CONTROVERSIES IN GASTROENTEROLOGY

Motion – All patients with GERD should be offered once in a lifetime endoscopy: Arguments against the motion

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The evidence for the recommendation that patients with gastroesophageal reflux disease (GERD) be offered once in a lifetime endoscopy is weak and is not supported by any clinical trials. GERD is a very prevalent condition, yet only 10% of patients with GERD have Barrett’s esophagus (BE). Esophageal adenocarcinoma (EAC) is a rare condition and is uncommon even among patients with BE. A decision analysis found that surveillance of BE patients is performed because of inflated estimates of the rate of progression from BE to EAC. Dysplasia more often regresses to more benign histological findings than to cancer, and transient dysplasia can also lead to a high rate of unnecessary endoscopy. Even though practice guidelines about endoscopic surveillance have been published, there is no consensus among gastroenterologists about appropriate protocols, and many physicians are more aggressive than the guidelines. It has not been proved that surveillance saves lives, in part because BE rarely leads to death from EAC. The favourable results from some specialized centres may not be widely applicable. The recommendation for ‘once in a lifetime’ endoscopy for GERD patients is premature.

Key Words: Barrett’s esophagus; Endoscopy; Esophageal carcinoma; Gastroesophageal reflux disease

Proposition : Tous les patients souffrant de RGO devraient être soumis à une endoscopie une fois dans leur vie – Arguments contre la proposition

RÉSUMÉ : Les preuves à l’appui de la recommandation selon laquelle les patients souffrant de reflux gastro-œsophagien (RGO) devraient être soumis à une endoscopie une fois dans leur vie sont faibles et non étayées par des essais cliniques. Le RGO est un trouble fortement prévalent, mais 10 % seulement des patients atteints présentent un œsophage de Barrett (OB). L’adénocarcinome de l’œsophage (ACO) est une maladie rare, peu fréquente même parmi les patients porteurs d’un OB. Selon une analyse de décision, ces patients font l’objet de surveillance en raison de prévisions exagérées du taux d’évolution de l’OB vers l’ACO. Le plus souvent, la dysplasie régresse vers des structures histologiques bénignes plutôt que de dégénérer en cancer, sans compter que la dysplasie transitoire peut donner lieu à un taux élevé d’endoscopies inutiles. Même si des directives cliniques ont été publiées sur la surveillance endoscopique, les gastroentérologues ne s’entendent pas sur les protocoles à suivre, et beaucoup de médecins adoptent des mesures plus énergiques que ne le proposent les lignes directrices. Rien ne prouve que la surveillance sauve des vies, en partie parce que l’OB aboutit rarement à la mort causée par l’ACO. Les résultats favorables obtenus dans certains centres spécialisés pourraient ne pas être applicables à grande échelle. La recommandation préconisant une « endoscopie une fois dans la vie » chez les patients souffrant de RGO est prématurée.

Patient management recommendations, particularly those that might become health care policy, should be based on the highest level of evidence. The evidence supporting the recommendation to perform a ‘once in a lifetime’ endoscopy in patients with gastroesophageal reflux disease (GERD) falls far short of this standard. In fact, the idea was invented in 1996 by a few opinion leaders who repaired to a bar to lament, among other things, the dwindling number of patients with esophagus adenocarcinoma (EAC), a rare condition that develops from Barrett’s esophagus (BE), a condition that affects about 10% of patients with GERD. A decision-analytic study estimated that surveillance is performed because of inflated estimates of the rate of progression from BE to EAC. Dysplasia more often regresses to more benign histological findings than to cancer, and transient dysplasia can also lead to a high rate of unnecessary endoscopy. Even though practice guidelines about endoscopic surveillance have been published, there is no consensus among gastroenterologists about appropriate protocols, and many physicians are more aggressive than the guidelines. It has not been proved that surveillance saves lives, in part because BE rarely leads to death from EAC. The favourable results from some specialized centres may not be widely applicable. The recommendation for ‘once in a lifetime’ endoscopy for GERD patients is premature.
of endoscopies for GERD, given managed care pressures and the fact that the vast majority of patients fully responded to treatment with proton pump inhibitors. In fairness, the lack of a consistent approach to the growing problem of Barrett’s esophagus (BE) and esophageal adenocarcinoma (EAC) no doubt fuelled enthusiasm for the novel concept, which, remarkably, quickly worked its way into educational programs and textbooks without sufficient supporting evidence.

