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Management of early invasive disease

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Massimiliano di Pietro, Consultant Gastroenterologist, Cambridge

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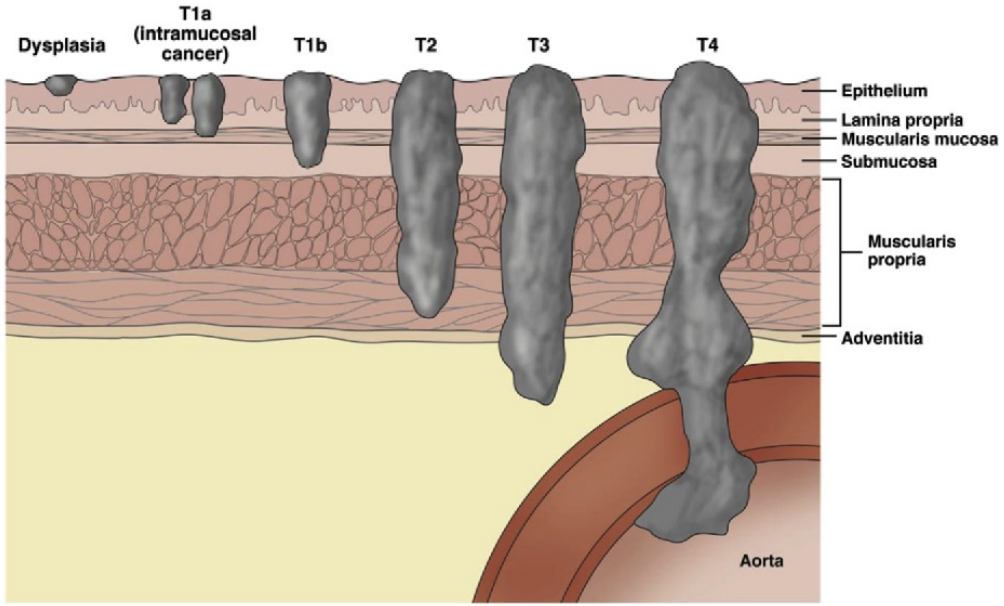
Management of early OG cancer



- T1a
  - Up to but not beyond MM
  - m1 / m2 / m3
- T1b
  - Submucosal, does not breach musc propria
  - sm1 / sm2 / sm3

However: a heterogenous group!

48yo female

- Routine OGD for reflux
- Dysplastic appearances at GOJ
- ESD → T1b sm2, LVI+
- Anxious and wants to avoid surgery

67yo female

- 2ww OGD for abdo pain
- Area of likely early invasive cancer seen
- ESD → T1b sm3 “at least”, with cells up to the diathermied deep margin
- Poorly differentiated
- CT / PET clear

- “Do what you think is best doc”

68yo male

- Longstanding reflux
- Long segment Barretts
- ESD for area of invasive cancer
- T1a, poorly differentiated, signet ring cells

- Now: complex stricture
- Further dysplastic areas

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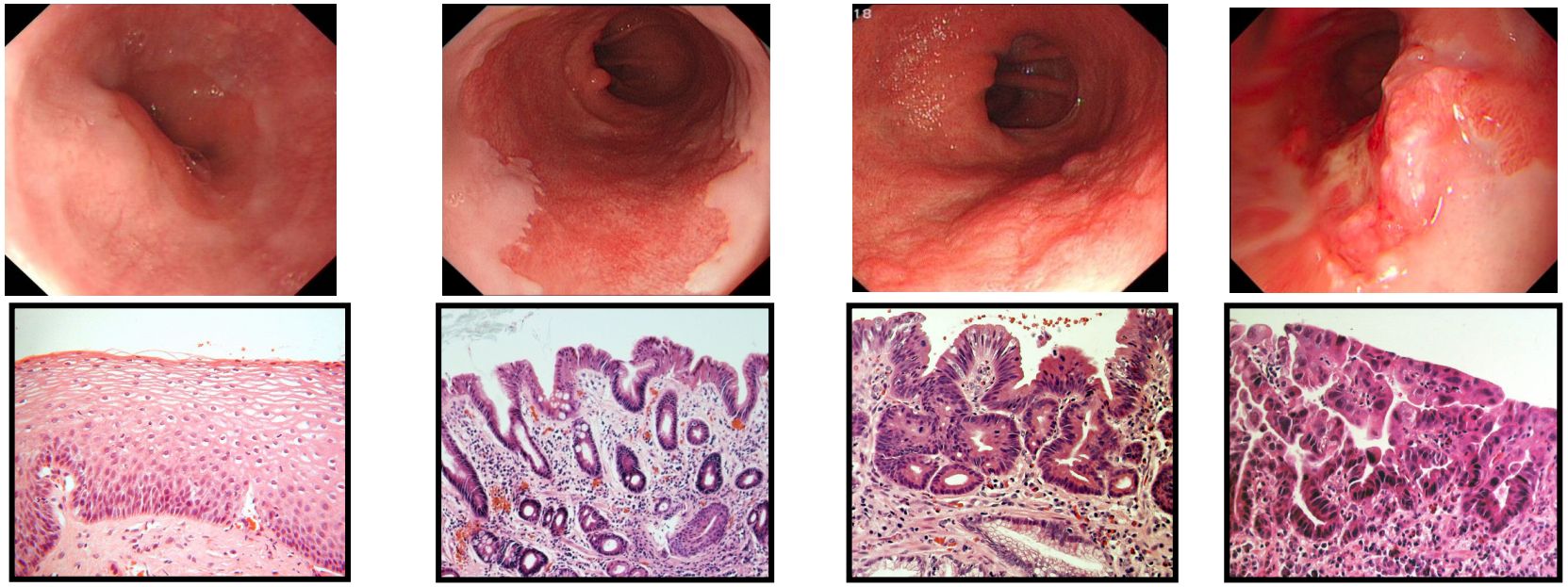
Early Disease and Endoscopic Management

Metaplasia – dysplasia – carcinoma sequence



Squamous epithelium → Barrett's with no dysplasia → Low-grade dysplasia (LGD) → High-grade dysplasia (HGD) → Oesophageal adenocarcinoma

5 - 20% per year

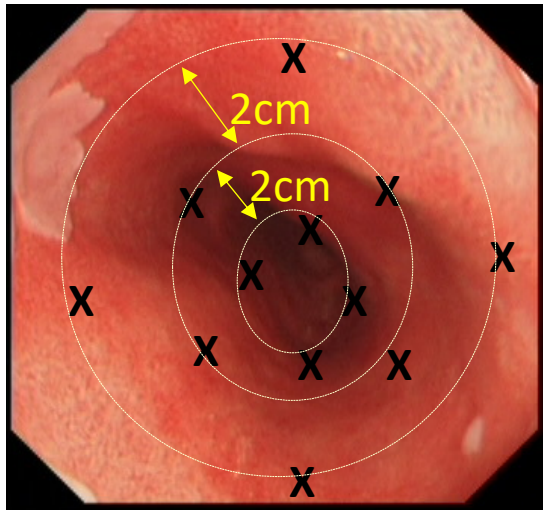
0.5 - 13% per year

0.12-0.5% per year

Desai, Gut 2011; Hvid-Jensen NEJM 2011; Bhat, JNCI 2011; Duits, Gut 2013 Shaheen, NEJM 2009

