Neoplasie dell'esofago e della giunzione gastroesofagea:
il trattamento bimodale, indicazioni e risultati

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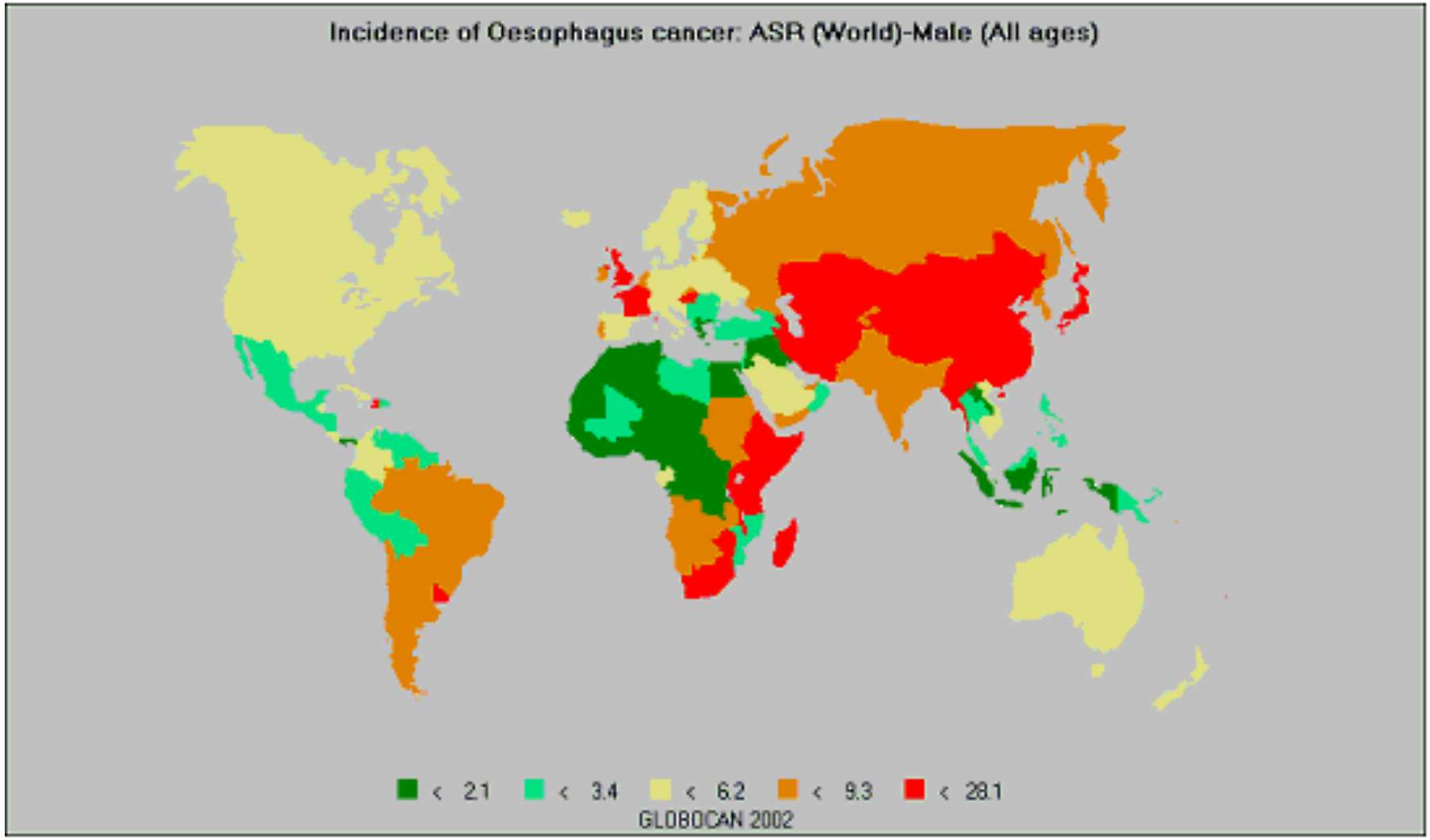
Incidence of oesophagus cancer in the male population of the world



Oesophageal cancer in the European Union (EU) is about 4.5 cases/100 000/year (43 700 cases) with considerable geographical differences within the EU ranging from 3/100 000 in Greece up to 10/100 000 in France

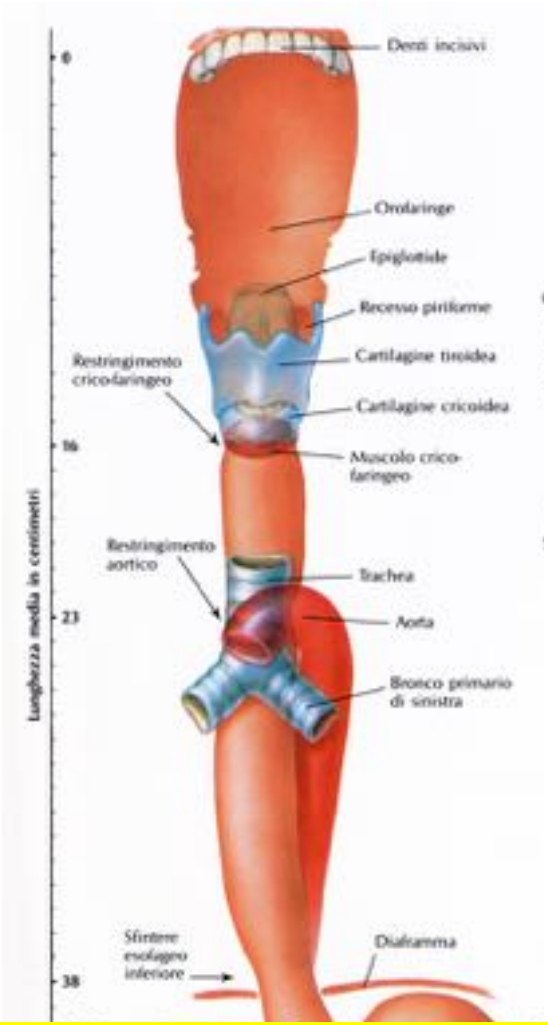
Kamangar 2006, ACS 2010

Sede Anatomica

Dal 1/3 superiore dell' esofago: 15%

Dal 1/3 medio: 50%

Dal 1/3 inferiore: 35%



Carcinoma Squamocellulare

Adenocarcinoma

Nei paesi occidentali, mentre l'incidenza di SCC rimane stabile, l'incidenza di AC è in rapido aumento e attualmente costituisce più della metà di tutti i casi di cancro esofageo.
In Italia è ancora prevalente l' SCC a differenza del Nord Europa e del Nord America dove l' AC ha superato l' SCC; tuttavia anche in Italia si assiste ad un aumento di AC con un incremento del 22% nel periodo 1980-1995 e del 35% nel periodo 1995-2004

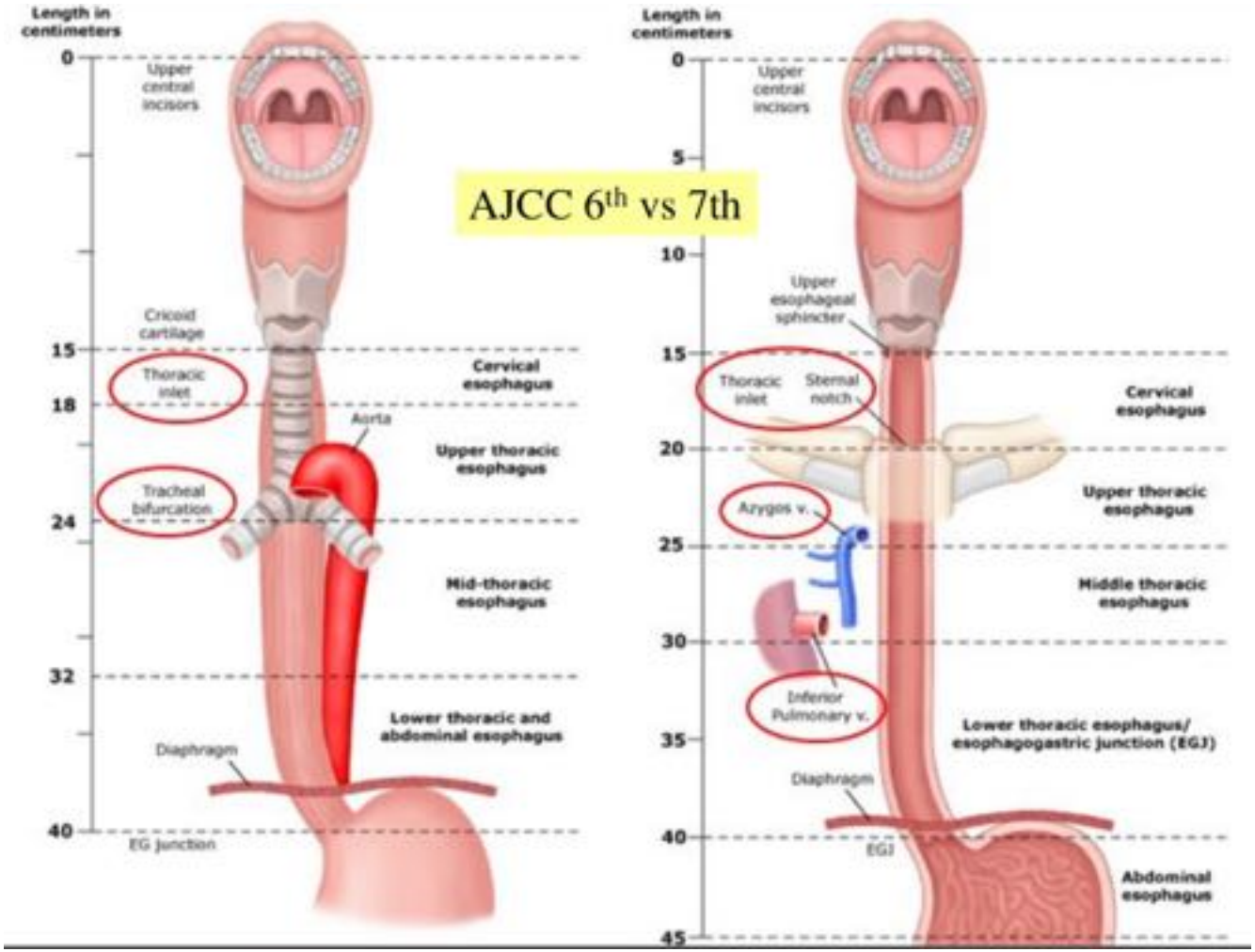
NCI 2008, Bollschweiler 2001, Registri Tumori 2012

