



THE UNIVERSITY OF TEXAS  
**MD Anderson**  
~~Cancer~~ Center  
Making Cancer History®

## **Current Approaches in the Management of Esophageal Cancer**

**Steven H. Lin, M.D., Ph.D.**

Associate Professor in Radiation Oncology, MD Anderson Cancer Center

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## Disclosures

**Grant funding:** CreatvMicrotech, Inc., Elekta Inc., Hitachi Chemical Diagnostics, Beyond Spring Pharmaceuticals, New River Labs, Genentech, Inc

**Advisory board:** AstraZeneca, Beyond Spring Pharmaceuticals

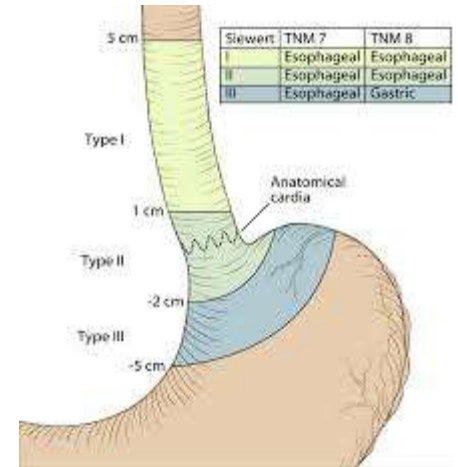
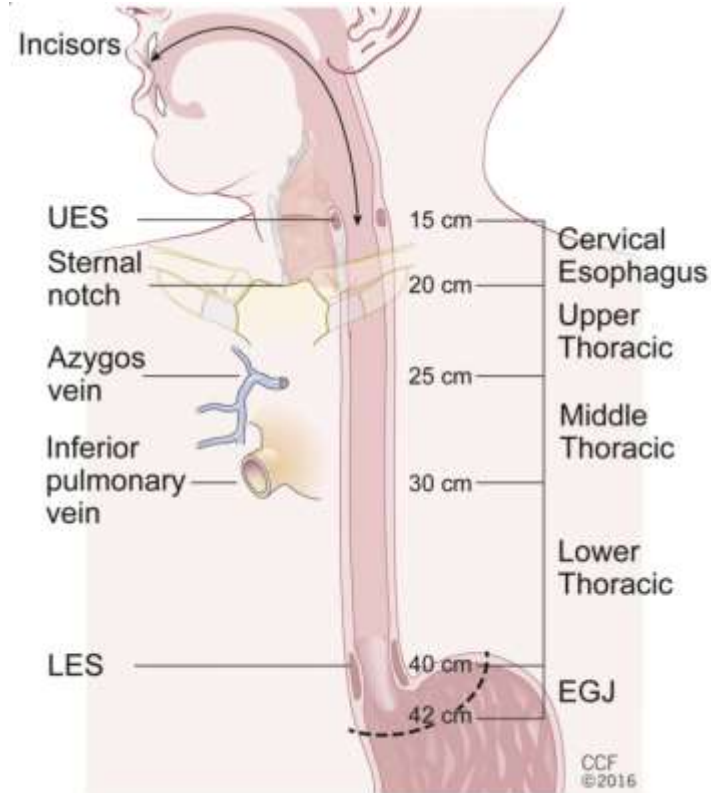
**Speaker bureau:** Varian Medical Systems, AstraZeneca

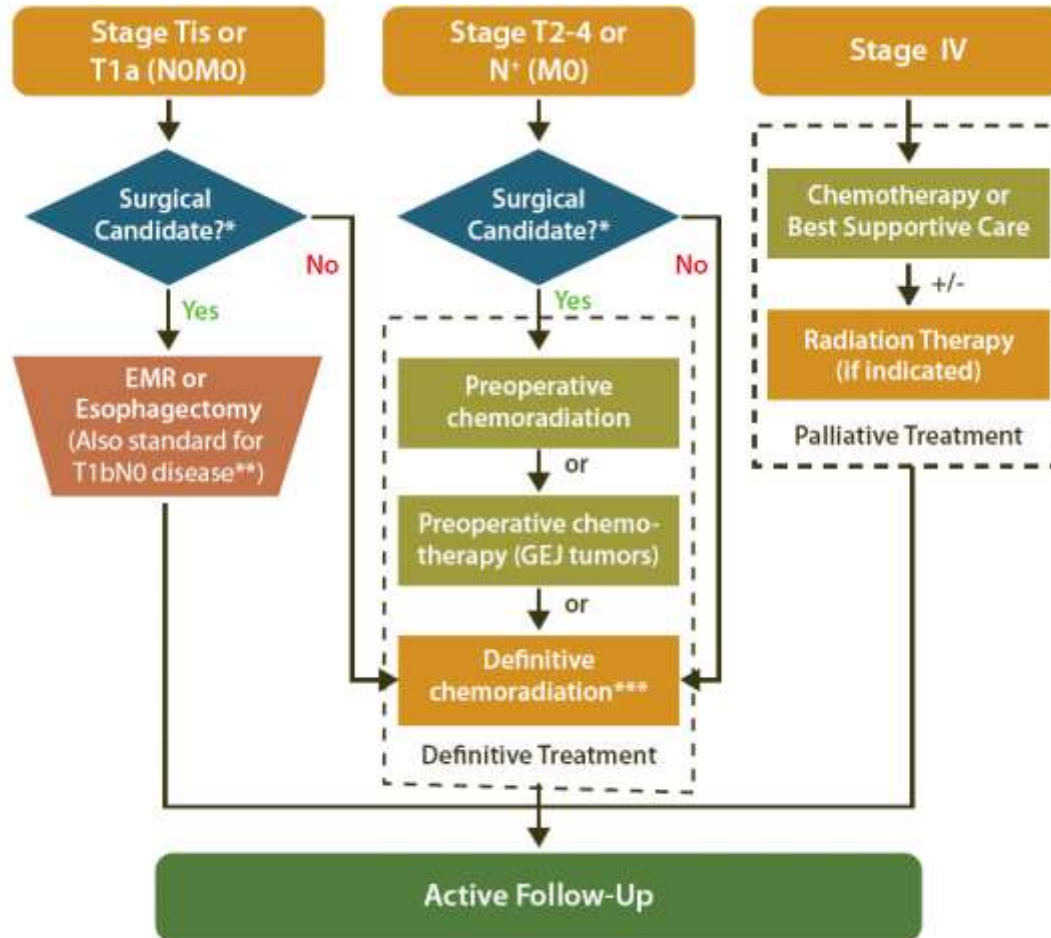
# Outline

- **Resectable disease: Role for preoperative CRT vs Chemotherapy**
- **Unresectable disease: Role for dose escalation**
- **Role of surgery after CRT**

**Red AND Underlined Statements: Please Pay Attention!**

# Esophageal anatomy





# Surgery alone is the single best modality for curative management

## Surgical resection

- **Best single modality therapy**
- **No other single modality options has proven superior in randomized clinical trials**
- **Greatest issue with upfront surgery is R0 resection**
  - Only 50-60% which significantly impacts prognosis
  - Neoadjuvant therapy was employed to improve resectability

**Table 2.** Five-Year Survival Rates for Esophageal Carcinoma, According to the Tumor–Node–Metastasis Classification.\*

Stage	Tumor	Node	Metastasis	5-Yr Survival %
0	Tis	N0	M0	>95
I	T1	N0	M0	50–80
IIA	T2-3	N0	M0	30–40
IIB	T1-2	N1	M0	10–30
III	T3	N1	M0	10–15
	T4	Any N	M0	
IVA	Any T	Any N	M1a	<5
IVB	Any T	Any N	M1b	<1

} ~30%

# Perioperative CRT trials prior to CROSS

## 3-year Survival

Study	# Pts	Surg	CMT	pCR%	Histology	Schedule	Weakness	Sig?
Le Prise	86	47%	47%	28	Squamous	Sequential to 20 Gy	Not concurrent chemo; low RT dose; split course RT; underpowered study	No
Bosset	297	34%	36%	26	Squamous	Sequential to 37 Gy	Not concurrent chemo; split course RT; low RT dose	No
Walsh	113	6%	32%	25	Adenoca	Concurrent to 40 Gy	Poor results with surgery	Yes
Urba	100	16%	30%	28	75% Adeno	Concurrent to 45 Gy	Underpowered	No
Burnmeister	256	19 mos	22 mos	16	62% adeno	Concurrent to 35 Gy	One cycle chemo only; lower RT dose	No
Tepper	56	1.8 yr	4.5 yr	40	75% adeno	Concurrent to 50.4 Gy	Closed to poor accrual with small numbers	Yes