The concept is appealing for several reasons. First, it appears to be a modest and sensible first step in addressing the rising incidence of EAC, which is a complication of GERD. Second, patients at risk of developing EAC can be readily identified because most are likely to have heartburn. Third, intestinal metaplasia is the only known precursor of EAC, and endoscopy readily detects this condition. The obvious economic incentive for endoscopists to tap into the motherlode of 60 million Americans who have heartburn is no doubt a minor consideration in advocating once in a lifetime endoscopy. It is, however, one that is likely to attract much attention if opinion leaders and gastroenterology organizations aggressively advocate this practice without substantial evidence that patients and the overall community would benefit. Such evidence is virtually nonexistent. Moreover, the scant evidence that has recently been cited actually raises more questions than answers, which underscores the fact that once in a lifetime endoscopy for patients with GERD cannot yet be advocated as a practice guideline, let alone a public policy. I will discuss the evidence against the adoption of such a policy.

All of the arguments against screening for BE as well as subjecting persons with this abnormality to surveillance apply to once in a lifetime endoscopy. These arguments are discussed by Chiba (pages 541-545), but some will be reiterated here because they are particularly relevant to this discussion.

**LOW YIELD OF SCREENING FOR EAC**

Approximately 42% of the American, white, adult population has heartburn, and 59% have either heartburn or acid regurgitation at least once per year (1). These persons are part of the potential pool for once in a lifetime endoscopy. On the other hand, only approximately 10% of patients with GERD have BE (2). Thus, 100 subjects would need to be screened to detect 10 cases of BE. How many of these patients would develop EAC? Very few. Precise figures are unavailable, but evidence indicates that the incidence of EAC in patients with BE has been exaggerated due to publication bias, ie, small, short term studies have reported an inflated incidence of cancer (3). Studies involving at least 150 patients with follow-up periods of more than four years have found that the incidence of EAC is only between one per 180 patient-years (4) and one per 300 patient-years (5). This helps to explain the low incidence of EAC, of less than 1.2 per 100,000 person-years, in the general population of several Western countries (6). This incidence is even lower than that of gastric cancer in Western countries, yet nobody is advocating endoscopic screening for that condition, even in the presence of a positive test for *Helicobacter pylori*.

**ABSENCE OF SUPPORTING STUDIES**

Retrospective studies have suggested that endoscopic surveillance of patients with BE would not dramatically reduce the rate of death from EAC (4-6). It is incumbent on physicians who advocate once in a lifetime endoscopy for GERD patients to present hard evidence that this approach does anything more than drive up health care costs. Even one supportive clinical trial would be helpful, but none exists.

To my knowledge, the only study that suggests a role for once in a lifetime endoscopy is a decision analysis that has appeared only in abstract form (7). In this study, Inadomi et al (7) calculated the incremental cost effectiveness ratio of screening and surveillance versus no screening at $23,738 per quality-adjusted life-year. The analysis was sensitive to the prevalence of BE, rate of progression of high-grade dysplasia (HGD) to cancer, utility of esophagectomy for cancer or HGD, and cost of (unsedated) endoscopy. All of these parameters vary widely according to the population and jurisdiction. For example, the study assumed that HGD progressed to EAC at an annual rate of 25%, but recent studies have found a much lower rate. Sontag et al (8) found that only 10 of 69 patients (14.5%) with HGD developed EAC within 6.9 years, for an annual rate of approximately 2%. Weston et al (9) found that unifocal HGD progressed to frank cancer at an annual rate of 9% over an average duration of follow-up of approximately three years. Reid et al (10) found an annual progression rate of about 12% over five years.

HGD commonly regresses to either low-grade dysplasia (LGD) or other benign abnormalities. Weston et al (9) reported that regression was considerably more frequent than progression to cancer among patients with HGD (47% versus 27%) during a mean follow-up of 43 months. Similarly, LGD progressed to cancer in 8%, but regressed in 75%, over a period of 28.5 months. It is apparent that modelling studies are unlikely to provide a solid basis for recommending once in a lifetime endoscopy for GERD patients unless a consensus is developed about the assumptions that are used in the models. In any case, guidelines that might result in massive increases in health care expenditures should be based on more than economic modelling studies. Such investigations are no better than second- or third-level evidence, and cannot substitute for prospective clinical trials or meta-analyses.

**LACK OF A PRECISE RECOMMENDATION**

It has become fashionable for educational programs to recommend endoscopic screening for patients over the age of 50 years who have chronic GERD symptoms. Recommendations should be more precise if they are to guide clinical practice. Should the recommendations apply equally to patients with mild or severe GERD? Is ‘long-standing’ defined as three, five, seven or 10 years? How about the fre-
The frequency of heartburn? These questions are relevant because the duration, frequency and severity of heartburn all contribute to the risk of developing EAC (11). In addition, the cancer risk is increased for white men who smoke cigarettes and have an elevated body mass index. These facts suggest that targeting persons at high risk might be more cost effective than general population screening.

