Endoscopic Submucosal Dissection for Gastric Cancer: Who Benefits?

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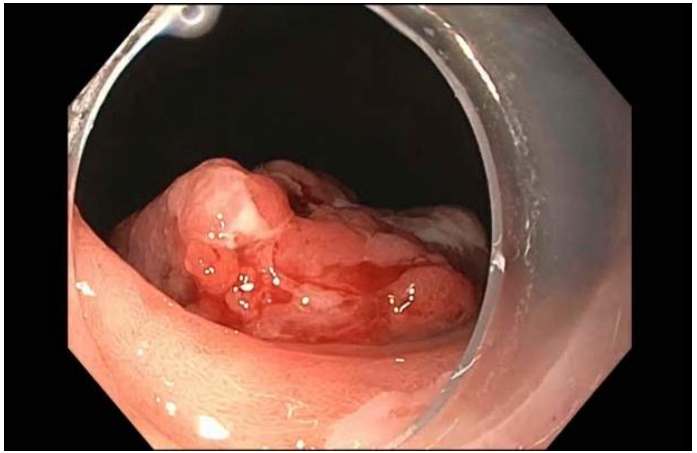
SOUTH FLORIDA GI CANCER SYMPOSIUM
April 11-12, 2025

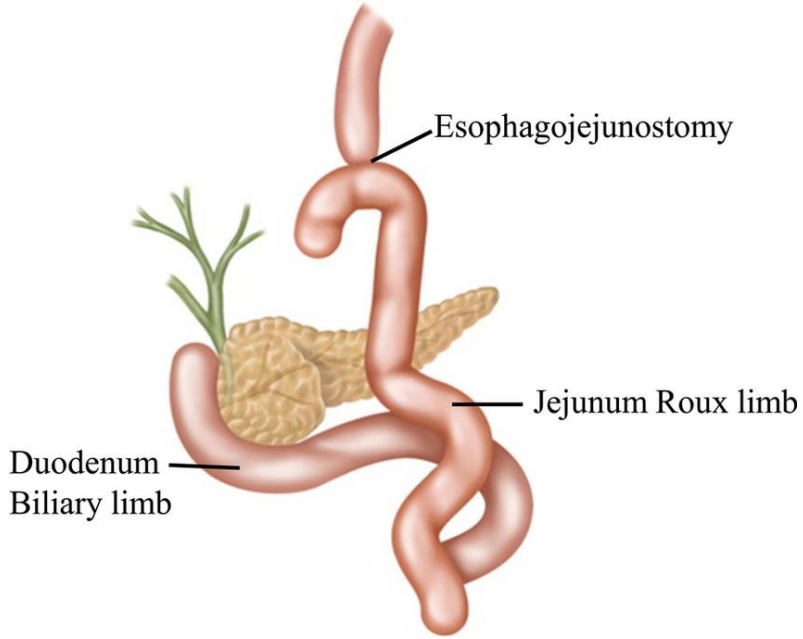
UVA Health

Who benefits from endoscopic resection (ER) of gastric dysplasia?

- Patients with **premalignant dysplasia**
- Patients with **early gastric cancer (EGC)** who
  - Can be cured by ER and would otherwise require surgery
    - T1a and early T1b with good pathological features
  - Are medically at high-risk for gastric surgery
    - T1a/early T1b with poor pathological features
    - Deep T1b
  - Might have difficulty adapting after gastric surgery
    - Proximal EGCs that would necessitate total gastrectomy
    - Elderly, cognitively limited



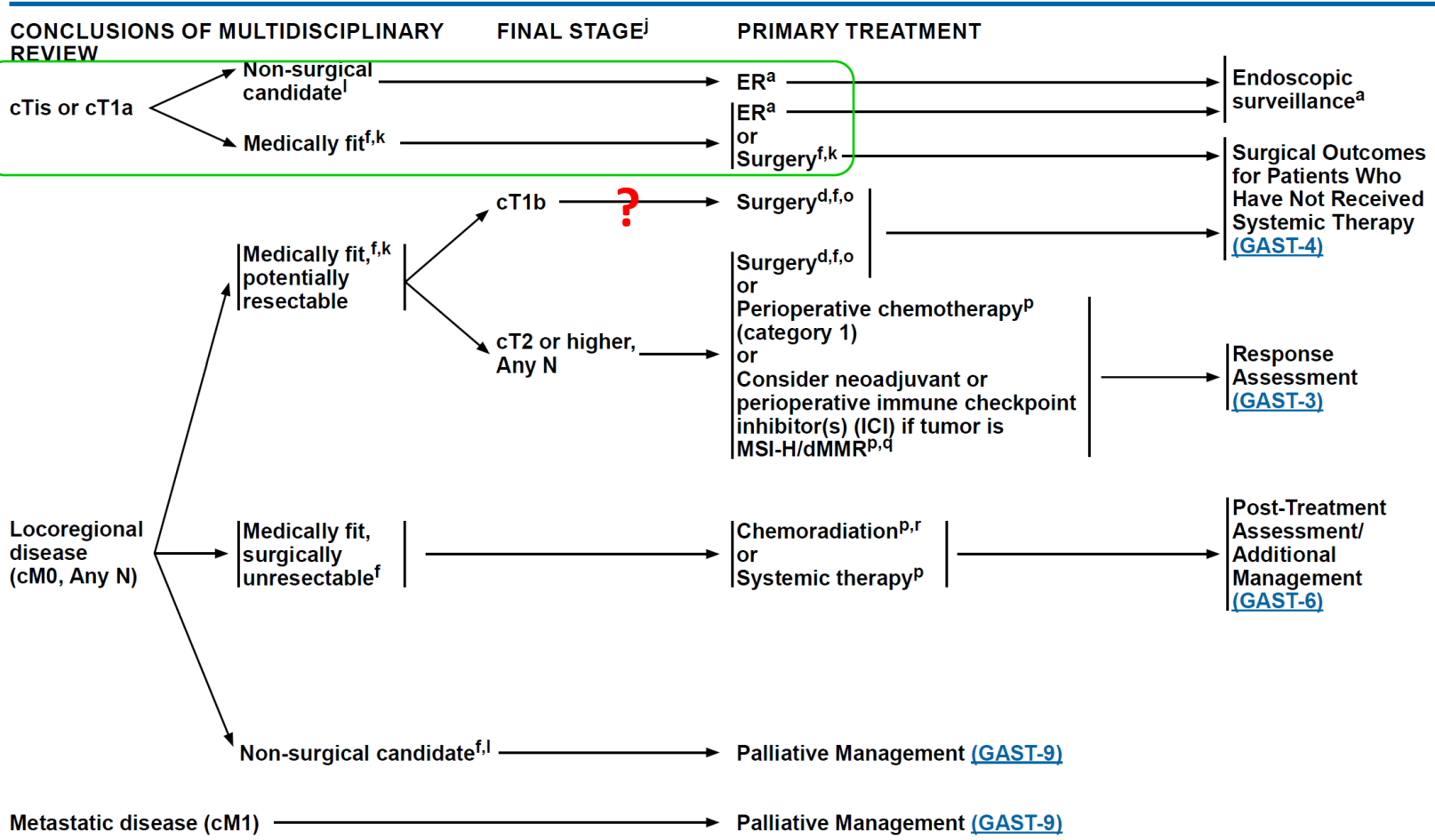
Who benefits from endoscopic therapy for dysplasia and EGC?



Anyone who can avoid a total gastrectomy and esophagojejunostomy with NED on follow-up!

Who would NOT benefit from endoscopic resection of gastric dysplasia?

