ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

SURGERY FOR GASTRIC AND GE JUNCTION CANCER

Primary, palliative – where and when?

Magnus Nilsson
Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden

DISCLOSURE OF INTERESTS

Member of the European Minimal Invasive Oesophagectomy Thinktank, sponsored by Medtronic Inc.

Surgery for gastric and GE junction cancer

Overview of surgical procedure types

Issues of controversy

- **The extent of lymph node dissection** – limited (D1) or extended (D2) lymphadectomy?
- **Open vs laparoscopic surgery**

Enhanced recovery after surgery programmes

Palliative surgery for gastric and GE junction cancers

- **Procedures and indications**

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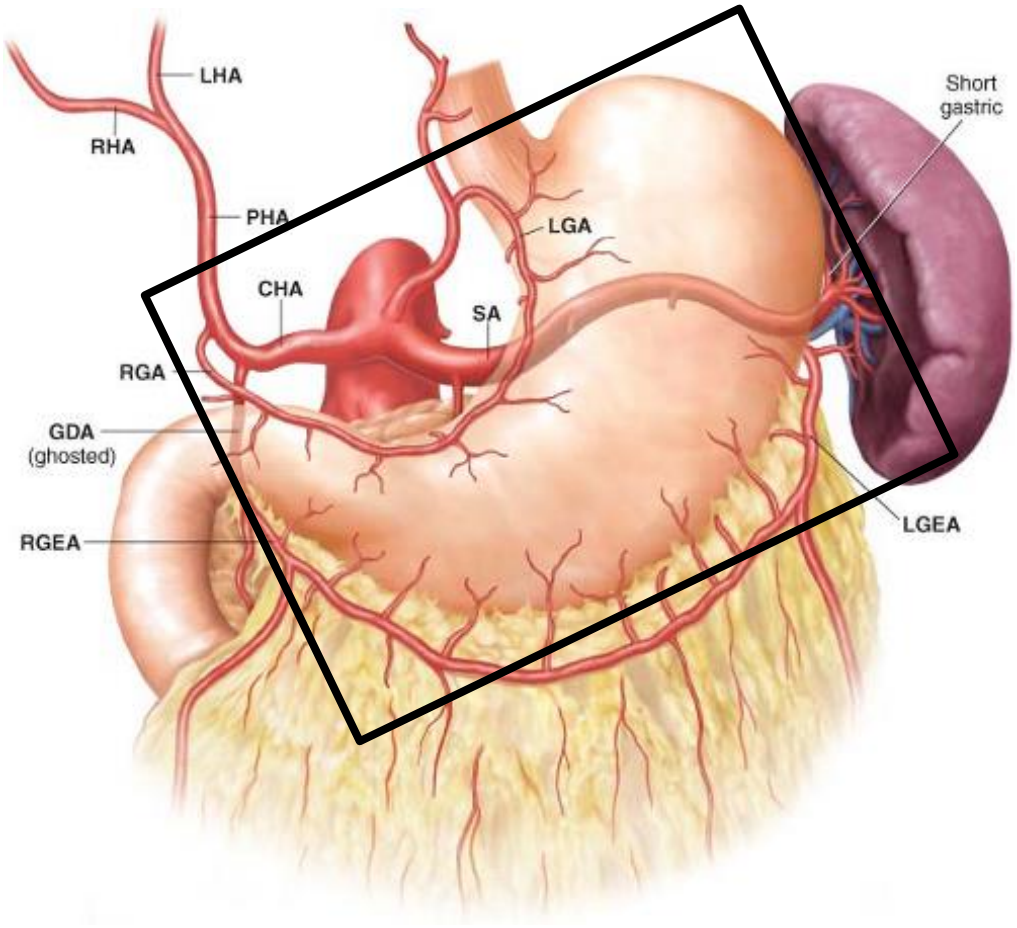
....basics

- **Standard procedures for gastric cancer**
  - Total gastrectomy
  - Distal gastrectomy (=subtotal gastrectomy)
  - Proximal gastrectomy



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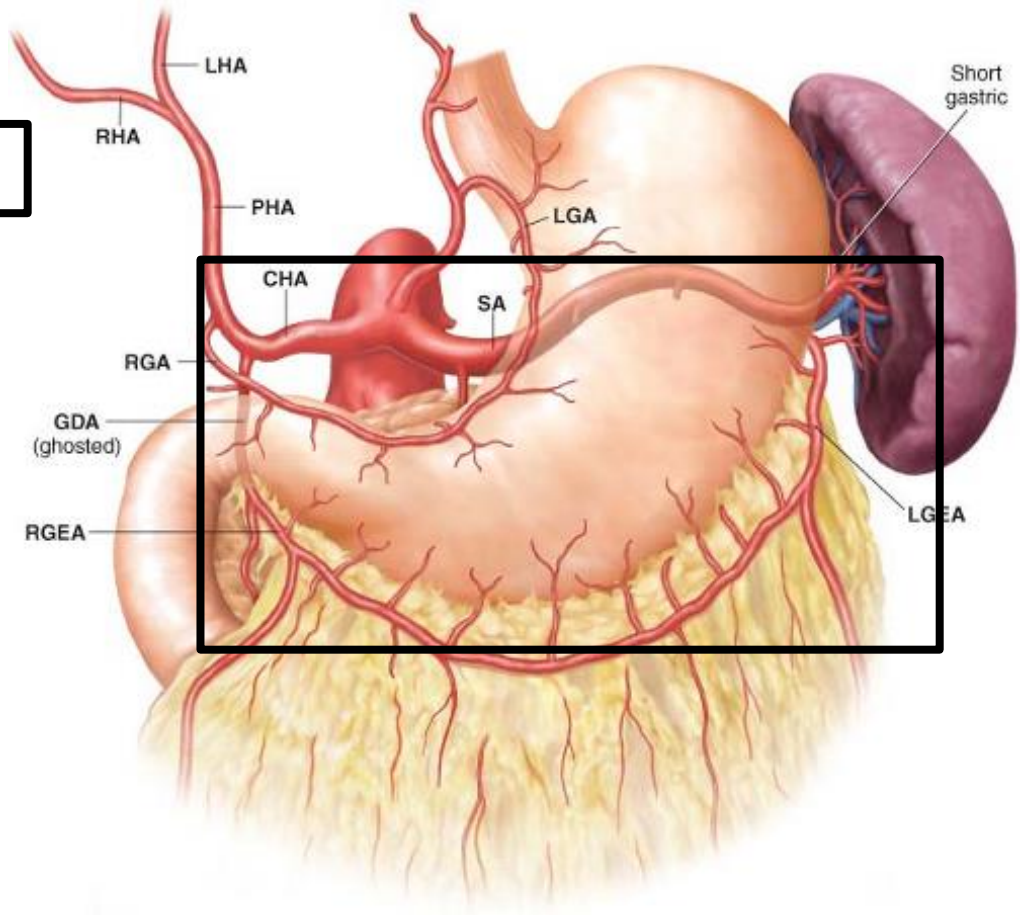

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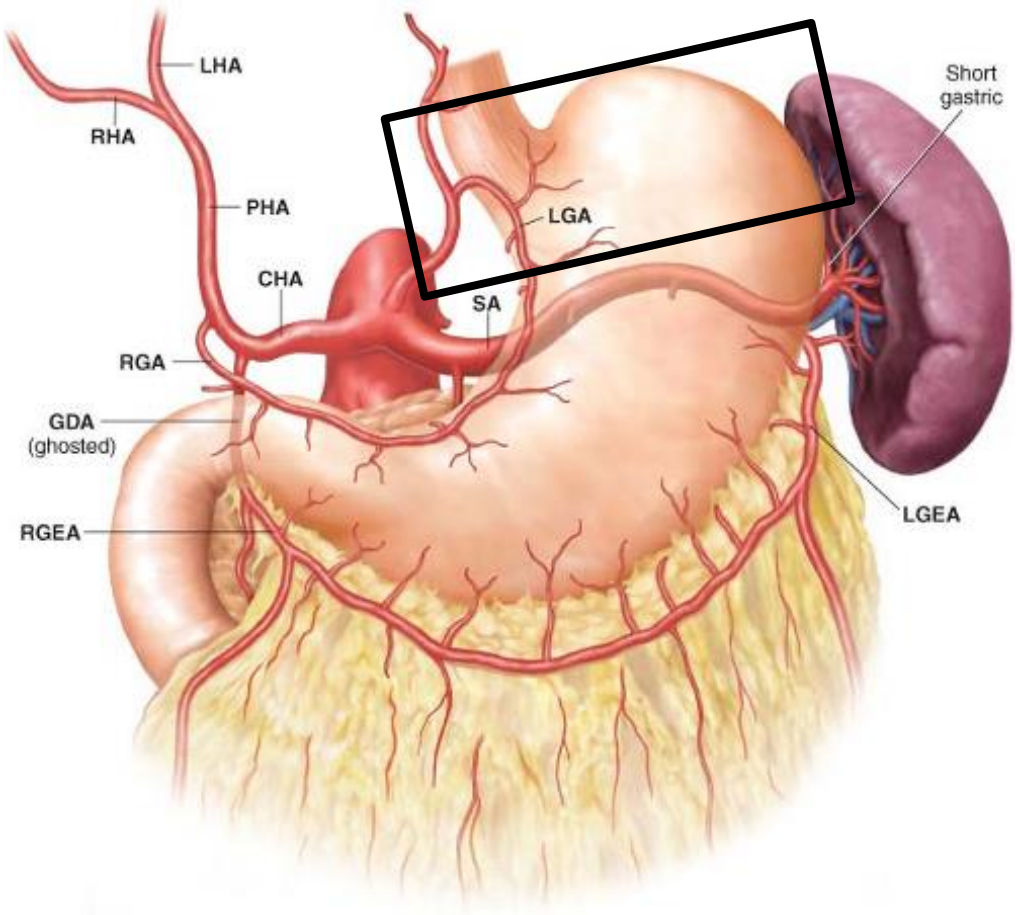
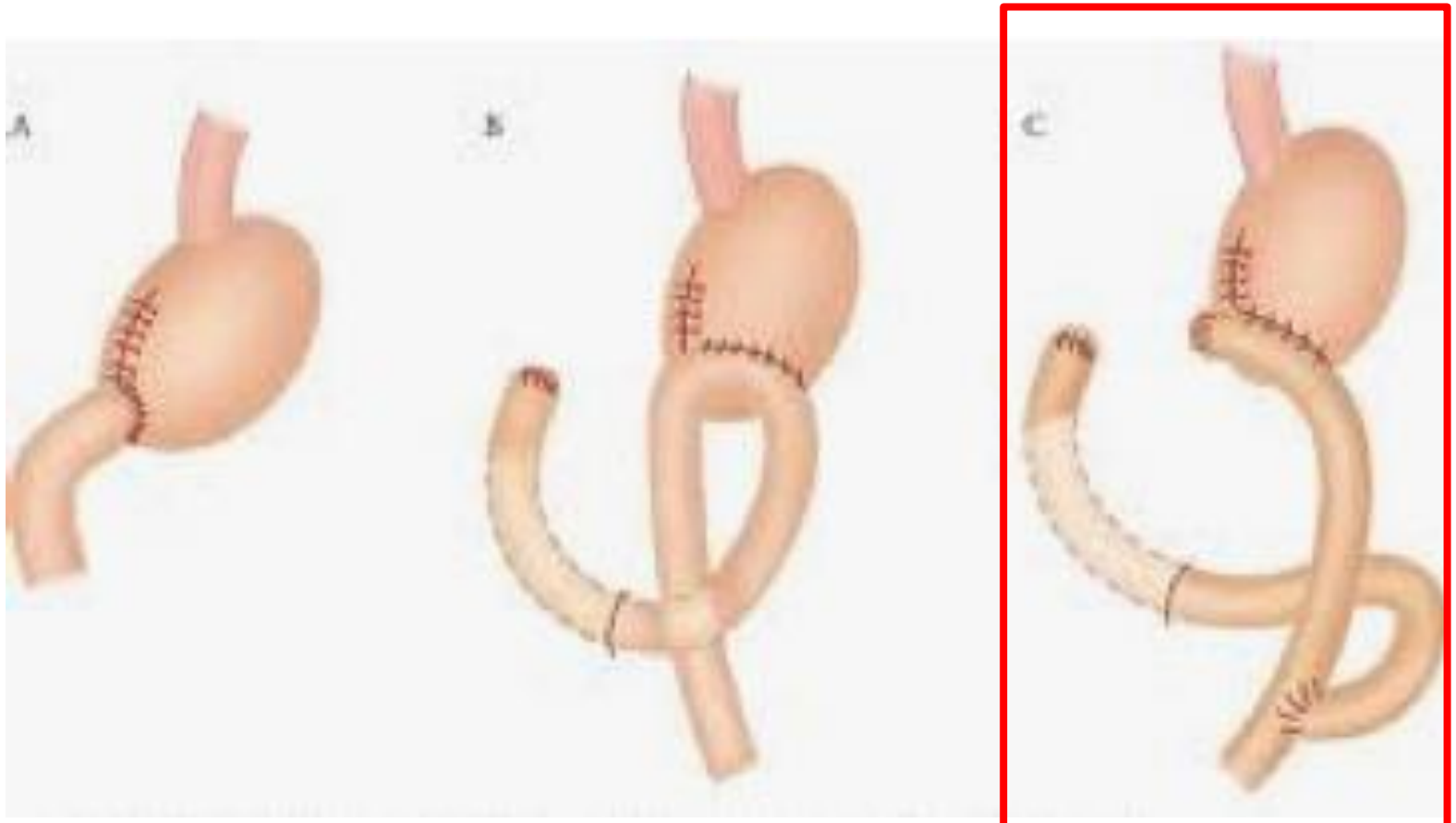


