ANNUAL

Advances and Innovations in Endoscopic Oncology and Multidisciplinary Gastrointestinal Cancer Care

The Role of the Endoscopist in Esophageal Organ Preservation

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Disclosures

- Consultant for Steris Endoscopy

The presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

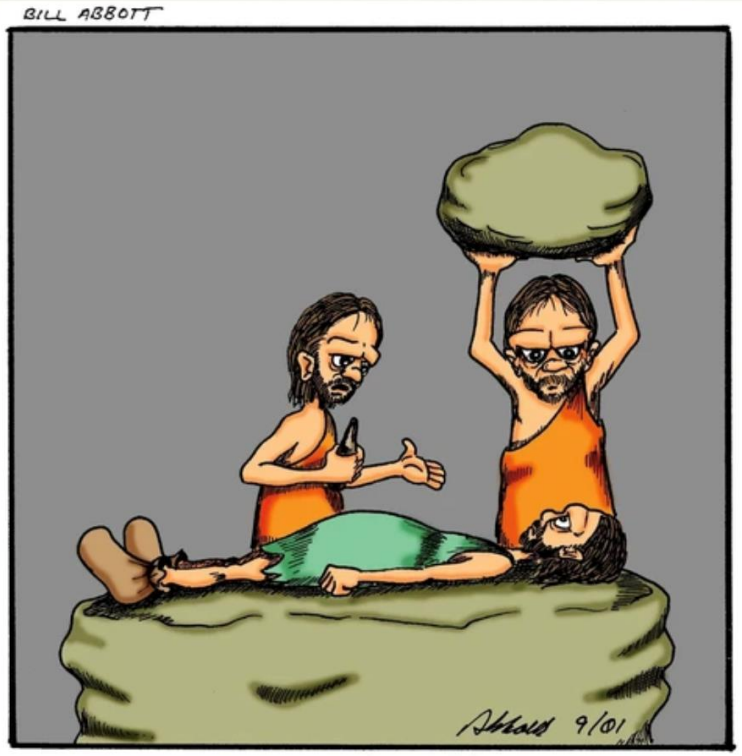
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- The appropriate impact of patient age on decision-making with respect to esophageal treatment.
- Recognition that esophageal adenocarcinoma does not arise solely in the obese white male population and must be considered in the differential diagnosis for patients presenting with dysphagia and other related symptoms.

Evolution of the Endoscopist's Role

- In the earliest days of upper endoscopy, we could just take a look and if something looked like a cancer
- Soon thereafter, we could take a biopsy and hopefully make a diagnosis
- But the concept of endotherapy for organ-threatening esophageal disease would take decades to mature



"...and this is Ralph, your anesthesiologist."

Case in Point: Barrett's Esophagus

- As the only known precursor to esophageal adenocarcinoma, Barrett's has been targeted for endoscopic surveillance in order to identify evolving neoplasia
- Initially, this was performed simply to diagnose early cancer or, with time, high grade dysplasia, when a suitable surgical candidate would be referred for an esophagectomy
    - Early endotherapy was inconsistent in effect, carried significant risk of stricture formation, perforation or undertreated disease, and in some cases was poorly tolerated by patients
- Only with the advent of newer therapeutic options (i.e. PDT, RFA, cryotherapy) did guidelines move toward inclusion of endotherapy and, ultimately, notation of a preference for an endoscopic to a surgical approach for HGD or intramucosal cancer

Where Are We Today?

- Endoscopists can play a critical (and expanded) role in management of esophageal disease that in the past would have been sent for esophagectomy
- Involvement spans the lifecycle of a malignancy:
  - Initial diagnosis and staging—is organ preservation even possible?
  - Delineation of lesion location prior to initiation of therapy
  - Delivery of therapy, as part of a single technique or a multi-modal approach
    - Can the lesion be removed completely with an endoscopic technique?
  - Evaluation of therapeutic outcomes/restaging
  - Post-treatment surveillance
  - Palliation when a cure is not possible
- Endoscopy can play a similar role for benign conditions as well

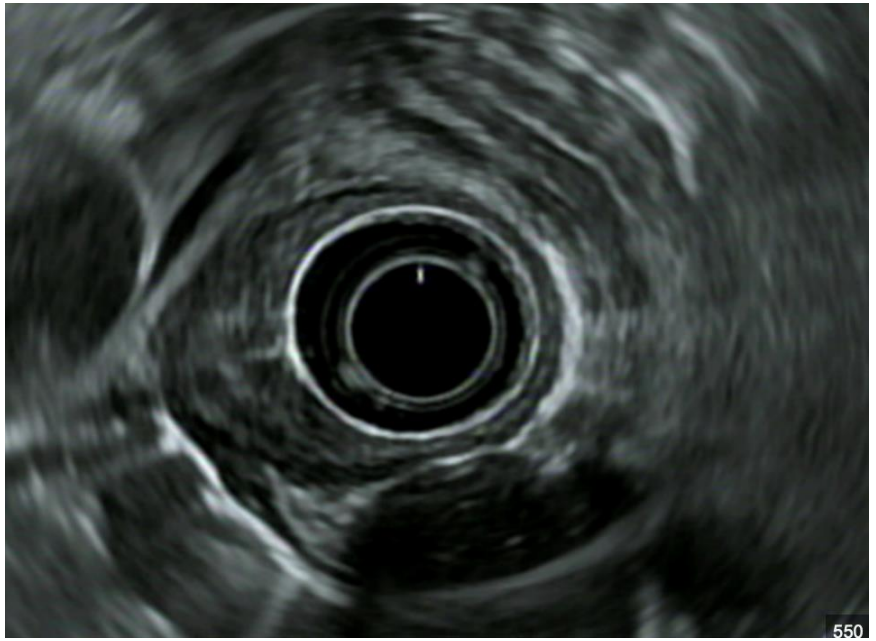
Making a Tissue Diagnosis

- Endoscopic tissue sampling allows for direct tissue acquisition without having to pass a tool through another organ, leading to potential tumor seeding
- A variety of tissue sampling tools are available for use:
  - Forceps (different sizes)
  - Brushes
  - Endoscopic resection kits
  - Fine needle aspiration or biopsy

- Is the diagnosis compatible with organ sparing interventions?

