HEALTH RELATED QUALITY OF LIFE
AND ASSOCIATED SYMPTOMS IN BARRETT'S ESOPHAGUS PATIENTS

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CHAPTER 1

1

General introduction

On a daily basis, people ask each other: “how are you?”. The answer to this question often refers to the status of one's health. A human's perception of their health status, their satisfaction with their current functioning and what the individual perceives as ideal are the main determinants of the concept of health-related quality of life (HRQoL). It is generally accepted that HRQoL is a multidimensional construct that consists of at least three broad domains – physical, psychological, and social functioning – that are affected by one’s disease and/or treatment[1,2]. Physicians depend on HRQoL outcomes to gain insight into the patients’ perspectives on their disease and the effect of treatment or interventions. The increasing prevalence of chronic diseases is a result of improved living conditions, better prevention, control of infectious diseases, medical-technological improvements, and the general aging of the population[3]. Therefore, more people are living with chronic diseases that can negatively affect their HRQoL.

The prevalence of gastroesophageal reflux disease (GERD) has also increased worldwide. The Montreal definition of GERD is “a condition that develops when the reflux of stomach contents causes troublesome symptoms (e.g., retrosternal burning, heartburn, regurgitation) and/or complications (e.g., esophagitis, esophageal stricture, Barrett’s esophagus)”[4]. The prevalence of upper gastrointestinal symptoms in the general population in the Netherlands was measured recently. This study indicated that the most commonly reported gastric symptom amongst the general population in the Netherlands is symptoms of belching with a prevalence of 11.2 %. Furthermore, 9.2% of the general population of the Netherlands experiences symptoms of regurgitation, 8.4 % epigastric pain, 8.2% heartburn[5].

A complication which occurs in about 10% to 15% of people with chronic or longstanding GERD is Barrett’s esophagus (BE). The diagnosis of BE is made if the distal esophagus is lined with columnar epithelium with a minimum length of 1cm (tongues or circular) containing intestinal metaplasia at histopathological examination[6]. The known factors that increase the risk of BE are as follows: >more than five years GERD symptoms, age >50 years, male sex, tobacco usage, central obesity[7] and the Caucasian race[8,9]. It is not clear when in life BE generally develops, but the diagnosis is most often made from the sixth decade of life[10,11]. After diagnosis, patients with BE should be included in a surveillance program, which entails undergoing an esophagogastroduodenoscopy (EGD) with an interval of one every 1 to 5 years. The goal of this surveillance program is to identify patients at risk for progression to esophageal adenocarcinoma (EAC). The risk of developing EAC in a BE is between 0.2-0.5% per year, depending on the length of the BE segment[12]. The risk of progression to EAC is cumulative over time, therefore, a patient with a BE and a long-life expectancy has a significant chance (>10%) of developing EAC. Patients undergo regular endoscopic surveillance for early detection of malignant transformation. Early EAC can be endoscopically (minimally invasive) removed while progression to more advanced stages require more extensive treatment.” Although early detection may lead to improved survival the efficacy of surveillance and the influence of BE on life expectancy are still questioned[13,14,15,16].

Patients acknowledge that EGD allows them to monitor progression of BE to cancer, and increases the likelihood of identifying problems at an early stage. Despite the fact that patients may tend to worry about BE, EGD can give them a sense of control[17]. According to a questionnaire study, performed in 2006, undergoing an EGD is associated with anxiety and distress before, and discomfort during, the procedure[18]. However, only 25% of patients received sedation in this study, which probably negatively affected the experienced anxiety and distress. Subgroup analysis showed that patients undergoing sedation had significantly better outcomes. Patients indicated that the sedation was effective and that they slept throughout the procedure and felt little or no discomfort afterwards.

Diagnosis of a pre-malignant condition such as BE can cause unnecessary anxiety and worry. This is further impacted by the difficulty for BE patients to accurately estimate their cancer risk. A significant percentage of these patients overestimate their annual risk of developing EAC[19,20,21]. It is unknown, whether the EAC risk perceived by BE patients is influencing their Health Related Quality of Life (HRQoL). The importance of a patient perceptions of the impact of the disease and their response to treatment is being widely recognized. Patient-reported outcomes (PROs), including HRQoL, measure the patient's health status from the patient's perspective. Previous studies show BE is associated with a significant decrease of HRQoL, measured with both generic and disease-targeted instruments[22]. These instruments, also known as Patient-Reported Outcome Measures instruments (PROMs) are validated questionnaires developed to assess a patient’s health status at a particular point in time. Generic PROMs are assessing a range of domains of QoL and are applicable to different patient populations. On the other hand, measurements with generic questionnaires may lack sensitivity to disease specific factors that have an impact on HRQoL. Disease specific PROMs are assessing concerns that may be particular to a disease, function, or population. Disease specific questionnaires are therefore more sensitive to determine HRQoL within specific patient groups. Currently there is no BE-specific PROM available.

An important measurement on psychological burden appears to be anxiety. Studies have shown that BE patients reported significantly higher anxiety scores compared to the general population[17,23,24,25]. This was associated with heightened perceived cancer risk, and less trust in their physicians[23] which remained elevated up to one month after an endoscopy[17]. Data on depression as psychological burden in BE patients are somewhat contradictory. Two Dutch studies[17,23] found depression levels lower than the general population with hardly any patients having depression or distress levels in the clinical range, whilst a Chinese study found heightened depression scores[25]. Another Dutch study found that concerns about developing cancer and overestimating cancer risk was associated with higher scores of depression[23].

Physical symptoms are also an important element in measuring HRQoL. Previous studies have shown that experiencing gastroesophageal reflux symptoms is associated with decreased perceived quality of life[26]. Some studies found BE patients to experience fewer symptoms than GERD patients[27,28]. GERD symptoms (e.g. heartburn, regurgitation, dyspepsia) are strongly associated with a reduced HRQoL in BE patients[22]. The use of proton pump inhibitors significantly improves HRQoL[29]. The majority of studies on HRQoL and perceptions on symptoms, treatment and diagnostics for BE were performed before 2008. Since then, diagnostics have improved and endoscopic treatment options for early cancer stage are now more widely available. The use of high-definition endoscopes, processors and displays, chromo-endoscopy and artificial intelligence (AI) are increasing and may lead to increased detection of early neoplasia. These improved detection methods allow the early neoplasia to be treated by endoscopy (e.g. endoscopic resection) and thus preventing more invasive surgery. BE can even be completely eradicated by ablation therapy techniques, such as radiofrequency ablation[30]. As such, previously published data on HRQoL for BE patients may no longer be reliable, due to the implementation of novel treatment options. They may not accurately reflect the patients' current perceptions of the diagnosis and treatment of BE. Therefore, for a complete understanding of HRQoL in BE patients both qualitative and quantitative research methods need to be used.

Aim and outline of this thesis

This thesis provides further insights into HRQoL and patients perspectives on the diagnosis of BE. Associated symptoms as well as perception on cancer risks and the potential influence of the use of artificial intelligence will be evaluated. Furthermore, it provides insight on how to measure HRQoL in patients with a BE.

In **chapter 2** patients' perceptions regarding factors influencing HRQoL were investigated in 34 patients from four different focus groups with non-dysplastic BE and with a history of endoscopic treatment for Barrett's dysplasia. **Chapter 3** provides an overview of all the instruments previously used for measuring HRQoL in BE patients and indicates which PROMs are most appropriate from the patient's perspective. In **chapter 4** we investigated how the EAC risk was perceived by 158 non-dysplastic BE patients. The associations with HRQoL, illness perception and gastroesophageal reflux symptoms were assessed using a cross-sectional questionnaire study. **Chapter 5** presents a multi-center study investigating factors associated with a negative illness perception of the diagnosis of BE in 859 BE patients. The outcomes were compared between patients treated in a specialized Barrett's esophagus center and in non-expert centers. Subsequently, **chapter 6** presents a cross-sectional study on cancer worry in patients endoscopically treated for Barrett's neoplasia. Results were compared with non-dysplastic BE patients included in an endoscopic surveillance program and patients with gastroesophageal reflux symptoms. In **chapter 7** a questionnaire study is presented on the knowledge, attitude, and experience of gastroenterology patients, gastroenterologists, and GE fellows on AI, particularly concerning implementation and application of AI (in assisting clinicians) in healthcare. **Chapter 8** describes the development of the Dutch-Flemish version of the PROMIS® Gastrointestinal symptom scales and the evaluation of their psychometric properties in a population of GERD/ BE patients, inflammatory bowel disease patients and irritable bowel syndrome patients.

References

1. Cella DF, Tulsky DS. Measuring quality of life today: methodologica l aspects. Oncol 1990; 4: 29–38. 7.
2. Siegrist J, Junge A. Conceptual and methodological problems in research on the quality of life in clinical medicine. Soc Sci Med 1989; 29: 463–8.
3. VZinfo.nl, https://www.vzinfo.nl/chronische-aandoeningen-en-multimorbiditeit, RIVM: Bilthoven, febr 2023.
4. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R; Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006 Aug;101(8):1900-20; quiz 1943
5. Tielemans MM, Jaspers Focks J, van Rossum LG, Eikendal T, Jansen JB, Laheij RJ, van Oijen MG. Gastrointestinal symptoms are still prevalent and negatively impact health-related quality of life: a large cross-sectional population based study in The Netherlands. PLoS One. 2013 Jul 29;8(7):e69876.
6. Weusten B, Bisschops R, Coron E, Dinis-Ribeiro M, Dumonceau JM, Esteban JM, Hassan C, Pech O, Repici A, Bergman J, di Pietro M. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy. 2017 Feb;49(2):191-198.
7. Singh S , Sharma AN , Murad MH et al. Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis . Clin Gastroenterol Hepatol 2013 ; 11 : 1399 – 412 .
8. Rubenstein JH , Morgenstern H , Appelman H et al. Prediction of Barrett's esophagus among men . Am J Gastroenterol 2013 ; 108 : 353 – 62.
9. Rubenstein JH , Mattek N , Eisen G . Age- and sex-specific yield of Barrett's esophagus by endoscopy indication. Gastrointest Endosc 2010 ;71 : 21 – 7.
10. Hvid-Jensen F, Pedersen L, Drewes AM, et al. Incidence of adenocarcinoma among patients with Barrett’s esophagus. N Engl J Med 2011;365:1375-83.
11. Bhat S, Coleman HG, Yousef F, et al. Risk of Malignant Progression in Barrett’s Esophagus Patients: Results from a Large Population-Based Study. J Natl Cancer Inst 2011;103:1049-57.
12. de Jonge PJF, van Blankenstein M, Grady WM, Kuipers EJ. Barrett’s oesophagus: epidemiology, cancer risk and implications for management. Gut. 2014;63:191–202.
13. Desai, T. K., Krishnan, K., Samala, N., et al. (2012). The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett’s oesophagus: A meta-analysis. Gut, 61, 970–976.

14. Caygill, C. P., Royston, C., Charlett, A., et al. (2012). Mortality in Barrett's esophagus: Three decades of experience at a single center. Endoscopy, 44, 892–898.

15. Solaymani-Dodaran, M., Card, T. R., & West, J. (2013). Causespecific mortality of people with Barrett's Esophagus compared with the general population: A population-based cohort study. Gastroenterology, 144, 1375–1383.

16. Sikkema, M., de Jonge, P. J. F., Steyerberg, E. W., & Kuipers, E. J. (2010). Risk of esophageal adenocarcinoma and mortality in patients with Barrett's Esophagus: A systematic review and meta analysis. Clinical Gastroenterology and Hepatology, 8, 235–244.

17. Arney J, Hinojosa-Lindsey M, Street RL Jr, Hou J, El-Serag HB, Naik AD. Patient experiences with surveillance endoscopy: a qualitative study. Dig Dis Sci. 2014 Jul;59(7):1378-85.

18. Kruijshaar ME, Kerkhof M, Siersema PD, Steyerberg EW, Homs MY, Essink-Bot ML; CYBAR Study Group. The burden of upper gastrointestinal endoscopy in patients with Barrett's esophagus. Endoscopy. 2006 Sep;38(9):873-8.

19. Shaheen NJ, Green B and Medapalli RK. The perception of cancer risk in patients with prevalent Barrett's esophagus enrolled in an endoscopic surveillance program. Gastroenterology 2005; 129: 429–436.

20. Kruijshaar ME, Siersema PD, Janssens ACJW, et al. Patients with Barrett's esophagus perceive their risk of developing esophageal adenocarcinoma as low. Gastrointest Endosc 2007; 65: 26–30.

21. Shaheen NJ, Peery AF, Hawes RH, et al, for the AIM Dysplasia Trial Investigators. Quality of life following radiofrequency ablation of dysplastic Barrett's esophagus. Endoscopy 2010; 42: 790–99.

22. Crockett SD, Lippmann QK, Dellon ES, et al. Health related quality of life in patients with Barrett's Esophagus: A systematic review. Clin Gastroenterol Hepatol 2009; 7: 613–623.

23. Essink-Bot ML, Kruijshaar ME, Bac DJ, Wismans PJ, ter Borg F, Steyerberg EW, Siersema PD. Different perceptions of the burden of upper GI endoscopy: an empirical study in three patient groups. Qual Life Res. 2007 Oct;16(8):1309-18.

24. Cooper SC, El-agib A, Dar S, Mohammed I, Nightingale P, Murray IA, Cooper BT, Trudgill NJ. Endoscopic surveillance for Barrett's oesophagus: the patients' perspective. Eur J Gastroenterol Hepatol. 2009 Aug;21(8):850-4.

25. Lee SW, Lien HC, Chang CS, Ko CW, Tung CF, Yeh HZ. Health-related quality of life of subjects with Barrett's esophagus in a Chinese population. PLoS One. 2017 Dec 21;12(12):e0190201.

26. Fuchs KH, Musial F, Eypasch E, Meining A. Gastrointestinal Quality of Life in Gastroesophageal Reflux Disease: A Systematic Review. Digestion. 2022;103(4):253-260

27. Loffeld RJ. Young patients with Barrett’s oesophagus experience less reflux complaints. Digestion 2001;64:151–4.

28. Madisch A, Miehlke S, Sell S, Wigginghaus B, Stolte M. Patients with Barretts esophagus experience less reflux complaints. Gastroenterology 2006;130:A263–A263.

29. Gerson LB, Shetler K, Triadafilopoulos G. Control of intra-oesophageal and intra-gastric pH with proton pump inhibitors in patients with Barrett’s oesophagus. Dig Liver Dis 2005;37:651–8.

30. Sharma P, Shaheen NJ, Katzka D, Bergman JJGHM. AGA Clinical Practice Update on Endoscopic Treatment of Barrett's Esophagus With Dysplasia and/or Early Cancer: Expert Review. Gastroenterology. 2020 Feb;158(3):760-769.

CHAPTER 2

2

Factors influencing health-related quality of life in patients with Barrett's esophagus: a qualitative focus group study

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Abstract

Introduction

Barrett's esophagus is a premalignant condition in the lower part of the esophagus, caused by gastroesophageal reflux disease. Previous studies found that having a Barrett's esophagus is associated with a significant decrease of health-related quality of life (HRQoL). Over the past decade, a considerable amount of literature has been published on the development of endoscopic treatment for (early) neoplasia in Barrett's esophagus. Though, currently very little is known about the impact of those endoscopic treatments on HRQoL from the perspective of patients. In this study, we aim to assess the factors influencing HRQoL according to Barrett's esophagus patients.

Methods

By using a qualitative focus group design, patients with non-dysplastic Barrett's esophagus and patients with a history of endoscopic treatment for Barrett's dysplasia were included. Data were analyzed following the conventional content analyses approach.

Results

A total of 34 patients participated in the four focus group sessions. Experiencing symptoms was valued as the most important factor in both groups. Other factors identified as important HRQoL influencers were: use of medication, fear of cancer and trust in physicians and endoscopic procedures.

Conclusions

In general, Barrett's esophagus patients experienced a good HRQOL, with a minimal emotional burden from the diagnosis of Barrett's esophagus. Most influencing factor on HRQOL was: experiencing reflux and dyspepsia symptoms. This study underlines the importance of adequate gastroesophageal reflux treatment and providing information to Barrett's esophagus patients, tailored to their personal needs.

Introduction

Barrett's esophagus is a condition in the lower part of the esophagus, caused by gastro esophageal reflux disease (GERD)[1,2]. It is considered to be a premalignant condition, because it is associated with an increased risk of development of esophageal adenocarcinoma (EAC). The relative risk of EAC in persons with non-dysplastic Barrett's esophagus is 30–125 times higher than that of the general population; however, their absolute risk is low (approximately 0.5% per year)[3]. As recommended in current guidelines, patients with a non-dysplastic Barrett's esophagus should undergo an upper gastrointestinal (GI) endoscopic surveillance every 3–5 years until the age of 75 years. A few studies reported discomfort and overall burden in Barrett's esophagus patients prior, during and after upper GI endoscopy[4,5].

Various definitions of health-related quality of life (HRQoL) can be found in the literature. Moreover, the term HRQoL is often described as: 'A term referring to the health aspects of quality of life, generally considered to reflect the impact of disease and treatment on disability and daily functioning; it has also been considered to reflect the impact of perceived health on an individual's ability to live a fulfilling life. However, more specifically HRQoL is a measure of the value assigned to duration of life as modified by impairments, functional states, perceptions and opportunities, as influenced by disease, injury, treatment and policy'[6]. There is no Barrett's esophagus-disease-specific instrument available for measuring HRQoL. Previous studies, predominant with a quantitative design, found that Barrett's esophagus is associated with a significant decrease of HRQoL, measured with both generic and disease-targeted instruments. In addition, patients with Barrett's esophagus are at risk for psychological consequences such as depression, anxiety and stress. These negative effects of Barrett's esophagus on HRQoL and psychological health may be related to the patient's perception of the risk of developing EAC[7] . However, many of these studies are dated[8].

Over the past decade, a considerable amount of literature has been published on the development of endoscopic treatment for (early) neoplasia in Barrett's esophagus. Though, currently very little is known about the impact of those endoscopic treatments on HRQoL from the perspective of patients. To date, only a limited number of qualitative research has been done investigating the perspective of non-dysplastic Barrett's esophagus patients regarding factors influencing their HRQoL[4,9,10]. None of these studies take note of the factors influencing the quality of life of both Barrett's esophagus patients with dysplasia BE (DBE) and the non-dysplastic BE (NDBE) patients. In the present study, we aim to assess the factors influencing HRQoL according to NDBE and DBE patients by using a qualitative focus group design.

Methods

This exploratory qualitative study with a focus group approach was part of larger research project in the development of a clinical assessment tool for measuring specific HRQoL in patients with Barrett's esophagus. The study was performed in the Catharina Hospital Eindhoven, a tertiary referral center for Barrett's esophagus in the Netherlands. A total of four focus groups (two NDBE groups and two DBE groups) were planned to establish saturation and thereby adequate data have been collected for a detailed analysis. Ethics approval was obtained from the medical research ethics committees united in the Netherlands. All participants provided signed informed consent before attending the focus group session and could withdrawal from the study at any time for any reason if they wish to do so without any consequences.

Participants

Patients were eligible when aged 18–75 years and had proven macroscopic and histologic Barrett's esophagus. Patients were subsequently included in the NDBE group, when undergoing surveillance upper GI endoscopy without visible abnormalities and no dysplasia in the random biopsies. Patients were included in the DBE group, if they currently or in the past had undergone endoscopic treatment [endoscopic resection and radio frequency ablation (RFA)] and proven dysplasia in Barrett's esophagus. Patients were excluded from both groups if they had undergone a surgical esophageal resection, history of a psychiatric disease or were not able to read, speak and understand the Dutch language.

Procedures

Participants were invited via mail by the investigator to partake in the study. We purposively invited predominantly male patients and patients between 65 and 70 years of age (80%) to ensure a good reflection of the sex and age distribution of a typical Barrett's esophagus population. In addition, a deliberate choice was made to invite a small number of patients (10%) with a complicated treatment course. Additional research information and an inform consent form were sent to patients. The focus group sessions were conducted in Dutch, audio-recorded and facilitated by the research team using a topic guide (Fig. 1). This topic guide was based on, first, topics provided by Barrett's esophagus patients at a patient meeting and, second, on a literature review performed by the investigator (M.v.d.E-v.L.) about HRQoL domains used for measuring HRQoL in Barrett's esophagus patients.

Each focus group session was led by the same experienced moderator (S.d.M.), and was attended by two observing researchers (M.v.d.E-v.L. and M.B.), who made field notes. All focus group sessions started with an introduction about the objectives of the study and an explanation of the role of the participants during this specific session. Starting with the standard open-ended question: "Which factors related to your BE are influencing your perceived HRQoL?" HRQoL was defined as "those aspects of self-perceived wellbeing that are related to or affected by the presence of disease or treatment"[11]. The participants were asked to discuss and comment on each factor, in particular, the degree of influence on HRQoL. At the end of each focus group session, the moderator summarized all factors discussed. Subsequently, participants were invited to make a top 10 list of factors, and prioritize and reach consensus on the various factors in terms of the degree of impact on HRQoL.

Data collection and analyses

The two researchers (M.v.d.E-v.L. and M.B.) independently made comprehensive notes at each focus group session. These detailed field notes descripted nonverbal behavior during the focus group discussion and the order of which participants communicated. The moderator took notes of essential comments and managed time of a maximum 90 min per focus group. Audio-recordings were transcribed verbatim and anonymized with pseudonyms by one member of the research team (M.v.d.E-v.L.) and were checked for accuracy by a second member (M.B.).

Transcripts were entered into ATLAS.ti, a qualitative data management software program (ATLAS. Ti 8 Scientific Software Development GmbH, Berlin, Germany) for further analyses. The analytical approach selected for this study was the conventional content analysis. This approach is used to interpret the content of the data through a systematic process and aims to describe the patients' experiences from different perspectives. The method is often used when the research literature in the area is limited[12]. Consistent with the procedures of conventional content analysis, the analysis was carried out independently by two members of the research team (M.v.d.E-v.L. and M.B.). The first step included reading the text as a whole to gain a general understanding. To ensure familiarity with the data, in the second step, the text was reread with a focus on identifying codes that captured key concept and thoughts. As the analysis proceeded, the two researchers (M.v.d.E-v.L. and M.B.) defined codes that were reflective of more than one key thought and together the codes resulted in the initial coding scheme. To achieve intercoder reliability, codes were subsequently discussed by the research team and consensus was achieved, thereafter a coding framework was developed. This framework contains the factors identified as influencing HRQoL; these factors were refined and reduced in number by clustering them together. Analysis was performed both at group and at individual level.

At the end of each focus group session, the participants reached consensus on a top 10 list of factors with the most impact on their HRQoL. When analyzing these data, we first gave a score to the various factors, where the first ranked factor was given 10 points, the second in the list 9, and so on. Subsequently, all factors mentioned in the different focus groups were combined in a final list. Factors that matched were pooled and scores added up. Furthermore, it was examined in what percentage of the focus groups the factors were identified as important and described whether this concerned an NDBE or the DBE group.

Results

Subject characteristics

A total of 34 consenting patients participated in the four focus group sessions and conducted in a meeting room at the hospital. These sessions took place between September and October 2019. The focus groups comprised of eight and nine participants in the DBE groups and seven and nine participants in the NDBE groups. The sessions lasted an average of 65 min (range 58–73 min). After the fourth focus group session, no new factors emerged and saturation had been reached.

The demographics of the study participants are shown in Table 1. Overall the mean age was 69 years (SD = 7.79) and 87% were males. The two groups of NDBE participants (NDBEp) contained a total of 16 participants with a median Barrett's esophagus duration of 8 years (1–29).

In the two groups of DBE participants (DBEp), all 17 participants had undergone endoscopic treatment, of which 10 patients for early EAC and 7 for dysplasia in Barrett's esophagus. The majority was treated with an endoscopic resection followed by RFA (13 participants) and four with monotherapy with endoscopic resection. A total of four participants had complications as a result of endoscopic treatment (three participants with strictures suffered multiple dilatations and one had poor recovery from ablated mucosa). Time from the last treatment was 18 months (35.5), and two patients were still in the treatment phase at the time of the focus group sessions. All participants in both groups were on a minimum daily dose of 40 mg proton pump inhibitor (PPI).

Open ended question starting the discussion:
Which factors related to your BE are influencing your perceived HRQOL?

Clarifying questions:

- What do you understand by the concept of quality of life?
- How does the Barrett diagnosis affect your life?
- What impact does the Barrett diagnosis have?
- How concerned are you about the diagnosis BE?
- What are your concerns about? Please indicate what affects / strengthens/ weakens these concerns.
- How or when does the Barrett diagnosis affect your mood?
- What factors do you think affect the quality of life in relation to the Barrett diagnosis?
- We would like to categorize these factors according to how they affect the quality of your life.
- What factors do you control yourself?

Factors influencing HRQOL according to participants on a BE patients meeting:

Impediments factors:
- Symptoms (reflux, passing symptoms, poor sleep)
- Thoughts of increased cancer risk
- Reassurance by upper GI endoscopy
- Fear of results
- Fear of cancer recurrence after treatment

Promoting factors:
- Endoscopic treatment gives reassurance
- Trust in the physician
- Support and information given by medical team
- Support from the family
- Sports / relaxation

Figure 1 Topic list

Identification of influencing factors on HRQoL according to Barrett's esophagus patients

Five factors were identified as most importantly influencing HRQoL, namely impact/burden of diagnosis, symptom control, use of medication, fear of cancer and trust in physician and endoscopic procedures. These factors may have both a positive and negative impact on HRQoL. Experiencing symptoms was valued as the most important factor (Table 2) by both groups.

	Overall N=33	NDBE group N=16	DBE group N=17
Male, *N* (%)	29(87%)	14 (88%)	15 (88%)
Age, mean (SD)	69(7.79)	67.4 (8.72)	70.7 (6.69)
Duration of diagnoses Barrett's esophagus Median (range)	5.0 (1–29y)	8.0 (1–29y)	3.0 (1–17y)
Worst histology, *N* (%)			
IM		16 (100)	
LGD			5 (29.4)
HGD			2 (11.8)
EAC			10 (58.8)
Treatment			
endoscopic resection + RFA, (*N* (%)			13 (76.4)
ESD/endoscopic resection monotherapy *N* (%)			2 (11.8)
RFA monotherapy, *N* (%)			2 (11.8)
Treatment complications			
Stenosis dilatations, *N* (%)			3 (17)
Poor healer, *N* (%)			1 (5.8)
Time from complete eradication Barrett's esophagus, *median months (range)*			18 (1–113)*
Time from last endoscopy, *median months (range)*	7 (1–56)	22 (7–56)	5 (1–29)

Table 1. Patients characteristics

DBE, dysplastic Barrett's esophagus; EAC, esophageal adenocarcinoma; ESD, endoscopic submucosal dissection; FG, focus group; HGD= high Grade dysplasia; HRQOL, health-related quality of life; IM, intestinal metaplasia; LGD, low grade dysplasia; NDBE, non-dysplastic Barrett's esophagus; RFA, radiofrequency ablation. * two patients still in treatment phase

Impact/burden of diagnosis

The DBEp were grateful that the neoplasia was discovered at an early stage during follow-up and/or by chance during gastroscopy because of symptomatic reflux disease.

DBEp2.2: I was happy that they discovered cells with first irregularities before becoming cancer.
DBEp2.3: I won the lottery! I feel very good, but I always have been very positive. I am happy that I got the treatment, otherwise it had gone completely wrong with me.

The general practitioner played an important role in the appropriate and timely referral to the hospital for an upper GI endoscopy. Participants experienced a minimal and temporary negative impact on their HRQoL at time of diagnosis, mainly due to uncertainties caused by a lack of knowledge about the diagnosis. In addition, a number of participants experienced the initial diagnosis as a relief, because it provided an explanation for their complaints. Both DBEp and NDBEp reported that their relatives had little knowledge of Barrett's esophagus. Overall, participants in the DBE groups felt well informed by the medical team (physician, nurse practitioner and endoscopy team); however, NDBEp experienced the need to be further informed, in particular, questions and uncertainties about how to notice changes in the esophagus and when to contact their physician. The group of DBEp considered emotional support from family to be important, in which the NDBEp considers it particularly important that possible diets, such as not eating spicy food, are taken into account while preparing food. Both the DBEp and NDBEp indicated that in general they experienced a good HRQoL, with a minimal emotional burden from the diagnosis of Barrett's esophagus. However, uncertainties just before and after an endoscopy increased the burden.

Factors influencing HRQOL (%)	FG discussed score	Total	Type of focus group
Symptoms of dyspepsia and dysphagia	100	29	2 × NDBE, 2 × DBE
Information given by medical team	100	27	2 × NDBE, 2 × DBE
Medication	100	25	2 × NDBE, 2 × DBE
Lifestyle and diet	75	22	2 × NDBE, 2 × DBE
Interval between upper GI endoscopy, perceived as long	50	17	2 × NDBE
Support of family	50	11	2 × DBE
Fear of cancer (recurrence)	50	10	2 × DBE
Support of general practitioner	50	8	2 × DBE
Sleeping position	50	7	2 × NDBE
Trust in physician	25	20	2 × DBE
Reassurance by upper GI endoscopy	25	18	2 × DBE
End of surveillance at 75 years	25	9	1 × NDBE
Explanation for complaints with diagnosis Barrett's esophagus	25	7	1 × DBE
Stress in daily life	25	6	1 × NDBE
When to contact the physician	25	5	1 × NDBE
Fear and uncertainty before upper GI endoscopy	25	5	1 × DBE
Diagnosis Barrett's esophagus is insidious	25	3	1 × DBE
EAC in family or friends	25	2	1 × DBE
Ignorance of environment about Barrett's esophagus	25	1	1 × DBE

Table 2. Prioriting influencing factors

Factors prioritized during the four focus groups: first, scored on percentage of FG discussed, and then scored on priority, giving position 1 with 10 points, position 2 with 9 points, and so on. DBE, dysplastic Barrett's esophagus; EAC, esophageal adenocarcinoma; GI, gastrointestinal; HRQOL, health-related quality of life; NDBE, nondysplastic Barrett's esophagus.

Symptoms

Experiencing symptoms such as reflux, dyspepsia, regurgitation and dysphagia was considered as the most influencing factors on HRQoL by both groups. In addition, DBEp indicated that they experienced just a few burdensome symptoms during the endoscopic treatment phase. Of these symptoms, pain after endoscopic procedures was the most stressful condition. Only patients with a complicated treatment phase, such as stenosis for which dilatation is required, experienced the process of treatment as more burdensome. It was remarkable that several DBEp reported less reflux and dyspepsia complaints after completing the process of endoscopic treatment and achieved complete remission of Barrett's esophagus. However, the majority still experienced mild daily symptoms of dysphagia, as a result of which they ate slower and chewed their food longer.

> *DBE1.4: For example, if I eat an apple, I hardly can swallow those pieces. Then I have to take a little water. (two participants confirm).*
>
> *NDBE4.8: Now it's actually not so bad, I have a few complaints when I eat certain things.*

NDBEp seemed to experience fewer symptoms in daily life than the DBEp. Specific food products and habits, such as drinking alcohol or orange juice, eating spicy or fatty food and eating late at night, were main triggers of developing symptoms of pyrosis, reflux and dyspepsia in both groups.

Experiencing symptoms of reflux at night was reported as most bothersome. Both DBEp and NDBEp indicated that adjusting their sleeping position was important, with the backrest of the bed being raised. The Barrett's esophagus diagnosis has no negative impact on the possibility to exercise and relax. Participants considered losing weight as a positive factor, experiencing fewer symptoms as a result.

Use of medication

> *DBEp1.1: I wouldn't dare go without the medication.*
>
> *NDBEp4.1: I can live very well with this. That pill works fantastic!*
>
> *NDBEp4.2: I have to take those medicines, if I don't take them, it will go wrong. Then, uh, then I'm having a really bad day.*

All patients in the focus groups used maintenance treatment with a daily dose of at least one PPI. The use of medication was highly prioritized (Table 2) in the list of factors influencing HRQoL. There was consensus within the focus groups that they cannot do without this medication. In addition, patients are aware that they have to use these medicines throughout the rest of their lives. The NDBEp indicate that they are concerned about possible side effects from lifelong use. Additionally, reports on the internet about possible side effects such as increased risk of dementia and low levels of vitamin B12 were mentioned. NDBEp indicate that they would value receiving more information about this subject. The DBEp did not share this concern. The participants in the NDBE group discussed the possibility of surgery instead of taking a daily dose of PPI. They concluded that they would appreciate if the physician would proactively inform them about the considerations between surgery and medical therapy.

Fear of cancer

> *DBE2.6: I also have some fear that it will return. But I also know if I regularly come in for the endoscopy, they will see progression in time and then they can do something about it.*
>
> *NDBE3.4: If I'm experiencing complaints in this region (epigastric) then I think what is going on? And then I feel a bit more insecure.*

Within the NDBEp as well the DBEp, there was consensus that the presence of EAC in family or friends increased fear of cancer. Patients referred to the poor prognoses with an advanced EAC and the poor HRQOL in the final stage of life of these patients. Experiencing symptoms of pain, reflux or dysphagia were additional important triggers for increased anxiety and fear of cancer.

All except one DBEp indicated that they infrequently think of cancer or dysplasia recurrence. This limited fear of recurrence was attributed to trust in their physician and in undergoing endoscopic surveillance procedures.

Trust in physician and endoscopic procedures

> *DBE1.5: Every time, before the endoscopy, I feel unsure. It gives me reassurance that everything is fine.*
>
> *NDBE3.7: I agree. It gives a peace of mind, we are under control. A lot of people don't have that and they may well be too late.*

NDBEp perceived the 3- to 5-year interval between upper GI endoscopies to be long. The majority of NDBEp did not understand the rationale for this interval. Participants aged 70 years and older indicated that having to discontinue upper GI endoscopies at 75 years of age made them feel anxious. Participants would have preferred surveillance endoscopies to continue as long as health permits. Both groups found it important to receive information about guidelines and arguments for the intervals or discontinuation of the surveillance endoscopies. Both NDBEp and the DBEp indicated that getting the results of the endoscopy is reassuring. Furthermore, sedation during the endoscopy was highly appreciated.

The DBEp experienced a high degree of trust in the medical team and the expertise of the physicians. They appreciated the easily accessible support provided by a nurse practitioner. There was consensus within the DBEp group that stress and tension increase just before the next treatment or follow-up endoscopy. DBEp stated the importance of early detection of dysplasia in Barrett's esophagus. Preferably, patients would like to have a preventive examination or a population screening in the form of a home test.

Discussion

This study aimed to assess the most important factors influencing HRQoL according to NDBE and DBE patients. To the best of our knowledge, this is the first qualitative study exploring factors influencing HRQoL among NDBE and DBE patients. Participants identified symptoms of reflux and dyspepsia, use of medication, fear of cancer and trust in physicians and endoscopic procedures as the most important factors influencing HRQoL. Fear of cancer (recurrence) was more prominently discussed in the DBEp groups than in the NDBEp groups. The importance of clear education on Barrett's esophagus, allowing patients to better understand, for example, the choice of interval of the upper GI surveillance endoscopies. This interval was a predominant theme in the NDBEp groups. Overall, DBEp and NDBEp indicated that they experienced a minimal emotional burden from the diagnosis Barrett's esophagus. These findings are consistent with those of Britton et al., who found three key potential impacts on HRQoL: symptom control, worry of esophageal cancer and burden of surveillance endoscopy[8]. There was consensus that experiencing reflux and dyspepsia was the most important factor influencing HRQoL. This finding is in line with previous studies in this area linking experiencing symptoms as reflux and dyspepsia with decreased HRQoL[13–15].

Previous quantitative studies showed a significantly decreased HRQoL among Barrett's esophagus patients[14-17]. In contrast, we found a good overall HRQoL with a minimal emotional burden from the diagnosis Barrett's esophagus in the present qualitative study as well as in the previous quantitative study of our group[15].

Consistent with the literature[4,8–10,15,18], the present study found that although a minority of patients (discussed more in the DBEp than NDBEp) mentioned that fear of cancer had a daily impact on their quality of life, all patients agreed that experiencing symptoms increased thoughts of developing cancer. Another factor increasing fear of cancer was the presence of EAC in family or friends. This finding seems consistent with our previous study, in which we found that the presence of cancer in family or friends was associated with overestimating one's own risk of developing EAC[15].

Trust in the medical team and expertise of the physician in endoscopic procedures was reported as an imported factor improving HRQoL in both groups, but most prominent in the DBEp group. A previous review stated that in NDBE patients' with heightened anxiety about the risk of cancer progression, almost universally relied on endoscopic surveillance as providing a safety net[19]. In addition, Arney et al. showed similar findings as trust in physicians and interpersonal interaction with staff as an important predictor of their intension to adhere to surveillance[4].

The participants in the DBE groups reported to be well informed about their Barrett's esophagus diagnosis and recommended (endoscopic) treatment. This finding is in contrast with previous studies suggesting that Barrett's esophagus patients have a limited knowledge and understanding of their condition[8–10]. It may be that participants in the present study benefitted from the fact that they were treated by physicians and nurse practitioner specialized in Barrett's esophagus in a referral center for Barrett's esophagus. We found that NDBEp often mentioned doubts and questions about the Barrett's esophagus diagnosis. Possibly these doubts and questions are due to the fact that NDBEp receive less intensive monitoring and support than DBEp with endoscopy results being discussed during telephone consultations.

This study with a qualitative focus group design has some limitations. First, the ability to generalize the findings in this study is somewhat limited because participants were included from a single, tertiary referral center for Barrett's esophagus. However, as European guidelines advice, DBE patients most likely are treated in a referral center for Barrett's esophagus[20]. Second, due to the fact that the observer is part of the medical team, patients may have been reluctant to give negative feedback about their experiences with this team. Third, particular disadvantage of a focus group design is the possibility that the participants may not have expressed their honest and personal opinions about the topic at hand. They may be hesitant to express their thoughts, especially when their thoughts oppose the views of another participant. These last two limitations have been overcome as much as possible by using an experienced moderator.

Conclusion

Patients with NDBE and DBE indicated symptoms of reflux and dyspepsia as most influencing factors on their HRQoL. In addition, the use of medication, fear of cancer and trust in their physician and endoscopic procedures are stated as important. In general, they are experiencing a good HRQoL, with a minimal emotional burden from the diagnosis Barrett's esophagus. This study underlines the importance of adequate treatment and providing the Barrett's esophagus patients information tailored to their personal needs. Further research should be undertaken to investigate, whether these factors, important for Barrett's esophagus patients, are actually included in the tools measuring HRQoL in Barrett's esophagus patients.

References

1. Barrett NR. Chronic peptic ulcer of the oesophagus and 'oesophagitis'. Br J Surg 1950; 38:175–182.
2. Allison PR, Johnstone AS. The oesophagus lined with gastric mucous membrane. Thorax 1953; 8:87–101.
3. Yousef F, Cardwell C, Cantwell MM, Galway K, Johnston BT, Murray L. The incidence of esophageal cancer and high-grade dysplasia in Barrett's esophagus: a systematic review and meta-analysis. Am J Epidemiol 2008; 168:237–249.
4. Arney J, Hinojosa-Lindsey M, Street RL Jr, Hou J, El-Serag HB, Naik AD. Patient experiences with surveillance endoscopy: a qualitative study. Dig Dis Sci 2014; 59:1378–1385.
5. Essink-Bot ML, Kruijshaar ME, Bac DJ, Wismans PJ, ter Borg F, Steyerberg EW, Siersema PD. Different perceptions of the burden of upper GI endoscopy: an empirical study in three patient groups. Qual Life Res 2007; 16:1309–1318.
6. Mayo N. Dictionary of Quality of Life and Health Outcomes Measurement. Milwaukee, WI: International Society for Quality of Life Research; 2015.
7. Crockett SD, Lippmann QK, Dellon ES, Shaheen NJ. Health-related quality of life in patients with Barrett's esophagus: a systematic review. Clin Gastroenterol Hepatol 2009; 7:613–623.
8. Britton J, Keld R, Prasad N, Hamdy S, McLaughlin J, Ang Y. Effect of diagnosis, surveillance, and treatment of Barrett's oesophagus on health-related quality of life. Lancet Gastroenterol Hepatol 2018; 3:57–65.
9. Britton J, Hamdy S, McLaughlin J, Horne M, Ang Y. Barrett's oesophagus: a qualitative study of patient burden, care delivery experience and follow-up needs. Health Expect 2019; 22:21–33.
10. Griffiths H, Davies R. Understanding Barrett's columnar lined oesophagus from the patients' perspective: qualitative analysis of semistructured interviews with patients. Frontline Gastroenterol 2011; 2:168–175.
11. Ebrahim S. Clinical and public health perspectives and applications of health-related quality of life measurement. Soc Sci Med 1995; 41:1383–1394.
12. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res 2005; 15:1277–1288.
13. Lee SW, Lien HC, Chang CS, Ko CW, Tung CF, Yeh HZ. Health-related quality of life of subjects with Barrett's esophagus in a Chinese population. PLoS One 2017; 12:e0190201.

14. Eloubeidi MA, Provenzale D. Health-related quality of life and severity of symptoms in patients with Barrett's esophagus and gastroesophageal reflux disease patients without Barrett's esophagus. Am J Gastroenterol 2000; 95:1881–1887.

15. van der Ende-van Loon MC, Rosmolen WD, Houterman S, Schoon EJ, Curvers WL. Cancer risk perception in relation to associated symptoms in Barrett's patients: a cross sectional study on quality of life. United European Gastroenterol J 2018; 6:1316–1322.

16. Gerson LB, Ullah N, Hastie T, Goldstein MK. Does cancer risk affect health-related quality of life in patients with Barrett's esophagus? Gastrointest Endosc 2007; 65:16–25.

17. Eloubeidi M, Uslick B, Provenzale D. Health related quality of life (HRQL) in patients with Barrett's esophagus. Gastroenterology 1997: 112:A14.

18. Shaheen NJ, Green B, Medapalli RK, Mitchell KL, Wei JT, Schmitz SM, et al. The perception of cancer risk in patients with prevalent Barrett's esophagus enrolled in an endoscopic surveillance program. Gastroenterology 2005; 129:429–436.

19. Hinojosa-Lindsey M, Arney J, Heberlig S, Kramer JR, Street RL Jr, El-Serag HB, Naik AD. Patients' intuitive judgments about surveillance endoscopy in Barrett's esophagus: a review and application to models of decision-making. Dis Esophagus 2013; 26:682–689.

20. Weusten B, Bisschops R, Coron E, Dinis-Ribeiro M, Dumonceau JM, Esteban JM, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy 2017; 49:191–198.

CHAPTER 3

3

How are we measuring health-related quality of life in patients with a Barrett Esophagus? A systematic review on patient- reported outcome measurements

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Abstract

Purpose

Barrett esophagus (BE) is associated with a significant decrease of health-related quality of life (HRQoL). Too often, patient-reported outcome measures (PROMs) are applied without considering what they measure and for which purposes they are suitable. With this systematic review, we provide researchers and physicians with an overview of all the instruments previously used for measuring HRQoL in BE patients and which PROMs are most appropriate from the patient's perspective.

Methods

A comprehensive search was performed to identify all PROMs used for measuring HRQoL in BE patients, to identify factors influencing HRQoL according to BE patients, and to evaluate each PROM from a patients' perspective.

Results

Among the 27 studies, a total of 32 different HRQoL instruments were identified. None of these instruments were designed or validated for use in BE patients. Four qualitative studies were identified exploring factors influencing HRQoL in the perceptions of BE patients. These factors included fear of cancer, anxiety, trust in physician, sense of control, uncertainty, worry, burden of endoscopy, knowledge and understanding, gastrointestinal symptoms, sleeping difficulties, diet and lifestyle, use of medication, and support of family and friends.

Conclusion

None of the quantitative studies measuring HRQoL in BE patients sufficiently reflected the perceptions of HRQoL in BE patients. Only gastrointestinal symptoms and anxiety were addressed in the majority of the studies. For the selection of PROMs, we encourage physicians and researchers measuring HRQoL to choose their PROMs from a patient perspective and not strictly based on health professionals' definitions of what is relevant.

Introduction

Barrett's esophagus (BE) is a premalignant condition involving metaplastic transformation of the lower esophageal lining from squamous to intestinal epithelium, due to gastroesophageal reflux disease (GERD)[1,2]. BE is associated with an increased risk of an esophageal adenocarcinoma (EAC). The relative risk of EAC in patients with non-dysplastic BE is 30–125 times higher compared to the general population. Patients therefore undergo regular endoscopic surveillance for early detection of malignant transformation. Although early detection may lead to improved survival, the absolute risk for malignant transformation is low (approximately 0.3–0.5% per year)[3, 4] and the efficacy of surveillance and the influence of BE on life expectancy are still questioned[4–7]. The effect of endoscopic surveillance programs on patient's perspective and quality of life should, therefore, not be neglected[8].

BE is associated with a significant decrease of health related quality of life (HRQoL), measured with both generic and disease-targeted instruments[9]. In addition, patients with BE are at risk for psychological consequences such as depression, anxiety, and stress. These negative effects of BE on HRQoL and psychological health may be related to patients' perception of the risk of developing EAC[9]. HRQoL is generally considered to encompass patients' physical, psychological, and social functioning, which can be affected by both the disease and treatment[10].

Nowadays, there is an increased awareness in international health care policy on the importance of measuring quality of care. Patient-reported outcomes (PRO) are an important instrument for measuring quality of care, enabling improvement and transparency in health care. The choice of what to measure (PRO) and how to measure is a complicated but important process. Too often, patient-reported outcome measurements (PROMs) are applied without considering what they should measure and for which purposes they are suitable. There is a rapid increase of questionnaires to choose from, however, it is often not clear which one is the best given its purpose. Currently, there is no BE-specific PROM available.

In this systematic review, we will identify all PROMs used for measuring HRQoL in BE patients, identify factors influencing HRQoL according to BE patients, and evaluate each PROM from a patient's perspective. This systematic review is part of a research project on the development of a person-centered measurement tool, measuring HRQoL in BE patients.

Materials and methods

This systematic review was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement[11].

Literature search

Two independent researchers (MvdE and AS) independently conducted a systematic search from inception to February 1, 2021 in the following electronic databases: Pubmed, EMBASE, CINAHL, and PsycINFO. To search the databases, we used medical subject headings (MeSH) and freetext words (Fig. 1). We additionally carried out reference and citation searches of all included articles and relevant review articles.

Inclusion and exclusion criteria

Studies were included when they were written in English and included only patients over 18 years old. Each article was judged against two sets of inclusion criteria (Fig. 1).

(1) Studies using HRQoL PROMs were included when they met the following criteria:
Using one or more PROMs for assessing HRQoL in BE patients. A PROM was defined as any self-administered QOL instrument assessing one of the three core domains described by the World Health Association: physical, social, and psychological wellbeing[12].
Measuring HRQoL in patients with a study population containing more than 25% BE patients. With this criterion, we aimed to ensure that the authors chose their PROMs from a perspective of the BE population. Subsequently, we used a criterion of inclusion of n>25 to guarantee an acceptable quality of the included articles with a quantitative approach.
Studies with primarily post-surgery measurements were excluded.
(2) Studies on influencing factors were included when they met the following criteria:

- Using a qualitative methodology (e.g., focus groups or in-depth interviews)
- Studies including only BE patients.

