

Progress in Gastric Cancer Therapy

IN SCIENTIA SALUS
Heilung durch Wissenschaft



Florian Lordick, M.D. – Heidelberg, Germany
National Center for Tumor Diseases

EORTC
ESMO

Interactive Question 1

48-year-old female, your surgeon is calling you!
uT3 Nx signet ring cell carcinoma of the corpus and antrum
Laparoscopy: no peritoneal carcinomatosis, resectable tumor

- Proceed with resection, then adjuvant RCTx
- Proceed with resection, then adjuvant CTx
- Stop the procedure and start with neoadjuvant CTx

Interactive Question 2

72-year-old fit male, your assistant is calling you!
uT3 Nx M1 (hep) intestinal type carcinoma of the cardia, minor dysphagia
ECOG 1

- Palliative resection
- Primary systemic treatment with DCF type CTx (docetaxel, cisplatin, 5-FU)
- Primary systemic treatment with XP type CTx (capecitabine, cisplatin)
- other treatment

Localized Disease

Surgery

**Risk Factors for Post-operative Mortality
in Surgery for Gastric Cancer**

| | p-value |
|--------------------------------|---------|
| • Karnofsky Index | 0.0001 |
| • Concomitant diseases | 0.0001 |
| • Lymph node metastases | 0.001 |
| • Tumor diameter | 0.001 |
| • Experience of surgical dept. | 0.001 |
| • Age | 0.026 |

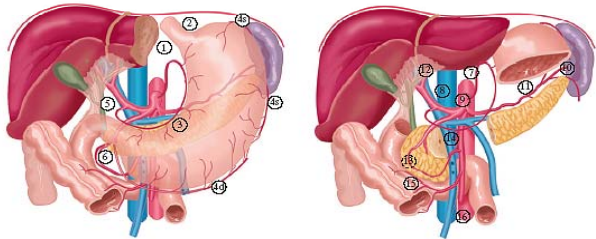
Theodor Billroth operating in the Auditorium of the Allgemeine Krankenhaus, Vienna (1889). Painting by Anton F. Seitzmann.

J. Rüdiger Siewert operating in the Klinikum rechts der Isar, Technische Universität München (2004)

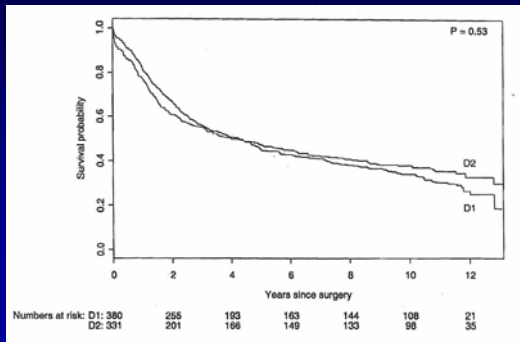
Böttcher et al. Chirurg 1994; 65:298-306

Surgery- Lymphadenectomy

D1 nodes adjacent to the stomach
D2 + branches celiac axis
D3 nodes along the aorta

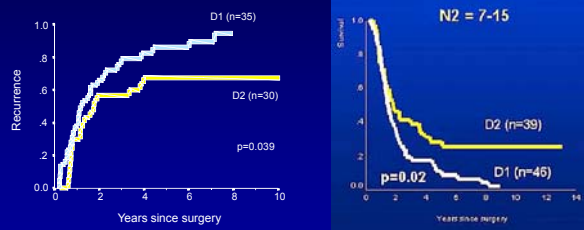


D1 versus D2 Lymphadenectomy Overall Survival



Hartgrink et al., J Clin Oncol 2004;22:2069-2077

D1 versus D2 Lymphadenectomy Relapse and Survival for N2 Patients



Dutch D1D2 trial

Hartgrink et al., J Clin Oncol 2004;22:2069-2077

Surgery

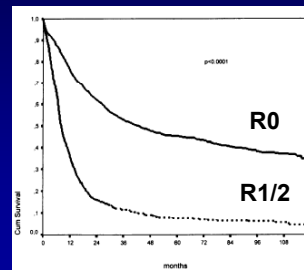
'In conclusion, the standard recommendation for surgery of resectable gastric/GE junction adenocarcinoma could be free-margin surgery with at least D1 resection combined with removal of a minimum of 15 lymph nodes.'



