

Esophageal and GEJ Cancer: What is the Optimal Preop Therapy?

David H. Ilson, MD, PhD

Gastrointestinal Oncology Service

Memorial Sloan-Kettering Cancer Center

Esophageal and GEJ Cancer: Adjuvant Therapy

- **Survival with surgery alone is poor**
 - < 20-40%
- **Adjuvant trials in esophageal cancer have evaluated preop therapy**
 - Preop Chemo
 - Preop Chemo + radiotherapy
 - Most common U.S. practice

Adjuvant Chemo: Esophagogastric Adenocarcinoma

- Addition of chemo has MODEST impact
- Periop Chemo vs Surgery
 - MAGIC, FFCD, OEO2
 - HR 0.67-0.86, 5 yr survival Δ 5%-15%
- Postop Chemo vs Surgery
 - ACTGS, CLASSIC
 - HR 0.66-0.67, 5 yr survival Δ 9-10%

Cunningham NEJM 355: 11; 2006; Ychou JCO 29: 1715; 2011; Allum JCO 27: 5062; 2009; Sasako JCO 29: 4387; 2011 ; Noh Lancet Oncol 15: 1389; 2014

Impact of Postop RT in Gastric Cancer Depends on Surgical Quality

- **INT 116**

- 54% < D1 resection
- 10% had D2

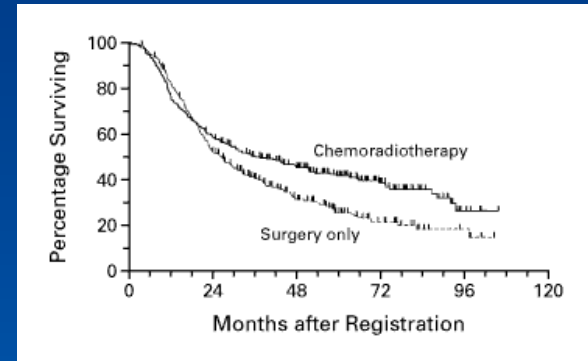
- **ARTIST**

- 100% D2 resection
- ? Benefit in intestinal, N+

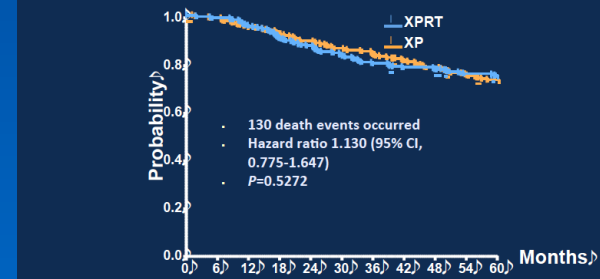
- **CRITICS**

- 87% D1-D2 resection

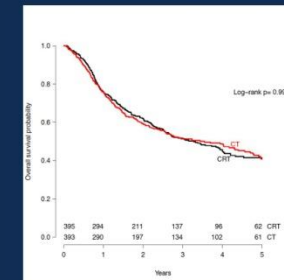
Macdonald NEJM 345:725; 2001; Park JCO 33:3030; 2015 Verheij JCO 34: 2016 (Abs 4000)



Overall Survival



Results: Overall Survival



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

Why Include Preop RT in Esophageal and GEJ Cancer?

- **Ensure R0 Resection**
- **Reduce Local Recurrence**
- **What are the data for Preop Chemo?**
 - Older studies
 - Contemporary Studies
- **The same results are obtained despite 30 years of trials!**

INT 113: Preop CF x 3, Post op CF x 2: Overall Survival

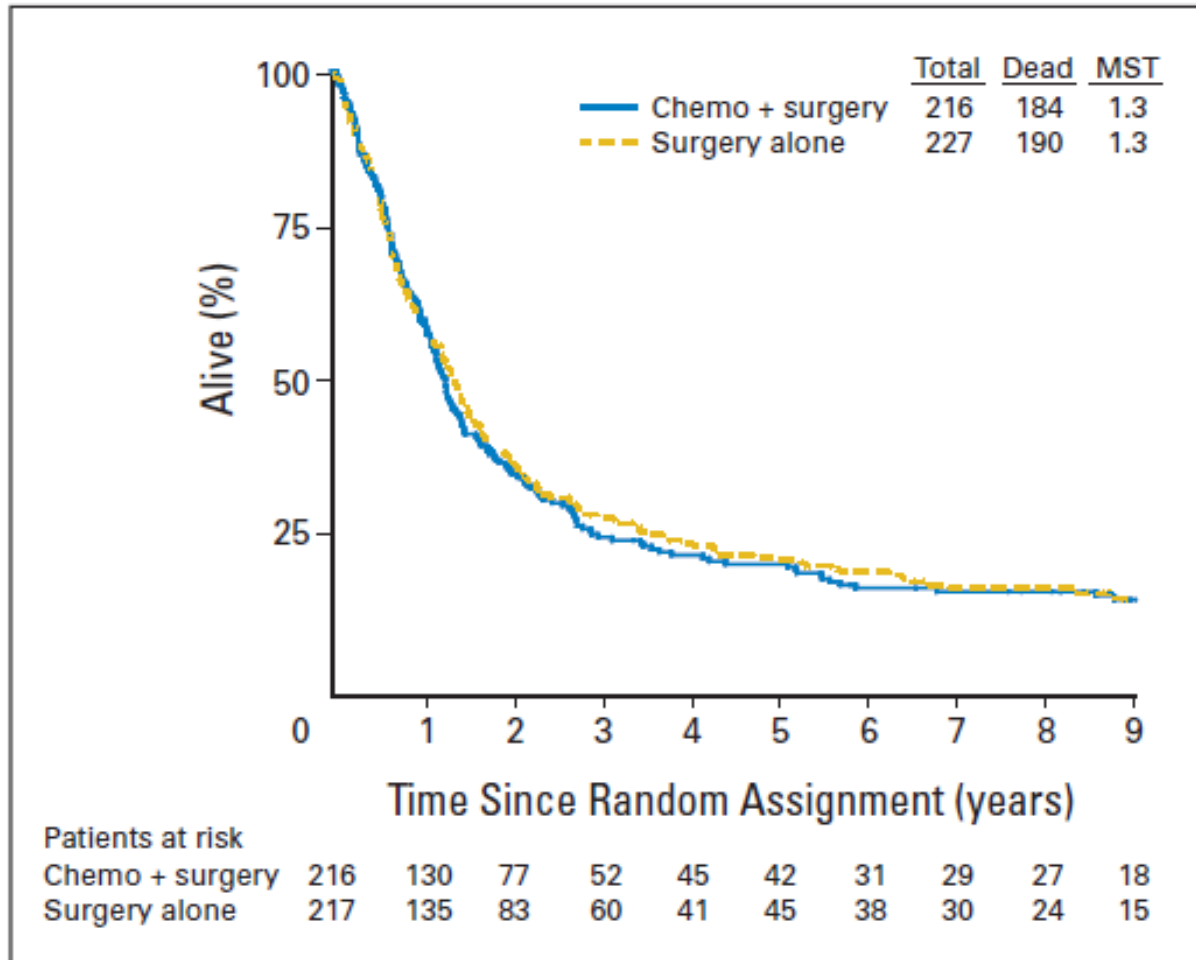


Fig 1. Overall survival by study arm for chemotherapy followed by surgery versus surgery only. MST, median survival time.