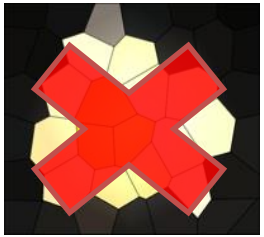
- Those with cancers that fall outside widely accepted criteria for pathologic cure who are fit candidates for surgery
  - G3/G4 (>2 cm), LVI (+), deep T1b
  - Diffuse/hereditary GC, ? signet-ring type GC
  - *Caveat:* ESD can offer accurate pathology to reassure patients about need for definitive surgery
- Frail patients with very limited lifespan


CONCLUSIONS OF MULTIDISCIPLINARY REVIEW
FINAL STAGE[j]
PRIMARY TREATMENT
cTis or cT1a
Non-surgical candidate[l]
Medically fit[f,k]
ER[a]
ER[a] or Surgery[f,k]
Endoscopic surveillance[a]
Surgical Outcomes for Patients Who Have Not Received Systemic Therapy (GAST-4)
Locoregional disease (cM0, Any N)
Medically fit,[f,k] potentially resectable
cT1b
?
Surgery[d,f,o]
cT2 or higher, Any N
Surgery[d,f,o] or Perioperative chemotherapy[p] (category 1) or Consider neoadjuvant or perioperative immune checkpoint inhibitor(s) (ICI) if tumor is MSI-H/dMMR[p,q]
Response Assessment (GAST-3)
Medically fit, surgically unresectable[f]
Chemoradiation[p,r] or Systemic therapy[p]
Post-Treatment Assessment/ Additional Management (GAST-6)
Non-surgical candidate[f,l]
Palliative Management (GAST-9)
Metastatic disease (cM1)
Palliative Management (GAST-9)

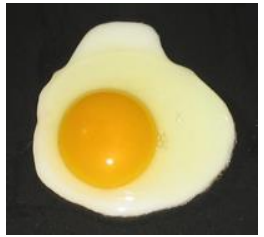
Ideal endoscopic resection

- **Curative resection**
  - **En bloc**
    - Affords pathology to determine **R0 resection**
    - Best chance to avoid residual/recurrent lesion
- **How to decide between EMR vs. ESD?**
  - **Size**
    - En bloc resection limited to 1-2 cm lesions by EMR
    - *EMR achieves similar oncological outcomes as ESD for gastric neoplasia of <1 cm, requiring less expertise, training and time*
  - **Morphology**
  - **Surface pattern**

If it might be cancer?



Piecemeal EMR

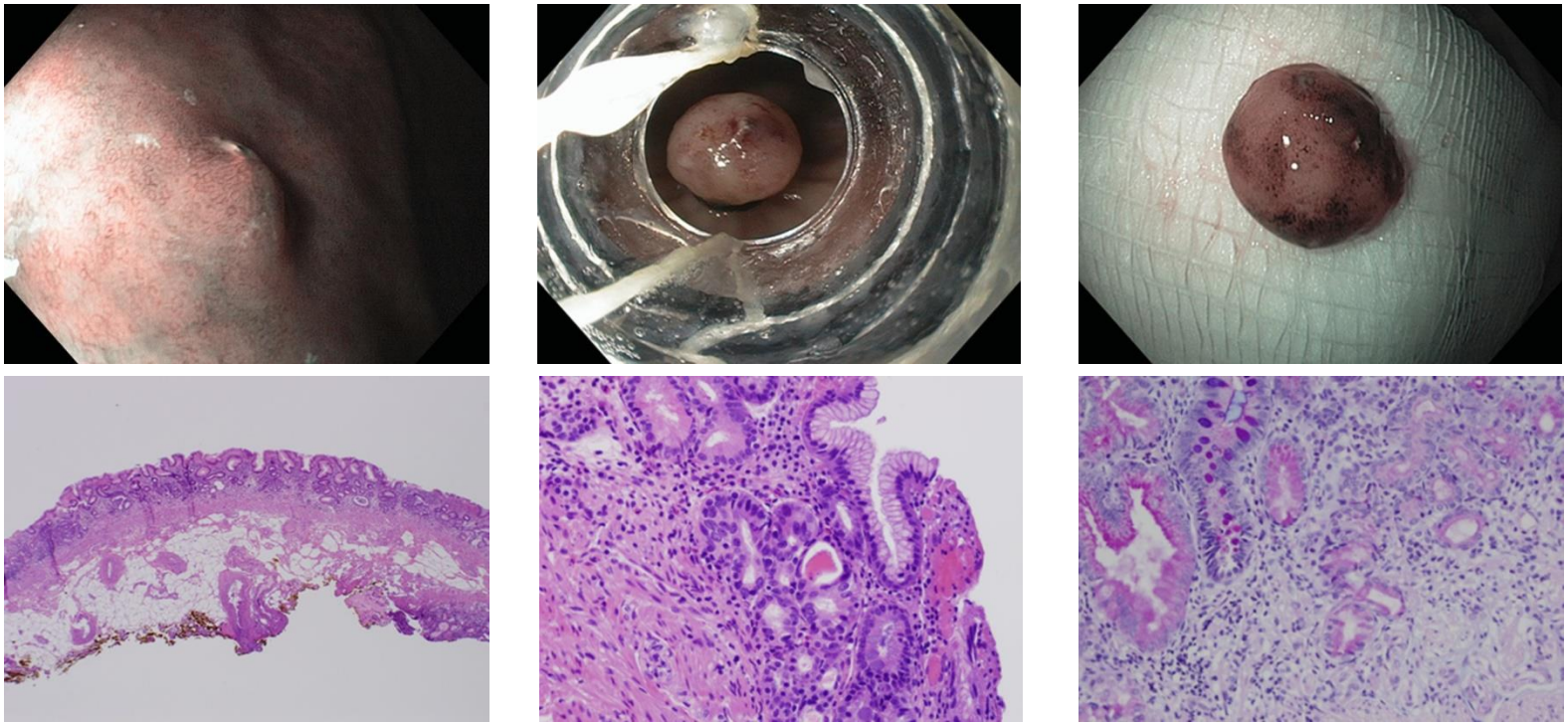


ESD

Banks M et al. Gut 2019;68

Images courtesy of Norio Fukami, MD

EMR of gastric LGD



Gomez JM, Wang AY. Gastroenterol Hepatol (NY) 2014;10

What is ESD?

- Endoscopic submucosal dissection (ESD) is an endoscopic technique developed in Japan to overcome the en bloc/size limitation of EMR, initially for treatment gastric dysplasia/EGC
- Requires
  - Training in lesion identification and endoscopic diagnosis
  - Specialized tools: ESD knives/tools, injection fluids, modern ESG
  - Skill in endoscopic resection, hemostasis and perforation management
- First performed in the late 1990s, ESD spread to nearby Asian countries, then to European early-adopters and later to the US
- In 2025, ESD is performed in many US academic medical centers

Early gastric ESD in Japan

Successful en bloc resection of a large superficial gastric cancer by using sodium hyaluronate and electrocautery incision forceps

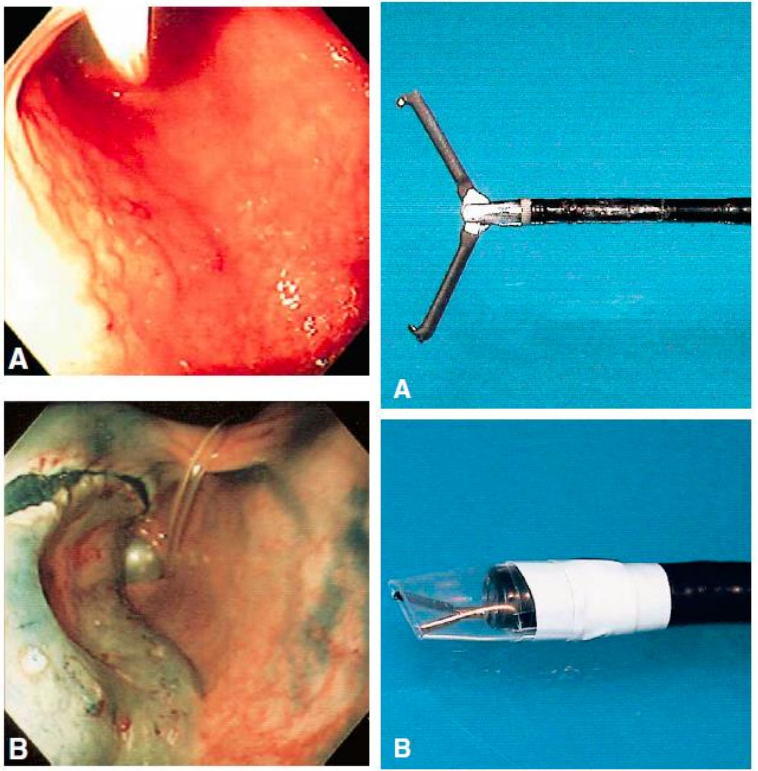
Hironori Yamamoto, MD, Yutaka Sekine, MD, Toshihiko Higashizawa, MD, Ken Kihira, MD, Yoshinari Kaneko, MD, Yoshinori Hosoya, MD, Kenichi Ido, MD, Ken Saito, MD, Kentaro Sugano, MD

Background: **The advisability of endoscopic mucosal resection (EMR) for treatment of large superficial gastric cancers has been challenged. For more reliable en bloc resection, a new method of EMR was developed that uses a viscous substance, sodium hyaluronate, and two newly designed devices.**

Methods: **A large superficial gastric cancer was treated with this new EMR technique. Sodium hyaluronate was injected into the submucosa and mucosal incisions were made with a needle-knife. The newly developed incision forceps and flat-ended transparent hood were used for submucosal incisions.**

Results: **The large cancer was successfully resected endoscopically as a single piece of mucosa 6 cm in diameter without complication. Histopathologic evaluation of the specimen confirmed that the resection was curative.**

