EPIDEMIOLOGY, RISK FACTORS, SURVEILLANCE AND DETECTION OF EARLY NEOPLASIA IN BARRETT'S OESOPHAGUS

PhD Thesis

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INTRODUCTION

1. Barrett's oesophagus

1. 1. Definition and pathomechanism

The condition was first described in 1946 by Philip R Allison (1) but the term Barrett's oesophagus (BO) was first used in the 1950s, coined after Normann Barrett, an eminent Australian surgeon in London (2).

BO is a diagnosis based on the endoscopic and histological investigation of the distal oesophagus. Gastroscopic assessment reveals a mucosal change above the level of the cardia at the top of the gastric folds. Biopsies form this salmon coloured mucosa finds the presence of columnar epithelium in place of the non-keratotic squamous epithelium (3).

1.2. Epidemiology

The prevalence of BO is increasing in developed countries. However, since an upper endoscopic investigation is needed to confirm the diagnosis, the increasing availability of this modality contributes to the rising trend. Current estimates suggest that the prevalence of BO is between 1-2% in the general population and around 10% in subjects with gastro-oesophageal reflux disease (GORD) (3).

1.3. Clinical presentation and symptoms

The diagnosis of BO is made after a diagnostic gastroscopy for upper gastrointestinal symptoms, that is dyspepsia, abdominal pain, heartburn or other signs of GORD most frequently, or after a gastroscopy for any other indication. It has to be noted that BO is often diagnosed when symptoms driven by the pathologies of the oesophagus or the cardia are investigated. A large proportion of patients diagnosed with BO does not have any BO-related symptoms (3).

1.4. Risk factors

According to current literature, the risk factors of BO are male gender, white ethnicity, older age, presence of GORD symptoms, large hiatal hernia, increased waist circumference, cigarette smoking and family history of GORD, BO or oesophageal adenocarcinoma (OAC) (3).

1.5. Barrett's oesophagus and *Helicobacter pylori*

The investigation of the association between BO and *Helicobacter pylori* infection (HPI) goes back to the late 1980s (4), soon after the discovery of the bacterium (5).

Results of individual studies demonstrated different associations between HPI and BO. Four previous meta-analyses analysed the association between *H. pylori* and BO, three of which concluded that HPI is associated with a lower BO prevalence (6-8). On the contrary a fourth did not find a clear relationship between HPI and BO (9).

1.6. Recognition and diagnosis

The columnar mucosal changes are conspicuous to the expert endoscopist, the mucosa which looks like the gastric mucosa can be seen above the top of gastric folds while the squamocolumnar junction is proximally displaced. There is evidence that the length of BO is directly associated with the risk of cancer conversion. Short segment BO (<3 cm) has a lower risk than long segment BO (≥3 cm), these are 0.19 and 0.33% anually, respectively (10). Biopsies must confirm the diagnosis of BO, and current guidelines recommend the use of the so-called Seattle protocol (11)

1.7. Surveillance and early neoplastic changes

Detection of the early neoplastic changes within the BO can prevent the development of advanced OAC as endoscopic treatment has a high success rate. Therefore, international and national guidelines give very detailed recommendations on the surveillance and treatment of early neoplasia in BO (12-14).

2. Adenocarcinoma of the oesophagus

2.1. Definition and pathomechanism

OAC is the malignant tumour most commonly in the distal third of the oesophagus. It arises from the columnar mucosa of the gastro-oesophageal junction or Barrett's segment (15).

2.2. Prognosis

Oesophageal cancer is currently the sixth leading cause of cancer-related mortality in the world (16). More than 85% of the patients die within 5-years following the diagnosis of oesophageal cancer (17). The absence of well-described precancerous states and the lack of early symptoms preclude effective screening programs for all oesophageal cancers (18), except for BO (discussed above) and OAC, where endoscopic surveillance is recommended (12, 13, 19).

2.3. International and Hungarian epidemiologic trends

Oesophageal cancer is the eighth most common cancer globally. It has an estimated annual incidence above 480,000 cases, and 410.000 patients die from it each year (20).

Previously, squamous cell cancer was the more common form of oesophageal cancer, but in recent decades, the incidence of OAC significantly increased in Western Europe and the United States, and in some countries OAC is now the leading histological type (21).

As part of our oesophageal cancer research, we collected and analysed data of 2,632 patients with primary oesophageal cancer between 1992 and 2018 in Hungary in a multicenter, longitudinal study. This study showed that the relative prevalence of OAC compared to the relative prevalence of squamous cell cancer of the oesophagus is quickly increasing, which trend attains the level of statistical significance. The rapid and concerning rise of the incidence of OAC points towards the change of environmental factors and also to the increasing life expectancy. The same risk factors of BO account for the rising prevalence of OAC.

