LEIDEN UNIVERSITY MEDICAL CENTER

Surgical management of localized gastric cancer

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Multidisciplinary interactive session

Management of localized gastric cancer

Case Presentation

Chest CT-scan: no lung or mediastinal mets

Abdominal and pelvic CT-scan:

No liver mets or peritoneal mets

Thickening of the whole gastric wall without invasion of any surrounding local structures

Multiple perigastric lymphonodes of 2 cm size, but no extraperigastric and paraortic lymph nodes.

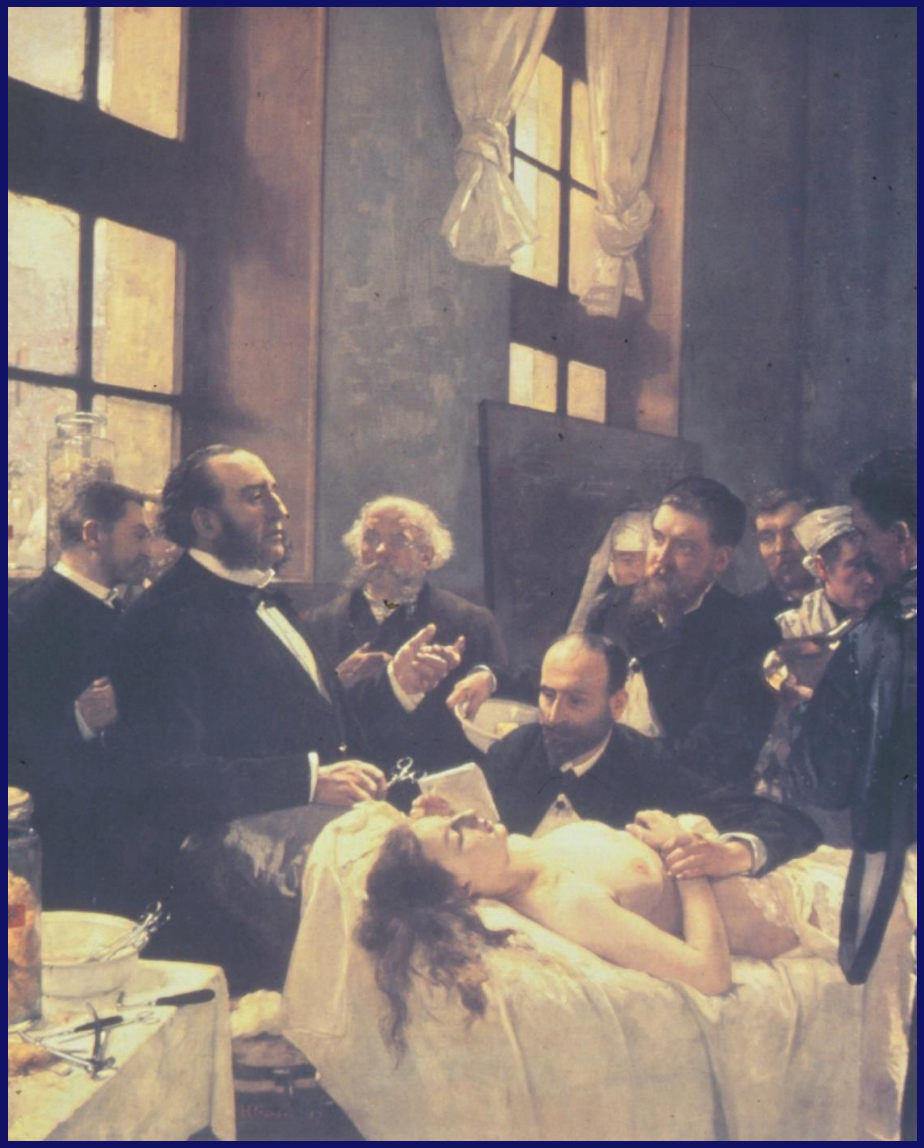
A laparoscopy and an endoscopic ultrasonography were not considered

cT3 cN+ cM0

Case

- Questions
  - What is the most appropriate surgical treatment for this patient?
  - What is the most appropriate hospital to refer this patient to?

The role of Surgery for gastric cancer



Pean and Billroth

Surgery for gastric cancer

Advanced gastric cancer

Surgery

- Goal: R0 resection
- Options:
  - Limited lymphadenectomy
  - extended lymphadenectomy
  - super extended lymphadenectomy

Definition of lymphadenectomy

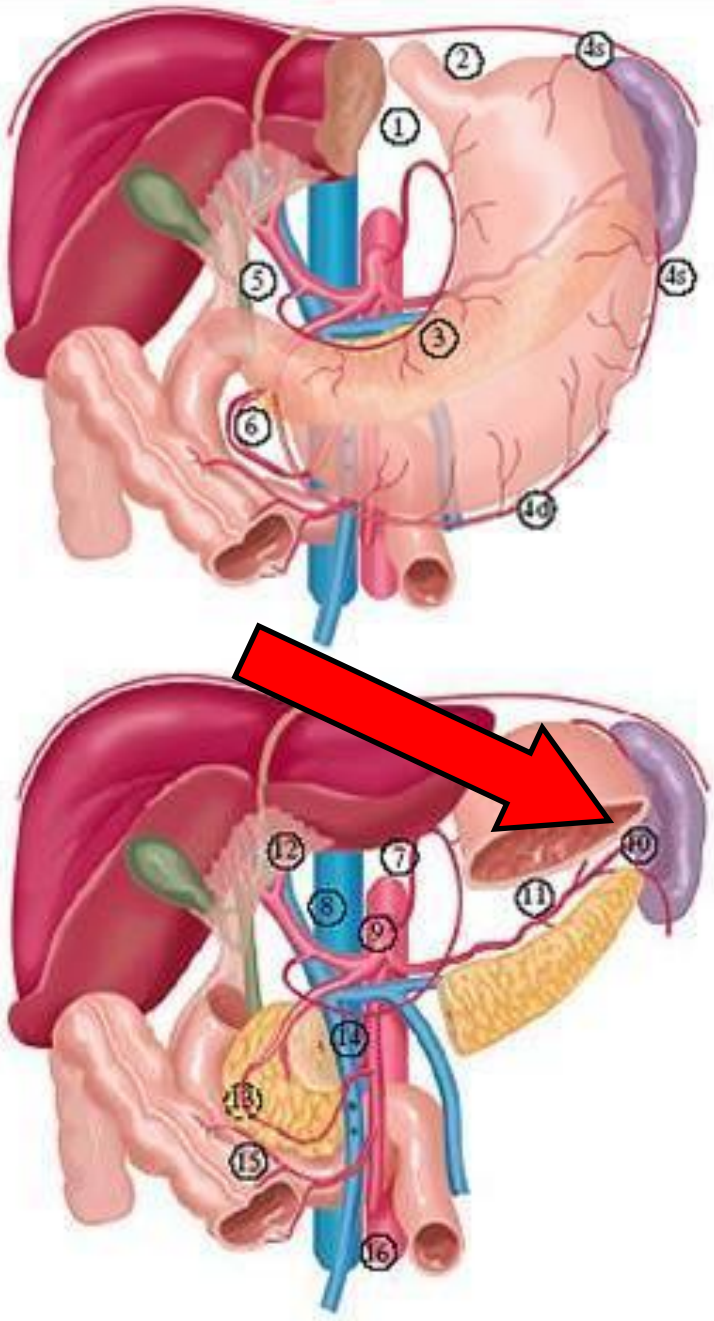
D1 nodes adjacent to the stomach

D2 + branches celiac axis

D3 nodes along the aorta

Station #10: in splenic hilus:

