Optimal Therapy for Achalasia and EGJOO in 2021

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Multidisciplinary Collaboration. Personalized Treatment Strategies. Patient Advocacy

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Disclosures

- Consultant: Medtronic

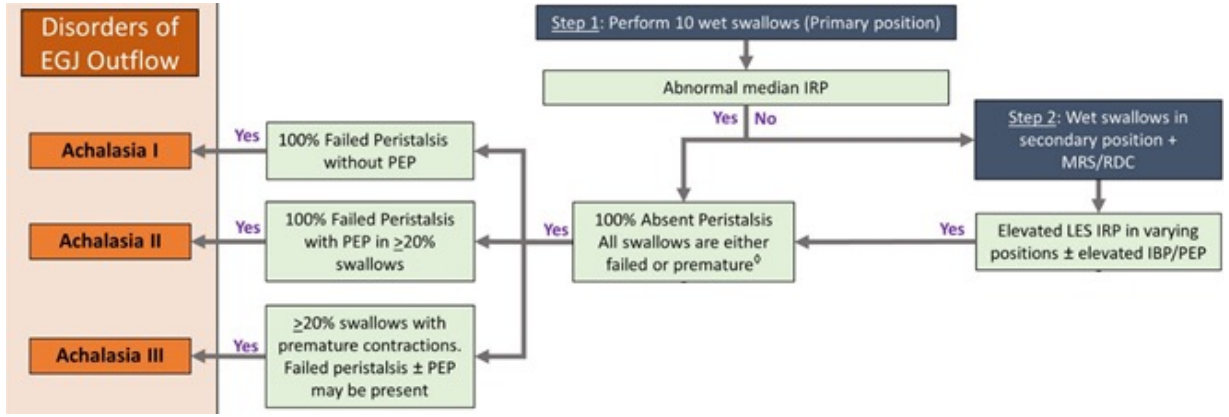
Objectives

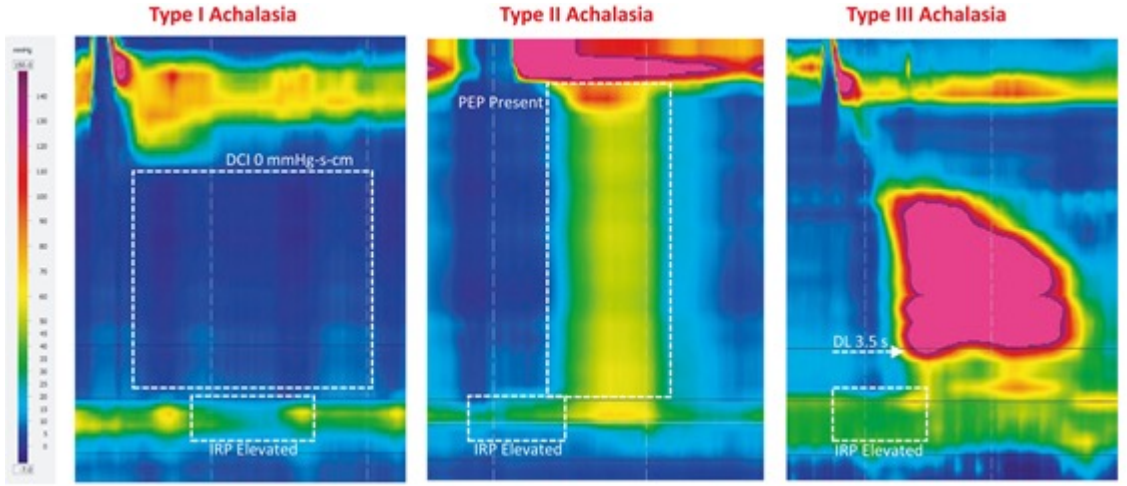
- To review:
  - The importance of an accurate diagnosis of achalasia or EGJ outflow obstruction (EGJOO) before considering treatment options
  - The evidence that guides optimal therapy for achalasia and EGJOO

Chicago Classification version 4.0 (CCv4.0): Hierarchical Classification Scheme

- Manometry remains standard tool to subtype achalasia based on pattern
  - Assumptions
    - Other diagnostic testing supports diagnosis
    - Pseudoachalasia excluded

- Conclusive achalasia on esophageal high-resolution manometry (HRM)
  - Abnormal median IRP in at least primary position
  - Type I: 100% failed peristalsis without PEP
  - Type II: 100% failed peristalsis with PEP ≥20% of swallows
  - Type III: ≥20% premature swallows and no peristalsis



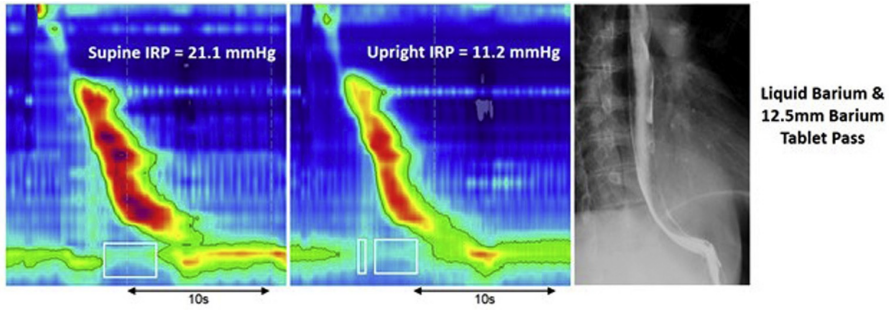


Khan A et al. Neurogastroenterol Motil 2021
Yadlapati R et al. Neurogastroenterol Motil 2021

EGJOO: Prior HRM Classifications

- Based on some peristalsis with elevated integrated relaxation pressure (IRP) suggesting potential poorly relaxing EGJ

- Natural history based on HRM diagnosis
  - 2015 study of 34 patients with idiopathic EGJOO with 82% requiring no treatment and only 3 patients developing achalasia within 2 years
  - 2017 study of 30 patients with EGJOO followed for a mean of 2.8 years with only 7 patients getting treatment (medical or procedural) and majority were asymptomatic
  - 2018 study of 112 patients with EGJOO and only 7 deemed to have a clinically significant idiopathic EGJOO