Data extraction and analysis

1. *Identification of PROMs*

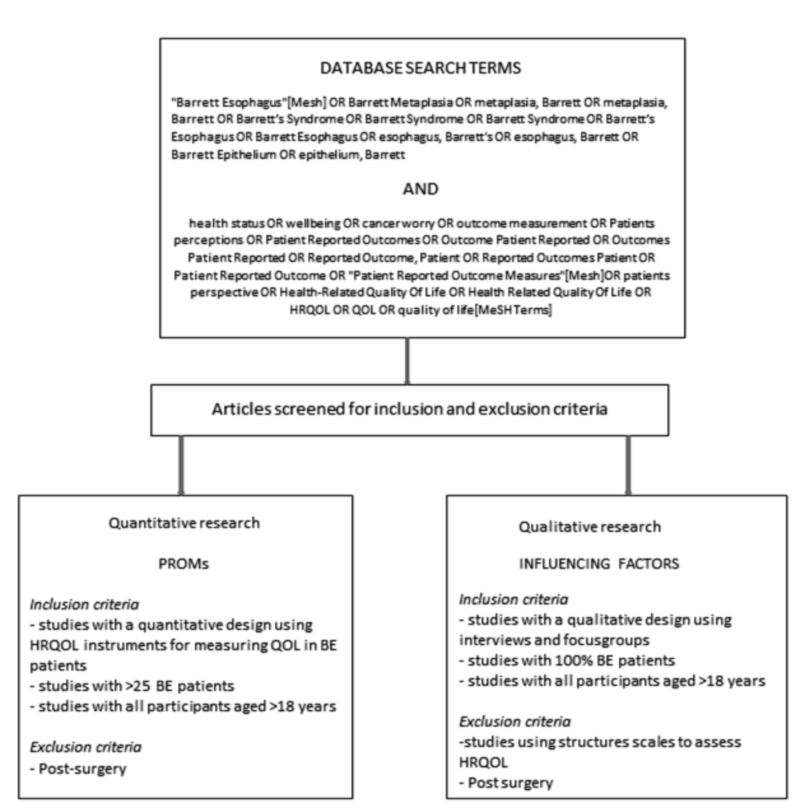
The details of all included studies (e.g., aim, sample sizes, study objectives, the level of evidence according to the Oxford Centre for Evidence-Based Medicine (OCEBM) criteria[13], and the PROMs used for measuring HRQoL) were reported in a summary table. Subsequently, it was determined whether a validation in the BE population was described in the reference literature of the included articles. Objectives and domains of each PROM were obtained. PROMs measuring perceived cancer risk, time trade-off, and standard gamble scores were not used for analyses.

2. *Identification of influencing factors according to BE patients*

To identify factors influencing HRQoL according to BE patients, quality assessment was independently conducted by two researchers (MvdE and AS) using the Critical Appraisal Skills Programme (CASP) criteria; a 10-item checklist designed for use in the appraisal of qualitative research studies[14]. In addition, factors were evaluated according to their relevance. To evaluate intra-rater and inter-rater reliability in the factors extracted from the literature review, two reviewers (MvdE and AS) each independently extracted a list of potential factors from the articles included. The two lists were compared, and differences resolved by consensus. All influencing factors identified were categorized into domains according to the patient-reported outcomes measurement information system (PROMIS) Adult Self-Reported Health model[15].

3. *Evaluation of each PROM*

Finally, each PROM was evaluated in terms of its ability to capture factors important to BE patients. For each factor, it was examined whether this was measured with an item of the PROM. A distinction was made between addressing a factor directly or indirectly in an item of the questionnaire. For example, when a questionnaire inquired about pain in general, the factor epigastric pain was considered to be measured indirectly.



DATABASE SEARCH TERMS

"Barrett Esophagus"[Mesh] OR Barrett Metaplasia OR metaplasia, Barrett OR metaplasia, Barrett OR Barrett's Syndrome OR Barrett Syndrome OR Barrett Syndrome OR Barrett's Esophagus OR Barrett Esophagus OR esophagus, Barrett's OR esophagus, Barrett OR Barrett Epithelium OR epithelium, Barrett

AND

health status OR wellbeing OR cancer worry OR outcome measurement OR Patients perceptions OR Patient Reported Outcomes OR Outcome Patient Reported OR Outcomes Patient Reported OR Reported Outcome, Patient OR Reported Outcomes Patient OR Patient Reported Outcome OR "Patient Reported Outcome Measures"[Mesh]OR patients perspective OR Health-Related Quality Of Life OR Health Related Quality Of Life OR HRQOL OR QOL OR quality of life[MeSH Terms]

Articles screened for inclusion and exclusion criteria

Quantitative research

PROMs

Inclusion criteria
- studies with a quantitative design using HRQOL instruments for measuring QOL in BE patients
- studies with >25 BE patients
- studies with all participants aged >18 years

Exclusion criteria
- Post-surgery

Qualitative research

INFLUENCING FACTORS

Inclusion criteria
- studies with a qualitative design using interviews and focusgroups
- studies with 100% BE patients
- studies with all participants aged >18 years

Exclusion criteria
-studies using structures scales to assess HRQOL
- Post surgery

Figure 1 Database search in- and exclusion criteria

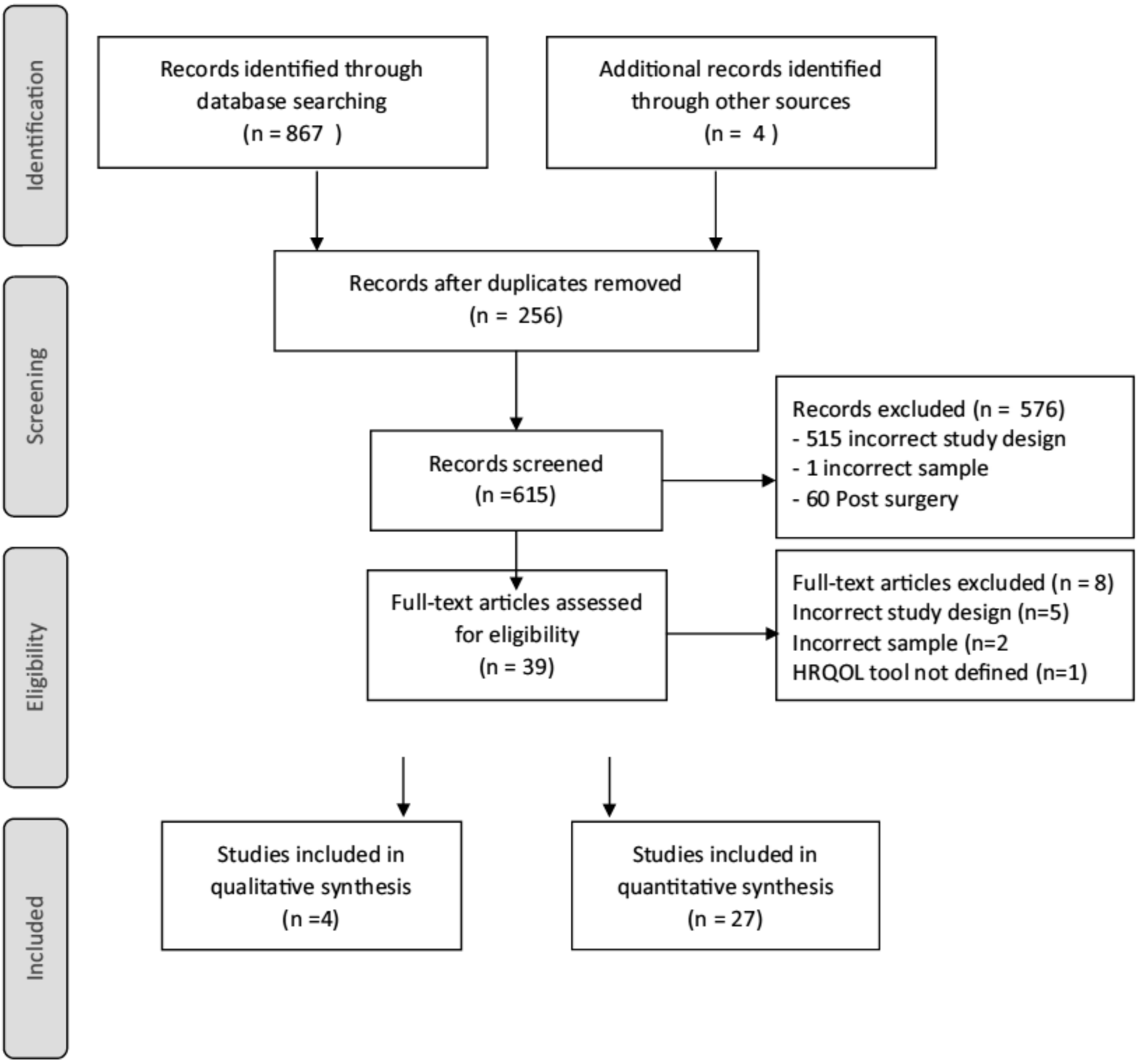


Figure. 2 PRISMA 2009 Flow diagram

Results

The literature search identified 402 articles. Twenty-seven articles met the inclusion criteria for HRQoL PROMs, after manual review of the full texts, and were included for analysis. Four qualitative studies that met the criteria for influencing factors were included (Fig. 2).

Identification of PROMs

Among the 27 studies[16–42], 32 different PROMs (Table 1) were identified. A total of nine studies[16,21,22,31,34,35,40–42] used PROMs that were not formally validated. The study of Shaheen et al.[31] used a disease-specific BE questionnaire. However, to our knowledge, this specific BE questionnaire has not been properly validated.

The study of Shaheen et al.[31] used a disease-specific BE questionnaire. However, to our knowledge, this specific BE questionnaire has not been properly validated.

An average of 3 (range 1–5) PROMs per study were used. Table 2 demonstrates a summary of sample and design characteristics of studies reporting HRQoL in BE patients. The mean number of PROMs used per study did not change over the years. Three Level 2 studies were found using PROMs in a RCT design. The majority (87.9%) were Level 3 studies per OCEBM criteria[13].

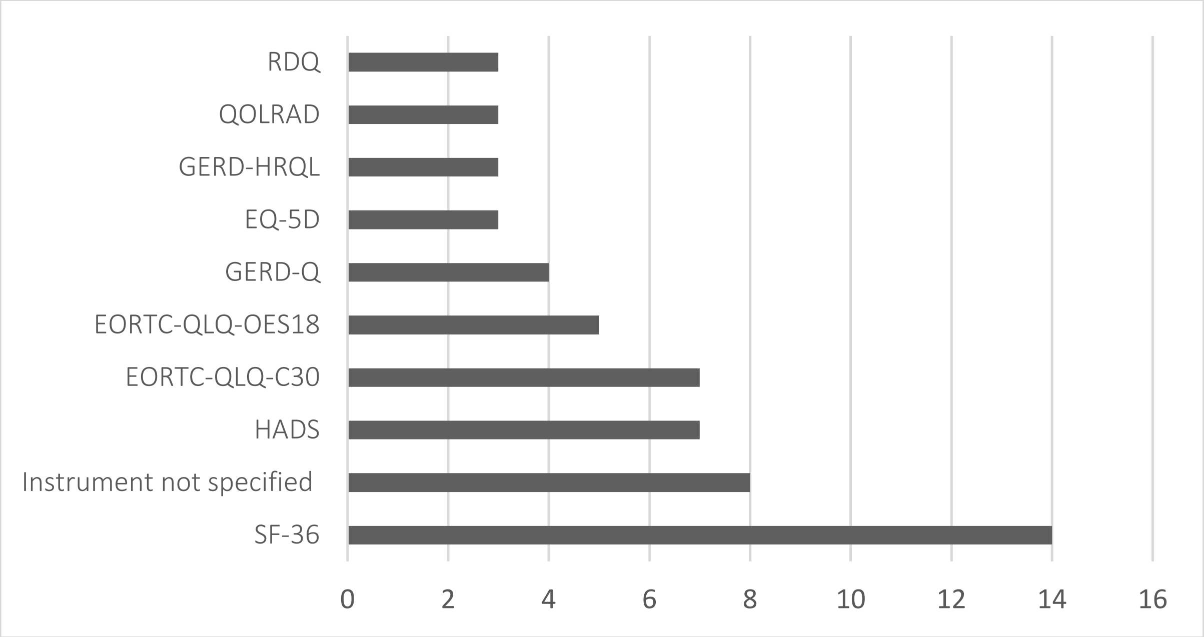


Figure 3. Top 10 most frequently reported PROMs

Abbreviations: RDQ: The Reflux Disease Questionnaire, QOLRAD: Quality of Life in Reflux and Dyspepsia, GERD- HRQL: The Gastroesophageal Reflux Disease-Health Related Quality of Life, EQ-5D: EuroQOL-5D, GERD-Q: Gastroesophageal reflux disease-questionnaire, EORTC-QLQ-OES18: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer Module, EORTC-QLQ-C30: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, HADS: Hospital Anxiety and Depression Scale, SF-36: The 36-Item Short Form Health Survey questionnaire

Seven different PROMs were used for measuring generic HRQoL (SF-36, SF-12, SF-6D, WHOQOL-BREF, LASA, PROMIS-10, and the EQ-5D for measuring health utility). Two disease-specific PROMs assessed the generic aspects of QOL in cancer patients (EORTC-QLQC30 and QLUC10D). Fourteen different disease-specific PROMs were used, measuring symptoms related to BE (GERD-Q, GERDHRQL, BSI, GSRS, GIQLI, SCL-90, QOLRAD, RDQ, EORTC-QLQOES18, the EORTC-QLQ OES, QLQ-OG25 and five different non-validated questionnaires)[16,34,35,40,41]. Cancer worry was measured with the WOCS, CWS, and a non-validated questionnaire[42]. Two PROMs measured sleeping difficulties (PSQI, BQ). Endoscopic burden was measured with three different PROMs (IES, DIS, and a non-validated Likert scale questionnaire[41]). An additional number of PROMs were identified, measuring trust in physician using the trust in physician scale (TIPS), anxiety and depression (HADS and a non-validated Likert questionnaire)[34], illness perceptions (B-IPQ), knowledge with non-validated questionnaire[42], and trust in the endoscopy with a non-validated Likert questionnaire[42]. The 10 most frequently cited PROMs are illustrated in Fig. 3. All studies except four[24, 26, 31, 36] used some form of a generic PROM for measuring HRQoL. The SF-36 was utilized most often, respectively, in 51.8% of the studies. Symptoms related to BE were measured in 85.2% of studies. The EORTC-QLQ-OES18, GERD-Q, QOLRAD, RDQ, and GERD-HRQL were most frequently used to measure reflux symptoms. Non-validated questionnaires were used in 30% of all included studies.

Table 1: PROMs used for measuring HRQoL in Barrett Esophagus patients.

Abbreviation	Type	Objective	Domains covered
SF-36	Generic	Measuring HRQoL of individuals with several chronic health conditions	36-questions on physical functioning, role- physical, bodily pain, general health, vitality, social functioning, role- emotional and mental health
SF-12	Generic	Measuring HRQoL of individuals with several chronic health conditions with substantially fewer questions than the SF-36	12- questions on physical functioning, role functioning, social functioning, mental health, health perceptions, pain
EQ-5D (3L or 5L)*	Generic	A simple, generic measure of health for clinical and economic appraisal.	5- items on mobility, self-care, usual activity, pain/ discomfort, and anxiety/ /depression and a visual analogue scale on self-rated health
PROMIS-10	Generic	Measurements of symptoms, functioning, and healthcare-related quality of life (HRQoL) for a wide variety of chronic diseases and conditions.	10- questions on overall physical health, mental health, social health, pain, fatigue, and overall perceived quality of life.
LASA	Generic	General measures of global QOL dimensional constructs in numerous settings	5- questions on physical well-being, emotional well-being, spiritual well-being, intellectual well-being, and overall QOL
WHOQOL-BREF	Generic	Assess the individual's perceptions in the context of their culture and value systems, and their personal goals, standards and concerns.	26- questions on Global items, Physical health, Psychological health, Social relationships, Environment QOL
EORTC-QLQC30	Cancer specific	Assessing the HRQoL of cancer patients participating in international clinical trials	30- questions on functional scales, symptom scales, global health status / QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients and perceived financial impact of the disease.
EORTC QLU-C10D	Cancer specific	Developed to capture cancer patients' QoL and to relate it to survival time and costs of treatment in health economic studies	10- items on physical functioning, role functioning, social functioning, emotional functioning, pain, fatigue, sleep, appetite, nausea, bowel problems
GERD-Q	Disease symptoms specific	Determine the presence or absence of symptoms of GERD in the general population	6- questions on symptoms of GERD

Table 1: PROMs used for measuring HRQoL in Barrett Esophagus patients continuation 1

Abbreviation	Type	Objective	Domains covered
BSI-18	Disease symptoms specific	Assessment of psychological distress	18- questions on somatization, anxiety, and depression
GSRS	Disease symptoms specific	A clinical rating scale for gastro intestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease	15- questions on reflux, abdominal pain, indigestion, diarrhea and constipation
GIQLI	Disease symptoms specific	Assess QoL specific for the gastrointestinal tract	36- questions on GI symptoms, emotion, physical function, social function and medical treatment
SCL-90	Disease symptoms specific	Evaluate a broad range of psychological problems and symptoms of psychopathology	90- items on somatization, obsessive compulsive disorder, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism
GERD-HRQL	Disease symptoms specific	Measure symptomatic change as a result of medical or surgical treatment of GERD.	16- questions on measuring symptom severity in GERD.
QOLRAD	Disease symptoms specific	Monitor changes in HRQOL in patients suffering from heartburn and dyspepsia.	25- questions on emotional distress, sleep disturbances, food/ drink problems, physical/ social functioning, vitality
RDQ	Disease symptoms specific	Assess the frequency and severity of heartburn, regurgitation, and dyspeptic complaints and to facilitate the diagnosis of GERD in primary care.	12- items on regurgitation, heartburn, and dyspepsia.

Table 1: PROMs used for measuring HRQoL in Barrett Esophagus patients continuation 2

Abbreviation	Type	Objective	Domains covered
The Ogilvie grading scale	Disease symptoms specific	To determine level of dysphagia	5- items on dysphagia
BE QOL	Disease symptoms specific	Not defined	10- questions on esophagostomy worry, adenocarcinoma worry, esophagus general worry, depression, daily QoL, amount of stress, difficulty to sleep, work or family life negatively impacted and worry dying due to esophagus
EORTC-QLQ OES18	Cancer symptom specific	Assess QOL in patients with esophageal cancer	18-questions on esophageal functional, symptomatic scales and the global QoL
TPS	Trust in Physician	Assess each patient's interpersonal trust in his primary care physician within the context of the management of chronic disease.	11-items on Trust in physician
IES	Endoscopic burden	Assess current subjective distress for any life event	15-items on episodes of intrusion, episodes of avoidance
DIS	Endoscopic burden	Measure of avoidance of and difficulty tolerating somatic sensations	7-items on ability to tolerate discomfort and pain, and avoidance of physical discomfort
PSQI	Sleeping difficulties	Assess sleep quality over a 1-month time interval	19- items on subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction.
Berlin- Q	Sleeping difficulties	Identifying patients with sleep apnea in primary care setting	10- questions on snoring behavior, wake time sleepiness or fatigue, obesity, hypertension

Table 1: PROMs used for measuring HRQoL in Barrett Esophagus patients continuation 3

Abbreviation	Type	Objective	Domains covered
HADS	Anxiety and depression	Measure symptoms of anxiety and depression	14- items on anxiety and depression
B-IPQ	Illness perceptions	Assess cognitive and emotional representations of illness	8- questions on cognitive illness, emotional perceptions, illness comprehensibility. And an open-ended response with three most important self-perceived causal factors of their illness.
WOCS	Fear of cancer	Undefined	4- questions on esophageal cancer in particular
CWS	Fear of cancer	Measure cancer specific worry and impact of worry on daily functioning	8- questions on worry and impact of worry on daily functioning

Abbrevations: RDQ: The Reflux Disease Questionnaire, QOLRAD: Quality of Life in Reflux and Dyspepsia, GERD-HRQL: The Gastroesophageal Reflux Disease-Health Related Quality of Life, EQ-5D: EuroQOL-5D, GERD-Q: Gastroesophageal reflux disease-questionnaire, EORTC-QLQ-OES18: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer Module, EORTC-QLQ-C30: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, HADS: Hospital Anxiety and Depression Scale, SF-16: The 16-Item Short Form Health Survey questionnaire, SF-12: The 12-Item Short Form Health Survey questionnaire, SF-6D: Short Form-6 dimension, PROMIS-10: Patient-Reported Outcomes Measurement Information Systems, LASA:Linear analog self-assessment, WHOQOL-BREF: World Health Organization Quality of Life Instruments, EORTC QLU-C10D: European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire–Core 10, BSI-18: Brief Symptom Inventory, GSRS: Gastrointestinal Symptom Rating Scale, GIQLI: Gastrointestinal Quality of Life Index SCL-90: The Symptom Checklist-90-Revised, QLQ-OG25: EORTC Quality of Life Questionnaire - Oesophago-Gastric Module, TPS: Trust in Physician Scale, IES: The Impact of Event Scale, DIS: The Discomfort Intolerance Scale, PSQI, Berlin-Q: Berlin Questionnaire, B-IPQ: Brief- Illness perception scale, CWS: Cancer worry scale, WOCS: Worry of cancer scale.

*The EQ-5D-5L differs from the EQ-5D-3L on the following points: 1) The number of levels of perceived problems per dimension was changed from 3 to 5, The most severe label for the mobility dimension was changed from “confined to bed” to “unable to walk about, and the instructions for the EQ VAS task were simplified.

Table 2: Study characteristics

Author, Year	Eloubeidi, 2000	Kulig , 2003	Gerson, 2005
Level of evidence	3	3	3
Analyse sample	NDBE=88, GERD =88	NDBE=702, NERD=2853 ERD=2660	NDBE=40, GERD =118
AIM	1)To compare HRQL of patients with BE and patients with GERD who do not have BE 2) to compare HRQL of GERD patients to that of normative data for the US general population 3) to examine the impact of GERD symptom severity and frequency on HRQL in these patients.	Describe the impact of GERD on the quality of life, to assess the changes in the QoL after 2 weeks of treatment with PPI and to define the factors that can predict these changes.	To derive health state utilities for patients with chronic reflux symptoms who required daily medication for adequate symptom control.
Baseline characteristics	Age, race, gender, nicotine use, alcohol use, PPI use, Charlson index (comorbidities), psychosomatic symptom checklist.	Age, gender education, marriage status, comorbidity, family history of GERD, nonsteroidal anti-inflammatory drug use, esophagitis, BMI	Age, gender, years of reflux, comorbidity, PPI use, 24-Kr potential of hydrogen test and esophageal motility assessment
PROMs used	2	3	2
Validated PROMs	SF-36 GERD-Q	SF-36 QOLRAD RDQ	QOLRAD GSRS
Non-validated questionnaires	N/A	N/A	N/A
Factors covered	7/18	8/18	7/18

Table 2: Study characteristics continuation 1

Author, Year	**Essink-Bot, 2007**	**Reddy, 2020**	**Gerson, 2007**	**Shaheen, 2010**
Level of evidence	3	3	3	2
Analyse sample	NDBE=180, NS=214, EAC= 82	DBE/EAC ET=239 DBE/EAC surgery=153	NDBE/ DBE =60 GERD= 40	DBE=127
AIM	Analyze potential determinants of the perceived burden of upper GI endoscopy by comparing BE patients with two additional patient groups, i.e., patients with non-specific upper GI symptoms (NS) and patients with a recent diagnosis of cancer of the upper GI tract (CA).	Compare long-term HR-QOL associated with ET or esophagostomy among patients with HGD or T1a EAC.	To determine whether Time Trade Of values would differ in patients with BE when patients were asked to trade away potential risk of esophageal adenocarcinoma rather than chronic heartburn symptoms.	To evaluate QoL before and after endoscopic treatment of dysplastic BE with RFA.
Baseline characteristics	Age, Gender, employment, civil status, education, sedation, hospital, endoscopy number	Age, gender, length BE diagnosis, histology, comorbidity	Age, gender, years of reflux, comorbidity, years on PPI, race, site of care, income	Age, gender, race, BMI, Length of BE, histology, time since diagnosis of BE, time since diagnosis of dysplasia
PROMs used	4	2	3	1
Validated PROMs	EQ-5D-3L IES HADS	EORTC-QLQ-C30 EORTC-QLQ-OES18	SF-36 QOLRAD RDQ	
Non-validated questionnaires	Non-validated questions on disease symptoms and endoscopic burden with Likert scale	N/A	N/A	Eight non-validated questions with range scale
Factors covered	3/18	7/18	8/18	0/18

Table 2: Study characteristics continuation 2

Author, Year	Lippmann, 2009	Cooper, 2009	Miller, 2010
Level of evidence	3	3	3
Analyse sample	NDBE= 168, GERD=361	NDBE =151	NDBE/DBE=489, EAC=212
AIM	To isolate any decrease in HRQoL associated with Barrett's esophagus by comparing BE patients to GERD patients with similar GERD symptom severity, and to measure any additional psychological distress that may be associated with BE, which could potentially be attributed to cancer risk. Additionally, we sought do determine whether any differences were present in quality of life based on gender and presence of erosive disease.	Examine the experience of patients undergoing endoscopic surveillance for BO, their levels of anxiety and depression, and quality of life and how the relationship with their physicians influences these factors.	To quantify the association of marital status and changes in QOL over time in patients with EC and patients with BE.
Baseline characteristics	Age, gender race, alcohol use, tobacco use, anti- reflux surgery, BMI, medication, comorbidities, prior mental health status,	Age, gender, number of gastroscopies, length BE,	Age, gender, marriage status, histology, surgical treatment, chemotherapy.
PROMs used	4	3	1
Validated PROMs	SF-36 GIQLI SCL-90-R GERD-HRQL	SF-36 TIPS HADS	LASA
Non-validated questionnaires	N/A	Non-validated question on trust physician an, fear of cancer and knowledge with and without Likert scale	N/A
Factors covered	10/18	3/18	1/18

Table 2: Study characteristics continuation 3

Author, Year	**Crockett, 2012**	**Vela, 2013**	**Rosmolen, 2017**	**Chang, 2016**
Level of evidence	3	3	3	3
Analysis sample	NDBE=235	NDBE=63, GERD=83 Control=75	NDBE=44, DBE/EAC ET=42 DBE/EAC surgery=21 Advanced EAC surgery=19	NDBE=84, control=168
AIM	To identify predictors of over or under-utilization of endoscopic surveillance including demographic factors, quality of life, healthcare numeracy, risk perception, and other health behaviors.	1) to compare the effect of GERD and BE on sleep quality and 2) to assess whether the association between sleep quality and GERD or its more severe form (i.e., BE) is independent of obstructive sleep apnea.	Investigate the overall QOL and the fear of cancer recurrence at multiple time points and included larger cohorts of patients.	Determine whether HRQOL of BE patients were worse than healthy referents in the ethnic Chinese population in Taiwan, adjusted for potential confounding factors.
Baseline characteristics	Age, gender, race, site, education, income, employment ,family history BE and EAC, Insurance, duration of BE	Age, gender, race, smoking, BMI, recruitment source	Age, gender, comorbidity, type of treatment, treatment related complications, treatment time, histology, recurrence during FU, additional treatment	Age, gender, BMI, comorbidity, marital status, education, employment, history of smoking and drinking
PROMs used	2	3	4	1
Validated PROMs	SF-36, GERD-HRQL	GERD-Q, PSQI BQ	SF-36, EORTC-QLQ-C30 EORTC-QLQ-OES18, HADS	WHOQOL-BREF
Non-validated questionnaire	Non-validated questions on disease symptoms, anxiety and worry with Likert scale	N/A	WOCS	N/A
Factors covered	7/18	6/18	8/18	3/18

Table 2: Study characteristics continuation 4

Author, Year	Han, 2018	Ende- van Loon, 2018	Rosmolen, 2019	Balamu, 2019
Level of evidence	3	3	2	3
Analysis sample	NDBE/DBE=193	NDBE=158	NDBE=49, DBE=47	NDBE/DBE/EAC= 97
AIM	1)Measure QOL impairment among patients with BE referred for Endoscopic eradication Therapy 2) identify factors associated with reduced QOL	To assess the EAC risk perceived by patients with NDBE in an endoscopic surveillance program and to associate these perceived EAC risks with Illness perception and QoL.	QOL and illness perceptions with confirmed Low Grade Dysplasia, comparing surveillance and ablation.	Investigate HRQoL and health utility scores for common progression states in patients.
Baseline characteristics	Age, gender, race, family history of BE and/or EAC, PPI use, duration of BE, length of BE (cm), histology, presence of Hiatus, Hernia Diaphragm, BMI	Age, gender BE diagnosis, marital status, education, employment status, comorbidity, Cancer in friends or family	Age, gender length of BE, time since diagnosis of BE in years, time since diagnosis of dysplasia in years, PPI use, Number of comorbidities	Age, gender comorbidity, treatment history previous 12 months, smoking, race, born in Australia, smoking, comorbidities, treatment characteristics
PROMs used	4	3	4	5
Validated PROMs	PROMIS-10 Gerd-Q DIS BSI	SF-36 GERD-Q B-IPQ	SF-36 EORTC-QLQ-C30 EORTC-QLQ-OES18 B-IPQ	SF-6D SF-36 EQ-5D-5L EORTC QLU-C10D EORTC-QLQ-C30
Non-validated questionnaire	N/A	N/A	N/A	N/A
Factors covered	7/18	9/18	7/18	3/18

Table 2: Study characteristics continuation 5

Author, Year	**Rosmolen, 2010**	**Schembre, 2010**	**Lee, 2017**
Level of evidence	3	3	3
Analysis sample	DBE/EAC ET=81 EAC surgery=33	DBE=40	NDBE=139
AIM	To explore QOL, fear of cancer recurrence, and anxiety in patients with a Barrett's esophagus treated for HGD or early cancer in the past, by comparing these outcomes between endoscopically and surgically treated patients.	Attempt to better understand the relative impact of esophagestomy and ET on patients' QOL after therapy and recovery are complete.	To investigate HRQoL in a Chinese population with BE.
Baseline characteristics	Age, gender, co-morbidity, Endoscopy treatment: type of treatment, duration of the treatment, HGD/early cancer during follow-up, . Surgically treated patients: type of surgical resection and reconstruction, length of hospital admission, complications, anastomotic stenosis, and histology of the resected specimen.	Age, gender, American Society of Anesthesiologists score, BE length	Age, BMI, Waist (cm), gender BE length, esophagocardiac junction, histology
PROMs used	4	2	3
Validated PROMs	SF-36 EORTC-QLQ-C30 EORTC-QLQ-OES18 HADS	SF-36 GIQLI	SF-12 RDQ HADS
Non-validated questionnaire	WOCS	N/A	N/A
Factors covered	8/18	9/18	7/18

Table 2: Study characteristics continuation 6

Author, Year	**Schwameis, 2020**	**Hauge,2020**	**Britton, 2020**
Level of evidence	3	3	3
Analysis sample	DBE/EAC=40	DBE/ EAC= 86	NDBE=305 DBE=48 GORD=131 Colonic- polyp=150 Control=47
AIM	To evaluate the workload associated with endotherapy, the frequency and type of recurrence, long-term, QOL, and late oncologic outcomes in a group of patients that were followed for a minimum of 5 years by 1 treating physician.	To evaluate the treatment of dysplasia and superficial esophageal cancer with Endoscopic Mucosal Resection and/or Radio Frequency Ablation and the post-procedural HRQL.	Assess HRQoL in patients with NDBE and endoscopically treated DBE compared with other common gastrointestinal disorders and healthy individuals.
Baseline characteristics	Age, gender, histology, no. Treatments, BE length, follow up length	Age, gender, BE length, histology	Age, gender, histology, employment, family history, career, smoking, PPI, anti-depressant, BE length, co-morbidities
PROMs used	3	3	4
Validated PROMs	SF-36 , GIQLI	EORTC-QLQ-C30 QLQ-OG25 The Ogilvie grading scale	SF-36, GSRS, CWS HADS
Non-validated questionnaire	Non-validated questions on disease symptoms	N/A	N/A
Factors covered	9/18	7/18	7/18

Table 2: Study characteristics continuation 7

Author, Year	Kruijshaar, 2006	Baldaque-silva, 2017
Level of evidence	3	3
Analysis sample	NDBE= 180	
AIM	To explore the burden of upper gastro intestinal endoscopy as perceived by patients.	NDBE=54
Baseline characteristics	Age, gender, marital status, employment status, education, number of endoscopies, histology, reflux esophagitis, PPI use, general health	Determine the impact of upwards titration of PPI on acid reflux, symptom scores and histology, compared to clinically successful fundoplication.
PROMs used	3	Age, gender BMI, smoking, BE length
Validated PROMs	EQ-5D-3L IES HADS	1
Non-validated questionnaire	Non-validated questions on disease symptoms with Likert scale	GERD-HRQL
Factors covered	3/18	N/A

Abbreviations: BE: Barrett Esophagus, NDBE: Non Dysplastic Barrett Esophagus, DBE: Dysplastic Barrett Esophagus, EAC: Esophageal Adeno Carcinoma, GERD: Gastroesophageal reflux disease, NERD: Nonerosive reflux disease, NS:non-specific upper GI symptoms, ET: Endoscopic Treatment, HRQoL: Health Related Quality of Life, QoL: Quality of Life, HGD: High grade dysplasia, BMI: Body Mass Index, PPI: Proton Pomp Inhibitor, RDQ: The Reflux Disease Questionnaire, QOLRAD: Quality of Life in Reflux and Dyspepsia, GERD-HRQL: The Gastroesophageal Reflux Disease-Health Related Quality of Life, EQ-5D: EuroQOL-5D, GERD-Q: Gastroesophageal reflux disease-questionnaire, EORTC-QLQ-OES18: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer Module, EORTC-QLQ-C30: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, HADS: Hospital Anxiety and Depression Scale, SF-16: The 16-Item Short Form Health Survey questionnaire, SF-12: The 12-Item Short Form Health Survey questionnaire, SF-6D: Short Form-6 dimension, PROMIS-10: Patient-Reported Outcomes Measurement Information Systems,LASA: Linear analog self-assessment, WHOQOL-BREF: World Health Organization Quality of Life Instruments, EORTC QLU- C10D: European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire–Core 10, BSI-18: Brief Symptom Inventory, GSRS: Gastrointestinal Symptom Rating Scale, GIQLI: Gastrointestinal Quality of Life Index SCL-90: The Symptom Checklist-90-Revised, QLQ-OG25: EORTC Quality of Life Questionnaire - Oesophago- Gastric Module, TPS: Trust in Physician Scale, IES: The Impact of Event Scale, DIS: The Discomfort Intolerance Scale, PSQI, Berlin-Q: Berlin Questionnaire, B-IPQ: Brief- Illness perception scale, CWS: Cancer worry scale, WOCS: Worry of cancer scale.

Identification of influencing factors according to BE patients

Four studies with a qualitative design were identified: one study used a focus group design and three used patient interviews43–46. The study characteristics and quality scores are demonstrated in Table 3. Studies were published between 2011 and 2020 and were conducted in the UK (n = 2), USA (n = 1), and the Netherlands (n = 1). All studies showed a minimal quality score of 7/10 according to CASP14. Within these studies, the following factors related to HRQoL according to BE patients were identified, namely fear of cancer, anxiety, trust in physicians, sense of control, uncertainty, worry, burden of endoscopy, knowledge and understanding, gastrointestinal (GI) symptoms (e.g., reflux or heartburn, regurgitation, dyspepsia, dysphagia, epigastric pain), sleeping difficulties, diet and lifestyle, use of medication, and support of family and friends. These factors were allocated into domains and displayed in a conceptual framework (see Fig. 4).

Coverage of factors in HRQOL PROMs relevant to patients

None of the 27 identified PROMs covered all factors important to BE patients (Table 4). Generic PROMs were used in 77.8% of all studies, and only a small number of factors were indirectly addressed. For instance, the commonly used SF 36 and SF12 contained items indirectly addressing anxiety and items on pain in general. The EQ-5D, PROMIS 10, LASA, WHOQOL-BREF had additional items on anxiety, and the EORTC-QLQC30 on worry.

The cancer-specific PROMs (EORTC-QLQ C30, EORTC-QLQ C10D) and the generic WHOQOL-BREF measured items of sleeping difficulties in addition to anxiety and pain and indirectly addressed the burden of the use of medication.

Looking at more disease-specific measures, we found that the GIQLI, GERD-HRQL covered all factors related to GI symptoms. Furthermore, the GERD-HRQL addressed an item on lifestyle, whereas the GIQLI contained an item on support of family.

The EORTC-QLQ-OES18 was the only PROM with items on diet and lifestyle; this factor was only indirectly addressed by the GERD-HRQL and the QOLRAD. The other cancer-specific PROM, the QLQ-OG25, addressed GI symptoms, as well as anxiety and worry. The factors 'sense of control' and 'knowledge and understanding' were measured by items of the B-IPQ. Although fear of cancer was stated as an important factor influencing HRQoL in the literature, it was only measured in one study using the CWS[38]. In another study by Rosmolen et al.[21, 22], the WOCS was used for assessing fear of cancer (recurrence). However, we found no accurate validation in the references.

The TPS was the only PROM measuring 'trust in the physician.' The factors uncertainty (QOLRAD) and endoscopic burden (IES) were only indirectly assessed. No PROMs with items on measuring the factor endoscopy as safety net were found. None of the studies address more than nine of the 18 factors important to patients with BE. Overall, a median of 7 (0–9) factors, stated as important to patients using validated PROMs, were covered.

Table 3: Summary list of domains and associated factors influencing HRQoL

Author, Year, country	Ende-van Loon, 2020, NL	Britton, 2018 UK	Arney, 2014 USA	Griffiths, 2011 UK
Aim	To assess the factors influencing HRQOL according to NDBE and DBE patients	To identify and explore factors impacting BO patients' health-related quality of life, follow-up needs and views on new models of follow-up care.	Identify elements of the EGD experience that frame patients' memories and overall perceptions of surveillance	To explore patients' views and perspectives on their experience of living with Barrett's columnar lined oesophagus (CLO) and being part of an endoscopic surveillance program.
Method	Focus group	Exploratory qualitative approach was adopted using semi-structured, in-depth, one-to- one interviews	structured in-depth, qualitative interviews	Qualitative semistructured interviews
Sample	NDBE =16 DBE/EAC ET=17	NDBE=20	NDBE / DBE= 20	NDBE=22
Quality score	10/10	10/10	8/10	7/10
1. Mental health				
Fear of cancer	√	√	√	√
Anxiety	√	√		√
Trust in Physician	√	√		√
Sense of control	√	√	√	√
Uncertainty	√	√	√	√
Worry	√	√		√
Burden of Endoscopy	√	√		√
Knowledge and understanding	√	√	√	√

Author, Year, country	Ende-van Loon, 2020, NL	Britton, 2018 UK	Arney, 2014 USA	Griffiths, 2011 UK
Gastrointestinal symptoms	√	√	√	√
Reflux	√		√	
Regurgitation	√			
Dyspepsia	√			
Dysphagia	√			
Epi gastric pain	√			
Sleeping difficulties	√			
Diet/ lifestyle	√			
Use of medication	√	√	√	
3. Social health	√			
Support of family and friends	√			

Table 3: Summary list of domains and associated factors influencing HRQoL

Abbreviation: NL: Netherlands, UK: United Kingdom, USA: United States of America, HRQOL: Health Related Quality of Life, BE: Barrett Esophagus, NDBE: Non Dysplastic Barrett Esophagus, DBE: Dysplastic Barrett Esophagus, EAC: Esophageal Adeno Carcinoma.

*Quality score using the CASP criteria; a 10-item checklist designed for use in the appraisal of qualitative research studies (CASP)16.

Discussion

In this systematic review, we identified 27 studies measuring HRQoL in BE patients; within these studies, 32 different PROMs were used. None of the identified PROMs were specifically validated to measure HRQoL in BE patients. Consequently, we found that a total of nine studies (33.3%) used some form of non-validated questionnaires. It is interesting to note that the total number of interventional studies that used HRQoL measurements is relatively low. These findings are in contrast with the increased number of endoscopic therapeutic options for BE patients resulting in publications[47].

The most frequently used PROMs for measuring generic HRQoL was the SF-36 (52.2%). Symptoms related to BE were frequently (83.4%) measured by the EORTC-QLQOES18, GERD-Q, GERD-HRQOL, QOLRAD, and the RDQ. The HADS was used to measure symptoms of anxiety and depression in 26% of studies.

We identified four studies with a qualitative design exploring factors influencing HRQoL according to BE patients. Within these studies, the following factors were addressed, namely fear of cancer, anxiety, trust in physician, sense of control, uncertainty, worry, burden of endoscopy, knowledge and understanding, GI symptoms, sleeping difficulties, diet and lifestyle, use of medication, and support of family and friends. These findings are fairly in line with those of Britton et al. [8]. In this study, symptom control, psychological effects as anxiety and depression, worry of cancer, patients' subjective perceived risk of cancer, frequency and severity of worry, and disease-specific knowledge were considered key factors for assessing HRQoL in BE patients.

None of the studies addressed more than nine of the 18 factors important to patients with BE. Disease-specific PROMs were more successful in covering factors important to BE patients, compared to generic PROMs. Interestingly, generic PROMs were used in 77.8% of all studies. However, generic PROMs are used to provide comparisons between diseases or to compare data with population normative values, not to evaluate specific patient populations. The selection of PROMs is a complex but essential process. Several documents for guidance in the appropriate selection of PROMs in clinical trials are available [48]. The current review confirms the need of a more patient centered approach in measuring HRQoL in BE patients. Since there is no BE-specific PROM available, the development of a new instrument seems inevitable. However, a wide variety of PROMs is currently available, and the development of a new measurement tool is time-consuming and complex. A combination of the following disease-specific PROMs GIQLI or GERD-HRQOL, with the CWS, TPS, the B-IPQ would be appropriate to measure factors influencing HRQoL in BE patients. This would, however, necessitate a large number of questions to be addressed by patients. Using the "Patient-Reported Outcomes Measurement Information System" (PROMIS) databank may be an appropriate solution for this problem. PROMIS is an easily accessible set of person-centered measures, using computerized adaptive testing from large item banks for over 70 domains relevant to a wide variety of chronic diseases[49–51]. PROMIS enables comparisons across populations and studies and can be integrated in several electronic health records. We advise clinicians to use the items: PROMIS® GI (disrupted and swallowing, reflux and gas and bloating), PROMIS® Anxiety, and PROMIS® Self-Efficacy (Managing medications and treatment, Managing Symptoms). Further research is needed to validate the PROMIS databank in BE patients. The current study has some limitations that need to be addressed. First, the aim of this review was to identify studies that measure HRQoL in BE patients. Using MeSH and free-text words focusing on areas of HRQoL, we may have underestimated the number of interventional studies that used HRQoL as a secondary endpoint. Second, we identified only four studies with a qualitative study design. Of these, two studies directly investigated factors important to BE patients, while the other two used an indirect manner by focusing on patients experiences with surveillance endoscopy and patient burden, care delivery experience, and follow-up needs. However, all factors identified in the latter two studies were confirmed in the first two studies. Third, the list of factors important to BE patients and the degree to which factors were addressed by the various PROMs is subjective. To increase the intra-rater and inter-rater reliability, an independent extraction of potential factors was performed by two researchers. In conclusion, none of the studies measuring HRQoL in BE patients sufficiently reflected the perceptions of HRQoL in BE patients. For the selection of PROMs, we encourage physicians and researchers measuring HRQoL to choose their PRO from a patient perspective and not strictly based on relevance according to health professionals' definitions. Using PROMs that are more patient centered will enhance knowledge of the true impact of surveillance and endoscopic treatment on the perceived) functioning of BE patients.

