City of Hope®

Annual

Advances and Innovations in Endoscopic Oncology and Multidisciplinary Gastrointestinal Cancer Care

Organ-preserving Esophageal Cancer Therapy: Are We Ready for the Next Frontier?



Biniam Kidane, MD, MSc

Thoracic & Foregut Surgery

Interventional Endoscopy

Professor, Department of Surgery, Western University

Disclosures

- Consultant for AstraZeneca, Bristol Myers Squibb, Johnson & Johnson MedTech, Medtronic, Olympus, and Roche.

This 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:

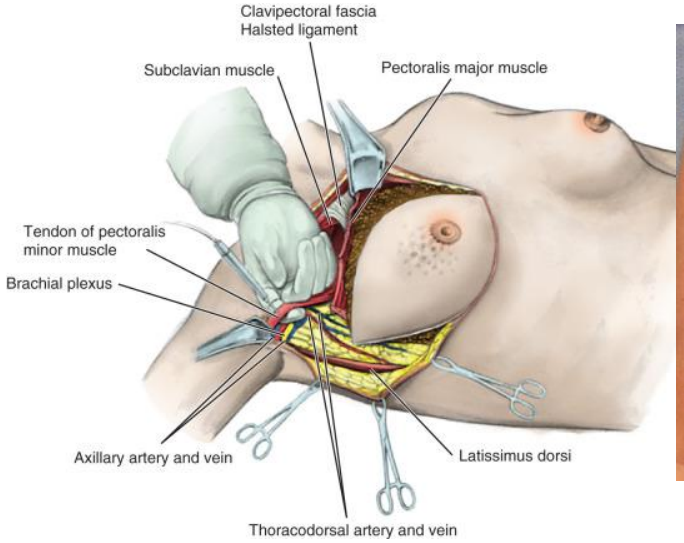
- Reduced access to organ-preservation in patients with low health literacy, low SES, rurality.

Objectives

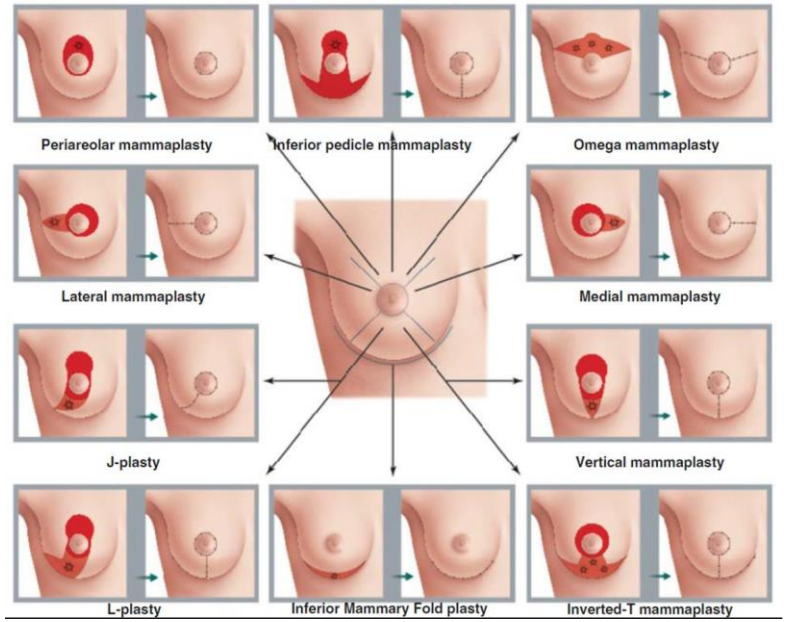
- What organ-sparing approaches are an option in patients with gastro-esophageal malignancies

- When should these be considered?

Western
UNIVERSITY · CANADA







EARLIER APPROACHES **CONTEMPORARY OPTIONS**

TREATMENT PARADIGMS EVOLVE OVER DECADES

Western UNIVERSITY · CANADA

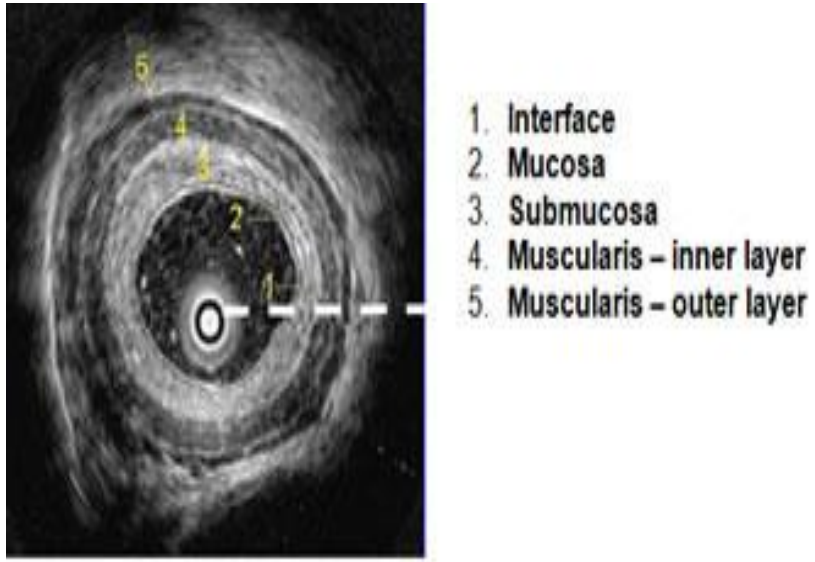
Early stage localized cancer

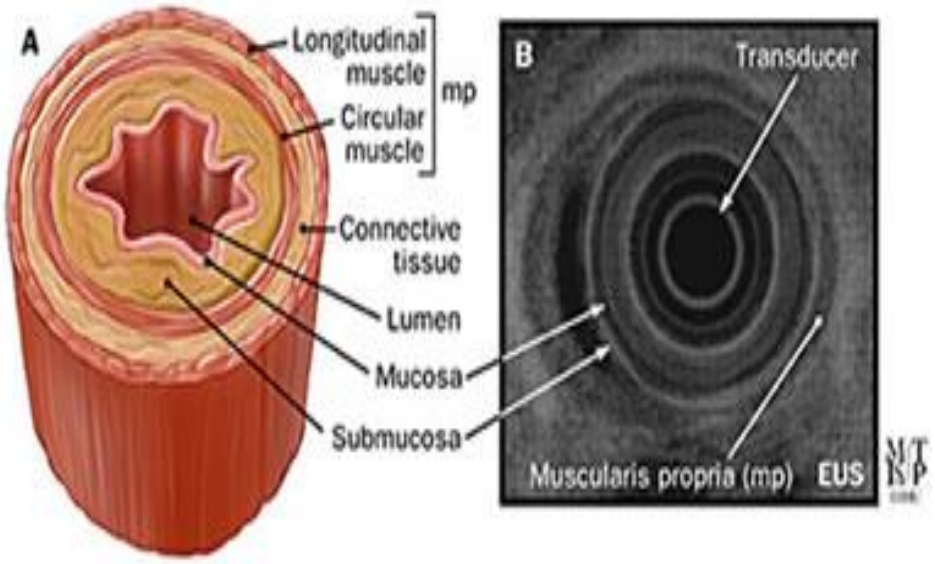
- Management of early/localized T1 esophageal cancer
  - Usually esophagectomy
  - More and more, endoscopic resection is favoured
    - Conventionally for pT1a

Western UNIVERSITY · CANADA

How can you tell if T1a?

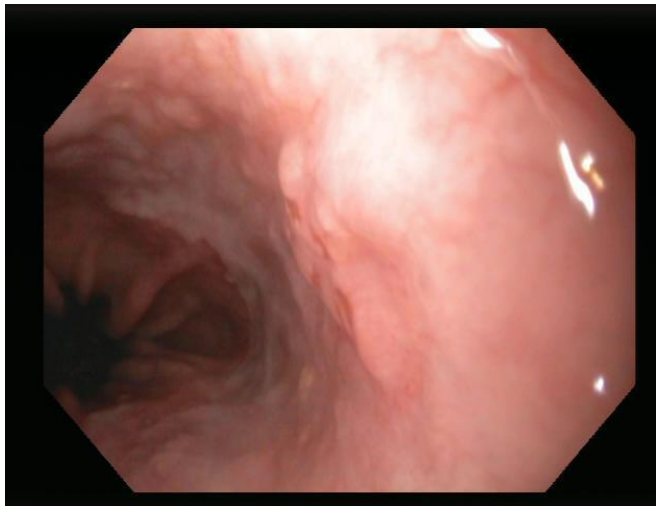
- Crux of management is distinguishing T1 vs T2, T1a?
- Traditionally→ EUS
  - Poor test characteristics for T1 vs T2
    - Worse for T1a vs T1b
- Solution: EMR!
  - Good pathologic assessment of T-stage



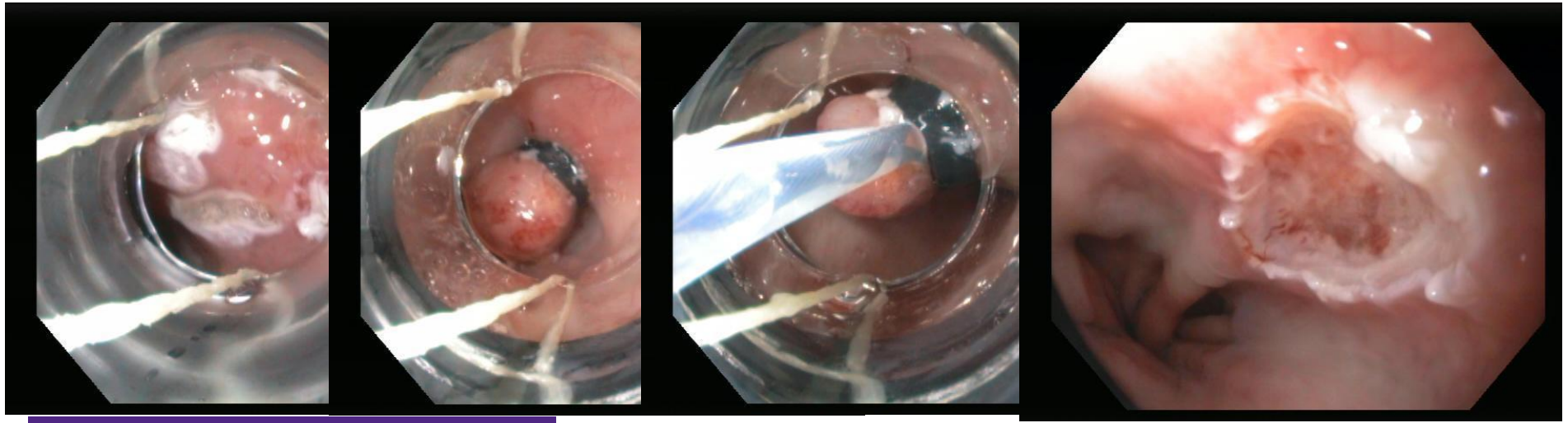


Western UNIVERSITY · CANADA

Endoscopic Mucosal Resection (EMR)







Western
UNIVERSITY · CANADA

Endoscopic Resection is standard of care!