EORTC Recommendation. Van Cutsem et al. Eur J Cancer 2008;44:182-194

Gastric Cancer

Prognosis after resection
German Gastric Cancer Study (n=1654)

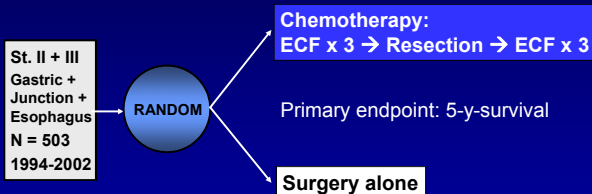


| Category | R0-Status (%) |
|----------|---------------|
| pT1 | 98.2 |
| pT2 | 86.7 |
| pT3 | 59.7 |
| pT4 | 40.6 |

Siewert et al. Ann Surg 1998; 228: 449-461

Peri-operative Chemotherapy

MAGIC-Trial



*ECF: Epirubicin 50mg/m2 d1, Cisplatin 60mg/m2 d1, 5-FU 200mg/m2/d cont iv, qd 22

Cunningham D et al. N Engl J Med 2006;355:11-20

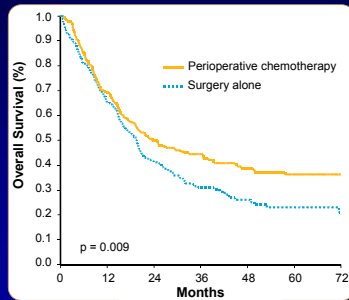
MAGIC Trial

Feasibility

| | CTX | SURG |
|------------------------------|-----|------|
| Pre-operative CTX completed | 88% | |
| Post-operative CTX started | 55% | |
| All 6 cycles completed | 43% | |
| Post-operative complications | 46% | 46% |
| Post-operative deaths (30 d) | 6% | 6% |

Cunningham D et al. N Engl J Med 2006;355:11-20

MAGIC Trial Survival



5-y-OS
36%
23%

Cunningham D et al. N Engl J Med 2006;355:11-20

ACCORD Trial

FNLCC 94012 FFCD 9703

St. II + III
Gastric +
Junction
N = 224
1995-2003

RANDOM

Chemotherapy:
CF x 2 → Resection → CF x 4

Primary endpoint: Survival
20% → 35% after 5 years, $\alpha=5\%$, $\beta=20\%$

Surgery alone

*CF: Cisplatin 100mg/m² d1, 5-FU 800mg/m²/d d1-5, qd 28

Boige V. et al. J Clin Oncol 2007; 25(18S):4510

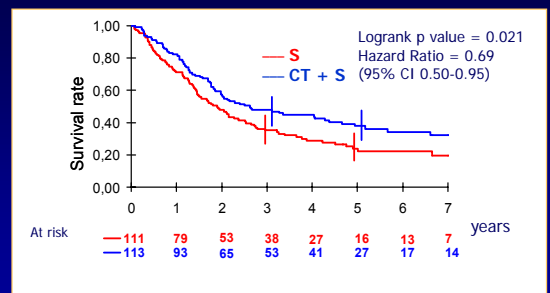
ACCORD Trial

Downsizing and resectability

| | Surgery alone (n=111) | CTx + Surgery (n=113) |
|-------------------------------|--------------------------|--------------------------|
| (y)pT category | | |
| - T0-2 | 32% | 42% |
| - T3/4 | 68% | 58% |
| (y)pN category | | |
| - N0 | 20% | 33% |
| - N1 | 80% | 67% |
| R0 resection p=0.04 | 73% | 84% |

Boige V. et al. J Clin Oncol 2007; 25(18S):4510

ACCORD Trial Survival



5-year-survival: 24% (16-33%) vs 38% (28-47%)

Boige V. et al. J Clin Oncol 2007; 25(18S):4510

Gastric Cancer – Peri-operative Chemotherapy

What has become clear?

Peri-operative chemotherapy

- is safe
- but post-op. CTx is more difficult to administer than pre-op. CTx
- pre-op. CTx reduces the tumor size
- and increases the R0 resection rate
- the peri-operative CTx concept improves the chance for cure

Adjuvant Chemotherapy

- Most studies carried out in the Western hemisphere are negative
- The effect seems to be slightly better for N+ disease
- Meta-analyses show, if any, only marginally positive results

| Meta-analyses | Studies (n) | Patients (n) | Odds ratio (CI) |
|---------------|-------------|--------------|------------------|
| Hermans 1993 | 11 | 2096 | 0.88 (0.78-1.08) |
| Earle 1999 | 13 | 1990 | 0.80 (0.66-0.97) |
| Mari 2000 | 21 | 3658 | 0.82 (0.75-0.89) |
| Janunger 2002 | 21 | 3962 | 0.84 (0.74-0.96) |

→ Adjuvant chemotherapy is not a standard of care

Adjuvant Chemotherapy

ATCS-GC Trial

St. II + III
(90% nodal+)
D2 resection
R0
n = 1059
(2001-2004)



