Treatment of Barrett's Esophagus and Prevention of Esophageal Cancer

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Barrett's Esophagus

Norman Barrett, in 1950,

British Journal of Surgery

he defined the esophagus as

"that part of the foregut, distal to the cricopharyngeal sphincter, which is lined by squamous epithelium"

Allison and Johnstone, 1953

- proposed that Barrett had misidentified the columnar lined intrathoracic structure as stomach and that in reality it was the esophagus lined with gastric mucus membrane. They had suggested the term "***lower esophagus lined with columnar epithelium***".

SURGERY

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Original Communications

THE LOWER ESOPHAGUS LINED BY COLUMNAR EPITHELIUM

N. R. BARRETT, LONDON, ENGLAND

DEFINITIONS

THE ideas discussed here are n statistics nor upon a large collection of specimens; they thinking about a few unusual cases of esophageal disease. rejected or modified in the light of future experiences. ecause I have changed my opinion relating to certain ot static and there is no subject which does not yiel pths are sounded.

This paper concerns is denied by some, misunderstood by others, and surgeons. It has been called a variety of names tory because they have suggested incorrect etiolog short esophagus, ectopic gastric mucosa, short esoph agus lined by gastric epithelium are but a few. At ost accurate description is that it is a state in which the phagus is lined by columnar epithelium. This does not com hich could be wrong, but it carries certain implications which rified.

- **Barrett accepted this terminology**
- **A more complete description of the disease in 1957.**

Definition of Barrett's esophagus

- The columnar-lined distal esophagus, extending proximally from the cardia mucosa of the stomach to involve the esophagus over distance raging from a few centimeters to its entire length.

Barrett's Esophagus

- Barrett's oesophagus is a sequel of gastro-esophageal reflux disease (GERD) and may be present in **5–15% of GERD** patients in the western population
- Barrett's esophagus is premalignant, with esophageal adenocarcinoma occurring at an overall incidence rate of **0.4–0.5% per year**.

S Seewald„Postgraduate Medical Journal 2007;**83**:367-372;