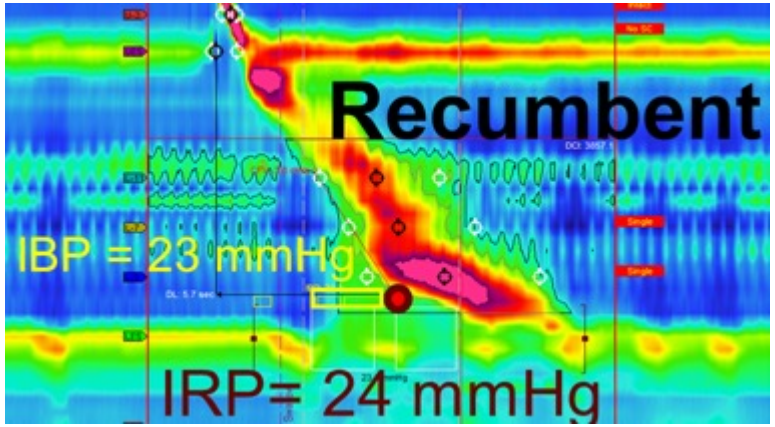


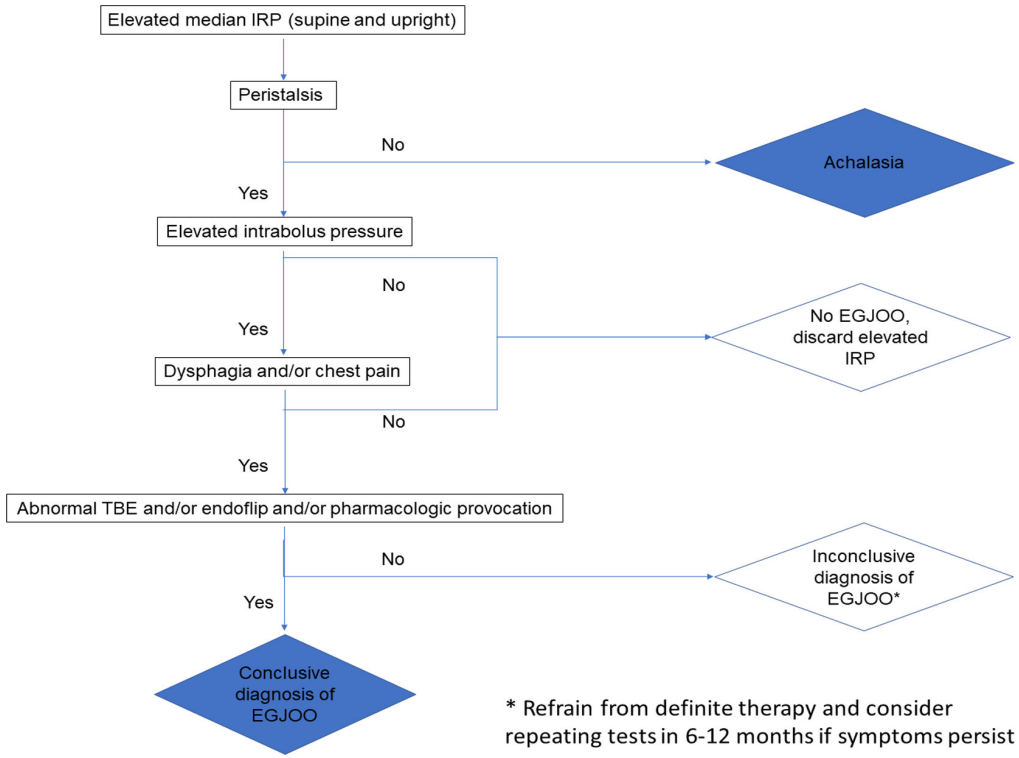
- A *manometry pattern*
  - It is not necessarily clinically relevant
    - Primary EGJOO based on HRM may not be related to inadequate LES smooth muscle relaxation
  - However: definitive achalasia treatment sometimes offered in carefully selected patients
    - Example: 2021 retrospective multicenter study of 55 POEMs for 'symptomatic' EGJOO
      - 94% success of Eckardt score ≤3 at mean 117 days; 66% GERD by pH study (18 patients)
    - Lack of long-term follow-up

Van Hoeij FB et al. Neurogastroenterol Motil 2015 *Song BG et al. Neurogastroenterol Motil 2018*
Schupack D et al. Neurogastroenterol Motil 2017 *Triggs JR et al. Clin Gastroenterol Hepatol 2019* *Jacobs CC et al. Clin Gastroenterol Hepatol 2021*

CCv4.0: EGJOO

- Assumption: negative careful endoscopy
- A manometric diagnosis of EGJOO is *always* considered clinically inconclusive (key update from prior versions and known *natural history*)
- Clinically relevant **conclusive** diagnosis of EGJOO
  - Elevated median IRP in the primary **and** secondary position **and** ≥20% swallows with elevated intrabolus pressure (IBP) in the supine position
  - Evidence of some peristalsis (not an achalasia pattern)
  - Clinically relevant symptoms: dysphagia and/or non-cardiac chest pain
  - At least one other investigation supporting obstruction: timed barium esophagram (TBE) or functional lumen imaging probe (FLIP)
- Additional considerations to support manometric evidence of EGJOO
  - Rapid drink challenge, solid food swallowing, pharmacologic provocation



