poor QOL: high-grade dysplasia and higher scores on the Brief Symptom Inventory. The proportion of patients with a poor QOL increased with higher degrees of dysplasia which contradict a recent study by Lee *et al.*, which found no difference in QOL (based on the Short Form-12) between dysplastic and non-dysplastic BE among a Chinese population of 139 patients.²⁴ Our study however suggests a progressive association between degree of dysplasia and QOL. We hypothesize that this association may be related to fear of cancer or recurrence of cancer as patients with HGD and EAC had the highest proportion of poor QOL.^{10,23,25} Similarly, the Brief Symptom Inventory primarily depicts somatization, depression, and anxiety, which may be contributory factors to the poor QOL in these patients. In a randomized sham controlled trial (AIM Dysplasia Trial) involving 127 patients, Shaheen *et al.* found that following EET (radiofrequency ablation), patient-reported depression, worry, stress, and dissatisfaction with the condition of their esophagus significantly decreased.²⁵ This study suggests an important role of EET on patient reported outcomes although this study was limited by the use of a nonvalidated questionnaire designed for the trial to measure QOL in BE. Thus, there is clearly a need to clarify the relationship between degree of dysplasia in BE and QOL, as this has important implications on treatment outcomes.

There are limitations of this study that merit discussion. QOL was measured using the generic PROMIS instrument since an externally validated BE-specific instrument is not currently available.²⁵ The potential for selection and participation bias in this study cannot be excluded. The potential selection bias arises from the inclusion of only patients referred for EET, as we did not include patients who opted for surgery or no treatment/surveillance alone. Additionally, as the study population was recruited from tertiary academic medical centers, these data should not be extrapolated to the general BE population. Relating to QOL, this study did not gather data on comorbidities that can also affect QOL, such as diabetes or psychiatric conditions, which also limits the generalizability to the general BE population. In addition, the possibility of survey fatigue needs to be considered given the combined length of surveys. Additionally, while

multivariable regression was performed in attempt to adjust for confounding, there exists the possibility of unmeasured confounders.

CONCLUSIONS AND FUTURE DIRECTIONS

In conclusion, this prospective multicenter cohort study highlights the significant QOL impairment among BE patients being referred for EET. Furthermore, these results emphasize the need for patient-centered care from onset of BE diagnosis and particularly with advanced dysplasia. Future work should focus on developing a BE-specific validated QOL instrument that incorporates the various issues patients with BE struggle with and examine the effect of EET on QOL and patient reported outcomes.

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