Ca Cardias e Stomaco: le diversita' e le terapie

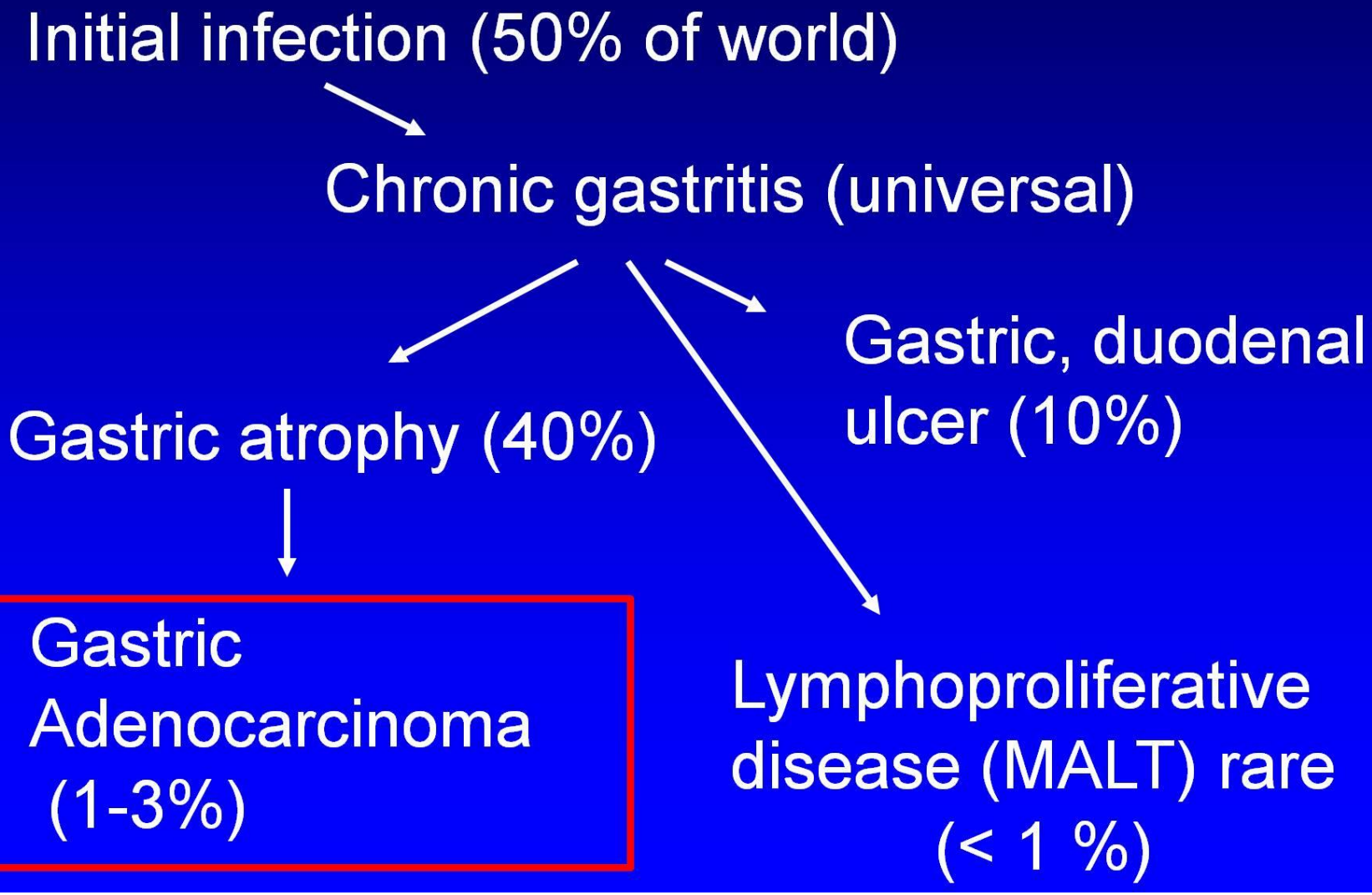
Maria Di Bartolomeo

s.s. Oncologia Medica Gastroenterologica
Fondazione IRCCS Istituto Nazionale Tumori
Milano

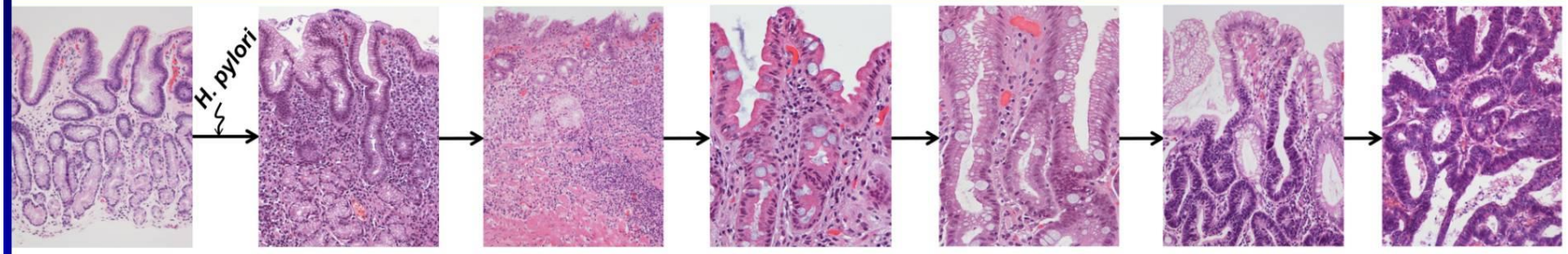
OUTLINE

- History of HP infection.
- Two concept of carcinogenesis.
- Morphological classification of Gastric, gastroesophageal junction (GEJ) and esophagous.
- Multimodality strategies:
  - postoperative CT+/-RT
  - perioperative CT
  - neoadjuvant CT+/-RT
- Molecular classification.

Natural History of *H. pylori* Infection



Natural History of *H. pylori* Infection- *Correa Cascade*



Hypothesis

A MODEL FOR GASTRIC CANCER EPIDEMIOLOGY

PELAYO CORREA

Department of Pathology, Louisiana State University Medical Center, 1542 Tulane Avenue, New Orleans, Louisiana 70112, U.S.A.

WILLIAM HAENSZEL

Biometry Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014, U.S.A.

CARLOS CUELLO

Department of Pathology, School of Medicine, Universidad del Valle, Cali, Colombia

STEVEN TANNENBAUM MICHAEL ARCHER

Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, U.S.A.

Summary It is postulated that one major subtype of gastric carcinoma (" intestinal type ") is the end-result of a series of mutations and cell transformation begun in the first decade of life. The mutagen could be a nitroso compound synthesised in the upper gastrointestinal tract by the action of nitrite (i.e., from food or saliva) on naturally occurring nitrogen compounds. Under normal conditions these nitroso compounds do not reach the gastric epithelial cell, presumably because their synthesis is inhibited by antioxidants present in food or because of their

[CANCER RESEARCH 52, 6735–6740, December 15, 1992]

Special Lecture

Human Gastric Carcinogenesis: A Multistep and Multifactorial Process— First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention[1]

Pelayo Correa

Department of Pathology, Louisiana State University Medical Center, New Orleans, Louisiana 70112-1393