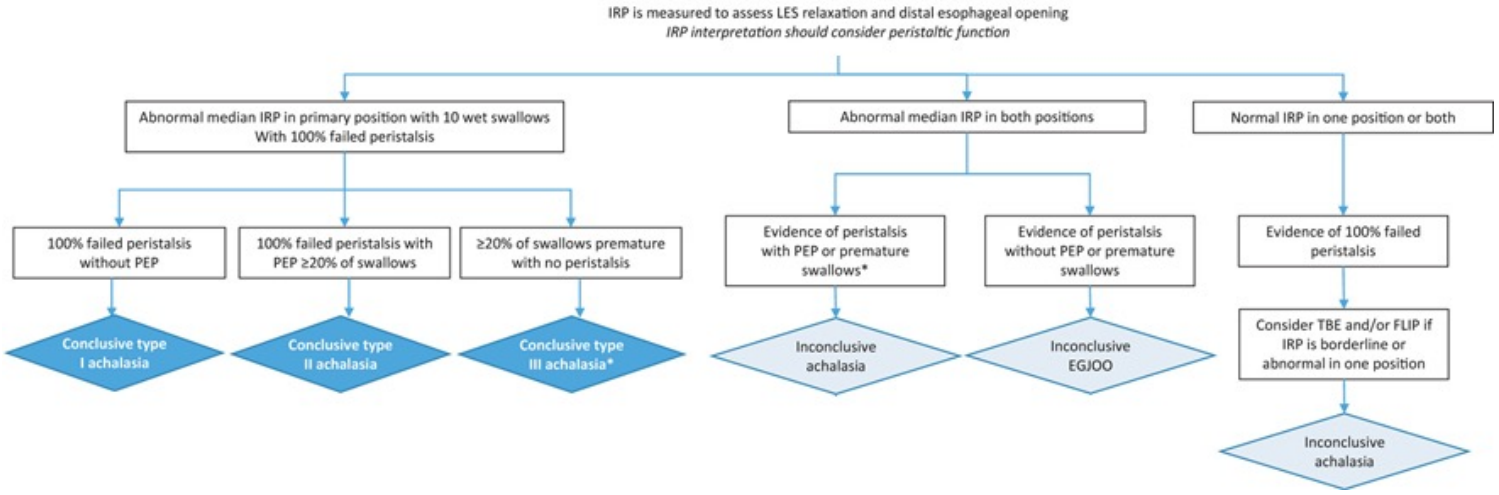


Bredenoord AJ et al. Neurogastroenterol Motil 2021
Yadlapati R et al. Neurogastroenterol Motil 2021

CCv4.0: Inconclusive Achalasia

- Inconclusive achalasia key possibilities
  - Absent contractility with median IRP at upper limit of normal in one or both positions
  - Some peristalsis in changing position from achalasia type I or II pattern in primary position
  - Abnormal median IRP with evidence of spasm and peristalsis: inconclusive type III achalasia
  - If patient is on opioids and has type III achalasia pattern
    - Suggested to study off opioids if possible

- Suggestion to do *TBE or FLIP* to determine if definitive achalasia therapy recommended



Khan A et al. Neurogastroenterol Motil 2021
Yadlapati R et al. Neurogastroenterol Motil 2021

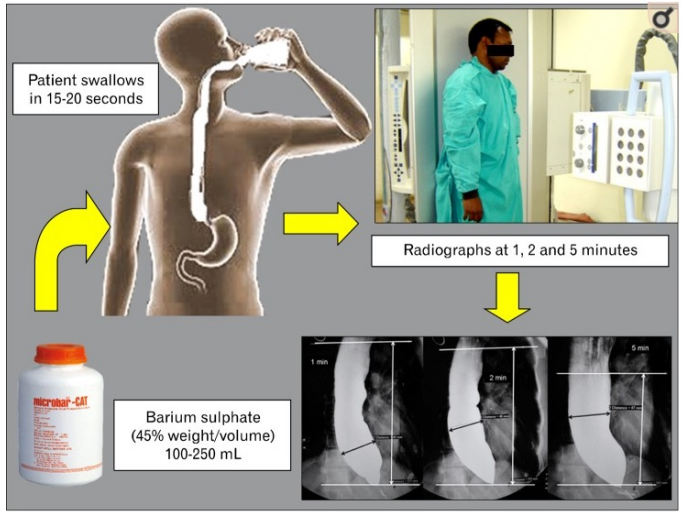
Further Investigation: TBE

- TBE utility
  - Different metrics have been used
  - Addition of barium tablet can increase the diagnostic yield for achalasia and EGJOO

Liquid Barium & 12.5mm Barium Tablet Pass

12.5mm Barium Tablet impaction

Barium column At 5 min



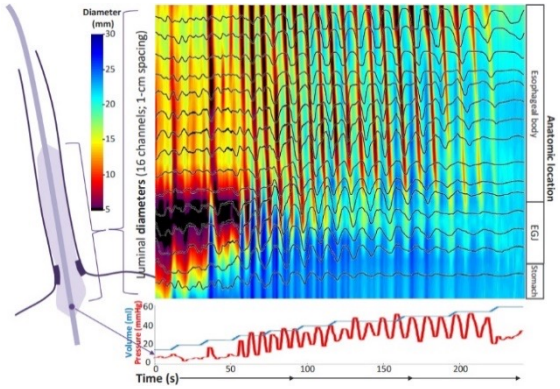
Neyaz Z et al. J Neurogastroenterol Motil 2013

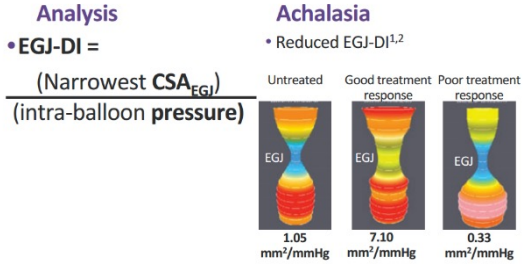
Blonski W et al. Am J Gastroenterol 2018