- Pathologic complete response after CRT is ~25-30% between 40-50 Gy (*there appears to be no dose response between 40-50 Gy*)

# Preop ChemoRT vs Surgery alone CROSS Trial (set the current standard)

366 pts (75% adenoca) randomized to preop CRT vs S alone

Somewhat unconventional chemo and radiation

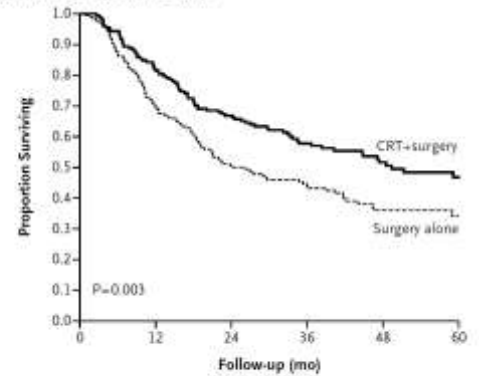
- Carboplatin/Taxol with 41.4 Gy

R0 Resection was significantly better in the CRT group vs Surgery (**92% vs. 69%**, [p<0.0001])

Pathologic complete response in 29% of CRT (**23% adenoca, 49% SCCA**)

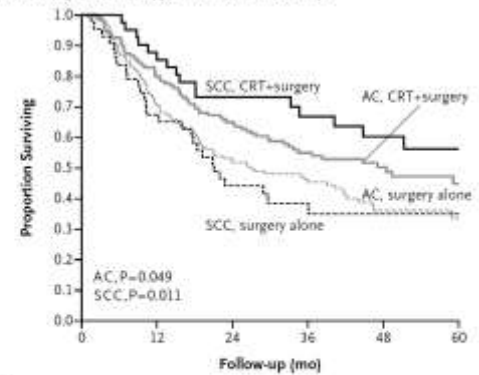
Median OS better in CRT (HR 0.66; 95% CI 0.49-0.87)

A Survival According to Treatment Group



No. at Risk	0	12	24	36	48	60
CRT+surgery	178	145	119	75	49	28
Surgery alone	188	131	94	62	31	17
Total	366	276	213	137	82	45

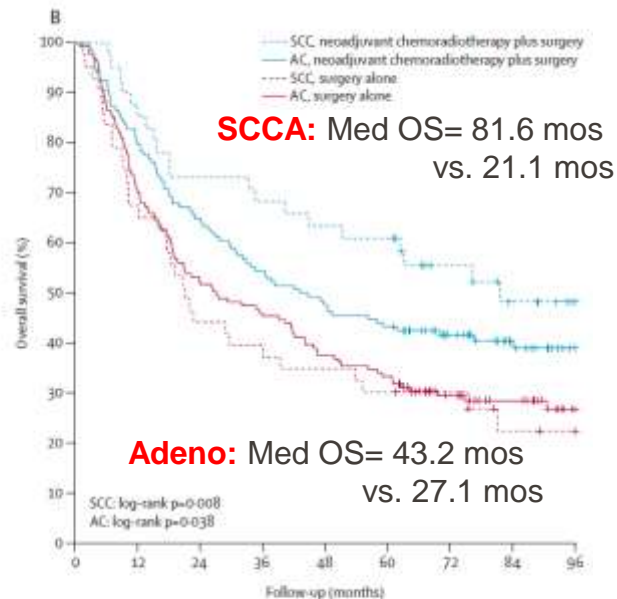
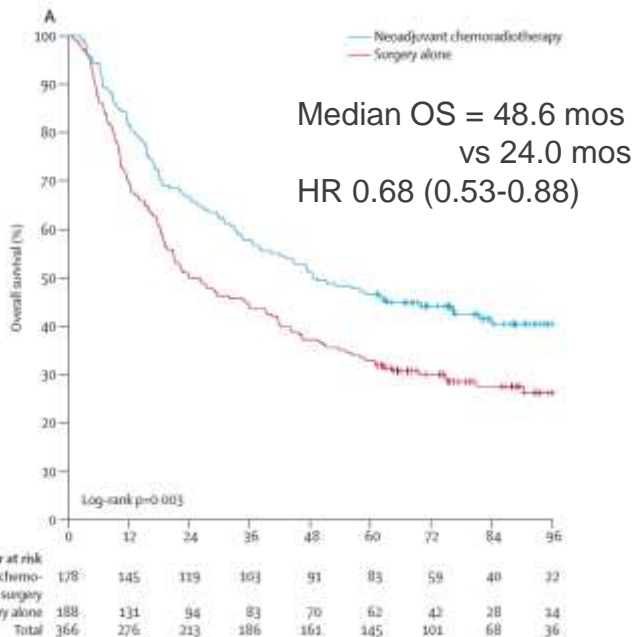
B Survival According to Tumor Type and Treatment Group



No. at Risk	0	12	24	36	48	60
AC, CRT+surgery	134	107	87	53	34	18
AC, surgery alone	141	99	73	50	25	10
SCC, CRT+surgery	41	35	30	21	15	8
SCC, surgery alone	43	29	19	11	8	4
Total	359	270	209	135	82	40



# CROSS Trial: Updated Survival



Number at risk	0	12	24	36	48	60	72	84	96
SCC, neoadjuvant chemo-radiotherapy plus surgery	41	35	30	28	26	25	17	11	6
SCC, surgery alone	43	29	19	17	16	13	9	5	4
AC, neoadjuvant chemo-radiotherapy plus surgery	134	107	87	73	64	58	42	29	16
AC, surgery alone	141	99	73	64	53	47	32	23	10
Total	359	270	209	182	158	143	100	68	36

# NEOCRTEC5010: Phase III nCRT vs S in ESCCA

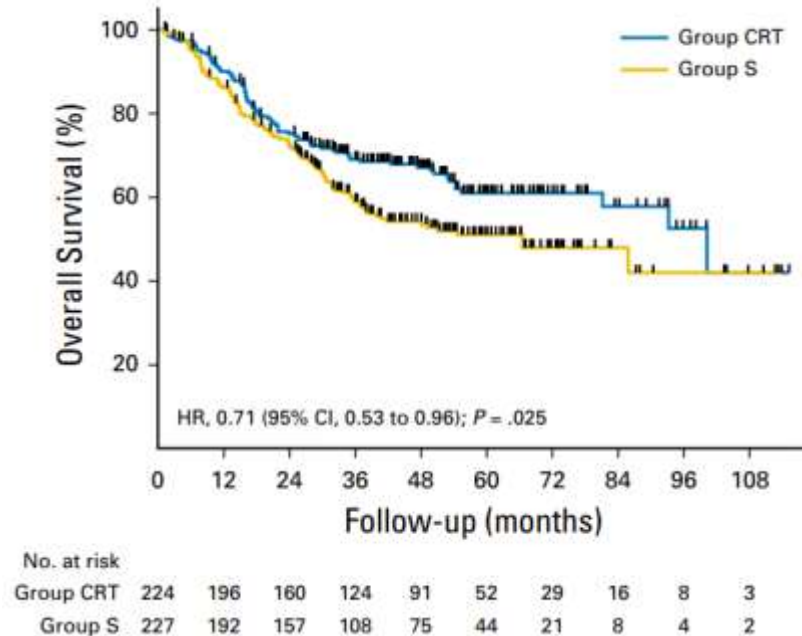
451 pts randomized

pCR = 43.2% with nCRT

CRT had higher R0 resection rate:  
**98.4% vs. 91.2%**, p=0.002

Median OS better in nCRT (HR 0.71)

No difference in postop complications



# **How about neoadj Chemo? Neoadj CRT is the preferred approach for locally advanced EC (at least for now)**

## **Three main reasons**

- **Neoadjuvant CRT improves resectability → increases curative resections**
- **Neoadjuvant improves pathologic complete response**
- **Neoadjuvant CRT is beneficial for both EADC and ESCCA**

# Pre-op Chemotherapy vs. Surgery alone Intergroup 0113

440 cases SCCA (46%) and adenoca (54%)

Surgery vs 3 cycles preop chemo (Cis/5FU) and 2 cycles postop chemo

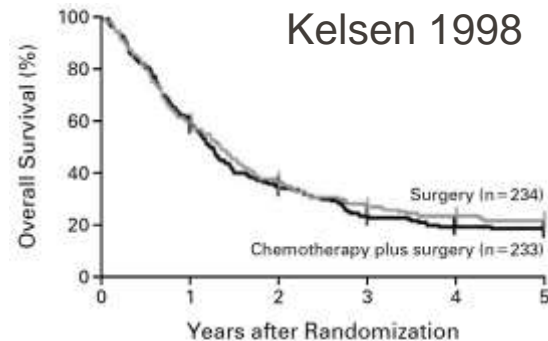
Only 71% received all 3 cycles of chemo, only 80% in chemo group got surgery (vs 96%)

