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

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INTRODUCTION
Barrett’s oesophagus (BO) is a common condition with a pooled prevalence of histologically confirmed BO of 7.2% in patients with gastro-oesophageal reflux symptoms worldwide.1 Patients with Barrett’s have an overall per annum risk of progression to oesophageal adenocarcinoma (OAC) in the order of 0.33%.2,3 OAC still carries a poor 10-year survival despite excellent advances in endoscopic therapy (ET) for pre-invasive disease.4 BO progresses through stages of non-dysplastic BO (NDBO) to low-grade dysplasia (LGD), high-grade dysplasia (HGD), intramucosal cancer to invasive OAC. National and international guidelines advise endoscopic surveillance to detect dysplasia and neoplasm amenable to ET such as endoscopic resection (ER) or radiofrequency ablation (RFA).5–8 Most patients with BO will never progress to dysplasia or OAC; factors influencing this include genetic predisposition,
WAT THIS STUDY ADDS

⇒ This large multicentre comparative cohort study shows patients undergoing treatment for dysplasia and early cancer had similar rates of worry of cancer pre and post endoscopic treatment.
⇒ Despite their intervention, there was no change in HRQOL across generic and gastrointestinal scores.
⇒ Non-dysplastic Barrett’s patients showed similar cancer worry and HRQOL scores to the pretreatment cohort with dysplasia, while those with colonic polyps, gastroesophageal reflux disease and healthy volunteers had lower cancer worry scores than the pretreatment group.
⇒ Patients with Barrett’s reported ongoing unanswered questions about their disease even when treated and satisfaction with follow-up services was mixed.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The provision of disease-specific knowledge around Barrett’s needs to be optimised, and practice around follow-up and education of Barrett’s patients could be studied to look for the best ways to deliver information.
⇒ Key aspects of symptom burden and cancer worry need particular attention in clinics and around endoscopic therapy to help reduce the HRQOL burden these patients’ experience.
⇒ The design and validation of a specific Barrett’s patient-reported outcome measure, which can be used to measure HRQOL in clinical interventions and research may be of value for this patient group.

Aims and objectives

⇒ To assess HRQOL in patients with BO and dysplasia or early OAC pre and post their ET.
⇒ To compare the pretreatment DBO group’s HRQOL with other comparator cohorts namely an NDBO group, those with gastro-oesophageal reflux disease (GORD), those with colonic polyps, healthy volunteers and a purely retrospective group who had received prior treatment for DBO.

METHODS

This study formed part of a concurrent mixed methods study exploring quantitative and qualitative aspects of BO HRQOL (quality of life measures in BO care pathways—CPMS ID 34114). Participants were recruited from four centres: two tertiary referral centres where BO ET is performed and two teaching hospitals in the Northwest of England.

Data from a questionnaire booklet consisting of a series of validated tools (outlined below) were obtained from a group of participants prior to their ET for DBO (pre-ET DBO group), the same patients were then invited to complete the questionnaire again (post-ET DBO group) >6 weeks to <6 months after completion of their ER or RFA 360 if this was the primary therapy or following a final surveillance not requiring further RFA 90 if this was their primary therapy.

Simultaneous data were collected from other groups for comparison to the pretreatment DBO group. These groups were:

⇒ Non-dysplastic Barrett’s cohort.
⇒ Retrospective only cohort—patients with DBO recruited following treatment.
⇒ GORD cohort—to determine the link with symptoms.
⇒ Colonic polyps—chosen as also a premalignant condition requiring surveillance to explore differences with lower gastrointestinal (GI) endoscopic surveillance versus upper GI.
⇒ Healthy individuals with no prior comorbidities—as a control group.