Triggs JR et al. Clin Gastroenterol Hepatol 2019

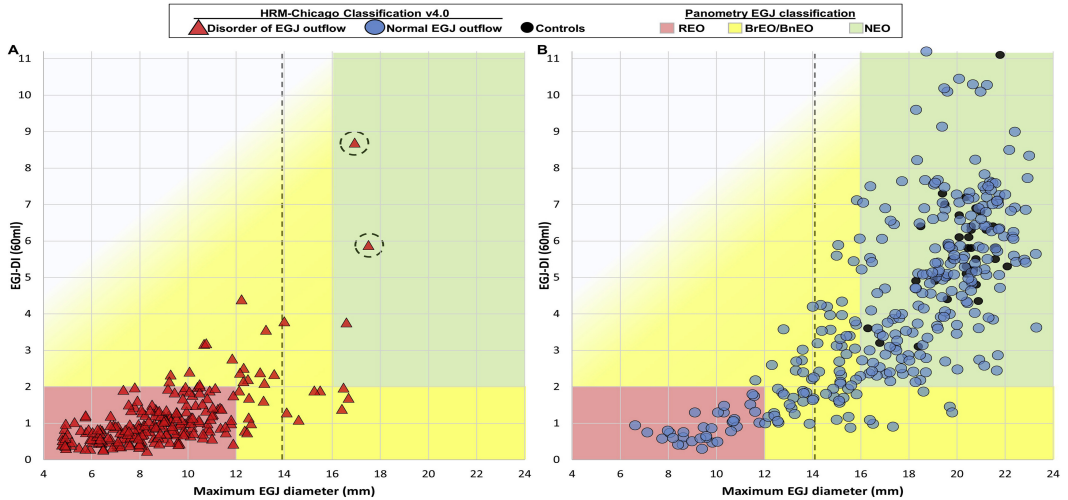
Further Investigation: FLIP

- FLIP Panometry Assessment
  - Contractile response to distension
  - EGJ opening
  - Both can be important in attempting to support achalasia diagnosis





- Current evidence
  - EGJ opening metrics can support potential achalasia physiology
    - More standardized delineation recently between reduced, borderline, and normal
  - 687 patients and 35 asymptomatic controls
    - 241 patients with reduced EGJ opening
      - 86% had conclusive disorder of EGJOO or achalasia on HRM CCv4.0
    - 203 patients with normal EGJ opening
      - 99% had normal EGJ outflow per HRM CCv4.0



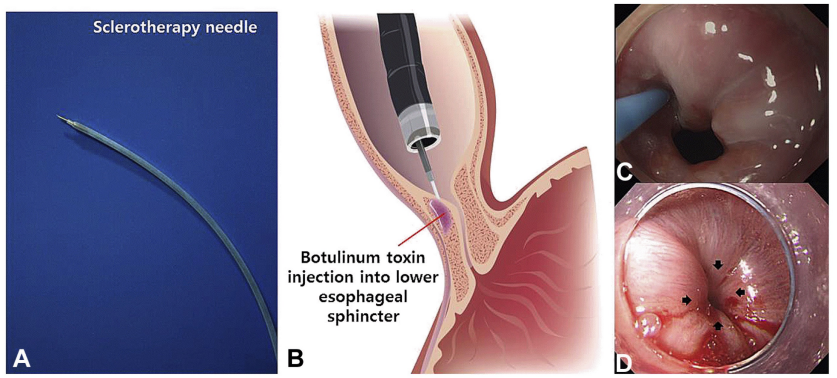
Carlson DA et al. Am J Gastroenterol 2016
Carlson DA et al. Neurogastroenterol Motil 2021
Carlson DA et al. Clin Gastroenterol Hepatol 2021
Rooney KP et al. Clin Gastroenterol Hepatol 2021

Before “Definitive” Treatments

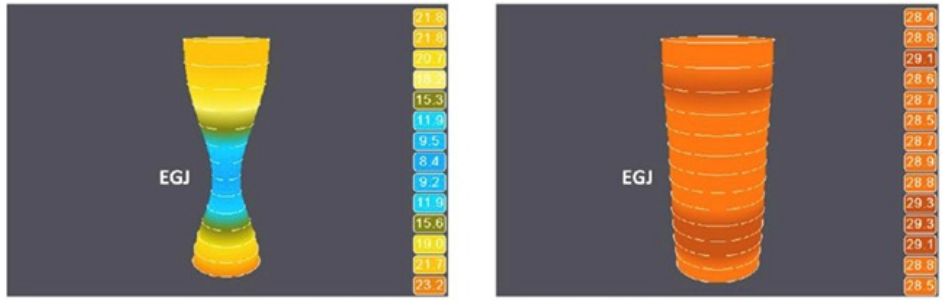
- Inconclusive achalasia physiology assessment remains

- Potential treatments
  - Medications very limited evidence
  - Botulinum toxin injection
    - Known short-term effectiveness in carefully selected EGJOO patients across several studies
  - Smaller dilations (not pneumatic)
    - Up to 20 mm, possibly combined with injection
    - EsoFLIP therapeutic balloon
      - Small studies showing benefit in achalasia patients
      - Can dilate 21-29 mm, potentially (theoretically) less risk of perforation compared to pneumatic dilation

- Can reassess in 6-12 months
  - Consider definitive achalasia therapy later



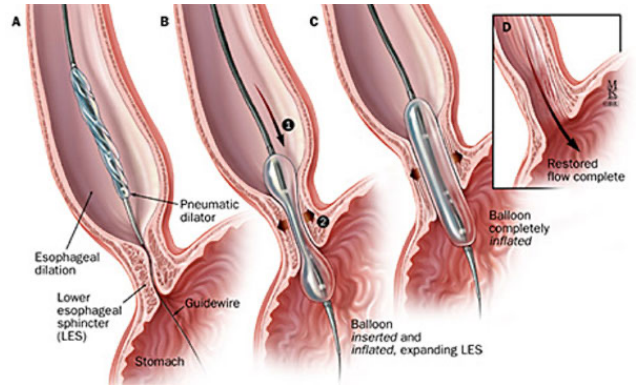
EsoFLIP

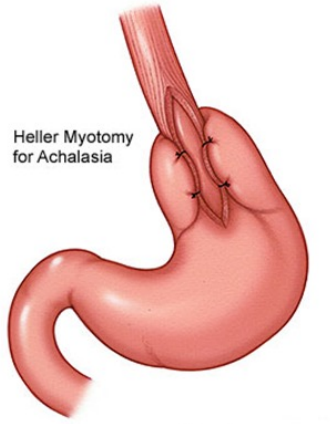


Van Hoeij FB et al. Neurogastroenterol Motil 2015
Schnurre L et al. Neurogastroenterol Motil 2020
Baumann AJ et al. Curr Opin Gastroenterol 2021

