Henderson Lecture
Current Management of Esophageal Cancer

Gail Darling MD FRCSC FACS
Dr D Alex Gillis Professor of Surgery
Head Department of Surgery
Dalhousie University and Nova Scotia Health

Toronto Thoracic Refresher Course June 13 2026

DALHOUSIE UNIVERSITY | Surgery



Presented by the Division of Thoracic Surgery,
Department of Surgery, University of Toronto

Surgery
UNIVERSITY OF TORONTO

50th Annual

Toronto Thoracic Surgery Refresher Conference

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Declaration of Conflict of Interest

No financial support

Relationships with financial sponsors: Not Applicable

Current Management of Esophageal Cancer

1. Surgery
2. Chemotherapy and Immunotherapy
3. Prehab

Current Management of Esophageal Cancer

Key Concepts:

1. Adenocarcinoma ≠ Squamous Carcinoma
2. Perioperative Chemotherapy + IO for Adenocarcinoma
3. Radiotherapy has limited role in curative treatment of Adenocarcinoma
4. Surgery may not be required for Squamous Cell Carcinoma
5. Palliation of Dysphagia is an important outcome
6. Oncologic principles of surgery apply: margins, lymph nodes
7. Esophageal cancer can be cured

Current Management of Esophageal Cancer

What's New?