Gastroenterology 2014;146:652–660

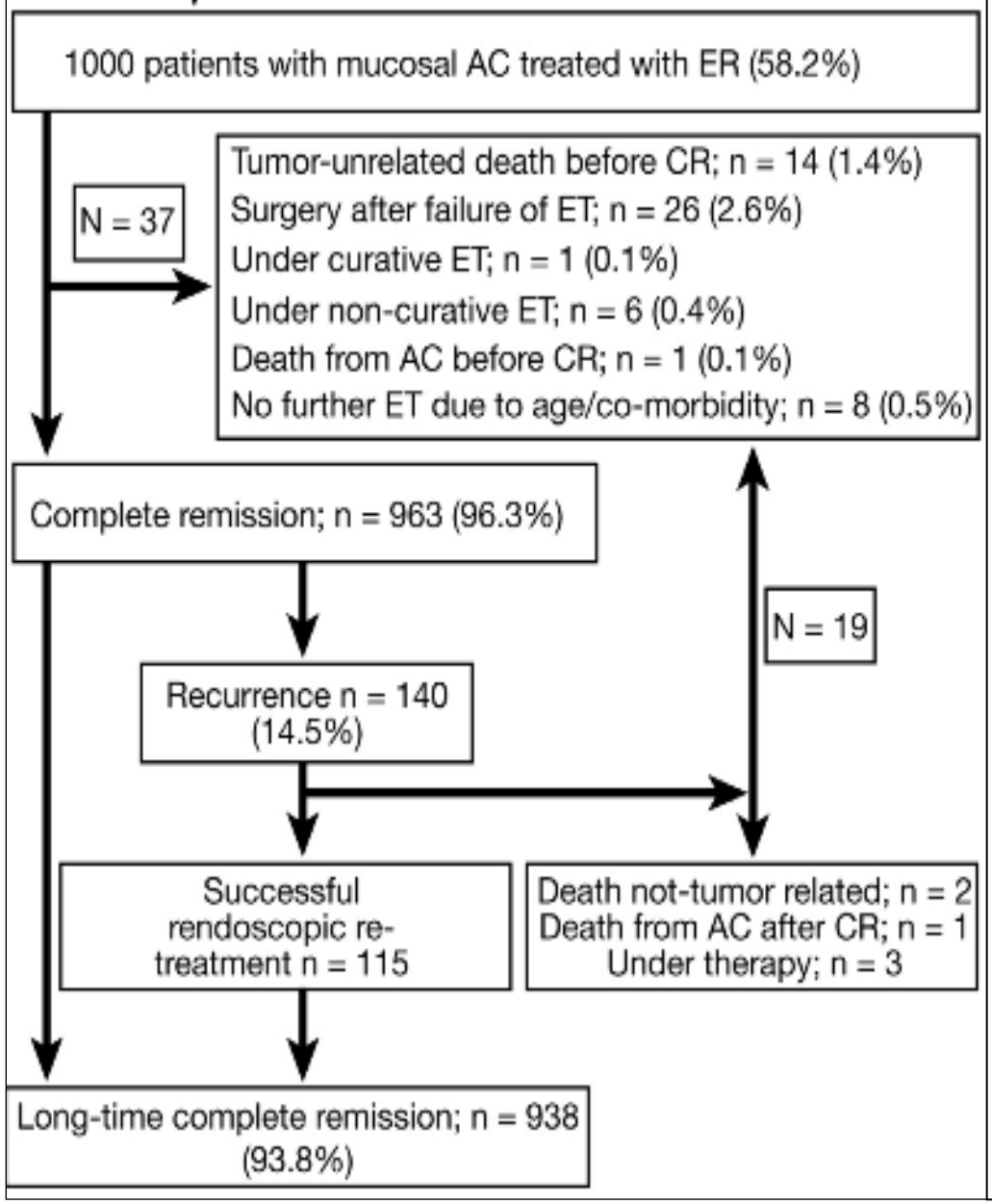
CLINICAL—ALIMENTARY TRACT

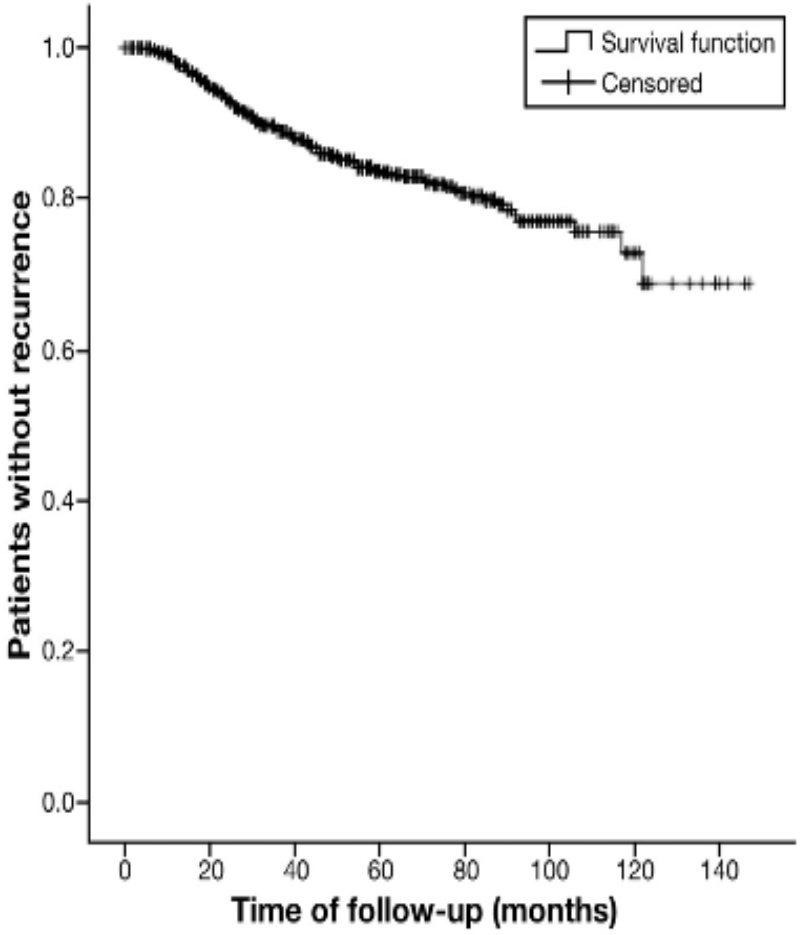
Long-term Efficacy and Safety of Endoscopic Resection for Patients With Mucosal Adenocarcinoma of the Esophagus

Oliver Pech,[1] Andrea May,[2] Hendrik Manner,[2] Angelika Behrens,[2] Jürgen Pohl,[2] Maren Weferling,[2] Urs Hartmann,[2] Nicola Manner,[2] Josephus Huijsmans,[2] Liebwin Gossner,[3] Thomas Rabenstein,[4] Michael Vieth,[5] Manfred Stolte,[6] and Christian Ell[2]

[1]Department of Gastroenterology and Interventional Endoscopy, St John of God Hospital, University of Regensburg, Regensburg; [2]Department of Internal Medicine II, HSK Wiesbaden, University of Mainz, Wiesbaden; [3]Department of Internal Medicine II, Klinikum Karlsruhe, Karlsruhe; [4]Department of Gastroenterology, Diakonissen Krankenhaus, Speyer; [5]Institute of Pathology, Bayreuth Hospital, University of Erlangen-Nuremberg, Bayreuth; [6]Department of Pathology, Klinikum Kulmbach, Kulmbach, Germany

Western UNIVERSITY · CANADA





Time (months)	12	24	36	48	60	72	84	96	108	120
Patients at risk	951	818	668	547	429	308	212	132	75	39

Figure 2. Kaplan–Meier plot for estimating freedom from tumor.