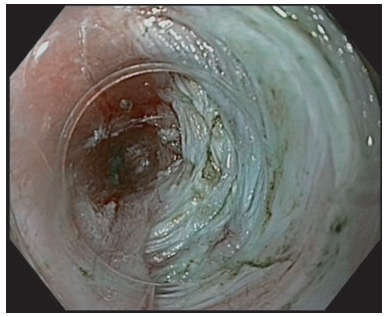
Approach to Achalasia Treatment

- Achalasia physiology confidently suspected → attempt at definitive treatment is indicated
  - If candidate considering risks of procedures
- Still do not reverse underlying pathophysiology…
- Overall aim
  - Decrease resting pressure in LES → gravity promotes esophageal emptying
    - Improved dysphagia, regurgitation, and aspiration
- Potential definitive benefit
  - Pneumatic dilation (PD) 30-40 mm
  - Laparoscopic Heller myotomy (LHM) with partial fundoplication
  - Peroral endoscopic myotomy (POEM)





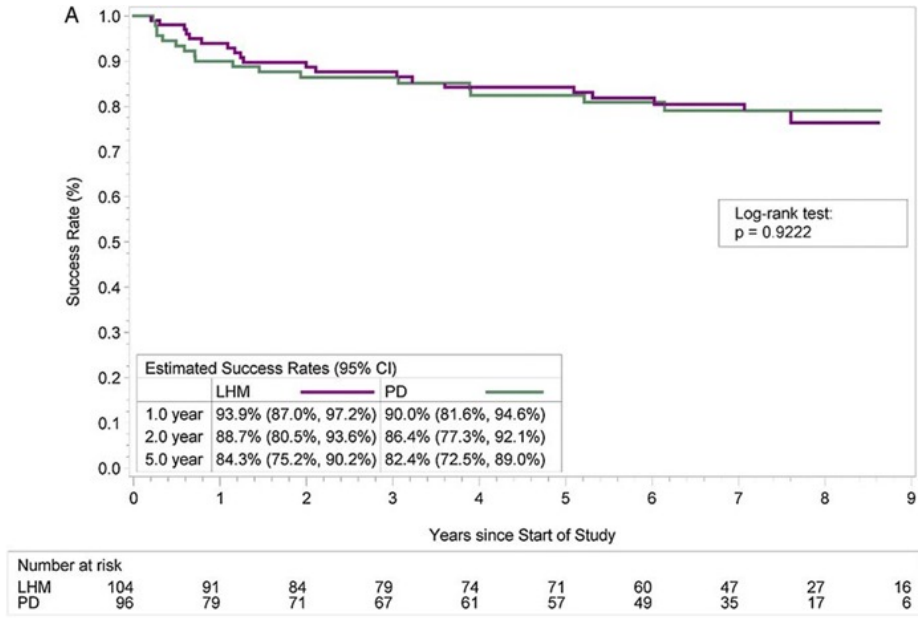
POEM



Kahrilas PJ et al. Gastroenterol 2013
Bredenoord AJ et al. Neurogastroenterol Motil 2014

European Achalasia Trial

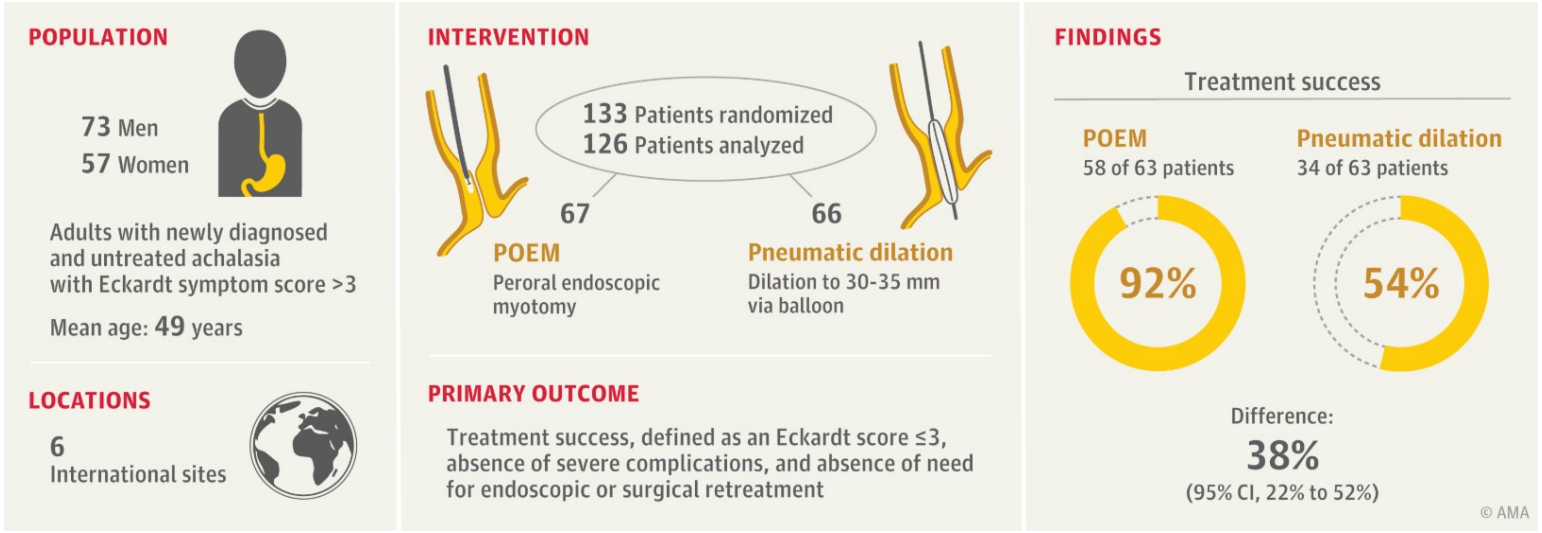
- PD versus LHM
  - 5-year success similar
    - Eckardt score, quality of life measures, esophageal emptying, LES pressure
  - PD patients allowed two sets of dilations first two years
    - 25% of PD patients had re-dilation performed after two years
  - Subtyping
    - 25% type I, 65% type II, 10% type III
    - Type I similar statistical success
      - 75% LHM, 69% PD
    - Type II better with PD
      - 88% LHM, 96% PD
    - Type III better with LHM
      - 86% LHM, 48% PD
  - Conclusion
    - Both can be offered as first-line options for type I and II achalasia