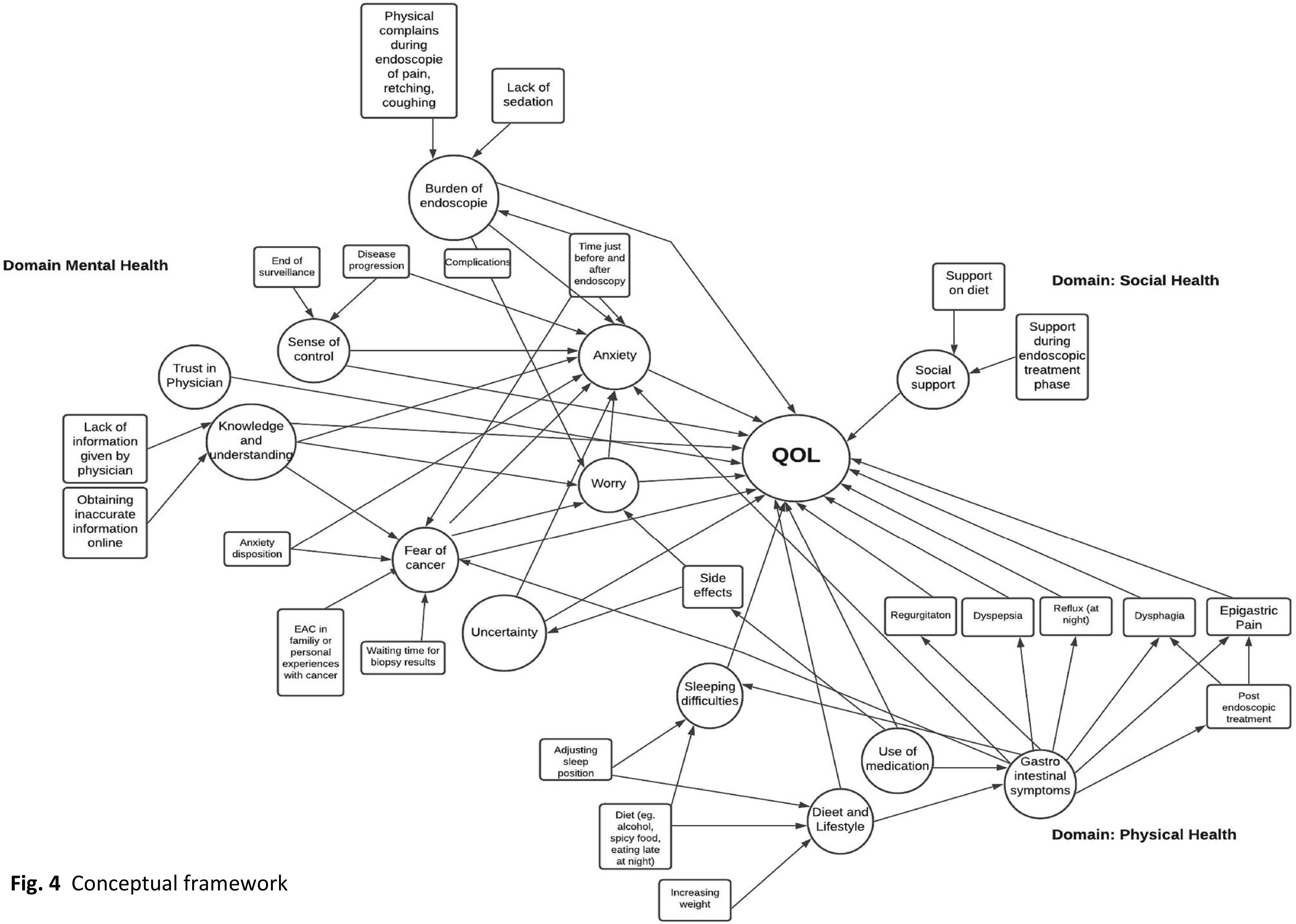


Fig. 4 Conceptual framework

Table 4: PROMs and the coverage of factors important to patients with BE

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	Total factors
GIQLI		√							√	√	√	√	√	√		√	√	9
GERD-HRQL									√	√	√	√	√	√	±	√		7 (1)
GERD-Q									√	√	√		√	√		√		6
QLQ-OG25		√				√			√		√	√	√					6
QOLRAD		√			±	√			√	√				√	±			5 (+2)
RDQ									√	√	√	√	√					5
EORTC-QLQ OES18									√	√		√	√		√			5
GSRS									√	√	√		√					4
WHOQOL-BREF		√											±	√		±	√	3 (2)
SCL-90		√				√					±			√				3 (1)
B-IPQ		±		√		√		√										3 (1)
EORTC-QLQC30						√							±	√		±		2 (2)
CWS	√					√												2
HADS		√				√												2
EORTC QLU-C10D													±	√		±		1 (2)
PROMIS-10		√											±				±	1 (2)
EQ-5D		√											±					1 (1)
IES							±							√				1 (1)
BSI-18		√																1
TPS			√															1
LASA		√																1
PSQI														√				1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	Total factors
Berlin-Q																		
The ogikvie grading scale																		
DIS				±									±			±		0 (3)
SF-36		±											±					0 (2)
SF-12		±											±					0 (2)
SF-6D		±											±					0 (2)

Table 4. PROMs and the coveragde of factors important to patients with BE

Abbrevations: RDQ: The Reflux Disease Questionnaire, QOLRAD: Quality of Life in Reflux and Dyspepsia, GERD-HRQL: The Gastroesophageal Reflux Disease-Health Related Quality of Life, EQ-5D: EuroQOL-5D, GERD-Q: Gastroesophageal reflux disease-questionnaire, EORTC-QLQ-OES18: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Oesophageal Cancer Module, EORTC-QLQ-C30: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, HADS: Hospital Anxiety and Depression Scale, SF-16: The 16-Item Short Form Health Survey questionnaire, SF-12: The 12-Item Short Form Health Survey questionnaire, SF-6D: Short Form-6 dimension, PROMIS-10: Patient-Reported Outcomes Measurement Information Systems, LASA:Linear analog self-assessment, WHOQOL-BREF: World Health Organization Quality of Life Instruments, EORTC QLU-C10D: European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire–Core 10, BSI-18: Brief Symptom Inventory, GSRS: Gastrointestinal Symptom Rating Scale, GIQLI: Gastrointestinal Quality of Life Index SCL-90: The Symptom Checklist-90-Revised, QLQ-OG25: EORTC Quality of Life Questionnaire - Oesophago-Gastric Module, TPS: Trust in Physician Scale, IES: The Impact of Event Scale, DIS: The Discomfort Intolerance Scale, PSQI, Berlin-Q: Berlin Questionnaire, B-IPQ: Brief- Illness perception scale, CWS: Cancer worry scale, WOCS: Worry of cancer scale. 1: Fear of cancer, 2: Anxiety, 3:trust in physician 4: Sense of control, 5: Uncertainty, 6: Worry, 7: Burden of endoscopy, 8: Knowledge and understanding, 9: reflux/ heartburn, 10: regurgitation, 11: dyspepsia, 12: dysphagia, 13: epigastric pain, 14: sleeping difficulties, 15: diet/ lifestyle, 16: use of medication, 17: social support,

√ factor was directly addressed **;** ± factor was indirectly addressed

References

1. Barrett, N. R. (1950). Chronic peptic ulcer of the oesophagus and “oesophagitis.” British Journal of Surgery, 38, 175–182.
2. Allison, P. R., & Johnstone, A. S. (1953). The oesphagus lined with gastric mucous membrane. Thorax, 8, 87–101.
3. Yousef, F., Cardwell, C., Galway, K., et al. (2008). The incidence of esophageal cancer and high-grade dysplasia in Barrett’s Esophagus: A systematic review and meta-analysis. American Journal of Epidemiology, 168(3), 237–249.
4. Desai, T. K., Krishnan, K., Samala, N., et al. (2012). The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett’s oesophagus: A meta-analysis. Gut, 61, 970–976.
5. Caygill, C. P., Royston, C., Charlett, A., et al. (2012). Mortality in Barrett’s esophagus: Three decades of experience at a single center. Endoscopy, 44, 892–898.
6. Solaymani-Dodaran, M., Card, T. R., & West, J. (2013). Causespecific mortality of people with Barrett’s Esophagus compared with the general population: A population-based cohort study. Gastroenterology, 144, 1375–1383.
7. Sikkema, M., de Jonge, P. J. F., Steyerberg, E. W., & Kuipers, E. J. (2010). Risk of esophageal adenocarcinoma and mortality in patients with Barrett’s Esophagus: A systematic review and metaanalysis. Clinical Gastroenterology and Hepatology, 8, 235–244.
8. Britton, J., Keld, R., Prasad, N., Hamdy, S., McLaughlin, J., & Ang, Y. (2018). Effect of diagnosis, surveillance, and treatment of Barrett’s Esophagus on health-related quality of life. The Lancet Gastroenterology Hepatology, 3(1), 57–65.
9. Crockett, S. D., Lippmann, Q. K., Dellon, E. S., et al. (2009). Health-related quality of life in patients with Barrett’s Esophagus: A systematic review. Clinical Gastroenterology and Hepatology, 7(6), 613–623.
10. Testa, M. A., & Simonson, D. C. (1996). Assessment of quality-of-life outcomes. New England Journal of Medicine, 334, 835–840.
11. Liberati, A., Altman, D. G., Tetzlaff, J., et al. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. PLoS Medicine, 6, e1000100.
12. WHOQOL-Group. (1995). The world health organization quality of life assessment (WHOQOL): Position paper from the world health organization. Social Science and Medicine, 41, 1403–1409.

13. OCEBM Levels of Evidence Working Group*. “The Oxford Levels of Evidence 2”. Oxford Centre for Evidence-Based Medicine. OCEBM Levels of Evidence — Centre for Evidence-Based Medicine (CEBM), University of Oxford.

14. Critical Appraisal Skills Programme. (CASP). CASP Checklists. Oxford: CASP, 2014. CASP - Critical Appraisal Skills Programme (casp-uk.net)

15. Terwee, C. B., van der Wees, P. J., en Sandra Beurskens, S., namens het NFU expertisenetwerk Patient-reported outcomes. (2015). Handreiking voor de selectie van PROs en PROMs; Utrecht: Nederlandse Federatie van Universitair Medische Centra (NFU).

16. Kruijshaar, M. E., Kerkhof, M., Siersema, P. D., Steyerberg, E. W., Homs, M. Y., Essink-Bot, M. L., & CYBAR Study Group. (2006). The burden of upper gastrointestinal endoscopy in patients with Barrett’s Esophagus. Endoscopy, 38(9), 873–878.

17. Han, S., Yadlapati, R., Simon, V., Ezekwe, E., Early, D. S., Kushnir, V., Hollander, T., Brauer, B. C., Hammad, H., Edmundowicz, S. A., Wood, M., Shaheen, N. J., Muthusamy, R. V., Komanduri, S., & Wani, S. (2019). Dysplasia severity is associated with poor quality of life in patients with Barrett’s Esophagus referred for endoscopic eradication therapy. Disease of Esophagus.

18. Miller, R. C., Atherton, P. J., Kabat, B. F., Fredericksen, M. B., Geno, D. M., Deschamps, C., Jatoi, A., Sloan, J. A., & Romero, Y. (2010). Marital status and quality of life in patients with esophageal cancer or Barrett’s Esophagus: The mayo clinic esophageal adenocarcinoma and Barrett’s esophagus registry study. Digestive Disease and Science, 55(10), 2860–2868.

19. Lippmann, Q. K., Crockett, S. D., Dellon, E. S., & Shaheen, N. J. (2009). Quality of life in GERD and Barrett’s Esophagus is related to gender and manifestation of disease. The American Journal of Gastroenterology, 104(11), 2695–2703.

20. Eloubeidi, M. A., & Provenzale, D. (2000). Health-related quality of life and severity of symptoms in patients with Barrett’s Esophagus and gastroesophageal reflux disease patients without Barrett’s esophagus. The American Journal of Gastroenterology, 95(8), 1881–1887.

21. Rosmolen, W. D., Nieuwkerk, P. T., Pouw, R. E., van Berge Henegouwen, M. I., Bergman, J. J., & Sprangers, M. A. (2017). Quality of life and fear of cancer recurrence after endoscopic treatment for early Barrett’s neoplasia: A prospective study. Disease of Esophagus, 30(3), 1–9.

22. Rosmolen, W. D., Boer, K. R., de Leeuw, R. J., Gamel, C. J., van Berge Henegouwen, M. I., Bergman, J. J., & Sprangers, M. A. (2010). Quality of life and fear of cancer recurrence after endoscopic and surgical treatment for early neoplasia in Barrett’s Esophagus. Endoscopy, 42(7), 525–531.

23. Rosmolen, W. D., Phoa, N. K. Y. N., Nieuwkerk, P. T., Pouw, R. E., Weusten, B. L. A. M., Bisschops, R., Schoon, E. J., Sprangers, M. A. G., & Bergman, J. J. G. H. M. (2019). Impact of ablation of Barrett's Esophagus with low-grade dysplasia on patients' illness perception and quality of life: A multicenter randomized trial. Gastrointestinal Endoscopy, 90(2), 215–221.

24. Gerson, L. B., Ullah, N., Hastie, T., & Goldstein, M. K. (2007). Does cancer risk affect health-related quality of life in patients with Barrett's Esophagus? Gastrointestinal Endoscopy, 65(1), 16–25.

25. Kulig, M., Leodolter, A., Vieth, M., Schulte, E., Jaspersen, D., Labenz, J., Lind, T., Meyer-Sabellek, W., Malfertheiner, P., Stolte, M., & Willich, S. N. (2003). Quality of life in relation to symptoms in patients with gastro-oesophageal reflux disease—An analysis based on the ProGERD initiative. Alimentary Pharmacology and Therapeutics, 18(8), 767–776.

26. Vela, M. F., Kramer, J. R., Richardson, P. A., Dodge, R., & ElSerag, H. B. (2013). Poor sleep quality and obstructive sleep apnea in patients with GERD and Barrett's Esophagus. Neurogastroenterology and Motility: The Official Journal of the European Gastrointestinal Motility Society, 26(3), 346–352.

27. Bulamu, N. B., Chen, G., Ratcliffe, J., Schloite, A., Bright, T., & Watson, D. I. (2019). Health-related quality of life associated with Barrett's Esophagus and cancer. World Journal of Surgery, 43(6), 1554–1562.

28. Chang, C. Y., Lee, L. J., Wang, J. D., Lee, C. T., Tai, C. M., Tang, T. Q., & Lin, J. T. (2016). Health-related quality of life in patients with Barrett's Esophagus. Health and Quality of Life Outcomes, 14(1), 158.

29. Lee, S. W., Lien, H. C., Chang, C. S., Ko, C. W., Tung, C. F., & Yeh, H. Z. (2017). Health-related quality of life of subjects with Barrett's Esophagus in a Chinese population. PLoS ONE, 12(12), e0190201.

30. Schembre, D., Arai, A., Levy, S., Farrell-Ross, M., & Low, D. (2010). Quality of life after esophagectomy and endoscopic therapy for Barrett's Esophagus with dysplasia. Disease of Esophagus, 23(6), 458–464.

31. Shaheen, N. J., Peery, A. F., Hawes, R. H., Rothstein, R. I., Spechler, S. J., Galanko, J. A., Campbell, M., Carr, C., Fowler, B., Walsh, J., Siddiqui, A. A., Infantolino, A., Wolfsen, H. C., & AIM Dysplasia Trial Investigators. (2010). Quality of life following radiofrequency ablation of dysplastic Barrett's Esophagus. Endoscopy, 42(10), 790–799.

32. van der Ende-van Loon, M. C. M., Rosmolen, W. D., Houterman, S., Schoon, E. J., & Curvers, W. L. (2018). Cancer risk perception in relation to associated symptoms in Barrett's patients: A cross sectional study on quality of life. United European Gastroenterology Journal, 6(9), 1316–1322.

33. Gerson, L. B., Ullah, N., Hastie, T., Triadafilopoulos, G., & Goldstein, M. (2005). Patient-derived health state utilities for gastroesophageal reflux disease. The American Journal of Gastroenterology, 100(3), 524–533.

34. Crockett, S. D., Lipkus, I. M., Bright, S. D., Sampliner, R. E., Wang, K. K., Boolchand, V., Lutzke, L. S., & Shaheen, N. J. (2012). Overutilization of endoscopic surveillance in nondysplastic Barrett's Esophagus: A multicenter study. Gastrointestinal Endoscopy, 75(1), 23–31.

35. Peerally, M. F., Bhandari, P., Ragunath, K., Barr, H., Stokes, C., Haidry, R., Lovat, L., Smart, H., Harrison, R., Smith, K., Morris, T., & de Caestecker, J. S. (2019). Radiofrequency ablation compared with argon plasma coagulation after endoscopic resection of high-grade dysplasia or stage T1 adenocarcinoma in Barrett's Esophagus: A randomized pilot study (BRIDE). Gastrointestinal Endoscopy, 89(4), 680–689.

36. Baldaque-Silva, F., Vieth, M., Debel, M., Håkanson, B., Thorell, A., Lunet, N., Song, H., Mascarenhas Saraiva, M., Pereira, G., Lundell, L., & Marschall, H. U. (2017). Impact of gastroesophageal reflux control through tailored proton pump inhibition therapy or fundoplication in patients with Barrett's Esophagus. World Journal of Gastroenterology, 23(17), 3174–3183.

37. Hauge, T., Franco-Lie, I., Løberg, E. M., Hauge, T., & Johnson, E. (2020). Outcome after endoscopic treatment for dysplasia and superficial esophageal cancer - A cohort study. Scandinavian Journal of Gastroenterology, 55(9), 1132–1138.

38. Britton, J., Taxiarchi, P., Martin, G., Willert, R., Horne, M., Hamdy, S., McLaughlin, J., & Ang, Y. (2020). Comparative quantitative survey of patient experience in Barrett's oesophagus and other gastrointestinal disorders. BMJ Open Gastroenterology, 7(1), e000357.

39. Reddy, C. A., Tavakkoli, A., Chen, V. L., Korsnes, S., Bedi, A. O., Carrott, P. W., Chang, A. C., Lagisetty, K. H., Kwon, R. S., Elmunzer, B. J., Orringer, M. B., Piraka, C., Prabhu, A., Reddy, R. M., Wamsteker, E., & Rubenstein, J. H. (2020). Long-term quality of life following endoscopic therapy compared to esophagectomy for neoplastic Barrett's Esophagus. Digestive Disease of Sciences.

40. Schwameis, K., Zehetner, J., Green, K. M., & DeMeester, S. R. (2020). Workload, recurrence, quality of life and long-term efficacy of endoscopic therapy for high-grade dysplasia and intramucosal esophageal adenocarcinoma. Annals of Surgery, 271(4), 701–708.

41. Essink-Bot, M. L., Kruijshaar, M. E., Bac, D. J., Wismans, P. J., ter Borg, F., Steyerberg, E. W., & Siersema, P. D. (2007). Different perceptions of the burden of upper GI endoscopy: An empirical study in three patient groups. Quality of Life Research, 16(8), 1309–1318.

42. Cooper, S. C., El-agib, A., Dar, S., Mohammed, I., Nightingale, P., Murray, I. A., Cooper, B. T., & Trudgill, N. J. (2009). Endoscopic surveillance for Barrett's oesophagus: The patients' perspective. European Journal of Gastroenterology Hepatology, 21(8), 850–854.

43. Britton, J., Hamdy, S., McLaughlin, J., Horne, M., & Ang, Y. (2019). Barrett's oesophagus: A qualitative study of patient burden, care delivery experience and follow-up needs. Health Expectation, 22(1), 21–33.

44. Arney, J., Hinojosa-Lindsey, M., Street, R. L., Jr., Hou, J., ElSerag, H. B., & Naik, A. D. (2014). Patient experiences with surveillance endoscopy: A qualitative study. Digestive Diseases and Sciences, 59(7), 1378–1385.

45. Griffiths, H., & Davies, R. (2011). Understanding Barrett's columnar lined oesophagus from the patients' perspective: Qualitative analysis of semistructured interviews with patients. Frontline Gastroenterology, 2(3), 168–175.

46. van der Ende-van Loon MCM, Brouwers M, Munnik S, et al. (2021) Factors influencing health related quality of life in patients with Barrett's Esophagus: A qualitative focus group study. European Journal Gastroenterology and Hepatology. Online ahead of print.

47. Tavankit, S., Madhusudhan, R. S., & Prashanthi, N. T. (2018). Endoscopic therapy for Barrett's esophagus and early esophageal cancer: Where do we go from here? World Journal of Gastrointestinal Endoscopy, 10(9), 165–174.

48. Crossnohere, N. L., Brundage, M., Calvert, M. J., King, M., Reeve, B. B., Thorner, E., Wu, A. W., & Snyder, C. (2020). International guidance on the selection of patient-reported outcome measures in clinical trials: A review. Quality of Life Research, 30(1), 21–40.

49. Cella, D., Yount, S., Rothrock, N., Gershon, R., Cook, K., Reeve, B., Ader, D., Fries, J. F., Bruce, B., & Rose, M. (2007). The patient-reported outcomes measurement information system (PROMIS): Progress of an NIH roadmap cooperative group during its first two years. Medical Care, 45, S3–S11.

50. Witter, J. P. (2016). Introduction: PROMIS a first look across diseases. Journal of Clinical Epidemiology, 73, 87–88.

51. PROMIS. Patient Reported Outcomes Measurement Information System 2018. PROMIS (healthmeasures.net)

CHAPTER 4

Cancer risk perception in relation to associated symptoms in Barrett's patients: A cross sectional study on quality of life

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Abstract

Background

Barrett’s oesophagus affects patients’ quality of life and may be a psychological burden due to the threat of developing an oesophageal adenocarcinoma.

Objective

Assessing the oesophageal adenocarcinoma risk perceived by non-dysplastic Barrett’s oesophagus patients and its association with quality of life, illness perception and reflux symptoms.

Methods

This cross-sectional questionnaire study included 158 Barrett’s oesophagus non-dysplastic patients aged 18–75 years. Based on their annual and lifetime oesophageal adenocarcinoma risk estimations measured with the Magnifier Scale, patients were classified as overestimating or underestimating. Associations between the groups where assed on demographics, reflux symptoms and results of the Outcomes Study Short-Form-36 (SF-36) and the Brief Illness Perception Questionnaire (B-IPQ).

Results

The annual oesophageal adenocarcinoma risk was overestimated by 41%. Overestimating patients had lower means on the SF-36 domains: bodily pain (annual p=0.007 and lifetime p=0.014), general health (annual p=0.011 and lifetime p=0.014), vitality (annual p=0.030), physical functioning (lifetime p=0.028), worse illness perception (total score p=0.001) and significantly more reflux symptoms.

Conclusions

Overestimation of the oesophageal adenocarcinoma risk by Barrett’s oesophagus patients was associated with decreased quality of life and worse illness perceptions, which is most likely caused by symptoms of dyspepsia and reflux. These symptoms should be adequately treated, and patients may be in need of extra support and specific information about their oesophageal adenocarcinoma risk.

Introduction

Barrett oesophagus (BO) is a premalignant condition involving a metaplastic transformation of the lower oesophageal lining from squamous to intestinal epithelium, which is caused by gastroesophageal reflux disease[1,2]. BO is associated with an increased risk of an oesophageal adenocarcinoma (OAC). The relative risk of OAC in persons with non-dysplastic BO is 30–125 times higher than that of the general population; however, their absolute risk is low (approximately 0.5% per year) [3].

A recent systematic literature review found that BO is associated with a significant decrease in quality of life (QoL), measured via both generic and disease-targeted instruments. In addition, patients with BO are at risk for psychological consequences such as depression, anxiety and stress.

These negative effects of BO on QoL and psychological health may be related to the patient's perception of the risk of developing OAC[4]. Nevertheless, a study of 92 US patients with BO who were undergoing endoscopic surveillance found that 68% of the patients overestimated their annual risk of developing OAC, and 38% overestimated their lifetime cancer risk[5]. Likewise, a European study found that 20% of BO patients overestimated their numeric annual OAC risk[6]. However, to date it is unknown whether the OAC risk perceived by BO patients is associated with QoL and illness perception.

To better understand the possible psychological burden due to the threat of developing an OAC, the aim of this study was to assess the OAC risk perceived by patients with non-dysplastic BO in an endoscopic surveillance program and to associate these perceived OAC risks with illness perception and QoL.

Materials and methods

Patients

A cross-sectional questionnaire study was performed by recruiting patients from a prospective database in an endoscopic BO surveillance program at the Catharina Hospital, Eindhoven, The Netherlands, a tertiary referral center for surveillance and endoscopic treatment of BO. Patients were invited to participate between November 2016 and January 2017, at a time independent of their gastroscopy.

Patients were eligible if aged between 18 and 75, and if they had prevalent non-dysplastic BO for longer than 6 months. BO was defined as red columnar lined oesophagus (>1 cm) above the proximal margins of the gastric folds on the gastroscopy, the histological presence of intestinal metaplasia in at least one biopsy, and the absence of dysplasia or OAC. Patients had to be able to read and understand the Dutch informed consent and the questionnaires. Patients were excluded if they had a history of BO endoscopic treatment or a surgical oesophageal resection, if their life expectancy was less than 5 years or if they were to undergo a gastroscopy within 1 week of inclusion. Patients who did not respond after 4 weeks received a one-time postal reminder.

Questionnaires.

Patients were asked to complete a questionnaire including demographic and clinical items, i.e. age, sex, marital status, employment status, educational level, duration of BO and comorbidity.

Perceived OAC risk was measured with the Magnifier Scale. This scale, which is presented in Figure 1, features a magnifying glass to represent probabilities between 0 and 100% on a logarithmic scale. This is a validated scale to assess the perceived cancer risk on a low probability range (<1%)[7]. The Magnifier Scale left of the line allows precise estimation of risks<1%. The questionnaire provided the patients with the average OAC risk in the general population of 0.002% per person-year. Patients were asked to indicate their estimation of their annual and lifetime risks of developing OAC by placing an ‘X’ in the magnifying glass or on the line.

The perceived OAC risk was further assessed with two additional questions: ‘How do you perceive your own risk of developing oesophageal carcinoma in the next year?’ and ‘How do you perceive your own lifetime risk of developing oesophageal carcinoma?’. These questions were assessed using a seven-point Likert scale with the responses ‘none’, ‘very small’, ‘small’, ‘neither small nor large’, ‘large’, ‘very large’ or ‘certain’.

Generic QoL was measured with the Outcomes Study Short Form-36 (SF-36). This widely used questionnaire has been validated for measuring generic QoL in multiple disease states.[8,9] The SF-36 measures health status in eight domains: physical functioning, social functioning, physical role functioning, emotional role functioning, vitality, bodily pain, mental health and general health. Scores on the SF-36 range from 0–100 on each dimension and on the summary scales, with higher scores indicating better QoL.

Cognitive and emotional representations of BO were assessed with the Brief Illness Perception Questionnaire (B-IPQ). A recent meta-analysis showed that the scales of this questionnaire had good concurrent validity and predictive validity[10–12]. The B-IPQ uses a nine single-item scale approach and each item is scored on a 0–10 scale. Five of the items assess cognitive illness perceptions, two items assess emotional perceptions and one item assesses illness comprehensibility. A higher score reflects greater perceived threat of the illness. The causal scale is an open-ended response item that asks patients to list the three most important self-perceived causal factors of BO.

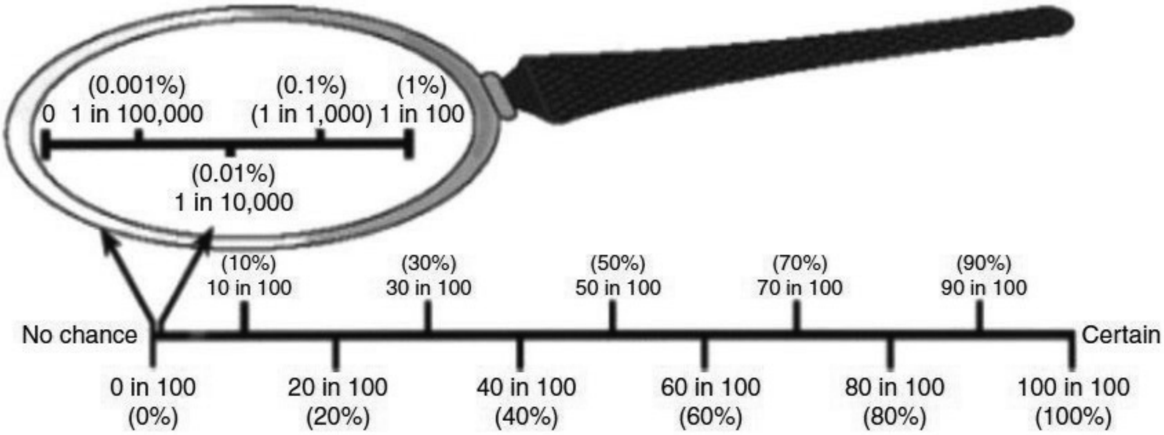

Figure 1. The magnifying glass scale. Reprinted with permission from Woloshin et al.[7]

The presence of reflux symptoms was measured with the Gastro Esophageal Reflux Disease Questionnaire (GerdQ). This validated, self-administered six-item questionnaire uses a four-point Likert scale (0–3) to score the frequency of four positive predictors of gastroesophageal reflux disease (GERD): heartburn, regurgitation, sleep disturbance due to reflux symptoms and use of over-the-counter medication. Furthermore, it uses a reversed Likert scale (3–0) for two negative predictors of GERD (epigastric pain and nausea), resulting in a total GerdQ score range of 0–18. A score higher than eight reflects the potential presence of GERD[13,14].

Statistical analysis

The cohort was divided into two groups according to their perception of developing OAC, as indicated on the Magnifier Scale. First, a dichotomous variable was created for the annual OAC risk overestimate group and for the underestimate group. Patients who perceived their annual risk to be greater than twice the annual OAC risk of 0.5% per year (>1%) were considered overestimating. A patient was considered underestimating their annual OAC risk when perceiving the OAC risk to be <0.025%.

Secondly, a dichotomous variable was created for the lifetime OAC risk over- and underestimate group. To classify patients as over- or underestimating their lifetime OAC risk, the average life expectancy was first calculated for each subject based on sex, age and the average life expectancy according to the Central Agency for Statistics in the Netherlands[15]. Then, the expected lifetime risk was calculated for each patient with the following formula: expected lifetime OAC risk = average life expectancy 0.5%. Overestimation of a lifetime OAC risk was defined as a lifetime risk estimated as 10% higher than the calculated expected lifetime OAC risk. If subjects estimated their lifetime OAC risk to 10% lower than the calculated lifetime OAC risk, they were classified as underestimating.

The results are presented as mean with SD or as median with interquartile range (IQR), as appropriate. Subjects with missing values on the Magnifier Scale were excluded. Missing values on the GerdQ, B-IPQ were not used for analysis. Differences between the demographics of both groups were identified with the Pearson^2 test or Fisher's exact test, as appropriate. Bivariate analyses were performed to detect differences between the annual and lifetime overestimate and underestimate groups in terms of QoL, illness perceptions and GerdQ, using the Student's t-test or Mann– Whitney U test (depending on normality) for continuous variables, and the Pearson^2 test or Fisher's exact test for categorical or ordinal variables. All tests were two-tailed.

Spearman's rho test was used to determine the correlation between the outcomes of the Magnifier Scale and the response rating scale. The level of significance was set at a p-value of $p<0.05$. Data management and analysis were performed using SPSS (IBM version 23). All authors had access to the study data, and they all reviewed and approved the final manuscript.

Results

After screening a total of 383 patient files, 233 patients were found eligible and were invited to participate in this study. In total, 170 patients (73%) signed informed consent and returned the questionnaire, and 158 patients (68%) completed the questionnaire sufficiently for analysis. Of the study population, patients were predominantly men (77%), the mean age of patients was 62.7 (36–76) years and the median time since BO diagnosis was 79 (6–383) months. The demographic and clinical baseline characteristics are shown in Table 1.

Perceived cancer risk

Annual OAC risk was overestimated by 65 of the 158 included patients (41%) and underestimated by 93 (59%). One patient estimated his annual risk correctly at 0.5%. The lifetime OAC risk was overestimated by 40 patients (25.1%) and correctly estimated by nearly one-half of the patients (48.4%). No significant differences were found between the groups in terms of demographic characteristics. In the overestimate groups, there were significantly more patients who had a friend or family member with cancer at the time of study participation (annual p=0.003 and lifetime p=0.019).

The annual risk perception on the response rate scale is presented in Figure 2. Risk perception on the Magnifier Scale significantly correlated with the OAC risk perception response rating scale (Rs=0.58, p=<0.001 for annual risk and R=0.66, p=< 0.001 for lifetime risk).

GERD symptoms

Overall, 88% of patients stated that they used the PPI as prescribed by their doctor. As shown in Table 2, the overestimate group reported significantly more symptoms of reflux and functional dyspepsia. However, the groups showed no significant differences in the total means of the GerdQ. There were significantly more scores above eight (p=0.027) in the lifetime overestimate group, suggesting the presence of GERD.

	Annual risk			Lifetime risk		
	Underestimate *n* 93 (59%)	Overestimate *n* 65 (41%)	*p*	Underestimate *n*42 (26%)	Overestimate *n* 40 (25%)	*p*
Male sex, *N* (%)	75 (80.6)	46 (70.8)	0.15	35 (83.3)	32 (80.0)	0.78
Age in years, mean (SD)	63.0 (9.1)	62.2 (8.9)	0.61	58.9 (9.5)	60.8 (9.5)	0.37
Time since Barrett diagnosis in months, median (IQR)	75.0 (6–383)	95.0 (7–319)	0.46	68.5 (6–205)	96.5 (7–319)	0.05
Marital status, *N* (%)			0.10			0.21
No relationship	4 (4.3)	4 (6.2)		0 (0)	3 (7.5)	
Married/living together	83 (89.2)	57 (87.7)		39 (92.9)	34 (85.0)	
Divorced	1 (1.1)	0 (0.0)		1 (2.4)	0 (0.0)	
Widow/widower	5 (5.4)	4 (6.2)		2 (4.8)	3 (7.5)	
Education, *N* (%)			0.71			0.35
<High school	29 (31.2)	25 (38.5)		9 (21.4)	12 (30.0)	
High school	30 (32.3)	21 (32.3)		13 (31.0)	16 (40.0)	
Bachelor's/university	33 (35.5)	19 (29.2)		19 (45.2)	12 (30.0)	
Missing value	1 (1.1)	0 (0.0)		1 (2.4)	0 (0.0)	
Employment status, *N* (%)			0.97			0.65
Employed	43 (46.2)	30 (46.2)		25 (59.5)	24 (60.0)	
Unemployed	9 (9.7)	8 (12.3)		5 (11.9)	3 (7.5)	
Retired	39 (41.9)	26 (40.0)		11 (26.2)	13 (32.5)	
Missing value	2 (2.2)	1 (1.5)		1 (2.4)	0 (0.0)	
Total comorbidity, mean (SD)	2.39 (1.82)	2.6 (1.92)	0.43	1.98 (1.71)	2.6 (1.68)	0.089
Missing value, *N* (%)	3 (2.8)					
Having a friend or family member with cancer, *N* (%)	14 (15.2)	23 (35.4)	0.003	7 (16.7)	16 (40.0)	0.019
Missing value	1 (0.93)					

Table 1. Demographic and clinical baseline characteristics

Demographic and clinical baseline characteristics in patients with non-dysplastic Barrett's oesophagus who underestimated or overestimated their annual and lifetime oesophageal adenocarcinoma risk. The lifetime risk was estimated correctly by 49%, this group was not used for analysis. A *p*-value < 0.05 was considered significant. IQR: interquartile range.

QoL

The results of the SF-36 summary scores are presented in Table 3. Both the annual and the lifetime overestimates group showed significantly lower means on three of the physical domains, namely physical functioning, bodily pain and general health.

Illness perception

Patients who overestimated their annual or lifetime OAC risk experienced more symptoms (p=0.001), had more concerns about their BO (p=0.000), were more emotionally affected by their BO (p=0.000), experienced more consequences of the BO (p=0.000) and were less satisfied with the treatment controlling their BO (p=0.034). No significant differences were found between the two groups regarding their understanding of BO, their personal control of the disease and their perception of the duration of their BO. The total scores of the illness perception scale were significantly higher/more threatening in the overestimate groups (annual p=0.000 and lifetime p=0.000).

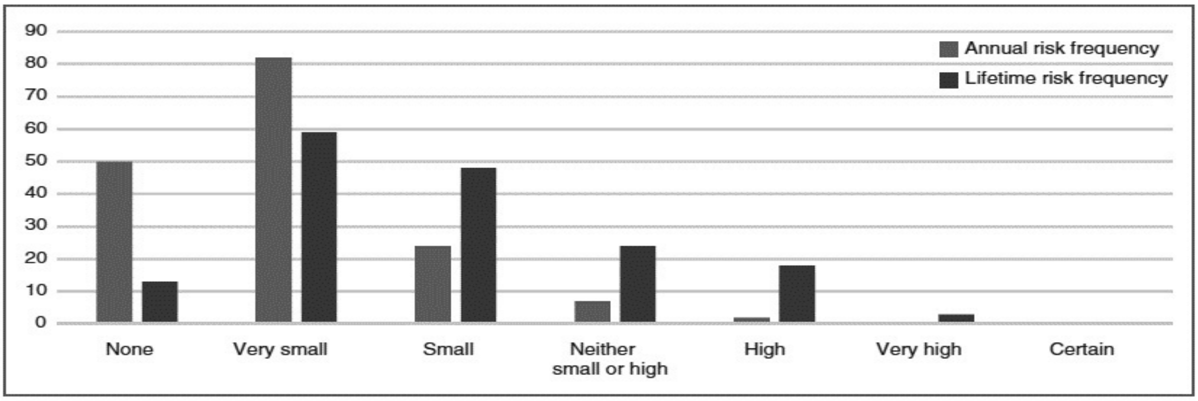

Figure 1 Perceived oesophageal adenocarcinoma risk for annual and lifetime risk scores on a response-rate Likert scale in patients with non-dysplastic Barrett’s oesophagus

	Annual risk Median (SD)			Lifetime risk Mean (SD)		
	Underestimate *n* 92 (IQR)	Overestimate *n* 63 (IQR)	*p*	Underestimate *n* 42 (IQR)	Overestimate *n* 38 (IQR)	*p*
Heartburn	0.00 (0.00–0.00)	0.00 (0.00–2.00)	0.001	0.00 (0.00–0.25)	0.00 (0.00–2.00)	0.024
Regurgitation	0.00 (0.00–0.00)	0.00 (0.00–1.00)	0.004	0.00 (0.00–0.00)	0.50 (0.00–2.00)	0.000
Epigastric pain	3.00 (3.00–3.00)	3.00 (1.00–3.00)	0.033	3.00 (3.00–3.00)	2.00 (1.00–3.00)	0.000
Nausea	3.00 (3.00–3.00)	3.00 (2.00–3.00)	0.28	3.00 (3.00–3.00)	3.00 (2.00–3.00)	0.011
Sleeping difficulties	0.00 (0.00–0.00)	0.00 (0.00–1.00)	0.065	0.00 (0.00–0.00)	0.50 (0.00–1.25)	0.001
Use of counter medication	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.32	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.23
Total	6.00 (6.00–7.00)	6.00 (6.00–9.00)	0.21	6.00 (6.00–7.00)	6.00 (6.00–9.00)	0.36
Score > 8, *N (%)*	22 (24)	24 (38)	0.074	7 (17)	15 (40)	0.027

Table 2. Reflux en dyspepsia symptoms. Gastro Esophageal Reflux Disease Questionnaire scores in patients with non-dysplastic Barrett’s oesophagus who underestimated or overestimated their annual or lifetime OAC risks. There were three patients with missing values; these patients were not used for analysis. A p-value < 0.05 was considered significant.. IQR: interquartile range.

	Annual risk Mean (SD)			Lifetime risk Mean (SD)		
	Underestimate *n* 91	Overestimate *n* 64	*p*	Underestimate *n* 42	Overestimate *n* 39	*p*
PF- physical functioning	84.0 (22.4)	80.4 (22.9)	0.024	90.5 (19.3)	83.1 (21.8)	0.064
RP- role functioning physical	82.1 (32.8)	72.6 (39.3)	0.11	85.1 (32.2)	75.0 (39.3)	0.14
RE- role functioning emotional	88.3 (27.8)	85.4 (31.6)	0.72	85.7 (31.4)	87.2 (29.2)	0.92
SF- social functioning	90.4 (17.9)	86.7 (21.0)	0.43	93.5 (12.1)	89.4 (21.0)	0.24
BP- bodily pain	82.3 (23.1)	72.8 (24.7)	0.004	85.9 (20.1)	73.1 (24.6)	0.008
MH- mental health	84.1 (15.6)	82.5 (16.4)	0.36	83.8 (19.4)	82.5 (14.2)	0.62
VT- vitality	71.3 (22.9)	66.8 (24.9)	0.030	73.7 (23.7)	65.3 (20.9)	0.068
GH- general health	69.8 (21.6)	58.19 (20.9)	0.012	71.0 (24.0)	59.2 (19.1)	0.015

Table 3. Quality of life. Outcomes Study Short Form-36 scores in patients with non-dysplastic Barrett’s oesophagus who underestimate or overestimate their annual and lifetime risk. There were three missing values; these patients were not used for analyses. A p-value < 0.05 was considered significant.

Discussion

As is already known, BO is a premalignant condition that affects patients' QoL and it may be a psychological burden due to the threat of developing OAC. This study is the first to show that overestimating the OAC risk is associated with a significantly lower QoL in the physical domains, more reflux and dyspeptic symptoms and worse illness perceptions. These differences were not associated with the number of comorbidities. It is important to point out that in comparison to the QoL results in other BO populations, our study population scored higher overall on all domains of the SF-36[16–18].

The association between overestimating the OAC risk, reduced QoL and worse illness perceptions may partly be explained by the presence of more symptoms of reflux and dyspepsia. This is consistent with the study of Shaheen et al.,[5] who found that patients overestimating their risk of developing OAC were more likely to have reflux symptoms. A Chinese study found that Health Related Quality of Life in BO patients was strongly associated with presentation of reflux symptoms[19].

Patients who overestimated their OAC risk were significant more likely to have a friend or family member with cancer at the time of study participation, hence this factor could most likely have influenced their illness perception. These results are in line with those of previous studies that concluded that a family history of cancer is associated with overestimating one's own cancer risk[20,21].

When assessing the OAC risk perceived by BO patients, previous studies used several instruments other than the Magnifier Scale. A Likert linear number scale was used by Kruyshaar et al.,[6] and time trade-off values were used by Gerson et al[16]. The linear number scale and the magnifying glass scale are similar in validity, reliability and usability. However, only the magnifying glass scale is validated for eliciting perceptions in the low-probability range (<1%)[11]. A previous study showed that time trade-off values may be less valid in patients aged over 60[22]. Since the average BO population is 60 or older, time trade-off values may not have been appropriate in our study population. In our opinion, by using the Magnifier Scale like Shaheen et al.[5]. this study used the best-validated scale available for assessing the perceived OAC risk within the BO population.

In contrast to the results of Shaheen et al[5]. this study showed that the majority underestimated their annual and lifetime OAC risk (68 versus 41%). A possible explanation for this difference might be that there are several culture differences as well as differences in healthcare systems. In contrast to Shaheen et al[5]. our questionnaire provided patients with the average OAC in the general population of 0.002% per person-year. This may have influenced our patients to perceive their OAC risk to be lower on the Magnifier Scale.

A limitation of this cross-sectional study is that although associations are confirmed, no causal factor of overestimating behavior can be identified. There is a potential bias in patients who experienced psychological stress caused by non-BO-related origins, which may have led to more reflux and dyspeptic symptoms. Also, this was a single-center study in a BO expert clinic, which implies that our study population may not be representative of the BO population worldwide.

Overall, this study confirms that overestimation of the OAC risk by non-dysplastic BO patients is associated with a decreased QoL and worse illness perception, which is most likely caused by symptoms of dyspepsia and reflux. Providers caring for patient with BO should be aware of the implications of the diagnosis. Patients may be in need of extra support and specific information about their OAC risk. BO patients experiencing reflux-related symptoms should receive adequate treatment.

Further research should be undertaken to investigate the causal factors that influence the OAC risk perceived by BO patients (e.g. patient information and reflux symptoms) in order to improve QoL in this patient group.

References

1. Barrett NR. Chronic peptic ulcer of the oesophagus and‘‘oesophagitis’’. Br J Surg 1950; 38: 175–182.

2. Allison PR and Johnstone AS. The oesophagus lined with gastric mucous membrane. Thorax 1953; 8: 87–101.

3. Yousef F, Cardwell C, Galway K, et al. The incidence oesophageal cancer and high-grade dysplasia in Barrett’s esophagus: A systematic review and meta-analysis. Am J Epidemiol 2008; 168: 237–249.

4. Crockett SD, Lippmann QK, Dellon ES, et al. Health related quality of life in patients with Barrett’s Esophagus: A systematic review. Clin Gastroenterol Hepatol 2009; 7: 613–623.

5. Shaheen NJ, Green B and Medapalli RK. The perception of cancer risk in patients with prevalent Barrett’s esophagus enrolled in an endoscopic surveillance program. Gastroenterology 2005; 129: 429–436.

6. Kruijshaar ME, Siersema PD, Janssens ACJW, et al. Patients with Barrett’s esophagus perceive their risk of developing esophageal adenocarcinoma as low. Gastrointest Endosc 2007; 65: 26–30.

7. Woloshin S, Schwartz LM, Byram S, et al. A new scale for assessing perceptions of chance (a validation study). Med Decis Making 2000; 20: 298–307.

8. McHorney CA, Ware JE and Raczek AE. The MOS 36item Short-Form Health Survey (SF-36):II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. MedCare 1993; 31: 247–263.

9. Ware JE Jr, Gandek B, Kosinski M, et al. The equivalence of SF-36 summary health scores estimated using standard and country-specific algorithms in 10 countries: Results from the IQOLA Project. International Quality of Life Assessment. J Clin Epidemiol 1998; 51: 1167–1170.

10. Broadbent E, Petrie KJ, Main J, et al. The brief illness perception questionnaire. J Psychosom Res 2006; 60: 631–637.

11. Weinman J and Petrie KJ. Illness perceptions: A new paradigm for psychosomatics? J Psychosom Res 1997; 42: 113–116.

12. Weinman J, Petrie KJ, Moss-Morris R, et al. The illness perception questionnaire: A new method for assessing the cognitive representation of illness. Psychol Health 1996; 11: 431–446.

13. Jonasson C, Wernersson B, Hoff DA, et al. Validation of the GerdQ questionnaire for the diagnosis of gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2013; 37: 564–572.

14. Jones R, Junghard O, Dent J, et al. Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. Aliment Pharmacol Ther 2009; 15: 30: 1030–1038.

15. Central Agency for Statistics in the Netherlands. Den haag/Heerlen. Jan 2017. Retrieved from the website of the Central agency for Statistics in the Netherlands https://opendata.cbs.nl/statline/#/CBS/nl/dataset/71950ned/table?ts=1535737814109 (accessed Jan 2017).

16. Gerson LB, Ullah N, Hastie T, et al. Does cancer risk affect health-related quality of life in patients with Barrett's esophagus? Gastrointest Endosc 2007; 65: 16–25.

17. Eloubeidi MA and Provenzale D. Health-related quality of life and severity of symptoms in patients with Barrett's esophagus and gastroesophageal reflux disease patients without Barrett's esophagus. Am J Gastroenterol 2000; 95: 1881–1887.

18. Eloubeidi M, Uslick B and Provenzale D. Health related quality of life (HRQL) in patients with Barrett's esophagus. Gastroenterology 1997; 112: A14.

19. Lee SW, Lien HC, Chang CS, et al. Health-related quality of life of subjects with Barrett's esophagus in a Chinese population. Plos One 2017; 12: e0190201.

20. Rini C, Jandorf L, Valdimarsdottir H, et al. Distress among inflammatory bowel disease patients at high risk for colorectal cancer: A preliminary investigation of the effects of family history of cancer, disease duration, and perceived social support. Psychooncology 2008; 17: 354–362.

21. Butler KM, Rayens MK, Wiggins AT, et al. Association of smoking in the home with lung cancer worry, perceived risk, and synergistic risk. Oncol Nurs Forum 2017; 44: E55–E63.

22. Dolan P, Gudex C, Kind P, et al. The time trade-off method: Results from a general population study. Health Econ 1996; 5: 141–154.

CHAPTER 5

5

Barrett Esophagus: Quality of life and factors associated with illness perception

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Abstract

Background

Health-related Quality of life (HRQoL) in patients with Barrett's esophagus (BE), a premalignant condition, may be influenced by gastroesophageal reflux disease (GERD) symptoms and the risk of developing esophageal adenocarcinoma.

Methods

We aim to investigate HRQoL in non-dysplastic Barrett Esophagus (NDBE) patients, identify factors associated with a negative illness perception of the diagnosis BE and compare outcomes between patients treated in a specialized BE center with non-expert centers. In this multi-center cross-sectional study, HRQoL of NDBE patients were assessed using the Short Form 36, Hospital Anxiety and Depression Scale, Cancer worry Scale, and Reflux Disease Questionnaire. A multivariable, linear regression analysis was conducted to assess factors associated with illness perception (Illness perception scale) of the BE diagnosis. Outcome parameters of patients from expert centers were compared to non-expert centers.