1.Immunotherapy

2. Adenocarcinoma of Esophagus and GE junction treated the same

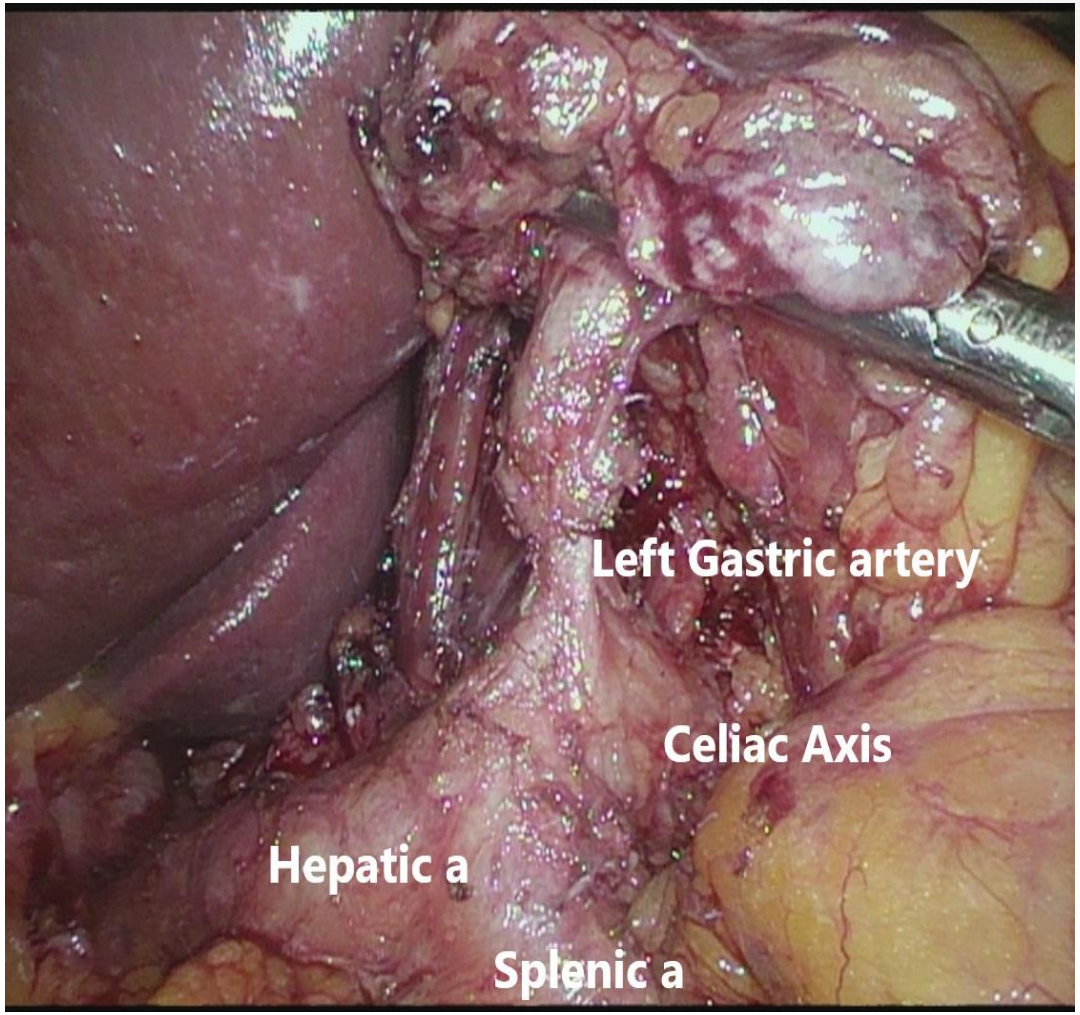
3. Robotic Esophagectomy

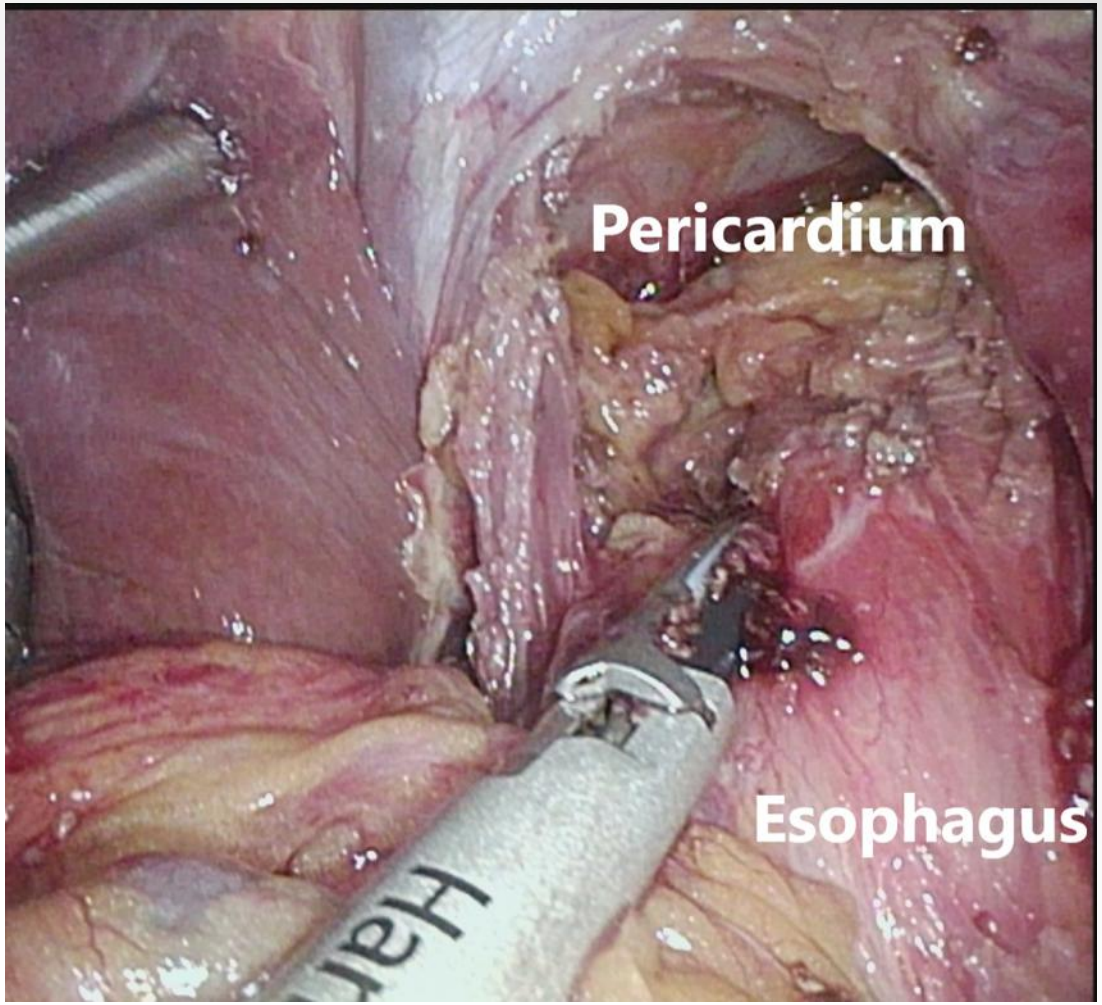


Surgery

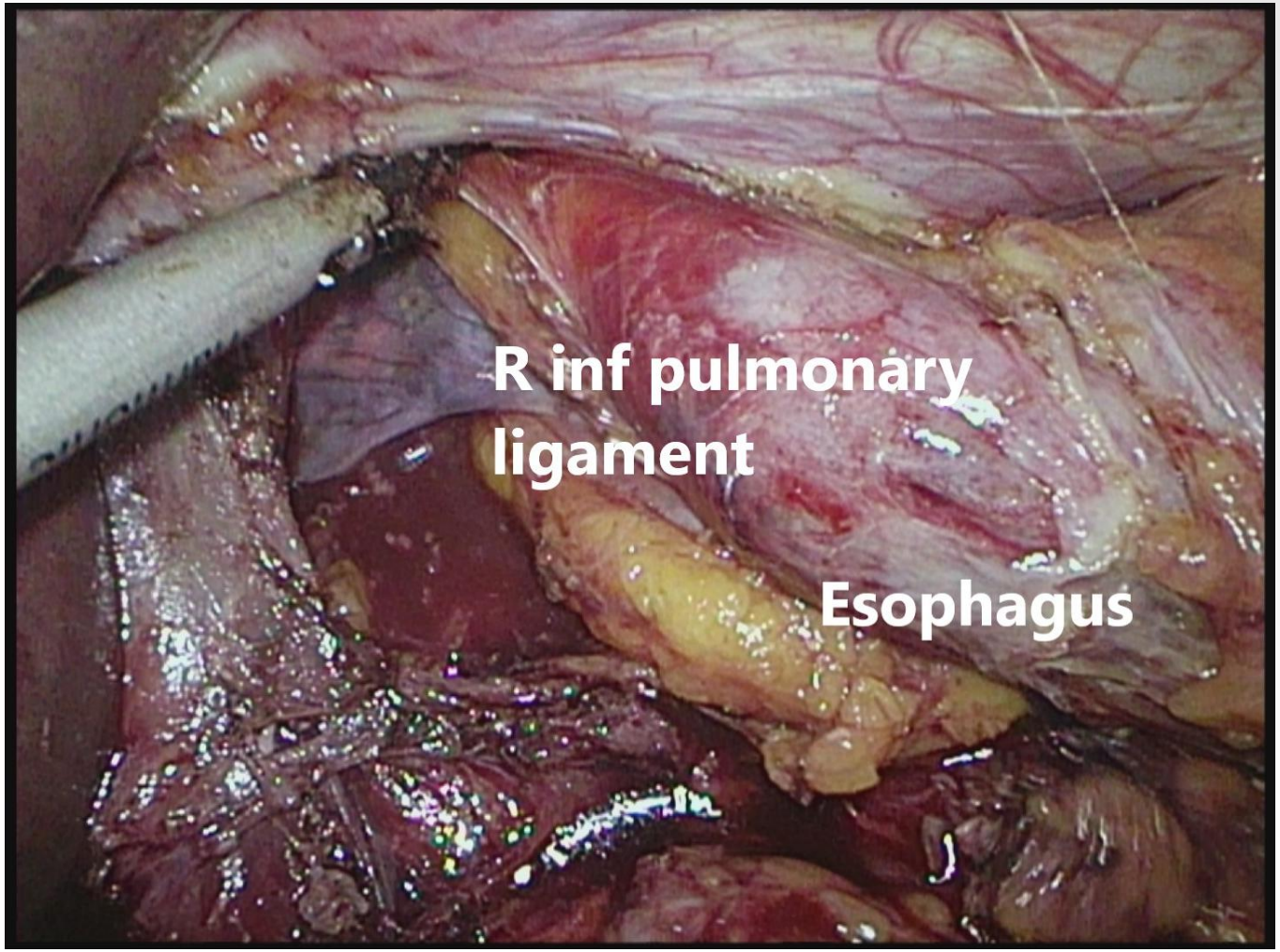
- Surgery is the mainstay of curative treatment
- Minimally Invasive esophagectomy = Laparoscopy + VATS
- RAMIE increasing
- Esophageal cancer can be cured
- There are longterm survivors
- As surgeons we owe it to our patients to do the best operation