INT 113: Resection Type

Chemotherapy +

Surgery

Surgery

| Variable | No. of Patients | % | No. of Patients | % |
|---------------------|-----------------|-----|-----------------|-----|
| Eligible patients | 227 | | 216 | |
| Surgery performed | 218 | | 180 | |
| Resections achieved | | | | |
| R0 | 135 | 59% | 135 | 63% |
| R1 | 34 | 15% | 9 | 4% |
| R2 | 33 | 15% | 24 | 11% |
| None | 25 | 11% | 48 | 22% |
| Postop deaths | 13 | 6% | 10 | 6% |

INT 113: Outcome by Resection

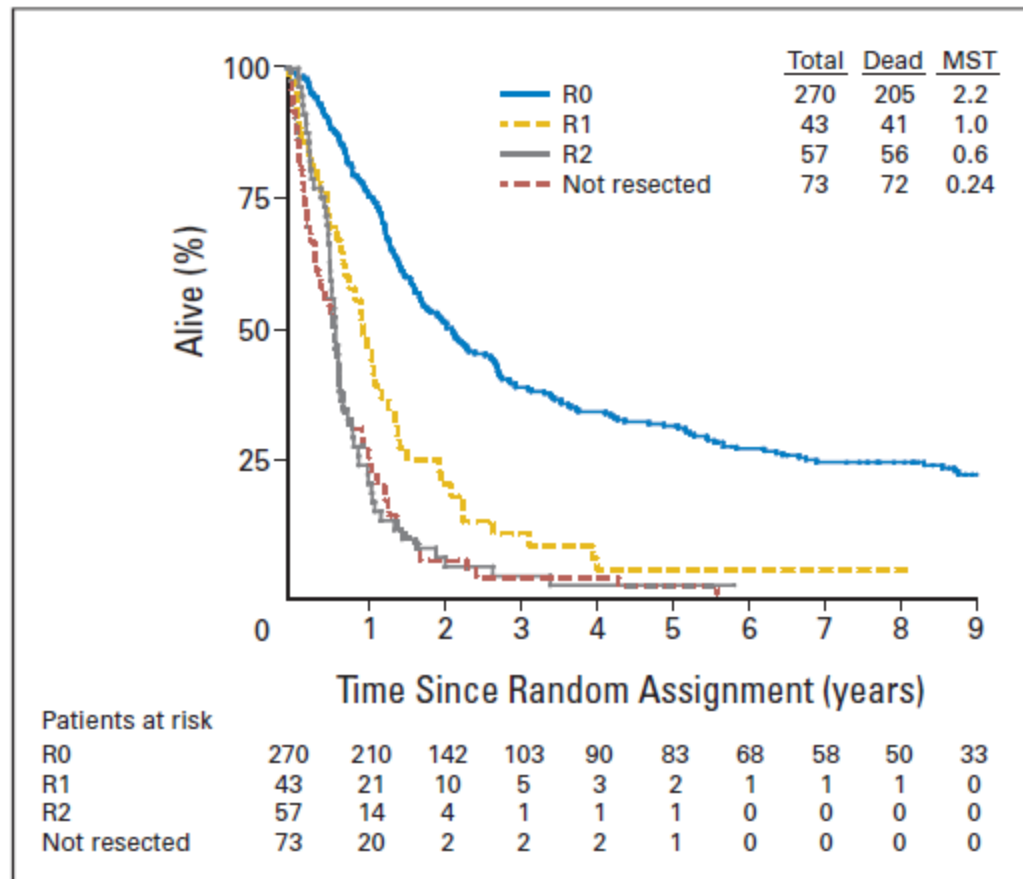
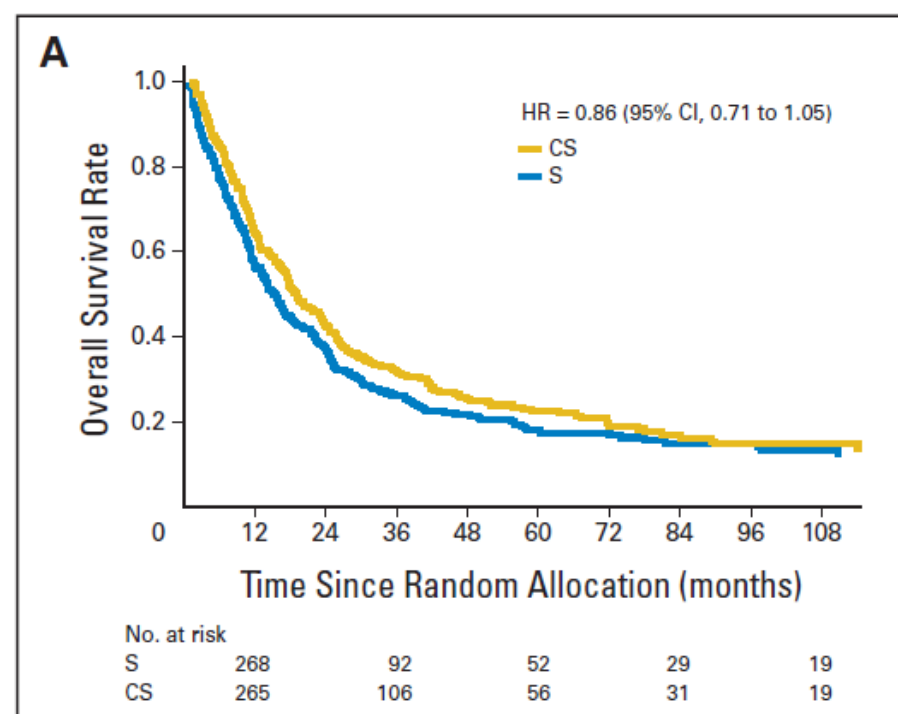
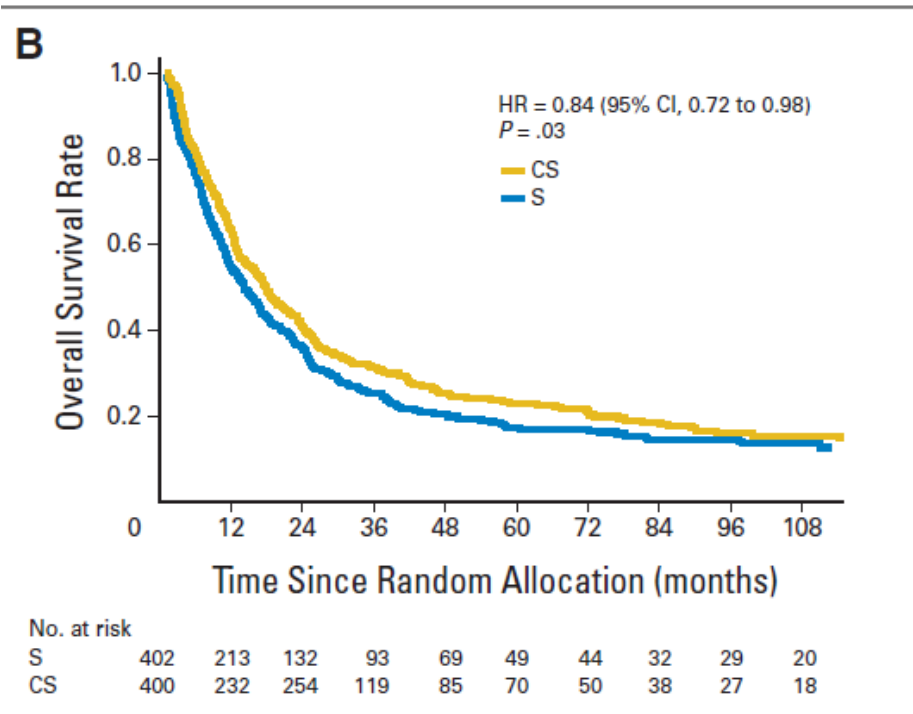


Fig 2. Overall survival by type of resection. R0, complete resection with negative microscopical margins; R1, all gross disease resected but microscopical examination reveals positive margins; R2, gross residual visible tumor; MST, median survival time.