Results

A total of 859 NDBE patients (mean age 63.6% and 74.5% male), of which 640 from BE expert centers were included. BE patients scored similar or higher means (i.e. better) on generic HRQoL in comparison with a Dutch norm population. The multivariable regression model showed that cancer worry, GERD symptoms, signs of anxiety and depression, and female gender were associated with a negative illness perception of BE. GERD symptoms were reported in the minority (22.4%) of BE patients. Levels of anxiety symptoms were comparable to a Dutch norm population (mean 3.7 vs. 3.9 p 0.183) and lower for depression symptoms (mean 6.8 vs.7.6 $p < 0.001$). Overall, there were no differences found on outcomes between expert centers and non-expert centers.

Conclusion

NDBE patients scored similar or better on generic HRQoL, anxiety and depression than an age and gender matched norm population. The presence of cancer worry, gastrointestinal symptoms, anxiety and depression, and female gender are factors associated with a negative illness perception of the diagnosis BE.

Introduction

The prevalence of gastroesophageal reflux disease (GERD) in Western countries has increased over the past few decades and is one of the most encountered conditions in primary care practice, with an estimated prevalence of between 18% and 27% in the USA and 9%–26% in Europe[1]. The diagnosis of GERD is associated with a 10%–15% risk of Barrett's esophagus (BE), involving a metaplastic transformation of the lower esophageal lining from squamous to intestinal type epithelium.[2] Current guidelines recommend endoscopic surveillance for patients with non-dysplastic Barrett's esophagus (NDBE) every 2–5 years[3,4]. Among those with BE (with or without GERD symptoms), 0.2%–0.5% will develop esophageal adenocarcinoma (EAC)[5]. Previous studies have shown it is difficult for patients to accurately estimate this cancer risk[6–8]. These perceptions on developing EAC may affect patients' HRQoL. HRQoL is generally considered encompassing patients' physical-, psychological-, and social functioning, which can be affected by both the disease and treatment[9]. Our recent study, performed in a Dutch single center, showed decreased HRQoL in those patients who overestimated their cancer risk[6]. Most BE patients reported a HRQoL compared to a general Dutch population, this in contrast to the results on HRQoL in previous studies[10]. Many of these studies are underpowered, single center or cannot be reliably compared with current patient pathways[14].

Several factors (e.g. fear of cancer, anxiety, trust in physicians, sense of control, gastrointestinal (GI) symptoms) were perceived as influencing HRQoL according to BE patients. None of the previously performed quantitative studies measuring HRQoL in BE patients sufficiently reflected these perceptions of HRQoL[11]. Quantitative data confirm associations between decreased HRQoL and fear of cancer, anxiety, and GI symptoms[7,10,12]. A more recent study on the prevalence of factors influencing HRQoL in patients receiving surveillance of their BE showed GERD symptom severity was associated with EAC cancer worry, anxiety and depression[7]. However, it is not known what factors are associated with negative illness perception by patients with the diagnosis BE. Illness perceptions are a representation of patients' beliefs and expectations about an illness or somatic symptoms. These perceptions have been found to be important determinants of behavior and have been associated with a number of important outcomes, such as treatment adherence and increased healthcare use[13].

Patients with BE are at risk for psychological consequences such as depression and anxiety. A recent German study showed high numeracy rates of depression (14.2%) and anxiety (9.9%), those were about 3–5 times higher in the study sample than in the general population. Rates of BE-related reflux and pain symptoms showed the strongest association with higher levels of depressive and anxiety symptoms. Though, absence of information on patients' disease characteristics limited generalizability of these results[14].

There is an increasing shift of care for BE patients to specialized BE centers. A previous review suggested delivering a focused BE-specific service for all BE patients[15]. However, it is not clear if patients are experiencing better HRQoL-outcomes in hospitals specialized in Barrett surveillance and treatment. In this multicenter study, we aim to assess the generic and disease specific QoL in NDBE patients, identify factors associated with negative illness perception of the diagnosis BE and compare outcomes between patients treated in a specialized BE center with non-expert centers. This may lead to a better understanding of the impact of the factors influencing HRQoL, which could be the start of a person-centered approach for measuring HRQoL in patients with BE.

Materials and methods

We performed a cross-sectional multi-center study, which was conducted between October 2019 and August 2021. Due to the COVID-19 pandemic, inclusion was interrupted between January 2021 and July 2021. For the collection of the data patients completed a self-administered questionnaire.

Patients

For this study, we analyzed the data collected from five expert centers for surveillance and endoscopic treatment of BE in the Netherlands (including two academic centers). BE expert-centers were defined according to the ESGE Barrett guideline (with dedicated gastroenterologist and nurse practitioners).[3] In addition, three non-expert centers for BE (of which one academic center) were included. All patients included in the endoscopic surveillance programs of the participating centers were asked to participate in the study. The inclusion criteria were (1) proven macroscopic and histologic BE, (2) aged 18–80 years (3) able to read, understand and complete the Dutch informed consent form and the study questionnaires. Patients were excluded if there was (1) a history of BE endoscopic treatment or a surgical esophageal resection, and (2) presence of low-or high-grade dysplasia or EAC in BE histology.

Patients were invited to participate with a postal invitation. Nonresponsive patients received a one-time postal reminder after 4 weeks. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Medical Ethical Committee United (MEC-U) with reference W19.068. Subsequently, all institutional review boards of the participating hospitals approved the protocol.

Questionnaires

Patients were asked to fill out demographic and clinical items (age, gender, marital status, employment status, educational level, knowledge of the diagnosis BE, use of medication treating GERD, and comorbidity). Generic HRQoL was measured with the Short Form 36 (SF-36). This widely used questionnaire has been validated for measuring generic QoL in multiple disease states[16,17]. Scores on the SF-36 range from 0 to 100 on each dimension (physical functioning, social functioning, physical role functioning, emotional role functioning, vitality, bodily pain, mental health and general health), with higher scores indicating better HRQoL. To compare data from our sample and Dutch normative data, the sample was age and gender standardized and based on a general Dutch population in the age of 61–70[18].

Cancer worry was measured using the Cancer Worry Scale (CWS)[19]. Scores range from 6 to 24, with a higher score indicating more cancer worry. Based on a previous Dutch validation study, we divided patients into three categories: no cancer worry (score <6), low level of cancer worry (score 7–9), and high level of cancer worry (score ≥10)[20].

To measure symptoms of anxiety and depression, the Hospital Anxiety and Depression Scale (HADS) was utilized.[21] Patient results were obtained by summing up each subscale (anxiety and depression), yielding values from 0 to 21. To compare to a general Dutch population, data of 1901 individuals were used including 48.8% men with a mean age of 61.3 (SD 2.3). A cut-off score of >8 was used, indicating moderate to severe signs of anxiety and/or depression[22].

The presence of GERD symptoms was measured using the Reflux Disease Questionnaire (RDQ)[23–26]. The mean of all three dimensions (dyspepsia, regurgitation, and heartburn) gives a total score ranging from 0 to 5. Where a score of 0 represents nil symptoms, a score of 1–2 mild symptoms, and 3–5 severe symptoms of GERD[27].

Cognitive and emotional perceptions of BE were assessed with the Brief Illness Perception Questionnaire (B-IPQ)[28–30]. The B-IPQ uses a nine single-item scale approach, and each item is scored on a 0–10 scale. Five of the items assess cognitive illness perceptions, two items assess emotional perceptions (e.g. sense of control and worry) and one item assesses illness comprehensibility (understanding of the diagnosis). A higher score reflects a more threatening perception of the illness.

Statistical analysis

Continuous sociodemographic data are presented with means and standard deviation. Categorical variables are summarized with frequency and percentages. The eight domains of the SF-36 score were converted to standard scores based on the scores of an age and gender matched representative reference sample of the Dutch population[18]. Standard scores were calculated by dividing the difference between the patients' SF-36 score and the mean score of the matched reference population by the SDs of the reference population. A standard score thus indicates how many SDs the observed SF36 score falls below or above the score of the reference population. Consequently, scores of the reference population are set at 0.

A mean standard score of 0.20 is considered to indicate a small deviation from the reference population, since it resembles the effect size calculation.[31] Mean standard scores of 0.20, 0.50 and 0.80 are considered to indicate small, moderate and large deviations from the reference population, respectively. To evaluate factors associated with a negative illness perception of the diagnoses Barrett (B-IPQ) a regression analysis was used. All variables were univariate tested on a significant correlation with BE illness perception. Variables with $P < 0.2$ in the univariable analyses were included in a multivariable model and R-squared was computed. To avoid multicollinearity, a correlation of the independent variables of less than 0.8 was accepted. For comparison of continuous variables between the BE expert centers and non-expert centers the student's *t*-test or Mann Whitney U (depending on normality) and for categorical variables a Chi-square test was used. $P < 0.05$ is considered statistically significant. Data were analyzed using the IBM Statistical Package for Social Sciences (SPSS), version 25.

Results

A total of 1731 BE patients were invited to participate, of whom 859 (49.6%) signed informed consent and completed the questionnaires. The mean age of BE patients was 63.6 years (SD = 13.4). Most patients were male (74.5%), married or cohabitating (81.5%), working (45.8%), and completed secondary or post-secondary education (74.3%). An overview with all demographic and clinical baseline characteristics is shown in Table 1. Most baseline characteristics showed no significant differences between the BE centers and nonexpert centers. However, participants in the non-expert centers reported significantly more comorbidities (two in the expert centers (0–14) versus three (0–11) in the non-expert centers).

Generic HRQoL

The participants treated in non-expert centers reported significantly lower scores on mental health (*p*.004), representing more psychological distress and less well-being. In addition, they scored lower on the vitality domain, however this was not significant (*p*.051).

Overall, BE patients had similar or higher mean scores on SF36 subscales than the Dutch reference population (Figure 1). The domains mental health, bodily pain, role functioning, and physical functioning showed a moderate but significant deviation with the reference population.

	All patients *n* = 859	**BE expert centers *n* = 640**	**Non-expert centers *n* = 219**	***P***
Male gender, *N (%)*	640 (74.5)	555 (74.4)	85 (75.2)	0.851
Age in years, *mean (SD)*	63.6 (10.4)	63.9 (9.1)	64.5 (7.9)	0.192
Marital status, *N (%)*				0.121
No relationship	72 (8.4)	63 (8.5)	9 (8.0)	
Married/living together	698 (81.5)	614 (82.5)	84(75.0)	
Divorced	46 (5.4)	36 (4.8)	10 (8.9)	
Widow/widower	39 (4.6)	30 (4.0)	9 (8.0)	
Education,[a] *N (%)*				0.408
< High school	219 (25.7)	186 (25.1)	33 (30.0)	
High school	363 (42.6)	322 (43.4)	41 (37.3)	
Bachelor/University	270 (31.7)	234 (31.5)	36 (32.7)	
Employment status, *N (%)*				0.192
Employed	340 (40.2)	300 (40.8)	40 (36.0)	
Unemployed	82 (9.7)	66 (9.0)	16 (14.4)	
Retired	377 (44.6)	326(44.4)	51 (45.9)	
Other	47 (5.6)	43 (5.9)	4 (3.6)	
Total comorbidity, *median (range)*	2 (0–14)	2 (0–14)	3 (0–11)	0.026

Table 1. Baseline characteristics
Note: BE expert centers represent five different hospitals and the Non-expert centers represent three different hospitals. Abbreviation: BE, Barrett Esophagus. a 3 missing values.

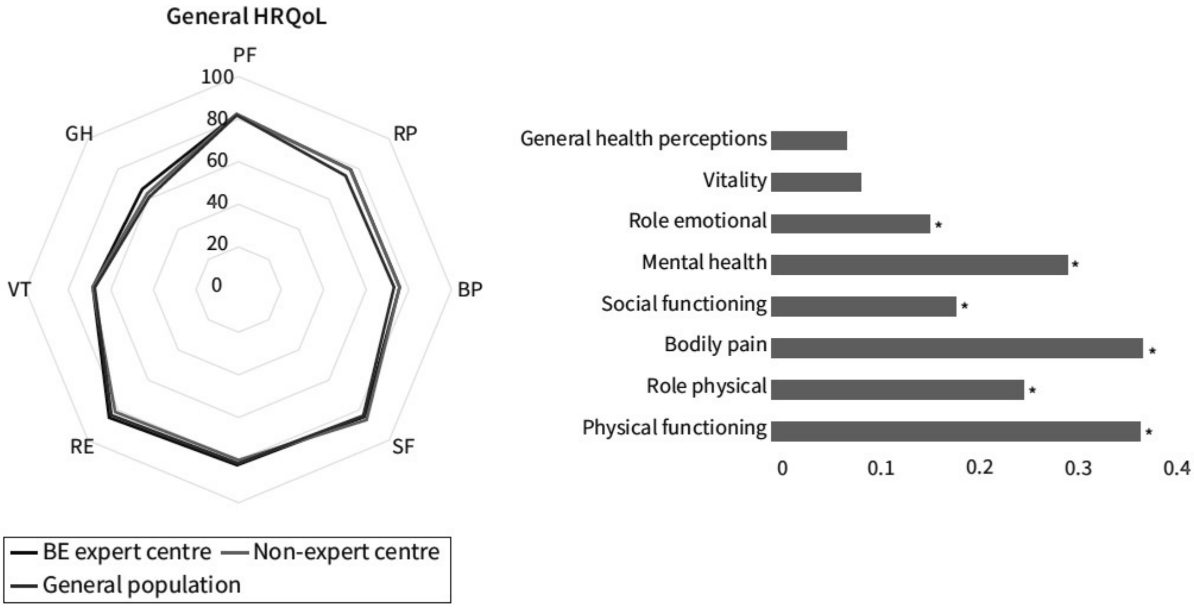

Figure 1. Health-related quality of life (HRQoL) scores for patients with Barrett Esophagus (BE). Standard scores of >0 indicate better HRQoL than a general Dutch population. Scores of 0.2, 0.5 and 0.8 indicate respectively a small, moderate, or large deviation from the reference population *$P < 0.005$

GERD symptoms

Overall, 92.4% of BE patients stated that they were using PPI as prescribed by their physician. Most patients experienced no GERD symptoms (77.6%), only 2.8% of patients reported severe GI symptoms. BE patients in the non-expert centers reported more symptoms of heartburn, however this was not significant ($X^2(2) = 5.529$, *p*.063) (Table 2).

Cancer worry

With a mean value of 9.14, BE patients reported low scores of cancer worry. As Table 3 shows, only 18.7% of patients scored lower than 6, indicating no cancer worry. 414 BE patients (48.8%) reported a low level of cancer worry, and 32.5% of the BE population reported a high level (>10) of cancer worry. This was not significantly different between the participating hospitals.

Anxiety and depression

Moderate to severe signs of a depression were found in 113 BE patients (13.2%). Additionally, 16.3% of patients reported moderate to severe signs of an anxiety disorder. Barrett patients reported lower means for depression (representing less signs of a depression) compared to the Dutch general population (mean 6.8 vs. 7.6 $p < 0.000$). The anxiety scores were comparable to the Dutch general population (mean 3.7 vs. 3.9 *p*.183). There were no significant differences between the participating hospitals.

	All BE patients	**BE expert centers**	**Non-expert centers**	***P***
Dyspepsia				0.481
None	674 (78.7)	590 (79.3)	84 (75.0)	
Mild	144 (16.8)	123 (16.5)	21 (18.8)	
Severe	38 (4.4)	31 (4.2)	7 (6.3)	
Regurgitation				0.517
None	604 (70.4)	529 (74.9)	75 (72.1)	
Mild	199 (23.2)	168 (22.6)	31 (27.4)	
Severe	55 (6.4)	48 (6.4)	7 (6.2)	
Heartburn				0.063
None	665 (77.7)	584 (78.5)	81 (72.3)	
Mild	156 (18.2)	134 (18.0)	22 (19.6)	
Severe	35 (4.1)	26 (3.5)	9 (8.0)	
Total				0.182
None	666 (77.6)	583 (78.3)	83 (76.9)	
Mild	168 (19.6)	144 (19.3)	24 (21.2)	
Severe	24 (2.8)	18 (2.4)	6 (5.3)	

Table 3. GERD symptoms.
Note: Gastro esophageal reflux disease symptoms measured with the Reflux Disease Questionnaire. Values are represented with mean (SD).
Abbreviation: BE, Barrett Esophagus.

	All patients	BE expert centers	Non-expert centers	P
Total cancer worry mean (SD)	9.14 (2.92)	8.98 (2.84)	9.14 (2.70)	0.938
No cancer worry	159 (18.7)	141 (19.1)	18 (16.1)	
Low cancer worry	414 (48.8)	360 (48.8)	54 (48.2)	
High cancer worry	276 (32.5)	236 (32.0)	40 (35.7)	
Positive history of cancer		93 (12.5)	18 (15.9)	0.309
Positive family history with cancer		197 (26.5)	20 (17.7)	0.044

Table 3 Cancer worry

Note: Cancer worry measured with the Cancer worry scale (CWS) Values are represented with *n* (%).

Variables	B	95%	R square	β	t	P
Cancer worry	0.990	0.769–1.211	0.260[a]	0.290	8.796	<0.000
GI symptoms	4.332	3.404–5.240	0.388[b]	0.302	9.246	<0.000
Symptoms of anxiety and depression	0.493	0.383–0.603	0.452[c]	0.290	8.776	<0.000
Gender	1.617	0.0048–3.186	0.456[d]	0.061	2.024	<0.043

Table 4 Factors associated with negative illness perceptions

Note: Regression Coefficients for identification of factors associated with negative illness perceptions of the diagnosis Barrett Esophagus. [a]Independent variable: (Constant), Total_CWS.

[b]Independent variables: (Constant), Total_CWS, totalRDQ.

[c]Independent variables: (Constant), Total_CWS, totalRDQ, TotalHADS.

[d]Independent variables: (Constant), Total_CWS, totalRDQ, TotalHADS, geslacht.

Factors associated with illness perception

Overall, values of cognitive and emotional perception of BE were low, representing a non-threatening perception of illness. No significant differences on BE illness perception were found between the BE expert centers and non-expert centers. Most patients stated a minimal effect on their life (3.00), moderate personal control over illness (4.78), good beliefs about the effectiveness of treatment (3.47); and little experience of symptoms (2.75). Only high values were found on timeline, a scale representing the expected duration of the illness (8.97). BE patients stated a minimal emotional representation of BE, an item questioning: How much does Barrett affect you emotionally? (e.g. does it make you angry, scared, upset or depressed) (2.12). Furthermore, concern about Barrett's was low (3.00) and there was a good understanding of the illness (3.77).

Regression analysis was used to determine the factors associated with illness perception of the diagnosis BE. As Table 4 shows, a negative illness perception of BE is associated with cancer worry, GI symptoms, signs of anxiety and depression, and female gender.

Discussion

The present multi-center study in NDBE patients was designed to investigate factors associated with a negative illness perception of the diagnosis BE. Overall, values of cognitive and emotional perceptions of BE were low, representing a non-threatening perception of Barrett's. The results of this study show that a negative illness perception of the diagnosis BE is associated with the female gender and more cancer worry, GI symptoms and symptoms of anxiety and depression.

The present study shows comparable or higher generic HRQoL compared to a Dutch reference population[18]. This finding suggests a minimal influence on generic HRQoL by the diagnosis of BE. This coincides with our earlier observations in focus-groups interviews[32] and a single center questionnaire study,[6] which showed Dutch BE patients experience a good HRQoL. Nevertheless, this finding contradicts previous studies, which have concluded that patients with BE reported decreased HRQol on the SF-36, compared to norm reference data. A more recent study in the UK showed NDBE patients had significantly lower scores across all domains of the SF-36 compared to a healthy cohort[7]. This study used propensity scores matching for age, gender and comorbidities. There are two probable causes for these differences in previous studies. Firstly, it could be argued that these results were due to the presence of GERD symptoms. BE patients in our study reported low values on GERD symptoms. A previous study in NDBE patients showed that experiencing moderate to severe GERD symptoms decreased HRQoL[33]. Secondly, Britton et al. compared HRQoL with a younger and healthy population (e.g mean age 50.3 and no comorbidities). The present study compared the data to a reflection of a general population in the age of 61–70 years with 50% experiencing one or more chronic conditions. In addition, sub-analyses in the age group 40–61 and >70 years similar results were found with comparable or higher HRQoL than the reference population.

As our regression model shows, cancer worry is an important factor associated with a negative illness perception of BE. Only 18.7% of NDBE patients in the present study scored lower than 6, indicating no cancer worry. Nearly half of the BE population (32.5%) reported a high level (>10) of cancer worry. These findings are inconsistent with that of Britton et al. who found 69.5% levels of >10 on the CWS[7].

Reporting higher levels of GI symptoms was associated with a negative illness perception of BE. However, patients reported good symptom control, representing with only 2.8% of patients reported severe GI symptoms. In accordance with the present result, the study of Britton et al.[7] demonstrated 10% moderate to severe acid regurgitation in comparison with the 6.4% found in the present study. The number of moderate to severe symptoms of heartburn were comparable between the expert centers in the Netherlands and an expert center in the UK (3.5% vs. 2.2%[7]). These comparison of data must be interpreted with caution because different instruments were used. GERD has been associated with functional deficiencies, such as sleeping difficulties, reduced ability to consume food, impaired sex life, thus affecting quality of life and increasing the risk for a comorbid mental disorder[34,35]. Appropriately adjusted medical treatment is essential for reducing GERD related symptoms. In addition, we suggest physicians to create an approachable and low threshold contact opportunity for BE patients to discuss flare ups of symptoms.

Most BE patients in the present study reported no symptoms of anxiety (81.7%) or depression (84.9%). In comparison with one Chinese[12] and two studies from the UK[7,36] the present population scored lower on the incidence of abnormal or borderline signs of depression (17.3%,[12] 19%,[7] 14%[36] vs. 13.2%) or symptoms of anxiety (25.2%,[12] 31%,[7] 39%[36] vs. 16.3%). This difference in results may be explained by several cultural differences, especially when considering that the HADS norm data of several reference populations between countries differ. Hanschmidt et al.[14] found levels of depression and anxiety 3–5 times higher in the study sample than in the general population. This rather contradictory result may be due the lack of information on patients' disease characteristics on the presence of BE dysplasia or EAC in that specific study. Another possible explanation for this is that Hansschmidt reported high presence of GERD symptoms. In general, increased anxiety levels, but not depression levels, are associated with greater severity of GERD symptoms such as retrosternal pain and retrosternal burning[37].

Female gender is known as a risk factor for experiencing more functional gastrointestinal diseases. The Rome Foundation Global Study on the Prevalence and Burden of Functional Gastrointestinal Disorders,[38] reported functional dysphagia as the most prevalent esophageal disorder. The rates for functional heartburn, reflux hypersensitivity, and esophageal chest pain were substantially lower. All esophageal disorders were more prevalent among women. Although reflux esophagitis is predominant in men (5:1 ratio for men: women), symptomatic GERD exhibits a female preponderance and this difference becomes more apparent during the perimenopausal period[39]. As known individuals with GERD symptoms have a decrement in their QoL, these scores are similar to patients with inflammatory bowel disease.[40] Beside experiencing more GERD symptoms, women have a higher risk for developing an anxiety disorder or depression. Anxiety disorders were more prevalent in Dutch women than in men (annual prevalence in 2020 age 60–65 years 16.6% in men vs. 35.3% in women) and women are almost twice as likely to ever develop a depressive disorder compared to men (24.3% vs. 13.1%)[41,42]. A recent study in BE patients showed that, women were more likely to be screened positive for depressive or generalized anxiety disorder[14]. These data underline the importance of accurate treatment and counseling to women with BE and functional esophageal disorders.

A secondary objective of the study was to compare outcomes on HRQoL between patients who undergo surveillance in a BE expert center with non-expert centers. In the current study, there were no differences found between the eight centers in experiencing illness perceptions and associated symptoms. Only the patients in the nonexpert centers scored worse on mental health. Since this difference has not been found on the BE specific questionnaires, it is probably not related to the diagnosis BE or the BE care patients received.

There is an increasing shift of care for BE patients to specialized BE centers. A previous review suggested delivering a focused BE-specific service for all BE patients. It concluded follow-up for BE patients appears inconsistent and often inadequate to meet patients' needs and expectations[15]. In our study, BE patients stated a good understanding of the diagnosis BE. Patients in the expert centers perceived they were not better informed, despite the presence of BE dedicated physicians and nurses working in those centers. There is no uniform procedure in the participating hospitals for informing patients. In general, patients are informed by telephone or short outpatient clinic visit about the results of their gastroscopy. Our data did not present patient-reported experience measures (PREMs). PREMs report information on patients' perceptions of their experience receiving care. In contrast to PROMs, PREMs do not look at the outcomes of care but the impact of the process of the care on the patient's experience for example, communication and timeliness of assistance.[43] We believe that it is beneficial to evaluate care through patient experiences. Previous qualitative studies found trust and communication with the physician as important factors influencing quality of life in BE patients[44–46].

Our multi-center study also has several limitations. The inclusion period of this study was interrupted due to the COVID-19 pandemic. This was a deliberate choice to minimize the influence of the pandemic as much as possible. Inclusion started again when most of the restrictive measures had been lifted. Secondary analysis of our data showed no differences on all primary and secondary outcomes between patients included before or during the pandemic. Secondly, despite the multi-center design of the study, data may not be representative for the BE population worldwide. Differences could be expected due to differences in the health care system as well as cultural differences. In addition, the response rate was only 49.6%. As this was a self-administered anonym questionnaire study, we could not compare baseline characteristics between responders and nonresponders. Considering the percentage of included males and the average age of 63.6 years a good representation of a Barrett population is provided[47]. Finally, a possible deficiency in the method of this study is the fact that not all factors that are considered important according to BE patients were included. Namely, trust in physicians, burden of endoscopy, sleeping difficulties, diet and lifestyle, were not included in the questionnaires. Therefore, factors influencing the outcome may have been missed in the regression model.

In conclusion, overall HRQoL in a multi-center BE population was comparable with an age and gender matched Dutch reference population. The presence of cancer worry, GI symptoms, anxiety and depression and female gender are associated with a negative illness perception of the diagnosis BE. There were no differences found on HRQoL outcomes between the expert centers with dedicated gastroenterologist and nurse practitioners and non- expert centers. We recommend that physicians offer an easy and approachable contact opportunity for BE patients to discuss symptom flares or fear of cancer.

References

1. El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2014;63:871–80.

2. Sikkema M, de Jonge PJF, Steyerberg EW, Kuipers EJ. Risk of esopghageal adenocarcinoma and mortality in patients with Barrett’s esophagus: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2010;8:235–44.

3. Weusten B, Bisschops R, Coron E, Dinis-Ribeiro M, Dumonceau JM, Esteban JM, et al. Endoscopic management of Barrett's esophagus: European society of gastrointestinal endoscopy (ESGE) position statement. Endoscopy. 2017;49(2):191–8.

4. Shaheen NJ, Falk GW, Iyer PG, Gerson LB, American College of Gastroenterology. ACG clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2016;111(1): 30–50. quiz 51Epub 2015 Nov 3. Erratum in: Am J Gastroenterol. 2016.

5. de Jonge PJF, van Blankenstein M, Grady WM, Kuipers EJ. Barrett’s oesophagus: epidemiology, cancer risk and implications for management. Gut. 2014;63:191–202.

6. van der Ende-vanLoon MC, Rosmolen WD, Houterman S, Schoon EJ, Curvers WL. Cancer risk perception in relation to associated symptoms in Barrett's patients: a cross sectional study on quality of life. UniEur Gastroenterol J. 2018;6(9):1316–22.

7. Britton J, Taxiarchi P, Martin G, Willert R, Horne M, Hamdy S, et al. Comparative quantitative survey of patient experience in Barrett's oesophagus and other gastrointestinal disorders. BMJ Open Gastroenterol. 2020(1):7.

8. Shaheen NJ, Green B, Medapalli RK, Mitchell K, Wei J, Schmitz S, et al. The perception of cancer risk in patients with prevalent Barrett's esophagus enrolled in an endoscopic surveillance program. Gastroenterology. 2005;129:429–36.

9. Testa MA, Simonson DC. Assessment of quality-of-life outcomes. N Engl J Med. 1996;334(13):835–40.

10. Crockett SD, Lippmann QK, Dellon ES, Shaheen NJ. Health-related quality of life in patients with Barrett's Esophagus: a systematic review. Clin Gastroenterol Hepatol. 2009;7(6):613–23.

11. van der Ende-van Loon MCM, Stoker A, Nieuwkerk PT, Curvers WL, Schoon EJ. How are we measuring health-related quality of life in patients with a Barrett Esophagus? systematic review on patient reported outcome measurements. Qual Life Res. 2021;8.

12. Lee SW, Lien HC, Chang CS, Ko CW, Tung CF, Yeh HZ. Healthrelated quality of life of subjects with Barrett's esophagus in a Chinese population. PLoS One. 2017;12(12):e0190201.

13. Schwille-Kiuntke J, Rüdlin SL, Junne F, Enck P, Brenk-Franz K, Zipfel S, et al. Illness perception and health care use in individuals with irritable bowel syndrome: results from an online survey. BMC Fam Pract. 2021;22(1):154.

14. Hanschmidt F, Treml J, Kreuser N, Gockel I, Kersting A. Anxiety and depression in patients with Barrett's esophagus: estimates of disorder rates and associations with symptom load and treatmentseeking. Eur J Gastroenterol Hepatol. 2021;33(6):825–31.

15. Britton J, Keld R, Prasad N, Handy S, McLaughlin J, Ang Y. Effect of diagnosis, surveillance, and treatment of Barrett's oesophagus on health- related quality of life. Lancet Gastroenterol Hepatol. 2018;3(1):57–65.

16. McHorney CA, Ware JE, Raczek AE. The MOS 36-Item Short- Form Health Survey (SF-36):II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. MedCare. 1993;31(3):247–63.

17. Ware JE, Jr., Gandek B, Kosinski M, Aaronson NK, Apolone G, Brazier J, et al. The equivalence of SF-36 summary health scores estimated using standard and country-specific algorithms in 10 countries: results from the IQOLA Project. Int Quality Life Assessment. JClinEpidemiol. 1998;51(11):1167–70.

18. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 health survey in community and chronic disease populations. J Clin Epidemiol. 1998;51:1055–68.

19. Douma KFL, Aaronson NK, Vasen HFA, Gerritsma MA, Gundy CM, Janssen EPA, et al. Psychological distress and use of psychosocial support in familial adenomatous polyposis. Psycho Oncol. 2010;19:289–98.

20. Custers JAE, Kwakkenbos L, van de Wal M, Prins JB, Thewes B. Revalidation and screening capacity of the 6-item version of the Cancer Worry Scale. Psycho Oncol. 2018;27(11):2609–15.

21. Snaith RP. The hospital anxiety and depression scale. Health Qual Life Outcome. 2003;1:29.

22. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med. 1997;27(2):363–70.

23. Kulig M, Leodolter A, Vieth M, Schulte E, Jaspersen D, Labenz J, et al. Quality of life in relation to symptoms in patients with gastrooesophageal reflux disease: an analysis based on the ProGERD initiative. Aliment Pharmacol Ther. 2003;18:767–76.

24. Nocon M, Kulig M, Leodolter A, Malfertheiner P, Willich SN. Validation of the reflux disease questionnaire for a German population. Eur J Gastroenterol Hepatol. 2005;17:229–33.

25. Shaw MJ, Talley NJ, Beebe TJ, Rockwood T, Carlsson R, Adlis S, et al. Initial validation of a diagnostic questionnaire for gastroesophageal reflux disease. Am J Gastroenterol. 2001;96:52–7.

26. Aanen MC, Numans ME, Weusten BLAM, Smout AJPM. Diagnostic value of the reflux disease questionnaire in general practice. Digestion. 2006;74:162–8.

27. Hsu CS, Liu TT, Wen SH, Wang CC, Yi CH, Chen JH, et al. Clinical, metabolic, and psychological characteristics in patients with gastroesophageal reflux disease overlap with irritable bowel syndrome. Eur J Gastroenterol Hepatol. 2015;27(5):516–22.

28. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. J Psychosom Res. 2006;60(6):631–7.

29. Weinman J, Petrie KJ. Illness perceptions: a new paradigm for psychosomatics? J Psychosom Res. 1997;42(2):113–6.

30. Weinman J, Petrie KJ, Moss-Morris R, Horne R. The illness perception questionnaire: a new method for assessing the cognitive represent ation of illness. Psychol Health. 1996;11:431–46.

31. Cohen J. Statistical power analysis for the behavioural sciences. Mahwah: Erlbaum; 1988.

32. van der Ende-van Loon M, Brouwers M, de Munnik S, Nieuwkerk P, Curvers W, Schoon E. Factors influencing health-related quality of life in patients with Barrett's esophagus: a qualitative focus group study. Eur J Gastroenterol Hepatol. 2021;18.

33. Chang CY, Lee LJH, Wang JD, Lee CT, Tai CM, Tang TQ, et al. Health-related quality of life in patients with Barrett’s esophagus. Health Qual Life Outcome. 2016;14:158.

34. Wiklund I. Review of the quality of life and burden of illness in gastroesophageal reflux disease. Dig Dis. 2004;22:108–14.

35. Lee Y-S, Jang B-H, Ko S-G, Chae Y. Comorbid risks of psychological disorders and gastroesophageal reflux disorder using the national health insurance service—national Sample Cohort: a STROBEcompliant article. Medicine (Baltimore). 2018;97(18):e0153.

36. Cooper SC, El-agib A, Dar S, Mohammed I, Nightingale P, Murray IA, et al. Endoscopic surveillance for Barrett's oesophagus: the patients' perspective. Eur J Gastroenterol Hepatol. 2009;21(8):850–4.

37. Kessing BF, Bredenoord AJ, Saleh CM, Smout AJ. Effects of anxiety and depression in patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol. 2015;13(6):1089–95.e1.

38. Sperber AD, Bangdiwala SI, Drossman DA, Ghoshal UC, Simren M, Tack J, et al. Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome foundation global study. Gastroenterology. 2021;160(1):99–114. e3.

39. Kim SY, Jung HK, Lim J, Kim TO, Choe AR, Tae CH, et al. Gender specific differences in prevalence and risk factors for gastroesophageal reflux disease. J Kor Med Sci. 2019;34(21):e158.

40. Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, et al. Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology. 2012;143(5):1179–87. e3.

41. Nivel zorgregistraties eerste lijn. Angststoornissen[Internet]. Volksgezondheid en Zorg. [cited 2022 jan 13]. Available from: Angststoornissen | leeftijd en geslacht | Volksgezondheid en Zorg (vzinfo.nl)

42. Nuijen J, van Bon-Martens M, de Graaf R, ten Have M, van der Poel A, de Beurs D, et al. Zicht op depressie: de aandoening, preventie en zorg. Themarapportage van de staat van volksgezondheid en Zorg. Utrecht: Trimbo-instituut; 2018.

43. Kingsley C, Patel S. Patient-reported outcome measures and patientreported experience measures. BJA Educ. 2017;17(4):137–44.

44. Britton J, Hamdy S, McLaughlin J, Horne M, Ang Y. Barrett’s oesophagus: a qualitative study of patient burden, care delivery experience and follow-up needs. Health Expect. 2019;22(1):21–33.

45. Griffiths H, Davies R. Understanding Barrett’s columnar lined oesophagus from the patients’ perspective: qualitative analysis of semistructured interviews with patients. Frontline Gastroenterol. 2011;2(3):168–75.

46. van der Ende-van Loon M, Brouwers M, de Munnik S, Nieuwkerk P, Curvers W, Schoon E. Factors influencing health-related quality of life in patients with Barrett's esophagus: a qualitative focus group study. Eur J Gastroenterol Hepatol. 2022;34(2):161–7.

47. Cook MB, Wild CP, Forman D. A systematic review and metaanalysis of the sex ratio for Barrett's esophagus, erosive reflux disease, and nonerosive reflux disease. Am J Epidemiol. 2005;162(11): 1050–61.

CHAPTER 6

Prevalence and associated factors of worry for cancer in patients with a Barrett's esophagus

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Abstract

Introduction

Although the risk of cancer progression in a Barrett's esophagus (BE) is very low, worrying about cancer is known as an important factor affecting HRQoL. The aim of this study was to determine the proportion of BE patients with high levels of worry for cancer, to compare outcomes of patients endoscopically treated for BE neoplasia (DBE), non-dysplastic BE patients (NDBE) and patients with reflux symptoms, and to examine associated factors.

Methods

We performed a cross sectional, exploratory, self-administered questionnaire study using the cancer worry scale, and the reflux disease questionnaire.

Results

A total of 192 DBE patients, 213 NDBE patients and 111 refractory reflux symptom patients were included from October 2019 until July 2021, 76.8% of BE participants were male and aged 66.9 years. High cancer worry was reported in 40.6% of the DBE patients and 36.2% of NDBE patient. Reflux patients scored statistically significant worse with 56.6% stated high cancer worry. Positive correlations were found between reflux symptoms and cancer worry in NDBE patients and reflux patients. In DBE patients' negative correlations were found between higher cancer worry and younger age as well as a family history of esophageal carcinoma.

Conclusions

A clinically significant group of BE patients reported high cancer worry, which was associated with reflux symptoms in NDBE patients and a younger age and a (family) history of esophageal carcinoma diagnosis in BE patients treated for (early) neoplasia. Physicians should communicate about the actual cancer risk, which leads to greater patient understanding and therefore may have a positive impact on health outcomes.

Introduction

Cancer is among the leading causes of death worldwide. In 2018, there were 18.1 million new cases and 9.5 million cancer-related deaths worldwide[1]. Cancer has been one of the most feared diseases for years[2]. Contrary to the negative image among the general public, epidemiological analyses show that cancer survival rates are gradually increasing. Comparable with numbers in Europe and the United States of America, the 5-year survival rate for esophageal adenocarcinoma (EAC) in the Netherland has risen from 8% in the early 1970s to 23% currently. In the past decades, substantial progress has been made in the diagnoses and treatment of EAC. The best chance for improved survival of patients with EAC remains detection of the cancer at an early and possibly curable stage. The main cause from which EAC can develop is the premalignant condition Barrett esophagus (BE). BE is a complication which occurs in about 10% to 15% of people with chronic or longstanding gastroesophageal reflux disease. The diagnosis of BE is made if the distal esophagus is lined with columnar epithelium with a minimum length of 1cm (tongues or circular) containing intestinal metaplasia at histopathological examination[3]. While pre-malignant conditions that are not under surveillance may eventually become cancer, in many cases the chances of progression is very low. Among patients with a BE, approximately 5% will develop EAC ultimately[4]. Previous studies have shown that it is difficult for individual BE patients to accurately estimate their cancer risk[5,6,7]. Therefore, a diagnosis such as BE, may cause anxiety and worry.

Over the past ten years, non-invasive endoscopic treatment (ET) techniques such as endoscopic resection (ER) or radio frequency ablation (RFA) have become the preferred treatment strategy for the removal of early neoplastic lesions (high grade dysplasia (HGD) and early EAC). Although, ET have shown to be effective for eradication of BE related neoplasia with remarkably low recurrence rates of neoplasia[8], high numbers of worry for cancer are descripted in the literature. Studies have shown that worry for cancer in patients before, and within 12 months after ET is high and comparable to those who have never had dysplasia[9,10,11]. However, little is known about the factors that influence these worries about cancer. For example, it is not clear whether actual risks for developing EAC (such as BE length and histology) actually increase cancer worry. In fact, a long-term follow up study[12] found endoscopically treated patients had statistical significantly higher levels of worry for cancer and general anxiety than surgically treated patients.

A previous systematic review identifying the key factors associated with fear of recurrence among cancer patients found there was strong evidence for an association between physical symptoms and fear of cancer recurrence[13]. Although previous studies found the majority of the BE patients reported good reflux symptom control, [7,14] reflux symptoms are known as an important factor for negative illness perception on BE[14]. In addition, it appears that patients who overestimate their cancer risk tend to experience more symptoms of reflux[7]. Due to the small number of studies on worry for cancer in BE patients, knowledge on factors associated with worry for cancer in BE patients is lacking. Identification of associated factors could help physicians to identify BE patients at risk of experiencing high levels of cancer worry. In order to better understand the impact of ET on cancer worry, it is important to investigate the level of cancer worry in a group of BE patients endoscopically treated for (early) neoplasia and in patients without neoplasia who are included in an endoscopic surveillance program. In addition, it is important to explore the potential impact of the label of Barrett's diagnosis and the presence of physical symptoms.

The aim of this study was to determine the proportion of BE patients with high levels of worry for cancer and to compare outcomes of patients endoscopically treated for BE neoplasia (DBE) and non-dysplastic BE patients (NDBE) with a non- BE control group of patients with reflux symptoms, and associated factors are studied. We hypothesized that the minority of BE patients would experience high cancer worry which would be associated with physical symptoms and not related to factors that would actually increase the risk of cancer such as Barrett’s length or histology outcomes.

Method

This was a cross sectional, exploratory, self-administered questionnaire study assessing worry for cancer in patients with a BE and refractory reflux symptoms. Patients were included from a single, tertiary referral centre for surveillance and endoscopic treatment of BE, the Catharina Hospital Eindhoven, the Netherlands. Participants completed the questionnaire before their endoscopy appointment from April 2018 until March 2022. Due to the COVID-19 pandemic, inclusion was interrupted between January 2021 and July 2021.

Dysplastic Barrett’s esophagus (DBE) group

This first group of patients had a history or presence of confirmed low grade dysplasia, high grade dysplasia or EAC (defined as R0 endoscopic resection of a pT1a or pT1b adenocarcinoma) in histology prevalent BE and treated with at least one endoscopic procedure, e.g. endoscopic submucosal dissection (ESD), endoscopic mucosal resection (EMR) or radio frequency ablation (RFA). Patients were excluded when treated with a surgical esophageal resection, R1 endoscopic resection, and patients who underwent neoadjuvant/adjuvant chemotherapy or radiation as part of treatment of EAC.

Non Dysplastic Barrett’s esophagus (NDBE) group

The patients in this second group were recruited from an endoscopic surveillance program for BE. All patients had proven macroscopic (metaplastic columnar epithelium above the gastro-esophageal (≥1 cm) junction, which was clearly visible endoscopically) and histologic (presence of intestinal metaplasia confirmed from esophageal biopsy) NDBE. Patients were excluded if there was presence of low-or high-grade dysplasia or EAC in BE histology.

Refractory reflux group

The group contained of patients with reflux symptoms referred for an upper endoscopy. In these patients symptoms of heartburn, regurgitation, and/or chest pain were present for at least three months and three times a week[15]. Patients used a standard-dose of Proton-Pump inhibitors (PPI) therapy for at least three months with a minimum of three times a week. Patients with pre-existing esophageal disorders or BE were excluded.

At the time of completing the questionnaire, all participants were above 18 years of age. Furthermore, patients were able to read, understand and complete the Dutch informed consent form and the study questionnaires. Patients were invited to participate with a postal invitation and received a one-time postal reminder when they did not respond after four weeks.

Questionnaires

The questionnaire asked participants to complete baseline items on age, gender, employment status, educational level, and comorbidity (diabetes, arthritis, mental illnesses, cancer, and diseases of hart, neurology, kidney, lung, and skin). In addition, data on the previous performed ET (date of procedure, histology and length of BE) were obtained from the medical record of the DBE patients.

Worry for cancer was assessed using the Cancer Worry Scale (CWS). The CWS is used in research to assess concerns about developing cancer or cancer recurrence and the impact of these concerns on daily functioning[16]. The CWS was translated in Dutch by Douma and colleagues[17]. The six items of the CWS are rated on a 4-point Likert scale ranging from “never” to “almost always”. Scores range from 6 to 32, with a higher score indicating more fear of cancer. Based on a previous Dutch validation study, patients were divided into three categories: no cancer worry (score <6), low level of cancer worry (score 7-9), and high level of cancer worry (score ≥ 10)[16].

The presence of reflux symptoms was measured using the Reflux Disease Questionnaire (RDQ). Extensive research has found this questionnaire to be reliable, valid, responsive and above all practical[18.] Furthermore, the RDQ outcome seems to correlate well with quality of life[19]. A Dutch validation study showed the RDQ is a valid and reliable questionnaire with excellent construct validity and a good relationship to quality of life[20]. RDQ includes 12 items assessing the frequency and severity of heartburn, acid regurgitation and dyspeptic complaints, which are scored on a 5-point Likert scale. The mean of all three dimensions gives a total score ranging from 0 to 5. Where a score of 0 represent nil symptoms, a score of 1-2 mild symptoms, and 3-5 severe symptoms of reflux[21].

Analyses

Continuous sociodemographic data, are presented with means and standard deviation (SD). Categorical variables are summarized with frequency and percentages(%). The DBE patients were allocated according to the time from the last ET (respectively 0-5, 6-11, 12-35, and >36 months), the worst pathology found (LGD, HGD, EAC and high risk EAC). A high risk EAC was defined as EAC with at least SM1 invasion or vascular invasion. NDBE patients were distributed according the length of their BE (<10cm and >10cm).

To answer the first research question, which was: what is the proportion of BE patients with high levels of worry for cancer? The scores of the CWS were divided into three categories: no cancer worry (score <6), low level of cancer worry (score 7-9), and high level of cancer worry (score ≥ 10).

The second research question was to investigate what the differences are on cancer worry and reflux symptoms between patients endoscopically treated for BE neoplasia (DBE), non-dysplastic BE patients(NDBE) and a non- BE control group of patients with reflux symptoms. Therefore, a one-way ANOVA was first was used to determine differences between the three patient groups (DBE, NDBE, refractory reflux). Then a post-hoc test was performed to identify differences on outcomes between the BE groups DBE and NDBE. Finally, a student t-test or Mann Whitney U (depending on normality), and the Chi-Square test for categorical variables were used to identify differences between all BE patients (DBE and NDBE) and the reflux control group.

For the final research question on exploring which factors were associated with worry for cancer, Spearman's rho or Pearson 'r (depending on continuous or categorical variables) were used. The outcome variable was total CWS score and the dependent variables: gender, age, marital status, employment status, total comorbidities, positive history of cancer, positive family history with cancer, months after ET, worst pathology and BE duration. Statistical analyses were performed using IBM Statistical Package for Social Sciences (SPSS) software (version 25). In this explorative study, significance levels were set at the 0.05 level (two-sided).

Results

The questionnaire was completed by a total of 405 BE patients: 192 DBE patients (response rate 60.1%) and 213 NDBE patients (response rate 60.3%). Sociodemographic characteristics of all patients are presented in table 1. The mean age of all BE patients was 67.1 years and the majority (77%) of participants were male. There were statistically significant more men included in the DBE group in comparison to the NDBE group ($X^2(2)=11.78$, p.001). There were no other differences between the two BE groups on sociodemographic characteristics. Just under half of the DBE patients previously treated with ET, had a follow-up of more than three The reflux group contained of 111 refractory reflux patients. The mean age of the reflux group was 60.2 years (SD = 16.8 years) and 36% were male. This group statistical significantly differed from the BE group on all sociodemographic characteristics. The reflux patients were predominately female and statistical significant younger than in comparison to the BE group. With 1.8 (SD 1.6) comorbidities per participant, reflux patients had fewer comorbidities in contrast to the 2.6 (SD 1.9) in de BE group.