Chemotherapy
S1 80-120mg/m²: 12 months

Primary endpoint: survival
HR 0.70; $\alpha=0.05$; power = 80%

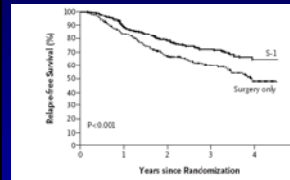
Observation

*S1 (Tegafur, Gimeracil, Oteracil): 80mg/m² d1-28, qd 43

Sakuramoto S et al. *N Engl J Med* 2007;357:1810-1820

Japanese Trial

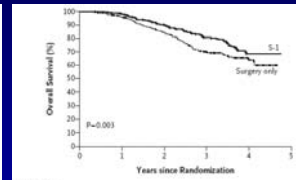
Recurrence-free Survival



No. at Risk
S-1 529 483 290 145 25
Surgery only 530 437 252 111 21

HR = 0.62 (95% CI, 0.50 to 0.77)
p < 0.001

Overall Survival



No. at Risk
S-1 529 515 304 196 46
Surgery only 530 504 312 183 40

HR = 0.68 (95% CI, 0.52 to 0.87)
p = 0.003

Sakuramoto S et al. *N Engl J Med* 2007;357:1810-1820

Adjuvant Chemotherapy

- Japan: Adjuvant S-1 standard of care in stage II and III tumors
- Western world: no proof of a survival advantage for adjuvant CTx
- Adjuvant S-1 should be re-assessed in a Western population

Adjuvant Chemoradiation

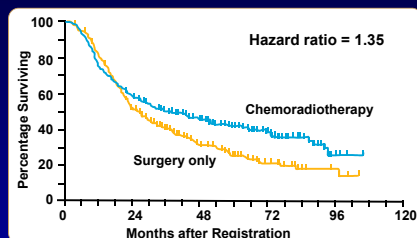
SWOG 9008 / INT 0116



Chemotherapy
Leucovorin 20mg/m² d1-5, 5-FU 425mg/m² d1-5, qd28
Modification cyc 2: Leucovorin 20mg/m² d1-4, 5-FU 400mg/m² d1-4
Modification cyc 3: Leucovorin 20mg/m² d1-3, 5-FU 400mg/m² d1-3

Macdonald et al., *N Engl J Med* 2001; 345: 725-730

Adjuvant Chemoradiation SWOG 9008 / INT 0116



But:
D2 lymphadenectomy 10%
D1 lymphadenectomy 36%
D0 lymphadenectomy 54%

Macdonald et al., *N Engl J Med* 2001; 345: 725-730

Adjuvant Chemoradiation SWOG 9008 / INT 0116

Subgroup analysis

- 54% D0: Effect
- 36% D1: Effect
- 10% D2: No Effect

Macdonald et al., *Proc WGCIC* 2004; abstr 85

- Does chemoradiation compensate for sub-optimal surgery?
- Survival advantage only in sub-optimally resected patients?

Adjuvant Chemoradiation

- Standard of care in the U.S.
- Europe: not accepted as standard of care
- Recommended after less than 15 removed lymph nodes
- Is currently re-evaluated after optimal resection (CRITICS study)

Advanced Disease

Chemotherapy in Advanced Gastric Cancer

What have we learned in the past 15 years?

Wagner AD et al. JCO 2006;24:2902-9

- Chemotherapy is superior to "Best supportive care"
- 5-FU-based combinations are better than single agent 5-FU
- There is a benefit to using cisplatin
- There is a potential benefit of adding anthracyclines

Chemotherapy in Advanced Gastric Cancer

Role of new chemotherapeutic agents

- Docetaxel
 - Irinotecan
 - S-1
 - Capecitabine
 - Oxaliplatin
- Superiority study designs
- Non-inferiority study designs

Docetaxel: DCF versus CF TAX 325

R
A
N
D
O
M

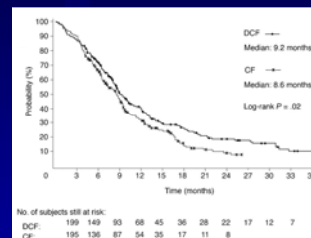
Docetaxel 75mg/m² d1
Cisplatin 75mg/m² d1
5-FU 750mg/m² d1-5
q3w

Primary Endpoint: Time to progression (superiority)