Conclusions: **EMR with sodium hyaluronate along with two new devices may be a reliable method for en bloc resection of large superficial gastric lesions.**



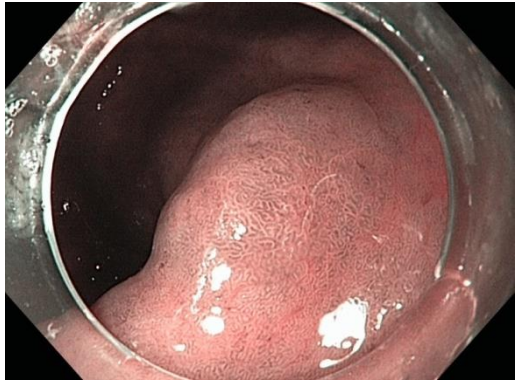
Yamamoto H et al. GIE 2001 54;5

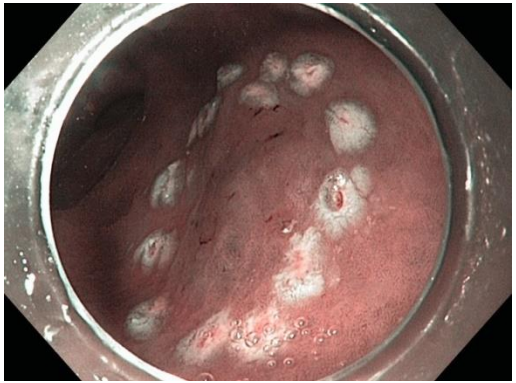
Endoscopic submucosal dissection with electrosurgical knives in a patient on aspirin therapy (with video)

Andrew Y. Wang, MD, Fabian Emura, MD, PhD, Ichiro Oda, MD, Dawn G. Cox, RN, Hyun-soo Kim, MD, Paul Yeaton, MD

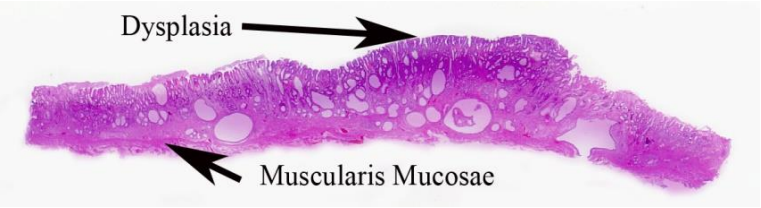
Charlottesville, Virginia, USA

Gastrointest Endosc 2010;72





- **1st ESD in a patient 1/2010 at UVA**
- First ESD in Virginia using new ESD knives



HGD, R0 resection, 120 min

Progression of ESD at UVA

POEM

1/2010

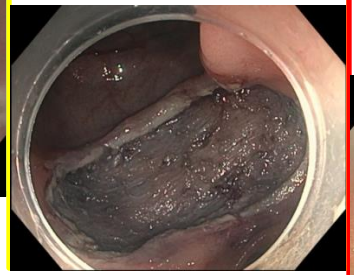
Gastric ESD

9/2012

Esophageal ESD

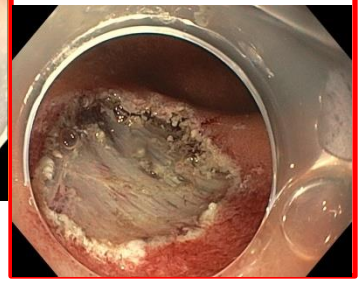
7/2015

Colonic ESD

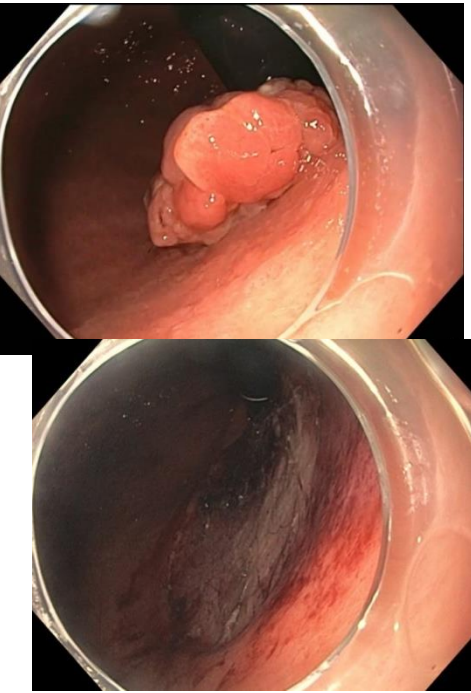


3/2017

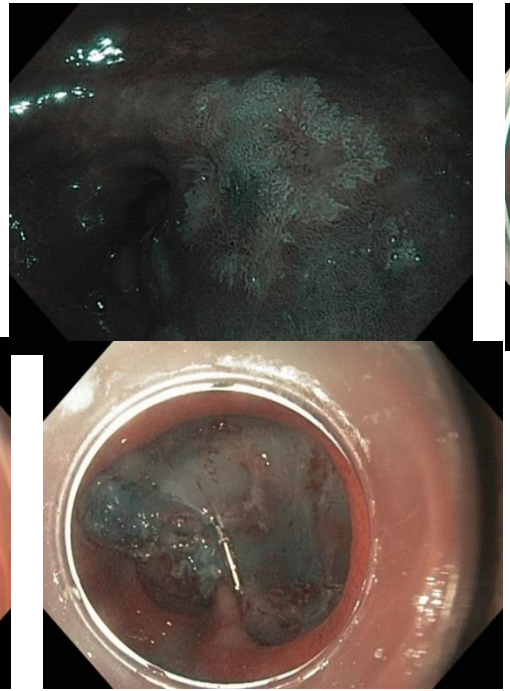
Duodenal ESD



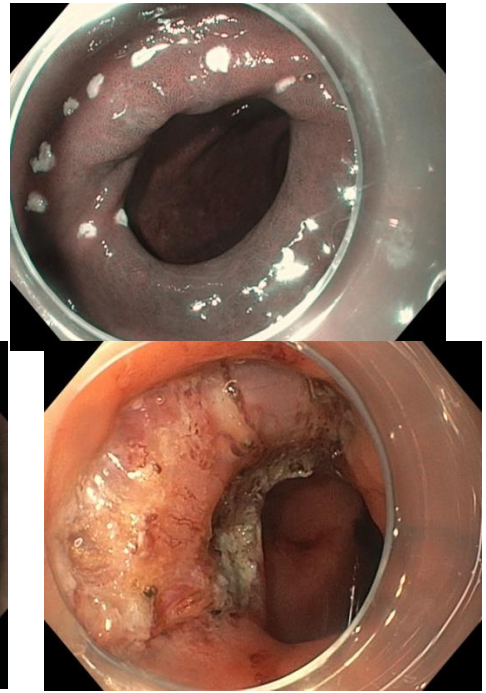
Gastric ESD



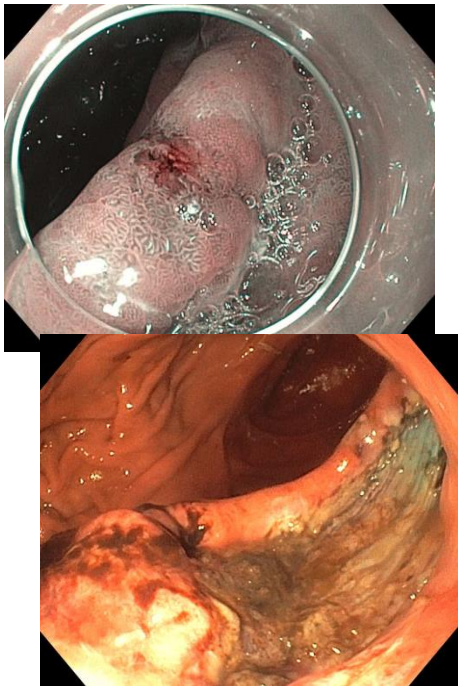
T1b (Sm cancer)
Cardia



HGD
Distal antrum



T1a (Mucosal cancer)
Pylorus



HGD
Prior Billroth II GJ

AGA Institute Clinical Practice Update: Endoscopic Submucosal Dissection in the United States

Peter V. Draganov,[*] Andrew Y. Wang,[‡] Mohamed O. Othman,[§] and Norio Fukami[‖]

Best Practice Advice 2

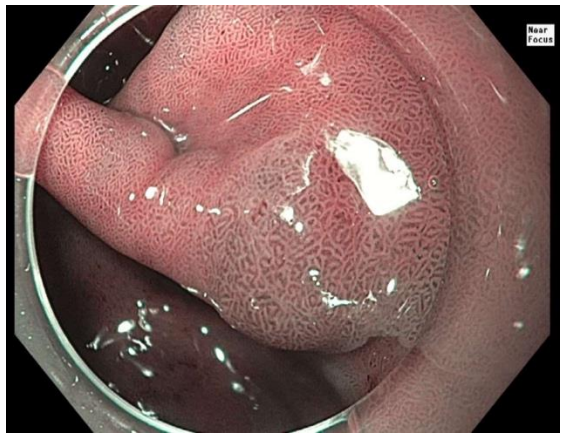
- The safety and feasibility of endoscopic submucosal dissection (ESD) for early gastric cancer is well established.
- The absolute indications for curative endoscopic resection include moderately and well-differentiated, nonulcerated, mucosal lesions that are <2 cm in size.