Very rarely used in in Western countries due to:

- Only oncogically suitable only for early (T1) cancers
- Leads to severe reflux problems

Gastrectomy reconstruction



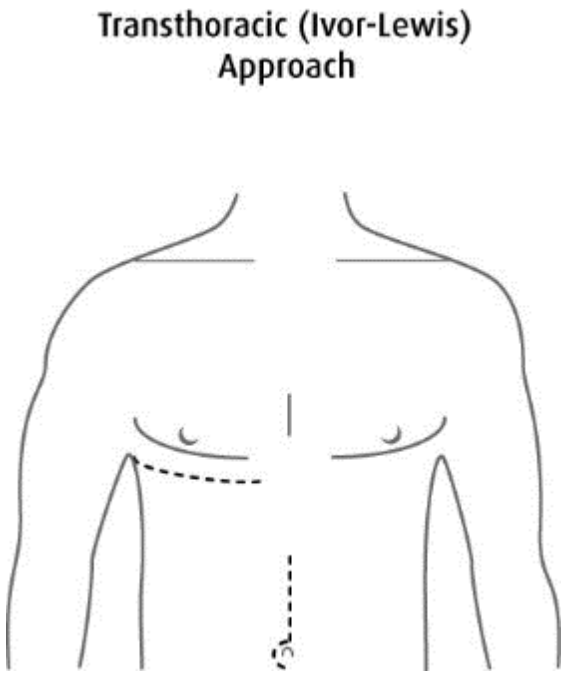
Billroth I

Billroth II

Roux-en-Y

....basics

- Standard procedures for GE junction cancer
  - Total gastrectomy – Siewert type III
  - Esophagectomy – types I and II
    - Ivor Lewis (intrathoracic anastomosis)
    - Transhiatal esophagectomy (cervical anastomosis)



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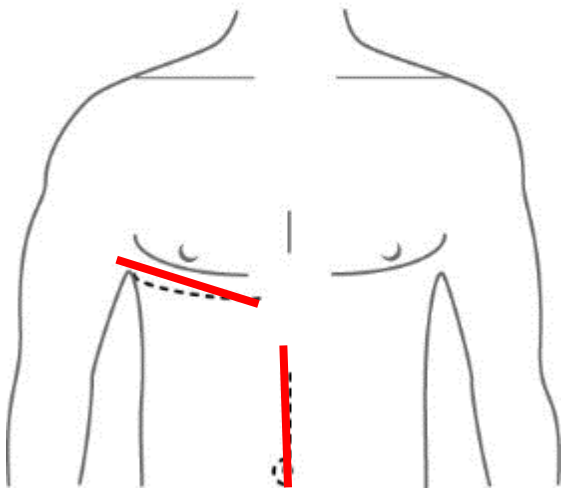
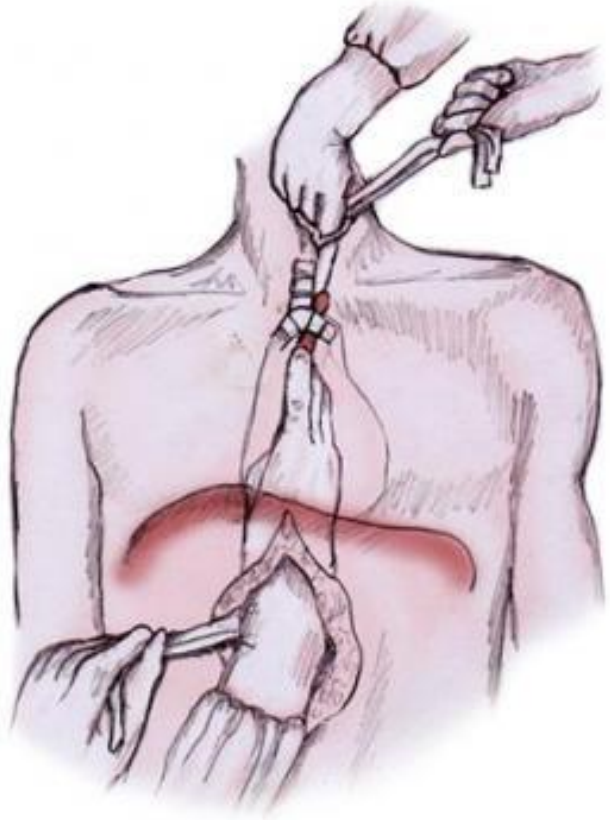


....basics

- Standard procedures for GE junction cancer
  - Total gastrectomy
  - Esophagectomy
    - Ivor Lewis (intrathoracic anastomosis)
    - Transhiatal esophagectomy (cervical anastomosis)
      - Mainly used for very frail patients (severe COPD)

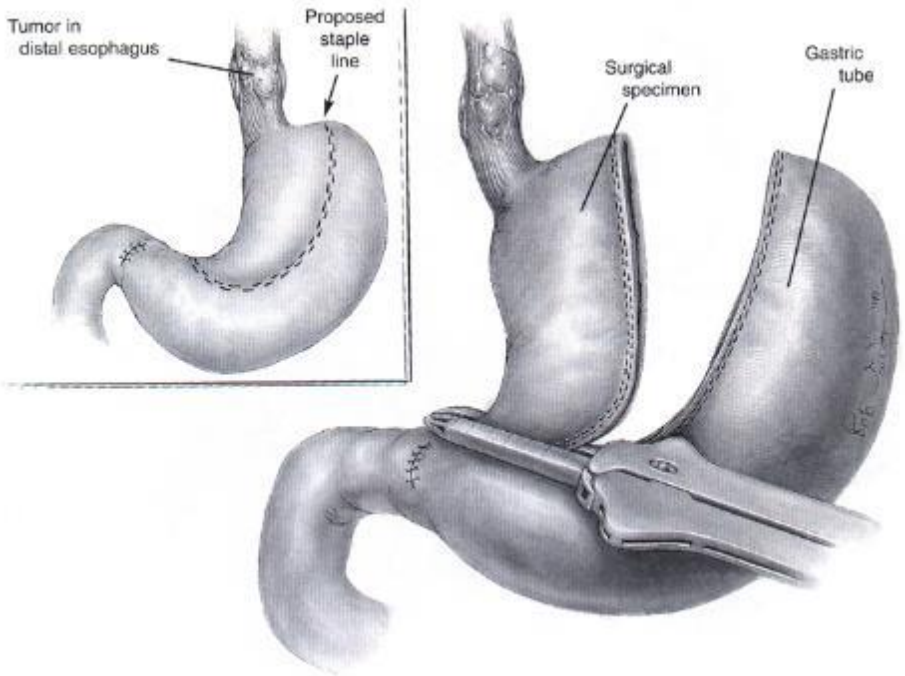


Esophageal mobilization on anterior aspect

Oesophagectomy reconstruction

- Using a **gastric tube** formed by the greater curvature is completely dominating (>95%)

- **Colonic interposition**, using left or right colon,is the second choice



To the issues of controversy:

Gastric and GE junction cancer surgery:

Lymph node dissection – limited (D1) or extended (D2) lymphadectomy?