Approach to patients with Barrett's

Seattle protocol



Good quality endoscopy

Visible lesions

no

4q bx
every 2 cm

No dysplasia

Surveillance

LGD/HGD

RFA or
EMR

yes

Targeted bx

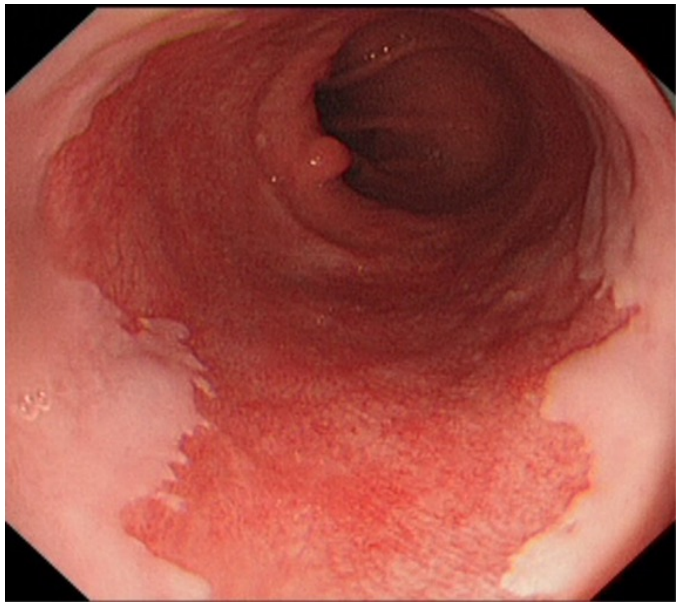
intramucosal
cancer

EMR or
ESD

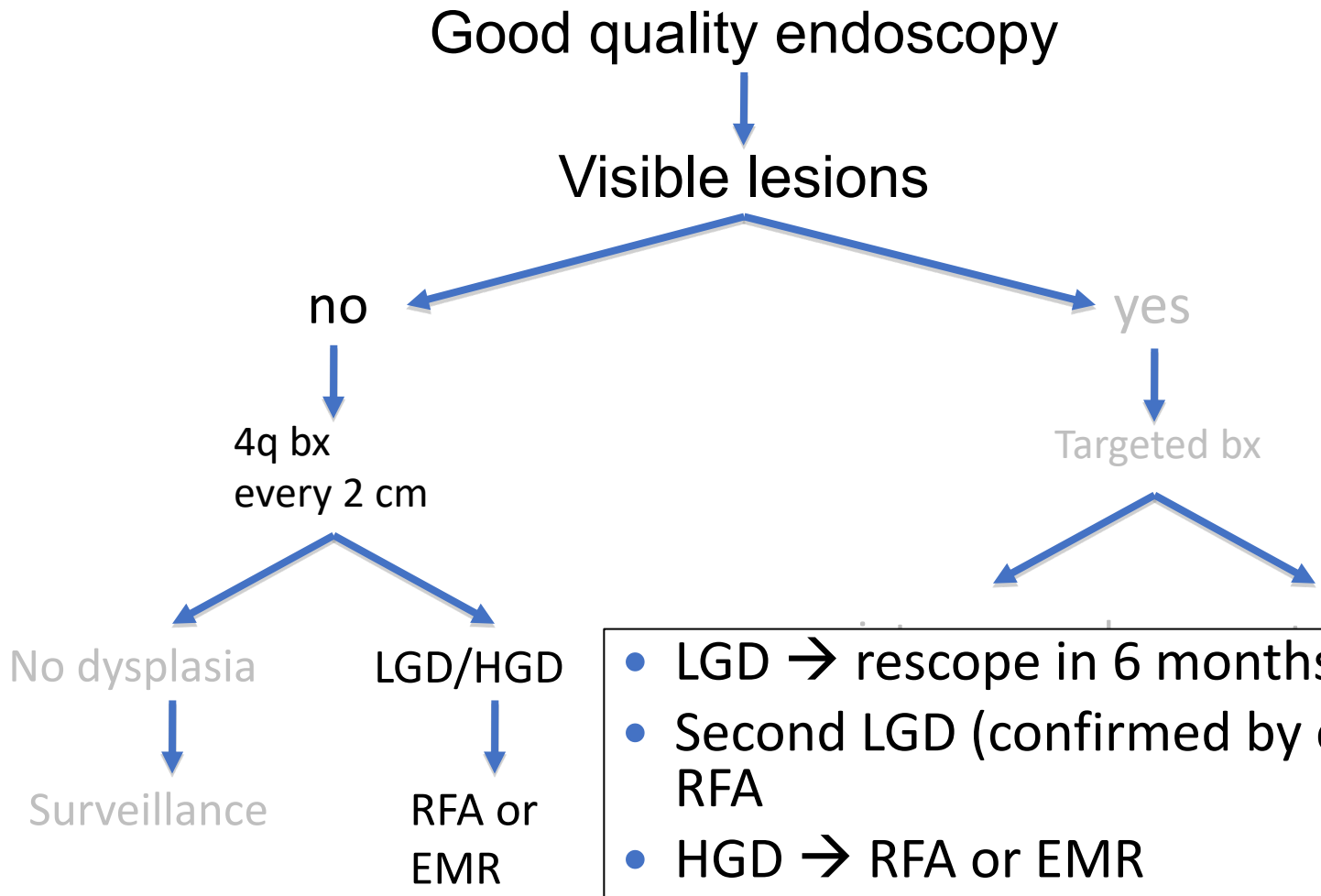
Invasive
cancer

Staging

Chemo +/-
surgery



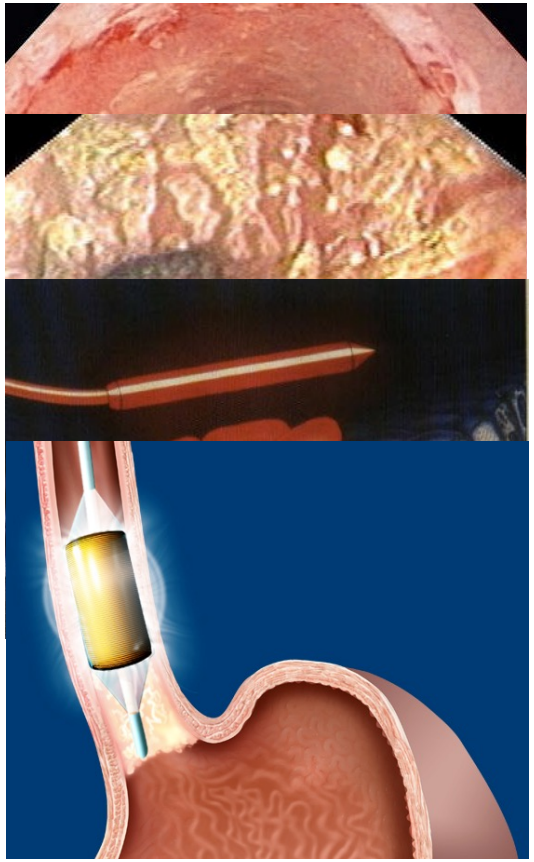
Approach to patients with flat dysplasia



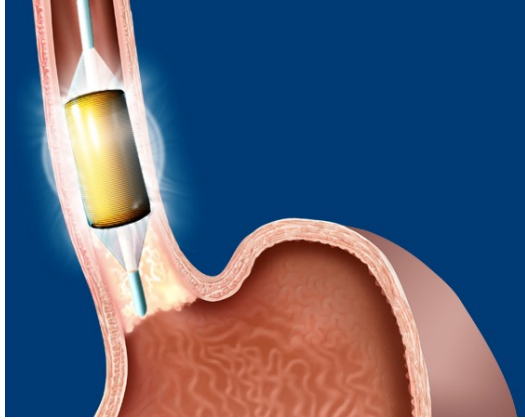
- LGD → rescope in 6 months
- Second LGD (confirmed by expert pathologist→ RFA
- HGD → RFA or EMR

Therapeutic Options for flat dysplasia

- Radical EMR
- Argon Plasma Coagulation
- Photodynamic therapy
- Radiofrequency ablation



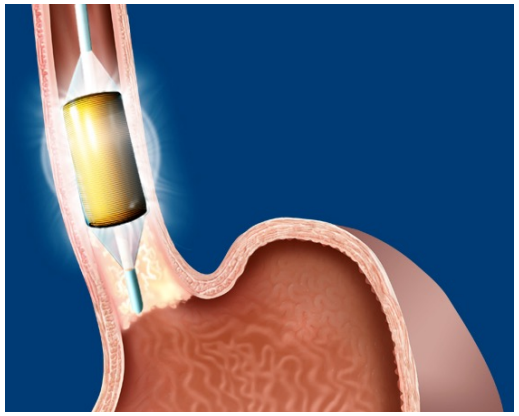
Radiofrequency Ablation



- Radiofrequency energy delivered by a bipolar electrode
- Thermal ablation to a depth of 500 µm
- Indicated only to ablate flat Barrett's mucosa
- NICE approved (2010) for treatment of HGD, BSG approved for persistent LGD (2014)