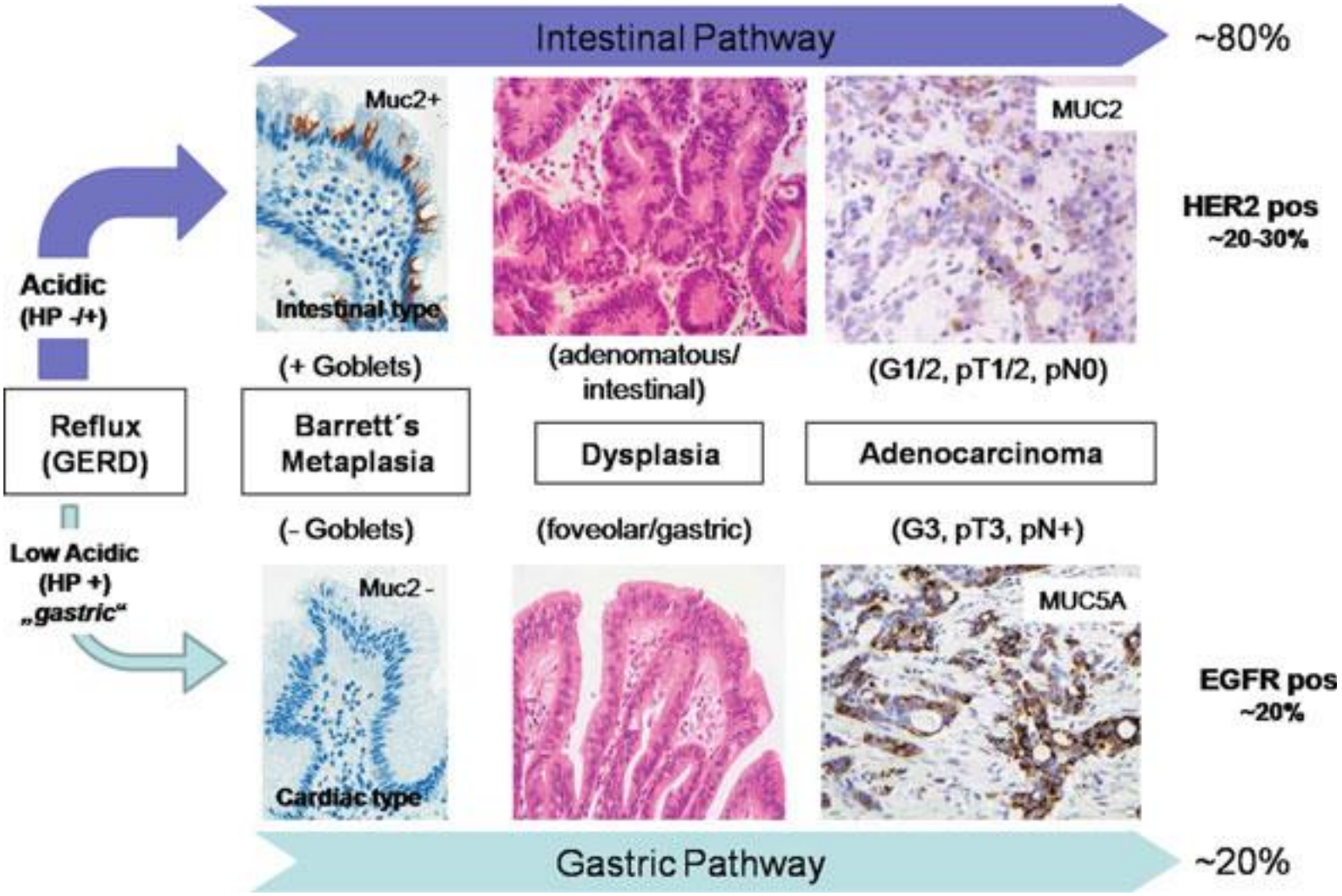
Abstract

Evidence from pathology and epidemiology studies has been provided for a human model of gastric carcinogenesis with the following sequential stages: chronic gastritis; atrophy; intestinal metaplasia; and dysplasia. The initial stages of gastritis and atrophy have been linked to excessive salt intake and infection with *Helicobacter pylori*. The intermediate stages have been associated with the ingestion of ascorbic acid and nitrate, determinants of intragastric nitrosation. The final stages have been linked with the supply of β-carotene and with excessive salt intake. Nitrosating agents are candidate carcinogens and could originate in the gastric cavity or in the inflammatory infiltrate.

phic gastritis (gland loss), small intestinal metaplasia, colonic metaplasia, and dysplasia (7, 8).

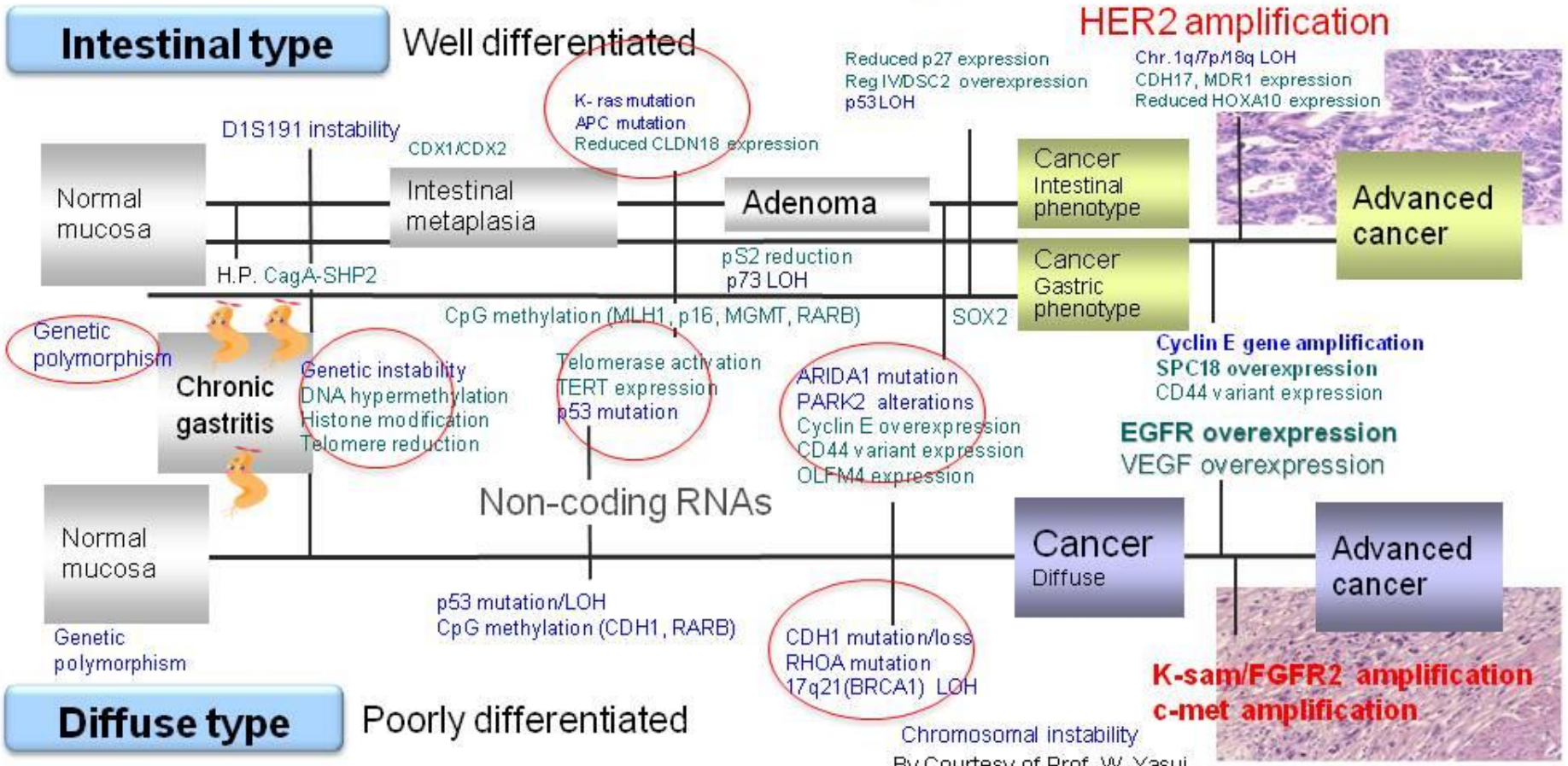
An etiological hypothesis, depicted in Fig. 2, has been proposed to explain the progressive tissular and cellular changes and to identify the etiological forces acting at different points in the chain of causation (9, 10). Research on the hypothesis has continued on several fronts and produced new information which will be reviewed briefly in this article. We will address the phenotypic markers, the etiological factors, and the pathways of carcinogenesis and conclude with remarks about the implications for cancer prevention.

