



*Theodor Billroth operating in the Auditorium
of the Allgemeine Krankenhaus, Vienna
(1899).*

Painting by Anton F. Seligmann.

Optimal treatment for Gastric cancer: Tailor made surgery

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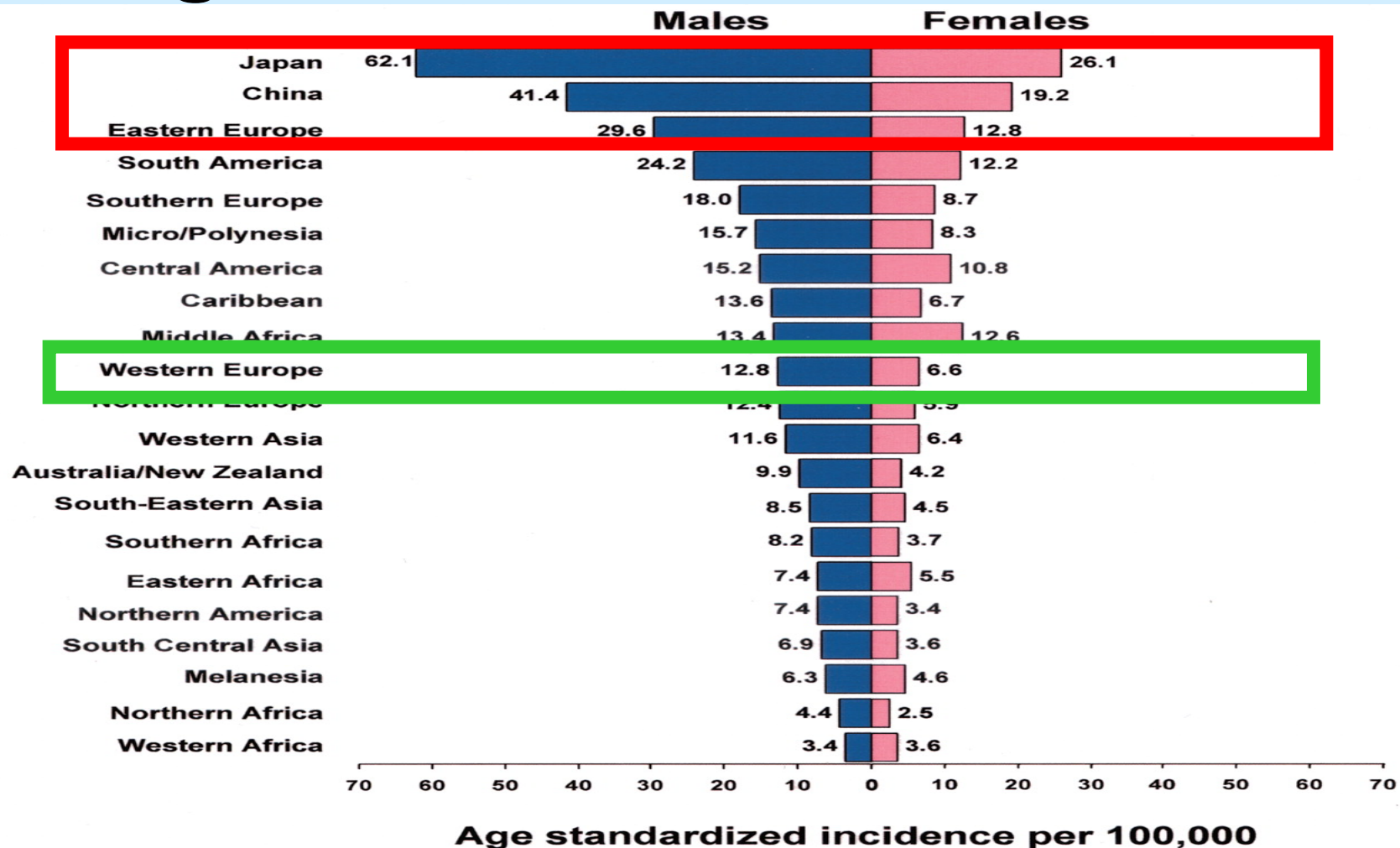
Topics

- I. Epidemiology/East-West differences**
- II. Tailoring treatment by translational research**
- III. Initial work up of gastric cancer patients**
- IV. Surgical treatment of gastric cancer; early, advanced and non-curative**
- V. Conclusions**

I. Epidemiology of Gastric Cancer

- **>1.4 million cases/year**
- **2nd cause of cancer death worldwide**
- **3rd cause (after lung and colorectal) of cancer death in Europe (138.000 / yr)**
- **Distal cancers decreasing; tumors of cardia or esophago-gastric junction increasing**
- **65% T3-T4; 85% N+; 30% liver metastases**

Is gastric Cancer in Asia different from gastric cancer in the West?



Gastric Cancer Surgery

Survival US vs. Japanese Centers

Stage	(%)	5-yr sur	(%)	5-yr sur
I	2004 (18.1)	50	1453 (45.7)	91
II	1976 (16.2)	29	377 (11.9)	72
III	3945 (35.6)	13	693 (21.8)	44
IV	3342 (30.1)	3	653 (20.6)	9

Comparing Asia and the West

Three hypothesis to explain the disparity

1. Differences in disease and patient characteristics
2. Differences in classification of disease stage
3. Differences in diagnosis and treatment

Biological and population differences

ASIA

- Distal localizations
- Intestinal type
- More MSI
- Younger
- Lower BMI

WEST

- Proximal localization
- Diffuse type
- More MSS
- Older
- Higher BMI

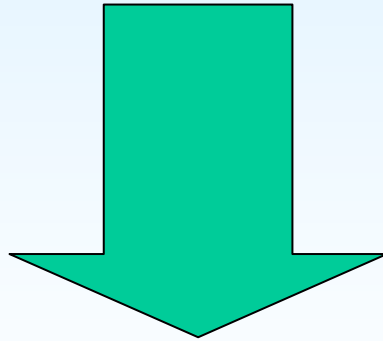
Disease stage classification differences

ASIA

WEST

**Surgeon-based
system**

**Pathology-based
system**



Stage Migration Effect

Diagnosis and treatment differences

ASIA

Screening

+

D2 gastrectomy

+

Aggressive

Chemotherapeutical
approaches

WEST

No screening

+

D1 gastrectomy

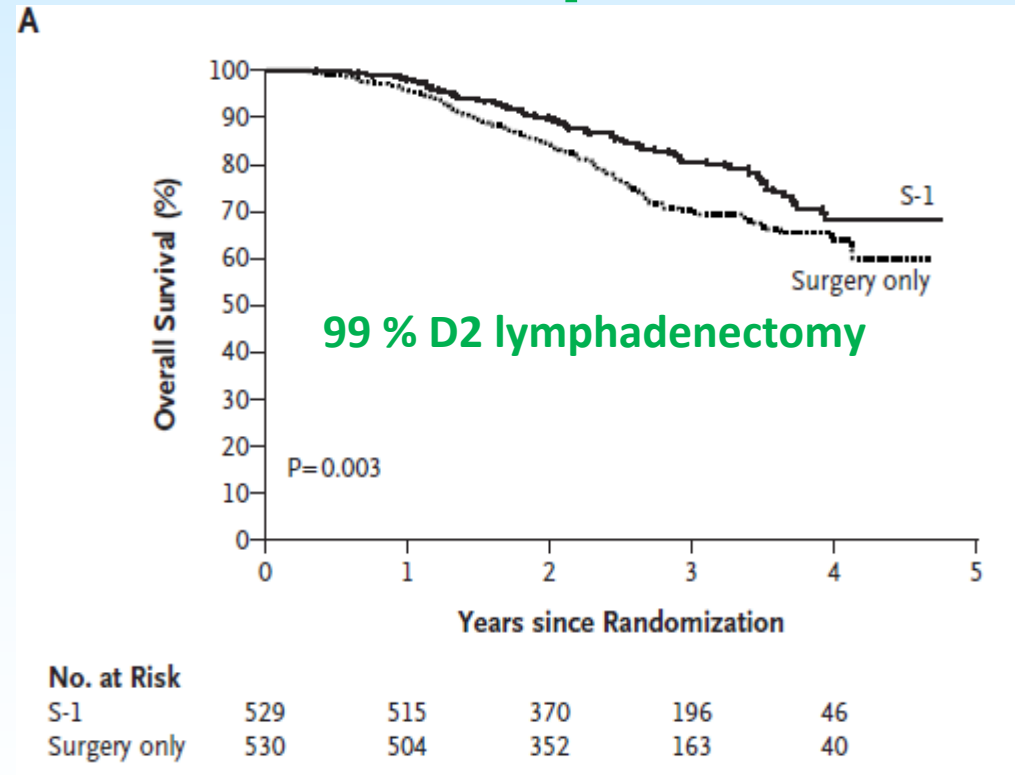
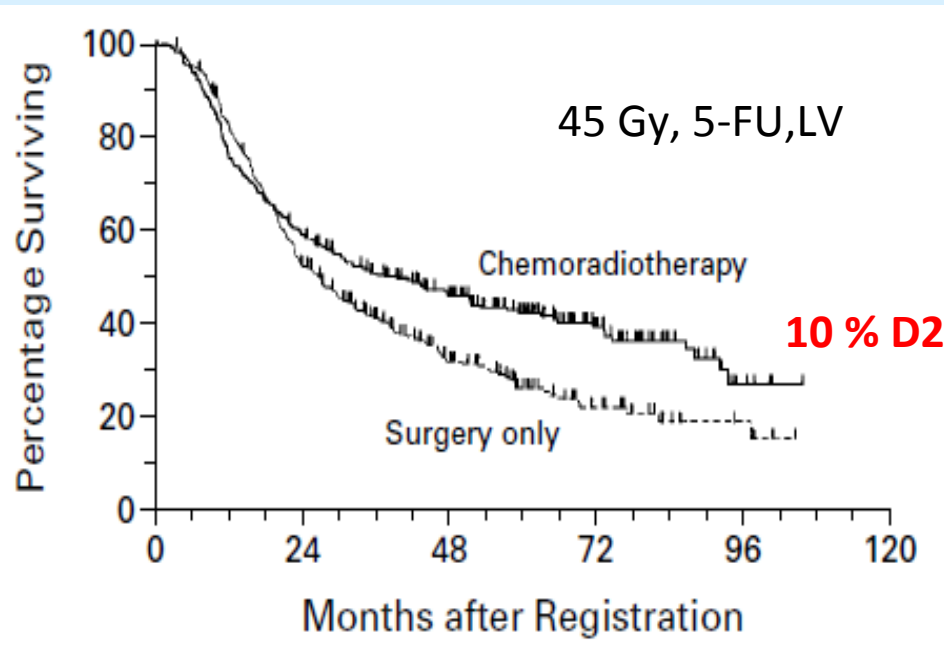
+

Less aggressive
chemotherapeutical
approaches

Treatment and outcome differences

McDonald Study
556 pts.