Best Practice Advice 3

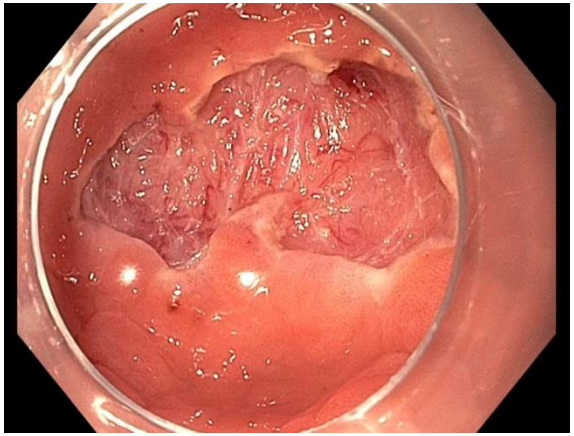
- Other relative (expanded) indications for gastric ESD include moderately and well-differentiated superficial cancers that are >2 cm, lesions <3 cm with ulceration or that contain early submucosal invasion, and poorly differentiated superficial cancers <2 cm in size.
- The risk of lymph node metastasis when ESD is performed for these indications is higher than when it is performed for absolute indications but remains acceptably low.

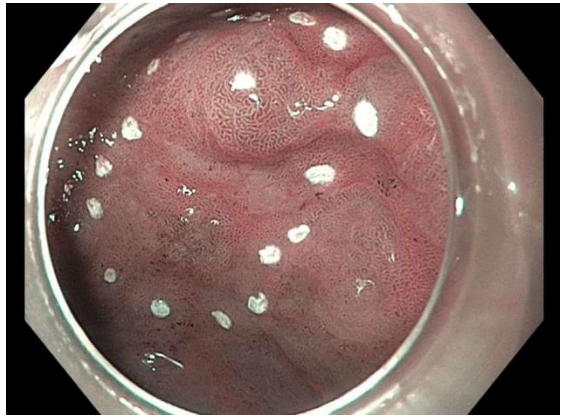
Clin Gastroenterol Hepatol 2019;17

Piecemeal UEMR and ESD

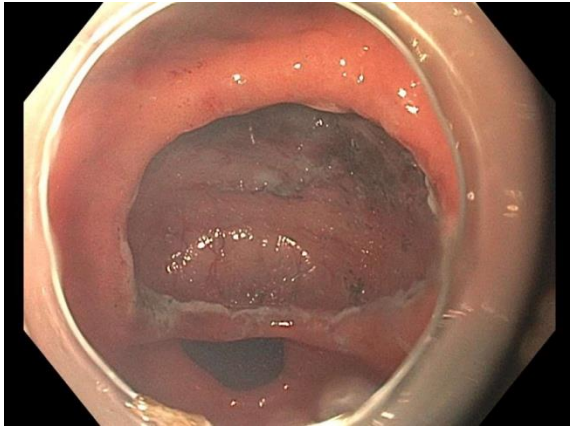


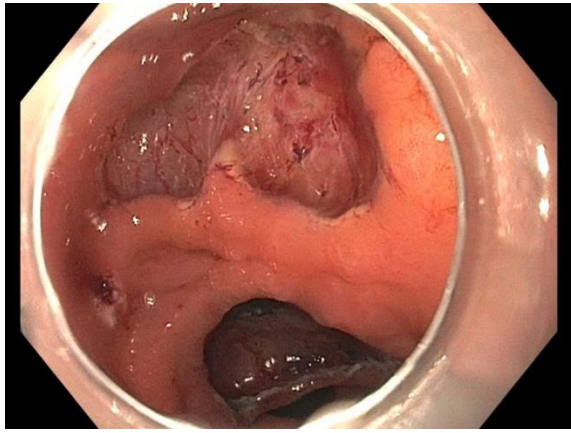
EMR





ESD





Consider ESD over EMR for gastric dysplasia

- **Gastric wall is thick**
  - Excellent place to start ESD
  - Piecemeal EMR in the stomach can be imprecise
- **Dysplasia and EGCs may have indistinct borders**
  - Need marking and wide margins
- EGCs do not follow a progressive colorectal adenoma to carcinoma pathway
  - **En bloc resection advantageous** for HGD lesions that harbor cancer

Shahidi N, Bourke MJ. Gut 2020;69

Gastric cancer recurrence: ESD vs EMR

Study or subgroup	ESD Events	ESD Total	EMR Events	EMR Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Oka	0	195	31	825	9.30%	0.06 [0.00, 1.06]	2006
Oda	6	303	27	411	17.30%	0.29 [0.12, 0.70]	2006
Hoteya	0	304	13	350	9.70%	0.04 [0.00, 0.69]	2007
Nakamoto	0	122	14	80	13.40%	0.02 [0.00, 0.32]	2009
Min	0	243	0	103		Not estimable	2009
Catalano	0	12	0	36		Not estimable	2009
Watanabe	5	219	39	146	35.30%	0.06 [0.02, 0.17]	2010
Hoteya 2010	0	40	2	22	2.40%	0.10 [0.00, 2.21]	2010
Tanabe	1	421	15	359	12.50%	0.05 [0.01, 0.42]	2014
Total (95%CI)		1859		2332	100.00%	0.09 [0.05, 0.17]	
Total events	12		141				

Heterogeneity: $\chi^2 = 8.48$ df = 6 ($P = 0.21$); $I^2 = 29\%$

Test for overall effect: $Z = 8.18$ ($P < 0.00001$)

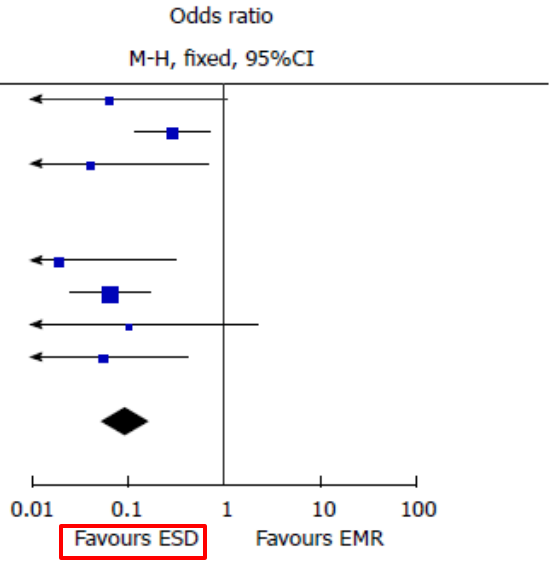
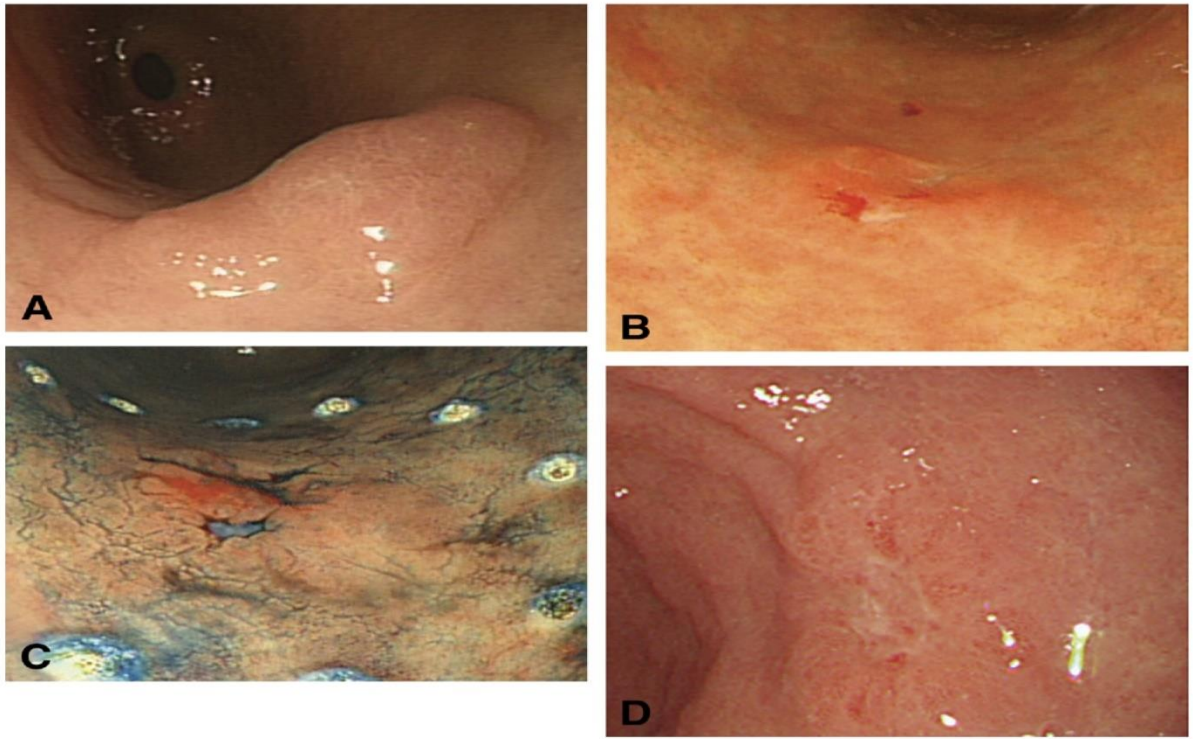