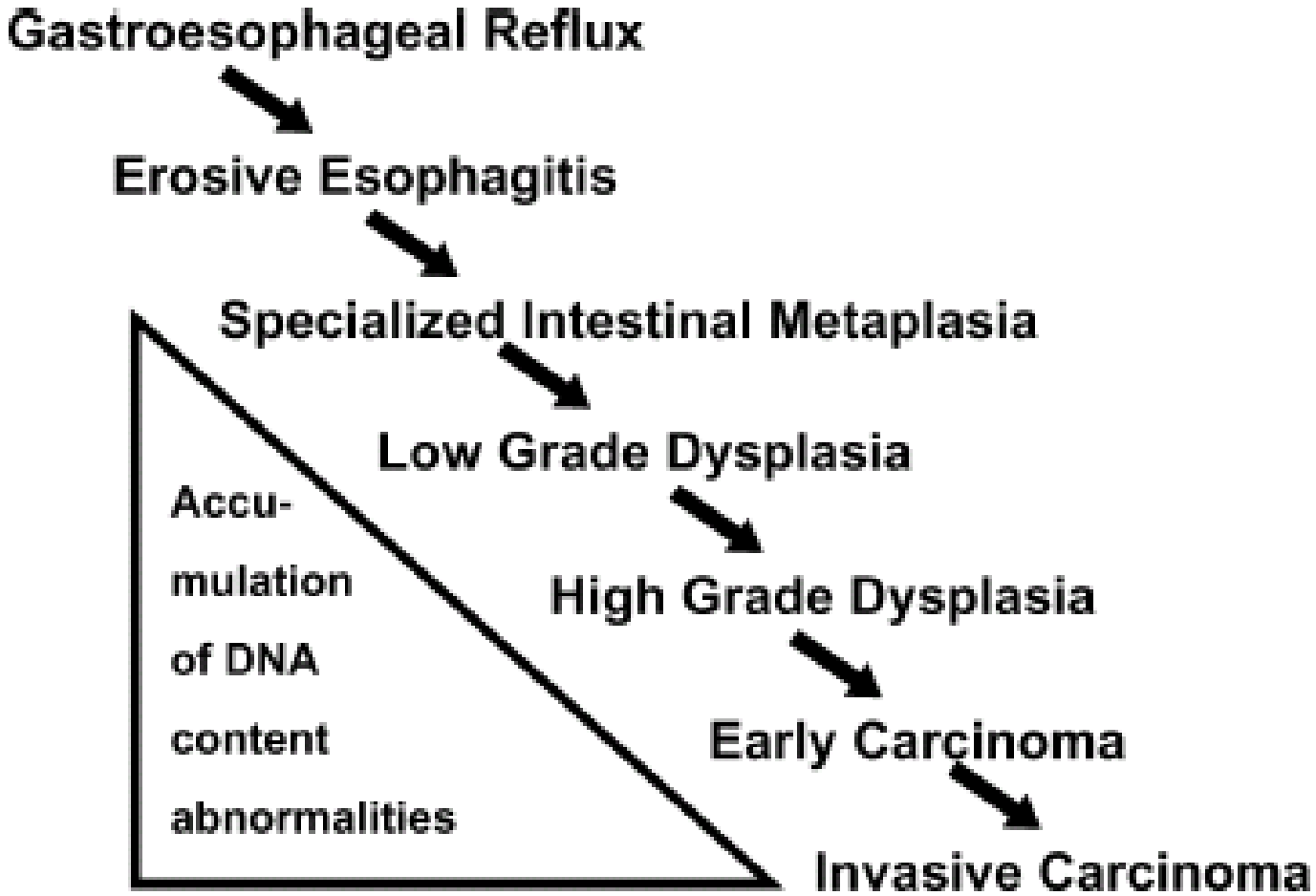

FIGURE 1. Development and stepwise histological progression of BE to invasive carcinoma.

Hiroshi M, J Clin Gastroenterol Volume 39, Supp. 2, April 2005

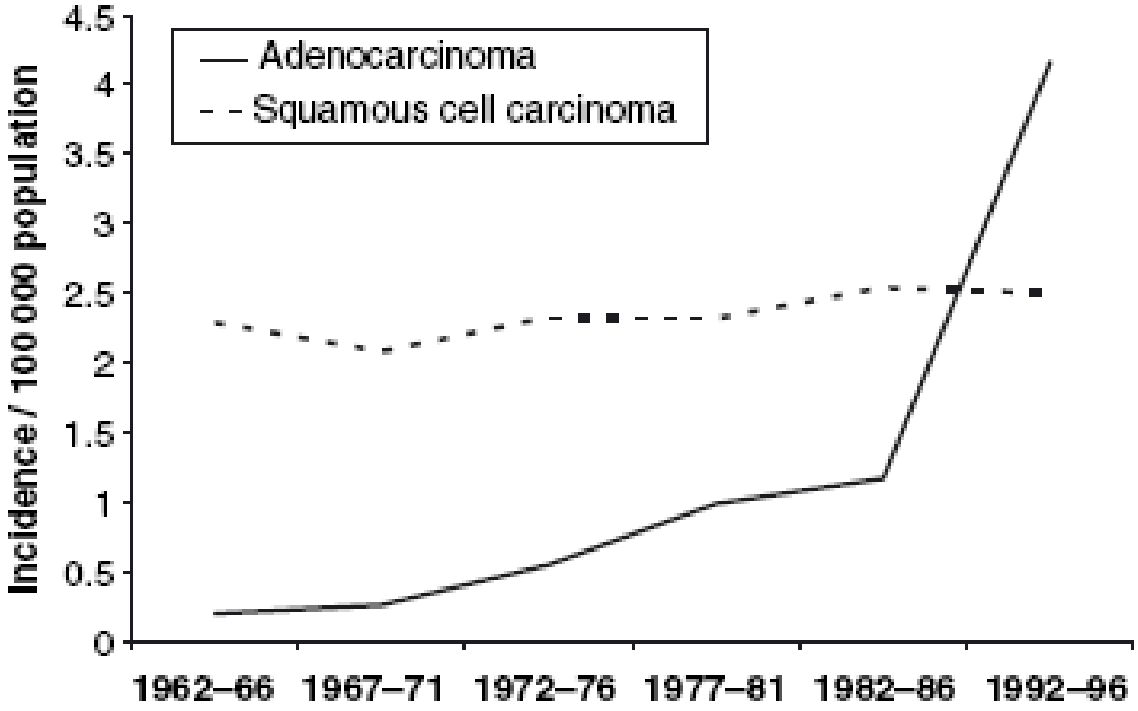

Figure 1. Historical change in the male incidence of oesophageal adenocarcinoma and squamous cell carcinoma (UK data).[1]

C. J . PETERS, Aliment Pharmacol Ther 25, 1253−1269

Barrett's Esophagus

- Patients without dysplasia and those with low grade intraepithelial neoplasia (LGIN) have low rates of disease progression.
- High grade intraepithelial neoplasia (HGIN), disease may progress at rates
  >10% per year

S Seewald„Postgraduate Medical Journal 2007;83:367-372;

Barrett's Esophagus

- Prevalence of 1% to 2% in the general population
- Up to 40% to 50% of patients with BE have not experienced frequent GERD symptoms.
- 15% to 66% risk of progression from HGD to cancer during a follow up of 9 months to 11.5 years;
- several series report rates of up to 50% within 5 years of diagnosis