Cisplatin 100mg/m² d1
5-FU 1000mg/m² d1-5
q4w

Van Cutsem et al. J Clin Oncol 2006;24:4991-4991

Docetaxel (TAX 325): DCF versus CF



Response rate
37% vs 25% p=0.01

Time to progression
5.6 vs 3.7 months p<0.01

Overall survival
9.2 vs 8.6 months p=0.02

2-year survival
18.4 vs 8.8 months p=0.02

Kaplan-Meier analysis: Overall survival

Van Cutsem et al. J Clin Oncol 2006;24:4991-4991

Tax 325: DCF versus CF Quality of Life and Clinical Benefit

Time until definitive deterioration of Karnofsky-Performance-Status

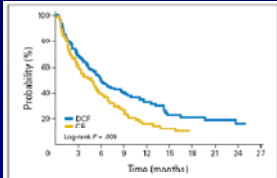


Fig 1. Kaplan-Meier curve of the primary clinical benefit parameter: time to definitive worsening of Karnofsky performance status (KPS). CF, cisplatin and fluorouracil; DCF, docetaxel, cisplatin, and fluorouracil.

Ajani et al. *J Clin Oncol* 2007; 25: 3205-3209

Time until definitive deterioration of EORTC Global QOL Score

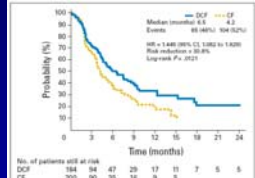


Fig 1. Kaplan-Meier curve of time to 5% definitive deterioration of global health status. CF, cisplatin, fluorouracil, cisplatin, and fluorouracil; DCF, docetaxel, cisplatin, and fluorouracil.

Ajani et al. *J Clin Oncol* 2007; 25: 3210-3216

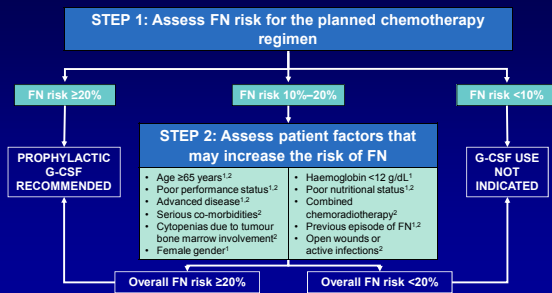
Tax 325: DCF versus CF Hematological Toxicities

| Regardless of secondary prophylactic treatment | % of evaluable patients | |
|--|-------------------------|------------|
| | DCF (n=221) | CF (n=224) |
| Neutropenia | 82.3 | 56.8 |
| Anaemia | 18.2 | 25.6 |
| Thrombocytopenia | 7.7 | 13.5 |
| Febrile neutropenia/neutropenic infection | 30.0 | 13.5 |

| -/+ secondary prophylactic G-CSF | - | | + | |
|--|---------|--------|---------|--------|
| | (n=219) | (n=41) | (n=222) | (n=20) |
| % of patients with febrile neutropenia/neutropenic infection | 28.3 | 12.2 | 13.1 | 15.0 |

Van Cutsem et al. *J Clin Oncol* 2006;24:4991-4991

DCF regimen: primary G-CSF prophylaxis recommended



This algorithm represents a combined interpretation of the 2006 G-CSF guidelines of EORTC and ASCO

¹ Apro MS, et al. *Eur J Cancer* 2006; 42:2433–2453.
² Smith TJ, et al. *J Clin Oncol* 2006; 24:3187–3205.

Modified Docetaxel-Platin-(FU) Combinations

| Study | Phase | Abstract |
|---|-------|--|
| GastroTax-1 TAX 40mg/m ² + Cisplatin 40mg/m ² d1 + LV 200mg/m ² + 5FU 2000mg/m ² d1+8, qd14 | 2 | Lorenzen et al. <i>Ann Oncol</i> 2007 |
| ATTAX: Weekly TCF vs weekly TX TAX 30mg/m ² d1+8 + Cisplatin 60mg/m ² d1 + 5FU 200mg/m ² c.i.v., qd22 versus TAX 30mg/m ² d1+8 + Capecitabine 1600mg/m ² d1-14, qd22 | 2 | Tebutt et al. <i>ASCO</i> 2007 |
| FLO-T TAX 50mg/m ² + Oxaliplatin 85mg/m ² d1 + LV 200mg/m ² + 5FU 2600mg/m ² d1, qd14 | 2 | Al-Batran et al. <i>Ann Oncol</i> 2008 |
| Docetaxel + FOLFOX-6 TAX 50mg/m ² + Oxaliplatin 85mg/m ² d1 + LV 400mg/m ² d1 + 5FU Bolus 400mg/m ² d1 + 3000mg/m ² c.i.v. d1-2, qd14 | 2 | Ajani et al. <i>ASCO</i> 2007 |
| Docetaxel + Oxaliplatin TAX 60mg/m ² + Oxaliplatin 130mg/m ² d1, qd 22 | 2 | Richards et al. <i>Ann Oncol</i> 2005 |
| Docetaxel + Oxaliplatin TAX 75mg/m ² + Oxaliplatin 80mg/m ² d1, qd 22 | 2 | Barone et al. <i>Gastric Cancer</i> 2007 |
| GATE: TE vs. TEF vs. TEX | 1-2 | Study ongoing |

