Role of Photodynamic Therapy, Brachytherapy and Cryotherapy in Esophageal Cancer

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PHOTODYNAMIC THERAPY

PDT: Indications

- **Esophageal Cancer**
  - Palliation of patients with completely obstructing esophageal cancer
- **High-Grade Dysplasia in Barrett's Esophagus**
  - Ablation of high-grade dysplasia (HGD) in Barrett's esophagus (BE) patients who do not undergo esophagectomy

PDT: Applications in Esophageal Cancer

- Treatment of esophageal stent ingrowth or overgrowth
- Anatomical locations which are not accessible with contact therapies
- Effective in multiple cell types
- Local treatment for fairly rapid control of symptoms
  - Improve dysphagia
  - Control bleeding
- Bridge to eventual definitive or palliative systemic therapy
- Resume adequate oral intake, improve nutritional status
- Avoid feeding tube

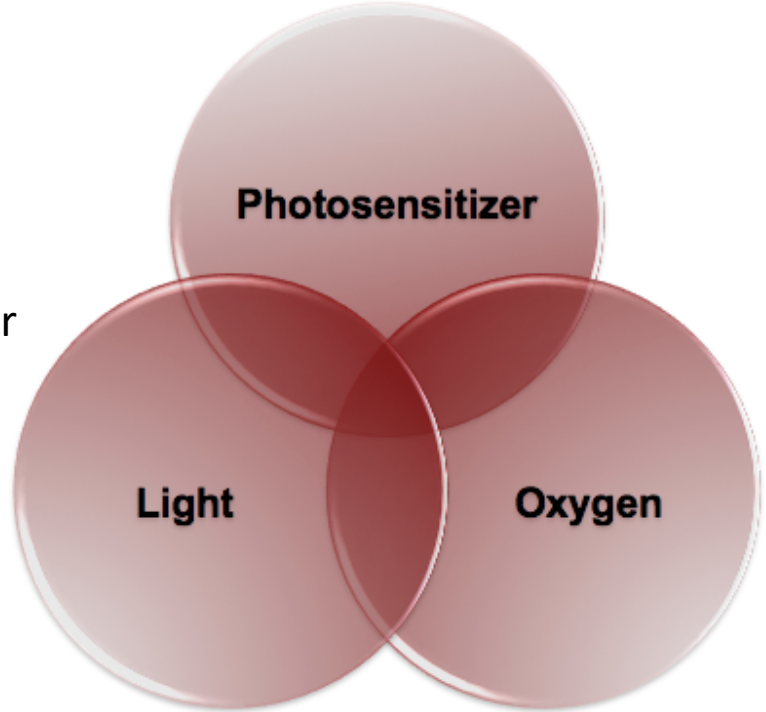
PDT: Contraindications

- PHOTOFRIN® is contraindicated in patients with porphyria
- Photodynamic therapy is contraindicated in patients with an existing tracheoesophageal or bronchoesophageal fistula
- Photodynamic therapy is contraindicated in patients with tumors eroding into a major blood vessel
- Photodynamic therapy is not suitable for patients with esophageal or gastric varices, or patients with esophageal ulcers >1 cm in diameter

PDT: Basic Initial Components

Photodynamic Therapy

- is a treatment that uses a drug, called a photosensitizing agent (Photofrin), and a particular type of light. When the photosensitizing agent is exposed to a specific waveform of light, they produce a form of oxygen (singlet oxygen) that destroys cells.



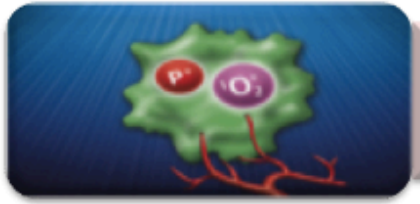
PDT: Photofrin Dosage & Administration

- 75 mg of porfimer sodium per vial
- Sterile dark red to reddish brown freeze – dried cake or powder
- Dosed at 2 mg/kg of body weight

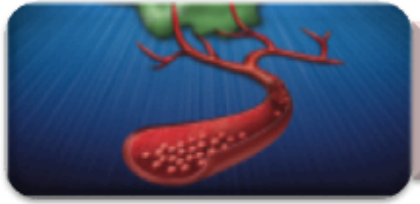
- Reconstituted with 31.8 mL of either 5% Dextrose or 0.9% Sodium Chloride
- Administered as a single slow intravenous injection over 3-5 minutes
- Injection is typically administered in an outpatient setting

PDT: Mechanism of Action

- Red light activates Photofrin to an excited state



- Energy transfer causes reactive singlet oxygen and tumor cell death



- Excited Photofrin causes vasoconstriction which leads to vascular occlusion and additional tumor cell death

- End result is lysis and ischemic necrosis of cancer cells

PDT: Depth of Penetration

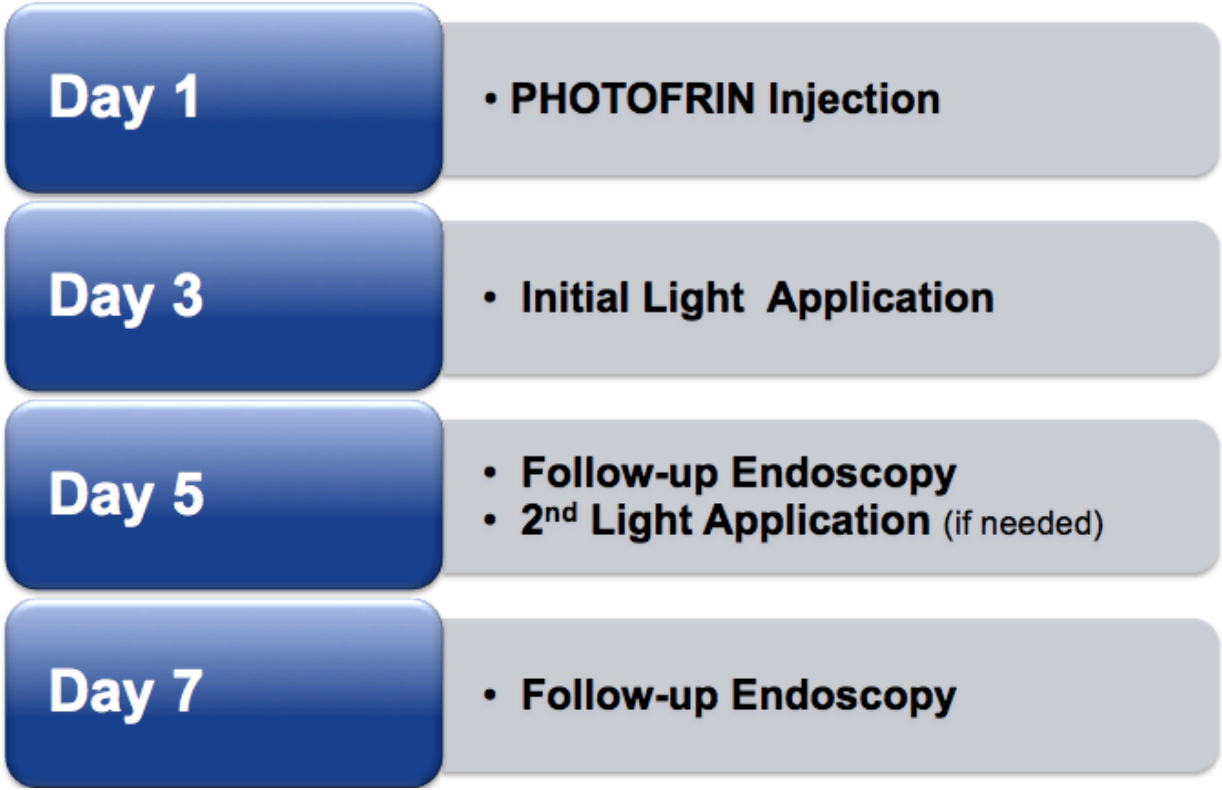
Table 1 Estimated depth of damage for various methods of endoscopic mucosal ablation