Jeffrey L., Semin Radiat Oncol 17:10-21 © 2006

Barrett's Esophagus

- Multifocal or diffuse HGD are at much greater risk for progression than patients with only a single focus of HGD on surveillance biopsies
- In a series of 100 patients at the Mayo Clinic,

  the cumulative incidence of esophageal

  adenocarcinoma at 3 years was

  56% for patients with multifocal disease and

  14% for patients with only focal abnormalities

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THE PROS AND CONS OF PPI THERAPY

- A prospective study over 13 years demonstrated that treatment with PPIs caused formation of squamous islands, but did not change the overall length of Barrett's oesophagus
- Excessive antisecretory medication use, beyond that required to heal esophagitis, may be detrimental in Barrett's esophagus

Simon Leedham, Am J Gastroenterol 2007;102:21-23

THE PROS AND CONS OF PPI THERAPY

- Patients receiving medical treatment of GERD had a higher risk of development of esophageal cancer (adjusted odds ratio 2.9) than the untreated.
- This negative effect of acid suppression could be mediated through gastrin that plays a complex role in regulation of epithelial proliferation and differentiation.

Simon Leedham, Am J Gastroenterol 2007;102:21-23

THE PROS AND CONS OF PPI THERAPY

- Hypergastrinemia is a common side effect of long-term PPI administration, with levels sometimes exceeding 400 pmol/L (normal range 10–59 pmol/L).
- Gastrin induces proliferation in Barrett's metaplasia via prevention of apoptosis, activation of the cholecystokinin 2 receptor, and upregulation of cyclo-oxygenase 2 (COX-2) expression.

Simon Leedham, Am J Gastroenterol 2007;102:21-23

Local Endoscopic Therapy for Dysplastic BE or Early-Stage Esophageal Cancer

- Endoscopic techniques used for treating superficial esophageal cancers and HGD in BE fall into 2 main categories.
- The first, endoscopic mucosal resection (EMR), is an endoscopic method to resect and preserve tissue for histologic staging and grading.

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Local Endoscopic Therapy for Dysplastic BE or Early-Stage Esophageal Cancer

- The second, ablative modalities,

  targeted mucosa is destroyed by any of several methods

- Thermal destruction by
  - Laser, multipolar electrocoagulation (MPEC), argon plasma coagulation (APC), radiofrequency ablation
  - Cryotherapy
  - Photodynamic therapy

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Several factors can influence the outcome of endoscopic treatment

1.The depth of treatment effect achieved.

- Barrett's epithelium is approximately 0.5mm (range, 0.39 to 0.59 mm) thick
- The presence of HGD may increase this thickness to 1 to 1.5 mm

Several factors can influence the outcome of endoscopic treatment

- 2. Pre-treatment staging
  - Once a carcinoma invades the submucosa, the chance of lymph node involvement may > 15% to 25% and the likelihood of achieving an endoscopic “cure” is diminished
- More desirable clinical outcomes when strict acid control is maintained posttreatment, facilitating healing and repopulation of the treated area by normal squamous epithelium

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TABLE 2. *Relationship between depth of tumor invasion and likelihood of lymph node metastases*

Tumor depth	Prevalence of lymph node metastases (%)[a]
Intramucosal	3–6
Submucosal	20–30
Intramuscular	45–75
Transmural	80–85

S. R. DEMEESTER, Ann. Surg. Oncol. Vol. 13, No. 1, 2006

bone marrow micrometastases

- High incidence of bone marrow micrometastases have led many physicians to consider this a systemic disease at the time of diagnosis

S. R. DEMEESTER, Ann. Surg. Oncol. Vol. 13, No. 1, 2006

bone marrow micrometastases

- Metastases of any type are extremely rare in patients with intramucosal tumors, nearly all patients are cured by resection alone.
- Further, the high cure rate in patients with limited lymph node metastases after en-bloc resection suggests that, similar to other cancers, esophageal adenocarcinoma starts locally and progresses in a stepwise fashion to nodal and systemic disease

S. R. DEMEESTER, Ann. Surg. Oncol. Vol. 13, No. 1, 2006

Major Concerns

- Pre-existing molecular abnormalities within dyplastic BE have been linked to reduced cellular apoptosis in response to photodynamic therapy (PDT)
- The persistence of genetic abnormalities in residual Barrett's mucosa after endoscopic treatments such as PDT.
- Intensive surveillance is thus required for all patients undergoing endoscopic therapy