Difficult to remove without splenectomy

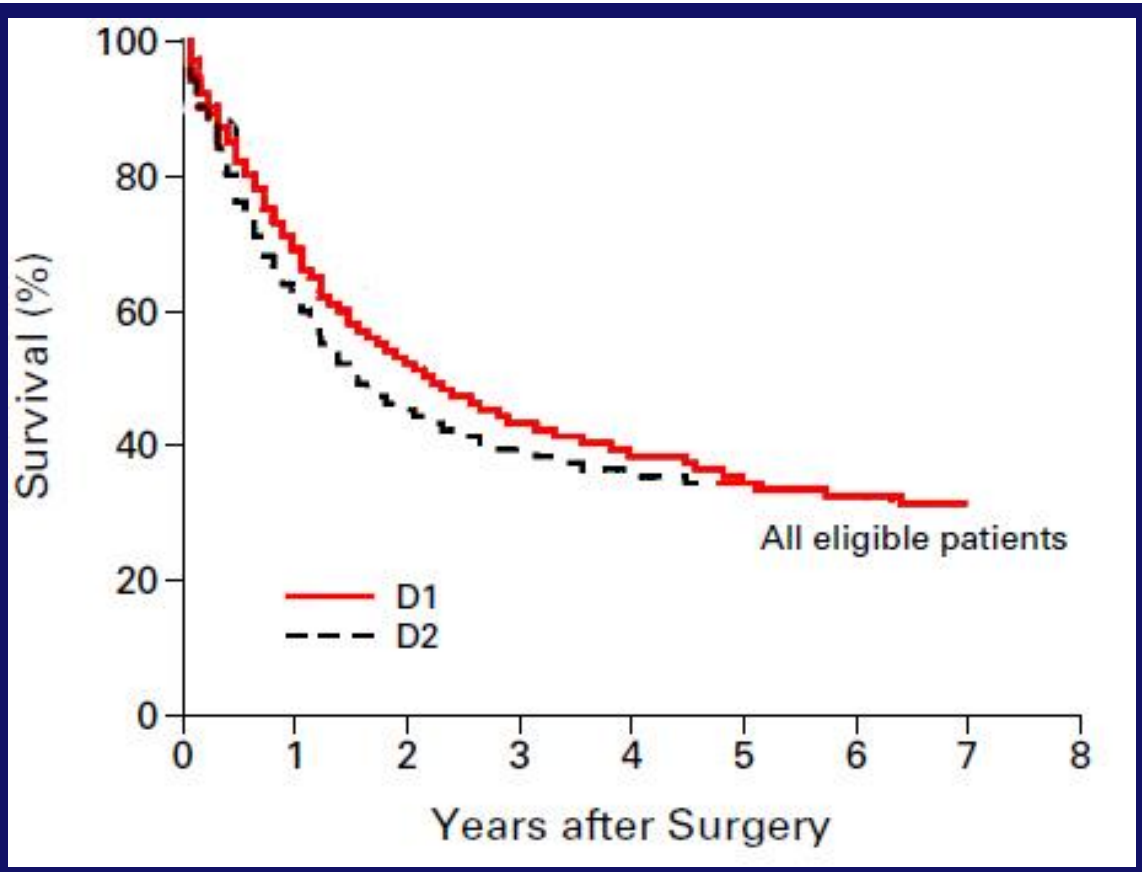


Randomized trials on extent of lymph node dissection

Study	N	Comparing	Conclusion	Journal
South Africa	43	R1/R2	R1	**Br J Surg 1998;110-2**
Hong Kong	55	R1/R3	R1	**Ann Surg 1994;176-82**
UK-MRC	400	D1/D2	D1	**Lancet 1996;995-9**
Dutch	996	D1/D2	D1 D1 **D2 when avoiding postoperative mortality**	**Lancet 1995;745-8** **NEJM 1999;908-14** **Lancet Oncol. 2010 11(5):439-49.**
Taiwan	221	D1/D2,3	D2,3	**Lancet Oncol 2006;309-15**
Japan	520	D2, D2+PAND	D2	**NEJM 2008;359:453-62**
Italy	267	D1/D2	No difference in mortality No survival data yet	**Br J Surg 2010; 97: 643–649**

Dutch Gastric Cancer Trial – 5-year follow-up

- 996 Patients
- D1 vs D2
- Mortality
  - D1: 4%
  - D2: 10%
- 5-Year Survival
  - D1: 45%
  - D2: 47%

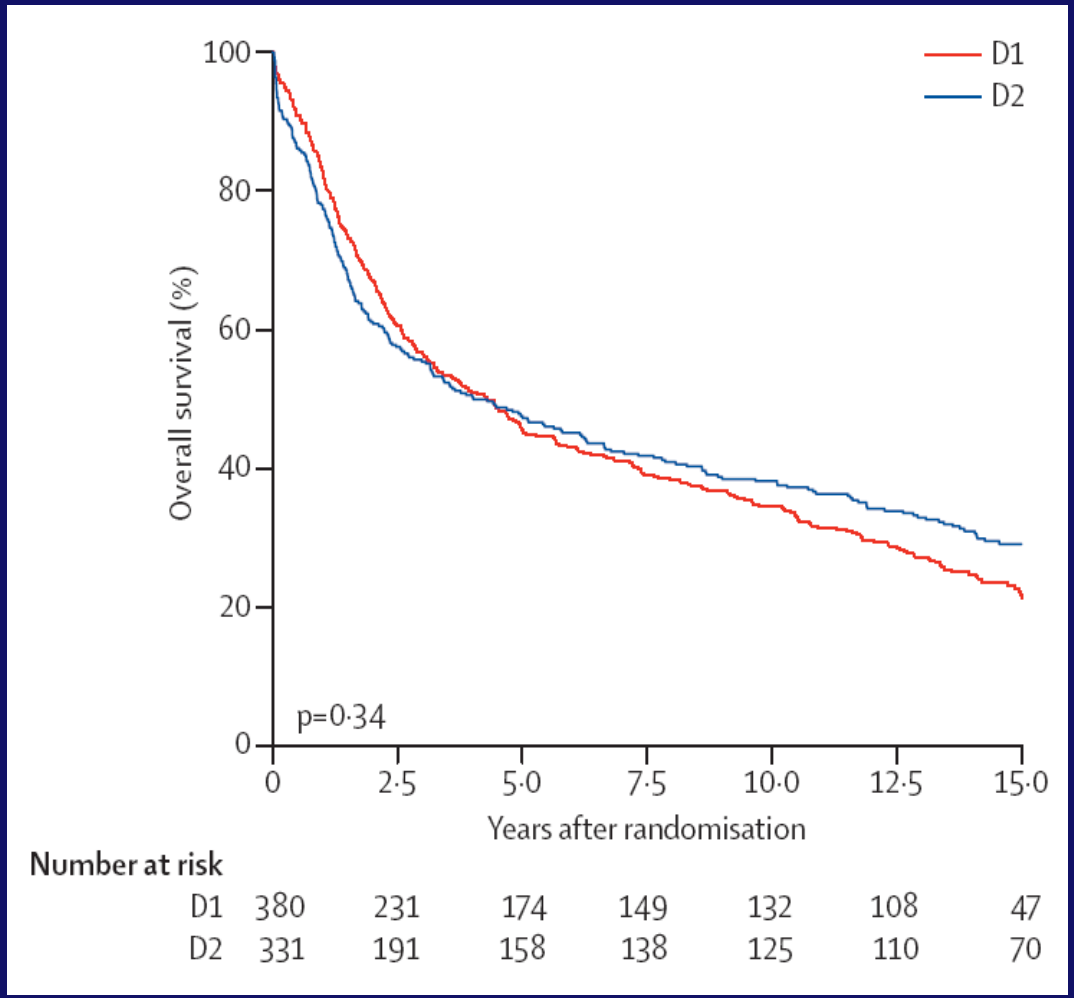


Conclusion: D1 dissection recommended

Bonenkamp, vd Velde et al., N Engl J Med 1999,340:908-14.

Dutch Gastric Cancer Trial – 15-year follow-up

711 Patients with curative resection



15-Year OS
- D1: 21%
- D2: 29%

P=0.34

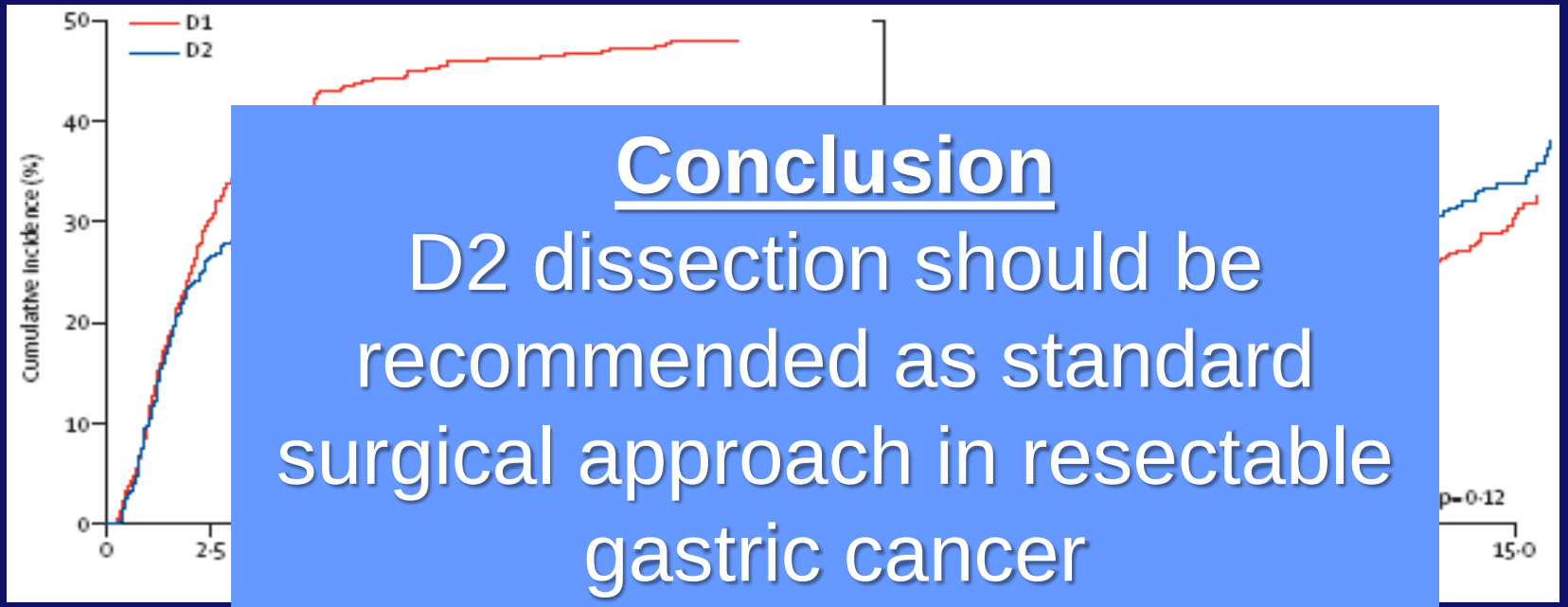
Local recurrence
- D1: 22%
- D2: 12%

Regional recurrence
- D1: 19%
- D2: 13%

Songun, vd Velde et al, Lancet Oncology 2010

Dutch Gastric Cancer Trial – 15-year follow-up

711 Patients with curative resection



Conclusion

D2 dissection should be recommended as standard surgical approach in resectable gastric cancer

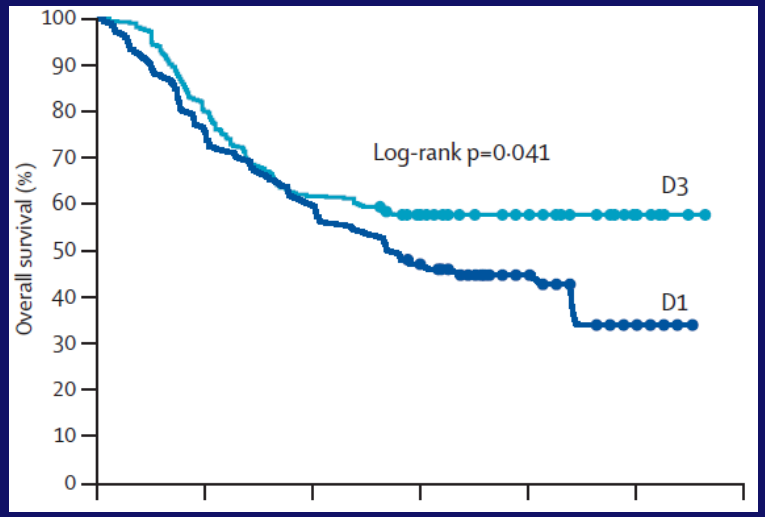
Death of Gastric Cancer
D1: 48%
D2: 37%
P=0.01