Proposal of two pathways concept of carcinogenesis



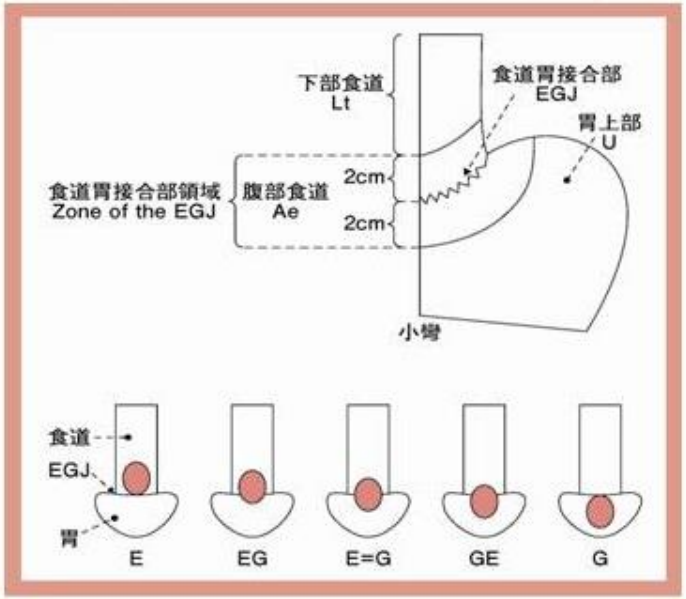
(Demicco EC, Mod Pathol,2011; Ruschoff J, Rec Res in Cancer Research 2012)

Genetic and molecular alterations during stomach carcinogenesis



Different definition of carcinoma of the EGJ

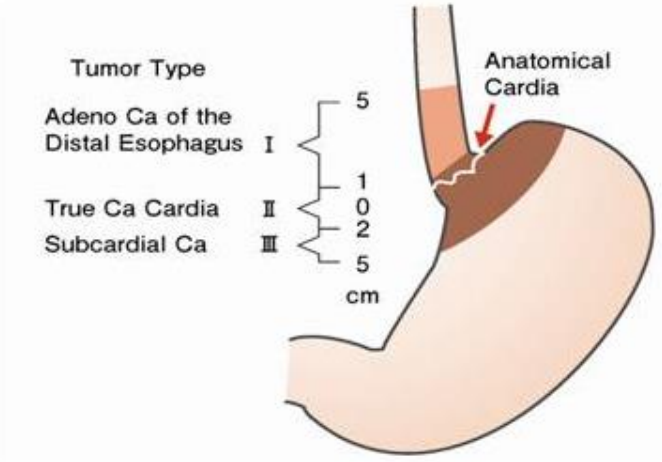
Japanese classification (Nishi's classification)

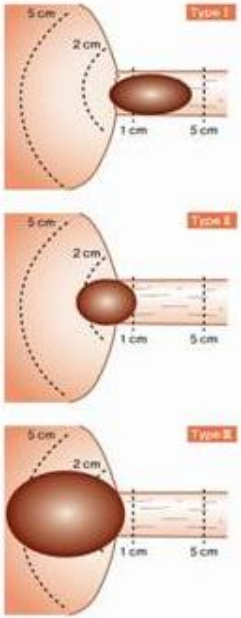


Center of the tumor is located above and below 2cm, regardless of pathology

UICC-TNM classification (7th ed.) (Adenocarcinoma of the esophagus)

Siewert's classification





Center of the tumor is located above and below 5cm, adenocarcimona

Factors affecting outcomes: East *vs* West

1. Tumor characteristics
2. Host characteristics:
   pharmacogenetics/pharmacogenomics
   tumor microenvironment
3. Treatment and practice pattern
4. Cultural and political issues

Drug tolerability and host genetics (pharmacogenetics)

Lower tolerable dose of S-1 in Caucasian than Asian: phase I/II studies

	Cycle (weeks)	S-1	Cisplatin	Cisplatin dose intensity	DLT	ORR
Japan	5	40-60 mg, bid, D1-21	60 mg/m^2, D8	36 mg/m^2/3 weeks	Anorexia, Neutropenia	54%
Korea	3	40 mg/m^2 bid, D1-14	60 mg/m^2, D1	60 mg/m^2/3 weeks	Diarrhea, Neutropenia	48%
USA	4	25 mg/m^2 bid D1-21	75 mg/m^2, D1	57 mg/m^2/3 weeks	Diarrhea, Fatigue	51%

- In Caucasian
  - higher 5-FU Cmax and AUC from S-1
  - higher CYP2A6 activity related to genetic polymorphism

Different immune signature for different outcome

- 1,016 GC gene expression analysis comparing Asian vs non-Asian GCs

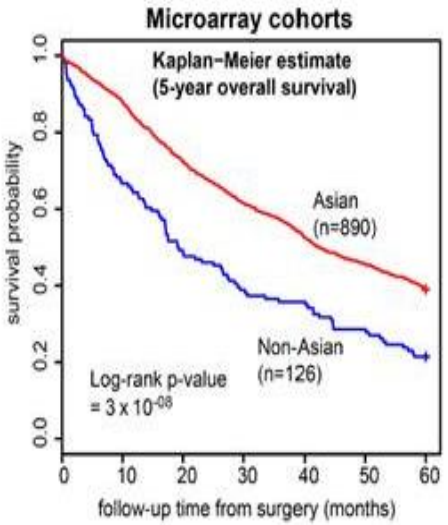
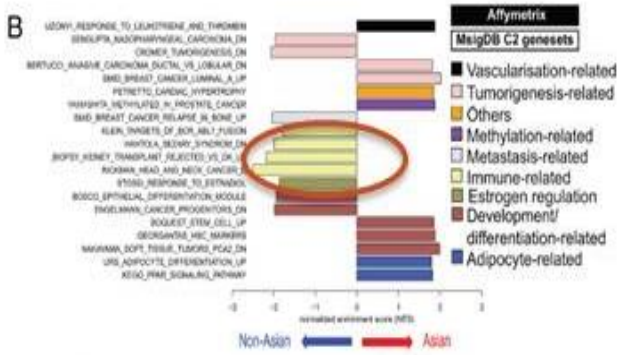
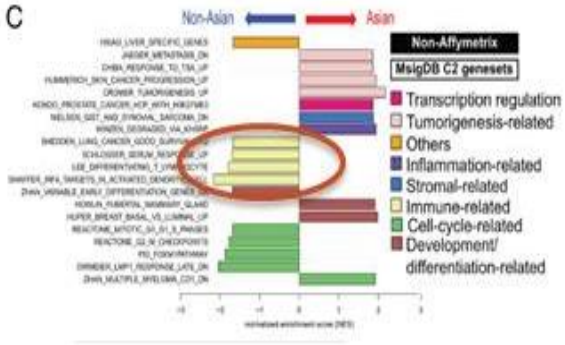
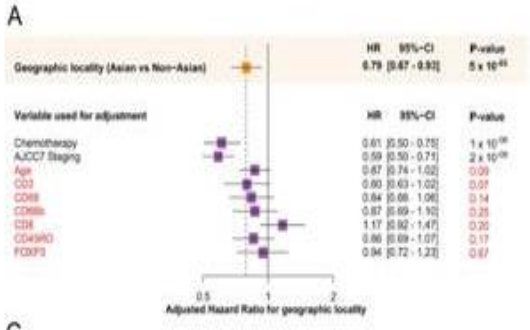
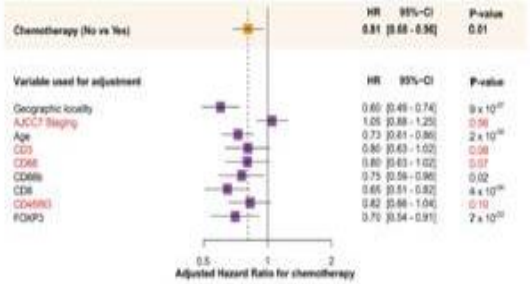


Figure 1 Five-year overall survival outcomes in the nine expression studies. Kaplan–Meier curves comparing Asian (red) versus non-Asian (blue) 5-year overall survival outcomes in the nine expression studies.