Intraabdominal Dissection

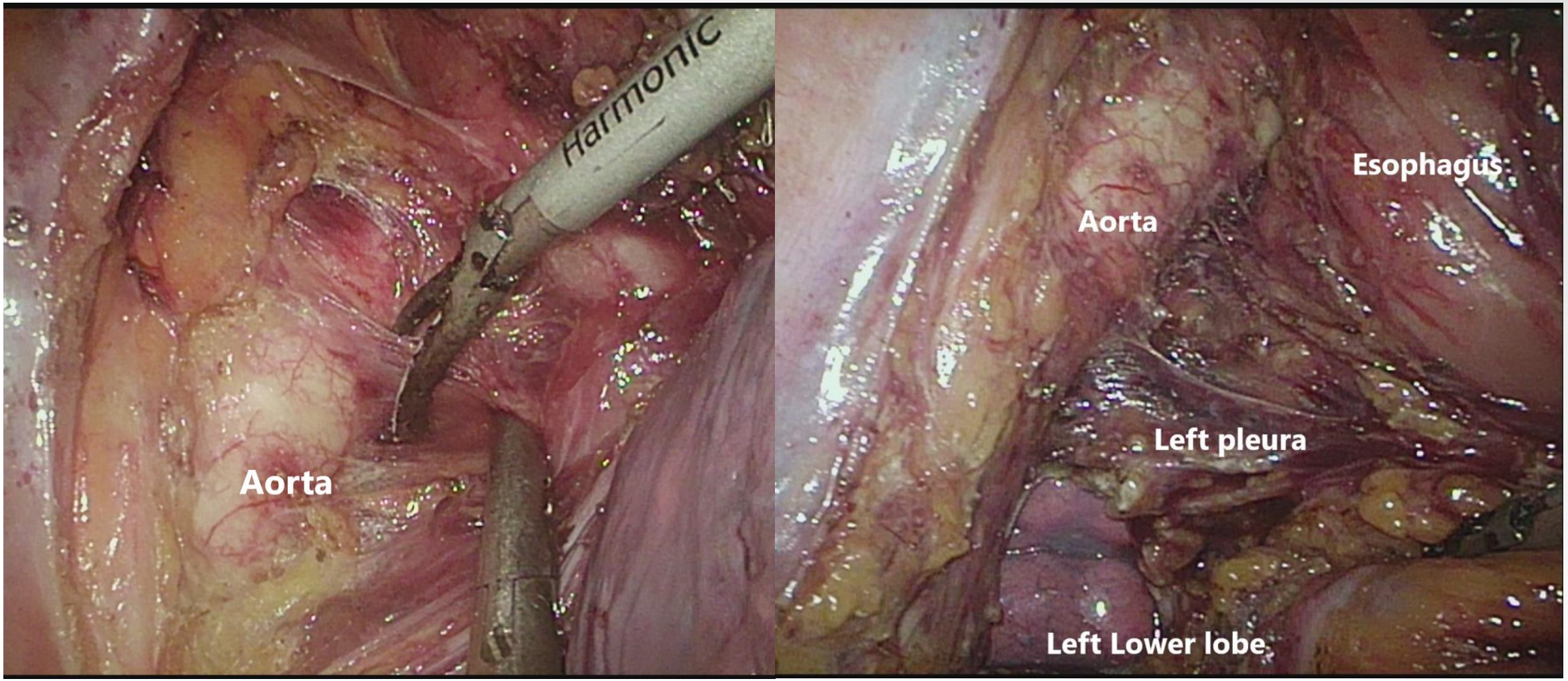




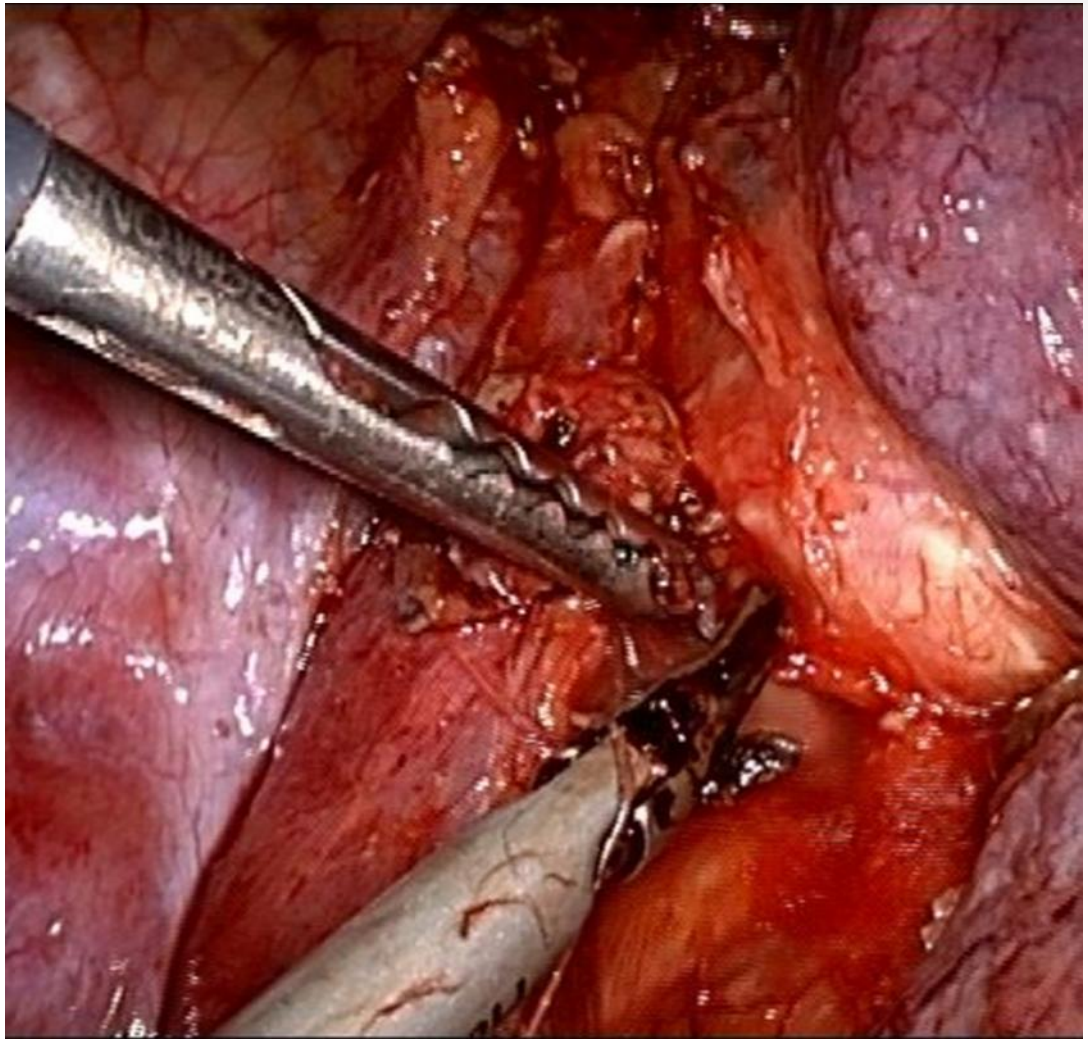
Intrathoracic Dissection through the hiatus