Death of Other Causes
HR=1.22
P=NS

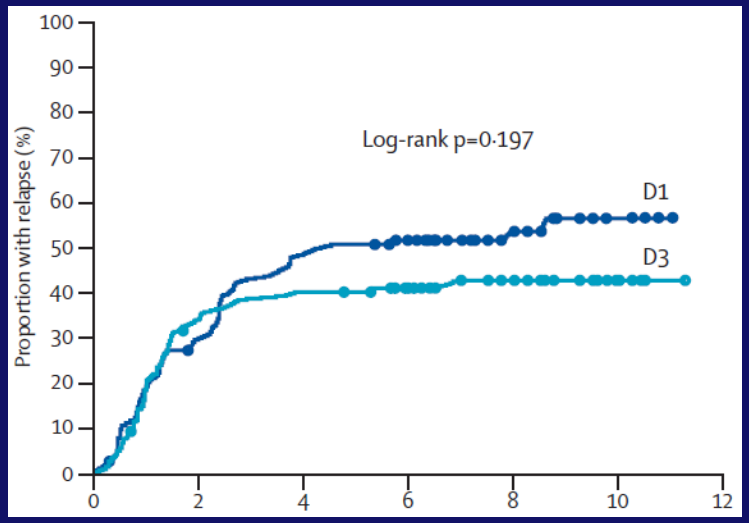
Songun, vd Velde et al, Lancet Oncology 2010

Taiwanese trial

- 221 Patients: small trial
- D1 vs D2,3



5-Year Overall Survival
D1: 54%
D2,3: 60%



5-Year Recurrence Rate
D1: 51%
D2,3: 40%

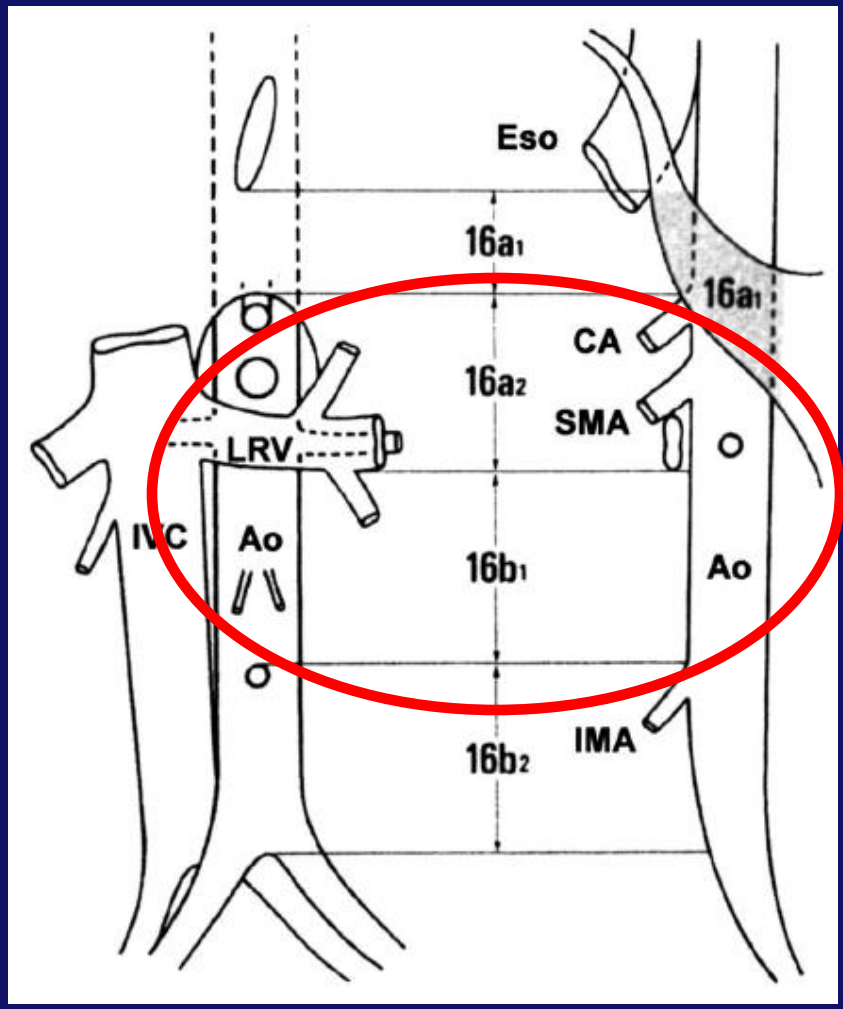
- Conclusion: in Asian population, extended lympadenectomy brings improved survival

Wu et al., Lancet Oncology 2006

Japanese Trial

- 523 Patients
- D2 vs D2 + PAND

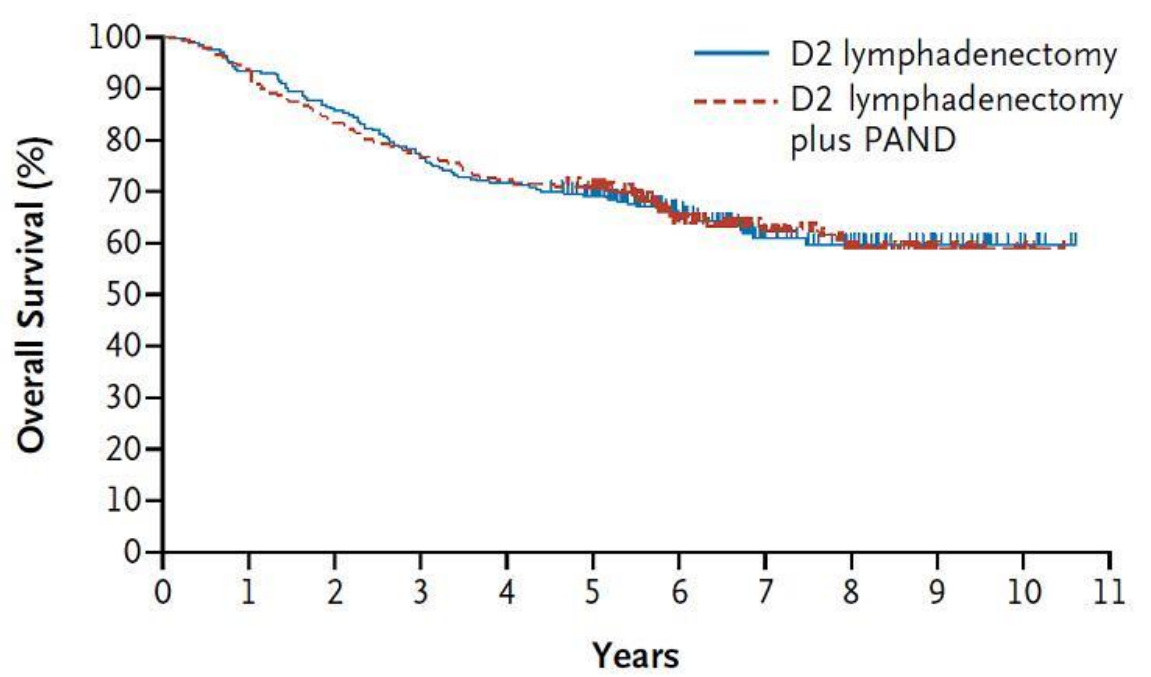
- Morbidity
  - D2: 20.9%
  - D2 + PAND: 28.1%
    P = 0.067



Sano et al., JCO 2004

Japanese Trial

- 5-Year overall survival
  - D2: 69%
  - D2 + PAND: 70%
  - *P* = 0.85
  - Conclusion: D2 + PAND should not be recommended



Sasako et al., NEJM 2008

Italian D1-D2 study

- 267 patients
- D1 vs D2 dissection in 5 specialized centers
- Only mortality data have been published

- Mortality
  - D1: 3.0%
  - D2: 2.2%

- Conclusion: D2-LND is safe in experienced centers
- Survival data to be awaited, but only 267 patients included

Degiuli et al., BJS 2010

Lymphadenectomy in recent Western trials

- Intergroup 0116 Trial:
  - D2 recommended
    - D0: 54%
    - D1: 36%
    - D2: 10%
- MAGIC Trial:
  - Surgeons decided extent of lymphadenectomy
    - D1: 19%
    - D2: 40%
- <u>Majority of patients: limited lymph node dissection</u>

MacDonald, NEJM 2001, Cunningham, NEJM 2006

Lymphadenectomy in Japan

- Differentiation extent of lymphadenectomy
- Different recommendation for every combination of T-stage and N-stage

Table 5. Japanese guidelines for surgical treatment (curative intention) by stage

	N0	N1	N2	N3
T1 (M)	IA A) ER (differentiated type, ≤2 cm, UL(-)) B) MGA (remainder)	IB A) MGB (≤2 cm) B) D2 (>2 cm)	II D2	IV D3
T1 (SM)	IA A) MGA (differentiated type, ≤1.5 cm) B) MGB (remainder)	IB A) MGB (≤2 cm) B) D2 (>2 cm)	II D2	IV D3
T2	IB D2	II D2	IIIA D2	IV D3
T3	II D2	IIIA D2	IIIB D2	IV D3
T4	IIIA D2 with combined resection	IIIB D2 with combined resection	IV D2 with combined resection	IV D3 with combined resection

ER, endoscopic resection; MGA, modified gastrectomy A; MGB, modified gastrectomy B; UL, with ulcerated lesion

Tanizawa, Gastric Cancer 2010

D1 vs D2: Results without splenectomy

	D1	D2	p-value
Morbidity (%)	**23**	**35**	**0.001**
Mortality (%)	**3.8**	**6.3**	**NS**
Survival			
mean (yrs)	**5.77**	**6.67**	**0.018**
5 year (%)	**47**	**56**	
7 year (%)	**42**	**52**	
11 year (%)	**33**	**47**	