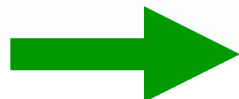
Japanese S1 Trial
1059 pts.



II. Tailoring by translational research

Biomarkers:

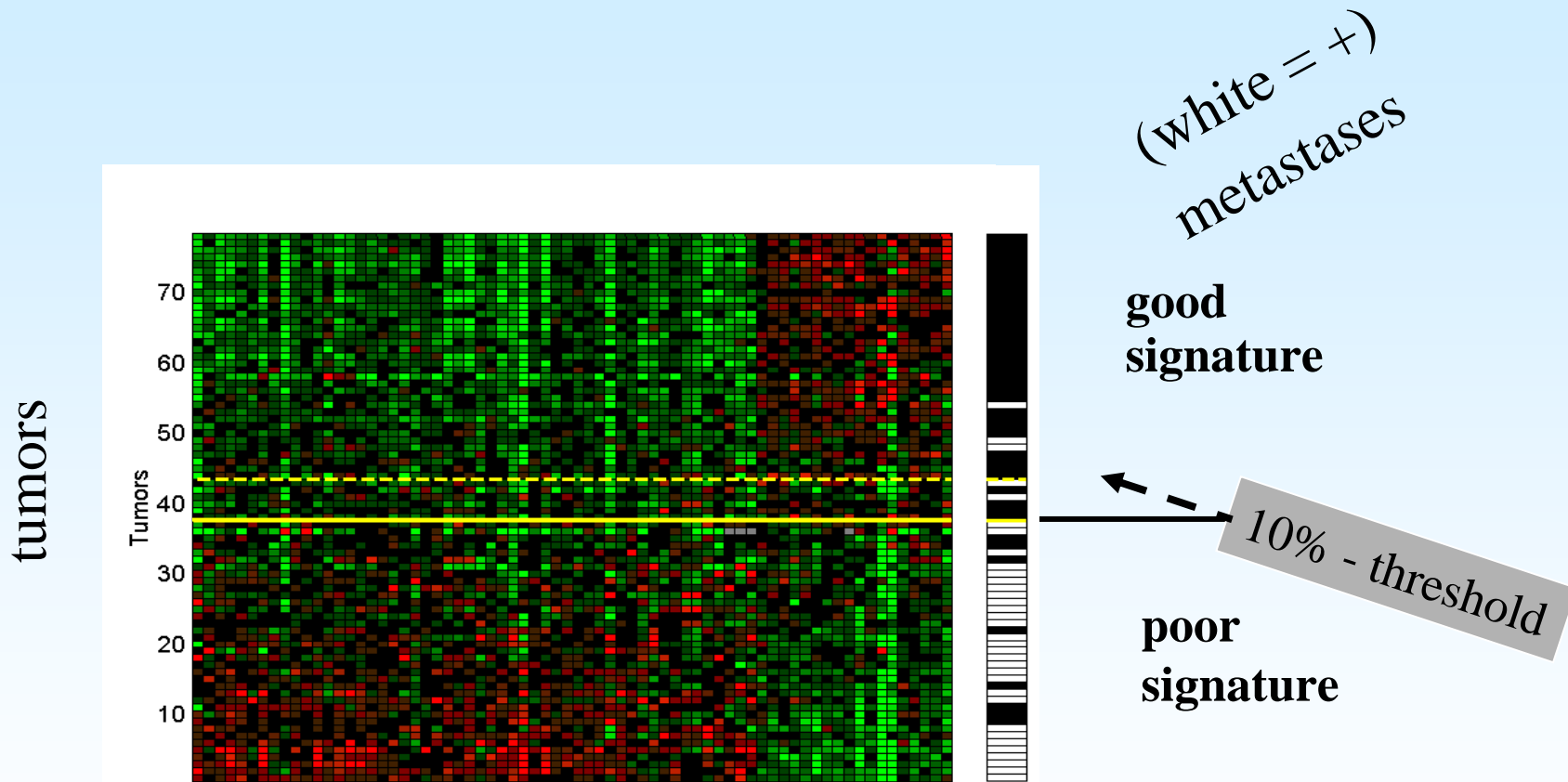
- Prognosis
- Predictive
- Target for diagnosis
- Target for therapy



Tailor made treatment

Differentially expressed genes

Genomic profiling predicts lymph node status and survival



threshold set with 10% false negatives
91 % sensitivity, 73% specificity

Differentially expressed genes

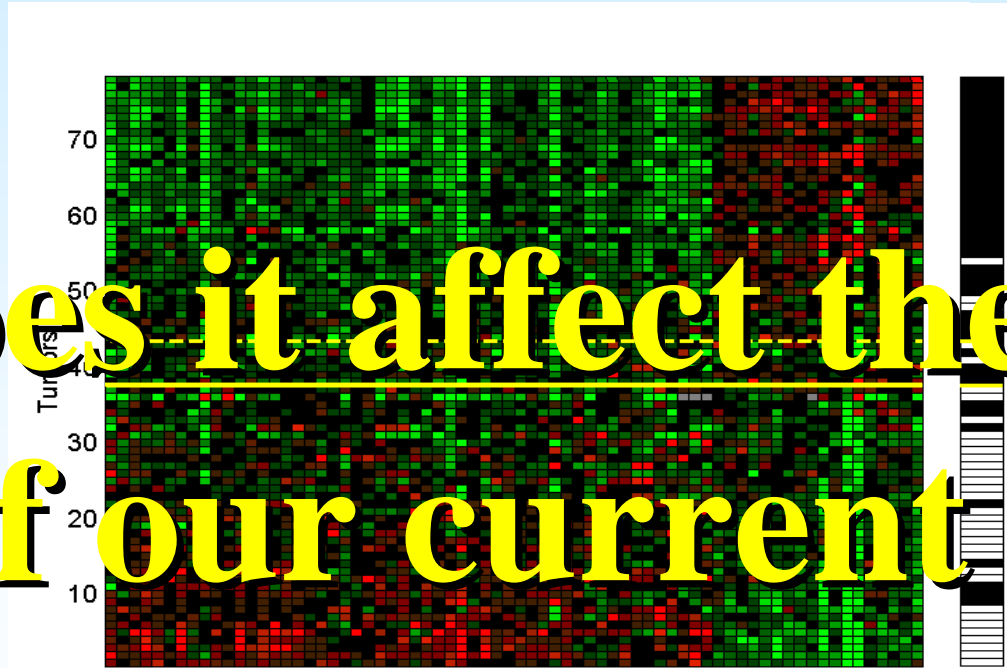
Genomic profiling predicts lymph node status and survival

(white = +)
metastases

good
signature

10% - threshold

Does it affect the prognosis
of our current patients?



threshold set with 10% false negatives
91 % sensitivity, 73% specificity

Differentially expressed genes

Genomic profiling predicts lymph node status and survival



(white = +)
metastases

good
signature

10% - threshold

Does it affect the prognosis of our current patients?

threshold set with 10% false negatives
91 % sensitivity, 73% specificity

III. Initial work up of gastric cancer

Diagnosis;

- No typical signs
- Gastric biopsy
- Clinical examination;
- No true tumor markers at hand

Classification;

- Japanese Classification of Gastric Cancer (JCGC); 13th edition
- International Union Against Cancer (UICC) TNM system; 7th edition.

III. Initial work up of gastric cancer

Imaging;

➤ T-stage;

Endoscopic ultrasound; differentiate T1/2 from T3/4

➤ Nodal involvement;

Multi-slice CT scan

➤ Metastasis;

- Liver and lung; CT scan
- Peritoneal; laparoscopy

**Response to
preoperative treatment**

PET = Promising

IV. Surgery for gastric cancer

Early gastric Cancer;

Endoscopic Submucosal Dissection (ESD)

Tumour	Diameter	Ulceration	Nr of pts	95% CI
Well diff. intramucosal	< 3cm	regardless	0/1230	0-0.3%
Well diff. intramucosal	regardless	no	0/929	0-0.4%
Well diff. Sub-mucosal	< 3cm	no	0/145	0-2.5%
Poor diff. intramucosal	< 2cm	no	0/141	0-2.6%

T1 tumours $\leq 40\text{mm}$

Sentinel node in gastric cancer

	Blue Dye	Radio guided
Detection rate	89-100%	90-96%
Sensitivity	73-90%	74-92%

Future; optical imaging of sentinel nodes

Seeing is Believing

- Extremely sensitive
- Very rapid + Real Time: acquisition time in seconds or a few minutes
- No extensive infrastructure needed
- Near infrared camera system + probes

Fluorescence imaging

- SLN detection with near-infrared fluorescence light
- Indocyanin green
- Intraoperative camera system (Frangioni Laboratory, Boston)



IV. Surgery for gastric cancer

Advanced gastric cancer;