3. Early neoplastic lesions of Barrett's oesophagus

3.1. Definition of early neoplasia

Both the prevalence of BO and the incidence of OAC are increasing (22), and OAC often develops in BO (3, 18). Early neoplasia of BO can be defined as OAC in very early histologic stages. Currently, low-grade dysplasia, high-grade dysplasia, intramucosal cancers are regarded as early neoplastic lesions. These are often tiny lesions, spreading superficially without invading deeper layers of the oesophageal mucosa (3, 13, 23). The annual cancer conversion rates of BO with early neoplasia are at around 10% and above (24, 25).

3.2. Recognition of early neoplasia

As early neoplastic lesions are very subtle, they can be missed on endoscopic assessment. Therefore it is pivotal that patients undergoing surveillance gastroscopies for BO need high-quality endoscopic evaluation (12, 13). To increase the detection rate of early neoplasia, numerous strategies and technical approaches are recommended, enabling targeted biopsy. Acetic acid (AAC) is a weak acid that can highlight irregular and suspicious surface patterns in Barrett's mucosa by an aceto-whitening reaction (26).

3.3. Treatment of early neoplasia

When early neoplasia is detected by endoscopy and confirmed by pathology, endoscopic therapy performs effectively. The treatment involves endoscopic resection of the dysplastic lesions, followed by the ablation of the residual Barrett's segment (3, 12, 13).

3.4. Clinical implications

In summary, we can conclude that increased detection of early neoplasia in BO is the ultimate goal of the endoscopic surveillance program.

OBJECTIVES

This thesis describes two research projects.

1) Inspired by the conflicting results from numerous publications about the role of HPI in the development of Barrett's oesophagus, we aimed to **perform a prognostic meta-analysis**, thereby synthesising all available evidence quantitatively.
2) Since lesion detection is often a challenge during Barrett surveillance endoscopy while the stake of missing a neoplastic lesion is high, we aimed to **develop and test training module** to increase the efficacy of the procedure.

THE STUDIES

4. Meta-analysis

4.1. Methods

4.1.1. Summary publications: the overview of meta-analyses

Considering the taxonomy of summary publications, systematic reviews and meta-analyses should be highlighted. A systematic review aims to collect and re-synthesize all evidence related to a specific question. If a systematic review performs quantitative synthesis with dedicated statistical methods, we call it a meta-analysis (27).

4.1.2. Clinical question

PECO items of the strategy were: (P) adult population, (E) past or current HPI, (C) patients without HPI, (O) BO.

4.1.3. Protocol

A prognostic meta-analysis and systematic review were performed using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (28).

4.1.4. Systemic literature search

A systematic search was conducted in MEDLINE (via PubMed), EMBASE and CENTRAL databases from inception to December 2016.

Keywords for the computer-aided search were (Barrett's OR Barrett's metaplasia OR Barrett metaplasia OR Barrett's oesophagus OR Barrett's esophagus OR Barrett oesophagus OR Barrett esophagus) AND (*Helicobacter pylori* or *H pylori or H. pylori* or *Helicobacter*). Additional articles were identified from the reference lists of eligible primary studies.

4.1.5. Inclusion and exclusion criteria

All studies with relevant information on HPI prevalence in BO patients and controls within the same population were included in our analysis. Full-text articles and abstracts were both included. All types of comparative observational studies were included, regardless of whether they were prospective or retrospective. Non-human studies and review articles were excluded.

4.1.6. Data extraction

Numeric data were extracted by two investigator. Data were collected on the year

of publication, study type, geographical location, number of cases and controls and basic demographics in both groups and method(s) of HPI testing. Most importantly, data were collected on the prevalence of HPI in BO cases and controls, also in dysplastic and non-dysplastic BO and in different segment lengths of BO, for further subgroup analysis.

4.1.7. Statistical analysis

We calculated odds ratios (ORs) and 95% confidence intervals (CIs) of HPI vs no HPI comparison for BO. Pooled estimates were calculated with the random-effects model. Results of the meta-analysis were displayed graphically on forest plots. Heterogeneity was quantified using the I^2 statistics, its probability was tested with chi^2 test. As suggested by the Cochrane Handbook, I^2 values were interpreted as negligible (<30%), moderate (30–60%), substantial (50–90%), and considerable (75–100%) heterogeneity. Publication bias of the included studies was checked by Egger's test and by visual assessment of funnel plots.