Method of ablation	Approximate depth of ablation (mm)	Author/ref
Argon laser (514 nm)	0.3	Weston 2003[50]
KTP laser (532 nm)	0.4	Dix 1996[35]
Diode laser (805 nm)	1.3	Dix 1996[35]
NdYAG laser (1064 nm)	4–6	Dix 1996[35]
APC (30–90 W)	1–3	Barham 1996,[31] Franchimont 2003[32]
MPEC 15–20 W	1.7–4.8	Sampliner 2003[30]
ALA PDT	2	Tan 1999,[41] Gossner 1998[40]
Exogenous PDT	4–6	Barr 1990,[39] Heier 1995[38]
Cryotherapy	1–4	Johnston 2003[29]

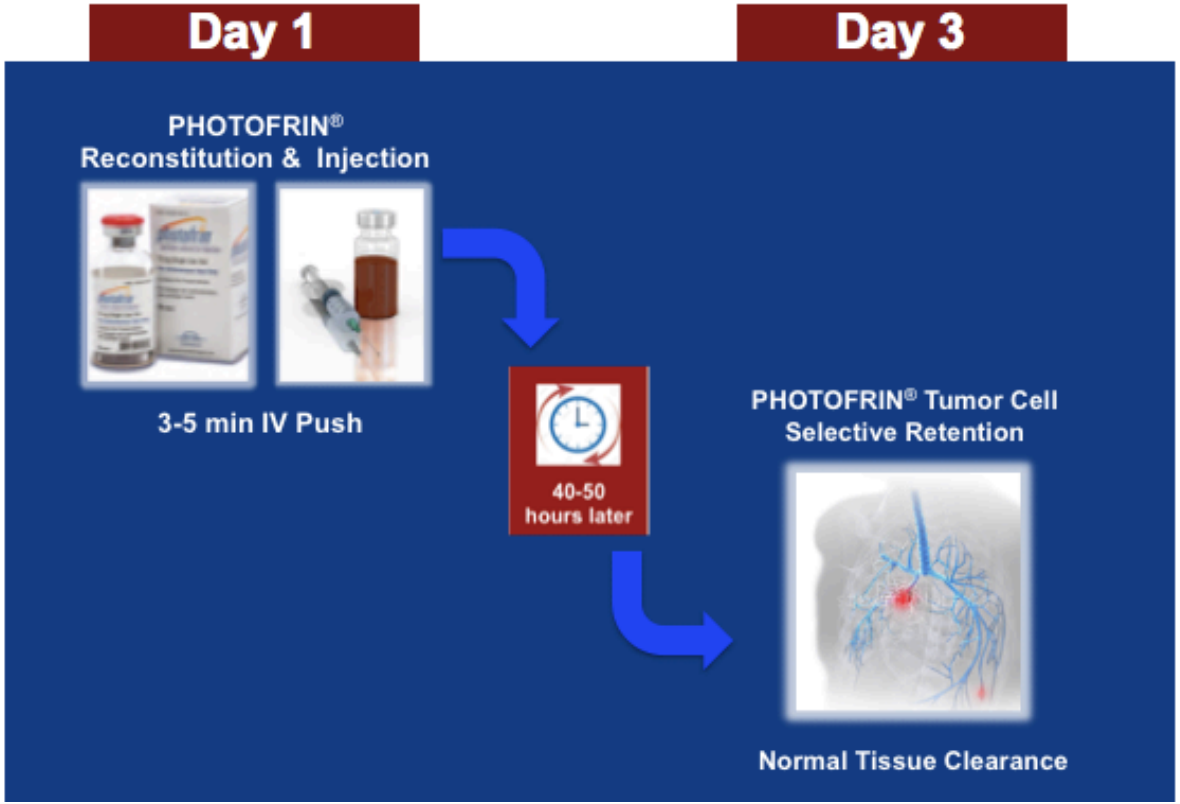
KTP, potassium titanyl phosphate; NdYAG, neodymium yttrium aluminium garnet; APC, argon beam plasma coagulation; MPEC, multipolar electrocoagulation; ALA PDT, 5-aminolaevulinic acid photodynamic therapy.