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Lord Moynihan in 1908:

"Surgery of malignant disease is not the surgery of organs; it is the anatomy of the lymphatic system"

Moynihan BGA. *Surg Gynecol Obstet* 1908;6:463–6:

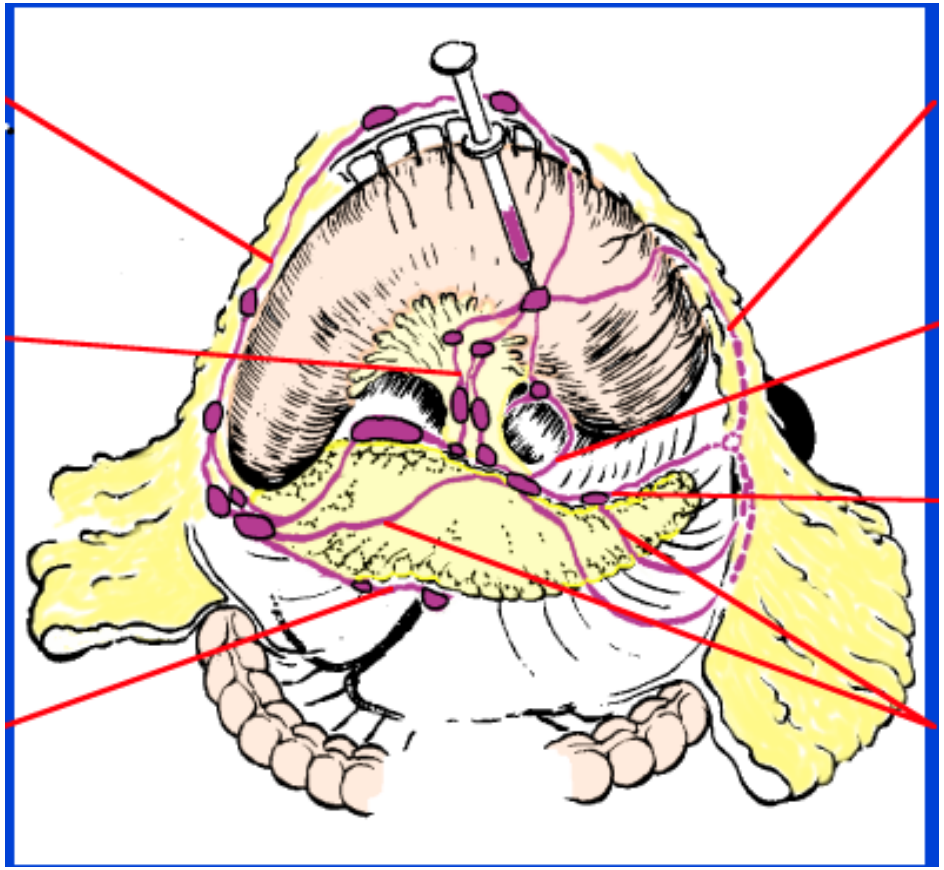
Japanese branch of research in gastric cancer:

Lymphatic Flow from the Stomach

Channels along the greater curve

Channels along the left gastric A.

Channels along the superior mesenteric V.



Channels along the lt. gastro-epiploic A.

Channels along the posterior gastric A.

Channels along the splenic A.

Channels crossing the pancreatic surface

Since 1970ies

National Cancer Center in Tokyo:

Database on specific lymph node station metastases

- **Database variables:**
  - **Sex, age, location** (upper, middle lower third), **position** (lesser/greater curvature, posterior/anterior, circumferential), **Borrmann classification, depth of invasion, max diameter, differentiation grade**

- **Accurate prediction of the risk of metastasis in each lymph node station**

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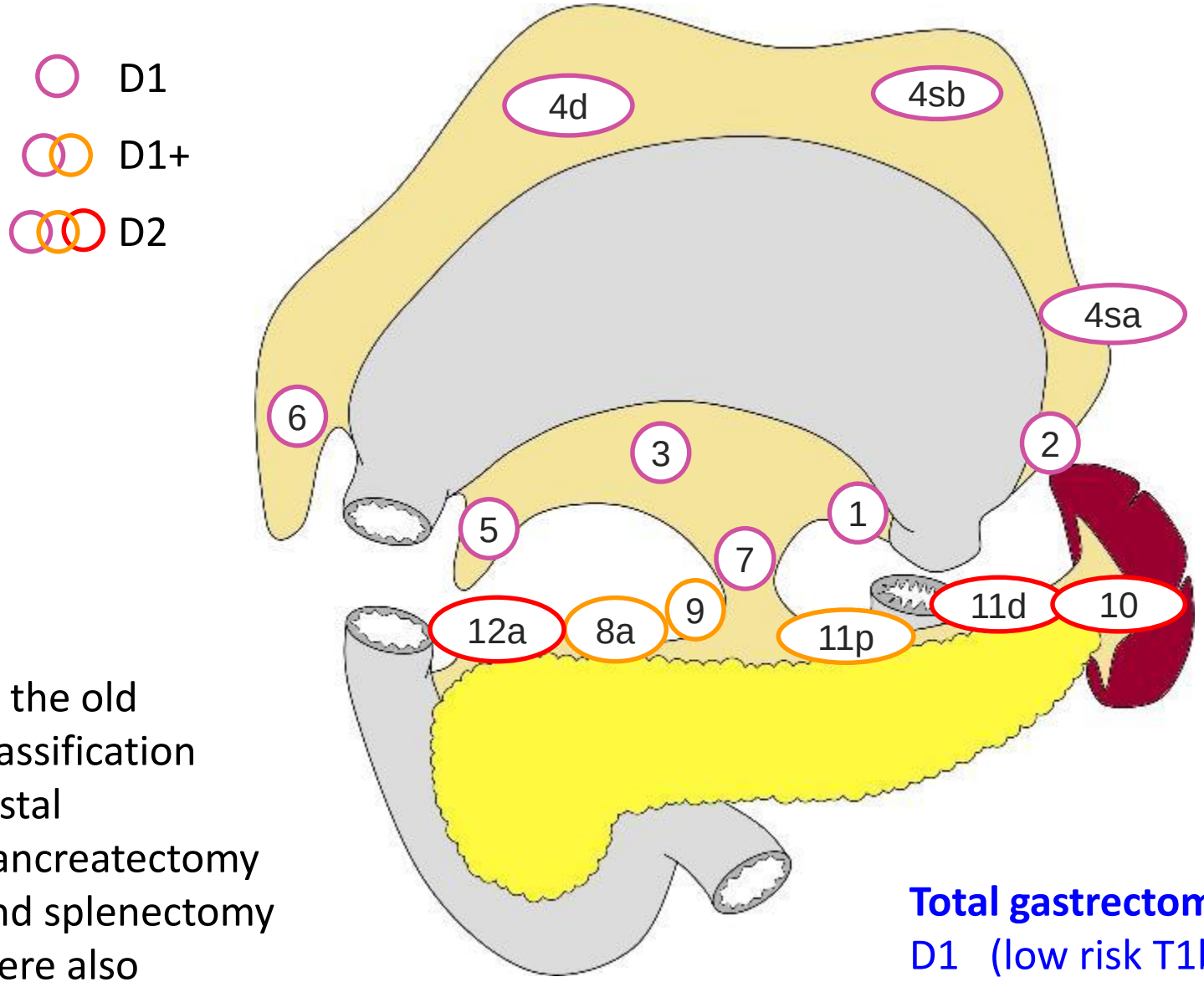


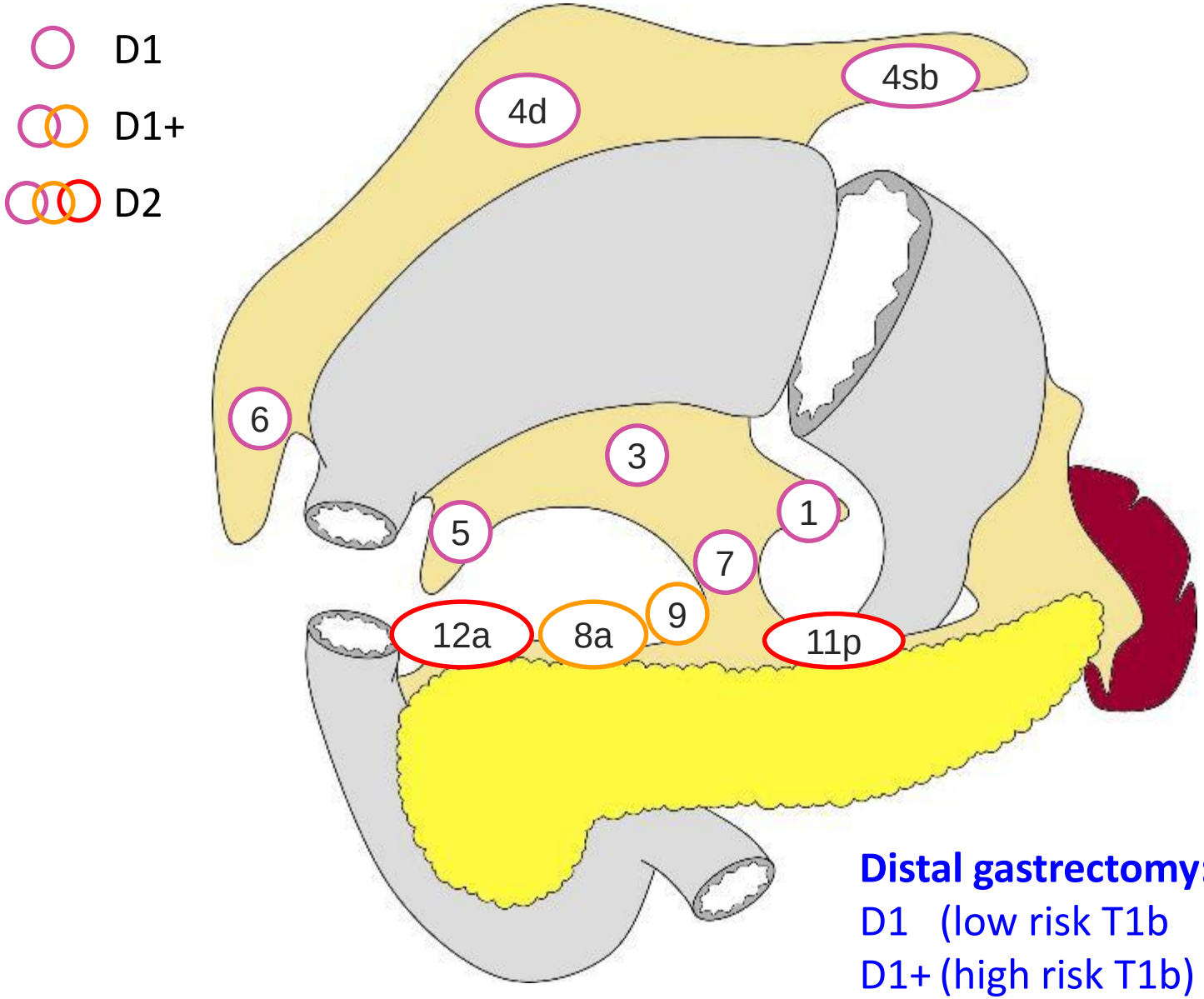
In the old classification distal pancreatectomy and splenectomy were also required

