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# **Esophageal and GEJ Adenocarcinoma: Preop Chemo + RT is Optimal Therapy**

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# Disclosure

- **Consulting**
  - AMGEN
  - Bayer
  - Lilly/Imclone
  - Pieris
  - Roche/Genentech
  - Astra Zeneca
  - Bristol Myers Squibb
  - Merck
  - Pfizer
  - Astellas

# Improving Outcomes in Esophageal and GEJ Adenocarcinoma

- What have current trials shown and what are the important endpoints?
- What are results for biomarkers?

# Esophageal and GEJ Cancer: Neoadjuvant Therapy

- **Survival with surgery alone: 20-40%**
- **Preop Chemo**
- **Preop Chemo + radiotherapy**
  - Most common U.S. practice
- **Both achieve survival improvements over surgery alone**
  - 6% to 14%
- **Why include RT?**
  - Enhance rate of R0 resection
  - Enhance pathologic CR

## Contemporary Trials: R0 Resection Rate

Trial	Regimen	Eso / GEJ	R0
OEO5	ECX x 4	907	66%
	CF x 2		59%
STO3	ECX + / - Bev	680	69% (61-75%)
FLOT4	ECX	201	77%*
	FLOT	200	84%*
POET	CF	59	70%
	CF → EP + RT	60	72%
CROSS	Surgery	141	69%**
	Carb/Pac /RT	134	92%**

\*GEJ + Gastric

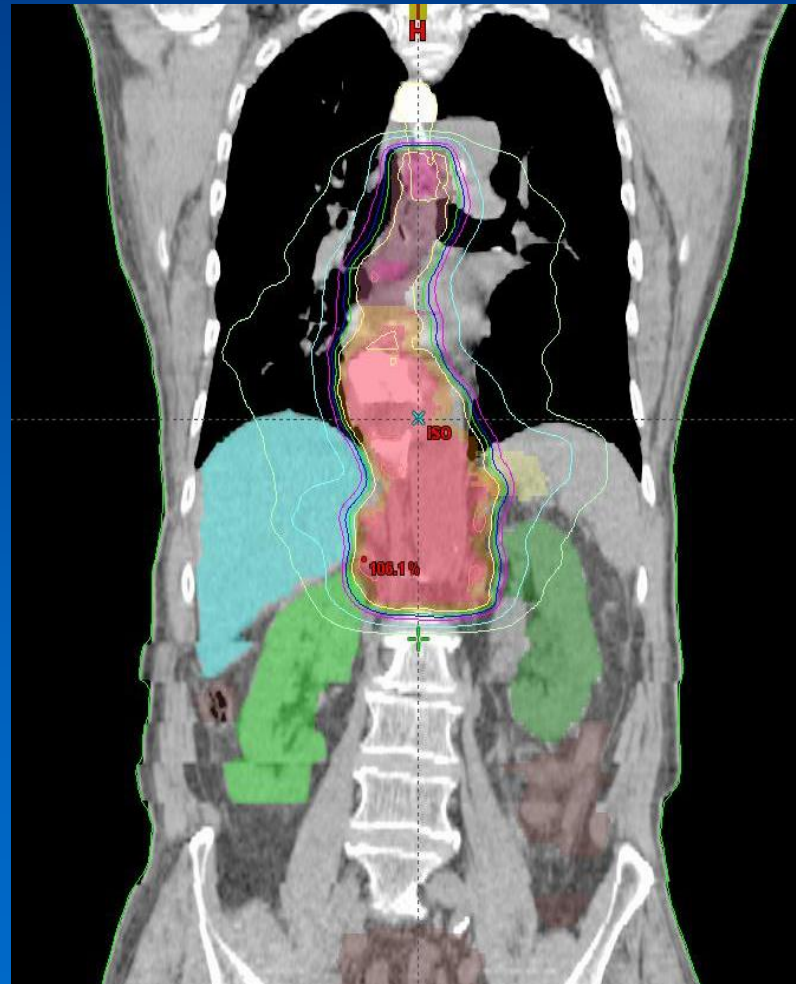
\*\*AC + Squam

# Gastric and Esophageal Cancer Margin Status with Preop ECF/X: ST03

	Patients	% R0
Total Resected	834	
Esophageal	116	66%
GEJ Type 1	102	61%
GEJ Type 2	148	72%
GEJ Type 3	157	75%
Stomach	304	87%
Eso/GEJ	523	69%

Cunningham Lancet Oncol 2017

# Salvage R1 Resection with Post Op Chemo + RT: Large RT field poorly tolerated



## Contemporary Trials: Rates of Path CR

Trial	Regimen	Eso / GEJ	PCR
OEO5	ECX x 4	907	7%
	CF x 2		1%
STO3	ECX + / - Bev	680	9%
FLOT4	ECX	201	6% Ph 2*
	FLOT	200	16% Ph 2*
POET	CF	59	2%
	CF → EP + RT	60	16%
CROSS	Surgery	141	0%
	Carb/Pac/ RT	134	23%

