Diagnosing dysplasia in Barrett's oesophagus still requires Seattle protocol biopsy in the era of modern video endoscopy: results from a tertiary centre Barrett's dysplasia database.

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ABSTRACT

Objectives: The role of random, four-quadrant biopsy (i.e. systematic biopsy) in Barrett's oesophagus surveillance has been questioned given its drawbacks and the emergence of high-resolution endoscopy and advanced imaging modalities. Our study aims to assess whether neoplastic pathology is typically diagnosed in routine clinical practice by random, four-quadrant or targeted biopsy whilst using high-resolution endoscopy.

Methods: The Nottingham University Hospital Barrett's oesophagus dysplasia database was retrospectively analysed. Endoscopic and histopathologic data pertaining to the initial endoscopy in which pathology was diagnosed was extracted from the medical records. The most advanced histopathologic abnormality at initial diagnosis and within twelve months were noted. The corresponding endoscopic impression at initial diagnosis was used to group cases per type of biopsy – random, four-quadrant or targeted. Pearson's chi-squared test of independence was used to analyse the relationship between the type of biopsy and diagnosis, indication for endoscopy, endoscopist level and advanced techniques used.

Results: Of the 222 patients involved in the study - a higher proportion were diagnosed through random, four-quadrant biopsy (72.97%) than targeted biopsy (27.03%). 90.91% of low-grade dysplasia, 71.43% of high-grade dysplasia and 50% of intramucosal adenocarcinoma cases were diagnosed by random, four-quadrant biopsy. Across all grades of clinicians, patients were typically diagnosed through random, four-quadrant biopsy. However, amongst specialist consultant endoscopists (n=10) the proportion was equal.

Conclusions: Our findings strongly emphasize the importance of random, four-quadrant biopsy in the detection of not only low-grade dysplasia, but also high-grade dysplasia and early invasive carcinoma as part of Barrett's oesophagus surveillance.

KEYWORDS
Barrett's oesophagus; surveillance; adenocarcinoma; dysplasia; endoscopy.

INTRODUCTION

Over the past forty years, the incidence of oesophageal adenocarcinoma has increased dramatically in the Western world (1). Coupled with its grim prognosis, a five-year overall survival rate of 15%, the epidemic of oesophageal adenocarcinoma is of significant concern (2). The major risk factor in the development of oesophageal adenocarcinoma is Barrett's oesophagus (BO) – a premalignant lesion characterized by the replacement of the normal squamous epithelium of the distal oesophagus with metaplastic columnar epithelium (3). Barrett's oesophagus is associated with an annual risk of 0.33% for adenocarcinoma development (4), which increases in proportion to length of the Barrett's segment (5–6). This occurs through a sequence of low- and high-grade dysplasia (7). In the presence of dysplasia the annual risk of cancer increases dramatically (8), thus necessitating treatment or intensified surveillance (11).

Barrett's surveillance is intended to detect oesophageal neoplasia at a pre-invasive stage, or if cancer does develop to diagnose it at an earlier stage, when it may be more amenable to intervention (9). The current standard of care in Barrett's surveillance is the Seattle protocol – targeted biopsies of visible lesions followed by random, four-quadrant biopsies at 1-2 cm intervals throughout the Barrett's segment (10–14). However, the Seattle protocol has significant limitations including sampling error, as well as its costly, labour- and time-intensive nature. This has resulted in widespread non-adherence by endoscopists that has been associated with reduced dysplasia detection (15–17).

The emergence of high-resolution white-light video endoscopy and advanced imaging modalities has raised the question of whether random, four-quadrant biopsies are still required in Barrett's surveillance, as it is believed that such modalities have the potential to improve the detection and characterization of mucosal lesions at an early stage. This is analogous to the situation in inflammatory bowel disease where random biopsies for dysplasia detection have largely been replaced by dye spray endoscopy (18). The diagnostic accuracy of high-resolution versus standard resolution white-light endoscopy has not been evaluated in a randomized controlled trial in Barrett's oesophagus, but a retrospective cohort study found that the former was associated with increased targeted dysplasia detection (19). The evaluation of advanced imaging modalities has largely been confined to clinical trials and surveillance programs involving selected patient populations in the context of academic medical centres, in which they have shown potential for identifying early neoplasia (12,20–23).

Our study aims therefore to assess whether the initial diagnosis of neoplastic pathology in the context of Barrett's oesophagus is typically made by targeted or random, four-quadrant biopsy in the era of high-resolution white-light video endoscopy and advanced imaging modalities.

METHODS

Study design

This is a retrospective cohort study involving two-hundred and twenty-two patients selected from the Nottingham University Hospital Barrett's Dysplasia Database.