- Non-Asian GCs were enriched with T cell infiltration and T cell related signatures

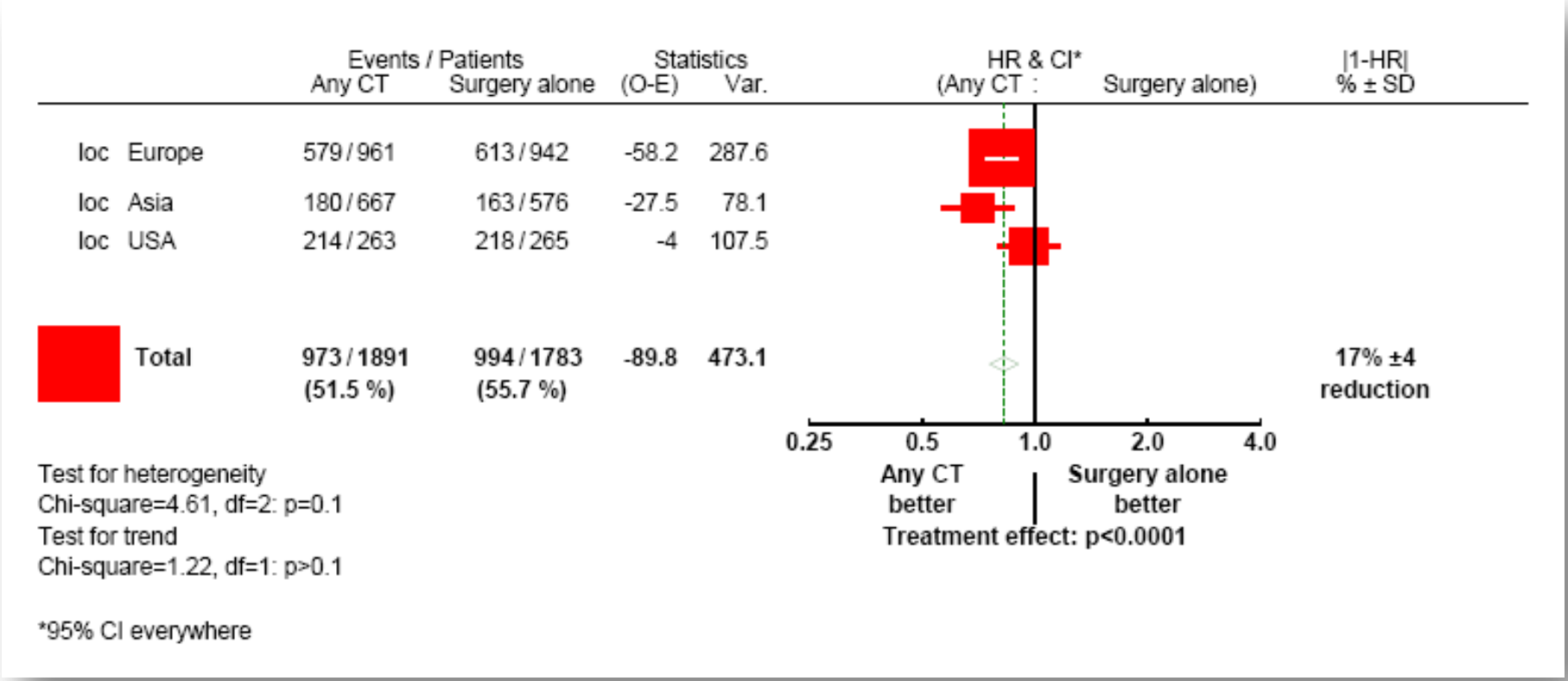
Might need different strategy for eastern and western patients!

Lin SJ, Gagnon-Bartsch JA et al. Gut 2015

Difference in treatment pattern

- Screening program (early diagnosis, low tumor burden, long-term survival)
- Extent of surgery: stage migration (standardized D2 surgery)
- Adjuvant Tx: Perioperative chemotherapy, Adjuvant radiotherapy vs adjuvant chemotherapy (different guidelines)
- Palliative chemotherapy: Doublet vs triplet, various regimens, lines of treatment
- Supportive care (stent, draining pigtail, palliative radiotherapy)

Interaction between CT and geographical area



Gastric Group et Al JAMA 2010

Comparison of Phase III adjuvant trials

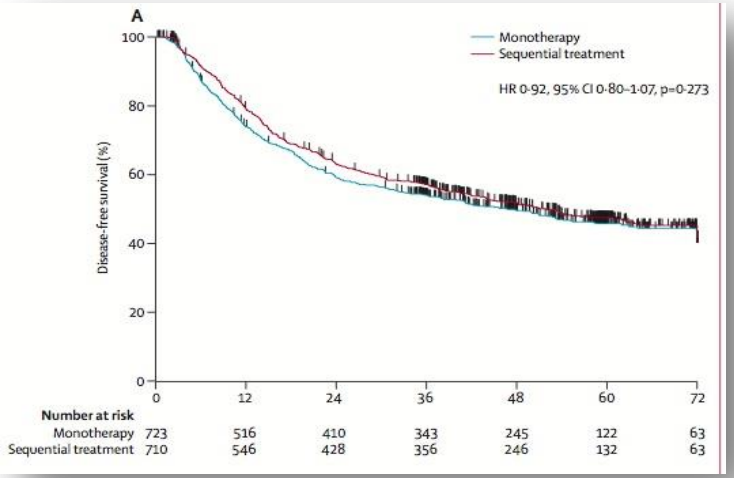
Study	N.Pz	Stage*	Location	Surgery	Regimen	5-DFS Rate (%)	5-OS Rate (%)
Western							
INT-0116	602	IB-IV (M0)	EGJ 20% Stomach 80%	D0:54% D1:36% D2:10%	postFL+RT vs CTL	42 vs 25	46 vs 28
CALGB 80101	540	IB-IV (M0)	GEJ 24% Stomach 76%	NA	postFL+RT vs ECF+RT	35 vs 38	41 vs 44
ITACA-S	1100	IB-IIIB	EGJ:12% Stomach :78%	D1:25% D2:75%	Post FL vs Folfiri→CDDP /Txt	44 vs 44	50 vs 51
Asian							
ACTS-GC	1056	II-III	All stomach	D2:100%	Post S1	53 vs 65	60 vs 71
Classic	1035	II-III	All stomach	D2:100%	Post XELOX	53 vs 68	69 vs 78
ARTIST	458	IB-IV (M0)	All stomach	D2: 100%	Post XP+RT vs XP	68 vs 71	75 vs 73
SAMIT	1495	IB-IV (M0)	All stomach	D2:100%	Post S1 vs S1→Pct	54 vs 57	55 vs 59

Different interpretation and different treatment guidelines!

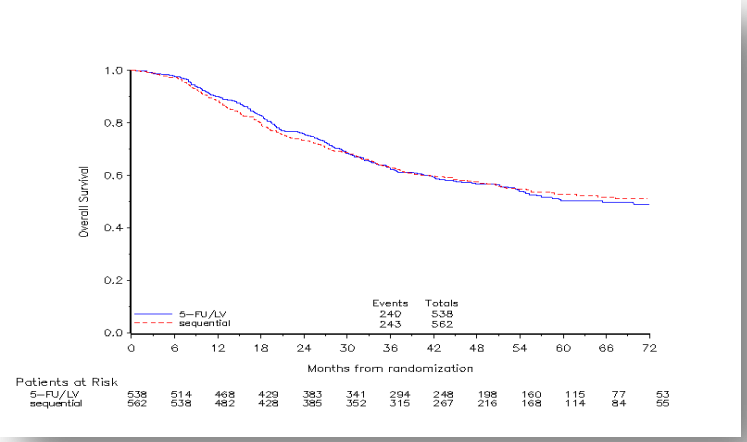
(*stage bases on AJCC 6th edition)

ADDING A TAXANE TO ADJUVANT CHEMOTHERAPY : FAILED TO IMPROVE OS IN 2600 PTS

- SAMIT[1]:1 yr S-1 or UFT after D2 gastrectomy +/- 3 month of paclitaxel
- 1495 pts
- No change in 3yrs DFS with taxane (57% vs 54%, HR 0.92, p=0.273) or 3 yr OS (59% vs 56%, HR 0.93, p=0.342)

