

CAGS AND ACS EVIDENCE BASED REVIEWS IN SURGERY. 38

Guidelines for the management of Barrett esophagus with high-grade dysplasia?

Harry J. Henteleff, MD
James C. Ellsmere, MD
Nabil Rizk, MD
for the Members of the
Evidence Based Reviews
in Surgery Group*

*The CAGS/ACS Evidence Based Reviews in Surgery Group comprises Drs. N.N. Baxter, K.J. Brasel, C.J. Brown, P. Chaudhury, C.S. Cutter, C.M. Divino, E. Dixon, L. Dubois, G.W.N. Fitzgerald, H.J.A. Henteleff, A.W. Kirkpatrick, S. Latosinsky, A.R. MacLean, T.M. Mastracci, R.S. McLeod, A.M. Morris, L.A. Neumayer, L.K. Temple and Ms. M.E. McKenzie.

Correspondence to:
Ms. Marg McKenzie, RN
Administrative Coordinator, EBRS
Mount Sinai Hospital, L3-010
60 Murray St., PO Box 23
Toronto ON M5T 3L9
fax 416 586-5932
mmckenzie@mtsinai.on.ca

DOI: 10.1503/cjs.027111

The term “evidence-based medicine” was first coined by Sackett and colleagues as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.”¹ The key to practising evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding. For clinicians to practise evidence-based medicine, they must have the skills to read and interpret the medical literature so that they can determine the validity, reliability, credibility and utility of individual articles. These skills are known as critical appraisal skills, and they require some knowledge of biostatistics, clinical epidemiology, decision analysis and economics, and clinical knowledge.

Evidence Based Reviews in Surgery (EBRS) is a program jointly sponsored by the Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS) and is supported by an educational grant from ETHICON and ETHICON ENDO-SURGERY, both units of Johnson & Johnson Medical Products, a division of Johnson & Johnson and ETHICON Inc. and ETHICON ENDO-SURGERY Inc., divisions of Johnson & Johnson Inc. The primary objective of EBRS is to help practising surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected for their clinical relevance to general surgeons and because they cover a spectrum of issues important to surgeons, including causation or risk factors for disease, natural history or prognosis of disease, how to quantify disease, diagnostic tests, early diagnosis and the effectiveness of treatment. A methodological article guides the reader in critical appraisal of the clinical article. Methodological and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS website, where they are archived indefinitely. In addition, a listserv allows participants to discuss the monthly article. Surgeons who participate in the monthly packages can obtain Royal College of Physicians and Surgeons of Canada Maintenance of Certification credits and/or continuing medical education credits for the current article only by reading the monthly articles, participating in the listserv discussion, reading the methodological and clinical reviews and completing the monthly online evaluation and multiple choice questions.

We hope readers will find EBRS useful in improving their critical appraisal skills and in keeping abreast of new developments in general surgery. Four reviews are published in condensed versions in the *Canadian Journal of Surgery* and 4 are published in the *Journal of the American College of Surgeons*. For further information about EBRS, please refer to the CAGS or ACS websites. Questions and comments can be directed to the program administrator, Marg McKenzie, at mmckenzie@mtsinai.on.ca.

Reference

1. Evidence-Based Medicine Working Group. Evidence-based medicine. *JAMA* 1992;268:2420-5.

SELECTED ARTICLE

Fernando HC, Murthy SC, Hofstetter W, et al. The Society of Thoracic Surgeons Practice Guideline Series: guidelines for the management of Barrett's esophagus with high-grade dysplasia. *Ann Thorac Surg* 2009;87:1993–2002.