When questioned whether DBE patients experienced reflux symptoms in the last seven days, 77.6% of the patients reported that they had experienced none (figure 1). There were significant more GI symptoms (e.g. heartburn, dyspepsia and regurgitation) in the reflux group in comparison with the two BE groups (t(514) -15.68= p=<.001). In which 24.3% of the reflux patients versus 1.5% in the BE patients were experiencing severe reflux symptoms. Patients currently under ET tended to have more regurgitation and dyspepsia symptoms compared to previously treated patients, however this difference was not statistically significant

Table 1: Sociodemographic characteristics.

	DBE **N=192(%)**	**NDBE** **n=213 (%)**	**Reflux** **N=111 (%)**	***P***
Male gender	161 (83.9)	149 (69.6)	40 (36.0)	<0.01
Age in years *mean (SD)*	70.9 (9.1)	63.3 (8.9)	60.4 (16.8)	<0.01
Marital status				<0.01
No relationship	25 (13.0)	17 (8.0)	31 (27.9)	
Married/ living together	145 (75.5)	178 (83.6)	71 (64.0)	
Divorced	1 (0.5)	9 (4.2)	2 (1.8)	
Widow/ widower	21 (10.9)	9 (4.2)	7 (6.3)	
Employment status				<0.01
Employed	48 (25.0)	90 (42.3)	51 (45.9)	
Unemployed	19 (9.9)	23 (10.8)	19 (17.1)	
Retired	125 (65.1)	100 (46.9)	41 (36.9)	
Total comorbidity *mean (SD)*	2.7 (1.9)	2.4 (2.0)	1.8 (1.6)	<0.01
Positive history of cancer	55 (30.4)	26 (12.2)	13 (11.7)	<.001
Positive family history with cancer	36 (18.8)	69 (32.4)	39 (36.1)	.002
Months after ET		n.a.	n.a.	na
0-5	13 (6.8)			
6-11	53 (27.6)			
12-35	31 (16.1)			
>36	95 (49.5)			
Worst pathology			n.a.	na
NDBE	-	213 (100)		
LGD	54 (28.1)			
HGD	46 (24.0)			
EAC	83 (43.2)			
High risk EAC	9 (4.7)			
Length BE	n.a.		n.a.	na
1-3cm		103 (48.4)		
4-9cm		82 (38.5)		
>10cm		28 (13.1)		

	DBE **N=192(%)**	**NDBE** **n=213 (%)**	**Reflux** **N=111 (%)**	***P***
Dyspepsia*				<.001
None	152 (79.2)	170 (79.8)	41 (36.9)	
Mild	32 (16.7)	40 (18.8)	36 (32.4)	
Severe	8 (4.2)	3 (1.4)	34 (30.6)	
Regurgitation*				<.001
None	141 (73.4)	146 (68.5)	46 (41.4)	
Mild	44 (22.9)	53 (24.9)	37 (33.3)	
Severe	7 (3.6)	14 (6.6)	28 (25.2)	
Heartburn*				<.001
None	147 (76.3)	168 (78.9)	27 (24.3)	
Mild	34 (17.7)	42 (19.7)	53 (47.7)	
Severe	11 (5.9)	3 (1.4)	31 (27.9)	
Total*				<.001
None	149 (77.6)	163(76.5)	25 (22.5)	
Mild	40 (20.8)	47 (22.1)	59 (53.2)	
Severe	3 (1.6)	3 (1.4)	27 (24.3)	

Table 1: Sociodemographic characteristics.

Results are described with *N (%)* DBE: dysplastic Barrett Esophagus, NDBE: non- dysplastic Barrett Esophagus, BE: Barrett esophagus, ET: Endoscopic treatment, LGD: Low grade dysplasia, HGD: high grade dysplasia, EAC: esophageal adenocarcinoma.

*A score of none represent a score of 0 on the RDQ, mild symptoms a score of 1-2, and severe.3-5

Cancer worry

Table 2 shows that both BE groups scored low on mean cancer worry (i.e. NDBE 9.13 and DBE 9.19) . Comparison of mean cancer worry scores between the BE groups showed no statistically significant differences (X^2 (2), N=400)=.880, *p*= .644). The reflux patients scored statistically significant worse on cancer worry in comparison to BE patients. Specifically, comparison of the level of high cancer worry between groups showed 56.6% of reflux patients versus 40.6% of the DBE and 36.2% of NDBE stated high cancer worry (X^2 (2 N=495)=21.8, *p*= <.001).

Of the patients endoscopically treated for EAC, only 33% reported they had cancer treatment in their medical history and 44.4% of the patients with high-risk EAC (lymfovascular invasion or >sm1) stated they were treated for cancer in the past. As shown in figure 2, scores of cancer worry did not correlate with time after the last endoscopic treatment (r=.-,048; p=.522 N 180)

	DBE	**NDBE**	**Reflux**	***P***
Total Cancer worry mean (SD)	9.19 (2.9)	9.13 (3.0)	10.28 (3.5)	.004
No cancer worry	42 (22.5) $_a$	50 (23.5)$_a$	18 (17.0)$_a$	
Low cancer worry	69 (36.9)$_{a,b}$	86 (40.4)$_a$	28 (26.4)$_b$	<.001
High cancer worry	76 (40.6)$_a$	77 (36.2)$_a$	60 (56.6)$_b$	

Table 2. Cancer worry measured with the Cancer worry Scale.
Results are described with N (%). A p-value<0.05 was considered statistically significant.
Each subscript letter denotes a subset of patient categories whose column proportions do not differ significantly from each other at the 0.05 level. DBE: dysplastic Barrett Esophagus, NDBE: non- dysplastic Barrett Esophagus

Associated factors

In the DBE group, a younger age had a low negative correlation with higher scores on cancer worry (r=.-190; p=.009 N 187). A DBE patient with a family or friend with a positive history of EAC scored higher on cancer worry (r= .192; p=.008 N 187). Likewise, having a medical history of cancer had a small negative correlation with more cancer worry in this group (r= .153; p=.037 N 187). The grade of histology and time from ET was not associated with higher scores on cancer worry. There was a moderate positive correlation found between the reflux symptoms and cancer worry in the NDBE group (r=.326; p=<.000 N 213) and a low correlation in the reflux group (r=.233; p= .019 N 111). This correlation was not found in de DBE group (r=.136; p=.063 N 187). There was no association found between the NDBE length and cancer worry (r=.460, p=.051 N 213).

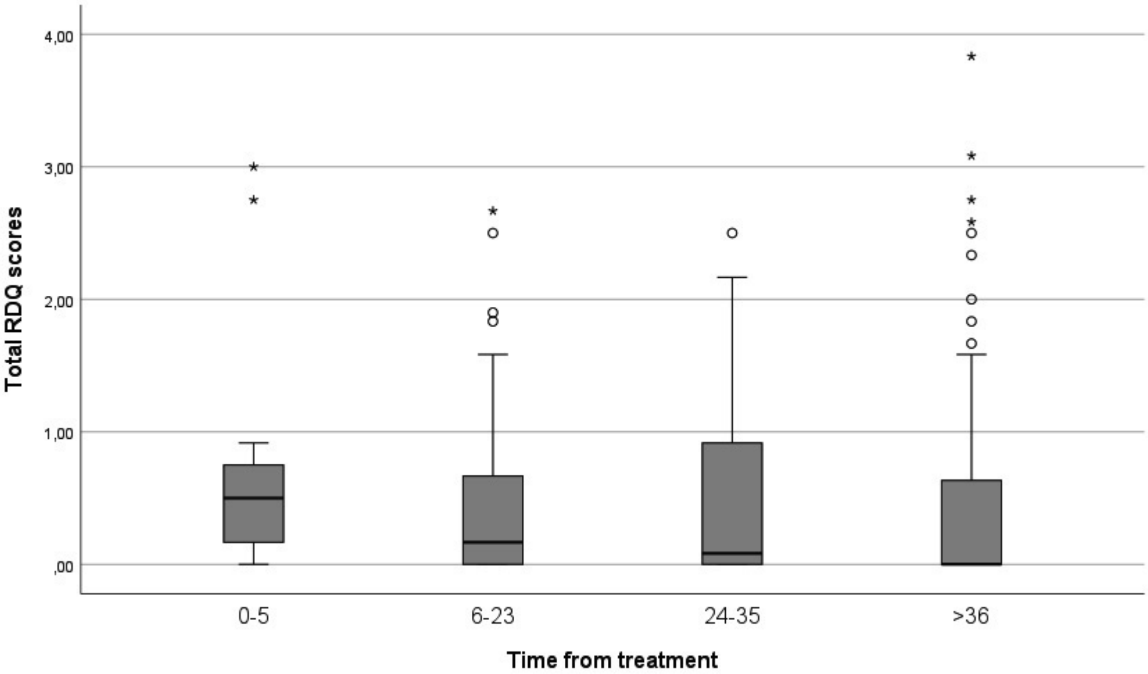

Figure 1: Reflux symptoms versus time after the last endoscopic treatment, measured with the Reflux Disease Questionnaire (RDQ).A score of 0 represent nil symptoms, a score of 1-2 mild symptoms, and 3-5 severe symptoms of reflux.

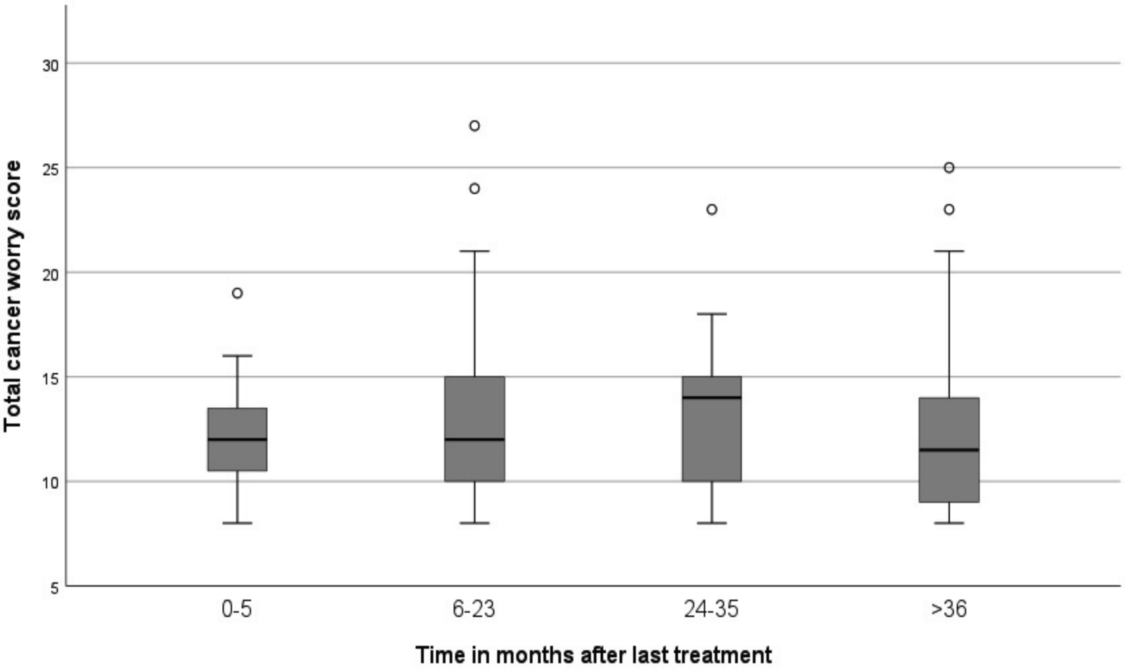

Figure 2. Comparison of cancer worry versus time after last endoscopic treatment,measured with the cancer worry scale. Scores of cancer worry did not change over time after the last endoscopic treatment (F (3,183) = ,598 p= .617).

Discussion

Although the chance of cancer progression in a Barrett's esophagus is very low, worry for cancer is known as an important factor influencing HRQoL and negative perceptions of the diagnosis BE[14]. In the present study, we determined the proportion of BE patients with high levels of worry for cancer and aimed to compare outcomes between patients endoscopically treated for BE neoplasia, non-dysplastic BE patients and patients with reflux symptoms. We hypothesized that the minority of BE patients would experience high cancer worry which would be associated with physical symptoms and not related to factors that would actually increase the risk of cancer such as Barrett's length or histology outcomes.

Overall, BE patients reported a low mean score on cancer worry, however still 40.6% of the DBE patients and 36.2% of the NDBE patients stated high cancer worry. In line with our results, a study from the UK showed no differences between cancer worry in a DBE group and NDBE group[11]. However, overall CWS scores of the BE groups in the UK study were higher (more cancer worry) than in the present study, specifically a mean of 12.8 in the UK patients versus 9.2 in the present study was found. The reason for this difference is not clear, but it might be related to the differences in care pathways, lower levels of education in the UK group. Although baseline characteristics of the two studies seemed to correspond, education level and ethnicity could be involved, but were not reported.

A possible explanation for the fact that the reflux patients in the present study were experiencing higher levels of worry for cancer than BE patients, is the fact that the data was used of patients with reflux symptoms refractory for PPI prior to their first upper GI endoscopy. Consequently, it is possible that these patients were more concerned about cancer because they missed the reassurance of an upper GI endoscopy. Previous studies have shown that BE patients felt a sense of control after undergoing upper GI endoscopy, which may have had a positive effect on cancer worries[22,23]. The

presence of high cancer worry in a group of patients with refractory reflux symptoms supports the hypothesis that experiencing reflux symptoms is related to worry for cancer. Experiencing reflux symptoms was moderately correlated with more cancer worry in the NDBE group and reflux group, this linear correlation was not found in the DBE group. Theoretical models of fear of cancer recurrence propose that somatic symptoms can trigger fear[24,25]. Studies have consistently found that higher prevalence of post cancer symptoms is associated with greater fear of cancer recurrence[26,27]. Furthermore, it has been demonstrated that experiencing symptoms of dysphagia, dyspepsia or heartburn in BE patients is associated with more fear of cancer[11,14].

Because reflux symptoms in BE patients appear to be an important factor in relation to worry for cancer, we further explored the prevalence and intensity of reflux symptoms. In the majority of DBE patients reflux symptoms were comparable with those with NDBE, and represent a good symptom control. Consistent with the literature[28,29], this study found that refractory reflux patients reported statistical significantly more reflux symptoms than BE patients. A possible explanation for these results may be the lack of esophageal sensitivity in BE patients instigated by significantly reduced esophageal acid sensitivity and an impaired ability to recognize acid reflux[30]. A second explanation could be the inadequate symptom control by the PPI prescribed. Although all reflux patients used a standard dose of PPI therapy for at least 3 times a week during a minimum of three months. It could be expected that the BE population had better PPI doses regulations then the reflux population who had been referred with refractory reflux symptoms. In addition to the impact on cancer worry, GERD has been associated with functional deficiencies, such as sleep difficulties, reduced ability to consume food, impaired sex life, thus affecting quality of life and increasing the risk for a comorbid mental disorder[31,32]. A previous study showed patients with BE have better disease-specific HRQoL when compared to patients with GERD. This difference was partially attributable to lower symptom severity amongst BE patients[33]. Appropriately adjusted medical treatment is essential for reducing GERD related symptoms.

To the best of our knowledge, this was the first study exploring factors associated with worry for cancer in BE patients. In addition to the association between reflux symptoms and worry for cancer, there was an association found between a younger age and high cancer worry in BE patients treated for (early) neoplasia. Previous research in cancer survivors have found that a younger age was a prominent factor associated with higher fear of cancer[34,35]. The underlying causes have not been determined, but the perception that cancer threatens the achievement of certain important life projects (e.g., career and marriage or having children) may play a role.

In DBE patients with a family or friend with a positive history of EAC, a higher cancer worry was found. This was in contrast with a review on fear of cancer recurrence in adult cancer survivors, which concluded that a family history of cancer was not associated with an increased fear of cancer[34]. Previous research in BE patients found patients with a friend or family member with cancer, were more likely to overestimate their risk for EAC[7]. Furthermore, there is some evidence that family caregivers report higher levels of fear of cancer than survivors[36]. As a physician, it is important to be aware of increased cancer worry if cancer is present in a family or friend or in their own medical history.

There was no correlation found between the degree of histology and the level of worry for cancer. Surprisingly, only 33% of the patients endoscopically treated for EAC, reported they had cancer treatment in their medical history. Of the patients with high-risk EAC (lymfovascular invasion or >sm1), this was 44.4%. A possible explanation for this might be that patients were associating a cancer treatment—or even the word cancer— with death and trepidation[2]. Endoscopic resection is the first-choice therapy for T1a EAC and is minimally invasive compared with surgical treatment. And therefore, this minimal invasive treatment may not be perceived as a cancer treatment. An important contributing factor is the possible lack of patient knowledge, specifically about histology outcomes. A previous qualitative study reported poor disease-specific knowledge in BE patients[37]. Thus, patient education needs to be comprehensive and easily understood.

Furthermore, there were no correlations found between the time after ET and the level of cancer worry. This in contrast to the studies of Shaheen and Rosmolen[9,12] et al, who found that post- ET cancer worry declined over time. There are several explanations for this difference. First, the cross-sectional design in the present study, could not demonstrate a change in scores of an individual patient. All we could demonstrate is that the mean scores of patients directly after ET and of patient's years afterwards do not vary. Additionally, the results of the two studies may not be comparable because different measurement instruments were used.

Three notable limitations affected this study. The first limitation was the cross-sectional design of this study, as a result change over time within an individual patient could not be detected. Further research with a longitudinal prospective design would determinate the true development of cancer worry over time. Second, the study was partly conducted during the Covid pandemic, which may have contributed to the patient's responses, although implementation of lockdown was not there during the data collection phase. However, a previously conducted sensitivity analysis showed no difference on primary and secondary outcomes before, during and after the COVID period. Third, this is an exploratory study, for this reason our findings are in need of replication before they can be accepted with confidence. Finally, no questionnaire was used on psychological distress, which is influencing worry for cancer.

The findings of this study have a number implications for daily practice. First, BE patients experiencing reflux related symptoms should receive adequate treatment. Furthermore, BE patients should receive adequate information on the diagnosis BE and the actual minor cancer risk. If high levels of cancer worries are persistent, cognitive behavioral therapy can be considered. Psychological interventions with cognitive behavioral therapy for fear of cancer recurrence revealed a small but robust effect at post intervention, which was largely maintained at follow-up[38].

In the present study, a significant group of BE patients reported high cancer worry which was associated with reflux symptoms in NDBE patients and a younger age, and a (family) history of the diagnosis esophageal carcinoma in BE patients treated for (early) neoplasia. Physicians should communicate about the actual cancer risk unambiguously, which leads to greater patient understanding and may therefore positively affects health outcomes.

References

1. American Cancer Society. Global Cancer Facts & Figures 4th Edition. Atlanta: American Cancer Society; 2018.
2. Robb KA, Simon AE, Miles A, Wardle J. Public perceptions of cancer: a qualitative study of the balance of positive and negative beliefs. BMJ Open. 2014 Jul 10;4(7):e005434.
3. Weusten B, Bisschops R, Coron E, Dinis-Ribeiro M, Dumonceau JM, Esteban JM, Hassan C, Pech O, Repici A, Bergman J, di Pietro M. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy. 2017 Feb;49(2):191-198.
4. de Jonge PJF, van Blankenstein M, Grady WM, Kuipers EJ. Barrett’s oesophagus: epidemiology, cancer risk and implications for management. Gut. 2014;63:191–202.
5. Kruijshaar ME, Siersema PD, Janssens ACJW et al. Patients with Barrett's esophagus perceive their risk of developing esophageal adenocarcinoma as low. Gastrointestinal Endoscopy, 2007; 65 (1): 26-30.
6. Shaheen NJ, Green B, Medapalli RK. The perception of cancer risk in patients with prevalent Barrett's esophagus enrolled in an endoscopic surveillance program. Gastroenterology, 2005; 129:429-436.
7. Ende MC, Rosmolen WD, Schoon EJ, Houterman S, Curvers WC. Cancer risk perception in relation to associated symptoms in Barrett's patients: A cross sectional study on quality of life. United European Gastroenterol J. 2018 Nov; 6(9): 1316–1322.
8. van Munster S, Nieuwenhuis E, Weusten BLAM, Alvarez Herrero L, Bogte A, Alkhalaf A, Schenk BE, Schoon EJ, Curvers W, Koch AD, van de Ven SEM, de Jonge PJF, Tang TJ, Nagengast WB, Peters FTM, Westerhof J, Houben MHMG, Bergman JJ, Pouw RE; Dutch Barrett Expert Centers. Long-term outcomes after endoscopic treatment for Barrett's neoplasia with radiofrequency ablation ± endoscopic resection: results from the national Dutch database in a 10-year period. Gut. 2022 Feb;71(2):265-276.
9. Shaheen NJ, Peery AF, Hawes RH, et al. Quality of life following radiofrequency ablation of dysplastic Barrett's esophagus. Endoscopy 2010;42:790–9.
10. Ratcliffe E, Britton J, Heal C, Keld R, Murgatroyd M, Willert R, McLaughlin J, Hamdy S, Ang Y. Quality of life measures in dysplastic Barrett's oesophagus are comparable to patients with non-dysplastic Barrett's oesophagus and do not improve after endoscopic therapy. BMJ Open Gastroenterol. 2023 Apr;10(1):e001091.
11. Britton J, Taxiarchi P, Martin G, et al. Comparative quantitative survey of patient experience in Barrett's oesophagus and other gastrointestinal disorders. BMJ Open Gastroenterol. 2020 Mar 31;7(1):e000357.
12. Rosmolen WD, Pouw RE, van Berge Henegouwen MI, Bergman JJ, Sprangers MA, Nieuwkerk PT. Long-term fear of cancer recurrence in patients treated endoscopically for early Barrett's neoplasia. Dis Esophagus. 2023 Apr 29;36(5):doac083.

13. Crist JV, Grunfeld EA. Factors reported to influence fear of recurrence in cancer patients: a systematic review. Psychooncology. 2013 May;22(5):978-86.

14. van der Ende-van Loon MCM, Nieuwkerk PT, van Stiphout SHC, et al. Barrett Esophagus: Quality of life and factors associated with illness perception. United European Gastroenterol J. 2022 Sep;10(7):721-729.

15. National Institute for Health and Care Excellence: Clinical guidelines. In Gastro-oesophageal Reflux Disease and Dyspepsia in Adults:Investigation and Management. National Institute for Health and Care Excellence (UCopyright © NICE 2019): London, 2019.

16. Custers JAE, Kwakkenbos L, van de Wal M, Prins JB, Thewes B. Re-validation and screening capacity of the 6-item version of the Cancer Worry Scale. Psychooncology. 2018;27(11):2609-2615.

17. Douma KFL, Aaronson NK, Vasen HFA, et al. Psychological distress and use of psychosocial support in familial adenomatous polyposis. Psychooncology. 2010; 19: 289–298.

18. Shaw MJ, Talley NJ, Beebe TJ et al: Initial validation of a diagnostic questionnaire for gastroesophageal reflux disease. Am J Gastroenterol 2001;96:52–57.

19. Nocon M, Kulig M, Leodolter A, Malfertheiner P, Willich SN: Validation of the Reflux Disease Questionnaire for a German population. Eur J Gastroenterol Hepatol. 2005; 17: 229–233.

20. M.C. Aanen, M.E. Numans, B.L.A.M. Weusten, A.J.P.M. Smout. Diagnostic Value of the Reflux Disease Questionnaire in General Practice Digestion 2006;74:162–168.

21. Hsu CS, Liu TT, Wen SH et al. Clinical, metabolic, and psychological characteristics in patients with gastroesophageal reflux disease overlap with irritable bowel syndrome. Eur J Gastroenterol Hepatol. 2015 May;27(5):516-22.

22. Arney J, Hinojosa-Lindsey M, Street RL Jr, Hou J, El-Serag HB, Naik AD. Patient experiences with surveillance endoscopy: a qualitative study. Dig Dis Sci. 2014 Jul;59(7):1378-85.

23. van der Ende-van Loon M, Brouwers M, de Munnik S, Nieuwkerk P, Curvers W, Schoon E. Factors influencing health-related quality of life in patients with Barrett's esophagus: a qualitative focus group study. Eur J Gastroenterol Hepatol. 2021 Jan 18.

24. Heathcote LC, Eccleston C. Pain and cancer survival: a cognitive-affective model of Symptom appraisal and the uncertain threat of disease recurrence. Pain. 2017; 158(7):1187-1191.

25. Fardell JE, Jones G, Smith AB, et al. Exploring the screening capacity of the Fear of Cancer Recurrence Inventory- Short Form for clinical levels of fear of cancer recurrence.PsychoOncol.2018;27(2):492-499.

26. Simard S, Thewes B, Humphris G, et al. Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. J Cancer Surviv 2013;7(3):300-322.

27. Crist JV, Grunfeld EA. Factors reported to influence fear of recurrence in cancer patients: a systematic review: Psycho Oncol 2013;22(5):978-986.

28. Kulig M, Leodolter A, Vieth M et al. Quality of life in relation to symptoms in patients with gastro-oesophageal reflux disease-- an analysis based on the ProGERD initiative. Aliment Pharmacol Ther. 2003 Oct 15;18(8):767-76.

29. Lippmann QK, Crockett SD, Dellon ES, et al. Quality of life in GERD and Barrett's esophagus is related to gender and manifestation of disease. Am J Gastroenterol 2009;104:2695–703.

30. Johnson DA, Winters C, Spurling TJ, Chobanian SJ, Cattau EL Jr. Esophageal acid sensitivity in Barrett's esophagus. J Clin Gastroenterol. 1987 Feb;9(1):23-7.

31. Wiklund I. Review of the quality of life and burden of illness in gastroesophageal reflux disease. Dig Dis. 2004; 22:108–14.

32. Lee Y-S, Jang B-H, Ko S-G, Chae Y. Comorbid risks of psychological disorders and gastroesophageal reflux disorder using the national health insurance service—National Sample Cohort: A STROBE-compliant article. Medicine (Baltimore). 2018; 97.

33. Lippmann QK, Crockett SD, Dellon ES, Shaheen NJ. Quality of life in GERD and Barrett's esophagus is related to gender and manifestation of disease. Am J Gastroenterol. 2009 Nov;104(11):2695-703.

34. Simard S, Thewes B, Humphris G, et al. Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. J Cancer Surviv. 2013;7(3):300–322.

35. Yang Y, Sun H, Liu T, et al. Factors associated with fear of progression in chinese cancer patients: sociodemographic, clinical and psychological variables. J Psychosom Res. 2018;114:18–24.

36. Old, M., Dunn, L. B., Phoenix, B., Paul, S. M., Hamolsky, D., Levine, J. D., et al. (2016). Co-occurrence of anxiety and depressive symptoms following breast cancer surgery and its impact on quality of life. Eur. J. Oncol. Nurs. 20, 97–105.

37. Britton J, Hamdy S, McLaughlin J, Horne M, Ang Y. Barrett's oesophagus: A qualitative study of patient burden, care delivery experience and follow-up needs. Health Expect. 2019 Feb;22(1):21-33.

38. Tauber NM, O'Toole MS, Dinkel A, Galica J, Humphris G, Lebel S, Maheu C, Ozakinci G, Prins J, Sharpe L, Smith AB, Thewes B, Simard S, Zachariae R. Effect of Psychological Intervention on Fear of Cancer Recurrence: A Systematic Review and Meta-Analysis. J Clin Oncol. 2019 Nov 1;37(31):2899-2915.

CHAPTER 7

Artificial intelligence in (gastrointestinal) healthcare: patients' and physicians' perspectives

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Abstract

Artificial intelligence (AI) is entering into daily life and has the potential to play a significant role in healthcare. Aim was to investigate the perspectives (knowledge, experience, and opinion) on AI in healthcare among patients with gastrointestinal (GI) disorders, gastroenterologists, and GI-fellows. In this prospective questionnaire study 377 GI-patients, 35 gastroenterologists, and 45 GI-fellows participated. Of GI-patients, 62.5% reported to be familiar with AI and 25.0% of GI-physicians had work-related experience with AI. GI-patients preferred their physicians to use AI (mean 3.9) and GI-physicians were willing to use AI (mean 4.4, on 5-point Likert-scale). More GI-physicians believed in an increase in quality of care (81.3%) than GI-patients (64.9%, $\chi^2(2) = 8.2$, $p = 0.017$). GI-fellows expected AI implementation within 6.0 years, gastroenterologists within 4.2 years ($t(76) = -2.6$, $p = 0.011$), and GI-patients within 6.1 years ($t(193) = -2.0$, $p = 0.047$). GI-patients and GI-physicians agreed on the most important advantages of AI in healthcare: improving quality of care, time saving, and faster diagnostics and shorter waiting times. The most important disadvantage for GI-patients was the potential loss of personal contact, for GI-physicians this was insufficiently developed IT infrastructures. GI-patients and GI-physicians hold positive perspectives towards AI in healthcare. Patients were significantly more reserved compared to GI-fellows and GI-fellows were more reserved compared to gastroenterologists.

Introduction

People living in western countries are facing artificial intelligence (AI) on a daily basis via facial recognition applications and speech processing tools. Recent developments in AI have led to the large-scale use of computer algorithms. Due to these successes, AI is starting to find practical applications in healthcare. AI can play a role in assisting physicians by providing (faster/more accurate) diagnoses, directing personalized treatment, making risk predictions, stratify diseases according to disease severity, and reducing medical errors[1,2].

AI has great potential in imaging analysis. Examples within gastrointestinal (GI) endoscopy include detection and classification of colorectal lesions[3], differentiation between superficial and deep invasive colorectal cancer[4], disease severity scoring of inflammatory bowel diseases[5], localizing blind spots during esophagogastroduodenoscopy[6], and detecting Barrett's neoplasia[7]. Some of these AI-systems diagnose diseases with expert-level accuracy or even outperform human experts[7–9].

AI-based systems can also be used in personalized healthcare[10]. Labovitz et al. (2017) showed that AI is helpful in improving compliance to therapy[11]. Furthermore, AI systems do not get distracted, are not influenced by fatigue, and can perform certain tasks with greater consistency, speed, and reproducibility than physicians[2]. Therefore, AI can potentially lead to an optimized care trajectory, increasing healthcare efficiency and quality, and save healthcare costs[12].

Despite the successes of AI in assisting in clinical tasks there is still some apprehension about the use of AI in healthcare by both patients and physicians. For smooth implementation, physicians need to have knowledge and willingness to use AI. Patients need to trust their physicians in using these techniques. AI product developers in healthcare, in turn, need to know the current bottlenecks and apprehensions in order to develop their products in such way that an optimal collaboration and joint performance between AI and physicians and between AI and patients is guaranteed. Since an intervention is only as successful as the target audience's acceptance to the intervention, physicians and patients need to have or gain confidence in AI prior to optimal implementation in healthcare[13]. The primary aim of this study was to investigate the perspectives of GI-patients, gastroenterologists, and GI-fellows towards AI in healthcare.

Methods

This non-interventional, prospective, questionnaire study was in accordance with the declaration of Helsinki and the General Data Protection Regulation. The Medical Ethical Review Committee of Maastricht UMC+ (METC2020-2281) and Catharina Hospital Eindhoven (W20.017, February 2020) approved the study (ClinicalTrials.gov NCT05214625).

Subjects.

GI-patients who underwent an endoscopic procedure at Maastricht UMC + or Catharina Hospital Eindhoven between April 2020 and August 2021 and aged ≥ 18 years, were eligible for inclusion. Physicians were gastroenterologists and GI-fellows from multiple Dutch hospitals. Participants were only included if they had appropriate understanding of the Dutch language and were able to read, understand, and fill in the Dutch questionnaire. There were no exclusion criteria for participation. Each participant could participate in the study only once, without follow-up. All GI-patients and GI-physicians provided written informed consent prior to participation. No incentives were offered.

Outcomes and questionnaires.

The primary outcome was the perspective, defined as knowledge, experience, and opinion, of GI-patients, gastroenterologists, and GI-fellows on AI in healthcare and possible differences between their perspectives. Secondary outcomes included the willingness to implement AI in healthcare and important (dis)advantages of AI use. Secondary outcomes only investigated among GI-physicians included the willingness to use AI, the preferred domains for AI use in healthcare, the use of imaging enhancement techniques during endoscopy, and the availability of the mandatory infrastructure for AI implementation. Data were obtained using self-assessed, paper questionnaires collecting both quantitative and qualitative data. GI-patients and GI-physicians were provided with different questionnaires. To the best of our knowledge, no validated questionnaire for the objective of our study existed at the time of execution of this study. Therefore, questionnaires were developed according to the checklist for reporting of survey studies after reviewing literature (Supplementary Methods S1 and S2). Perspectives on AI and availability of the infrastructures were investigated using closed-ended (‘yes’, ‘no’, or ‘I don’t know’) and open questions. Responses concerning opinion and willingness were given on a 5-point Likert-scale, ranging from strongly disagree (1) to strongly agree (5). Questions regarding (dis)advantages of AI and domains in healthcare were multiple response questions in which a maximum of three answers could be chosen. In the questionnaire AI was explained briefly (Supplementary Methods S3). Questionnaires were handed out to patients during a visit at the outpatient clinic. GI-physicians completed the questionnaire during a yearly training day.

Statistical analysis

Sample size calculations were performed using www. check market. com/ sample- size-calculator. To estimate a proportion (e.g. knowledge on AI) with a margin of error of 5% and a confidence level of 95%, 377 GI-patient and 209 GI-physician respondents were needed. All questionnaires were taken into account, including incomplete questionnaires. Baseline characteristics are presented as proportions (%) for categorical variables or as mean (standard deviation [SD]) for numerical variables. Multiple response questions were analyzed using descriptive statistics and reported as percentages of the total number of answers (%answers) and percentages of the GI-patients or GI-physicians that selected these answers (%GI-patients, %GI-physicians). For normally distributed data, differences between (sub)groups were analyzed using Chi-square test or Fisher's exact test for categorical variables and independent sample t-test for numerical variables. The Mann–Whitney U test was used for non-normal distributions. Two-sided *p*-values ≤ 0.05 were considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics (IBM Corp., Armonk, NY, USA).

Results

Study population

In total, 377 GI-patients participated of which 257 (68.2%) handed in a fully completed and 120 (31.8%) a partially completed questionnaire. The most prevalent indication for an endoscopic procedure was a colonoscopy because of the national screening program for colorectal cancer (61.5%, n = 232) (Table 1). The majority of GI-patients (94.1%, n = 351) used at least one electronic device in the past month. Computers and smartphones were used most. Devices were used for medical purposes by 44.5% (n = 157) of GI-patients (defined as users), while 55.5% (n = 196) never used a device for medical purposes (non-users). The purposes of medical device use are listed in Table 1. Of GI-patients, 62.5% (n = 228) reported to be familiar with AI. Patients (n = 258) reported associated words as 'robot' (31.0%, n = 80), 'computer' (23.6%, n = 61), and 'digitalization', 'automation', or 'information technology' (14.3%, n = 37). GI-patients with complete questionnaires had a significantly higher level of education, underwent significantly more often a colonoscopy because of screening, significantly more often were (medical) device users, and significantly more often were familiar with AI.

In total, 35 gastroenterologists and 45 GI-fellows fully completed the questionnaire. The majority of gastroenterologists (82.9%, n = 29) used medical applications in their clinical work, in contrast to 57.8% (n = 26), $\chi^2(1) = 5.8$, $p = 0.016$) of GI-fellows (Table 2). Applications used by more than five GI-physicians are listed in Supplementary Table S3. Work-related experience with AI was reported by 37.1% (n = 13) of gastroenterologists and by 15.6% (n = 7) of GI-fellows. Personal exposure with AI was mainly research related (n = 6).

	GI-patients N = 377
Gender, female n (%)	155 (41.1)
Age in years, mean (SD)	64.5 (20.8)
Level of education, n (%) (N = 372)	
Elementary education	35 (9.4)
Secondary education	211 (56.7)
Higher education	126 (33.9)
Indication for endoscopic procedure, n (%)	
CRC screening colonoscopy	232 (61.5)
Symptoms or surveillance*	145 (38.5)
Device use, yes n (%) (N = 373)	**351 (94.1)**
Computer or laptop	321 (86.1)
Smartphone	303 (81.2)
Smartwatch	65 (17.4)
Medical device use, yes n (%) (N = 353)	157 (44.5)
Purpose of medical device use, yes n (%^) (N = 144)	
Communication with physicians	26 (18.1)
Searching information	79 (54.9)
Tracking heartbeat and blood pressure	32 (22.2)
Tracking sport activities	16 (11.1)
Making appointments	5 (3.5)
Access to medical file	12 (8.3)
Monitor disease activity	8 (5.6)
Reminders for medication use	6 (4.2)
Other	11 (7.6)
Familiar with AI, yes n (%) (N = 365)	228 (62.5)

Table 1. Baseline characteristics for GI-patients.

*Endoscopic procedures for symptoms or because of surveillance were both gastroscopies and colonoscopies. ^Percentage of GI-patients using a medical device for this purpose *AI* artificial intelligence; *CRC* colorectal cancer; *GI* gastrointestinal; *SD* standard deviation.

	Gastroenterologists N = 35	GI-fellows N = 45	*p* value
Gender, female n (%)	13 (37.1)	33 (73.3)	0.001
Age in years, mean (SD)	49.7 (7.6)	32.7 (2.9)	< 0.001
Year of education, n (%)*			
Year 2	–	1 (1.3)	–
Year 3	–	19 (42.2)	–
Year 4	–	10 (22.2)	–
Year 5	–	9 (20.0)	–
Year 6	–	6 (13.3)	–
Application use in clinical (GI) work, yes n (%)	29 (82.9)	26 (57.8)	0.016
Experience with AI in clinical (GI) work, yes n (%)	13 (37.1)	7 (15.6)	0.079

Table 2. Baseline characteristics for GI-physicians.

*No GI-fellows were in the first year of their education. App mobile application; GI gastrointestinal; SD standard deviation.

GI-patients' perspectives.

On a 5-point Likert-scale, GI-patients preferred their physicians to use AI (mean 3.9 [SD 1.0]) in their clinical work (Table 3). On average, GI-patients expected AI implementation in healthcare within 6.1 years (SD 4.6). The majority of GI-patients was not anxious for AI (68.8%, n = 238) and thought that implementation of AI in healthcare will increase the quality of care (64.9%, n = 231). Subgroup analyses showed that GI-patients reporting to be familiar with AI (62.5%, n = 228) had a significantly more positive perspective towards AI compared to GI-patients unfamiliar with AI. Their preference of AI use by their physicians was 4.0 (SD 1.0 vs 3.6 [SD 1.0], t(343) = -2.8, $p = 0.005$), they expected AI implementation within 5.6 years (SD 4.4 vs 7.7 [SD 5.5], t(116) = 3.0, $p = 0.003$), more believed in an increase in quality of care with AI (76.4% [n = 172] vs 45.0% [n = 58], $\chi^2(2) = 35.8$, $p < 0.001$), and only a few were anxious for AI (2.8% [n = 6] vs 8.1% [n = 10], $\chi^2(2) = 27.5$, $p < 0.001$) (Supplementary Table S4). Patients with fully completed questionnaires were also significantly more positive towards AI regarding AI use by their physicians, increase in quality of care, and anxiety compared to patients with partially completed questionnaires (Supplementary Table S4). The same accounted for male gender. Subgroup analysis for medical device use only showed a significantly earlier expectation of AI implementation for users compared to non-users. Higher level of education showed a positive trend towards AI compared to lower levels of education.

	GI-patients N = 377
Willingness of AI use by physicians*, mean (SD) (N = 347)	3.9 (1.0)
Years to implementation, mean (SD) [range] (N = 270) 5	6.1 (4.6) [0–25]
years, n (%)	186 (68.9)
10 years, n (%)	64 (23.7)
15 years, n (%)	8 (3.0)
20 + years, n (%)	12 (4.4)
Anxious for AI, n (%) (N = 346)	
Yes	18 (5.2)
No	238 (68.8)
I don't know	90 (26.0)
Increase in quality of care with AI, n (%) (N = 356)	
Yes	231 (64.9)
No	13 (3.7)
I don't know	112 (31.5)

Table 3. Artificial intelligence in healthcare—GI-patients' perspective.

*On a 5-point Likert scale. *AI* artificial intelligence; *GI* gastrointestinal; *SD* standard deviation.

	GI-physicians N = 80	**Gastro-enterologists N = 35**	**GI-fellows N = 45**	***p* value^**
Expectation of work changes by AI*, mean (SD)	4.5 (0.7)	4.8 (0.4)	4.3 (0.7)	< 0.001
Years to implementation, mean (SD) [range]	5.2 (3.0)	4.2 (2.7)	6.0 (3.0)	0.011
5 years, n (%)	61 (78.2)	29 (85.3)	32 (72.7)	–
10 years, n (%)	15 (19.2)	5 (14.7)	10 (22.7)	–
15 years, n (%)	2 (2.6)	0 (0.0)	2 (4.5)	–
20 + years, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	–
Willingness to use AI as physician*, mean (SD)	4.4 (0.7)	4.6 (0.7)	4.3 (0.7)	0.014
Willingness for physicians to use AI as patient*, mean (SD)	4.1 (0.8)	4.2 (0.8)	4.0 (0.9)	0.243
Increase in quality of care with AI, n (%)				0.433
Yes	65 (81.3)	29 (82.9)	36 (80.0)	–
No	1 (1.3)	1 (2.9)	0 (0.0)	–
I don't know	14 (17.5)	5 (14.3)	9 (20.0)	–

Table 4. Artificial intelligence in healthcare- GI physicians'perspective.

*On a 5-point Likert scale. ^*p* value reported for differences between gastroenterologists and GE fellows. *AI* artificial intelligence; *GI* gastro intestinal; *SD* standard deviation.

Reported advantages of a virtual nurse, a technique performing tasks normally performed by nurses, were the availability at any time (GI-patients 50.0%, n = 177), the technique's possibility to make appointments (GI patients 49.4%, n = 175), and to control and monitor disease activity (GI-patients 35.0%, n = 124) (Supplementary Table S5). GI-patients preferred mobile applications as digital communication tool with their healthcare professionals (GI-patients 47.5%, n = 168), followed by text massages (GI-patients 26.6%, n = 94), and websites (GI-patients 26.0%, n = 92) (Supplementary Table S6).

GI-physicians' perspectives.

GI-physicians expected their work to change by AI (gastroenterologists mean 4.8 [SD 0.4] vs GI-fellows mean 4.3 [SD 0.7], t(73) = 3.9, *p* < 0.001, on a 5-point Likert-scale) (Table 4). Gastroenterologists expected AI implementation in healthcare within 4.2 years (SD 2.7), while GI-fellows expected this within 6.0 years (SD 3.0, t(76) = -2.6, *p* = 0.011). GI-physicians were willing to use AI for their patients (mean 4.4 [SD 0.7]).

The majority of GI-physicians believed that the implementation of AI in healthcare will increase the quality of care (81.3%, n = 65).

Subgroup analyses among GI-physicians showed that more application users had a positive perspective towards AI than non-users. Their expectation of work changes by AI was 4.6 (SD 0.6) compared to 4.2 (SD 0.7) for non-users (t(78) = -2.3, *p* = 0.022). They expected earlier AI implementation (4.7 years [SD 2.4] vs 6.4 years [SD 3.8], t(32) = 2.0, *p* = 0.052), were more willing to use AI as physicians (mean 4.5 [SD 0.7] vs mean 4.2 [SD 0.7], t(78) = -1.7, *p* = 0.093), and more believed in an increase in quality of care with AI (85.5% [n = 47] vs 72.0% [n = 18], $\chi^2(2) = 3.1$, *p* = 0.209).

GI-physicians expect the most benefits of AI in the domain of diagnostics: diagnostics within endoscopy (72.5%, n = 58), diagnostics within radiology (61.3%, n = 49), and diagnostics within histopathology (45.0%, n = 36) (Table 5).

To investigate whether the infrastructure of GI-endoscopy in Dutch hospitals is ready for AI implementation, GI-physicians reported the ability to save endoscopic images and videos within their hospitals. In total, 85.0% (n = 68) of the GI-physicians had the ability to save endoscopic images in high definition quality and 71.3% (n = 57) for high definition videos. In addition, 92.5% (n = 74) could save those images in the electronic patient file (Table 6). The mean number of images taken during a colonoscopy and gastroscopy were similar for gastroenterologists and GI-fellows. Imaging enhancement techniques such as narrow band imaging, use specific wavelengths of light in order to optimize the visualization of vessels and mucosal patterns. The standard use of these imaging enhancement techniques was significantly lower among GI-fellows (48.9%, n = 22) compared to gastroenterologists (80.0% [n = 28], $\chi^2(2) = 9.8$, $p = 0.007$).

	GI-physicians **n (% of physicians)** **N = 80**	**n (% of answers)** **N = 234***
Diagnostics—endoscopy	58 (72.5)	58 (24.8)
Diagnostics—radiology	49 (61.3)	49 (20.9)
Diagnostics—histopathology	36 (45.0)	36 (15.4)
Identify risk profiles	26 (32.5)	26 (11.1)
Telemonitoring	18 (22.5)	18 (7.7)
Education about diseases and patient self-management	13 (16.3)	13 (5.6)
Robot assisted treatment	12 (15.0)	12 (5.1)
(Personalized) treatment	12 (15.0)	12 (5.1)
Communication (virtual nurse)	10 (12.5)	10 (4.3)

Table 5. Fields of application of AI in healthcare and domains within gastroenterology and hepatology.

*Multiple response questions. *GI* gastrointestinal.

	GI-physicians **N = 80**	**Gastroenterologists** **N = 35**	**GI-fellows** **N = 45**	***p* value**
Ability to save HD images, yes n (%)*	68 (85.0)	–	–	–
Ability to save HD videos, yes n (%)*	57 (71.3)	–	–	–
Ability to save HD images in electronic patient file, yes n (%)*	74 (92.5)	–	–	–
Number of images taken per colonoscopy, mean (SD)	–	10.0 (4.8)	8.6 (4.1)	0.187
Number of images taken per gastroscopy, mean (SD)	–	7.3 (2.6)	7.6 (2.7)	0.695
Use of imaging enhancement techniques, yes n (%)	–	28 (80.0)	22 (48.9)	0.007

Table 6. **I**maging during endoscopy.

*Gastroenterologists and GI-fellows were working in the same hospitals. Therefore, only numbers for the total group (GI-physicians) are provided. *GI* gastrointestinal; *HD* high definition; *SD* standard deviation.

Comparing GI-patients and GI-physicians

GI-patients and GI-physicians both believed in a quality of care increase with AI, but significantly more GI-physicians were convinced (81.3%, n = 65) than GI-patients (64.9% [n = 231], $\chi^2(2) = 8.2$, $p = 0.017$). The expectation of GI-fellows was that AI will have a place in healthcare within 6.0 years (SD 3.0), whereas gastroenterologists expected this within 4.2 years (SD 2.7, t(76) = -2.6, $p = 0.011$, compared to GI-fellow) and GI-patients within 6.1 years (SD 4.6 vs 5.2 years [SD 3.0], t(193) = -2.0, $p = 0.047$, compared to GI-physicians). GI-patients and GI-physicians agreed on the most important advantages of AI in healthcare: improving quality of care (GI-patients 66.1% [n = 228] vs GI-physicians 90.0% [n = 72]), time saving (GI-patients 38.0% [n = 131] vs GI-physicians 55.0% [n = 44]), and faster diagnostics and shorter waiting times (GI-patients 71.3% [n = 246] vs GI-physicians 51.3% [n = 41]) (Table 7).