- **Surgery**

Goal; R0 resection

Options; D1 or D2 Resection

- **Adjuvant strategies**

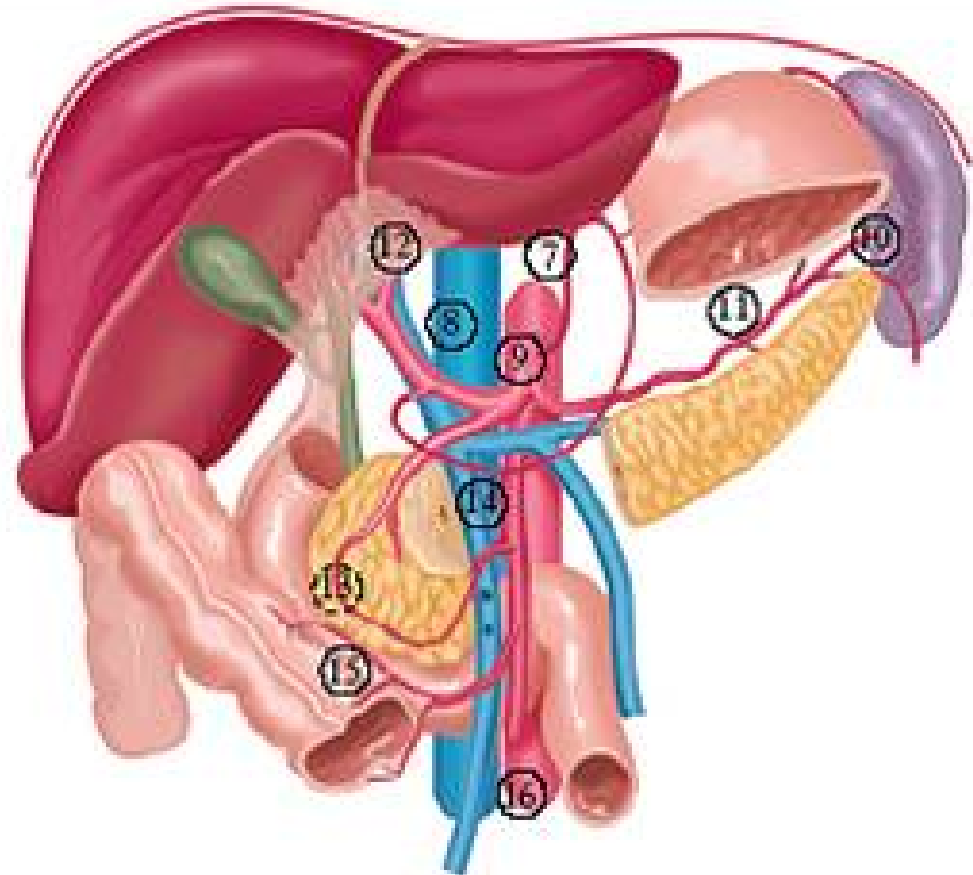
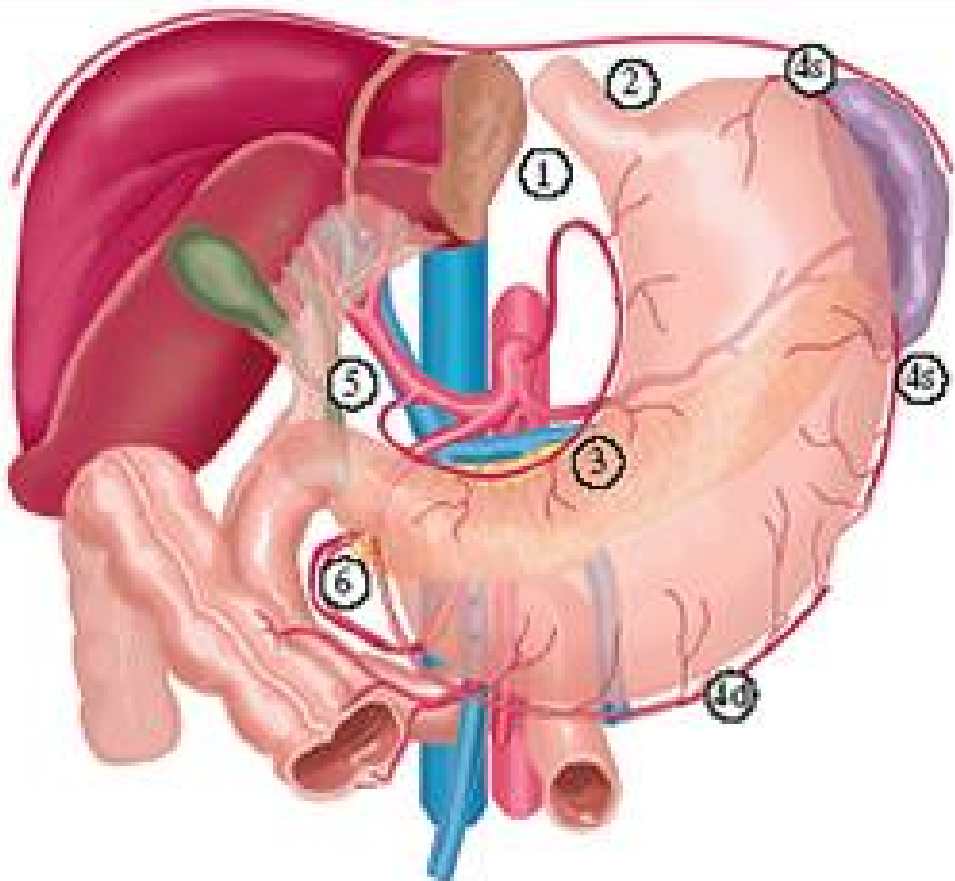
Goal; Depends on approach

Options; pre, peri- or postoperative chemo- or chemoradiation therapy.

D1 nodes adjacent to the stomach

D2 + branches celiac axis

D3 nodes along the aorta



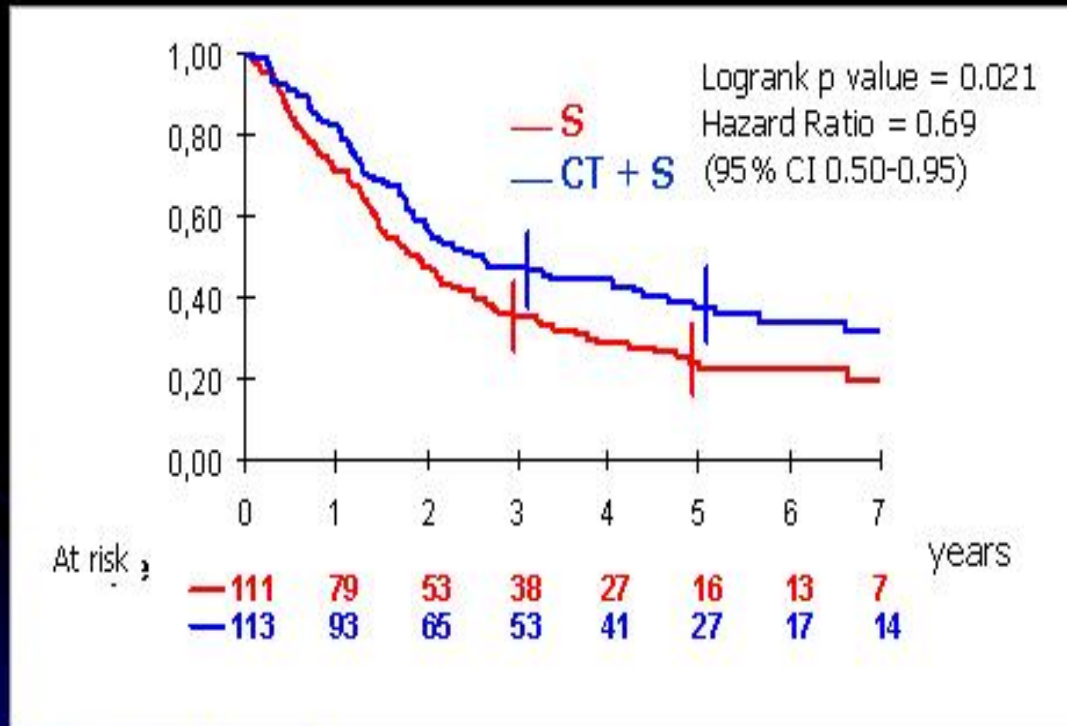
Surgical treatment of advanced gastric cancer;

Randomized trials on extend of surgery

N	Journal	Study		Conclusion
43	Br J Surg 1998;110-2	South Africa	R1 / R2	R1
55	Ann Surg 1994;176-82	Hong Kong	R1 / R3	R1
400	Lancet 1996;995-9	UK-MRC	D1 / D2	D1
996	Lancet 1995;745-8 NEJM 1999;908-14 JCO 2004;22:2069-77 ,Lancet Oncology 2010	Dutch	D1 / D2	D1 D1+ present update indicates D2
221	Lancet Oncol 2006;309-15	Taiwan	D1 / D2,3	D2,3
520	NEJM 2008;359:453-62	Japan	D2,3 / D4	D3 = D4

FCDD Trial

Overall survival



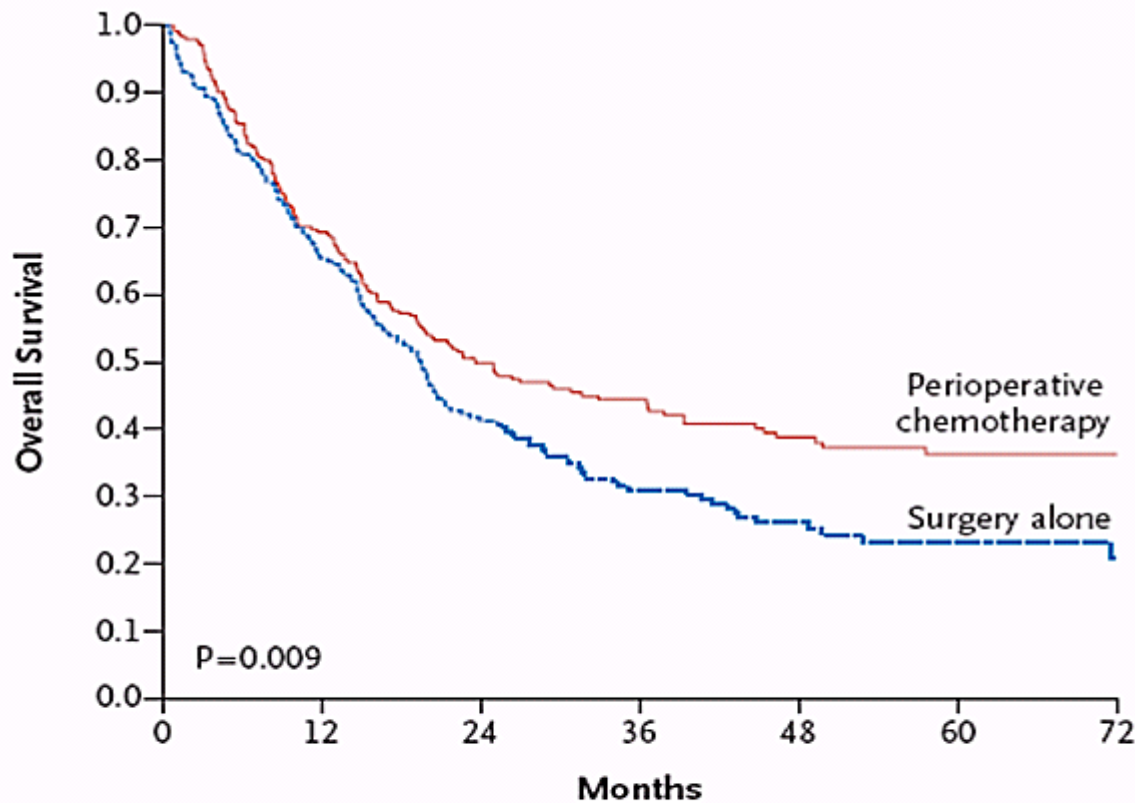
Pre-operative
chemotherapy

Vs.

