Endoscopic treatment of high-grade dysplasia and early cancer in Barrett's oesophagus

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Barrett's oesophagus is the premalignant precursor of oesophageal adenocarcinoma. Non-dysplastic metaplasia can progress to low-grade dysplasia, high-grade dysplasia, and finally to invasive cancer. Although the frequency of adenocarcinoma in patients with Barrett's oesophagus is low, surveillance is justified because the outcome of adenocarcinoma is poor. Oesophagectomy remains the standard treatment for patients with high-grade dysplasia and superficial carcinoma. However, it has been associated with substantial morbidity and mortality and some patients are judged unfit for surgery. In this review, the present status of less invasive procedures is discussed. Endotherapy preserves the integrity of the oesophagus and allows a better quality of life to patients at low risk of developing lymph-node metastases. Opposition to endoscopic treatment is based mainly on the identification of undetected foci of cancer and high-grade dysplasia in oesophagectomy samples. The current ablative techniques used are photodynamic therapy, argon plasma coagulation, laser treatment, and endoscopic mucosal resection.

Introduction

Oesophageal cancer is associated with high mortality. Despite advances in treatment, including surgical resection, radiation, and chemotherapy, the overall survival at 5 years is 12·5–13·7%.[1] 30–40 years ago, most oesophageal cancers in more developed countries were squamous-cell carcinomas, mostly related to smoking and alcohol consumption. Since then, the proportion of oesophageal adenocarcinomas, related to gastroesophageal reflux and Barrett's oesophagus has risen to constitute 46–50% of new cases of oesophageal cancer.[2]

Barrett's oesophagus is the premalignant precursor of adenocarcinoma (figure 1). After reflux-induced damage, the distal oesophageal squamous epithelium is replaced by columnar epithelium, as seen at endoscopy. Oesophageal biopsies confirm intestinal-type columnar metaplasia. Many patients with oesophageal adenocarcinoma have a long history of heartburn and acid regurgitation.[3] Barrett's oesophagus is a complication of long-standing gastro-oesophageal reflux disease, which is present in about 5–10% of patients undergoing endoscopy for reflux symptoms.[4] Nevertheless, of patients presenting with adeno-carcinoma in a previously undiagnosed Barrett's oesophagus, only about 60% had chronic reflux symptoms.[5]

The prevalence of Barrett's oesophagus longer than 3 cm in people older than 60 years, based on endoscopy and autopsy studies, is about 1%.[6] The mean age at diagnosis is about 60 years, but the disorder probably develops many years before it is found. Like adenocarcinoma, the prevalence of Barrett's oesophagus has also increased. One study estimated that only about one in five cases in the population have been identified.[7,8] What is not clear, is whether there has been a true increase in the frequency of Barrett's oesophagus or the rise in the number of diagnosed cases is the result of improved detection by endoscopy.

High-grade dysplasia and superficial cancer

Cancer can develop in patients with Barrett's oesophagus over several years, with rising cellular abnormalities from non-dysplastic metaplasia to low-grade dysplasia to high-grade dysplasia, and finally invasive adenocarcinoma.[4] High-grade dysplasia is found in fewer than 5% of patients with Barrett's oesophagus.[9] It is defined as intraepithelial neoplasia that has not infiltrated the basement membrane. Histological features of high-grade dysplasia include hyperchromatic nuclei, nuclear atypia, nuclear crowding, loss of cellular polarity, lack of cellular maturation at the epithelial surface, and complexity of the epithelial architecture. When high-grade dysplasia is diagnosed, slides should be reviewed by an expert pathologist because there is substantial variation within and between observers.[10]

The definition of superficial neoplasias includes those without invasion of the lamina propria, and intramucosal carcinoma invading the lamina propria. The Vienna classification of gastrointestinal epithelial neoplasias

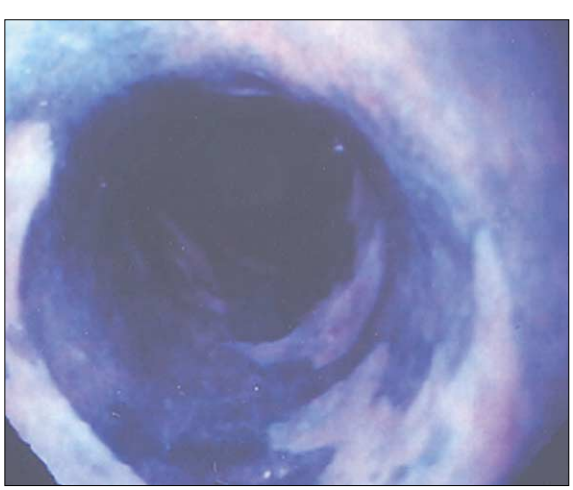

Figure 1: **Chromoendoscopy of methylene-blue-stained Barrett's oesophagus**

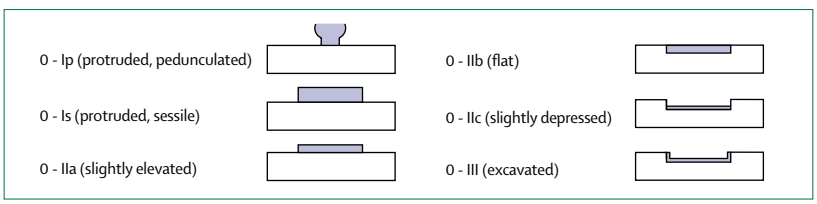

Figure 2: **Morphology of superficial neoplastic oesophageal lesions**

includes intraepithelial neoplasia (low-grade dysplasia and high-grade dysplasia), mucosal carcinoma (pT1a), submucosal carcinoma (pT1b), and advanced cancer (pT2).[11]

Figure 2 shows the morphology of superficial neoplastic lesions. Polypoid lesions are easily removed, but have a minor role in the onset of cancer of the oesophagus. Flat lesions are more difficult to diagnose, and careful endoscopy is needed. The most common lesions in Barrett's oesophagus are type 0–II, representing 70% of the total. Depressed type IIc lesions are commonly associated with submucosal invasion.