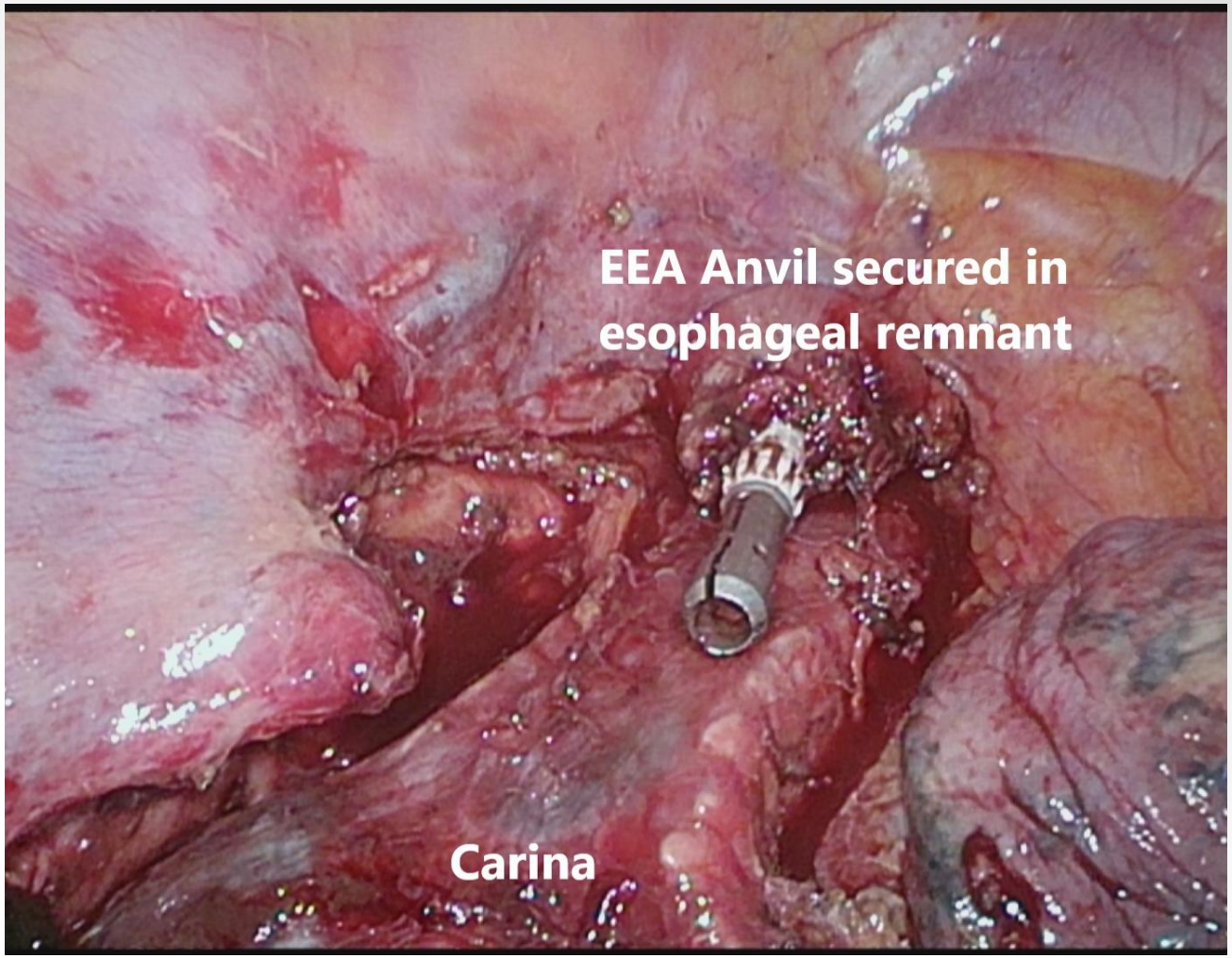


Intrathoracic Dissection



Intrathoracic Dissection





Surgery

- Best operation: Minimally Invasive (Robotic)
- Lowest mortality: 1-2%
- Lowest morbidity: anastomotic leak < 5%
- Good quality of life: swallowing, eating, reflux, pain,
- Good cancer operation: margins, lymph node harvest



Crossing the Finish Line

5 years after treatment for esophageal cancer with a supraclavicular node

Multimodality Therapy

Clinical Trials Smorgasbord: What do you need to know?

- FLOT4
- D-FLOT
- NeoAegis
- TOPGEAR
- Esopec
- Checkmate 577
- KeyNote 585
- Matterhorn

Old News:
MAGIC
CROSS
CRITICS

Pivotal RCTs: Chemotherapy +/-RT

MAGIC	G/GEJ/LE	503	Periop ECF Vs Surgery	5 yr OS 36% vs 23%	HR = 0.75 P=0.009
CROSS	G/GEJ/LE	368	Neoadj Carbo+Paclitaxel +RT+S Vs Surgery alone	Median OS: 49 vs 24 mo	HR = 0.66 P= 0.003
CRITICS	E/GEJ	788	Adj ECX/EOX +RT Vs Adj ECX/EOX	Median OS: 43 vs 37 mo	HR =1.01 P=0.90
FLOT 4	G/GEJ	716	Periop FLOT Vs Periop ECF/ECX	5 yr OS 45% vs 36%	HR = 0.77 P= 0.012
Neo-AEGIS	E/GEJ	362	Neoadj Carbo paclitaxel+RT Vs Periop ECF/ECX/FLOT	Median OS 49 vs 48 mo	HR= 1.03 P=0.82
TOPGEAR	G/GEJ	574	Periop ECF/ECX/FLOT+CRT Vs Periop ECF/ECX/FLOT	Median OS 46 vs 49 mo	HR = 1.05
ESOPEC	E/GEJ	438	Periop FLOT Vs neoadj Carbo Paclitaxel+ RT	3 yr OS 57% vs51%	HR=0.70 P=0.01

Okemoto et al. Gastroenterology Report 2026; http://doi.org/10.1093/gastro/goag010

Immunotherapy Trials

CheckMate577	E/GEJ	794	Neadj Carbo-paclitaxel +RT + adj nivo vs Neoadj Carbo Paclitaxel + RT	Median DFS 22 vs 11 months	HR = 0.69 P<.0001
KEYNOTE-585	G/GEJ	1007	Periop FLOT/ FP/XP+ pembro Vs Periop FLOT/FP/XP	PCR13%vs2% Median EFS 44 vs 26mo Median OS 72 vs 56 mo	P<0.00001 HR=0.81 p=0.0198 HR 0.86
MATTERHORN	G/GEJ	948	Periop FLOT +Durva vs Periop FLOT	24mo EFS 67% vs 59%	HR 0.71 P<0.001

Okemoto et al. Gastroenterology Report 2026; http://doi.org/10.1093/gastro/goag010

Summary of Clinical Trials for Adenocarcinoma

- Periop D FLOT
- No role for RT
- IO preop (Durva (Pembro?)) vs postop (Nivo)

Current ESMO recommendation: D FLOT

- If no preop IO but no pCR : adjuvant Nivo
- If PCR after FLOT: no postop FLOT

Questions

- Is there really a difference between Durva, Pembro and Nivo?
- Is Neoadjuvant IO better than Adjuvant?
- Postop Chemo: FLOT4 only 46% completed postop cycles
  Matterhorn only 48% completed post op cycles
- FLOT for elderly or frail patients? Alternative regimen or dose reduction?