Initial Staging of the Neoplastic Lesion

- Endoscopy, either through more extensive resection or advanced imaging, can identify depth of injury and likelihood of metastatic spread beyond the esophageal wall
    - The presence of a positive deep margin on a resection specimen suggests a greater possibility of lymphatic spread
    - Endosonography (EUS) can provide a T stage for the lesion that will help determine whether what treatment modalities are appropriate



Delineation of Lesional Extent

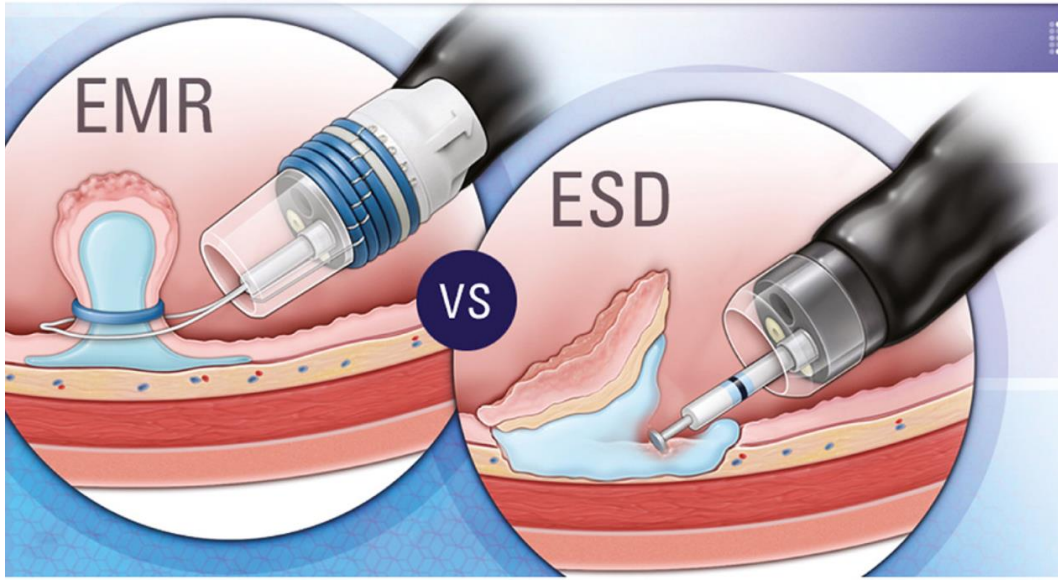
- The size and location of the lesion can be determined relative to aerodigestive tract landmarks through conventional endoscopy, and with respect to adjacent anatomic structures endosonographically
- Accurate determination of size and anatomic positioning can facilitate selection of optimal treatment(s), increasing the likelihood of a successful outcome that may preclude the need for esophagectomy
- Endoscopically placed markers, such as fiducials, tattoos and clips may be used to focus therapies in order to maximize results and minimize side effects

How About… Cut it Out?!

- Neoplastic lesions involving only the mucosa and submucosa may be amenable to endoscopic resection as a means of providing both diagnostic and therapeutic value, while preserving the esophagus
- Endoscopic Mucosal Resection (EMR) actually reaches the superficial submucosa (SM1) and is most effective when used on smaller lesions (<1.5 cm diameter)
- Endoscopic Submucosal Dissection (ESD) works better on larger lesions and those with known invasion into the submucosa