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Major Concerns

- The possibility for residual, untreated specialized intestinal metaplasia (SIM) to dwell beneath the squamous epithelium that repopulates the treated areas of the esophagus.
- In clinical protocols utilizing PDT this subsquamous intestinal metaplasia is found in 4.9% to 51.5% of cases

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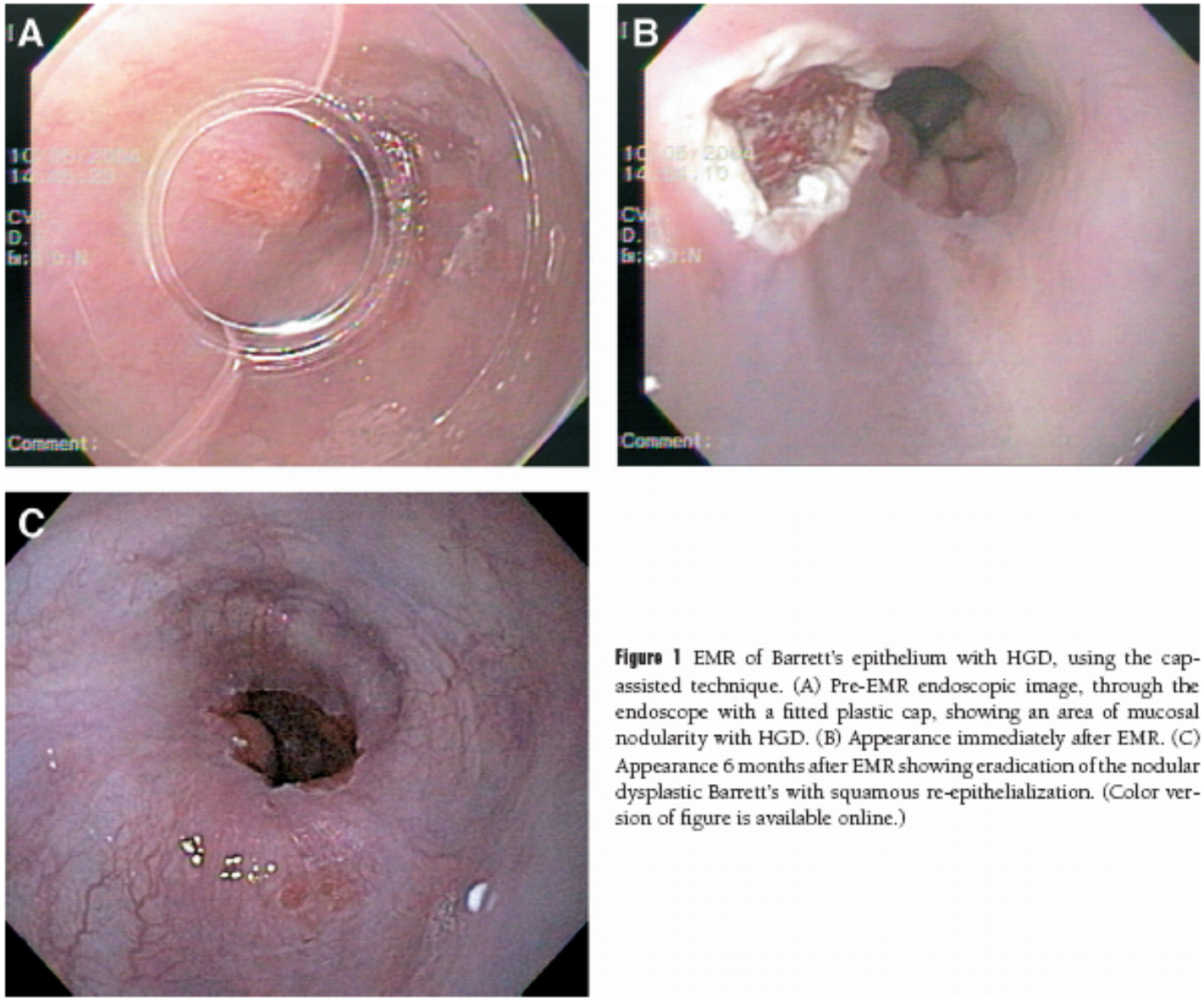

Figure 1 EMR of Barrett's epithelium with HGD, using the cap-assisted technique. (A) Pre-EMR endoscopic image, through the endoscope with a fitted plastic cap, showing an area of mucosal nodularity with HGD. (B) Appearance immediately after EMR. (C) Appearance 6 months after EMR showing eradication of the nodular dysplastic Barrett's with squamous re-epithelialization. (Color version of figure is available online.)