The risk of nodal metastases increases with the depth of malignant invasion. The oesophageal mucosa is divided into three layers: epithelium (m1); lamina propria (m2); and muscularis mucosae (m3). The submucosa is classified in much the same way, with three equal thickness sections: sm1; sm2; and sm3. The best possible histological assessment requires full-thickness oesophageal resection. For squamous-cell carcinomas, Japanese investigators[12] choose an empirical cut-off for submucosal cancer invasion. When the value is less than 200 μm the risk of nodal metastases is low. The same method has been proposed for cancer in Barrett's oesophagus.[13] The risk of lymph-node metastases in the presence of submucosal infiltration ranges from 20% to 25%.[14]

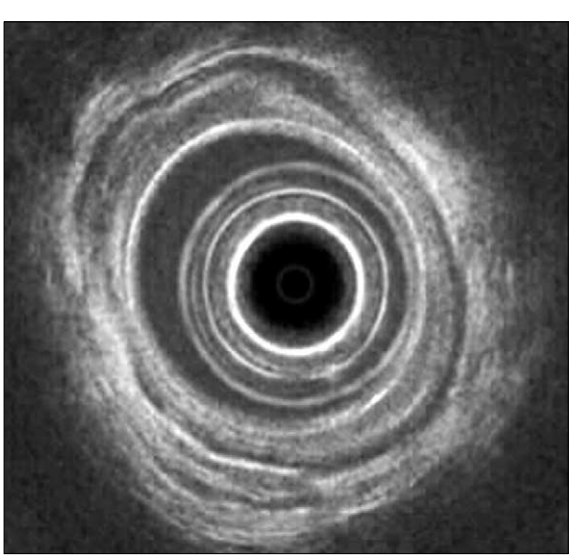

Figure 3: **Early cancer detected by endoscopic ultrasound in patient with high-grade dysplasia**
Hypoechoic thickened area imaged in superficial layer.

A review[15] of many large series estimated the cancer risk in patients with Barrett's oesophagus to be about one cancer per 200 patient years, with about 5% of patients with Barrett's oesophagus dying from oesophageal cancer.[16] Pathological examination showed unrecognised cancers in 38–73% of patients having surgery for high-grade dysplasia.[17,18] However, no detectable cancers were found in 1 year of intensive searching after the diagnosis of high-grade dysplasia by Schnell and colleagues.[19] In the few reported long-term surveillance studies (up to 10 years), the frequency of adenocarcinoma in patients with high-grade dysplasia was 16–26%.[19]

Endoscopic diagnosis

In many cases, high-grade dysplasia and early adenocarcinoma in Barrett's oesophagus are not visible on routine endoscopy. Therefore, a better technique is needed to identify dysplasia, which works in or near real time. Focal cellular changes in a Barrett's oesophagus that can be up to 15 cm in length need to be identified, meaning that the technique has to be moderately specific and not easily affected by oesophageal inflammation. Interobserver agreement should be greater than that for histopathology without prohibitive cost.

The following endoscopic methods for identification of dysplasia have been tested or are being developed: cytology; chromoendoscopy; laser-induced fluorescence; reflectance spectroscopy; light-scattering spectroscopy; trimodal spectroscopy; Raman spectroscopy; endoscopic ultrasonography; high-magnification endoscopy; optical-coherence tomography; and endoscopic-confocal microscopy. No method has yet solved the issue of identifying focal microscopic cellular changes in a large area of Barrett's epithelium

Cytology

Abrasive balloons have been developed to obtain cytological material from the oesophageal surface. Their advantage is an ability to sample a large area of the oesophagus at a low cost and without sedation. However, cytological interpretation of dysplasia is even more difficult than histological interpretation. Therefore, the sensitivity for identifying high-grade dysplasia with cytology is restricted, and the sensitivity for identifying low-grade dysplasia is poor.[20] If a cellular biomarker strongly associated with dysplasia could be identified, then this technique might become clinically useful.

Chromoendoscopy

Chromoendoscopy is based on the differential colour staining of abnormal epithelium with dyes such as methylene blue. The dye is taken up by absorptive intestinal-type cells, but not by dysplastic cells, in the small bowel and colon. Methylene blue (figure 1) stains short-segment Barrett's oesophagus in a focal pattern and long-segment Barrett's oesophagus in a diffuse

pattern.[21] Methylene-blue-directed biopsy samples can aid in the differential diagnosis of short-segment Barrett's oesophagus and metaplasia at the gastro-oesophageal junction and cardia.[21] In dysplastic Barrett's oesophagus, nuclei increase and there is less cytoplasm and fewer goblet cells for uptake of methylene blue. Hence, dysplastic tissue takes up less dye; close to 90% of all samples of dysplastic tissue are either unstained or more lightly stained.[22] However, many studies[21,23] of methylene-blue-directed biopsies have given conflicting results. The technique is operator dependent and the sensitivity for identifying dysplasia is not sufficiently high.

Laser-induced fluorescence

Dysplastic and malignant tissues fluoresce differently from healthy tissue when excited by light because of differences in the concentrations of endogenous fluorophores. The sensitivity for detecting high-grade dysplasia and cancer is about 90%.[24] However, auto-fluorescence still has a very low sensitivity for detection of low-grade dysplasia, and inflammation can also lead to false-positive results. Endoscopic-fluorescence detection might be improved by systemic or local 5-aminolaevulinic acid, which is metabolised by dysplastic and malignant tissue into protoporphyrin-IX.[25] Further improvements in sensitivity and specificity can be affected by temporal as well as spectral resolution of the fluoresced light. This technique remains a promising area for further research, possibly for the development of better fluorophores.