4.2. Results

4.2.1. Selected studies

Our search strategy initially identified 1,705 potential studies. Removal of duplicates was followed by screening first the titles, and then the abstracts. Our statistical analysis included 72 studies. The summary of the characteristics of the studies included in our review is shown in **Table 1**.

Table 1 Main characteristics of the studies included. BO: Barrett's oesophagus, C: culture, GORD: gastro-oesophageal reflux disease, H: histology, HPI: H. pylori infection, PCR: polymerase chain reaction, S: serology, SA: stool antigen, R: rapid urease test, U: urea breath test, †: studies only in the subgroup analysis for BO segment length, ‡: HPI tested in esophageal or gastro-oesophagal junction samples only.

Study author and year	Country	Number of cases / controls	HPI testing method	Definition of controls	Only new BO cases
Abbas et al. 1995 (29)	Pakistan	29 / 29	H, R	GORD	No
Abe et al. 2009 (30)	Japan	36 / 108	H, R, S	Population	Yes
Abouda et al. 2003 (31)	UK	60 / 25	H, R, S	Endoscopy	No
Ackermack et al. 2003 (32)	The Netherlands	51 / 62	S	Endoscopy	Not stated
Ahmed et al. 2004 (33)	Sudan	11 / 47	R	GORD	Not stated
Anderson et al. 2008 (34)	Ireland	224 / 260	S	Population	Yes
Blaser et al. 1991 (35)	The USA	58 / 41	H,S	Population	Not stated
Carmona et al. 2003 (36)	Mexico	24 / 232	R	Endoscopy	Not stated
Chacaltana et al. 2009 (37)	Peru	11 / 911	H	Other	No
Chang et al. 2010 (38)	China	32 / 41	H	Endoscopy	No
Chen et al. 2016 (39)	Taiwan	161 / 644	R	Endoscopy	Not stated
Cooper et al. 1991 (40)	UK	26 / 30	H	GORD	No
Corley et al. 2008 (41)	The USA	318 / 299	S	Population	Yes
Csendes et al. 1997(42)	Chile	100 / 190	H	Endoscopy	No
Dore et al. 2016 (43)	Italy	131 / 1772	H, R, U	Endoscopy	No
El Serag et al. 1999 (44)	The USA	36 / 72	H	GORD	No
Fassan et al. 2009 (45)	Italy	210 / 210	H	Endoscopy	Not stated
Ferrandez et al. 2006 (46)	Spain	104 / 213	H, R, S, PCR	Population	No

Table 1 (continued)

Study author and year	Country	Number of cases / controls	HPI testing method	Definition of controls	Only new BO cases
Goldblum et al. 2002 (47)	The USA	70 / 60	H, S	Endoscopy	No
Hackelsberger et al. 1998 (48)	Germany	16 / 315	H, R	Endoscopy	No
Henihan et al. 1998 (49)	Ireland	82 / 40	H oesophagus	GORD	No
Hilal et al. 2016 (50)	The USA	323 / 1849	H	Endoscopy	No
Hirota et al. 1999 (51)	The USA	104 / 738	H oesophagus	Endoscopy	No
Inomata et al. 2006 † (52)	Japan	36 / 80	H, R, S	Endoscopy	Not stated
Johansson et al. 2007 (53)	Sweden	21 / 498	H oesophagus	Endoscopy	No
Jonaitis et al. 2011 (54)	Lithuania	33 / 160	H, R	GORD	Not stated
Kala et al. 2007 (55)	Czech Rep.	22 / 173	H, R	GORD	No
Katsienlos et al. 2013 (56)	Greece	75 / 1915	H, R	Endoscopy	Not stated
Keyashian et al. 2013 (57)	The USA	52 / 391	H, SA	Endoscopy	No
Kiltz et al. 1999 (58)	Germany	35 / 320	R, S	Endoscopy	No
Kim et al. 2006 (59)	South Korea	31 / 224	H, R	Endoscopy	Not stated
Laheij et al. 2002 (60)	The Netherlands	23 / 528	H, R, C	Endoscopy	Not stated
Lam et al. 2008 (61)	The USA	56 / 280	S	Endoscopy	Yes
Lee et al. 2011 (62)	Malaysia	15 / 104	H, R	Endoscopy	Not stated
Loffeld et al. 1992 (63)	The Netherlands	71 / 200	H oesophagus, S	Population	Not stated

Table 1 (continued)