No difference in resectability

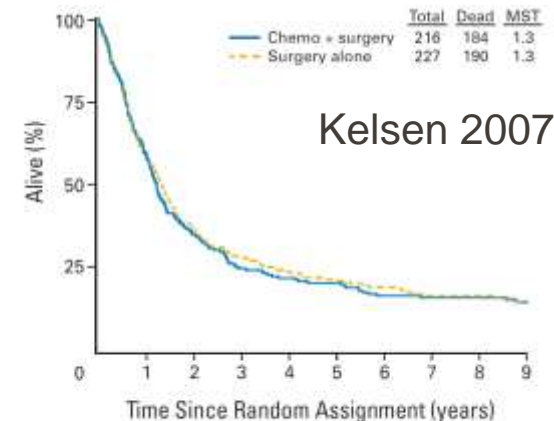
- R0 resection similar (59% vs 62%), with less R1 resection in preop chemo (4% vs 15%, p=0.001)

pCR = 2.5%; no difference between SCCA vs Adeno

No difference in 4 yr OS (26% vs 23%) or MS (16 mo vs 15 mo) between arms



	0	1	2	3	4	5
Chemotherapy plus surgery	136	73	42	28	15	
Surgery	138	81	45	27	16	



	0	1	2	3	4	5	6	7	8	9
Chemo + surgery	216	130	77	52	45	42	31	29	27	18
Surgery alone	217	135	83	60	41	45	38	30	24	15

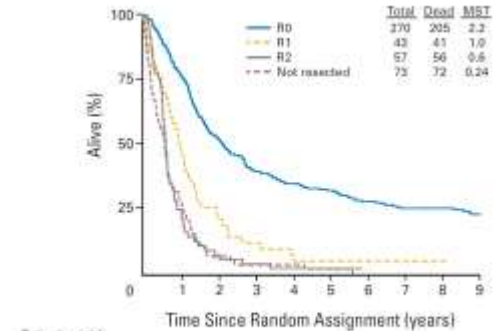
# Long term survival results of INT0113

**The most important predictor of long-term survival was an R0 resection**

**5-year survival for R0 resection = 32%; R1 resection 5%**

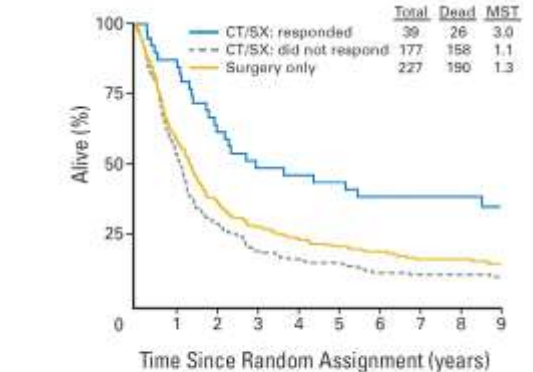
**No difference in survival if R1/R2 or no resections**

**Clinical or radiographic responses to chemo (19%) had better survival than no response and compared to surgery alone**



Patients at risk

R0	270	210	142	103	90	83	68	58	50	33
R1	43	21	10	5	3	2	1	1	1	0
R2	57	14	4	1	1	1	0	0	0	0
Not resected	73	20	2	2	2	1	0	0	0	0



Patients at risk

CT/SX; responded	39	34	25	19	18	17	13	12	12	9
CT/SX; did not respond	177	98	52	33	27	25	18	17	15	9
Surgery only	227	135	83	60	51	45	38	30	24	15

# Pre-op Chemotherapy vs. Surgery alone MRC OE02

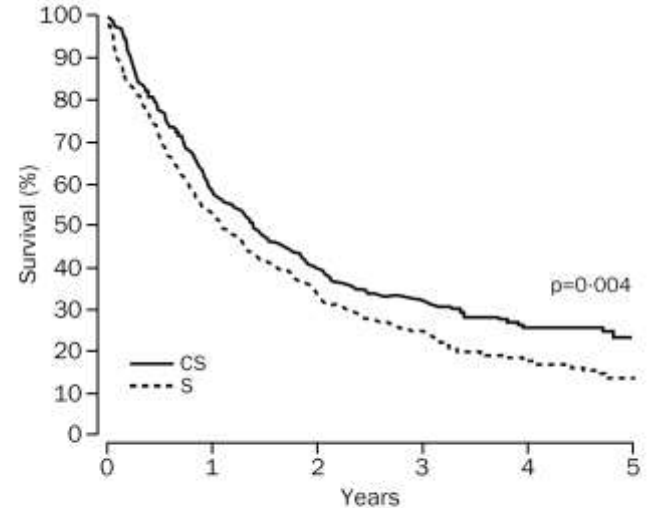
802 pts (31% SCCA and 66% Adenoca)

Preop chemo (2 cycles cis/5FU) vs surgery

92% received surgery in the chemo arm

R0 resection higher in chemo group (60% vs 54%)

2 year OS and MS better with preop chemo (43% vs 34% and 16.8 mo vs 13.3 mos,  $p=0.004$ )



Patients at risk (events)

CS	400 (164)	231 (73)	143 (26)	81 (13)	36 (2)	14
S	402 (185)	212 (76)	124 (32)	70 (18)	28 (5)	10

# Pre-op Chemotherapy vs. Surgery alone MRC MAGIC Trial

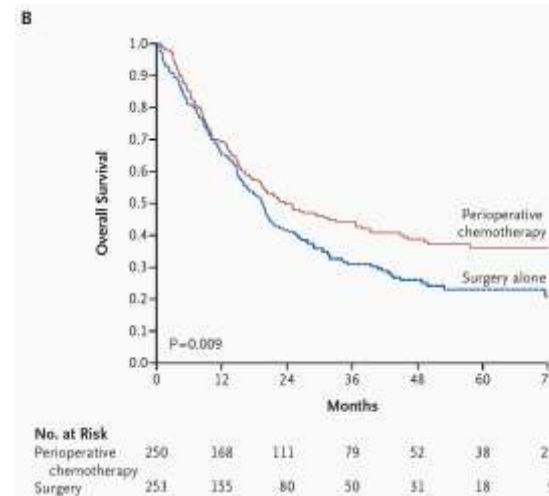
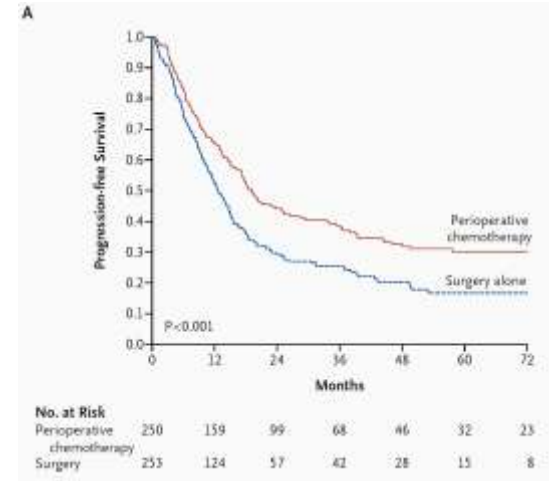
503 pts Gastric/GEJ tumors (~25% GEJ/EC)

3 cycles of ECF preop and 3 cycles postop vs surgery alone

Complications similar between the two groups – 92% preop vs 96% S alone had surgery

R0 resection slightly higher in chemo group (**69% vs 66%**), greater downstaging with chemo, no pathologic complete response

2 year OS and MS better with preop chemo (43% vs 34% and 16.8 mo vs 13.3 mos, p=0.004)



# Head-to-Head Preop Chemo vs Preop CRT trials

## Phase III POET Trial (all Adeno)

Trial terminated at 119 of 354 due to poor accrual

Arm A: 2.5 cycles platinum/leuc/5FU (PLF) → Surg

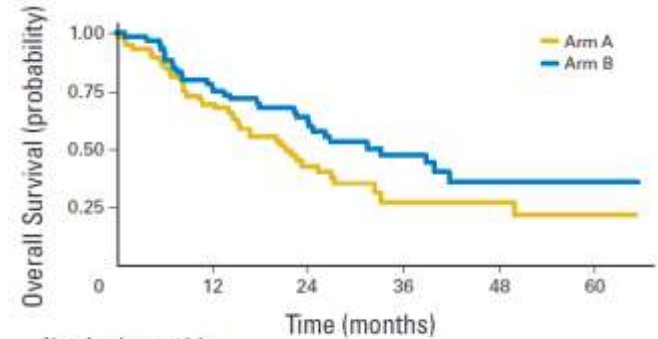
Arm B: 2.0 cycles of PLF → CRT (30 Gy) w/ PE → Surg