Figure 7 Forest plot of recurrence rate. ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; M-H: Mantel-Haenszel; df: Degrees of freedom.

Facciorusso A et al. World J Gastrointest Endosc 2014;6

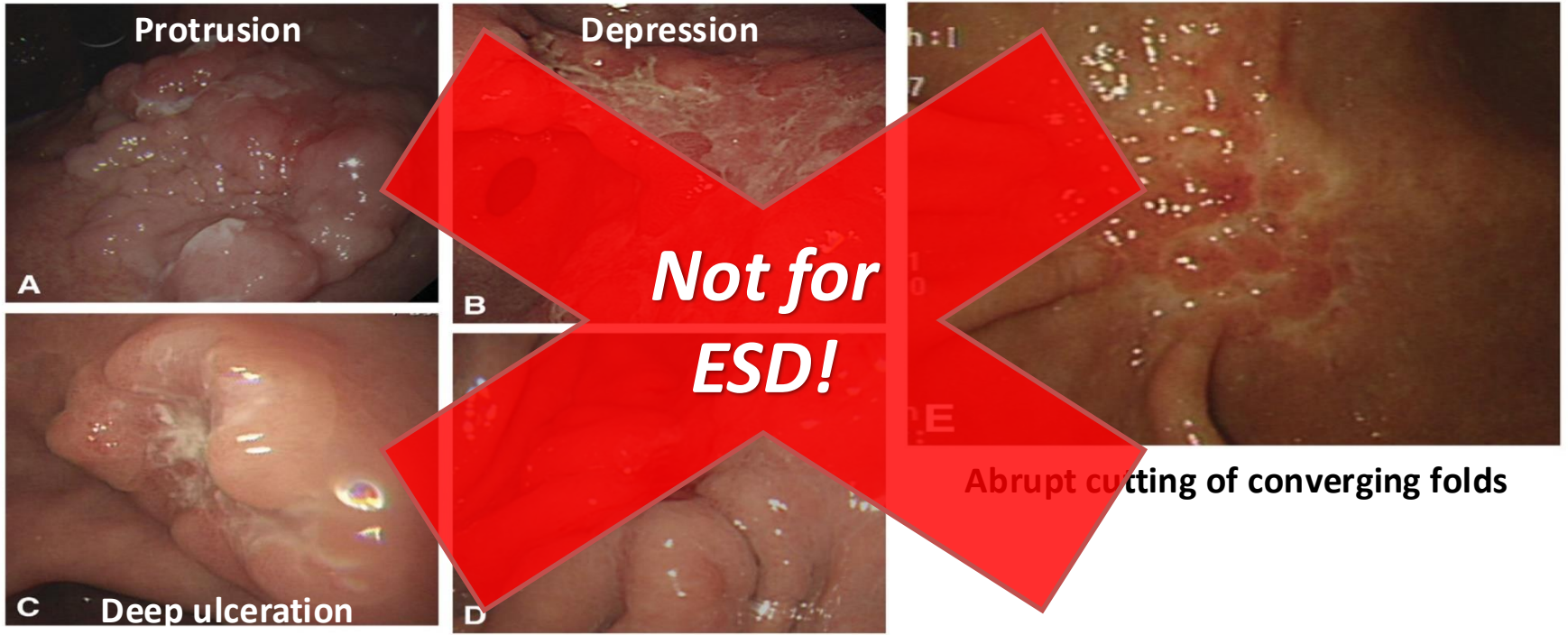
Mucosal gastric cancer



Choi J et al. Gastrointest Endosc 2011;73

Deep submucosal gastric cancer

Irregular/nodular surface



Choi J et al. Gastrointest Endosc 2011;73

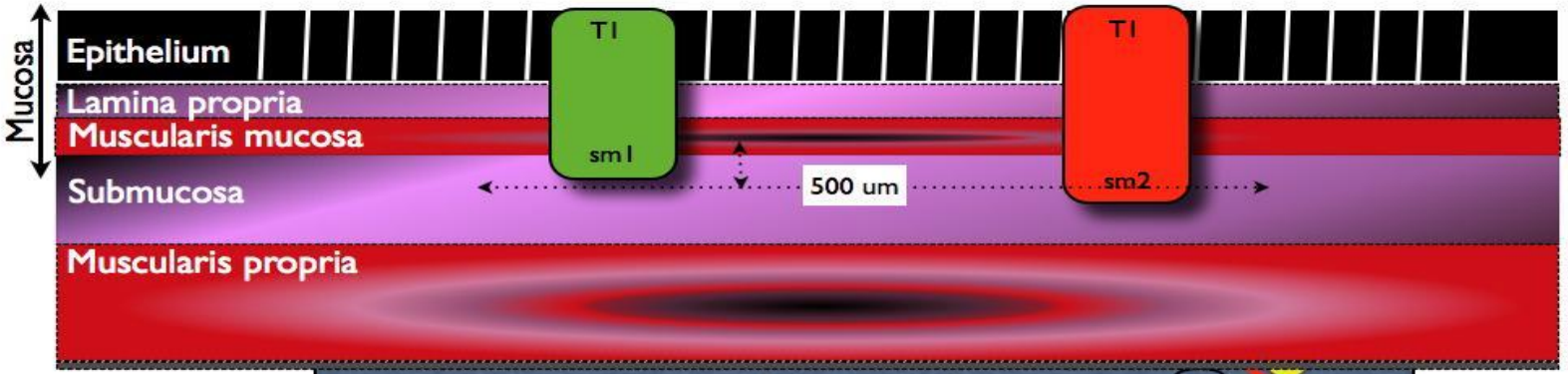
Foundation for ESD for EGC in Japan

Table 1. Early gastric cancer with no risk of lymph node metastasis

Criteria	Incidence	95% CI
Intramucosal cancer Differentiated adenocarcinoma No lymphovascular invasion Irrespective of ulcer findings Tumor less than 3 cm in size	0/1230; 0%	0–0.3%
Intramucosal cancer Differentiated adenocarcinoma No lymphovascular invasion Without ulcer findings Irrespective of tumor size	0/929; 0%	0–0.4%
Undifferentiated intramucosal cancer No lymphovascular invasion Without ulcer findings Tumor less than 2 cm in size	0/141; 0%	0–2.6%
Minute submucosal penetration (SM 1) Differentiated adenocarcinoma No lymphovascular invasion Tumor less than 3 cm in size	0/145; 0%	0–2.5%

Gotoda et al. Gastric Cancer 2007;10

EGC Sm (T1b) invasion and LN mets



Nodal invasion	
< 500 um	> 500 um
15/265	171/826
6%	21%

(<u>All</u> lesion sizes)

Paris Workshop. Gastrointest Endosc 2003;58

Clinical Gastroenterology and Hepatology 2019;17:16–25

CLINICAL PRACTICE UPDATE: EXPERT REVIEW

AGA Institute Clinical Practice Update: Endoscopic Submucosal Dissection in the United States