Role of Splenectomy: Italian study

- 618 Patients
- Randomized between
  - Total gastrectomy
  - Subtotal gastrectomy
- Multivariate analysis:
  - Splenectomy associated with worse survival

Bozetti, Ann Surg 1999; 230: 170-8

Splenectomy vs. preservation

- N = 207
- 5 years survival rate: 49% vs. 55%, p = 0.50
- Median no of lymph nodes dissected: 40 vs. 40, p = 0.96
- **Prophylactic splenectomy cannot be justified**

Yu W. et al. Br J Surg. 2006 May; 93(5):559-63

Total vs Subtotal gastrectomy for distal gastric cancer

	Surgery	N	Mortality (%)	Morbidity (%)	5 year survival rate
Gouzi et al., Ann Surg 1989;**209**: 162-166	TG	93	3.2	32	48
	SG	76	1.3	34	48
Bozetti et al., Ann Surg 1999;**230**: 170-180	TG	303	2	13	62.4
	SG	315	1	9	65.3

Conclusion on surgery

- D2 dissection should be recommended
  - No splenectomy or pancreatectomy
  - In experienced centers

- PAND does not improve survival any further

Surgical quality assurance

Dutch Gastric Cancer Trial

Hospital volumes

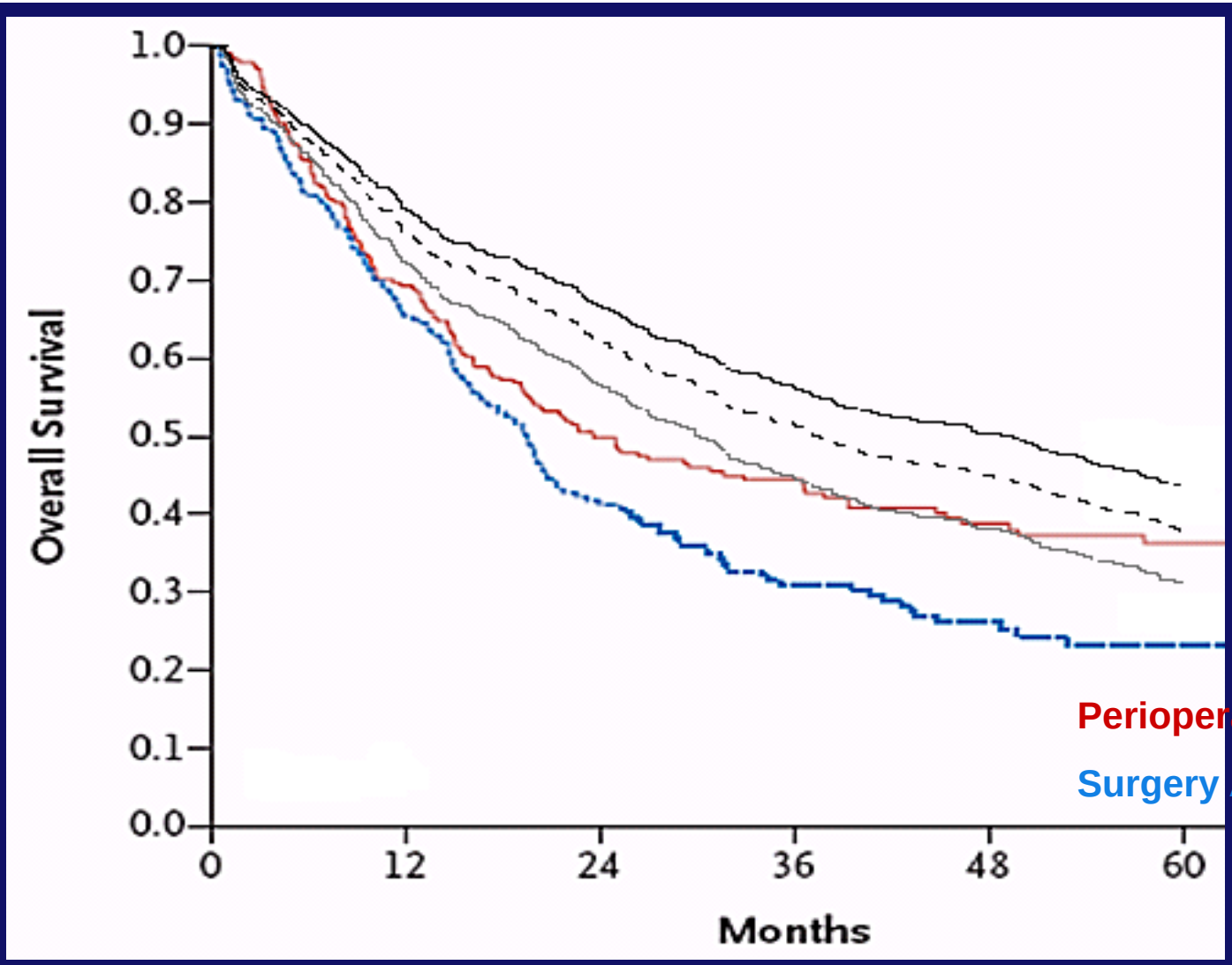
- 711 gastrectomies, 80 participating hospitals
- Average of 2.2 gastrectomies/hospital/year

  (registered in study)

Quality Assurance

- Instruction in operating room by Japanese surgeon
- ‘Supervising surgeons’ present with every D2 gastrectomy
- Book and video
- Teaching meetings for surgeons

The effect of improvement of surgical quality over the introduction of adjuvant therapy



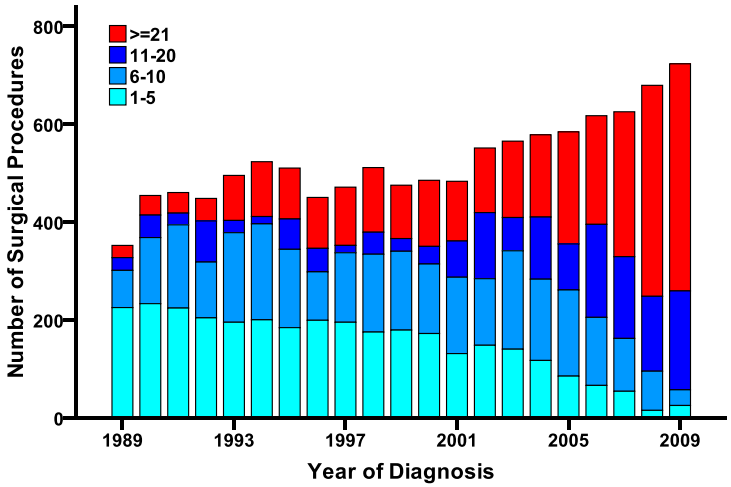
Krijnen et al., EJSO 2009

Trials vs nationwide improvements

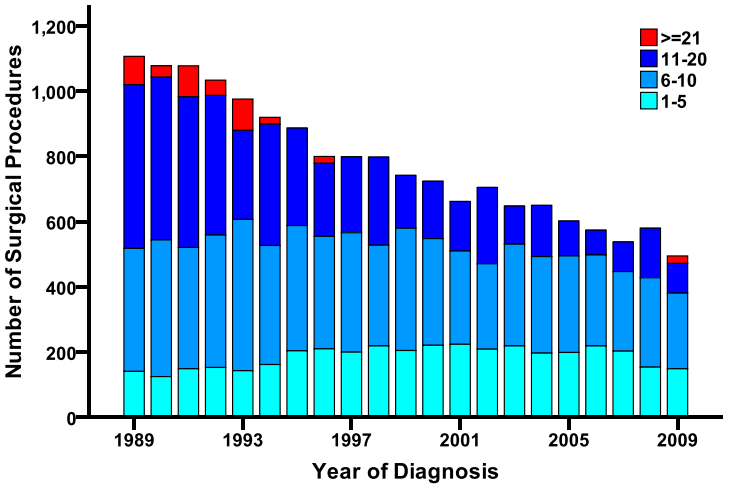
- Trials → improve outcomes by
  - Providing better treatment options
  - Training surgeons
- Most patients treated outside trials
  - → analyze outcomes on nationwide level

