

Motion – Screening and surveillance of Barrett’s epithelium is practical and cost effective: Arguments against the motion

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The issue of whether to screen individuals for Barrett’s esophagus (BE) to prevent esophageal adenocarcinoma (EAC) is highly controversial. Important considerations are that BE is not highly prevalent in the general population and that not many patients with BE develop or die from EAC. Studies that suggest an improved prognosis from surveillance programs are susceptible to lead-time bias. Most of the principles for effective screening, as outlined by the World Health Organization, are not met by endoscopic screening and surveillance protocols. The diagnosis of BE (and dysplasia) is often unclear. Most patients with BE are not identified by screening, and few deaths would be prevented by surveillance. A decision analysis found that the most cost effective screening protocol would be every five years, but the costs associated with prolongation of life are very high, even if a group at high risk for EAC could be identified.

Key Words: *Barrett’s esophagus; Esophageal adenocarcinoma*

Proposition : Le dépistage et la surveillance de l’épithélium de Barrett sont pratiques et rentables – Arguments contre la proposition

RÉSUMÉ : La question du dépistage de l’œsophage de Barrett (OB) pour prévenir l’adénocarcinome de l’œsophage (ACO) suscite une forte controverse. Il convient de souligner que l’OB est faiblement prévalent dans la population générale et que peu de patients le voient dégénérer en ACO ou en meurent. Les études qui laissent entendre que les programmes de surveillance pourraient améliorer le pronostic sont susceptibles d’un biais de délai d’exécution. Le dépistage endoscopique et les protocoles de surveillance ne répondent pas à la plupart des principes d’un dépistage efficace, comme ceux formulés par l’Organisation mondiale de la santé. Le diagnostic de l’OB (et de la dysplasie) est souvent flou. La majorité des patients atteints ne sont pas repérés par le dépistage, et la surveillance ne permettrait pas de sauver beaucoup de vies. Selon une analyse de décision, le protocole de dépistage le plus rentable recommanderait un examen tous les cinq ans, mais les coûts associés à la prolongation de la vie seraient énormes, et ce, même si on cernait un groupe de patients prédisposés à l’ACO.

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BARRETT'S ESOPHAGUS AND THE RISK OF CANCER

Barrett's esophagus (BE) is a complication of gastroesophageal reflux disease (GERD), in which normal esophageal squamous epithelium is replaced with columnar epithelium. In the Canadian Adult Dyspepsia Empiric Therapy – Prompt Endoscopy (CADET-PE) study, which involved endoscopy within 10 days of referral for previously uninvestigated dyspepsia, only 25 patients out of a study population of 1040 with BE were identified (unpublished data). The Alberta endoscopy database identified BE in only 6.3% of patients undergoing endoscopy for GERD symptoms (1). Other investigators have reported BE in up to 12% of patients with reflux symptoms (2), but most of these patients did not have intestinal (specialized columnar) epithelium. In a prospective study, classic long-segment (3 cm or greater) BE was identified in only 5% of subjects, whereas 14% had short segment BE (SSBE) (3). Thus, SSBE is much more common than the classic variety and is easily overlooked if biopsies are not taken. The prevalence of BE increases with age, and the prevalence of esophageal adenocarcinoma (EAC) increases with increasing frequency and duration of gastroesophageal reflux (4,5).

There is little debate that BE is a risk factor for EAC – a cancer that is increasing in incidence (6). Only a small part of this apparent increase can be attributed to misclassification of cancers of the gastric cardia as EAC. This increasing risk and the fact that BE is the only known precursor of EAC have led to recommendations that surveillance endoscopy and biopsies be undertaken every two to three years for patients with BE who do not have dysplasia (7). Estimates of the risk of EAC in patients with BE, which have ranged from one in 46 to one in 441 patient-years of follow-up, appear to be susceptible to publication bias, and the actual risk is probably close to 0.5% per year (8). This means that one cancer would be detected in a population of 200 patients followed for one year. Overall, EAC arising in Barrett's epithelium is a rare disorder, with fewer than 10,000 cases per year in the United States.