Advantages of AI	GI-patients			GI-physicians		
	n N = 345	% of patients N = 345	% of answers N = 1004*	n N = 80	% of physicians N = 80	% of answers N = 237*
Improving quality of care	228	66.1	22.7	72	90.0	30.4
Personalized care	54	15.7	5.4	22	27.5	9.3
Time saving (for the physicians)	131	38.0	13.0	44	55.0	18.6
Faster diagnostics and shorter waiting times (for the patient)	246	71.3	24.5	41	51.3	17.3
Solutions for complex care tasks	74	21.4	7.4	17	21.3	7.2
Availability at any time (24/7)	85	24.6	8.5	5	6.3	2.1
Remote communication	67	19.4	6.7	12	15.0	5.1
Education about diseases and health for the patient^	21	6.1	2.1	–	–	–
Education about diseases and health for physicians	27	7.8	2.7	8	10.0	3.4
Costs	62	18.0	6.2	13	16.3	5.5
No benefits	6	1.7	0.6	1	1.3	0.4
Other advantages‡	3	0.9	0.3	2	2.5	0.8

Table 7. Advantages of artificial intelligence in healthcare—GI-patients' and GI-physicians' perspectives.

*Multiple response questions. ^Answer options not given to physicians. ‡For 'other advantages' patients reported continuity in treatment (n = 1), independent of humans (n = 1), and research (n = 1). Gastroenterologists reported a different healthcare perspective for patients (n = 1) and more control for physicians (n = 1). AI: artificial intelligence; GI: gastrointestinal; IT: information technology.

The most important disadvantage for GI-patients was the potential loss of personal contact with healthcare professionals (66.4%, n = 227), where this was insufficiently developed information technology infrastructures for GI-physicians (56.3%, n = 45) (Table 8). For both GI-patients and GI-physicians this was followed by the lack of (technical) knowledge by physicians (GI-patients 27.8% [n = 95] vs GI-physicians 50.0% [n = 40]) and uncertainty about laws and regulations (responsibility) (GI-patients 48.5% [n = 166] vs GI-physicians 35.0% [n = 28]). A difference between gastroenterologists and GI-fellows was seen in the concern for the loss of skills by AI. None of the gastroenterologists reported this as a disadvantage, while it was reported by 42.2% (n = 19) of GI-fellows (Supplementary Table S7). A smaller difference in concerns between gastroenterologists and GI-fellows was seen for the loss of employment (gastroenterologists 0.0% [n = 0] vs GI-fellows 6.7% [n = 3]) and lack of human supervision (gastroenterologists 20.0% [n = 7] vs GI-fellows 28.9% [n = 13]).

Disadvantages of AI	**GI-patients**			**GI-physicians**		
	n N = 342	**% of patients N = 342**	**% of answers N = 861***	**n N = 80**	**% of physicians N = 80**	**% of answers N = 214**
Loss of personal contact with physicians^	227	66.4	26.4	–	–	–
Fear that your physician is using the technique incorrectly^	57	16.7	6.6	–	–	–
Fear that you as a patient are using the technique incorrectly^	47	13.7	5.5	–	–	–
Lack of (technical) knowledge by physicians	95	27.8	11.0	40	50.0	18.7
Insufficiently developed IT infrastructure	78	22.8	9.1	45	56.3	21.0
Uncertainty about laws and regulations (responsibility)	166	48.5	19.3	28	35.0	13.1
Insufficient privacy protection	81	23.7	9.4	12	15.0	5.6
Insufficient support from hospital administration	10	2.9	1.2	10	12.5	4.7
Problems with health insurance reimbursement	39	11.4	4.5	8	10.0	3.7
Costs	23	6.7	2.7	20	25.0	9.3
No disadvantages	25	7.3	2.9	8	10.0	3.7
Other disadvantages‡	13	3.8	1.5	1	1.3	0.5
Loss of employmentϕ	–	–	–	3	3.8	1.4
Loss of skills[Φ]	–	–	–	19	23.8	8.9
Lack of human supervision[Φ]	–	–	–	20	25.0	9.3

Table 8. Disadvantages of artificial intelligence in healthcare—GI-patients' and GI-physicians' perspectives.

*Multiple response questions. ^Answer options not given to physicians. ‡For 'other disadvantages' patients reported loss of expertise by the physicians (n = 5), unseen misdiagnosis (n = 3), cuts in healthcare (n = 3), loss of employment for physicians (n = 2). One gastroenterologist reported a loss of the human dimension (n = 1). ΦAnswer options not given to GI-patients.

Discussion

This study compared the perspectives of GI-patients, gastroenterologists, and GI-fellows on artificial intelligence in healthcare. We showed that there is a general positive perspective towards AI and AI implementation in healthcare, but GI-patients were more reserved compared to GI-fellows and GI-fellows in their turn were more reserved compared to gastroenterologists.

AI-research has focused on studies investigating accuracy of AI-based systems, while there is a gap in knowledge on patients' and physicians' perspectives towards AI. Successful implementation of AI into routine clinical practice depends not only on technical challenges, but also on the public's trust and acceptance of AI[14]. Trust in AI is determined by the way people interact with the technology and dependent on the ease of use, reliability, transparency, explainability, security and privacy protection, and communication on the use of AI systems[13].

Here, GI-patients preferred their physicians to use AI (mean 3.9 on a 5-point Likert-scale) and GI-physicians were willing to use AI for their patients (mean 4.4). This positive attitude is largely consistent with literature[15–18], although concerns were raised by Yakar et al. (2022) who observed distrust towards AI in medicine among the Dutch general population[19]. In the current study, gastroenterologists were significantly more progressive towards AI than GI-fellows. Gastroenterologists had higher expectations of their work to change by AI and believed in a significant faster implementation of AI compared to GI-fellows. These results are interesting and somewhat controversial since GI-fellows are from a younger generation raised with digitalisation compared to gastroenterologists. A possible explanation may be found in the reporting of deskilling, employability, and negative career impacts by GI-fellows, while gastroenterologists did not report these concerns. Literature also shows limited impact of those specific issues[18,20]. Furthermore, we might speculate that gastroenterologists oversee their own shortcomings, the field, and its impossibilities better than GI-fellows. Partly supported by the routine use of imaging enhancement techniques by gastroenterologists, but much less by GI-fellows.

In line with literature, the majority of GI-patients (68.9%) and GI-physicians (78.2%) expected implementation of AI in healthcare within five years[17,18]. GI-patients (64.9%) and GI-physicians (81.3%) believed that AI will improve quality of care, again comparable with literature[21]. Human interaction in addition to AI use was considered critical for the experience of high-quality care[22]. The importance of human interactions is further supported by evidence showing that patients' compliance was higher for physicians and for physicians using AI compared to an AI-system alone[8]. This so called augmented intelligence emphasizes that AI enhances or assists human intelligence rather than replacing it, expressing the importance of symbiosis between humans and AI[16,23,24].

Medical device use among patients was low compared to literature[15,23] and did not show a positive trend towards AI for users compared to non-users. In contrast, perspectives of GI-patients familiar with AI were significantly more positive compared to those unfamiliar with AI. Familiarity led to a higher willingness of GI-patients for their physicians to use AI, an earlier expected implementation of AI, and more GI-patients believed in an increase in quality of care compared to GI-patients unfamiliar with AI. Familiarity was self-reported and as high as 62.5%, which is comparable to literature[20,25,26]. However, this means that still one third of patients was unfamiliar with artificial intelligence, leaving room for better dissemination of information. It was not investigated to what extend GI-patients were familiar with AI, while AI acceptance was found to be higher in patients who assigned a higher rating to their AI knowledge[27]. Castagno et al. (2020) showed that 87% of healthcare staff did not know the difference between machine learning and deep learning[20]. The fast evolutions and developments in AI may result in an overflow of information, unmanageable for patients and physicians. This may paradoxically discourage further developments and implementation, emphasizing the importance of education and training[14,17].

Acceptance of AI is also driven by patients' and physicians' understanding of potential (dis)advantages[13]. Hence, in this study the most frequently mentioned advantages of AI in healthcare were improved quality of care and time saving for both patients and physicians. Other perceived advantages are reducing risks of medical errors, more time available for physician–patient interaction, standardization in the interpretation of results, more objective diagnosis, gain in efficiency, and reduced costs[17,23,28]. Important disadvantages of AI were insufficiently developed information technology infrastructures, potential loss of personal contact, lack of (technical) knowledge by physicians, and uncertainty about laws and regulations. Other perceived disadvantages are overdependence on AI, increased procedural time, privacy protection, lack of (non-)verbal communication, and increased costs[12,15,16,20,23,25,28,29.]

Current literature is inconclusive about the effects of AI on workload. AI use is believed to save time, time that physicians could invest in personal contact with their patients, improving the physician–patient relationship[16,25]. In contrast, others reported a distortion of the physician–patient relationship as a concern of AI[20,30]. Remarkably, time for physician–patient interaction, procedural time, and costs are both perceived advantages and disadvantages, highlighting the importance of clear information, education, and studies investigating these outcomes.

Agreement existed on the fields of application of AI. Diagnostics within endoscopy, radiology, and histopathology were reported most promising by GI-physicians. Previous studies among gastroenterologists showed high interest for AI-assistance in colorectal polyp detection and in capsule endoscopy[29,30]. In contrast to the interest of GI-physicians in AI in diagnostic processes, patients preferred physician decision makers over AI decision makers, resulting in lower levels of trust when decisions were made by AI rather than by humans[24]. In addition, patients' expressed a significantly higher confidence in AI-assisted interpretation than in AI-assisted management[15].

An important requirement for implementation of AI in clinical practice is the technical infrastructure to be aligned with AI needs. Servers, data storage capacity, and (endoscopic) equipment need to meet these demands. Routine use of high definition endoscopes and digital imaging enhancement techniques are recommended by the European Society of Gastrointestinal Endoscopy[31]. Gastroenterologists in this study routinely used imaging enhancement techniques (80.0%) compared to less than half of GI-fellows (48.9%). One reason for GI-fellows not routinely using these imaging enhancement techniques might be the lack of experience. Although the use of these techniques is in line with a survey among US gastroenterologists[29], this may hamper the added value of AI since most endoscopic AI-systems are built on using these imaging techniques.

The results of the current study should be considered in light of potential limitations. Unfortunately, the sample size for GI-physicians was not reached leading to a larger margin of error. In the Netherlands, there are around 800 practicing GI-physicians. Since we only recruited GI-physicians during one single Dutch training day, including 209 GI-physicians was not feasible using this approach. However, we do consider our sample of 80 GI-physicians representative. Due to COVID-19 restrictions, inclusions were temporary discontinued. Therefore, the total inclusion period for GI-patients was ten months. Selection bias may have occurred as responders more likely held strong opinions (both positive and negative) towards AI or were either more or either less informed about AI than non-responders. Response bias cannot be excluded as participants may have given assumed desirable answers, although they were explicitly asked not to do so. The order of response options of multiple response questions were not randomized in the questionnaires. This may have caused bias due to the primacy and recency effects, the tendency to better remember information or response options that are presented first or last, respectively[32]. Furthermore, the framing effect (bias caused by the manner in which questions are presented by using positive or negative words) may have influenced patients' responses[33]. We did not investigate how well informed respondents were on AI or if they understood or were aware of potential shortcomings of AI, while insufficient or incorrect information could have biased the answers. We included GI-patients and GI-physicians. Therefore, these results may not be directly generalizable to other patient groups or medical specialties. Answers were self-reported and the questionnaires were not validated.

In summary, both GI-patients and GI-physicians hold positive perspectives towards AI and AI implementation in healthcare. GI-patients are more reserved compared to GI-fellows and GI-fellows are more reserved compared to gastroenterologists. One third of patients was unfamiliar with AI. AI will only have a beneficial role in healthcare if patients and physicians are knowledgeable and supportive towards AI. Therefore, AI developments should be conducted in a patient and physician-centric manner. Misconceptions and perceived (dis) advantages should be conquered by better disseminating information in layman's terms and by educating physicians and patients.

References

1. Miller, D. D. & Brown, E. W. Artificial intelligence in medical practice: The question to the answer?. Am. J. Med. 131, 129–133.
2. He, J. et al. The practical implementation of artificial intelligence technologies in medicine. Nat. Med. 25, 30–36.
3. Weigt, J. et al. Performance of a new integrated CADe/CADx system for detection and characterization of colorectal neoplasia. Endoscopy 2022 Feb;54(2):180-184.
4. Luo, X. et al. Artificial intelligence-enhanced white-light colonoscopy with attention guidance predicts colorectal cancer invasion depth. Gastrointest. Endosc. 94, 627-638.e621.
5. Stidham, R. W. et al. Performance of a deep learning model vs human reviewers in grading endoscopic disease severity of patients with ulcerative colitis. JAMA Netw. Open 2, e193963.
6. Wu, L. et al. Randomised controlled trial of WISENSE, a real-time quality improving system for monitoring blind spots during esophagogastroduodenoscopy. Gut 68, 2161–2169.
7. de Groof, A. J. et al. Deep-learning system detects neoplasia in patients with Barrett's esophagus with higher accuracy than endoscopists in a multistep training and validation study with benchmarking. Gastroenterology 158, 915-929.e914.
8. Soellner, M. & Koenigstorfer, J. Compliance with medical recommendations depending on the use of artificial intelligence as a diagnostic method. BMC Med. Inform. Decis. Mak. 21, 236.
9. van der Sommen, F. et al. Computer-aided detection of early neoplastic lesions in Barrett's esophagus. Endoscopy 48, 617–624.
10. Shaban-Nejad, A., Michalowski, M. & Buckeridge, D. L. Health intelligence: how artificial intelligence transforms population and personalized health. NPJ Digit. Med. 1, 53.
11. Labovitz, D. L., Shafner, L., Reyes Gil, M., Virmani, D. & Hanina, A. Using artificial intelligence to reduce the risk of nonadherence in patients on anticoagulation therapy. Stroke 48, 1416–1419.
12. Griffin, J. & Treanor, D. Digital pathology in clinical use: Where are we now and what is holding us back?. Histopathology 70, 134–145.
13. Siau, K. & Wang, W. Building trust in artificial intelligence, machine learning, and robotics. Cutter Bus. Technol. J. 31, 47–53 (2018).
14. Aggarwal, R., Farag, S., Martin, G., Ashrafian, H. & Darzi, A. Patient perceptions on data sharing and applying artificial intelligence to healthcare data: a cross sectional survey. J Med Internet Res. 2021 Aug 26;23(8):e26162.

15. York, T., Jenney, H. & Jones, G. Clinician and computer: A study on patient perceptions of artificial intelligence in skeletal radi-ography. BMJ Health Care Inform. 2020 Nov;27(3):e100233.

16. Maassen, O. et al. Future medical artificial intelligence application requirements and expectations of physicians in German university hospitals: Web-based survey. J. Med. Internet Res. 23, e26646.

17. Waymel, Q., Badr, S., Demondion, X., Cotten, A. & Jacques, T. Impact of the rise of artificial intelligence in radiology: What do radiologists think?. Diagn. Interv. Imaging 100, 327–336.

18. Sarwar, S. et al. Physician perspectives on integration of artificial intelligence into diagnostic pathology. NPJ Digit. Med. 2, 28.

19. Yakar, D., Ongena, Y. P., Kwee, T. C. & Haan, M. Do People favor artificial intelligence over physicians? A survey among the general population and their view on artificial intelligence in medicine. Value Health 25, 374–381.

20. Castagno, S. & Khalifa, M. Perceptions of artificial intelligence among healthcare staff: A qualitative survey study. Front. Artif. Intell. 3, 578983.

21. Ardon, O. & Schmidt, R. L. Clinical laboratory employees' attitudes toward artificial intelligence. Lab. Med. 51, 649–654.

22. Lennox-Chhugani, N., Chen, Y., Pearson, V., Trzcinski, B. & James, J. Women's attitudes to the use of AI image readers: A case study from a national breast screening programme. BMJ Health Care Inform. 2021 Mar;28(1):e100293.

23. Nelson, C. A. et al. Patient perspectives on the use of artificial intelligence for skin cancer screening: A qualitative study. JAMA Dermatol. 156, 501–512.

24. Formosa, P., Rogers, W., Griep, Y., Bankins, S. & Richards, D. Medical AI and human dignity: Contrasting perceptions of human and artificially intelligent (AI) decision making in diagnostic and medical resource allocation contexts. Comput. Hum. Behav. 133, 107296.

25. Jutzi, T. B. et al. Artificial intelligence in skin cancer diagnostics: The patients' perspective. Front. Med. (Lausanne) 7, 233. (2020).

26. Cho, S. I., Han, B., Hur, K. & Mun, J. H. Perceptions and attitudes of medical students regarding artificial intelligence in dermatology. J. Eur. Acad. Dermatol. Venereol. 2021 Jan;35(1):e72-e73

27. Lennartz, S. et al. Use and control of artificial intelligence in patients across the medical workflow: single-center questionnaire study of patient perspectives. J. Med. Internet Res. 23, e24221.

28. Valikodath, N. G. et al. Evaluation of pediatric ophthalmologists' perspectives of artificial intelligence in ophthalmology. J. Aapos 25(164), e161-164.e165.

29. Wadhwa, V. et al. Physician sentiment toward artificial intelligence (AI) in colonoscopic practice: a survey of US gastroenterologists. Endosc. Int. Open 8, E1379-e1384.

30. Leenhardt, R. et al. PEACE: Perception and expectations toward artificial intelligence in capsule endoscopy. J. Clin. Med. (2021).

31. Bisschops, R. et al. Advanced imaging for detection and differentiation of colorectal neoplasia: European Society of Gastrointestinal Endoscopy (ESGE) Guideline—Update 2019. Endoscopy 51, 1155–1179. (2019).

32. Krosnick, J. & Alwin, D. An evaluation of a cognitive theory of response-order effects in survey measurement. Public Opin. Q. (1987).

33. in The Psychology of Survey Response (eds Kenneth Rasinski, Lance J. Rips, & Roger Tourangeau) 230–254 (Cambridge University Press, 2000).

CHAPTER 8

Dutch-Flemish translation and validation of the gastrointestinal symptom scales from the patient reported outcomes measurement information system (PROMIS)®

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Abstract

Purpose

To translate the eight PROMIS® Gastrointestinal Symptom Scales into Dutch-Flemish and to evaluate their psychometric properties.

Methods

This study consisted of two parts: (1) translation according to the Functional Assessment of Chronic Illness Therapy (FACIT) translation methodology and (2) evaluation of psychometric properties: structural validity, using confirmatory factor analysis; and construct validity using hypothesis testing.

Results

In the first part of the study, in 19 out of the 77 items (24.7%) translation was challenging. After discussion between the translators, consensus could be achieved. In the cognitive debriefing interview phase, ten minor changes in the wording of items were made. A universal Dutch- Flemish translation for all 77 items was obtained.

In de second part of the study a good fit was found for three DF-PROMIS GI Scales: Bowel Incontinence, Gas and Bloating, and Belly Pain. Four scales (Reflux, Disrupted Swallowing, Diarrhea, and Constipation) did not show sufficient fit and fit for the Nausea and Vomiting scale could not be assessed because of skewed responses. Construct validity was considered sufficient for six out of eight DF-PROMIS GI Scales. Less than 75% of hypothesis for de Constipation and Disrupted Swallowing scales could be confirmed.

Conclusion

The PROMIS GI Symptom Scales were successfully translated into Dutch-Flemish. The findings suggest a sufficient structural validity for the PROMIS GI Scales. Bowel Incontinence, Gas and Bloating and Belly Pain. Construct validity was sufficient for the Scales Gas and Bloating, Incontinence, Nausea and Vomiting, Reflux, Belly Pain, and Diarrhea.

Introduction

Gastrointestinal (GI) symptoms are widespread and bring substantial economic and social consequences. The prevalence of gastrointestinal diseases in Western countries has increased over the past few decades and is one of the most commonly encountered conditions in primary care practice. A large-scale multinational study, found that more than 40% of persons worldwide have functional *gastrointestinal disorders* (FGID). Data from the Netherlands show a prevalence of 30.6% and 35.6% in Belgium. Functional constipation and IBS were most prevalent[1]. Individuals with any FGID showed lower global physical health and global mental health, as measured with the PROMIS® Global Health Scale, compared with subjects with no FGID, which affects quality of life and increases health care use[1].

The importance of patients' perspectives on the impact of disease and response to treatment is widely recognized. Patient-reported outcome measures (PROMs) measure the patient's health status from the patient's perspective. For measuring patients' perspectives on GI symptoms, over the past two decades investigators have developed over 100 disease-targeted PROMs[2]. However, scores from these different questionnaires are not comparable since they utilize different measurement scales. Furthermore, it is often unclear which changes in scores are relevant in daily practice. It is important to standardize outcome measurements and use the same PROMs as much as possible across all GI disorders for clinical and research purposes.

The eight National Institutes of Health (NIH) PROMIS GI Symptom Scales capture GI symptoms experienced by people with a wide range of digestive disorders. Unlike disease-targeted measures, which are designed for specific patient populations, the PROMIS-GI Symptom Scales are system-targeted measures, designed for anyone experiencing GI symptoms, whether patients or members of the population at large[3]. This is an important unique value of PROMIS measures, because disease-targeted PROMs are not useful across the population as a whole[3,4]. The original PROMIS-GI Symptom Scales were developed by Spiegel et al. in the Unites States of America. The scales correlated significantly with both generic and disease- targeted legacy instruments, and demonstrate evidence of reliability[3]. The PROMIS-GI symptom scales can be used together or individually in clinical practice and clinical research and are broadly applicable across populations, GI symptoms, GI diseases, and demographics.. The PROMIS GI symptom Scales have been translated and validated in different languages, however there is no data published yet on the psychometric properties of these translations.

By translation of the PROMIS Gastrointestinal Symptoms Scales into Dutch-Flemish we will make these instruments available for use in the Netherlands and Flanders (the Dutch-speaking part of Belgium) in patients with a broad range of GI diseases. This study aimed to translate the PROMIS Gastrointestinal Symptom Scales into Dutch-Flemish and to evaluate their psychometric properties structural validity and construct validity in patients with a variety of GI conditions.

Methods

This study consisted of two parts: (1) translation of the PROMIS -GI Scales v1.0 into Dutch-Flemish (DF) and (2) evaluation of psychometric properties structural validity using confirmatory factor analysis (CFA) and construct validity using hypothesis testing in GI patients. Authorization to translate the eight PROMIS GI Symptom Scales was obtained from the Health Measures translation team in June 2021. For both parts of this study, patients were recruited from the Catharina Hospital in the Netherlands and the University Hospital UZ Leuven in Belgium. Patients were eligible if aged 18 years, and confirmed diagnosis of Inflammatory bowel disease (IBD), irritable bowel syndrome (IBS) or gastroesophageal reflux disease (GERD) with or without a Barrett’s esophagus, had to be able to read, understand and complete the Dutch informed consent form and the study questionnaires. Informed consent was obtained from all participants.

1. Translation and cognitive debriefing

The translation process followed the Functional Assessment of Chronic Illness Therapy (FACIT) translation methodology5. The steps of the FACIT translation methodology included two forward translations (by 1 Dutch and 1 Flemish native-speaker), and one backward translation (English native-speaker), independent review by two reviewers (ME and CT), harmonization with previous PROMIS translations and assessment of translation quality by the Dutch-Flemish PROMIS National Center (CT), and pilot testing including cognitive debriefing (Figure 1).

To assess comprehensibility, cognitive debriefing interviews were performed with 10 native Dutch-speaking participants in the Netherlands and 10 native Flemish-speaking participants in the Flemish-speaking part of Belgium. Participants included five persons from the general population and five patients with GI symptoms in each country. Participants from the general population were recruited from the social network of employees working in the GI department of the two hospitals. Participants were selected based on age, gender, education level, and disease to obtain heterogeneity in the population sample. Informed consent was obtained from all participants. The interview script was based on the retrospective verbal prompting technique, following prior PROMIS work6. During the interviews, participants first completed all translated items in writing. Subsequently, participants were asked about difficulties in understanding each item and the meaning of the items were discussed to ensure comprehensibility. After completing the interviews with 10 Dutch participants, some adjustments were made to the translations of the response categories and items. Thereafter, another 10 interviews were completed with participants from Belgium to test the modified versions of the items. All interviews were audio recorded.

2. Psychometric testing

The aim of the psychometric testing phase was assessing structural validity and construct validity of the DF-PROMIS GI Symptom Scales using a cross-sectional study design in patients with GI conditions. For assessing construct validity, all patients completed the DF-PROMIS GI questionnaire Gastrointestinal Symptom Rating Scale (GSRS). In addition, Inflammatory Bowel Disease (IBD) patients completed the Inflammatory Bowel Disease Questionnaire (IBDQ) and Irritable Bowel Syndrome (IBS) patients completed the Irritable Bowel Syndrome Quality of Life Questionnaire (IBS-QOL).

For validation purposes, COSMIN guidelines recommend a sample of 7 times the number of items per scale and at least 100 for a study of very good quality[7]. Questionnaires were completed at home, with a postal or digital return of the questionnaire in Research manager (version 5.2.2).

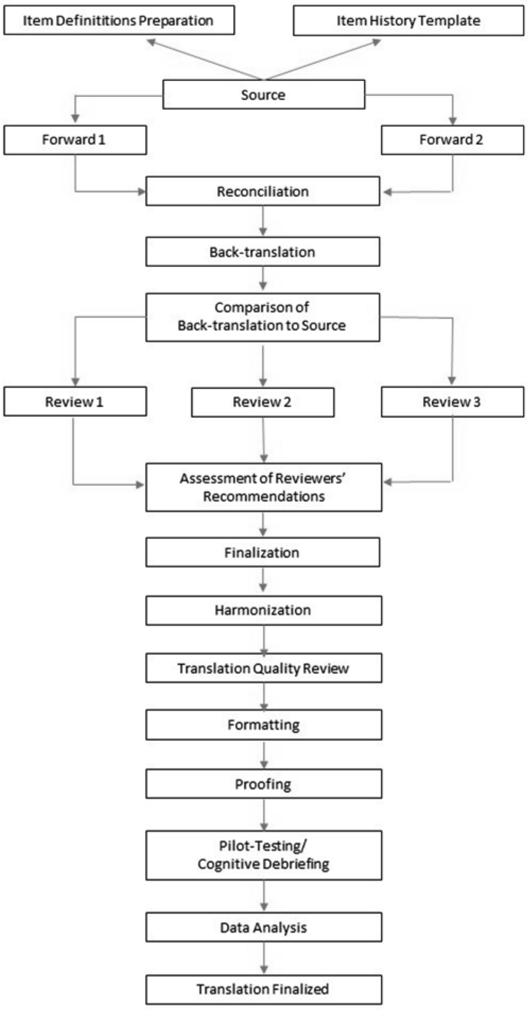

Figure 3: FACIT translation methodology chart

Measurements

Patients were asked to fill out several demographic and clinical questions (age, sex, and educational level)

PROMIS GI

The DF-PROMIS GI Symptom Scales consist eight scales: Reflux (13 items), Disrupted Swallowing (7 items), Diarrhea (5 items), Bowel Incontinence (4 items), Nausea and Vomiting (4 items), Constipation (9 items), Belly Pain (6 items), and Gas and Bloating (12 items). The PROMIS GI scales can be used individually or in combination and are subsequently scored and reported individually. All items, except for one, are administered using a 5-point categorical response scale. The first item in Gas and Bloating is an unscored item (GISX94). Its response options are "A=yes" and "B = no" and do not contribute to the summed score. There were expected missing responses on items in the Scales Reflux, Diarrhea, Bowel Incontinence, Nausea and Vomiting, Belly Pain, and Gas and Bloating. These scales contain response instructions with "if never, go to…" As a result, patients without symptoms skipped one or more items.

For all scales, except the Bowel Incontinence Scale, T-scores were calculated using the response pattern scoring service available at the Health Measures website. T-scores were based on the underlying Item-response theory (IRT) models. IRT models are used for establishing whether a set of items intended to measure a particular attribute, together constitute a scale for measurement[8].

Higher T-scores indicate more symptoms. Each GI scale was calibrated by the original developers using a IRT graded response model and IRT scores were converted to T scores with a mean of 50 and SD of 10 in the US general population, by PROMIS convention[11]. However, previous studies did not produce an IRT based T-score for the Bowel Incontinence scale. Therefore, simple summed scores for this scale were used in analysis.

The Gastrointestinal Symptom Rating Scale (GSRS)

The GSRS is a 15-item questionnaire that evaluates the five common symptom clusters of GI disorders: abdominal pain, reflux, indigestion, constipation and diarrhea[9]. Items ask about the past week using a 7-point categorical response scale ranging from no discomfort to very severe discomfort. The self-administered version of the GSRS utilized in this study showed an acceptable reliability, validity, and responsiveness to change in patients with different GI disorders[10,11]. The GSRS has five-symptom domains representing reflux, abdominal pain, indigestion, diarrhea and constipation. A score for each domain was calculated based on the average score of the questions in that domain with higher scores indicating more symptoms.

In addition to completing the DF- PROMIS GI Scales and the GSRS, patients completed a relevant disease-targeted legacy instrument: IBS patients completed the IBS-QOL, IBD patients completed the IBDQ.

Irritable Bowel Syndrome Quality of Life Questionnaire (IBS-QOL)

The IBS-QOL is a well-established 34-item measure assessing the degree to which IBS interferes with a patient's quality of life. Each item is rated on a 5-point Likert scale, ranging from not at all to extremely or a great deal, yielding a total score that ranges from 34 to 170[12,13]. As per the IBS-QOL scoring manual, all items were reversed and raw summary scores were transformed into a 0 to 100 scale with higher scores indicate better QOL[14].

Inflammatory Bowel Disease Questionnaire (IBDQ)

The validated Dutch version of the IBDQ was used in IBD patients. The IBDQ is a 32-item questionnaire assessing bowel symptoms, systemic symptoms, emotional function, and social function. All items use 7-point Likert scales for capturing symptom-related experiences during the past two weeks, where 1 represents the highest symptom frequency/severity and 7 indicates the lowest symptom frequency/severity. The total score ranges from 32 (poor quality of life) to 224 (good quality of life). IBDQ total score higher than 170 is usually associated with patients in clinical remission [15,16].

Analysis

Demographics and clinical characteristics of the participants were summarized with descriptive statistics.

Structural validity

A confirmatory factor analysis (CFA) with weighted least square mean- and variance-adjusted estimator was performed to assess unidimensionality of the PROMIS-GI Scales. The distribution of answers for all items was reviewed. If a CFA could not be completed due to a highly skewed distribution of answers, response categories that were chosen by fewer than five patients were merged with an adjacent response category until a minimum of five answers were obtained in each response category.

To evaluate model fit comparative fit index (CFI), Tucker–Lewis Index (TLI), the root mean square error of approximation (RMSEA) and the standardized root mean square residual (SRMR) were used. Representative of a good fit was a CFI value >0.95, RMSEA value <0.08, TLI >0.95, and a SRMR <0.10[17].

Construct validity - Hypothesis testing

To assess the extent to which the DF-PROMIS-GI Scales are measuring the same or similar constructs as the scales of the three legacy instruments (IBDQ, IBS-QOL and GSRS), convergent validity was assessed. This was evaluated by calculating Pearson's correlations of the DF-PROMIS GI Scale T-scores with the total scores of the disease specific instruments. According to COSMIN guidelines[18], hypotheses were formulated a priori regarding the expected correlations based on previous research[3] (Table 1). A moderate to strong correlation was considered (r >0.40) between the DF-PROMIS GI Scales and the three legacy instruments, based on the results of the original PROMIS GI development study. Convergent validity was considered to be adequate if at least 75% of the results were in accordance with the hypotheses.

IBM® SPSS® Statistics for Windows version 29.0., Armonk, NY was used for descriptive statistics and hypotheses testing. The R-package "lavaan (v0.6.14)" [19] was used for structural validity.

	GSRS reflux	GSRS Indiges-tion	GSRS belly pain	GSRS diarrhea	GSRS constipation	GSRS total	IBD-Q	IBS-QOL
PROMIS Gastroesophageal Reflux	>0.40[a]	>0.40	>0.40	<0.40[b]	>0.40	>0.40	>-0.40	<-0.40
PROMIS Disrupted Swallowing	>0.40	>0.40	>0.40	<0.40	>0.40	>0.40	<-0.40	<-0.40
PROMIS Diarrhea	<0.40	>0.40	<0.40	>0.40	<0.40	>0.40	>-0.40	>-0.40
PROMIS Incontinence	<0.40	<0.40	<0.40	>0.40	<0.40	>0.40	>-0.40	<-0.40
PROMIS Nausea and vomiting	>0.40	>0.40	>0.40	<0.40	>0.40	>0.40	>-0.40	>-0.40
PROMIS Constipation	<0.40	>0.40	>0.40	<0.40	>0.40	>0.40	>-0.40	<-0.40
PROMIS Abdominal pain	>0.40	>0.40	>0.40	>0.40	>0.40	>0.40	>-0.40	>-0.40
PROMIS Gas and Bloating	>0.40	>0.40	>0.40	>0.40	>0.40	>0.40	>-0.40	>-0.40

Table 1 Hypotheses of PROMIS Gastrointestinal Symptom Scales with legacy measures.

[a] Pearson ʻs r of >.040 represent a moderate to strong correlation

[b] Pearson ʻs r of <.040 represent a weak correlation

GSRS, Gastrointestinal Symptom Rating Scale; IBDQ, Inflammatory Bowel Disease Questionnaire; IBS-QOL, Irritable Bowel Syndrome-Quality of Life; PROMIS, Patient-Reported Outcomes Measurement Information System.

Results

1. Translation and cognitive debriefing

Eight PROMIS GI Scales were translated into Dutch-Flemish (DF), and all of them had translation issues to be resolved. Nineteen out of the 77 items (24.7%) were challenging for translation and required specific linguistic attention. The term ‘how much’ was used in 12 source items and was translated into ‘in welke mate’ (to what extent), to ensure consistency with previously translated PROMIS measures. Two source items use the phrase ‘make it to the bathroom’. After discussion this was translated as ‘bij het toilet kon zijn’ (get to the toilet). The term bathroom is not used in Dutch for going to the toilet, but for going to the shower instead. In the Scale Diarrhea the term loose is used three times, which in Dutch means ‘losse’. Since ‘losse’ is not a commonly used term to describe stool consistency, therefore ‘dunne’ (thin) was chosen. Two items of the Scale Gastrointestinal Disrupted Swallowing use the phrase ‘in your chest’. In Dutch, symptoms of dysphagia are explained as that food gets stuck or does not lower behind the breastbone. Therefore, the phrase ‘achter het borstbeen’ (behind the breastbone) was chosen.

Subsequently, the DF-PROMIS GI Scales were tested for comprehensibility in the Netherlands and Belgium. In total 20 respondents (10 from the Netherlands, and 10 from Belgium) participated in the interviews, of which 60% were men (n = 12) with an average age of 50.5 years (19-77). Five IBD patients were included, two IBS patients, three GERD/ Barrett’s esophagus patients and ten people from the general population with no GI diseases. Ten minor changes in wording of the items were made after the interviews (Appendix A). In addition, changes were made to the translations of the response options: ‘never’, ‘one day’, ‘2-6 days’, ‘once a day’, ‘more than once a day’. Particularly, the difference between ‘one day’ and ‘once a day’ was not clear in the first ten interviews. The translation was changed to: ‘nooit (never)’, ‘een keer tijdens de afgelopen 7 dagen (once in the last 7 days)’, ‘2-6 keer tijdens de afgelopen 7 dagen (2-6 times during the last 7 days)’, ‘vaak (eenmaal per dag) often (once per day)’, and ‘meer dan eenmaal per dag (more than ones per day)’.

The term breastbone is used in multiple Scales, but only in the Scale Gastrointestinal Reflux an image of the location of the breastbone is used for explanation. Respondents stated that adding the image also to the Scale Gastrointestinal Disrupted Swallowing would help them identify the location of the breastbone. This is particularly important for respondents who will not complete all GI Scales in the future. Therefore, the image was added to the DF-PROMIS GI Gastrointestinal Disrupted Swallowing Scales.

2. Psychometric testing

The DF-PROMIS GI Scales and legacy instruments were completed by a total of 216 patients with GI conditions (IBD n= 95; IBS n= 50; GERD/Barrett's esophagus n=66, other GI disease =2). The mean (SD) age was 54.8 (17.2) years, 50% were male, and 83.7% had a minimum of college education (Table 2)

Scores of all the DF-PROMIS GI Scales and legacy instruments are shown in Table 3. The mean score of the DF- PROMIS GI Gas and Bloating Scale was above 50 (53.0), indicating that our patients reported more or more severe symptoms on average than the US general population. All other Scale mean scores were lower than 50, which means that the included patients scored fewer or less severe symptoms than the US general population.

Patients characteristics	**n=216 (%)**
Male gender	109 (50.4)
Age in years, *mean (SD)*	54.8 (17.2)
Belgium/ Flanders	74 (34.3)
Netherlands	142 (65.7)
Diagnosis	
Inflammatory bowel disease	96 (44.4)
Irritable Bowel Syndrome	51 (23.6)
Barrett's esophagus/ GERD	67 (31.0)
Other GI condition*	2 (1.0)
Education	
High school graduate or less	24 (11.1)
Some college	88 (40.7)
Bachelor/ University graduate	93 (43.0)
Missing	12 (5.2)

Table 2: patients characteristics

Other GI conditions were: cirrhosis of the liver=1, coeliac disease=1 GERD: gastro esophageal reflux disease, SD: standard deviation

Questionnaires	**Mean**	**(SD)**
DF- PROMIS Gastrointestinal Reflux	45.7	(8.0)
DF- PROMIS Gastrointestinal Disrupted Swallowing	46.3	(7.0)
DF- PROMIS Gastrointestinal Diarrhea	48.7	(8.8)
DF- PROMIS Gastrointestinal Bowel Incontinence [a]	5.5	(2.6)
DF- PROMIS Gastrointestinal Nausea and Vomiting	47.5	(8.0)
DF- PROMIS Gastrointestinal Constipation	49.8	(8.5)
DF- PROMIS Gastrointestinal Belly Pain	49.7	(12.0)
DF- PROMIS Gastrointestinal GI Gas and Bloating Scale	53.0	(8.9)
IBD-Q	182	(29.2)
IBS-QOL	71.1	18.6
GSRS Reflux	2.28	1.2
GSRS Abdominal pain	1.67	1.0
GSRS Indigestion	2.79	1.2
GSRS Diarrhea	2.58	1.6
GSRS Constipation	2.39	1.3
GSRS	2.48	1.0

Table 3 Scores DF-PROMIS GI Scales and legacy instruments

[a] The Health Measures version of the PROMIS Bowel incontinence Scale does not produce an IRT-based T-score. Therefore a summed scores was used (possible score range 4 to 20).

SD= standard deviation, DF= Dutch Flemish; PROMIS=Patient-Reported Outcomes Measurement Information System, GSRS= Gastrointestinal Symptom Rating Scale, IBDQ= Inflammatory Bowel Disease Questionnaire, IBS-QOL= Irritable Bowel Syndrome-Quality of Life;

Structural validity

For the Scales DF-PROMIS GI Bowel Incontinence and Disrupted Swallowing, a CFA could be performed. For the other Scales the distribution of answers was highly skewed and a CFA could not be completed. After merging response categories in the Scales Reflux, Diarrhea, Constipation, Belly Pain and Gas and Bloating a CFA could be performed in these Scales. The data of the PROMIS Scale Nausea and Vomiting was still highly skewed after merging response categories and therefore CFA could not be performed.

The CFA for the Scales Gas and Bloating, Belly Pain and Bowel Incontinence showed a good fit (Table 4). The Reflux, Disrupted Swallowing, Diarrhea, and Constipation scales did not show a sufficient fit.

DF- PROMIS Gastrointestinal Scales	CFI	RMSEA	TLI	SRMR
Reflux*	0.463	0.135	0.356	0.170
Disrupted Swallowing	0.871	0.068	0.806	0.057
Diarrhea*	0.905	0.135	0.842	0.064
Bowel incontinence	0.999	0.068	0.999	0.013
Constipation*	0.664	0.131	0.553	0.116
Belly Pain*	0.998	0.030	0.967	0.020
Gas and Bloating*	0.952	0.071	0.942	0.067

Table 4 Confirmative factor analysis

DF= Dutch Flemish, PROMIS, Patient-Reported Outcomes Measurement Information System, CFI =Comparative fit index, RMSEA= root mean square error of approximation, TLI= Tucker–Lewis Index, SRMR= standardized root mean square residual

*Distribution of response categories was highly skewed, and responses were merged. The complete overview of the merged categories is descripted in Appendix B.

Construct validity - Hypothesis testing

Table 5 summarizes the correlations between the DF-PROMIS GI T-scores and the legacy instrument scores. Six out of eight Scales (Reflux, Diarrhea, Bowel Incontinence, Nausea and Vomiting, Belly Pain, and Gas and Bloating) showed sufficient convergent validity with more than 75% of hypothesis confirmed.

Although only five out of eight hypothesis of the PROMIS Scale Constipation were consistent with the hypotheses, a high correlation (0.78) was found with de GSRS constipation scale. Low correlations were found for the PROMIS Disrupted Swallowing Scale and only four out of the eight hypothesis good be confirmed.

As Table 5 shows, high correlations were found (*r* .56- .79) between scales measuring the same construct.

DF- PROMIS Gastrointestinal Scales	GSRS reflux	GSRS Indigestion	GSRS belly pain	GSRS diarrhea	GSRS Consti-pation	GSRS total	IBD-Q	IBS-QOL	Confirmed (%)
Reflux	.55	.47	.47	.19	.33	.53	-.33	-.38	75
Disrupted Swallowing	.42	.30	.36	.15	.29	.38	-.19	-.26	50
Diarrhea	.06	.37	.39	.79	.21	.56	-.66	-.40	88
Bowel incontinence	.06	.20	.18	.45	.19	.30	-.46	-25	75
Nausea and vomiting	.31	.48	.64	.34	.33	.58	-.54	-.41	75
Constipation	.20	.42	.34	.17	.78	.49	-.27	-.29	63
Belly Pain	.31	.63	.65	.57	.52	.75	-.75	-.53	88
Gas and Bloating	.33	.74	.51	.35	.49	.65	-.48	-.47	75

Table 5 Correlations of DF-PROMIS gastrointestinal Scales with legacy measures.

GSRS= Gastrointestinal Symptom Rating Scale, IBDQ= Inflammatory Bowel Disease Questionnaire, IBS-QOL= Irritable Bowel Syndrome-Quality of Life, PROMIS= Patient-Reported Outcomes Measurement Information System.

Pearson correlation coefficients were calculated. Results in accordance with a priori hypothesized correlations are underlined.

Discussion

With this study, the PROMIS GI Symptom Scales were translated in Dutch-Flemish and their psychometric properties, structural validity and construct validity, were evaluated. The translation was performed using a rigorous, standardized methodology. The FACIT translation methodology was developed based on comprehensive research in the HRQOL field to ensure that the translations are conceptually equivalent to the English source and are rendered in a language that is culturally acceptable and relevant to the target audience. Nineteen out of the 77 items (24.7%) were challenging for translation and required specific linguistic attention. Those items were discussed between the translators, after which consensus was achieved. Subsequently, in the cognitive debriefing phase, ten minor changes in the wording of the items were made. There were no cross-cultural issues identified. In general, patients stated that they had no difficulty understanding the DF-PROMIS GI items, and could use these items to self-report their GI symptoms. We finally succeeded in developing one universal Dutch- Flemish translation for all 77 items.

To our knowledge, this is the first study investigating the psychometric properties of the PROMIS-GI Scales v1.0 outside the US. CFA analysis could initially only be performed on the two Scales Incontinence and Disrupted Swallowing. The highly skewed data on all of the other Scales were probably due to the expected missings, the low variation in reported symptoms, and patients being more likely to have fewer or less severe symptoms. After merging response categories, a CFA analysis for the majority of the Scales could be performed. The Scale Nausea and Vomiting was still highly skewed after merging the responses and therefore CFA could not be performed on this Scale. Remarkably, Spiegel et al[3] were able to run CFA without merging response categories. This may be explained by the fact that our respondents reported fewer and less severe symptoms, resulting in skewed data with more scores of one or two. Also the variation in responses was higher in the sample of Spiegel et al, compared to our sample.

A good fit was found for three Scales: Gas and Bloating, Bowel Incontinence, and Belly Pain. This means that these Scales are considered unidimensional and that there is a single latent trait underlying the responses. Poor fit was found for the Scales Reflux, Disrupted Swallowing, Diarrhea, and Constipation, in contrast to the findings of the original development study. A possible explanation for this might be the skewed data or the heterogeneous sample. Alternatively, (some of) the concepts aimed to be measured by these scales might be more multidimensional in the Dutch and Belgian cultures. This should be tested in a future study.

Construct validity was considered sufficient for six out of eight DF-PROMIS GI Scales. For the Bowel Incontinence and Disrupted Swallowing Scales less than 75% of the hypothesis could be confirmed. The hypotheses were predefined based on the first and only study validating the PROMIS GI Scales. In line with the original PROMIS-GI data, this study showed high correlations between the DF-PROMIS GI Scales and subscales of the legacy instruments measuring the same constructs. For example, the DF-PROMIS GI Diarrhea Scale showed a Pearson correlation of .79 with the GSRS diarrhea subscale, which support the validity of the GI Scales.

Interestingly, mainly weak correlations were found between the Disrupted Swallowing Scale and the legacy instruments. This may be explained by the fact that the legacy questionnaires do not contain questions about difficulties with swallowing or passage of food through the esophagus, although higher correlations were found in the original development study. This may be explained by the fact that the participants in Spiegel's study reported more symptoms, thus making overlap of different GI symptoms more likely. It is well known that some patients with FGID can have more than one FGID. This overlap could affect the primary symptomatology of different disorders [20,21,22].

Only 63% of the hypothesis for the Constipation Scale could be confirmed. The a priori defined hypotheses were entirely based on the work of Spiegel et al[3]. Surprisingly, Spiegel et al. found moderate correlations between Scales that were not measuring the same construct (e.g. PROMIS GI Constipation versus IBD-Q r= 0.54). In general, and in contrast to the present study, Spiegel et al. reported more moderate correlations (.40-.70) between the PROMIS GI Scales and the legacy instruments IBDQ and IBS-QOL. Possibly this was caused by the fact that the patients included in the study of Spiegel et al. reported more and more severe symptoms than the patients in the current study. This may have caused that there was more overlap in the GI symptoms present, and therefore higher correlations were found for the study of Spiegel et al. compared to the current study. There was also more variation in T-scores in the sample of Spiegel et al, which leads to higher correlations.