Western UNIVERSITY · CANADA

Table 2. Acute and Long-term Results

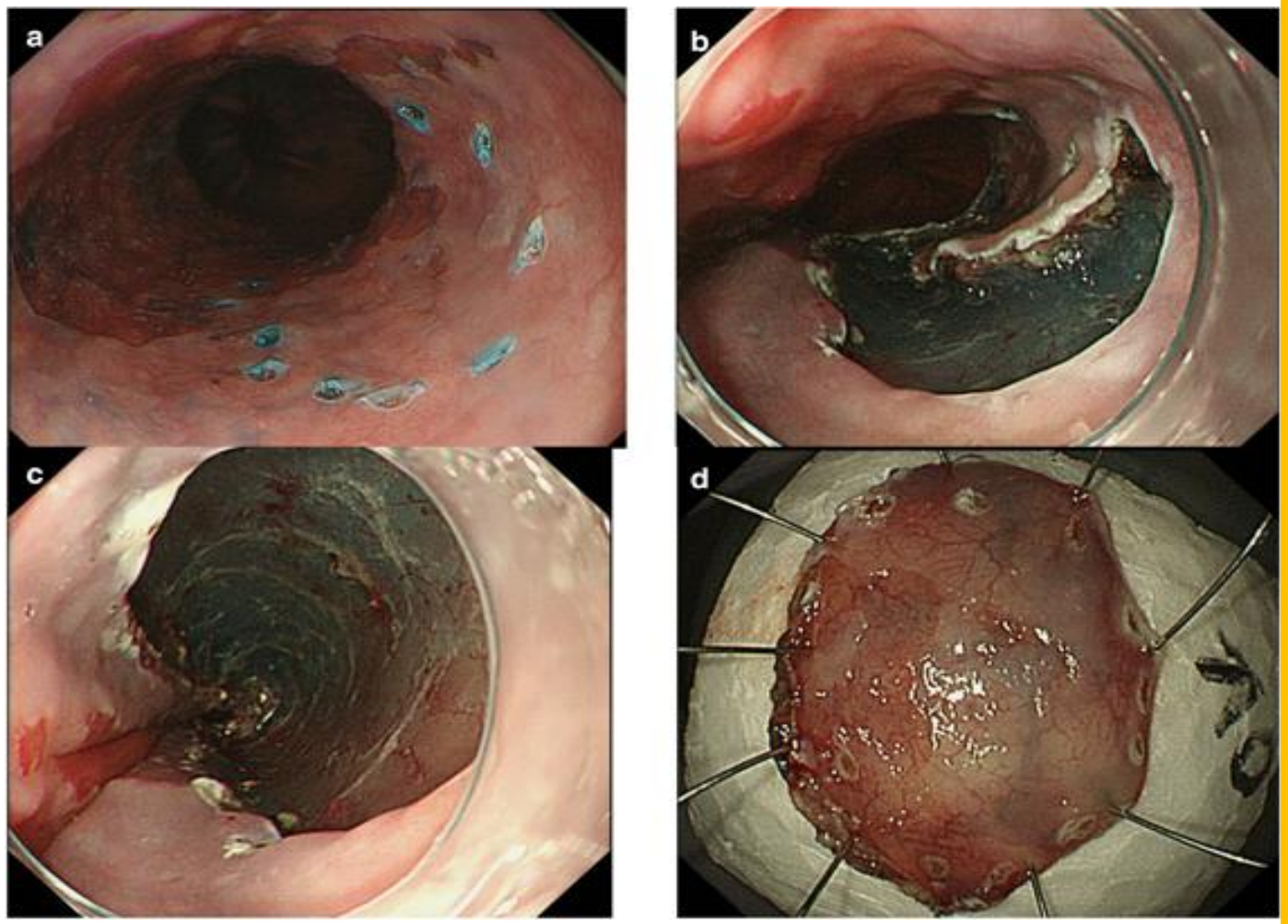
ERs (n)	2687
ERs per patient; median (interquartile range)	1 (1–3)
Major complications, n (%)	15 (1.5%)
Major bleeding	14
Perforation	1
Complete local remission, n (%)	963/1000 (96.3)
Time until complete local remission (*mo*), median (interquartile range)	1 (1–3)
Follow-up (*mo*), mean ± SD	56.6 ± 33.4
Metachronous lesions, n (%)	140/963 (14.5)
Long-term complete local remission after repeat ER, n (%)	938/1000 (93.8)

Endoscopic resection is curative for pT1a!

N.B. Most of these were EMR

Western UNIVERSITY · CANADA

Endoscopic Submucosal Dissection (ESD)



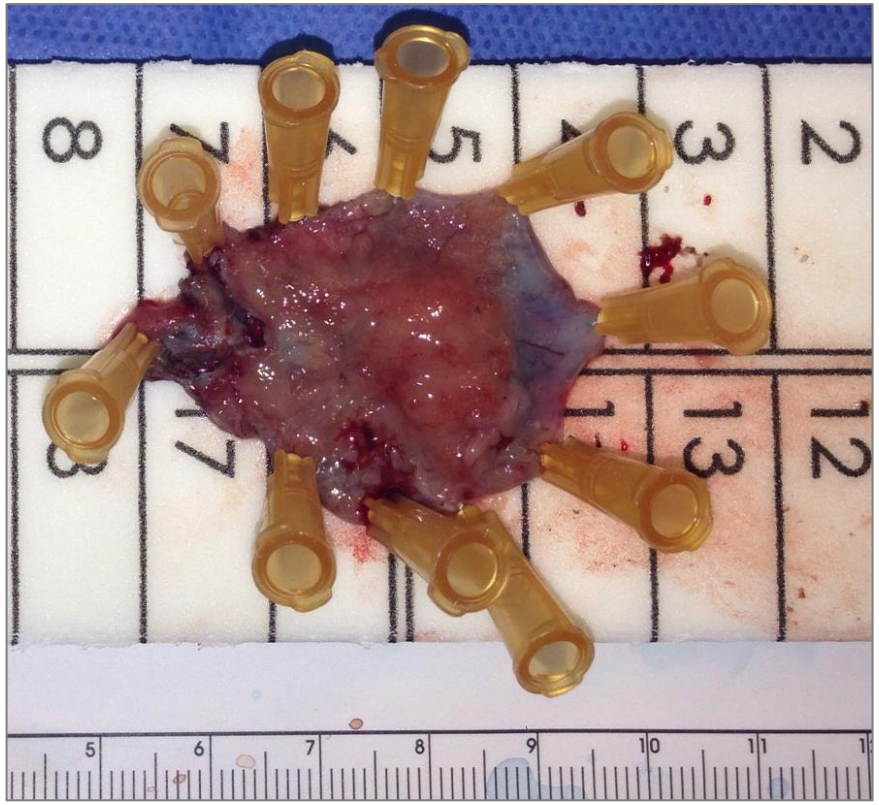
- Mark
- Submucosal injection
- Mucosotomy
- Submucosal dissection
- En bloc resection

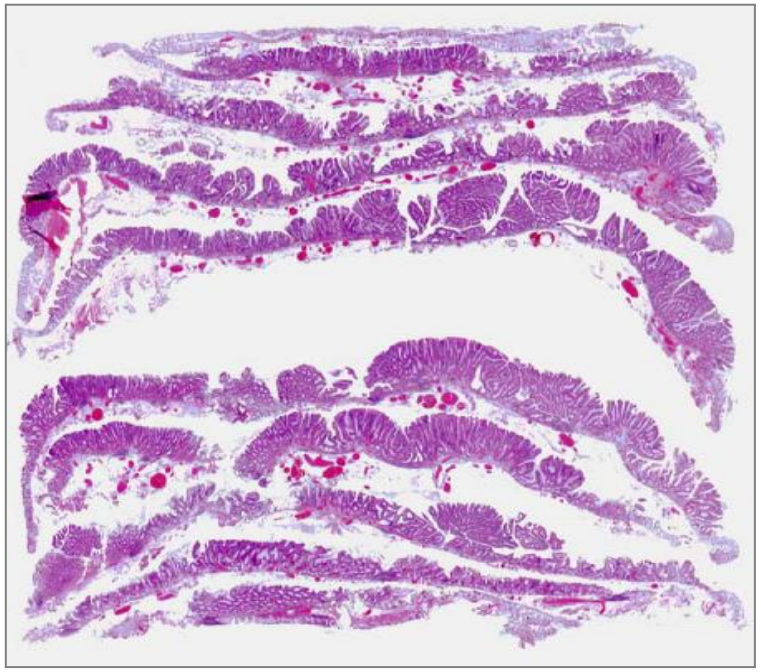
Why ESD vs EMR?

- Larger lesions
  - Avoid piecemeal EMR
    - Better margin assessment, reduced local recurrence
- Previous endoscopic treatments (cause submucosal fibrosis)
  - RFA
  - EMR

Western UNIVERSITY · CANADA

ESD allows for en-bloc resection





Circumferential Margin

Deep Margin

Lower rate of recurrence than EMR

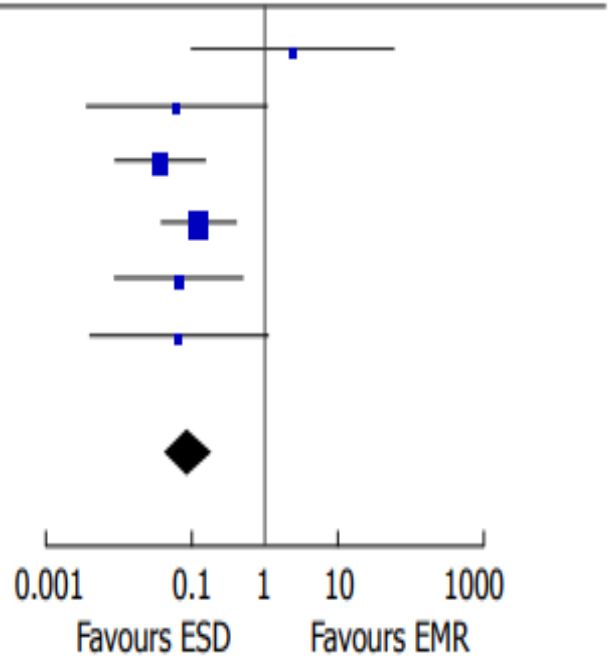
Courtesy of Dr Lorenzo Ferri

Lower local recurrence with ESD

Study or subgroup	ESD Events	ESD Total	EMR Events	EMR Total	Weight	Odds ratio IV, fixed, 95%CI
Kim YJ 2013	1	115	0	91	5.5%	2.40 [0.10, 59.55]
Kobayashi N 2012	0	28	12	56	6.9%	0.06 [0.00, 1.10]
Lee EJ 2012	2	257	31	177	27.3%	0.04 [0.01, 0.16]
Saito Y 2010	3	145	33	228	39.5%	0.12 [0.04, 0.42]
Tajika M 2011	1	84	16	104	13.7%	0.07 [0.01, 0.51]
Terasaki M 2011	0	83	14	176	7.1%	0.07 [0.00, 1.14]
Total (95%CI)		712		832	100.0%	0.09 [0.04, 0.19]
Total events	7		106			