Surgery

➤ 14 % survival benefit
chemotherapy with
surgery

Magic Trial



No. at Risk

Perioperative chemotherapy	250	168	111	79	52	38	27
Surgery	253	155	80	50	31	18	9

**Peri-operative
chemotherapy**

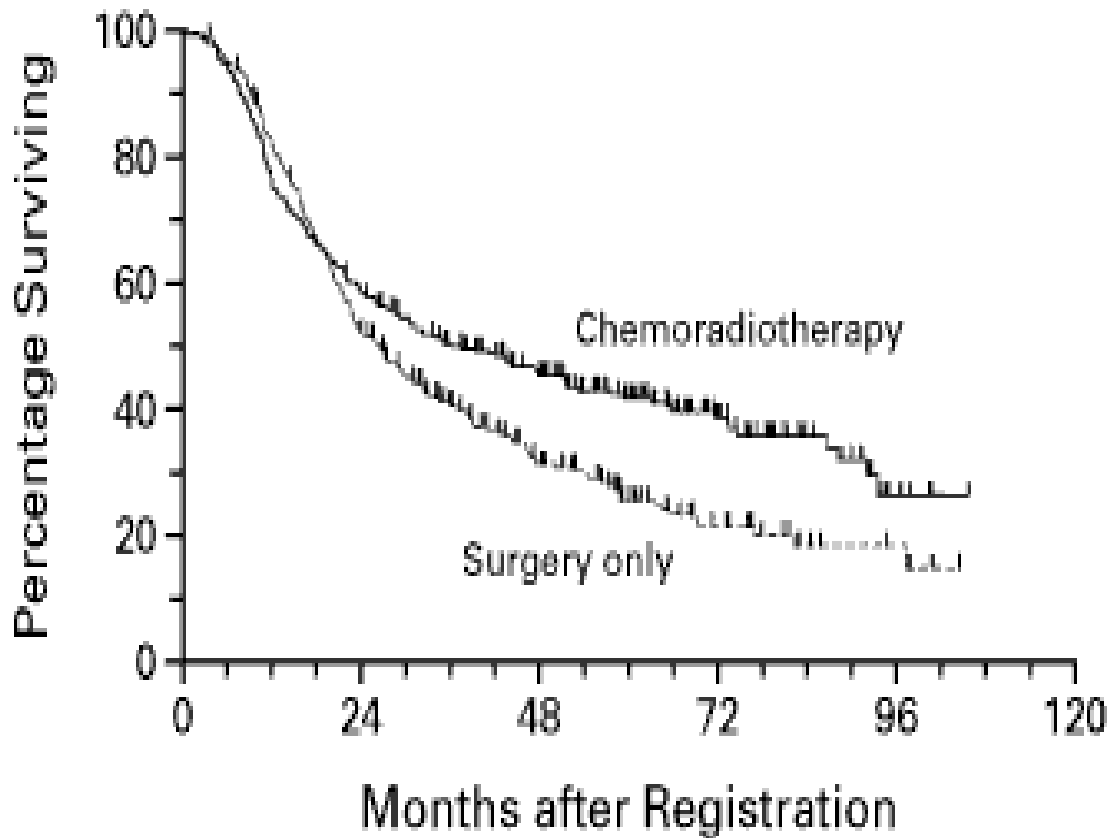
Vs.

Surgery

➤ **13 % overall
survival benefit**

➤ **10 % more
resectability**

SWOG trial



**Post-operative
chemoradiation**

Vs.

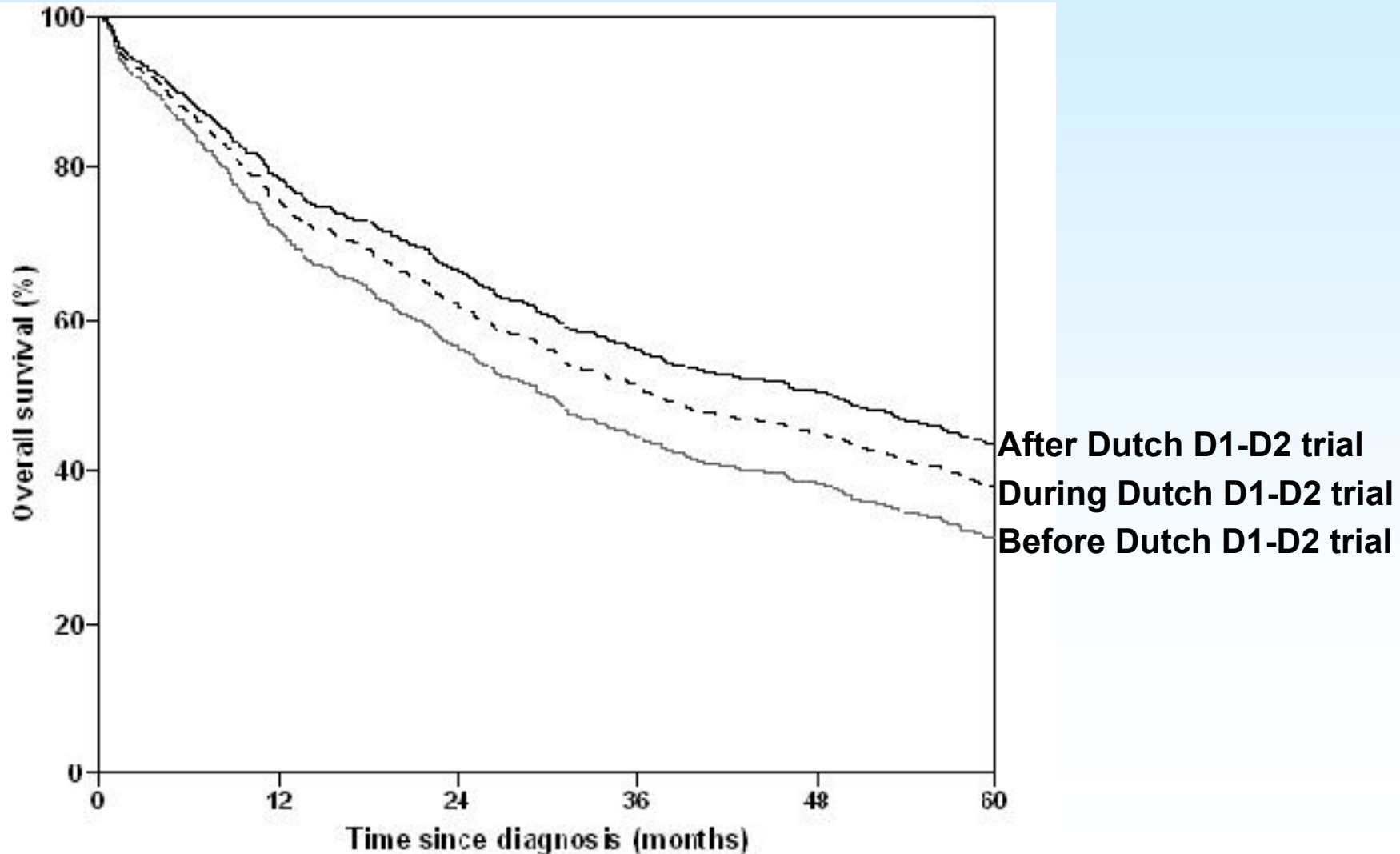
Surgery

- **73 % grade $\frac{3}{4}$ toxicity**
- **64% completed CRT**
- **9% survival benefit Adjuvant CRT**

Reasons no postoperative chemotherapy

	MAGIC <i>n=94</i>	FFCD <i>n=50</i>	SWOG <i>n=100</i>
• PD or early death	40%	8%	17%
• Patient's request	12%	10%	23%
• Complication postoperative	10%	28%	
• C(R)T toxicity	6%	20%	49%

National effect of improved and extended surgery



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	

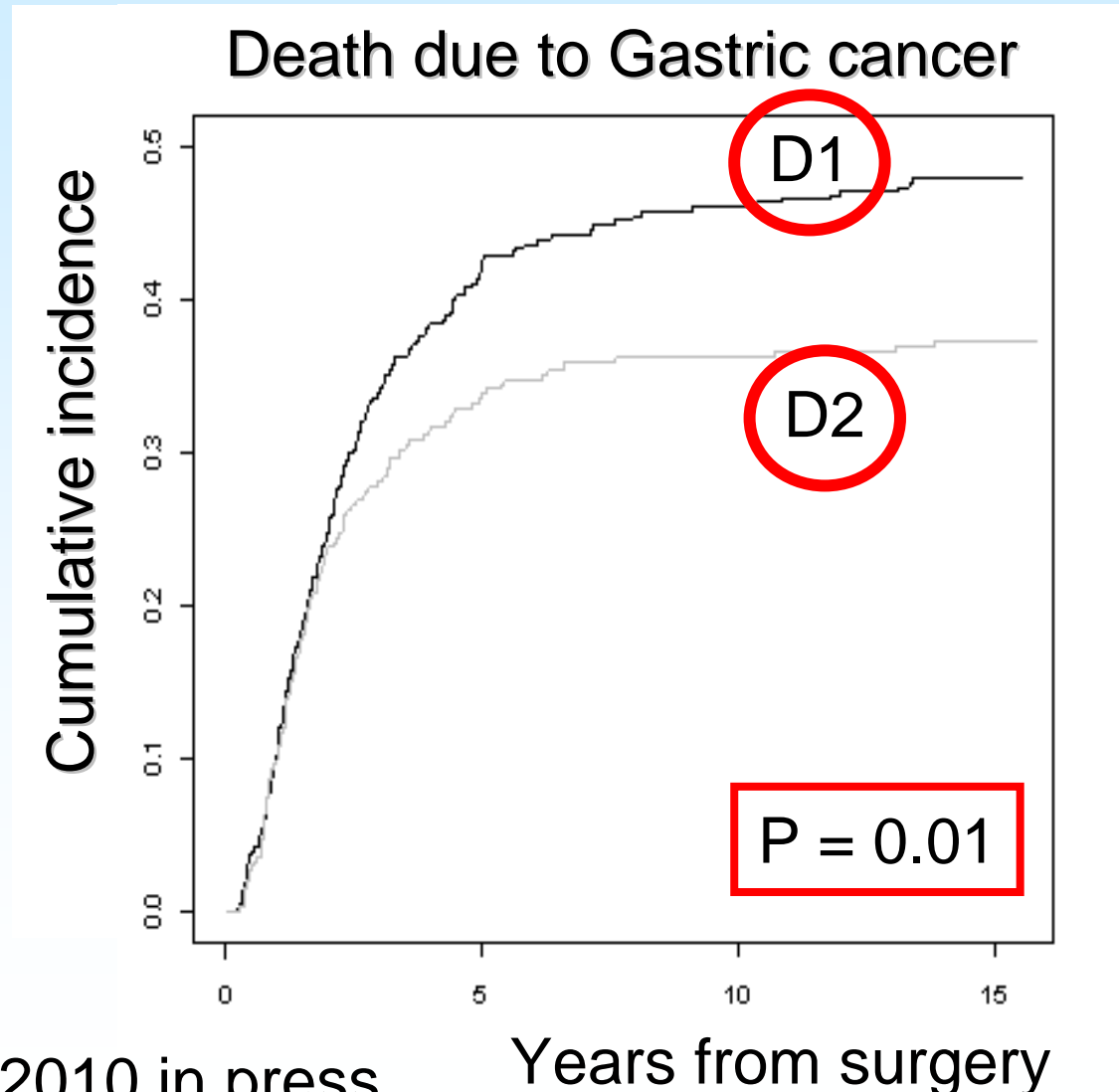
15 year Follow Up results Dutch D1/D2 trial

Some figures;