Endoscopic Mucosal Resection

- EMR has become an accepted treatment for squamous-cell carcinoma confined to the superficial mucosa and not extending beyond the muscularis mucosa
- EMR has been applied to early neoplastic changes in BE as a possible alternative to surgery
- risk of bleeding 0 to 14%
- risk of perforation of 1.8%
- facilitating pathologic diagnosis and staging

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Thermal Ablation

- laser; MPEC; APC; and radiofrequency ablation
- The relatively high risk of recurrent BE, higher bleeding rates and the paucity of centers with the necessary equipment and training have limited the enthusiasm for this option

Multipolar Electrocoagulation

- Ablate BE by using MPEC, a modality in which thermal energy is applied by an electrode probe placed in direct contact with the mucosa
- Side effects are uncommon with MPEC, but there is limited published experience of ablating dysplastic BE or early cancers with this modality

Argon Plasma Coagulation (APC),

- The development of APC, a noncontact thermal ablation technique, has supplanted the use of MPEC in many centers.
- The depth of injury can be varied by adjusting several factors, including the generator setting, the rate of argon gas flow, the distance between the probe and the tissue, and the duration of application

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Argon Plasma Coagulation (APC),

- Although the depth of injury is thought to be less than PDT or laser,

  complication rates as high as 24% have been reported and include pneumatosis, pneumoperitoneum, subcutaneous emphysema, pain, perforation, ulceration, bleeding, stricture, and death

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Radiofrequency Ablation (RFA)

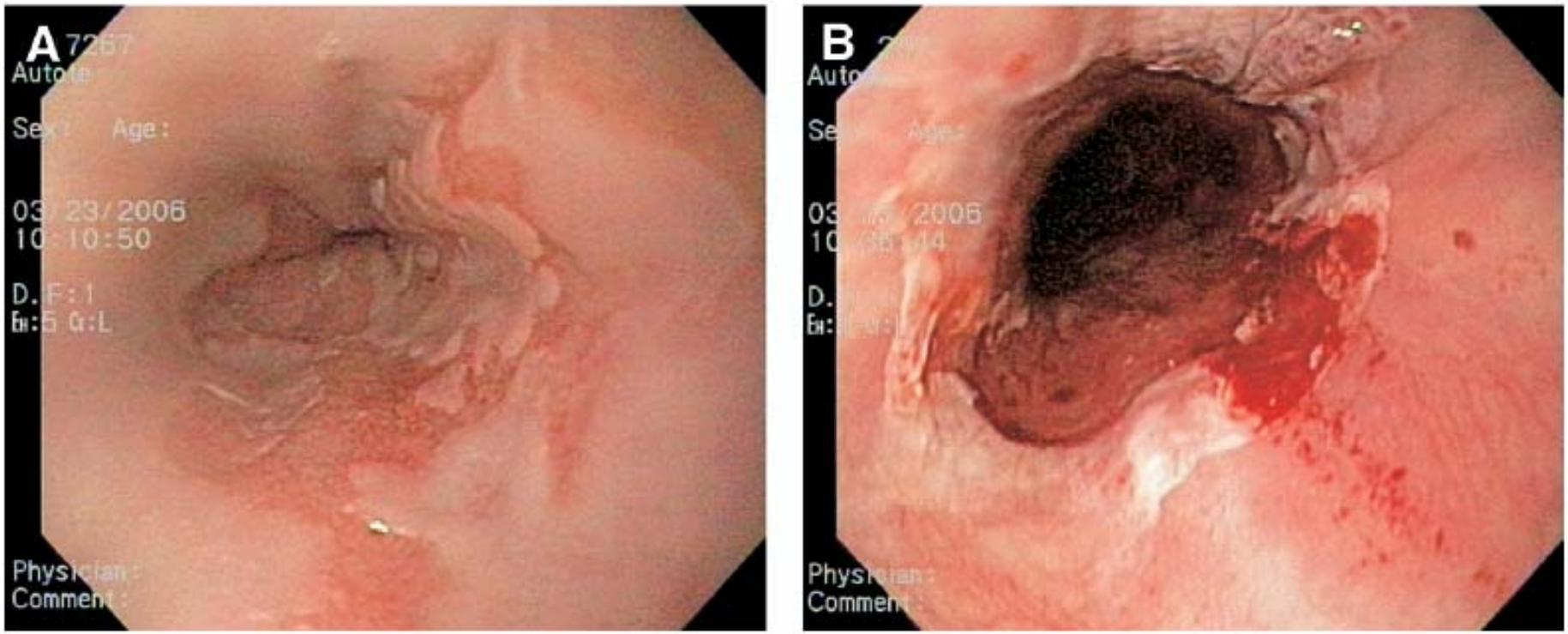

Figure 2 Barrett's epithelium: (A) before and (B) immediately after a session of RFA. (Color version of figure is available online.)