INT 113: Pattern of First Failure for R0 Patients

| Variable | Surgery | | Chemotherapy + Surgery | |
|---------------------------------|---------|-----|---------------------------|-----|
| | No. | % | No. | % |
| Resection R0 | 129 | | 126 | |
| Failure pattern | | | | |
| Local/regio nal only | 27 | 21% | 24 | 19% |
| Local/regio nal + distant | 10 | 8% | 10 | 8% |
| Distant only | 56 | 43% | 52 | 41% |
| Any local/regio nal | 37 | 29% | 34 | 27% |
| Any distant | 66 | 51% | 62 | 49% |

OEO2: Preop CF x 2: Updated Survival for All Patients, Adenocarcinoma

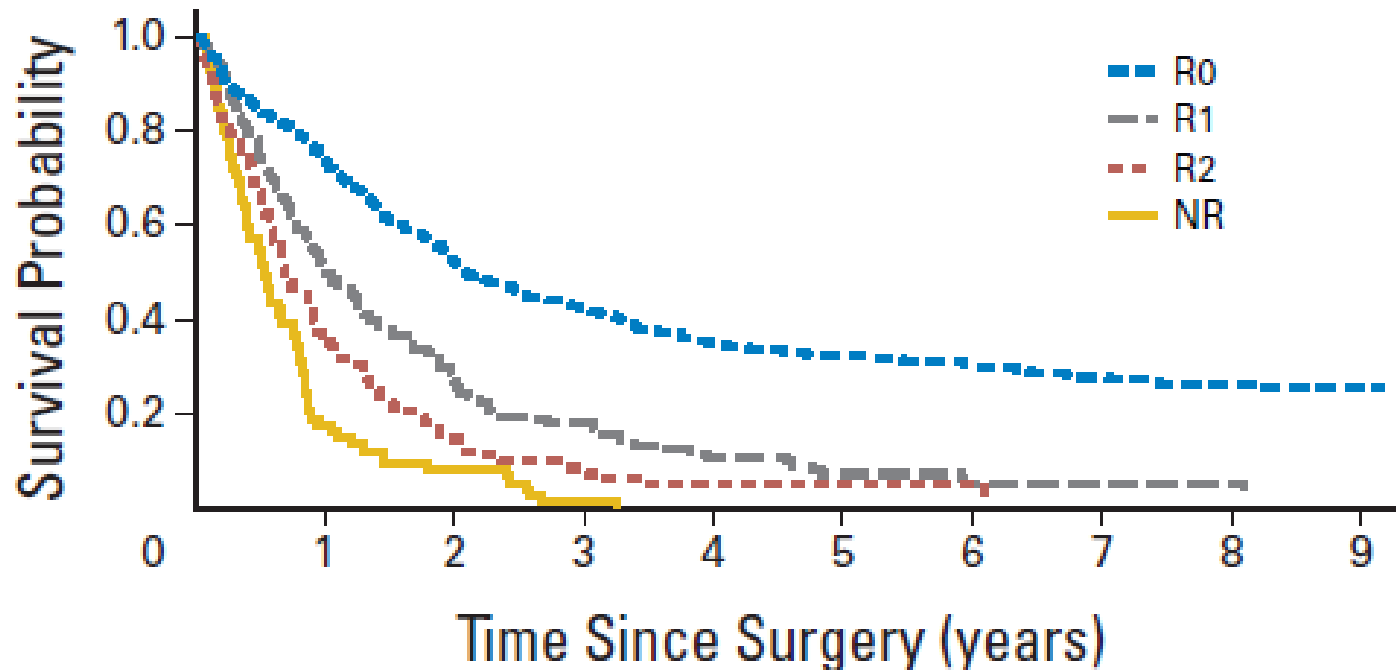


Survival Δ 5%

OEO2: Resection Type

| | CS group (n=400) | S group (n=402) | Total (n=802) |
|----------------------------------|-----------------------------|----------------------------|--------------------------|
| Extent of resection | | | |
| Macroscopically complete | 303 (78%) | 278 (70%) | 581 (74%) |
| Microscopically complete (R0) | 233 (60%) | 215 (54%) | 448 (57%) |
| Microscopically incomplete | 70 (18%) | 63 (16%) | 133 (17%) |
| Macroscopically incomplete | 35 (9%) | 52 (13%) | 87 (11%) |
| Not possible | 21 (5%) | 54 (14%) | 75 (10%) |
| No surgery | 31 (8%) | 13 (3%) | 44 (6%) |
| Extent not recorded | 2 | 2 | 4 |
| No surgical information received | 8 | 3 | 11 |
| Postoperative death* | 36 (10%) | 40 (10%) | 76 (10%) |

OEO2: Overall Survival by Resection Status



| | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|----|----|----|----|----|
| R0 | 396 | 290 | 205 | 162 | 122 | 96 | 78 | 60 | 78 | 33 |
| R1 | 141 | 72 | 38 | 24 | 13 | 8 | 5 | 4 | 4 | 2 |
| R2 | 88 | 32 | 12 | 6 | 4 | 4 | 2 | 1 | 1 | 1 |
| NR | 75 | 13 | 6 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

OEO2: Recurrence Pattern After Surgery

| Table 2. Nature of First Disease-Free Survival Event | | | | | | |
|---|---------|------|----------|------|-------|------|
| Event | S Group | | CS Group | | Total | |
| | No. | % | No. | % | No. | % |
| Disease free | 50 | 12.4 | 72 | 18.0 | 122 | 15.2 |
| Macroscopic residual disease | 52 | 12.9 | 36 | 9.0 | 88 | 15.2 |
| Resection not possible | 54 | 13.4 | 21 | 5.3 | 75 | 9.4 |
| Local recurrence | 49 | 12.2 | 46 | 11.5 | 95 | 11.8 |
| Distant metastases | 60 | 14.9 | 68 | 17.0 | 128 | 16 |
| Local recurrence and distant metastasis | 18 | 4.5 | 29 | 7.2 | 47 | 5.9 |
| Death from cancer but site of failure not specified | 69 | 17.2 | 71 | 17.8 | 140 | 17.5 |
| Death from other or unspecified cause | 50 | 12.4 | 57 | 14.2 | 107 | 13.3 |
| Total | 402 | 100 | 400 | 100 | 802 | 100 |

Abbreviations: S, surgery alone; CS, two cycles of combination cisplatin and fluorouracil before surgery.