Heterogeneity: $\chi^2 = 5.94$, df = 5 ($P = 0.31$); $I^2 = 16\%$

Test for overall effect: $Z = 6.31$ ($P < 0.00001$)



Western UNIVERSITY · CANADA

Complications

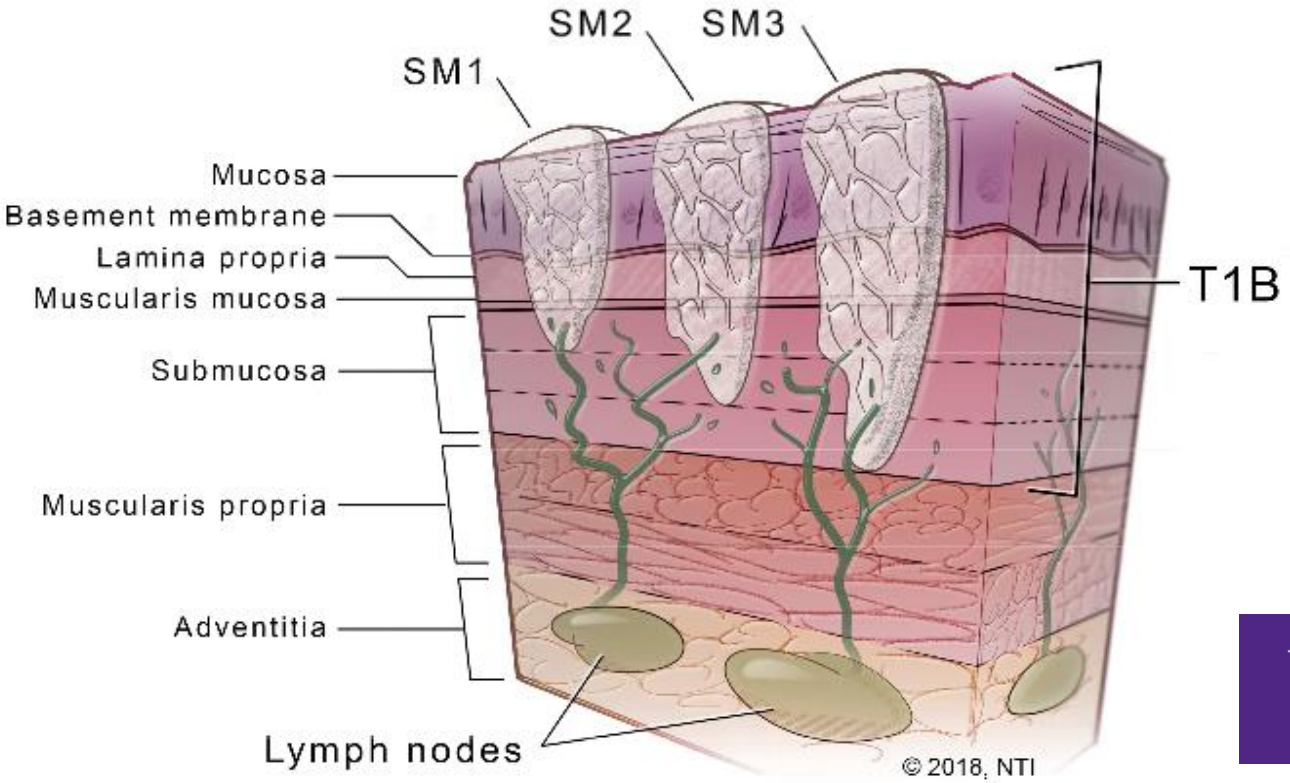
- Death: 0%
- Perforation: 3-5%
  - less problematic than esophagectomy leak → Mostly managed endoscopically
- All complications (major/minor): ~11%
- QOL implications: minimal (organ preservation!)
- Our outcomes (>150 ESD cases)
  - Perforation: <1% (Rx: intra-op stent)
  - Hospital stay: 0-2 days
    - started in OR with LOS 2 days → now as outpatient day procedure
  - Offering cure to patients not otherwise eligible for curative therapy

Western UNIVERSITY · CANADA

ESD killed the esophagectomy star?

- ❖Absolutely for pT1a!
- ❖How about pT1b?

High risk of LN mets → esophagectomy



Risk of occult LN mets in pT1b is ~30-40% overall:

-SM1→ up to 27%
-SM2→ up to 38%
-SM3→ up to 54%

Western UNIVERSITY · CANADA

Controversial/gray area

- Fully resected pT1b (SM2/3) or pT2 via ESD
  - Negative margins

- Relevant factors to consider:
  - LN+ risk factors (length of tumor, LVI, differentiation)
  - Age
  - Fitness of patient (competing risks non-cancer death)
  - Alternative therapies or adjuncts available/possible
    - Chemo, RT, clinical trial (esp IO)

Western UNIVERSITY · CANADA

What to do with pT1b or higher post ESD?

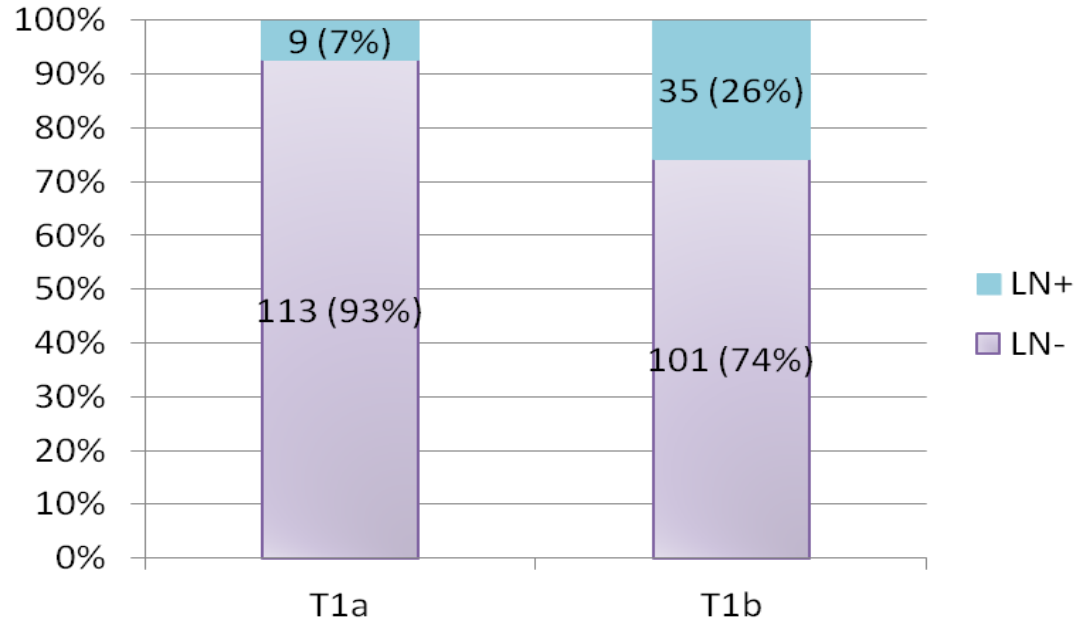
- SOC = esophagectomy
- What if cannot tolerate esophagectomy?
  - Surveillance
  - Adjuvant RT
  - Adjuvant CRT
  - Clinical trial
- "Why would I have that big surgery?"

Western UNIVERSITY · CANADA

Predicting Lymph Node Metastases in Early Esophageal Adenocarcinoma Using a Simple Scoring System

Lawrence Lee, MD, MSc, Ulrich Ronellenfitsch, MD, PhD, Wayne L Hofstetter, MD, FACS, Gail Darling, MD, FACS, Timo Gaiser, MD, Christiane Lippert, MD, Sebastien Gilbert, MD, FACS, Andrew J Seely, MD, PhD, FACS, David S Mulder, MD, FACS, Lorenzo E Ferri, MD, PhD, FACS

Metastatic Lymph Nodes



258 pts with pT1 ADC post esophagectomy:
McGill/Ottawa/Toronto/
Mannheim/MD Anderson

JACS June 2013

Scoring Nomogram

Variable		Points
Size		+1 per cm
Depth		
T1a		+0
T1b		+2
Differentiation		
Well		+0
Moderate		+2
Poor		+2
Lymphovascular invasion		+4
Risk Category	**Risk of LNM**	**Points**
Low	1% - 4%	0 - 1
Moderate	7 – 10%	2 - 3
High	>17%	4+

Western UNIVERSITY · CANADA

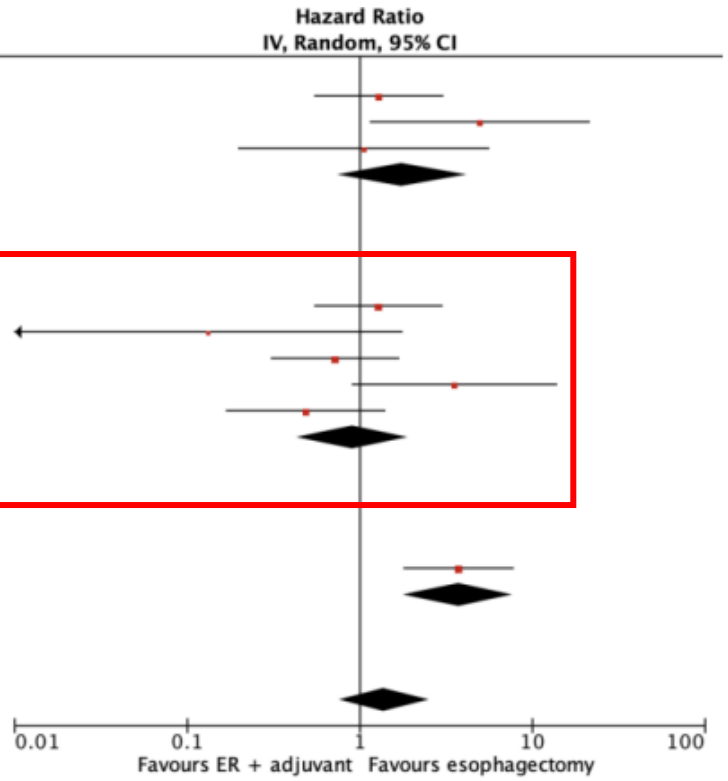
Systematic Review

Esophagectomy Versus Endoscopic Resection with Adjuvant Therapy for T1b/T2 Esophageal Cancer: A Systematic Review and Meta-Analysis