Recruitment technique and inclusion criteria

All participants recruited to the study were over 18 years of age and had capacity to consent for the study, detail of inclusion criteria for each cohort is provided in online supplemental appendix 1.
<table>
<thead>
<tr>
<th></th>
<th>Pre-DBO N=69</th>
<th>Post DBO N=42</th>
<th>NDBO N=379</th>
<th>Retro DBO N=49</th>
<th>GORD N=132</th>
<th>Colonic N=152</th>
<th>Healthy N=48</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response rate %</strong></td>
<td>70%</td>
<td>61%</td>
<td>40%</td>
<td>65%</td>
<td>28%</td>
<td>47%</td>
<td>33%</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>70.7</td>
<td>65.1</td>
<td>71.0</td>
<td>60.9</td>
<td>68.6</td>
<td>48-89</td>
<td>50.3</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>60% Male</td>
<td>66.2% Male</td>
<td>89.8% Male</td>
<td>72</td>
<td>100</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td><strong>Employment status</strong></td>
<td>20.3% Retired</td>
<td>31.2% Retired</td>
<td>8.2%</td>
<td>35.9%</td>
<td>17.3%</td>
<td>85.1%</td>
<td>10.6%</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td>18.8% Cancer</td>
<td>20.3% Cancer</td>
<td>24.5%</td>
<td>27.8%</td>
<td>16.9%</td>
<td>22.5%</td>
<td>50.0%</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>27.5% Never</td>
<td>42.9% Never</td>
<td>26.5%</td>
<td>49.6%</td>
<td>39.7%</td>
<td>70.8%</td>
<td>8.3%</td>
</tr>
<tr>
<td><strong>PPI use</strong></td>
<td>92.8% Yes</td>
<td>94.9% Yes</td>
<td>100%</td>
<td>84.6%</td>
<td>45.7%</td>
<td>0.0%</td>
<td>33.3%</td>
</tr>
<tr>
<td><strong>Comorbidity prevalence</strong></td>
<td>6.2% Range</td>
<td>3.7</td>
<td>3.9</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

CRC, colorectal cancer; DBO, dysplastic Barrett's oesophagus; GORD, gastro-oesophageal reflux disease; NA, not applicable; NDBO, non-dysplastic Barrett's oesophagus; OAC, oesophageal adenocarcinoma; PPI, proton pump inhibitor.
Participants were approached by post or in-person at endoscopy lists or clinic appointments and deemed recruited when they had returned the completed questionnaire booklet. When provided in-person, participants were encouraged to complete the questionnaire 4 weeks after their intervention or clinic appointment.

**Data collected**

**All participants**

- Demographics: age, sex, family history, carer status, employment status, smoking status, proton pump inhibitor usage, antidepressant usage.
- Comorbidities (see questionnaire pack in online supplemental material).

Additional group-specific information was obtained and is outlined in online supplemental appendix 2.

**HRQOL tools**

Prior literature review regarding HRQOL and BO was used as the basis to choose the tools for this study as there is currently no specific BO PROM.

The tools used were:

- Gastrointestinal Symptom Rating Scale (GSRS) (15 items, 5 domains, 4-point Likert scale).
- Hospital Anxiety and Depression Score (HDAS) (2 domains, 14 items, 4-point Likert scale).
- Cancer Worry Scale (CWS) (6 domains, 4-point Likert Scale).
- Short Form-36 (SF-36).

The questionnaire booklet is available on request.

**Statistical analysis**

The impact of each disease state was assessed with the HRQOL tools, initially focusing on the pretreatment

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**Figure 1** A flow chart depicting the responses for each cohort and reasons for non-response or exclusion. DBO, dysplastic Barrett’s oesophagus; NDBO, non-dysplastic Barrett’s oesophagus; GORD, gastro-oesophageal reflux disease; RIP, deceased.
DBO group (N=69) and the comparison with their post-treatment responses (N=42) performed using Wilcoxon rank test. Comparisons using multiple linear regression analysis were performed comparing the pre-treatment group with the following groups: non-DBO (N=390), gastro-oesophageal reflux (GORD) (N=128), colonic polyps (N=146), healthy participants (N=45) and a purely retrospective post therapy DBO group (N=56) adjusted for a set of prespecified confounders from 4 hospital sites. These confounders were age, smoking history, sex, comorbidities and history of anxiety or depression. Independent t-test was used to compare BO groups’ mean CWS pre and post January 2020 to assess the impact of the COVID-19 pandemic. Significance was determined with a p value<0.05, using Stata V.14 software.

**RESULTS**

**Data quality**

Greater than 90% completion of questions was deemed satisfactory—in this study 812/894 (90.8%) of the participants completed>90% of the questionnaire. A response consistency index (RCI) score of 0 means no contradictory responses and is calculated on the SF-36 software. Ideally a study should achieve>90% of respondents with an RCI of 0, this study achieved 89% with an RCI of 0. Cronbach alpha is a measure of scale reliability—all the tools used in this study had greater than satisfactory scores for their Cronbach alpha (SF-36>0.85, HDAS 0.83, CWS 0.89, GSRS 0.6–0.85).

**Response rates and demographics**

The response rate overall for all groups was 39.4%; this reflected the use of postal recruitment used for some of the cohorts. Demographics of the responders have been outlined in table 1. Responder versus non-responder characteristics for the pre-DRO group have been outlined in the online supplemental appendix 3.

