Management of Precancerous Lesions and Early Esophageal Carcinoma with Endoscopic Advancements

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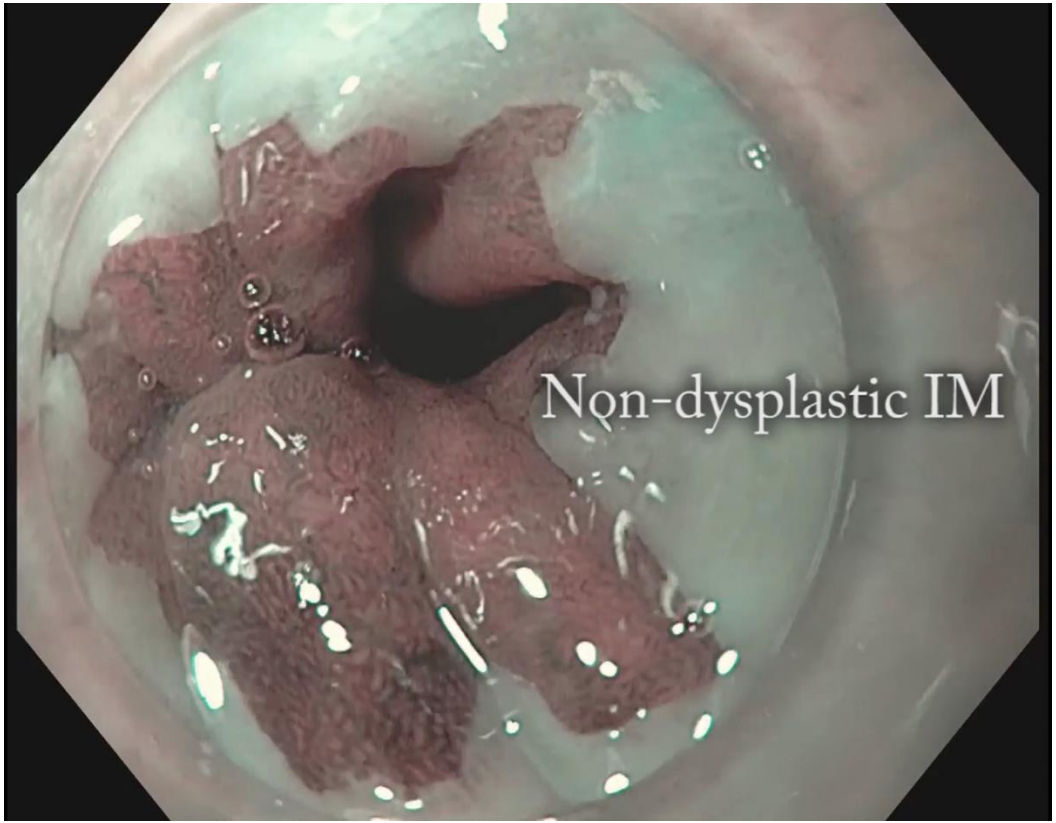
SOUTH FLORIDA GI CANCER SYMPOSIUM
April 11-12, 2025

UVA Health

Esophageal squamous dysplasia

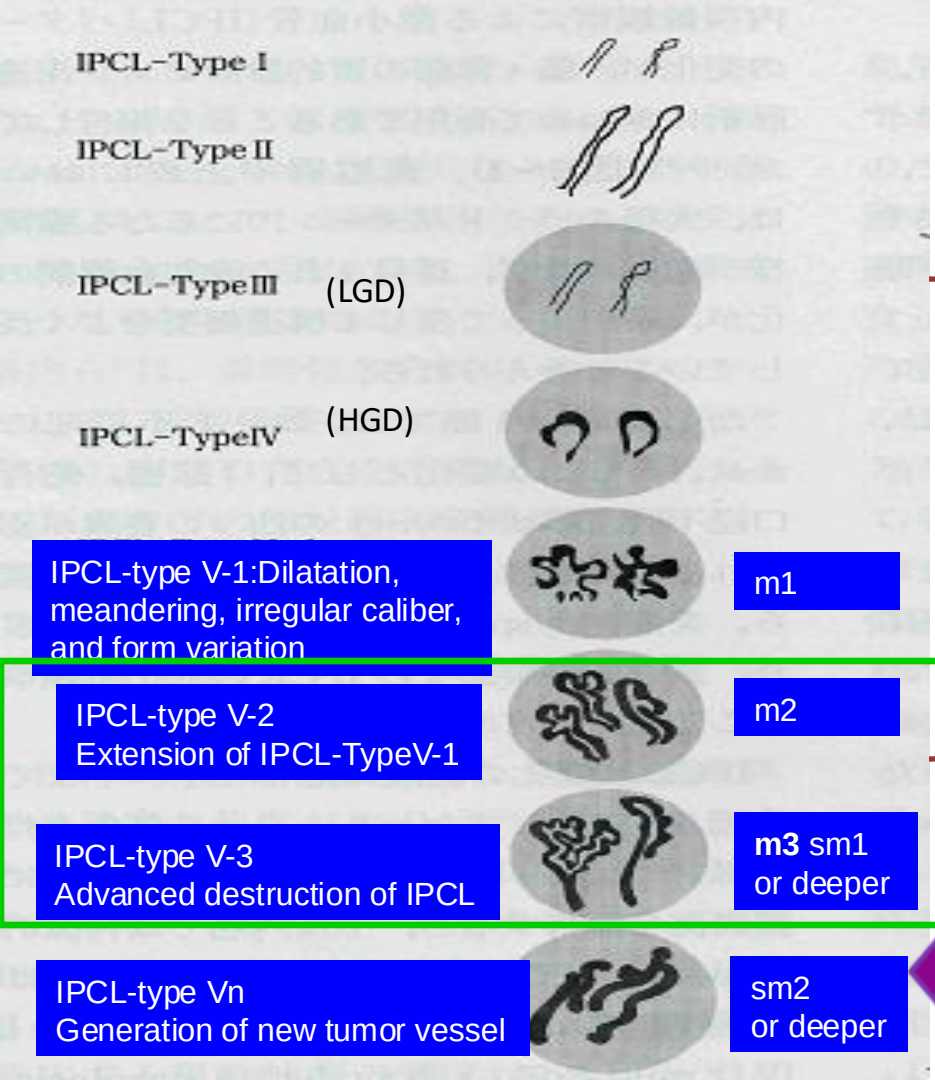
- 61 yo M with 24 pk-yrs of tobacco use who drinks 1 bottle wine/day
- Had h/o non-dysplastic Barrett's at the GEJ, **with squamous epithelium and severe dysplasia (plaque at 30-32 cm) on EGDs done 3 months apart**
- Subsequent EGD/EUS showed abnormal mucosa from 31-34 cm, taking up 25% of the circumference. **EUS showed thickened mucosa but no deeper invasion and no pathologic LNs**
- Patient was referred for ESD

Detailed endoscopic examination



IPCL classification

Inoue H. Dig Endosc 2001;13
Inoue H et al. Annals of Gastroenterol 2015; 28

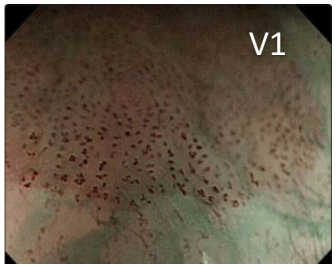


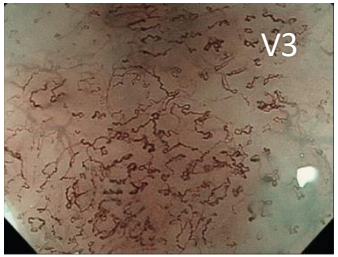
Local treatment through EMR/ESD

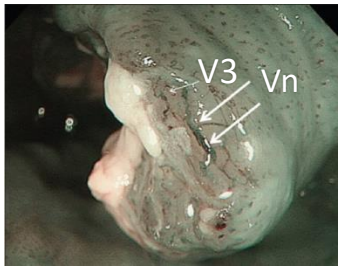
Definitely applied: V-1, V-2

Relatively applied: V-3

Comprehensive treatment through surgery: Vn

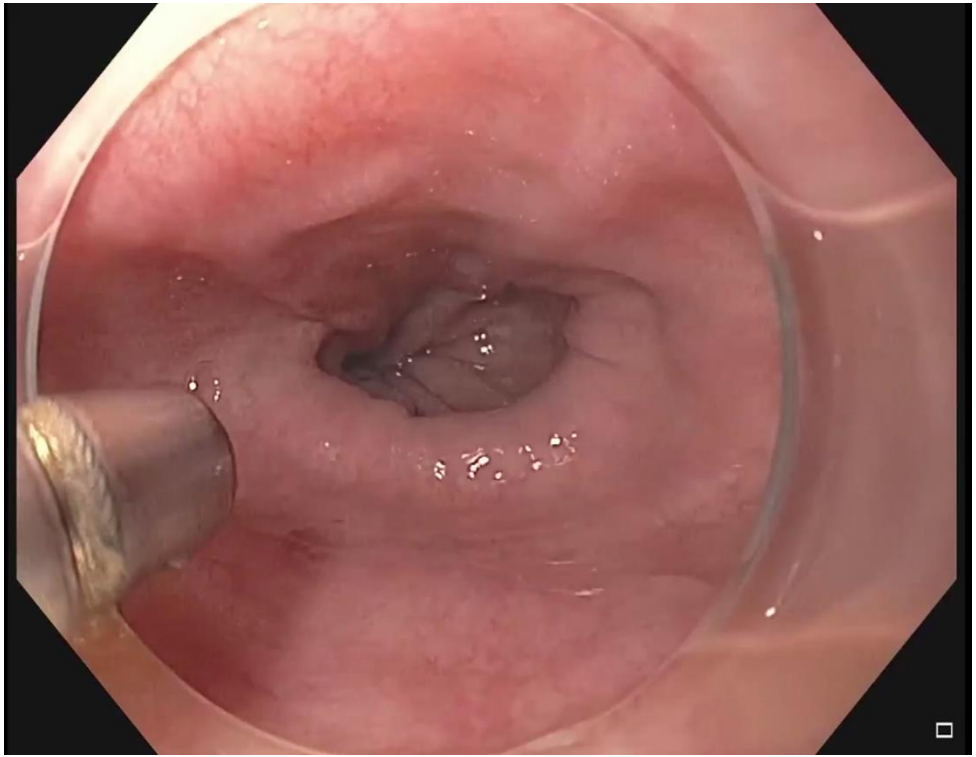






Endoscopic findings

- EGD found a large hemi-circumferential mass
  - From 32 to 35 cm from the incisors
  - 7 o'clock to 2 o'clock (gravity at 6 o'clock)
  - Paris 0-IIa and 0-II b
- Near focus NBI and Lugol's iodine used
  - **From 32-34 there was an area where the IPCLs c/w V2 and possibly V3 suggestive intramucosal ESCCA**
  - No deeply invasive cancer suggested



