

## Leading article

# Barrett's oesophagus – to screen or not to screen?

Barrett's oesophagus lined with columnar epithelium (CLO) is usually the consequence of gastro-oesophageal reflux. Basing the diagnosis on circumferential involvement of at least the lowermost 3 cm of the oesophagus, CLO is found at endoscopy in 10–16% of patients with reflux oesophagitis.<sup>1-5</sup> Within two years of Barrett's description of the disorder in 1950<sup>6</sup> its association with adenocarcinoma was reported<sup>7</sup> and it is now well established that the prevalence of adenocarcinoma in CLO is of the order of 8–15%.<sup>18</sup> Although CLO carries a clear risk of adenocarcinoma, the magnitude of this risk and therefore the value of endoscopic screening remains highly controversial. In this issue Van der Veen *et al*<sup>9</sup> in Rotterdam reporting a postal follow up of 155 patients with CLO conclude that systematic endoscopic surveillance is not indicated in this disease.

One of the major difficulties in this field lies in deciding what to take as a yardstick for comparative purposes and to compare the incidence of adenocarcinoma in CLO with that of squamous carcinoma in the general population is fallacious. Squamous carcinoma in association with CLO has been reported,<sup>10</sup> but there is no evidence that its incidence is increased. Comparison of adenocarcinoma in CLO with adenocarcinoma of the oesophagus without demonstrable CLO, presents insuperable problems, because it is usually impossible to be certain whether these growths have arisen in the stomach and subsequently extended upwards. Furthermore, it is arguable that nearly all adenocarcinomas of the oesophagus arise on a basis of CLO.<sup>11</sup> Decisions must therefore be based on assessments of the incidence of adenocarcinoma in CLO in terms of patient year follow up of those who had no detectable neoplasm at the initial examination. Here estimates differ widely and in six studies reported since 1984 the incidence has varied between one adenocarcinoma per 46<sup>13</sup> to one per 441<sup>8</sup> patient year follow up (Table). Such variation is probably to be expected, as none of the series reported more than four carcinomas, and four of the six collected only one or two. Hence the presence, or absence of a single carcinoma would affect the reported incidence profoundly. Another source of possible error is that carcinomas developing within one year of the initial diagnosis of CLO might have been missed at the initial examination. Variation in incidence may be related to the method of follow up – for example, two of the three lowest reported incidences were obtained from follow up by postal enquiry. The more thorough the follow up, the more carcinomas might be revealed, because the growth may be present for some years before producing symptoms and in the elderly death from other causes may occur before it has declared itself.

Surveys in which regular endoscopy is used give a better estimate of the incidence of carcinoma in CLO and often yield higher incidence rates (Table). It is now apparent that in its early stages adenocarcinoma

Table Screening for adenocarcinoma in Barrett's oesophagus

|  | Screening method | Patients (n) | Mean follow up (yr) | Adenocarcinomas (n) | Incidence per pt-yr follow up |
|--|------------------|--------------|---------------------|---------------------|-------------------------------|
| Spechler <i>et al</i> 1984 <sup>12</sup>   | Endoscopy        | 105          | 3.3                 | 2                   | 1/175                         |
| Sprung <i>et al</i> 1984 <sup>13</sup>     | Endoscopy        | 15           | 3.1                 | 1                   | 1/46                          |
| Cameron <i>et al</i> 1985 <sup>*</sup>     | Post             | 122          | 8.5                 | 2                   | 1/441                         |
| Sampliner <i>et al</i> 1985 <sup>14</sup>  | Endoscopy        | 25           | 2.1                 | 1                   | 1/92                          |
| Robertson <i>et al</i> 1988 <sup>15</sup>  | Endoscopy        | 56           | 3.0                 | 4                   | 1/56                          |
| Van de Veen <i>et al</i> 1988 <sup>*</sup> | Post             | 155          | 4.4                 | 4                   | 1/170                         |
| Total                                      |                  | 478          | 4.6                 | 14                  | 1/166                         |
| Endoscopically screened patients           |                  | 201          | 3.0                 | 8                   | 1/77                          |

complicating CLO is often impossible to diagnose on gross endoscopic appearances, even when biopsy or cytology are unequivocally positive.<sup>15 16</sup> If only those studies in which endoscopic surveillance was used are considered, the incidence of adenocarcinoma becomes one in 77 patient-years of follow up. With yearly endoscopy this would imply that 77 endoscopies would be necessary to detect one adenocarcinoma, although a number of these would be necessary for other reasons, such as management of oesophageal strictures which occur in about 40% of patients with CLO.<sup>5 17</sup> Endoscopic surveillance has the potential advantage that carcinomas can be detected in the presymptomatic stage, at which surgery is more likely to be curative.