Types of RFA devices

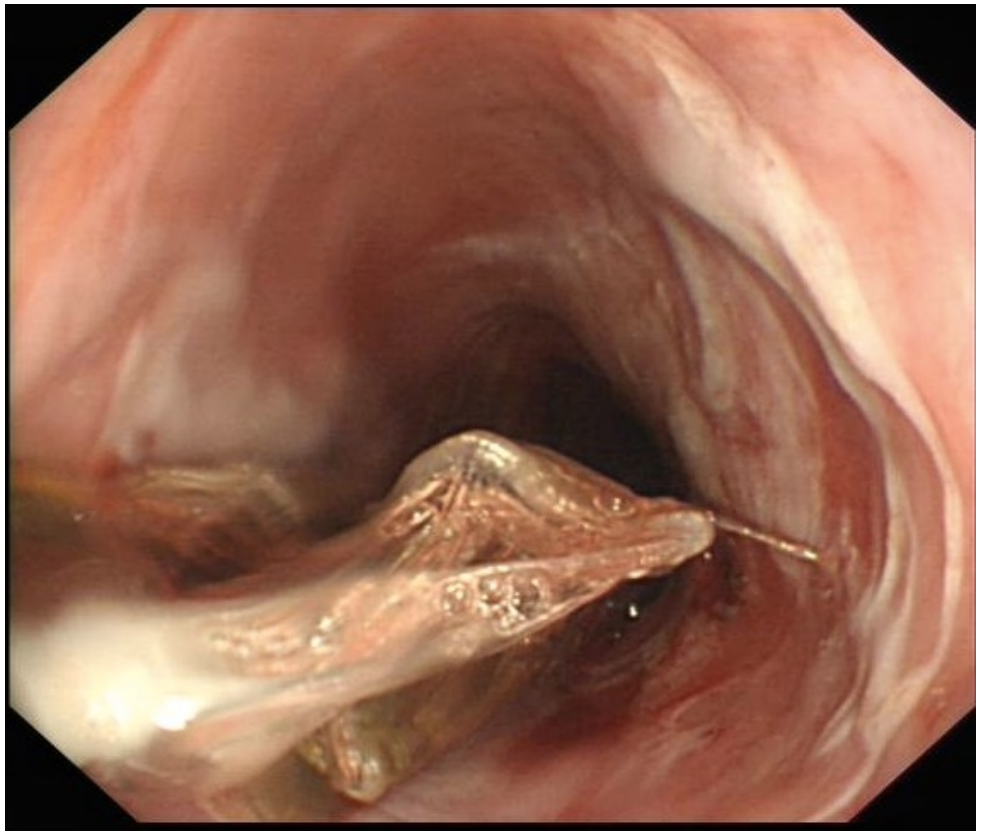
- HALO360 Primary circumferential ablation long segment BE



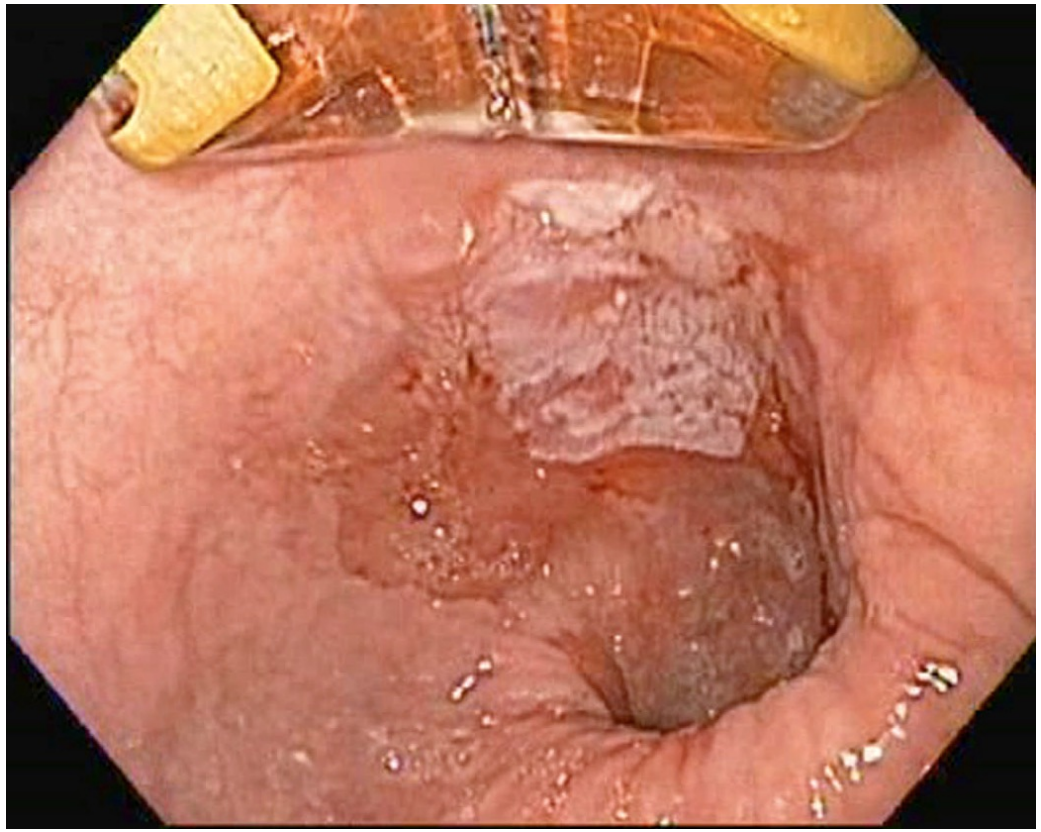
- HALO90
  - Secondary ablation of residual Barrett's
  - Primary ablation short segment BE

Circumferential and focal RFA

HALO 360



HALO 90



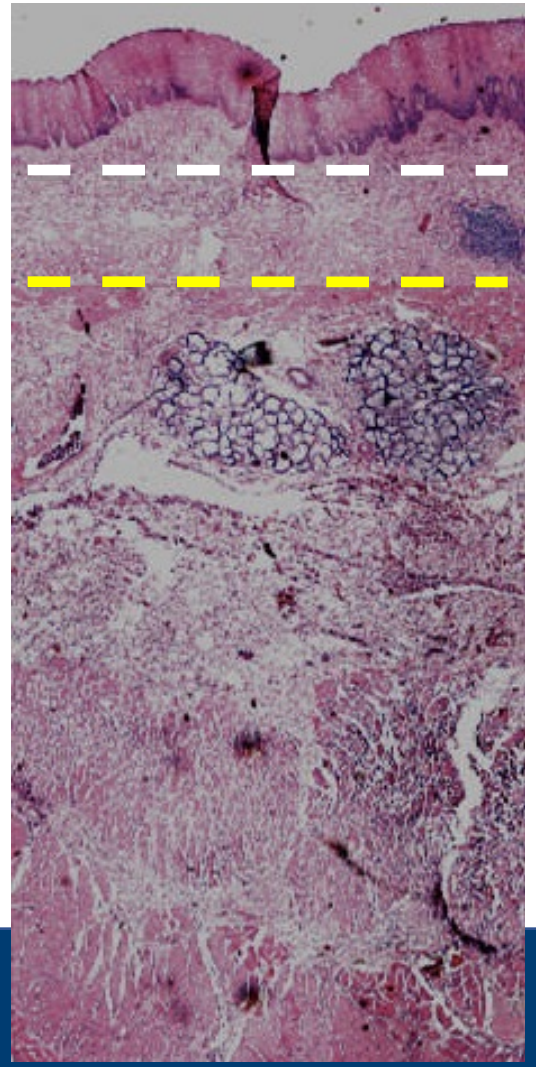
RFA - Ablation depth

Ablation depth

RFA – ALA PDT

EMR

Porfimer PDT

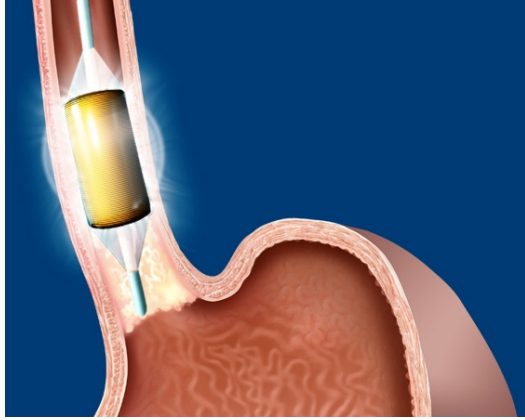


Evidence for RFA

- Prospective multicentre trial for non-dysplastic BE (5y follow up): CR-IM 92%
- Sham controlled RCT for dysplastic BE (1y follow up): CR-D 90.5% vs 22.7%, CR-IM 77.4% vs 2.3%
- Durability at 3 year: CR-D 98%, CR-IM 91%
- UK HALO Registry: >700 patients (335 complete treatment): CR-D 81%, CR-IM 62%
- 2 RCTs for BE with LGD: 25% risk reduction for HGD/Cancer and 35- 88% remission rate