Centralization in the Netherlands

Esophagectomy



Gastrectomy

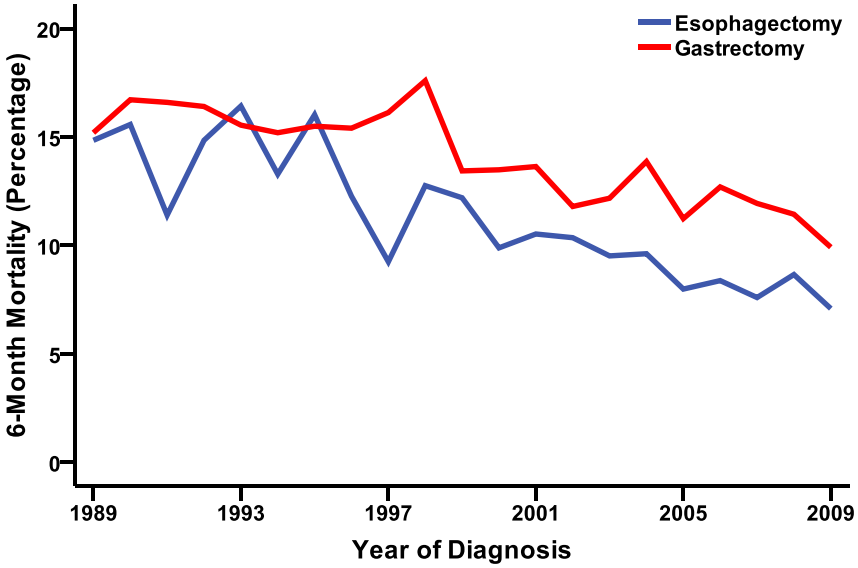


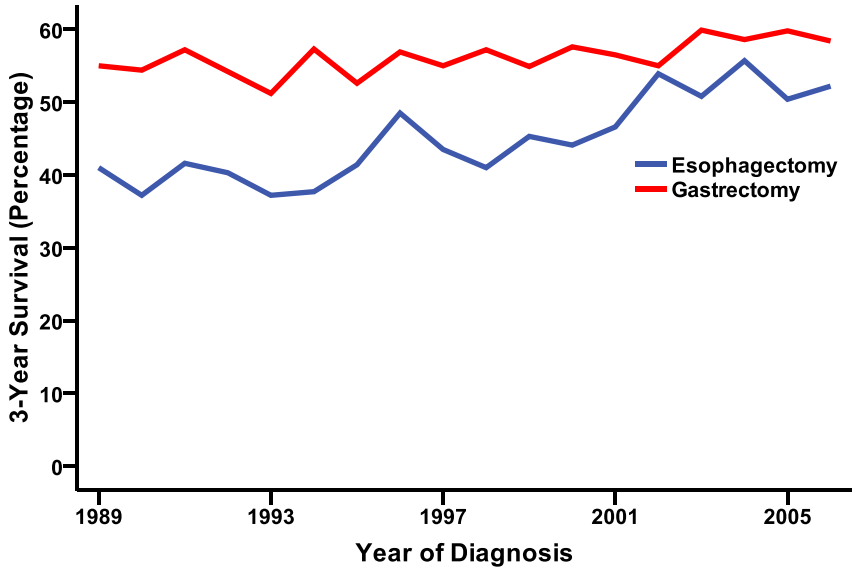
RED = High-volume surgery (>20/year)

- Esophagectomy: centralization effect
- Gastrectomy: decreasing number, no centralization

Dikken, vd Velde et al, EJC 2012

Outcomes esophagectomy vs gastrectomy

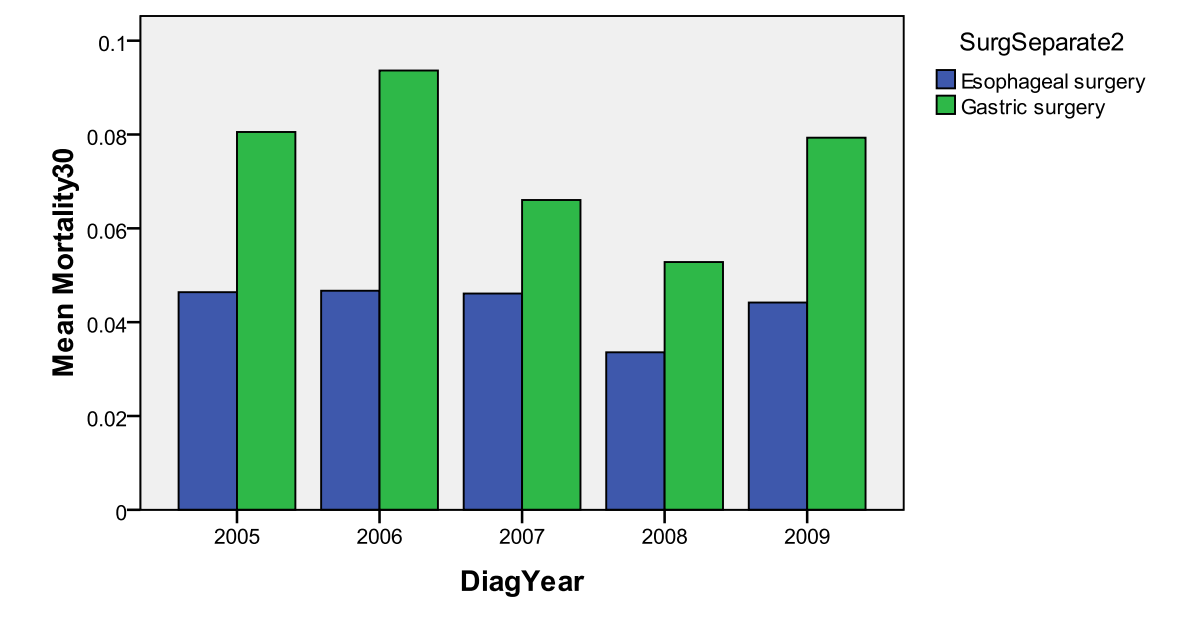




- 6-Month mortality:
  - Gastrectomy → non-significant decrease
  - Esophagectomy → significant decrease
- 3-Year survival:
  - Gastrectomy → no improvement
  - Esophagectomy → catch-up with gastric cancer

Dikken, vd Velde et al, EJC 2012

30-Day mortality in the Netherlands



Blue: esophagectomy ~ 4%

Green: gastrectomy ~ 8%

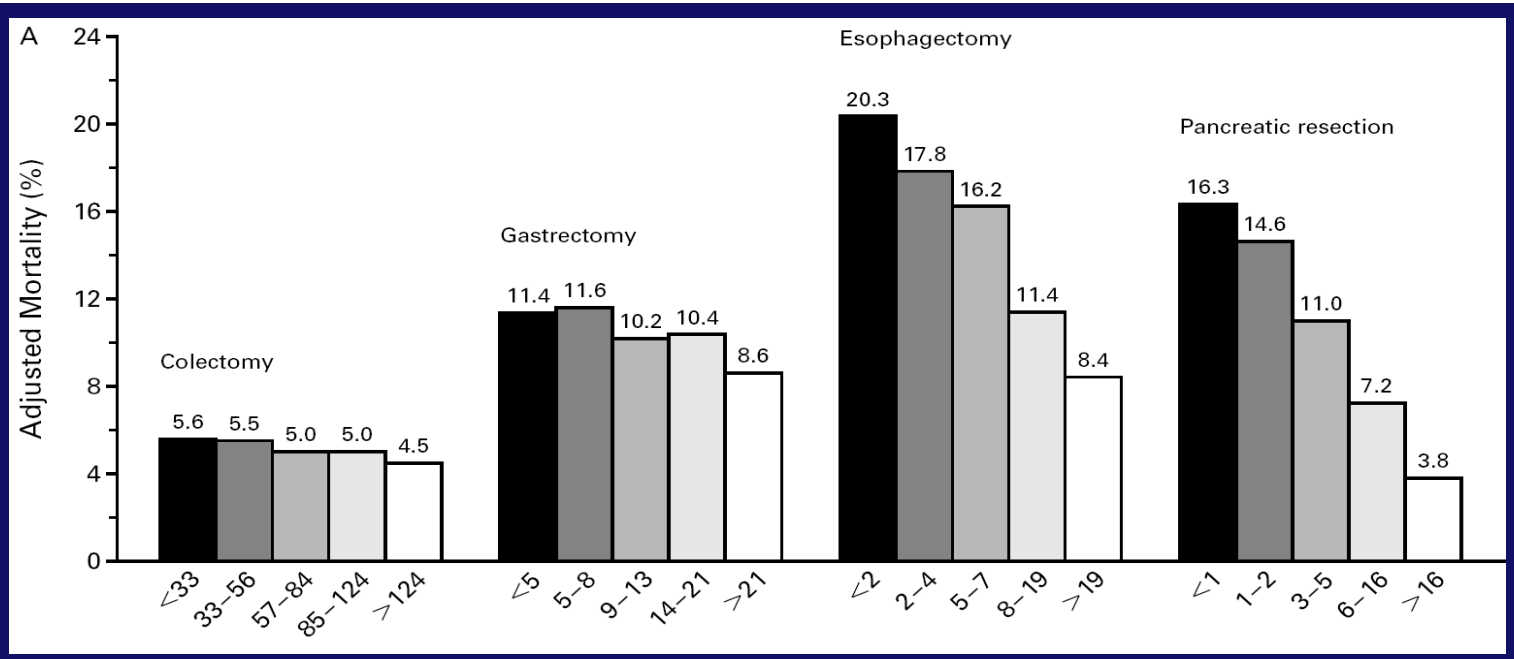
Higher mortality after gastrectomy for past 5 years

Dikken, vd Velde et al, EJC 2012

Conclusion

- Urgent need for improvement of gastric cancer care in the Netherlands
  - Centralization
  - Auditing
  - Use of multi-modality treatment

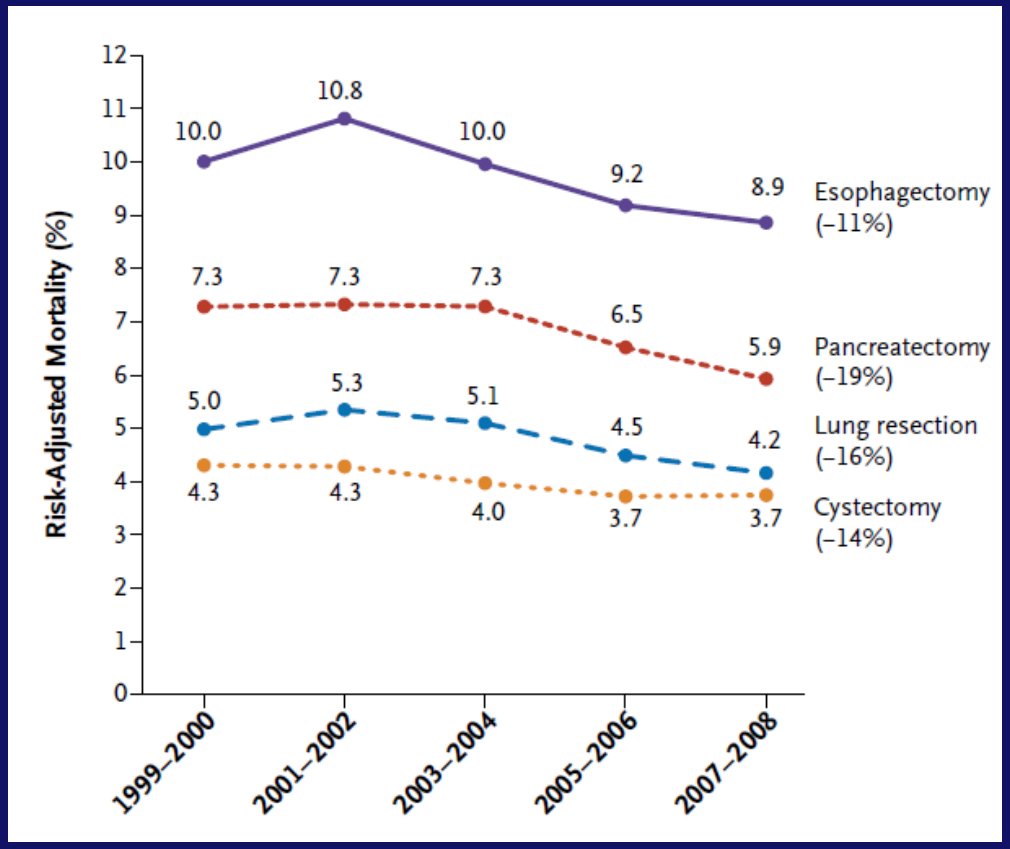
Centralization: volume-outcome relation US