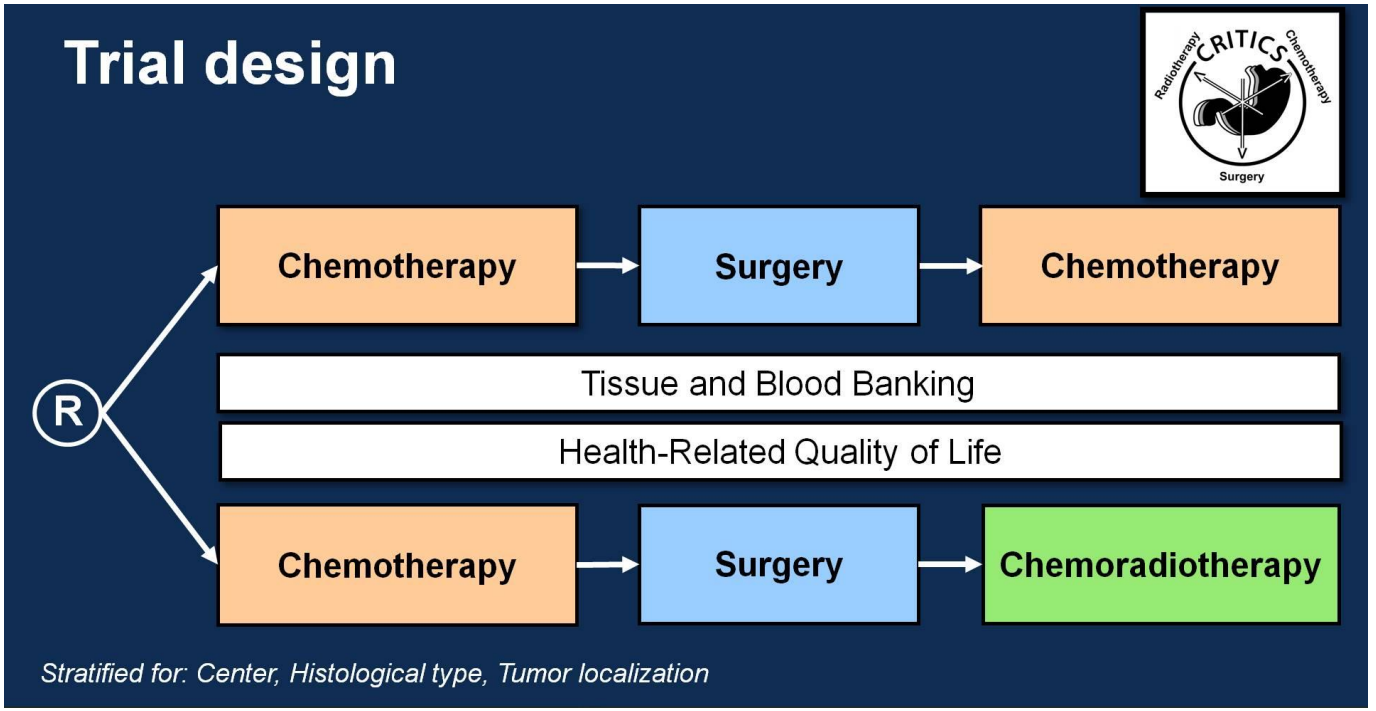


- ITACA-S[2]: FU/LV cycles vs FOLFIRI x 4 cycles →docetaxel/cisplatin for 3 cycles
- 1106 pts with gastric cancer
- No change in DFS HR:1 p=0.974 or OS HR 0.98 p=0.865



[1]Tsuburaya A, Lancet 2014; [2]Bajetta, Ann Oncol, 2014

CT: 393 pts
CT+RT: 395 pts



Treatment Details

Chemotherapy: Pre-operative and post-operative: 3x ECC or EOC q3 wks

Epirubicin 50 mg/m² day 1; Cisplatin 60 mg/m² day 1; Capecitabine 1000 mg/m² b.i.d. 1-14
Epirubicin 50 mg/m² day 1; Oxaliplatin 130 mg/m² day 1; Capecitabine 625 mg/m² b.i.d. 1-21

Surgery: Total / partial gastrectomy + *en bloc* N1 and N2 lymph nodes

D1⁺ resection: lymph node stations 1-9 and 11; no splenectomy or pancreatectomy
Removal of ≥15 lymph nodes
Quality assurance: Maruyama Index

Chemoradiotherapy: Post-operative: 45 Gy in 25 fractions combined with CC

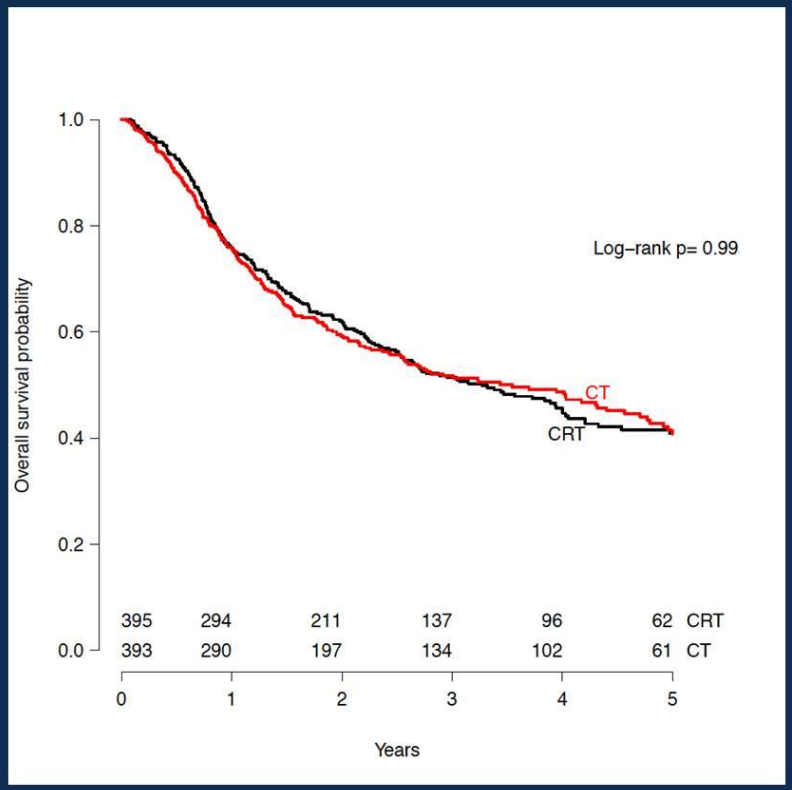
3D-CRT or IMRT; CTV includes tumor bed, anastomoses, draining lymph node stations
Concurrent during RT: Cisplatin 20 mg/m² weekly; Capecitabine 575 mg/m² b.i.d./d.d.w.d.
Quality assurance: central review of RT plans

Pts characteristics:
GEJ: 17%

Surgery:
D1 49%
D2 38%

Presented at ASCO 2016

Results: Overall Survival



	CT	CRT
5-year OS (%)	40.8	40.9
Median OS (yrs)	3.5	3.3

Conclusions:

No difference in overall survival has been observed

Median survival are comparable with other studies!!!