Local Failure 17-19%

For RO Only: 31% for S, 32% for CS

FFCD: CF x 2-3 Pre, CF x 2-3 Post: Esophageal and Gastric

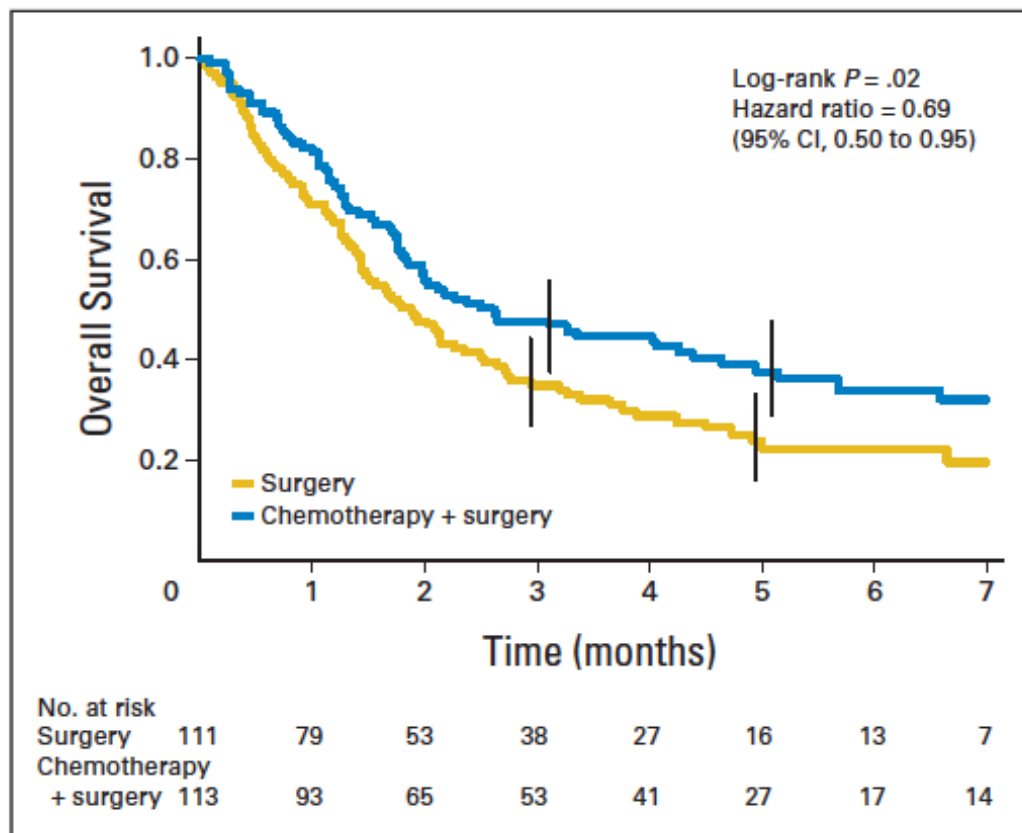


Fig 2. Kaplan-Meier curve showing overall survival from date of random assignment.

R0 Resection, Local Recurrence

- ❑ R0 Resection improved from 74%
➔ 84%
- ❑ Local recurrence all 24-26%
- ❑ Local recurrence R0: 29-36%

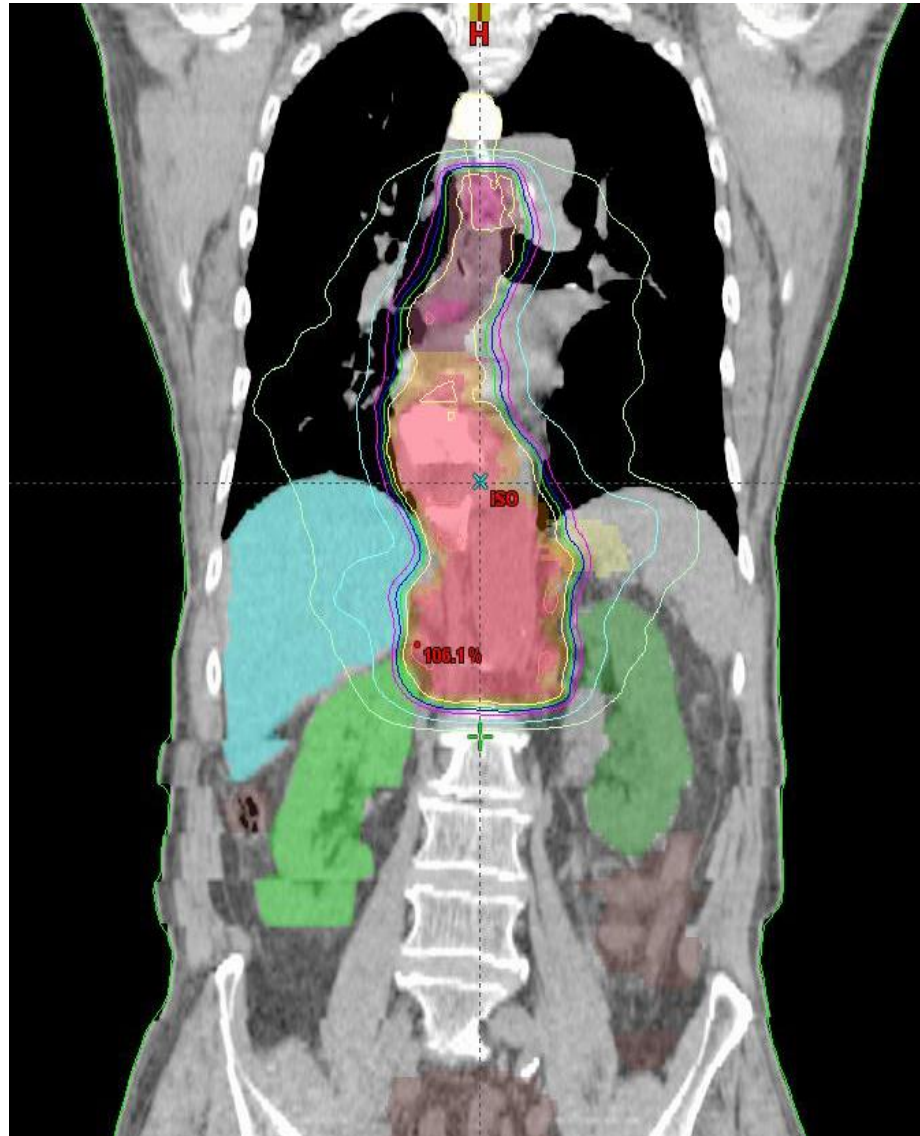
| Table 4. Patterns of Recurrence, Survival Status, and Cause of Death | | | | |
|---|-----------------------|------|----------------------|----|
| Parameter | CS Group (n = 113) | | S Group (n = 111) | |
| | No. | % | No. | % |
| Recurrence | 63 | 55 | 71 | 64 |
| Locoregional only | 14 | 12 | 9 | 8 |
| Distant only | 35 | 30 | 42 | 38 |
| Both | 14 | 12 | 20 | 18 |
| Death | 71 | 63.8 | 85 | 77 |
| Cancer related | 59 | | 70 | |
| Surgery related | 5 | | 5 | |
| Drug related | 1 | | 1* | |
| Other | 6 | | 9 | |

Abbreviations: CS, perioperative chemotherapy and surgery; S, surgery.
*One of the patients who received postoperative chemotherapy.

Salvage R1 Resection

- Anything Less than R0 Resection = Death
- INT 113: 18 of 34 Surgery alone R1 pts received post op chemo RT
 - 7 (21%) long term survivors
- OEO2: Pre op RT was allowed (given in 9%)
 - No comment on post op RT

Post-op Chemoradiation: GE junction: Larger post op
RT field poorly tolerated



What have we learned?