Barr, H et al. Gut 2005; 54:875-884

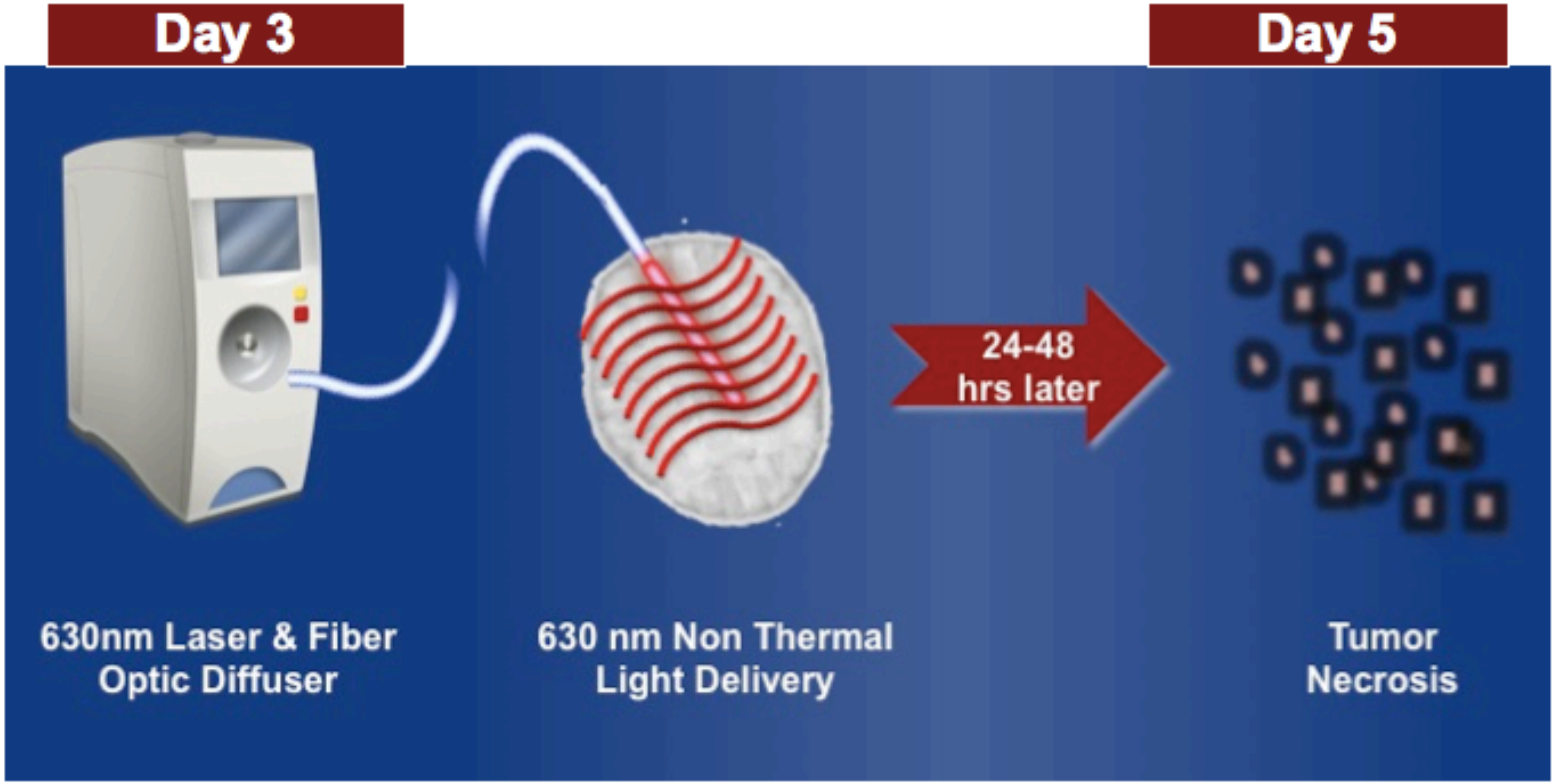
PDT: Esophageal Treatment Schedule



PDT: Esophageal Treatment Schedule

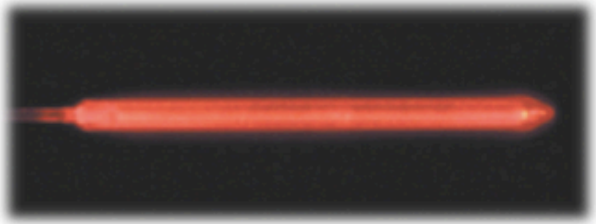


PDT: Esophageal Treatment Schedule

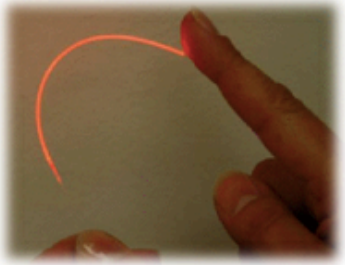


PDT: Fiber Optic Types and Sizes

Rigid Diffuser Tip



Flexible Diffuser Tip



PDT: Photoactivation – Light Dose

- **Esophageal Cancer**
  - Laser light **dose of 300 J/cm** of fiber optic diffuser length 40–50 hours following injection with PHOTOFRIN; repeated, if needed, 96-120 hours after initial injection

- **High-Grade Dysplasia in Barrett's Esophagus**
  - Laser light **dose of 130 J/cm** of fiber optic diffuser length 40–50 hours following injection with PHOTOFRIN; repeated, if needed, with a light dose of 50 J/cm of fiber optic diffuser length 96-120 hours after initial injection

PDT: Benefits

- Non contact
- Non thermal
- Selectively retained in cancer cells
- Treatment of diffuse area
- Treatment of visible and nonvisible disease
- Selective necrosis of target lesion up to 6 mm
- Compatible with any level of FiO_2 level

PDT: Timing of Treatments

- **Before Radiation**
  - Recommended that **2 - 4 weeks** to be allowed **after PDT** before commencing radiotherapy

- **After Radiation**
  - the acute inflammatory reaction from radiotherapy usually subsides within **4 weeks** after completing radiotherapy, after which PDT may be given

PDT: Safety Tips

- Tracheoesophageal or bronchoesophageal fistula can occur if esophageal tumor is eroding into trachea or bronchial tree.
- Gastrointestinal perforation can occur.
- Esophageal stenosis occurs frequently after treatment of HGD in Barrett's esophagus
- After treatment of high-grade dysplasia (HGD) in Barrett's esophagus, monitor endoscopic biopsy every three months, until four consecutive negative evaluations for HGD have been recorded

PDT: Safety Tips

- **Photosensitivity can be expected; ocular sensitivity is possible.**
  - **Avoid UV light – can cause severe sunburn**
  - **Patients should wear hats, long sleeve shirts, pants, gloves, and sunglasses while outdoors**
  - **Fluorescent light is OK**
- **Patients with hepatic or renal impairment may need longer precautionary measures for photosensitivity (possibly more than 90 days)**