0.5% Lugol's iodine chromoendoscopy

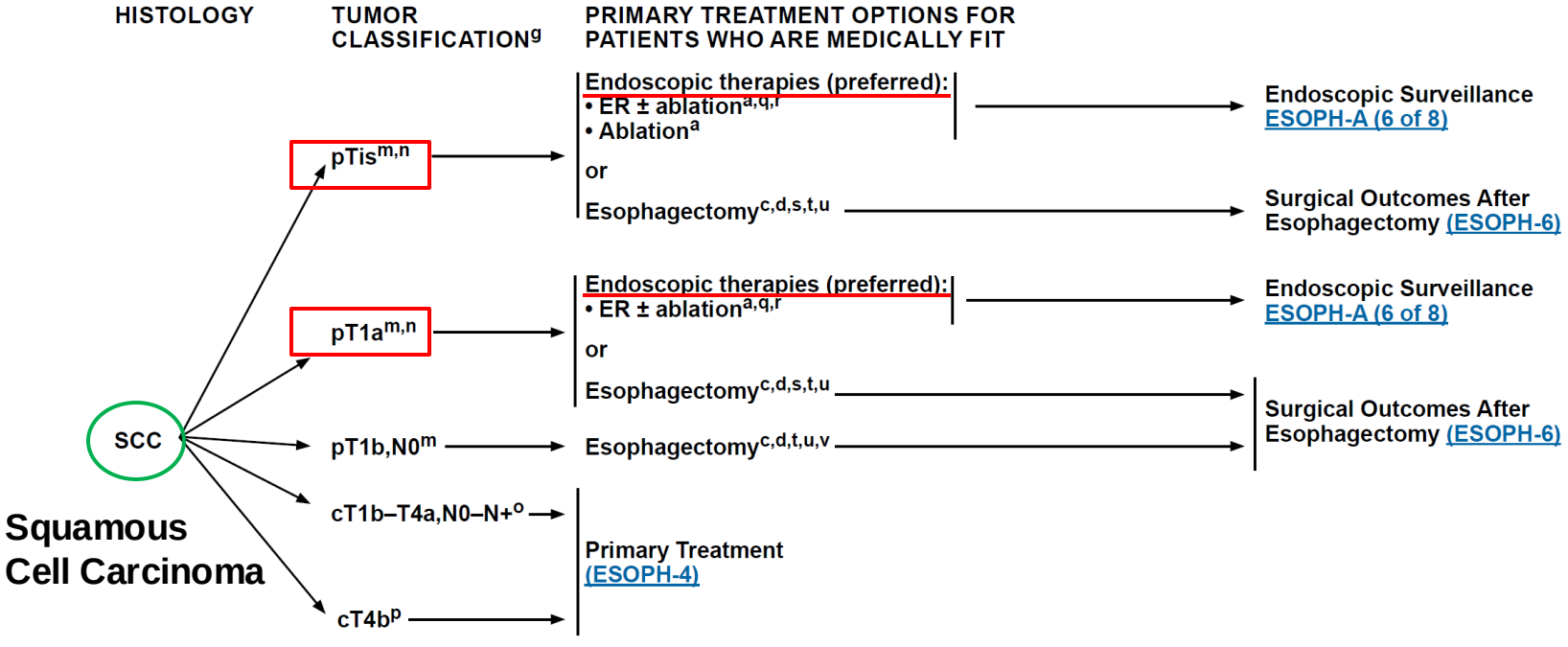
Indications for ESD of esophageal SCCA

Table 2. Japanese Esophageal Society Guidelines for esophageal endoscopic submucosal dissection (ESD) -- Squamous dysplasia

Absolute indications	T1a esophageal cancer involving the epithelium or lamina propria	<2/3 the circumference of the esophagus
Relative indications	Esophageal cancer involving the muscularis mucosa or <200 μm invasion of the submucosa	

Organ	Indications for ESD
Esophagus	
Squamous cell carcinoma	HGD to well (G1) to moderately (G2) differentiated Paris 0-II lesions *Absolute indications*: m1-m2 involvement with ≤2/3 of the esophageal circumference *Expanded indications*: m3 or sm < 200 μm involvement, any size, clinically N0

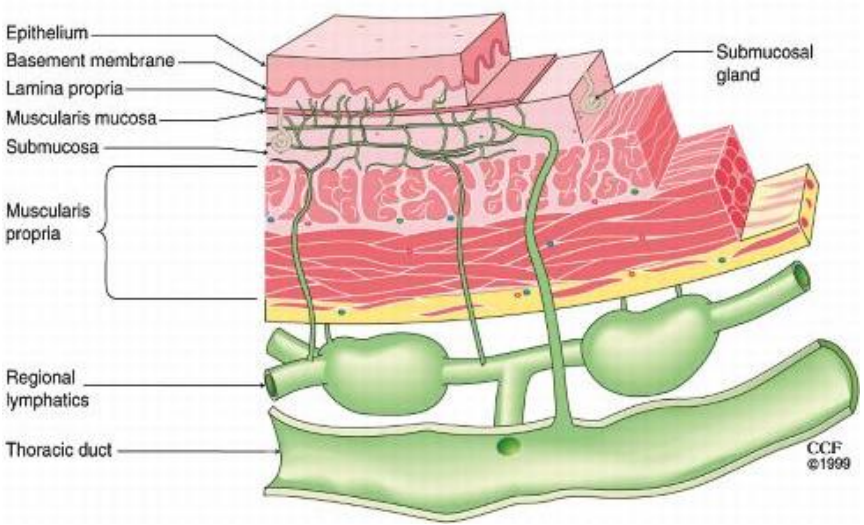
Bhatt A, Abe S, Kumaravel A, Vargo J, Saito Y. Am J Gastroenterol 2015;110
Draganov PV, Wang AY, Othman MO, Fukami N. Clin Gastroenterol Hepatol 2019;17



[a] Principles of Endoscopic Staging and Therapy (ESOPH-A).
[c] Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[d] Principles of Surgery (ESOPH-C).
[g] See Staging (ST-1) for tumor classification.
[m] pTis, pT1a, superficial pT1b, pT1b, N0 tumor classifications are defined by pathology of the diagnostic ER specimen. See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[n] The initial diagnostic ER procedure may prove therapeutic for some patients, but

[q] For pTis and pT1a, the level of evidence for ablation of SCC after ER is low. However, additional ablation may be needed if there is multifocal high-grade dysplasia (HGD)/carcinoma in situ. Ablation may not be needed if all lesions are completely excised. For references, see Principles of Endoscopic Staging and Therapy (ESOPH-A).
[r] ER followed by ablation may be used to completely eliminate residual dysplasia.
[s] Esophagectomy is indicated for patients with extensive carcinoma in situ (pTis or HGD) or pT1a, especially nodular disease that is not adequately controlled by ablation or ER followed by ablation.

Esophagus: lymphatic drainage & LN met risk



Absi A, et al. https://www.clevelandclinicmeded.com

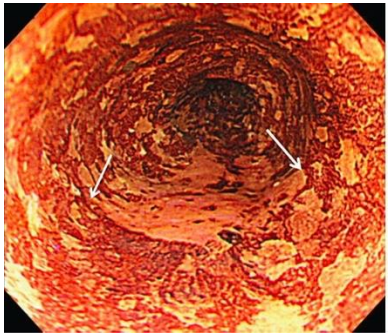
2017 Esophageal cancer practice guidelines edited by the Japan Esophageal Society: part 2
Esophagus 2019;16

Risk of LN mets for ESCCa:

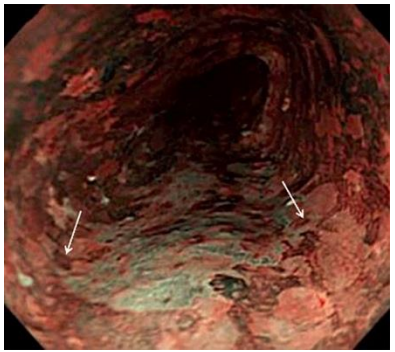
pT1a-EP/LP (m1/2):	**0.36%** (1/280)
pT1a-MM (m3):	**4.29%** (3/70)
pT1b-SM1:	**11.7%** (2/17)
pT1b-SM2:	**25.7%** (9/35)

ESD should be the first option for superficial esophageal squamous dysplasia

- ESCCA is a field defect
- For lesions ≥10 mm wide, **en bloc excision by ESD indicated**
  - Excludes obvious Sm invasion
  - Enables accurate path staging



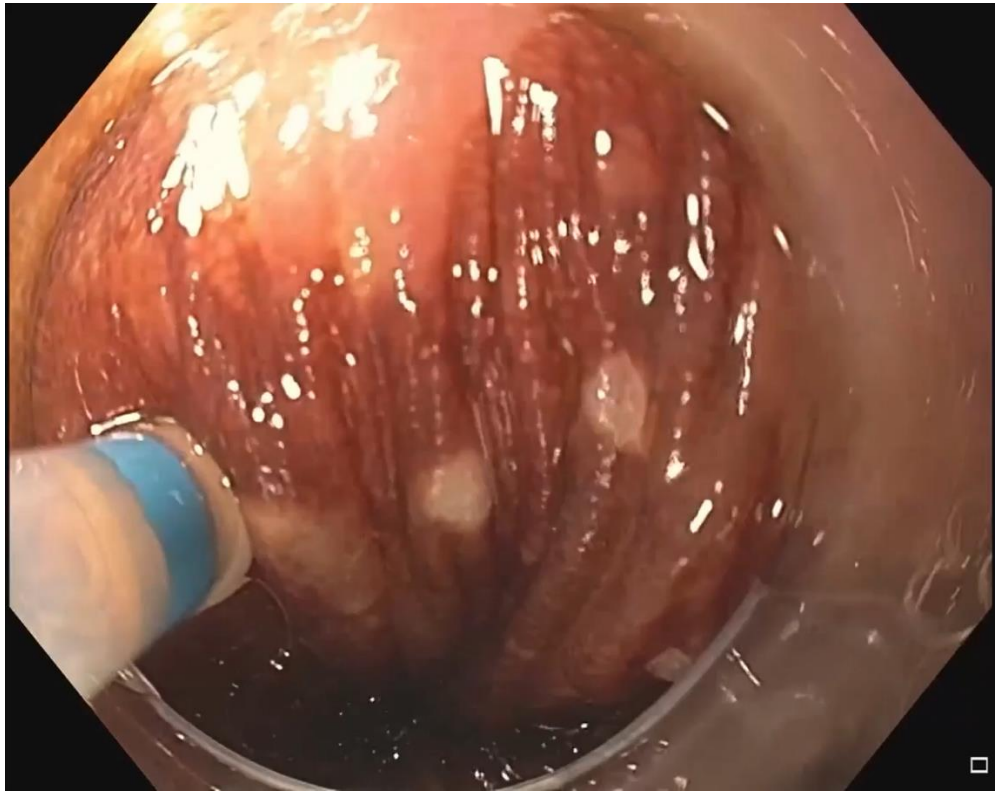
Lugol's iodine

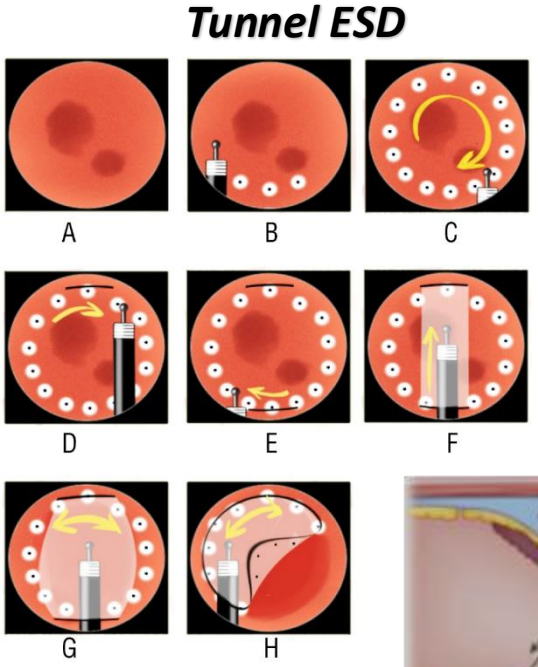


NBI

Pimentel-Nunes P, et al. ESGE Guideline. Endoscopy 2015;47Inoue H et al. Annals of Gastroenterol 2015; 28