esofago cervicale: dal bordo inferiore della cartilagine cricoide allo stretto toracico superiore (circa 18cm dagli incisivi superiori)

esofago toracico superiore: dallo stretto toracico alla biforcazione tracheale (circa 24cm dagli incisivi superiori)

esofago toracico medio: tra biforcazione tracheale ed esofago distale appena sopra la giunzione gastro-esofagea (circa 32cm dagli incisivi superiori)

esofago toracico inferiore: porzione intra-addominale dell' esofago e giunzione gastro-esofagea (circa 40cm dagli incisivi superiori).



Upper thoracic	20–25 cm from incisors
Middle thoracic	>25 to 30 cm from incisors
Lower thoracic	>30 to 40 cm from incisors
Esophagogastric junction	Includes cancers whose epicenter is in the distal thoracic esophagus, esophagogastric junction, or within the proximal 5 cm of the stomach (cardia) that extend into the esophagogastric junction or distal thoracic esophagus (Siewert III). These stomach cancers are stage grouped similarly to adenocarcinoma of the esophagus

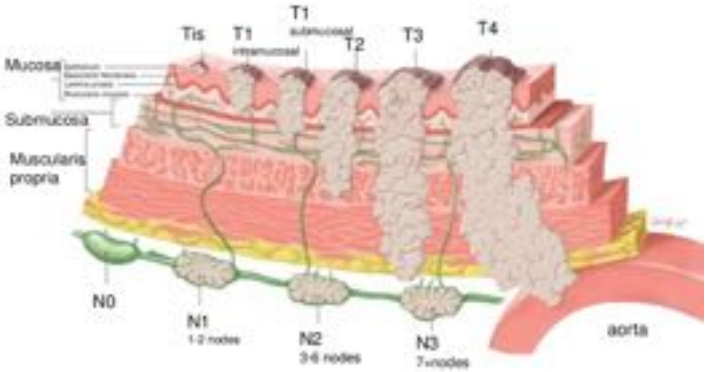
AJCC 7th

TNM VII[a] Edizione- Esofago
(In giallo sono evidenziate le variazioni introdotte dalla 7° Edizione)

- T is carcinoma in situ / displasia di alto grado
- T 1 lamina propria o sottomucosa
  - T1a lamina propria o muscolaris mucosae
  - T1b sottomucosa
- T2 muscolare propria
- T3 Avventizia
- T4 strutture adiacenti
  - T4a pleura, pericardio, diaframma
  - T4b altre strutture adiacenti come aorta, corpi vertebrali, trachea

- N0 assenza di metastasi nei linfonodi regionali
- N1 metastasi in 1-2 linfonodi regionali
- N2 metastasi in 3-6 linfonodi regionali
- N3 metastasi in 7 o più linfonodi regionali

M metastasi a distanza
- M1 presenza di metastasi a distanza



Spesso, soprattutto nei tumori in fase avanzata, non è possibile separare i carcinomi dell' esofago distale che si estendono allo stomaco, da quelli dello stomaco prossimale che si estendono all' esofago, per le difficoltà nel riconoscere l' esatta sede di origine.

L' attuale versione del TNM facendo riferimento alla localizzazione dell' epicentro del T, ed al coinvolgimento della GEG per discriminare l' appartenenza alle lesioni esofagee o gastriche, ha accorpato lesioni del GEG a quelle esofagee

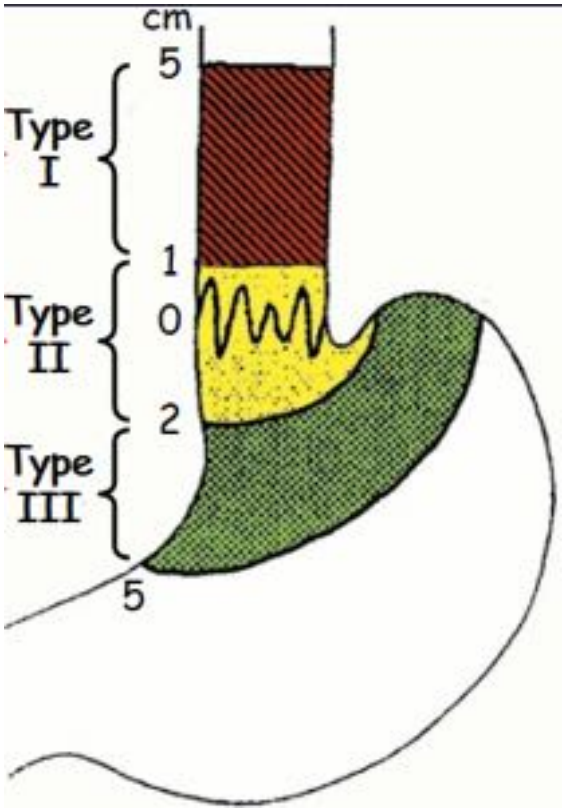
Edge 2010

TNM 7°, diversamente dalla precedente edizione, classifica i carcinomi della GEG (**nei 3 tipi di lesione sec. Siewert**) insieme a quelli dell' esofago e li differenzia nettamente dai tumori gastrici.

Tipo1 il centro della neoplasia è localizzato a 1-5cm sopra il cardias

Tipo2 il centro della neoplasia è localizzato tra 1cm sopra e 2cm sotto il cardias

Tipo3 il centro della neoplasia è localizzato a 2-5cm sotto il cardias



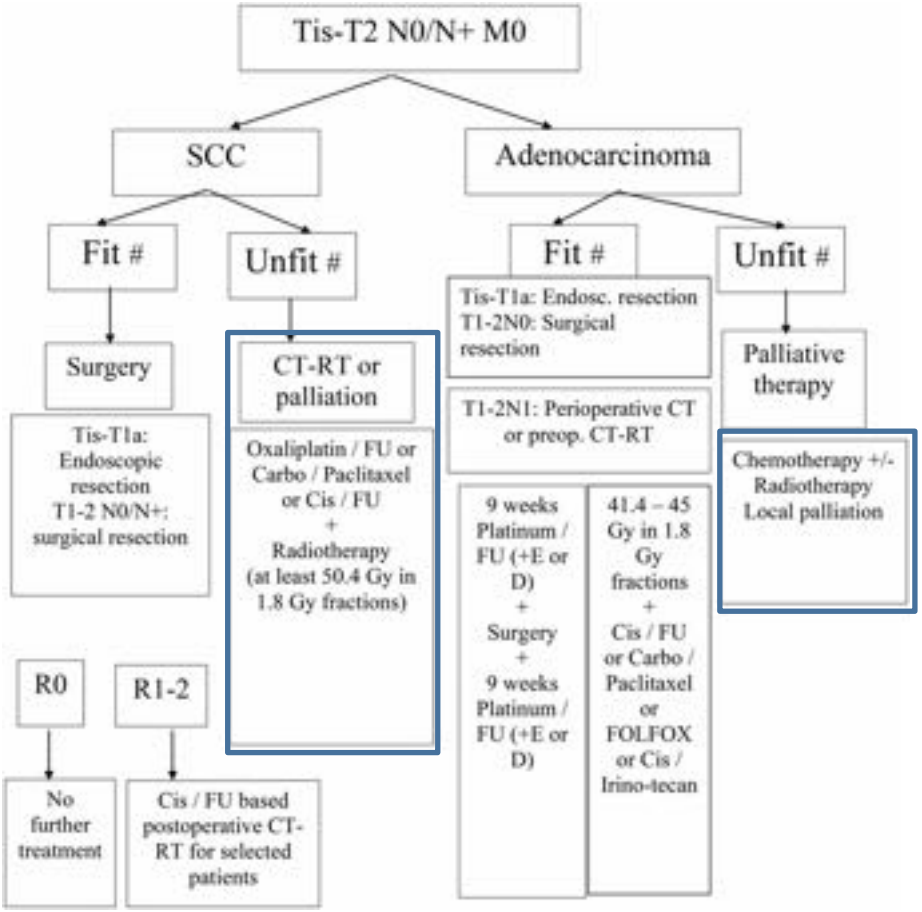
I tumori il cui epicentro è situato entro 5cm dalla giunzione gastroesofagea e che si estendono anche all' esofago vanno classificati e stadiati come i tumori dell' esofago.
I tumori con epicentro entro 5cm dalla giunzione senza estensione nell' esofago, i tumori con epicentro a più di 5cm dalla giunzione gastroesofagea e quelli nello stomaco vanno classificati e stadiati come i tumori gastrici.