"Patients can often improve their chances of survival substantially, even at high volume hospitals, by selecting surgeons who perform the operations frequently"

Birkmeyer et al, NEJM 2002

Centralization: volume-outcome relation US



- 10 years after initial US paper
  - Decrease in postoperative mortality
  - Esophagectomy: completely due to centralization

Finks et al, NEJM 2012

Centralization in Denmark

2003
- Gastric cancer surgery restricted to 5 hospitals
- Introduction national clinical guidelines
- Introduction nationwide database

Study period	1999-2003	2003-2008
No. of departments	**37**	**5**
No. of operations	537	416
Anastomotic leakages (%)	6.1	5.0
Hospital mortality (%)	**8.2**	**2.4**

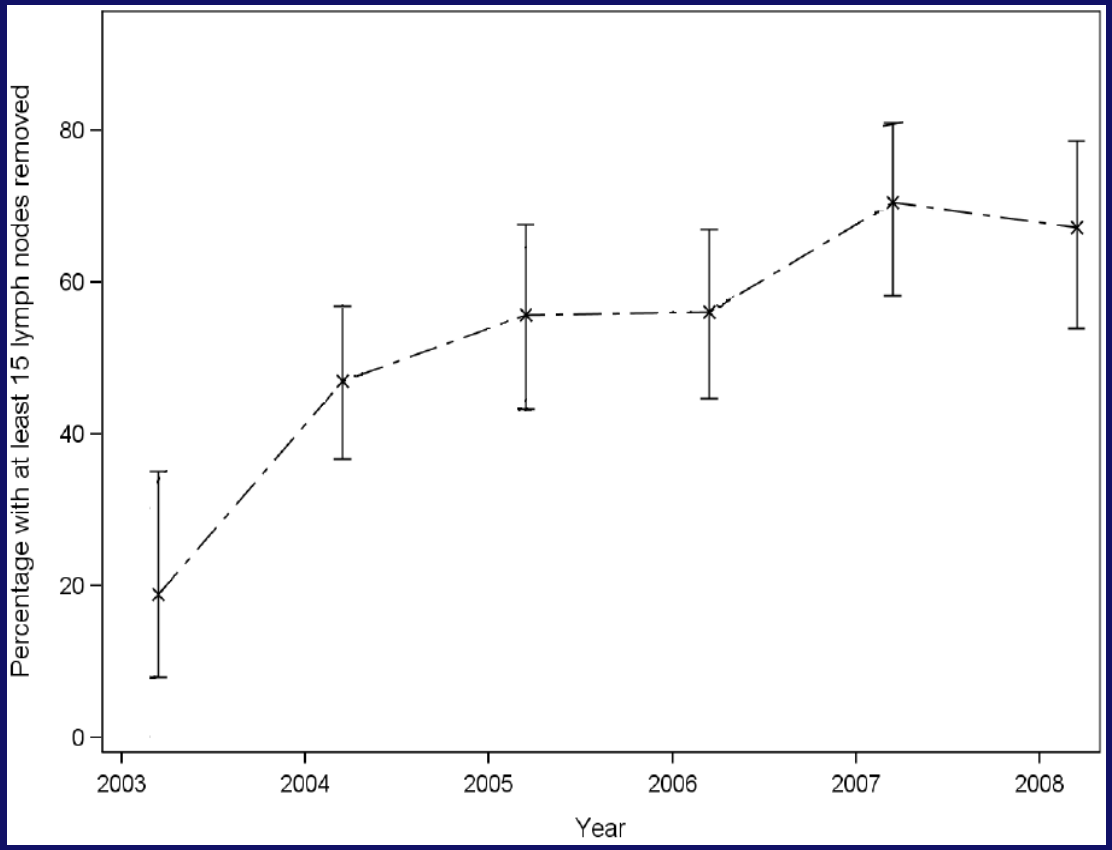
Jensen et al, EJSO 2002

Centralization in Denmark

Cases with at least 15 lymph nodes removed

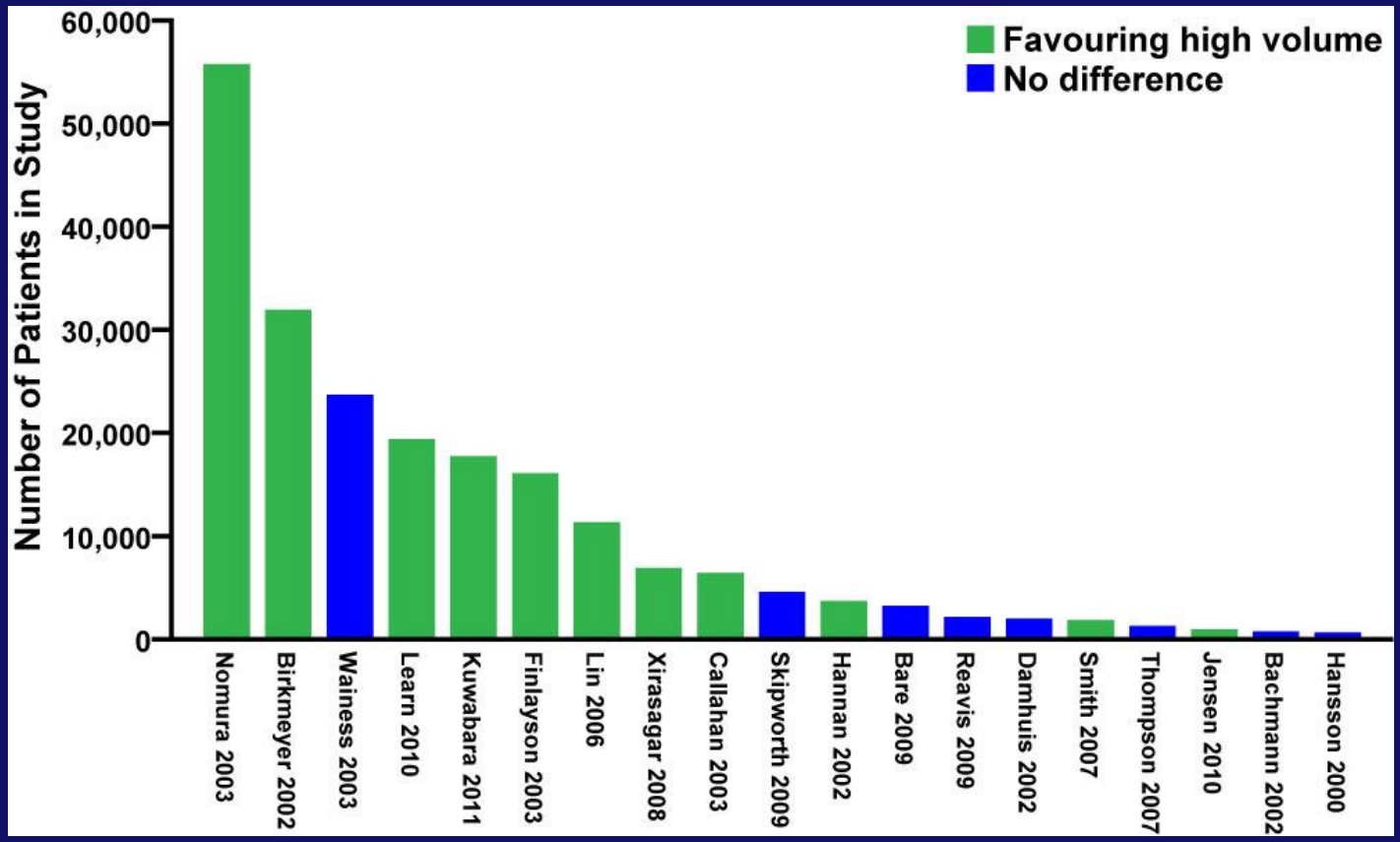
2003: 19%

2008: 67%



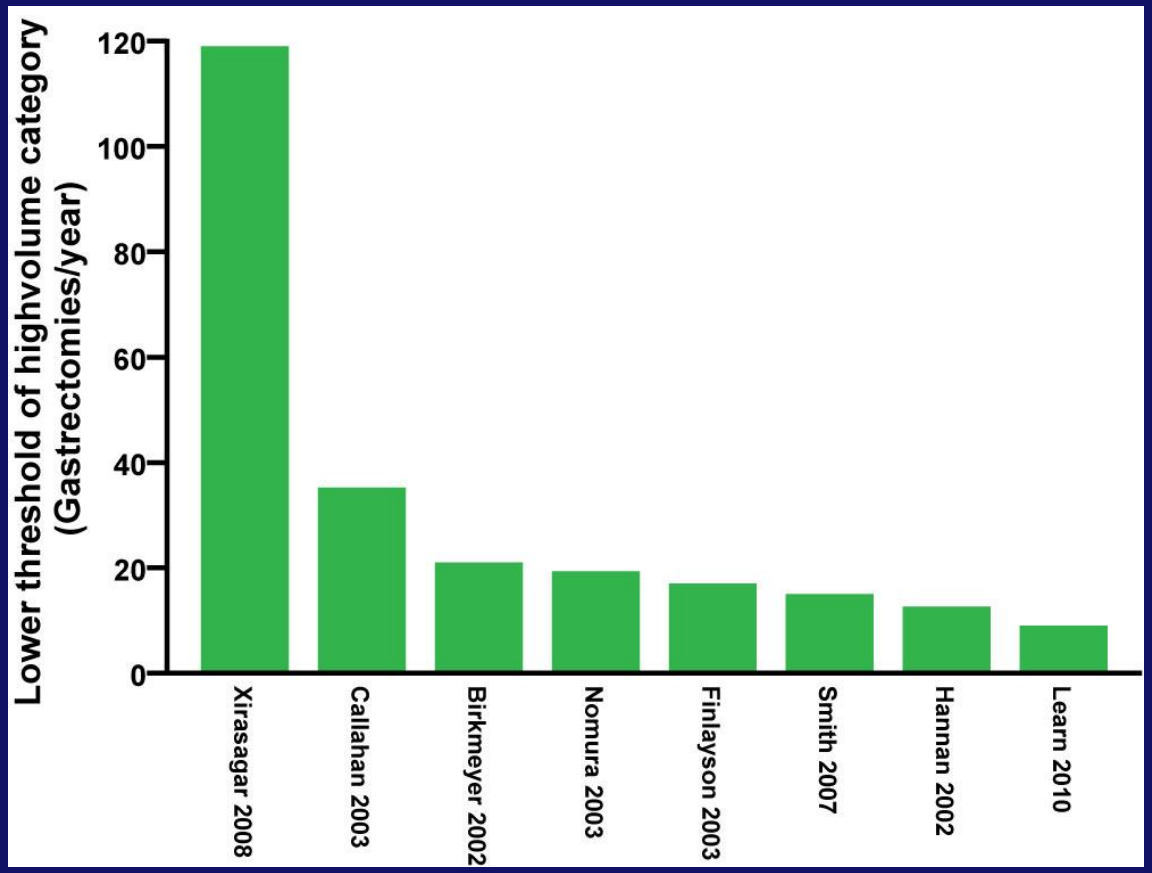
Jensen et al, EJSO 2002

Literature on Gastrectomies
Number of patients in volume-outcome studies



- Smaller studies: often no volume-outcome effect