(Fleischer 2008, Fleischer 2010, Shaheen 2009, Shaheen 2011, Haidry 2013, Phoa JAMA 2014, Barret Gut 2021)

PROs and CONs of RFA



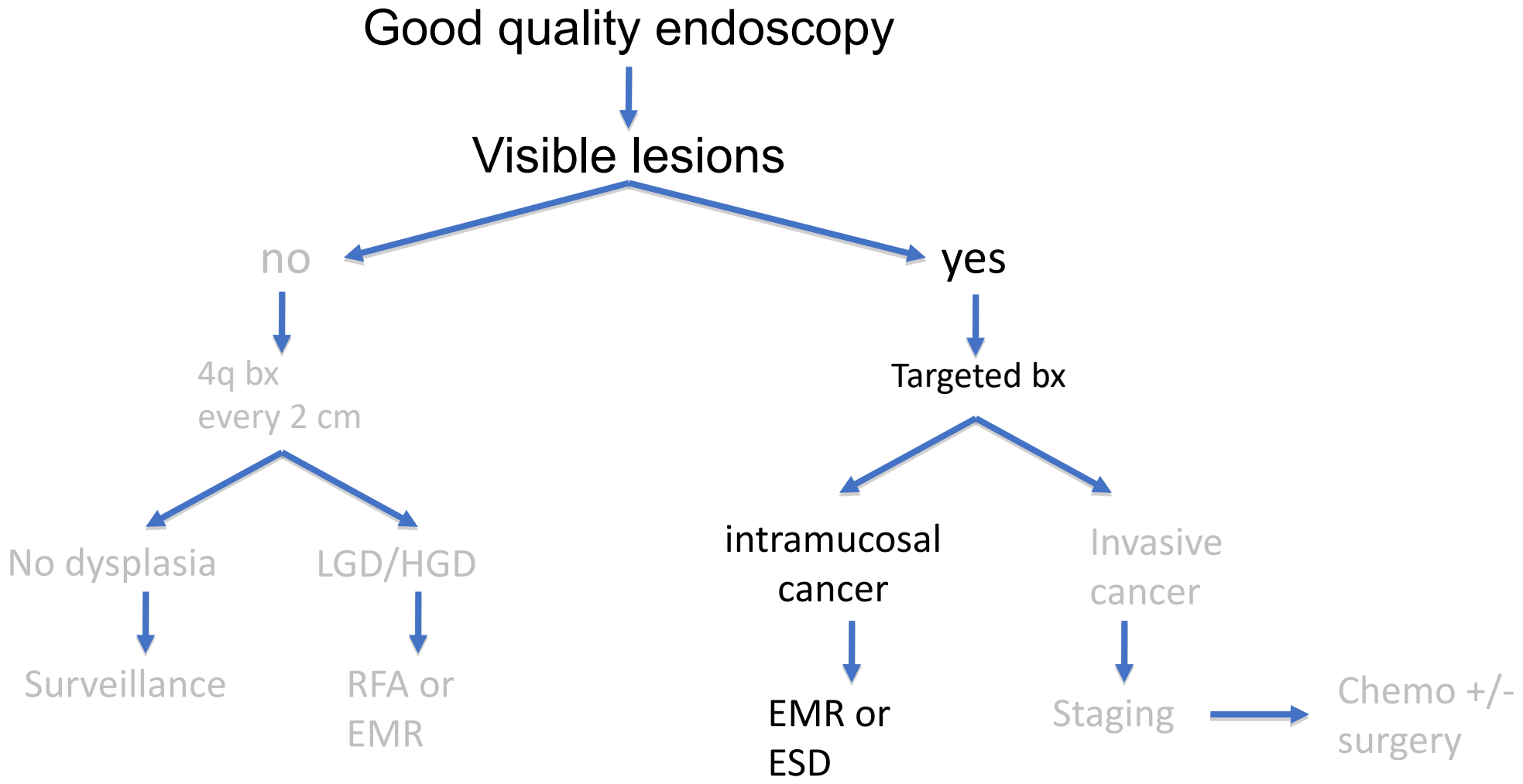
PROs

- Excellent response rate for dysplasia
- RCT available
- Good safety profile (stricure 0-6%)
- Low incidence of buried glands

CONs

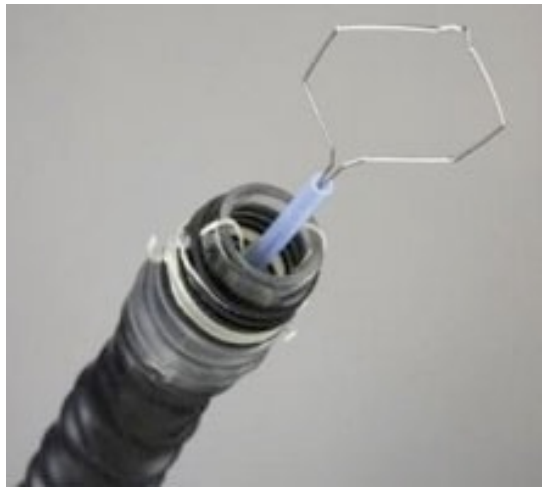
- Costs
- Multiple treatments required (average 2)
- 6-10% stricture rate

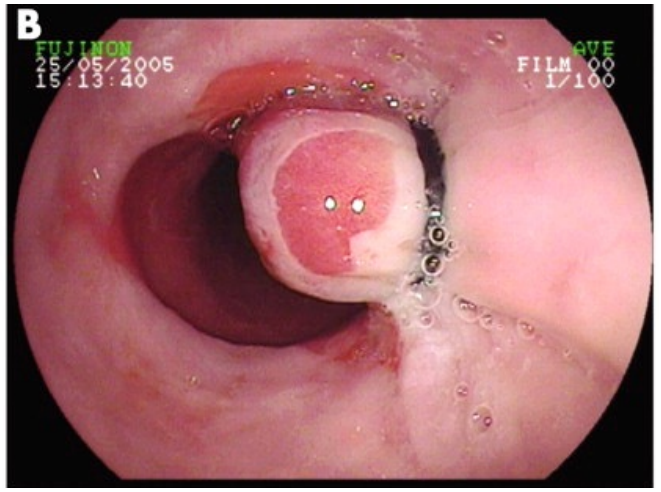
Approach to patients with early visible lesions



