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CLINICAL PRACTICE

Barrett's Esophagus

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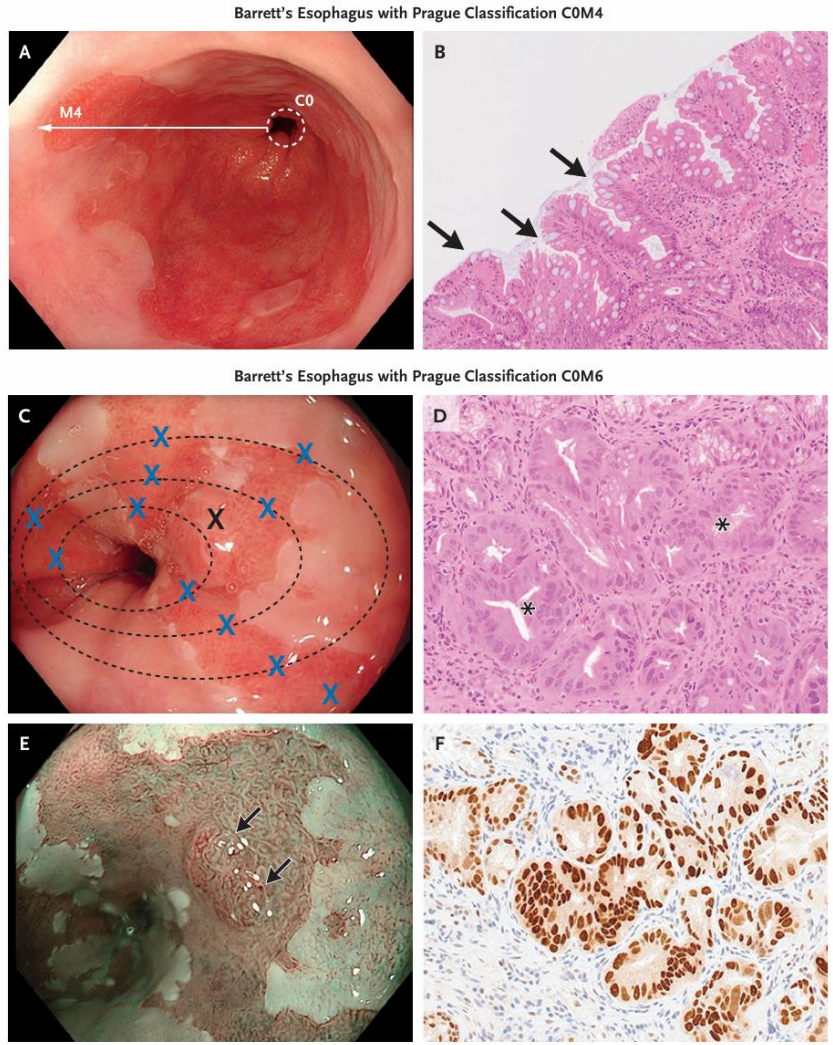
Barrett's Esophagus

- Detected in 3-14% of patients with GERD undergoing EGD
- Chronic reflux -> Replacement of distal esophageal squamous epithelium by columnar epithelium
- Diagnosis requires:
  - Visible columnar segment >= 1cm
  - Histologically confirmed intestinal metaplasia with goblet cells
- Longer segments(>=3cm) -> greater molecular instability and progression risk
- More prevalent in Western populations
- Increasing incidence in Asia
  - Changing lifestyle
  - Declining H.pylori prevalence
- Associated with increased risk of esophageal adenocarcinoma(EAC)



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Barrett’s Esophagus

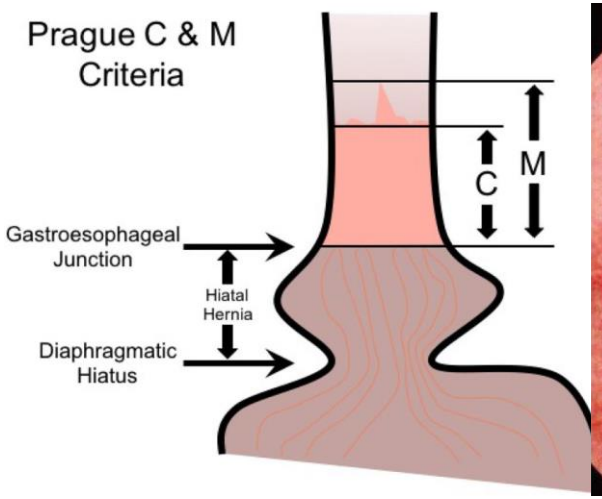
- Molecular features of Barrett’s esophagus may persist even when overt BE is not evident at EAC diagnosis
- No specific symptoms, often incidental finding
- Up to 80% of patients with Barrett’s esophagus remain undiagnosed
- Acid suppression does not reverse the underlying metaplasia