Peter V. Draganov,* Andrew Y. Wang,‡ Mohamed O. Othman,§ and Norio Fukami‖

Table 2. Suggested Indications for ESD in the United States

Organ	Indications for ESD	References
Stomach	*Absolute indications:* Mucosal adenocarcinoma (and lesions with HGD), intestinal type, G1 or G2 differentiation, size ≤2 cm, no ulceration *Expanded indications:* Adenocarcinoma, intestinal type, G1 or G2 differentiation, any size, without ulceration Adenocarcinoma, intestinal type, G1 or G2 differentiation, sm-invasive (<500 μm) Adenocarcinoma, intestinal type, G1 or G2 differentiation, ≤3 cm, with ulceration Adenocarcinoma, diffuse type, G3 or G4 differentiation, size ≤2 cm, without ulceration	19,72,74

Determination of curative resection following ESD for early gastric cancer based on risk of lymph node metastasis

	T1a				T1b	
	No ulcer		Ulcer		Submucosal invasion	
					<500 μm	≥500 μm
Lesion diameter / Histologic type	≤2 cm	>2 cm	≤3 cm	>3 cm	≤3 cm	any size
Differentiated	<1%	<1%	<1%	3.0%	2.6%	1-9%
Undifferentiated	<1%	2.8%	5.1%		10.6%	

Curative resection (absolute criteria[1]) if no lymphovascular invasion and negative pathological margins

Curative resection (former expanded criteria[2]) if no lymphovascular invasion and negative pathological margins

Non-curative resection (in patients who are surgical candidates)

References: 1) Ono H, Yao K, Fujishiro M, et al. Dig Endosc 2021;33:4-20
2) Ono H, Yao K, Fujishiro M, et al. Dig Endosc 2016;28:3-15

Wang AY et al. Gastroenterology 2021;161

LN met rates may differ by country/populations

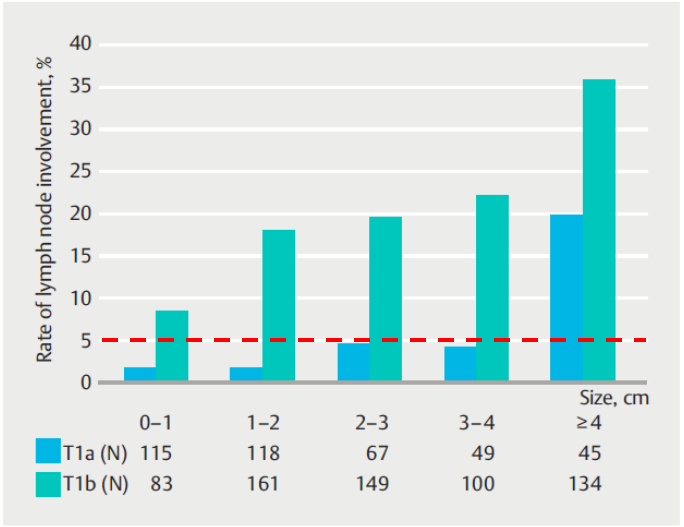
S. Korea, 3,951 pts mGC radical gastrectomy

	LNM rate (%)
Expanded indication	0.4% (11/2678)
Absolute indication	0.3% (3/1065)
Differentiated tumor <1 cm without ulceration	0.5% (2/414)
Differentiated tumor <0.5 cm with ulceration	1.6% (2/123)

TABLE 2. Multivariate analysis of risk factors for lymph node metastasis in mucosal gastric cancer (N = 3951)

Variable	Odds ratio	95% CI	*P* value
Age	0.99	0.97-1.02	.502
Sex	1.14	0.74-1.76	.502
Size of tumor	1.25	1.15-1.37	< .001
Tumor differentiation	7.49	2.91-19.24	< .001
Lauren classification[11]			.911
Intestinal		Reference	
Diffuse	1.01	0.45-2.28	.985
Mixed	1.24	0.40-3.85	.714
Microscopic ulceration	4.07	2.21-7.51	< .001
Lymphatic invasion	20.65	10.62-40.12	< .001
Perineural invasion	23.45	1.96-280.43	.013

USA SEER database

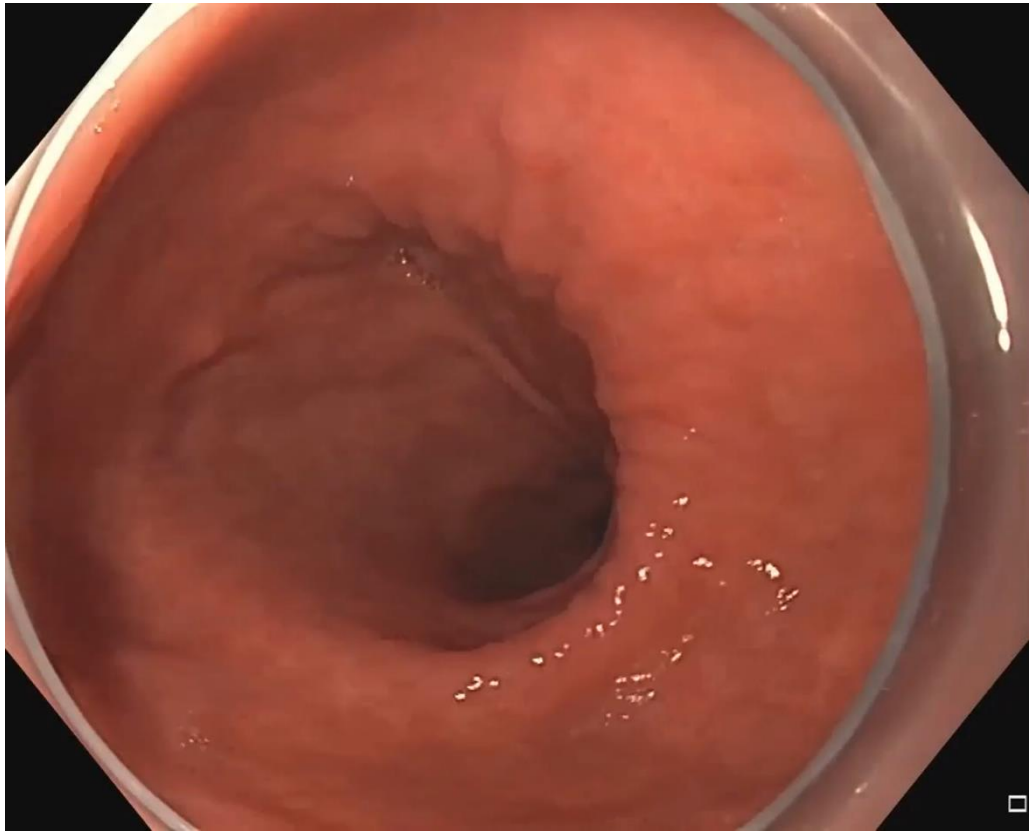


▶ **Fig. 2** Rate of nodal metastasis in early[1] low grade[2] gastric adenocarcinoma by tumor stage and size. [1] Early-stage was defined as Tis, T1a, and T1b tumors, according to the American Joint Committee on Cancer staging manual [16]. [2] Low grade was defined as well differentiated or moderately well differentiated.