- Larger studies: volume-outcome effect

Literature on Gastrectomies
Definition of 'high volume' in positive studies



- Definition of 'high volume' in most studies ~20/year
- But studies with higher volumes

Centralization: type of referral

Should centralization only be based on case volume?

Volume-based vs. Outcome-based referral

Gruen et al, CA Cancer J Clin 2009

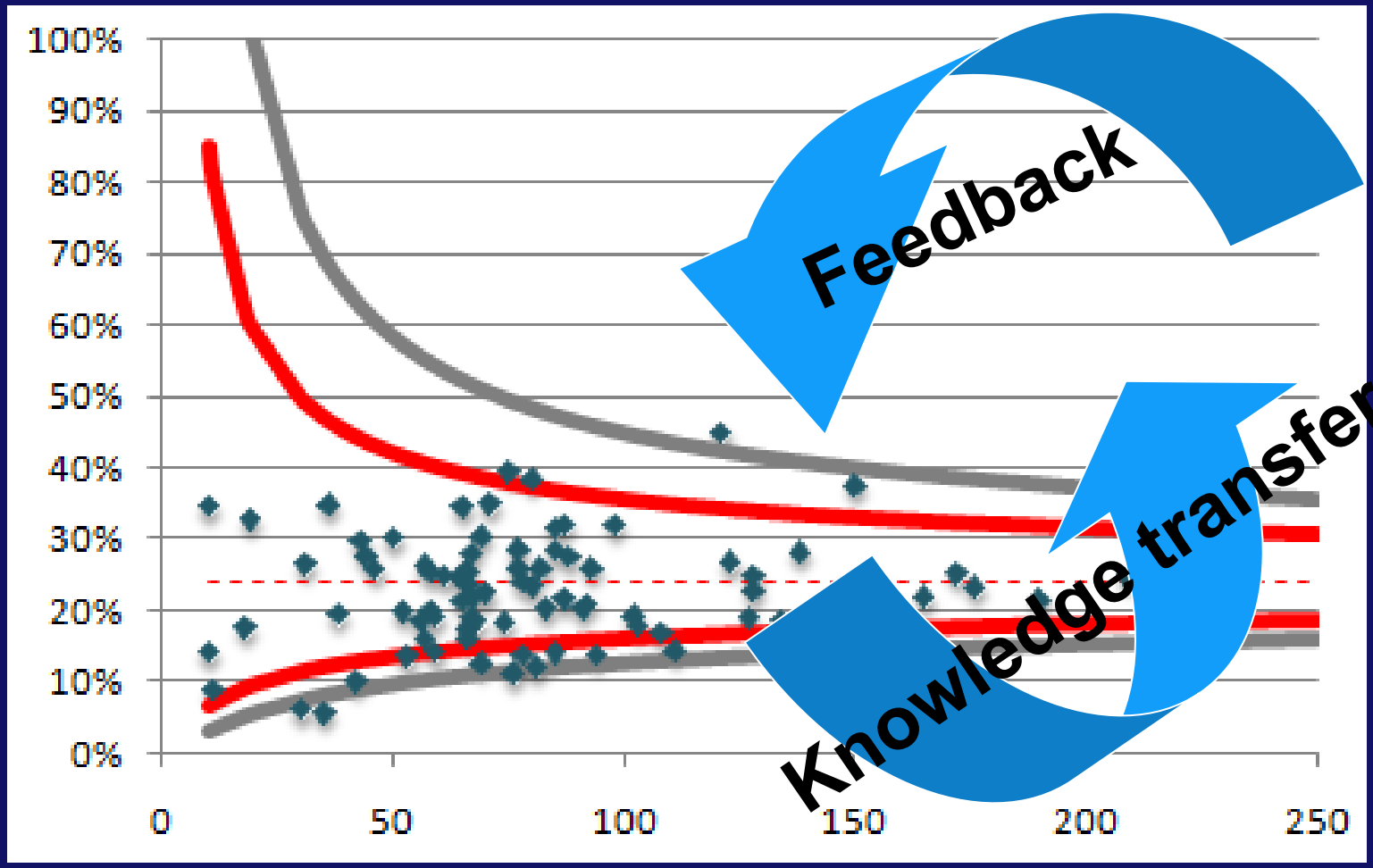
Auditing

- Definition
- “providers of care are monitored and their performance is benchmarked against their peers”

- Surgical Hawthorne effect

- Gastric cancer audits currently performed in several European Countries
  - United Kingdom
  - Denmark
  - Sweden
  - Netherlands

Effect of auditing

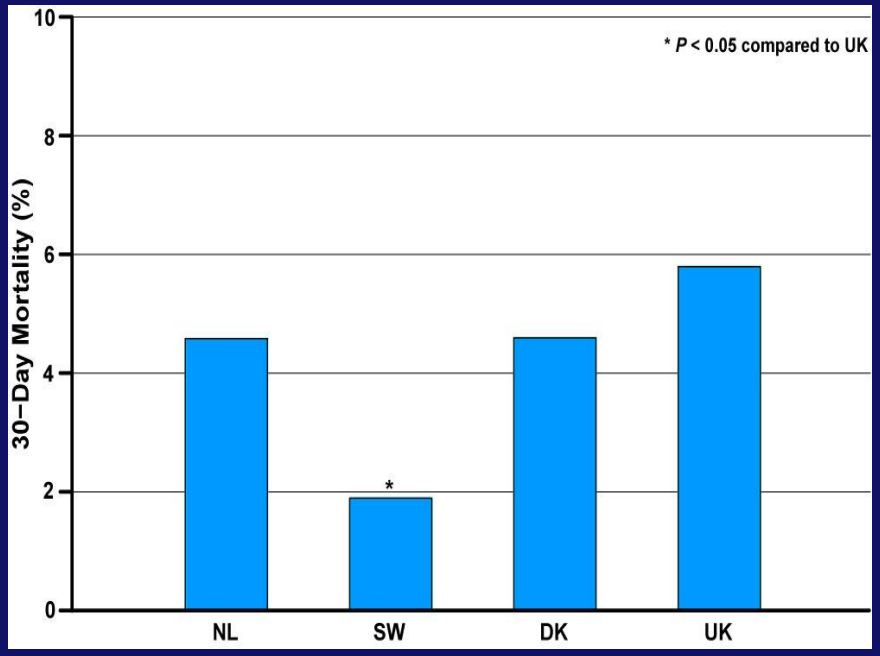


International comparison

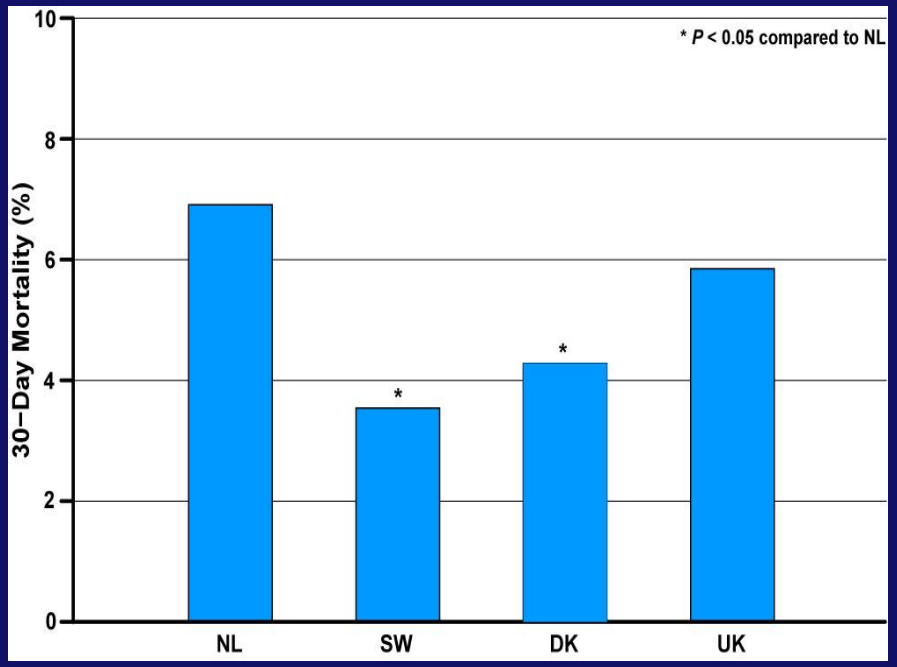
- Compare national audits and cancer registries
- Esophageal and gastric resections 2004-2009
  - Netherlands: N = 5,791
  - Sweden: N = 653 (part of Sweden)
  - Denmark: N = 1,420
  - England: N = 12,000
- Goals
  - Compare differences between countries
  - Analyse possible volume-outcome relation