Of the 378 patients in our Barrett's Dysplasia Database, approximately forty percent (n=156) were excluded. We excluded patients who never received a diagnosis greater than ID, those diagnosed prior to 2008 (to ensure that our analyses reflect the use of modern endoscopic modalities), and those for whom the relevant endoscopy or histopathology reports were not available. The remaining patients who were included in this study (n=222) had been diagnosed with Barrett's oesophagus with dysplasia between 2008 to 2016. The majority (n=152) were initially assessed at the tertiary referral centre, however, 70 were initially assessed at one of four district general hospitals, before referral to the tertiary referral centre for expert evaluation, typically for newly-diagnosed HGD or IMCA.

The study was performed under approval from Nottingham Health Science Biobank ACP 00035, and received a waiver of informed consent. Permission to access medical records was granted by the appropriate senior clinician and/or administrator affiliated with each hospital involved in this study.

Data collection

We retrieved and analysed the medical records for each patient initially evaluated at the tertiary referral centre or district general hospitals. We defined as the 'index endoscopy' the first occurrence of LGD, HGD or IMCA for each patient except in the small number of cases (n=17), where there was a history of ID or above which had previously remitted for a variable time period without treatment. In these few cases, the index endoscopy was that which first detected the currently observed period of dysplasia. The findings were independently verified by two expert gastrointestinal histopathologists in each case. The following relevant data was extracted from the medical and pathological records for each index endoscopy:

Age (at time of index endoscopy).

Sex.

Length of Barrett's segment.

The endoscopic equipment and advanced imaging modalities used:
- All index endoscopies were high-resolution, white-light video endoscopies. Of these, some were aided by advanced imaging modalities (n=16), such as acetic acid, auto-fluorescence imaging and narrow-band imaging.
- All endoscopies were performed using the Olympus endoscopy system.

Prevalent versus Incident cases

- Dysplasia was considered to be **prevalent** where an initial diagnosis of Barrett's dysplasia was made at the time of Barrett's diagnosis being prompted by patient symptoms.

- Dysplasia was considered to be **incident** when diagnosed during ongoing surveillance of Barrett's oesophagus .

- **Prior diagnosis of ID or above** refers to incident cases in whom there is a prior history of indefinite for dysplasia or above.

The type of biopsy used – random, four-quadrant or targeted – was ascertained using the endoscopists record or request form corresponding to the biopsy exhibiting the most advanced histological abnormality at index endoscopy. The endoscopist impression was codified into one of the following seven groups, which accommodate a variety of descriptive terms that were noted in endoscopy reports. Groups 1-3 were categorized as random, four-quadrant biopsy (although being a retrospective study, this group also includes all randomly taken non-targeted biopsies). Groups 4-7 were categorized as targeted biopsy.

1. "Barrett's oesophagus"
2. "Inflammation"
3. "Barrett's oesophagus with inflammation"
4. "Slight irregularity"
5. "Suspicious"
6. "Cancer"

7. "Ulcer"

The most advanced histological diagnosis noted at index endoscopy (i.e. ID, LGD, HGD or IMCA).

The most advanced histological diagnosis noted within in twelve months after index endoscopy (i.e. LGD, HGD or IMCA). The rationale for acquiring this data was to ensure that the true histological diagnosis at index endoscopy was ascertained, and not underestimated as a result of sampling error.

The endoscopist grade:

- Barrett's specialist endoscopist – a consultant gastroenterologist who specializes in Barrett's oesophagus
- Consultant – any other type of consultant or associate specialist
- Fellow
- Registrar
- Nurse practitioner

Data analysis

We calculated proportions of each category of dysplasia detected by random, four-quadrant and targeted biopsies. We then similarly calculated the proportions of cases detected by random, four-quadrant and targeted biopsies among cases where dysplasia was incident, prevalent or

recurrent and stratified this result by the level of dysplasia (HGD, LGD, IMCA). Proportions of dysplasia diagnosed by random, four-quadrant and targeted biopsies were similarly calculated for differing levels of expertise of the examining endoscopist.

We went on to examine the proportions of each level of dysplasia detected by standard white light endoscopy – Olympus Lucera video endoscopy system with GIF Q260 and H260 gastroscopes – and by more advanced modalities, and the proportions associated with differing clinical endoscopic impressions at the index endoscopy.

For all of these comparisons the hypothesis of difference between categories was tested using a chi-square test. Analysis was performed using Stata version 14.

RESULTS

Of the 222 patients identified, more than 80% were male with a mean age of 67.43 years, and mean length of Barrett's segment of 5.39 cm.