➤ Gastric cancer related death rate; D1 group (48%) vs D2 group (37%)

➤ Local recurrence (22% in D1 vs. 12% in D2)

➤ regional recurrence (19% in D1 vs. 13% in D2)

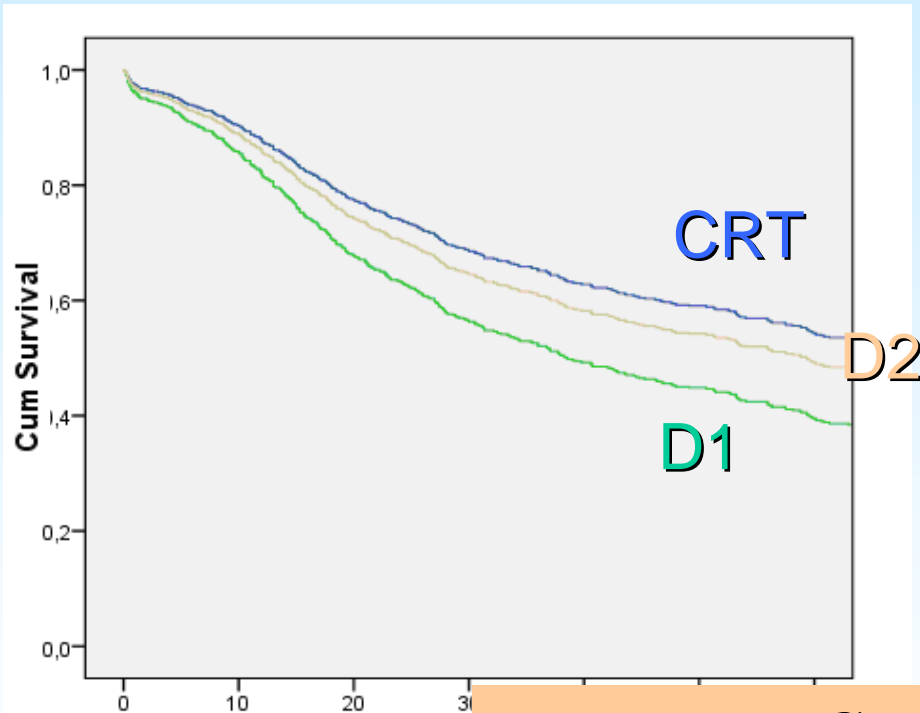


Lancet oncology 2010 in press

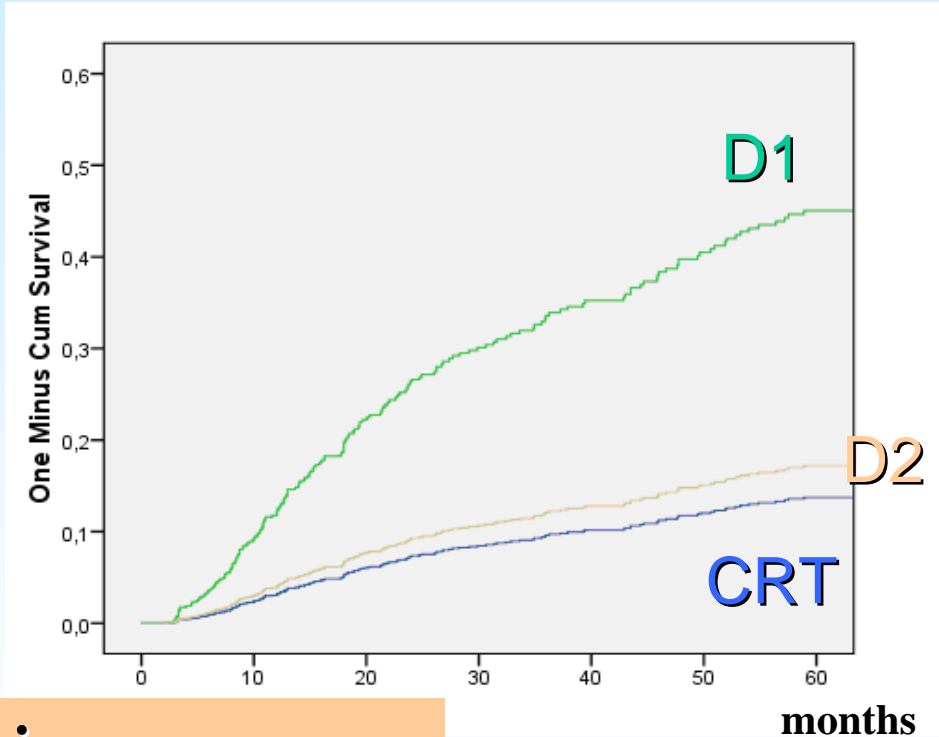
Years from surgery

D1/D2 surgery VS. post-operative chemotherapy

Overall Survival



Time to Local Recurrence



Conclusion

adjuvant CRT has survival/
recurrence benefit over D1 BUT
NOT over D2 surgery

HR CRT vs. D1 1.4051 p < 0,000

HR CRT vs. D2 1.277 p 0,579

1.4051 p < 0,000

1.277 p 0,579

elde et al JCO in press 2010

The adjuvant treatment of gastric cancer

Reasons for (neo-)adjuvant therapy

Post-Operative

- Treat occult residual metastases
- Successful in other tumor types
- Better patient selection

Peri-operative

- Downstaging
- Better tolerance
- Eliminating occult micrometastases



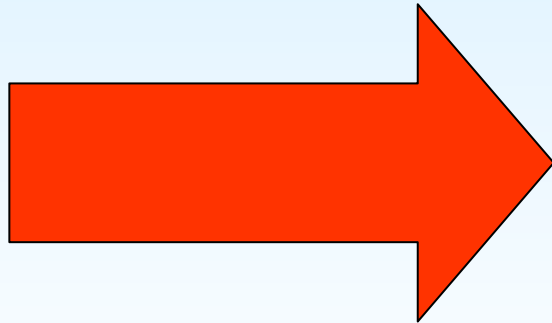
R0 resection

+

Better compliance

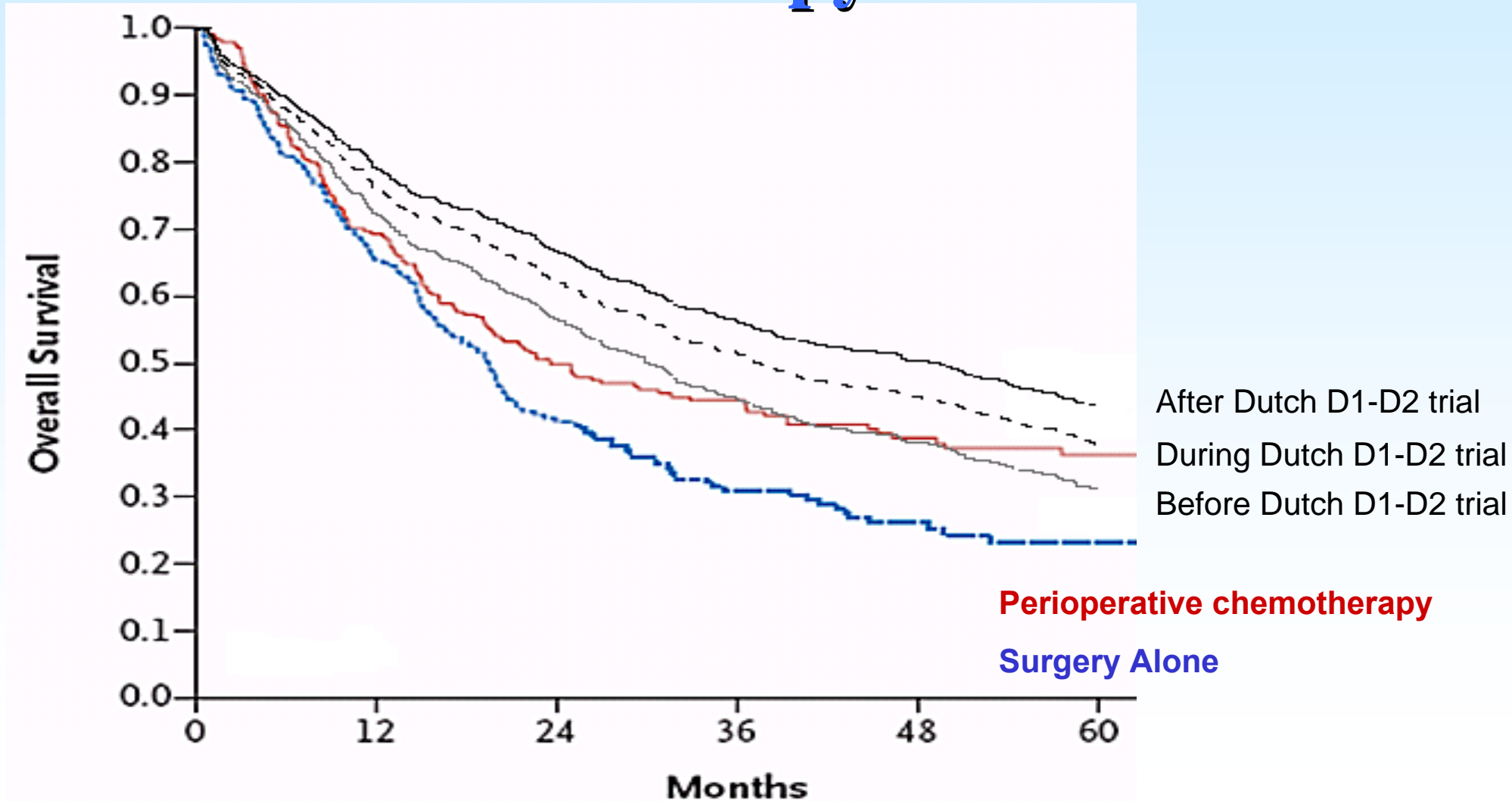
Treatment of Advanced Gastric Cancer

- Surgery remains the primary curative treatment
- To improve treatment outcome



**Improve surgical
quality**

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



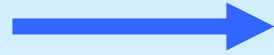
Quality assurance

Definition

The complete set of systematic actions that is required to achieve a treatment result that meets a certain standard

Working definition for quality

The right patients



Getting the right operation

In the right setting

While minimizing complications

And maximizing effectiveness

And patient satisfaction

•appropriateness

•access to care

Working definition for quality

The right patients

Getting the right operation → **Procedure comparisons**

In the right setting

While minimizing complications

And maximizing effectiveness

And patient satisfaction

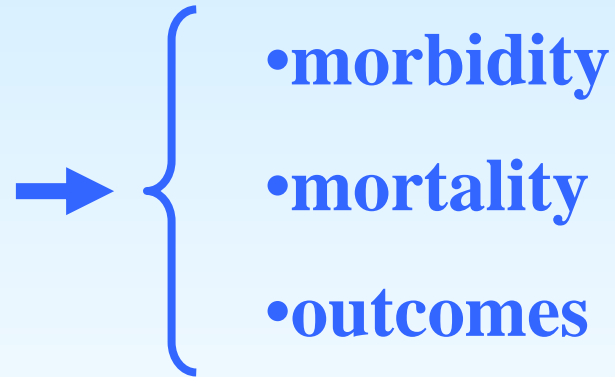
Working definition for quality

The right patients
Getting the right operation
In the right setting →
While minimizing complications
And maximizing effectiveness
And patient satisfaction