Study author and year	Country	Number of cases / controls	HPI testing method	Definition of controls	Only new BO cases
Loffeld et al. 2000 (64)	The Netherlands	36 / 454	H	Endoscopy	Yes
Loffeld et al. 2004 (65)	The Netherlands	307 / 5341	H, C	Endoscopy	No
Lord et al. 2000 (66)	Australia	91 / 214	H	Endoscopy	No
Martinek et al. 2003 (67)	Czech Rep.	31 / 259	H, R	Endoscopy	Not stated
Meng et al. 2008 (68)	The USA	28 / 104	PCR	Endoscopy	Not stated
Monkemuller et al. 2008 (69**)**	Germany	97 / 97	H	Endoscopy	No
Nandurkar et al. 1997 (70)	Australia	46 / 112	H oesophagus	Endoscopy	Yes
Newton et al. 1997 (71)	UK	16 / 25	H, R	Endoscopy	No
Pascareno et al. 2014 (72)	Romania	24 / 218	H	Endoscopy	Not stated
Paull et al. 1988 (4)	The USA	26 / 26	H	Endoscopy	No
Peng et al. 2009 (73)	China	27 / 110	R	GORD	Not stated
Rajendra et al. 2004 (74)	Malaysia	123 / 1741	H, R	Endoscopy	Not stated
Rajendra et al. 2007 (75)	Malaysia	55 / 53	H, S	Endoscopy	No
Rex et al. 2003 (76)	The USA	48 / 764	R	Population	Yes
Rodriguez et al. 2014 (77)	Spain	8 / 192	H	Endoscopy	Yes
Ronkainen et al. 2005 (78)	Sweden	16 / 984	H, C, S	Population	Not stated
Rubenstein et al. 2014 (79)	The USA	150 / 177	S	Endoscopy	No

Table 1 (continued)

Study author and year	Country	Number of cases / controls	HPI testing method	Definition of controls	Only new BO cases
Rugge et al. 2001 (80)	Italy	53 / 53	H	Endoscopy	Not stated
Schenk et al. 1999 (81)	Netherlands	49 / 88	H	GORD	No
Sharifi et al. 2014 (82)	Iran	34 / 702	H, R	GORD	Not stated
Sonnenberg et al. 2010 (83)	The USA	2510 / 76475	H	Endoscopy	No
Sonnenberg et al. 2016 (84)	The USA	76475 / 284552	H	Endoscopy	No
Thrift et al. 2012 (85)	Australia	0/ 398	S	Population	Yes
Toruner et al. 2004 (86)	Turkey	29 / 306	H	Endoscopy	Yes
Uno et al. 2011 (87)	Japan	126 / 100	H, S, R	Endoscopy	No
Vaezi et al. 2000 † (88)	The USA	83 / 60	H, S	GORD	Not stated
Veldhuyzen et al. 2006 (89)	Canada	25 / 1015	H	Endoscopy	Yes
Vicari et al. 1998 (90)	The USA	48/57	H,S	GORD	No
Vieth et al. 2000 (91)	Germany	1054 / 712	H	Endoscopy	No
Watari et al. 2009 (92)	Japan	88 / 52	H, C	Other	No
Werdmuller et al. 1997 (93)	Netherlands	13 / 399	H, C, R, S	Endoscopy	Not stated
Weston et al. 2000 (94)	The USA	208 / 217	H	GORD	No
White et al. 2008 (95)	Canada	39 / 29	H oesophagus	Endoscopy	No
Wong et al. 2002 (96)	China	10 / 448	H, R, U	Endoscopy	Yes
Wu et al. 2000 (97)	Hong Kong	6 / 85	H, R	GORD	Not stated

Table 1 (continued)

Study author and year	Country	Number of cases / controls	HPI testing method	Definition of controls	Only new BO cases
Zaninotto et al. 2002 (98)	Italy	34 / 32	H oesophagus	GORD	No
Zullo et al. 2014 (99)	Italy	17 / 1037	H	Endoscopy	Not stated

4.2.2. The association of *H. pylori* infection with Barrett's oesophagus

Our results confirmed that BO was significantly less frequent in patients with HPI compared to those without HPI: OR=0.68 (CI: 0.58-0.79, p<0.001) based on the data of the 70 studies, including a total of more than 90,000 BO cases and nearly 400,000 controls. Heterogeneity was substantial, I^2=84.0% (**Table 2**).

Table 2 Odds ratios from 70 studies included in the overall analysis and subgroups for continents.