Reflectance spectroscopy

This technique assesses the reflectance of diffuse light, which after multiple scattering events, provides morphological information about the underlying tissue. The spectrum can be analysed to obtain information about the haemoglobin concentration, the oxygen saturation, and the density of the scattering tissue.[26] However, this technique alone does not have sufficient discrimination for clinical application.

Light-scattering spectroscopy

Another interaction of light with tissue that can be used to identify cellular characteristics is based on its scattering pattern.[27] The spectrum and intensity of the scatter is based on the size and density of the scattering particle, namely the nucleus. Wallace and colleagues[27] undertook studies in vitro and found that composite measurements of the spectrum based on scatter size and clustering could be used to differentiate dysplastic epithelium from healthy epithelium with a sensitivity and specificity of over 90%. The processing of data using this technology is not yet real time and it can only be used to investigate the spectrum of a small volume of tissue.

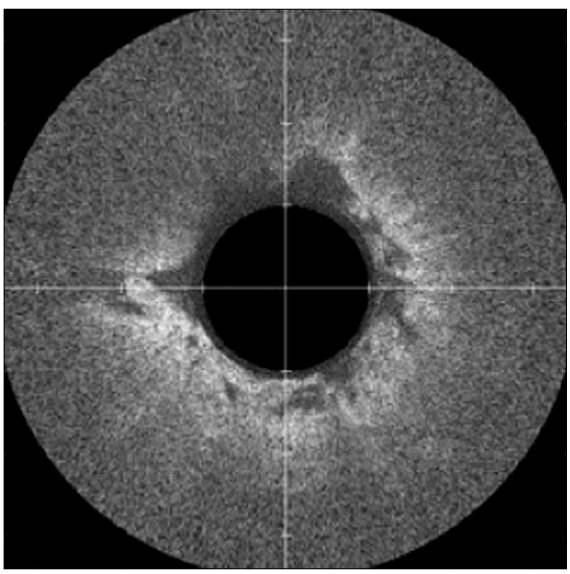

Figure 4: Real-time optical coherence tomography image of high-grade dysplasia with low reflectance areas and disordered architecture

Trimodal spectroscopy

Trimodal spectroscopy is a newly proposed technique that combines fluorescence, reflectance, and scattering spectroscopy.[26,28] This combination allows information to be obtained about the architecture of the biochemical and cellular tissue. Perhaps this technique will provide the sensitivity and discrimination needed for reliable identification of dysplastic changes. However, the combination of several methods could make it prohibitively expensive.

Raman spectroscopy

Chemical bonds in biological molecules absorb small amounts of vibrational energy, leading to the Raman effect. Although Raman spectroscopy provides a very specific signature of biological tissue, the spectrum is very low in intensity. This technique might accurately identify dysplasia and cancer at specific points[29] but will need to be combined with other surveillance techniques for clinical application.

Endoscopic ultrasonography

Endoscopic ultrasonography is another high-resolution-imaging technique based on the reflectance of sound waves from tissue interfaces. High-frequency ultrasound provides a higher resolution but lower penetration into tissue. The frequencies used for imaging tissue do not provide the resolution of cellular structures needed to identify dysplasia. Clinically, endoscopic ultrasonography might be of use for detection early cancers and lymph nodes in patients known to have high-grade dysplasia, and for selection of patients with high-grade dysplasia for endoscopic mucosal resection (figure 3). Whereas few occult cancers are diagnosed by endoscopic ultrasonography alone, the

technique could be of use in localisation of cancers when findings from endoscopy and biopsy samples are inconclusive. Endoscopic ultrasonography is restricted in that it does not have sufficient resolution to detect low-grade dysplasia or high-grade dysplasia; the studies are scarce and mixed as to whether the technique can identify cancer or nodal metastases reliably.[30]

High-magnification endoscopy

High-magnification endoscopes provide images of the gastrointestinal epithelium. Magnification of 115 times can be achieved with this technology. Although specialised intestinal metaplasia cannot be identified morphologically by conventional endoscopy, enhanced-magnification endoscopy by use of contrast agents, such as acetic acid, indigo carmine, or methylene blue, allows the identification of specific pit patterns of the oesophageal epithelium, which correspond to intestinal metaplasia, with a sensitivity of more than 95%.[31] High-grade dysplasia seems to distort the pattern, but this technique cannot distinguish low-grade dysplasia from non-dysplastic-intestinal metaplasia. Whether this technique can be used to investigate the entire oesophageal surface under magnification is not clear. However, the results are preliminary and need to be replicated.

Narrow-band imaging is a method for enhancing the contrast during high-magnification endoscopy. Preliminary studies[32] are under way to test the usefulness of this technology for identification of dysplastic changes and early cancers in patients with Barrett's oesophagus.

Optical-coherence tomography

Optical-coherence tomography is based on the scattering interaction of light and tissue. The technique measures the optical delay of back-scattered or reflected light, which is a function of the distance between the source and the scatterer. It measures the path length of the emitted beam plus that of the scattered light from tissue by use of an optical technology known as low-coherence interferometry. Data from optical-coherence tomography are converted into grey-scale images. Optical-coherence-tomography imaging of the oesophagus (figure 4) can identify distinctive features associated with Barrett's epithelium.[33] Preliminary experience[34] in patients with Barrett's oesophagus indicates that endoscopic-optical-coherence tomography can detect dysplasia as a loss of epithelial-surface architecture and that dysplastic tissue scatters or poorly reflects light compared with ordered, healthy epithelium. New technologies, specifically sapphire lasers, have become available that should improve the resolution of endoscopic-optical-coherence-tomography instrument to as much as 3–4 μm. The volume of tissue in a single-optical-coherence-tomography image is small, so imaging of a large surface area is difficult. New system designs are needed for imaging of large surfaces.