- surgeon volume
- hospital volume
- specialization
- regionalization
- surgeon training
- multidisciplinary
approach
- systems
- processes resources

Working definition for quality

The right patients
Getting the right operation
In the right setting
While minimizing complications
And maximizing effectiveness
And patient satisfaction



Working definition for quality

The right patients

Getting the right operation

In the right setting

While minimizing complications

And maximizing effectiveness

And patient satisfaction

•survival

•recurrence rates

•quality of life

•reduction in morbidities

•adj/neoadj therapy use

Working definition for quality

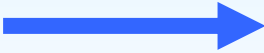
The right patients

Getting the right operation

In the right setting

While minimizing complications

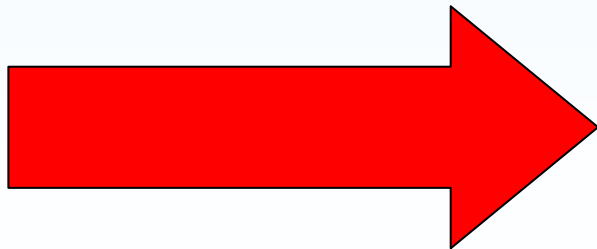
And maximizing effectiveness

And patient satisfaction  rarely considered

Maruyama index (MI)

“Low Maruyama Index (MI)” is associated with significantly enhanced survival and is an **independent** predictor of survival

The Maruyama index valid quantitative yardstick for assessing the adequacy of lymphadenectomy

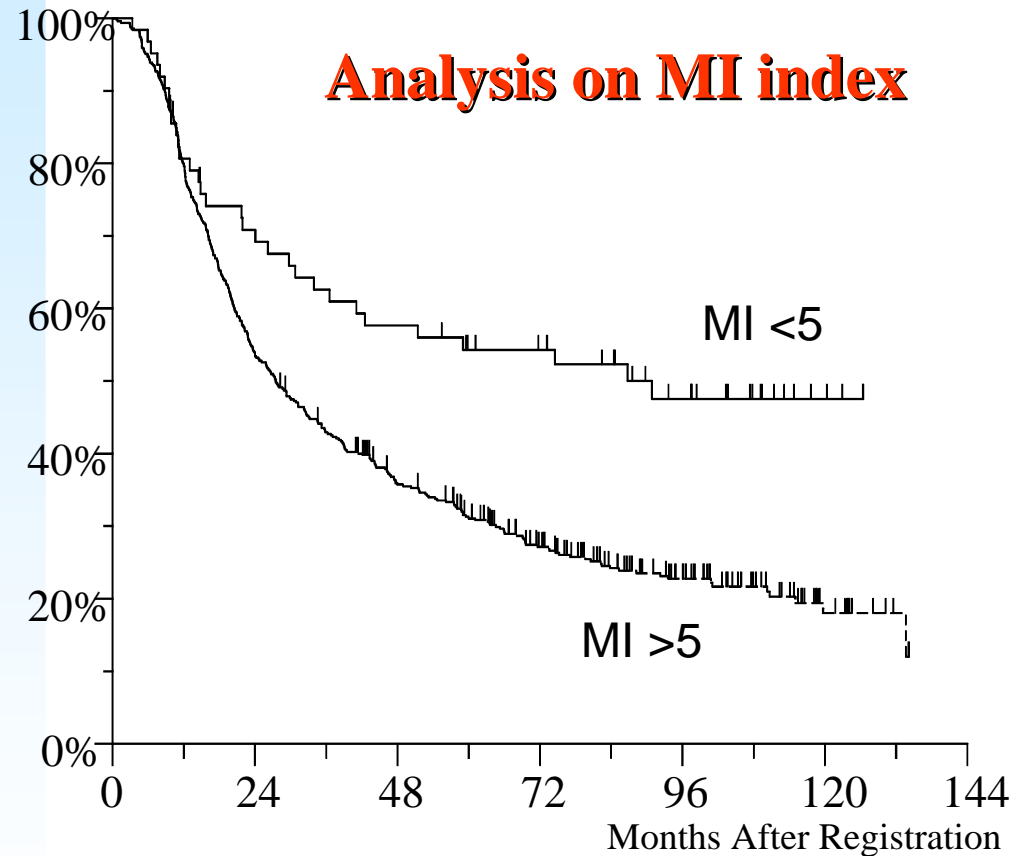
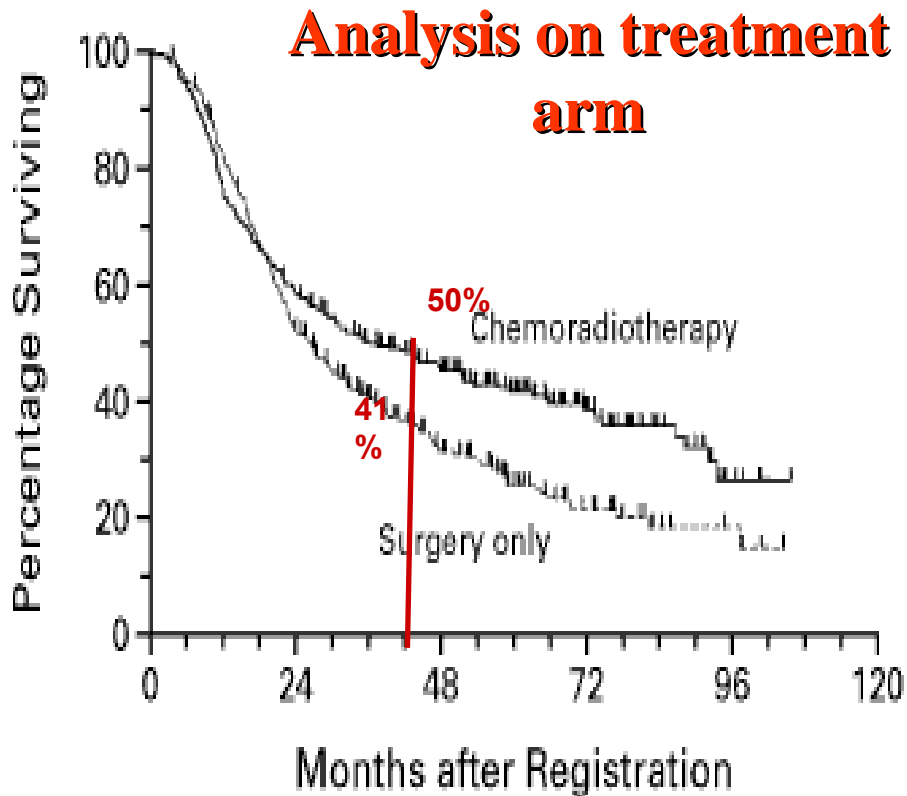


Tested in:

- **SWOG trial**
- **D1/2 trial**

Overall Survival in the SWOG

The effect of MI based analysis



p=0.005

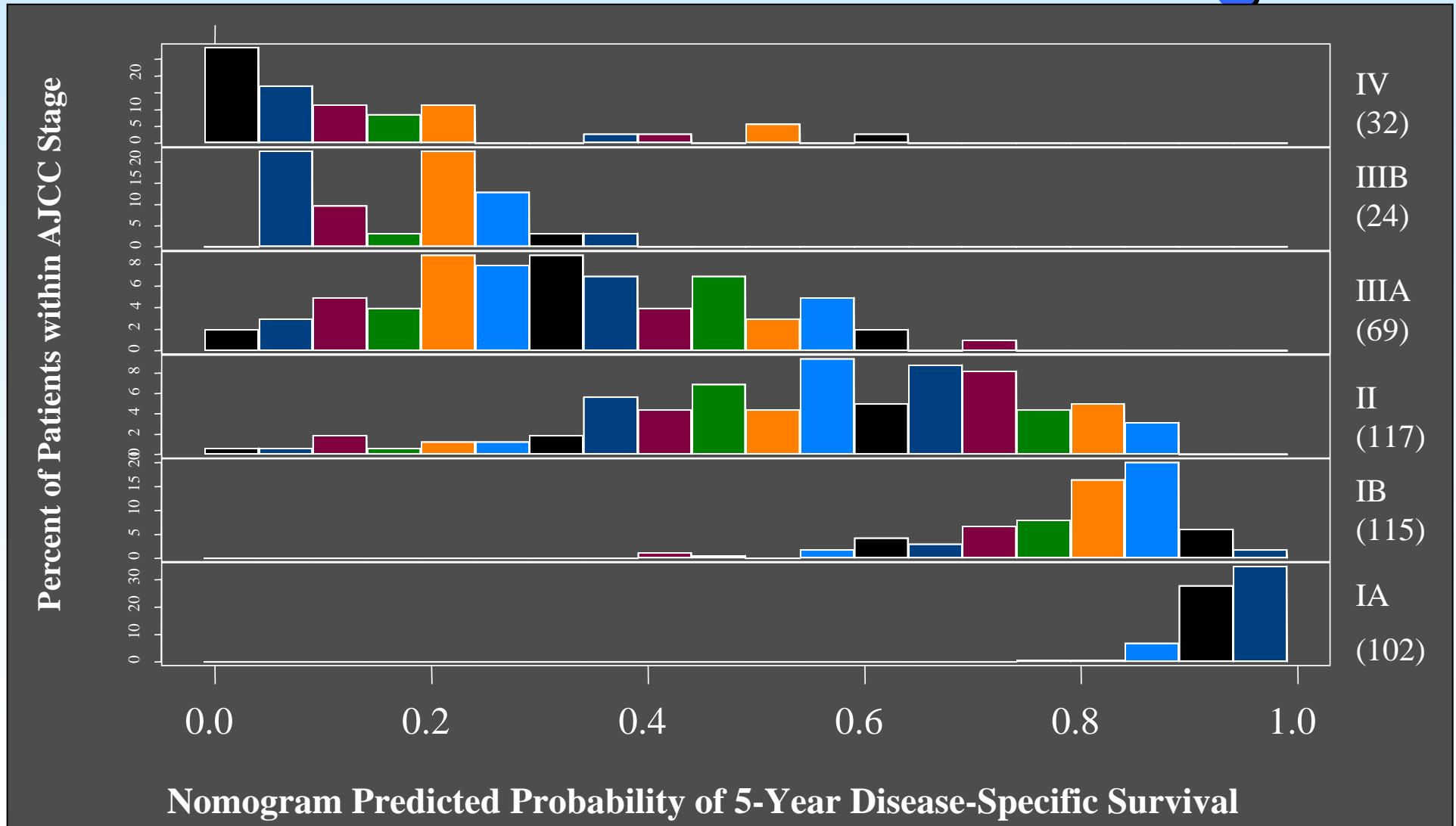
VS

p= 0.0005

Normogram

- **Prediction tool for disease specific survival**
- **Takes into account all factors that are prognostic according to the multivariate Cox regression analysis**
- **Enables tailored (adjuvant) treatment**