Those who advocate screening and surveillance for BE have argued that such techniques detect cancer earlier and thus improve prognosis (9), but this effect might be due to lead-time bias. In fact, no randomized, controlled study has demonstrated a prolongation of survival from screening. Provenzale's decision analysis has shown that surveillance at five-year intervals is expensive, although cost effective, with a cost of \$98,000 per quality-adjusted life year (QALY) (10).

DIFFICULTIES IN THE DIAGNOSIS OF BE

Consider the principles of early disease detection (Table 1) proposed by the World Health Organization, to determine whether screening for BE is justified (11). Only some of the principles (items 1, 3, 5 and possibly 9 and 10) are met by endoscopic screening of BE. On the other hand, there is a dearth of information about the pathogenesis and treatment of this disorder. On the whole, there are more com-

TABLE 1
World Health Organization principles for early disease detection

The target health problem is important
There should be an accepted and effective treatment for the target problem
Facilities for diagnosis and treatment should be available
There should be a recognized latent or early symptomatic stage
There should exist a suitable screening test or examination
The test should be acceptable to the patient (and population) to be screened
The pathogenesis of the target problem should be adequately understood
There should be an agreed policy on whom to treat
The process of case finding should be cost effective
Case finding should be a continuing process and not a 'once only' procedure

**Data from reference 11*

elling reasons (based on items 2, 4, 6, 7, 8 and possibly 9) not to undertake endoscopic screening.

Now consider some arguments against screening and surveillance for BE. First, is this condition clearly defined and understood by everyone? This is unfortunately not the case. BE refers to the presence of metaplastic columnar epithelium instead of the normal squamous epithelium of the esophagus. Because it is recognized that only intestinal metaplasia (as indicated by the presence of goblet cells) confers an increased risk of EAC, the definition of BE has been revised to include only cases in which this abnormality is identified (12). BE, as so defined, cannot reliably be diagnosed by its endoscopic appearance alone and requires histological confirmation (13). Ideally, four-quadrant biopsies, using jumbo biopsy forceps, should be taken at every 1 to 2 cm of endoscopically abnormal mucosa. However, in practice, how many biopsies are actually taken?

Traditionally, BE has been defined as the presence of columnar epithelium more than 3 cm beyond the gastroesophageal junction. This criterion was established because of difficulties ascertaining the location of the gastroesophageal junction, due to the presence of a transition zone (the cardia) and the irregular contour of the squamocolumnar junction, as identified at endoscopy. The meaning of 'cardia' is also unclear (14). Endoscopists are well aware of how difficult it is to determine where the esophagus ends and a hiatus hernia begins. At issue is the concept of SSBE, which is defined as a segment of metaplastic epithelium of less than 3 cm in length. The diagnosis of SSBE requires keen observation by the endoscopist, as well as histological confirmation. It appears that patients with SSBE are at an increased risk of EAC, although to a much lesser degree than are those with classic BE (15). A careful review concluded that surveillance of patients with SSBE is not warranted (14). Therefore, the diagnosis of BE itself, and thus the identification of patients at risk of EAC, is not as straightforward as one would wish.

IS SCREENING FOR BE WORTHWHILE?

Most patients with BE die of unrelated causes (16). Of a cohort of 155 patients with BE who were subjected to 1440 patient-years of follow-up, only eight were found to have EAC. Of these patients, three underwent 'successful' resections, three died of other disorders and only two died of esophageal cancer. The important message is that few patients actually die of EAC. Moreover, even if surgery were feasible, the advanced age of these patients means that this option does not substantially prolong life.