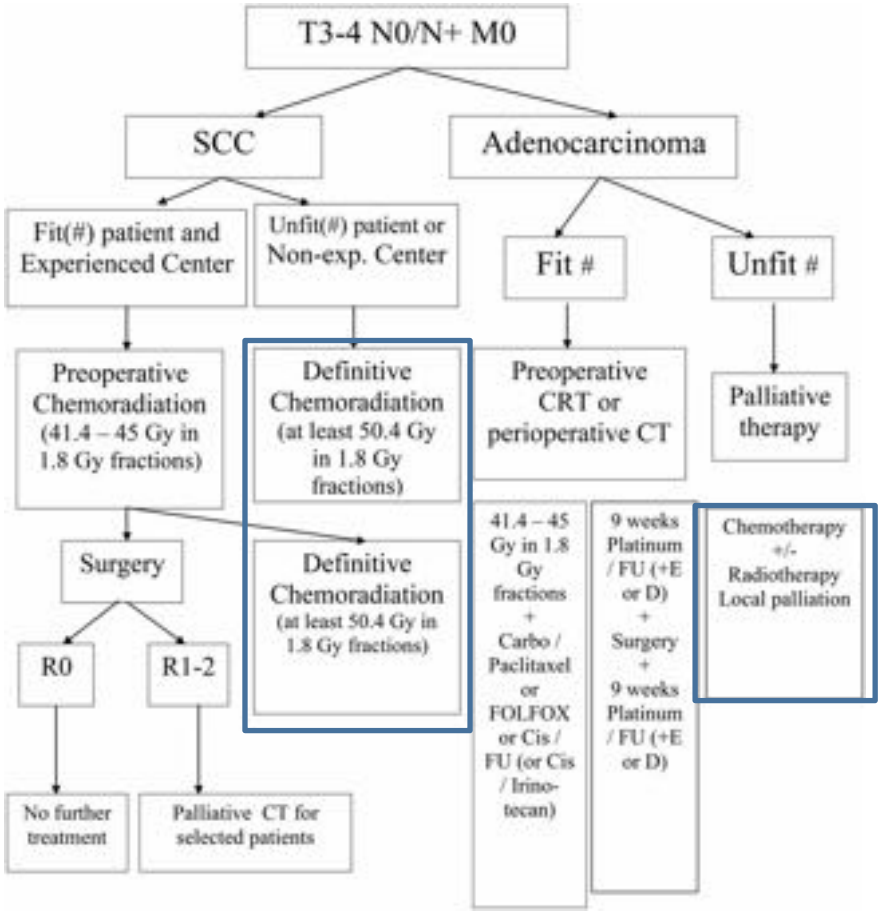
L'approccio interdisciplinare del trattamento è necessario e mandatorio!

I principali fattori prognostici indipendenti per la sopravvivenza a lungo termine e che risultano fondamentali per la scelta terapeutica sono:

- lo stadio (Te N)
- il tipo istologico
- la sede del tumore (prevalentemente per SCC)
- PS (ECOG 0-1)

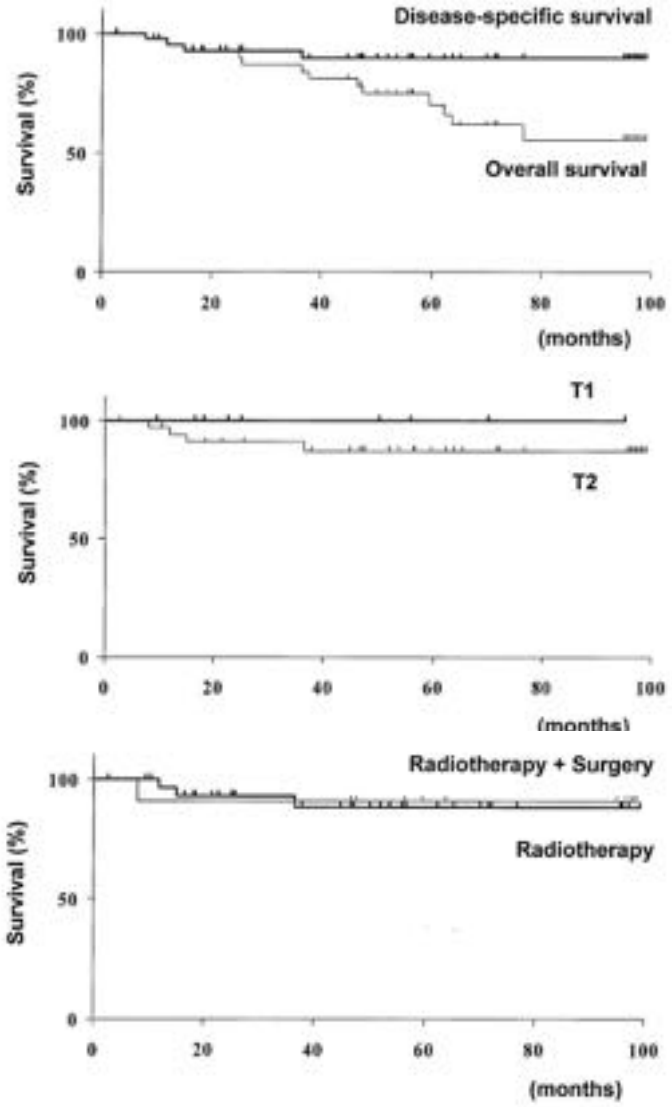
ESMO Clinical Practice Guidelines





ChemioRadioterapia Definitiva – Esofago cervicale

43 patients with Stage I–II: Thirty-two patients (74.4%) who demonstrated a complete response continued to receive further radiotherapy, with a median total dose of 61.2 Gy. Eleven other patients (25.6%) received surgery.



Local control with laryngeal voice preservation in:
- 88.9% of Stage I patients
- 67.6% of Stage II patients.

The overall and disease-specific 5-year survival rates for all patients were 70.4% and 89.5%, respectively

The 5-year disease-specific survival rates according to the T category were 100% for patients with T1 disease and 87.2% for patients with T2 disease ($p = 0.32$)

No significant differences in 5-year disease-specific survival rates between patients receiving radical radiotherapy or a combination of radiotherapy and surgery (88.4% vs. 90.9%) ($p = 0.90$)

Nakamura 2005

RTOG 85-01 randomized, phase III trial

Primary outcome = overall survival

cT1-T3, N0-1, M0 SCC or AD
50 Gy, 25 fs over 5 weeks & CDDP + 5Fu vs
64 Gy, 32 fs over 6.4 weeks

129 patients, 1986-1990 when a planned interim analysis revealed a difference that satisfied the "early stopping rule." Over the next year, 73 consecutive patients were treated uniformly by CRT.

Studio	N° paz	RT dose	CT	2 y	5 y
ECOG	59	40-60	FU/MMC	27	9
EST1282 [96]	60	40-60	–	12	7
RTOG	61	50	FU/CDDP	38	27
85-01 [97]	62	64	–	10	0
BNCI [98]	28	50	MMC/BLM/FU	38	16
	31	60	–	22	6
EORTC [99]	110	40	CDDP	20	8
	111	40	–	16	10

Overall Survival by Treatment Group*

Time, y	No. (%) Alive Following Radiation Therapy Only (Randomized)	No. (%) Alive Following Combined Modality Therapy	
		Randomized	Nonrandomized
0	62 (100)	61 (100)	69 (100)
1	21 (34)	32 (52)	43 (62)
2	6 (10)	22 (36)	24 (35)
3	0 (0)	18 (30)	18 (26)
4	0 (0)	17 (30)	13 (19)
5	0 (0)	14 (26)	10 (14)
6	0 (0)	12 (22)	6 (10)†
7	0 (0)	12 (22)	2 (6)†
8	0 (0)	10 (22)	. . .
9	0 (0)	4 (20)†	. . .
10	0 (0)	3 (20)†	. . .
Total dead (median, mo)	62/62 (9.3)	48/61 (14.1)	65/69 (16.7)

*Percentages are estimated. Data compiled by Kaplan-Meier method. Statistical test results of the log-rank test are randomized comparison, $P<.001$; and combined modality therapy and radiation therapy (randomized vs nonrandomized), $P = .24$ (stratified by tumor stage). Ellipses indicate data not available because follow-up lasted less than 8 years.
†Percentages are unreliable due to the small number of people at risk.