Subgroup	Odds ratio, 95% confdence interval	N0 of studies	Statistical heterogenety
Asia	0.53, 0.33-0.84	14	I^2=75.7%, p<0.001
Europe	0.77, 0.60-0.98	31	I^2=75.1%, p<0.001
North America	0.59, 0.47-0.74	19	I^2=79.2%, p<0.001
Australia	0.56, 0.39-0.80	3	I^2=0.0%, p=0.580
South America	0.95, 0.56-1.64	2	I^2=0.0%, p=0.737
Africa	3.05, 0.59-15.73	1	Not applicable
Total	0.68, 0.58-0.79	70	I^2=84.0%, p<0.001

4.2.3. The association of *H. pylori* infection and early neoplasia in Barrett's oesophagus

Prevalence of HPI in association with the presence of dysplasia in BO was detailed in 7 studies (45, 49, 84, 85, 90, 91, 94). Dysplastic BO was less common with HPI than without it, OR=0.37 (CI: 0.26-0.51, $p<0.001$).

4.4. Discussion of the meta-analysis

Our meta-analysis showed an inverse association between HPI and BO. However, there are several previous studies with altogether different conclusions: reporting that HPI has no correlation with BO (42, 73) or even a positive association (49, 63) (describing HPI as a risk factor). As to why and how exactly could HPI reduce the risk of BO development, several theories exist, but none of them is considered proven. Multiple articles attribute this fact to the effect of HPI on the gastric mucosa: the microorganism causes corpus-predominant gastritis, which leads to a decreased gastric output. In this case, the oesophagus is less exposed to the harmful effect of gastric acid; thus, it has a reduced risk for developing BO and OAC (6, 8, 100, 101).

In a meta-analysis on the subject, Fischbach et al. describe another theory that aims to explain the inverse relationship between HPI and BO. They speculate that HPI is associated with reduced risk for obesity, thus not only reducing the likeliness for acidic reflux but also the insulin level in the blood. This leads to the decreased production of insulin-like growth factor (IGF), which normally acts as an agent that potentiates the proliferation of Barrett's epithelium (6). With the reduced amount of circulating IGF due to HPI, BO is less likely to develop (24).

According to our results and the majority of conclusions available in the literature, a persistent HPI would be desirable for the prevention of BO. However, we have to emphasise that there is no evidence that should prevent us from eradicating *H. pylori*, regardless of coexisting reflux esophagitis or BO. HPI needs treatment, when it is identified.

5. Development of a training module in endoscopy

5.1. Methods

5.1.1. Objectives

We aimed to develop and test a training program for the use of AAC in Barrett's endoscopic surveillance for experts and novices. To do so, we organised a prospective,

educational evaluation study at the Queen Alexandra Hospital (Portsmouth, United Kingdom) – an expert centre for BO – between March and April 2015.

5.1.2. Ethical approval

The study was approved by the National Health Service Research Ethics Committee (reference number REC 15/SC/0085).

5.1.3. Study design

The study had two phases: an online training module and a live interactive session Diagnostic performance of participants was measured at three cross-sections in time at study entry, after the completion of the online module and after the live session with a diagnostic assessment test to determine the learning curves (**Figure 1**).

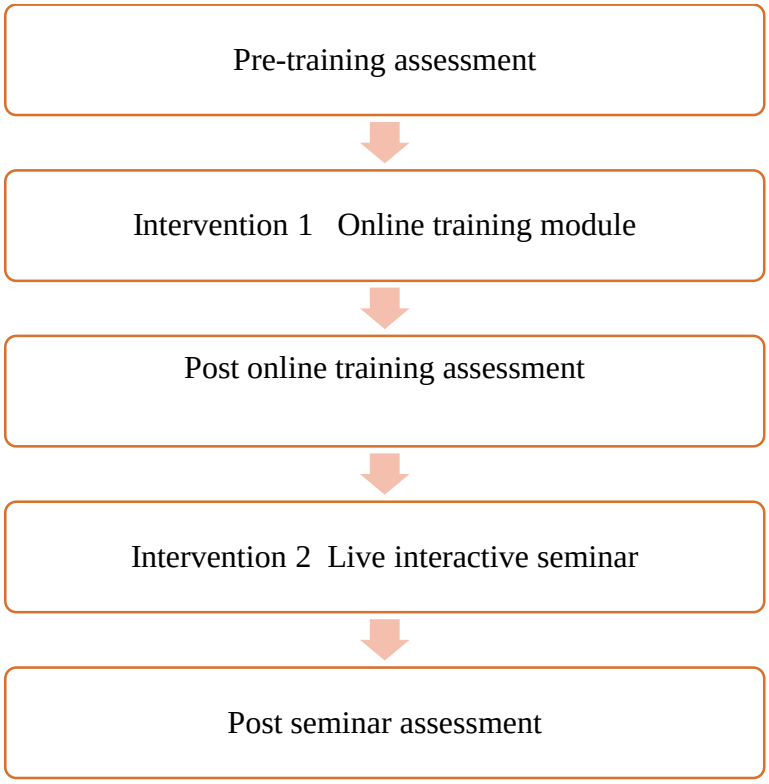

Figure 1 Flow chart of the study

5.1.4. Online training module

5.1.4.1. Platform development

First, we performed a comprehensive search and a review to determine the key features of the use of AAC in BO surveillance. As a result, a new classification of AAC was developed and validated (102) and learning objectives for the training module were defined.

