Digestive and Liver Disease xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

How to get the most out of costly Barrett's oesophagus surveillance

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ARTICLE INFO

Article history:
Received 21 February 2018
Received in revised form 11 April 2018
Accepted 12 April 2018
Available online xxx

Keywords:
Advanced endoscopic imaging
Dysplasia
Early oesophageal cancer
Endoscopic therapy

ABSTRACT

Current endoscopic surveillance protocols for Barrett's oesophagus have several limitations, mainly the poor cost-effectiveness and high miss rate. However, there is sufficient evidence that patients enrolled in a surveillance program have better survival chances of oesophageal cancer due to earlier tumor stages at diagnosis compared to patients with de novo diagnosed oesophagus cancer. Risk stratifications aim to identify patients at highest risk of developing adenocarcinoma of the oesophagus; most of them base on the length of the Barrett's segment and the presence of dysplasia.

This review discusses prognostic factors and provides practical guidance on how to improve the efficacy and outcome in Barrett's surveillance programs.

1. Challenges for endoscopic surveillance programs

The presence of Barrett's oesophagus has been identified as the main risk factor for developing oesophageal adenocarcinoma and epidemiologic studies show that the incidence of oesophageal adenocancer has been rising alarmingly over the past decades. Despite advances in surgery and oncology, the overall 5 years survival rate of oesophagus cancer remains still disappointingly low (15–25%) [1]. However, the vast majority (about 95%) of all patients with Barrett's oesophagus will never develop cancer. Patients with Barrett's oesophagus will ten times more likely die from other unrelated causes than from oesophageal cancer [2]. Only about 0.1–0.5% of patients with Barrett's oesophagus will progress to high grade dysplasia or adenocancer within one year (Table 1).

On the other hand, we have diagnosed only a fraction of the patients with Barrett's oesophagus; the prevalence of Barrett's oesophagus in the population is about 1–2%. This means that the majority of the individuals affected with Barrett's oesophagus have never been endoscoped and are not aware of the risk factor.

These facts render it difficult to run any surveillance programs efficiently and its cost-effectiveness is still disputed. Published studies on the cost-effectiveness of Barrett's surveillance programs have demonstrated mixed results [7–9]. Hopefully, the results of the BOSS trial will answer whether the actual risk: benefit ratio favours an endoscopic surveillance strategy but the data will not be available for some years (estimated publication date in 2024) [10,11]; http://www.nets.nihr.ac.uk/projects/051201.

2. Why is endoscopic surveillance in patients with Barrett's oesophagus recommended?

Patients with adenocarcinoma of the oesophagus have earlier tumor stages and better survival rates when they were detected on surveillance programs.

Surveillance programs have been recommended by many Gastroenterological societies (BSG [12], ACG [13]) and indeed many studies (Table 2) demonstrate that patients participating in these endoscopic surveillance programs have earlier stage cancers when it is detected compared to the general population where oesophageal cancer is generally found only in advanced stages when patients present with symptoms.

The detection of oesophagus cancer in early stages when curative treatment might still be possible is associated with a better outcome compared to more advanced stages. High grade dysplasia and intramucosal cancer are nowadays treated endoscopically by endoscopic resection followed by radiofrequency ablation of the remaining Barrett's epithelium. A recent meta-analysis, showed a reduction in mortality risk from oesophageal cancer by 61% when patients underwent endoscopic surveillance [26].

3. Risk stratification

Current surveillance programs are expensive and time consuming [27]. The costs are estimated to range between $10 000 and $100 000 per quality-adjusted life year [9]. Ideally, we should have

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https://doi.org/10.1016/j.dld.2018.04.012
1590-8658/

Table 1
Annual progression rate from non-dysplastic Barrett's oesophagus to high grade dysplasia and oesophageal cancer.

Study	Patients	Follow-up [years]	High grade dysplasia	Adenocancer
Bhat et al. [3]	8522 (3917 IM)	7.0	0.22%/year	0.16%/year (0.38%/year)
Hvid-Jensen et al. [4]	11,028 IM	5,2	0.26%/year	0.12%/year
Desai et al. [2]	11,434	5.1	na	0.33%/year
Sharma [5]	1376	4.1		0.5%/year
Rugge [6]	841	3.7	0.49%/year	0.23%/year

Table 2
Patients with adenocarcinoma of the oesophagus have earlier tumor stages and better survival rates when they were detected on surveillance programs.