R0 resection higher with CRT (96% vs 85%)

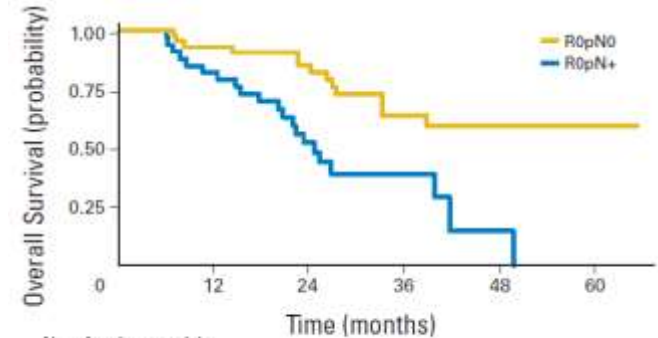
High rates of pCR with CRT (15.6 vs 2.0%, p=0.03)

OS trended in favor of CRT (3 yr OS 47.4% vs 27.7%, p=0.07)

Postop mortality slightly higher with CRT (10.2% vs 3.8%, p=NS)



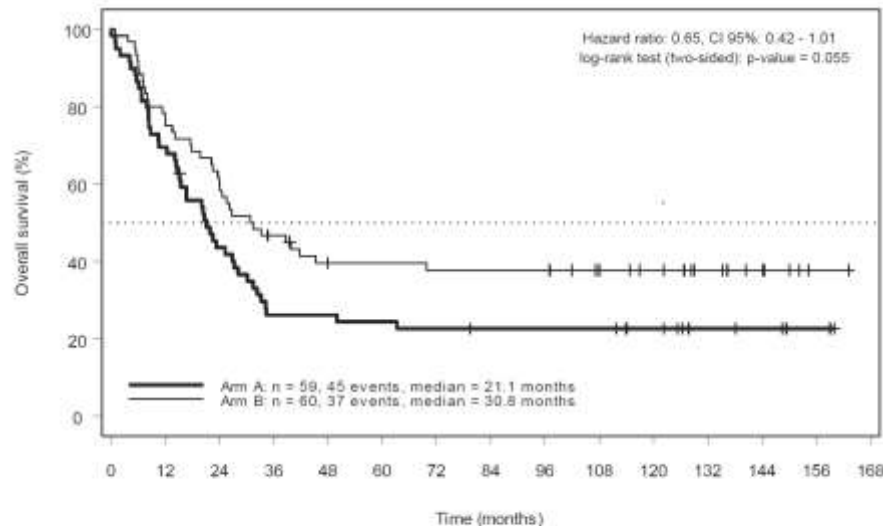
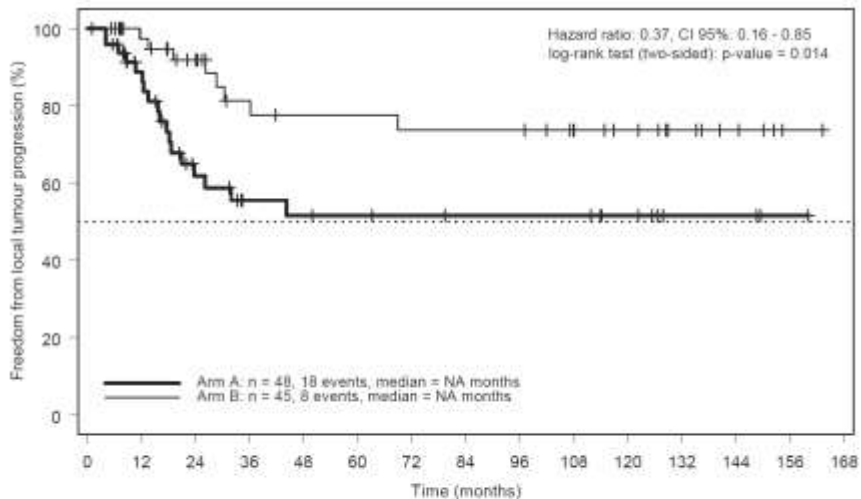
	0	12	24	36	48	60
A:	59	41	19	6	5	2
B:	60	45	30	15	7	1



	0	12	24	36	48	60
pN0	45	42	30	14	11	3
pN+	34	28	13	4	1	0



# POET trial update with 126 months median f/u



Number at risk

n = 48	35	20	14	13	12	11	10	10	10	7	3	3	1	Arm A
n = 45	37	30	22	20	20	19	19	19	15	12	8	5	1	Arm B

Number at risk

n = 59	41	25	15	15	14	13	12	12	9	5	4	2	Arm A	
n = 60	45	36	27	21	21	20	20	20	16	13	9	6	1	Arm B

# Head-to-Head Preop Chemo vs Preop CRT trials

## Phase II NeoRes Trial (75% adeno)

181 pts randomized trial:

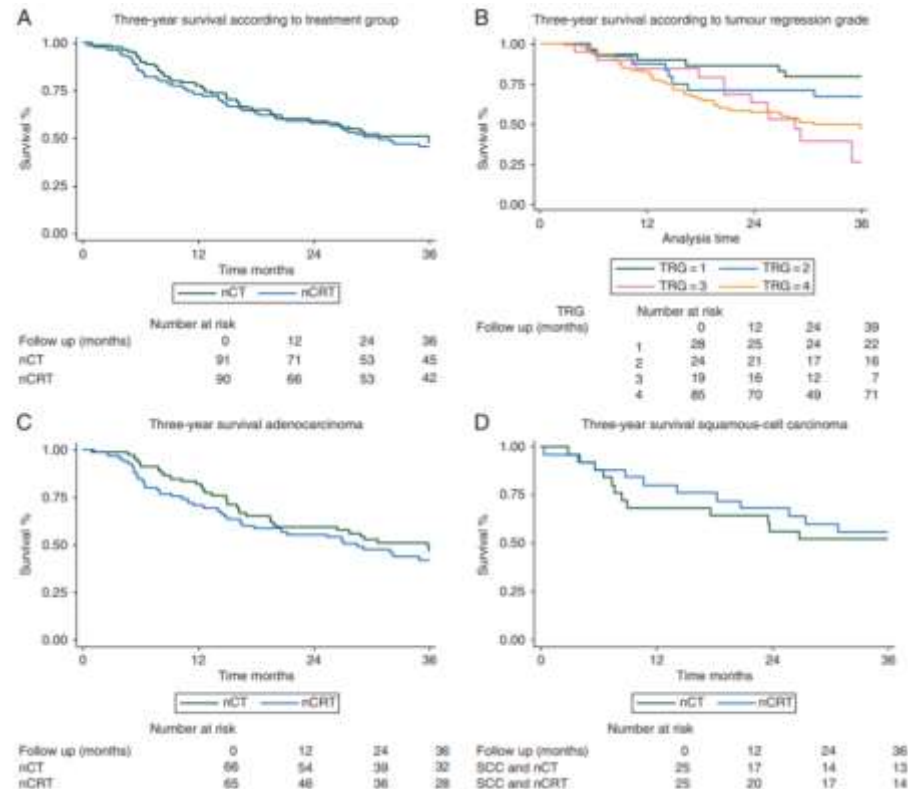
CRT: 40 Gy/20 fx, 5FU/platin

CT: 5FU/platin x 3 cycles

**Met the Primary endpoint: Better pCR rate, R0 resection rate**

- Higher pCR **28% nCRT vs 9% nCT**
- R0 resection: **87% nCRT vs 74% nCT**
- Nodal mets at path: 35% nCRT vs 62% nCT

Not powered for survival



# The importance of R0 resection and the role of neoadjuvant therapy

A review of 28 studies analyzed prognostic value of positive circumferential resection margin (R1+) per either College of American Pathologist (CAP) (at ink) or Royal College of Pathologist (RCP) (<1 mm) definitions

A wide range of CRM involvement (8.6-83.1%) was reported

Available single studies and meta-analysis found **significant association between positive CRM and OS irrespective of margin definition** (RCP: OR 2.52 (95% CI 1.96-3.25),  $p < 0.001$ ) or CAP: OR 4.02 (95% CI 2.25-7.20),  $p < 0.001$ )

# Meta-analysis of preop CT vs CRT (7 studies, 4188 pts)

## Preop CRT vs Surgery

- Overall: HR 0.78 (95% CI 0.70-0.88,  $p < 0.0001$ )
- **SCCA: HR 0.80 (0.68-0.93,  $p = 0.004$ )**
- **Adeno: HR 0.75 (0.59-0.95,  $p = 0.02$ )**