Endoscopic-confocal microscopy

Endoscopes and endoscopic probes have been developed to enable confocal microscopy in vivo. A clinical trial[35] in 27 patients with a confocal colonoscope has shown sharp images of cells, nuclei, and other subcellular structures. This technology, which is still at an early stage of development, will undoubtedly be able to identify dysplastic changes in specific focal areas of Barrett's oesophagus. However, it will need to be coupled with a wide-area surveillance method, such as fluorescence endoscopy, for clinical usefulness.

When high-grade dysplasia is detected, three options are available: endoscopic surveillance, oesophagectomy, and endoscopic treatments.

Surveillance endoscopy of Barrett's oesophagus

No or low-grade dysplasia

Surveillance of Barrett's oesophagus is justified by the poor outcome of adenocarcinoma despite its low frequency in patients with Barrett's oesophagus. Surveillance has been associated with improved survival in retrospective studies but is still controversial.[4] The proposed strategy consists of a screening endoscopy of older patients with chronic gastro-oesophageal-reflux disease, and then periodic endoscopic surveillance with random biopsy in patients with Barrett's oesophagus, even those with short extensions of metaplastic epithelium. Consequently, many patients would need surveillance, with a substantial increase in health expenditure. The recommended policy is to take biopsy samples from all visible mucosal abnormalities, followed by random samples from all four quadrants, preferably with jumbo forceps, every 1–2 cm.[36] Surveillance should be done every 2–3 years if there is no dysplasia and every 0·5–1·0 years if low-grade dysplasia is present.

High-grade dysplasia

In the management of high-grade dysplasia, some authorities advocate surgical resection, whereas others suggest endoscopic surveillance every 3 months until cancer is detected.[19,37–42] The uncertainty of the natural history of high-grade dysplasia and its low progression rate could justify a conservative approach. Aggressive sampling might detect invasive adenocarcinoma in patients with high-grade dysplasia undergoing endoscopic follow-up. Endoscopic surveillance is restricted by the inability to investigate the overall surface of the metaplastic epithelium. Cancer and dysplasia can be multifocal and scattered in patches, so they might be missed even with many random biopsies.[43] The so-called Seattle protocol, which uses frequent jumbo-forceps biopsies with intervals of 1 cm, is cumbersome.[44] Most endoscopists do not comply with even a modified protocol needing biopsies every 2 cm. Finally, the overall strategy of periodic endoscopic surveillance is very expensive with, as yet, unproven

benefit. Therefore, perhaps this approach should be offered only to patients who cannot undergo more aggressive treatment.

Oesophagectomy

Oesophagectomy continues to be the standard treatment for patients with superficial cancer. However, it is a major operation involving substantial risks. In a US study,[45] the mortality was 2·5% in hospitals with high surgical volume, and 15% in hospitals with low surgical volume. Postoperative complications, including pneumonia, cardiac arrhythmia, anastomotic leakage, and infections, were reported after 12–50% of oesophagectomies.[42,46–48] Regurgitation, aspiration, and cough were recorded in 60–80% of patients.[49] Table 1 summarises the surgical studies in patients with high-grade dysplasia or cancer arising in Barrett's oesophagus. By removing all of the Barrett's oesophagus cells, oesophagectomy would prevent death from metastatic adenocarcinoma.[17,37] However, some patients are poor candidates for major surgery because of their age and comorbidity. For these reasons, we review the current status of other, less invasive procedures to remove dysplastic Barrett's oesophagus.

Endoscopic treatment

The aims of endotherapy are to preserve the integrity of the oesophagus and to offer better quality of life to patients. Oppositions to endoscopic treatment are based mainly on the common detection in oesophagectomy samples of undetected foci of adenocarcinoma and high-grade dysplasia. Patients need to be selected carefully to avoid the risk of missing lymph-node metastases. They should also be involved in the decision-making process, involving a discussion with them about the outcomes of endoscopic and surgical treatments.

The theory behind endotherapy is that the removal of the dysplastic Barrett's oesophagus should stop the neoplastic progression and restore a neosquamous epithelium. Since Barrett's oesophagus is caused by chronic gasto-oesophageal reflux disease, patients undergoing endotherapy need continuous pharmacological suppression of gastric secretion or antireflux surgery. Treatment with proton-pump inhibitors is associated with a substantial reduction in the onset of dysplasia in patients with Barrett's oesophagus.[52]

The ablative techniques that have been used in patients with high-grade dysplasia and superficial adenocarcinoma are: photodynamic therapy, argon-plasma coagulation, laser therapy, and endoscopic mucosal resection.

Photodynamic therapy

This non-thermal chemical method involves the activation of a photosensitiser given to the patient in advance. The drug is an inactive compound until its exposure to light delivered by a dye laser or a diode laser. The light can be delivered by a cylindrical diffusing fibre passed through the biopsy channel of the endoscope, or by means of an air-filled cylindric balloon, which has a fibre in its centre. Single oxygen molecules are generated that are cytotoxic for the mucosa and cause its necrosis. Photodynamic therapy has the theoretical advantage of destroying unrecognised foci of cancer. Table 2 summarises on photodynamic therapy for high-grade dysplasia or cancer arising in Barrett's oesophagus.