Persistence of disease was the most common mode of treatment failure

CRT: (34/130 [26%]) vs
RT only (23/62 [37%]).

Cooper , JAMA 1999

ChemioRadioterapia vs Radioterapia

Pooling seven randomized trials with concomitant RTCT, 687 patients

RTCT

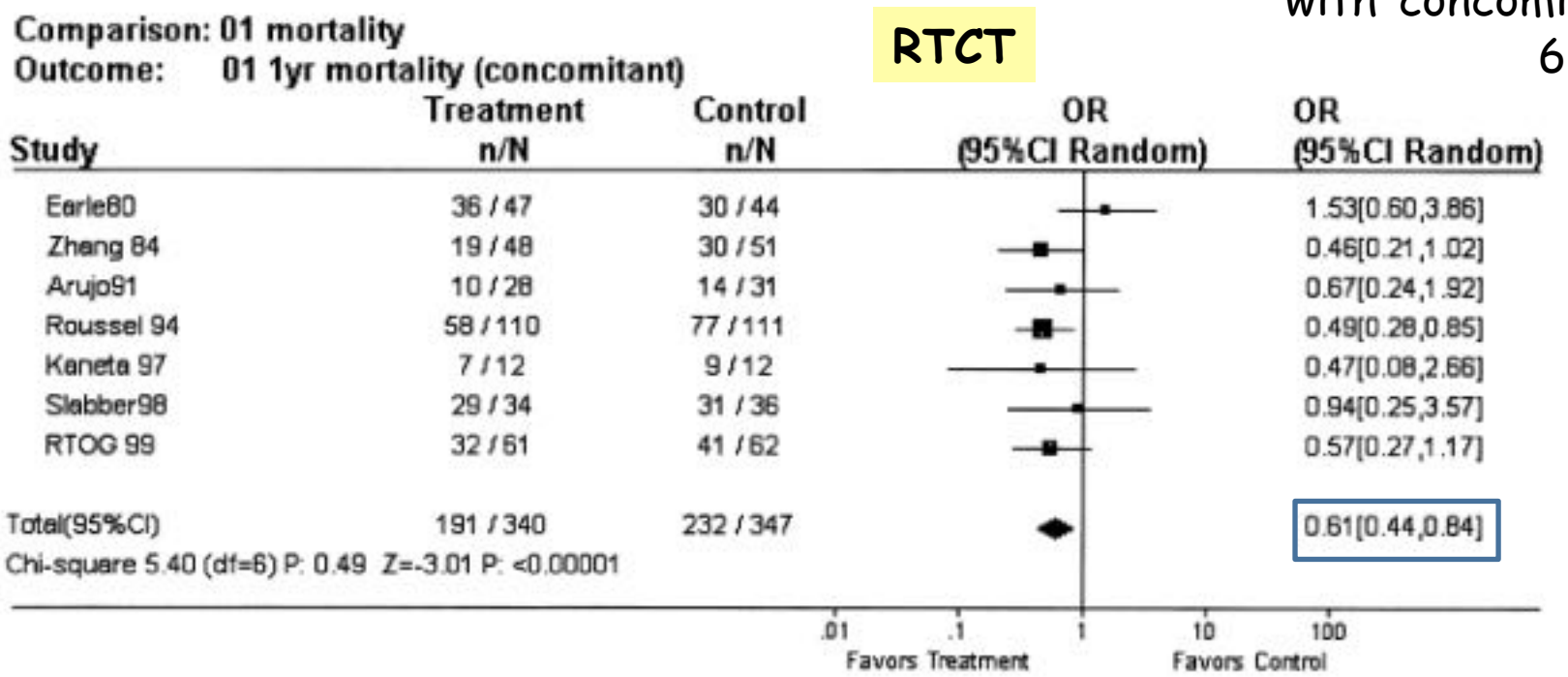


Fig. 1. Pooling of 1-year mortality data from trials of concomitant RTCT vs. RT.

CDDP

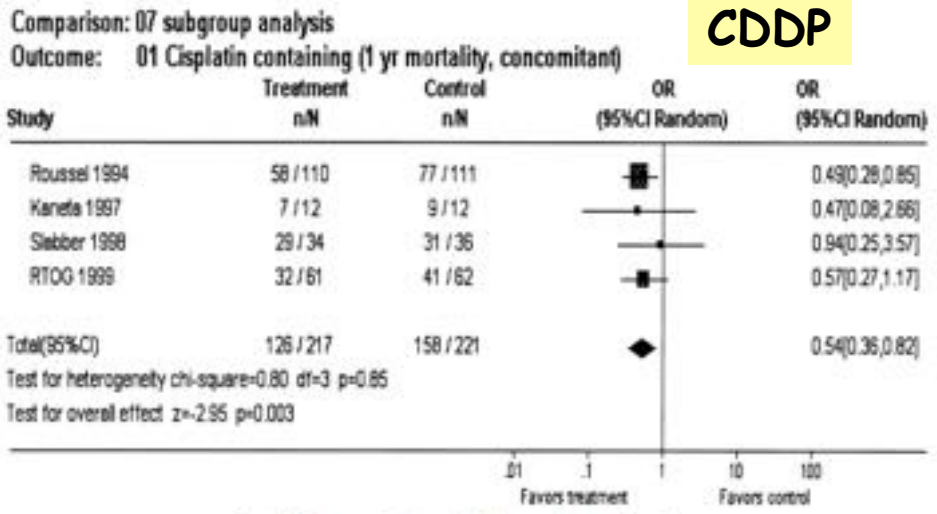


Fig. 3. Subgroup analysis: cisplatin-containing studies only.

However, these advantages are associated with a significant increase in potentially life-threatening and severe adverse effects (Grade 3-4).

Wong 2003

ChemioRadioterapia vs Radioterapia

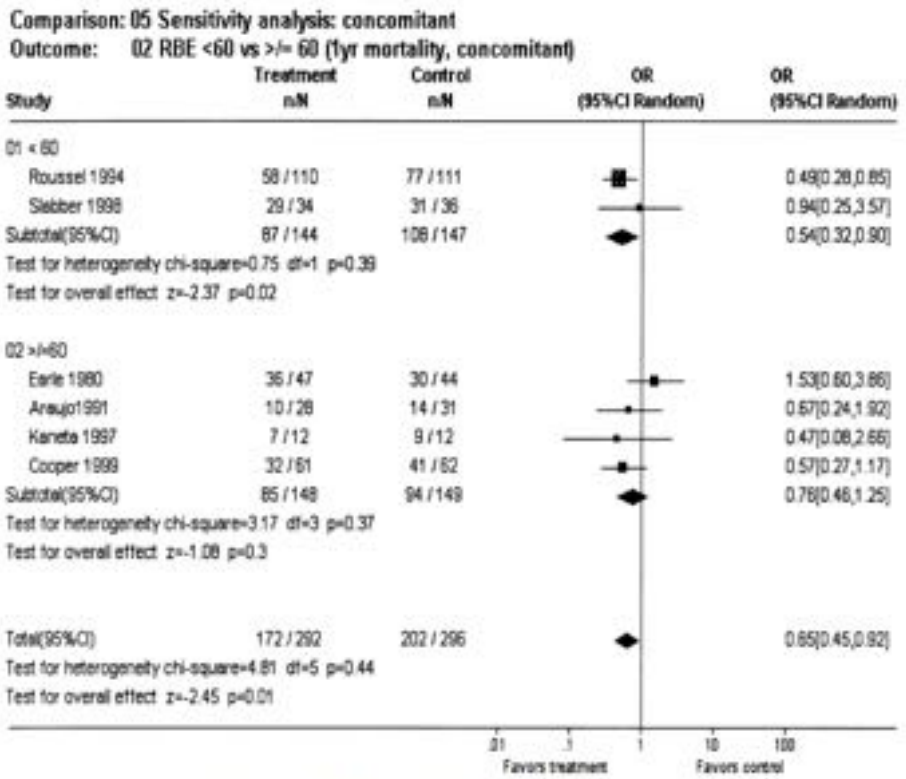


Fig. 4. Sensitivity analysis results (BED <60 Gy vs. ≥60 Gy).

No statistically significant survival benefit was detected for studies using a BED ≥ 60 Gy

This observation infers that the survival benefit observed might be a result of chemotherapy compensating for suboptimal RT dosing rather than augmenting survival beyond what optimal RT alone could provide.

In patients with a favorable PS and who have a reasonable chance of completing concomitant RTCT, this approach is a reasonable option compared with RT alone.