Eagan J. Peters [1], Madeline Robinson [2], Noopur Patel [3] and Biniam Kidane [4,5,6,7,*]

Cancers **2025**, *17*, 680

Study or Subgroup	log[Hazard Ratio]	SE	ER + adjuvant 5yOS (%)	ER + adjuvant Total	Esophagectomy 5yOS (%)	Esophagectomy Total	Weight	Hazard Ratio IV, Random, 95% CI
5.3.1 Majority without LVI + CRT								
Berger 2023 [23]	0.2554	0.4353	61.3	46	70.0	15	13.9%	1.29 [0.55, 3.03]
Li 2023 [30]	1.6024	0.7418	51.4	7	90.2	23	9.1%	4.96 [1.16, 21.25]
Tanaka 2019 [42]	0.0549	0.8492	80.3	33	89.5	19	7.8%	1.06 [0.20, 5.58]
Subtotal (95% CI)				**86**		**57**	**30.8%**	**1.76 [0.75, 4.15]**
Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 2.80$, df = 2 (P = 0.25); $I^2 = 29\%$								
Test for overall effect: Z = 1.30 (P = 0.19)								
5.3.2 Majority with LVI + CRT								
Emi 2022 [24]	0.2487	0.4319	81.0	36	92.6	29	14.0%	1.28 [0.55, 2.99]
Kadota 2022 [26]	−2.0228	1.3176	98.0	50	87.7	18	4.2%	0.13 [0.01, 1.75]
Katada 2023 [28]	−0.3285	0.4299	91.6	131	85.6	58	14.0%	0.72 [0.31, 1.67]
Miyata 2021 [33]	1.2615	0.6918	79.9	123	94.3	37	9.7%	3.53 [0.91, 13.70]
Ota 2003 [35]	−0.7213	0.536	83.0	18	64.9	111	12.2%	0.49 [0.17, 1.39]
Subtotal (95% CI)				**358**		**253**	**54.1%**	**0.90 [0.43, 1.88]**
Heterogeneity: $Tau^2 = 0.34$; $Chi^2 = 8.28$, df = 4 (P = 0.08); $I^2 = 52\%$								
Test for overall effect: Z = 0.28 (P = 0.78)								
5.3.3 Majority without LVI + ablative								
Otaki 2020 [36]	1.3164	0.3718	59.0	73	89.0	68	15.1%	3.73 [1.80, 7.73]
Subtotal (95% CI)				**73**		**68**	**15.1%**	**3.73 [1.80, 7.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.54 (P = 0.0004)								
Total (95% CI)				**517**		**378**	**100.0%**	**1.38 [0.76, 2.51]**
Heterogeneity: $Tau^2 = 0.48$; $Chi^2 = 21.27$, df = 8 (P = 0.006); $I^2 = 62\%$								
Test for overall effect: Z = 1.06 (P = 0.29)								
Test for subgroup differences: $Chi^2 = 7.22$, df = 2 (P = 0.03), $I^2 = 72.3\%$								



Western UNIVERSITY · CANADA

Methods

OPERA-RADIO (NCT05667298) · Phase I prospective trial

Two eligible pathways

DE NOVO EARLY-STAGE EC

1. Upfront ESD
2. High-risk pT1b/pT2N0M0
3. Adjuvant IO-RT: 41.4–45 Gy / 23–25 fractions
4. Concurrent + consolidation Durvalumab every 4 weeks × 13 cycles

PROTOCOL AMENDMENT

1. Locally advanced EC
2. Neoadjuvant concurrent chemoradiotherapy (CROSS regimen)
3. Complete clinical response amenable to ESD (induced early-stage disease) · declined esophagectomy
4. ESD
5. Adjuvant Durvalumab only · 13 cycles

Across both pathways: endoscopic complications prospectively captured using Clavien–Dindo classification.

OPERA RADIO trial

- Preliminary findings
  - Feasible
    - Enrolled 11 patients in <1 year
      - 10 patients got IO and 1 got CROSS CRT
  - Safe
    - Only grade 1-2 AEs
    - 2 discontinuations after 7 of 13 cycles

Western UNIVERSITY · CANADA

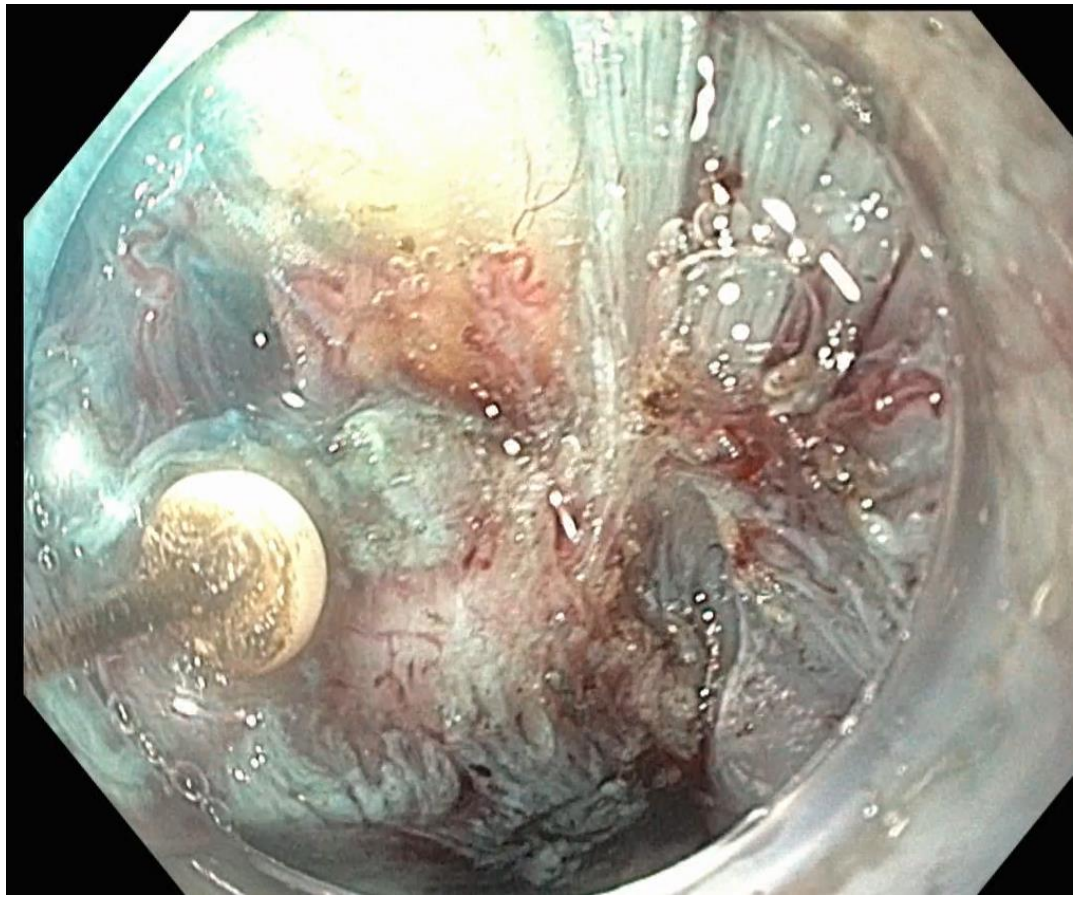
OPERA RADIO trial: prelim outcomes

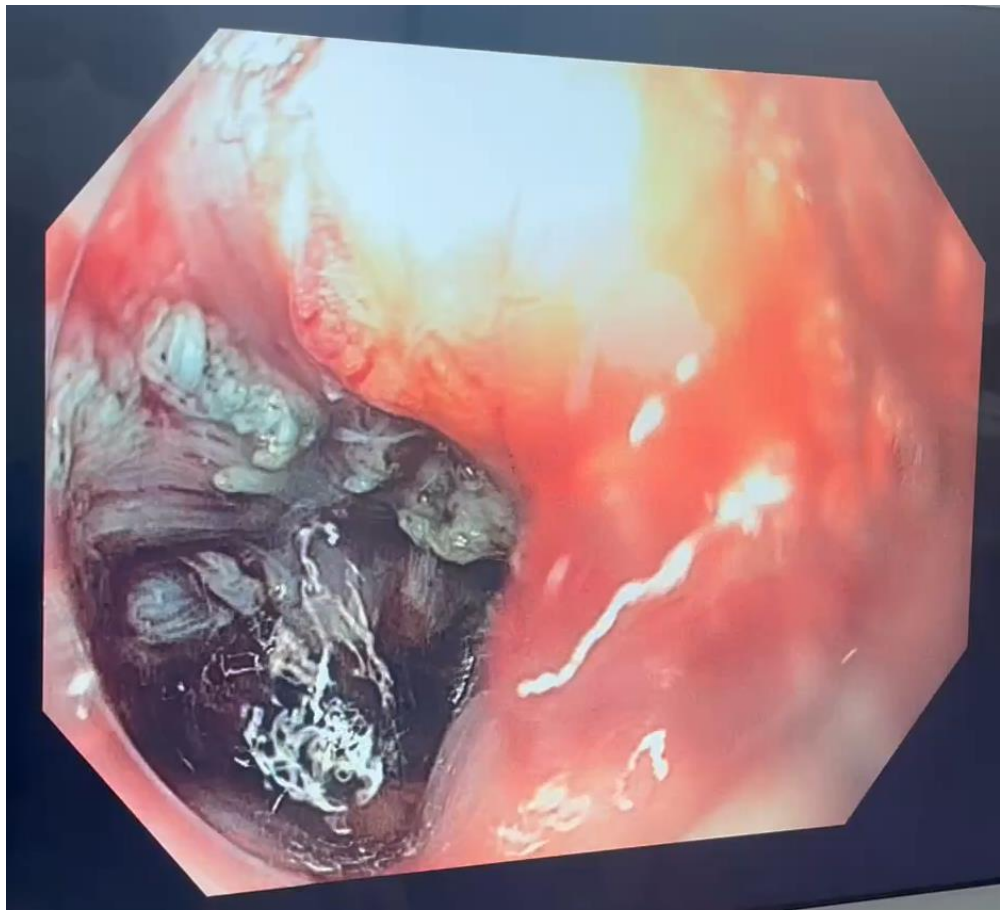
- Quality of life
  - High preservation of quality of life
  - Better than stage-matched patients who receive standard of care esophagectomy
- Survival analysis
  - Not yet mature
- Translational biology studies→ pending analysis

Western UNIVERSITY · CANADA

Is pT2 and pT3 resection by ESD really possible !?!