EMR vs. ESD: Recent Meta-Analysis

EMR versus ESD for Barrett's Neoplasia and Esophageal Adenocarcinoma

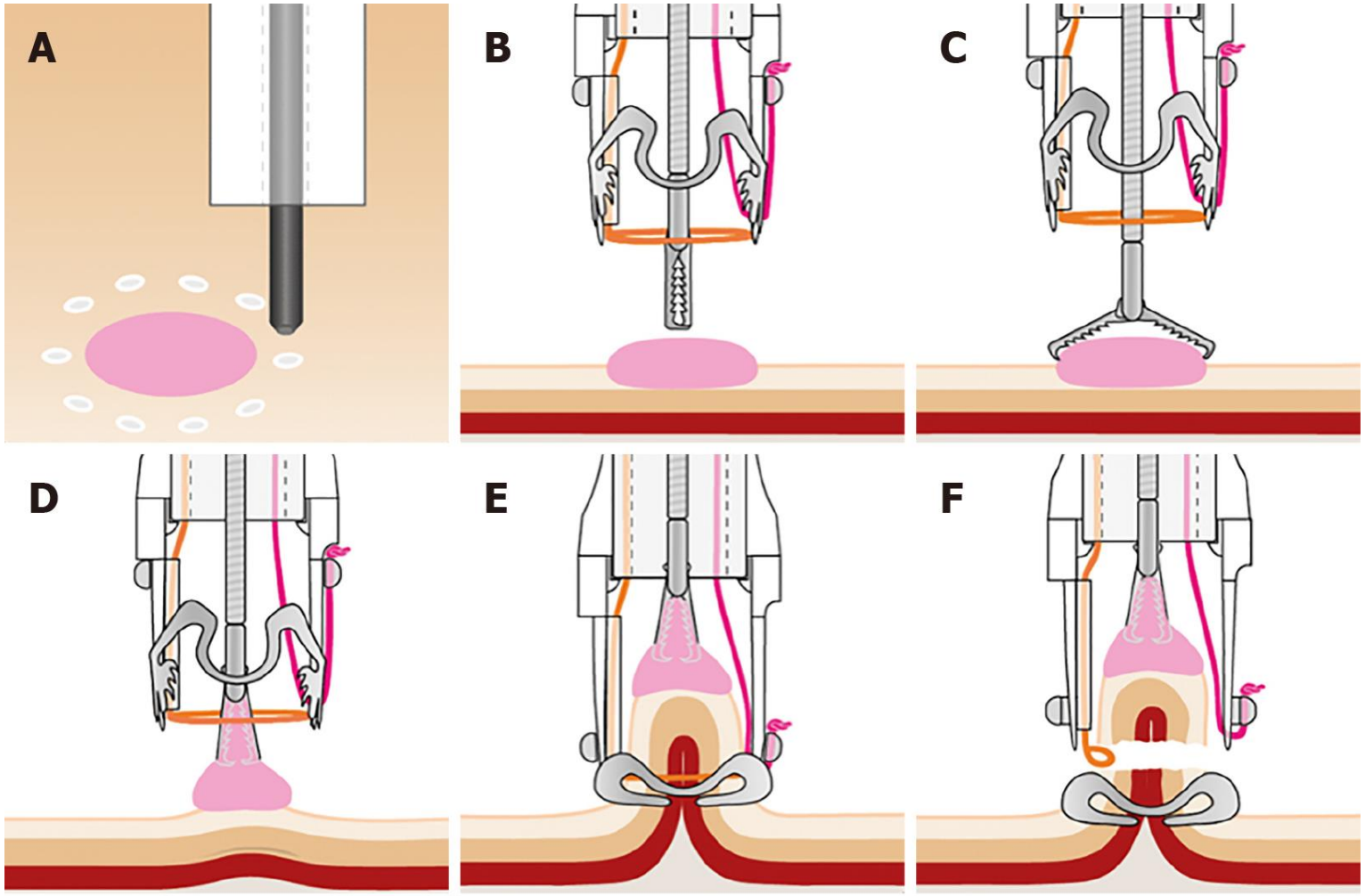


Systematic Review and Meta-Analysis | 11 studies, 2209 total patients

	Outcomes	Odds ratio of ESD to EMR (95% CI)	p-value
Primary	En Bloc Resection	31.53 (10.02 - 99.19)	<0.01
	R0 Resection	5.73 (2.32 - 14.16)	<0.01
	Curative Resection	3.49 (0.86 - 14.14)	0.080
	Complete Remission of Dysplasia	0.92 (0.37 - 2.26)	0.86
	Local Recurrence	0.35 (0.11 - 1.04)	0.058
Secondary	Bleeding	0.67 (0.30 - 1.50)	0.33
	Perforation	1.82 (0.50 - 6.67)	0.36
	Postoperative Stricture	1.01 (0.58 - 1.75)	0.98

Fujiyoshi Y et al. Gastrointestinal Endoscopy 2024. 100(5):P817-828.

Endoscopic Full Thickness Resection (EFTR)



Mun EJ and Wagh MS. *World J Gastroenterol* 2023; 29(25): 4009-4020.

Submucosal Tunnel Endoscopic Resection (STER)

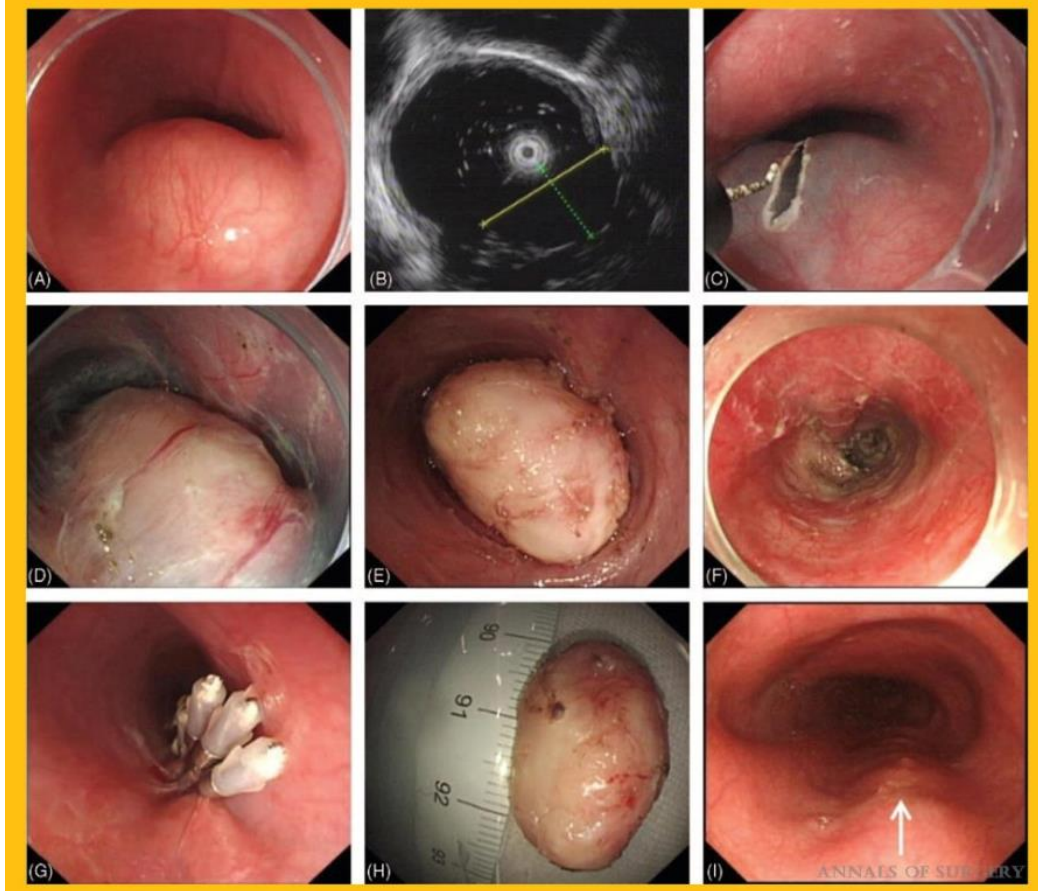


FIGURE 1. Submucosal tunneling endoscopic resection (STER) for an esophageal submucosal tumor.