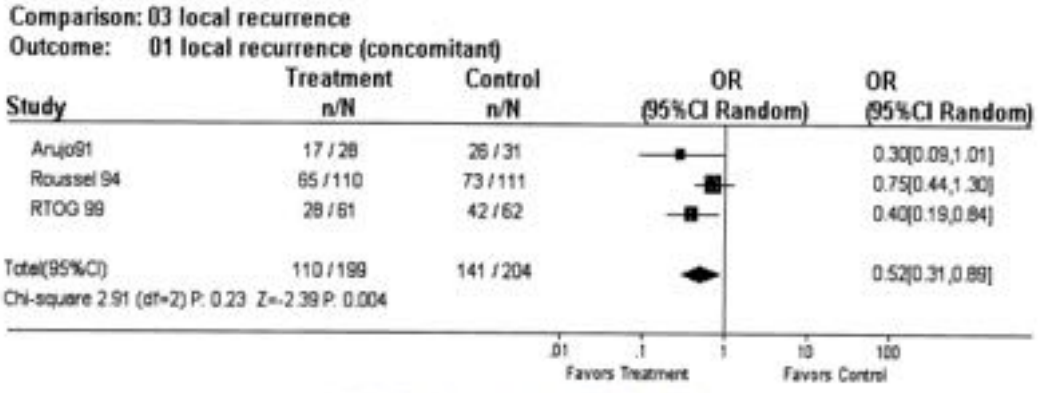


Fig. 5. Trials of concomitant RTCT vs. RT.

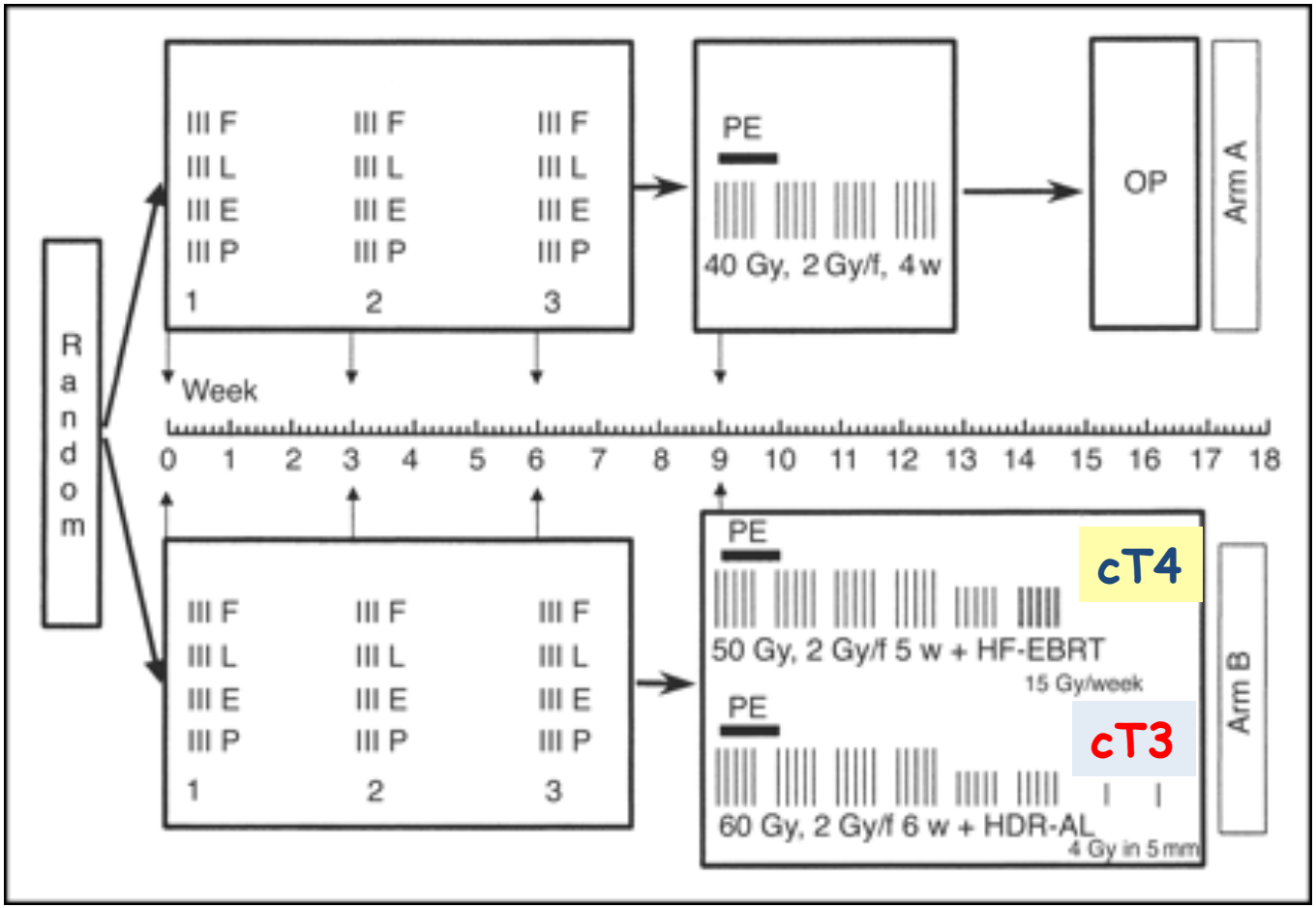
Wong 2003

ChemioRadioterapia + Chirurgia vs ChemioRadioterapia Definitiva

172 patients (86 patients per arm),
T3-4, N0-1, M0, SCC

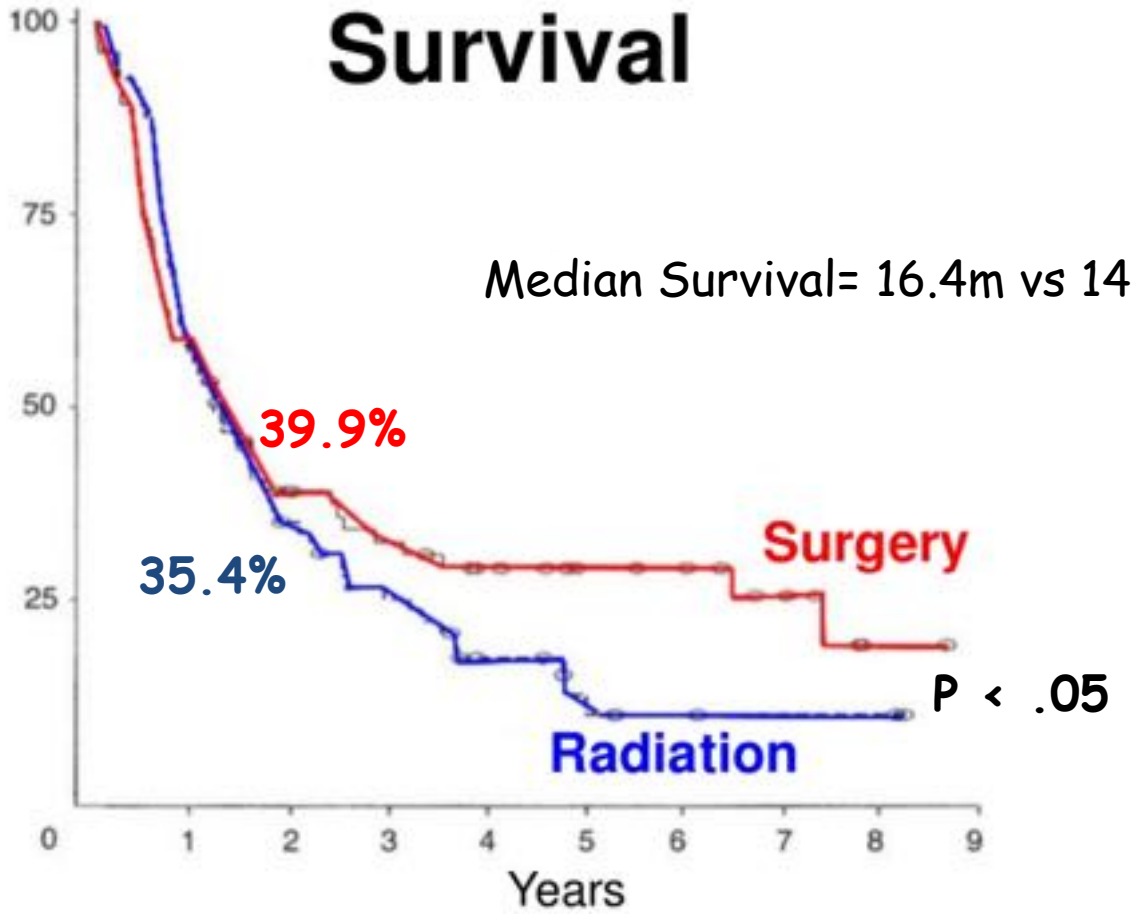
University of Essen
1994-2002

Primary outcome = overall survival



Stahl 2005, Stahl 2008

Equivalent Overall survival at 2 years between both treatment groups



Median Survival= 16.4m vs 14.9m

Treatment-related mortality was significantly increased in the Surgery group than in the CRT group (12.8% v 3.5%, respectively; P = .03).