**Pre and post endotherapy DBO groups**

A total of 69 pretreatment DBO cases were obtained (response rate 70%), of which 42/69 (60%) completed the follow-up questionnaire post treatment. Participants of the pre and post cohort and their outcomes are outlined in the flow chart figure 1.
Cancer worry

Comparing pretreatment DBO versus other groups

There was no significant difference in total CSRS scores (median 4, IQR 2–10, post=5, p=0.47). When broken down to disease-specific scores, the reflux scores were similar pre and post therapy. When assessing their own risk of OAC, 67% of individuals pre treatment had a significant CWS and 75% thereafter.

Table 3 Cancer Worry Score and perception of risk for pretreatment dysplastic Barrett’s oesophagus compared with the other cohorts.

<table>
<thead>
<tr>
<th>Cancer Worry Score</th>
<th>Category % Borderline (10-11)</th>
<th>Category % Positive (12+)</th>
<th>Coefficient (95% CI)</th>
<th>Pretreatment DBO versus p value</th>
<th>Pretreatment DBO versus other domains for VAS scoring p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment DBO</td>
<td>22.7% N=15</td>
<td>67.2% N=44</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>NDBO</td>
<td>31.8% (121)</td>
<td>50.9% (194)</td>
<td>–0.99 (–2.12 to 0.13)</td>
<td>0.084</td>
<td>0.713</td>
</tr>
<tr>
<td>Retro DBO</td>
<td>33.3% (16)</td>
<td>50.0% (24)</td>
<td>0.59 (–0.94 to 2.12)</td>
<td>0.451</td>
<td>0.967</td>
</tr>
<tr>
<td>GORD</td>
<td>45.7% (59)</td>
<td>43.4% (56)</td>
<td>–3.30 (–4.61 to –1.98)</td>
<td>&lt;0.001*</td>
<td>0.003*</td>
</tr>
<tr>
<td>Colonic polyps</td>
<td>36.2% (54)</td>
<td>51.0% (76)</td>
<td>–1.29 (–2.53 to –0.46)</td>
<td>0.042*</td>
<td>0.438</td>
</tr>
<tr>
<td>Healthy</td>
<td>47.9% (23)</td>
<td>22.9% (11)</td>
<td>–4.26 (–6.00 to –2.53)</td>
<td>&lt;0.001*</td>
<td>0.773</td>
</tr>
</tbody>
</table>

Table 4

<table>
<thead>
<tr>
<th>VAS</th>
<th>Category %</th>
<th>Total mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal (&lt;10)</td>
<td></td>
</tr>
<tr>
<td>Pretreatment DBO</td>
<td>22.7% N=15</td>
<td>12.55 (4.85)</td>
</tr>
<tr>
<td>NDBO</td>
<td>31.8% (121)</td>
<td>12.19 (4.57)</td>
</tr>
<tr>
<td>Retro DBO</td>
<td>33.3% (16)</td>
<td>12.67 (4.95)</td>
</tr>
<tr>
<td>GORD</td>
<td>45.7% (59)</td>
<td>10.88 (4.98)</td>
</tr>
<tr>
<td>Colonic polyps</td>
<td>36.2% (54)</td>
<td>11.58 (3.93)</td>
</tr>
<tr>
<td>Healthy</td>
<td>47.9% (23)</td>
<td>10.02 (3.31)</td>
</tr>
</tbody>
</table>

* Denotes statistical significance; DBO, dysplastic Barrett's oesophagus; GORD, gastroesophageal reflux disease; NDBO, non-dysplastic Barrett's oesophagus; VAS, Visual Analogue Scale.
COVID-19 impact
The SARS-COVID-19 pandemic spread across the globe from December 2019 and caused disruption to endoscopy services. The time from pretreatment recruitment to ET prior to December 2019 was median 62 days (range 13–243) excluding one case who declined treatment multiple times and waited 999 days. Time to ET post December 2019 was median 114 days (range 54–383). However, despite delay for the pre-ET DBO cohort, there was no significant difference in total CWS using independent t-test pre Jan 2020 versus post Jan 2020 (−1.606, 95% CI −4.323 to 1.11, p=0.242) and again for the post DBO cohort (−0.381, 95% CI −3.179 to 2.417 p=0.784). For the NDBO cohort: −1.861 (95% CI −4.327 to 0.120, p=0.64). All other cohorts were recruited prior to January 2020.