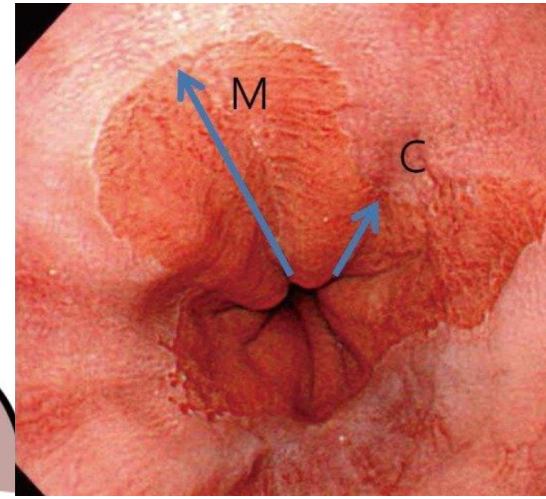
Diagnosis – Whom to test

- **Risk Factors for Barrett's Esophagus**
  - Several factors are associated with higher risk of Barrett's esophagus
  - History of **reflux symptoms** and three of the following(**White race, male sex, age over 50, central obesity, tobacco use, first-degree relative with BE or EAC**)

- **Pooled Barrett's esophagus prevalence estimates from meta-analysis**
  - Low risk general population : 0.8%
  - Age > 50 6.1%
  - Obesity 1.9%
  - Male 6.8%
  - GERD 3.0%
  - GERD + >=1 risk factor 12.2%
  - Family history of BE and EAC 23.4%
  - Western vs. Non-Western 3.0% vs. 1.0%

Diagnosis – How to test





- **Endoscopy = Diagnostic standard**
  - Identify GEJ landmarks, distinguishing Barrett's esophagus from hiatal hernia
  - Measure the extent using Prague classification
  - Multiple biopsies to minimize sampling error due to tissue heterogeneity
- **Nonendoscopic triage**
  - Increasing interest because many BE cases remain undiagnosed
  - Cell-collection device(ex.cytosponge) + protein-based biomarkers(ex.TFF3) -> detection of intestinal metaplasia
- **Pragmatic RCT: Cytosponge–based screening**
  - High risk population: age >50 yr + acid suppression >6 mo
  - Cytosponge/TFF3(Trefoil factor 3) screening offer(endoscopy if positive) vs. usual care
  - ITT -> **BE detection**: 140(**2.0%**) vs **0.2%**, Adjusted rate ratio **10.6** (95% CI, 6.0–18.8), P<0.001
  - Positive triage test(221) → EGD: 59.3% BE/cancer
  - Usual gastroscopy in symptomatic reflux: 4.1% BE yield

Treatment

- **Reflux control**
  - PPI -> Reflux symptoms and inflammation-related complications, including stricture
  - Does not regress Barrett's esophagus
- **Confirmed dysplasia or early-stage T1 adenocarcinoma**
  - Depend on the focality of the lesion, the depth of invasion, length of the overall segment, skills and equipment available, physical fitness of the patient
  - <20mm -> EMR, >20mm or suspicious SM invasion -> ESD
  - Deep margin(+) or unfavorable features -> consider oncologic treatment, multidisciplinary team
  - Acid-suppressing therapy after resection or RFA to maintain the squamous re-epithelialization