→NeoAegis: Cross similar to Periop Chemo (ECF/ECX/FLOT)

→BUT Esopec: PeriopFLOT superior to CROSS

- Dante: periop FLOT + atezolizumab vs periop FLOT
- Circulating tumour DNA ?

Biomarkers in Adenocarcinoma

- HER 2+ve: trastuzumab in stageIV gastric cancer (ToGa) beneficial
- No Phase III trials of anti Her 2 +chemo + surgery; phase II promising
- Drug –antibody conjugates under development/testing

MSI-H/ dMMR:

- ICI + chemo in stage IV disease beneficial

Resectable:

- Phase II Trials (NEONIPIGA, INFINITY) Dual ICI : PCR 60%
- NICE: torilumimab+CAPOX: PCR 80%
- DANTE (resectable) MSI-H/ dMMR Atezolizumab+ FLOT: PCR = 50%

Biomarkers in Adenocarcinoma PD-L1

- PD-L1: NCCN ESMO recommend ICI for stage IV disease CPS ≥ 1%
- PD-L1: NCCN recommends ICI for CPS/TPS ≥ 1%
- PD-L1: ↑ PCR with ↑ TPS score (Matterhorn, KeyNote- 585)
- **Matterhorn included all comers**– not limited to + PDL1 expression
- *PD-L1 survival benefit not limited to positive TPS score*

Claudin18.2 novel molecular biomarker

Weijie Cao et al. doi: 10.1186/s40364-022-00385-1.

- CLDN18.2 : normal gastric mucosa epithelial tight junctions
- With malignant transformation, CLDN18.2 epitopes become exposed.
- Highly selective biomarker with limited expression in normal tissues
- CLDN18.2 : unique molecule for targeted therapy in GC;
- CLDN18.2 → proliferation, differentiation and migration of tumor cells.

- mAb agents such as zolbetuximab (claudiximab, IMAB362)
- Immunotherapy targeting CLDN18.2: bispecific antibodies (BsAbs), chimeric antigen receptor T (CAR-T) cells redirected to target CLDN18.2, antibody-drug conjugates (ADCs).

Biomarkers in Adenocarcinoma Claudin18.2

- ↑ in tumors with signet-ring-cell features (P=0.0391, univar; P=0.0113, multi)
- Including CLDN18.2 ↑ cases with at least one actionable biomarker to 92%
- In triple-negative (HER2-neg, PD-L1-neg, and MMR-proficient) tumors, →CLDN18.2 was positive in 52% overall and 50% of cases with metastasis,
- CLDN18.2 low intratumoral heterogeneity,
- 72% either no staining (<10% tumor cells staining) or diffuse staining (≥90% of tumor cells staining)

Biomarkers in Adenocarcinoma

Reflex testing recommended for Adenocarcinoma (PS(PD-L1), MSI, Her 2, Cldn18.2

Canadian Consensus Recommendations for Predictive Biomarker Testing in Gastric and Gastroesophageal Junction Adenocarcinoma

Christine Brezden-Masley . doi: 10.3390/curroncol31120572.

Zolbetuximab Trials

- Zolbetuximab plus chemo vs placebo + chemo
- Unresectable gastric or GE junction
- Zolbextuximab : monoclonal antibody targets Claudin 18.2
- **FAST** EOX +/- Zolbetuximab n= 223 Cldn18.2 > 40% (phase II)
- **GLOW** CAPOX +/- Zolbetuximab n=507 (phase III)
- **SPOTLIGHT** mFOLFOX 6 +/- Zolbetuximab n=565 Cldn18.2>75% (phase III)
- **↑ PFS and OS**

- FAST Sahin et al. 2021 May:32(5) 609-619 doi: 10.1016/j.annonc.2021.02.005. Epub 2021 Feb 19
- GLOW Shah et al. 2023 Aug;29(8):2133-2141. doi: 10.1038/s41591-023-02465-7. Epub 2023 Jul 31
- SPOTLIGHT Shitara. 2023 May 20;401(10389):1655-1668. doi: 10.1016/S0140-6736(23)00620-7. Epub 2023 Apr 15.

Role of Radiotherapy

Adenocarcinoma:

- CROSS: CRT better than surgery alone, well tolerated
- TOPGEAR: no benefit (gastric and Siewert II/III)

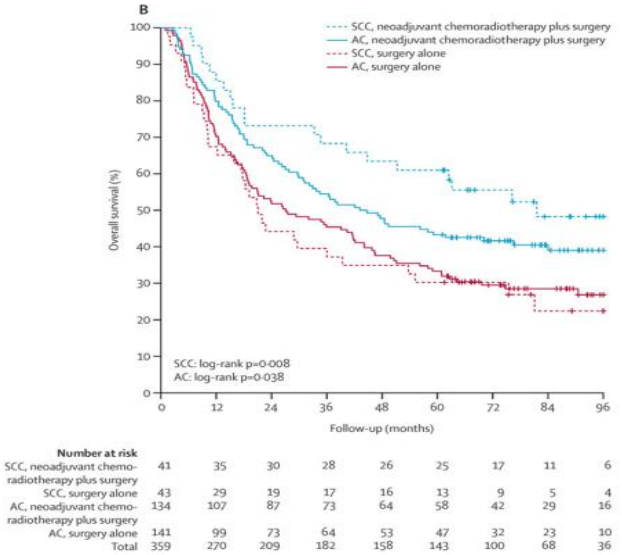
ESCC

- CROSS: ESCC 50% PCR → NEEDS trial
- NEEDS: ESCC CRT + active surveillance vs CRT+ S

NEEDS trial

Background and Rationale

- *Curative intent treatment for locally advanced esophageal cancer involves trimodality therapy (CRT+surgery)*
  - *CROSS trial*
  - *5-y OS for SCC = 60%, pCR = 49%*
  - *Surgical morbidity post esophagectomy (ECCG) high*
    - *Overall incidence of complications 59%*
    - *30/90 day mortality 2.4/45%*
    - *Reduced quality of life post esophagectomy*
- *Can we avoid surgery (and maintain similar oncologic outcomes)? And can we salvage patients who recur locally? Will organ preservation lead to improved QoL?*