Total gastrectomy:

D1 (low risk T1b

D1+ (high risk T1b)

D2 (all T2-T4)



Distal gastrectomy:

D1 (low risk T1b

D1+ (high risk T1b)

D2 (all T2-T4)

Randomised trials addressing lymphadenectomy for gastric cancer

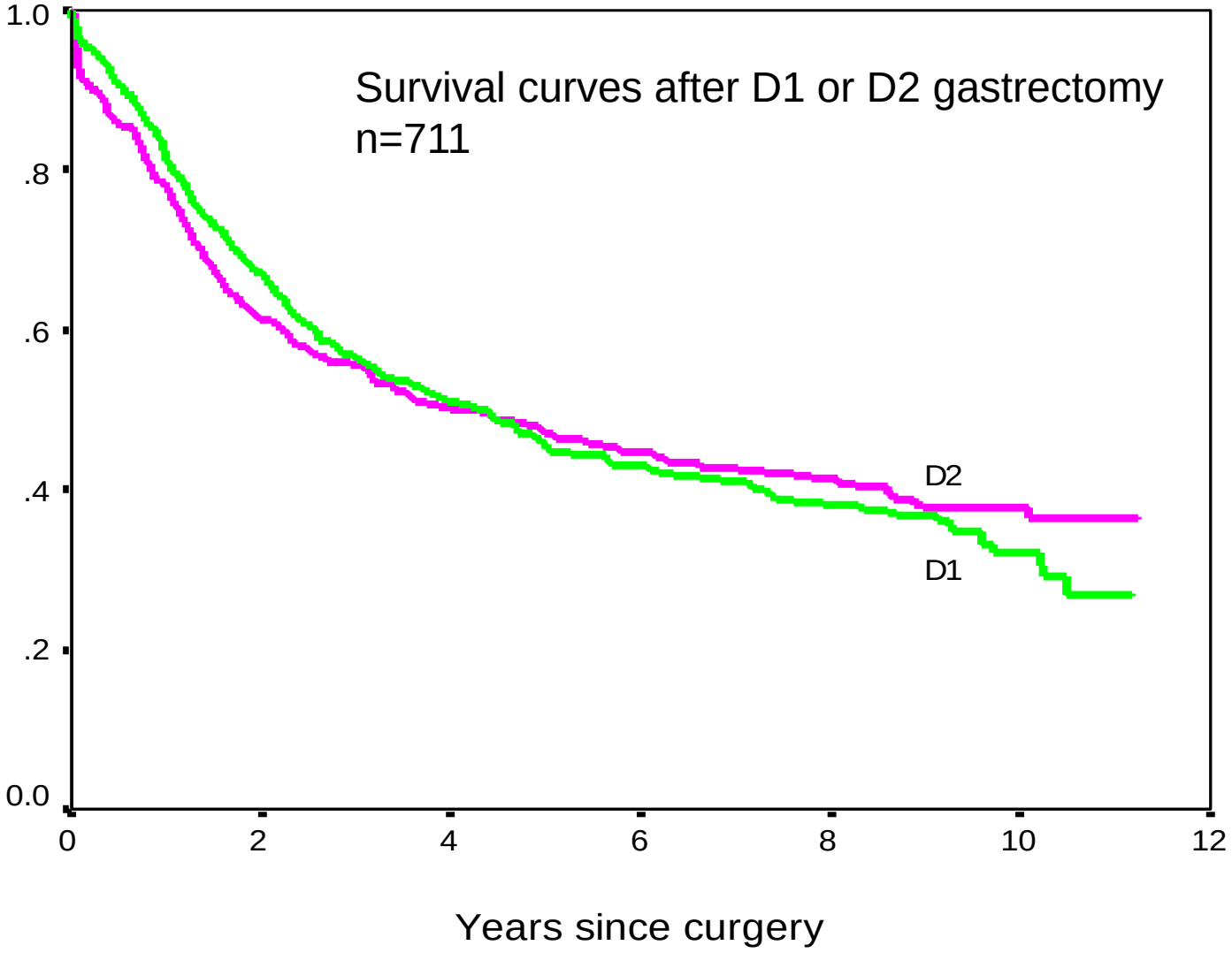
Trial	Author, year	No. Pts	Results
Dutch	Bonenkamp, 1999	711	No survival benefit of D2. High mortality.
British MRC	Cuschieri, 1999	400	No survival benefit of D2. High mortality.
Chile	Csendes, 2002	187	Splenectomy is not necessary.
Taegu	Yu, 2006	207	Prophylactic splenectomy is not justified.
Taipei	Wu, 2006	221	D3 (actually more like D2) > D1
JCOG 9501	Sasako, 2008	523	Prophylactic D3 should not be done.
Italian D1-D2	Deguili, 2014	267	Low morbidity and mortality, no overall survival difference, subgroup differences (N+ patients)

Dutch D1/D2 Trial

Accrual and publlication history:

- 1989-1993 996 randomized; 711 curative
- 1995 Morbidity/mortality (Lancet)
- 1999 Survival (N Engl J Med)
- 2004 “Final” results (J Clin Oncol)
- 2010 15-yr follow-up (Lancet Oncol)
- 2015 Lymph node dissection per protocol data (BJS)

Dutch D1/D2 Trial



Bonenkamp et al NEJM 1999

Inhospital Mortality
Dutch D1/D2 trial

	D1	D2
Hosp. Death (%)	3.9	9.7
Male	4.2	14.0
Female	3.7	4.1

Mortality largely attributed to splenectomy and distal pancreatectomy

Bonenkamp et al NEJM 1999

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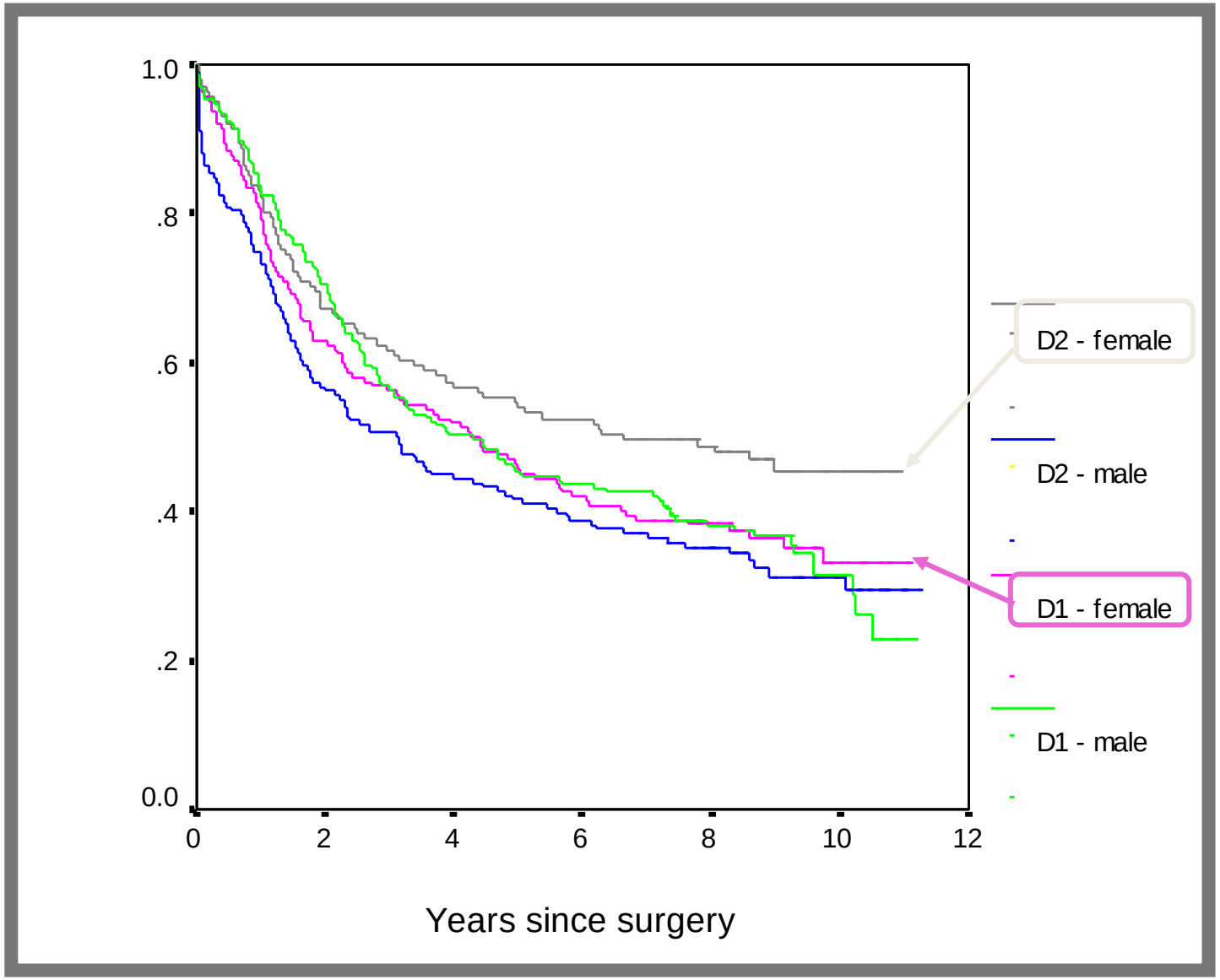
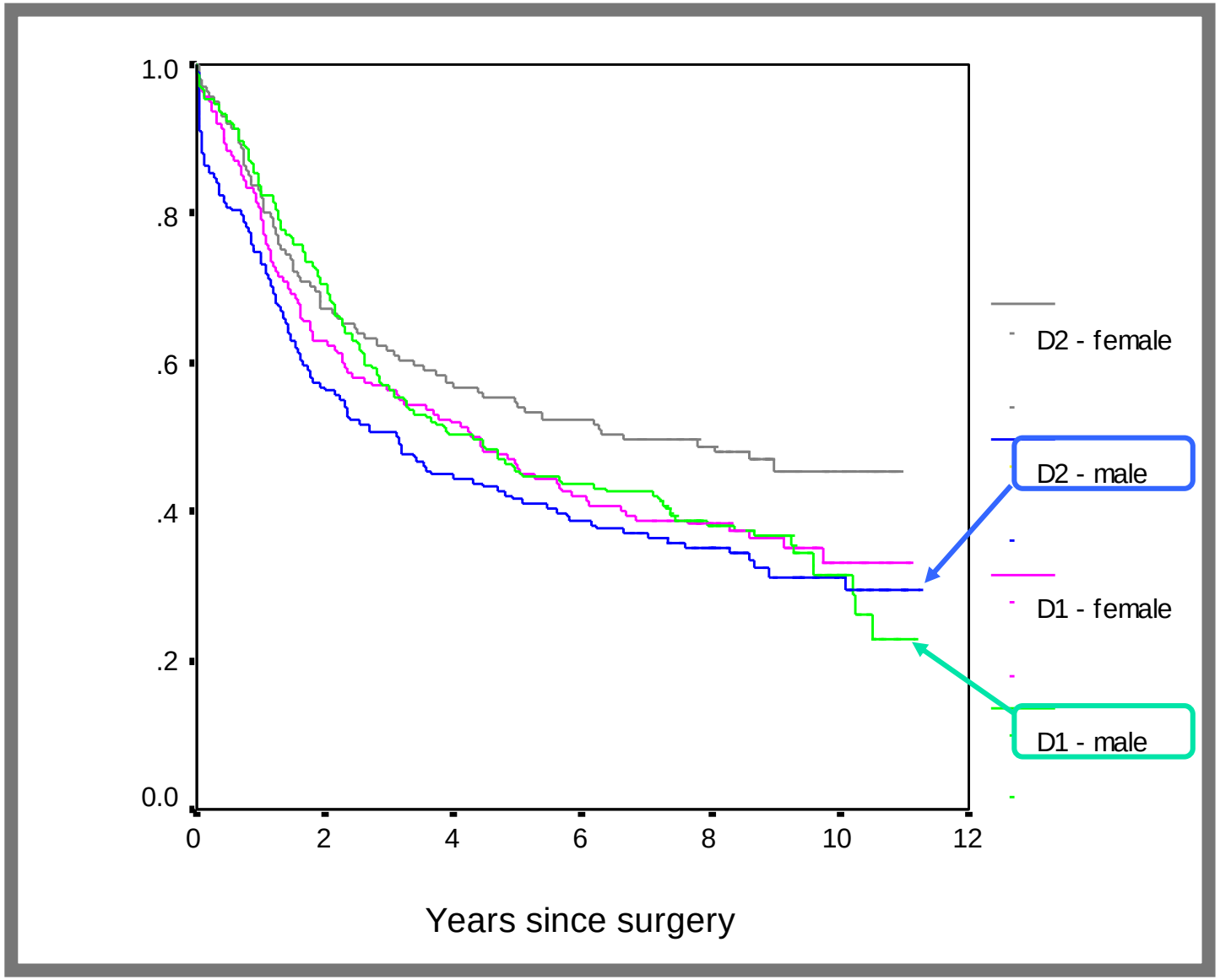
Dutch D1 *vs.* D2