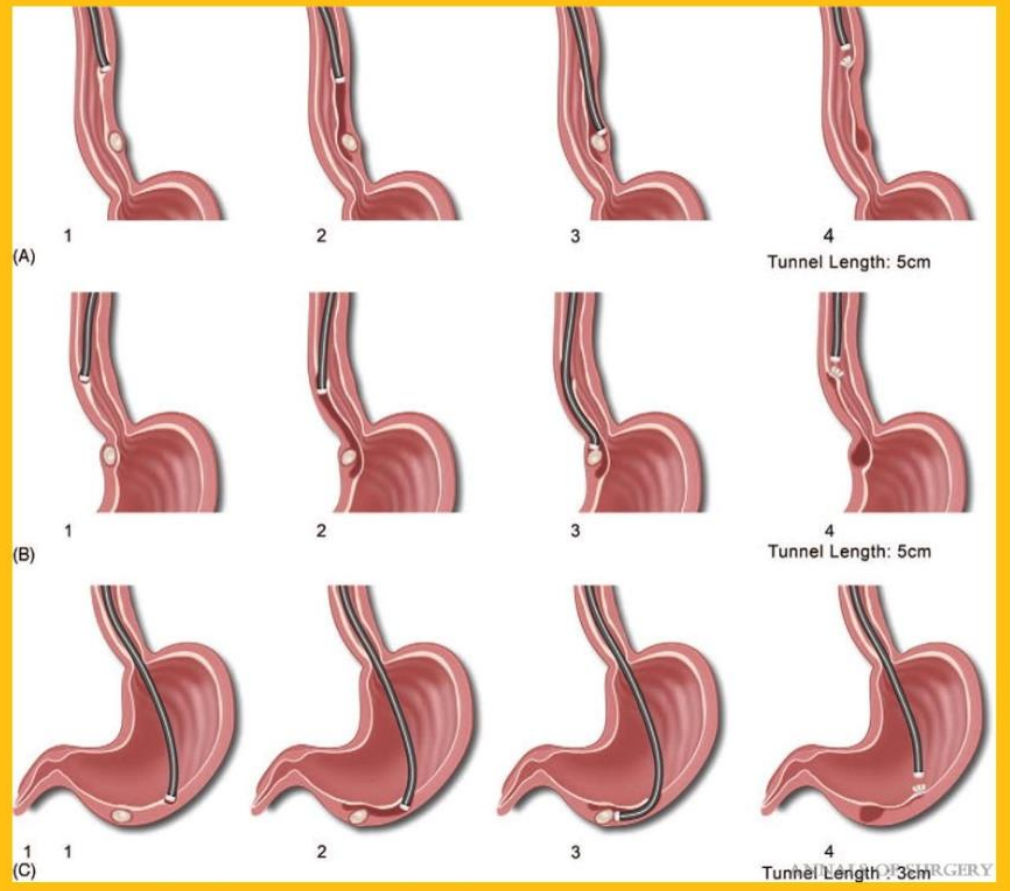


FIGURE 2. Schematic STER procedures for submucosal tumors in 3 typical upper gastrointestinal locations.

Chen et al. Ann Surg. Feb 2017.

Field Ablation of Esophageal Neoplasia

- Multiple devices exist that can treat a focal or more diffuse abnormality, with proper selection based on diagnosis, lesion size and depth, concerns for adverse effects, and patient preferences

- Esophageal Treatments include:
  - Liquid nitrogen spray cryotherapy (LNC)
  - Nitrous oxide cryoballoon focal ablation system (CbFAS)
  - Photodynamic therapy (PDT)
  - Hybrid argon plasma coagulation (H-APC)
  - Pulsed electrical field (PEF)
  - Water vapor
  - Radiofrequency ablation (RFA)—limited to flat lesions (HGD, ?IMCA)

Liquid Nitrogen Spray Cryotherapy (LNC)

- Extreme Cold (-196ºC) Liquid Nitrogen contacts tissue prior to phase shift
- Rapid, efficient energy transfer (~25 Watts) at low pressure (<3 psi at treatment site)
- Treatment delivered via spray catheter placed through the scope (even ultra-thin)
- No direct tissue contact required for delivery of treatment
- Treats over and through stents, mesh and other appliances; no risk of fire
- *Does not require a flat surface to treat*
- Can treat in retroflexion
- No debridement required for treated tissue
- FDA indication: ablation of benign or malignant tissue
- Included in NCCN guidelines

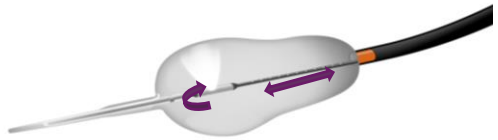
Systematic Review & Meta-Analysis: Efficacy of LNC in Early Esophageal CA

Author	Year	Publication Type	Design	No. of centers	N	Age (yrs)	Male (%)	# T1a	# T1b	Histology	BE segment length (cm)	Median Treatment Sessions	Prior Treatment (%)[a]	Concurrent EMR (%)[b]	CE-C	CE-D	CE-IM	Median Follow Up (mo)
Alshelleh et al.	2020	abstract	retrospective	1	13	62.3	84.6%	13	0	IMC	3.08 +/- 0.47	3	0%	100%	/	92%	85%	17.3
Coyle et al.	2020	manuscript	retrospective	1	2	67.5	50.0%	0	2	EAC	NA	NA	0%	0%	100%	/	/	18
Eluri et al.	2019	abstract	prospective	15	27	68	77.0%	27	0	IMC	NA	3	35%	25%	/	78%	67%	21
Ramay et al.	2018	abstract	prospective	15	39	69.7	82.1%	39	0	IMC	5.2 +/- 6.2	2	85%	10.2%	69%	56%	41%	20
Trindade et al.	2018	manuscript	retrospective	3	27	68	89.0%	27	0	IMC	4.5 +/- 1.5	3	0%	100%	89%	82%	70%	24
Suchniak-Mussari et al.	2017	manuscript	retrospective	1	8	66	64.0%	8	0	IMC	NA	NA	25%	100%	75%	75%	50%	27.6
Tsai et al.	2017	manuscript	retrospective	11	62	76	81.4%	38	24	EAC	NA	3	97%	17%	T1-66% T1a-76% T1b-46%	/	/	18.4
Chan et al.	2016	abstract	prospective	1	4	67	65.0%	4	0	IMC	7.4 +/- 0.8	2	100%	0%	100%	50%	0%	NA
Johnston et al.	2016	abstract	retrospective	1	11	75.6	81.8%	11	0	IMC	4.82	2	0%	100%	/	100%	91%	36.9
Sengupta et al.	2015	manuscript	retrospective	1	2	68	80.0%	2	0	IMC	7	3	100%	0%	/	100%	100%	7.5
Ghorbani et al.	2013	abstract	prospective	>1	25	76	75.0%	6	19	90% EAC 10% SCC	NA	3.5	69%	0%	T1-68% T1a-83% T1b-63%	/	/	NA
Greenwald et al.	2010[c]	manuscript	retrospective	10	43	76	79.0%	25	18	95% EAC	NA	3.5	67%	23%	T1-75% T1a-92% T1b-50%	/	/	28
Dumot et al.	2008	abstract	prospective	1	8	71	71.0%	8	0	IMC	5 +/- 3	4	25%	0	75%	50%	38%	18

Xie, M & Smith, MS. Oral Presentation DDW 2021.