Chemotherapy in Advanced Gastric Cancer

- Docetaxel DCF superior to CF
- Irinotecan Irinotecan 5-FU/FS not superior to CF
- S-1 S1 plus cisplatin not superior to CF
- Capecitabine } equally effective as compared to 5-FU
- Oxaliplatin } equally effective as compared to Cisplatin

Van Cutsem et al. *J Clin Oncol* 2006;24:4991-4991
Dank et al. *Ann Oncol* 2006; 19: 1450-1457
Ajani JA et al. *Proc GI Symposium* 2008; abstract 8
Kang et al. *Ann Oncol* 2009; Jan 19 [Epub ahead of print]
Cunningham D et al. *N Engl J Med* 2008;358:36-46
Al-Batran et al. *J Clin Oncol* 2008; 26: 1436-1442

Chemotherapy in Advanced Gastric Cancer

New options – new choices

- Docetaxel adds activity but also some toxicity. There is a well documented clinical benefit from adding docetaxel to platin/5-FU DCF is an approved regimen. Alternative regimens are being investigated
- Oxaliplatin equals cisplatin in terms of efficacy and reduces overall toxicity. FOLFOX is active.
- Capecitabine equals 5-FU infusions. XP, ECX and EOX are approved new regimens with proven efficacy

Biologically targeted drugs

Bio-chemotherapy in Gastric Cancer

Randomized phase III trials

Growth factor receptor antagonists

| | |
|-------------|---|
| Trastuzumab | TOGA: Cisplatin/Capecitabine +/- Trastuzumab (Herceptin) in Her2 overexpressing advanced gastric cancer |
| Cetuximab | EXPAND: Cisplatin/Capecitabine +/- Cetuximab (Erbix) in advanced gastric cancer |
| Panitumumab | REAL-3: EOX +/- Panitumumab in advanced gastric cancer |
| Lapatinib | LOGIC: Oxaliplatin/Capecitabine +/- Lapatinib (Herceptin) in Her2 positive advanced gastric cancer |
| | Paclitaxel +/- Lapatinib (Herceptin) in Her2 amplified advanced and pretreated gastric cancer |

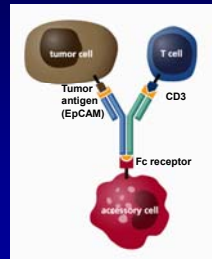
Anti-angiogenic drugs

| | |
|-------------|---|
| Bevacizumab | AVAGAST: Cisplatin/Capecitabine +/- Bevacizumab |
| Bevacizumab | MAGIC-B: Perioperative ECX +/- Bevacizumab (Avastin) in resectable gastric cancer |

Bio-chemotherapy in Gastric Cancer i.p. Catumaxumab – a bispecific monoclonal Ab

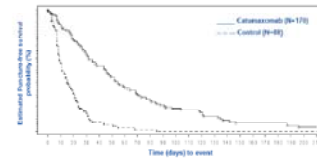
Binds to three cell types:

- tumor cells via EpCAM
- T-lymphocytes via CD3
- FC γ R I positive accessory immune cells
 - macrophages, dendritic cells
 - => phagocytosis
- FC γ R III positive accessory immune cells
 - natural killer [NK] cells
 - => ADCC



Lordick et al. *Expert Opin Biol Ther* 2008;8:1407-1415

Bio-chemotherapy in Gastric Cancer i.p. Catumaxumab – a bispecific monoclonal Ab



Median Puncture Free Survival in days (d)

| | Pooled Population | Ovarian Cancer Stratum | Non-Ovarian Cancer Stratum |
|-------------------------|-------------------|------------------------|----------------------------|
| Catumaxumab | 45d | 52 | 37 |
| Control | 11 | 11 | 14 |
| Difference [Median] | 35 [4.2] | 41 [4.7] | 23 [2.6] |
| p-value (log-rank-test) | p < 0.0001 | p < 0.0001 | p < 0.0001 |

Parsons et al. ASCO 2008; abstract 3000

Gastric Cancer Therapy 2009

- Peri-operative treatment for locally advanced tumors: standard of care
- New active drugs, new reference regimen
 - Docetaxel
 - Capecitabine
 - Oxaliplatin
- Important new trials on “biologics”