5.1.4.2. Selection of images and videos

High-definition still images and videos of BO surveillance with 2.5% AAC and corresponding biopsy results were selected from a repository of more than 500 such procedure, which were recorded in Queen Alexandra Hospital Enodscopy Unit before the development of the module. Images and videos were reviewed for quality and visibility of the critical features of AAC. Altogether 40 still images (21 non-dysplastic, 19 early neoplasia) and 20 videos (ten non-dysplastic, ten early neoplasia) were selected from 60 individuals.

5.1.4.3. Structure and operation

The training module consisted of eight images (four non-dysplastic and four dysplastic) and nine videos (three benign and six neoplastic), explaining the critical features of AAC-assisted lesion recognition. Included within the training module was a sample quiz of eight questions that provided immediate feedback, with a clear explanation of the diagnosis, surface pattern, loss of acetowhitening reaction, and morphology. On completion of the training module, the test of baseline assessment was immediately repeated without feedback on prior performance.

5.1.5. Live interactive seminar

The seminar was held in Queen Alexandra Hospital on 24th April 2015. At the end of the interactive seminar, endoscopists immediately repeated the same assessment exercise without feedback on performance.

5.1.6. Inquiry about confidence and preferences

Before the pre-training assessment, participants were asked to complete a questionnaire regarding their confidence in the use of AAC; the same questionnaire was completed after all training.

5.1.7. Study participants

A total of 13 endoscopists took part in the study. The endoscopists were independent endoscopists with experience in BO endoscopy but without formal training in AAC-assisted lesion recognition.

5.1.8. Statistical analysis

To examine the content validity of the training module, a 10% improvement in sensitivity between pre- (70%) and post-training (80%) performance was deemed to be

clinically relevant. For a chi^2 test with a 5% significance level and 80% power, and again assuming the data are not truly independent, at least 291 observations would be required. Yet, because the data are not truly independent, we assumed 780 observations for each stage of assessment, from 13 observers, would more than satisfy the power calculation.

Sensitivity, specificity, accuracy, positive predictive value (PPV), and NPV were calculated for each observer (n = 13) at each time point, using histopathological diagnosis as the reference standard. All analyses were performed using these summary values. Confidence intervals were calculated to illustrate the uncertainty in the estimated values, and the two-sided paired t-test was used to compare between time points.

Interobserver agreement for images and videos was assessed using the multirater Fleiss kappa (κ) statistic. A κ value of <0.2 was regarded as poor agreement, 0.21-0.40 as fair agreement, 0.41-0.60 as moderate agreement, 0.61-0.80 as substantial agreement, and 0.81-1.00 as almost perfect agreement.

5.2. Results

5.2.1. Online and live interactive training

A total of 13 endoscopists (experts and learners) participated in online training. Assessment images and videos were completed before and repeated after the online training module, and demonstrated a significant improvement in sensitivity and negative predictive value (NPV) following the online training module (**Table 3**).

Table 3 Baseline vs post-online training assessment. CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

	Accuracy, % (95%CI)	Sensitivity, % (95%CI)	Specificity, % (95%CI)	PPV, % (95%CI)	NPV, % (95%CI)	Kappa
Images						
• **Baseline**	79 (0.75-0.83)	83 (0.79-0.86)	76 (0.73-0.79)	76 (0.72-0.79)	83 (0.79-0.86)	0.48
• **Post online training**	86 (0.83-0.88)	95 (0.92-0.97)	79 (0.76-0.81)	80 (0.78-0.82)	94 (0.91-0.98)	0.67
• ***P* value**	<0.01	<0.01	0.522	0.459	<0.01	
Videos						
• **Baseline**	78 (0.72-0.83)	73 (0.67-0.78)	83 (0.77-0.88)	81 (0.75-0.87)	76 (0.70-0.80)	0.41
• **Post online training**	82 (0.77-0.86)	91 (0.86-0.95)	74 (0.69-0.78)	78 (0.73-0.81)	89 (0.83-0.94)	0.51
• ***P* value**	0.281	0.011	0.194	0.505	0.041	

Following the completion of the interactive training, the assessment tool was repeated and showed a significant improvement in sensitivity and NPV for videos and a trend for improvement for images (**Table 4**).