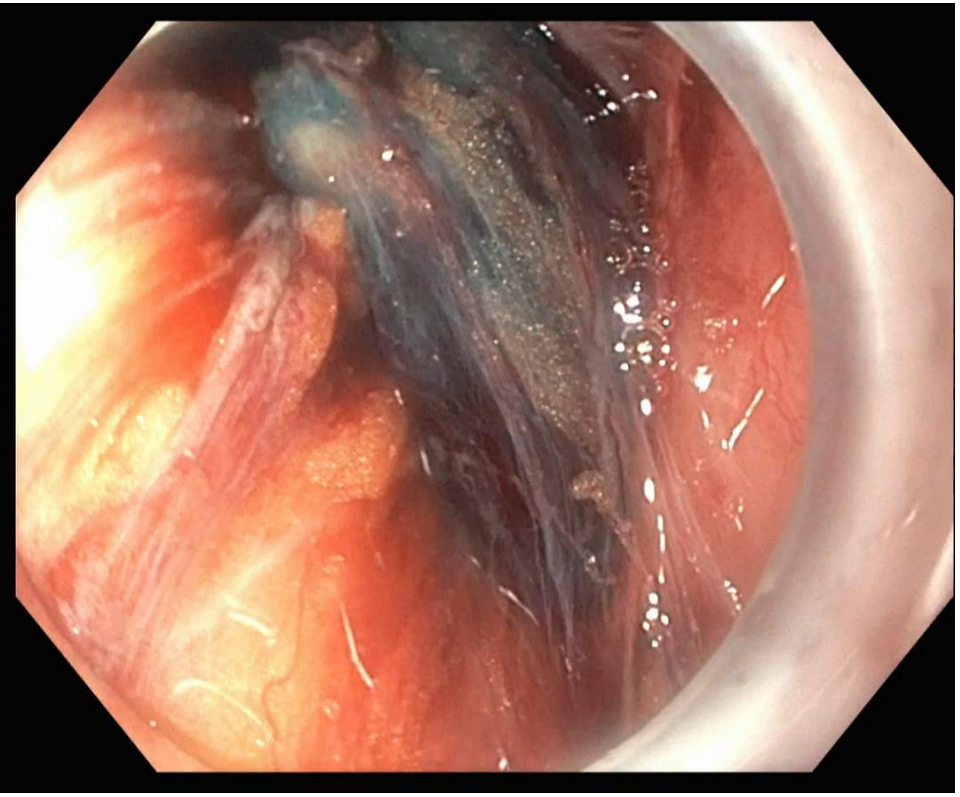
ypT3 resection post CROSS, met SANO CCR criteria, no leak

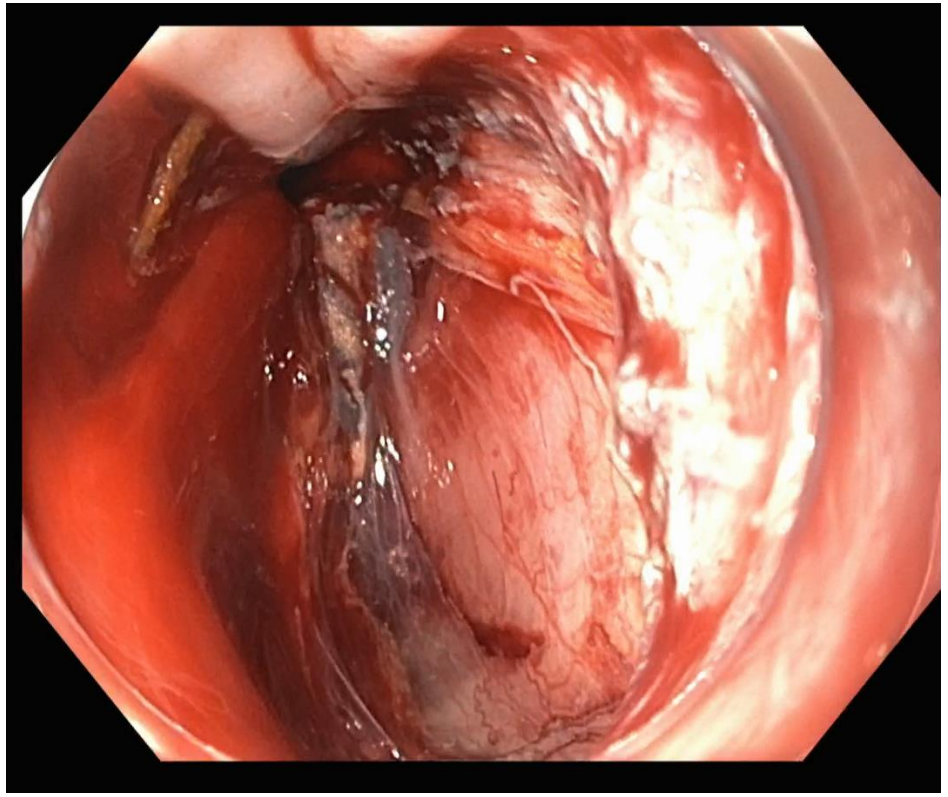


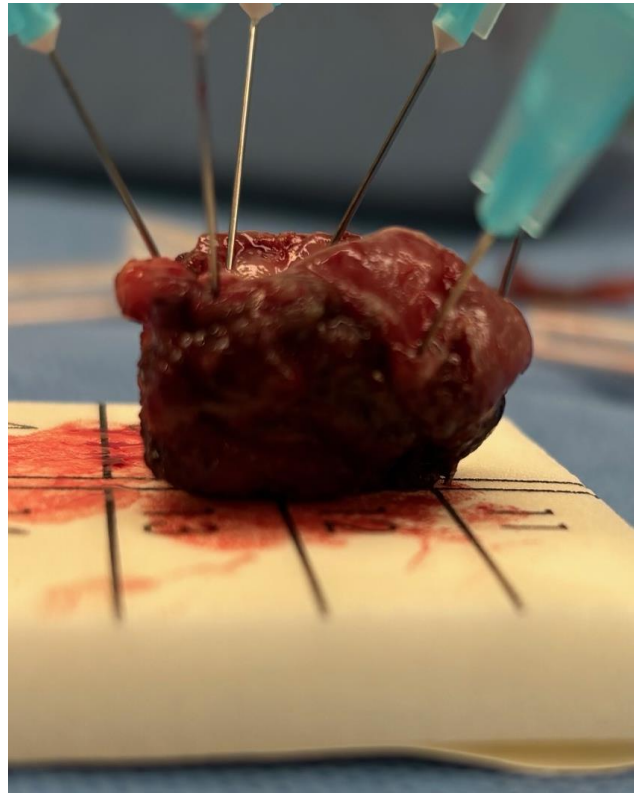


- Microscopic deep margin positive → underwent hybrid MIE
  - ypT0N1
  - LOS=5 days, no complications