Tunnel ESD aided by clip-floss & suture-pulley traction

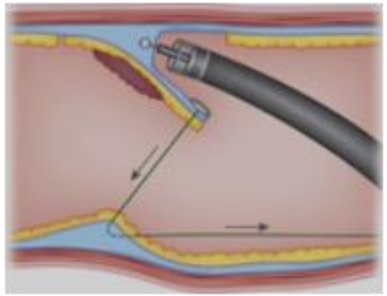




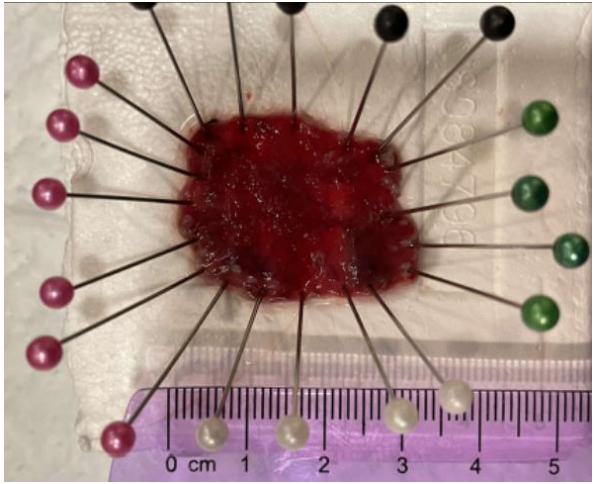
Ge PS…Aihara H. GIE 2019;89

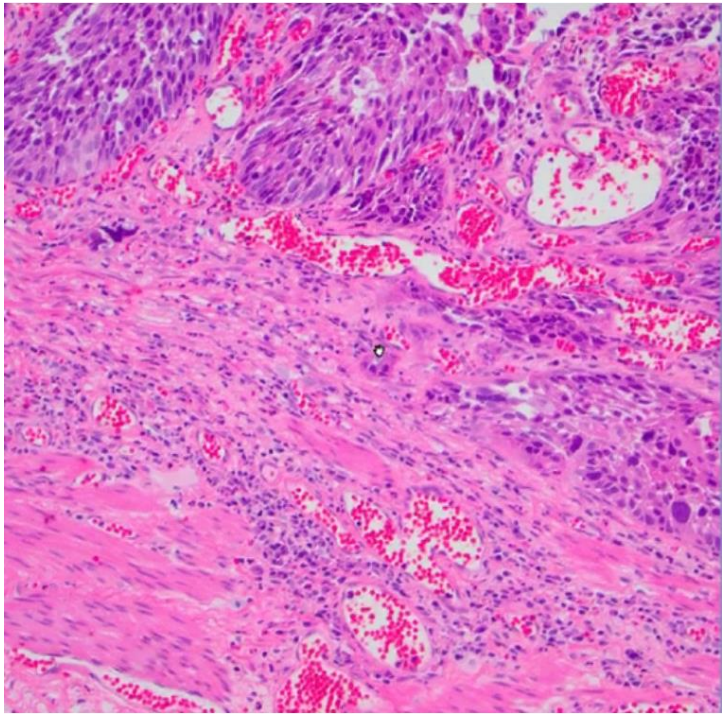
Riberiro TML, Arantes VN et al. Arq Gastroenterol 2021;58

Suture-pulley



Pathology/pathologists are not perfect!





Initial path read:

ESOPHAGUS, MID, ESOPHAGEAL SUBMUCOSAL DISSECTION:

EXTENSIVE SEVERE SQUAMOUS DYSPLASIA (HGD), FOCALLY SUSPICIOUS FOR INTRAMUCOSAL INVASION

Final pathology

- Given near focus NBI finding of V2 or V3 IPCLs, we asked for deeper cuts

- ESOPHAGUS, MID, ESOPHAGEAL SUBMUCOSAL DISSECTION:
- ***INVASIVE MODERATELY DIFFERENTIATED SQUAMOUS CELL CARCINOMA.*** (See comment.)

- Amendment Comment: Additional levels were performed on blocks A3 and A4. On Slide A3-5, there is a **focus of invasive squamous cell carcinoma extending into the lamina propria and abutting the muscularis mucosa**. The focus is approximately 2mm by 0.5mm (depth). Adjacent to this focus, **there is lymphovascular invasion**. **The invasive carcinoma is widely excised (as is the severe squamous dysplasia)**

- **Final ESD path:** pT1a-M2 ESCCa, G2, LVI (+), R0

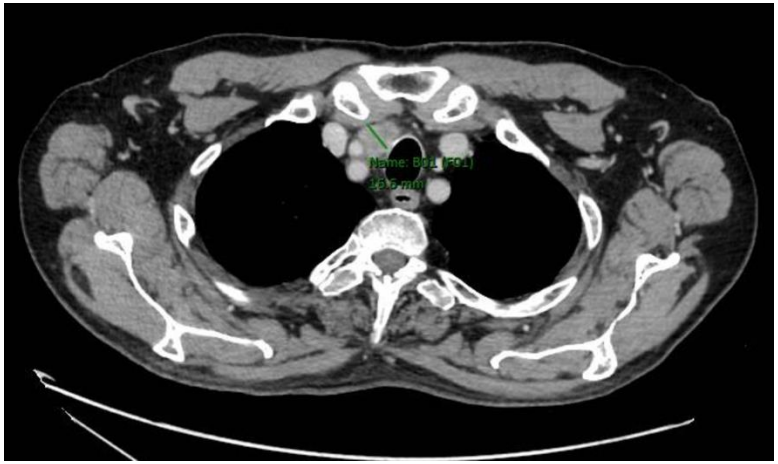
Next steps?

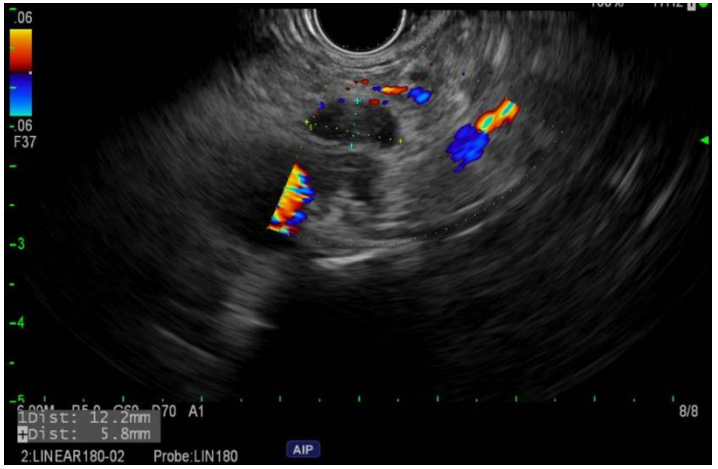
- Endoscopic surveillance alone?
- Endoscopic and radiographic surveillance?
- Radiotherapy?
- Esophagectomy?

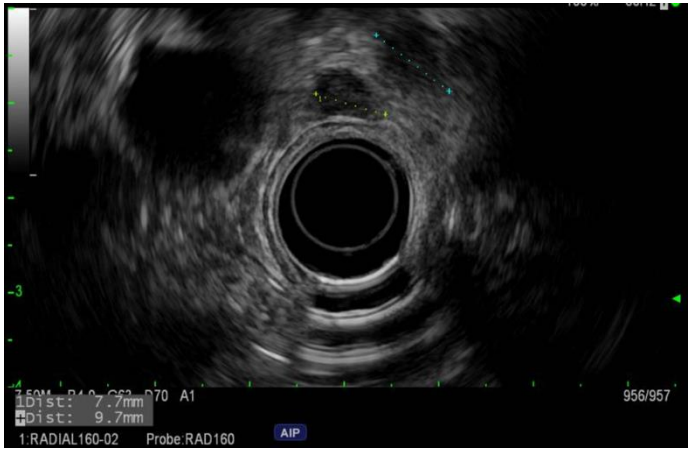
Follow-up

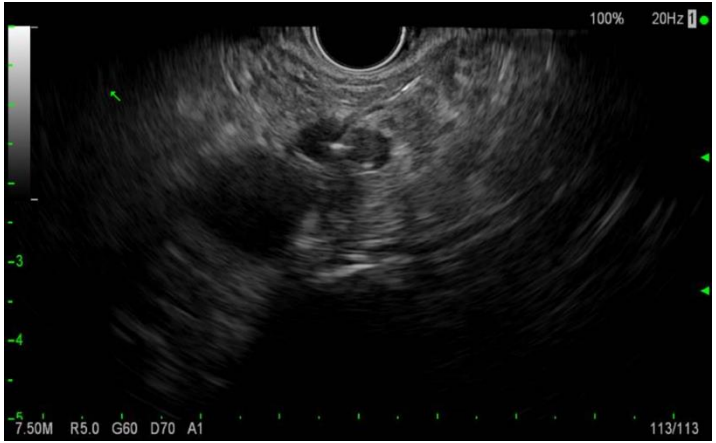
- Patient declined surgery as well as XRT
  - Plan was EGD ± EUS and CT scans
- CT chest/abd 2 months later – no LN mets
- EGD 4 months later normal
- CT chest/abd 9 months later – **concerning 1.7 cervical LN**

Metastatic squamous cell carcinoma



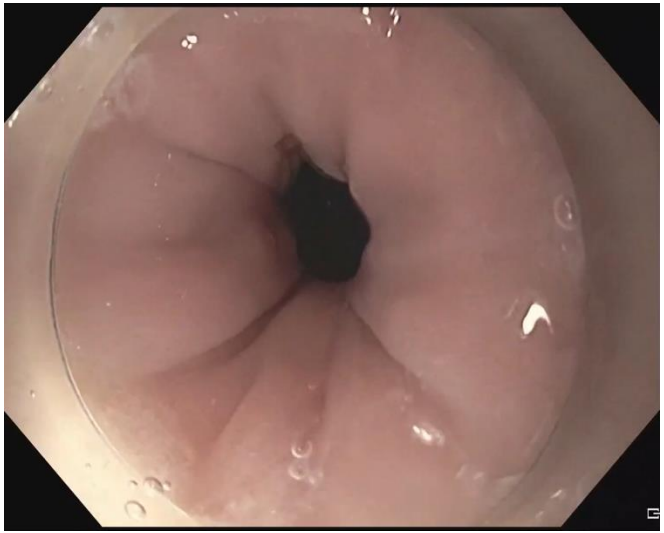


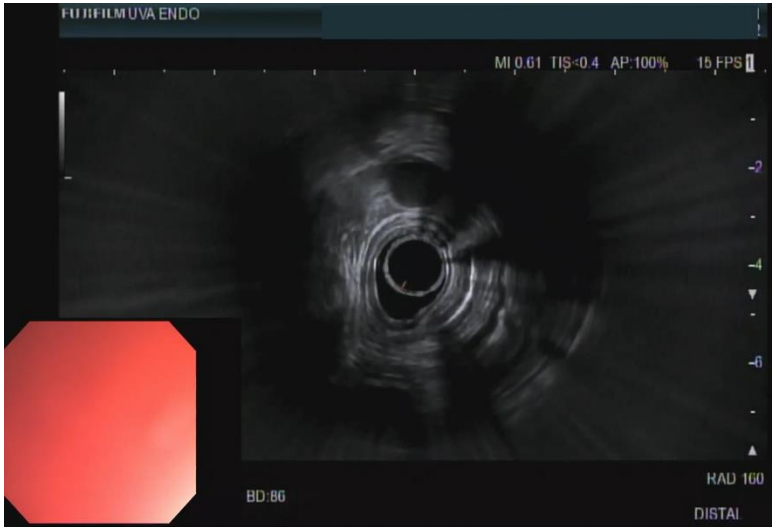




Long-term follow-up

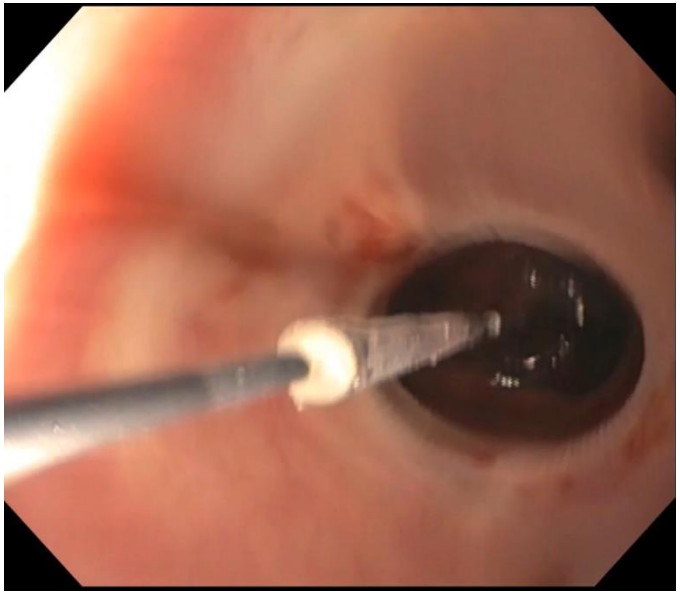
- **For stage IIb ESCCa (pT1a, N1, M0)**
  - Carbo/taxol and radiation to RT paratracheal LN and mid esophagus
- **2.5 yrs after Chemo/RT no evidence of disease by EGD/EUS**