Table 4 Post-online training vs post-interactive training assessment. CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

	Accuracy, % (95%CI)	Sensitivity, % (95%CI)	Specificity, % (95%CI)	PPV, % (95%CI)	NPV, % (95%CI)	Kappa
Images						
• **Post online training**	86 (0.83-0.88)	95 (0.92-0.97)	79 (0.76-0.81)	80 (0.78-0.82)	94 (0.91-0.98)	0.67
• **Post interactive seminar**	82 (0.80-0.84)	98 (0.95-0.99)	68 (0.66-0.69)	74 (0.72-0.75)	97 (0.94-0.99)	0.75
• ***P* value**	0.028	0.084	0.007	0.002	0.131	
Videos						
• **Post online training**	82 (0.77-0.86)	91 (0.86-0.95)	74 (0.69-0.78)	78 (0.73-0.81)	89 (0.83-0.94)	0.51
• **Post interactive seminar**	79 (0.75-0.81)	99 (0.95-1.0)	60 (0.56-0.61)	71 (0.68-0.72)	98 (0.91-1.0)	0.63
• ***P* value**	0.322	0.003	0.005	0.035	0.004	

5.2.2. Confidence of the endoscopist in the use of acetic acid

Endoscopist confidence in the use of the AAC for BO increased during the training, with a mean confidence level of 2.5 (5-point scale) before and a confidence level of 3.9 ($P < 0.001$) after the training. Confidence in the diagnosis for images also improved during training, with 41% of diagnoses made with high confidence pre-training, rising to 63% after the online training module ($P < 0.001$).

5.3. Discussion of results

This study involved the development of a new training module for AAC-assisted in vivo diagnosis of BO early neoplasia. The well-validated training module proved to be feasible for training in AAC BO surveillance and lesion recognition.

Endoscopists of various backgrounds and expertise participated and all of them demonstrated clinically relevant improvements in the detection of early neoplasia in BO with AAC. The results showed the validity, effectiveness, and widespread applicability of this tool. The technique of AAC is simple and can be performed by any endoscopist. However, our results showed that recognition of early neoplasia after AAC is not easy and necessitates training. Baseline assessment data showed poor performance (before

training) from both expert and non-expert BO endoscopists, thus justifying the need for our training tool. The interobserver agreement significantly improved after training, with substantial agreement by the end of training.

Our study showed that the technique of in vivo diagnosis for early neoplasia in BO using AAC could be taught using images and videos. But it appears that endoscopists find it more challenging to identify neoplasia from videos compared with still images. It may be explained by the fact that still images have been pre-selected and edited to focus on neoplasia, whereas videos focus on the entire BO, requiring more complex assessment. Video performance improved following training. Sensitivity and NPV improved following the interactive seminar, but accuracy and specificity worsened. It can be explained by a higher number of false-positive results, making AAC safer by reducing the risk of missed early neoplasia. At the end of the study, participant's sensitivity was 98% for images and 99% for videos.

The same is true for NPV, with mean scores of 97% for images and 98% for videos, reaching the ASGE PIVI criteria of ≥98%. We believe that the high NPV is the most important parameter, as it suggests that the early neoplasia miss rate is minimal, making the technique safe. The most recent ASGE Technology Committee review endorses AAC targeted-biopsy in expert hands (103), but our data show that training by our module can ensure that participants achieve the same thresholds as experts.

Training modules on endoscopic lesion recognition and in vivo diagnosis previously relied on still images. In real life, assessments are made on live endoscopic images. Therefore, evaluation and training of endoscopists in AAC BO surveillance would be better performed using videos that more closely reflect real-time practice. However, the results of our study showed no significant difference in performance when endoscopists were assessed using images or videos.

The study had a robust design with a well-validated library of images and videos, and the performance of the library was validated prior to its use. The study proved the effectiveness of an online training module for AAC and demonstrated the added clinical value of an interactive training day incorporating expert endoscopists and live cases.

SUMMARY OF THE RESULTS AND CONCLUSIONS

- The results of the meta-analysis confirmed that HPI is associated with lower prevalence of BO; therefore, it can be considered as a protective factor.
- The results of the meta-analysis confirmed that HPI is associated with lower prevalence of dysplastic BO as well.
- The findings from the study about the development of our training module support the usefulness of the tool in improving lesion recognition during Barrett's surveillance endoscopy.
- The learning curves from this study suggest that both experts and trainees may benefit from using this cheap and easily accessable training module.