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Radiofrequency Ablation (RFA)

- RFA uses an endoscopically placed balloon-based electrode composed of tightly spaced bipolar rings. Uniform energy is delivered to simultaneously ablate circumferential esophageal segments of BE.
- the procedure easy to perform, with no complications. Depth of tissue injury was limited to the muscularis mucosa

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Cryoablation

- The most recent addition to the ablation armamentarium
- Uses low-pressure liquid nitrogen to provide a "cryospray" under direct endoscopic visualization, which causes delayed mucosal injury
- Johnston and coworkers reported on their preliminary clinical experience the device, achieving complete reversal of Barrett's epithelium in 9 of 11 patients (78%).

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Photodynamic Therapy (PDT)

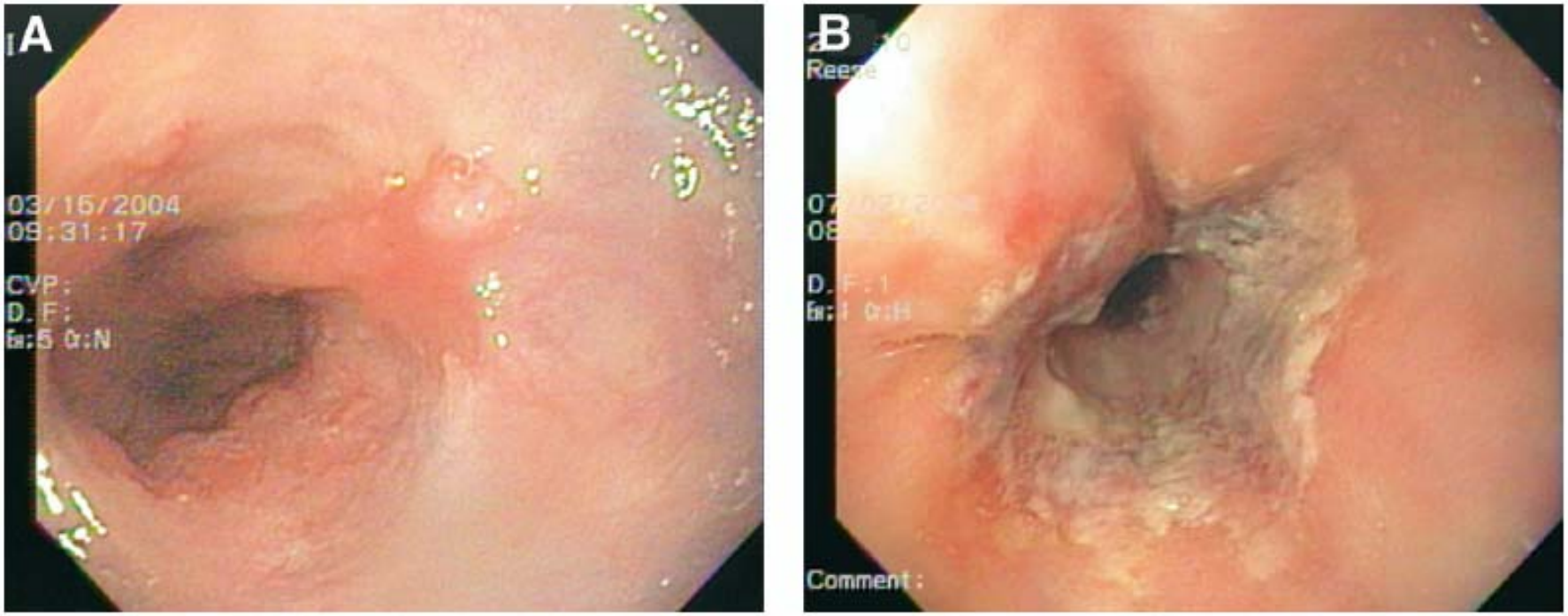

Figure 3 Barrett's epithelium (A) before and (B) immediately after a session of PDT using sodium porfimer as a photosensitizer. (Color version of figure is available online.)

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Photodynamic Therapy (PDT)

- PDT is a 2-step photochemical treatment results in relatively selective tissue injury and necrosis
- The first step involves intravenous or oral administration of a photosensitizing agent that concentrates with greater affinity in neoplastic tissue relative to normal cells.
- The second step involves local application of laser light to the target tissue which results in formation of free oxygen radicals and subsequent tissue necrosis

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Photodynamic Therapy (PDT)

- PDT is the most expensive of the endoscopic treatment options and has the greatest risk for treatment-related side effects and complications, particularly when porfimer sodium is used
- uptake in normal tissue still occurs. Cutaneous photosensitivity reactions (sunburn-like), which are occasionally severe, remain a major clinical limitation
- Patients must therefore avoid sunlight for 4 to 6 weeks after treatment.