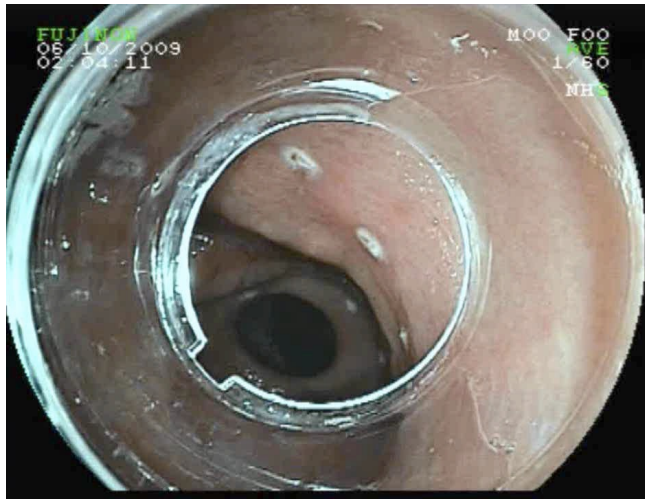
Endoscopic options: Conventional EMR

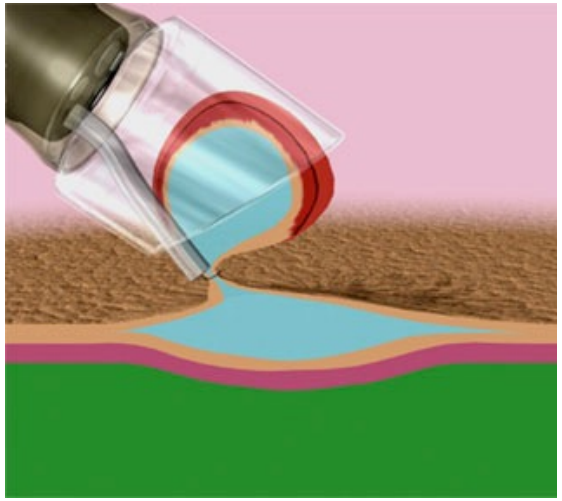
Multiband mucosectomy



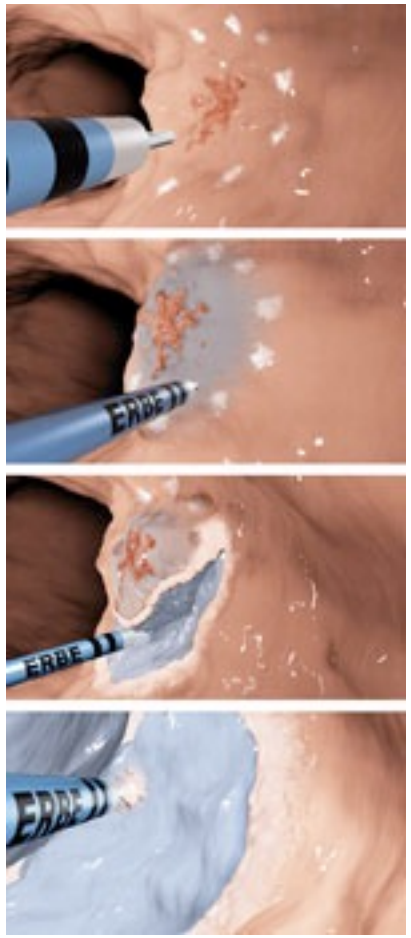


Snare & Cap





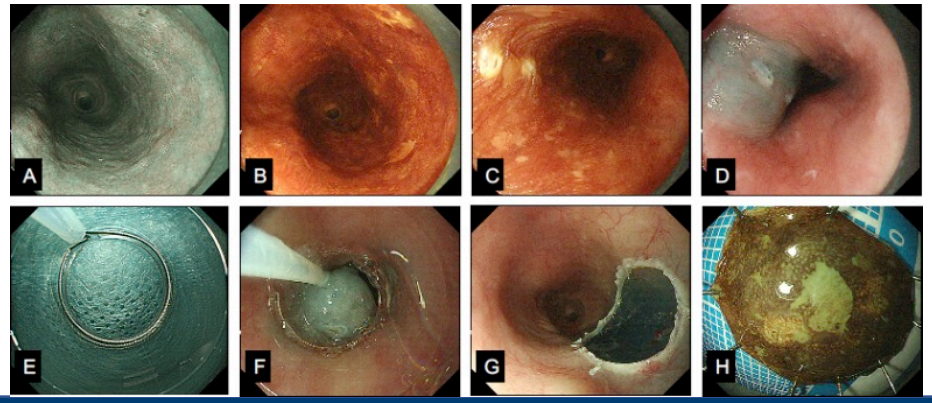
Endoscopic options: Endoscopic submucosal dissection (ESD)

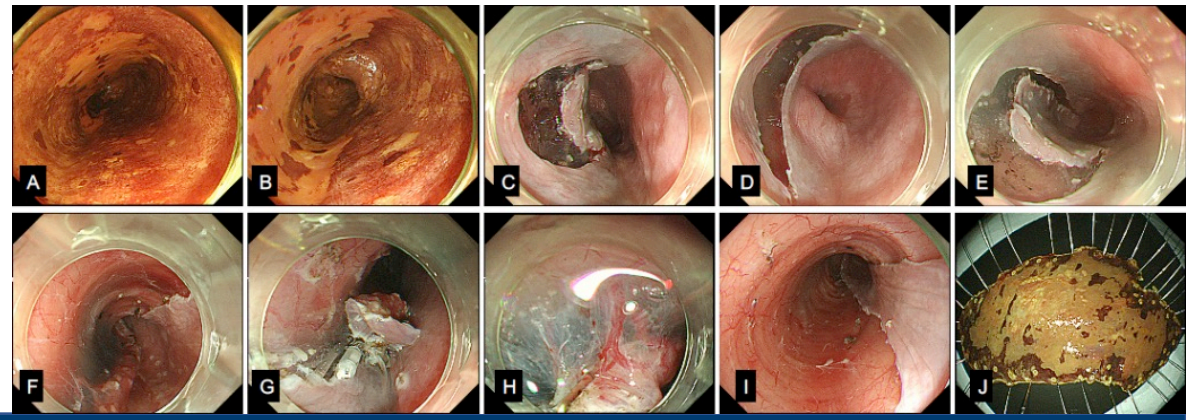


- PROs
  - Allows en block resection (lesions >15mm)
  - Oncologically sound
  - Lower R1 resection rate of superficially elevated lesions
- CONs
  - Technically difficult
  - Long learning curve
  - Higher risk of acute and late complications

ESD vs EMR for OSCC

- No RCT available
- Large retrospective series (mainly from Asia but now Europe too) show that ESD associated to
  - higher R0 resection rate than EMR (100 vs 53%, p<0.05)
  - lower local recurrence rate (0.9 vs 9.8%; p<0.05)
  - higher 5-year survival rates (95.2% vs 73.4%; p<0.01)



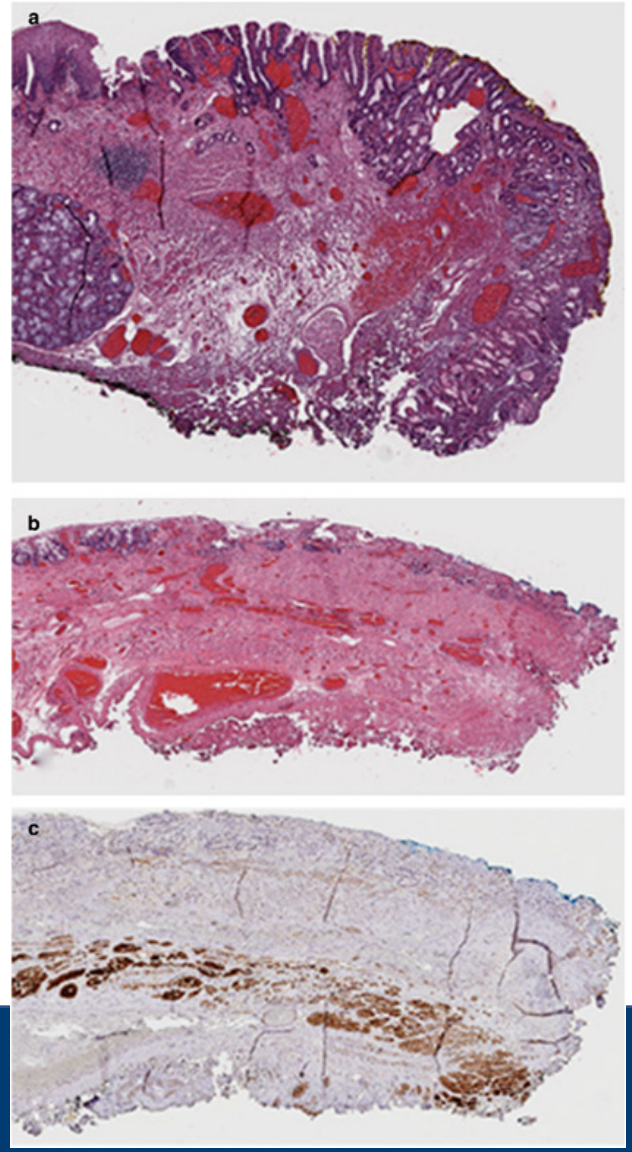


Probst 2015, Takahashi 2010, Park 2016, Nagami 2017

Pathological implications – EMR vs ESD

EMR

ESD



Martelli, Am J Gastro, 2016

ESGE guidelines for endoscopic therapy in ESCC

4.1 Esophageal SCC lesions

RECOMMENDATION

4 ESGE recommends ESD as the treatment of choice for most esophageal squamous cell and gastric (or junctional non-Barrett's) superficial lesions, mainly to provide an en bloc potentially curative resection with accurate pathologic staging.

Strong recommendation, moderate quality evidence.

RECOMMENDATION

5 ESGE suggests that ESD might also be considered for en bloc resection of noncircumferential clinically staged T1a-m3/T1b-sm1 or for circumferential clinically staged T1a-m1/m2 esophageal squamous cell carcinoma (SCC).

Weak recommendation, moderate quality evidence.