The majority of the PROMIS Scales use a T-score metric with a mean score of 50 (representing the mean score of the US reference population) and a standard deviation of 10. A remarkable finding of this study was that the T-scores of all Scales except the DF-PROMIS Gas and Bloating Scale were below 50. This seems to show that the enrolled patient group as a whole (IBD, IBS and reflux) reported fewer and less severe symptoms than a US general population. Another explanation could be the presence of differential item functioning (DIF). Additional research can determine whether there is DIF between US and DF patients within the PROMIS GI Scales, after allowing for overall subgroup differences in that scale.

When we analyzed the disease groups separately, we found that only the IBS patients reported an average T-score above 50 on four out of the eight Scales (Diarrhea, Constipation, Belly Pain and Gas and Bloating). IBD patients in clinical remission generally report a score of 170 or higher on the IBD-Q[15]. The included Dutch and Belgian patients in the present study scored an average of 182, which suggest that we mainly included patients in remission. However, one would expect IBD patients in remission to report more GI symptoms than a

generic population. Previous research found that IBD patients in remission often experience symptoms similar to those of IBS[23].
When comparing the mean T-scores of the DF-PROMIS GI with the study from Spiegel at al. who included US patients with similar GI diseases, it is also notable that the American population with GI diseases reported relatively low T-scores (e.g. 51-57). However, in contrast to T-scores found in the present study, always slightly above 50. A possible explanation for the discrepancies may be the differences in experiencing GI symptoms between countries. A world-wide study on the prevalence of FGID showed that persons living in the US reported a higher percentage of any FGID in comparison to persons living in the Netherlands (39.9 in the US versus 30.6 in the Netherlands). Specifically, the US population reported double the amount of functional dyspepsia as compared to Dutch and Belgium residents. This raises the question if the interpretation of a T- score of 50 as the mean score of the general population would also be applicable to the Dutch population. To determine the true differences between the Dutch and US (norm) population, further research should be undertaken to investigate T-scores in a Dutch general population. Another possible explanation for the differences in observed T-scores between the two studies is the difference in disease severity. There were no mean scores described of the legacy instruments IBS-QOL, IBDQ and GSRS in the article of Spiegel et al. As a result, it is unclear whether the study populations are comparable.

A limitation of our study is that our sample may not accurately reflect the population of Dutch and Belgian patients with a GI condition, considering the low T-scores. Another limitation is that we only assessed convergent validity and did not have data to test discriminant validity. Another limitation is the highly skewed data of all of the PROMIS GI Scales, indicating that the patient sample was not very heterogeneous. These have negatively influenced the outcomes of the CFA analysis and may also have influenced the correlations with the legacy instruments. Since the present study did not assess other psychometric properties such as discriminant validity, test–retest reliability and cross-cultural validity, for the population of Dutch and Belgian patients with a GI condition, nor the Dutch and Belgian general population, future research should address these properties. Furthermore, it is important to obtain both T-scores of the Dutch and Belgian general population.

In conclusion, The PROMIS GI Symptom Scales were successfully translated into Dutch-Flemish. The findings suggest a sufficient structural validity for the PROMIS GI Scales Bowel Incontinence, Gas and Bloating and Belly Pain. Construct validity was considered sufficient for the Scales Gas and Bloating, Incontinence, Nausea and Vomiting, Reflux, Belly Pain, and Diarrhea. The DF-PROMIS GI Symptom Scales are available on request from the Dutch-Flemish PROMIS National Center (www.dutchflemishpromis.nl).

References

1. Sperber AD, Bangdiwala SI, Drossman DA, Ghoshal UC, Simren M, Tack J, WhiteheadWE, Dumitrascu DL, Fang X, Fukudo S, Kellow J, Okeke E, Quigley EMM, Schmulson M, Whorwell P, Archampong T, Adibi P, Andresen V, Benninga MA, Bonaz B, Bor S, Fernandez LB, Choi SC, Corazziari ES, Francisconi C, Hani A, Lazebnik L, Lee YY, Mulak A, Rahman MM, Santos J, Setshedi M, Syam AF, Vanner S, Wong RK, Lopez-Colombo A, Costa V, Dickman R, Kanazawa M, Keshteli AH, Khatun R, Maleki I, Poitras P, Pratap N, Stefanyuk O, Thomson S, Zeevenhooven J, Palsson OS. Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study. Gastroenterology. 2021 Jan;160(1):99-114.e3.

2. Khanna P, Agarwal N, Khanna D, et al. Development of an online library of patient reported outcome measures in gastroenterology: the GI-PRO database. Am J Gastroenterol. 2014;109:234–48.

3. Spiegel BM, Hays RD, Bolus R, Melmed GY, Chang L, Whitman C, Khanna PP, Paz SH, Hays T, Reise S, Khanna D. Development of the NIH Patient-Reported Outcomes Measurement Information System (PROMIS) gastrointestinal symptom scales. Am J Gastroenterol. 2014 Nov;109(11):1804-14.

4. Khanna D, Hays RD, Shreiner AB, Melmed GY, Chang L, Khanna PP, Bolus R, Whitman C, Paz SH, Hays T, Reise SP, Spiegel B. Responsiveness to Change and Minimally Important Differences of the Patient-Reported Outcomes Measurement Information System Gastrointestinal Symptoms Scales. Dig Dis Sci. 2017 May;62(5):1186-1192.

5. Eremenco SL, Cella D, Arnold BJ (2005) A comprehensive method for the translation and cross-cultural validation of health status questionnaires. Eval health prof 28(2):212–232.

6. DeWalt DA, Rothrock N, Yount S, et al. Evaluation of item candidates: the PROMIS qualitative item review. Med Care. 2007;45:S12–21.

7. Mokkink LB, Prinsen CAC, Patrick DL, Alonso J, Bouter LM, De Vet HCW, et al. COSMIN Study Design checklist for Patient-reported outcome measurement instruments Amsterdam2018 [Available from: https://www.cosmin.nl/wp-content / uploads /COSMIN-study-designing-checklist_final.pdf.]

8. Sijtsma, K., & Van der Ark, L. A. (2017). A tutorial on how to do a Mokken scale analysis on your test and questionnaire data. British Journal of Mathematical and Statistical Psychology, 70(1), 137–158

9. Revicki DA, Wood M, Wiklund I, Crawley J. Reliability and validity of the Gastrointestinal Symptom Rating Scale in patients with gastroesophageal reflux disease. Qual Life Res. 1998; 7:75–83.

10. Glia A, Lindberg G. Quality of life in patients with different types of functional constipa-tion. Scand J Gastroenterol. 1997; 32:1083–1089.

11. Dimenas E, Glise H, Hallerback B, Hernqvist H, Svedlund J, Wiklund I. Well-being and gastrointestinal symptoms among patients referred to endoscopy owing to suspected duodenal ulcer. Scand J Gastroenterol. 1995;30:1046-1052.

12. Patrick DL, Drossman DA, Frederick IO, et al. Quality of life in persons with irritable bowel syndro- me: development and validation of a new measure. Dig Dis Sci. 1998; 43:400–11.

13. Drossman DA, Patrick DL, Whitehead WE, Toner BB, Diamant NE, Hu Y, Jia H, Bangdiwala SI. Further validation of the IBS-QOL: a disease-specific quality-of-life questionnaire. Am J Gastroenterol. 2000 Apr;95(4):999-1007.

14. Information Sheet on the Irritable Bowel Syndrome- Quality of Life Measure (IBS-QOL) htps://depts.washington.edu/seaqo l/docs/IBS-QOL_Info.pdf

15. Russel MG, Pastoor CJ, Brandon S, Rijken J, Engels LG, van der Heijde DM, Stockbrügger R Validation of the Dutch translation of the Inflammatory Bowel Disease Questionnaire (IBDQ): a health-related quality of life questionnaire in inflammatory bowel disease. Digesti Digestion. 1997;58(3):282-8.

16. Irvine EJ. Development and subsequent refinement of the inflammatory bowel disease question- naire: a quality-of-life instrument for adult patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 1999; 28:S23–7.

17. Schermelleh-Engel, K., Moosbrugger, H., & Müller, H. (2003). Evaluating the fit of structu- ral equation models: Tests of signifcance and descriptive goodness-of-fit measures. Met- hods of Psychological Research Online, 8(2), 23–74.

18. Mokkink LB et al. COSMIN Study Design checklist for Patient- reported outcome measure-ment instruments. Version July 2019 (www.cosmin.nl)

19. Rosseel, Y. (2012). lavaan: An R package for structural equation modeling. Journal of Statistical Software, 48(2), 36.

20. Von Wulffen M, Talley NJ, Hammer Jet al. Overlap of irritable bowelsyndrome and functional dyspepsia in the clinical setting: prevalenceand risk factors.Dig Dis Sci2019;64: 480–6.7

21. de Bortoli N, Tolone S, Frazzoni Met al. Gastroesophageal refluxdisease, functional dyspep- sia and irritable bowel syndrome: commonoverlapping gastrointestinal disorders. Ann Gastroenterol2018;31:639–48.8

22. Park KS, Jee SR, Lee BEet al. Nationwide multicenter study for overlaps of common functional gastrointestinal disorders in Korean patients with constipation. J Neurogastroenterol Motil2017;23:569–77.

23. Teruel C, Garrido E, Mesonero F. Diagnosis and management of functional symptoms in inflam- matory bowel disease in remission. World J Gastrointest Pharmacol Ther. 2016 Feb6;7(1):78-90.

Appendix A: Adjustments made after the debriefing interviews of the translated PROMIS Gastro Intestinal Scales.

Item Number	Source item	Dutch version English equivalent	Final Dutch version	Reason for adaptation
GISX45	How often did you have bowel incontinence—that is, have an accident because you could not make it to the bathroom in time?	How often did you have bowel movements – that is to say soil your underwear because you did not get to the toilet in time?	Hoe vaak had u ongewenst ontlasting verlies – dat wil zeggen bevuilde u het ondergoed omdat u niet op tijd bij het toilet kon zijn?	The term "darmincontinentie" is not clear. After adjusting to “ongewenst ontlasting verlies" no more comments were made. The term " een ongelukje krijgen" was not clear and could also be interpreted as having an accident (falling). After adjustment to "soiling your underwear," no more comments were made.
GISX66	How much did you usually strain while trying to have a bowel movement?	To what extent did you have to press hard when you tried to get bowel movement?	In welke mate moest u hard persen wanneer u probeerde ontlasting te krijgen?	Three out of 10 respondents recommended to delete the word ‘gewoonlijk’ . After adjustments no comments in the next ten interviews were made
GISX68	How often did you feel pain in your rectum or anus while trying to have bowel movements?	How often did you feel pain in your last part of the bowel or anus while trying to have bowel movements?	Hoe vaak voelde u pijn aan uw laatste stukje van de darm of anus wanneer u probeerde ontlasting te krijgen?	Nine out of 10 respondents did not know what "rectum" means. And indicated that this is probably the same as the anus. After adjusting to "laatste stukje van de darm," no comments were made in the last ten interviews.

GISX42	How often did you feel like you needed to empty your bowels right away or else you would have an accident?	How often did you feel like you needed to empty your bowels right away or else you would soil your underwear.	Hoe vaak had u het gevoel dat u uw darmen meteen moest legen, anders zou u uw ondergoed bevuilen?	The term ‘een ongelukje krijgen’ was not clear and can also be interpreted as getting into an accident. After adjustment to ‘uw ondergoed bevuilen’ no comments were made
GISX43	How much did feeling you needed to empty your bowels right away interfere with your day-to-day activities?	How much did feeling you needed to empty your bowels right away interfere with your daily activities?	In welke mate belemmerde het gevoel dat u uw darmen meteen moest legen uw dagelijkse activiteiten?	In the first 10 interviews, there were problems with the readability of this sentence. After modification to " In welke mate belemmerde het gevoel dat u uw darmen meteen moest legen u bij dagelijkse activiteiten??" still 2/10 respondents in Belgium found it difficult to understand. Both the original question and the translation are difficult to interpret but difficult to simplify.
GISX94	Did you have swelling in your belly?	Did you have a swollen belly?	Had u een opgezwollen buik?	Five out of ten respondents had difficulty with the term "zwelling" after adjusting to "opgezwollen buik" no comments were made by Belgian respondents.

GISX95	How bad did the swelling in your belly get?	How bad was the swollen belly?	Hoe erg was de opgezwollen buik?	The part of the sentence '…is uw buik geworden?' is not well understood by the first 10 respondents. Participants recommended deleting this last part because it has no additional value. As in the previous question, "zwelling" was changed to 'opgezwollen buik'. No more comments were made in the last 10 interviews.
GISX96	How much did the swelling in your belly interfere with your day-to-day activities?	How much did the swollen belly interfere with your day-to-day activities?	In welke mate belemmerde de opgezwollen buik u bij uw dagelijkse activiteiten?	As in item, 'zwelling' is adjusted to 'opgezwollen buik' . No comments were made in the final ten interviews
GISX97	How much did having swelling in your belly bother you?	How much did having a swollen belly bother you?	In welke mate had u last van een opgezwollen buik?	As in item, 'zwelling' is adjusted to 'opgezwollen buik'. No comments were made in the final ten interviews
GISX28	How often did you feel like there was a lump in your throat?	How often did you feel like you had a lump in your throat that you had to swallow?	Hoe vaak had u het gevoel dat er een brok in uw keel zat die u weg moest slikken?	Three of 20 respondents questioned whether it was meant figuratively or proverbially. Changed to: Hoe vaak had u het gevoel dat er een brok in uw keel zat die u weg moest slikken? There were no comments after this in Belgium

Appendix B: . Overview of the merged categories used in the confirmative factor analysis

	reflux_GISX2	reflux_GISX3	reflux_GISX9	reflux_GISX10	reflux_GISX11	reflux_GISX12	reflux_GISX14	reflux_GISX21	reflux_GISX22	reflux_GISX24	reflux_GISX25	reflux_GISX28
1	150	18	22	25	174	141	148	152	52	74	115	137
2	38	38	21	25	30	37	40	38	40	60	62	46
3	21	5	17	11	7	17	17	18	60	15	30	23
4	5	0	3	1	3	17	6	5	62	13	5	6
5	0	3	1	2	0	2	3	1	0	0	2	2
999	0	0	0	0	0	0	0	0	0	0	0	0
empty	2	152	152	152	2	2	2	2	2	54	2	2

	Nausea_GISX49	Nausea_GISX52	Nausea_GISX55	Nausea_GISX59
1	136	34	112	198
2	32	21	61	13
3	31	15	21	1
4	14	7	18	1
5	1	1	2	0
999	0	0	0	0
empty	2	138	2	3

	gas_GISX95	gas_GISX96	gas_GISX97	gas_GISX98	gas_GISX99	gas_GISX100	gas_GISX101	gas_GISX102	gas_GISX103	gas_GISX104	gas_GISX105	gas_GISX109
1	5	24	7	70	12	16	17	72	53	24	16	56
2	42	39	38	49	63	47	62	29	60	66	96	62
3	26	16	16	56	35	24	38	25	14	29	78	53
4	17	9	24	33	29	46	22	9	13	21	24	39
5	0	4	6	3	1	7	2	4	0	0	0	2
999	0	0	0	0	0	0	0	0	0	0	0	0
empty	126	124	125	5	76	76	75	77	76	76	2	4

	Const_GISX63	Const_GISX64	Const_GISX65	Const_GISX66	Const_GISX67	Const_GISX68	Const_GISX69	Const_GISX72	Const_GISX74
1	124	12	91	4	28	112	25	55	182
2	46	36	42	48	39	46	44	65	17
3	36	24	54	33	25	36	24	57	7
4	7	15	19	34	26	14	5	27	5
5	0	2	6	2	2	4	2	7	1
999	1	1	1	1	1	1	1	1	1
empty	2	126	3	94	95	3	115	4	3

	Swal_GISX31	Swal_GISX32	Swal_GISX33	Swal_GISX34	Swal_GISX35	Swal_GISX36	Swal_GISX37
1	151	176	166	157	199	199	164
2	38	25	32	43	11	14	27
3	21	10	13	11	3	1	13
4	3	1	2	3	0	0	7
5	1	1	0	0	0	0	1
999	0	0	0	0	0	0	0
empty	2	3	3	2	3	2	4

	Inco_GISX45	Inco_GISX46	Inco_GISX47	Inco_GISX48
1	173	162	161	139
2	28	38	38	44
3	9	9	8	26
4	1	2	3	5
5	3	2	2	0
999	0	1	2	0
empty	2	2	2	2

	Diarrhea_GISX38	Diarrhea_GISX40	Diarrhea_GISX41	Diarrhea_GISX42	Diarrhea_GISX43	Diarrhea_GISX44
1	120	21	10	121	16	7
2	28	40	37	44	40	34
3	24	17	29	25	21	25
4	21	10	10	16	12	16
5	19	4	6	5	0	7
999	1	1	1	1	1	1
empty	3	123	123	4	126	126

	Pain_GISX78	Pain_GISX79	Pain_GISX90	Pain_GISX91	Pain_GISX92
1	93	11	34	9	53
2	51	53	45	52	60
3	36	33	24	32	52
4	14	21	14	20	36
5	20	0	3	6	8
999	0	0	0	0	0
empty	2	98	96	97	7

CHAPTER 9

General discussion

Barrett's esophagus (BE) is the precursor to esophageal adenocarcinoma (EAC) which is an aggressive tumor that has a poor prognosis[1]. Over the past two decades there has been a significant improvement in the field of surveillance endoscopic imaging modalities, resulting in an increase detection of (pre-) cancerous lesions in BE. Furthermore, endoscopic treatment has replaced esophagectomy for the management of early Barrett's neoplasia. Thereby allowing for the curative treatment of intramucosal EAC and dysplastic BE with minimal morbidity and no mortality. Previous studies on Health Related Quality of Life (HRQoL) in BE patients found that BE is associated with a significant decrease of HRQoL, measured with both generic- and disease-targeted instruments. In addition, patients with BE seem to be at risk for psychological consequences such as depression, anxiety and stress[2]. These negative effects of BE on HRQoL and psychological health may be related to the patient's perception of the risk of developing EAC. However, the majority of the studies published on HRQoL are outdated and can therefore not be projected onto the current patient care pathways. Other limitations of these studies are: underpowered samples, use of a single measurement tool and/or a lack of appreciation of the patients' perspectives on what to measure. As a result, the actual important influencing factors for HRQoL in patients with BE remains largely unknown. Therefore, the aim of this thesis was to gain more insight into their HRQoL and the current patients perspectives on the diagnosis of BE. Associated symptoms, as well as perception on cancer risks, and the potential influence of the use of artificial intelligence were evaluated. Furthermore, this thesis provides insight on how to measure HRQoL in patients with BE. This may lead to new initiatives in the field to further improve individual care for these patients in the future.

Generic Health related Quality of life

Various definitions of HRQoL can be found in the literature. Moreover, the term HRQoL is often described as: 'a term referring to the health aspects of quality of life, generally considered to reflect the impact of disease and treatment on disability and daily functioning; it has also been considered to reflect the impact of perceived health on an individual's ability to live a fulfilling life'. More specifically, HRQoL is a measure of the value assigned to duration of life as modified by the impairments, functional states, perceptions and social opportunities that are influenced by disease, injury, treatment and policy'[3]. Studies in the field of HRQoL in patients with BE, performed between 1997 and 2017, found that their HRQoL was significantly decreased[4]. However, our large multi-center study in **chapter 5** and the cross-sectional questionnaire study in **chapter 4** found BE patients to have comparable or higher generic HRQoL compared to a Dutch age and gender reference population.

Generic HRQoL was measured in previous studies using the Short Form-36 (SF-36). This widely used questionnaire has been validated for measuring generic QoL in multiple disease states[5,6]. The SF-36 contains eight domains: physical functioning, social functioning, physical role functioning, emotional role functioning, vitality, bodily pain, mental health and general health. The majority of BE patients, reported in **chapter 5**, reported high scores on all domains. The domains mental health, bodily pain, role functioning, and physical functioning showed a moderate but significant increase in comparison to the reference population. These findings suggest a minimal influence on generic HRQoL due to the diagnosis of BE. This corresponds with our earlier observations in focus-groups interview results in **chapter 2**, in which participants stated a minimum influence of BE on their experienced HRQoL. These findings are contradictory with previous studies, that showed patients with BE reporting decreased HRQoL on the SF-36 compared to norm reference data[2,7]. A more recent study in the United Kingdom (UK) showed Non Dysplastic Barrett's esophagus (NDBE) patients to have lower scores on all domains of the SF-36 compared to a healthy cohort[8]. The patients scores were specifically lower on bodily pain. There are two probable causes for these contradicting results. One explanation may be the presence of more gastroesophageal reflux symptoms in the UK study. BE patients in **chapter 5** reported low values on gastroesophageal symptoms, in contrast to the patients in the UK study that reported moderate symptoms. Secondly, Britton et al. compared HRQoL results of a NDBE group versus a younger and healthy population with a mean age of 50.3 years and without comorbidities[8]. The study in **chapter 5** compared the HRQoL data to a more reflective general population aged 61–70 years old of which 50% had at least one chronic condition. In addition, the subgroup analysis of the study in **chapter 5** indicates that the age group 40-61 and the age group over 70 had similar or even higher HRQoL compared to the reference population in the same age categories.

Although we found that the most frequently used PROM for measuring generic HRQoL in studies on the HRQoL of BE patients was the SF-36 (52.2%), as described in **chapter 3,** it must be debated whether this is the appropriate PROM to choose. The SF-36, focuses to a large extent on how patients are functioning, including their ability to take care of themselves and carry out their usual roles in life. BE is not likely to have a large effect on how patients are functioning. Therefore, it is questionable whether the SF-36 is truly measuring the HRQL in BE patients.

Factors influencing health related quality of life

In this thesis we have concluded that generic HRQoL is not influenced by the diagnosis of BE in Dutch patients. There are, however, several disease specific factors influencing the HRQoL in BE patients. We explored which factors are influencing HRQoL in BE patients using two different research strategies. For the focus-group study descripted in **chapter 2** we asked patients to discuss all factors related to BE and how these influence their lives. And in **chapter 5** we describe the result from a large multi-center questionnaire study (n= 859) on factors influencing the illness perception of patients diagnosed with BE. In both studies we found that experiencing gastroesophageal symptoms was perceived as the most important factor influencing HRQoL. Other important factors identified as influencing HRQoL of BE patients were: use of medication, cancer worry, and trust in physicians and endoscopic procedures. Female gender and predisposition to anxiety and depression symptoms were associated with negative perceptions of the diagnoses of BE.

Gastroesophageal reflux symptoms

Nowadays it is common practice to treat patients with BE with a proton pump inhibitor (PPI). PPIs significantly reduce stomach acid production and symptoms often disappear completely. In studies, presented in this thesis, 88-100% of patients take their PPI as prescribed by their doctor. Therefore, the majority of patients included in the multi-center study experienced no gastroesophageal reflux symptoms (77.6%) and only 2.8% of patients reported severe symptoms. A previous study of Britton et al.[8] demonstrated higher values of moderate to severe acid regurgitation (10%) and heartburn (11.2%). However, the comparison of these data must be interpreted with caution since different PROMs tools were used. The study described in **chapter 6** found that patients with symptoms of gastroesophageal reflux reported significantly more reflux symptoms than BE patients. A possible explanation for these results may be the lack of esophageal sensitivity in BE patients, which is instigated by significantly reduced esophageal acid sensitivity and an impaired ability to recognize acid reflux[9]. Patient reported outcomes on reflux symptoms in NDBE patients were compared with patients after endoscopic treatment (ET) for BE neoplasia. As expected, gastro-intestinal symptoms of dysphagia and regurgitation were more prevalent in patients within five months after endoscopic treatment. Similar as in the study of Britton et al[8] no statistical differences were found between the patients endoscopically treated and patients with non-dysplastic BE. We also explored the symptoms related to ET within the focus groups, as described in **chapter 2.** Patients indicated that they experienced just a few burdensome symptoms during the ET phase. Of these symptoms, pain in the first week after endoscopic procedures was the most stressful condition. Only patients with a complicated treatment phase, such as stenosis, for which dilatation is required, experienced the process of treatment as more burdensome. It was remarkable that several patients endoscopically treated for BE neoplasia reported less reflux and dyspepsia complaints after completing the process of ET. A possible explanation for this may be the fact that PPI was prescribed with a maximum dose of two times 40mg a day in all patients. Another explanation may be that the post radiofrequency ablation scarring has resulted in narrowing the Z-line with less regurgitation as a result. The majority still experienced mild daily symptoms of dysphagia, resulting in patients eating slower and chewing their food longer.

It is known that gastroesophageal reflux symptoms have a significant impact on HRQoL and has been associated with several functional deficiencies, such as sleeping difficulties, reduced ability to consume food, impaired sex life, and increased risk for a comorbid mental disorder[10,11]. Appropriately adjusted medical treatment is essential for reducing GERD related symptoms. Reporting higher levels of gastroesophageal reflux symptoms was associated with a negative illness perception of BE in **chapter 5**. When we further explored these symptoms within BE patients in **chapter 2**, experiencing symptoms of reflux at night was reported as the most bothersome. In general, symptoms of reflux, dyspepsia, regurgitation, and dysphagia were the important factors influencing HRQoL. Patients were aware of triggering foods and thus avoided drinking alcohol or orange juice, eating spicy or fatty food and eating late at night. The use of medication was highly prioritized in the list of factors improving HRQoL and there was a consensus within the focus groups that they cannot do without it. Simultaneously, patients indicated they are concerned about possible side effects from lifelong use of medication. Although, there is low evidence for an increased risk of osteoporosis, traveler's diarrhea and pneumonia in patients on the intensive care unit[13,] patients worry about non proven side effects as well. Reports on the Internet about possible side effects such as increased risk of dementia and low levels of vitamin B12 were mentioned and experienced as worrisome. Patients indicated that they would value to receive more information about this subject.

Cancer worry and anxiety

Cancer has been one of the most feared diseases for years as it is one of the leading causes of death worldwide[14]. Contrary to the negative image among the general public, epidemiological analyses show that cancer survival rates are gradually increasing. Comparable with numbers in Europe and the United States of America, the overall 5-year survival rate for esophageal cancer (EAC) in the Netherlands has risen from 8% in the early 1970s to 23% currently[15]. In the past decades, substantial progress has been made in the diagnosis and treatment of EAC. The introduction of high-definition endoscopy and advanced imaging techniques have improved the detection of early neoplasia. Patients with a BE diagnosis, approximately 5% will ultimately develop EAC[16]. When diagnosed with a pre-malignant condition, feelings of anxiety and panic may occur. Previous studies have shown it is difficult for individual patients to accurately estimate this cancer risk. A study from 2005 found that the majority of BE patients tend to overestimate their cancer risk[17]. These results contrast with our study descripted in **chapter 4**. In line with the study of Kruyshaar et al. from

2007[18] we found that most of BE patients underestimated their risk for developing EAC. A possible explanation for the difference between the Dutch studies and data from the USA may be due to culture differences, as well as differences in healthcare systems.

Misperception of cancer risk can have important behavioral and psychological consequences. For example, patients who overestimate their risk may be unnecessarily anxious and have high expectations of the benefits of surveillance. Consistent with the literature[12,17] our study found that overestimating cancer risk was associated with the presence of more symptoms of reflux and dyspepsia in patients. The presence of these symptoms in the overestimating group may have negatively influenced the findings of decreased HRQoL. Patients who underestimate their risk may overlook the potential benefits of surveillance. However, the study of Kruyshaar et al[18]. showed nearly all patients who perceived their cancer risk as low adhered to the endoscopic surveillance program.

Two studies in this thesis investigate the presence of cancer worry in patients with BE. The first study in **chapter 5** found a mean score of 9.14 on the cancer worry scale (an 8-item scale with a minimum worry score of 8 to maximum worry score of 32) indicating an overall low cancer worry. The second study in **chapter 6** further explored these results and compared a group of patients endoscopically treated for BE neoplasia and a group of patients with gastroesophageal reflux symptoms refractory for PPI. The reflux patients scored significantly worse on the cancer worry scale in comparison to BE patients. More specifically, 56.9% of reflux patients versus 31.8% of BE patients scored a high level of cancer worry. A possible explanation for these differences may be caused by the fact that patients with reflux symptoms refractory for PPI were administered the questionnaire prior to having had their first upper GI endoscopy. As a result, it is expected that these patients are experiencing higher levels of cancer worry caused by the lack of the reassurance of an upper GI endoscopy. An earlier study demonstrated that there are no cancer worry differences between a DBE group and NDBE group[8], which is in accordance with the results presented in this thesis. However, the overall scores of the DBE group in the UK study were higher (more cancer worry) than those in the present study. No clear explanation for this difference has been found, nevertheless they may be caused by differences in the health care systems and/or variances in the study populations (e.g. levels of education, ethnicities). The baseline characteristics of the two studies seem to correspond, but their education level and ethnicity were not described.

The levels of cancer worry in patients previously treated for BE neoplasia do not correlate with the time from treatment or the grade of dysplasia. Consistent with previous studies[19-21], we found that a younger age showed a small negative correlation with higher scores on the cancer worry scale. In addition, having a family member or friend with a history of EAC was also associated with a higher cancer worry. This association was also reported by BE patients included in the focus groups in **chapter 2**. Patients referred to the poor prognoses with an advanced EAC and the poor HRQoL in the final stage of life of these patients.

In addition to the statement of patients in the focus groups on the relationship between symptoms of pain, reflux or dysphagia and an increased fear of cancer. Experiencing reflux symptoms was moderately correlated with more cancer worry in the non-dysplastic BE group, as described in **chapter 5** and previous research[8]. Theoretical models of fear of cancer recurrence confirm that somatic symptoms can trigger fear[21,22]. Studies have consistently found that higher prevalence of post cancer symptoms is associated with greater fear of cancer recurrence[23,24].

A surprising finding in **chapter 6** was that only 33% of the patients endoscopically treated for EAC, indicate this as a cancer treatment in their medical history. Of the patients endoscopically treated for a high-risk EAC (lymfovascular invasion or >sm1) only 44.4% reported ET as cancer treatment. There are several possible explanations for this misinterpretation of the EAC diagnosis. First, the information given by the physician or nurse practitioner may not be adequately reproducible by patients. Second, a recent quantitative study showed that, the majority of participants associated a cancer diagnosis—or even the word cancer— with death and trepidation[25]. Endoscopic treatment and the minimal post-procedural symptoms may therefore not meet the expectations of a cancer diagnosis and the required treatment.

Next to anxiety surrounding an endoscopy, previous studies on anxiety in BE patients also reported a significantly higher anxiety scores in day-to-day life of these patients compared to the general population[26]. In the large multi-center study descripted in **chapter 5** we found that the anxiety scores were comparable to the Dutch general population. Although the deposition of anxiety was associated with a negative illness perception of the diagnosis BE. However, in comparison with a Chinese[12] and two studies from the UK[8,26] the population included in our multi-center study scored lower on the incidence of abnormal or borderline symptoms of anxiety (respectively 25.2%[12], 31%[8], 39%[26] vs. 16.3%). These differences may be explained by several cultural differences, especially when considering that the anxiety and depression norm data of several reference populations between countries differ. Hansschmidt et al.[27] found levels of depression and anxiety 3–5 times higher in the study sample than in the general population. This rather contradictory result may be due lack of information on the patients' disease characteristics i.e the presence of BE dysplasia or EAC in that specific study. Another possible explanation for this is that Hansschmidt reported high presence of GERD symptoms. In general, increased anxiety levels, are associated with greater severity of GERD symptoms such as retrosternal pain and retrosternal burning[28].

Trust in physician and surveillance endoscopy

Although, BE itself does not cause symptoms, the majority of BE patients are referred by their general practitioner with longstanding symptoms of heartburn and acid regurgitation. Once BE has been diagnosed, patients are offered surveillance endoscopy every 2–5 years, depending on the length of their BE. The patients included in the focus group study descripted in **chapter 2,** stated a minimal and temporary negative impact on their HRQoL at time of diagnosis, mainly due to uncertainties caused by a lack of knowledge about the diagnosis. Previous studies from the UK have shown that BE patients lack disease-specific knowledge, as well as showing that less than half of patients with BE-associated EAC knew about the diagnosis of BE despite multiple prior endoscopies [29,30]. This contrasts with our findings in **chapter 2 and 5** where a good understanding of the diagnosis of BE was found. Patients who experienced the need to be further informed, had questions and uncertainties about how to notice changes in the esophagus and when to contact their physician. It seems possible that differences in results are due to the fact that patients in our study were included from a referral center for Barrett's diagnostics and treatment. The majority of those patients received patient centeric information by a nurse practitioner about the diagnoses, treatment and importance of a surveillance endoscopy. Literature has shown that patient education improves medication compliance and persistence across a broad range of conditions and disease severity; and should be considered as an integral part of any disease management program[31].

A qualitative study found that BE patients who felt informed, respected, and experienced little or no discomfort during an EGD have a high degree of trust in their doctors and in the endoscopy center in general. Whilst patients who felt under-informed, disrespected, or experienced pain during an EGD often discussed a loss of trust in their doctors[32]. Trust in physicians and interpersonal interaction with staff was an important predictor of patients' intension to adhere to surveillance[26]. Patients included in our focus groups in **chapter 2** stated a high degree of trust in the medical team and the expertise of the physicians. Furthermore, patients appreciated easily accessible support provided by a nurse practitioner. Trust in the medical team and expertise of the physician in endoscopic procedures were reported as important factors for improved HRQoL and decreased fear of (recurrent) cancer. A recent meta-analysis demonstrated that in general patients reported more beneficial health behaviors, less symptoms, and higher quality of life when they had a higher level of trust in their health care professionals. The same authors also found a small, but significant correlation, between trust and health-related quality of life and symptom-related outcomes and a strong association between trust and patient satisfaction[34].

As mentioned earlier, undergoing an EGD is associated with higher levels of anxiety and distress before, and discomfort during the procedure[35]. However, these data are from 2006 and only 25% of the patients received sedation. The lack of sedation likely negatively affected these results, as the group that was sedated scored significantly better on all outcomes. A qualitative study in 20 BE patients reported that some patients indicated that the sedation was so effective that they slept throughout the procedure and felt little or no discomfort afterwards[33]. In **chapter 2** many patients acknowledged that the EGD allows them to monitor progression of BE to cancer and increases the likelihood of identifying cancer in an early stage. It is important to point out that patients included in the focus groups all underwent their EGD under sedation and reported no stress related to the EGD. Patients acknowledged that while they may tend to worry about BE, EGD gives them a sense of control. In this regard, the three-to-five-year interval between EGDs was perceived to be too long. Participants aged 70 years and older indicated that having to discontinue surveillance via EGD at age of 75 made them feel anxious. Participants would have preferred surveillance endoscopies to continue as long as health permits. Patients found it important to receive information about guidelines and arguments for the intervals or discontinuation of the surveillance endoscopies.

Several advanced imaging techniques have been introduced over the past two decades with the goal of improving the detection of neoplasia in BE - from traditional dye-spray chromoendoscopy to more practical virtual chromoendoscopy technologies and high-definition endoscopy,. However, detecting early neoplasia with these new techniques is challenging without adequate training. Further improvements in the quality of the endoscopy and in training are crucial to reduce the high miss rate for early neoplastic lesions[36]. Detection of both dysplasia and early adenocarcinoma enables curative endoscopic treatment, and to this end, profound endoscopic assessment is crucial and improves outcomes. The burden of missed neoplasia in BE is still far from negligible, probably due to inadequate knowledge and training in recognizing neoplastic lesions. As shown in other fields[37], artificial intelligence (AI) has revolutionized the field of diagnostic endoscopy and will play a central role in BE as well[38]. In **chapter 7** we investigated the perspectives (knowledge, experience, and opinion) on AI in healthcare amongst patients with gastrointestinal (GI) disorders, gastroenterologists, and GI-fellows. We showed there is a general positive perspective towards AI and AI implementation in healthcare, but GI-patients were more reserved compared to GI-physicians. GI-patients and GI-physicians agreed on the most important advantages of AI in healthcare, which are: improving quality of care, faster diagnostics and shorter waiting times. The most important disadvantage mentioned by GI-patients was the potential loss of personal contact. These results are confirmed by a qualitative study from Australia, who found patients preferred physician decision makers over AI decision makers, resulting in lower levels of trust when decisions were made by AI rather than by humans[39]. AI will only have a beneficial role in healthcare if patients and physicians are knowledgeable and supportive towards AI. Therefore, AI developments should be conducted in a patient and physician-centered manner. Misconceptions and perceived (dis)advantages should be conquered by better disseminating information in layman’s terms and by educating physicians and patients.

Patient reported outcome measurements

One of the most important steps in using PROMs in health systems is selecting the appropriate measure(s) for the purpose and context of the measurement. However, the availability of many different PROMs makes this choice rather difficult. In determining which

PROMs best to use in the BE population, we identified all the PROMs used for measuring HRQoL in BE patients and then evaluated each PROM from a patient's perspective.

The most relevant outcomes to BE patients were examined via a literature search and focus group discussions. In the literature study in **chapter 3** we evaluated 27 studies measuring HRQoL in BE patients. Within these studies, 32 different PROMs were used. Consequently, we found that a total of 9 studies (33.3%) used some form of non-validated questionnaires. Comparison and appreciation of PROMs between the various studies is therefore problematic. None of the all the 27 studies addressed more than 9 of the 18 factors important to patients with BE. Increasing the probability that important factors according to BE patients are missed.

The importance of the patient perspectives on the impact of disease and their response to treatment has being widely recognized. It is therefore of interest to note that the total number of interventional studies that used HRQoL measurements was relatively low. These findings are in contrast with the increased number of endoscopic therapeutic options for BE patients resulting in publications[40].

Since there is no BE-specific PROM available, the development of a new instrument seems inevitable. However, a wide variety of PROMs are already available, and the development of a new measurement tool is time-consuming and complex. Furthermore, the comparison with other diseases would not be possible. Using the "Patient-Reported Outcomes Measurement Information System" (PROMIS®) databank may be the right way forward. PROMIS is an easily accessible set of person-centered measures, using computerized adaptive testing from large item banks for over 70 domains relevant to a wide variety of chronic diseases[41,42]. PROMIS enables comparisons across populations and studies and can be integrated in several electronic health records. The eight PROMIS gastrointestinal (GI) symptom scales capture GI symptoms experienced by people with a wide range of digestive disorders. Unlike disease-targeted measures, which are designed for specific patient populations, the PROMIS GI symptom scales are system-targeted measures designed for anyone experiencing GI symptoms — whether patients or members of the population at large[43]. In **chapter 8** The PROMIS GI Symptom Scales were successfully translated into Dutch-Flemish. Sufficient structural validity was found for the PROMIS GI Scales Bowel Incontinence, Gas and Bloating and Belly Pain. Construct validity was sufficient for the Scales Gas and Bloating, Incontinence, Nausea and Vomiting, Reflux, Belly Pain, and Diarrhea. Although the scales are available on request, further research should be undertaken to investigate T-scores in a Dutch norm population and perform a cross-cultural validation study using differential item functioning (DIF) analysis.

References

1. Coleman HG1 BS, Murray LJ, McManus D, O'Neill OM, Gavin AT, Johnston BT. Symptoms and Endoscopic Features at Barrett's Esophagus Diagnosis: Implications for Neoplastic Progression Risk. Am J Gastroenterol. 2014
2. Crockett SD, Lippmann QK, Dellon ES, Shaheen NJ. Health-related quality of life in patients with Barrett's esophagus: a systematic review. Clin Gastroenterol Hepatol 2009; 7:613–623.
3. Mayo N. Dictionary of Quality of Life and Health Outcomes Measurement. Milwaukee, WI: International Society for Quality of Life Research; 2015
4. Britton J, Keld R, Prasad N, et al. Effect of diagnosis, surveillance, and treatment of Barrett's oesophagus on health-related quality of life. Lancet Gastroenterol Hepatol 2018;3:57–65. 9
5. McHorney CA, Ware JE and Raczek AE. The MOS 36item Short-Form Health Survey (SF-36):II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. MedCare 1993; 31: 247–263.
6. Ware JE Jr, Gandek B, Kosinski M, et al. The equivalence of SF-36 summary health scores estimated using standard and country-specific algorithms in 10 countries: Results from the IQOLA Project. International Quality of Life Assessment. J Clin Epidemiol 1998; 51: 1167–1170.
7. Chang CY, Lee LJH, Wang JD, Lee CT, Tai CM, Tang TQ, et al. Health-related quality of life in patients with Barrett's esophagus. Health Qual Life Outcome. 2016;14:158.
8. Britton J, Taxiarchi P, Martin G, Willert R, Horne M, Hamdy S, et al. Comparative quantitative survey of patient experience in Barrett's oesophagus and other gastrointestinal disorders. BMJ Open Gastroenterol. 2020(1):7.
9. Johnson DA, Winters C, Spurling TJ, Chobanian SJ, Cattau EL Jr. Esophageal acid sensitivity in Barrett's esophagus. J Clin Gastroenterol. 1987 Feb;9(1):23-7.
10. Wiklund I. Review of the quality of life and burden of illness in gastroesophageal reflux disease. Dig Dis. 2004; 22:108–14.
11. Lee Y-S, Jang B-H, Ko S-G, Chae Y. Comorbid risks of psychological disorders and gastroesophageal reflux disorder using the national health insurance service—National Sample Cohort: A STROBE-compliant article. Medicine (Baltimore). 2018; 97.

12. Lee SW, Lien HC, Chang CS, Ko CW, Tung CF, Yeh HZ. Health-related quality of life of subjects with Barrett's esophagus in a Chinese population. PLoS One. 2017 Dec 21;12(12):e0190201.

13. Haastrup PF, Thompson W, Søndergaard J, Jarbøl DE. Side Effects of Long-Term Proton Pump Inhibitor Use: A Review. Basic Clin Pharmacol Toxicol. 2018 Aug;123(2):114-121.

14. American Cancer Society. Global Cancer Facts & Figures 4th Edition. Atlanta: American Cancer Society; 2018.

15. Netherlands Comprehensive Cancer Organisation. https://iknl.nl/nieuws/2021/slokdarm-en-maagkanker-in-nederland-kerncijfers.

16. de Jonge PJF, van Blankenstein M, Grady WM, Kuipers EJ. Barrett’s oesophagus: epidemiology, cancer risk and implications for management. Gut. 2014;63:191–202.

17. Shaheen NJ, Green B, Medapalli RK, Mitchell K, Wei J, Schmitz S, et al. The perception of cancer risk in patients with prevalent Barrett's esophagus enrolled in an endoscopic surveillance program. Gastroenterology. 2005;129:429–36.

18. Kruijshaar ME, Siersema PD, Janssens ACJW et al. Patients with Barrett's esophagus perceive their risk of developing esophageal adenocarcinoma as low. Gastrointestinal Endoscopy, 2007; 65 (1): 26-30.

19. Simard S, Thewes B, Humphris G, et al. Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. J Cancer Surviv. 2013;7(3):300–322.

20. Yang Y, Sun H, Liu T, et al. Factors associated with fear of progression in chinese cancer patients: sociodemographic, clinical and psychological variables. J Psychosom Res. 2018;114:18–24.

21. Hartl K, Janni W, Kästner R, et al. Impact of medical and demographic factors on long-term quality of life and body image of breast cancer patients. Ann Oncol. 2003;14(7):1064–1071.

23. Heathcote LC, Eccleston C. Pain and cancer survival: a cognitive-affective model of Symptom appraisal and the uncertain threat of disease recurrence. Pain.2017;158(7):1187-1191.

23. Fardell JE, Jones G, Smith AB, et al. Exploring the screening capacity of the Fear of Cancer Recurrence Inventory- Short Form for clinical levels of fear of cancer recurrence.PsychoOncol.2018;27(2):492-499.

24. Crist JV, Grunfeld EA. Factors reported to influence fear of recurrence in cancer patients: a systematic review: Psycho Oncol 2013;22(5):978-986.

25. Robb KA, Simon AE, Miles A, Wardle J. Public perceptions of cancer: a qualitative study of the balance of positive and negative beliefs. BMJ Open. 2014 Jul 10;4(7):e005434.

26. Cooper SC, El-agib A, Dar S, Mohammed I, Nightingale P, Murray IA, et al. Endoscopic surveillance for Barrett's oesophagus: the patients' perspective. Eur J Gastroenterol Hepatol. 2009;21(8):850–4.

27. Hanschmidt F, Treml J, Kreuser N, Gockel I, Kersting A. Anxiety and depression in patients with Barrett's esophagus: estimates of disorder rates and associations with symptom load and treatment seeking. Eur J Gastroenterol Hepatol. 2021;33(6):825–31.

28. Kessing BF, Bredenoord AJ, Saleh CM, Smout AJ. Effects of anxiety and depression in patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol. 2015;13(6):1089–95.e1.

29. Murphy SJ, Anderson LA, Johnston BT, et al. Patients with Barrett esophagus have poor understanding of the diagnosis and its implications. J Clin Gastroenterol 2008;42:431–2.

31. Britton J, Hamdy S, McLaughlin J, et al. Barrett's oesophagus: a qualitative study of patient burden, care delivery experience and follow-up needs. Health Expect 2019;22:21–33.

31. Gold DT, McClung B. Approaches to patient education: emphasizing the long-term value of compliance and persistence. Am J Med. 2006 Apr;119(4 Suppl 1):S32-7.

32. Hinojosa-Lindsey M, Arney J, Heberlig S, et al. Patients' intuitive judgments about surveillance endoscopy in Barrett's esophagus: a review and application to models of decision-making. Dis Esophagus 2013;26:682–9.

33. Arney J, Hinojosa-Lindsey M, Street RL Jr, Hou J, El-Serag HB, Naik AD. Patient experiences with surveillance endoscopy: a qualitative study. Dig Dis Sci. 2014 Jul;59(7):1378-85.

34. Birkhäuer J, Gaab J, Kossowsky J, Hasler S, Krummenacher P, Werner C, Gerger H. Trust in the health care professional and health outcome: A meta-analysis. PLoS One. 2017 Feb 7;12(2):e0170988.

35. Kruijshaar ME, Kerkhof M, Siersema PD, et al. The burden of upper gastrointestinal endoscopy in patients with Barrett’s esophagus. Endoscopy. 2006; 38:873–878.

36. Codipilly DC, Chandar AK, Singh S, Wani S, Shaheen NJ, Inadomi JM, Chak A, Iyer PG. The Effect of Endoscopic Surveillance in Patients With Barrett's Esophagus: A Systematic Review and Meta analysis. Gastroenterology. 2018;154:2068–2086.e5

37. Nelson, C. A. et al. Patient perspectives on the use of artificial intelligence for skin cancer screening: A qualitative study. JAMA Dermatol. 156, 501–512.