Stahl 2005, Stahl 2008

The patient group in this study was extremely homogeneous. Only patients with T3 and T4 tumors according to EUS and CT and only patients with SCC histology were eligible.

2 years LC = 43%,
2 years survival = 35%.

Table 1. Pretreatment Patient Characteristics

Characteristic	Total (N = 172) No.	%	Arm A (n = 86) No.	%	Arm B (n = 86) No.	%
Age						
< 60 years	112	65	53	62	59	69
60-70 years	60	35	33	38	27	31
Median, years	57		57		57	
Range, years	36-71		37-70		36-71	
Stage						
uT3 N0	31	18	14	16	17	20
uT3 N1	112	65	56	65	56	65
uT4 N0-1	29	17	16	19	13	15
Endoscopic ultrasound						
Complete	99	58	53	62	46	53
Incomplete*	73	42	33	38	40	47

Table 2. Phase III Trials With Definitive Radiochemotherapy in Esophageal Cancer

Trial	No. of Patients	Proportion of Patients With T3-4 Tumors (%)	Radiation Dose (Gy)	Crude Rate of Local Failure (%)	Local Failure at 2 Years (%)
RTOG 85-01[3]	61	8	50	45	47
INT 0123[20]	109	43	50	55	52
INT 0123	109	48	64	50	56
Present trial	86	100	> 65	51	58

2-year LPFS was better in the Surgery group (64.3%) than in the CRT group (40.7%; P = .003).

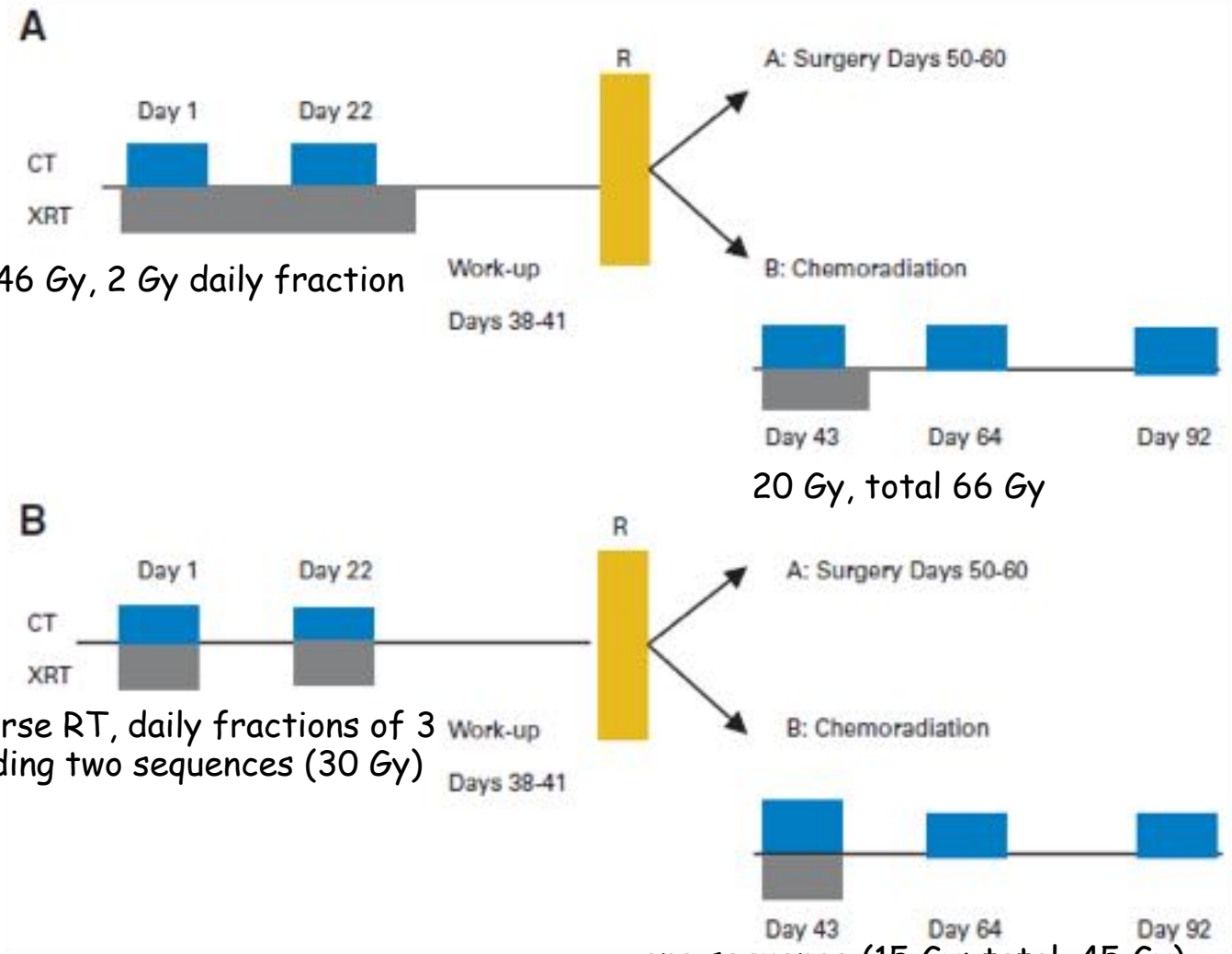
Stahl 2005, Stahl 2008

ChemioRadioterapia + Chirurgia vs ChemioRadioterapia Definitiva

FFCD 9102

259 Patients with operable T3N0-1M0, SCC = 88%

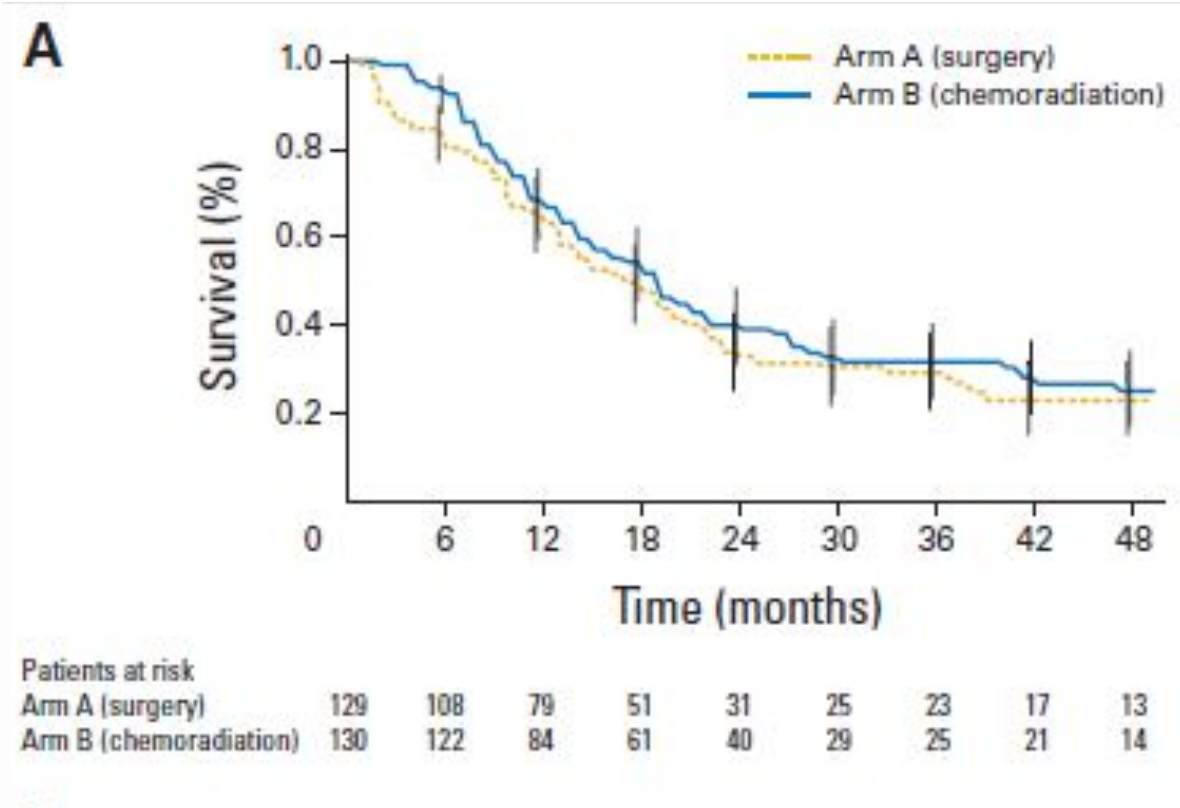
Primary outcome = overall survival



Bedenne 2007

2y survival rate was 34% in arm A vs 40% in arm B (P = .44).