Authors	Oesophageal adenocancer	On surveillance	Earlier cancer stage	Improved survival
Streitz et al. [14]	77	11	P = .006	P = .007
Peters et al. [15]	52	17	P = .01	P = .05
Van Sandick et al. [16]	70	16	P = .0001	P = .003
Corley et al. [17]	23	15	P = .02	P = .001
Cooper et al. [18]	1633	159	P = .001	P = .01
Incarbone et al. [19]	97	12	P = .01	P = .01
Fountoulakis et al. [20]	91	17	P = .001	P = .008
Cooper et al. [21]	2754	23	P = .001	P = .001
Ferguson et al. [22]	80	12	P = .001	P = .001
Grant et al. [23]	224	36	P = .0001	P = .001
El-Serag et al. [24]	424	209	P = .001	P = .0001
Tramontano et al. [25]	4978	577	P = .0001	P = .0001

better risk stratification as the progression rate for non-dysplastic Barrett's oesophagus is low (Table 1). Future research should aim at biomarkers selecting patients with higher progression risk [28–30].

The BSG guidelines [12] have recommended surveillance intervals reflecting the risk of the patient to develop cancer which depends on the length of the Barrett's oesophagus. Patients with long Barrett's segment >3 cm should be endoscoped every 2–3 years, while short Barrett's segments have a lower risk to progress and 3–5 years intervals are recommended. Advanced age, central obesity, male gender and smoking are known risk factors for the progression of Barrett's oesophagus to Barrett's cancer [31].

For patients with non-dysplastic Barrett's epithelium, the annual risk of progression to high grade dysplasia or cancer ranges between 0.1% and 0.5% (Table 1). In a recent meta-analysis, low grade dysplasia confirmed by at least two expert pathologist had an annual incidence rate of 10.35% to progress to high grade or early adenocancer while after endoscopic finding of high grade dysplasia 28.63% developed cancer per year [32].

Patients with a long Barrett's oesophagus of more than 10 cm, confirmed low grade dysplasia, high grade dysplasia or early cancer should be referred to a high volume center [33,34] with endoscopic interventional, surgical and pathology expertise in the management of complicated Barrett's oesophagus.

4. How to perform Barrett's oesophagus surveillance

4.1. High definition white light endoscopy

Barrett's oesophagus is often diagnosed using standard white light endoscopy. For surveillance purposes high definition endoscopes should be preferred as improved image quality aides the detection of subtle mucosal abnormalities. The sensitivity to detect dysplasia/early neoplasia is higher using high definition endoscopes [35].

Meticulous clearing of the oesophagus from mucus and residual bubbles is mandatory to achieve adequate views. A pre-procedure drink containing simethicone and *N*-acetylcysteine improves the mucosal visibility [36].

Attaching a transparent cap at the tip of the endoscope can facilitate the visualization of the mucosa which is often impaired by frequent peristaltic movement, especially around the cardia.

Correctly defining and detecting Barrett's oesophagus is the first important step. Often endoscopists overestimate the risk for the individual patient by calling an irregular Z-line (the squamocolumnar junction) with short extensions of the columnar-lined epithelium over a few mm a short Barrett's segment. The distal end of a Barrett's oesophagus is defined by the top of the gastric folds and this can be best identified when partially deflating. Only if there is a clearly visible columnar-lined epithelium (>1 cm, [ESGE [33], BSG] [12]) in the distal oesophagus proximal to the top of the gastric folds (or the palisade vessels in the Japanese definition), should this be labeled as Barrett's oesophagus. A pitfall that often occurs is to take biopsies from the gastric cardia which then demonstrates intestinal metaplasia and the patient is falsely labeled as having Barrett's oesophagus although there is no visible columnar epithelium in the distal oesophagus.

The British and Asian guidelines rely on the endoscopically visible presence of columnar lined epithelium proximal to the top of the gastric folds, but the European and American guidelines also require confirmation of intestinal metaplasia present on biopsies.

Documenting the length of the Barrett's epithelium according to the Prague classification (C—circumferential length, M—maximal length) allows risk stratification and selecting surveillance intervals which are also based on the presence of dysplasia in the biopsy results.

Describing any visible lesions within the Barrett's mucosa according to the Paris classification helps to predict the presence of invasive malignancy.

Rarely, inlet patches are mistaken for Barrett's oesophagus although the location in the cervical oesophagus should make it clear. Inlet patches are a common developmental abnormality (about 5%) and easier seen when using narrow band imaging during withdrawal from the oesophagus [37]. Inlet patches can cause unspecific symptoms of dysphagia and discomfort but usually do not harbor intestinal metaplasia. The development of adenocarcinoma from inlet patches is extremely rare; therefore patients with inlet patches do not require endoscopic surveillance.

Current surveillance protocols recommend the so-called Seattle protocol which advises to take one random biopsy in every quadrant of the Barrett's oesophagus in every 1–2 cm of Barrett's length. In long Barrett's segments of more than 10 cm this can result in more than 40 biopsies that will be sent to histology. In a long Barrett's segment the time to take all these biopsies can easily amount

Please cite this article in press as: Braden B, Jones-Morris E. How to get the most out of costly Barrett's oesophagus surveillance. Dig Liver Dis (2018), https://doi.org/10.1016/j.dld.2018.04.012