Follow-up care and patient education
A crucial factor in patient HRQOL is disease-specific knowledge and education, in this questionnaire patient participants with BO were asked about their experience receiving information regarding BO (summary table in online supplemental appendix 4). Most information was acquired by patients from the medical team via face-to-face appointments or when they came for a procedure, with fewer gaining online information. Written information was provided to the majority of patients, with around 1/3 in each group seeking out self-taught information. Overall satisfaction with follow-up care and information was higher among patients who were going to or had received ET, with NDBO ratings being less satisfied. Overall, 73.2% of the NBDO participants reported being satisfied or very satisfied versus 90%–100% in those who have had or will have therapy. The overall satisfaction was good despite 10%–30% of respondents still reporting they have unanswered questions.

DISCUSSION
BO carries overall a low risk of cancer, but those with known dysplasia or neoplasia would be expected to have greater worry of cancer given they have a localised early cancer already or are at greater risk given their dysplasia. Those who have received ET are still at higher risk of developing cancer but we aimed to see if there was any change pre and post treatment. Though we are unable to attribute this to the treatment given the cohort design, there was no significant change in the mean scores or proportions of those with higher cancer worry. Overall, both the pre and post groups had high CWS suggesting background concern about this, appropriate for their increased risk of progression compared with the NDBO. However, this was not significantly higher than the NDBO, again confirming that this non-dysplastic group still has a high cancer worry despite overall low risk of progression. Other studies confirm this and have shown that anxiety and depression appear to be associated with greater cancer worry; likewise, a high symptom burden is seen in those with high cancer worry. Despite their high CWS, a large proportion of the pretreatment and post-treatment groups underestimate their risk (79.7% pre and 57.9% post therapy); this may be reflective of patients finding the understanding of numerical estimates of risk difficult to interpret.

Pre and post groups overall showed no significant differences between their HRQOL scores, particularly their CWS. One factor at play here may be that for DBO treatment it can be unclear to patients when their treatment

Table 4  Breakdown of gastro-oesophageal symptom rating scale (GSRS) scores overall and for reflux symptoms alone for the pretreatment group versus the other cohort groups

<table>
<thead>
<tr>
<th></th>
<th>Total GSRS Mean (SD)</th>
<th>Reflux score Mean (SD)</th>
<th>Coefficient (95% CI)</th>
<th>Pretreatment DBO versus p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment DBO</td>
<td>5.96 (5.4)</td>
<td>0.9 (1.3)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>NDBO</td>
<td>6.95 (6.1)</td>
<td>0.95 (1.33)</td>
<td>−0.92 (−1.52 to 1.33)</td>
<td>0.900</td>
</tr>
<tr>
<td>Retro DBO</td>
<td>6.43 (5.73)</td>
<td>0.7 (0.9)</td>
<td>0.77 (−1.19 to 2.73)</td>
<td>0.441</td>
</tr>
<tr>
<td>GORD</td>
<td>10.42 (7.41)</td>
<td>1.81 (1.75)</td>
<td>1.88 (0.22 to 3.54)</td>
<td>0.027*</td>
</tr>
<tr>
<td>Colonic polyps</td>
<td>5.29 (5.4)</td>
<td>0.49 (0.96)</td>
<td>−1.47 (−3.04 to 0.11)</td>
<td>0.068</td>
</tr>
<tr>
<td>Healthy</td>
<td>1.96 (2.48)</td>
<td>0.25 (0.53)</td>
<td>−5.93 (−8.14 to −3.72)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

*n* Denotes statistical significance; DBO, dysplastic Barrett’s oesophagus; GORD, gastro-oesophageal reflux disease; GSRS, Gastro-oesophageal Symptom Rating Scale; NDBO, non-dysplastic Barrett’s oesophagus.
has concluded, their surveillance frequency might increase and they may require repeated treatments especially for RFA. In a study by Shaheen et al of RFA versus sham procedure, the RFA group at 12 months post treatment showed a reduction in worry of cancer (p=0.003), depression (p=0.02), stress (p=0.05), dissatisfaction with their oesophageal disease (p=<0.001) and reduced worry about esophagectomy (p=0.009) compared with the sham arm participants. This may reflect the timing of their post-treatment follow-up questionnaire—at 12 months rather than within 6 months. As part of the LGD RFA or surveillance only RCT performed by Rosmolen et al they assessed HRQOL in each of the study groups.