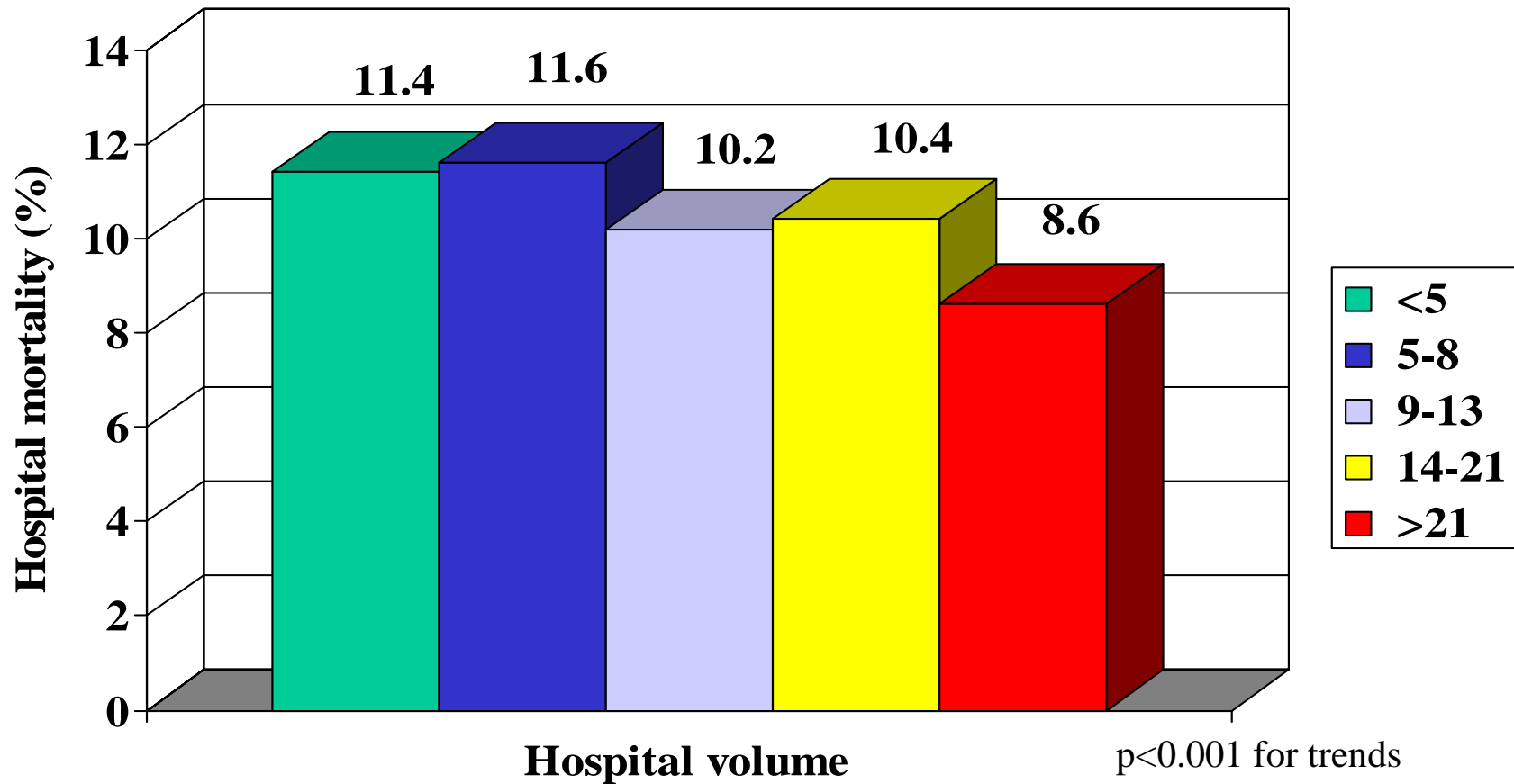
Normogram; predicted probabilities within each of the AJCC stages



Volume

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

Surgical mortality and hospital volume: gastrectomy



Radiotherapy

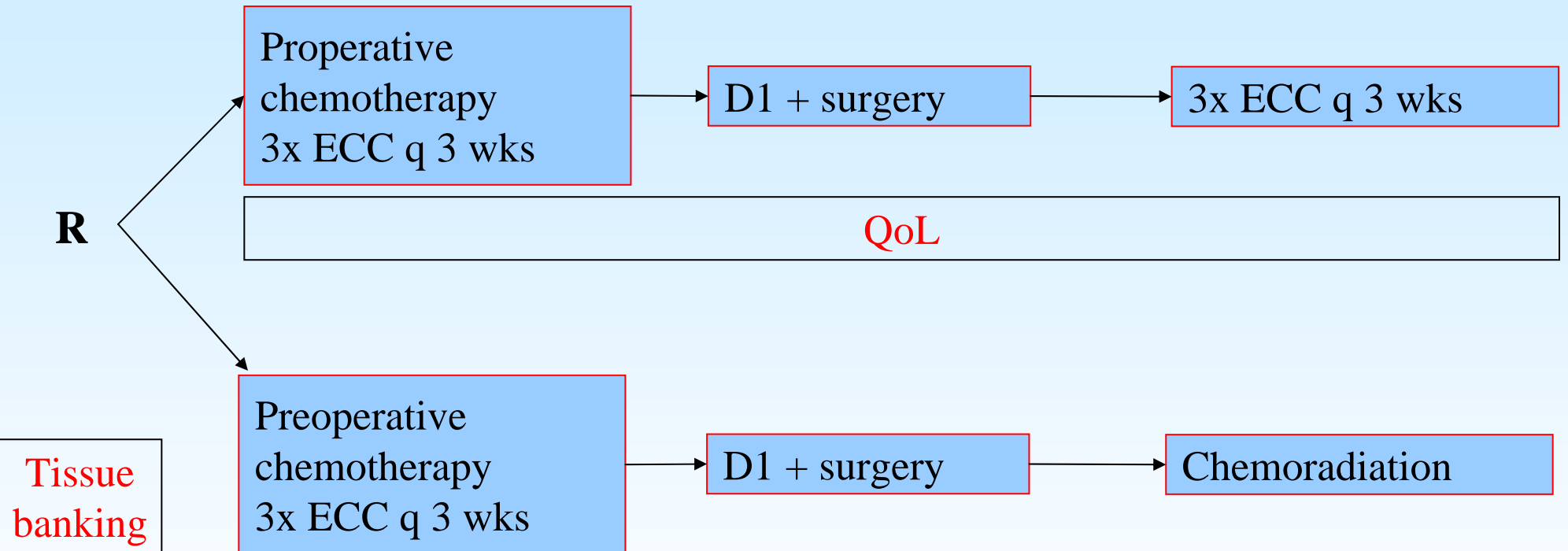


Surgery

Chemotherapy

To assess if post-operative CRT prolongs OS compared to chemotherapy only after pre-operative chemotherapy combined with **ADEQUATE** surgery

CRITICS



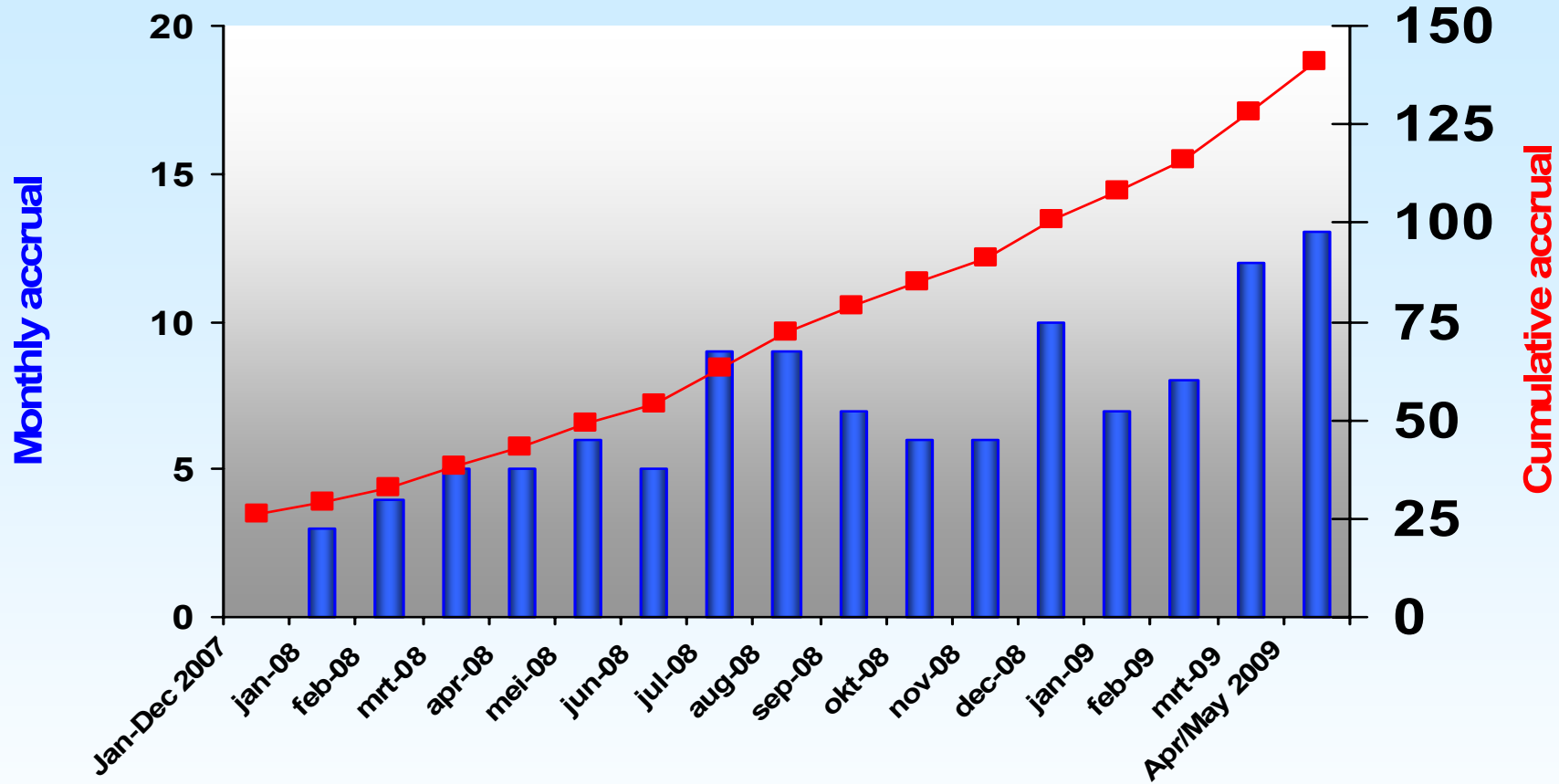
“MAGIC”(3xECC)