Overall survival

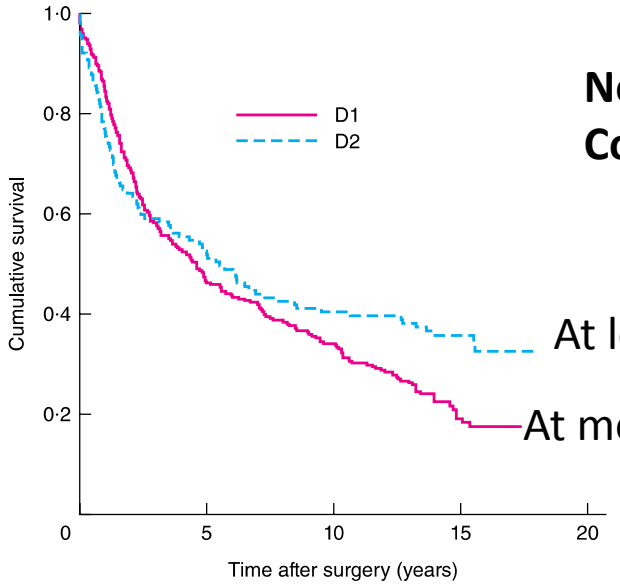


Dutch D1 *vs.* D2

Overall survival



Dutch trial per protocol (quality assured pathology)



No. at risk

D1	282	133	96	32
D2	139	73	55	29

Fig. 3 Survival curves for D2 compliant + contaminated (139 patients) and D1 without contamination (282) subgroups. $P = 0{\cdot}041$ (log rank test)

At least D2

At most D1

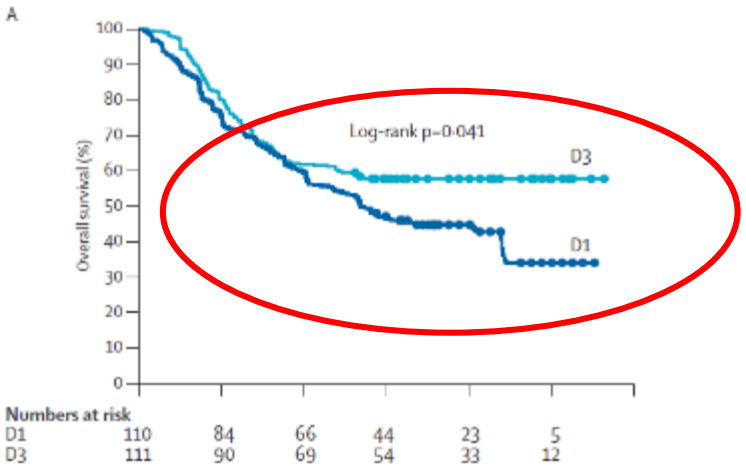
Treatment delivery problems in D1-D2 trials:

Non-compliance = less lgll dissection than required for D2
Contamination = more lgll dissection than required for D1

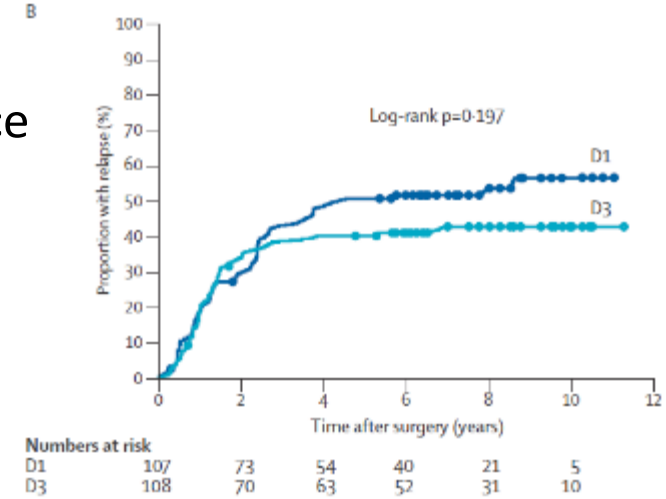
W.O. de Steur et al. BJS 2015

Taipei D1 vs extended lymphadenectomy trial

Overall survival



Recurrence after R0



- Single institutional RCT
- N=221
- No adjunct therapy

Significantly better overall survival after extended lymphadenectomy

Wu et al. Lancet Oncology 2006

Extent oflymphadenectomy in gastric cancer surgery

Take home message:

Extended lymphadectomy (D2) improves the oncological outcome in gastric cancer

Under the condition that postoperative mortality is kept low (SURGERY IS STANDARDIZED = High volume centers)

ESMO guidelines 2016:

Consensus opinion is that, in Western countries, medically fit patients should undergo D2 dissection that is carried out in specialised, high-volume centres with appropriate surgical expertise and postoperative care [I, B] [25–27]. As a result, perioperative

Smyth et al. Ann Oncol 2016

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Next issue of controversy:

Gastric and GE junction cancer surgery:

Laparoscopic /minimal invasive or open surgery?

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Minimal invasive or open surgery

What's the actual difference?

- Entry wound trauma
- Vision

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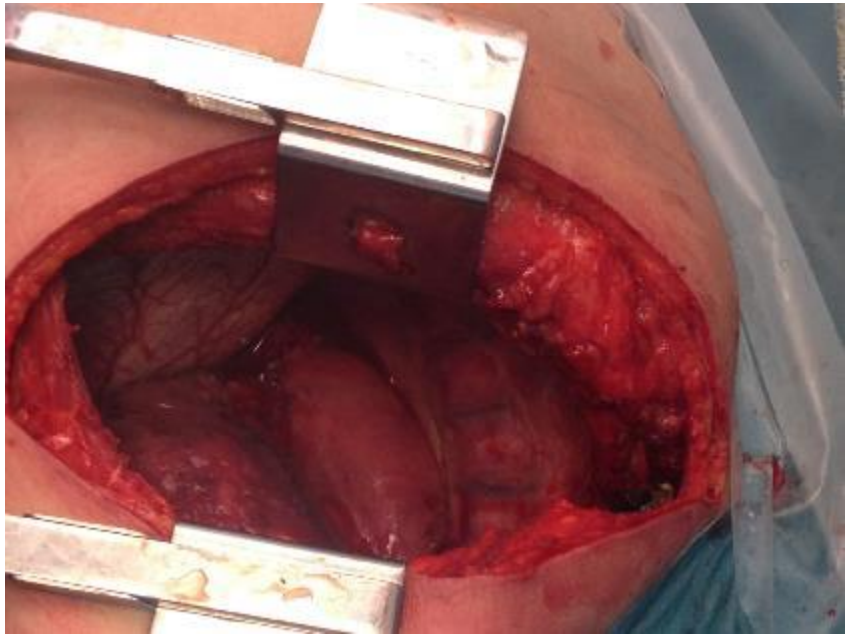
Minmal invasive oesophagectomy (MIO) for GE junction cancer:

Less entry wound trauma

Open

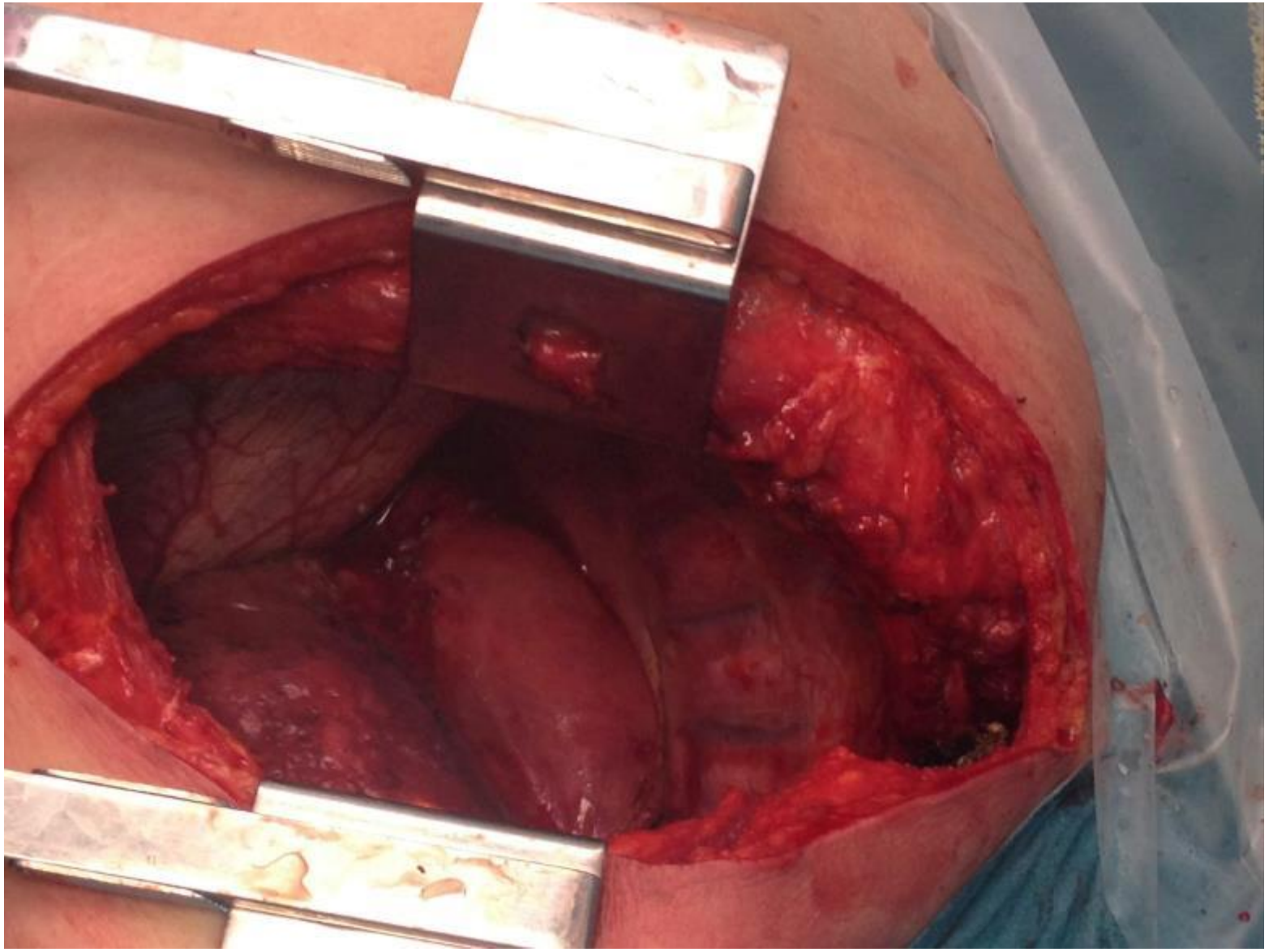


VS

MIO

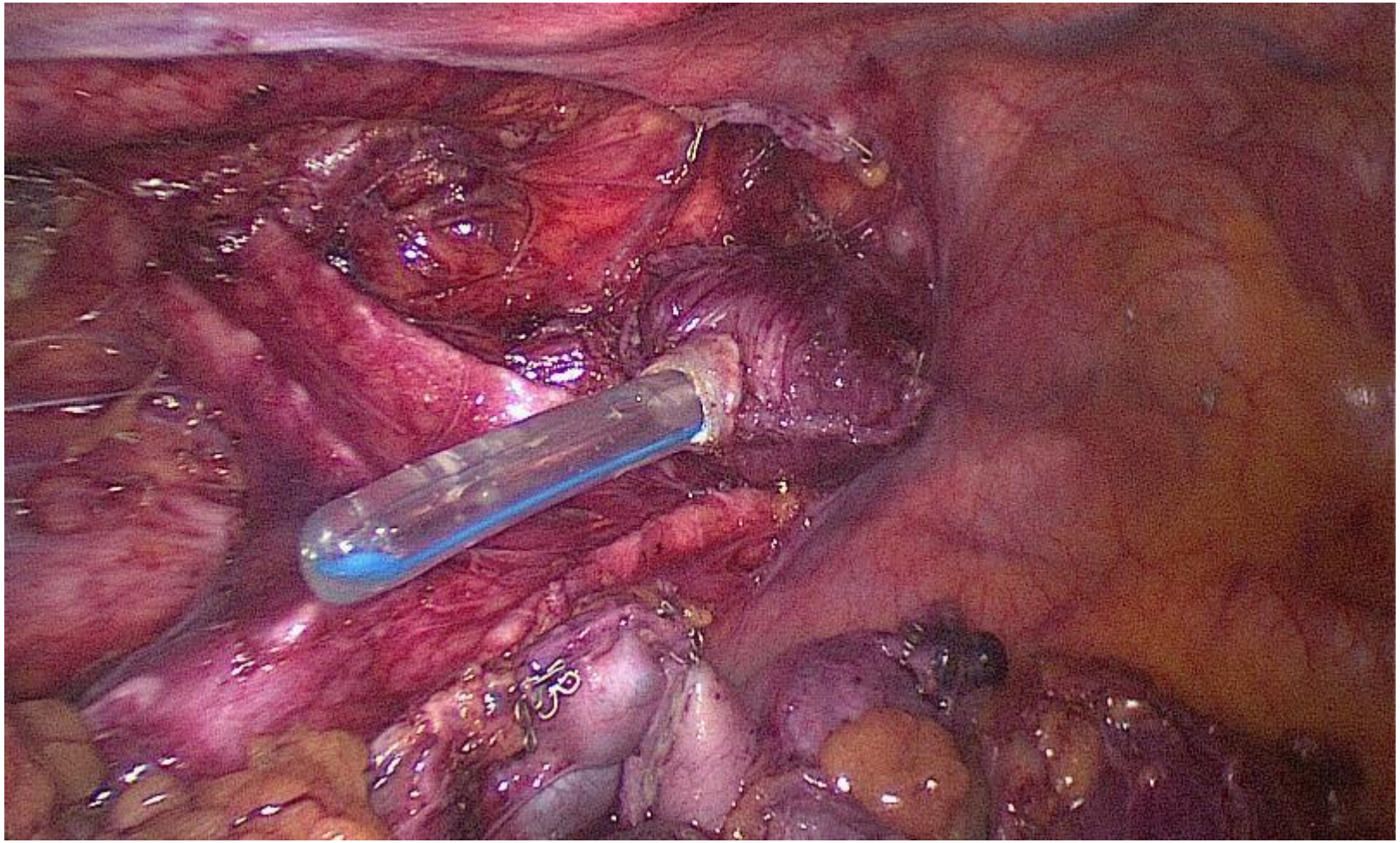
True both for abdominal and thoracic parts of the operation

Vision in open oesophagectomy



Vs

Vision in MIO



Enhanced vision in MIO →More precise dissection→

→Less bleeding

→Potential for better lymph node dissection and radicality

→Less unintentional tissue damage

First port placement

Laparoscopic or open gastrectomy?

Major randomized trials comparing open to laparoscopic gastrectomy for gastric cancer

Trial	Patients	Primary outcome	Sample size	Status	Finding
JCOG0703	Stage I, DG only	Morbidity	176	Published	Equal
Cai et al.	Stage II-III	R0, lgll counnt, morbidity, recovery	123	Published	Equal R0, lgll yield, lap less pulmonary morbidity
Cui et al.	Stage II-III	R0, Lgll count + recovery	296	Published	Equal R0/lgll, lap faster recovery
KLASS-01	Stage I, DG only	Overall survival	1416	Published	Non-inferiority for OS, Lap less morbidity
JCOG 0912	Stage I, DG only	Overall survival	920	Published	Non-inferiority regarding OS, less blood oss, less wound complications
KLASS02	Stage II-III, DG only	Relapse-free survival, complications	1050	Preliminary results	Non-inferiority for relapse free survival, less w.c.
JLSSG0901	Stage II-III, DG only	Relapse-free survival, complications	507	Preliminary, early results	No difference in morbidity, less blood loss and analgetics in lap
LOGICA	Stage II-III, DG only	Postop stay	210	Preliminary results	No difference
STOMACH	Stage II-III, TG only	Lymph node yield	168	Preliminary results	No difference

- **Non-inferiority for lap in survival**
- **Lap: minor reduction in**
  - **Blood loss**
  - **Analgetic use**
  - **Morbidity**

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Minimally invasive or open oesophagectomy?

Three randomised trials comparing open to minimal invasive oesophagectomy for oesophageal or GE junction cancer

Trial	Patients	Primary outcome	Sample size	Status	Finding
TIME trial, open vs MIO	Esophageal and GE types I and II	Pulmonary complications	N=115	Published 2012	MIO: less pulmonary complications, quicker recovery, better QoL
Robot trial, open vs robotic MIO	Esophageal and GE types I and II	All complications	N=112	Published 2018	RMIO: less overall complications, quicker funct recovery better QoL
MIRO trial, Open vs hybrid	Esophageal and GE types I and II	All complications	N=207	Published 2019	HMIO: less overall complications, better OS (P=0.06)

MIO:

- Less complications
- Quicker functional recovery
- Better quality of life (up to 1 year after)
- No signs of oncological disadvantages

Biere et al. Lancet 2012
Van der Sluis et al. Ann Surg 2018
Mariette et al. NEJM 2019

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Enhanced recovery programmes (standardized clinical pathways)

Enhanced recovery programmes in oesophagogastric surgery

Original article

Impact of a multidisciplinary standardized clinical pathway on perioperative outcomes in patients with oesophageal cancer

S. R. Preston[1], S. R. Markar[2], C. R. Baker[1], Y. Soon[1], S. Singh[1] and D. E. Low[2]

[1]Oesophago-Gastric Unit, Royal Surrey County Hospital, Guildford, UK and [2]Department of Thoracic Surgery, Virginia Mason Medical Center, Seattle, Washington, USA

Correspondence to: Dr D. E. Low, Department of Thoracic Surgery, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, Washington 98111, USA (e-mail: Donald.low@vmmc.org)

Key components:

- Standardisation of perioperative clinical pathway
- ”Aggressive” mobilisation

Preston et al. BJS 2011

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Preston et al. BJS 2011

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Clinical care pathway from Royal Surrey County Hospital 2011, adopted at Karolinska in 2013