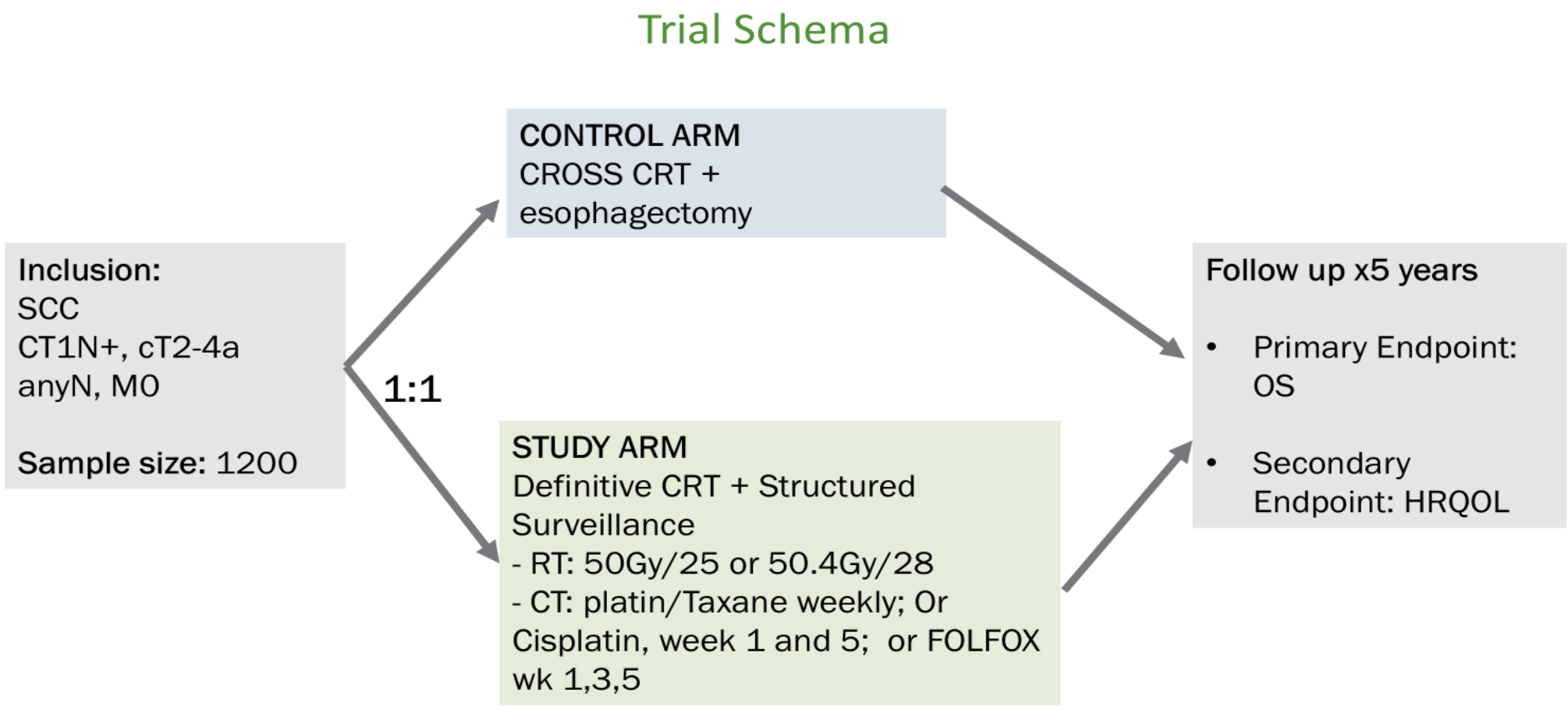
> Ann Surg. 2015 Aug;262(2):286-94. doi: 10.1097/SLA.0000000000001098.

International Consensus on Standardization of Data Collection for Complications Associated With Esophagectomy: Esophagectomy Complications Consensus Group (ECCG)

Donald E Low [1], Derek Alderson, Ivan Cecconello, Andrew C Chang, Gail E Darling, Xavier Benoit D'Journo, S Michael Griffin, Amulf H Hölscher, Wayne L Hofstetter, Blair A Jobe, Yuko Kitagawa, John C Kucharczuk, Simon Ying Kit Law, Toni E Lerut, Nick Maynard, Manuel Pera, Jeffrey H Peters, C S Pramesh, John V Reynolds, B Mark Smithers, J Jan B van Lanschot

Canadian Cancer Trials Group | Groupe canadien des essais sur le cancer

NEEDS Trial



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Prehabilitation

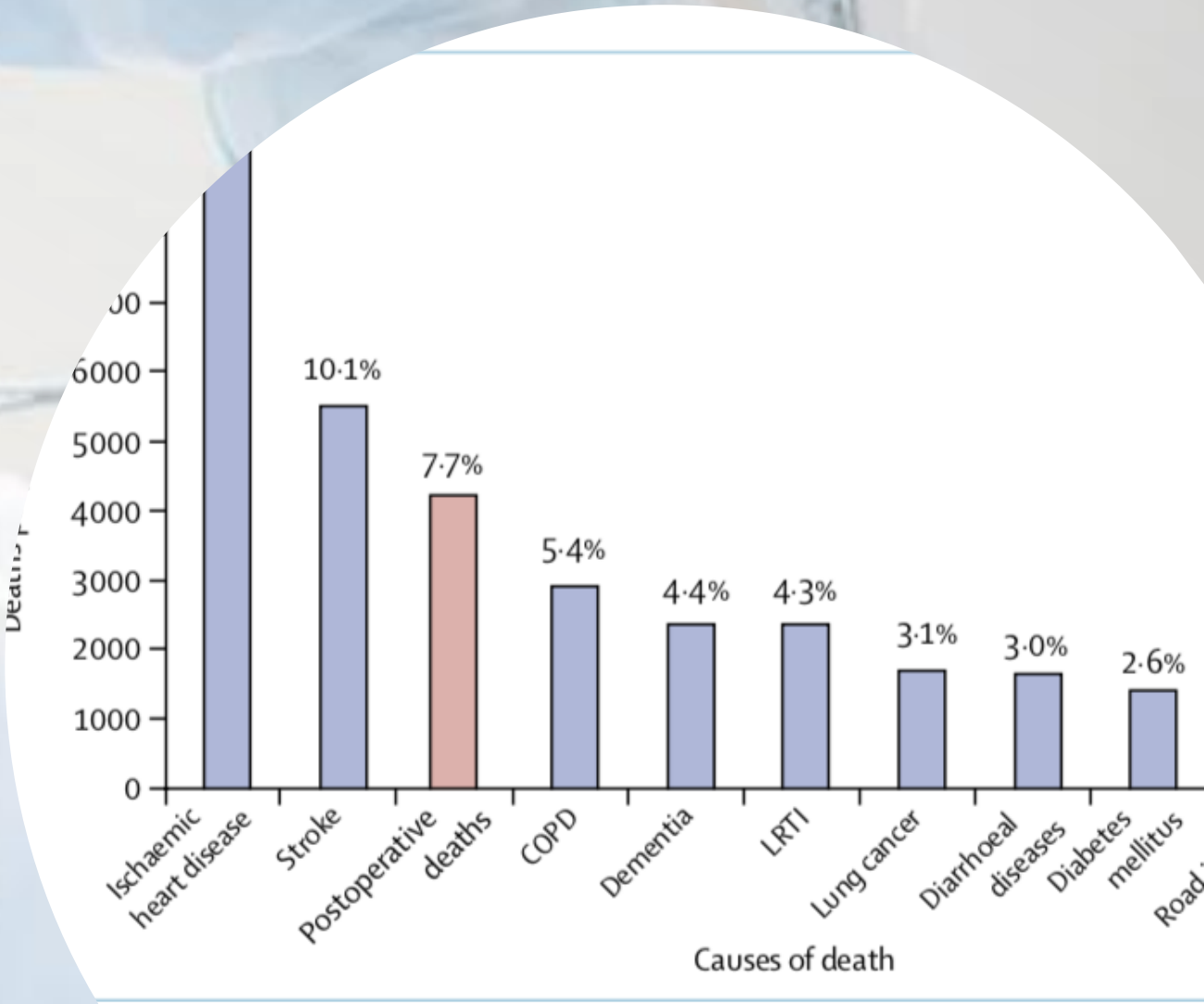
The following slides were provided to me by