Epirubicine /Cisplatin /Capecitabine

³ 15 Lymph nodes
no splenectomy

45 Gy/25 fx +
capecitabine dd
cisplatin 1-5x pw
3D-CRT/IMRT

CRITICS ACCRUEL



So far 260 patients included (April 6, 2010)

For further information on the CRITICS trial:

www.critics.nl

Principle investigators:

E.P.M. Jansen

Prof. M. Verheij

Dr. A. Cats

Prof. C.J.H. van de Velde

Study coördinator

Maurits Swellengrebel

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VU medisch centrum



IV. Surgery for gastric cancer

Advanced gastric cancer

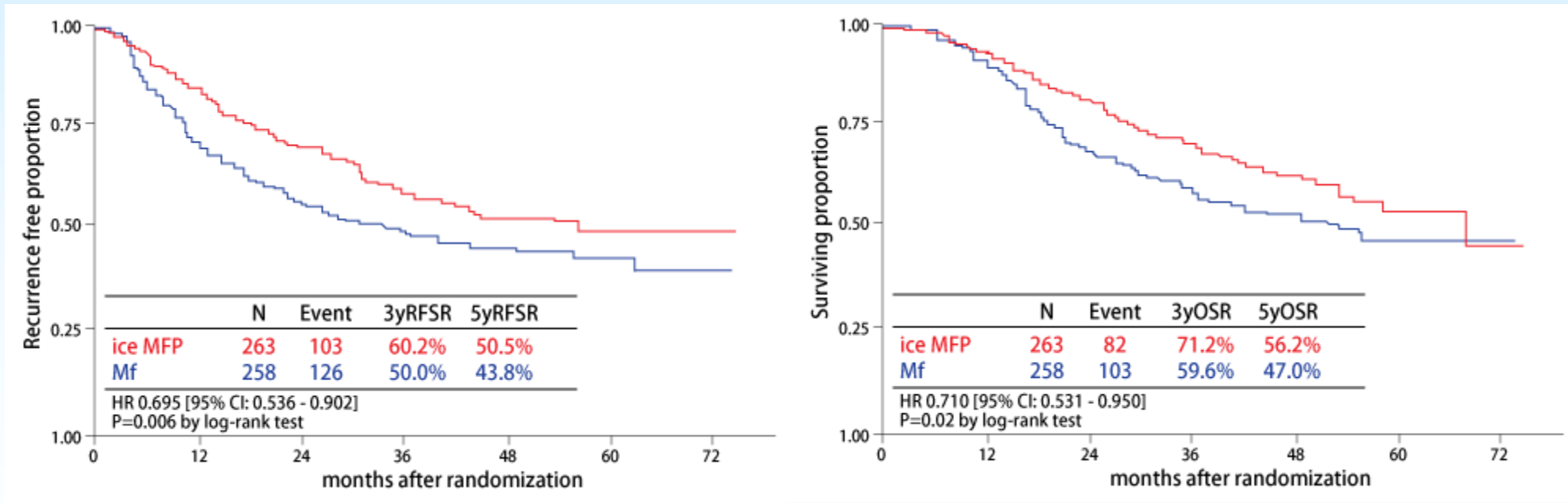
	Surgery + chemotherapy	Chemotherapy alone	
Survival times	351 days	182 days	$p = .008$

Gastrectomy only independant prognostic factor

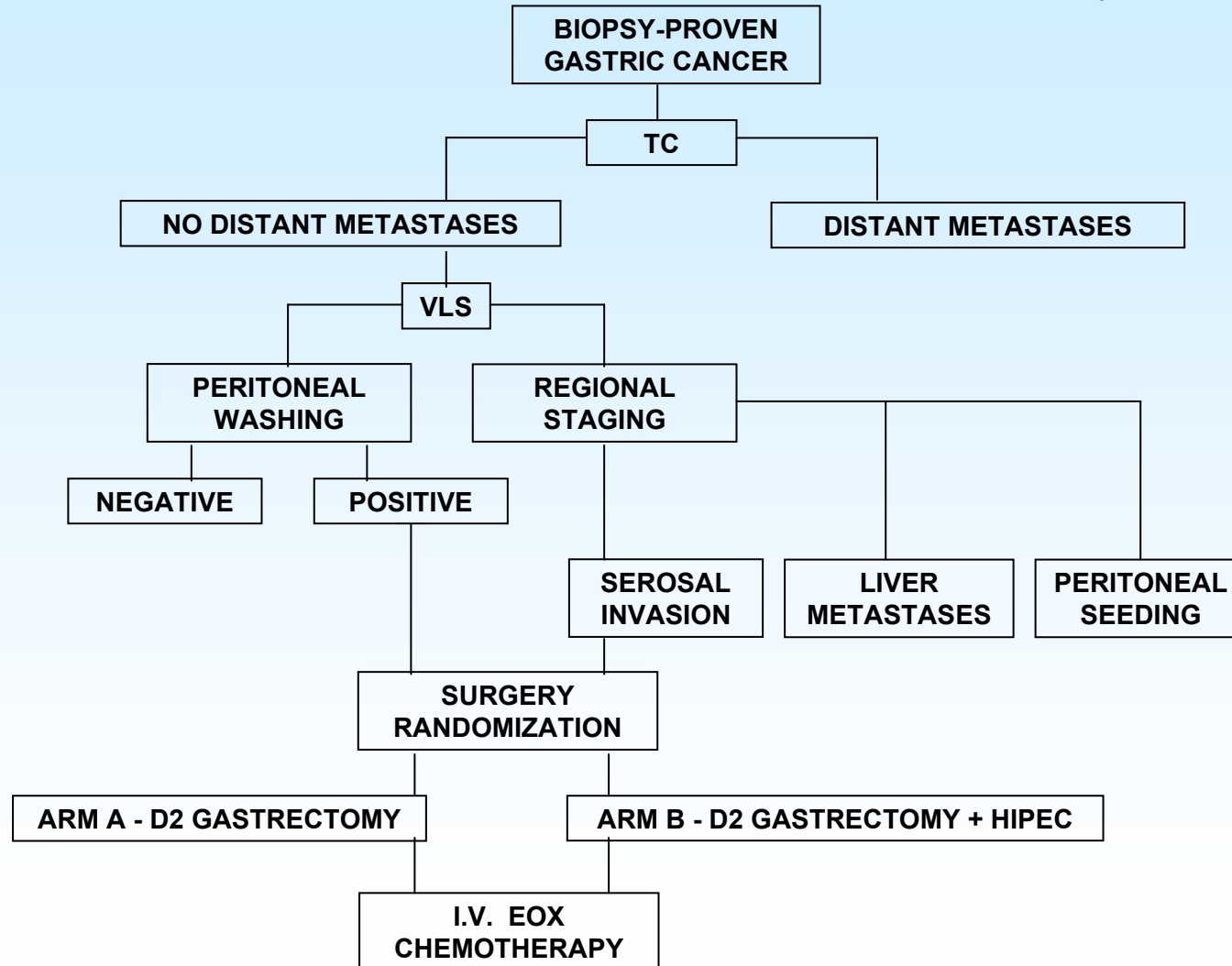
Miyagaki H *Anticancer Res* 2008

Intraperitoneal chemotherapy

- Phase III trial: intraperitoneal cisplatin and early mitomycin-C plus long-term doxifluridine plus cisplatin (iceMFP) *versus* mitomycin-C plus short-term doxifluridine (Mf)



RADICAL RESECTION AND INTRAOPERATIVE HYPERTHERMIC CHEMOPERFUSION IN GASTRIC CARCINOMA PATIENTS AT HIGH RISK OF PERITONEAL RECURRENCE (Phase III study)



V Conclusions

- **Optimal surgery is crucial; *D2 in selected cases***
- **QA and audit of surgeons and hospitals; *M index, normograms, centers of excellence***
- **Preoperative CTx: new standard of care**
- **Postoperative chemoradiation**
 - To be studied after appropriate surgery (CRITICS)
 - Indicated if lymphadenectomy was inappropriate

Future directions

- **Optical imaging of sentinel nodes and metastatic disease**
- **Robot-assisted/laparoscopic gastrectomy (RAG) with lymph node dissection for gastric cancer?**
- *RAG with lymphadenectomy can be applied safely and effectively for patients with gastric cancer.*

Song J, Oh SJ, Kang WH, Hyung WJ, Choi SH, Noh SH. Ann Surg. 2009 Jun;249(6):927-32

Initiative European Society of Surgical Oncology

One European Cancer Audit

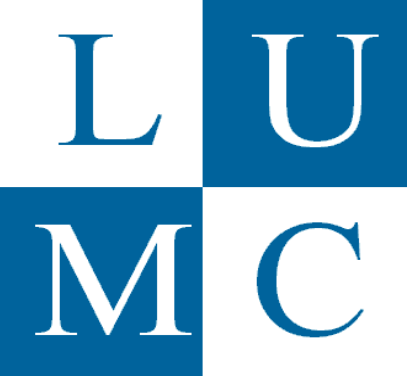
Quality



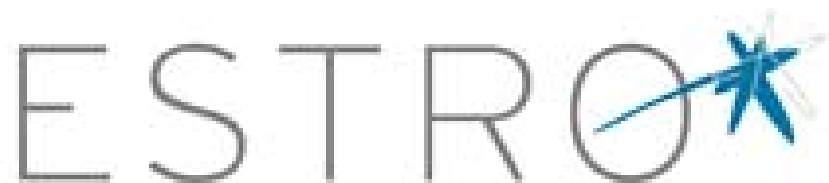
Variation



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



European Audit on Cancer Treatment Outcome



EURECCA Objectives (European Registration of Cancer Care)

- To perform research on the currently available population-based registries**
- defining “core quality treatment strategies” as well as treatment recommendations.**
- To integrate “core treatment quality strategies” in clinical practice**
- To optimize the level of knowledge and experience**

A top-down photograph showing approximately 12 hands of various skin tones (ranging from light to dark brown) reaching towards the center of the frame. The hands are resting on a light-colored, textured surface that appears to be sand or fine gravel. The composition is circular, with the hands forming a ring around a central point. The lighting is even, highlighting the textures of the skin and the ground.

collaboration
is everything

ESSO 2010

Surgical outcome: can we do better?

15th Congress of the
European Society of Surgical Oncology

BORDEAUX | FRANCE

15-17 September 2010



esso

THE EUROPEAN SOCIETY
OF SURGICAL ONCOLOGY