30-Day mortality

Esophagectomies



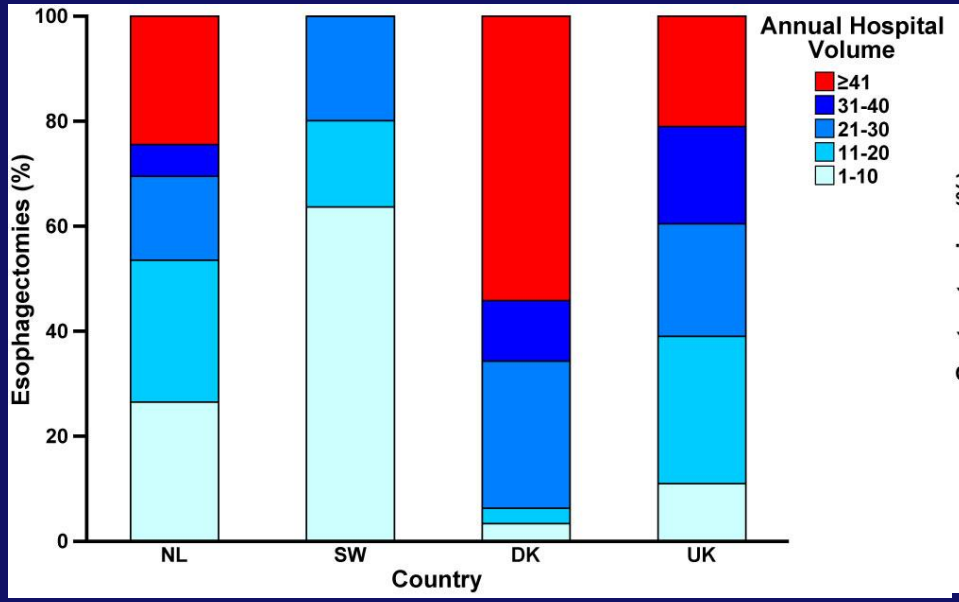
Gastrectomies



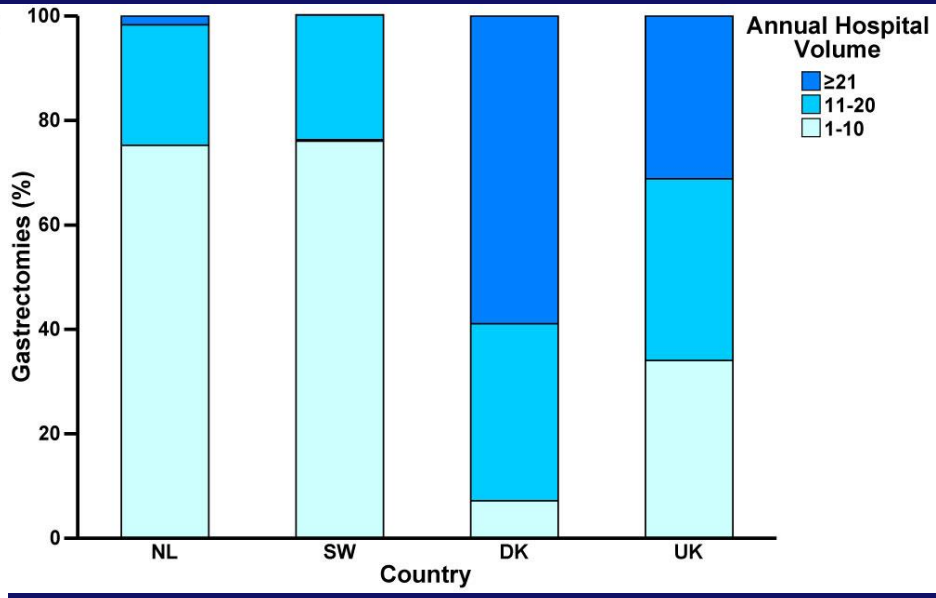
Significant differences between countries

Differences in annual hospital volumes

Esophagectomies



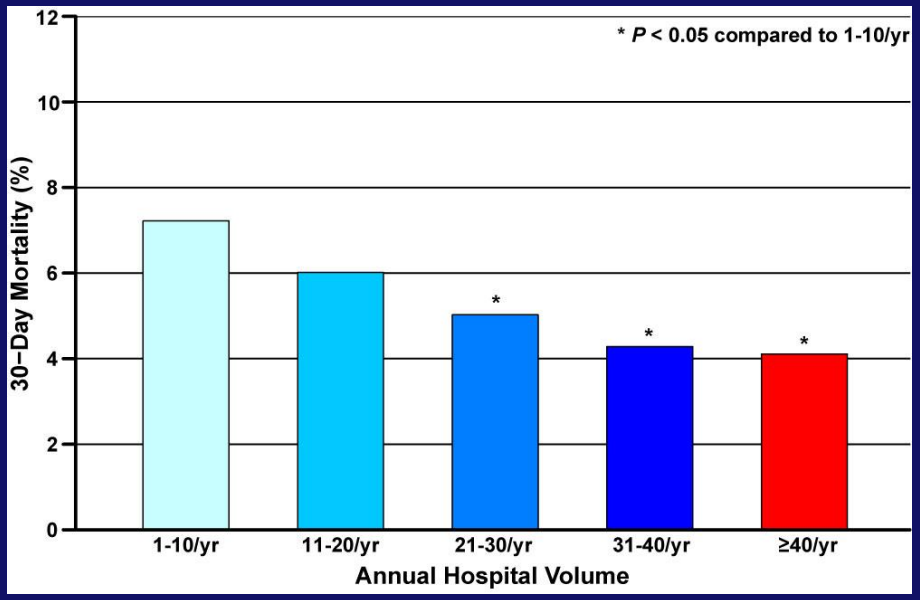
Gastrectomies



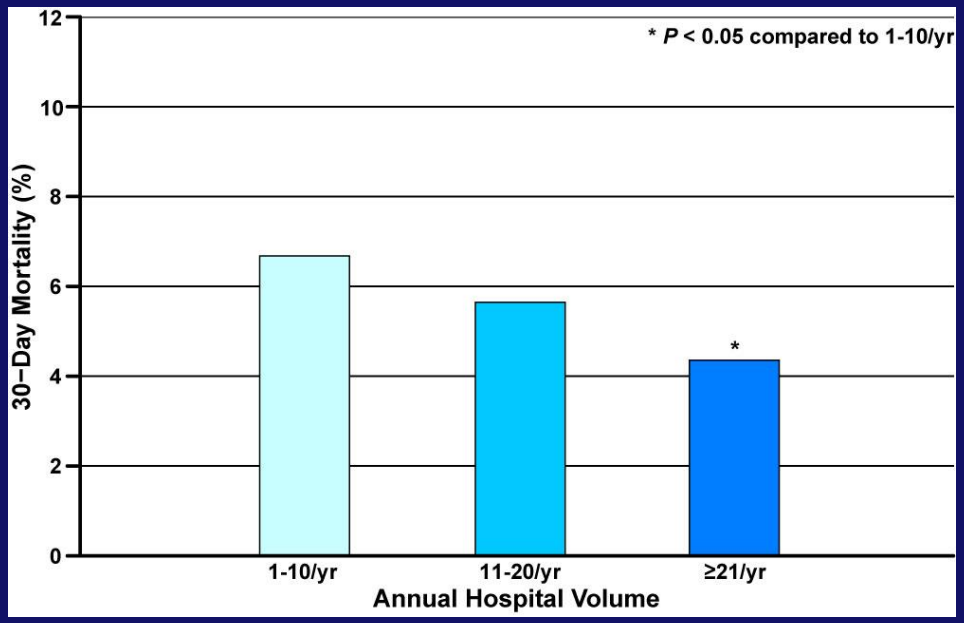
- Large differences in annual hospital volumes
- Denmark: centralization of esophagectomies and gastrectomies

Effect of hospital volume on 30-day mortality

Esophagectomies



Gastrectomies



Lower 30-day mortality with increasing hospital volume

- **Esophagectomies: up to >40/jaar**
- **Gastrectomies: up to >20/jaar**

Conclusions

- Participating countries:
  - **Considerable variation** in hospital volumes and 30-day mortality
- Significant relation between **volume** and **30-day mortality**
  - But not the only explanation for differences between countries
- Need for a uniform European Upper GI Cancer Registry:founded in Valencia sept 2012

European Upper GI Registry

Possible purposes	Data required
Compare outcomes after surgery	Type of surgery, case-mix (comorbidity), complications, short-term mortality
Compare resection rates	All patients with a diagnosis of oesophagogastric cancer, type of surgery
Compare patterns of care	Type of surgery, chemotherapy, radiotherapy, etc.
Compare long term outcomes	Follow-up data, TNM stage

One European Cancer Audit

Quality  **Variation**

- **Identify and spread Best Practice**
- **Research**
- **Outcome monitoring (feedback)**
- **Guidelines Development**


LUMC
ecco
esso
EURECCA
EUROPEAN REGISTRATION OF CANCER CARE
ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE
ESTRO
EORTC
European Organization for Research and Treatment of Cancer

Conclusion

- **Nationwide improvements require nationwide interventions**
  - Centralization
  - Auditing

‘The best care, for <u>every</u> cancer patient’

Amsterdam
September 2013

Multidisciplinary care: can we do better?