Dr Heather Gill Associate Professor

Vascular Surgery Dalhousie University



2016 – post operative deaths were the 3rd leading cause of death representing 7.7% of global deaths

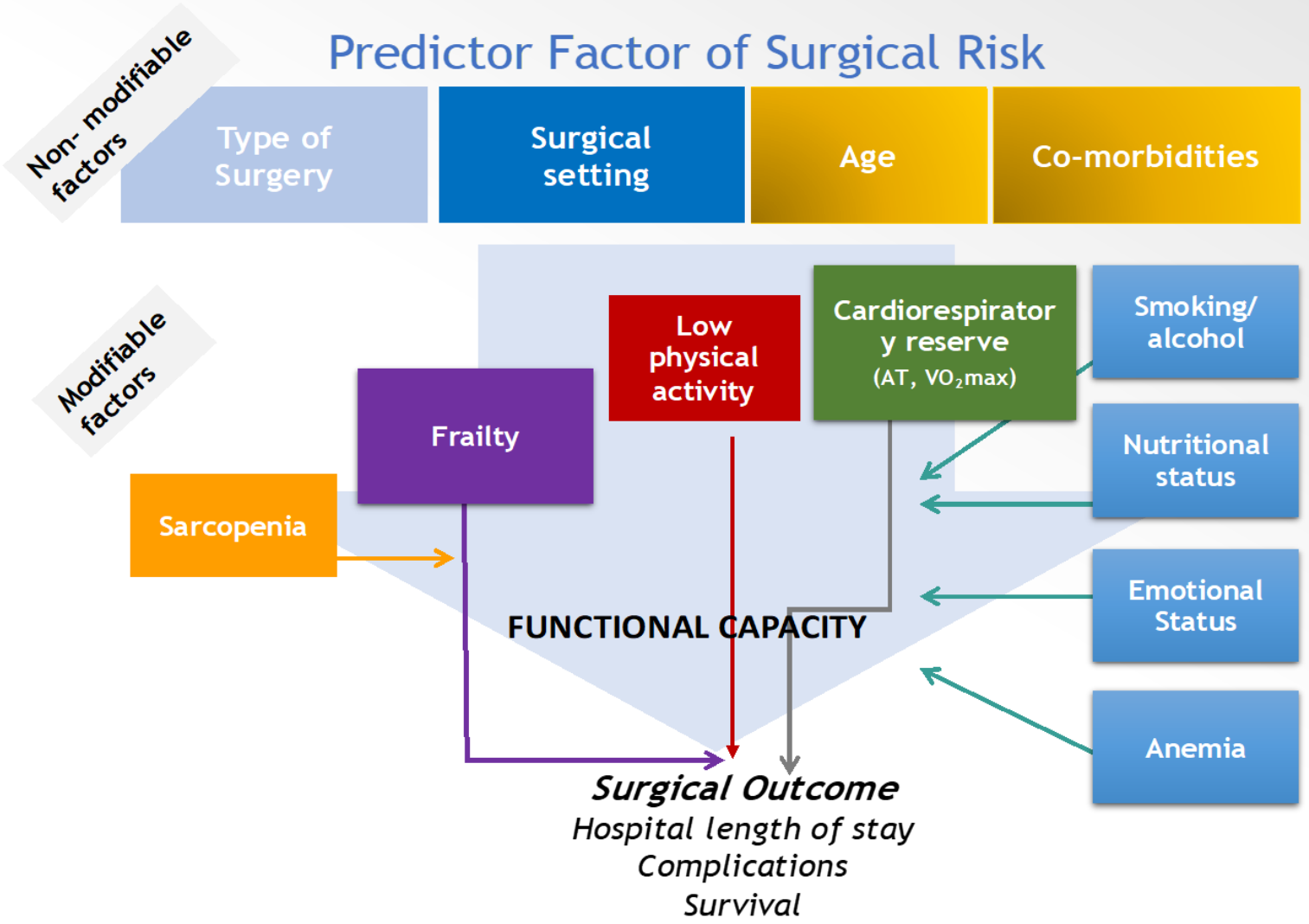


ten global causes of death, 2016

re the proportion of total global deaths attributable to each cause. Data, e
aths, are from the Global Burden of Disease Study 2016.[4] COPD=chr
RTI=lower respiratory tract infections.

The *Lancet* Commission on Global Surgery . www.thelancet.com Vol 393 February 2, 2019

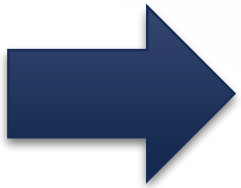
Predictor Factor of Surgical Risk



Anaesth, 2009;64:883
BJAnaesth, 2010;105(3):297
J Am Coll Surg 2010;210:901-908
Anaesth, 2013; 68:67
Lancet 2018; 391:2631