pT3 resection post previous ESD, negative margin, no leak

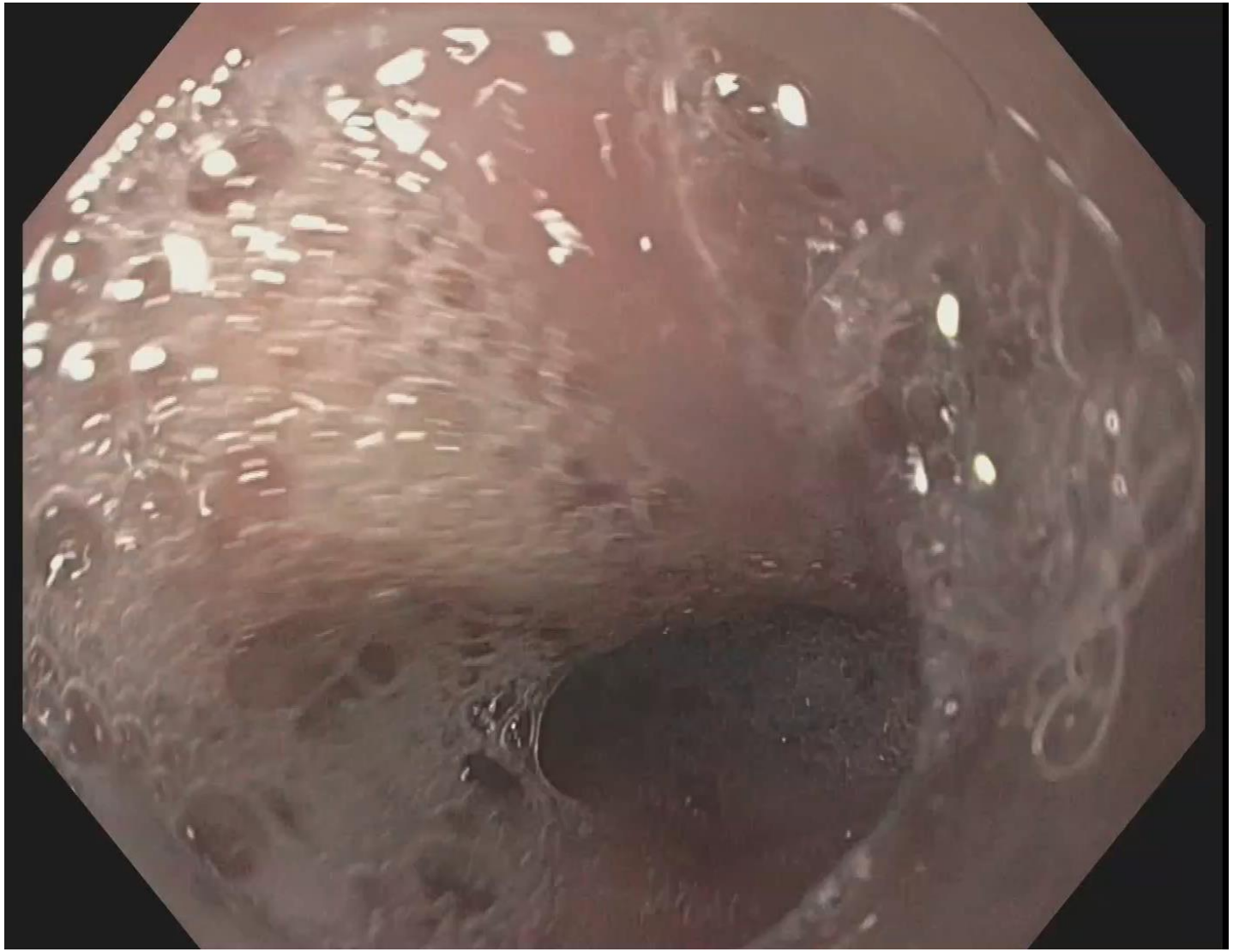






- Declined esophagectomy→ definitive CRT to address nodal/systemic risk

84M uT1b ESCC, not candidate for CRT



- pT2, R0 , no LVI, mod differentiated
- MDT discussion
  - *Surveillance*
  - *CV too high risk for CRT*
  - *No SOC indications for RT (& +risk)*
- Outcomes
  - *Went home POD1, no complications*
  - *Stricture with 3 dilations*
  - *Good HRQOL*
- Death 3 years later of CV causes
  - *No evidence of cancer*

Surveillance Versus Resection Following Induction Therapy for Esophageal Cancer



Organ preservation is aspirational!

- Why would we want to avoid esophagectomy?
  - ↓complications
  - ↓costs
  - ↑quality of life
- In Stage 1-3
  - esophagectomy remains standard workhorse

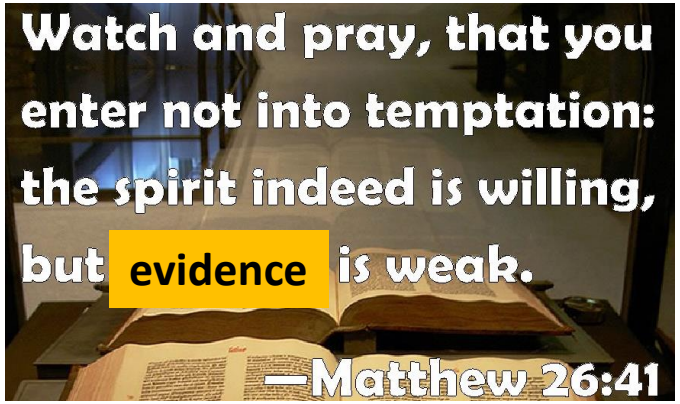
Western UNIVERSITY · CANADA

Organ preservation is aspirational!

- Stage 1 → EMR or ESD
  - supplanting esophagectomy

- Stage 2-3
  - growing desire for TNT or SANO

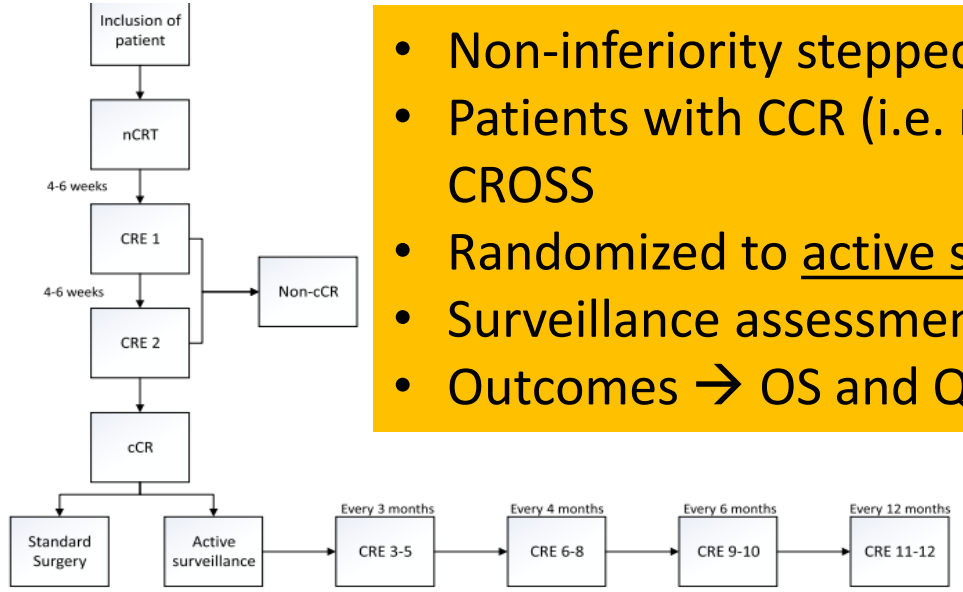
…but…



Neoadjuvant chemoradiotherapy followed by active surveillance versus standard surgery for oesophageal cancer (SANO trial): a multicentre, stepped-wedge, cluster-randomised, non-inferiority, phase 3 trial

Lancet Oncol 2025; 26: 425–36

Berend J van der Wilk*, Ben M Eyck*, Bas P L Wijnhoven, Sjoerd M Lagarde, Camiel Rosman, Bo J Noordman, Maria J Valkema, Tanya M Bisseling, Peter-Paul L O Coene, Marc J van Det, Jan Willem T Dekker, Jolanda M van Dieren, Michail Doukas, Stijn van Esser, W Edward Fiets, Henk H Hartgrink, Joos Heisterkamp, I Lisanne Holster, Bastiaan Klarenbeek, David van Klaveren, Eva Kouw, Ewout A Kouwenhoven, Misha D Luyer, Bianca Mostert, Grard A P Nieuwenhuijzen, Liekele E Oostenbrug, Jean-Pierre Pierie, Johanna W van Sandick, Meindert N Sosef, Manon C W Spaander, Roelf Valkema, Edwin S van der Zaag, Ewout W Steyerberg, J Jan B van Lanschot, SANO Study Group†

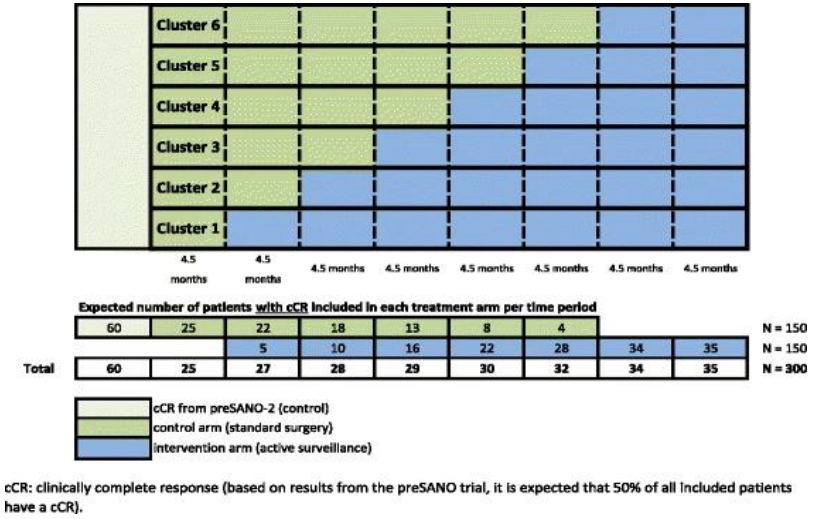


- Non-inferiority stepped-wedge cluster RCT
- Patients with CCR (i.e. no residual disease) after CROSS
- Randomized to active surveillance vs standard surgery
- Surveillance assessments: EGD/EUS & PET-CT
- Outcomes → OS and QOL

Western UNIVERSITY · CANADA

The devil is in the details

- Non-inferiority trial
  - Non-inferiority margin of 15%
  - Based on patient survey experiment
- Design is…complex



cCR: clinically complete response (based on results from the preSANO trial, it is expected that 50% of all included patients have a cCR).



"It's a big misconception. Everyone thinks hell is all fire. Actually, it's all paperwork."