Ablative therapy ESCCA

- Data for cryotherapy and RFA are sparse, and of limited methodologic rigor, for treatment of ESCCA

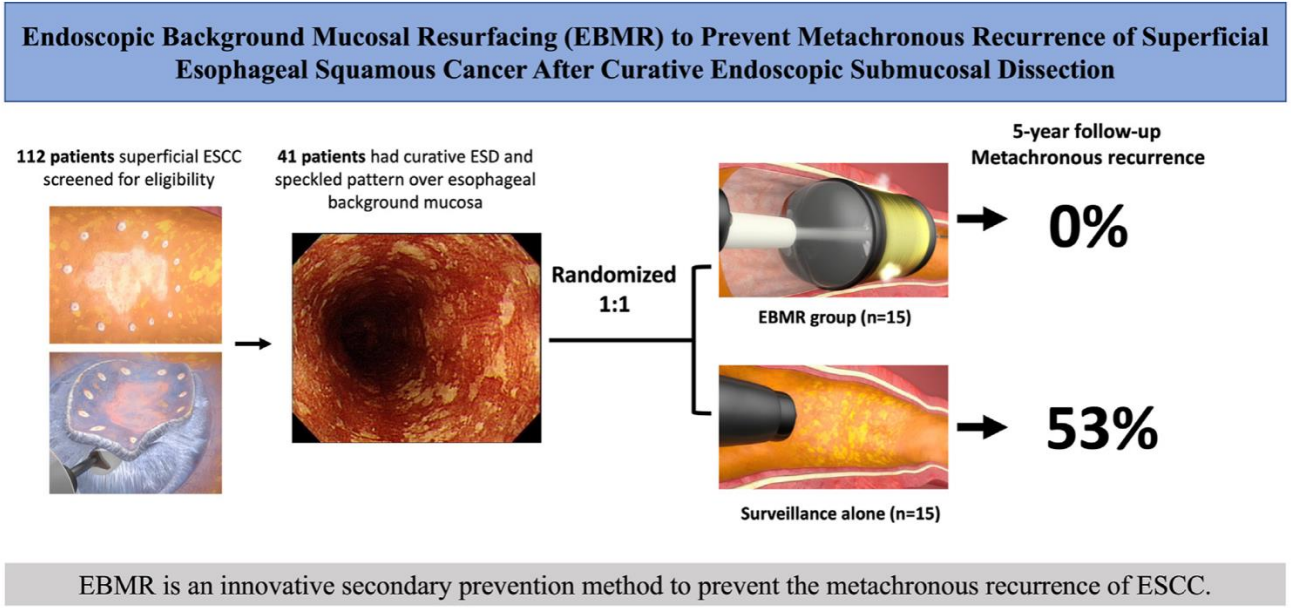


Endoscopic background mucosal resurfacing to prevent metachronous recurrence of superficial esophageal squamous cell cancer after curative endoscopic submucosal dissection: randomized pilot study with 5-year follow-up (with video)

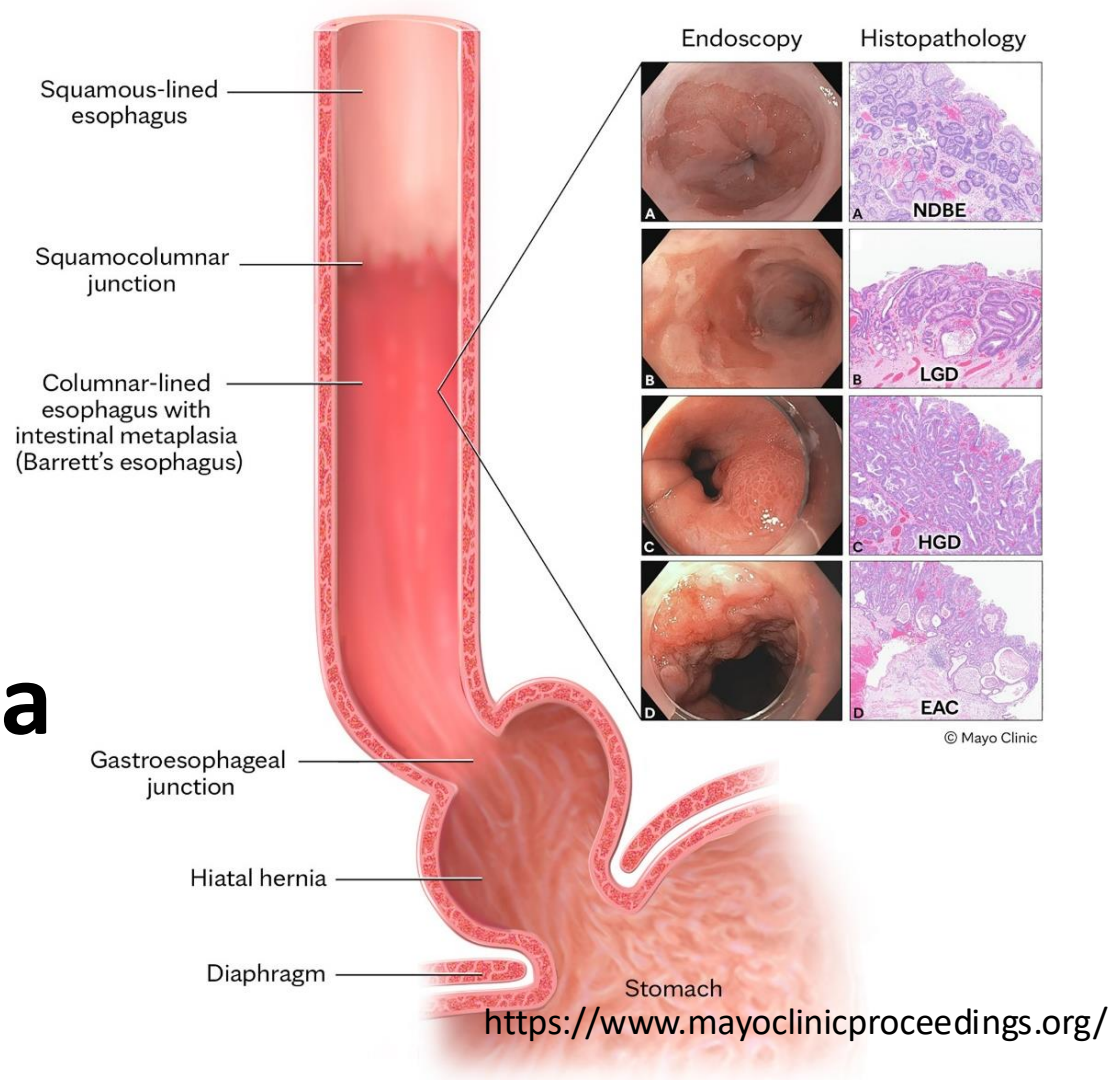
Wen-Lun Wang, MD, PhD,[1,2] Ying-Nan Tsai, MD,[3] Ming-Hung Hsu, MD,[1] Jaw-Town Lin, MD, PhD,[1,2] Hsiu-Po Wang, MD,[4] Ching-Tai Lee, MD[1]

Kaohsiung, Taipei, Taiwan

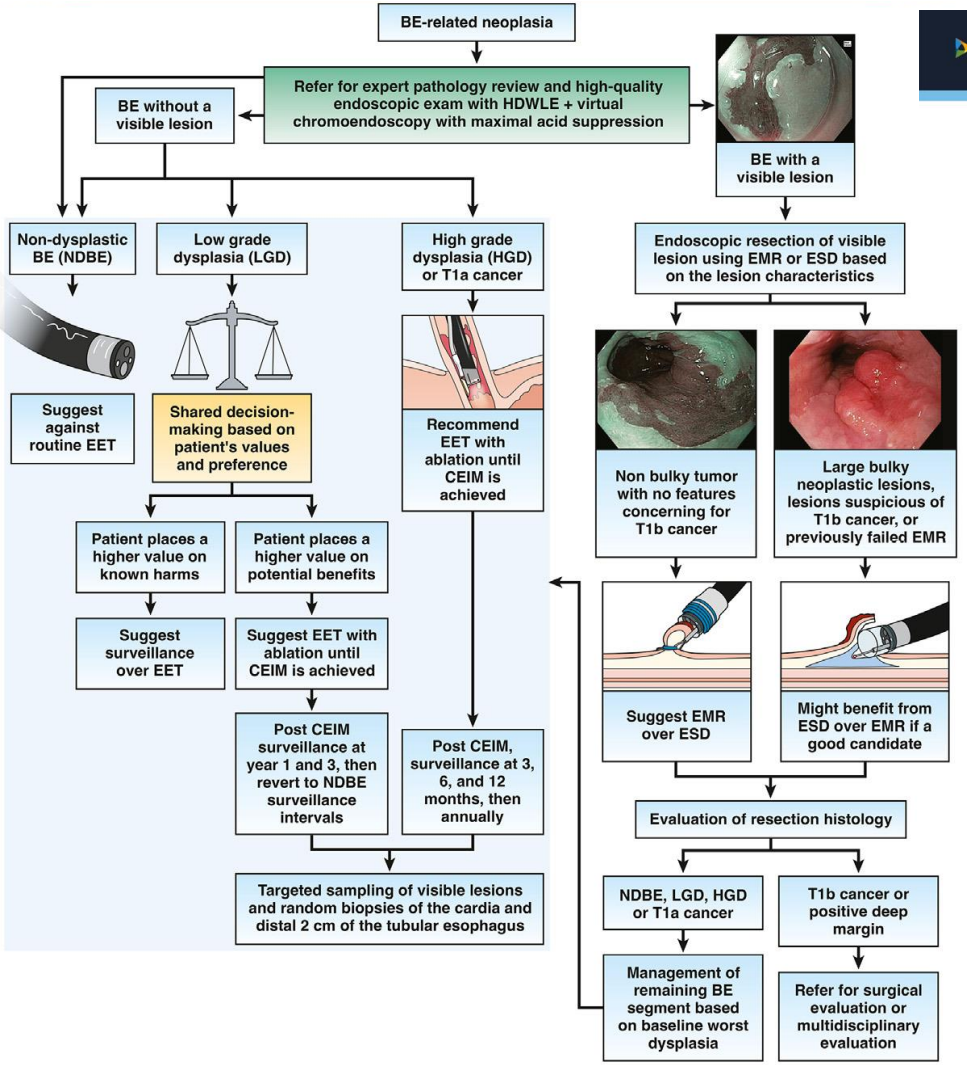
GRAPHICAL ABSTRACT



Barrett's neoplasia & esophageal adenocarcinoma (EAC)



https://www.mayoclinicproceedings.org/



aga American Gastroenterological Association
Gastroenterology Spotlight

Spotlight: Endoscopic Eradication Therapy (EET) of Barrett's Esophagus and Related Neoplasia