Only few patients with BE potentially benefit from endoscopic cancer surveillance. Gudlaugsdottir et al (11) reviewed the charts of all 395 patients who had been found to have BE over a five-year period at their endoscopy unit in the Netherlands. Demographic and other factors that are associated with a low risk of EAC (less than one case per 200 patient-years of surveillance) were considered exclusion criteria for screening. These criteria included white males younger than 60 years or older than 75 years, female sex and SSBE. In addition, screening was deemed to be inappropriate for patients who were not suitable candidates for esophagectomy, including persons with a life expectancy of less than five years. Finally, 60 patients in whom EAC or high-grade dysplasia (HGD) had already been discovered were excluded from the study. Of the remaining 335 patients, only 52 (15.5%) were thought to benefit from endoscopic surveillance.

An additional problem is that most patients with BE remain undiagnosed. A population-based study from the Mayo Clinic, Rochester, Minnesota, found that the prevalence of BE was 21 times greater in an autopsy series than in a clinical series based on endoscopy records (17). This means that fewer than 5% of cases of BE are identified clinically. In a Danish retrospective population-based study, the incidence of EAC increased eightfold between 1970 and 1990 (6). Of the 524 patients who were found to have EAC, only 1.3% had a previous diagnosis of BE. This means that more than 98% of patients with EAC would not have been enrolled into an endoscopic surveillance program. These data provide strong arguments against a population-based screening program.

An additional purpose of screening is the identification of patients with dysplasia. Even when the appropriate biopsies are taken, the histological diagnosis of dysplasia remains difficult, and there is limited agreement, even between experienced pathologists (18).

IS SCREENING COST EFFECTIVE?

Provenzale et al (19) published, in 1994, an excellent Markov modelling decision analysis of 10,000 hypothetical 55-year-old men with BE, and evaluated 12 strategies:

- A: No surveillance; endoscopy for alarm symptoms; surveillance every six months for low grade dysplasia (LGD) or every three months for HGD; surgery for cancer

- B: No surveillance; endoscopy for alarm symptoms; surgery for HGD
- C1-C5: Surveillance every one to five years; increased to every six months for LGD or every three months for HGD; surgery for cancer
- D1-D5: Surveillance every one to five years; surgery for HGD

The authors used an estimate of the risk of EAC in BE of 1.3% per year of follow-up. Based on this estimate, the life-time cancer risk for a 55-year-old man who does not undergo surveillance would be 27%. A yearly surveillance protocol would reduce the lifetime cancer risk to 15% to 18%, which would be reduced to 3% to 7% if surgery were undertaken for HGD (strategy D1). The life expectancy of a 55-year-old man was assumed to be 24.5 years. With no surveillance, the life expectancy would fall to 20.6 years. The most aggressive protocol of yearly surveillance and esophagectomy for HGD (strategy D1) was calculated to prolong life expectancy by one to 1.2 years, compared with no surveillance (strategy A). Therefore, if only life expectancy were considered, and not the cost or morbidity associated with screening procedures, then the preferred strategy would be yearly surveillance endoscopy and surgery for HGD (strategy D1).

However, the costs and complications of endoscopy and surgery must also be considered. When considering these issues, surveillance with esophagectomy for cancer added only 0.5 to 0.6 QALY, which is approximately one-half of the estimate based only on life expectancy statistics. The morbidity associated with the high numbers of endoscopies and esophagectomy, as well as the early timing of surgery, erode the gains associated with yearly surveillance, so that the yearly gain in QALY was only 0.05 year (or 0.6 months). After considering all factors, the authors calculated that the optimum surveillance interval was actually two to three years (19).

All interventions have a monetary cost; thus, one must calculate the cost of each year of life gained and compare this with other medical practices. The authors used a 5% yearly discount rate for costs, which is the standard method of compensating for the effects of inflation. They calculated that surveillance every five years increased life expectancy by 3.4 months. The incremental cost utility ratio (ICUR) of screening every five years was \$27,400 per QALY. Surveillance every four years provided the greatest gain in quality-adjusted life expectancy but with a dramatically increased ICUR of \$276,700 per QALY gained. Even shorter surveillance intervals actually led to decreased quality-adjusted life expectancy. By comparison, the estimated cost of colon cancer screening is \$20,000 to \$25,000 per QALY gained (20), and that of mammography screening for breast cancer is \$22,000 per QALY gained (21).