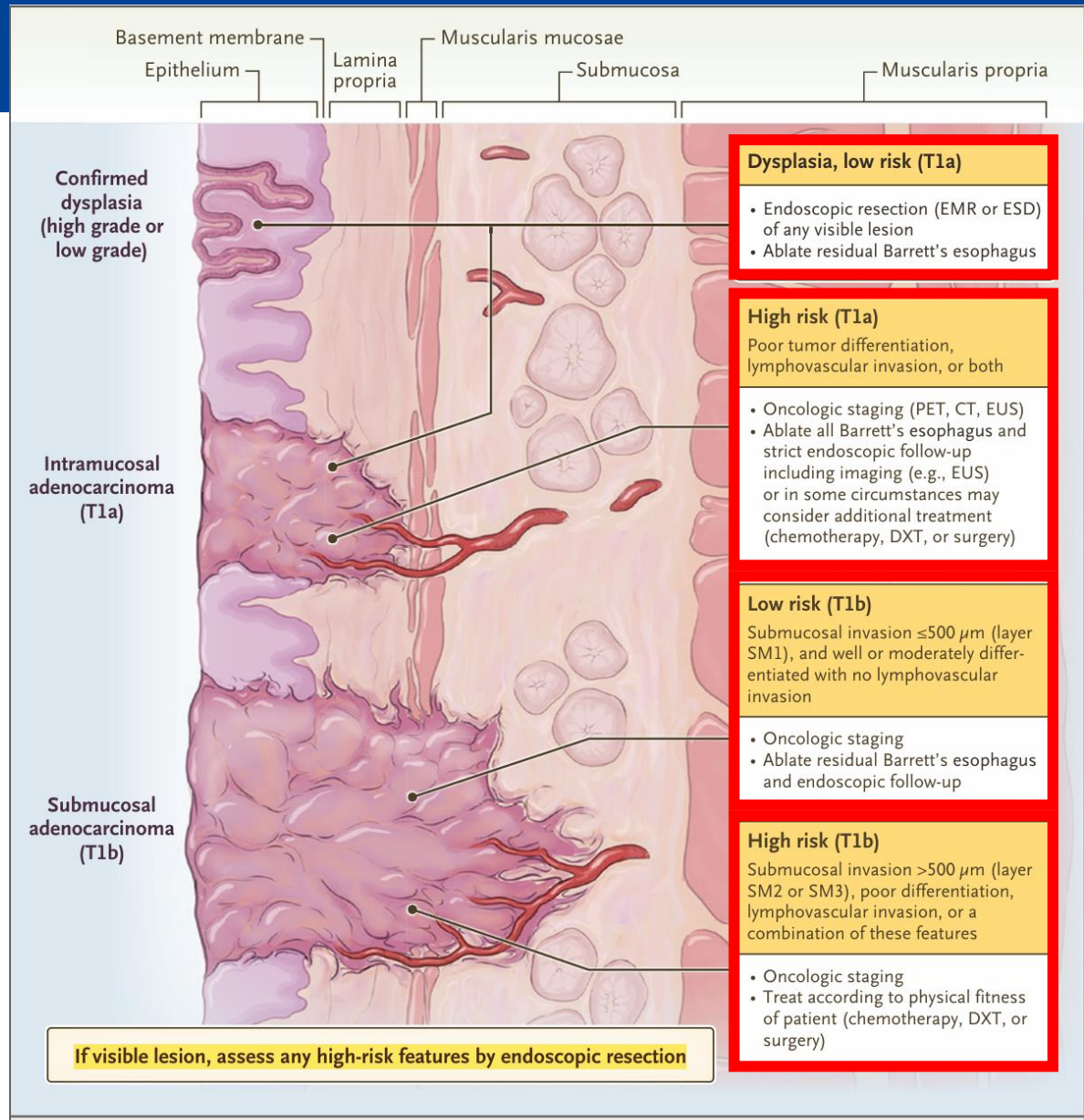


Figure 2. Disease Extent, Features, and Therapy Recommendations in Barrett's Esophagus.

Risk of Cancer Progression & Rationale for Surveillance

- **Nondysplastic Barrett's esophagus**
  - Reported annual risk varies substantially(**0.12%/year~11.8/person-year**)
  - Variation reflects differences in case selection and diagnostic criteria
  - One study showed a standardized incidence ratio to risk of progression to cancer **11.3** (95% CI, 8.8 to 14.4) among patients with Barrett's esophagus as compared with the general population
- **Low absolute risk, increased relative risk**
- **Surveillance**
  - Early detection of HGD/EAC for curative endoscopic therapy

Evidence for Endoscopic Surveillance – Mortality Benefit

- **Case-control study**
  - Corley et al., Barrett's esophagus patients -> EAC death case or no EAC death control -> surveillance within 3 years
  - Adjusted Odds ratio 0.99 (95% CI, 0.36 to 2.75)
  - **Surveillance every 3 years -> No reduction in mortality**

- **Meta-analysis of 12 cohort studies**
  - Surveillance-detected Esophageal carcinoma vs. Symptom-detected Esophageal carcinoma
  - Relative risk, 0.73 [95% CI, 0.57 to 0.94]; hazard ratio, 0.59 [95% CI, 0.45 to 0.76])
  - BUT, **Lead-time bias & Length-time bias** adjustment substantially attenuated the benefit

- **BOSS Trial(Barrett's Oesophagus Surveillance vs. Endoscopy at Need Study)**
  - N= 3453, Surveillance every 2 years vs. Endoscopy only when clinically indicated, **RCT**, median follow-up 12.8 years
  - EAC diagnosis 2.3% vs 1.8%, HR 1.32(**95% CI 0.82-2.11**)
  - Overall mortality HR 0.95 (**95% CI 0.82–1.10**)
  - EAC-related death 1.2% vs 1.1%, Cancer-specific survival HR 1.01 (**95% CI 0.77–1.33**)