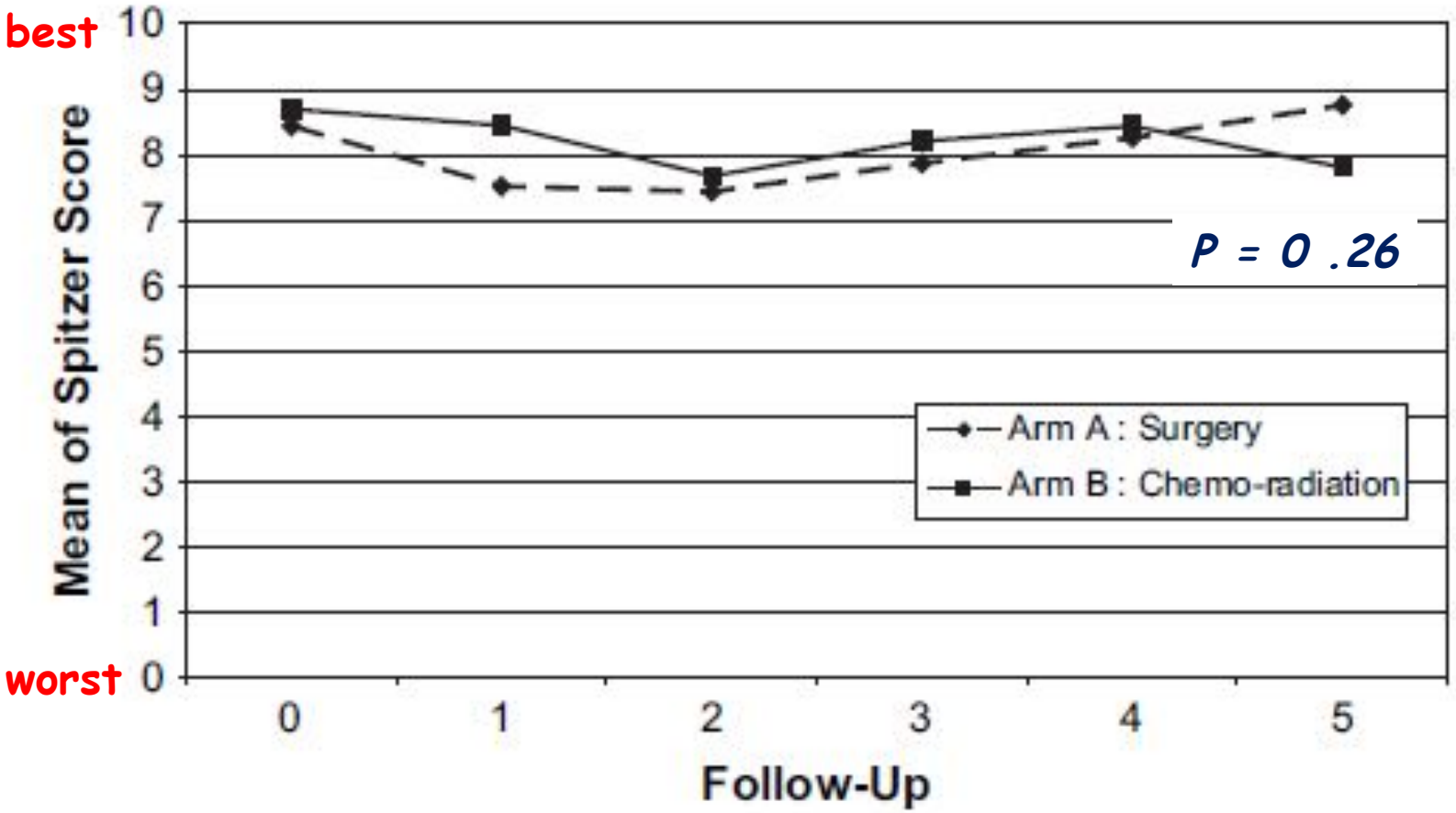
Median survival time was 17.7 ms in arm A versus 19.3 ms in arm B.



2-year local control rate: 66.4% in arm A versus 57.0% in arm B

Bedenne 2007

The longitudinal quality-of-life study



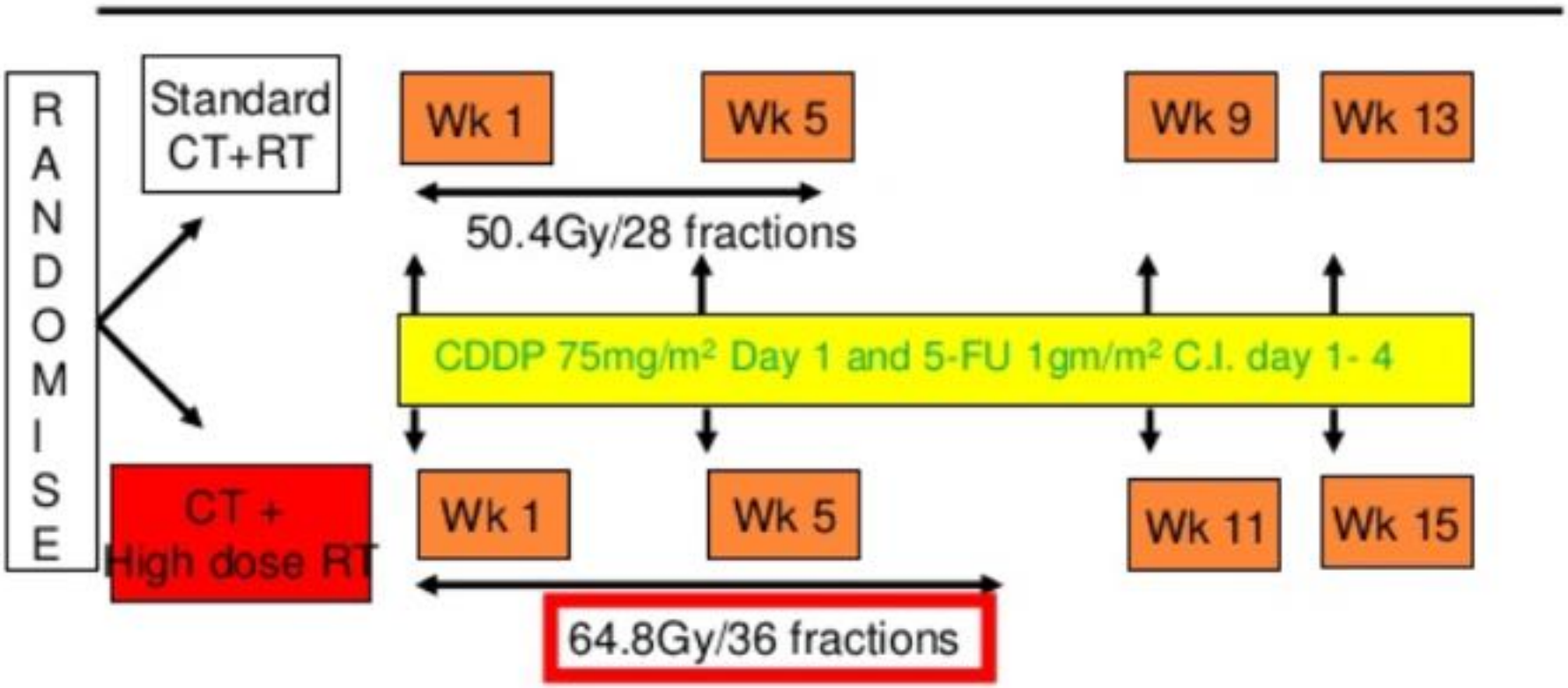
In univariate analysis, the mean Spitzer quality-of-life index score was higher in arm B only at the first follow-up period 6 months after inclusion (*P = 0.01*).

Bonnetain 2006

The Intergroup 0123 phase III trial (RTOG 94-05)

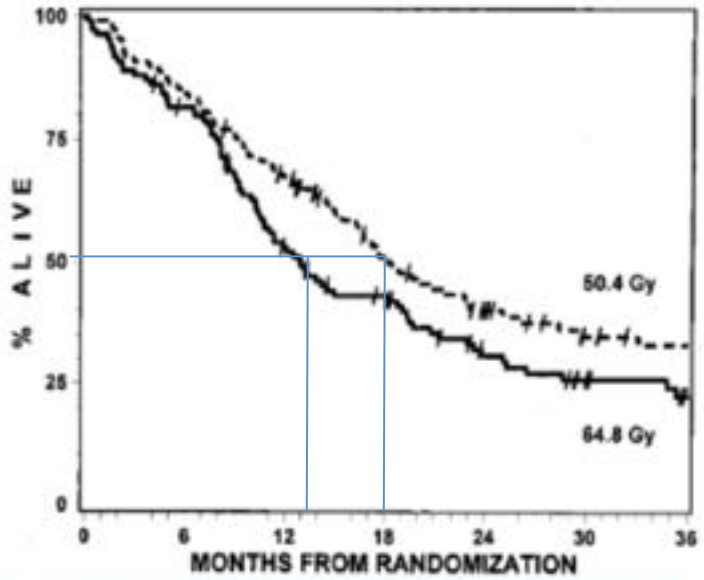
236 patients with T1-4, N0-1, M0, 218 eligible