Our principal finding was that over seventy percent of all cases were diagnosed through random, four-quadrant biopsy, almost three times as many as targeted biopsy (Table 1). Only 9.09% of low-grade dysplasia was diagnosed through targeted biopsy; but more surprisingly, only 28.57% of high-grade dysplasia and 50% of intra-mucosal adenocarcinomas were detected through targeted biopsy. This means that half of early Barrett's neoplasia was diagnosed by random, four-quadrant biopsy. High-grade dysplasia was over three times as likely to be diagnosed by targeted biopsy as low-grade dysplasia, and intra-mucosal adenocarcinoma was almost twice as likely to be diagnosed through targeted biopsy as high-grade dysplasia.

Greater than a third of prevalent cases were diagnosed through targeted biopsy, almost three times as many as incident cases, and approximately sixty percent of cases in which a prior diagnosis of indefinite for dysplasia or above was made were diagnosed through targeted biopsy (Table 2).

Barrett's specialist endoscopists diagnosed fifty percent of cases through targeted biopsy - almost twice the proportion so diagnosed by the other endoscopist grades combined (Table 3), but the

absolute number of cases was small (n=10), and the differences between groups of endoscopists did not reach statistical significance.

The vast majority of targeted biopsies were performed using white-light endoscopy – with only sixteen cases diagnosed using advanced imaging modalities.

There were eight cases in which "inflammation" alone was listed as the endoscopist impression. However, histological analysis found that LGD was noted in four of these cases. Notably, the other four cases were found to have IMCA.

Table 1. The relationship between histological diagnosis and the type of biopsy used

	Random, four-quadrant	Targeted	
LGD	80 (90.91%)	8 (9.09%)	88
HGD	50 (71.43%)	20 (28.57%)	70
IMCA	32 (50.00%)	32 (50.00%)	64
	162 (72.97%)	60 (27.03%)	222

$\chi^2 = 31.56$, degrees of freedom $= 2$, $p < 0.001$

Table 2. The type of biopsy used in prevalent versus incident cases

	Random, four-quadrant	Targeted	
Prevalent	63 (63.64%)	36 (36.36%)	99
Incident	92 (86.79%)	14 (13.21%)	106
Prior ID + *	7 (41.18%)	10 (58.82%)	17
	162 (72.97%)	60 (27.03%)	222

$\chi^2 = 23.35$, degrees of freedom $= 2$, $p < 0.001$
* prior indefinite for dysplasia or above

Table 3. The relationship between endoscopist grade and the type of biopsy used

	Random, four-quadrant	Targeted	
Barrett's specialist endoscopist	5 (50.00%)	5 (50.00%)	10
Consultant	67 (70.53%)	28 (29.43%)	95
Fellow	36 (72.00%)	14 (28.00%)	50
Registrar	16 (84.21%)	3 (15.79%)	19
Nurse practitioner	32 (78.05%)	9 (21.95%)	41
	156 (72.56%)	59 (27.44%)	215

$\chi^2 = 4.68$, degrees of freedom = 3, p = 0.322

DISCUSSION

Advances in endoscopy have held out the tantalising prospect of replacing random, four-quadrant biopsies as per the Seattle protocol as standard of care in Barrett's surveillance. Whilst it is generally agreed that random, four-quadrant biopsy as part of the Seattle protocol is important (10–14), the emergence of high-resolution white-light endoscopy and advanced imaging modalities has raised the question as to whether it may be possible to use targeted biopsies in lieu of random, four-quadrant biopsies without compromising neoplasia detection (22). This has the obvious advantage of reducing endoscopy and pathology workload, but is only viable if detection of dysplasia is not compromised. A switch from random to targeted biopsies has to some extent been successfully adopted in surveillance of inflammatory bowel disease (IBD) (18,24), with dye-spray endoscopy replacing random biopsies in some centres. However, there are substantial differences in this respect between BO and IBD. Firstly, the overall length of BO mucosa is much smaller than that required to be surveilled in IBD. This means that it would be impossible in IBD to achieve the same coverage with random biopsies as per the four-quadrant biopsy per two centimetres in Barrett's oesophagus. There is also good evidence that random sampling of the large bowel mucosa is relatively ineffective in detecting dysplasia in IBD.

This study has clearly demonstrated that in routine endoscopy practise within our region, encompassing several district general hospitals and one tertiary referral centre, which should be generalisable to the entire NHS – random, four-quadrant biopsy is much more effective in

detecting dysplasia than targeted biopsy alone. Over seventy percent of all cases were detected through random, four-quadrant biopsy – an observation that strongly emphasizes the role of random, four-quadrant biopsy in Barrett's surveillance. The consensus in the literature is that non-adherence with the Seattle protocol amongst endoscopists is widespread, and is associated with a reduction in dysplasia detection (15–17). In light of our results, this is a significant concern.

