

## Bartrett's esophagus registries

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## ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Issue: *Barrett's Esophagus: The 10th OESO World Congress Proceedings***Barrett's esophagus registries**Piers A.C. Gatenby,<sup>1</sup> Christine P.J. Caygill,<sup>2</sup> Anthony Watson,<sup>2</sup> Liam Murray,<sup>3</sup> and Yvonne Romero<sup>4</sup>

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The following on Barrett's esophagus registries contains commentaries on the data sets to be included, organizational issues, and the demographic, lifestyle, and diagnostic differences between the United States and Europe. The importance of collaborative studies is also discussed.

**Keywords:** Barrett's registries; cancer risk; surveillance; esophageal cancer; tissue bank; quality of life

**Concise summaries**

- The crucial future role of registries is likely to involve further examination and refinement of surveillance strategies to assess risk, cost, and benefit with the result of targeting surveillance appropriately for individual patients. The associated symptoms of gastro-esophageal reflux are increasing, and it is expected that current trends in increased diagnosis of Barrett's esophagus and development of esophageal cancer are likely to continue.
- Registries have been set up to help to clarify the answers to some questions such as current trends in increased diagnosis of Barrett's esophagus and development of esophageal cancer, the natural history of the metaplastic segment, factors influencing cancer risk. They may be institution-based or population-based, and may provide infrastructure for central pathological confirmation, and coordination and recruitment of clinical studies.
- The method of data collection may be retrospective, which limits available information to patient identifiers, demographic data, date of diagnosis, and histological features, but allows a larger number of cases, where a long follow-up has already elapsed, to be collected in a short period of time at lower cost. They can be prospective, allowing standardization of procedures with direct data collection from patients. The data collected vary depending on the organization of the registry and the purpose that it is intended to fulfill.
- Follow-up of registered patients is crucial as the registered cases then form a cohort, allowing study of outcomes.
- The common data set collected by existing registries includes patient identifiers, demographic data, and date of diagnosis. Further data include histological and endoscopic features, other clinical data and follow-up data. The registries differ in the subjects of interest, categorized by their specific disease phenotype at baseline, and the type of specimen collected.
- As an indirect consequence of registries, practice homogeneity and quality is improved with the introduction of standardization for the measurement of endoscopic landmarks and biopsy protocols at each site. The crucial future role of registries is likely to involve further examination and refinement of surveillance strategies to assess risk, cost, and benefit with the result of targeting surveillance appropriately for individual patients.
- There are a small number of Barrett's registries worldwide and collaboration is important for allowing comparison between different

regions and pooling of data to improve study power. Collaboration among investigators, clinicians, patients, and registries may facili-

tate identification of translational discoveries that reduce the mortality rate of esophageal adenocarcinoma.

## 1. Do Barrett's registries have a role to play in research?

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The management of Barrett's esophagus presents a particular challenge in modern healthcare. This is an apparently new condition, or one whose presence has only been detected over recent decades. If the increasing rates of diagnosis have resulted from more than simply improvements in recognition of the metaplastic mucosa, the epidemiology of Barrett's esophagus is changing.

This hypothesis (that the observations represent a true increase in incidence of Barrett's esophagus) is supported by the rapid increase in esophageal adenocarcinoma. The rapid escalation in cases of esophageal adenocarcinoma is most marked in non-Hispanic white men in developed countries (with the highest global incidence being seen in Scotland and the highest in the U.S. in Massachusetts, where this conference has been held).<sup>1</sup> Furthermore, the associated symptoms of gastroesophageal reflux are increasing, and it is expected that current trends in increased diagnosis of Barrett's esophagus and development of esophageal cancer are likely to continue.

The natural history of the metaplastic segment is not fully documented. Overall, studies agree that the overall risk of progression to adenocarcinoma is around 0.6% per annum following diagnosis of Barrett's and exclusion of prevalent cancers, and 1% for development of high-grade dysplasia and adenocarcinoma.<sup>2</sup> While the risk of progression is relatively low, this means that typical surveillance centers will see a small number of cases of high-grade dysplasia or cancer and rely on larger studies, meta-analyses, and expert guidelines to direct their clinical practice.