ABSTRACT

Objective: To address the role of esophageal resection and other approaches that are becoming increasingly adopted for the management of Barrett esophagus with high-grade dysplasia (HGD). **Data sources:** MEDLINE, Cochrane Library and the Trip databases were searched for the terms “Barrett’s or high-grade dysplasia” and “surgery,” “photodynamic therapy,” (PDT) “radiofrequency ablation” (RFA) or a combination of these. **Study selection:** Studies were selected based on the best evidence supporting these commonly used strategies for HGD. **Data extraction:** The guideline was divided into 4 major components: endoscopic surveillance, mucosal ablation, endoscopic mucosal resection (EMR) and esophagectomy. **Main results:** Regarding endoscopic surveillance, HGD is an entity distinct and distinguishable from intramucosal carcinoma, and it does not invariably progress to carcinoma. If there is progression, it can be reliably detected at an early, curable stage. Patients undergoing surveillance are reliable for follow-up and are candidates for further therapy if progression is diagnosed. Regarding mucosal ablation, several methods have been reported for HGD; of these, PDT is the most widely used. Radiofrequency ablation has been introduced into practice and is being studied in many of the same centres that have advocated for PDT (RFA is useful for high-risk surgical patients and typically requires multiple endoscopic sessions for therapy and follow-up.) The EMR method has been used to excise discrete esophageal mucosal nodules that were small, flat or polypoid in nature and that did not invade deeper than the submucosa. Owing to the frequent multifocality of Barrett esophagus, a concomitant mucosal ablative procedure is often required to assure complete eradication of disease (EMR can evaluate and treat discrete mucosal nodules in the esophagus). Most cancers found incidentally in patients with HGD are cured by esophagectomy. It can be performed safely with an operative mortality approaching 1% (it remains the standard of care for patients deemed to have good operative risk). **Conclusion:** Given the complexities in decision-making in the management of HGD, the nuances in diagnosis and therapy, and the risks associated with either over- or undertreatment, Barrett esophagus with HGD is best managed in a centre of excellence, preferably with input from experienced surgeons, gastroenterologists and pathologists with a focused interest in treating this disorder.

COMMENTARY

This practice guideline on the management of Barrett esophagus with associated HGD was produced by the Society of Thoracic Surgeons (STS) and published in 2009.¹ Once there is HGD in Barrett mucosa, there is a high risk of cancer. The STS guideline considers 4 treatment options: endoscopic surveillance, mucosal ablation, EMR and esophagectomy. Historically, esophagectomy has been the treatment recommended by surgeons to eligible patients, whereas other therapies are offered to those who are ineligible or unwilling to undergo surgery.

In general, guidelines can be very useful when there is controversy regarding the best way to manage a disease. They summarize the current evidence, weigh the quality of the evidence and make treatment recommendations. The value of guidelines often depends on their methodologic quality and the strength of the evidence used to make the recommendations. Optimally, there should be a focused guideline question, the target patient population should be defined, a systematic review of the literature should be performed, the evidence should be graded, and experts in all fields relevant to the topic should review the evidence and come to a consensus on the guideline recommendations. Sometimes a Delphi process can be used to facilitate consensus. Guidelines should then be submitted for peer review to a wide range of potential users and revised based on the reviewers' comments.

The STS guideline on the management of Barrett esophagus was developed by a group of thoracic surgeons who met at the annual meetings of the 2 major North American thoracic surgical societies (American Association for Thoracic Surgery and STS) and by conference call. It seems that gastroenterologists and other specialists were not involved, which is a significant limitation because gastroenterologists play a major role in the management of Barrett esophagus. The authors state that their guideline was developed in response to the one produced by the American College of Gastroenterology (ACG). Consensus was achieved by members of the guideline task force, and the guideline was posted on the STS website for comments.

A major weakness of the STS guideline is that the quality of its evidence is low (mainly type B data derived from observational studies) and is therefore subject to interpretation. The recommendations are mostly class II, indicating conflicting evidence or a divergence of opinion. Regarding the management of Barrett esophagus and HGD, there are 3 fundamental issues for which the literature provides conflicting data:

1. In patients evaluated according to the strictest screening guidelines, what is the prevalence of invasive cancer?
2. In patients with “low-risk” HGD who are followed with close screening, what is the likelihood of incident cases of invasive cancer developing? Furthermore, do these incident cases represent progression of disease or

identification of previously missed cancers? In the latter case, is there any potential harm in delaying treatment?

3. If screening alone is believed to be insufficient in managing low-risk HGD, does the addition of ablative therapies effectively treat and prevent progression to invasive cancer?