## Preop Chemo vs Surgery

- Overall: HR 0.87 (0.79-0.96,  $p = 0.005$ )
- **SCCA: HR 0.92 (0.81-1.04,  $p = 0.18$ )**
- **Adeno: HR 0.83 (0.71-0.95,  $p = 0.01$ )**

**Preop CRT is best for both histologies, preopCT is best for adeno**

# Indirect comparison of all-cause mortality for preop CRT vs chemo

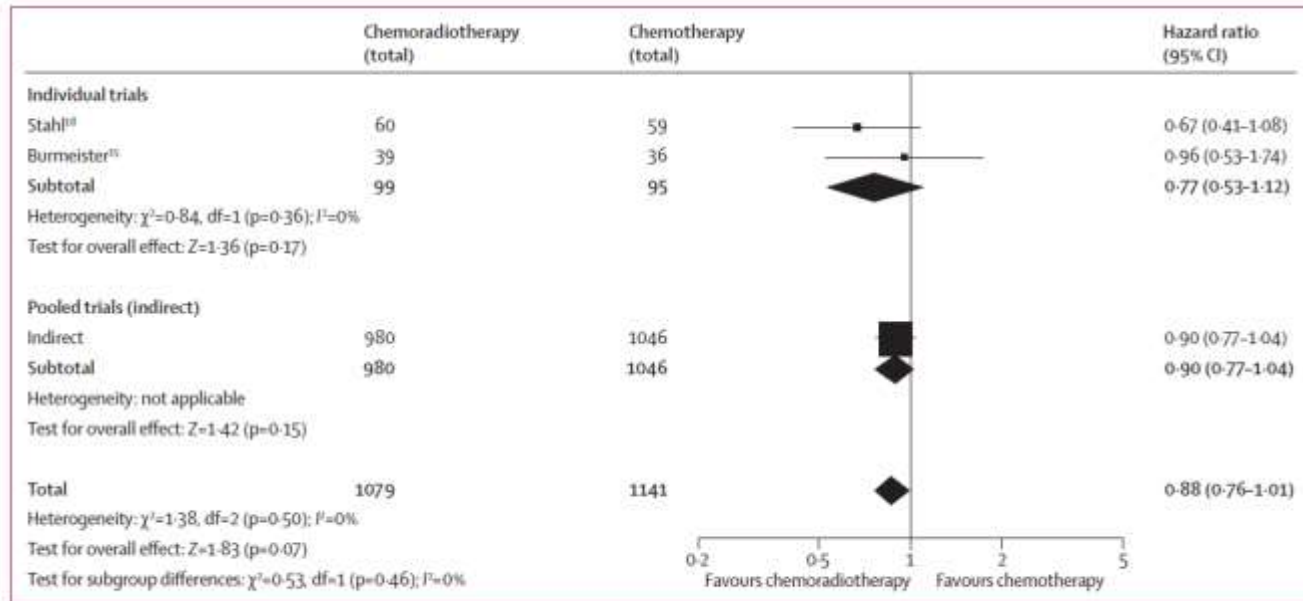
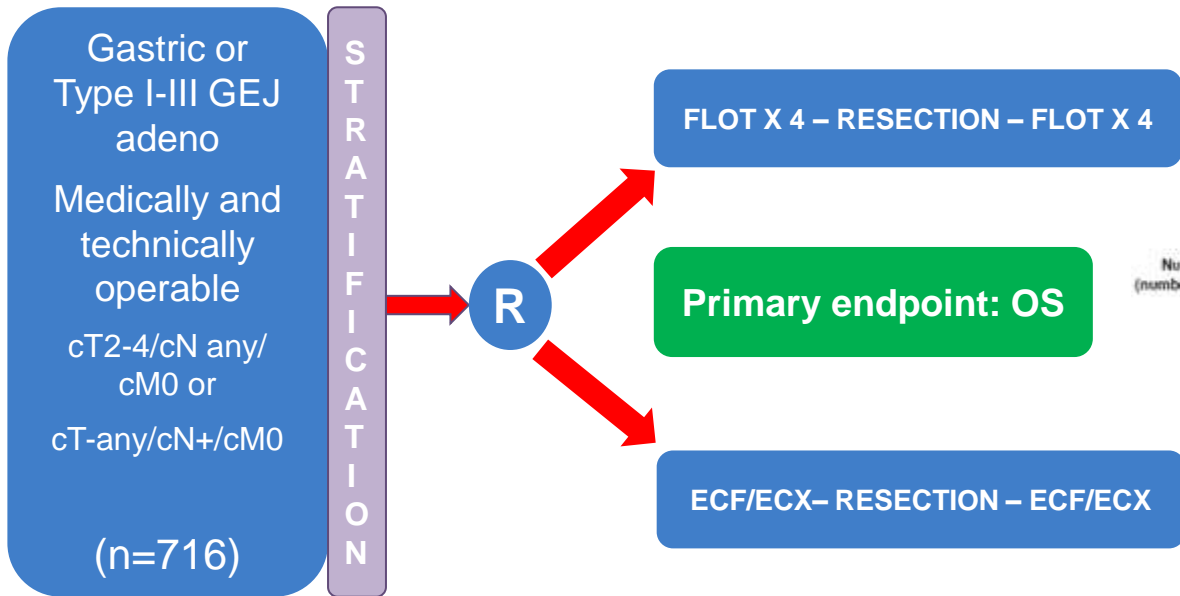
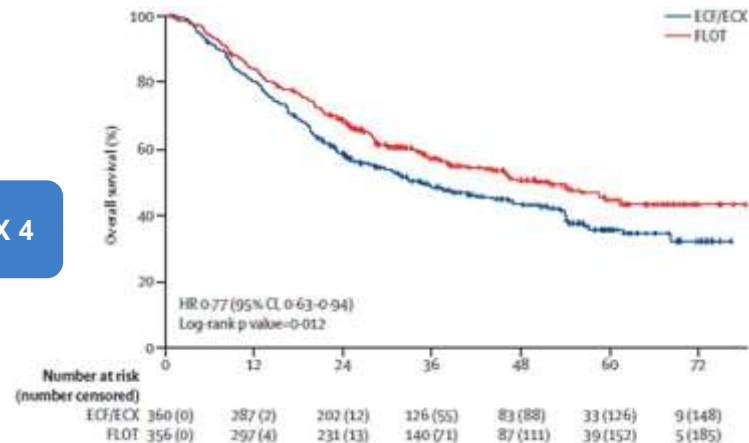


Figure 4: Indirect comparison of all-cause mortality for chemoradiotherapy and chemotherapy

# FLOT4-AIO



GEJ 56%  
 Gastric 44%



Treatment	Median OS (months) (95% CI)	Hazard ratio (95% CI)
ECF/ECX	35 (27.4 to 46.3)	0.77 (0.63-0.94)
FLOT	50 (38.3 to not reached)	

# Pathological CR and R0 rates in adenocarcinoma following neoadjuvant therapies

Trial	Treatment arm	R0 resection (%)	Pathological CR (%)
MAGIC	ECF	69	5
OEO5	CF	60	3
OEO5	ECX	67	11
ST03	ECX	75	8
ST03	ECX + bevacizumab	76	10
<b>FLOT4-AIO</b>	<b>FLOT</b>	<b>84</b>	<b>16</b>
<b>CROSS</b>	<b>C/P + RT</b>	<b>92</b>	<b>23</b>

# Clinical trials of perioperative chemo vs CRT in adenocarcinoma **in the FLOT era**

Trial	N	Key Eligibility Criteria	Treatment	Primary Endpoint
<b>ESOPEC</b> NCT02509286 Germany	438	Adeno of esophagus or GEJ	<b><u>CROSS vs FLOT4</u></b> PC/XRT → Surgery <b>versus</b> FLOTx4 → surgery → FLOTx4	OS
<b>NEO-AEGIS</b> NCT01726452 Ireland	540	Adeno of esophagus or GEJ	<b><u>CROSS vs. MAGIC</u></b> PC/XRT → Surgery <b>versus</b> ECFx3 or FLOTx4 → surgery → ECFx3 or FLOTx4	OS
<b>RACE</b> Germany	340	Adeno of esophagus or GEJ, T3, T4	FLOTx2 + 5FU/Oxa/XRT → Surgery → FLOTx4 <b>versus</b> FLOTx4 → surgery → FLOTx4	PFS
<b>TOP GEAR</b> NCT01924819 Australia/New Zealand/Europe/Canada	570	Adeno of stomach or GEJ Siewert type II and III	ECFx2 or FLOT x3 + 5FU/XRT → surgery → ECFx3 <b>versus</b> ECFx3 or FLOTx4 → surgery → ECFx3 or FLOTx4	OS