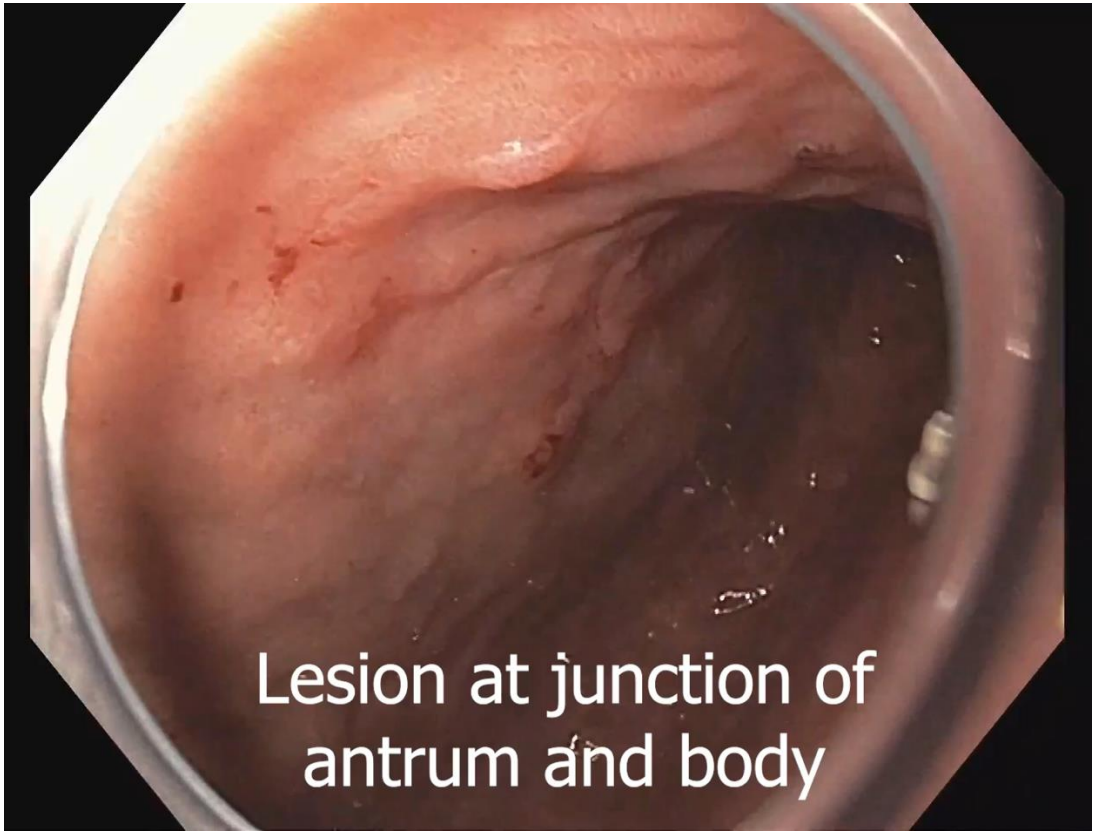
Pokala SK et al. Endoscopy 2018; 50

Choi KK et al. GIE 2016;83

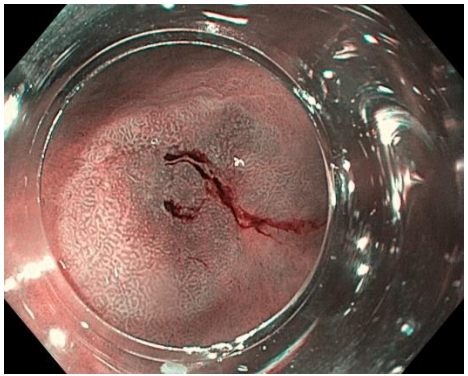
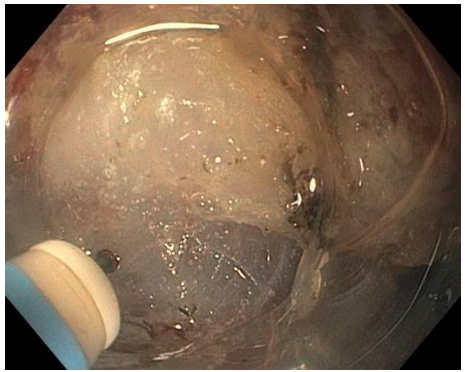
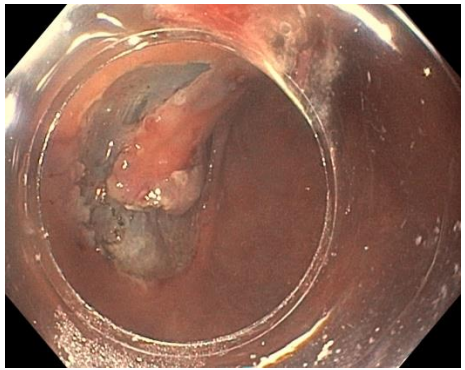
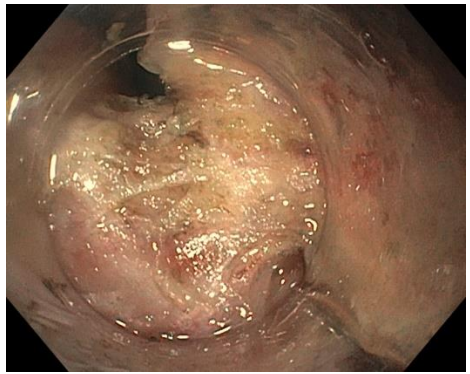
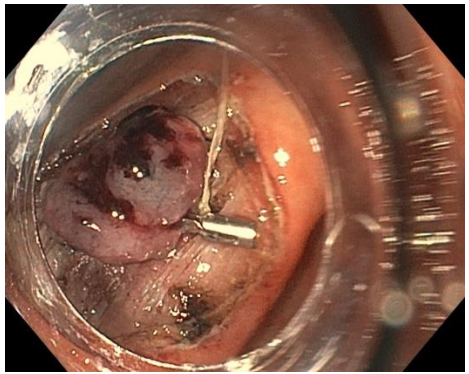
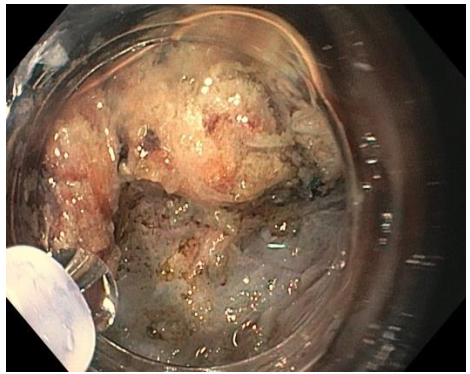
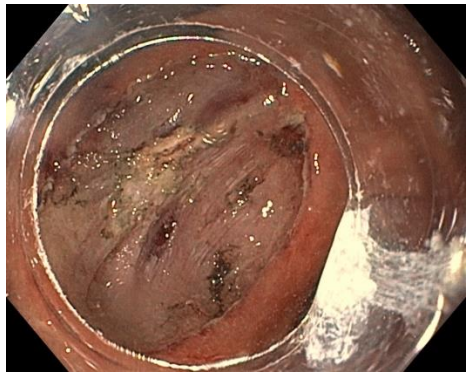
Typical outpatient ESD in the U.S.



Gastric ESD, F2 fibrosis, traction-wire device



T1a EGC s/p EMR followed by cryoablation with HGD recurrence → THEN referred for ESD!

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CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on Surveillance After Pathologically Curative Endoscopic Submucosal Dissection of Early Gastrointestinal Neoplasia in the United States: Commentary

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Suggested surveillance

Table 3. Suggested Surveillance for Gastric Dysplasia and Adenocarcinoma Removed by Endoscopic Submucosal Dissection That Met Histopathologic Criteria for Curative Resection (Absolute and Expanded Japanese Criteria Used)

Variable	First follow-up endoscopy, *mo*	Second follow-up endoscopy, *mo*	Subsequent endoscopic examinations	Need for EUS surveillance	Need for radiographic surveillance	Estimated risk of LN metastasis (affected by size, ulceration), %
LGD	6–12	12	Annually	No	No	0
HGD	6–12	6-12	Annually	No	No	0
T1a EGC[a]	6	6	Annually	No[b]	No[b]	<1–5.1[a]
T1b, Sm1 EGC (<500 μm submucosal invasion)[a]	3–6	3–6	Annually	Yes, CT chest and abdomen and/or EUS every 6–12 mo for 3–5 y		2.6–10.6[a]

[a]Refer to Supplementary Figure 1 for additional details regarding what factors constitute a curative resection for T1a and T1b EGCs, which correlate with the estimated risk of LN metastasis.
[b]CT scans and/or EUS can be considered for T1a EGCs.

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Efficacy of Endoscopic Submucosal Dissection for Superficial Gastric Neoplasia in a Large Cohort in North America

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Gastric ESD in North America

Table 3. Resection Outcomes

	Total	EGC[a,b]	Adenoma/low-grade dysplasia	High-grade dysplasia	Neuroendocrine tumor
Outcomes					
En bloc resection	320/347 (92.2)	130/139 (93.5)	84/90 (93.3)	73/82 (89.0)	33/36 (91.7)
R0 resection	384/347 (81.8)	104/139 (74.8)	83/90 (92.2)	71/82 (86.6)	27/36 (75)
Additional surgery at index ESD	28/334 (8.9)	22/126 (17.6)[c]	0/90 (0)	2/82 (2.4)	4/36 (11)
Follow-up outcomes					
Residual/local recurrence	8/203 (3.9)	5/70 (7.1)	1/59 (1.7)	2/57 (3.5)	0/17 (0)
Metachronous gastric lesions	14/203 (6.9)	6/70 (8.6)	2/59 (3.38)	5/57 (8.9)	1/17 (5.9)
Metastasis during follow-up	1/203 (0.49)	0/70 (0)	1/59 (1.7)	0/56 (0)	0/17 (0)
Death					
Gastric cancer	1/277 (0.4)	0/111 (0)	1/75 (1.3)	0/64 (0)	0/27 (0)
Nongastric cancer	9/277 (3.2)	8/111 (7.2)	1/75 (1.3)	0/64 (0)	0/27 (0)