PUBLICATIONS, PRESENTATIONS AND SCIENTIFIC METRICS (20.01.2020.)

Number of publications: ; All citations: 71; Independent citations: 65; Sum of all impact factors: 100.529; Hirsch index: 5

Publications related to the topic of the PhD thesis (IF:9.981)

1. Chedgy FJQ, Kandiah K, Barr H, De Caestecker J, Dwerryhouse S, **Eross B**, Gordon C, Green S, Li A, Brown J, Longcroft-Wheaton G, Bhandari P. Development and validation of a training module on the use of acetic acid for the detection of Barrett's neoplasia. Endoscopy. 2017;49(2):121-9. **IF:6.629 (Q1), citations: 4**
2. **Eross B**, Farkas N, Vincze A, Tinusz B, Szapary L, Garami A, Balasko M, Sarlos P, Czopf L, Alizadeh H, Rakonczay Z, Jr., Habon T, Hegyi P. Helicobacter pylori infection reduces the risk of Barrett's esophagus: A meta-analysis and systematic review. Helicobacter. 2018;23(4):e12504. **IF:3.352 (Q1) citaions: 17**
3. **Eross B**, Tinusz B, Farkas N, Hegyi P. Reply: Does Helicobacter pylori infection increase the risk of Barrett's esophagus and esophageal adenocarcinoma? Helicobacter. 2018;23(6):e12539.

Poster presentations at international conferences related to the topic of the PhD thesis

1. Clisby C, **Eross B**, Gordon C. The safety of oesophageal endoscopic mucosal resection for early neoplasia in Barrett's oesophagus, experiences from a general district hospital in the UK. Gut. 2017;66:A187.
2. Clisby C, Gordon C, **Eross B**. Efficacy and complications in palliative oesophageal stenting, experinces of a tertiary referral center in the UK. United European Gastroenterology Journal. 2017;5(5):A707-A8.
3. **Eross B**, Clisby C, Foria B, Gordon C. The efficacy of endoscopic mucosal resection in managing early neoplasia in Barrett's oesophagus, experiences of a tertiary referral center in the uk. United European Gastroenterology Journal. 2017;5(5):A360.
4. **Eross B**, Clisby C, Gordon C. Outcomes of treatment of patients with early-stage adenocarcinoma of the esophagus with incipient submucosal invasion, retrospective analysis of 19 cases from a tertiary referral center in the UK. United European Gastroenterology Journal. 2017;5(5):A803.

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6. **Eross BM**, Clisby C, Gordon C, Foria B. The efficacy of oesophageal endoscopic mucosal resection in managing early neoplasia in Barrett's oesophagus, experiences of a district general hospital in the UK. Gut. 2017;66:A179.
7. John C, Jamal S, Gordon C, **Eross B**. Palliative stenting in oesophageal cancer. Gut. 2015;64:A289-A90.

OWN WORK IN WIDER CLINICAL CONTEXT

My goal was to simultaneously develop clinical research expertise and advance the clinical services for BO and oesophageal cancer.

I have been involved in these research projects while I developed outstanding expertise in the management of these pathologies. I have learned the multidisciplinary clinical approach to oesophageal cancers and developed the upper gastrointestinal services in one of the large tertiary referral centres of the United Kingdom since 2011. I contributed to the advancement of the BO surveillance program and was involved in the revision of important guidelines on BO and oesophageal stenosis guidelines of the UK.

Since my move back to Hungary in 2017, I have been focusing my efforts on building an upper gastrointestinal clinical research team. With the help and support of the clinical staff and the team of the Institute for Translational Medicine, University of Pécs, we have built a multidisciplinary team, involving senior clinicians, trainees, under- and postgraduate students and have started registries on oesophageal cancer and gastrointestinal bleeding. We completed many other successful meta-analytical research projects and a significant and relevant epidemiologic study on oesophageal cancer in Hungary.

I have also significantly contributed to other research projects in different fields of gastroenterology, such as pancreatology, inflammatory bowel disease and coeliac disease.

While completing my research, I have continued to work as a clinician in gastroenterology, contributing to the service developments in gastroenterology.

In the future, I plan to continue the ongoing work in both registries and would like to contribute to the continued development of an upper gastrointestinal clinical and research team, mentoring young talents.

Through this work, I believe I can significantly contribute to better care for patients with upper gastrointestinal pathologies.

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