Moonen A et al. Gut 2016

PD versus POEM

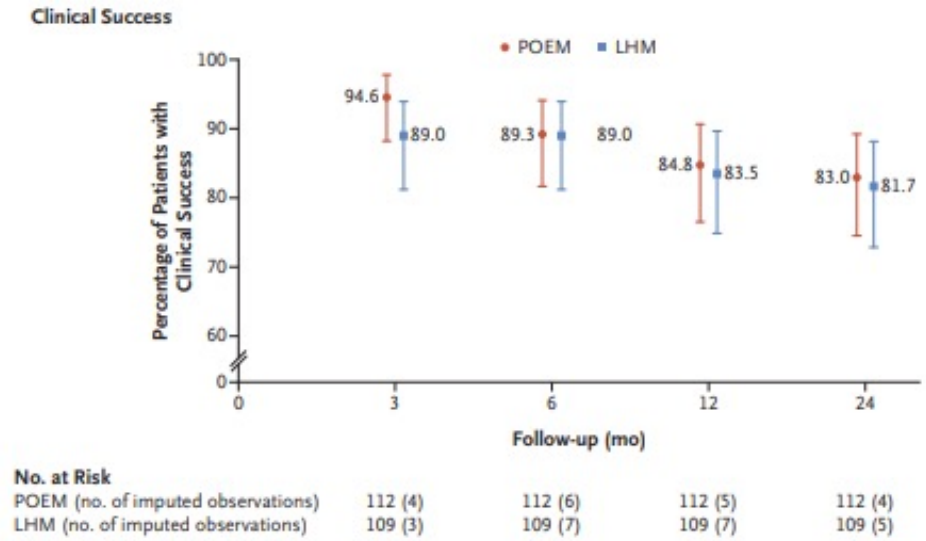
- Randomized international study of 133 achalasia patients
  - Treatment success defined by two year follow-up Eckardt score ≤3
    - Favors POEM
  - 16 of PD patients only had one 30 mm dilation (group allowed one 30 mm and one 35 mm)
  - >50% type II achalasia in both groups
  - PD group one perforation and one hospitalization, no serious adverse events in POEM group
  - POEM had more reflux esophagitis (41% versus 7%, p=0.002)



Ponds FA et al. JAMA 2019

LHM versus POEM

- NEJM randomized study of 221 achalasia patients
  - POEM versus LHM (with Dor fundoplication)
  - Primary end point Eckardt score ≤3 at two years
    - Analyzed as a noninferiority study
    - POEM noninferior at 2 years
  - Over 70% in both groups type II achalasia
  - Two year GERD follow-up
    - Reflux esophagitis higher in POEM (44% versus 29%, significant)
    - pH study positivity similar (30% versus 30%) but only 126 patients had pH studies
    - PPI use higher with POEM (53% versus 27%)

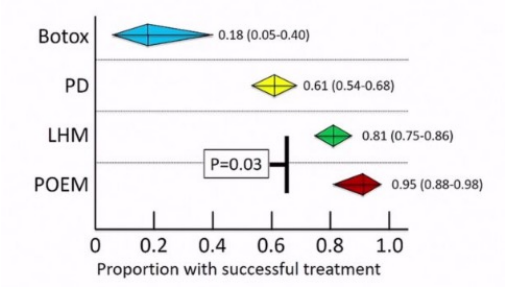


Werner YB et al. N Engl J Med 2019

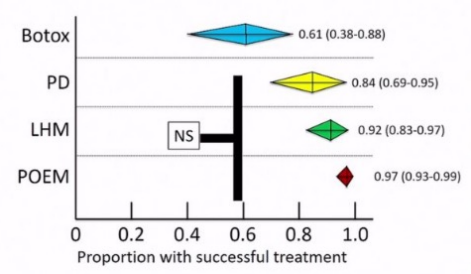
Comparing Treatments

- Meta-analysis comparing treatments by subtype
  - 1575 achalasia patients
  - POEM best for type I and type III achalasia
  - PD, LHM and POEM equivalent for type II achalasia

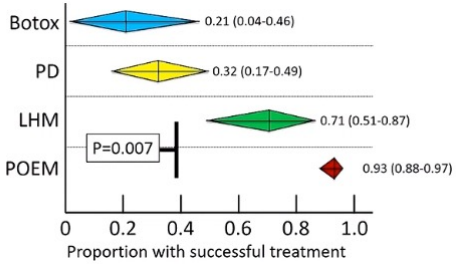
Type I Achalasia



Type II Achalasia



Type III Achalasia



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Andolfi C et al. B J Surg 2019

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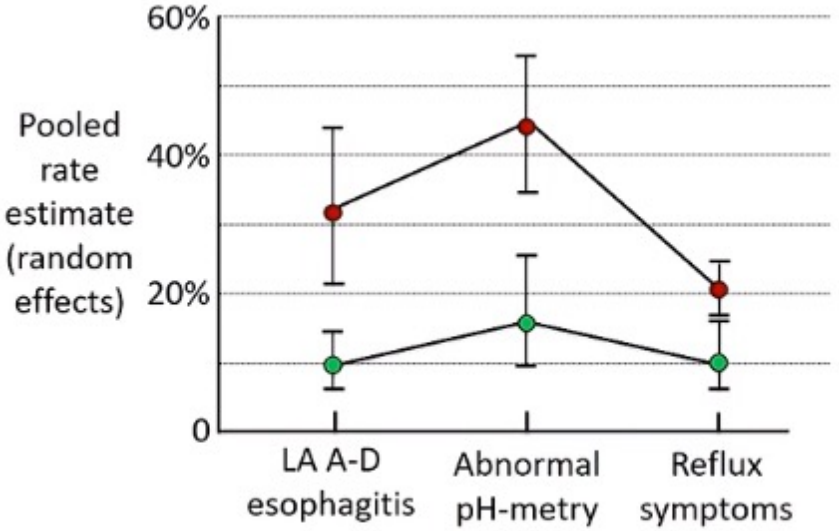
GERD Post-treatment