As endoscopic surveillance in all CLO patients is a formidable workload and very expensive, a knowledge of factors which indicate increased risk of malignant change might be useful in selecting which patients should be offered screening. It has been suggested that alcohol abuse and heavy smoking, known risk factors for squamous carcinoma of the oesophagus, predispose to adenocarcinoma in CLO, but the evidence for this is as yet not convincing. The extent of gastric epithelialisation of the oesophagus may relate to the likelihood of malignant change in CLO.<sup>18</sup> In each of the four patients with adenocarcinoma in Van der Veen's study and in four described by Robertson *et al*,<sup>14</sup> the gastric lined portion of the oesophagus was at least 10 cm long. On the other hand the development of malignancy does not correlate with the rate of extension of gastric epithelium up the oesophagus.<sup>15</sup>

Bile reflux into the oesophagus may be of aetiological importance in CLO, CLO is reported to follow gastric surgery and duodenogastric reflux of bile is more severe in CLO patients with complications such as stricture or ulcer, than in those without.<sup>19</sup> Intestinal metaplasia in gastric mucosa is a recognised predisposing factor for gastric cancer<sup>20</sup> and bile reflux has been implicated in the causation of intestinal metaplasia and stump cancer after partial gastrectomy.<sup>21</sup> Specialised (intestinal) epithelium is often found in CLO and might be related to contact of gastric epithelium in the oesophagus with bile. Be that as it may, there is stronger evidence that malignant change occurs only in specialised (intestinal) epithelium in CLO.<sup>22 23</sup> Biopsy material, however, suggests that such specialised mucosa is present in most patients with CLO<sup>16 24</sup> and its presence is of little value in deciding who should be offered regular endoscopic screening. Sulphomucin secretion, a marker for specialised (intestinal) epithelium, is by the same token too common a finding in CLO to predict the likelihood of malignant

change.<sup>24</sup> Other histochemical markers, including alkaline phosphatase and disaccharidases, are unlikely to be helpful in this respect.

Other markers which have been examined include the carcinoembryonic antigen – which is of little value in predicting malignant change – and neuro endocrine substances. Argrophil cells are found in 90% of biopsies and resection specimens in CLO and the expression of serotonin may help to distinguish Barrett's tumours from gastric cancer involving the cardia,<sup>25</sup> but is unlikely to be of predictive value for malignancy.

Undoubtedly the most important indicator of impending malignant change and at present the only reliable morphological marker is dysplasia in oesophageal biopsies in CLO.<sup>15 16 22</sup> High grade dysplasia, which is synonymous with carcinoma *in situ*, indicates that invasive adenocarcinoma is imminent<sup>15</sup> and is often taken as an indication for immediate oesophagectomy in CLO.<sup>26</sup> Low grade dysplasia is of less certain predictive value, but it often progresses to high grade dysplasia and adenocarcinoma over several years. Its presence in biopsies is a clear indication that endoscopic surveillance is advisable. DNA analysis using flow cytometry<sup>27 28</sup> and the more recent technique of DNA image cytometry<sup>29</sup> offer hope of more reliable predictability of malignant change in CLO in the future, but their worth has still to be evaluated.

Any practical approach to endoscopic surveillance in CLO must first take into consideration the value of early diagnosis of adenocarcinoma in the individual patient. Obvious unfitness for oesophagectomy because of age or other disease, makes early diagnosis pointless. As it is known that screening will detect carcinoma sometimes years before symptoms appear, the patient's life expectation may be limited on account of reasons other than the oesophageal carcinoma. Patients with short, gastric lined segments of oesophagus are less likely to develop carcinoma and endoscopic surveillance might only be offered to those with a segment of more than 8 cm in length. Dysplastic changes in CLO are a clear indication for endoscopic surveillance. Here sampling error must be considered and the fewer biopsies are taken the more likely is dysplasia to be missed. As yet there is no clear guidance available on this point, but it would seem advisable to take 4 quadrant biopsies at levels of 3 cm up the columnar lined segment and in addition target biopsies from any suspicious lesion should be taken. This represents a considerable workload for clinicians and pathologists, but they will be heartened in their tasks by the satisfaction of occasionally diagnosing an early symptomless and surgically resectable carcinoma in an otherwise fit middle aged person.

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