Nitrous Oxide Cryoballoon (CbFAS)

- N_2O (-89ºC) released into a self-sizing compliant polyurethane balloon (~30 mm)
- Self-contained Low pressure system (~3.5-4.5 psi)
- Catheter requires therapeutic endoscope (3.7 mm) working channel, or is placed alongside the endoscope (“sidecar”)
- Balloon must contact mucosal surface to generate cryogenic heat transfer
- Multiple balloon configurations to match anatomy
- Treatment depth controlled by duration
- Diffuser rotates and moves axially to direct treatment
- Stricture rate 12-19% in published studies
- FDA Indication: cryosurgical tool for use, including dysplastic Barrett’s esophagus



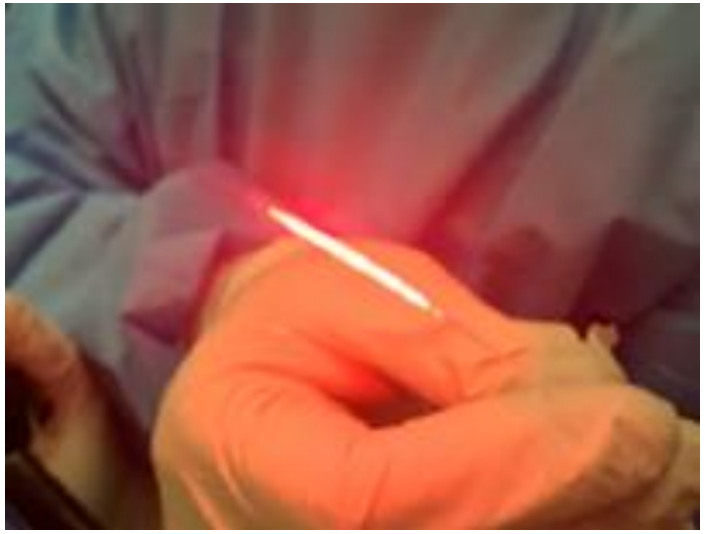
CbFAS for Esophageal Squamous Neoplasia

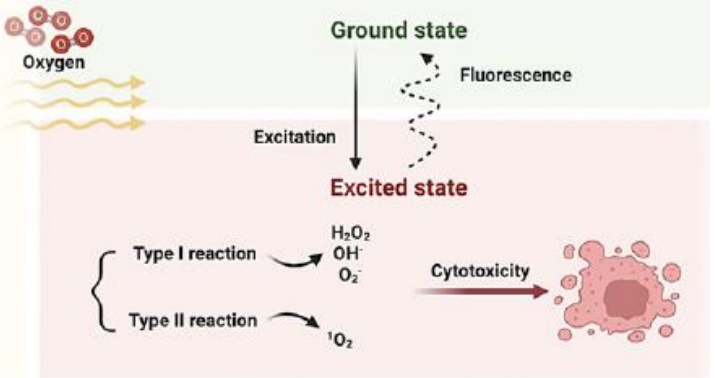
- Design
  - Patients with esophageal squamous cell neoplasia (ESCN)
  - Treatment naïve or recurrent, previously treated
  - Retrospective and prospective, multi-center, non-randomized
- Patients
  - 10 Patients
  - 7 HGIN, 3 LGIN
- Efficacy
  - 100% response on treated areas at 3 months
- Safety
  - No SAEs
  - 2 patients with circumferential tx developed strictures
- Tolerability
  - No pain requiring narcotics lasting > 24 hours.

Canto MI, Abrams JA, Kunzli HT, et al. Gastrointest Endosc. 2018 Feb;87(2):574-581.

Photodynamic Therapy (PDT)

- Uses a combination of photosensitizers, specific wavelength of light and reactive oxygen species to target neoplasia
- Photosensitizing agent collects preferentially in neoplastic tissue, creating more selective/targeted treatment
- Device is non-thermal
- Tumor ablation depths: 4-6 mm (adjacent) and 10 mm (interstitial)
- Ok for use when stents and PPM are present
- Included in NCCN Guidelines