Barrett's-related neoplasia: RCT EMR vs ESD

Table 2 Procedural characteristics and outcome at 30 days

	ESD	EMR	p Value
Included patients	20	20	
Type of anaesthesia			
Sedation with propofol	18	19	1.00
Mean amount (±SD) (mg)	724 ±539	362 ±187	0.007
General anaesthesia	2	1	1.00
Mean procedural duration (±SD) (min)	54±33	22±13	0.0003
Circumferential incision for ESD (±SD) (min)	20±12	NA	
Dissection for ESD (±SD) (min)	30±20	NA	
Complete resection of the targeted area	20		
Mean number of pieces (±SD)	1±		
En-bloc resection			
Mean maximal diameter of the large specimen (±SD)			
Length (mm)			
Width (mm)			
Intraprocedural AE			
Perforation			
Postprocedural AE			
Mediastinitis			1.00
Temporary chest discomfort			1.00
Severe AE		0	0.49
30-day mortality (%)	0	0	
Complete resection of HGIN or AC (R0)	10/17	2/17	0.01

Table 4 Follow-up of >30 days

	ESD	EMR	p Value
Included patients	20	20	
Patients refer	4	3	1.00
Patient	0	1	1.00
		16	1.00
		23.6 ±5.0	0.66
	15/16	16/17	1.00
dual neoplasia	16/16	17/17	1.00
estinal neoplasia	6/16	10/17	0.30
estinal metaplasia	10	5	0.08
eradication of intestinal metaplasia	8	3	0.60
eatment ongoing	2	2	1.00
Delayed AEs	0	0	0
Recurrent/metachronous neoplasia	1	0	1.0

AE, adverse event; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; RFA, radiofrequency ablation.

No evidence that ESD should be preferred to EMR for Barrett's neoplasia

ESGE guidelines for endoscopic therapy in Barret's associated lesions

4.2 Barrett's esophagus (BE)-associated lesions

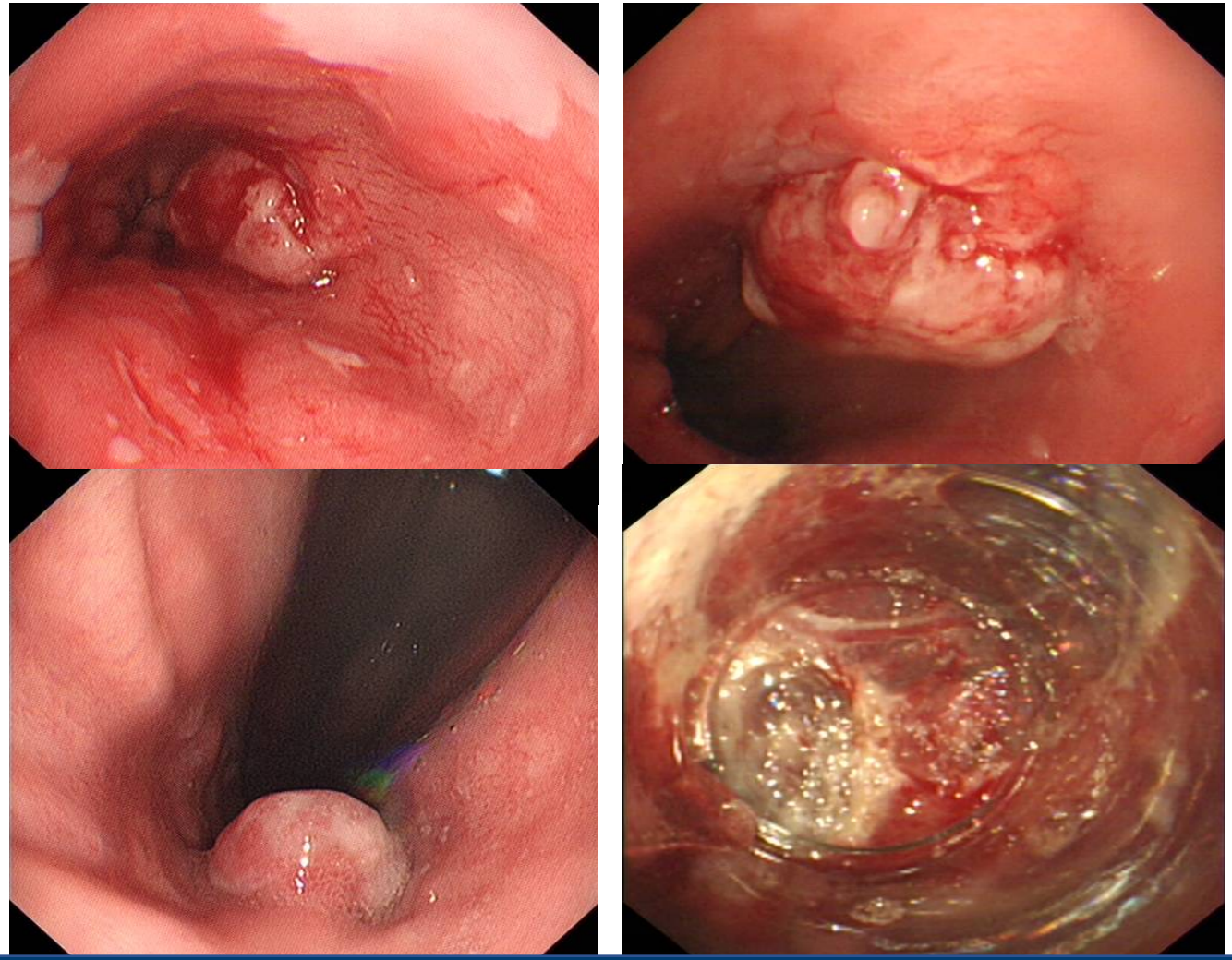
RECOMMENDATION

6 For BE-associated lesions, ESGE recommends to use EMR for ≤ 20 mm visible lesions with low probability of submucosal invasion (Paris type 0-IIa, 0-IIb) and for larger or multifocal benign (dysplastic) lesions.
Strong recommendation, high quality evidence.

RECOMMENDATION

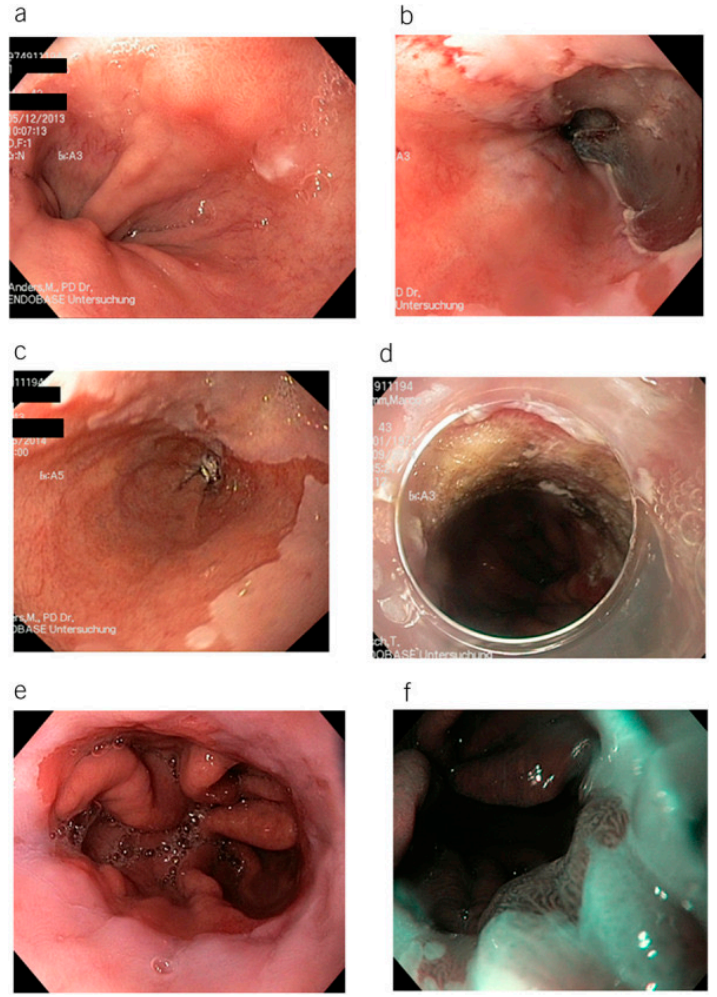
7 For BE-associated lesions, ESGE suggests to use ESD for lesions suspicious for submucosal invasion (Paris type 0-Is, 0-IIc), for malignant lesions > 20 mm, and for lesions in scarred/fibrotic areas.
Weak recommendation, low quality evidence.