The photosensitisers used in the clinical setting are: porfimer, haematoporphyrin derivative, and 5-aminolaevulinic acid. These photosensitisers differ in the way they are given, the depths of distribution at the tissue level, and the clearing time from the body.

Porfimer is given intravenously 48 h before photodynamic therapy at a dose of 2 mg/kg. It accumulates

n	Histology		Complications	Follow-up (months)	Residual disease or recurrence	Death	Ref
	Before surgery	After surgery					
30	High-grade dysplasia (30)	High-grade dysplasia (17), adenocarcinoma (13)	Death (1); small or large bowel necrosis; abdominal wound (3); minor (3)	Mean, 40	Residual high-grade dysplasia developed in adenocarcinoma (1)	3 (not cancer)	37
18	High-grade dysplasia (18)	High-grade dysplasia (9), adenocarcinoma (9)	Cervical leak (2); chylothorax (1); colon necrosis (1)	Median, 34	2	3 (not cancer)	41
11	High-grade dysplasia (11)	High-grade dysplasia (3), adenocarcinoma (8)	Delayed gastric emptying (2) Anastomotic leak or stricture (1)	Mean, 32	Adenocarcinoma (1)	1 (adenocarcinoma)	42
15	High-grade dysplasia (15)	Carcinoma-in-situ (3), adenocarcinoma (8), high-grade dysplasia (4)	Pulmonary, cardiovascular, or infectious (11)	Mean, 41	0	0	46
15	High-grade dysplasia (15)	High-grade dysplasia (10), adenocarcinoma (5)	Pleural effusion, pneumonia,urinary retention, diabetic decompensation, bleeding, chylothorax (8); late stenosis (4)	Median, 46	0	2 (not cancer)	47
60	High-grade dysplasia (60)	High-grade dysplasia (42), adenocarcinoma (18)	Major (4); death (1)	Not detectable	Not detectable	3	48
33	High-grade dysplasia (21), adenocarcinoma (12)	High-grade dysplasia (13), adenocarcinoma (20)	Not detectable	Not detectable	Adenocarcinoma (5)	Not detectable	50
12	High-grade dysplasia (12)	High-grade dysplasia (7), adenocarcinoma (5)	Small bowel perforation (1), respiratory insufficiency (2), delayed gastric emptying (3); minor (1)	Mean, 12·6	0	0	51

Table 1: **Selected surgical studies in patients with high-grade dysplasia or cancer in Barrett's oesophagus**

n	Mean size of lesion (cm)	Photosensitiser	Pretreatment histology	Complications	Surgery	Follow-up (months)	Residual disease or recurrence	Ref
100	Not detectable	Photofrin	High-grade dysplasia (73) Low-grade dysplasia (14) Adenocarcinoma (13)	Stenosis (34)	2 (high-grade dysplasia) 2 (adenocarcinoma)	Mean, 19	Residual high-grade dysplasia (7); residual low-grade dysplasia (8 of 73 with high-grade dysplasia); progression from low-grade to high-grade dysplasia (1)	53
60	Not detectable	Photofrin	High-grade dysplasia (43) Adenocarcinoma (17)	Stenosis (14)	0	Mean, 12	Residual high-grade dysplasia(4%); residual adenocarcinoma (0%)	54
32	2	5-aminolaevulinic acid	High-grade dysplasia (10) Cancer (22)	Mild transaminase increase 66%	2	Mean, 9·9	Early cancer (2 of 22 with early cancer)	55
103	Not detectable	Porfimer	High-grade dysplasia (80) Early cancer (9) Near early cancer (22)	Stenosis (31)	7 (high-grade dysplasia) 5 (adenocarcinoma)	Not detectable	Residual high-grade dysplasia (4); residual adenocarcinoma (1 of 9 with early cancer); progression to adenocarcinoma (2 of 80 with high-grade dysplasia)	56
48	Not detectable	Photofrin	High-grade dysplasia (34) Adenocarcinoma (14)	Stenosis (11); Photosensitivity (7); atrial fibrillation (1); congestive heart failure (1); perforation (1, high-grade dysplasia)	1 (adenocarcinoma)	Median, 18·5	0	57

Table 2: **Selected studies on photodynamic therapy in high-grade dysplasia or cancer in Barrett's oesophagus**

in both healthy and diseased mucosa, with more in the dysplastic tissue. Porfimer causes skin photosensitivity that lasts for up to 3 months and patients should avoid sunlight. Using porfimer, Overholt and co-workers[53] completely removed superficial cancer in 77% of patients with Barrett's oesophagus, and high-grade dysplasia in 88% of patients with Barrett's oesophagus over a mean follow-up period of 19 months. In many of these patients neodymium:yttrium-aluminium-garnet laser therapy was given as well as photodynamic therapy. The major drawback of photodynamic therapy with porfimer is that about 30% of patients have severe oesophageal strictures. The Mayo Clinic group eradicated high-grade dysplasia in 88% of 26 patients with the use of haematoporphyrin derivative.[58]

5-aminolaevulinic acid is a natural compound of the heme biosynthetic pathway that is metabolised to the photosensitive compound protoporphyrin. The drug is given orally at a dose of 60 mg/kg, 4–6 h before treatment. This prodrug accumulates in the cells of the mucosal layer, by contrast with porfimer and haematoporphyrin derivative, which are distributed in the submucosa. The necrosis is superficial, without risk of oesophageal perforation and stenosis. For this reason, 5-aminolevulinic acid is more suitable for mucosal ablation of non-complicated Barrett's oesophagus. The rapid clearing of the drug (after 24–48 h), substantially reduces the risk of photosensitivity.[59]

Whether photodynamic therapy reduces the incidence of adenocarcinoma is not known. Long-term results after photodynamic therapy and additional laser therapy have been reported. After mean follow-up of 58·5 months, high-grade dysplasia had regressed in 60 of 65 patients, whereas three patients developed subsquamous adenocarcinoma. Of the nine patients with cancer, three had elimination of cancer and Barrett's oesophagus. The length of Barrett's oesophagus was also reduced. Oesophageal strictures occurred in 18% of patients receiving one session of photodynamic therapy and in 50% of patients receiving two sessions (30% overall). Subsquamous metaplastic epithelium was found in 5% of patients.