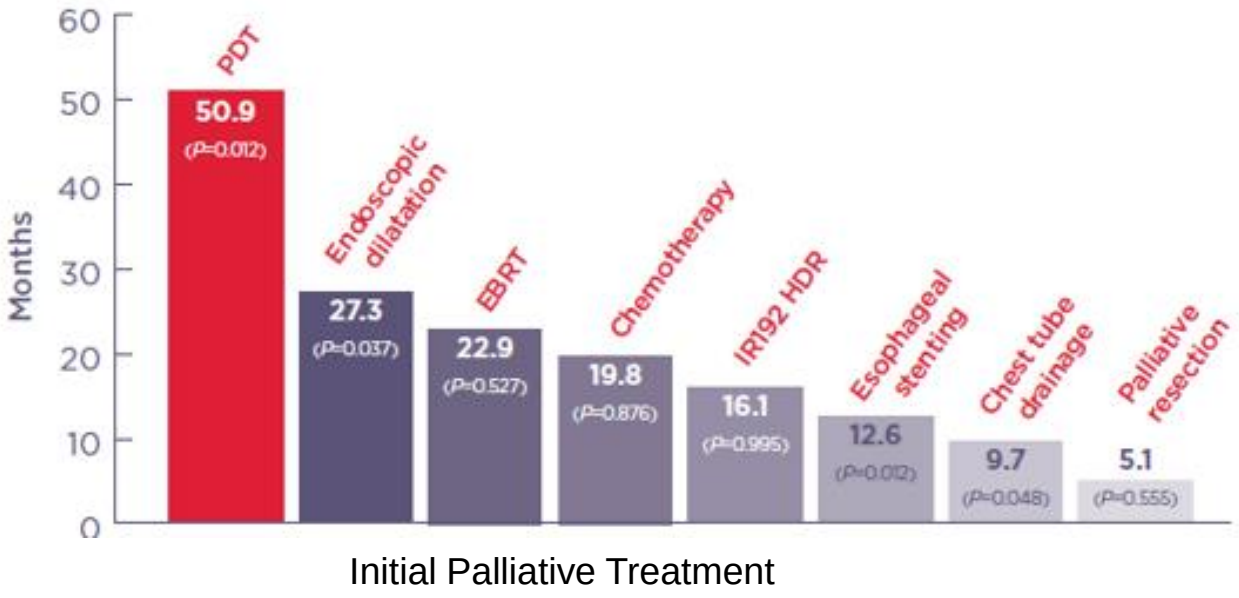




Juarranz et al, 2008; Clin Transl Oncol

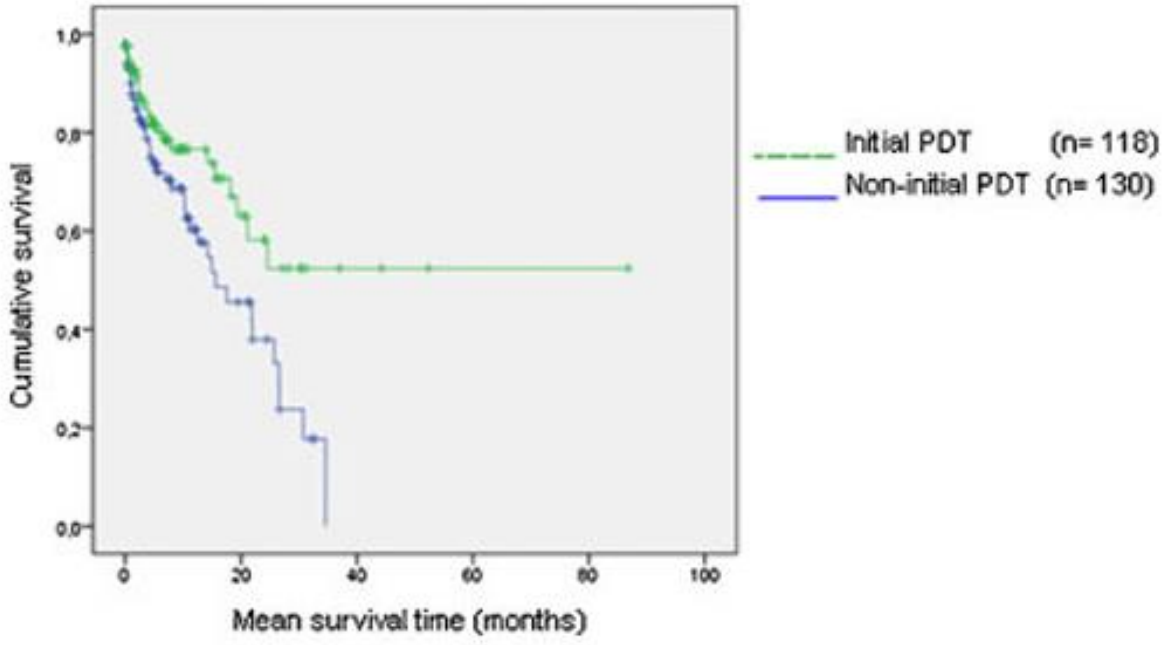
PDT For Esophageal Cancer

Median Survival by treatment modality



The long median survival time of 50.9 months recorded in patients following initial PDT was biased as it was used as first therapeutic step only in the absence of gross tumor infiltration into the mediastinum, the great vessels or the trachea-bronchial tree.

Median Survival



Median survival in 118 patients in whom PDT was used as first treatment was 50.9 months Compared to 17.3 months for those in whom other options were used as the initial modality (P=0.012)

Lindenmann, et al. 2012, Lasers Surg. Med.

Is Multi-Modality Therapy the Future?

Endoscopic resection after downstaging of oesophageal carcinoma by neoadjuvant chemoimmunotherapy: – a new multimodal concept?

Mingyan Cai [1], Baohui Song [1], Dongli He [2], Chen Xu [3], Rongkui Luo [3], Yang Qian [4], Sikei Kam [1], Xucheng Huo [1], Jian Wang [5], Michael Vieth [6], Yunshi Zhong [1]

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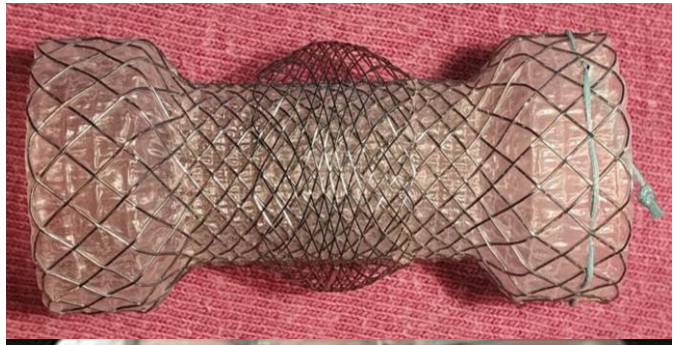
https://doi.org/10.1136/gutjnl-2024-333337

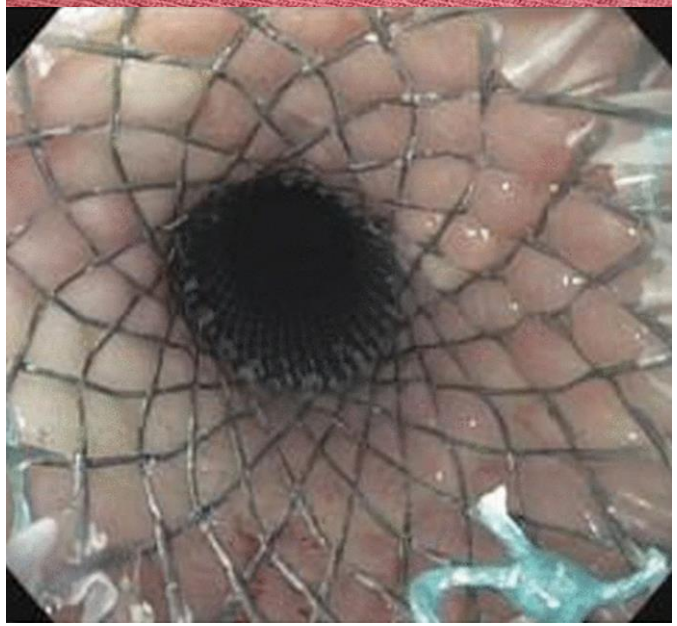
Endoscopic Symptom Palliation

- Maintaining a patent esophageal lumen can provide many benefits to the patient:
  - Continued enteral nutrition
  - Ability to take oral medications
  - Relief of being able to swallow and handle secretions
- Multiple tools to reduce tumor bulk and preserve patency
  - Endoscopic stenting
  - Cryotherapy
  - PDT
  - Laser (less frequently used now)