- **Preop Chemo Alone for Esophageal and GEJ Cancer**
- **R0 resection rate of 60%**
 - Consistent for trials treating only esophageal and GEJ Cancer
 - FFCD trial, included gastric, fewer pts, is outlier
- **In R0 patients local failure rate of 30%**
 - FFCD: 29%
- **Have we improved outcome in contemporary trials?**

Neoadjuvant Chemotherapy for Resectable Oesophageal and Junctional Adenocarcinoma: Results from the UK MRC OE05 trial

**Professor David Cunningham
on behalf of the OE05 Trial Management Group
Abstract #4002**



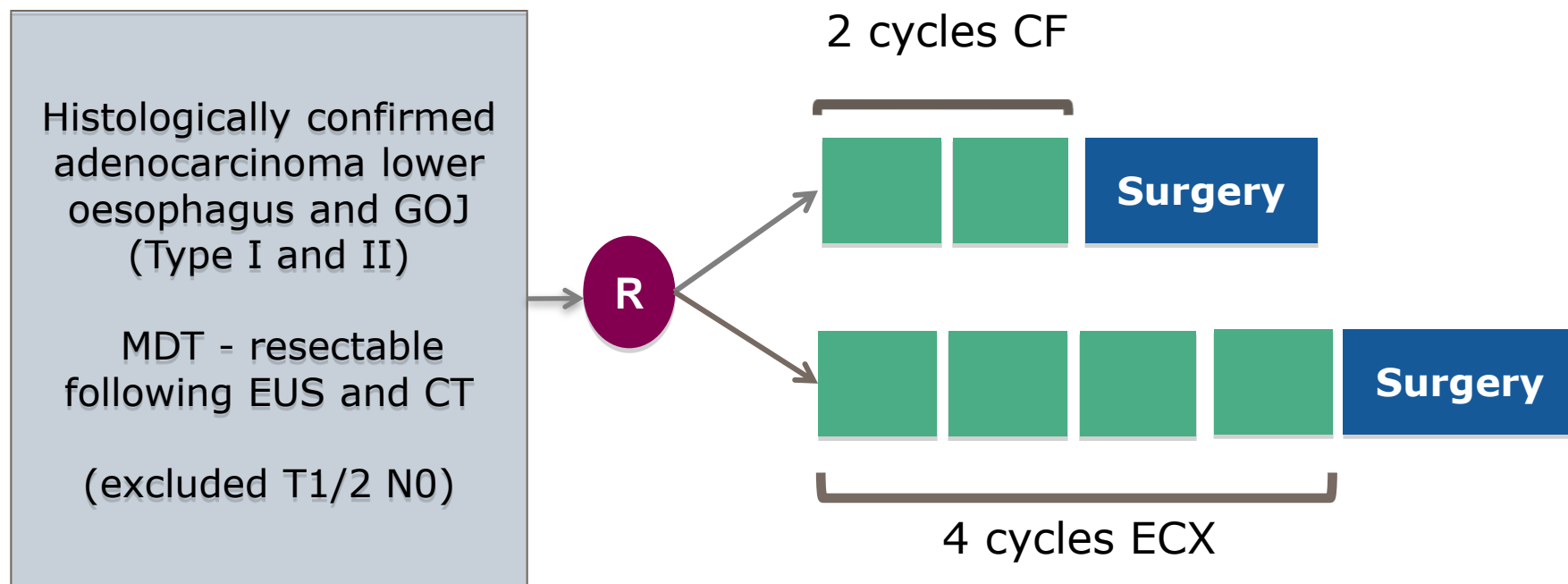
SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

PRESENTED AT:  **ASCO** Annual '15 Meeting

Cunningham JCO 33: 2015 (Abs 4002)

Presented By Geoffrey Ku at 2015 ASCO Annual Meeting

OE05 Trial Design



- **CF:** Two 3-weekly cycles of cisplatin ($80\text{mg}/\text{m}^2$ D1) and 5FU ($1\text{g}/\text{m}^2$ D 1-4)
- **ECX:** Four 3-weekly cycles of epirubicin ($50\text{mg}/\text{m}^2$ D1), cisplatin ($60\text{mg}/\text{m}^2$ D1) and capecitabine ($1250\text{mg}/\text{m}^2$ daily)

Baseline characteristics

| 897 patients, Jan 2005 – Oct 2011 72 UK centres | | CF (N=451) | | ECX (N=446) | |
|--|-------------------|---------------|-----|----------------|-----|
| | | n | % | n | % |
| Age (years) | Median (Range) | 62 (27 – 81) | | 62 (33 – 80) | |
| Sex | Male | 412 | 91% | 398 | 89% |
| WHO PS | 0 | 311 | 69% | 292 | 65% |
| | 1 | 140 | 31% | 154 | 35% |
| Stage (TNM6) | T1 N1 | 3 | 1% | 5 | 1% |
| | T2 N1 | 49 | 11% | 41 | 9% |
| | T3 N0 | 97 | 22% | 99 | 22% |
| | T3 N1 | 287 | 64% | 289 | 65% |
| | T4 N0 | 3 | 1% | 1 | <1% |
| | T4 N1 | 12 | 3% | 11 | 2% |
| Laparoscopy | Yes | 216 | 48% | 213 | 48% |
| PET | Yes | 271 | 60% | 270 | 61% |

87%T3

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76% N1

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Surgery

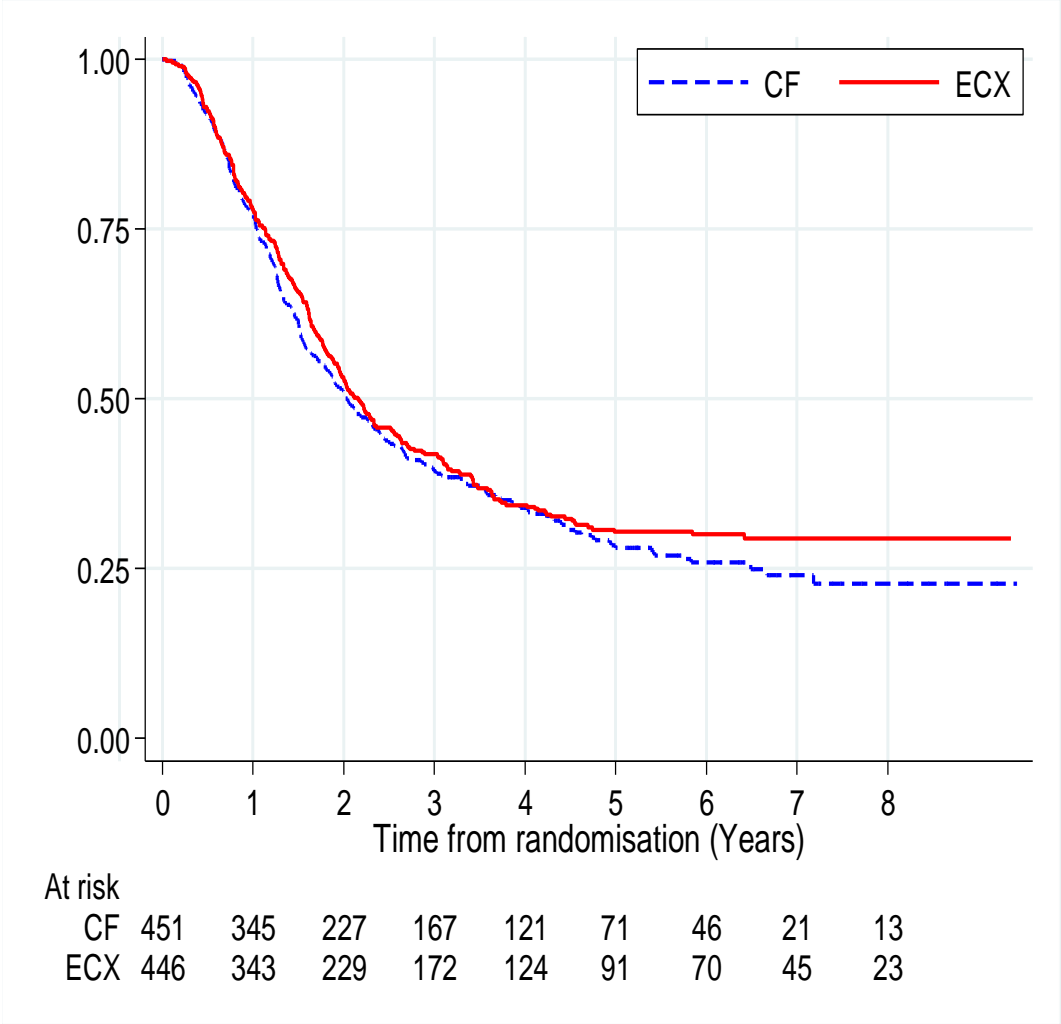
| | | CF (N=451) | | ECX (N=446) | | P-value |
|------------------------------|-----------------------------|---------------|-----|----------------|-----|---------|
| | | n | % | n | % | |
| Surgery performed | Yes | 411 | 91% | 387 | 87% | 0.043 |
| | No | 40 | 9% | 59 | 13% | |
| Reason for no surgery | PD, inoperable, comorbidity | 37 | | 44 | | |
| | Patient choice | 2 | | 7 | | |
| | Died | 1 | | 8 | | |
| Resection | Yes | 387 | 94% | 364 | 94% | 1.000 |
| | No | 24 | 6% | 23 | 6% | |