PDT for Obstructing Esophageal Cancer

Overview

- PDT performed for palliation of bleeding or obstructing esophageal cancer
- 215 patients underwent 318 courses of PDT for the following reasons:
  - Bleeding 15, Obstruction 277, Bleeding and Obstruction 18, Other 8
- Tumor types include: n=179 Adenocarcinoma, n=33 SQCC, n=3 undifferentiated carcinomas

Results

- 85% of PDT treatment courses for obstruction resulted in a reduction of at least one unit in the pre-PDT dysphagia score.
- Mean dysphagia score changed from 3 to 2 post PDT treatment
- Mean dysphagia-free interval was 66 days

Conclusion

- **PDT is an effective palliative treatment and improves malignant dysphagia in patients with obstructing esophageal carcinoma.**
- **PDT also is effective at controlling bleeding tumors and ablating tumor ingrowth or overgrowth of esophageal stents.**

Litle, Luketich et al. Ann Thorac Surg, 2003; 76:1687-93

PDT: Case Scenario

Patient History

- 70 year old female
- Presenting Symptoms:
  - Weight loss
  - Dysphagia

Diagnostic Assessment

- New partially obstructing GEJ adenocarcinoima

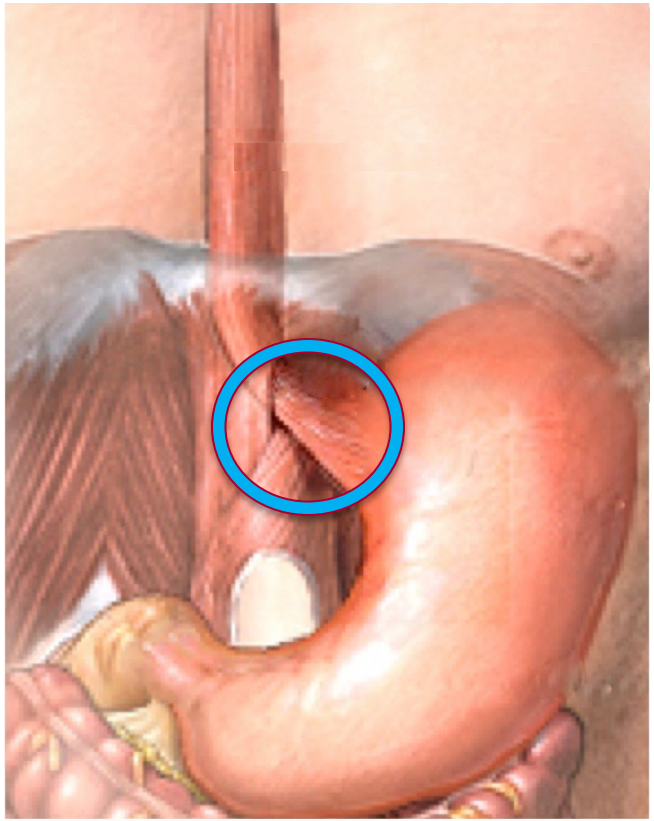
Pretreatment Considerations

- Referred for induction chemorads
- Found to have metastatic disease post neoadjuvant tx
- Persistent 90% obstruction
- Failed stent placement - migration
- No longer a surgical candidate

Treatment Plan

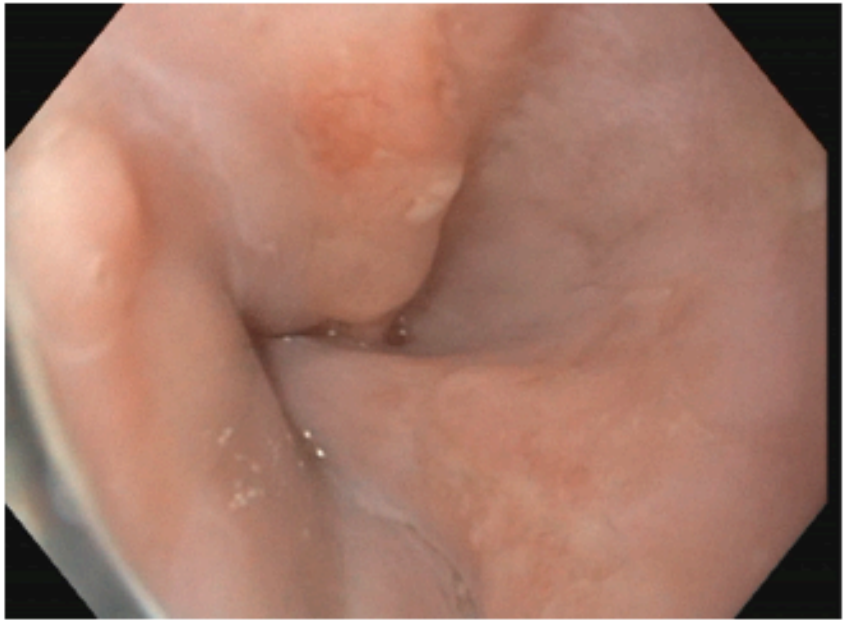
- Photodynamic Therapy
- Clinical trials