The authors recognized that the results of their analysis depended on the baseline assumptions that they used, and thus undertook sensitivity analyses (19). When the risk of

cancer was adjusted to less than 0.5% (one per 200 patient-years of follow-up), no surveillance became the preferred strategy for maximizing quality-adjusted length of life. On the other hand, if the cancer risk were greater than 2%, annual surveillance was preferred. They then examined the effect of changes in the age of diagnosis of BE. For men aged 20 to 54 years, surveillance every two years (with esophagectomy for HGD) provided the greatest quality-adjusted life expectancy, with a gain of up to eight years compared with no surveillance. With increasing age at diagnosis, the preferred surveillance interval increased; for example, for men aged 70 to 80 years, the interval was five years. The authors assumed a willingness to pay threshold of \$50,000 per QALY gained. Surveillance every four years was below this willingness to pay threshold for men aged 20 to 31 years; for those aged 31 to 66 years, the acceptable surveillance interval was deemed to be five years; and for men over age 66 years, only the 'no surveillance' strategy fell within the threshold of acceptability.

The same investigators, in 1999, repeated their Markov modelling analysis because of revised estimates of the risk of EAC in BE (10). They used the new estimated risk of EAC in patients with BE of 0.4% annually (one per 227 patient-years of follow-up) (22), and evaluated strategies involving no surveillance or surveillance every one to five years with esophagectomy for HGD. Their conclusion was that the only acceptable strategy was surveillance endoscopy every five years. The ICUR with this strategy was \$98,000 per QALY gained. This cost was comparable with the ICUR of heart transplantation, which is estimated to be \$160,000 per QALY gained (23). Although surveillance endoscopy every five years for patients with BE was deemed to be cost effective, one must realize that a decreased risk of EAC was associated with a marked increase in ICUR.

CONCLUSIONS

It is apparent that screening and surveillance of BE are not practical or cost effective for all patients with BE. So what should be done with the patient who is known to have BE? It would be difficult to suddenly inform the patient that all the screening procedures that he or she had undergone, for years, were inappropriate.

To design a cost effective protocol, patients who are truly at increased risk for EAC must be identified. Persons at low risk of cancer would not benefit from endoscopic surveillance and should not be enrolled in programs. The following risk factors have been identified, although this list is not exhaustive:

- White men, particularly those over the age of 60 years
- A long history of reflux symptoms
- Cigarette smoking
- Putative biomarkers of high risk, such as cytometrically determined aneuploidy (which is more reliable than histological assessments of

dysplasia) (24) and certain gene mutations (eg, *p53* and *p16*) (25)

- Greater than 6 cm of Barrett's epithelium (26)
- Dysplasia, whether high- or low-grade, especially if extensive (27)
- Ulceration or stricture in the presence of BE

Contraindications for surveillance include the presence of serious concomitant disease that either limits survival or precludes esophagectomy (or alternative procedures, such as photodynamic or ablative therapies). Only persons who are both healthy enough and willing to undergo aggressive treatment should be considered for screening and surveillance. In addition, a practical limit of screening only persons who are younger than perhaps 70 years of age should be considered.

It is not feasible to screen the general population or persons who are at low risk for EAC, including women, persons of Asian or African descent, or those with SSBE. Because there is evidence that the duration and frequency of GERD symptoms might be risk factors for BE, endoscopy with multiple biopsies above the gastroesophageal junction in areas of suspected columnar epithelium should be undertaken to exclude BE and dysplasia. Patients with such findings should be offered endoscopic surveillance, if they are otherwise suitable candidates.

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