Pathology

| Data | | CF | | ECX | | P-value |
|---------------------|-------------|-----|--------------|-----|--------------|---------|
| | | n | % | n | % | |
| Mandard TRG | 1-3 | 43 | 15% | 93 | 32% | <0.001 |
| | 4-5 | 244 | 85% | 194 | 68% | |
| | Unavailable | 99 | | 75 | | |
| R0 resection | Yes | 211 | 59% (47%) | 222 | 67% (50%) | 0.058 |
| | No | 144 | 41% | 111 | 33% | |
| | Unavailable | 32 | | 29 | | |

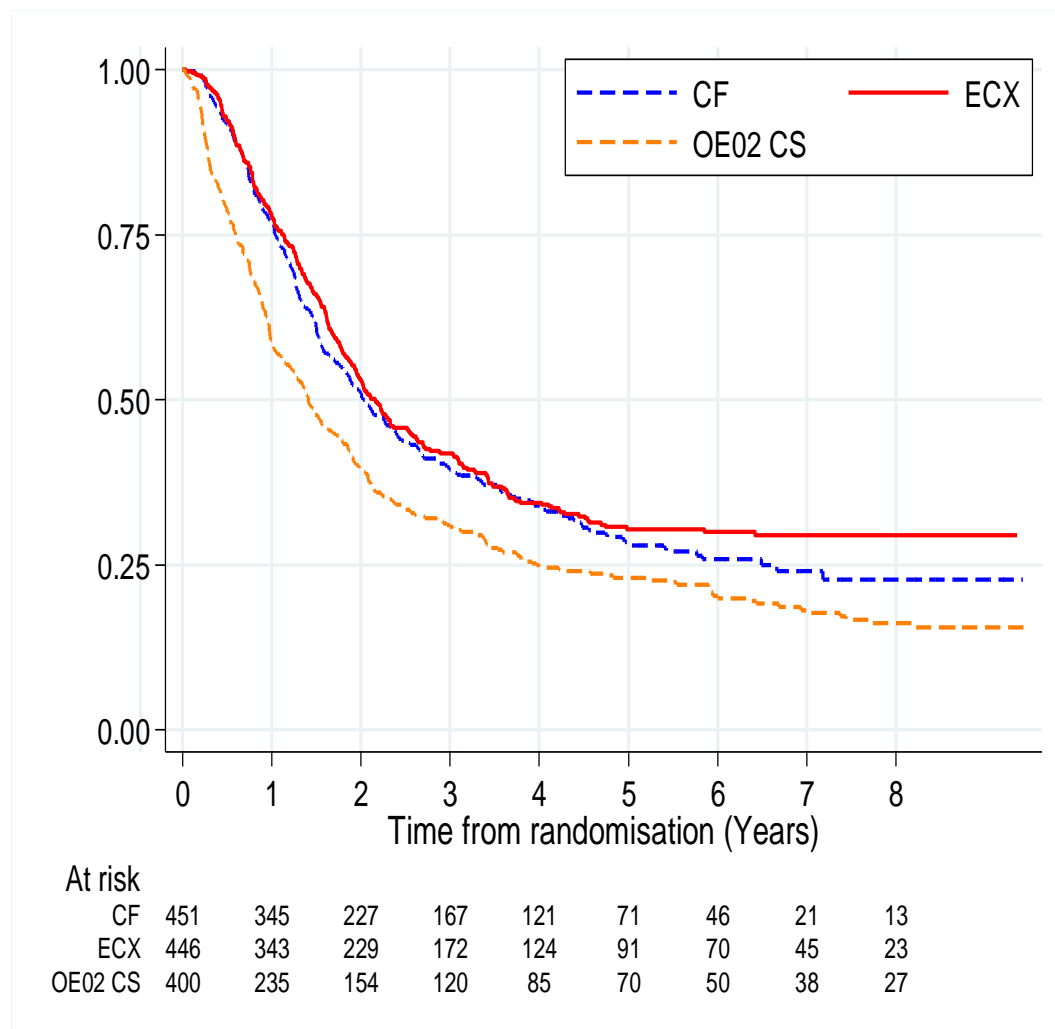
- Mandard grade 1 rate was 9 (3%) CF vs 32 (11%) ECX.
- A central pathology review of all patients is currently ongoing.

Overall survival



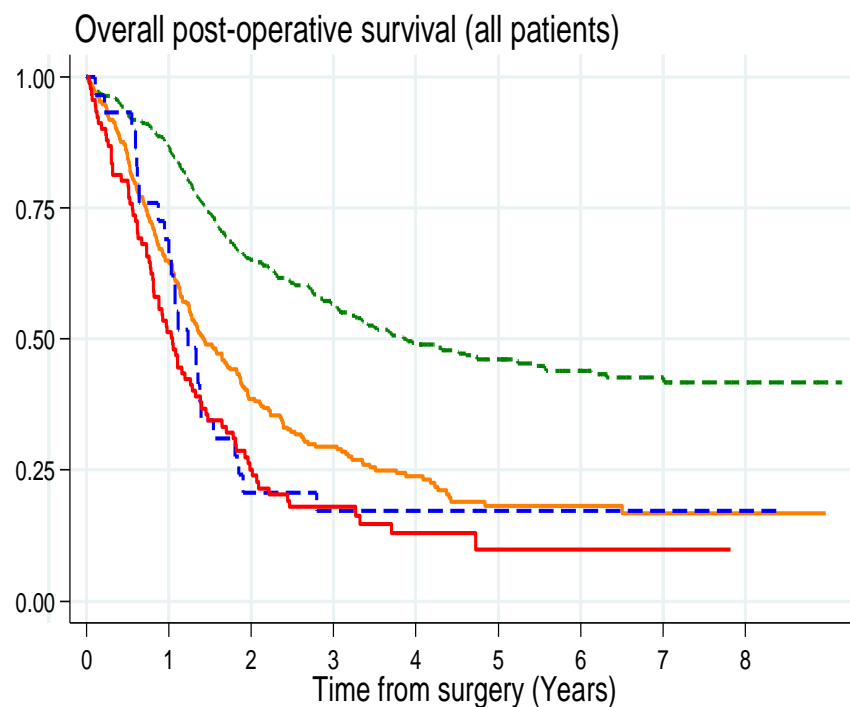
| Median survival (95% CI) | |
|--------------------------|-------------------|
| CF | 2.02 (1.80, 2.38) |
| ECX | 2.15 (1.93, 2.53) |
| HR | 0.92 (0.79, 1.08) |
| P-value | 0.8582 |
| 3-year survival (95% CI) | |
| CF | 39% (35%, 44%) |
| ECX | 42% (37%, 46%) |

