Barrett’s esophagus: Is it all that bad?

GNJ Tytgat MD PhD

An alarmingly rapid rise in the number of adenocarcinomas at the level of the gastroesophageal junction and distal esophagus has been noted over the past two decades. Intestinal metaplasia is considered to be the main precursor lesion for such adenocarcinomas. Given the low five-year survival rate in patients with advanced esophageal cancer, strategies for early detection have been developed. Because superficial cancers only rarely cause symptoms, detection of cancer at such an early curable state can only be achieved through surveillance of patients at risk. Therefore, implementation of an endoscopic surveillance program for patients in whom intestinal metaplasia has been detected in the distal esophagus or at the esophagogastric junction seems to be a reasonable option.

Key Words: Adenocarcinoma; Barrett’s esophagus; Endoscopy; Intestinal metaplasia

L’œsophage de Barrett : est-ce si grave?

RÉSUMÉ : Depuis deux décennies, on observe une augmentation alarmante du nombre d’adénocarcinomes au niveau de la jonction gastro-œsophagienne et de l’œsophage distal. La métaplasie intestinale est considérée comme la principale lésion précurseure de ces adénocarcinomes. Compte tenu du faible taux de survie après cinq ans chez les patients atteints d’un cancer de l’œsophage avancé, des stratégies de dépistage précoce ont été mises au point. Compte tenu que les cancers superficiels ne provoquent que rarement des symptômes, le dépistage du cancer à un stade où la maladie est curable, ne s’obtient que par la surveillance des patients à risque. Par conséquent, la mise en place de programmes épidémiologiques endoscopiques pour les patients chez qui la métaplasie intestinale a été décelée dans l’œsophage distal ou à la jonction œsophago-gastrique semble une option envisageable.
program for patients in whom intestinal metaplasia has been detected in the distal esophagus or at the esophagogastric junction seems to be a reasonable option.

ENDOSCOPIC DETECTION OF COLUMNAR METAPLASIA

The proximal extent of the gastric folds provides a reliable endoscopic landmark to identify the junction between the esophagus and stomach (13-15). Any length of pinkish mucosa in the lower esophagus above the proximal extent of the gastric folds that contains intestinalized mucosa or intestinal metaplasia on biopsy qualifies for a diagnosis of esophageal columnar metaplasia or Barrett’s esophagus, regardless of the length of this segment. Histology is, therefore, essential to diagnose columnar metaplasia when only short, pink tongues are present in the distal esophagus. The combined hematoxylin and eosin-alcian blue pH 2.5 stain is invaluable for the histologic definition of intestinal-type mucosa (16-18; Personal communication, W Polkowski et al). A short segment esophageal columnar metaplasia is most often arbitrarily defined as columnar metaplasia less than 2 to 3 cm in length above the esophagogastric junction (19-21). In the case of long segment Barrett’s esophagus, the length of the metaplastic segment extends beyond 2 to 3 cm. Whether small tongues or patches of columnar mucosa with evidence of intestinal metaplasia in the vicinity of the squamocolumnar junction correspond to ultrashort segments of Barrett-type columnar metaplasia or intestinal metaplasia of the cardia in patients with a somewhat irregular squamocolumnar junction is impossible to tell from an endoscopic point of view, because the histological appearance is identical.

INTESTINAL METAPLASIA-DYSPLASIA-CARCINOMA SEQUENCE

Many studies have shown that malignant progression occurs through stages of increasing severity of dysplasia (7,18,22-26). The rate at which low grade dysplasia develops into high grade dysplasia and ultimately cancer is highly variable. High grade dysplasia is an ominous sign and indicates impending malignancy within a short period of time. Commonly, malignant foci are already present but are not discovered when high grade dysplasia is detectable in biopsies.

Ideally disease should be detected at the stage of high grade dysplasia, before overt or occult malignancy has developed.

ENDOSCOPIC DETECTION OF DYSPLASIA

The endoscopic detection of dysplasia is problematic. In general, no peculiar endoscopic features permit a distinction between dysplastic and nondysplastic mucosas.

Exceptionally dysplastic areas may be suspected when the mucosa is somewhat more whitish, although usually such more whitish plaques consist of patches of nondysplastic mucosal thickening. Equally exceptional is the detection of dysplasia in areas that disclose a somewhat peculiar vascularity or have an inflamed appearance. Finally, dysplasia may also be suspected in areas with conspicuous villiform appearance.

It has been claimed that toluidine blue staining may be helpful in detecting areas of high grade dysplasia, suitable for targeted biopsy, but this is rather questionable (27). In contrast, methylene blue-directed biopsy may improve the detection of intestinal metaplasia and by doing may also detect dysplasia, if present (28).

HISTOLOGIC DETECTION OF DYSPLASIA

Usually, dysplasia is detected in random biopsies taken at intervals of 1 to 2 cm from all quadrants of the metaplastic segment. The use of large calibre biopsy forceps (9 French or 8 mm open span) is advisable, but this requires an endoscope with a large (greater than 3.5 mm) instrumentation channel. In routine practice, biopsies are often taken with standard biopsy forceps, and often only two biopsies are taken from opposite walls at 2 cm intervals (29,30).

ENDOSCOPIC APPEARANCE OF EARLY MALIGNANCY

Superficial esophageal cancer is often subdivided in three macroscopic subtypes, according to the differences in height in relation to the noncancerous adjacent mucosa (31). Type 1 is characterized by an elevated or protruded lesion; type 2 is a superficial flat lesion; type 3 corresponds to a depressed or excavated type.