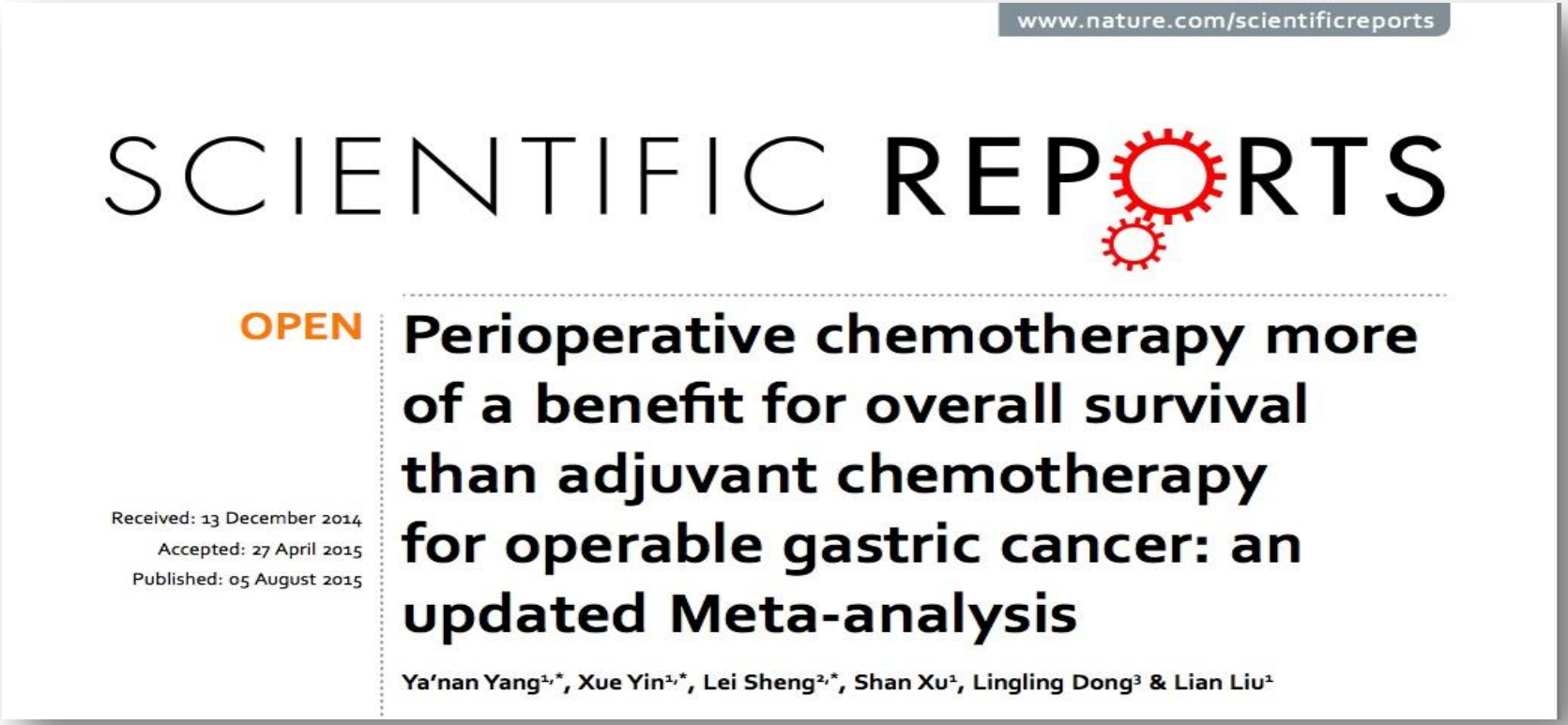
No advice can be given on the preferred adjuvant strategies

More enphasis on preoperative strategies should be considered

Would neoadjuvant chemotherapy (NAC) have alone benefits for operable gastric cancer? NO

NAC should be combined to adjuvant chemotherapy (AC) (i.e PC)? YES

PC has more advantages than AC? YES



www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN

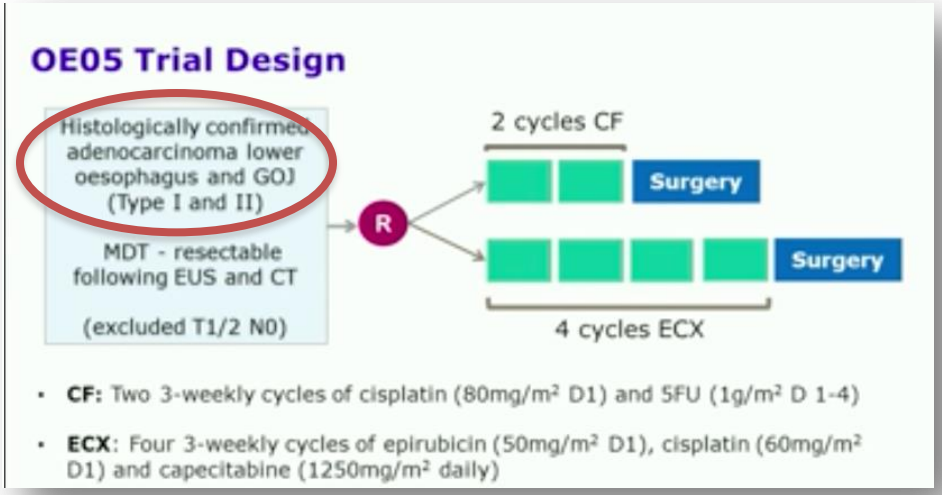
Received: 13 December 2014
Accepted: 27 April 2015
Published: 05 August 2015

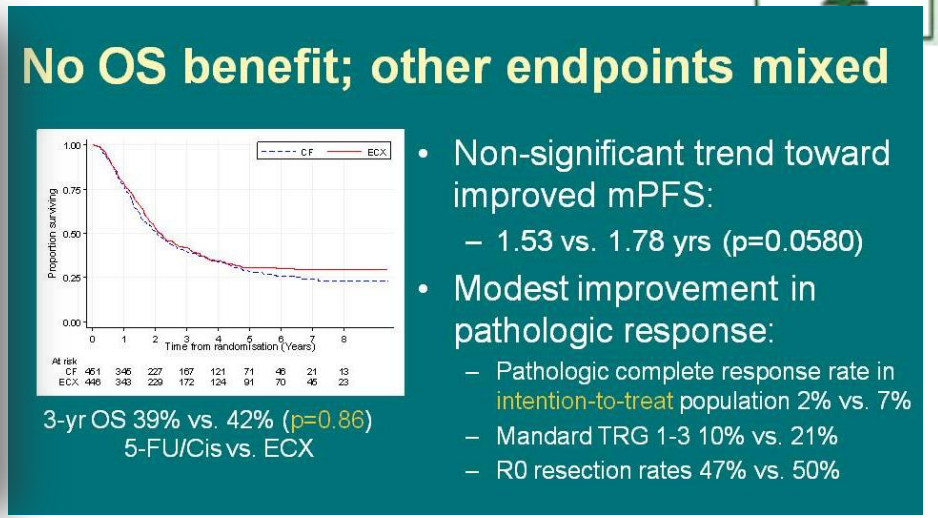
Perioperative chemotherapy more of a benefit for overall survival than adjuvant chemotherapy for operable gastric cancer: an updated Meta-analysis

Ya'nan Yang[1,*], Xue Yin[1,*], Lei Sheng[2,*], Shan Xu[1], Lingling Dong[3] & Lian Liu[1]

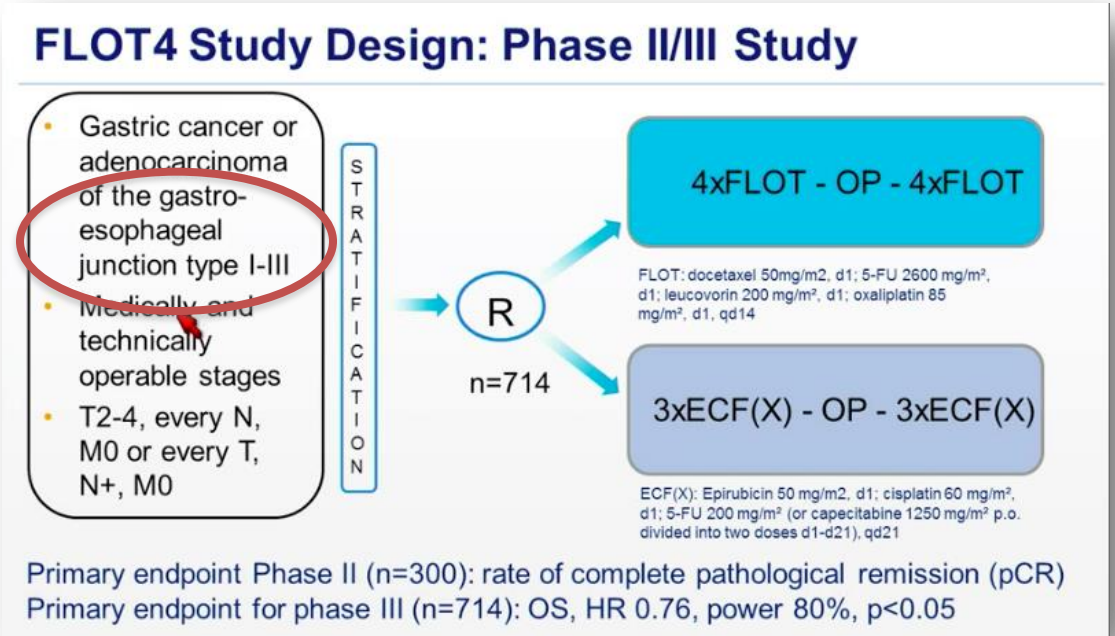
(DOI:10.101038/serep12850)