We also made several other observations. Firstly, prevalent cases - those whose dysplasia was detected at the initial diagnosis of Barrett's - were three times more likely to be diagnosed through targeted biopsy than incident cases - those with known Barrett's who had dysplasia detected arising under surveillance. It is reasonable to suggest that prevalent cases – that is, patients whose gastroscopy is likely to have been prompted by clinical symptoms – are more likely to have an underlying macroscopic lesion, which may then be sampled by targeted biopsy, as opposed to patients undergoing routine surveillance. Secondly, approximately sixty percent of cases with a prior diagnosis of indefinite for dysplasia or above were diagnosed through targeted biopsy. It is possible that those with prior indefinite for dysplasia or above have a greater likelihood of developing a visible neoplastic lesion, which is subsequently diagnosed through targeted biopsy. On the other hand, it is also possible that knowledge of prior pathology may lead endoscopists to conduct a more careful inspection, through which more lesions are detected by targeted biopsy. Thirdly, we found an association between the severity of pathology and likelihood of diagnosis through targeted biopsy, in that, more advanced pathology was typically diagnosed by targeted biopsy. This is in keeping with the general belief that low-grade dysplasia is often invisible endoscopically. Surprisingly, however, most high-grade lesions were also

detected by random, four-quadrant biopsy and of particular interest, only fifty percent of intra-mucosal adenocarcinoma was diagnosed by targeted biopsy. This included 4 cases where intra-mucosal adenocarcinomas were detected by biopsies taken for suspected oesophagitis without a clinical diagnosis of Barrett's oesophagus. This has implications not only for biopsy schedules in Barrett's oesophagus, but also in oesophagitis.

Barrett's specialist advanced endoscopists diagnosed fifty percent of cases through targeted biopsy - almost twice the proportion so diagnosed by the other endoscopist grades combined. It is likely that advanced training and experience played a role in the greater diagnostic yield of Barrett's specialist endoscopists. However, the number of cases was small, and it is questionable whether it is feasible for the majority of endoscopists diagnosing and surveilling BO to develop the concentrated experience necessary to recognise more subtle abnormalities. Similarly, other studies have also found that specialist endoscopist cohorts were associated with greater dysplasia detection (25–26). It has been suggested that – in the hands of an expert endoscopist – the ability to dispense with random, four-quadrant biopsies may become a reality in the near future. However, our findings challenge this perspective, suggesting that even Barrett's specialist endoscopists only diagnosed fifty percent of cases through targeted biopsy.

The vast majority of cases diagnosed by targeted biopsy were made using high-resolution white-light endoscopy rather than advanced imaging modalities. In fact, only sixteen cases were diagnosed using advanced imaging modalities, approximately one-third of that of white-light endoscopy. It is therefore reasonable to suggest that advanced imaging modalities play only a minor role in Barrett's surveillance at present – a conclusion that reflects current medical society

guidelines, which have not recommended advanced imaging modalities for routine use (10–14,22), as well as the realities of current endoscopy practice in the UK.

The main strength of this study is its generalizability. It includes patients evaluated in both tertiary referral and district general hospitals, as well as a range of endoscopist grades. However, we readily accept that there are also certain limitations. Firstly, the retrospective, observational study design could increase risk of bias. However, by including virtually every case of dysplasia this should be ameliorated. Secondly, the small sample size reduces confidence in certain results, such as those involving Barrett's specialist endoscopists and advanced imaging modalities. However, we believe that this does not affect the strength of our main conclusions. Thirdly, we do not know the extent to which all endoscopists applied the Seattle protocol fully, but from previous audits elsewhere we know that that fewer biopsies than recommended are often taken. This is however a conservative bias relative to our main conclusion, in that if the Seattle protocol had been followed it is likely that random, four-quadrant biopsy would have picked up even a greater number of dysplastic cases (17,27).

In conclusion, we found that half of intra-mucosal adenocarcinomas and over seventy percent of all cases in our study were detected through random, four-quadrant biopsy. These findings strongly emphasize the importance of random, four-quadrant biopsy in the detection of not only low-grade dysplasia, but also high-grade dysplasia and intra-mucosal adenocarcinoma as part of Barrett's surveillance. It is therefore clear that the Seattle protocol remains the gold-standard in the era of high-resolution video endoscopy and advanced imaging modalities. This study highlights several future directions. Firstly, it is important to tackle the problem of endoscopist

non-adherence with regards to the Seattle protocol. Secondly, it is important to place emphasis on clinical training in order to improve the diagnostic yield of targeted biopsy using modern high-resolution video endoscopy. Thirdly, any new imaging modality or technique requires further assessment in unselected patient populations in order to determine clinical utility in routine practice.

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The authors report no conflict of interest.

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This dataset utilized in this research may be provided upon request.