## **How to determine if dz is unresectable (preoperative vs definitive CRT)? NCCN v4.2019**

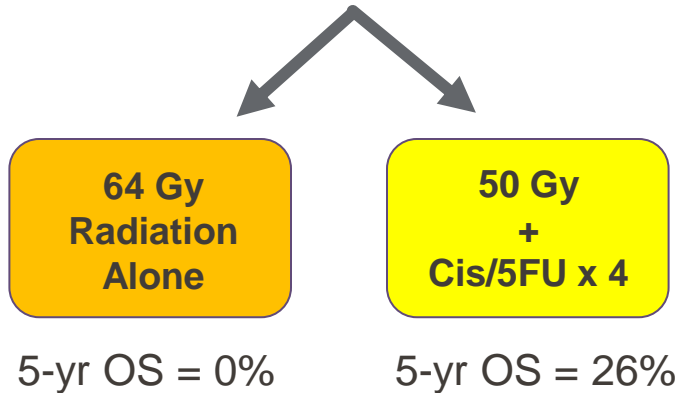
- **Metastatic dz, including non-regional node**
- **Siewert type III for GEJ tumors (manage as gastric paradigm)**
- **Cervical / upper thoracic dz**
- **T4b with involvement of heart, great vessels, trachea, and adjacent organs (liver, pancreas, lung, spleen)**
- **Multi-station, bulky, lymphadenopathy**
- **Poor performance status, or cardiovascular co-morbidities that preclude safe resection**

# Is there a role for dose escalation for definitive therapy for esophageal cancer?

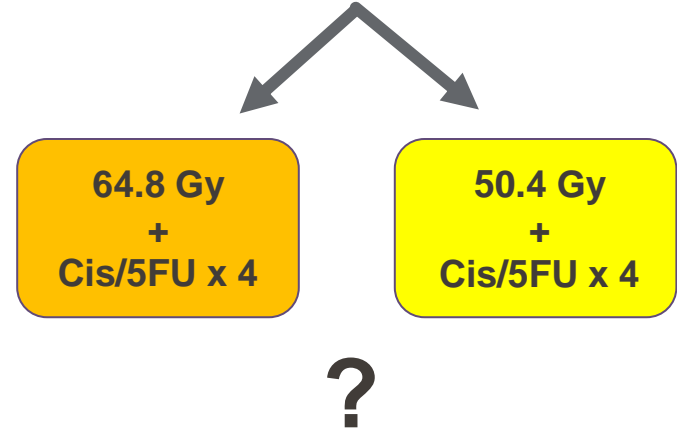
## Chemoradiotherapy of Locally Advanced Esophageal Cancer

Long-term Follow-up of a Prospective Randomized Trial (RTOG 85-01)

## INT 0123 (Radiation Therapy Oncology Group 94-05) Phase III Trial of Combined-Modality Therapy for Esophageal Cancer: High-Dose Versus Standard-Dose Radiation Therapy



Cooper JAMA 1999



Minsky JCO 2002

# Intergroup 0123 trial

	Grade 3/4 acute tox	Grade 3/4 late tox	Grade 5 (death)
50.4 Gy	79%	37%	2
64.8 Gy	67%	45%	<b>**11</b>

**\*\*7 of 11 deaths occurred before 50.4 Gy**

	N	Persistent Dz or LRR	Compliance
50.4 Gy	109	52%	83%
64.8 Gy	109	56%	<b>67%</b>

Table 4. Treatment-Related Deaths (grade 5)

Dose Received	Toxicity
High dose (64.8 Gy)	
5.4 Gy	Cardiac
5.4 Gy	Cardiac, genitourinary
9.0 Gy	Cardiac, hematologic
37.8 Gy	Respiratory
43.2 Gy	Hematologic, infection, genitourinary
50.4 Gy	Infection
50.4 Gy	Genitourinary
54.0 Gy	Infection
61.2 Gy	Hematologic
64.8 Gy	Infection
64.8 Gy	Fistula, gastrointestinal
Standard dose (50.4 Gy)	
50.4 Gy	Infection
50.4 Gy	Infection

# Intergroup 0123 trial

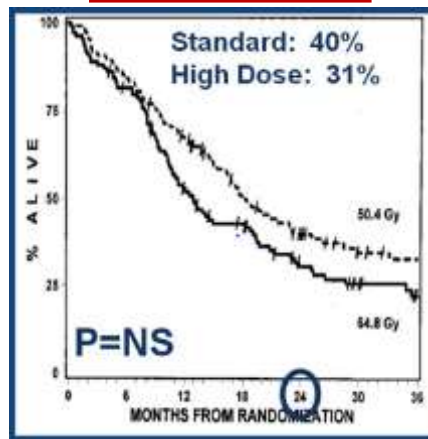
	Grade 3/4 acute tox	Grade 3/4 late tox	Grade 5 (death)
50.4 Gy	79%	37%	2
64.8 Gy	67%	45%	<b>**11</b>

**\*\*7 of 11 deaths occurred before 50.4 Gy**

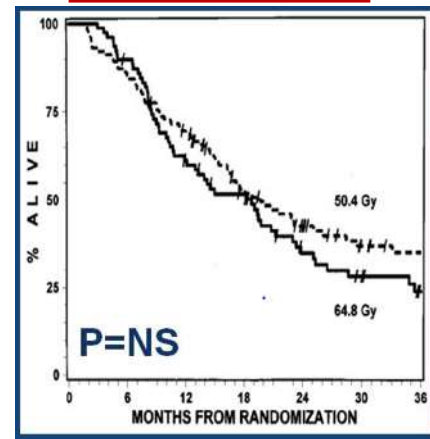
	N	Persistent Dz or LRR	Compliance
50.4 Gy	109	52%	83%
64.8 Gy	109	56%	<b>67%</b>

Minsky JCO 2002

Survival according to Intent to Treat



Survival according to Dose Received



- Caveats:** Old RT techniques, Bad luck, etc.

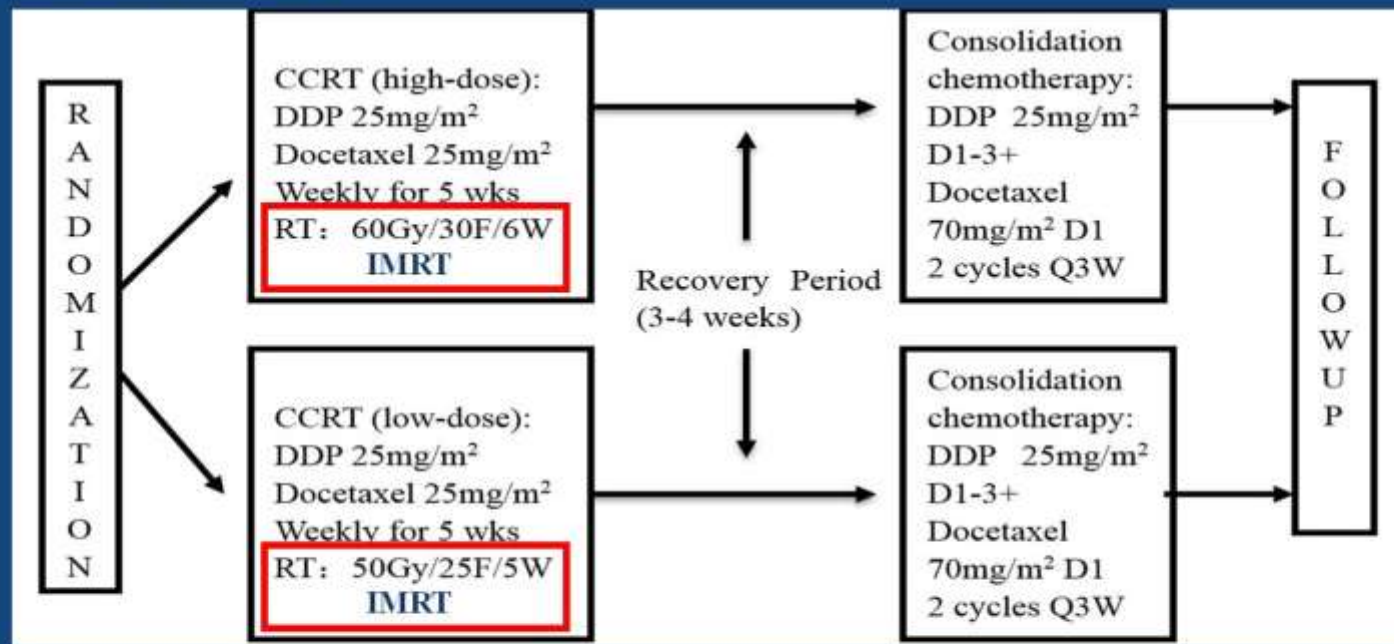
# Modern Randomized Trials

- **Chinese phase III trial (All SCCA)**
- **ARTDECO (Dutch) (2/3 SCCA)**

# Abstract 4013 (221203): A multi-center, randomized, prospective study evaluating the optimal radiation dose of definitive concurrent chemoradiation for inoperable esophageal squamous cell carcinoma