Overall survival



| 3-year survival (95% CI) | |
|--------------------------|----------------|
| CF | 39% (35%, 44%) |
| ECX | 42% (37%, 46%) |
| OE02 CS | 31% (27%, 36%) |

Survival by R0 status



At risk

| | | | | | | | | | |
|-------------|-----|-----|-----|-----|-----|-----|----|----|----|
| R0 | 442 | 381 | 279 | 223 | 163 | 122 | 79 | 48 | 20 |
| R1 | 232 | 149 | 89 | 62 | 39 | 22 | 17 | 11 | 4 |
| R2 | 29 | 20 | 6 | 5 | 4 | 2 | 2 | 2 | 1 |
| Unavailable | 91 | 46 | 21 | 12 | 5 | 3 | 1 | 1 | 0 |

3-year survival (95% CI)

R0

57% (52%, 61%)

R1

30% (24%, 36%)

R2

17% (6%, 33%)

Unavailable

18% (11%, 27%)

HR (R0 vs others)

2.41 (2.02, 2.88)

P-value

<0.001

STO3: Preop Chemo in GEJ and Gastric Cancer: ECX + / - Bevacizumab

- **1063 pts**
- **63-64% esophagus or GEJ**
- **ECX x 3 cycles pre and post op**
- **+ / - Bevacizumab**
- **No survival benefit with Bevacizumab (median OS 34 mos, 3 year 48-50%)**
- **Higher leak rate with Bev, esophageal cancers**

Margin Status with Preop Chemo : ST03

- Counting all patients: R0 resection 57-59%
- Counting 80-84% were resected: 872 patients: R0 resection 74-75%

| | Patients | % R0 |
|------------|----------|------|
| Total | 872 | |
| Esophageal | 124 | 61% |
| Type 1 | 110 | 60% |
| Type 2 | 157 | 71% |
| Type 3 | 164 | 75% |
| Stomach | 317 | 87% |
| Eso/GEJ | 555 | 67% |

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ORIGINAL ARTICLE

Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer

P. van Hagen, M.C.C.M. Hulshof, J.J.B. van Lanschot, E.W. Steyerberg, M.I. van Berge Henegouwen, B.P.L. Wijnhoven, D.J. Richel, G.A.P. Nieuwenhuijzen, G.A.P. Hospers, J.J. Bonenkamp, M.A. Cuesta, R.J.B. Blaisse, O.R.C. Busch, F.J.W. ten Kate, G.-J. Creemers, C.J.A. Punt, J.T.M. Plukker, H.M.W. Verheul, E.J. Spillenaar Bilgen, H. van Dekken, M.J.C. van der Sangen, T. Rozema, K. Biermann, J.C. Beukema, A.H.M. Piet, C.M. van Rij, J.G. Reinders, H.W. Tilanus, and A. van der Gaast, for the CROSS Group*

| | M | T | W | T | F | S | S | M | T | W | T | F | S | S | M | T | W | T | F | S | S | M | T | W | T | F | S | S |
|-----|--------|-------|-------|-------|-------|-------|-------|--------|-------|-------|-------|-------|-------|-------|--------|-------|-------|-------|-------|-------|-------|--------|-------|-------|-------|-------|-------|-------|
| | Week 1 | | | | | | | Week 2 | | | | | | | Week 3 | | | | | | | Week 4 | | | | | | |
| | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
| XRT | ▼ | ▼ | ▼ | ▼ | ▼ | | | ▼ | ▼ | ▼ | ▼ | ▼ | | | ▼ | ▼ | ▼ | ▼ | ▼ | | | ▼ | ▼ | ▼ | ▼ | ▼ | | |
| CTX | ■ | | | | | | | ■ | | | | | | | ■ | | | | | | | ■ | | | | | | |

- Paclitaxel 50mg/m² + Carboplatin AUC=2 on days 1, 8, 15, 22 and 29
- Concurrent radiotherapy of 41.4 Gy in 23 fractions of 1.8 Gy
- Surgery within 6 weeks after completion of chemoradiotherapy (THE/TTE)

CROSS and OEO5 Demographics: Similar

| Tumor location — no. (%)† | | | |
|-----------------------------|----------|----------|----------|
| Esophagus | | | |
| Proximal third | 4 (2) | 4 (2) | |
| Middle third | 25 (14) | 24 (13) | |
| Distal third | 104 (58) | 107 (57) | |
| Esophagogastric junction | 39 (22) | 49 (26) | |
| Missing data | 6 (3) | 4 (2) | |
| Clinical T stage — no. (%)‡ | CROSS | | |
| cT1 | | 1 (1) | 1 (1) |
| cT2 | | 26 (15) | 35 (19) |
| cT3 | | 150 (84) | 147 (78) |
| cT4 | | 0 | 1 (1) |
| Could not be determined§ | | 1 (1) | 4 (2) |
| Clinical N stage — no. (%)¶ | | | |
| N0 | 59 (33) | 58 (31) | |
| N1 | 116 (65) | 120 (64) | |

T3:78-85%
N1:64-65%

| Stage (TNM6) | T1 N1 | 3 | 1% | 5 | 1% |
|--------------|-------|-----|-----|-----|-----|
| | T2 N1 | 49 | 11% | 41 | 9% |
| | T3 N0 | 97 | 22% | 99 | 22% |
| OEO5 | T3 N1 | 287 | 64% | 289 | 65% |
| | T4 N0 | 3 | 1% | 1 | <1% |
| | T4 N1 | 12 | 3% | 11 | 2% |

T3:87-88%
N1:77-79%

CROSS Trial: Resection rate and resection margins

Resection rate of all randomized patients

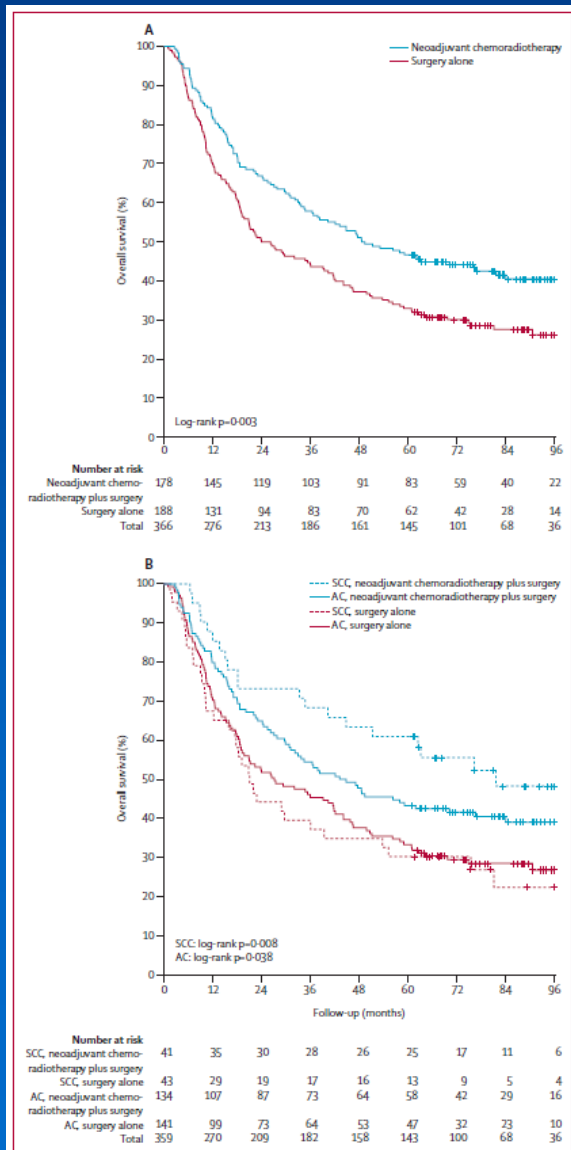
| Surgery alone | CRT + surgery |
|---------------|---------------|
| 186/188 (99%) | 168/178 (95%) |