Although the evidence base used to develop the ACG and STS guidelines was similar, their recommendations often diverge. For example, the ACG guideline recommends that low-risk HGD can be safely followed, whereas the STS guideline recommends that surveillance of low-risk HGD qualifies as only a class IIB recommendation (usefulness and efficacy is less well established). Three key references were used by both groups to support their recommendations. Studies by Schnell and colleagues² (cohort of 75 patients) and Buttar and colleagues³ (cohort of 100 patients) strongly argue that patients with low-risk lesions (flat, unifocal lesions) can be safely followed with intense endoscopic surveillance. Conversely, a study by Weston and colleagues⁴ (smaller cohort of 15 patients) argues that even low-risk HGD lesions are at significant risk for progression. The STS guideline put more weight on the study by Weston and colleagues, whereas the recommendations by the ACG were mainly based on the observations reported by Schnell and colleagues and Buttar and colleagues.

A similar example of a biased interpretation involves the review of the evidence from the retrospective study by Prasad and colleagues⁵ on long-term survival following PDT compared with surgical treatment of HGD (cohort of 199 patients). Although the authors reported equivalent overall and disease-free survival, the results of the study were potentially affected by selection biases. The ACG authors simply state that these 2 treatments yielded similar outcomes without mention of any potential biases, whereas the STS authors point out that the PDT group was older and had greater comorbidities than the surgery group and therefore likely did not survive long enough for cancer to develop (despite the overall survival being the same).

Another example of more subtle yet pervasive differences in the interpretation of the evidence is the STS authors' concern that a strict endoscopic screening regimen may not be practical outside specialized centres, whereas the surgical outcomes quoted list the best available results in the literature. Likewise, the ACG authors tend to underestimate the difficulties associated with the frequency of endoscopies needed to appropriately screen patients and neglect some of the surgical series with better outcomes. They also fail to appreciate that esophagectomies performed for early-stage disease are associated with better outcomes than those performed for advanced-stage disease.

Considering the limitations in both sets of guidelines,

the recommended management for Barrett esophagus with HGD remains unclear.

In the STS guideline, strict endoscopic surveillance of patients is recommended but may not be practical outside of specialized centres. Multiple mucosal ablation techniques are discussed, but neither the STS nor the ACG guidelines included what is now considered to be a landmark paper on the use of RFA in HGD, which appeared in the *New England Journal of Medicine*⁶ after the guidelines were published. This technique and complex EMR are unlikely to be available in nonspecialized centres. Finally, vagal sparing esophagectomy, considered to be a less morbid type of surgery, is also not widely practised.

Although the STS guideline summarizes the limited evidence on the management of Barrett esophagus with HGD and makes soft recommendations with a surgical slant, given the current uncertainty it seems that the most balanced approach would be to follow patients with low-risk HGD closely with an intense regimen of endoscopies, biopsies and mucosal resection of any nodular lesion (with or without the addition of ablative therapies), whereas patients with high-risk HGD should likely undergo an esophagectomy owing to the high likelihood of unsuspected invasive cancers. It is clear that the management of this clinical problem remains controversial, and stronger recommendations useful to those practising outside specialized centres are not yet available.

Competing interests: None declared.

References

1. Fernando HC, Murthy SC, Hofstetter W, et al. The Society of Thoracic Surgeons Practice Guideline Series: guidelines for the management of Barrett's esophagus with high-grade dysplasia. *Ann Thorac Surg* 2009;87:1993-2002.
2. Schnell TG, Sontag SJ, Chefec G, et al. Long-term nonsurgical management of Barrett's esophagus with high-grade dysplasia. *Gastroenterology* 2001;120:1607-19.
3. Buttar NS, Wank KK, Sebo TJ, et al. Extent of high-grade dysplasia in Barrett's esophagus correlates with risk of adenocarcinoma. *Gastroenterology* 2001;120:1630-9.
4. Weston AP, Sharma P, Topalovski M, et al. Long-term follow-up of Barrett's high-grade dysplasia. *Am J Gastroenterol* 2000;95:1888-93.
5. Prasad GA, Wang KK, Buttar NS, et al. Long-term survival following endoscopic and surgical treatment of high-grade dysplasia in Barrett's esophagus. *Gastroenterology* 2007;132:1226-33.
6. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med* 2009;360:2277-88.