PDT: Case Scenario

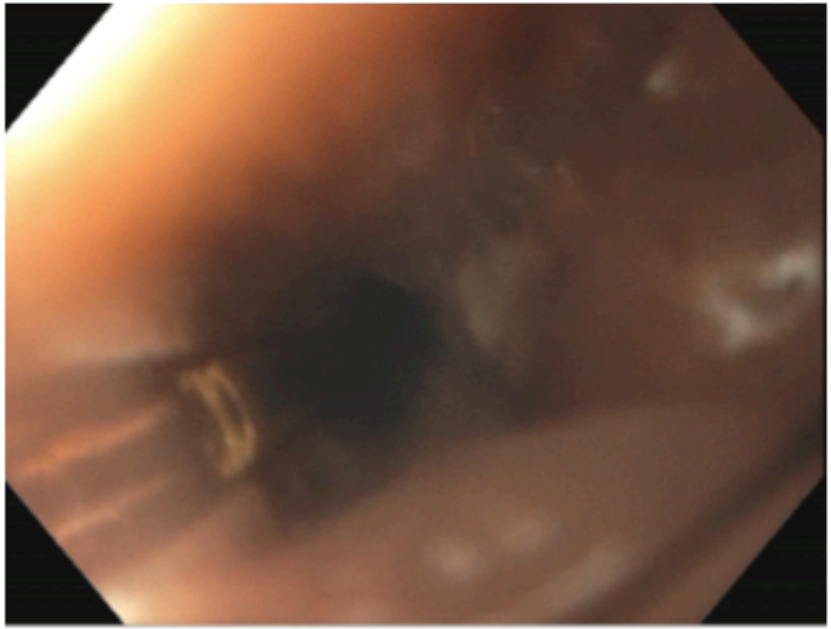


GE Junction Adenocarcinoma

PDT: Case Scenario



Nearly complete obstruction of distal GEJ



Just enough lumen for PDT catheter

PDT: Case Scenario

Day 1

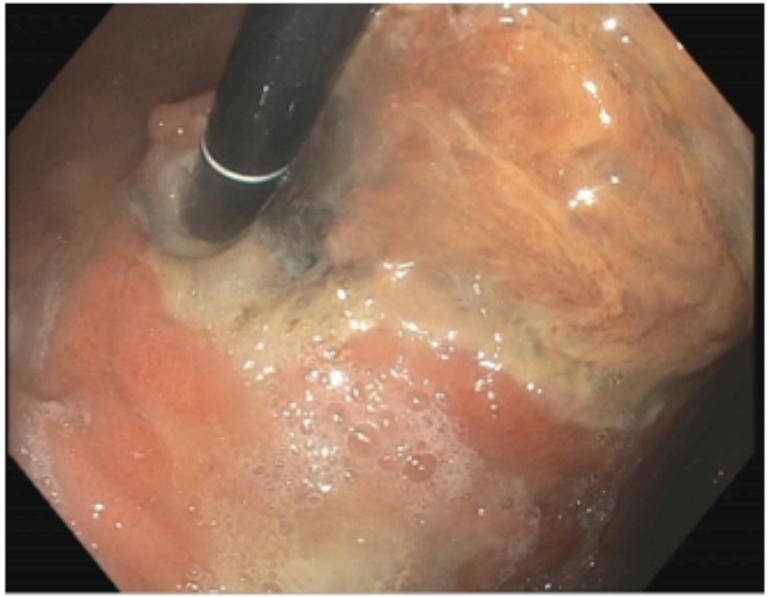
Drug Administration	
Photofrin Injection	2 mg/kg IV Push

Day 3, 5, 8, 14

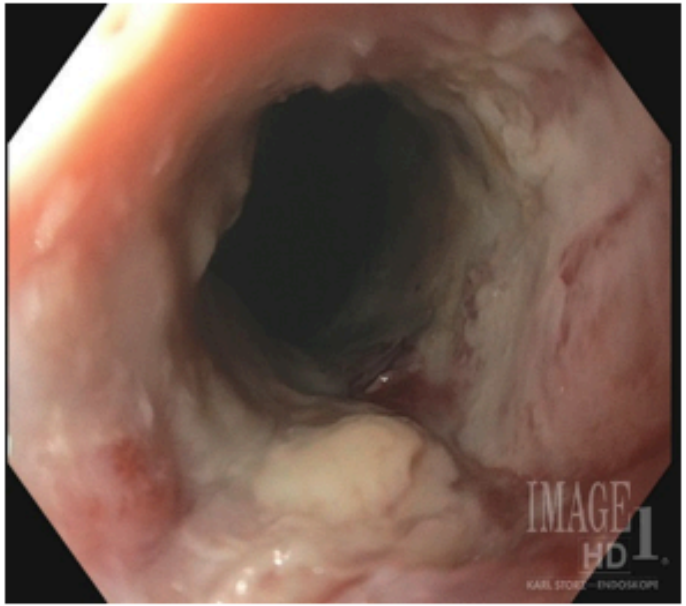
Fiberoptic Diffuser Selection	
Fiber Type	Rigid Fiberoptic Diffuser
Fiber Length	5cm
Fiber Placement	Endoscopic

Endoscopy & Light Application	
Initial Light Application	300 J/cm x 12.5 min

PDT: Case Scenario



Now able to pass scope into stomach, view of GEJ tumor upon retroflexion



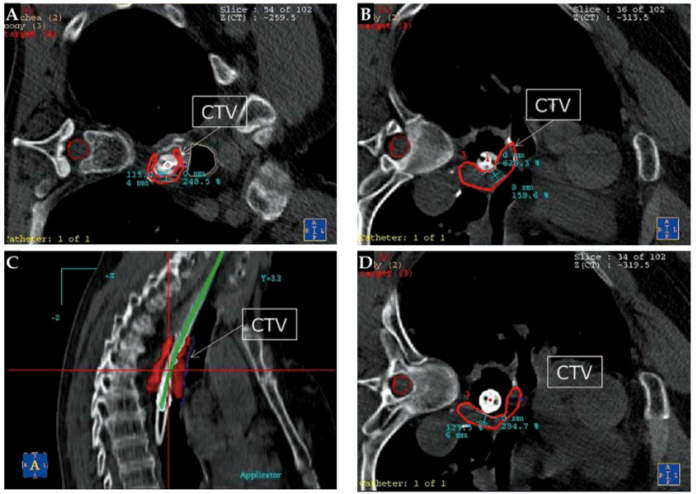
Post 3rd PDT session

BRACHYTHERAPY

Brachytherapy

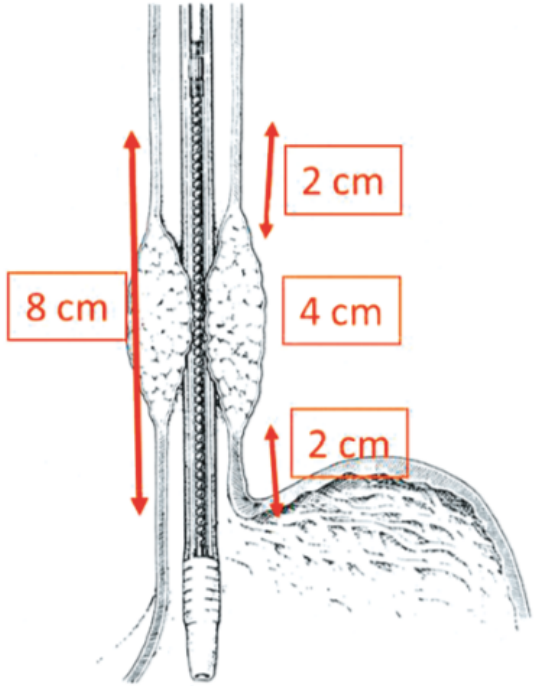
- Radiotherapy has played a major role, both as an adjunct and alternative to surgical approaches, in the treatment of esophageal cancer