As previously mentioned, the healing process causes the development of severe scarring and stenosis, with the need for endoscopic dilations. To overcome this complication, prednisone use has been assessed. Panjehpour and colleagues[54] showed the ineffectiveness of this treatment and reported the elimination of cancer in all

n	Mean size of lesion (cm)	Technique	Histology before laser argon-plasma coagulation	Complications	Mean follow-up (months)	Residual disease or recurrence	Death	Ref
14	>2	Neodymium: yttrium-aluminum garnet	High-grade dysplasia (9) Intramucosal cancer (5)	Odynophagia (31%); dysphagia (14%); chest pain (20%)	12·8	0	0	62
10	Not detectable	Argon-plasma coagulation	High-grade dysplasia (7) Adenocarcinoma (3)	Stenosis (1)	24	High-grade dysplasia (1) High-grade dysplasia recurred in adenocarcinoma 3 months later (1)	Adenocarcinoma (1)	63
55	Not detectable	Argon-plasma coagulation	High-grade dysplasia (9)	Perforation (2)	20·8	0	High-grade dysplasia with perforation (1)	64

Table 3: **Selected studies on laser argon-plasma coagulation in high-grade dysplasia or cancer in Barrett's oesophagus**

n	Mean size of lesion (cm)	Histology		Complications	Surgery	Mean follow-up (months)	Recurrence	Ref
		Before procedure	After procedure					
17	Not detectable	Intramucosal carcinoma (7) Adenocarcinoma (10)	Intramucosal carcinoma (7) Adenocarcinoma (10)	Bleeding (1)	1	13	0	67
12	Not detectable	High-grade dysplasia (3) High-grade dysplasia or intramucosal carcinoma (2) Intramucosal carcinoma (7)	Barrett's oesophagus (2) Low-grade dysplasia (1) High-grade dysplasia (5) Adenocarcinoma (4)	Bleeding (4) Stenosis (2)	0	Median: 9	0	68
21	1·6	Intramucosal carcinoma (12) Adenocarcinoma (9)	High-grade dysplasia (12) Adenocarcinoma (9)	Bleeding (4)	Adenocarcinoma (1)	18	0	69
80	Not detectable	High-grade dysplasia (7) Early cancer (73)	Adenocarcinoma (11)	Bleeding (48) Stenosis (3)	0	34	24	70
25	Not detectable	Barrett's oesophagus (2) Low-grade dysplasia (8) High-grade dysplasia (5) Adenocarcinoma (9) Other (1)	Barrett's oesophagus (2) Low-grade dysplasia (3) High-grade dysplasia (5) Adenocarcinoma (13) Other (2)	0	Adenocarcinoma (2/13)	14·6	Adenocarcinoma (4/13)	71
35	0·9	High-grade dysplasia (3) Early cancer (32)	High-grade dysplasia (3) Early cancer (32)	Bleeding (7)	Not detectable	12	4	72

Table 4: **Selected studies on endoscopic mucosal resection in high-grade dysplasia or cancer in Barrett's oesophagus**

four patients, high-grade dysplasia in 41 of 43 patients, and Barrett's oesophagus in 25 of 60 patients.

Eradication of the dysplastic tissue and squamous re-epithelialisation was obtained with 5-aminolaevulinic acid in all five patients with high-grade dysplasia, and in 77% of those with mucosal cancer in Barrett's oesophagus.[55,60] The superficial necrosis obtained with 5-aminolaevulinic acid meant that there was a risk of buried metaplastic epithelium underneath the neosquamous epitelium.[61]

Laser therapy and argon-plasma coagulator

Lasers have been used almost exclusively in palliation of cancers (table 3). The use of laser therapy is declining because metal stents have shown a better outcome in this setting. An attempt to revitalise laser therapy has been made in the specialty of oesophageal mucosal ablation, with or without high-grade dysplasia. Three lasers have been used: neodymium:yttrium-aluminum-garnet (1064 nm), potassium titanyl phosphate (532 nm), and argon (514·5 nm). Their depth of penetration is related to the wavelength; neodymium:yttrium-aluminium-garnet can reach up to 4 mm, compared with 1 mm for potassium titanyl phosphate and argon.

A few studies, involving a small amount of patients, have analysed the effectiveness of laser therapy in early malignant disorders. Sharma and co-workers[65] reported the favourable outcome for six patients with early Barrett's oesophagus managed with neodymium:yttrium-aluminium-garnet laser and multipolar electrocoagulation. Only one recurrence of cancer was noted 36 months later. In a second study, Weston and co-workers[62] enrolled 14 patients with high-grade dysplasia and adenocarcinoma. All had complete elimination of high-grade dysplasia and cancers.

An argon-plasma coagulator is a non-contact electrocoagulation device that involves a high-frequency monopolar current conducted to the tissue by a flow of ionised argon gas. The depth of necrosis varies according to the power setting of the generator, the distance of the tip of the probe from the mucosa, the amount of gas flow, and the duration of the application. The depth of the injury can reach up to 6 mm.

In a study by Van Laethem and coworkers[63] involving a series of ten patients (seven high-grade dysplasia, three adenocarcinoma), eight showed complete regression of malignant disease. One patient progressed to cancer, and one had persistent high-grade dysplasia. May and colleagues[66] treated three patients with intramucosal carcinoma. One patient had a recurrence 2 years later and was treated with argon-plasma coagulator.