Surveillance frequency and estimation of cancer risk are primarily based upon the detection of dysplasia at biopsy and although adjuncts to standard endoscopy and systematic biopsy are used in

research and specialized centers, most patients' biopsies are not targeted by these techniques and adherence to biopsy protocols is variable. The reported rate of progression to high-grade dysplasia or cancer following a diagnosis of low grade dysplasia (which is further complicated by the difficulties with diagnosis in the center of the histological spectrum) is variable, and frequent resolution of findings of dysplasia at subsequent endoscopy make this a difficult area in Barrett's esophagus for clinicians to manage well.<sup>3</sup>

Other factors influencing cancer risk such as age, sex, metaplastic segment length, obesity, smoking, method of reflux control, and other medications have been examined, but overall, our ability to treat optimally, explain the associated risks clearly, and undertake targeted surveillance tailored to stratification of an individual patient's risk remain poor.

Registries have been set up to help to clarify the answers to some of these questions. They may be population-based (such as the Northern Ireland, Danish [reported at this conference], and Dutch registries), which usually register patients from histopathology databases or institution-based (such as the Mayo Clinic Barrett's Registry, Cleveland Clinic Barrett's Registry, Venice Region Barrett's Registry, and UK Barrett's Oesophagus Registry). The pathological databases are able to provide the appropriate population denominator and the institution-based registries can draw from multiple units to provide a large volume of Barrett's cases and may be able to access other clinical information for studies of associations. Barrett's registries may also provide infrastructure for central pathological confirmation, coordination, and recruitment of clinical studies such as the two large U.S. studies of radiofrequency ablation.<sup>4,5</sup>

The crucial future role of registries is likely to involve further examination and refinement of surveillance strategies to assess risk, cost, and benefit with the result of targeting surveillance appropriately for individual patients. Registries should also examine further for differences in geographical variation and variation in time. Further work should

involve catalyzing collaboration and looking for opportunities to intervene earlier in the metaplasia–dysplasia–neoplasia sequence that can subsequently be tested by cohort and intervention studies.

## 2. Barrett's registries: what data set should be included?

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Defining a core data set for Barrett's registries is a complex question and perhaps the best way to approach it is by looking at the structure of existing Barrett's registries and the data set they include. Barrett's registries may be classified as those that are population-based or institution based. The method of data collection may be retrospective or prospective, and the data collected vary depending on the organization of the registry and the purpose that it is intended to fulfill.

### *Population-based registries*

These may be further subdivided into those who have complete registration for a geographical area, which are usually based on national/regional histopathological databases and include the Dutch (PALGA) and Northern Irish nationwide pathology registries, the Rochester Epidemiology Project (U.S.), and the retrospective component of the Amsterdam Gastroenterological Association Barrett's Registry. Other registries such as the UK Barrett's Oesophagus Registry (UKBOR), the prospective component of the Amsterdam Gastroenterological Association Barrett's Registry, and Veneto Region Barrett's Registry (EBRA) are population representative.

These registries contain data from either all or a proportion of centers providing management of Barrett's esophagus in a region. They do not have the robust processes for identifying all cases from national data and, in examining their data, it is important to consider what reference population the cases are drawn from. Population-based registries allow the calculation of rates of Barrett's diagnosis and trends in these rates.

### *Hospital/Institution-based registries*

Other registries may be hospital or institution-based such as the Mayo Clinic (EABE) and Cleveland Clinic Barrett's Register. Institutions may be

able to specify data collection protocols more easily than multicenter registries, and those institutions with high expertise may have large numbers of Barrett's patients comparable to some of the regional population-based registries.

### *Retrospective data collection*

Data collection may be prospective or retrospective. The Northern Irish Barrett's Registry and Dutch Pathology Registry collect data from pathology reports, which limits available information to patient identifiers, demographic data, date of diagnosis, and histological features (presence of specialized intestinal metaplasia and dysplasia).