Xu Y, Zhu W, Zheng X, Wang W, Li J, Huang R, He H, Chen J, Liu L, Sun Z, Yang X, He H, Zeng M, Pu J, Hu W, Bao Y, Liu Z, Ma J, Chen M

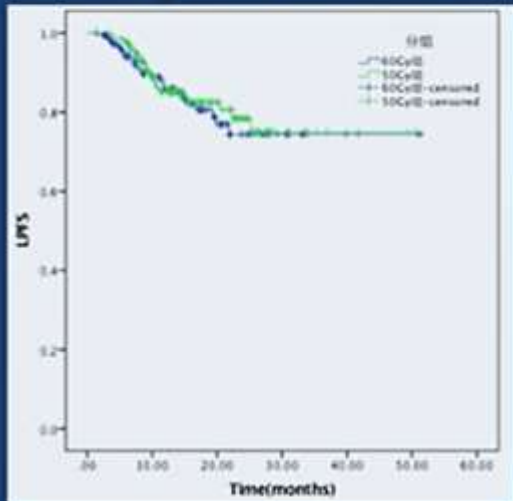
SCCA



Median follow-up - 14.4 months

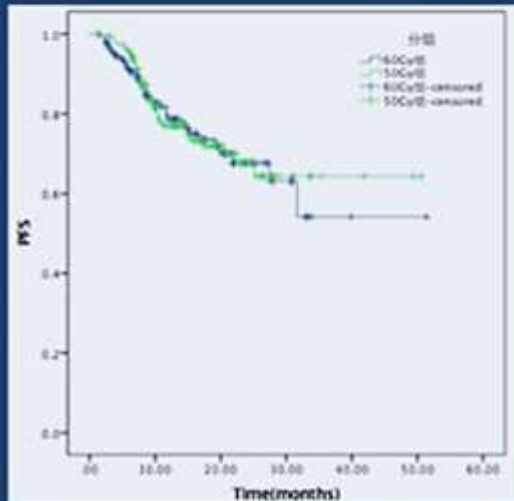
# No improvement in outcomes with dose escalation

## Local-regional Prog free survival



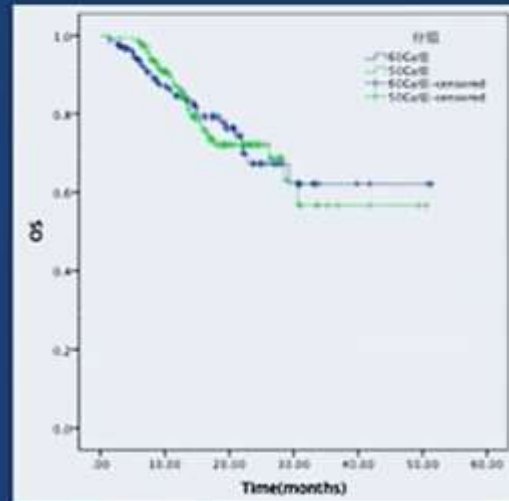
	1y	2y	P
60 Gy	85.8%	74.4%	
50 Gy	85.1%	78.4%	0.68

## Prog free survival



	1y	2y	P
60 Gy	78.6%	67.6%	
50 Gy	76.9%	67.7%	0.88

## Overall Survival



	1y	2y	P
60 Gy	84.6%	67.3%	
50 Gy	86.4%	72.2%	0.98



# A randomized phase III multicenter study on dose escalation in definitive chemoradiation for patients with locally advanced esophageal cancer

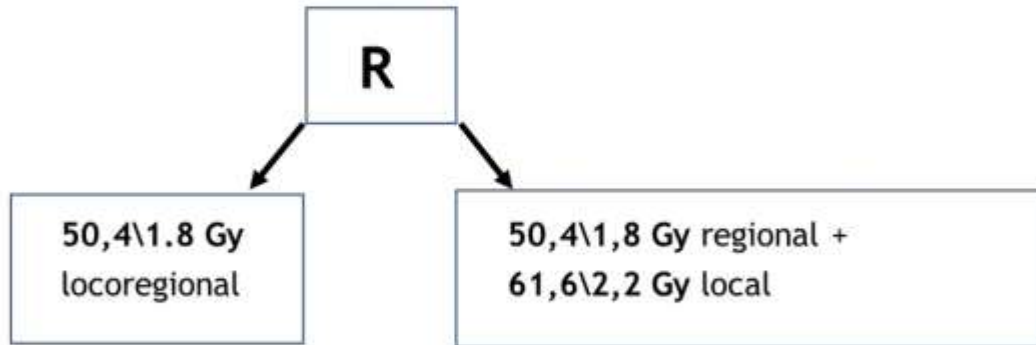
- The ARTDECO trial -  
Maarten CCM Hulshof

Elisabeth D Geijsen, Tom Rozema, Vera Oppedijk, Jeroen Buijsen, Karen J Neelis, Joos JME Nuyttens, Maurice JC van der Sangen, Paul M Jeene, Maartje AH Piet, Jannie G Reinders, Mark I van Berge Henegouwen, Hanneke WM van Laarhoven, Ate van der Gaast.