- PD evidence: generally low frequency
  - 15% at one year by pH study in European achalasia trial

- Meta-analysis comparing LHM (2581 patients) to POEM (1582 patients)
  - Higher rates of GERD by esophagitis, pH-metry or symptom analysis
  - Studies heterogeneous without standardization
  - Consider partial fundoplication after?



Boeckxstaans et al. N Engl J Med 2011
Repici A et al. Gastrointest Endosc 2018

Achalasia Treatment Summary

- Two network meta-analyses
  - Surgical Endoscopy 2020
    - POEM and LHM have comparable efficacy and may increase treatment success compared to PD with low confidence in estimates
    - POEM may have lower rate of serious adverse events compared to LHM and PD, but higher risk of GERD
  - The Lancet 2021
    - POEM and LHM should be the preferred treatments for idiopathic achalasia
    - PD performed worse, and its role is less certain

- Society guidelines summary: ACG 2020 and ASGE 2020 most updated
  - LHM, PD and POEM are effective treatment options for type I and type II achalasia
  - Preference for tailored and longer myotomy for type III achalasia
  - Local expertise and shared decision-making are relevant

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Vaezi MF et al. Am J Gastroenterol 2020
Khashab MA et al. Gastrointest Endosc 2020
Facciorusso A et al. Surg Endosc 2020
Mundre P et al. Lancet Gastroenterol Hepatol 2021

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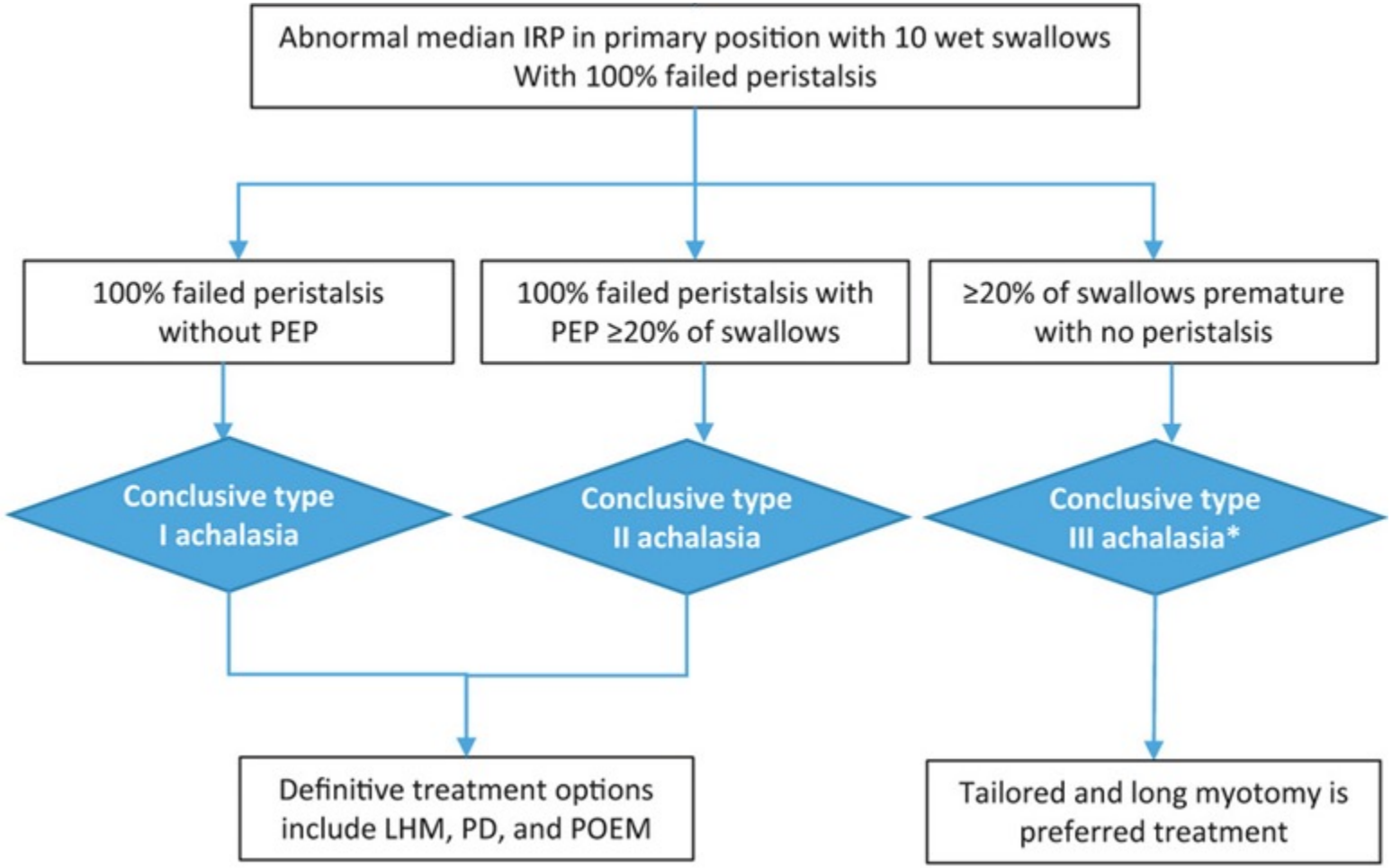
General Recommendations