Endoscopic Stenting

- Multiple stent types and configurations to match the patient's need
  - Variable length and diameter
  - Uncovered vs. partially covered vs. fully covered
- Displace the tumor to maintain patency, but do not relieve the tumor burden
- Once deployed, they can be painful due to radial expansion forces, and sometimes need to be removed right away
- Occasionally (less common with malignancy), migration can occur





LNC Palliates Malignant Dysphagia: A Systematic Review and Meta-Analysis

- Studies utilizing LNSC for dysphagia palliation in patients with advanced esophageal cancer
- 230 patients (86.5% EAC/13.5% SCC), 773 LNSCT sessions from 5 studies
- Dysphagia improved or did not deteriorate in **81.63%** of patients
- Significant improvement reported by **54.70%**
- Pooled major AE rate 3.6% (1.1% bleeding, 1.4% perforation, 2.6% delayed stricture)
- ***Conclusion:* Endoscopic liquid nitrogen spray cryotherapy can effectively and safely treat dysphagia in esophageal cancer. It could be considered as an option for dysphagia palliation in centers with expertise and equipment.**

Puli S. et. al., Endoscopic Spray Cryotherapy for Dysphagia Palliation in Esophageal Cancer: A Systematic Review and Meta-Analysis. GIE Journal 2024. https://doi.org/10.1016/j.gie.2024.04.2192

LNC for Refractory Benign Strictures

- 33 patients from 5 Centers
- Anastomotic (15), Peptic (6), XRT-induced (6) most common
- Others: post-endotherapy (3), caustic (1), congenital (1), idiopathic (1)
- Dosimetry: 20-30 seconds + Balloon dilation X 1-2 sessions
- Measuring dilation efficacy: reviewed number of dilations in the 6 months before and after cryodilation

Results:

Mean Dilations per Patient: Pre-Cryodilation	Mean Dilations per Patient: Post-Cryodilation	p Value
3.8 Dilations	.7 Dilations	p < 0.001

Mean Lumen Size: Pre CryoDilation	Mean Lumen Size: Post CryoDilation
8.4mm	12.4 mm

Safety:

- No recorded bleeding or perforation

Conclusion: ***For benign upper gastrointestinal strictures, cryodilation appears to be an effective and safe technique to decrease the frequency of repeated endoscopic interventions. Further prospective studies are needed to further evaluate the safety and efficacy of this novel technique.***

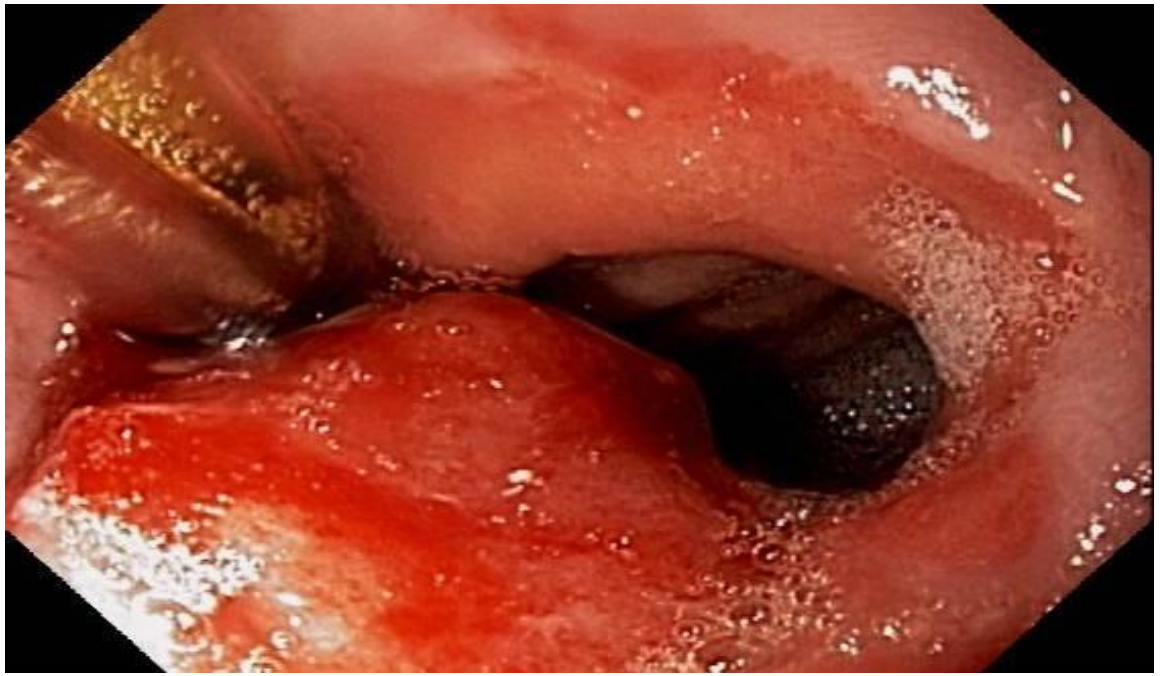
Canto MI, Abrams JA, Kunzli HT, et al. Gastrointest Endosc. 2018 Feb;87(2):574-581.