Joel H. Rubenstein, MD, MSc[1,2,3*]; Tarek Sawas, MD, MPH[4*]; Sachin Wani, MD[5*]; Swathi Eluri, MD, MSCR[6]; Shailendra Singh, MD[7,8]; Apoorva K. Chandar, MD[9]; Ryan B. Perumpail, MD[10]; John M. Inadomi, MD[11]; Aaron P. Thrift, PhD[12]; Alejandro Piscoya, MD, MSc[13]; Shahnaz Sultan, MD[14,15]; Siddharth Singh, MD, MS[16]; David Katzka, MD[17]; Perica Davitkov, MD[18,19]

General endoscopic strategy for BE neoplasia:

- Consent pts undergoing EGD for BE surveillance for EMR of nodules
- Carefully examine the esophagus using WL and IEE, a distal cap may help
- If a nodule is found that is small (<1 cm, not bulky, and no features to suggest T1b), remove by EMR
- Ablate flat BE (including HGD/T1a EAC) typically with RFA with close follow-up until CEIM achieved
- If a large/bulky lesion is found that is not deep cancer, or T1b disease suspected, consider ESD

Gastroenterol 2024; 166

AGA Clinical Practice Guideline on Endoscopic Eradication Therapy of Barrett's Esophagus and Related Neoplasia

Joel H. Rubenstein,[1,2,3,*] **Tarek Sawas**,[4,*] **Sachin Wani**,[5,*] Swathi Eluri,[6] Shailendra Singh,[7,8] Apoorva K. Chandar,[9] Ryan B. Perumpail,[10] John M. Inadomi,[11] Aaron P. Thrift,[12] Alejandro Piscoya,[13] Shahnaz Sultan,[14,15] Siddharth Singh,[16] David Katzka,[17] and Perica Davitkov[18,19]

Recommendation 4: In patients undergoing EET, the AGA suggests resection of visible lesions followed by ablation of the remaining BE segment over resection of the entire BE segment. ***(Conditional recommendation, very low certainty of evidence)***

Implementation Considerations:

- In patients with only a small area of BE beyond the visible lesion, completion endoscopic resection in the same setting is acceptable and may be preferred over repeated procedures to perform ablation.
- RFA is the preferred ablative modality.

Gastroenterol 2004;166

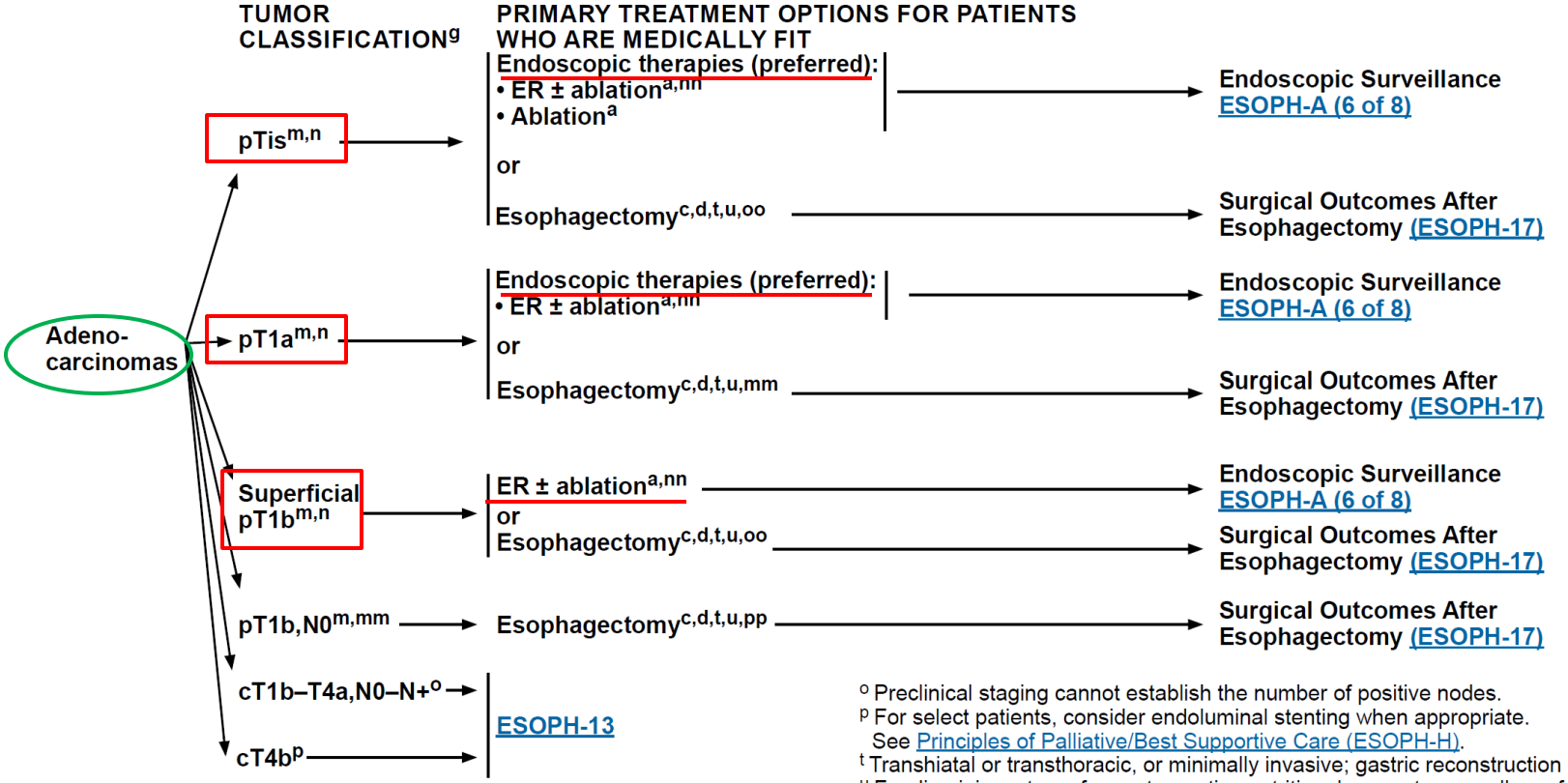
Recommendation 5: In individuals with BE with visible neoplastic lesions that are undergoing endoscopic resection, the AGA suggests the use of either EMR or ESD based on lesion characteristics. *(Conditional recommendation, very low certainty of evidence)*

Rubenstein JH et al. Gastroenterol 2004;166

Implementation Considerations:

- Patients suspected of having T1 EAC should be referred for consideration of EET.
- Endoscopic resection is the test of choice over endoscopic ultrasound for distinguishing EAC from HGD and for staging depth of invasion in early cancer.
- The vast majority of neoplastic lesions may be managed with EMR rather than ESD.
- Patients with large bulky neoplastic lesions or lesions highly suspicious of at least T1b invasion (for instance those with depressed, Paris IIc, or IIa+c lesions) and deemed candidates for endoscopic resection might benefit from ESD over EMR.
- Patients with previously failed EMR might benefit from ESD.

NCCN Guidelines Version 1.2025
Esophageal and Esophagogastric Junction Cancers



[a] Principles of Endoscopic Staging and Therapy (ESOPH-A).
[c] Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[d] Principles of Surgery (ESOPH-C).
[g] See Staging (ST-1) for tumor classification.

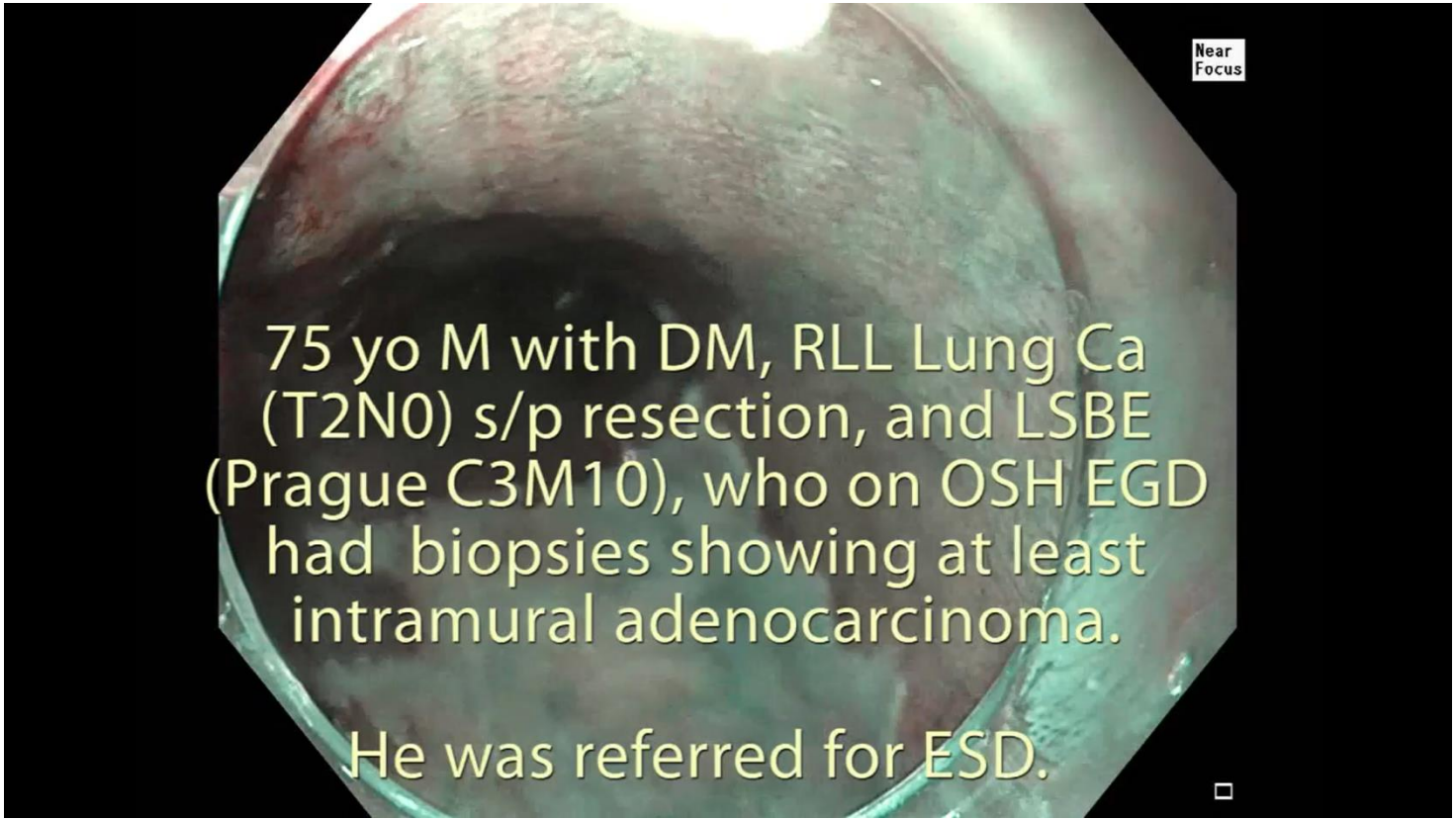
[o] Preclinical staging cannot establish the number of positive nodes.
[p] For select patients, consider endoluminal stenting when appropriate. See Principles of Palliative/Best Supportive Care (ESOPH-H).
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[mm] Diagnostic ER can be considered to confirm the pathologic staging and for treatment in select patients.
[nn] ER followed by ablation may be used to completely eliminate residual dysplasia or Barrett epithelium.

Suggested indications for esophageal ESD in the U.S.