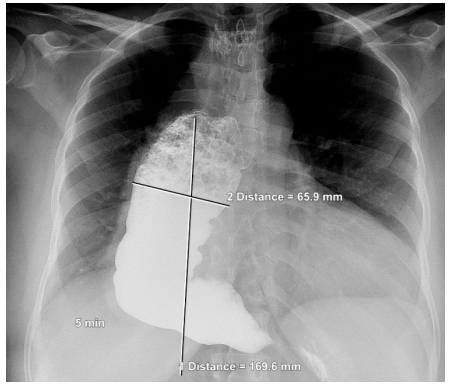
Khan A et al. Neurogastroenterol Motil 2021

Pearls of Treatment

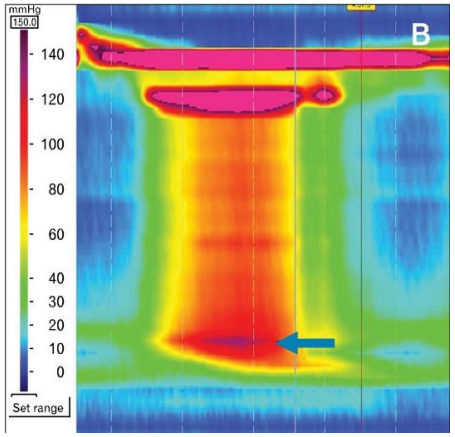
- Type I and type III achalasia: multi-disciplinary discussion often important
  - Progressive type I: does anatomy guide surgical benefit (e.g. esophageal straightening?)
  - Type III or potential embedded spasm in type II: where does spasticity proximally start?
    - May have to rely on FLIP and/or esophagram

- Blown-out myotomy (BOM)
  - Increasingly recognized adverse event and pseudo-diverticulum from LHM or POEM
  - Mechanism? → wall strain in the area weakened by myotomy
    - From residual spastic contractility and/or continued EGJOO
    - Importance of ensuring complete EGJ disruption and lack of spastic contractions proximally
  - Precision myotomy based on diagnostic studies may be needed
    - Long POEM for type III achalasia; limited to EGJ for non-spastic achalasia
    - More outcome studies needed
      - Recent type II achalasia study of 91 POEMs randomized to short versus standard POEM: similar 1-year success; less GERD by pH study in short POEM group

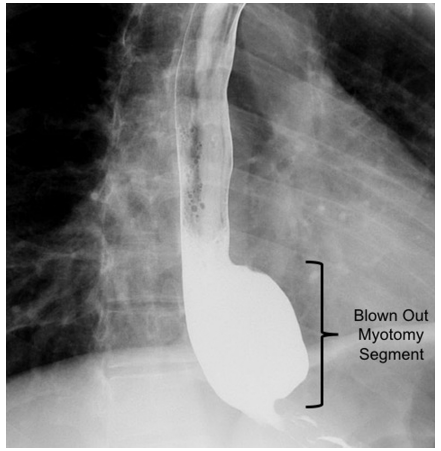
Type I Achalasia



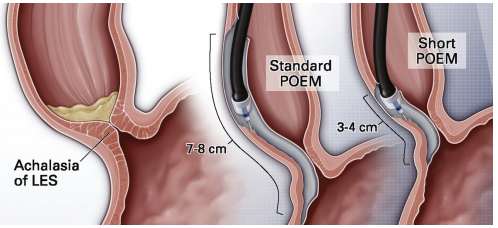
Type II Achalasia



BOM



POEM Length



Kim HH et al. J Neurogastroenterol Motil 2013
Vaezi MF et al. Am J Gastroenterol 2020
Triggs JR et al. Gastrointest Endosc 2021
Gu L et al. Gastrointest Endosc 2021

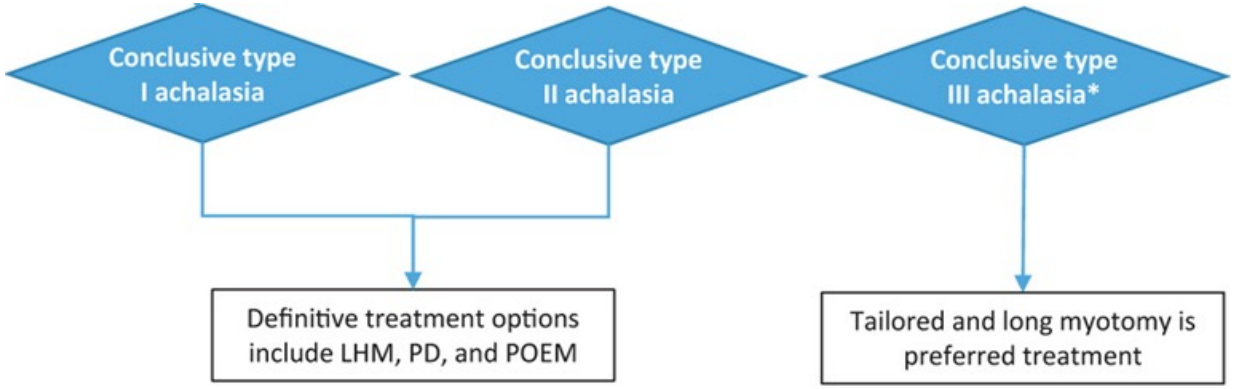
Refractory Disease and Future Directions

- Failed treatment
  - Reassess carefully diagnostically → was therapy incomplete?
  - PD, LHM and POEM can all be options for retreatment after individual assessment
    - Local expertise important
  - Esophagectomy
    - Surgically fit patients with megaesophagus failing other therapies

- Future
  - Further understanding of subtypes across the achalasia spectrum with diagnostic tools
  - More tailored treatments in this spectrum
    - Designed to minimize GERD risks as well as complications and esophageal remodeling (e.g. BOM)

Conclusion

- An accurate diagnosis of achalasia and primary EGJOO is paramount before deciding upon therapy.
- Subtyping achalasia guides evidence-based treatment decisions
- Local expertise and a multi-disciplinary approach are often vital in optimally treating patients with achalasia and EGJOO



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