A common appearance is that of a circumscribed polypoid or protruded lesion (type 1). Early malignancy may also appear as a plaque-like lesion in which the cancerous area appears slightly elevated with a granular knobby surface or a circumscribed area of altered pliability or patch of mucosal discoloration (type 2). Superficial cancer can also present as a slightly depressed area with grey erosive spots against a reddish background (type 3). A rather exceptional but most intriguing presentation is ‘occult type’ cancer where in essence no suspicious endoscopic abnormalities are visible. It should be stressed that multiple biopsies have to be taken at various levels within the columnar segment to establish the spread of the malignancy. If only high grade dysplasia is found, biopsies should be repeated because high grade dysplasia is often associated with superficial malignancy (27,32-35; Personal communication, JW Sandick et al).

CONSEQUENCES OF DETECTION OF HIGH GRADE DYSPLASIA

When high grade dysplasia is detected, a clinical dilemma is often encountered. In expert centres with a low operative morbidity and mortality for esophageal resection, high grade dysplasia is increasingly regarded as the end point of surveillance for patients who are good surgical risks and who can withstand a major operation (35-39). Other experts advise deferring esophagectomy until proven invasive adenocarcinoma is documented. In the meantime, these experts propose that surveillance should be continued at very short intervals (three months) with strict endoscopic biopsy protocols (18,40,41). It should be stressed that high grade dysplasia has been identified as a predictor of future cancer development. Also, it may indicate the presence of a coexis-
tent covert invasive adenocarcinoma. A recent collective series of 96 patients who underwent esophagectomy for high grade dysplasia revealed a 41% incidence of endoscopically undetected adenocarcinoma, with an overall postoperative mortality of 4% (42). In the study of Van Sandick et al (43), four of six patients with a biopsy diagnosis of high grade dysplasia were identified to have invasive adenocarcinoma in the resection specimen. Such findings emphasize the limitations of the random biopsies in detecting foci of malignancy in such patients. The frequency of finding a coexisting adenocarcinoma is high and, therefore, justifies esophageal resection in patients with an unequivocal diagnosis of high grade dysplasia who are likely to tolerate a major surgical procedure.

COST EFFICACY CONSIDERATIONS
Although the cost efficacy of surveillance in columnar metaplasia has been questioned by some authors (44,45), two recent studies indicate that the cost of endoscopic surveillance to detect adenocarcinoma in patients with esophageal columnar metaplasia compares quite favourably with the cost of screening mammography to detect early breast cancer (46,47).

A much greater concern is the ultimate lack of evidence that surveillance ultimately reduces the mortality due to esophageal adenocarcinoma. The ideal methodology for the evaluation of the efficacy of surveillance is a randomized trial. Such a trial not only seems impractical in terms of the number of patients needed and the many years of follow-up (48) but also may pose several ethical dilemmas for the physicians who would be asked to withhold a potentially life-saving procedure from an individual with a premalignant condition. Provenzale et al (49) estimated that, if the annual risk of cancer development in esophageal columnar metaplasia is 1.3%, then a randomized trial designed to show an efficacy of endoscopic surveillance would require 5000 patients to be followed for 10 years. For patients with short segment intestinal metaplasia at the gastroesophageal junction, whose annual cancer risk is substantially less than the 1.3%, even larger numbers of patients and longer duration of follow-up would be required for a study to show a significant benefit. It is, therefore, unlikely that a randomized study will ever be performed to prove the value of cancer surveillance in columnar metaplasia. The logistics of conducting such enormous long term studies are truly daunting and the ethics highly questionable.

EFFECT OF SURVEILLANCE ON CANCER MORTALITY RATES
Indirect proof of efficacy may be derived by evaluating the effect of surveillance on cancer mortality rates. The method most commonly used compares the outcomes of surveillance-detected cancer cases with those of symptom-diagnosed cases.

Several studies have indicated that endoscopic biopsy surveillance may provide a beneficial effect on resectability and mortality from cancer in esophageal columnar metaplasia (46,50,51; personal communication). Patients who have undergone some form of endoscopic surveillance were operated on at significantly earlier stages of their disease with a subsequent survival advantage over patients who were not part of a surveillance program.

However, such nonrandomized types of evaluation harbour a number of pitfalls (42,52). A first pitfall is selection bias. Patients undergoing regular surveillance tend to be health conscious and may be the ones who would have presented with early stage cancer even if their disease were diagnosed because of symptoms. A second pitfall is lead-time bias, which operates in all screening and surveillance programs (53). An observed survival benefit may be due only to the advancement of the diagnosis of cancer in time and not to the postponement of death. A third pitfall is length bias (54). Length bias occurs because screening programs are more likely to detect slow growing lesions, with a favourable prognosis, than lesions with a more aggressive nature and relatively more unfavourable prognosis.

The stage distribution and the duration of survival in the surveillance group of our patients may partly reflect lead time and length bias for cancer in Barrett’s esophagus. Despite such shortcomings of evaluating cancer surveillance in such patients, efforts to do so should continue in order to clarify factors that affect outcome.

CONCLUSIONS
Endoscopic biopsy surveillance of patients with high grade dysplasia or early cancer in esophageal columnar metaplasia allows the detection of cancer at an early, curable stage. None of the patients in surveillance groups had advanced stage cancer compared with 50% to 60% of patients in non-surveillance groups who had stage 3 or 4 tumours. Patients from the surveillance group appeared to have a significant survival advantage after resection. The striking difference in survival strongly suggests that a long term reduction in cancer mortality by widespread surveillance of patients with columnar metaplasia is indeed possible.

REFERENCES
Tytgat