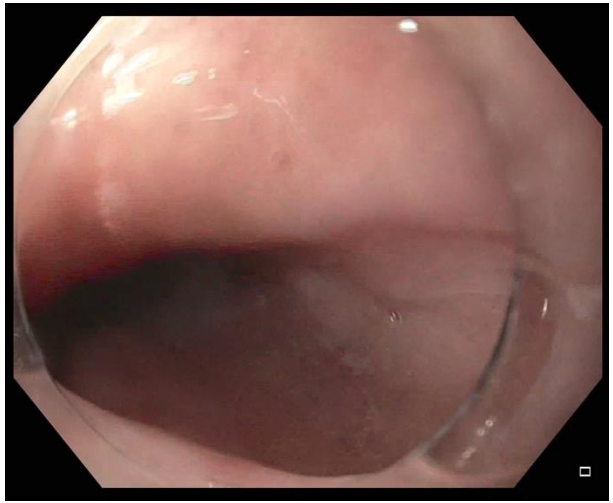
Organ	Indications for ESD
Esophagus	
Squamous cell carcinoma	HGD to well (G1) to moderately (G2) differentiated Paris 0-II lesions *Absolute indications*: m1-m2 involvement with ≤2/3 of the esophageal circumference *Expanded indications*: m3 or sm < 200 μm involvement, any size, clinically N0
Barrett's esophagus	HGD to moderately (G1/G2) differentiated T1a (m1-m3) lesions ≥15 mm (not amenable to en bloc resection by EMR) Patients with Barrett's esophagus and the following features: Large or bulky area of nodularity Equivocal preprocedure histology Intramucosal carcinoma Suspected superficial submucosal invasion Recurrent dysplasia EMR specimen showing invasive carcinoma with positive margins

Wang AY, Draganov PV. Techniques Gastrointest Endosc 2017;19
Draganov PV, Wang AY, Othman MO, Fukami N. Clin Gastroenterol Hepatol 2019;17

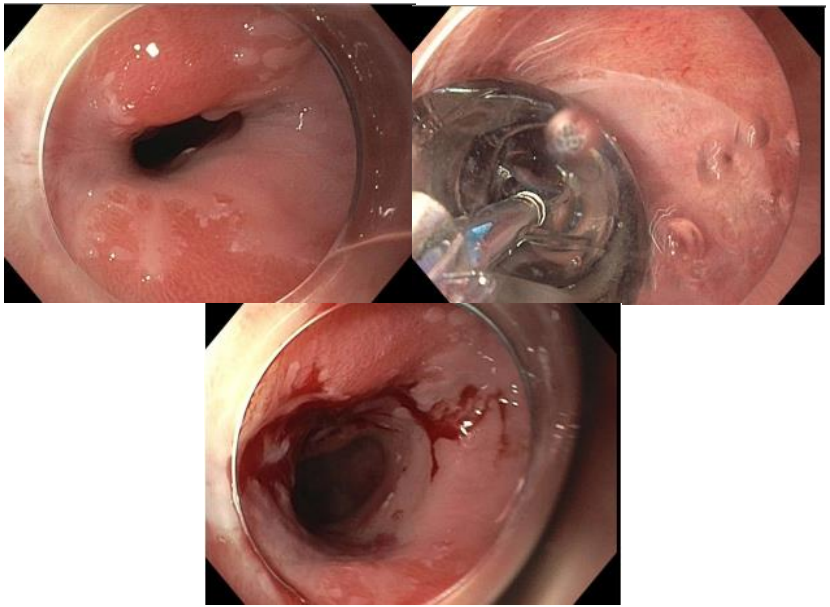
Near circumferential ESD



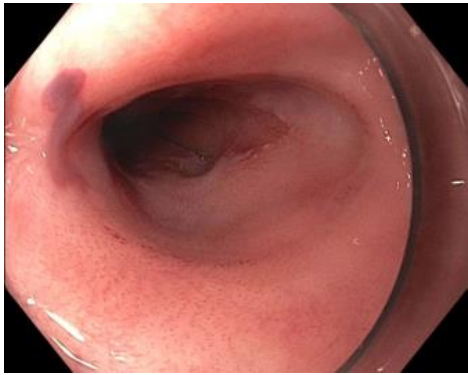
Post-ESD stricture



3 weeks after ESD



2 weeks later



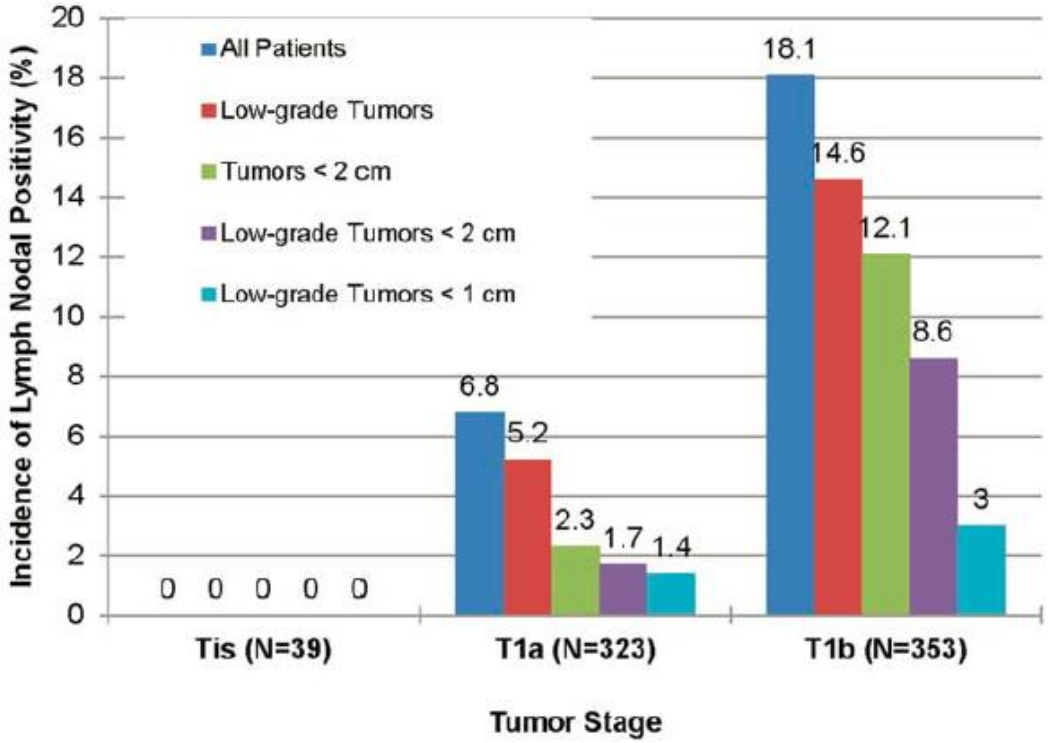
3 years later:
Non-obstructing

Post-ESD stricture prevention

- Most studies of prevention modalities show limited effect/uncertain benefit or lack statistical rigor
- Steroids
  - Sm injection after ESD (avoid MP)
  - PO prednisone, IV methylprednisolone, PO viscous budesonide
- Tissue shielding
  - PGA sheets
  - Self-assembling peptide hydrogel
- Prophylactic stenting

Yang D et al Gastrointest Endosc 2024;100
Bhatt A, Mehta NA. Gastrointest Endosc 2020;92
Takahashi H et al. BMC Gastroenterology 2015;15

Incidence of LN mets in early EAC



Gamboa AM…Willingham FF et al. Cancer 2016;122

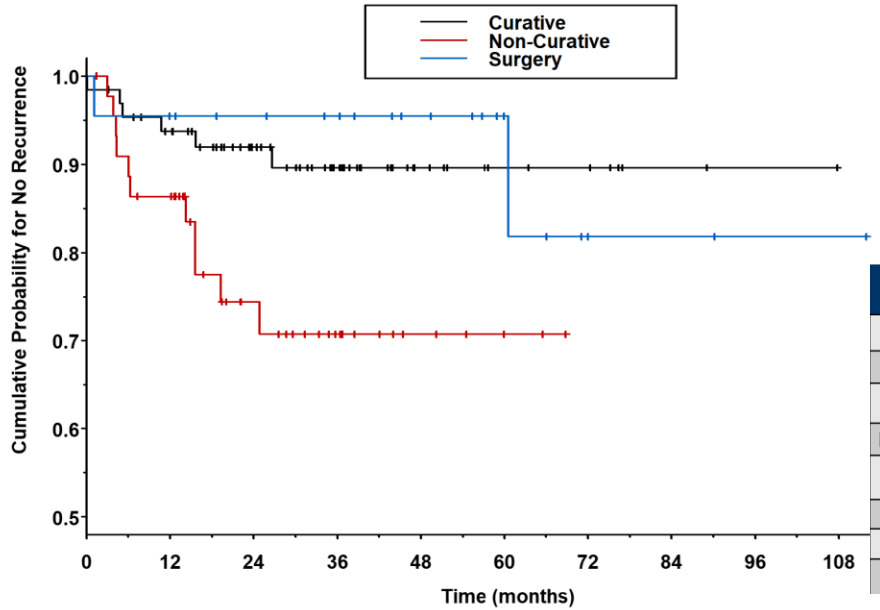
Meta-analysis: ESD for early Barrett's EAC

- Eleven studies — 501 patients, 524 lesions
- Mean lesion size — 27 mm (95% CI: 20.9%-33.1%)
- **Pooled estimates**
  - En bloc resection — **92.9%** (95% CI: 90.3%-95.2%)
  - Curative resection — **64.9%** (95% CI: 55.7%-73.6%)

Yang D…Draganov PV. Gastrointest Endosc 2018

ESD for EAC with curative pathology is reassuring at 3-year follow-up

Figure 1. Recurrence after ESD



*The cumulative distribution functions differed between curative and non-curative pathology recommendation cases (**p=0.019**) and marginally between non-curative and surgical resection pathology recommendation cases (**p=0.061**), but not between curative and surgical resection pathology recommendation cases (**p=0.787**).*

Table 4. Recurrence Rate Analyses

	Univariate Odds Ratio [95% CI]	P-value
Non-Curative vs. Curative	3.2 [1.1, 10.0]	0.01
Surgical Resection vs. Curative	1.0 [0.1, 5.1]	0.98
Non-Curative vs. Surgical Resection	3.2 [0.7, 23.1]	0.15
	Multivariate Odds Ratio [95% CI]	**P-value**
Non-Curative vs. Curative	4.9 [1.4, 17.6]	0.01
AJCC T1b vs. T1a	0.9 [0.3, 2.4]	0.89
Lymphovascular Invasion vs. no LVI	0.4 [0.1, 1.4]	0.12

Schenck RJ…Wang AY. DDW 2024

Original research

Long-term outcomes after endoscopic treatment for Barrett's neoplasia with radiofrequency ablation ± endoscopic resection: results from the national Dutch database in a 10-year period