- Although these tumors are radiosensitive, curative doses of radiation are difficult to achieve due to the close proximity of vital organs (lungs, heart, spinal cord)



Brachytherapy

- Intraluminal brachytherapy offers a way of delivering high doses of radiation to the esophageal wall while avoid the need to traverse organs-at-risk
- Delivered endoscopically
- Both curative and palliative indications



Brachytherapy: Indications & Dose

CURATIVE INDICATIONS	PALLIATIVE INDICATIONS
Uni-focal thoracic adeno- or squamous esophageal cancers	Unresectable local disease progression or recurrence after initial treatment
Maximum length of 10cm	Distant metastatic disease
No metastatic disease	Stenosis
	Dysphagia
	Tumor hemorrhage
	Alternative to stent placement
Dose: HDR 10-12 Gy in 2 weekly fractions of 5-6 Gy each (3-4 weeks after 50-60 Gy EBRT)	**Dose: HDR 7-28 Gy in fractions of 5-7 Gy**

Lettmaier, S et al. J Contemp Brachytherapy 2014; 6(2):236-241

Brachytherapy: Curative Setting

- Limited data on using as a sole treatment – considered experimental
- Main use of brachytherapy in the curative setting is in the context of definitive treatment schedules as boost following EBRT.

Table 1. Selected clinical series employing brachytherapy as boost

Author	*n*	EBRT dose	iBT dose	Local control	Overall survival
Mujis *et al.*	62	60 Gy	12 Gy (2 fractions)	45% (3y)	11% (5y)
Murakami *et al.* (2011)	87	50-61 Gy	10 Gy (4-5 fraction)	49-75% (5y)	31-84% (5y)
Tamaki *et al.* (2011)	54	56-60 Gy	10 Gy (2 fractions) 9 Gy (3 fractions)	79% (5y)	61% (5y)
Gaspar *et al.*; phase I/II – RTOG 9207 trial (2000)	49	50 Gy	10-15 Gy (2-3 fractions)		49% (1y)
Yorozu *et al.* (1999)	169	40-61 Gy	8-24 Gy (2-4 fractions)	40-80% (2y)	20-70% (2y)
Okawa *et al.*; phase III trial (1999)	103	60 Gy	10 Gy (2 fractions)		20% (5y)
Kumar *et al.* (1993)	75	40-55 Gy	8-10 Gy 10-12 Gy 12-15 Gy	38% (1y)	39% (1y)

Lettmaier, S et al. J Contemp Brachytherapy 2014; 6(2):236-241

Brachytherapy: Procedure

1. TREATMENT PLANNING

- Endoscopy to visualize the tumor. Proximal and distal borders marked with metal clips.

2. PLACEMENT OF BRACHYTHERAPY SOURCE APPLICATORS

- Applicator inserted over guidewire and under fluoroscopy
- CT scan obtained to ensure correct positioning of applicator

3. CREATING A VIRTUAL PATIENT & OPTIMIZING THE TREATMENT PLAN

- 3D visualization plan is created to refine the planned delivery. Contouring of organs at risk and allows for variations of the shape and size of tumor

4. TREATMENT DELIVERY

- Reference dose placed at 5mm tissue depth and 2cm longitudinal margins

Stent insertion or endoluminal brachytherapy as palliation of patients with advanced cancer of the esophagus and gastroesophageal junction. Results of a randomized, controlled clinical trial

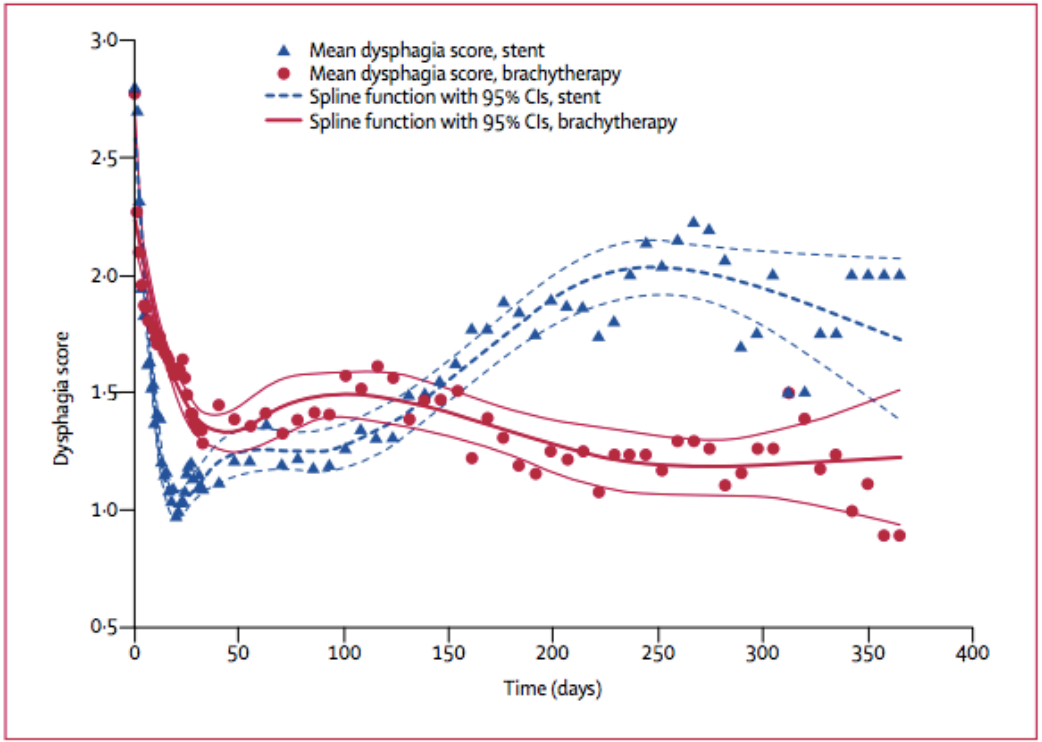
- 65 patients with inoperable esophageal cancer; randomized
  - n=28 Ultraflex expandable stent
  - n=24 high-dose-rate endoluminal brachytherapy (7Gy x3 over 2-4 weeks)
- Patient follow-up at 1, 3, 6, 9 and 12 months after treatment and assessed with a variety of validated questionnaires
- Results
  - At 1-month follow-up the stent group reported statistically significantly improvement of dysphagia
  - After 3 months, the brachytherapy group had a more improved quality of life
  - Median survival was similar in both groups (120 days)
- **Conclusion**
  - Patients that present with more advanced disease with decreased survival may have more initial relief with stenting, however, patients predicted to survive more than 3 months, brachytherapy may offer a better quality of life in the long term.