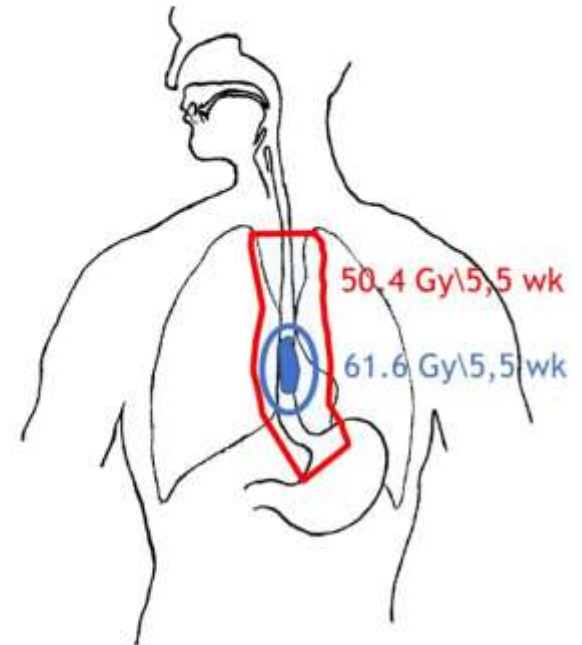
## Trial design

Inclusion T2-4a,N0-3,M0

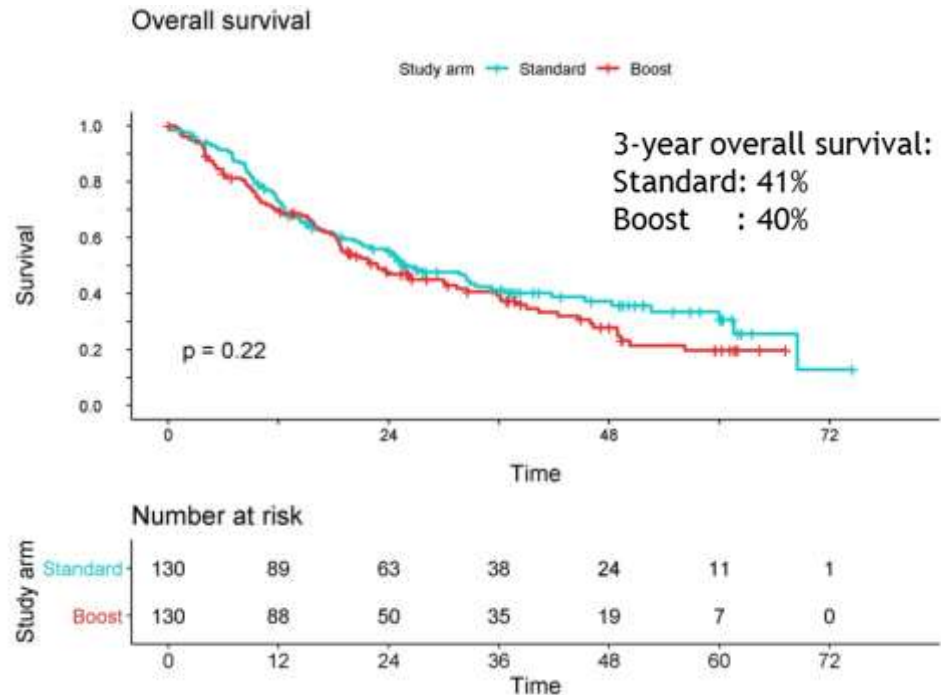
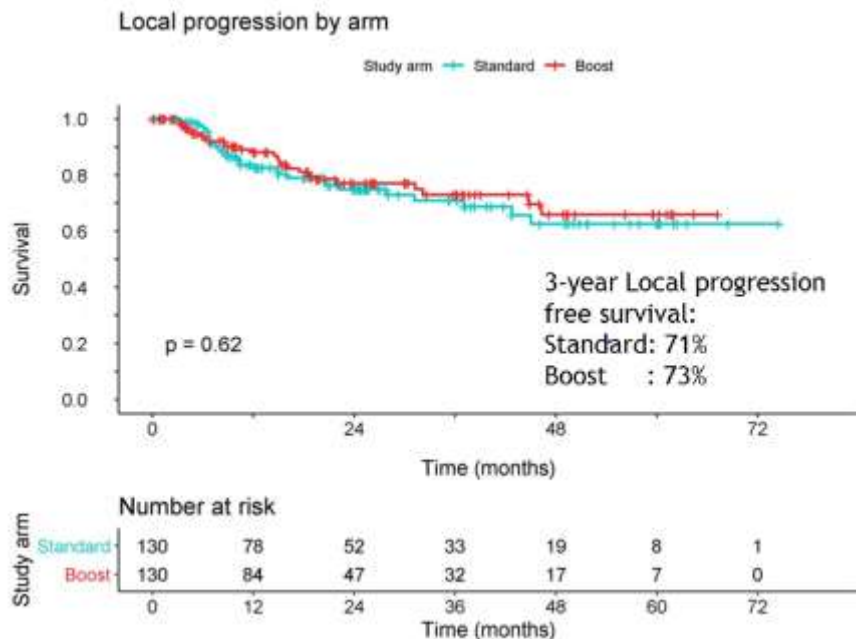


Weekly (6 times) concurrent Carboplatin ( 2x AUC) and Paclitaxel (50 mg\m<sup>2</sup>)

Stratification for histological subtype



# CRT dose escalation does not improve LRC or OS



# Toxicities were worse on the high dose arm

## Overall toxicities

CTC AE scoring	Standard arm (n=120)	Boost arm (n=118)
1	3.3%	0%
2	25.8%	15.3%
3	55.0%	61.0%
4	10.8%	13.6%
5	5.0%	8.5%

## Grade 5 toxicities

	c	Boost arm
GE\lung bleeding	1	3
Esophageal fistula\perforation	2	2
Respiratory failure		2
Sepsis	1	1
Total	4	8

## **Radiation dose: Even with modern trials, no role for dose escalation**

**Preoperative: 41.4 – 50.4 Gy (1.8-2.0 Gy/day)**

**Postoperative (type III or positive margin after surgery): 45-50.4 Gy (1.8-2.0 Gy/day)**

**Definitive: 50-50.4 Gy (1.8-2.0 Gy/day) (for cervical esophagus, higher dose may be indicated esp. if surgery not planned)**

- **At MDACC, ~50% of patients go to surgery (since salvage surgery for local only recurrent dz after CRT is safe and effective)**
- **50.4 Gy for all patients regardless of resectability**
- **40 Gy can be used as initial PTV if the volume is too large or if pts develop toxicities during CRT → boost to 50-50.4 Gy to iGTV+1cm**

# Role of surgery after CRT?

## Preoperative CRT vs CRT alone (**German trial**)

172 pts with SCCA (No Adenocarcinoma)

Arm A: Induction chemo → RT 40 Gy+EP → S

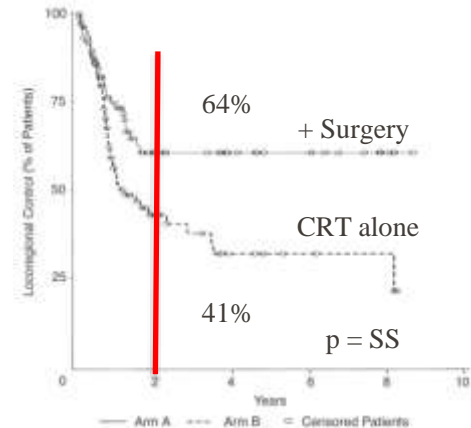
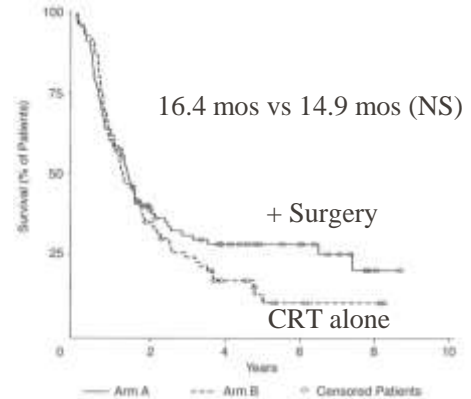
Arm B: CRT alone

- Induction chemo → Arm A + 10 Gy to large field → Boost to 65 Gy
  - T4 or obstructing T3 tumors (15 Gy/1.5 Gy BID)
  - T3 tumors (10 Gy + 5 Gy brachytherapy)

Trend towards survival benefit with surgery (NS)

Better local control with surgery after CRT

Treatment-related mortality much higher with surgery  
**(12.8% vs 3.5%, p=0.03)**



# Role of surgery after CRT?

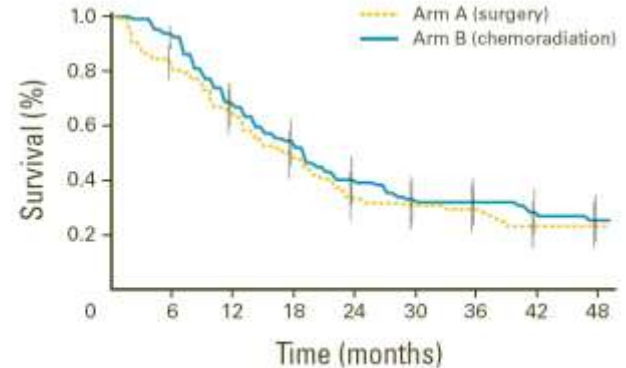
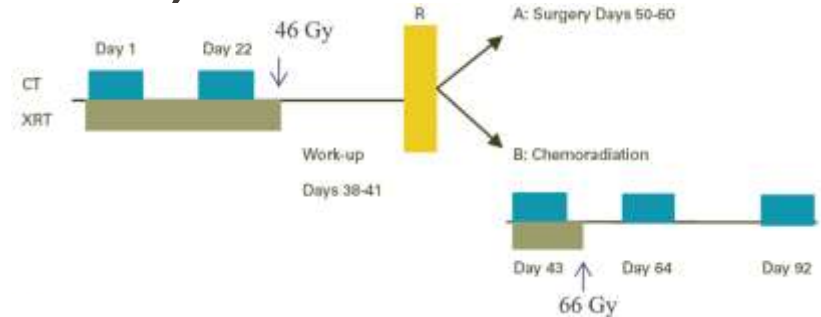
## Preoperative CRT vs CRT alone (French Trial)

Started with 444 eligible pts, only 259 pts randomized

2-year local recurrence was improved in the surgery arm (34% vs 43%,  $p=0.02$ )

No difference in OS

3-month mortality rate higher in surgery arm (9.3% vs. 0.8%,  $p=0.002$ )



Patients at risk	0	6	12	18	24	30	36	42	48
Arm A (surgery)	129	108	79	51	31	25	23	17	13
Arm B (chemoradiation)	130	122	84	61	40	29	25	21	14

## Role of surgery after CRT?

While there is no clear role for upfront surgery after nCRT based on clinical trials, there is still a role of surgery as local recurrence is high (~30-50%) after dCRT

Competing risk of DM is of concern

DM at 6 mos after CRT+surgery (21% with pCR up to 42% with nCR) (MDACC series of 624 pts)

At MDACC, depending on the treatment response, patient's preference, age and comorbidities, we take a selective approach

# Conclusions

**Neoadjuvant therapy with CRT is the optimal curative therapy for esophageal cancers**

**nCRT increases R0 resections and enhance pathologic complete response → both increases cure rates**

**Neoadjuvant chemo is not sufficient for ESCCA and only nCRT or dCRT enhances cure rates for ESCCA**

**41.4-50.4 Gy is the standard dose range, higher is not better**

**Selective use of surgery → wait and see approach is reasonable considering the response and patients' condition**



# Thank you