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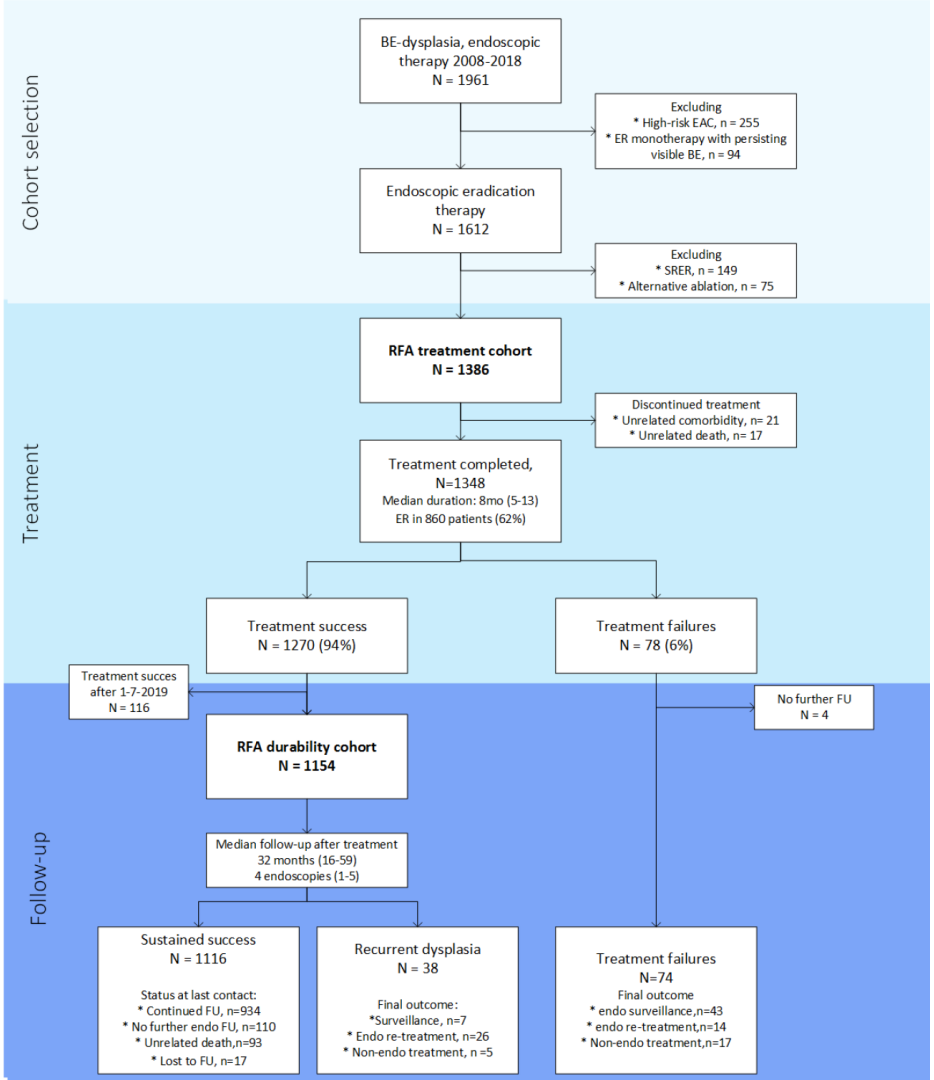

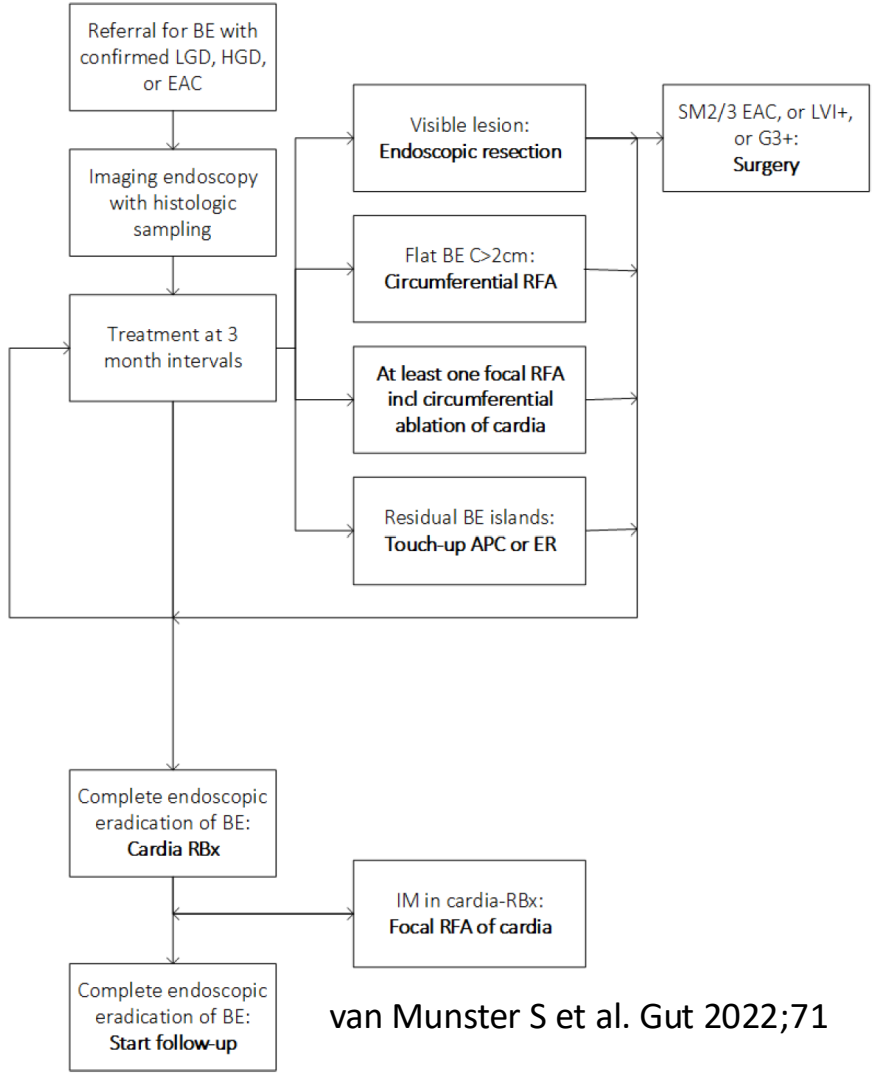

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National Dutch Study BE RFA: Results

- Adverse events occurred in 21% (268/1386), most commonly esophageal stenosis (15%), all were managed endoscopically.
- 1,154 patients with CE-BE were analyzed for long-term outcomes.
- Median 43 months (22–69) and 4 endoscopies (1–5), **38 patients developed dysplastic recurrence (3%, annual recurrence risk 1%)**, all were detected as endoscopically visible abnormalities.

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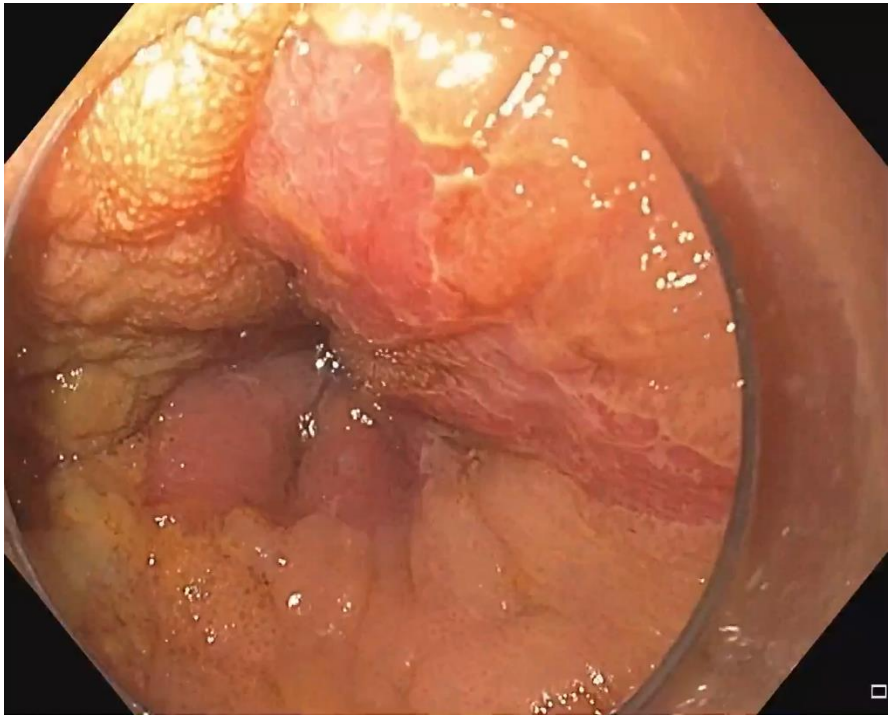
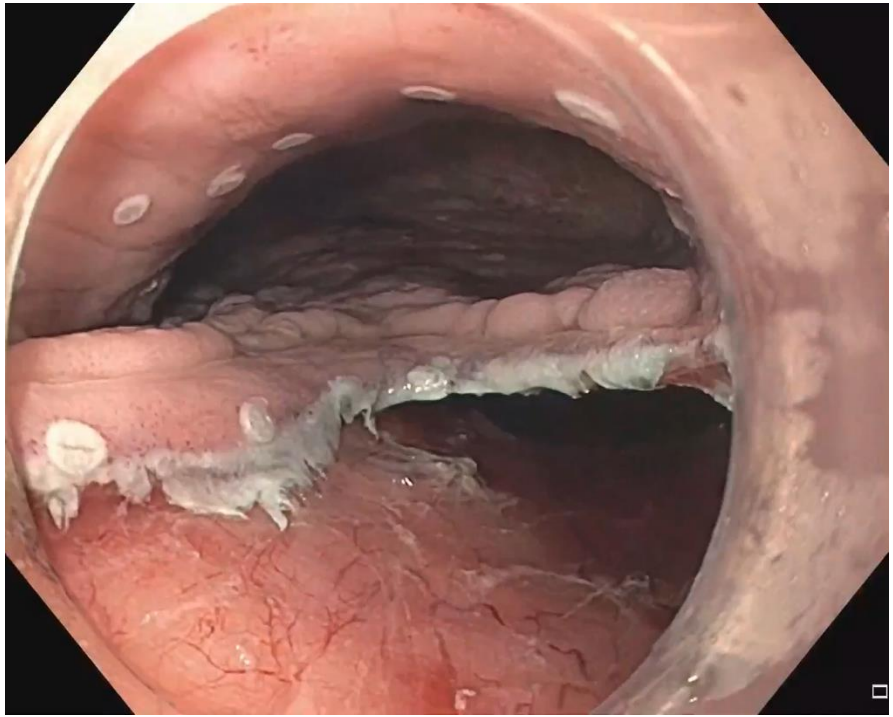
Extensive severe esophageal squamous dysplasia

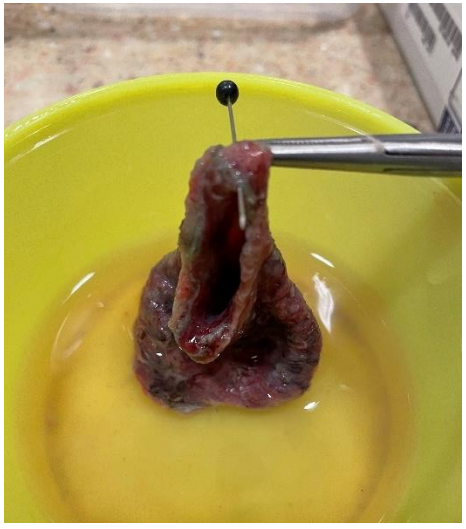
- 47 yo AAM h/o SLE Nephritis, FSGS s/p 3 renal transplants (first 2 from father and cousin failed)
- Hiatal hernia s/p fundoplication at OSH 2016
- On Tacrolimus, Mycophenolate and Prednisone.
- Referred for ESD after EGD/EUS for severe squamous dysplasia from 28 to 35 cm