\*GEJ + Gastric



## Contemporary Trials: OS

Trial	Regimen	Eso / GEJ	3 yr OS
OEO5	ECX x 4	907	42%
	CF x 2		39%
STO3	ECX + / - Bev	680	48%-50%*
FLOT4	ECX	201	37%*
	FLOT	200	46%*
POET	CF	59	28%
	CF → EP + RT	60	47%
CROSS	Surgery	141	45% 5 yr 33%
	Car/Pac/ RT	134	54% 5 yr 43%

\*GEJ + Gastric

# Esophageal Cancer: Neoadjuvant Therapy

- **Why include RT?**

- Potential higher R0 resection rate over chemo alone
- Potential higher rate of path CR
- FLOT is superior to CF or ECX in R0 and pCR rate

- **Why include RT?**

- Reduce local recurrence
- Enhance N0 status at surgery

## Contemporary Trials: Local Failure

Trial	Regimen	Eso or GEJ Adeno	Local Failure
OEO5	CF vs ECX	907	10%-13%
STO3	ECX +/- Bev	680	NR
FLOT4	FLOT vs ECX	401	NR
CROSS	Chemo+ RT	134	14%*
	Surgery	141	34%*
POET	Chemo + RT	60	23%
	Chemo	59	41%

\*AC + Squam

Older Trials: INT 113 27-29%, FFCD 29-36%

## N0 Status at Surgery

Trial	Treatment	N0
OEO5	CF	30%
	ECX	39%
STO3	ECX	NR
	ECX + Bev	NR
FLOT	ECX	41%*
	FLOT	49%*
CROSS	Surgery	24%**
	Car/Pac/RT	64%**
POET	CF	37%
	CF + EP/RT	68%
		*Includes squamous cancer

\*GEJ + Gastric

\*\*AC + Squam

# The Importance of Path CR and N0 Status

- Rates of path response relatively low for Chemo or Chemo + RT
- N0 status is also prognostic
- Smyth MAGIC trial: 340 resection specimens
  - pCR (5%) or near pCR (18%): Improved OS
  - Multivariate analysis: only N0 status at surgery was independently prognostic for survival
    - Pathologic response was not prognostic for OS
  - In N0 pts, 5 yr OS in responder pts (66%) = non responder pts (72%)

## Results for Current Preop Therapy Trials

- **Survival improved with preop chemo + / - RT**
- **Largest series OEO5, STO3: poor rates of R0 resection with preop chemo alone**
  - FLOT is superior to ECX: R0
  - Chemo + RT: superior rate of R0
- **Chemo + RT: higher rate of pCR and more patients N0 post chemo + RT**
  - N0 status may be more important than response to therapy
- **FLOT is superior to ECX: pathologic response, N0 status**

# Ongoing Randomized Trials of Preop Chemo + / - RT

- **ESOPEC (NCT 92509286)**
  - FLOT vs CROSS, Eso and GEJ, 438 pts
- **NEO-Aegis (NCT 0172645)**
  - MAGIC ECF/X vs CROSS, Eso and GEJ, 366 pts
- **TOPGEAR (NCT 01924819)**
  - Perioperative ECF/X
  - + / - Preoperative RT
  - GEJ and Gastric cancer, 752 pts
- **Chemo on Neo, TOPGEAR changed to FLOT**
- **ECF is no longer appropriate for esophageal and GEJ cancers**

# Biomarkers in Gastroesophageal Cancer

- Need to be developed and validated in oncologic therapy
- Genomics may ID candidate pathways
- It is unlikely that one or even a series of biomarkers / pathways will advance the success of therapy
- Networks, patterns of multiple biomarkers



# Biomarkers

- **Chemotherapy biomarkers**
  - ERCC1 not useful for platinum response in metastatic disease (SWOG 1201)
- **PET Scan (CALGB 80803)**
  - PET responders to induction FOLFOX → FU/Oxali/RT → Surgery
    - Path CR: 38%
    - Carboplatin / Paclitaxel PET responders: low rate of pCR: 13%
  - PET non responders to induction chemo
    - Cross over to alternative chemo + RT: pCR 17-19%
- **SCOPE2 (UK): definitive CRT, PET non responders to induction chemo**
  - + / - change chemo, + / - RT dose escalation, AC and SC

# HER2 Targeted Neoadjuvant Trials

- **RTOG 1010 (NCT01196390):** Esophageal and GEJ Cancers, Carbo/Pac/RT + / - Trastuzumab
- **TRAP (NL) (NCT02120911):** Phase II Carbo/Pac/Tras/Pertuz + RT
- **PETRARCA (NCT02581462):** FLOT + / - Trastuzumab + Pertuzumab, gastric and GEJ
- **INNOVATION (EORTC) (NCT02205047):** FU or Cape/Cisplatin + Trastuzumab + / - Pertuzumab, gastric and GEJ