Table 2 Clinical care pathway at Royal Surrey County Hospital, 2011

Postoperative day	Aim or goal
Evening of day of surgery	Goal-directed fluid therapy with LiDCO™ Rapid* for 6 h to maximize fluid status
	Epidural analgesia ± additional intravenous analgesia
	Sits up in bed for 4 h
Day 1	Mobilizes twice in the day as far as the patient is able
	Sits up in chair/bed for 4 h
	Start jejunal feeding (30 ml/h)
	Start 30 ml/h water orally
	Commence prophylactic anticoagulation
Day 2	Mobilizes three times in the day
	Increase jejunal feeding to 50 ml/h continuously
	Remove nasogastric aspirate if < 300 ml per 24 h
	Transfer to surgical HDU
Day 3	Mobilizes four times in the day
	Basal chest drain may be removed if serous output < 250 ml per 24 h
Day 4	Mobilizes five times in the day
	When flatus passed, increased jejunal feeds to 80 ml/h, and oral intake to 50 ml/h including cups of tea/coffee
Day 5	Mobilizes six times in the day, increasing distance of walks
	Consider discontinuation of epidural following pain team review
	Central line removal
	If bowels opened, discontinue urinary catheter
	Convert intravenous proton pump inhibitor to oral formulation
Day 6	Commence free fluids
	Remove apical chest drain if clear fluid is draining
	Receive pump training for jejunostomy
Day 7	Commence puréed diet and free (non-fizzy) fluids
	Dietitian education on postoperative diet and enteral feeding regimen
	Planned discharge, following physiotherapy assessment and instructions

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Two hours post oesophagectomy

Photo shown after patient's permission

First walk postop day 1

Photo shown after patient's permission

A worn down track in the floor by now

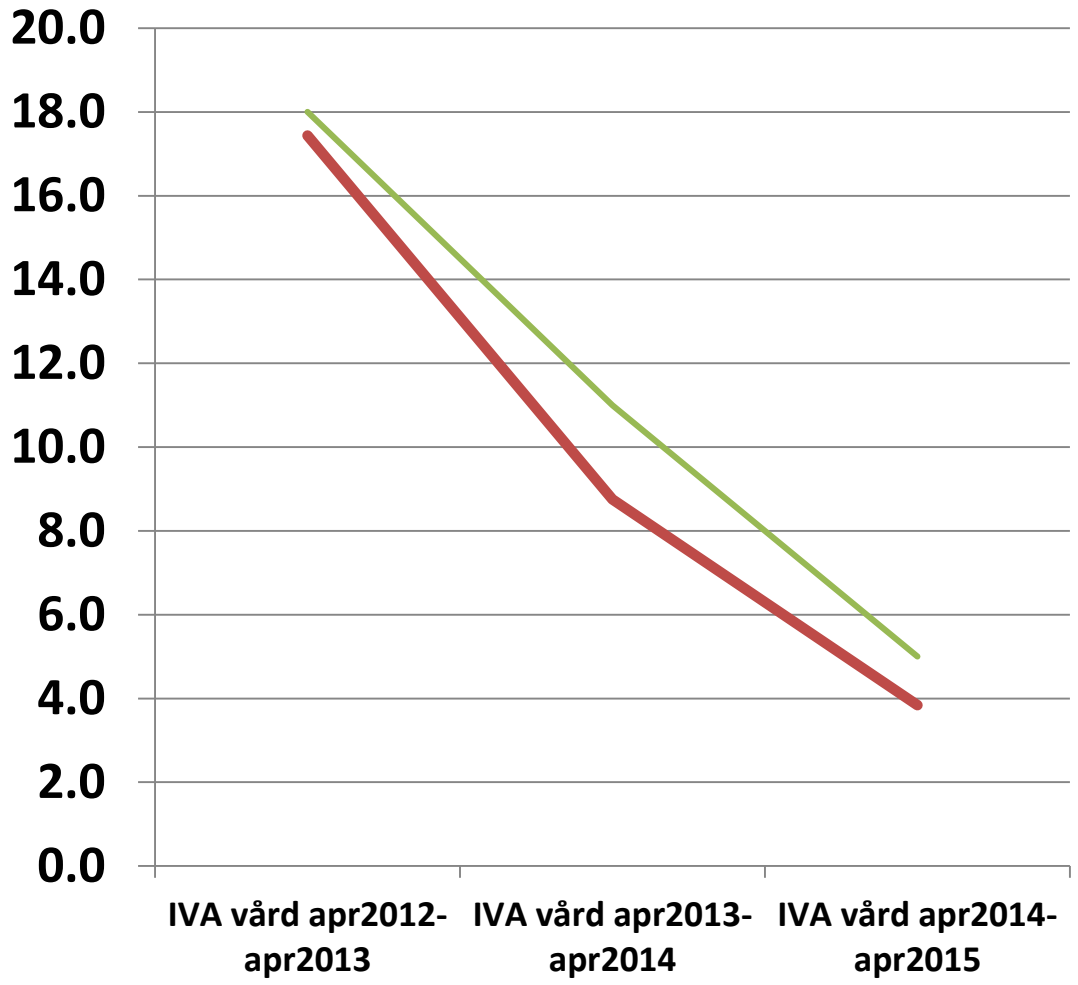
Leaving the hospital at postop day 10

Total game changer for us:

- Major reduction in all types of complications (incidence and severity)
- ICU-time most reduced (unplanned ICU admittance 20% → <5%)

Photo shown after patient's permission

Annual ICU costs after oesophagectomy 2012-2015 (millions of SEK)



Palliative surgery

for gastric and GE junction cancer

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Palliative surgery for gastric and GE junction cancer

What types of palliative surgery may be indicated?

- Distal gastrectomy
  - For severe bleeding
- Gastro-jejunostomy bypass
  - For gastric outlet obstruction
- Palliative gastrectomy in general for reduction of tumour burden???

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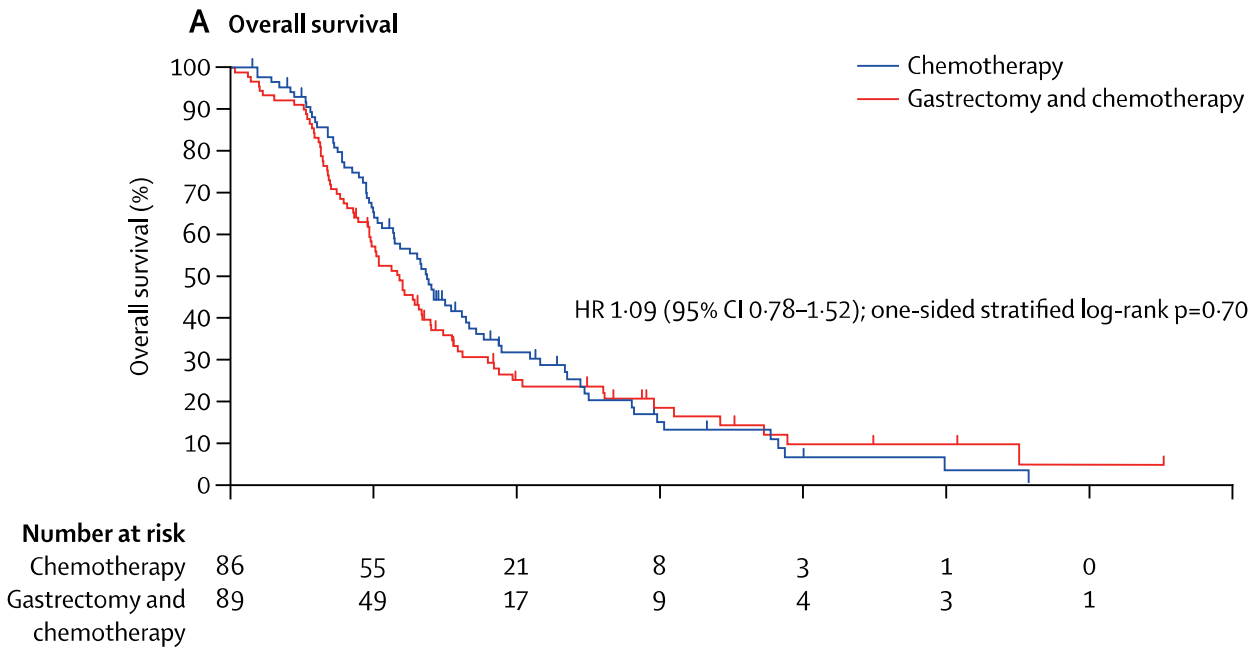
Does resection of primary tumour improve survival in metastatic gastric cancer?

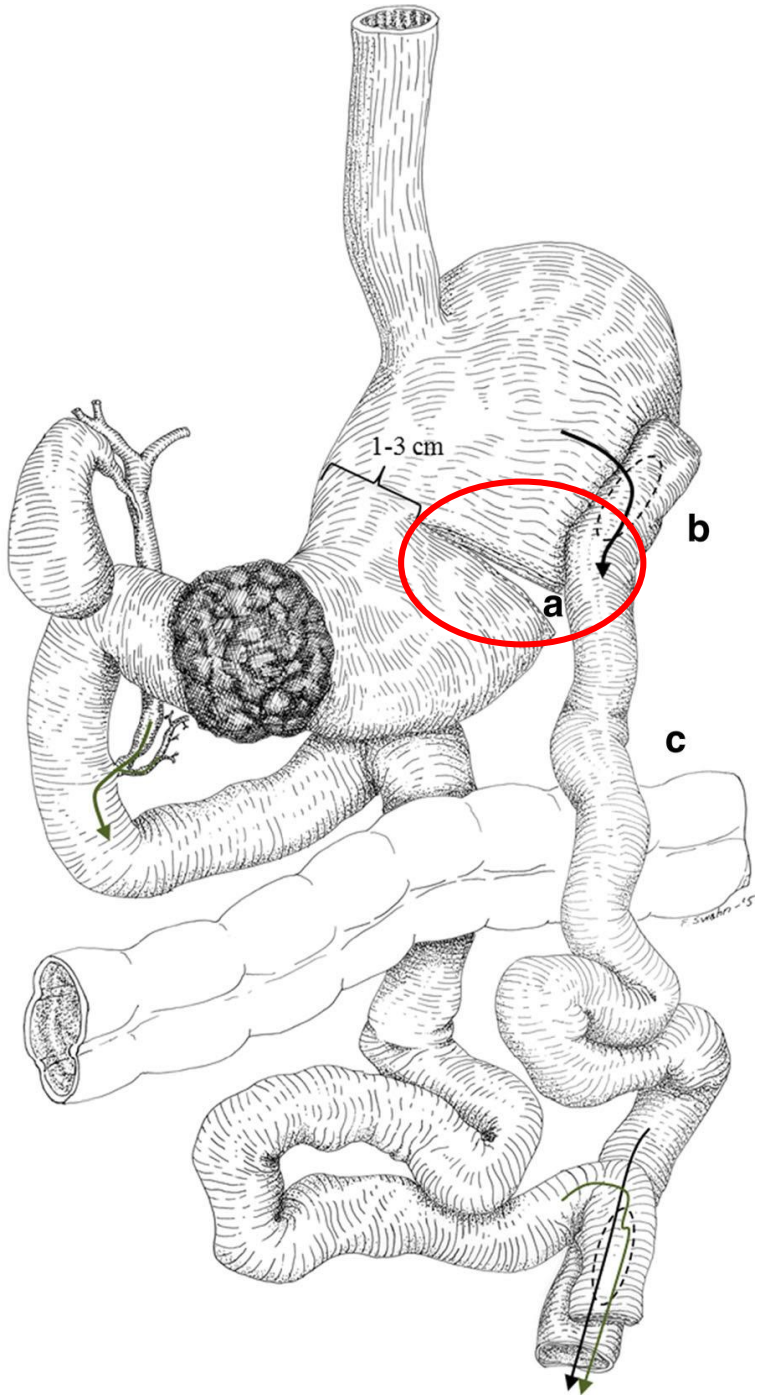
Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial

Kazumasa Fujitani, Han-Kwang Yang*, Junki Mizusawa, Young-Woo Kim, Masanori Terashima, Sang-Uk Han, Yoshiaki Iwasaki, Woo Jin Hyung, Akinori Takagane, Do Joong Park, Takaki Yoshikawa, Seokyung Hahn, Kenichi Nakamura, Cho Hyun Park, Yukinori Kurokawa, Yung-Jue Bang, Byung Joo Park, Mitsuru Sasako, Toshimasa Tsujinaka, for the REGATTA study investigators†*



- RCT palliative chemo vs palliative chemo + distal gastrectomy for metastatic disease in one organ
- N=175
- Trend towards worse OS

Fujitani et al. Lancet Oncol 2016



Illustrator: Swahn F.

How should the gastro-jejunostomy bypass for gastric outlet obstruction be performed?

- Conventional vs
- ”Modified Devine procedure” = bypass with partial stomach partioning

How should the gastro-jejunostomy bypass for gastric outlet obstruction be performed

Langenbecks Arch Surg (2016) 401:777–785
DOI 10.1007/s00423-016-1470-8

SYSTEMATIC REVIEWS AND META-ANALYSES

A systematic review and meta-analysis comparing partial stomach partitioning gastrojejunostomy versus conventional gastrojejunostomy for malignant gastroduodenal obstruction

Koshi Kumagai[1] · Ioannis Rouvelas[1] · Annika Ernberg[1] · Saga Persson[1] · Apostolos Analatos[1] · Daniela Mariosa[2] · Mats Lindblad[1] · Magnus Nilsson[1] · Weimin Ye[2] · Lars Lundell[1] · Jon A. Tsai[1]

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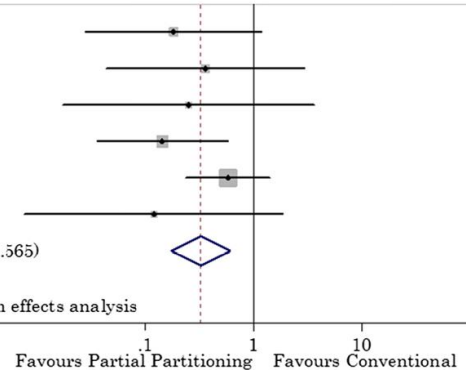
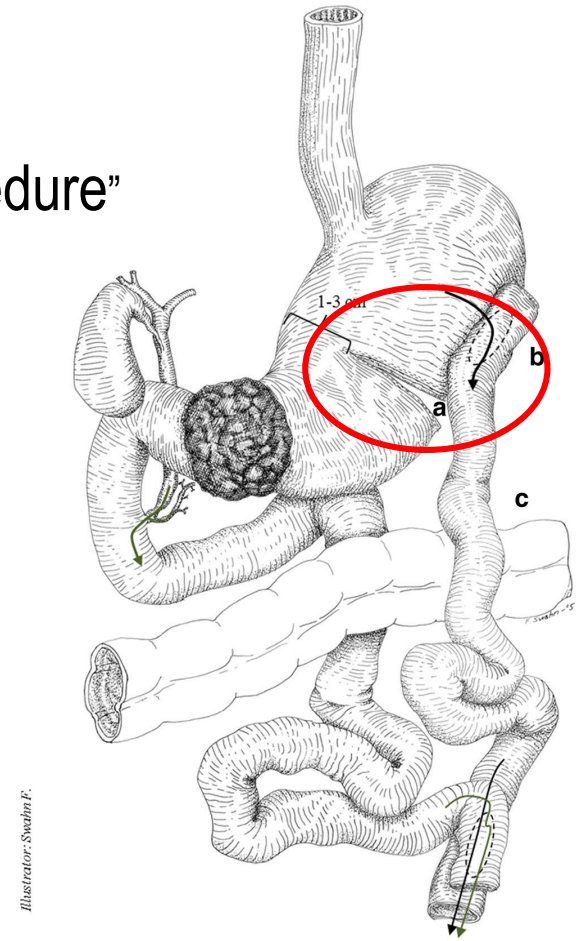


Study ID	RR (95% CI)	Events, Partial Partitioning	Events, Conventional
Kaminishi 1997	0.18 (0.03, 1.17)	1/8	9/13
Kato 2001	0.36 (0.04, 2.94)	1/7	2/5
Yamagishi 2004	0.25 (0.02, 3.62)	0/3	4/8
Oida 2009	0.14 (0.04, 0.57)	2/30	14/30
Usuba 2011	0.58 (0.24, 1.40)	6/26	8/20
Ernberg 2015	0.12 (0.01, 1.88)	0/8	6/13
Overall (I-squared = 0.0%, p = 0.565)	0.32 (0.17, 0.60)	10/82	43/89

NOTE: Weights are from random effects analysis

"Modified **Devine** procedure"



Modified Devine:

- Better gastric emptying
- Shorter length of stay

Kumagai et al. Langenbeck Archives of Surgery 2016

Take home message:

- **Extended (D2) lymphadenectomy is recommended** in curative intent surgery for locally advanced gastric cancer (ESMO)
- **Laparoscopic gastrectomy and minimal invasive oesophagectomy are safe and oncologically non-inferior** in curative intent surgery for gastric and GE junction cancer
- **Palliative gastrectomy is not recommended**, except for palliation of specific symptoms such as severe bleeding
- **Gastro-jejunostomy bypass with partial stomach partitioning (modified Devine) is the most recommendable palliative procedure for malignant gastric outlet obstruction**

ESMO


Thank you

Surgery for gastric and GE junction cancer

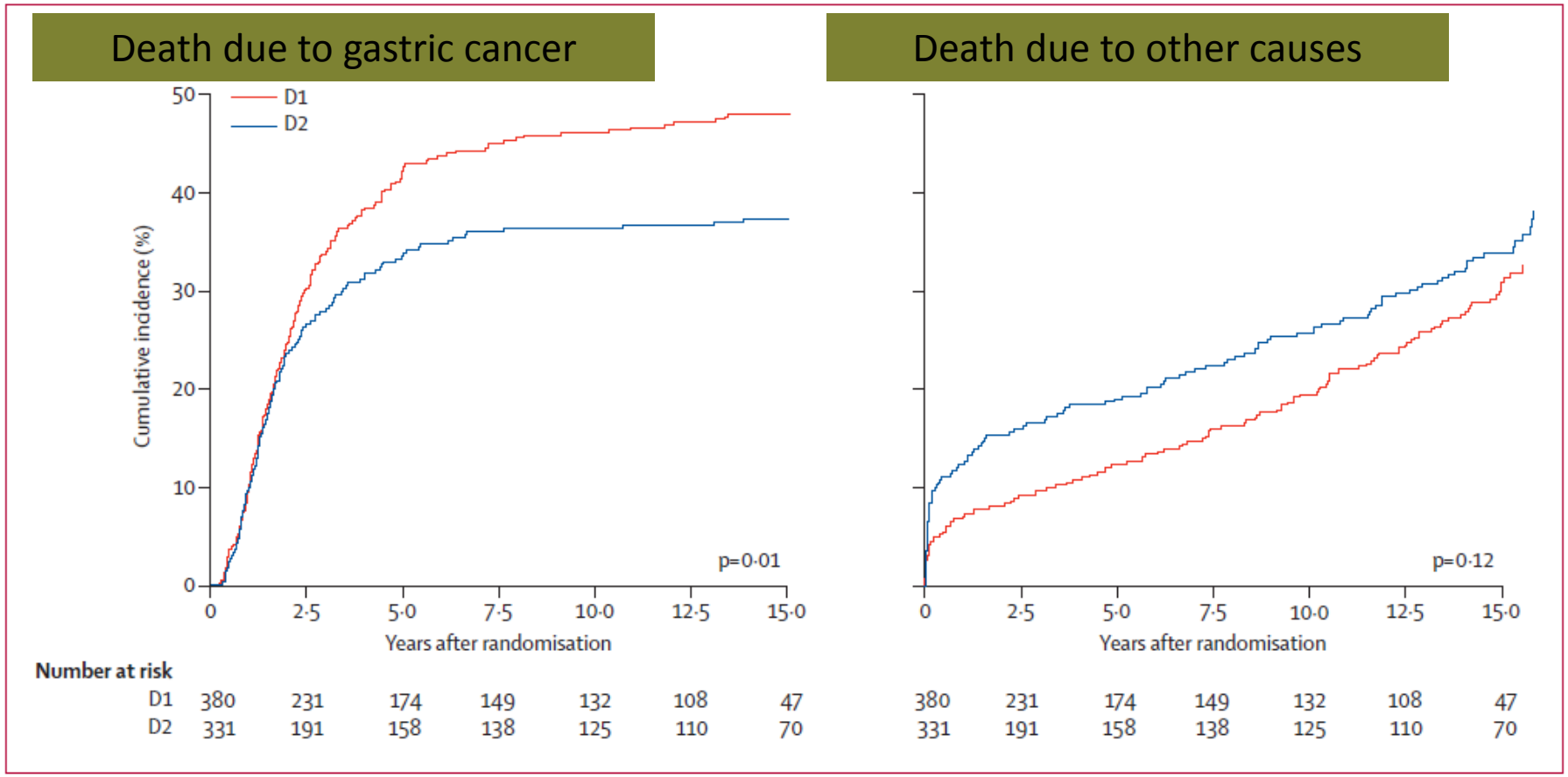
The dilemma of oncological surgery

High level of radicality
→Increased risk of morbidity

Low level of radicality
→Increased risk of cancer recurrence

Dutch D1/D2 trial: 15-yr results
Post hoc analyses

Cumulative risk of death



Songun I, et al. Lancet Oncol 2010;11:439-49