FUNCTIONAL CAPACITY - OF SURGICAL OUTCOMES

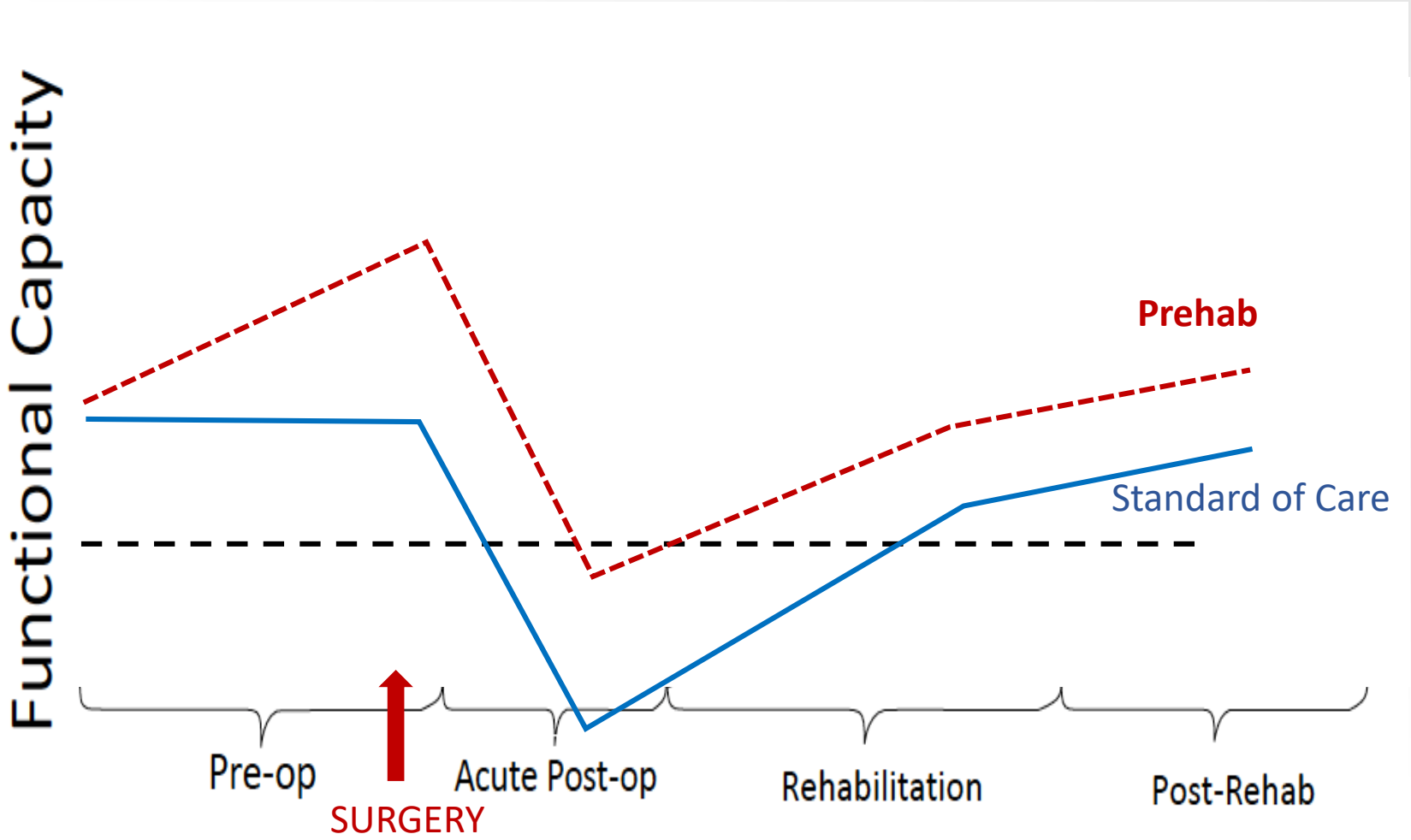
Functional Capacity



- **Postoperative mortality and morbidity**
- **Length of stay**
- **Recovery**
- **Quality of life**
- **Degree of independence**

Baldini et al. Surg Clin North Am. 2018; 98 (6): 1149-1169
Wijeysundera et al. Lancet. 2018; 391 (10140): 2631-2640
West et al. Br J Surg. 2016; 103 (6): 744-752
Moran et al. Br J Anaesth. 2016; 116 (2): 177-91
Snowden et al. Ann Surg. 2013; 257 (6): 999-1004
Wilson et al. Br J Anaesth. 2010; 105 (3): 297-303
Hightower et al. Br J Anaesth. 2010; 104 (4): 465-71
Snowden et al. Ann Surg. 2010; 251: 535-541

PREHABILITATION



PREHABILITATION: The use of the preoperative time to optimize functional status with the Goal of improving surgical recovery and perioperative morbidity

2011



Unimodal Prehabilitation

2013



Trimodal Prehabilitation

2018



Multimodal Prehabilitation

PREHABILITATION EVIDENCE: POSTOP OUTCOMES

Meta- Analysis

Review > Br J Sports Med. 2018 Mar;52(5):344. doi: 10.1136/bjsports-2017-098032. Epub 2018 Feb 1.

Preoperative exercise halves the postoperative complication rate in patients with lung cancer: a systematic review of the effect of exercise on complications, length of stay and quality of life in patients with cancer

- Lung Resection

↓ Post op complication RR0.52 (0.36-0.71) ↓LOS -2.86d (-5.4--0.33)

- Esophageal Ca – ↓Complications
- No change in LOS

Review > Ann Surg Oncol. 2025 Feb;32(2):1236-1247. doi: 10.1245/s10434-024-16527-8. Epub 2024 Nov 30.

Prehabilitation Outcomes in Surgical Oncology Patients Undergoing Major Abdominal Surgery: A Meta-analysis of Randomized Control Trials

- ↓Complications OR 0.60 (0.46-0.78)
- No change in readmission or LOS

Meta-Analysis > Sci Rep. 2024 Jul 11;14(1):16012. doi: 10.1038/s41598-024-66633-6.

Multimodal prehabilitation and postoperative outcomes in upper abdominal surgery: systematic review and meta-analysis

↓Odd of complications
-0.38 (-0.75--0.004)
↓Pulmonary complications
–0.96(-1.38--0.54)

PREHABILITATION EVIDENCE: SURVIVAL & TUMOR REGRESSION

Clinical Trial > Br J Sports Med. 2022 Apr;56(7):402-409. doi: 10.1136/bjsports-2021-104243. Epub 2022 Feb 1.

Exercise prehabilitation during neoadjuvant chemotherapy may enhance tumour regression in oesophageal cancer: results from a prospective non-randomised trial

- ↑Tumor regression
- Differences in markers of immunity and inflammation

Meta-Analysis > Support Care Cancer. 2024 Oct 28;32(11):749. doi: 10.1007/s00520-024-08941-1.

Prehabilitation for patients undergoing neoadjuvant therapy prior to cancer resection: a systematic review and meta-analysis

- ↑ treatment tolerance
- ↑ completion rates

Clinical Trial > N Engl J Med. 2025 Jul 3;393(1):13-25. doi: 10.1056/NEJMoa2502760. Epub 2025 Jun 1.

Structured Exercise after Adjuvant Chemotherapy for Colon Cancer

- 8 year - ↓(Disease recurrence, new primary or death)
- ↑5Year DFA ↑OS

Summary

- Adenocarcinoma and Squamous Carcinoma are treated differently
- Surgery remains mainstay of curative intent treatment (so far)
- FLOT D + Surgery for fit patients
- CROSS regimen for less fit patients
- ICI for PD-L1 expression ≥ 1% (or maybe all comers?)
- Dual ICI for MSI-H/dMMR
- Multimodal Prehabilitation improves patient outcomes