# Immunotherapy Neoadjuvant/Adjuvant Trials

- **Adjuvant nivolumab vs placebo after chemo + RT + surgery**
  - 760 pts, esophageal and GEJ cancer (NCT02743494)
- **ECOG: Carboplatin/Paclitaxel/RT + / - Nivolumab → Surgery**
  - → Observation vs Nivolumab + Ipilimumab
- **AIO: Dante: FLOT4 + / - Atezolizumab**
- **Merck: Cape or FU/Cis periop + / - Pembrolizumab**
- **Pilots: combining anti PD-1 or PDL-1 agents with chemo + RT**

# Esophageal and GEJ Adenocarcinoma: Current Outcomes + Future Directions

- **Neoadjuvant Therapy**

- FLOT is the new standard periop chemo
- Chemo + RT CROSS is a standard alternative
- R0 resection, pCR, N0 status, failure pattern
  - All outcomes favor chemo + RT, FLOT
- Comparative studies pending

- **Biomarkers**

- Use of PET scan to guide neoadjuvant therapy

- **On the Horizon: new agents from metastatic disease trials, identify pathways, networks from genomic analysis**





# Targeted Therapy Post Op?

- **Maintenance therapy with a novel targeted agent , high risk residual disease pts (N+)**
- **Suppress rather than eradicate micro metastatic disease**
- **CALGB/Alliance, GEJ cancer**
  - High risk N+ pts post chemo rt and surgery
  - 1 year Regorafenib (Anti VEGF TKI) vs Placebo
- **Targeted agents should not be used outside of a clinical trial**
  - Phase III validation
  - Agents may do harm
    - Bevacizumab, cetuximab in CRC adjuvant therapy

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

- Paclitaxel 50mg/m<sup>2</sup> + 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 FLOT 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. (%)‡		
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)

CROSS

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

	ECF/ECX N=360		FLOT N=356	
<b>cT-stage</b>				
T1	2	1%	3	1%
T2	59	16%	49	14%
T3	253	70%	267	75%
T4	33	9%	28	8%
unclear	13	4%	9	3%
<b>cN-stage</b>				
N-	70	19%	77	22%
N+	290	81%	279	78%

T3:70-75%  
N+:78-81%

# CROSS Trial: Resection rate and resection margins

Resection rate of all randomized patients

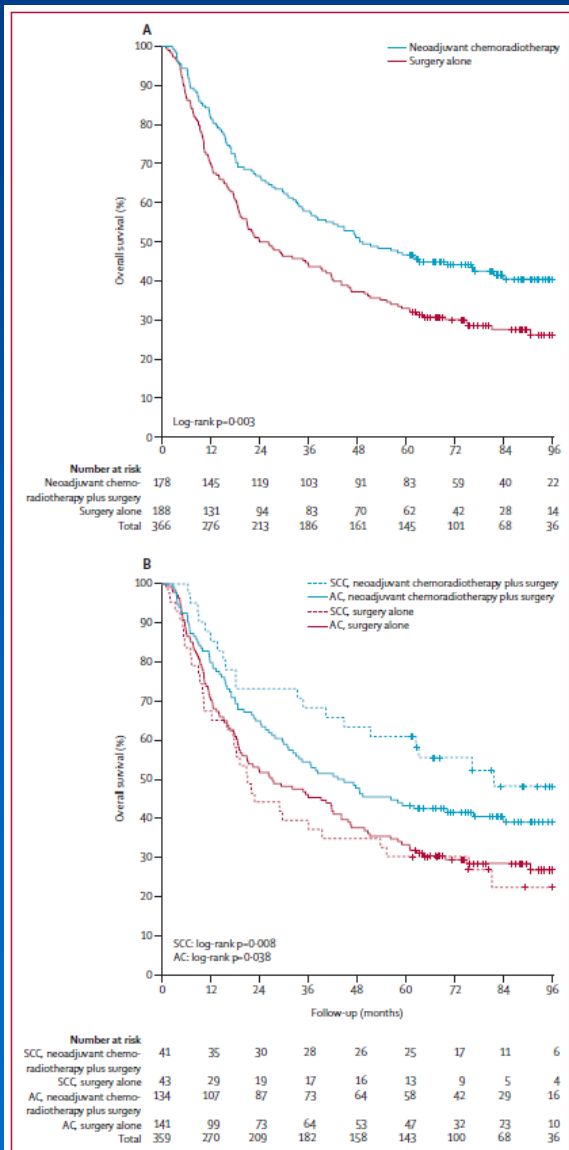
Surgery alone	CRT + surgery
186/188 (99%)	168/178 (95%)

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%

# 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
- 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 tumors
- Consistent outcome 3 decades of studies
- **Less than R0 = DEATH**
- **Chemo + RT is the optimal backbone for future studies**

# 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

- **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)
- Trastuzumab: RTOG 1010: HER2+, Carbo/Paclitaxel/RT → Surgery + / - Tras
  - INNOVATION: Cape or FU/CIS, + Tras, + Tras/Pertuz ongoing