Laser and argon-plasma coagulation might not provide homogeneous ablation of the mucosa, and glands can persist under the neosquamous epithelium. Perforation and death have been reported.[64] Argon-plasma coagulation, photodynamic therapy, and neodymium:yttrium-aluminum-garnet have disadvantages such as the need for repeated sessions and the risk that an invasive cancer will be missed.

Panel: **Techniques of endoscopic mucosal resection**

Without suction (freehand techniques)
Strip-off biopsy (injection and snaring)
Lift-and-cut with double-channel endoscope
Insulated-tip diathermic knife (injection+incision+snaring)
Barbed snare

With suction
Endoscopic mucosal resection, cap-assisted (plastic-cap. Injection and snaring)
Suck-and-ligate with a variceal ligating device

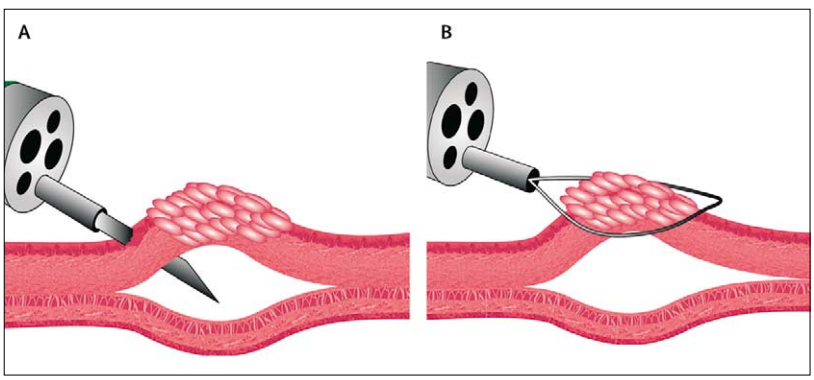

Figure 5: **Strip-biopsy**
(A) Submucosal injection. (B) Grasping of lesion.

Endoscopic mucosal resection

Japanese researchers introduced endoscopic mucosal resection in 1984, and have shown outcomes comparable with those of surgery for superficial squamous-cell carcinomas and early gastric cancers. Most of the studies describe endoscopic mucosal resection of endoscopically visible areas of high-grade dysplasia or early adenocarcinoma (table 4); however, the number of reported series remains small. Randomised control studies comparing endoscopic mucosal resection with surgery are still lacking. In addition, there is restricted information on the long-term effectiveness of this technique.

By removing full thickness mucosa, endoscopic mucosal resection maximises the histological assessment of the lesion, allowing definition of both its lateral extent and its depth. It changes the pathological stage in many patients. Reclassification has been reported in up to 75% of patients after endoscopic mucosal resection, possibly owing to biopsy sampling error and observer interpretation (table 4). Compared with endoscopic mucosal resection, ablative methods (photodynamic therapy, laser, and argon-plasma coagulation) prevent any histopathological assessment.

Treatment	Advantages	Disadvantages	Outcome
Endoscopic mucosal resection	Histological assessment; complete removal of circumferential short-segment Barrett's oesophagus; 1 to 2 sessions	Incomplete treatment of invisible foci of high-grade dysplasia in long-segment Barrett's oesophagus	Favourable in superficial cancer; long-term results awaited
Photodynamic therapy	Easy to perform; 2 sessions	Lack of adequate histological examination; photosensitivity and oesophageal stenosis needing periodic bougienage	Favourable in superficial cancer
Laser	Non-contact techniques; deep penetration	Lack of adequate histological examination; many sessions; persistence of buried metaplastic epithelium	Few data available
Argon plasma coagulation	Non-contact; technically simple	Lack of adequate histological examination; many sessions; persistence of buried metaplastic epithelium; perforation	Few data available
Oesophagectomy	Complete remove of Barrett's oesophagus; histological assessment of lymph nodes	Morbidity and mortality not negligible; worsening of quality of life	Radical treatment for superficial cancers

Table 5: **Therapeutic options for high-grade dysplasia or cancer in Barrett's oesophagus**

The sequential use of endoscopic mucosal resection to remove the visible areas of high-grade dysplasia, followed by photodynamic therapy for invisible foci of malignant disease has been proposed. Buttar and co-workers[67] successfully treated 17 non-surgical patients with superficial oesophageal cancer. Endoscopic mucosal resection improved staging in 47%. Stenosis after photodynamic therapy was recorded in 30% of patients.

When high-grade dysplasia is detected in short-segment Barrett's oesophagus (≤30 mm), even without endoscopic abnormalities, endoscopic mucosal resection can remove all the metaplastic epithelium. The safety of circumferential endoscopic mucosal resection in patients with non-visible high-grade dysplasia has been assessed in five patients with multifocal high-grade dysplasia and intramucosal carcinoma, and seven with invisible high-grade dysplasia. During each session, endoscopic mucosal resection removed 30–40 mm in length and three-quarters of the circumference. No recurrences were seen after median follow-up of 9 months. Two strictures arose but were treated by bougienage.[68]

Circumferential endoscopic mucosal resection has been attempted in 21 patients with high-grade dysplasia or mucosal cancer. The resection was done in two sessions, the second 1 month after the first, to prevent stenosis. Endoscopic mucosal resection was completed in 18 of the patients. Of the three patients with residual disease, one underwent surgery and the two remaining received chemoradiation. These patients are free of disease after 18 months and 24 months. Two local recurrences were treated again by endoscopic mucosal resection.[69]

An attempt to remove large areas of oesophageal mucosal in six pigs has been made. Mucosal strips of 5 cm long have been successfully resected.[73]

Endoscopic mucosal resection allows the complete resection of nodular and flat lesions. Only cancer confined to m1 and m2 can be treated safely. A study of 742 samples obtained at endoscopic mucosal resection from 326 patients with superficial neoplasia arising in Barrett's oesophagus showed that most of the lesions were localised to the mucosa and that infiltration by blood and lymphatic vesseal was rare.[74] Endoscopic mucosal resection must be done after endoscopic ultrasonography, to assess the depth of penetration and the status of regional lymph nodes.