38. Struyvenberg MR, de Groof AJ, Bergman JJ, van der Sommen F, de With PHN, Konda VJA, Curvers WL. Advanced Imaging and Sampling in Barrett's Esophagus: Artificial Intelligence to the Rescue? Gastrointest Endosc Clin N Am. 2021 Jan;31(1):91-103.

39. Formosa, P., Rogers, W., Griep, Y., Bankins, S. & Richards, D. Medical AI and human dignity: Contrasting perceptions of human and artificially intelligent (AI) decision making in diagnostic and medical resource allocation contexts. Comput. Hum. Behav. 133, 107296.

40. Tavankit, S., Madhusudhan, R. S., & Prashanthi, N. T. (2018). Endoscopic therapy for Barrett's esophagus and early esophageal cancer: Where do we go from here? World Journal of Gastrointestinal Endoscopy, 10(9), 165–174.

41. Cella, D., Yount, S., Rothrock, N., Gershon, R., Cook, K., Reeve, B., Ader, D., Fries, J. F., Bruce, B., & Rose, M. (2007). The patient-reported outcomes measurement information system (PROMIS): Progress of an NIH roadmap cooperative group during its first two years. Medical Care, 45, S3–S11.

42. Witter, J. P. (2016). Introduction: PROMIS a first look across diseases. Journal of Clinical Epidemiology, 73, 87–88.

43. Spiegel BM, Hays RD, Bolus R, et al. Development of the NIH Patient-Reported Outcomes Measurement Information System (PROMIS) gastrointestinal symptom scales. Am J Gastroenterol. 2014 Nov;109(11):1804-14.

CHAPTER 10

English summary

Barrett’s esophagus (BE) is a condition in the lower part of the esophagus, caused by gastro esophageal reflux disease. It is considered to be a premalignant condition, due to its association with an increased risk in developing esophageal adenocarcinoma (EAC). The relative risk of EAC in persons with non-dysplastic BE is 30 to 125 times higher than that of the general population, however, their absolute risk is low (approximately 0.5% per year). As recommended in current guidelines, patients with a non-dysplastic BE should undergo an upper gastrointestinal endoscopic surveillance every 2–5 years until the age of 75. BE has been associated with a significant decrease of health related quality of life (HRQoL), measured with both generic and disease-targeted instruments. However, the majority of studies on HRQoL of BE patients and their perceptions on the symptoms, treatment and diagnostics for BE are dated before 2008. Since then, diagnostics have improved and endoscopic treatment options have increased. High-definition endoscopes, processors and displays, chrome endoscopy and artificial intelligence (AI) are enabling the earlier detection of neoplasia. This timely detection allows the early neoplasia to be treated endoscopically (e.g. endoscopic resection and radiofrequency ablation) and thus preventing invasive surgery . Therefore, previously published data on HRQoL cannot be reliably compared with current patient care and may not accurately reflect the patients' current perceptions of the diagnosis of BE.

The aim of this dissertation was to provide further insights into HRQoL and patients perceptions on the diagnosis of Barrett’s esophagus. Associated symptoms as well as perception on cancer risks and the use of artificial intelligence were evaluated. Furthermore, it provides insight on how to measure HRQoL in patients with BE.

In **chapter 2**, we performed a qualitative study with a focus group design. A total of 34 patients with non-dysplastic Barrett and patients endoscopically treated for early neoplasia participated in four focus group sessions. In general, BE patients experienced a good HRQoL, with a minimal emotional burden from the diagnosis of BE. Experiencing symptoms was rated as the most important factor by both groups. Other factors identified as important HRQOL influencers were: use of medication, fear of cancer and trust in physicians and endoscopic procedures.

In order to investigate whether the factors deemed important by BE patients are actually included in the instruments measuring HRQoL in BE patients, we performed a systematic review in **chapter 3**. A comprehensive search was performed to identify all patient reported outcome measurement (PROM) tools used for measuring HRQoL in BE patients. Also, to identify factors influencing HRQoL according to BE patients and to evaluate each PROM from a patients’ perspective. Amongst the 27 studies reviewed, a total of 32 different HRQoL tools were identified. None of these instruments were designed or validated for use on BE patients. Four qualitative studies were identified exploring factors influencing HRQoL in the perceptions of BE patients. These influencing factors included fear of cancer, anxiety, trust in physician, sense of control, uncertainty, worry, burden of endoscopy, knowledge and understanding, gastrointestinal symptoms, sleeping difficulties, diet and lifestyle, use of medication, and support of family and friends. None of the quantitative studies measuring HRQoL in BE patients sufficiently reflected the perceptions of HRQoL in BE patients. Only gastrointestinal symptoms and anxiety were addressed in the majority of the studies.

BE affects patients' quality of life and may be a psychological burden due to the fear of developing an EAC. In **chapter 4** we described a cross-sectional questionnaire study which included 158 patients with a non-dysplastic BE. Based on their annual and lifetime EAC risk estimations measured with the Magnifier Scale, patients were classified as overestimating or underestimating their cancer risk. Associations between the groups where assessed based on demographics, reflux symptoms, results of the Outcomes Study Short-Form-36 (SF-36) and the Brief Illness Perception Questionnaire (B-IPQ). The annual EAC risk was overestimated by 41% of the patients. The overestimating patients reported lower mean scores on the SF-36 on the dimensions of: bodily pain, general health, vitality, physical functioning. In addition, the overestimating patients had a worse illness perception of the diagnosis of BE and experienced significantly more reflux symptoms.

As previously described, patients with BE may be at risk of psychological consequences such as depression and anxiety and decreased HRQoL. However, many of these studies were underpowered, single center and cannot be reliably compared with current patient pathways. In **chapter 5** we investigated HRQoL in non-dysplastic BE patients, and identified factors associated with a negative illness perception of the BE diagnosis. There is an increasing shift of care for BE patients to specialized BE centers. However, it is not clear if patients are experiencing better HRQoL-outcomes in hospitals specialized in BE surveillance and treatment. In the study descripted in chapter 5 we additionally compare outcomes between patients treated in a specialized BE center with non-expert centers. In this multi-center, cross-sectional study the HRQoL of non-dysplastic BE patients was assessed using the Short Form 36, Hospital Anxiety and Depression Scale, Cancer worry Scale, and Reflux Disease Questionnaire. A multivariable, linear regression analysis was conducted to assess factors associated with illness perception (using the Illness perception scale) of the BE diagnosis. This included a total of 859 non-dysplastic Barrett's esophagus patients (mean age of 63.6 years and 74.5% male), of which 640 were patients from BE expert centers. BE patients scored similar or higher means (i.e. better) on generic HRQoL in comparison to a Dutch norm population. The multivariable regression model showed that cancer worry, GERD symptoms, signs of anxiety and depression, as well as the female gender, were associated with a negative illness perception of BE. GERD symptoms were reported in the minority (22.4%) of BE patients. Levels of anxiety symptoms were comparable to a Dutch norm population (mean 3.7 vs. 3.9) and lower for depression symptoms (mean 6.8 vs.7.6). In general, no differences found in the outcomes between expert and non-expert centers.

Endoscopic treatment has become the preferred treatment for (early) neoplasia in a BE diagnosis. The treatment of this pre-malignant condition may trigger cancer worry. Reflux symptoms is known to be an important factor for the negative illness perception of BE. The aim of the study descripted in **chapter 6** was to assess the worry for cancer and reflux symptoms in patients endoscopically treated for (early) neoplasia. As well as comparing the outcomes with non-dysplastic BE patients and with patients with reflux symptoms only. A cross-sectional self-administered questionnaire study was performed using the cancer worry scale, and the reflux disease questionnaire. A total of 192 dysplastic BE patients, 213 non-dysplastic BE patients and 111 refractory reflux symptom patients were included (76.8% of participants were male with an average age of 66.9). High cancer worry was reported in 40.6% of the dysplastic BE patients and 36.2% of non-dysplastic BE patients. Reflux patients scored significant worse with 56.6% stated high cancer worry. A positive correlation was found between reflux symptoms and cancer worry in both non-dysplastic BE patients and reflux patients. In dysplastic BE patients correlations were also found between higher cancer worry and younger age and/or a (family) history of diagnosis of esophageal carcinoma.

Artificial intelligence (AI) is entering into our daily lives and has the potential to play a significant role in healthcare. In **chapter 7** we have investigated the perceptions (knowledge, experience, and opinion) on AI in healthcare among patients with gastrointestinal disorders, gastroenterologists, and gastrointestinal-fellows. In this prospective questionnaire study 377 gastrointestinal-patients, 35 gastroenterologists, and 45 gastrointestinal-fellows participated. Of the gastrointestinal-patients, 62.5% reported to be familiar with AI whilst 25.0% of gastrointestinal physicians indicated work-related experience with AI. Gastrointestinal-patients preferred their physicians to use AI (mean 3.9 on 5-point Likert-scale) and physicians indicated a wiliness to use AI (mean 4.4 on 5-point Likert-scale). More physicians believed AI leads to an increased quality of care (81.3%) compared to gastrointestinal patients. Fellows expected AI implementation within 6.0 years, gastroenterologists within 4.2 years, and gastrointestinal-patients within 6.1 years. Gastrointestinal patients and physicians agreed on the most important advantages of AI in healthcare. These being improving quality of care, and faster diagnostics and shorter waiting times. The most important disadvantage for patients was the potential loss of personal contact, whilst physicians concerns were insufficiently developed IT infrastructures. In summary, both gastrointestinal-patients and physicians hold positive perspectives towards AI and AI implementation in healthcare.

The importance of patient perceptions on the impact of the disease and response to treatment is being widely recognized. Measuring patients reported outcomes on gastrointestinal symptoms over the past two decades has led to development of over 100 disease-targeted PROMs. However, the field remains in need of a standardized, rigorously developed, electronically administered set of PROs that span the breadth and depth of gastrointestinal symptoms, which can be used across all gastrointestinal disorders for clinical and research purposes. In **chapter 8** we developed a Dutch-Flemish version of the PROMIS Gastrointestinal (GI) symptom scales and evaluated their psychometric properties in patients with BE, inflammatory bowel disease and irritable bowel syndrome. Sufficient structural validity was found for the PROMIS GI Scales Bowel Incontinence, Gas and Bloating and Belly Pain. Construct validity was sufficient for the Scales Gas and Bloating, Incontinence, Nausea and Vomiting, Reflux, Belly Pain, and Diarrhea.

In **chapter 9** the main findings on HRQoL and the factors influencing this HRQoL according to BE patients as descripted in this thesis were discussed in depth by comparing our results with the findings of (recently) published literature. We concluded that HRQoL in BE patients was similar compared to an age and gender match norm population. Experiencing esophageal reflux symptoms, cancer worry, (disposition of) anxiety were pointed out as the most important factors influencing HRQoL. Furthermore, we emphasized the importance of trust in the treating physician and adequate communication to the patient.

CHAPTER 11

Nederlandse samenvatting

Een Barrett slokdarm is een aandoening van het onderste deel van de slokdarm, veroorzaakt door gastro-oesofageale refluxziekte. Het wordt beschouwd als een premaligne aandoening, vanwege de associatie met een verhoogd risico op de ontwikkeling van een adenocarcinoom van de slokdarm. Het relatieve risico voor het ontstaan van een adenocarcinoom in de slokdarm bij personen met een niet-dysplastisch Barrett slokdarm is 30-125 maal hoger dan dat van de algemene bevolking; hun absolute risico is echter laag (ongeveer 0,3-0,5% per jaar). Zoals aanbevolen in de huidige richtlijnen moeten patiënten met een niet-dysplastisch Barrett slokdarm tot aan de leeftijd van 75 jaar oud, iedere 2 tot 5 jaar een endoscopische controle (gastroscopie) van het bovenste deel van het maag-darmkanaal ondergaan.

Kwaliteit van leven van Barrett patiënten, gemeten met zowel generieke- als gezondheid specifieke instrumenten, tonen significante lagere scores dan een algemene populatie. De meeste studies naar gezondheid gerelateerd kwaliteit van leven en patiënten percepties over symptomen, behandeling en diagnostiek dateren echter van vóór 2008. Sindsdien is de diagnostiek verbeterd en zijn de endoscopische behandelmogelijkheden van Barrett toegenomen. HD-endoscopen, HD-processoren, HD-beeldschermen en virtuele-, chromo-endoscopie, vergroten de vroegtijdige detectie van neoplasie. Door deze vroege detectie kan deze neoplasie vervolgens worden behandeld middels endoscopische behandeling (bijvoorbeeld endoscopische resectie en/of radiofrequente ablatie) en kan een invasieve operatie worden voorkomen. Eerder gepubliceerde uitkomsten over gezondheid gerelateerd kwaliteit van leven kunnen daarom niet betrouwbaar worden gegeneraliseerd met de huidige patiënten en weerspiegelen de resultaten mogelijk niet accuraat de huidige perceptie van patiënten over de diagnose Barrett slokdarm.

Het doel van dit proefschrift was om meer inzicht te verschaffen in gezondheid gerelateerde kwaliteit van leven en perspectieven van patiënten op de diagnose Barrett slokdarm. Zowel symptomen geassocieerd met een Barrett, als de perceptie van kankerrisico's en kunstmatige intelligentie werden geëvalueerd. Verder geeft het inzicht in hoe gezondheid gerelateerde kwaliteit van leven te meten bij patiënten met een Barrett slokdarm.

In **hoofdstuk 2** wordt een kwalitatieve studie met een focusgroep design beschreven. In totaal namen 34 patiënten met niet dysplastisch Barrett en patiënten die endoscopisch werden behandeld voor een vroege neoplasie deel aan vier focusgroep sessies. In het algemeen ondervonden patiënten met een Barrett slokdarm een goed gezondheid gerelateerde kwaliteit van leven, met een minimale emotionele belasting door de diagnose Barrett slokdarm. Het ervaren van symptomen werd in beide groepen als belangrijkste belemmerende factor gewaardeerd. Andere factoren die als belangrijke gezondheid gerelateerde kwaliteit van leven beïnvloedende factoren werden aangemerkt waren: medicijngebruik, angst voor kanker en vertrouwen in artsen en in de endoscopische procedures.

Om te onderzoeken of de factoren die door patiënten met een Barrett-slokdarm als belangrijk zijn gewaardeerd ook daadwerkelijk werden opgenomen in de eerder gebruikte instrumenten voor het meten van kwaliteit van leven, is er in **hoofdstuk 3** een systematische literatuurstudie uitgevoerd om alle instrumenten voor het meten van gezondheid gerelateerd kwaliteit van leven bij Barrett slokdarm patiënten te identificeren. Daarnaast zijn factoren geïdentificeerd die volgens Barrett slokdarm patiënten gezondheid gerelateerde kwaliteit van leven beïnvloeden. Als laatste is elk instrument (PROM) geëvalueerd vanuit het perspectief van Barrett patiënten. Onder de 27 studies, welke kwaliteit van leven bij Barrett patiënten onderzochten, werden in totaal 32 verschillende PROMs geïdentificeerd. Geen van deze instrumenten was ontworpen of gevalideerd voor gebruik bij Barrett slokdarm patiënten. Er werden vier kwalitatieve studies geïdentificeerd die factoren onderzochten die de gezondheid gerelateerde kwaliteit van leven beïnvloeden in de perceptie van Barrett-slokdarm patiënten. Deze factoren waren zorgen voor kanker, angst, vertrouwen in de arts, gevoel van controle, onzekerheid, zorgen, belasting van de endoscopie, kennis en begrip, maag- en slokdarm symptomen, slaapproblemen, dieet en levensstijl, gebruik van medicatie en steun van familie en vrienden. Geen van de kwantitatieve studies die gezondheid gerelateerde kwaliteit van leven bij Barrett-slokdarm patiënten meten, weerspiegelde accuraat de perceptie van Barrett slokdarm patiënten op het gezondheid gerelateerde kwaliteit van leven. Met name gastro-intestinale symptomen en angst kwamen in de meeste studies aan bod.

Een Barrett-slokdarm beïnvloedt mogelijk de kwaliteit van leven van patiënten en kan een psychologische belasting vormen vanwege de dreigende ontwikkeling van een slokdarm adenocarcinoom. In **hoofdstuk 4** werd een cross-sectioneel vragenlijst onderzoek beschreven, waaraan 158 patiënten met een niet-dysplastisch Barrett slokdarm deelnamen. Op basis van hun schatting van het jaarlijkse- en levenslange risico op een slokdarm adenocarcinoom, werden de patiënten ingedeeld in groepen die hun kankerrisico overschatten of onderschatten. Associaties tussen de groepen werden beoordeeld op demografische gegevens, de aanwezigheid van reflux symptomen, resultaten van de Outcomes Study Short-Form-36 (SF-36) en de Brief Illness Perception Questionnaire (B-IPQ). Door 41% van de patiënten werd het jaarlijkse risico op slokdarm adenocarcinoom overschat. Patiënten die het kankerrisico overschatte rapporteerden lagere scores op de SF-36 domeinen: lichamelijke pijn, algemene gezondheid, vitaliteit en fysiek functioneren. Bovendien ervaarde de overschattende patiënten een meer negatieve ziekteperceptie over de diagnoses Barrett oesophagus en rapporteerde zij significant meer reflux symptomen.

Zoals eerder beschreven, hebben patiënten met een Barrett slokdarm mogelijk een hoger risico op psychologische gevolgen zoals depressie, angst en een verminderde gezondheid gerelateerde kwaliteit van leven. Echter veel van deze studies includeerde een laag aantal patiënten en veelal vanuit één enkel centrum. In **hoofdstuk 5** onderzochten we ziekte gerelateerd kwaliteit van leven bij patiënten met een niet-dysplastische Barrett slokdarm en identificeerden we factoren die samenhangen met een negatieve ziekteperceptie van de Barrett slokdarm diagnose. Er is een toenemende verschuiving van zorg voor Barrett slokdarm patiënten naar gespecialiseerde Barrett centra. Het is echter niet duidelijk of patiënten behandeld in een expertise centrum voor Barrett betere gezondheid gerelateerde kwaliteit van leven ervaren. In de studie beschreven in **hoofdstuk 5** werden de uitkomsten vergeleken tussen patiënten behandeld in een gespecialiseerd Barrett centrum en niet-gespecialiseerde centra. In deze multi-center, cross-sectionele studie werd gezondheid gerelateerde kwaliteit van leven van niet-dysplastische Barrett-slokdarm patiënten beoordeeld met behulp van de vragenlijsten: Short Form 36 (generiek) , Hospital Anxiety and Depression Scale (angst en depressie), Cancer worry Scale (zorgen om kanker), en Reflux Disease Questionnaire (reflux symptomen). Een multivariabele, lineaire regressieanalyse werd uitgevoerd om factoren te identificeren die samenhangen met ziekteperceptie (Illness perception scale) van de Barrett slokdarm diagnose. In totaal werden 859 patiënten met een niet-dysplastische Barrett slokdarm geïncludeerd (gemiddelde leeftijd 63,6 jaar en 74,5% man), waarvan 640 uit Barrett expertisecentra. Barrett slokdarm patiënten scoorden vergelijkbare of hogere gemiddelden scores (d.w.z. beter) op generiek gezondheid gerelateerd kwaliteit van leven in vergelijking met een Nederlandse normpopulatie. Het multivariabele regressiemodel liet zien dat zorgen over kanker, gastro-intestinale symptomen, tekenen van angst en depressie en het vrouwelijk geslacht geassocieerd waren met een negatieve ziektebeleving van een Barrett slokdarm. Gastro-intestinale symptomen werden gerapporteerd in de minderheid (22,4%) van de Barrett slokdarm patiënten. Gemiddelde scores van angstsymptomen waren vergelijkbaar met een Nederlandse normpopulatie (3,7 versus 3,9) en lager voor depressiesymptomen (gemiddeld 6,8 versus 7,6). Over het geheel genomen werden er geen verschillen gevonden in uitkomsten tussen de Barrett expertise centra en de centra zonder Barrett expertise.

Endoscopische behandeling is de voorkeursbehandeling voor (vroege) neoplasie in een Barrett slokdarm. De diagnose en behandeling van deze premaligne aandoening zouden kunnen leiden tot bezorgdheid over kanker. Refluxklachten staan bekend als een belangrijke factor voor negatieve ziekteperceptie bij Barrett patiënten. Het doel van de studie beschreven in **hoofdstuk 6** was het beoordelen van zorgen over kanker en refluxklachten bij patiënten die endoscopisch werden behandeld voor een niet-dysplastische Barrett slokdarm in vergelijking met patiënten met alleen refluxklachten. Het betrof een cross-sectionele vragenlijst studie, waarbij gebruik werd gemaakt van de Cancer worry scale (vragenlijst over zorgen over kanker) en de Reflux Disease Questionnaire (vragenlijst over reflux symptomen). In totaal werden 192 endoscopisch behandelde Barrett patiënten, 213 niet-dysplastische Barrett slokdarm patiënten en 111 patiënten met reflux klachten geïncludeerd; 76,8% van de deelnemers was man met een gemiddeld leeftijd van 66,9 jaar. Er werd een hoge mate van zorgen om kanker gemeld door 40,6% van de patiënten met een dysplastisch Barrett slokdarm en 36,2% door de niet-dysplastische Barrett slokdarm patiënten. Reflux patiënten scoorden significant slechter: 56,6% gaf aan zich ernstig zorgen te maken over kanker. Bij patiënten met een niet dysplastisch Barrett slokdarm en refluxpatiënten werden positieve correlaties gevonden tussen reflux symptomen en zorgen over kanker. Bij dysplastische Barrett slokdarm patiënten werden correlaties gevonden tussen een hogere bezorgdheid

over kanker en een jongere leeftijd en de aanwezigheid van een (familie)geschiedenis met de diagnose slokdarmcarcinoom.
Kunstmatige intelligentie (AI) doet zijn intrede in het dagelijks leven en heeft daarnaast het potentieel om een belangrijke rol te spelen in de gezondheidszorg. In **hoofdstuk 7** werd bij patiënten met gastro-intestinale aandoeningen, gastro-enterologen en gastro-enterologen in opleiding de perspectieven (kennis, ervaring en mening) op AI in de gezondheidszorg onderzocht. Aan deze prospectieve vragenlijst studie namen 377 gastro-enterologie patiënten, 35 gastro-enterologen en 45 gastro-enterologen in opleiding deel. Van de gastro-intestinale patiënten gaf 62,5% aan bekend te zijn met AI en 25,0% van de gastro-intestinale artsen had werk gerelateerde ervaring met AI. Gastro-intestinale patiënten staan positief tegenover het gebruik van AI door hun artsen (gemiddeld 3,9 op een 5-punts Likertschaal) en ook artsen waren bereid AI te gebruiken (gemiddeld 4,4). Artsen hadden meer geloof in een toename van de kwaliteit van zorg (81,3%) dan gastro-intestinale patiënten. Gastro-enterologen in opleiding verwachtten AI-implementatie binnen 6 jaar, gastro-enterologen binnen 4.2 jaar, en gastro-intestinale patiënten binnen 6.1 jaar. Gastro-intestinale patiënten en artsen waren het eens over de belangrijkste voordelen van AI in de zorg, namelijk: verbetering van de kwaliteit van zorg, tijdsbesparing en snellere diagnostiek en kortere wachttijden. Het belangrijkste nadeel van gebruik van AI in de zorg voor patiënten was het mogelijke verlies van persoonlijk contact, voor artsen was dit onvoldoende ontwikkelde IT-infrastructuren. Kortom, gastro-intestinale patiënten en artsen staan positief tegenover AI in de gezondheidszorg.

Het belang van patiënten perspectieven op de impact van ziekte en respons op behandeling wordt steeds meer erkend. Voor het meten van patiënten perspectieven op gastro-intestinale symptomen hebben onderzoekers de afgelopen twee decennia meer dan 100 ziektegerichte PROMs ontwikkeld. Het veld heeft echter nog steeds behoefte aan een gestandaardiseerde, grootschalig ontwikkelde en elektronisch beheerde set van PROs die gastro-intestinale symptomen in zijn geheel omvat en kan worden gebruikt voor alle gastro-intestinale aandoeningen voor klinische en onderzoeksdoeleinden. In **hoofdstuk 8** ontwikkelden we een Nederlands-Vlaamse versie van de PROMIS Gastro-intestinale symptoom schalen en evalueerden we de psychometrische eigenschappen bij patiënten met een refluxklachten of Barrett slokdarm, inflammatoire darmziekten en prikkelbare darmsyndroom. Er werd een voldoende structurele validiteit gevonden voor de PROMIS GI-schalen Darmincontinentie, Gas en Opgeblazen gevoel en Buikpijn. De constructvaliditeit was voldoende voor de schalen Gas en Opgeblazen gevoel, Incontinentie, Misselijkheid en Braken, Reflux, Buikpijn en Diarree.
In **hoofdstuk 9** werden de belangrijkste bevindingen uit dit proefschrift samengevat en bediscussieerd. Studies met betrekking tot gezondheid gerelateerde kwaliteit van leven bij patiënten met een Barrett slokdarm en de factoren die deze beïnvloedt werden diepgaand besproken. Dit is gedaan door de resultaten uit dit thesis te combineren met de bevindingen

van (recent) gepubliceerde literatuur. Er werd geconcludeerd dat de gezondheid gerelateerde kwaliteit van leven van patiënten met een Barrett slokdarm vergelijkbaar is met die van een normpopulatie gematched op basis van leeftijd en geslacht. Het ervaren van reflux klachten, zorgen over kanker, (dispositie van) angst werden aangewezen als belangrijkste factoren die de gezondheid gerelateerde kwaliteit van leven beïnvloeden. Verder werd er benadrukt wat het belang is van vertrouwen in de behandelend arts en een goede communicatie met de patiënt.

CHAPTER 12

Impact paragraph

Gastroesophageal reflux is common in western countries with a prevalence of 18.1%–27.8% in North America and 8.8%–25.9% in Europe. Barrett's esophagus (BE) is known to be a result of longstanding gastroesophageal reflux disease (GERD). However, only a small proportion (10-15%) of patients with GERD are at risk of developing BE[1]. The diagnosis of BE is made if the distal esophagus is lined with columnar epithelium with a minimum length of 1cm (tongues or circular) containing intestinal metaplasia at histopathological examination[2]. BE affects 2–7% of adults in Western countries[3] and is predominantly diagnosed in middle-aged white men[4,5,6]. Other factors associated with the development of BE is a family history with BE, current or past smoking and being overweight. BE is a pre-malignant condition that places patients at risk for developing esophageal adenocarcinoma (EAC). The relative risk of EAC in patients with non-dysplastic BE is 30–125 times higher compared to the general population. Patients therefore undergo regular endoscopic surveillance for early detection of malignant transformation. Although early detection may lead to improved survival, the absolute risk for malignant transformation is low (approximately 0.3–0.5% per year)[7,8]. When diagnosed with a pre-malignant condition, the message can cause anxiety and uncertainties to the patient. The importance of patient perceptions on the impact of the disease and response to treatment is being widely recognized. Illness perception is descripted by Broadbent as a patient's cognitive appraisal and personal understanding of a medical condition and its potential consequences[9]. This may include both positive and negative illness beliefs that can influence the ability to cope with the disease and to perceive it as manageable or threatening [10].

The main goal for this thesis was to gain more insight into health-related quality of life (HRQoL) and perceptions of patients with a Barrett's esophagus on associated symptoms, cancer risks and the use of artificial intelligence. Furthermore, to provide healthcare professionals knowledge on how to measure HRQoL in patients with BE. The perceptions of patients were investigated using a variety of research techniques (focus groups, cross-sectional self-administered questionnaire studies, a multi-center study and a literature review). The results of the studies outlined in this dissertation have been published or submitted in international peer-reviewed journals in gastro-enterology or quality of life. In addition, the study findings were presented at (inter)national congresses including Digestive Disease Days (DDD, Veldhoven, The Netherlands), Digestive Disease Week (DDW, Washington, USA) and the United European Gastroenterology Week (UEGW, Vienna, Austria)

Implications for patients

Patient perceptions have been the main focus in this thesis. Gaining more insight into which factors are influencing the lives of BE patients will benefit the patients through a more patient centered care. The identification of patient’s perceptions can be helpful to healthcare professionals in better understanding patient’s needs and delivering more patient centered care. Results of the focus group discussions (chapter 2) and its systematic review (chapter 3) found that BE patients perceive having trust in their healthcare professionals and receiving adequate information on the diagnosis are highly important. It was even indicated that having a good relationship with healthcare professionals reduced their cancer worry. We, therefore, encourage patients to ask their physician the questions: “What are my treatment or surveillance options?”, “What are the advantages and disadvantages of these options?”, “What does this mean for my situation?” These questions will invite the physician to provide adequate information and leads to an more open conversation. Shared decision making starts with the realization by the medical specialist and the patient that they need each other. The medical specialist has the medical knowledge, and patients are specialized on their personal situation.

Patients with a good reflux symptom control were found to report less negative illness perceptions on the diagnosis of Barrett (chapter 5), higher (e.g. better) HRQoL scores (chapter 5), a lower cancer risk perception (chapter 2 and 4) and low cancer worry (chapter 6). Furthermore, results from the focus group study confirmed that taking proton pomp inhibitors and a good reflux symptom control was perceived as an important factor for improving HRQoL. To prevent reflux related symptoms we would advise patients to use their proton pump inhibitors and to avoid certain foods (such as mint, fatty foods, spicy foods, tomatoes, onions, garlic, coffee, tea, chocolate, and alcohol). Furthermore, it is advised to sleep on an inclineand if necessary lose weight and /or quit smoking.

Implications for healthcare professionals

Healthcare professionals caring for patients with BE should be aware of the implications of this diagnosis. This thesis provides insights on the perceptions of the diagnoses of BE. These findings can be used for counselling in daily clinical practice. We would like to make healthcare professionals aware of the importance of communicating with patients on gastroesophageal reflux symptoms and treat with adequate medication as needed. Experiencing symptoms of gastroesophageal reflux in BE patients is related to overestimating their cancer risk (chapter 4), more cancer worry (chapter 6), lower generic HRQoL and worse illness perceptions on the diagnosis BE (chapter 5). This underlines the importance of awareness amongst physicians that less burden of gastroesophageal reflux symptoms will enhance quality of life and decrease cancer worry (chapter 6) in BE patients. When communicating with patients it is essential to provide BE patients information tailored to their personal needs. We recommend that physicians offer an easy and approachable contact opportunity for BE patients to discuss symptom flares or fear of cancer. Our results have shown that overall cancer worry scores were lower in BE patients who had undergone endoscopic treatment. These scores, however, were not correlated to time from treatment or histology. Therefore, it is a misconception that eliminating BE with endoscopic treatment may reduce cancer worry.

Previous studies have shown it is difficult for individual patients to accurately estimate their cancer risk, these findings were confirmed in chapter 4. None of the patients accurately estimated their annual cancer risk (59% underestimated and 41% overestimated), the lifetime risk was overestimated by 25% and 26% underestimated their cancer risk. Physicians should keep on communicating with patients about the actual low cancer risk. On the contrary, with the patients who underestimate their risk it is advised to discuss the importance of endoscopic surveillance. This will lead to greater patient understanding and may therefore positively affect health outcomes. In addition to the presence of cancer worry and gastroesophageal reflux symptoms, we found that anxiety and depression symptoms and the female gender were also associated with a negative illness perception of the diagnosis of BE.

Physicians, nurse practitioners, nurses and physician assistants should be aware that patients' trust in their healthcare professionals and endoscopic surveillance is perceived by BE patients as very important. BE patients rely on endoscopic surveillance for the early detection of EAC. Trust in the medical team and expertise of the physician in endoscopic procedures was reported as an imported factor improving HRQoL (chapter 2), which was most prominent in patients endoscopically treated for Barrett's neoplasia. However, patients are possibly too reliant on this reassurance and therefore healthcare professionals must, for this exact reason, be aware that discontinuing EGD at 75 years of age can make patients feel anxious. Patients interviewed in the focus groups found it important to receive information about guidelines and arguments for the intervals or discontinuation of the surveillance endoscopies.

Artificial intelligence (AI) is new development in clinical medicine and especially in gastrointestinal (GI) endoscopy. AI has the potential to improve the quality of GI endoscopy. We found that patients with gastrointestinal symptoms hold positive perceptions towards Artificial Intelligence (AI) and the implementation of AI in healthcare. The majority of GI-patients were not anxious about AI and thought the implementation of AI in healthcare will increase the quality of care. One third of patients was unfamiliar with AI, those patients stated a less positive perspective towards AI. Half of the GI patients reported beneficially to a virtual nurse, a technique that performs tasks normally conducted by nurses and is available at any time. AI will only play a significant role in healthcare if patients and physicians are knowledgeable and supportive towards AI.

Implications for research

Patient-reported outcomes (PROs), including HRQoL, measure the patient's health status from the patient's perspective. For the selection of PROMs, we encourage physicians and researchers measuring HRQoL to choose their PRO from a patient perspective and not strictly based on relevance according to health professionals' definitions. Using PROMs that are more patient-centered will enhance knowledge of the true impact of surveillance and endoscopic treatment on the (perceived) functioning of BE patients. In chapter 3 we have developed a conceptual framework on factors influencing HRQoL according to Barrett patients. This framework can be used by researchers to determine which construct to be measured. Within qualitative studies, the following factors influencing HRQoL were addressed by patients, namely: fear of cancer, anxiety, trust in physician, sense of control, uncertainty, worry, burden of endoscopy, knowledge and understanding, GI symptoms, sleeping difficulties, diet and lifestyle, use of medication, and support of family and friends. Furthermore, this thesis provides insights on how HRQoL has been measured in BE patients and provides healthcare professionals with an advice on which PROM's to choose. A combination of the disease-specific PROMs: GIQLI or GERD-HRQOL, with the CWS, TPS, the B-IPQ would be appropriate. However, this would necessitate a large number of questions to be addressed by patients. Using the "Patient-Reported Outcomes Measurement Information System" (PROMIS®) databank may be an appropriate solution for this problem. PROMIS is an easily accessible set of person-centered measures (www.promishealth.org), using computerized adaptive testing from large item banks for over 70 domains relevant to a wide variety of chronic diseases. PROMIS enables comparisons across populations and studies and can be integrated in several electronic health records. We advise clinicians to use the items: PROMIS GI (disrupted and swallowing, reflux and gas and bloating), PROMIS Anxiety, and PROMIS Self-Efficacy (Managing medications and treatment, Managing Symptoms). Our study on translation and validation of the Dutch-Flemish version of the PROMIS Gastrointestinal symptom scales (chapter 8) found good psychometric properties for the use in Barrett patients, but not only Barrett patients. Further research is required to validate the item bank against objective tests such as upper GI endoscopy, motility studies, or other diagnostics.

The studies in this thesis were almost entirely based on research with a cross-sectional design. Therefore, the associations and correlations that were found must be interpreted with some caution, because no causality has been investigated. Further research should be undertaken to investigate the causal factors that influence the HRQoL in BE patients. We advise to perform studies with a longitudinal design to develop a prediction model in HRQoL. Furthermore, we hope investigators in the field of endoscopic treatment of BE would integrate PROMs in their study protocol for randomized control trials. Further longitudinal research in patients treated with ET is needed to measure cancer worry and burden over time. Finally, it would be interested to perform a RCT in patients with negative illness perception on the diagnosis BE and determine the effect of treatment optimalisation or counseling.

The findings of this dissertation resulted in a collaboration between Mirjam van der Ende-van Loon and a group of researchers from the University of Cambridge. They are currently working on the project: ‘Psychological and behavioral aspects of Cytosponge screening for Barrett’s esophagus’. Cytosponge-trefoil factor 3 (TFF-3) testing is effective at identifying Barrett’s esophagus in people with acid reflux and heartburn. Within clinical trials, participants have reported high acceptability of the Cytosponge. However, past trials have not examined barriers to uptake or the psychological impact of a Barrett’s diagnosis in this context. Moreover, this project aims to understand the psychological outcomes and information needs of the potentially large numbers of people who may be diagnosed with Barrett’s, leading to long-term surveillance. Based on current clinical and research work, the PhD student Mirjam van der Ende- van Loon has been invited as an expert in the field of quality of life in BE patients to contribute to this project.

Implications for society

In addition to reporting important patient-reported outcome measures in studies presented in this thesis, the PhD student is dedicated to promoting research conducted by nurses. Florence Nightingale stated more than 150 years ago: “Let us never consider ourselves finished nurses…. we must be learning all of our lives". Research from the nursing perspective will provide more deepening in the advancement of healthcare. The findings from nurse led research can help shape health policy and global healthcare. The use of evidence-based practices by nurses improves standards of care. Patients rely on nurses for information to make informed decisions about their health. Furthermore, research helps to professionalize the nursing profession as it evolves with the needs of society and advances in medical science, and helps nurses provide effective, evidence-based care. The PhD student has given several lectures on nursing research to (inter)national nurses and donors of the Catharina Research Fund. In addition, an article was published in the Eindhovens Dagblad entitled, "Doctor maar geen arts” (Doctor but not a physician), and an interview with the PhD student about the nursing research was published in a magazine of the Catharina Hospital titled ‘trots’ (pride). By spreading her enthusiasm for research, the doctoral candidate hopes to inspire other nurses or Nurse Practitioners to start their own research project.

List of publications

Ende-van Loon, MCM. Bewuster omgaan met psychische gevolgen bij diagnose Barrett. Tijdschrift voor Verpleegkunde in praktijk en wetenschap. 2018 Jun: 49.

Ende-van Loon, MCM, Rosmolen WD, Houterman S, Schoon EJ, Curvers WL. Cancer risk perception in relation to associated symptoms in Barrett's patients: A cross sectional study on quality of life. United European Gastroenterol J. 2018 Nov; 6(9): 1316–1322.

I. C. Noordzij, **M.C.M. Van Loon van de Ende**, W.L. Curvers, G. van Lijnschoten, C.J. Huysentruyt, E.J. Schoon. Dysplasia in Random Biopsies from Barrett’s Surveillance Is an Important Marker for More Severe Pathology. Digestive Diseases and Sciences. 2020 Jul 13.

Renske A.B. Oude Nijhuis, Wouter L. Curvers, **Mirjam van der Ende**, Thomas V.K. Herregods, Jeroen M. Schuitenmaker, Andreas J.P.M. Smout and Albert J. Bredenoord, MD, PhD. Utility of Routine Esophageal Biopsies in Patients With Refractory Reflux symptoms. Am J Gastroenterol 2020;00:1–5.

van der Ende-van Loon M, Brouwers M, de Munnik S, Nieuwkerk P, Curvers W, Schoon E. Factors influencing health-related quality of life in patients with Barrett's esophagus: a qualitative focus group study. Eur J Gastroenterol Hepatol. 2021 Jan 18.

Gilissen LPL, Heinen SGH, Rijpma-Jacobs L, Schoon E, Schreuder RM, Wensing AM, van der **Ende-van Loon MCM**, Bloemen JG, Stapelbroek JM, Stronkhorst A. Neither inflammatory bowel disease nor immunosuppressants are associated with an increased risk of severe COVID-19: an observational Dutch cohort study. Clin Exp Med. 2021 Sep 20:1–12.

van der Ende-van Loon MCM, Stoker A, Nieuwkerk PT, Curvers WL, Schoon EJ. How are we measuring health-related quality of life in patients with a Barrett Esophagus? A systematic review on patient-reported outcome measurements. Qual Life Res. 2022 Jun;31(6):1639-1656.

van der Ende-van Loon MCM, Nieuwkerk PT, van Stiphout SHC, Scheffer RCH, de Ridder RJJ, Pouw RE, Alkhalaf A, Weusten BLAM, Curvers WL, Schoon EJ. Barrett Esophagus: Quality of life and factors associated with illness perception. United European Gastroenterol J. 2022 Jul 6.

van der Zander QEW, **van der Ende-van Loon MCM**, Janssen JMM, Winkens B, van der Sommen F, Masclee AAM, Schoon EJ. Artificial intelligence in (gastrointestinal) healthcare: patients' and physicians' perspectives. Sci Rep. 2022 Oct 6;12(1):16779.

Stoker AMH, Logghe L, **van der Ende-van Loon MCM**, Schoon EJ, Schreuder RM, Stronkhorst A, Gilissen LPL. Relapse rates after withdrawal versus maintaining biologic therapy in IBD patients with prolonged remission. Clin Exp Med. 2023 Jan 12:1–9.

Stoker AMH, Gruters A, **Loon MCMVE**, Postulart D, Czuber-Dochan W, Gilissen LPL. Translation, validation and psychometric properties of the Dutch version of the Inflammatory Bowel Disease-Fatigue (IBD-F) self-assessment scale. J Patient Rep Outcomes. 2023 Oct 30;7(1):108.

van der Ende-van Loon, M., Korteling, D., Willekens, H. et al. Dutch–Flemish translation and validation of the gastrointestinal symptom scales from the patient-reported outcomes measurement information system (PROMIS)®. J Patient Rep Outcomes 7, 125 (2023).

MCM van der Ende-van Loon, RAB. Oude Nijhuis MD, WL Curvers MD, EJ Schoon. Prevalence and associated factors of worry for cancer in patients with a Barrett's esophagus: .Sci Rep. 2024 Feb 4;14(1):2878.

Submitted

Nikki C.M. van Ham, Sofie Glazemakers, **Mirjam van der Ende-van Loon**, Grard A.P. Nieuwenhuijzen Harm J.T. Rutten, Jip L Tolenaar, Anne Jacobs, Jacobus W.A. Burger , Stijn H.J. Ketelaers, Johanne G. Bloemen. Factors Associated with One-Year Mortality after Curative Surgery for Primary Clinical T4 and Locally Recurrent Rectal Cancer in Older Patients .

Quirine Eunice Wennie van der Zander, Ramon M. Schreuder, Ayla Thijssen, Carolus HJ Kusters, Nikoo Dehghani, Thom Scheeve, Bjorn Winkens, **Mirjam CM van der Ende - van Loon**, Peter HN de With, Fons van der Sommen, Ad AM Masclee and Erik J Schoon. Artificial Intelligence for Characterization of Diminutive Colorectal Polyps: A Feasibility Study Comparing Two Computer-aided Diagnosis Systems

Scientific presentations

MCM van der Ende-van Loon, W. Rosmolen, EJ Schoon, S. Houterman, WL Curvers.
Barrett patients overestimating their esophageal cancer risk have more reflux symptoms and a decreased quality of life.

- Digestive Disease Days, Veldhoven, Netherlands, 2017 (oral presentation)
- Digestive Disease Week, Washington, United states of America, 2018 (poster presentation)

MCM van der Ende-van Loon
Inschatting van het kanker risico door patiënten met een Barrett slokdarm

- Digestive Disease Days, Veldhoven, Netherlands, 2017 (invited speaker)

MCM van der Ende-van Loon, M Brouwers, S de Munnik, P Nieuwkerk, W Curvers, E Schoon. Factors influencing health-related quality of life in patients with Barrett's esophagus: a qualitative focus group study.

- Digestive Disease Days, Online congres, Netherlands, 2021 (oral presentation)

MCM van der Ende-van Loon, PT Nieuwkerk, RAB Oude Nijhuis, SHC van Stiphout, RCH Scheffer, RJJ de Ridder, RE Pouw, A Alkhalaf, BLAM Weusten, WL Curvers, EJ Schoon.
Factors associated with health related quality of life in patients with Barrett Esophagus.

- 30th UEGW, Vienna, Austria,2022 (moderated poster presentation)

MCM van der Ende- van Loon. Quality of life in patients with a Barrett Esophagus – what nurses need to know-

- 30th UEGW, Vienna, Austria, 2022 (invited speaker)

References

1. Shaheen NJ, Falk GW, Iyer PG, Gerson LB American College of G. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol. 2016;111:30–50.

2. Weusten B, Bisschops R, Coron E, Dinis-Ribeiro M, Dumonceau JM, Esteban JM, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy 2017; 49:191–198.

3. Naini BV, Souza RF, Odze RD. Barrett's Esophagus: A Comprehensive and Contemporary Review for Pathologists. Am J Surg Pathol. 2016;40:e45–66

4. Rex DK, Cummings OW, Shaw M, et al. Screening for Barrett's esophagus in colonoscopy patients with and without heartburn. Gastroenterology 2003;125:1670–1677.

5. Ronkainen J, Aro P, Storskrubb T, et al. Prevalence of Barrett's esophagus in the general population: An endoscopic study. Gastroenterology. 2005;129:1825–1831.

6. Hayeck TJ, Kong CY, Spechler SJ, et al. The prevalence of Barrett's esophagus in the US: estimates from a simulation model confirmed by SEER data. Dis Esophagus. 2010;23:451–457.

7. Yousef, F., Cardwell, C., Galway, K., et al. (2008). The incidence of esophageal cancer and high-grade dysplasia in Barrett's Esophagus: A systematic review and meta-analysis. American Journal of Epidemiology*, 168*(3), 237–249.

8. Desai, T. K., Krishnan, K., Samala, N., et al. (2012). The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: A meta-analysis. Gut*, 61*, 970–976.

9. Broadbent E, Wilkes C, Koschwanez H, et al. (2015) A systematic review and meta-analysis of the brief illness perception questionnaire. Psychology & Health 30: 1361–1385.

10. Bonsaksen T, Lerdal A, Fagermoen MS. (2015) Trajectories of illness perceptions in persons with chronic illness: An explorative longitudinal study. Journal of Health Psychology 20: 942–953.

ADDENDUM

A

Dankwoord
Curriculum vitae

Dankwoord

Bij het schrijven van dit laatste deel van mijn thesis, kwamen verschillende herinneringen, van de afgelopen zes jaar die ik heb besteed aan het uitvoeren van mijn promotietraject, voorbij. Het is een bewogen hoofdstuk in mijn leven geweest, met al zijn ups en downs, maar ik ben trots en dankbaar dat ik deze reis heb mogen maken. Dit was niet mogelijk geweest zonder de steun van velen en daarom wil ik op deze wijze iedereen die (on)bewust heeft bijgedragen aan de totstandkoming van mijn proefschrift bedanken.

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Curriculum Vitae

Mirjam, Cornelia, Maria van der Ende- van Loon was born on April 3, 1982 in the Catharina Hospital in Eindhoven. She grew up in Son en Breugel and received her MAVO diploma in 1998 at the Christiaan Huygens College in Eindhoven. Following this she started nursing school at the Kempenpoort in Eindhoven. In 2000 she received her diploma and she started a bachelor of nursing at Fontys in Eindhoven. After graduating in 2002 she started as a nurse at the internal medicine/gastroenterology department in the Catharina Hospital in Eindhoven. After four years she obtained the diploma of specialized gastroenterology nurse at the HAN in Nijmegen. In 2016 she started the study Master Advanced Nursing Practice at Fontys University of applied science in Tilburg. During this study, she performed scientific research which resulted in the start of this PhD thesis in 2017. She is currently working as a nurse practitioner at the gastroenterology out-patient clinic in the Catharina hospital in Eindhoven. She also works as a teacher within the curriculum knowledge development and research at the Master Advanced Nursing Practice at Fontys University of applied science in Tilburg and is the president of the Dutch Gastroenterology Nursing society. Mirjam is married to Tim and together they have two sons Boaz (2009) and Sil (2011).