Bergquist et al. Diseases of the Esophagus, 2005; 18:131-139

Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial

- 209 patients with inoperable esophageal cancer; randomized
  - n=108 stent placement
  - n=101 single-dose 12Gy brachytherapy
- Patient follow-up at 14 days, 1 month, and then monthly for a year
- Primary outcome was relief of dysphagia during follow-up
- Secondary outcomes were complications, treatment for persistent or recurrent dysphagia, HRQL, and costs

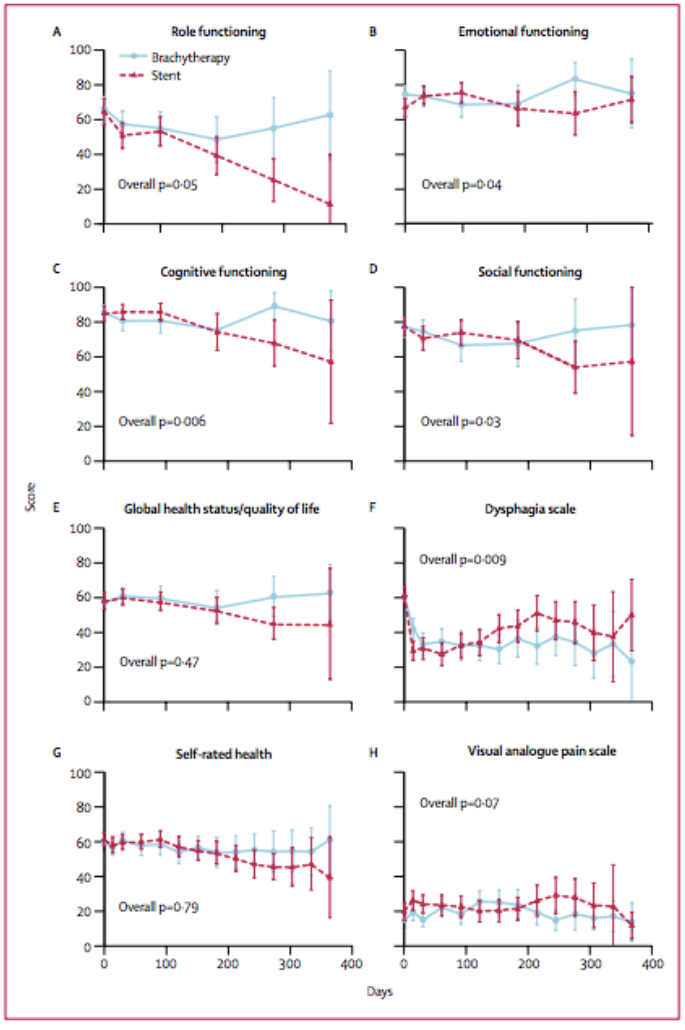
Homs et al. Lancet, 2004; 364:1497-504



Results

- Dysphagia score improved more rapidly after stent placement
- At 30 days, dysphagia score improvement was similar in both groups
- After 30 days, the dysphagia score was better after brachytherapy

Homs et al. Lancet, 2004; 364:1497-504



Results

- Quality of life scores were in favor of brachytherapy compared with stent placement

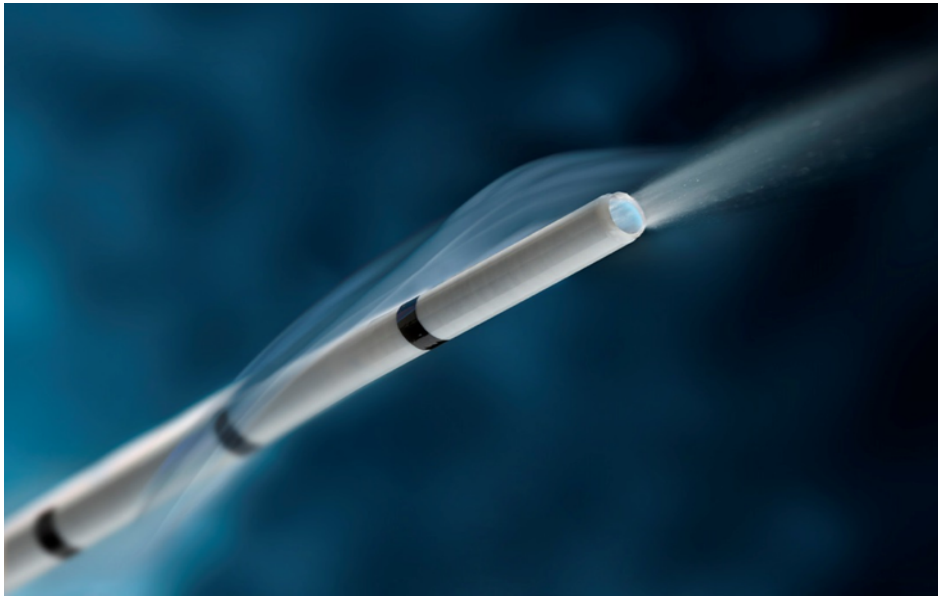
Other results

- Complications occurred more frequently after stent placement (perforation, tumor hemorrhage)
- Cost was similar between groups

- **Conclusion**
  - Recommend single-dose brachytherapy as the primary treatment for palliation of dysphagia from esophageal cancer

Homs et al. Lancet, 2004; 364:1497-504

CRYOTHERAPY

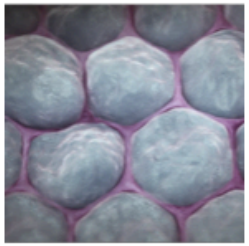


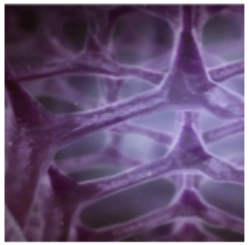
Cryotherapy

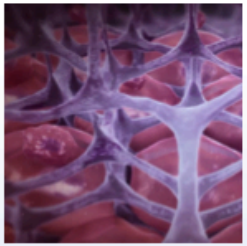
- Cryogenic destruction of tissue using Liquid Nitrogen spray that has a boiling point of -196 ºC