1) The role of Epirubicin





2) The role of Taxan



Conclusion:

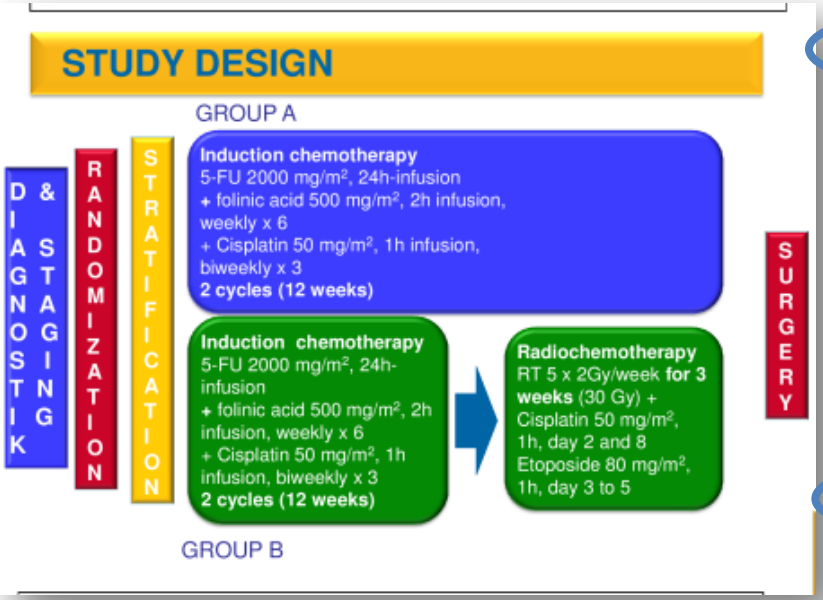
- FLOT →higher rates of pCR than ECX(F)
- The results in line with previous NR studies
- The Phase III will show if pCR improvement will traslate into a survival advantage

Preoperative chemoradiotherapy tends to win the long-term run in curative treatment of locally advanced oesophagogastric junction adenocarcinoma: Update of the POET phase III study

M. Stahl[1], J. Riera-Knorrenschild[2], M.Stuschke[3], R. Engenhart-Cabillic [4], M. Bitzer [5], W. Budach[6], A. Sandermann [7], G. Folprecht[8], L. Mantovani-Löffler[9], M.K. Walz[10], H. Wilke[1]

[1]Department of Medical Oncology, Kliniken Essen-Mitte, Essen; [2] Department of Hematology and Oncology, Universitätsklinikum Giessen und Marburg, Marburg; [3]Department of Radiation Oncology, West German Cancer Center, Universität Duisburg-Essen, Essen; [4]Department of Radiation Oncology, Universitätsklinikum Giessen und Marburg, Marburg;[5]Department of Gastroenterology, Universitätsklinikum Tübingen; [6]Department of Radiation Oncology, Universitätsklinikum Düsseldorf; [7]Biostatistics Wissenschaftlicher Service Pharma GmbH, Langenfeld; [8]University Cancer Center, Universitätsklinikum Gustav Carus, Dresden; [9]Department of Medical Oncology and Hematology, St. Georg Hospital, Leipzig; [10]Department of Surgery and Center of Minimal Invasive Surgery, Kliniken Essen-Mitte, Essen; Germany

STUDY DESIGN



PATIENT CHARACTERISTICS

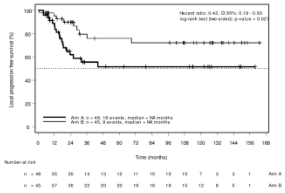
	CT + S N=59	CT + CRT + S N=60	Total N=119
Weight loss			
<10%	43 (73%)	44 (73%)	87 (73%)
≥ 10%	16 (27%)	16 (27%)	32 (27%)
Localisation			
Siewert type I	32 (54%)	33 (55%)	65 (55%)
Siewert type II	27 (46%)	27 (45%)	54 (45%)
T-category			
T3	54 (92%)	54 (90%)	108 (91%)
T4	5 (8%)	6 (10%)	11 (9%)
PS			
WHO °0 #	38 (69%)	33 (58%)	71 (63%)
WHO °1 #	17 (31%)	24 (42%)	41 (37%)

values missing from 4 / 3 patients

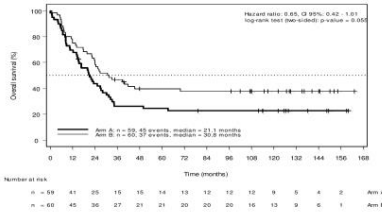
RESULTS AT SURGERY

	CT + S N=59	CT + CRT + S N=60	P value
Surgery	52 (88%)	49 (82%)	
R0-Resection	40 (77%)	43 (88%)	ns
R1-Resection	8 (15.4%)	2 (4.1%)	
Histology			
Pathologic CR	1 / 52 (1.9%)	7 / 49 (14.3%)	0.03
Treatment deaths			
Overall	4 (6.8%)	6 (19%)	ns
Postop. 30-day	1 (1.9%)	2 (4.1%)	
Postop. In-hospital	2 (3.8%)	5 (10.2%)	ns

LOCAL PROGRESSION FREE SURVIVAL AFTER R0/R1 RESECTION

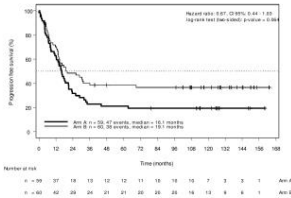


OVERALL SURVIVAL



	CT + S (Arm A)	CT+CRT+ S (Arm B)	Log-rank p
Median Survival Time	21.1 mo	30.8 mo	ns
3-year survival rate (95%-CI)	26.1% (16.9-40.3)	46.7% (35.6-61.2)	0.055
5-year survival rate (95%-CI)	24.4% (15.5-38.4)	39.5% (28.8-54.2)	