Resection techniques

Resection techniques are either with or without suction (panel). The lesion can be removed in a single piece (en bloc) or in several fragments (piecemeal). Removal of a malignant lesion en bloc is ideal, to improve the radicality of the treatment and to allow better assessment of the resection margins. However, in many instances, piecemeal resection is unavoidable.

Submucosal injection

The gastrointestinal wall has two components, mucosal and muscle layers, attached by a loose connective tissue of submucosa. Injection of a fluid into the submucosa creates a cushion between the lesion and the deeper layers of the gut wall before removal.

Several solutions have been proposed, some of which have been tested only experimentally: saline with or without adrenaline, 50% dextrose, glyceol (10% glycerol and 5% fructose), hyaluronic acid, and hydroxypropyl methylcellulose. In our endoscopic practice, we use saline plus adrenaline solution (1/200 000). When an infiltrating cancer is present, the injection aids indirect diagnosis, because the lesion does not lift. In these patients, endoscopic mucosal resection should not be attempted.

Strip biopsy

After a submucosal injection to raise the lesion, the open polypectomy snare is placed around it and pressed against the mucosa (figure 5). Excess air is aspirated to decrease distension and grasp the targeted lesion. The size of the samples obtained with this procedure range between 10 mm and 15 mm.

Endoscopic mucosal resection (cap-assisted)

A transparent, hard, plastic cap is preloaded on a standard front-viewing endoscope tip (figure 6). Inside the distal end of the cap is a gutter that positions the opened polypectomy snare. After creation of the submucosal fluid cushion, the cap is applied against the lesion, which is aspirated into it. The opened snare is then secured around the tissue.

Suck-and-ligate technique

Endoscopic mucosal resection can be done by use of a variceal-band ligator. An artificial polyp is created and the resection is done with a polypectomy snare. A randomised study[75] comparing two techniques of endoscopic mucosal resection has been done in patients with early oesophageal cancer. 50 procedures were done with the suck-and-ligate technique without submucosal injection, and 50 with endoscopic mucosal resection cap after submucosal injection. No difference was noted between the two techniques. At the first follow-up, 57% of patients had residual neoplasia.

Complication rates for endoscopic mucosal resection range from up to 50%. The most frequent is bleeding, reported in a median 10% of patients. Haemorrhage can be controlled endoscopically in most cases. Oesophageal stenosis is a late complication of endoscopic mucosal resection, reported in up to 30% of cases (table 4). The perforation risk is generally less than 1%.

Conclusions

Oesophagectomy is still the standard treatment for patients with high-grade dysplasia and superficial carcinoma arising in Barrett's oesophagus. However, it has been associated with much morbidity and mortality.

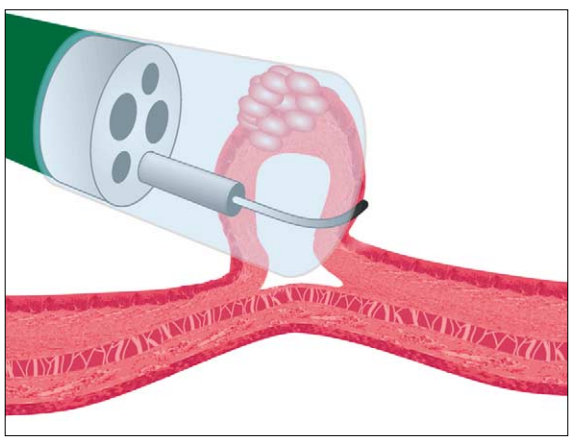

Figure 6: Endoscopic mucosal resection, cap assisted

Endotherapy is gaining support in a subset of patients with superficial cancer, at low risk of lymph-node metastases. It could become an alternative to surgery, affecting the quality of life, and lowering cost (table 5).

Data from published work are encouraging on the use of endoscopic mucosal resection. Nevertheless, randomised trials comparing this technique with surgery or other ablative endoscopic techniques are lacking. At present, only patients who are unfit for surgery or those who decline such aggressive treatment have been considered for endoscopic mucosal resection. The improvement of diagnostic methods will allow careful selection of patients, minimising the risk of under treatment in case of long segment Barrett's oesophagus.

Technical improvement of the devices and the ability to control the healing process after endoscopic mucosal resection, avoiding scarring and consequent stenosis, will increase its use. Long-term follow-up of many patients is needed to confirm the effectiveness of this treatment.

Endoscopic mucosal resection should be done by skilled endoscopists, who can cope with procedural complications, such as bleeding and perforation. Owing to the small number of patients with superficial neoplasias in oesophageal Barrett's oesophagus, the performance of endoscopic mucosal resection should be restricted to referral centres.

Search strategy and selection criteria

Data for this review were identified by searches of PubMed and selected references from relevant articles with the search terms "high-grade dysplasia", "HGD", "cancer", "therapy", "endoscopy", "photodynamic therapy", "PDT", "argon plasma coagulator", "APC", "laser", "EMR" linked with the Bolean operator OR and combined with "Barrett's oesophagus". Only papers published between 1984 and 2004 were included.

Conflict of interest

We declare no conflicts of interest.

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