- **Indications:**
  - Ablation of benign lesions (Barrett's esophagus with HGD or LGD)
  - Ablation of malignant lesions (esophageal cancer)
  - Stricture or stent management

Cryotherapy: Mechanism of Action

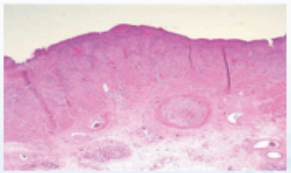






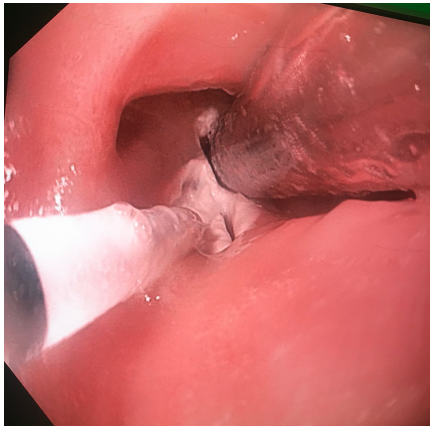
- Flash freezes benign and malignant tissue, causing instant cell death
- Combination of fast, deep freeze & subsequent thaw destroys cellular components while preserving extracellular matrix (ECM)
- Intact ECM enables healing response with limited scarring and fibrosis

  Not possible with heat ablation
- Tissue remains amenable to future therapeutic options

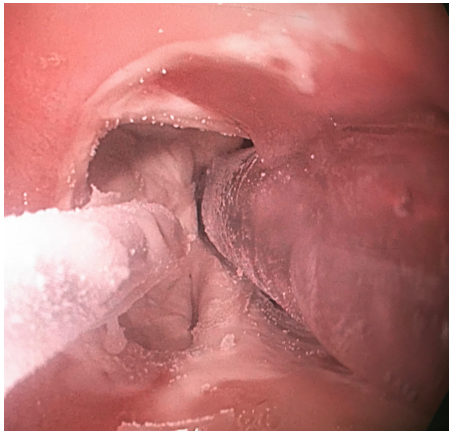


Cryotherapy: Procedure

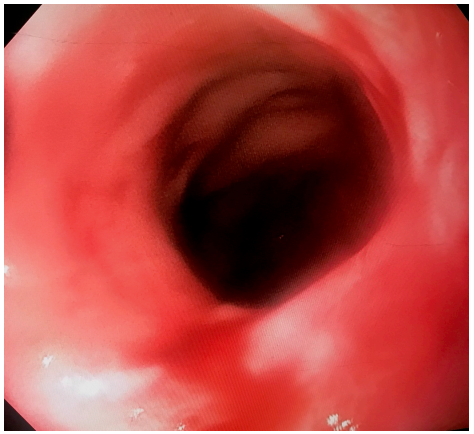
Tight stricture; unable to pass the EGD scope. Spray catheter introduced through the working channel of the scope



Suction initiated with start of liquid nitrogen spray



Frozen for 20 seconds for 3 cycles. Complete thaw in between cycles.

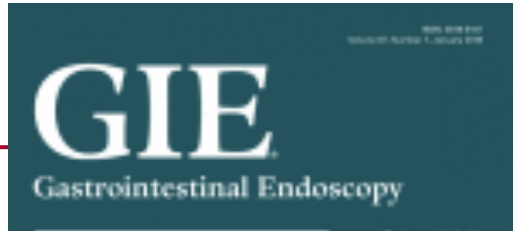


After balloon dilation to 19mm

Cryotherapy: Safety Tips

- Requires suction through an orogastric tube to facilitate the escape of excess nitrogen out of the body and thus prevents perforation of GI viscus.
- Contraindicated in patients with mucosal breaks, eosinophilic esophagitis or coagulopathy.
- Allow 4-6 weeks between cryospray treatments.

Endoscopic spray cryotherapy for esophageal cancer: safety and efficacy



- 49 patients completed treatment
  (median age 76 years, 81% male, 94% with adenocarcinoma)
- Tumor stage T1=60, T2=16, T3/4=3; mean tumor length was 4.0cm
- Results
  - 61.2% (n=30) demonstrated complete response with cryotherapy
  - 75% (18 out of 24) with mucosal cancer demonstrated complete response
  - mean follow-up of 10 months
  - Median number of cryotherapy sessions = 3
  - No serious events reported, however, benign stricture noted in 13%
- Conclusion
  - Short-term results demonstrate that cryotherapy is effective in those that could not receive conventional treatment

Greenwald B et al. Gastrointest Endosc, 2010; 71(4):686-693

Safety and efficacy of endoscopic spray cryotherapy for esophageal cancer

- Multi-institutional study (11 academic and community practices)
- Patients with adenocarcinoma who failed or were not candidates for conventional therapy
- 88 patients (median age 76, 80.7% male, mean length 5.1cm) underwent 359 treatments (median 4.4 per patient)
- Tumor stage T1a=39, T1b=25, unspecified T1=9, T2=15
- Results
  - 55.8% (n=48) demonstrated complete response with cryotherapy
  - 76.3% forT1a, 45.8% for T1b, 66.2% for all T1, and 6.7% for T2 demonstrated complete response
  - mean follow-up of 18.4 months
  - No serious events reported, however, benign stricture noted in 13.6%
- Conclusion
  - Endoscopic spray cryotherapy is a safe, well-tolerated, and effective treatment option for early esophageal adenocarcinoma

Tsai F et al. Diseases of the Esophagus, 2017; 30:1-7

Liquid nitrogen spray cryotherapy for dysphagia palliation in patients with inoperable esophageal cancer

- Multi-center, retrospective case series
- 49 patients with inoperable esophageal cancer undergoing palliative endoscopic cryotherapy
- Primary outcomes were change in dysphagia scores between pre- and –post cryotherapy
- Results
  - Mean dysphagia score improved significantly from 2.4 precryotherapy to 1.7 postcryotherapy (improvement of 0.7 points $p<0.001$)
- Conclusion
  - Liquid nitrogen spray cryotherapy may be safe and effective for dysphagia palliation in inoperable esophageal cancer

Kachaamy T et al. Gastrointestinal Endoscopy, 2018; 88(3):447-55

Conclusions

- **Photodynamic therapy, brachytherapy and cryotherapy are effective palliation treatments to relieve dysphagia.**

- **Brachytherapy and cryotherapy may also have curative benefits in patients with esophageal cancer that are no candidates for conventional.**

Thank You

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