Current Surveillance & Emerging Biomarkers

- **Current Standards**
  - Endoscopic inspection + Targeted biopsy of visible abnormality
  - Systematic biopsy : 4 samples/2cm, to detect microscopic dysplasia
  - Systematic biopsies may still miss small or focal lesions

- **Emerging tools**
  - WATS-3D(Wide-Area TransEpithelial Sampling with 3-Dimensional analysis)
  - Tissue Systems Pathology Test(TSP-9 or **TissueCypher**, Biomarker-based risk stratification)
    - FFPE -> 15 protein features including TP53 + morphometric features(nuclear size, morphology…) -> Low/Intermediate/High
    - Predicts the risk of progression to HGD/EAC
    - Pooled analysis, **High risk** vs Low/Intermediate : **OR 6.0 (95% CI, 2.9 to 12.0)**
    - Specificity 94%, **Sensitivity 38%**

Risk-stratified surveillance: Nonendoscopic Triage

- **Cytosponge-based Surveillance Triage Test**
  - **Nonendoscopic** cell collection using cytosponge
  - Clinical risk factors(**Age, Sex, Segment length**) + cellular biomarkers(**TP53, Atypia**)
  - Prospective validation Study, **AUC 91%**(95% CI, 86 to 95) for **HGD or cancer**
  - **Sensitivity 80%**[95% CI, 66 to 91], **Specificity 87%**[95% CI, 83 to 91]
  - Real-world implementation, **High risk 15.2% -> Neoplasia detected in 37.7%**
  - **Low risk 53.7% -> HGD 0.4%, EAC 0%**

Chemoprevention

- **AspECT trial**
  - N= 2557, median 8.9 years of follow-up
  - **High dose esomeprazole 40mg bid** vs. **Low dose 20mg qd**
  - Primary composite endpoint : All cause mortality or EAC or HGD
  - 10.9% vs. 13.8%, p=0.04
  - No placebo arm -> **High-dose PPI may reduce progression-related events** in patients with Barrett's esophagus

- **Future Surveillance** may shift from universal endoscopic monitoring

  Toward **Risk-stratified surveillance using biomarkers**

  while **PPI therapy may provide chemopreventive benefit**.

Societal Guidelines

- **Screening**
  - In patients with GERD + >= additional risk factors
  - GERD in not a prerequisite according to AGA
- **Surveillance**
  - Generally recommended once Barrett's esophagus is diagnosed
  - Surveillance interval should consider the length of Barrett's segment
  - SSBE : benefit of surveillance remains uncertain
- **Treatment**
  - Confirmed dysplasia or cancer -> Endoscopic eradication therapy
  - After focal resection, eradicate residual Barrett's esophagus
  - Nondysplastic Barrett's esophagus -> No endoscopic treatment recommended

Future Directions & Emerging Strategies

- **Improving Risk Stratification**
  - Currently, Dysplasia & clinical risk factors
  - Emerging : Germline predisposition + Influences of ancestry + Molecular biomarkers

- **Ongoing Clinical Trials**
  - BEST4 Screening Trial : High risk individuals enriched by age, sex, heartburn symptoms 120000 participants
    - **Capsule sponge screening -> confirmatory endoscopy** vs. **usual care**
    - **Longterm follow-up for early detection of BE-related neoplasia and reduction of EAC mortality**
  - PREFER study: Prospective single arm study, **High risk T1b EAC** R0 resection, N0M0 -> Strict endoscopic follow-up
    - Potential alternative to Esophagectomy
  - SURVENT trial : Barrett's esophagus & confirmed **LGD** -> **Endoscopic surveillance** vs. Endoscopic eradication therapy
    - **Universal EET for LGD may lead to overtreatment** because its natural history is heterogeneous

- **AI-assisted Diagnosis**
  - AI for endoscopic and histopathologic assessment -> Detection of subtle/early dysplasia, Interobserver variability

Future Management Paradigm

- **Current approach : Diagnosis of BE -> lifelong surveillance -> treatment when dysplasia is detected**

- **Baseline screening -> Risk stratification -> Individualized management**
  - Low risk -> discharge from surveillance
  - High risk -> Intensified surveillance/treatment

Conclusion : Risk-stratified surveillance and treatment

- **Screening**
  - GERD + multiple risk factors(High-risk population) -> Endoscopy or nonendoscopic triage test
- **Reflux management**
  - Optimize lifestyle + medications, PPI, antireflux surgery
- **If Barrett's Esophagus is diagnosed**
  - Surveillance interval based on BE segment length
    - >3cm : every 3 years
    - 1-3cm : every 5 years
  - Confirmed dysplasia -> Endoscopic eradication therapy
- **Chemoprevention**
  - PPI
  - Aspirin/statins : insufficient evidence to replace surveillance