In a recent study, Gerson et al (12) employed a simple questionnaire to enhance endoscopic screening for BE. They found that men with severe heartburn, nocturnal symptoms and odynophagia were more likely to have BE, but that dysphagia was a negative predictor. Although this preliminary study indicated that targeted screening protocols could improve the diagnostic yield, it has not been proven to be cost effective. Lagergren et al (11) calculated that, if endoscopic surveillance were restricted to men older than 40 years with reflux symptoms severe enough to entail a risk that was 20 times higher than normal, a Swedish physician would need to follow more than 1400 patients for one year to encounter a single case of EAC. Moreover, Soni et al (13) determined that an effective screening program requires a false-positive rate for endoscopy of less than 10%, a decrease in health-related quality of life after esophagectomy of 15% or less, and a prevalence of HGD or EAC in BE patients of 10% or higher. None of these requirements has been demonstrated with any consistency.

SCREENING LEADS TO SURVEILLANCE
Reid (14) and Chiba (pages 541-545) have reviewed the arguments for and against surveillance. Although the evidence supporting surveillance, under certain conditions, is far more compelling than that for once in a lifetime screening, some additional shortcomings of surveillance are emphasized here because they accentuate the problems (including the costs) engendered by inappropriate screening.

THE PROBLEM OF MATCHING PRACTICE TO EVIDENCE OF COST EFFECTIVENESS
Several guidelines have been promulgated to help clinicians select endoscopy intervals according to the degree of dysplasia found at biopsy. Sampliner et al (15) advocated that endoscopy be performed every two to three years if there is no dysplasia, every six months for two occasions in cases of LGD (and yearly thereafter if there is no progression) and every three months if HGD is confirmed. Esophagectomy is an alternative procedure for patients with HGD. Falk et al (16) demonstrated that actual clinical practice patterns are more aggressive and, presumably, more costly than these guidelines. In the absence of dysplasia, most gastroenterologists (88%) performed endoscopy every one to two years, and only 8% did so at three-year intervals. For LGD, 69% of gastroenterologists undertook endoscopy every three to six months, and only 26% did so once per year. Both the guidelines (15) and clinical practice (16) are at variance with the results of, arguably, the best economic modelling study of surveillance, undertaken by Provenzale et al (17), which found that a five-year interval might be cost effective.

THE PROBLEM OF TRANSIENT DYSPLASIA
Several investigators have found that even HGD can regress on subsequent biopsies, although sampling error and interobserver variability are confounding factors. Ofman et al (18) recently calculated the costs of ‘transient’ dysplasia. They followed 95 patients with BE over two years and identified 19 patients who had a histological finding of dysplasia on at least one occasion but no dysplasia on the biopsy taken at 24 months. They modelled the effect of transient dysplasia over a 10-year period, assuming that endoscopy would be undertaken every two years if there were no dysplasia and every six months if dysplasia were detected. The model predicted that 1072 surveillance endoscopies would be performed, at a cost of $1,587,184. Of these endoscopies, 61% would be for transient findings of dysplasia, and their incremental costs would be $509,545 (for only 19 patients).

PATIENTS WITH BE RARELY DIE OF EAC
Once in a lifetime endoscopy should not be recommended unless the placement of patients with BE into surveillance programs is expected to result in improved outcomes. Such benefits might not be realized, however, because many older patients die of causes other than EAC. For example, van der Burgh et al (4) reported a cohort of 155 BE patients who were followed for a mean of 9.3 years without endoscopic surveillance. The median age of subjects upon entry into the study was 62 years. Of the 72 deaths, only two were due to EAC (2.5%); 97.5% of the subjects died of other causes, even if they had EAC.

Reid (14) summarized the evidence that persons with BE who are enrolled in an endoscopic surveillance program have a higher five-year survival rate than those who are not in such a program. However, such improvements cannot be attributed to periodic endoscopies alone. Well developed programs have several attributes: endoscopists who obtain biopsies extensively and systematically, pathologists who reliably identify and grade dysplasia, and surgical teams that can perform esophagectomy with low morbidity and mortality rates. All of these resources contribute to favourable outcomes, but they rarely exist outside of specialized centres. Therefore, the optimistic outcomes in published studies cannot necessarily be generalized.

CONCLUSIONS
Once in a lifetime endoscopy for GERD patients is a self-serving recommendation that is not based on evidence, most notably from any clinical trial. A single modelling study supports the concept, but it has not been confirmed or subjected to peer review, and is based on overly optimistic baseline assumptions. No level 1 or 2 evidence has been produced to demonstrate an improvement in outcomes. Recommendations for such a protocol are not specific, and practice patterns vary widely. Given the large pool of
patients with GERD who could be screened, and the small incidence of EAC, it is likely that adoption of this policy would substantially increase health care costs without measurable benefit to either patients or society in general. The recommendation is, at best, premature.

REFERENCES
14. Reid BJ. Motion – Screening and surveillance of Barrett's epithelium is practical and cost effective: Arguments for the motion. Can J Gastroenterol. (In press)