Not all early Barrett's cancer are curable by EMR



What after curative resection of Barrett's neoplasia

- Risk of recurrence approx. 15% at 5 years
- Subsequent EMR allows curative resection of residual neoplasia in >90%
- Ablation of residual Barrett's (RFA or APC) reduces 10-fold risk of recurrence
- Post ER ablation induces sustained Barrett's remission in 87-90% of cases



(Pech O, Gastoenterology 2014, Knabe Am J Gastro 2022, Manner Endoscopy 2014, Phoa Gut 2016)

NICE Guidelines on Barrett's Oesophagus *Revised in 2023*

Coming soon!

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What comes after ESD?

Current guidelines

- Current recommendations for T1bN0 oesophageal cancer are to offer radical treatment (i.e. surgery for ACC, dCRT or surgery for SCC)
- Based on theoretical risk of nodal metastasis (commonly cited 4-16%)
- …Survival rate after surgery does not start at 100%

1.4.4 Offer radical resection for people with T1bN0 oesophageal adenocarcinoma if they are fit enough to have surgery.

1.4.5 Offer people with T1bN0 squamous cell carcinoma of the oesophagus the choice of:

- definitive chemoradiotherapy **or**
- surgical resection.

T1a, T1b sm1

- Low risk of spread

- 114 patients 1996-2009
- 6.6% local recurrence rate
- No metastatic disease

Comparison Between Endoscopic and Surgical Resection of Mucosal Esophageal Adenocarcinoma in Barrett's Esophagus At Two High-Volume Centers

Oliver Pech, MD, PhD, Elfriede Bollschweiler, MD, PhD, Hendrik Manner, MD, PhD, Jessica Leers, MD, Christian Ell, MD, PhD, and Arnulf H. Hölscher, MD, PhD

High risk T1b?

- >=500nm
- Poorly diff
- LVI+

- Plenty of studies citing low (5-10% rate of nodal metastasis), but…

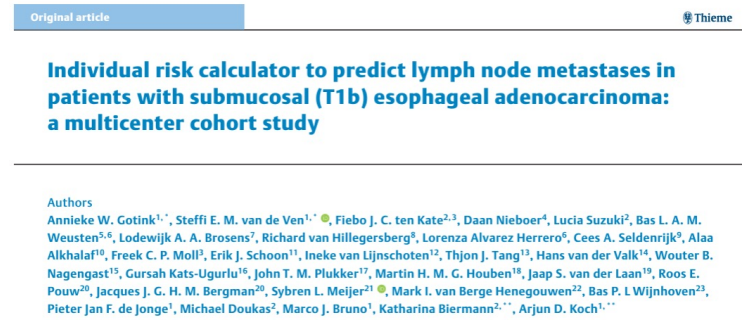
- 75 T1a, 51 T1b
- 21.6% nodal met rate, 36% if LVI+

- 248 T1b patients (any T1b)
- 30.9% nodal metastasis rate over 5y f/u

The Prevalence of Lymph Node Metastases in Patients With T1 Esophageal Adenocarcinoma

A Retrospective Review of Esophagectomy Specimens

Jessica M. Leers, MD, Steven R. DeMeester, MD*, Arzu Oezcelik, MD*, Nancy Klipfel, MD†, Shahin Ayazi, MD*, Emmanuele Abate, MD*, Jörg Zehetner, MD*, John C. Lipham, MD*, Linda Chan, PhD‡, Jeffrey A. Hagen, MD*, and Tom R. DeMeester, MD**



Original article

Thieme

Individual risk calculator to predict lymph node metastases in patients with submucosal (T1b) esophageal adenocarcinoma: a multicenter cohort study

Authors

Annieke W. Gotink[1,*], Steffi E. M. van de Ven[1,*], Fiebo J. C. ten Kate[2,3], Daan Nieboer[4], Lucia Suzuki[2], Bas L. A. M. Weusten[5,6], Lodewijk A. A. Brosens[7], Richard van Hillegersberg[8], Lorenza Alvarez Herrero[6], Cees A. Seldenrijk[9], Alaa Alkhalaf[10], Freek C. P. Moll[3], Erik J. Schoon[11], Ineke van Lijnschoten[12], Thjon J. Tang[13], Hans van der Valk[14], Wouter B. Nagengast[15], Gursah Kats-Ugurlu[16], John T. M. Plukker[17], Martin H. M. G. Houben[18], Jaap S. van der Laan[19], Roos E. Pouw[20], Jacques J. G. H. M. Bergman[20], Sybren L. Meijer[21], Mark I. van Berge Henegouwen[22], Bas P. L Wijnhoven[23], Pieter Jan F. de Jonge[1], Michael Doukas[2], Marco J. Bruno[1], Katharina Biermann[2,**], Arjun D. Koch[1,**]

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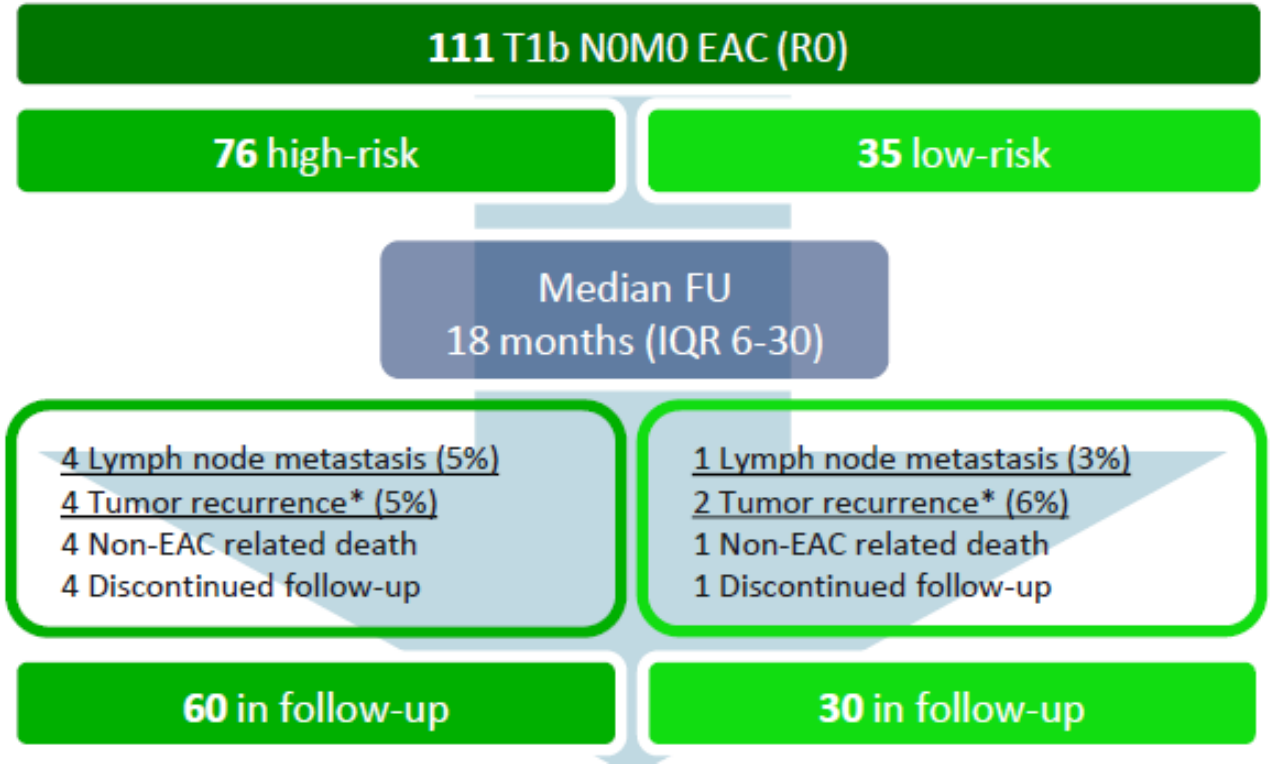
PREFER study

- Retrospective: 120 patients over 11 years
- Prospective: 9 units, 2017-22



ueg week

So what do we know about T1b…

- Small numbers
- Hugely variable outcome reports
- Lack of prospective trials

So what happened to those patients…

48yo female

- Routine OGD for reflux
- Dysplastic appearances at GOJ
- ESD → T1b sm2
- Anxious and wants t surgery

No residual disease in surgical specimen

67yo female

- 2ww OGD for abdo pain
- Area of likely early invasive cancer seen
- ESD → T1b sm3 "a
  cells up to the diath
  margin
- Poorly differentiated
- CT / PET clear

No residual disease in surgical specimen

- "Do what you think is best doc"

68yo male

- Longstanding reflux
- Long segment Barretts
- ESD for area of invasive cancer
- T1a, poorly differen
  signet ring cells

- Now: complex stricture
- Further dysplastic areas, at least one area of adenoca


We need better data!