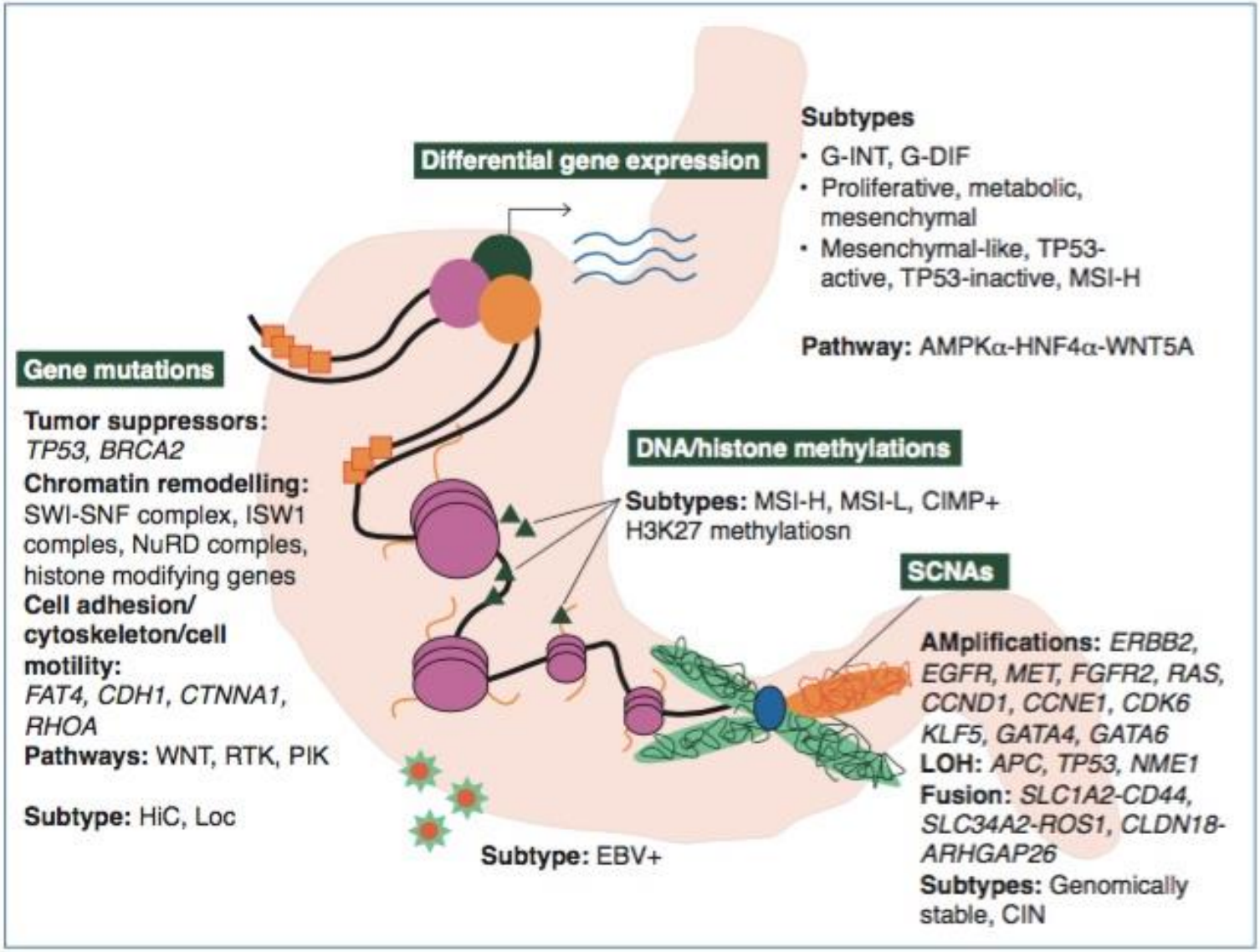
PROGRESSION FREE SURVIVAL (ITT)



	CT + S (Arm A)	CT+CRT+ S (Arm B)	Log-rank p
Median Progression Free Survival	21.1 mo	30.8 mo	ns
3-year PFS (95%-CI)	22.7% (14.1-36.6)	40.0% (29.3-54.5)	ns
5-year PFS (95%-CI)	21.0% (12.7-34.7)	38.3% (27.8-52.8)	ns

Presented at ASCO2016

Molecular classification of GC



Chia N, Ann Oncol, 2016

Immunotherapy: RESULTS

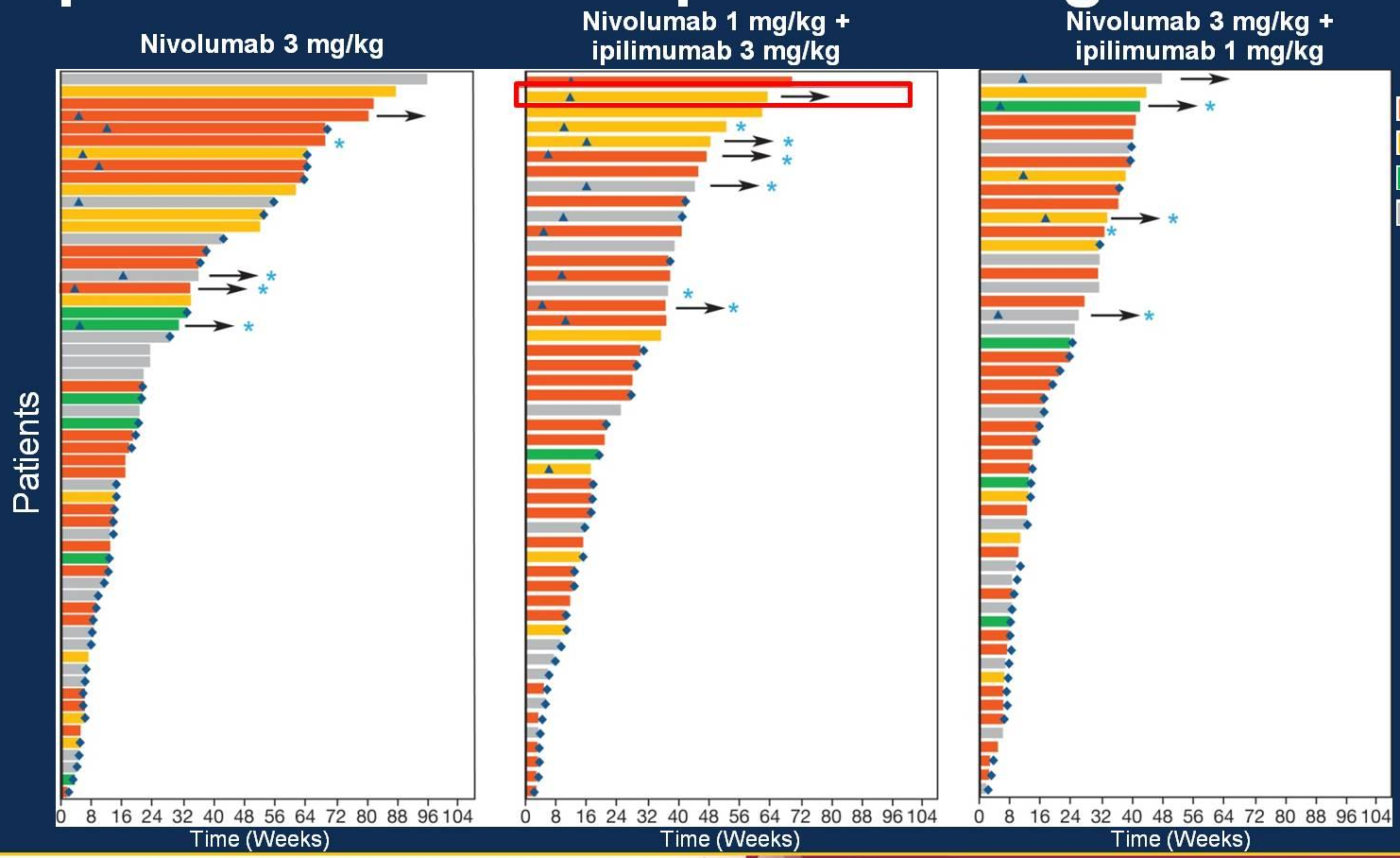
Target	Drug	Phase	Setting	Pts	Results	Reference
CTLA-4	Tremelimumab	2	II line	18	1 PR; 4 SD	Ralph, *Clin Can Res 2010*
	Ipilimumab	2 rand	Maintenance	143		*ASCO2016*
PD-1■	Pembrolizumab	1	Different lines	39	ORR 22%; OS 11.4 m; PFS 1.9 m	Bang, *ASCO 2015*
PD-L1	Avelumab	1b	pretreated	20Jpn	ORR15%PFS 11.6w	Yamada, *ASCO 2015*
	Durvalumab (MEDI4736)	1	pretreated	16	ORR 25%	Segal, *ASCO 2014*
	Atezolizumab	1	pretreated	1	1 PR	Herbst, *ASCO 2013*

■ pts with PD-L1 staining in stroma or ≥1% of tumor cells.

Correlation of PD-L1 and RR

Alsina M. Targ Oncol Feb, 2016

Ipi + Nivo active in pre-treated gastric cancers



Adapted from poster by Yelena Jangigian, et al
ASCO 2016, 6/4 Poster discussion

Conclusions

The characterization of oesophageal and gastric cancer into subtype based on genotype has evolved in the last decade.

The molecular landscapes of gastroesophageal cancer provide a guide to assist the development of new drugs and their combination.

Trastuzumab is the only approved treatment for gastroesophageal cancer that overespress HER2.

Ramucirumab, anti –VEGFr therapy is the first biological treatment to produce survival benefit in an unselected population of pts.

The role of biomarker-driven targeted therapy has been investigated in the metastatic and in the perioperative setting.