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Photodynamic Therapy (PDT)

- A second major drawback is the development of esophageal strictures in 30% of treated patients, although they are typically amenable to endoscopic treatment
- Cardiac arrhythmias and pleural effusions are less common and typically not severe

Photodynamic Therapy (PDT)

- Some European endoscopists prefer ALA over porfimer sodium because it has a more favorable side effect profile (self-limited nausea, vomiting, and hepatic transaminitis), a shorter duration of photosensitivity risk (1-2 days), and a significantly lower stricture rate than with porfimer sodium

PDT for Dysplastic Barrett's or Early-Stage Esophageal Adenocarcinoma

- PDT was used to successfully eradicate HGD and early cancers (T_1 or less) in 97% to 100% of 66 patients followed for a median duration of approximately 37 months

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PDT for Dysplastic Barrett's or Early-Stage Esophageal Adenocarcinoma

- During endoscopic follow-up for initially successful treatment, recurrent or metachronous cancers were found in 6% of the HGD group and 29% of the early cancer group
- Most of these were successfully treated endoscopically or surgically, and calculated 5-year survival rates of the HGD and early cancer patients were 97% and 80% respectively

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PDT vs. PPI

- Complete ablation of HGD:
  77% in the PDT vs 39% omeprazole-alone,
  benefit persisted up to 18 months.
- Complete elimination of all Barrett's mucosa
  52% in the PDT vs 7% in omeprazole alone
- the need for alternative interventions, such as esophagectomy or other ablative interventions was significantly delayed in the PDT arm

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Endoscopic Treatment

- At the current time, decisions regarding which approach to use are largely based on equipment availability local expertise, and the endoscopist's preference
- Candidates must recognize the need for intensive endoscopic surveillance to identify recurrent or metachronous lesions which are often amenable to endoscopic retreatment

Surgery vs. Medical Treatment

- Antireflux surgery is significantly reduced ***incidence rate of esophageal adenocarcinoma*** when compared with medically treated patients 2.8/1000 vs. 6.8/1000 patient-years *(p 0.034)*
- Surgically treated patients demonstrated a higher incidence of disease ***regression***, which was observed in 15.4% of surgically treated patients compared with 1.9% of medically treated patient *(p 0.004)*
- No difference in disease ***progression***,

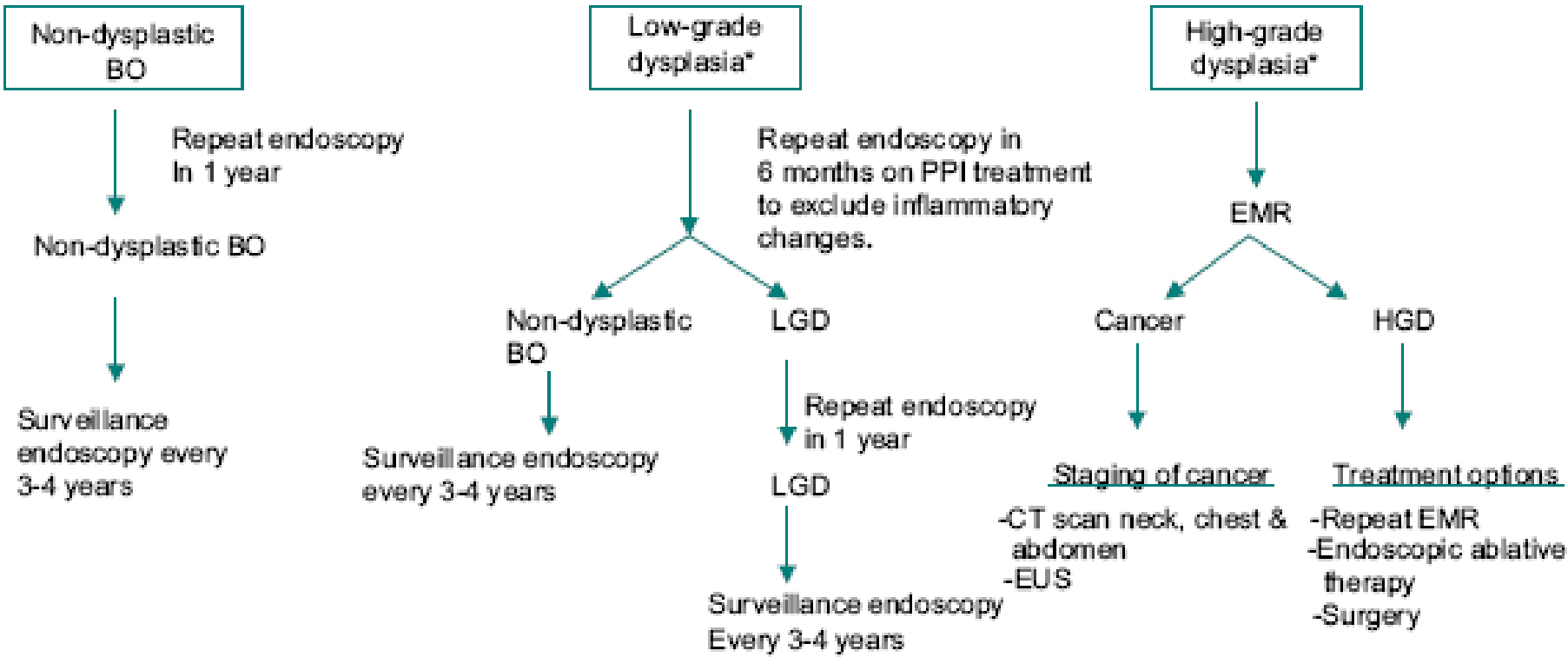
Chang, Annals of Surgery • **Volume 246, Number 1, July 2007**