Using these methods of data collection means that missing data are common, and these registries lack other important information such as the endoscopic features of the metaplastic segment. Diagnostic coding of the nonstandardized free text pathological reports can be difficult. These data can be enhanced by case note and endoscopy note review or histopathological review of biopsy specimens, but these are time consuming and expensive. The medical record review may still not be able to collect all missing data. Retrospective collection also allows little opportunity for standardization of diagnostic criteria and procedures (such as biopsy protocol and histopathological reporting). Furthermore, there may be difficulty in locating and retrieving records and specimens.

The advantages of retrospective data collection are that it allows a larger number of cases where a long follow-up has already elapsed to be collected in a short period of time at lower cost. The unselected cases may be more representative of the real life situation and analysis may be undertaken as soon as the data have been collected rather than having to wait for the accrual of cases prospectively.

### *Prospective data collection*

This allows standardization of procedures with direct data collection from patients. Registries using prospective collection procedures have been able to collect data including identifiers, demographics, clinical data (indication for endoscopy, symptoms, lifestyle factors, anthropometry, comorbidities, medications, and treatment decisions), endoscopic data (segment length—often using the Prague classification,<sup>6</sup> presence of esophagitis, ulceration, and nodularity), specification of the biopsy protocol (e.g., quadrantic biopsies and biopsies

from the stomach and squamous esophagus), pathology data (presence of specialist intestinal metaplasia, dysplasia, inflammation, and *Helicobacter Pylori*) and the collection of other biospecimens for storage and analysis (such as blood for genetic analysis).

### *Follow-up of registry cases*

Follow-up of registered patients is crucial as the registered cases then form a cohort. This allows study of outcomes: disease progression (and regression), development of high-grade dysplasia and esophageal adenocarcinoma, extraesophageal malignancies, and mortality. The influence of management: antireflux surgery, acid suppression, entry into surveillance, NSAIDs, and statins can be examined.

Passive follow-up may involve death registration, links to cancer registration, identification of high-grade dysplasia, and surveillance biopsies, and following cessation of active surveillance or moving away from their surveillance center, patients may still be followed-up to a limited degree using these tools.

Active follow-up may be either opportunistic or at scheduled surveillance appointments and further samples may also be taken at this time.

### *Organizational issues*

Running an effective registry requires good management and is a multidisciplinary task involving gastroenterology, gastrointestinal surgery, pathology, epidemiology, database management/IT, and specialist nurses. A steering committee is required, which generally includes representatives from the involved disciplines as well as funders and lay representatives. It will be involved in strategic decision making, acquisition of funding (which is often insecure), and govern access to data.

Registries will need to have ethical/IRB permission for the study from the appropriate board and are increasingly requiring informed consent from patients for use of their data (although this may not always be required for some population-based studies). The registry will also need to take steps to ensure data security and confidentiality.

### *Comparability and collaboration*

There are a small number of Barrett's registries worldwide, and collaboration is important allowing comparison between different regions and pool-

ing of data to improve study power. There are challenges with data harmonization in particular between those registering retrospectively and prospectively, but early steps have been taken and a workshop of European Barrett's Registries met in Venice in 2007.<sup>7</sup>

### *Conclusion*

Ideally, registries will contain as much data as is practical. The common data set collected by existing registries includes patient identifiers, demographic data, and date of diagnosis. Further data include histological and endoscopic features, other clinical data, and follow-up data.