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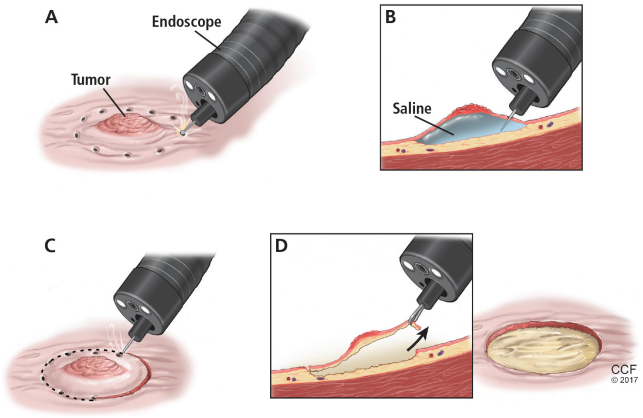
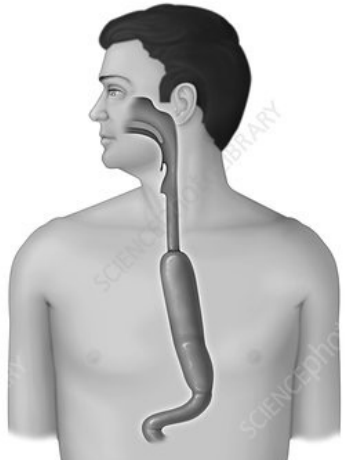
CONGRESS

endosCopic resectiON, esophaGectomy or gastrectomy foR Early oeSophagogastric cancerS

A national retrospective audit of management and outcomes for early OG cancers

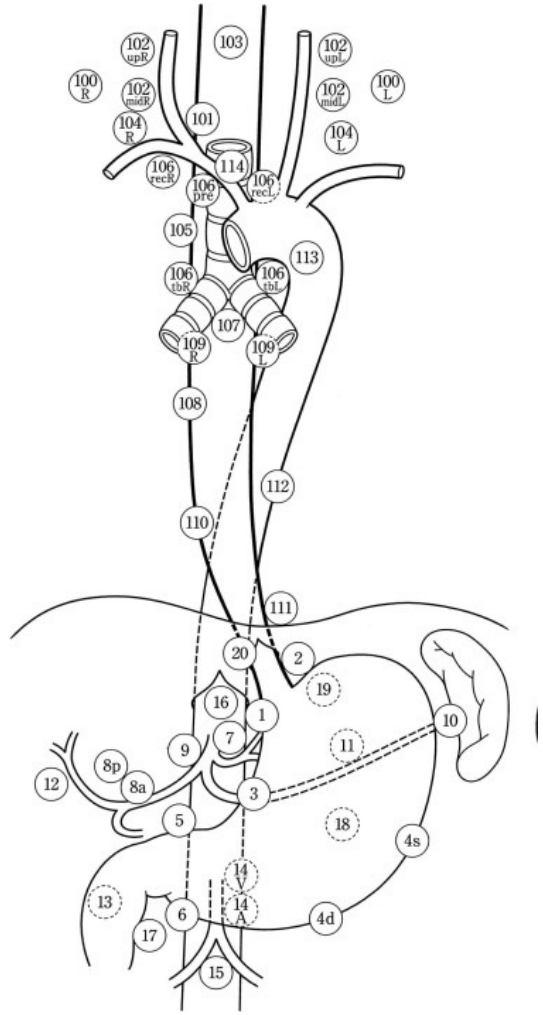


AUGIS
Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland



The problem

- Massive risk of overtreating patients who may not have residual disease
- A lack of large datasets to gauge true risk of nodal metastasis
- The (un)known variability of practice nationally
- What about T1a? Gastric?



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The solution

- **CONGRESS: a national retrospective audit**
- Early OG cancers: T1a/T1bN0 (clinically or ESD staged)

- REDCap online data capture

- Standard collaborative authorship model
- Local lead consultant + named local collaborators

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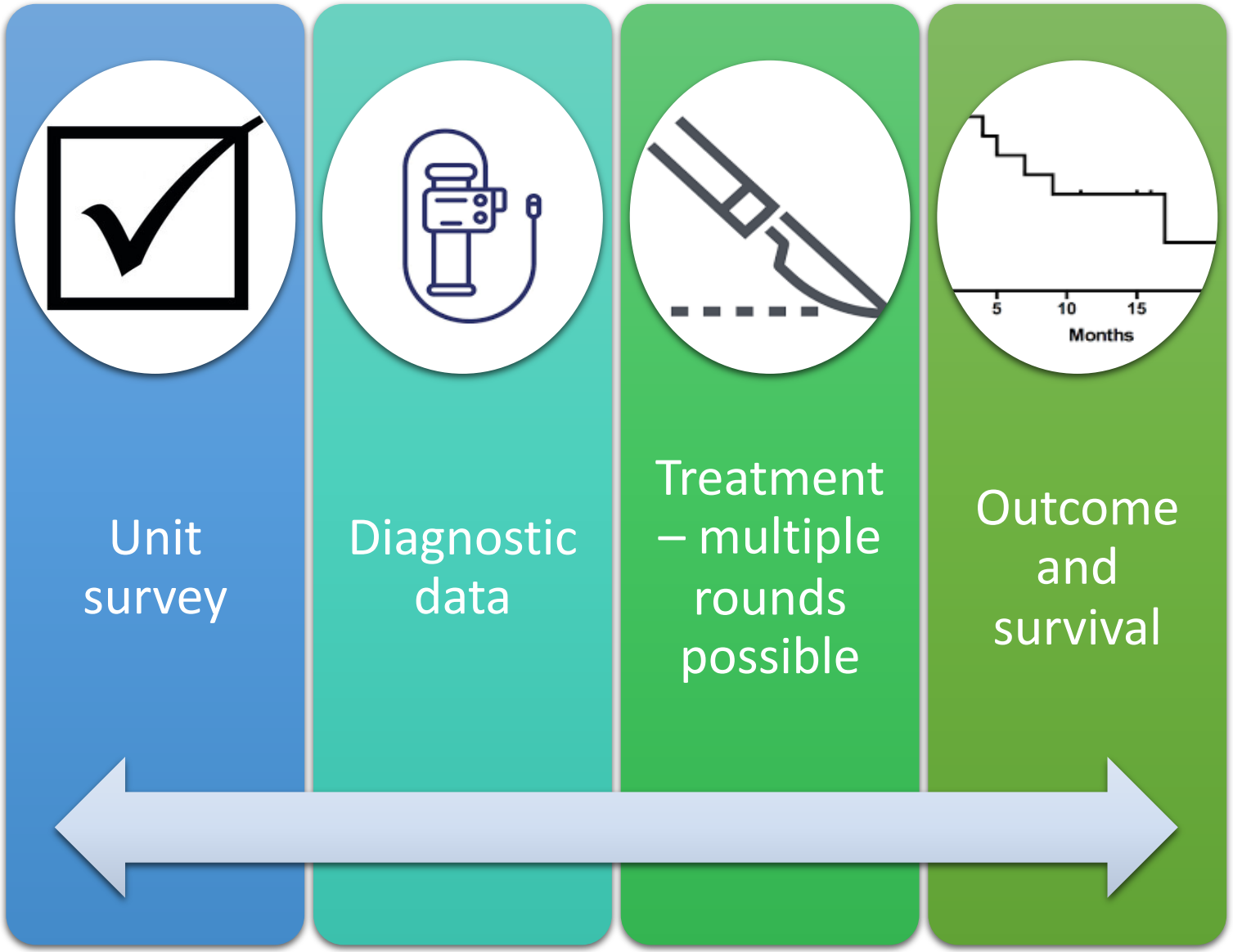
CONGRESS

- Anonymised patient, disease, treatment, and outcome variables
- 2015 - 2022



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Next steps

- Currently in RedCAP final piloting phase
- Wider advertising, recruitment, and opening to data entry soon
- Please contact me or steering group for questions!

Philip Pucher (Portsmouth)

Sivesh Kamarajah (West Midlands)

Natalie Blencowe (Leeds)

Sheraz Markar (Oxford/Utrecht)

Ewen Griffiths (Birmingham)

Tim Underwood (Southampton)

Pradeep Bhandari (Portsmouth)

Rich Evans (West Midlands)

Tom Crosby (Cardiff)

Nigel Trudgill (Birmingham)

James Gossage (St Thomas', London)

Thank you