Guidelines by the American College of Gastroenterology

- A systematic endoscopic biopsy protocol, generally accepted to be four quadrant biopsy specimens taken every 1-2 cm of Barrett's mucosa starting at the gastro-oesophageal junction using standard or jumbo biopsy forceps, can provide tissue for histologic diagnosis of dysplasia

Sachin Wani, Best Practice & Research Clinical Gastroenterology Vol. 20, No. 5, pp. 829-842, 2006

Surveillance and treatment of Barrett's oesophagus.



BO, Barrett's oesophagus; PPI, Proton pump inhibitor; EMR, endoscopic mucosal resection; EUS, endoscopic ultrasound; LGD, low grade dysplasia; HGD, high grade dysplasia

* Confirm all dysplasia reading by expert pathologists.

Sachin Wani, Best Practice & Research Clinical Gastroenterology Vol. 20, No. 5, pp. 829-842, 2006

Prevention of esophageal SCC

- Changes in lifestyle, especially the avoidance of alcohol and tobacco use.
- Additional benefits may be realized by the elimination of high salt foods that may be contaminated with microbial toxins, nitrosamines and their precursors
- Increased consumption of vegetables and fruit

G.D. Stoner et al. / Toxicology and Applied Pharmacology 224 (2007) 337–349

Chemoprevention for SCC

Table 4
Agents tested in clinical trials for inhibitory effects against human esophageal SCC

Agents	Activity				References
	No Effect	Inhibition	Enhancement	Mechanism	
Daily supplementation with vitamins and minerals	+				Rao et al. (1994)
Calcium	+				Wang et al. (1993)
Antitumor-B,		+		?	Lin et al. (1990)
4-ECPR [a],	+	+		?	
Riboflavin					
Celecoxib+Selenomethionine	+	+		?	Limburg et al. (2005)
Green tea	+				Wang et al. (2002)

[a] 4-ECPR: 4-ethoxycarbophenylretinamide.

G.D. Stoner et al. / Toxicology and Applied Pharmacology 224 (2007) 337–349

Selective vs. Non-selective cox-2

- 9 epidemiological studies involving 1813 cases of esophageal cancer, suggest a protective effect between aspirin and other NSAIDs use and the occurrence of esophageal cancer (SCC and adenocarcinoma)
- These results suggest that agents which inhibit COX-1 or both COX-1 and COX-2 might be more effective against esophageal cancer than specific inhibitors of COX-2.

(Corley et al., 2003).

Practice points

- The role of screening and surveillance in patients with Barrett's oesophagus remains extremely controversial.
- Recent guidelines recommend that patients with chronic gastro-oesophageal reflux disease symptoms are those most likely to have Barrett's oesophagus and should undergo endoscopy for the presence of Barrett's oesophagus.

Sachin Wani, Best Practice & Research Clinical Gastroenterology Vol. 20, No. 5, pp. 829-842, 2006

Practice points

- Existing data do not show that screening for Barrett's oesophagus is cost effective or improves mortality from esophageal adenocarcinoma.
- Currently, endoscopy with four-quadrant random biopsies remains the clinical standard method for obtaining surveillance biopsies and grade of dysplasia determines surveillance intervals.

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Practice points

- Proposed management strategies for high-grade dysplasia in Barrett's oesophagus include oesophagectomy, endoscopic ablative therapies and endoscopic mucosal resection and intensive endoscopic surveillance.

Sachin Wani, Best Practice & Research Clinical Gastroenterology Vol. 20, No. 5, pp. 829-842, 2006

Thank You For Your Attention