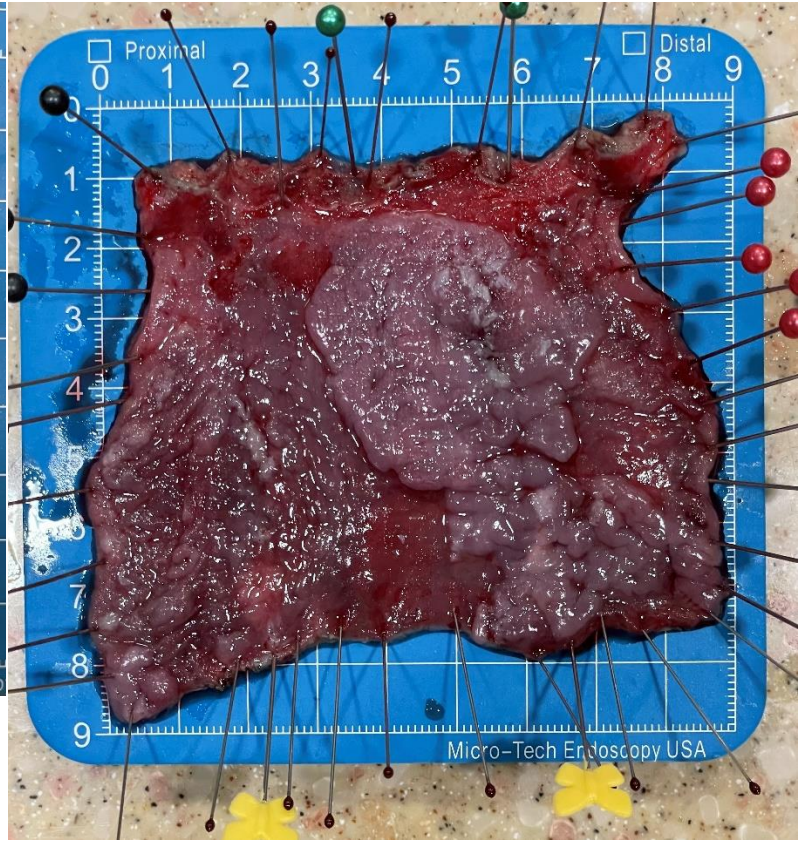
2 tunnel circumferential ESD



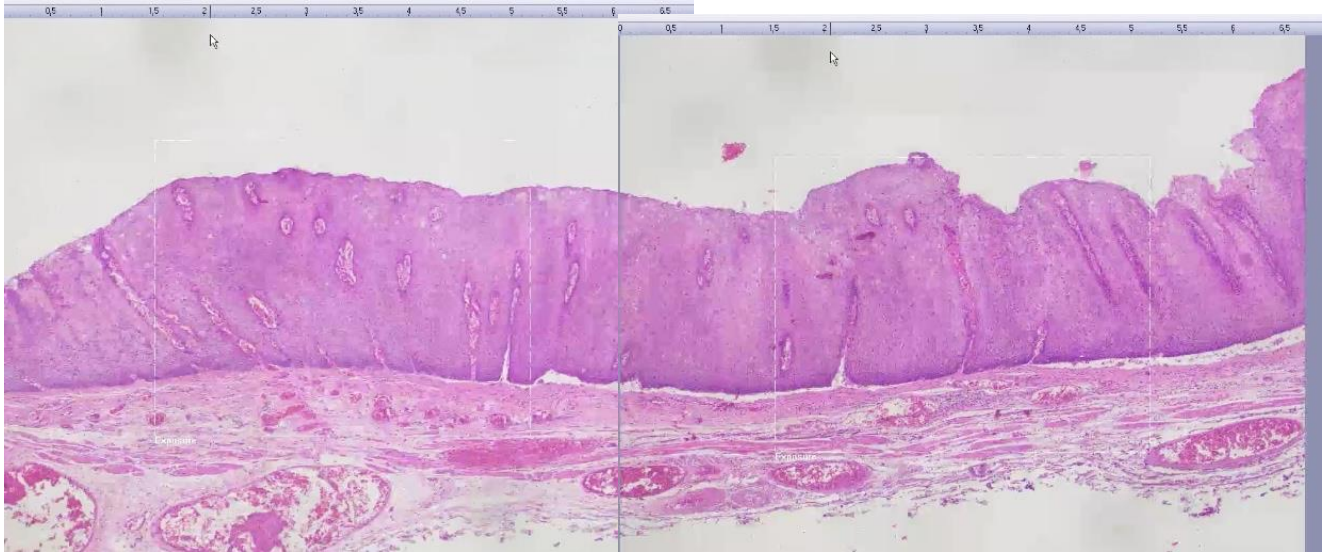


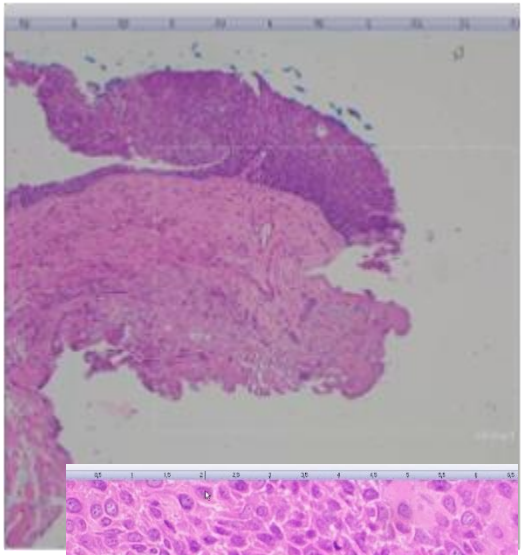
Tubular ESD specimen

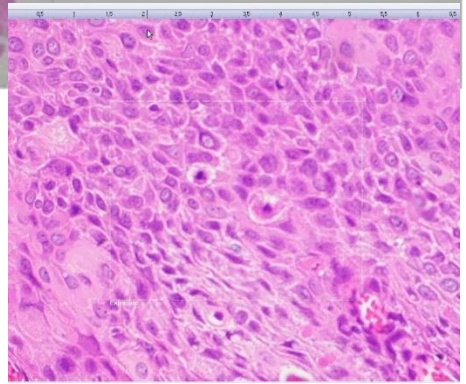




Squamous HGD, positive prox margin

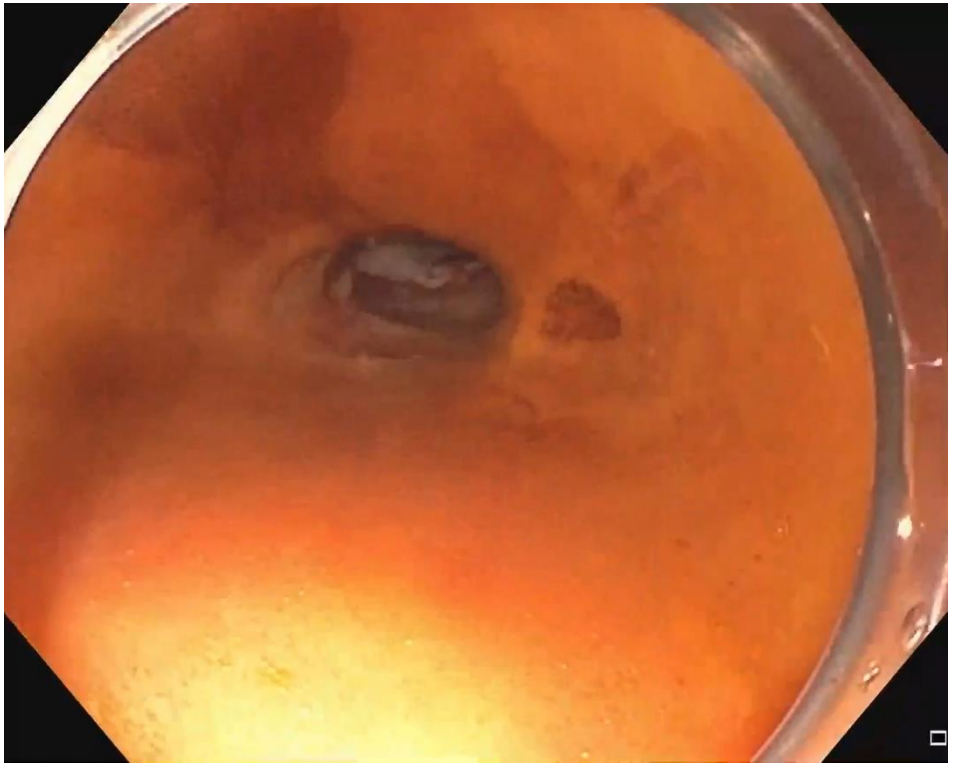




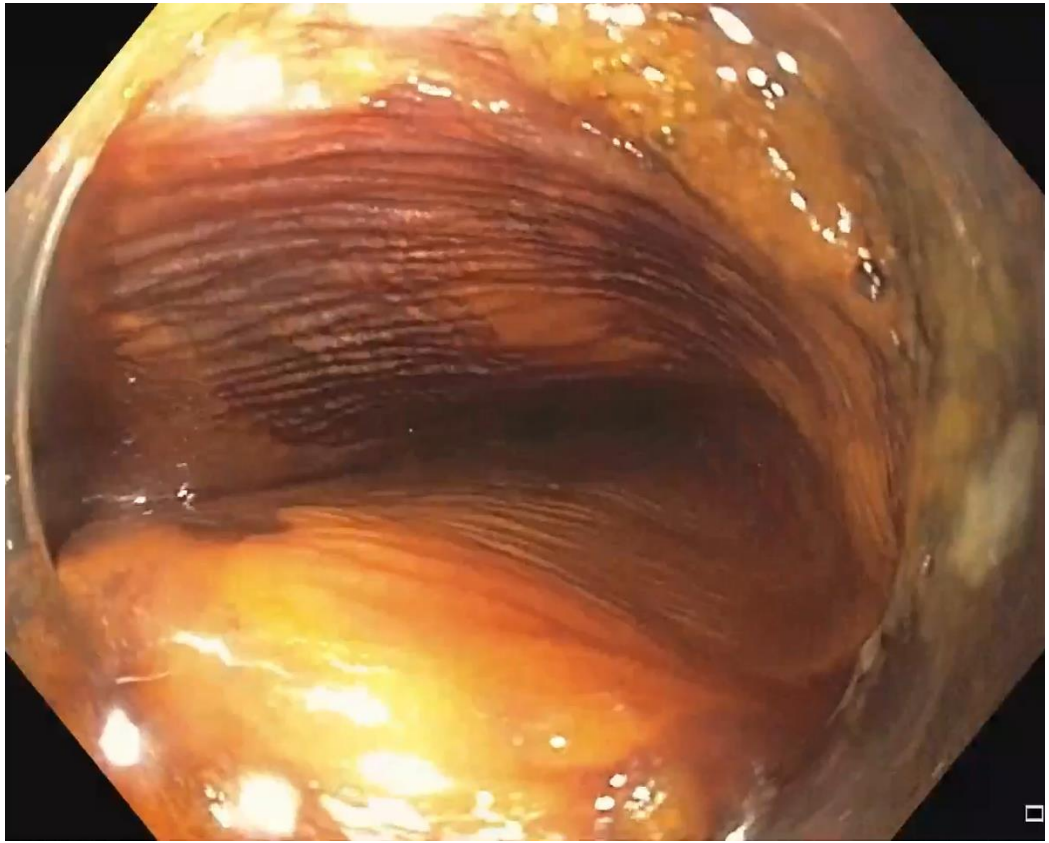


Post-ESD follow-up

- EGD at 3 weeks scope could pass
- 2 weeks later required EGD and dilation, and EGD and dilation every 2-3 weeks (total x7)
- Biopsies showed HGD proximal to ESD scar/stricture
- Focal RFA applied (EGD #5)
- 360 RFA applied (EGD #6)



Squamous severe dysplasia remains!



Takeaways

- Esophageal squamous cell carcinoma (ESCCA) is a diffuse disease, and superficially invasive cancer is associated with higher rates of LN metastasis. As such, en bloc ESD is recommended.
- Barrett's neoplasia and esophageal adenocarcinoma (EAC)—when confined to small nodules/flat changes and the mucosa (HGD or T1a EAC)—is amenable EMR and ablation (typically RFA, but cyro-therapy is acceptable).
- In patients with bulky disease and/or when T1b EAC is suspected, then ESD is advised for accurate diagnosis and possibly cure.
- Patients who undergo more than 75% circumferential esophageal endoscopic resections will develop strictures and early, planned dilation therapy is recommended