Resection margins

| | Surgery alone | CRT + surgery | |
|--------|---------------|---------------|---------|
| R0 | 111/161 (69%) | 148/161 (92%) | p<0.002 |
| ITT R0 | 111/188 (59%) | 148/178 (83%) | |

R0 = no tumor within 1 mm of the resection margins

Overall Survival Improved with Chemo RT + Surgery



- 5-year survival 47% versus 34%

- Median survival 48.6 versus 24 months, HR 0.68, $p = 0.003$

- Squamous HR 0.48 ($p = 0.008$)

- Adeno HR 0.73 ($p = 0.038$)

Cross Trial: Patterns of Failure

| | # Pts. | Local Failure | Peritoneal | Distant Mets |
|---------------------|--------|---------------------|--------------------|--------------------|
| Neoadjuvant ChemoRT | 213 | 14% Δ 20% | 4% Δ 10% | 29% Δ 6% |
| Surgery | 161 | 34% | 14% | 35% |

Preop Chemo vs Chemo RT: Stahl

- EUS, laparoscopy staged pts
- Siewert I-III, T3-4 adenocarcinoma

| Arm | Pts | R0 | pCR | N0 | Median Survival | 3 yr OS | Local Control |
|----------|-----|-----|-----|-----|-----------------|-----------------|-----------------|
| Chemo | 59 | 70% | 2% | 37% | 21 mos | 28% | 59% |
| Chemo RT | 60 | 72% | 16% | 64% | 33 mos | 47% P = 0.07 | 77% P = 0.06 |

Stahl J Clin Oncol: 27: 836; 2009

What is Optimal Preop Therapy for Esophageal and GEJ Cancer?

- Chemo improves OS by 5-15%
- Adding RT to Chemo: is favored over chemo alone: increases R0, reduces local recurrence
- 30% local recurrence + / - Chemo after R0
- Poor rates of R0 resection with preop chemo
 - 1600 Eso/GEJ contemporary pts in UK trials
 - R0 still only 59-67%
 - EUS/PET/laparoscopic staging
 - Worst R0 rates in ESO/GEJ Type I-II tumors
- Consistent outcome 3 decades of studies
- **Less than R0 = DEATH**
- Chemo + RT is the optimal backbone for future studies

Are more trials needed? Ongoing Trials

- **FLOT4: FLOT x 8 vs ECF x 6, 714 patients**
 - Will adding a taxane improve survival?
 - Sequencing a taxane with 5-FU adjuvant: failed in gastric SAMIT and ITACA-S trials
 - Impact of higher path CR? R0 rates for primary site
 - OEO5: pCR 11% ECX > 3% CF: R0 67% > 59%
- **TOPGEAR (AGITG), 752 patients, GEJ and stomach**
 - ECF x 3 vs ECF x 2 + FU/RT
 - → Surgery → ECF x3
 - OEO 5: ECX x 4 no better than CF x 2
- **CROSS vs MAGIC (Ireland)**
- **ESOPEC: FLOT vs CROSS**
- **Will reshuffling the deck of marginally active therapies move the field forward?**

Next Steps in Chemo RT

- **Biomarkers of Chemo Response**

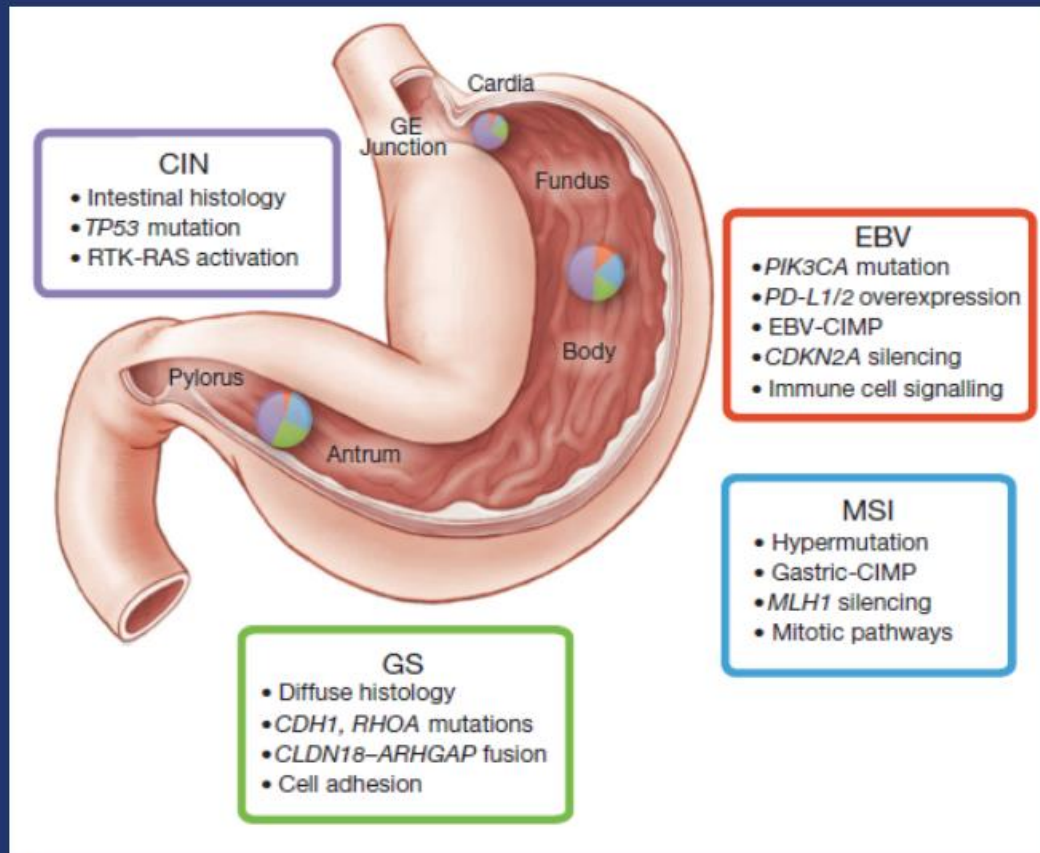
- PET Scan assessment of response to chemo
- CALGB 80803: Induction chemo → PET → ChemoRT
 - Change chemo during RT in PET Non responders
- Chemo response: ERCC1 ?

- **Targeted Agents**

- EGFR: Cetuximab failed in 2 phase III Trials
- Bevacizumab: Failed in 2 phase II trials (Esophageal) and 1 phase III trial (Gastric and GEJ)
 - Ramucirumab likely not to perform better
- Trastuzumab: RTOG 1010: HER2+, Carbo/Paclitaxel/RT → Surgery + / - Tras
 - INNOVATION: Cape or FU/CIS, + Tras, + Tras/Pertuz ongoing

Next Steps in Chemo + RT: Genomic Profiling and Molecular Subsets

Comprehensive Molecular Characterization



Next Steps in Chemo + RT

- **Immunotherapy**

- Anti PD-1, PD-L1
 - 10-20% response rate with half durable
- Give as adjuvant in high risk
- Chemo RT → Surgery + / - Nivolumab
- Combine with RT
 - Antigen release during RT
 - Abscopal Effect

- **Measures of minimal residual disease**

- Circulating tumor DNA



第005窟 弥勒佛 元代
Room No.005 Maitreya Yuan