Questionnaires were given at baseline (before randomization) and at 2, 9, 14, 26 and 38 months after randomisation. The Illness Perception Questionnaire (IPQ) showed that patients in their ablation group perceived their disease lasted for a shorter period (p=0.001) and experienced fewer symptoms (p=0.001). Over time, there were improved outcomes at each of the further time points in the ablation group significantly compared with the surveillance group. This may reflect the positive reinforcement of each RFA session showing improvement/reduction in the presence of glandular mucosa and hence participants felt their condition was not as threatening as the surveillance-only group. Future time points could be assessed in the current study cohort to see if HRQOL improves.

Comparing the pre-treatment DBO group with all cohorts, it is striking that NDBO have a similar worry of cancer. Education is an important factor in patient’s understanding of BO. Shaheen et al attempted to evaluate this after the 12-month follow-up, when they had informed them of their current disease status, for example, dysplasia or intestinal metaplasia was eradicated, and asked participants to consider what they understood in their disease state. Only 59% of participants could correctly identify their disease state, this echoes our findings that despite satisfaction with follow-up, many participants with NBDO or DBO had unanswered questions about their disease. In the UK, currently, BSG guidelines advise an initial clinic appointment to discuss the diagnosis, and thereafter patients receive limited contact other than at surveillance. Practical improvements could include improving the quality of the initial contact by focusing on the key areas of symptom management, burden of surveillance, cancer-worry and disease-specific knowledge. Then, as Barrett’s patients will undergo years of surveillance, opportunities should be created for patients to flag concerns, perhaps via an email or telephone link and health professionals could detect patients in need of support using a Barrett’s-specific PROM provided at intervals between surveillance.

Limitations

As this was a cohort study, we were unable to attribute cause or effect to the treatment for the pre and post groups. There was an unfortunate loss of recruited subjects between pre and post groups, this was in part due to the clinical picture changing but there was a considerable issue with COVID-19 causing delays to treatment and some patients were still awaiting their ET at completion of the study. A similar cohort study halted their recruitment during the initial phase of the pandemic; however, as ET procedures were protected in the UK, we continued recruitment during this time. Nonetheless, fewer patients were seen face to face in clinic, front-line working was required of the clinical research staff and research nurses were redeployed. The COVID-19 pandemic may have impacted patients’ support networks and usual activities, which may have affected generic aspects of HRQOL.

Response rates overall were good and comparable to other survey studies; however, there is always an element of self-selection bias with questionnaires, though clinic recruitment improved rates of return. The tools used for this study, though all validated, were not specific to BO. In a systematic review, Van der Ende-van Loon et al assimilated the key areas of importance in HRQOL in BO according to patients from four qualitative works. They outlined that individually the tools used in prior QOL work in BO did not address a full range of these issues, which could be true of the tools used in this study. To overcome this, we used multiple tools to address different aspects of HRQOL; however, this may have resulted in a burden to patients given the length of the questionnaire pack, though missing data proportions were low. A more streamlined tool designed specifically for BO patients and validated in this patient group would be beneficial for future studies.

CONCLUSIONS

To the authors knowledge, this is the largest UK multicohort, multicentre study of DBO patients comparing to other disease states, and the first to explore the pre–post DBO experience prospectively. Our study shows high burdens of cancer worry across all stages of BO, and a need for improved education, reassurance and follow-up care for these patients.

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Contributors All authors contributed significantly to this work. ER, YA, JM, SH and JB devised and designed the study. ER, JB, RK, MM, RW and YA were responsible for driving recruitment at each site. ER and JB performed the data collection and data analysis was undertaken by ER and CH. ER wrote the initial manuscript, all authors reviewed and revised the final manuscript. ER and YA are guarantors for the study and overall content of this manuscript.

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Competing interests ER and YA have research funding from Medtronic, YA has research funding from Cancer Research UK. ER has received honoraria for a podcast recording with Janssen and for a focus group with Takeda. SH is the director and chief scientific officer for Phagenesis and holds founder shares, he holds a patent for Anisys Go and Lyt device, and received honoraria for ESSD meeting Brussels and Chinese Dysphagia research forum.

Patient consent for publication Not applicable.

Ethics approval Prior ethical approval was obtained for the study from the Health Research Authority Yorkshire and Humbers ethics committee (REC reference number 16/NW/0335). All participants received a participant information sheet alongside a questionnaire pack. Written consent was not required as completion and return of the questionnaire pack implied consent and no changes were made to the individual’s care. This is in accordance with the UK Health Research Authority guidance.

Provenance and peer review Not commissioned; externally peer reviewed.

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