### **3. Barrett's esophagus registries: what are the demographic, lifestyle, and diagnostic differences between the United States and Europe, and can these be overcome for future collaborative studies?**

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As per the Centers for Disease Control, a registry is a "system for collecting and maintaining in a structured record, information on specific persons from a defined population with specified health characteristics." Although there are at least 20 registries of patients with Barrett's esophagus throughout Europe and the United States, for simplicity, comparisons will be made using four prominent registries: the Mayo Clinic Esophageal Adenocarcinoma and Barrett's Esophagus (EABE) Registry,<sup>8</sup> the Italian European Barrett's Registries Association (EBRA),<sup>9</sup> the Northern Ireland Barrett's Register (NIBR),<sup>10</sup> and the United Kingdom National Barrett's Oesophagus Registry (UKBOR).<sup>11</sup>

The registries differ in the subjects of interest, categorized by their specific disease phenotype at baseline (Table 1), the type of specimen (e.g., blood and tissue) collected, and how it is processed (e.g., fresh-frozen, formalin-fixed paraffin embedded). Three of the registries store formalin-fixed tissue, the exception being UKBOR. The EABE Registry additionally collects fresh-frozen tissue. Blood is only collected in the EABE Registry. The registries also differ in the manner in which clinical information (e.g., demographics, symptoms, risk factors, and quality of life) is collected (retrospective chart review,

**Table 1.** Phenotypes collected in each registry at baseline

Registry	Phenotypes of Interest					
	Cancer			Barrett's esophagus (BE)		
	Adenocarcinoma		Esophageal squamous cell carcinoma	LSBE	SSBE	Endoscopic BE without biopsy confirmation
Esophageal	GEJ					
EABE	X	X	X	X		
EBRA				X	X	
NIBR				X	X	
UKBOR				X	X	X

*Note:* Endoscopic BE without biopsy confirmation = any endoscopic length of salmon-colored mucosa thought to be in the esophagus without confirmation of columnar cells, intestinal metaplasia, or goblet cells.

LSBE, long-segment ( $\geq 3$  cm) BE (specialized intestinal metaplasia); SSBE, short-segment ( $< 3$  cm) BE (specialized intestinal metaplasia). EABE, Mayo Clinic Esophageal Adenocarcinoma and Barrett's Esophagus registry; EBRA, Italian European Barrett's Registries Association; NIBR, Northern Ireland Barrett's Register; UKBOR, United Kingdom National Barrett's Oesophagus Registry. This table is the work and intellectual property of Yvonne Romero.

prospective annual questionnaires) and annotated (Table 2). Another difference is in the diagnostic criteria used by registries. In UKBOR a patient is considered as having Barrett's esophagus if the diagnostic biopsy shows gastric type mucosa but no intestinal metaplasia.

There are advantages to each registry. Prospectively collected fresh-frozen tissue and blood may be particularly helpful in biomarker discovery, while formalin-fixed specimens serially collected over time will be helpful in confirming the utility of biomarker panels, especially on a population-wide

basis. Registries help to define the natural history of disease.

As an indirect consequence of registries, practice homogeneity, and quality is improved with the introduction of standardization for the measurement of endoscopic landmarks and biopsy protocols at each site. Patients with nondysplastic Barrett's esophagus have a low (0.5%) annual risk of progression to esophageal adenocarcinoma.<sup>12</sup>

Due to the infrequent event rate, informal sample size calculations have suggested that 10,000 patients followed for 10 years would be required

**Table 2.** Method and type of clinical information collected in each registry

Registry	Prospective self-report questionnaires								Retrospective medical record abstraction
	Baseline				Follow-up				
	Sx	Risk factors	Dem/Life	QOL	Sx	Risk factors	Dem/Life	QOL	
EABE	X	X	X	X	X	X	X	X	
EBRA	X								X
NIBR									X
UKBOR									X

Sx, symptoms; dem/Life, demographic information and lifestyle factors; QOL, quality of life; EABE, Mayo Clinic Esophageal Adenocarcinoma and Barrett's Esophagus registry; EBRA, Italian European Barrett's Registries Association; NIBR, Northern Ireland Barrett's Register; UKBOR, United Kingdom National Barrett's Oesophagus Registry. This table was created by Yvonne Romero.

to discover and validate biomarkers of neoplastic transformation.

Thus, collaboration among investigators, clinicians, patients, and registries may facilitate identification of translational discoveries that reduce the mortality rate of esophageal adenocarcinoma.

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### Conflicts of Interest

The authors declare no conflicts of interest.

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