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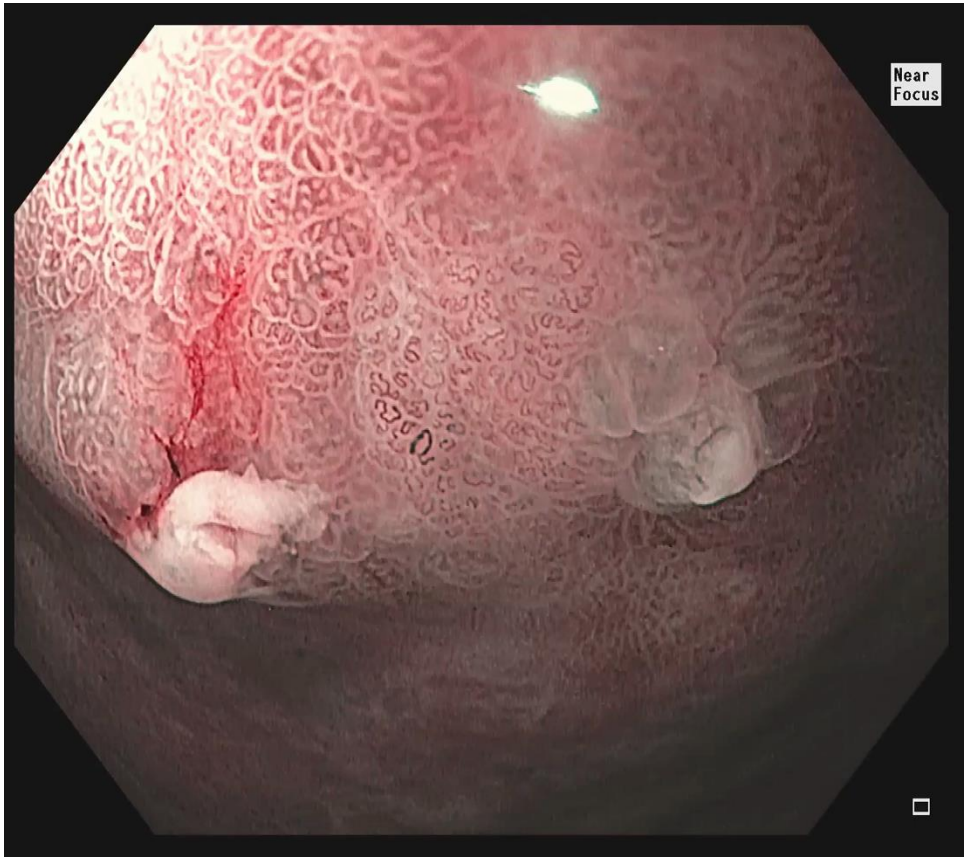
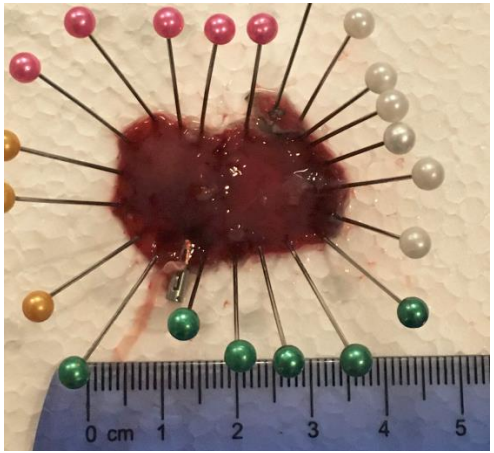
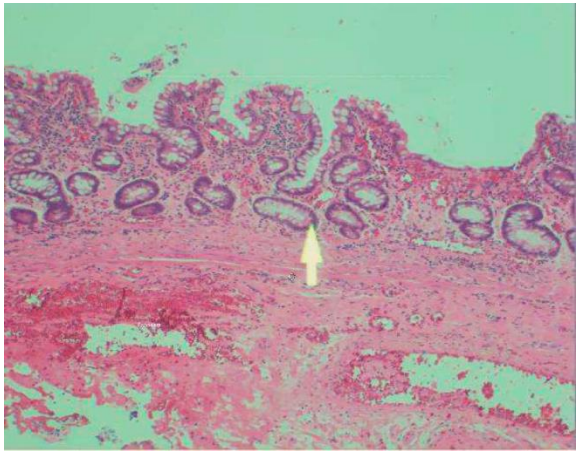
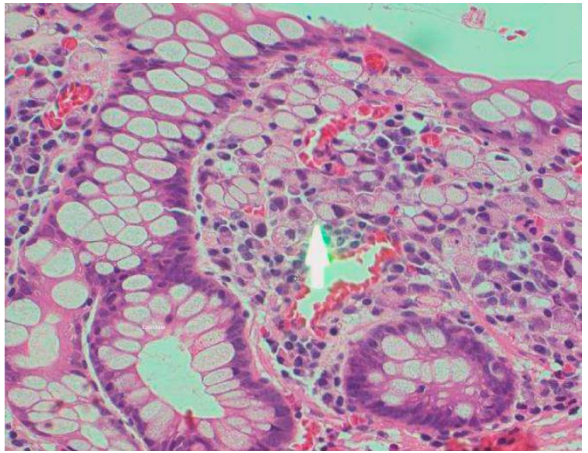
Referral: ImCA, signet type, ant/lesser



ESD Path: T1a, signet-ring type (G3), LVI (-), R0

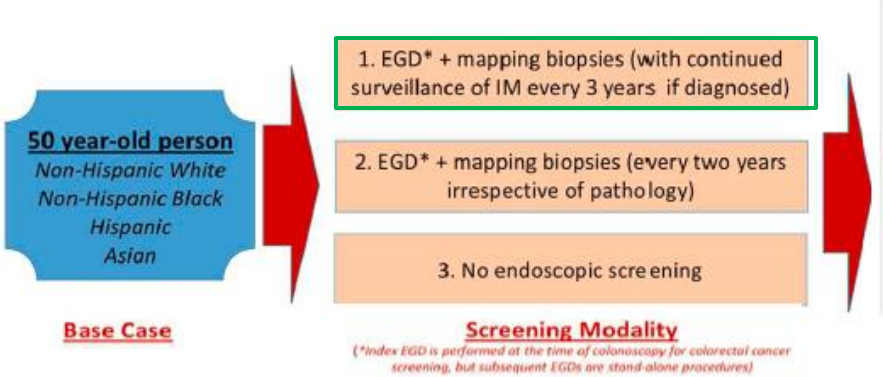


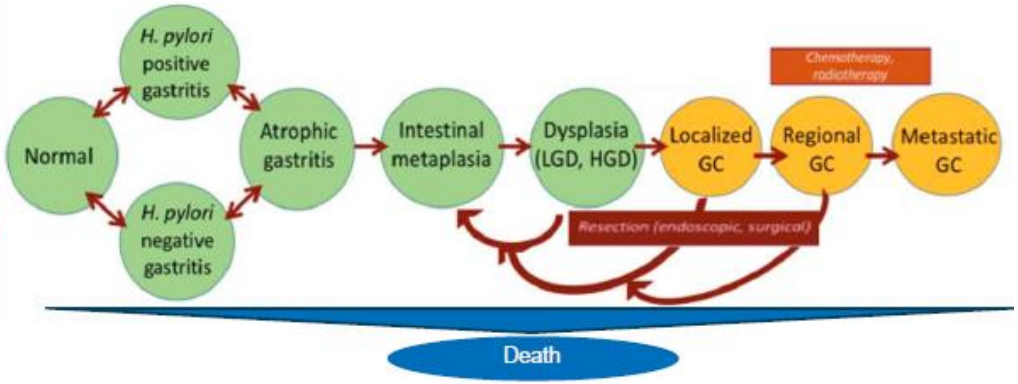




Next steps?

Markov model simulating gastric cancer screening (index EGD at time of 1st screening CY)





Gastric cancer screening with EGD + mapping biopsies (+/- surveillance) might be cost effective for Asians, Hispanics, and non-Hispanic Blacks compared to a no screening strategy

Asian:	$ 71,451 / QALY
Hispanic:	$ 76,070 / QALY
Non-Hispanic Black:	$ 80,278 / QALY
Non-Hispanic White:	$ 122,428 / QALY

Saumoy M…Shah SC, Gastroenterology 2018;155

Takeaways

- Endoscopic resection benefits patients with gastric dysplasia and EGC with low risk of LN mets, as they can avoid gastric surgery
- ESD is generally preferred over EMR for gastric dysplasia/EGC
- Gastric ESD likely has an important role in diagnosing and curing selected T1b EGCs, though the NCCN has not firmly adopted this stance yet
- The stomach is a good place to begin ESD, particularly for dysplasia that is not cancer
- Screening in individuals/populations at increased risk for GC may be cost effective when endoscopic surveillance and endoscopic resection are included alongside surgery and other treatments

Thank you!