Case Study: LNC for EAC Palliation

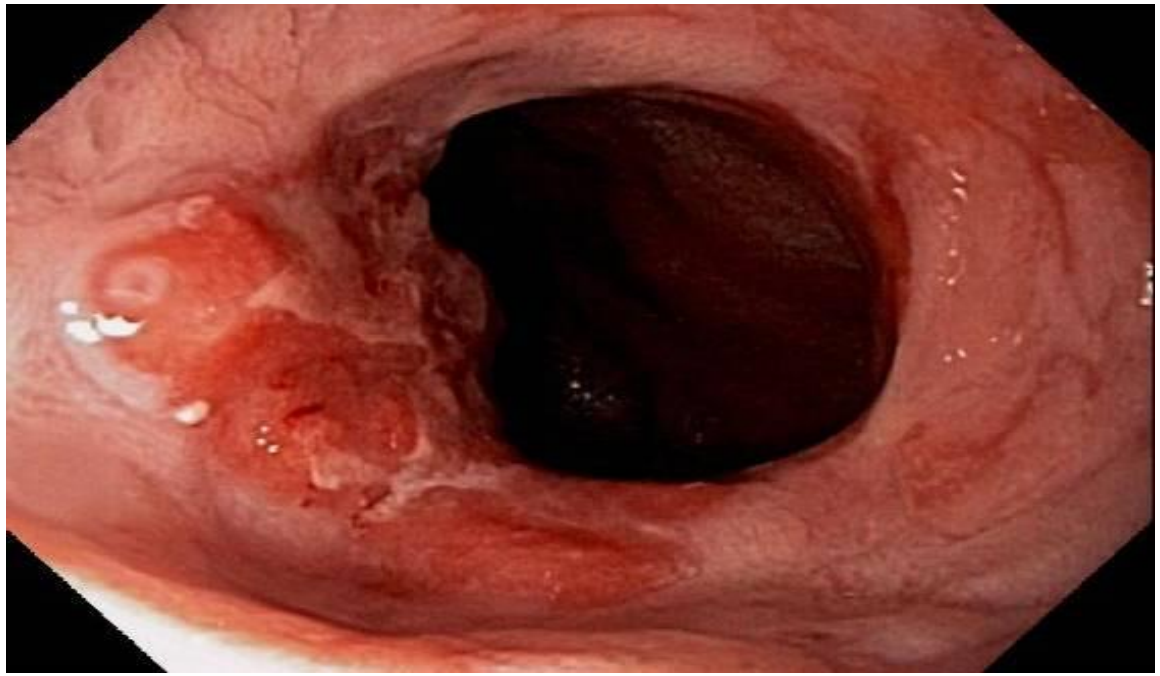
- 80 year old Caucasian male
- First diagnosed with Barrett's/Esophageal AdenoCA 2004
- Ivor-Lewis esophagectomy
- Negative surveillance until nodule seen at anastomosis during endoscopy February 2009
- Given chemotherapy/XRT with resolution of lesion
- Subsequent 1 cm nodule noted on surveillance EGD September 2010 (pathology: invasive adenocarcinoma)
- Reluctant to undergo repeat chemo or radiation, so he was referred by his local GI for possible palliative ablation

Marked Tumor Response After 3 Months

Initial Endoscopy



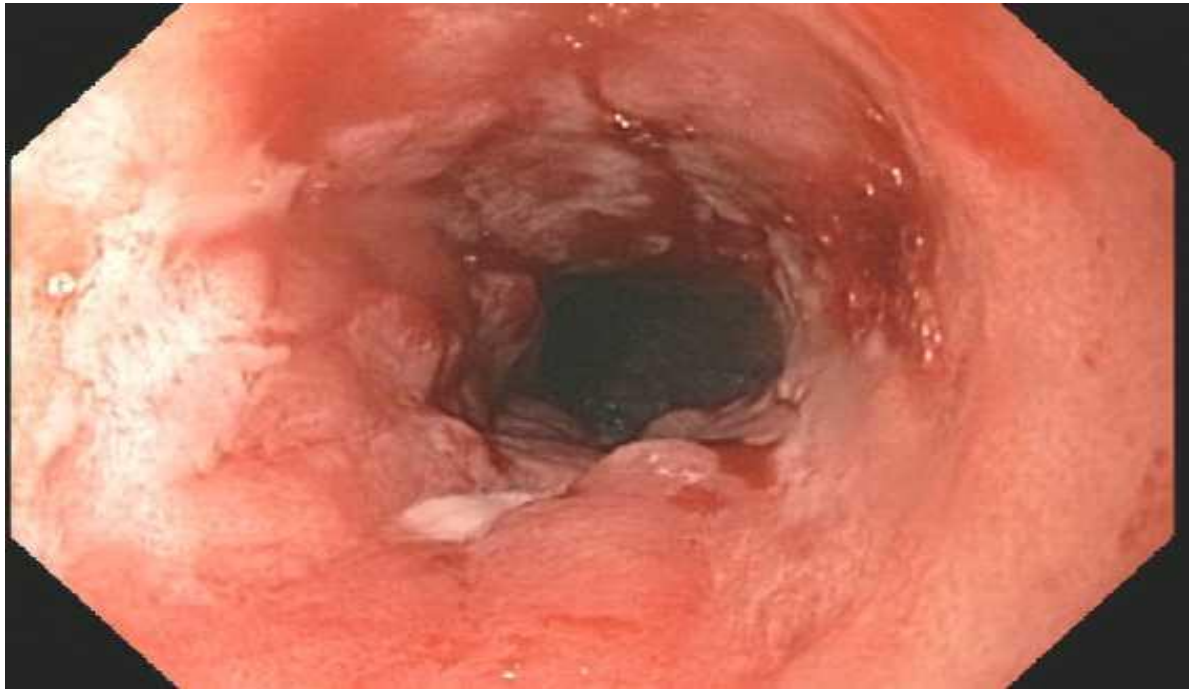
After 3 Treatments (1 per month)



Long-Term Success of Palliative LNC

12 months

24 months



- A total of 27 sessions of were performed over the course of 32 months
- No post-procedure dysphagia or chest pain; energy “back to normal” 4-5 days after ablations
- PET-CT scans at 6 and 18 months showed no change or metastasis
- After skipping some treatments, PET-CT scan at 30 months showed adrenal/subcutaneous metastases, and subsequent endoscopy showed tumor ingrowth requiring stent placement

Putting It All Together

- The endoscopist plays a major role in esophageal organ preservation for both malignant and benign disease, from initial characterization of the lesion through endoluminal treatment and perhaps cure
- Newer endoscopic techniques for resection and field ablation open the door to successful eradication of disease without esophagectomy
- Especially with esophageal neoplasia being found in younger patients, as well as those who do not fit the traditional demographic of an esophageal cancer patient, it is important to collaborate with the patient and other members of the care team to arrive at an optimal treatment plan

Thank you!