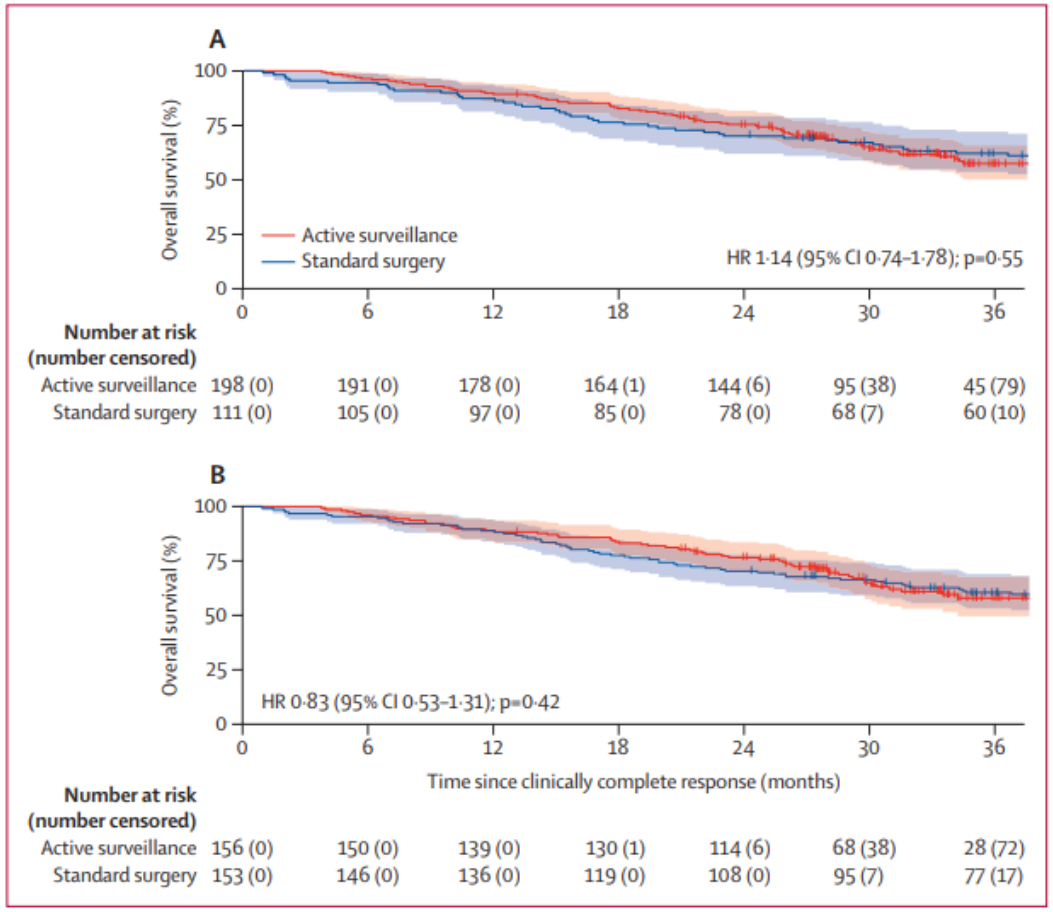


Figure 2: **Kaplan–Meier estimates of overall survival according to modified intention-to-treat analysis (A) and intention-to-treat analysis (B)**

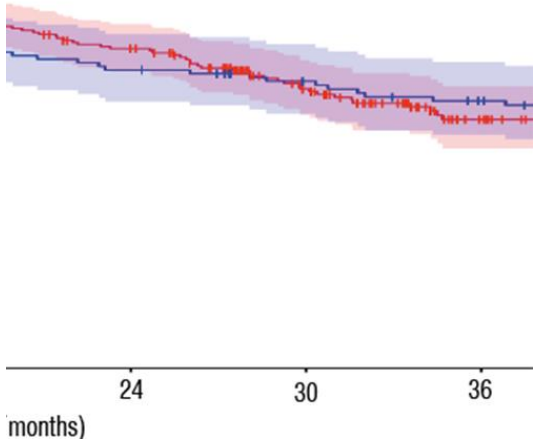
- non-inferior OS
- global QOL better in surveillance arm
  - But not after 1 year
- At 30 months, distant mets in
  - 43% of surveillance group
  - 34% of surgery group

Western UNIVERSITY · CANADA

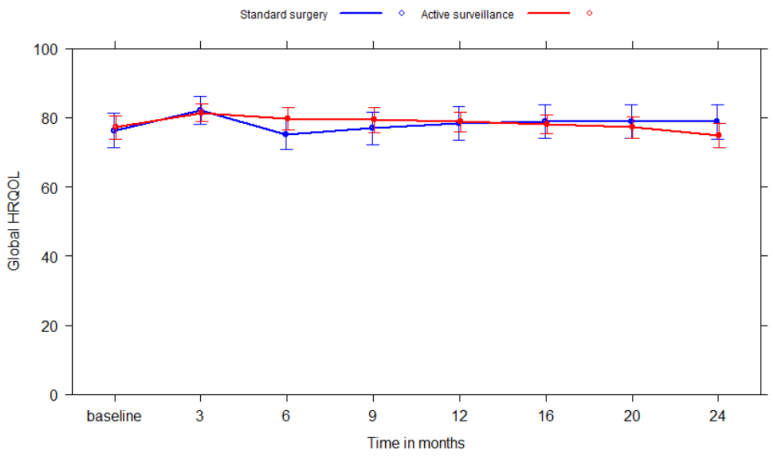
Time to abandon routine esophagectomy?



After 1-2 years, SANO is worse!



- After 2 years, curves cross!
  - Esophagectomy has higher OS
- After 2 years, 9% higher distant mets in surveillance group
- In real world, this effect may be heightened
  - Esophagectomy patients have access to adjuvant IO
- After 1 year, QOL is the same



Sub-standard control arm!

- Easy way to make anything look superior
  - Have poor performing control group

I was told once that the most important part of a fight is making sure your opponent looks worse than you do when you're through.

Julia Quinn

	Active surveillance (n=83)	Standard surgery (n=101)
Any complication	68 (82%)	85 (84%)
Anastomotic leakage	18 (22%)	27 (27%)
Severity of anastomotic leakage		
Subclinical, spontaneous recovery	2 (2%)	3 (3%)
Subclinical, requiring surgery	1 (1%)	0
Clinical, spontaneous recovery	10 (12%)	15 (15%)
Clinical, requiring surgery	5 (6%)	9 (9%)
Pulmonary complications		
Any	39 (47%)	64 (63%)
Pneumonia	20 (24%)	29 (29%)
Respiratory failure requiring reintubation	2 (2%)	5 (5%)

Western UNIVERSITY · CANADA

Sub-standard control arm!

Benchmarking Complications Associated With Esophagectomy

Donald E. Low, MD, FACS, FRCSC, Madhan Kumar Kuppusamy, MD, FRCS,* Derek Alderson, FRCS,† Ivan Cecconello, MD, PhD,‡ Andrew C. Chang, MD,§ Gail Darling, MD, FRCSC, FACS,¶ Andrew Davies, MD, FRCS,|| Xavier Benoit D'Journo, MD, PhD,** Suzanne S. Gisbertz, MD, PhD,†† S. Michael Griffin, OBE, MD, FRCSEd, FRCS,‡‡ Richard Hardwick, MD, FRCS,§§ Arnulf Hoelscher, MD, FACS, FRCS,¶¶ Wayne Hofstetter, MD,|||| Blair Jobe, MD, FACS,*** Yuko Kitagawa, MD, PhD, FACS,††† Simon Law, MS, PhD, FRCS,‡‡‡ Christophe Mariette, MD, PhD,§§§ Nick Maynard, MS, FRCS,¶¶¶ Christopher R. Morse, MD,|||||| Philippe Nafteux, MD, PhD,**** Manuel Pera, MD, PhD,†††† C. S. Pramesh, MS, FRCS(Edin),‡‡‡‡ Sonia Puig, MD,§§§§ John V. Reynolds, MCh, FRCSI,¶¶¶¶ Wolfgang Schroeder, FACS,|||||||| Mark Smithers, FRACS, FRCS,***** and B. P. L. Wijnhoven, MD, PhD†††††*
(Ann Surg 2019;269:291–298)

Methods: The Esophageal Complications Consensus Group (ECCG) involving 24 high-volume esophageal surgical centers in 14 countries developed a standardized platform for recording complications and quality measures associated with esophagectomy. Using a secure online database (ESODA-TA.org), ECCG centers prospectively recorded data on all resections according to the ECCG platform from these centers over a 2-year period.

of patients. The overall incidence of complications was 59% with the most common individual complications being pneumonia (14.6%) and atrial dysrhythmia (14.5%). Anastomotic leak, conduit necrosis, chyle leaks, recurrent nerve injury occurred in 11.4%, 1.3%, 4.7%, and 4.2% of cases,

Simulated Patient Summary

The Society of Thoracic Surgeons

Procedure Type: Open Ivor Lewis

Operative Outcome	Estimate %	95% CI
Operative Mortality	18.2%	10.6% - 28.1%
Morbidity & Mortality	53.5%	47.2% - 59.7%
Morbidity	51.1%	44.7% - 57.3%

Copy

Clinical Summary

Planned Surgery:	Open Ivor Lewis, ASA Classification: III (Severe systemic disease), ECOG Score: 2 - capable of all self car, unable to carry out work activity, Elective
Demographics:	69 year old, White, male, 70kg, 70inches, BMI: 22.1 kg/m², BSA: 1.87m²
Insurance/Payor:	Commercial; Non-U.S. Plan
Clinical Cancer Staging:	T3N1M0 Histology: Adenocarcinoma
Tumor Location:	Lower Thoracic, including EG Junction (30 – 42 cm)
Induction Treatment:	Chemotherapy, Radiation
Risk Factors/Comorbidities:	Smoking History: Current smoker, Diabetes
Cardiovascular Disease:	Hypertension, Coronary Artery Disease (CAD)
Vascular Disease:	Cerebrovascular Accident (CVA)
Kidney Function:	Last Creatinine: 71 umol/L

Western UNIVERSITY · CANADA

Can you apply the intervention?

- Assuming you believe SANO results
  - Can you apply it in real world?



- PET-CT & EGD/EUS
  - Every 3 months for 1st year
  - Every 4 months for 2nd year
  - Every 6 months for 3rd year
  - Annually for 4th and 5th years
- Challenging for regionalized/centralized care
- Patients may not be able to afford costs of surveillance

Western UNIVERSITY · CANADA

Who is organ-preservation appropriate for?

- Assuming meet criteria for SANO
- Patient factors
  - Older
  - More frail
  - Higher comorbidity
  - Higher risk
  - Capacity/willingness to undertake intense surveillance
  - **Hesitant about surgery**

Who is organ-preservation appropriate for?

- Surgical/Institutional factors
  - High complication rates for esophagectomy
    - Closer to SANO results vs STS/ECCG estimates
  - Capacity for salvage esophagectomy
    - With similar outcomes to index/upfront esophagectomy
  - Capacity for intense surveillance

Who is organ-preservation appropriate for?

- Future-oriented factors
  - Better assessment of complete responders
    - i.e. ESD, sentinel LN biopsies
  - Better “liquid biopsies” for surveillance
    - ctDNA, miRNA
  - Use of better systemic therapies (i.e. adjuvant IO or chemoIO)
    - Via personalized risk assessment or routine for all comers?
  - Can we use this with FLOT? Matterhorn?
    - Unanswered but likely even more reasonable theoretically

organ-preservation is the future

- No doubt that patients want this

Thank you!



biniam.Kidane@lhsc.on.ca