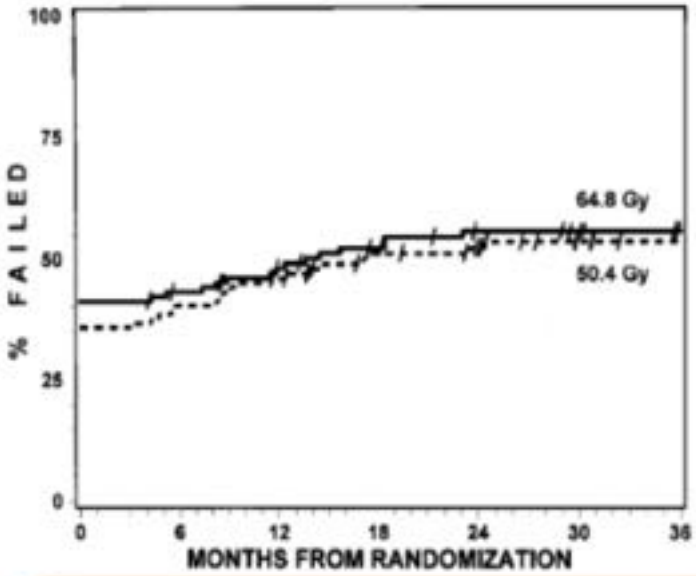
PURPOSE: To compare the local/regional control, survival, and toxicity



Minsky 2002

The Intergroup 0123 phase III trial (RTOG 94-05)





No significant difference in survival(p=NS)

MS-18 v/s 13 months
2 yr survival—40% v/s 31%

No significant difference in time to first failure(52% v/s 56%)
(local /regional failure or locoregional persistance of cancer)

This trial demonstrated that for patients who receive concurrent chemotherapy with radiation, **higher doses of radiation therapy do not offer a local/regional control or survival advantage**.

Minsky 2002

RTOG 92-07 phase I/II trial

49 patients

50 Gy + CDDP & 5FU followed 2 ws later by HDR 5 Gy of 15 Gy or LDR of 20 Gy

Life-Threatening and Fatal Toxicities in RTOG 9207 (n = 49)

	Life-threatening	Fatal	All (%)
Upper aerodigestive tract excluding fistulas[a]	3	0	3 (6%)
Fistula	3	3	6 (12%)
Gastrointestinal tract[b]	2	0	2 (4%)
Hematologic[c]	8	1	9 (18%)
Infection	2	3	5 (10%)
Skin[d]	0	1	1 (2%)
Renal	0	1	1 (2%)
Cardiac	0	1	1 (2%)

24%

10 %

[a] For the lungs and esophagus, life-threatening effects included ulceration, necrosis, perforation, and formation of a stricture.

[b] Life-threatening gastrointestinal side effects were nausea and vomiting for more than 6 days, requiring hospitalization.

[c] Life-threatening hematologic effects included a leukocyte count below 1.0×10^9 cells per liter, a platelet count below 25×10^9 cells per liter, and a hemoglobin concentration below 50 g per liter.

[d] Fatal side effects of skin involved moist desquamation.

17% 1y actuarial risk of treatment-related fistulas

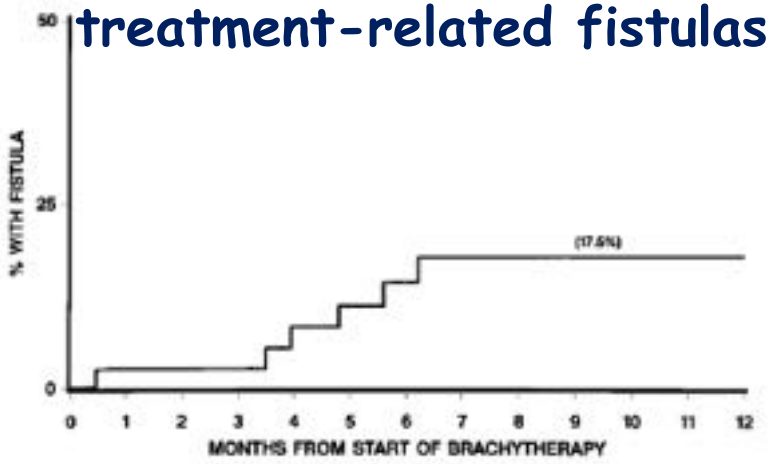


FIGURE 2. The cumulative incidence of esophageal fistulas in Radiation Therapy Oncology Group Study 9207 is shown.

The estimated survival rate at 12 months was 49%, with an estimated median survival of 11 months.

Gaspar 2000

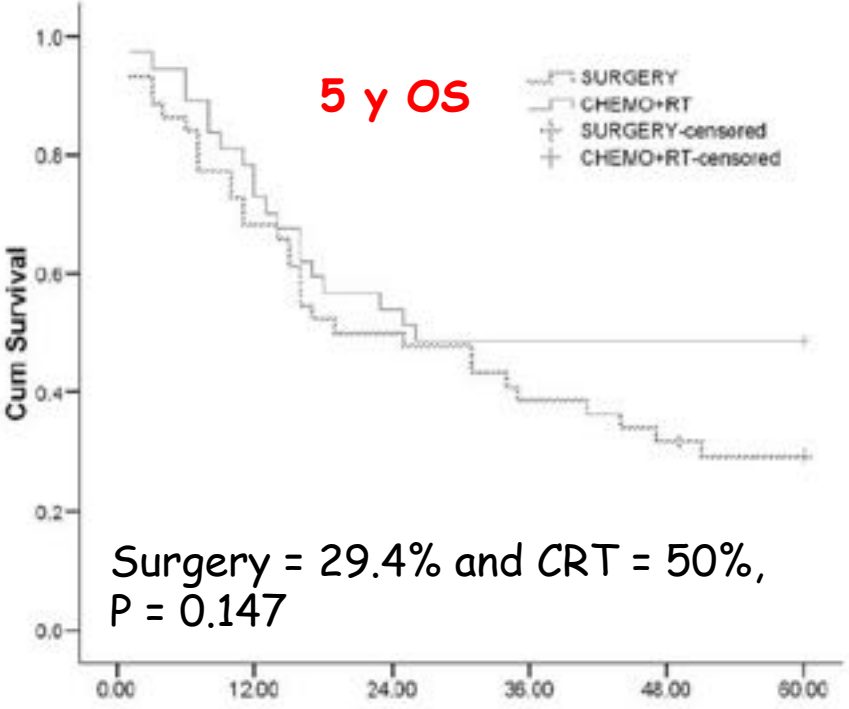
ChemioRadioterapia vs Chirurgia

Chinese University of Hong Kong
2000-2004

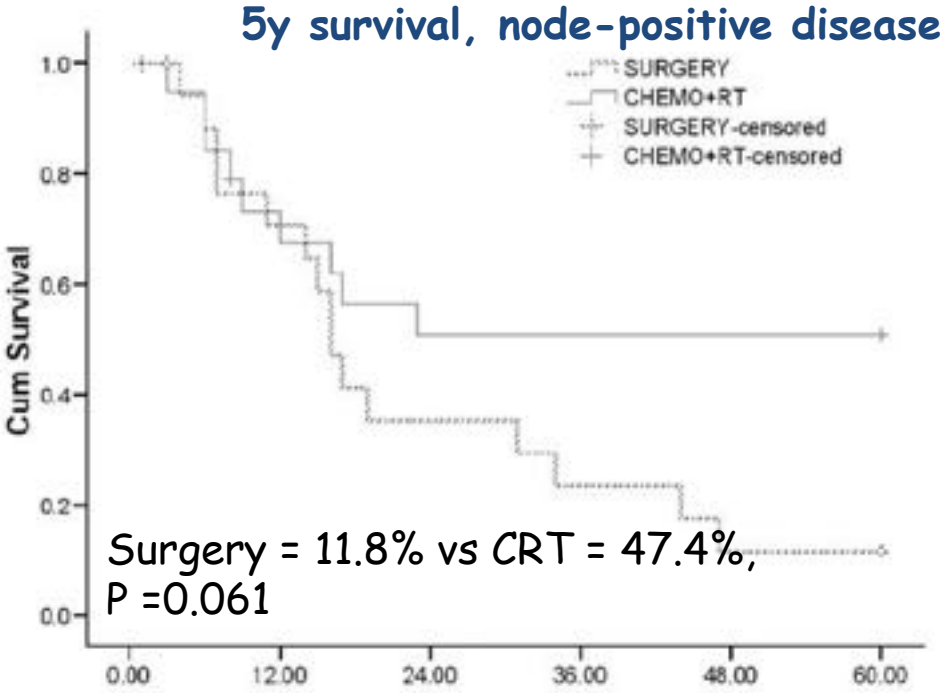
81 pts with resectable SCC,
44 Surgery vs 36 CRT (CDDPp + ic 5FU & 50–60 Gy, 25–30 fs over 5–6 ws)

Primary outcome = overall survival

Secondary outcomes = disease-free survival, morbidities and mortalities



Surgery = 29.4% and CRT = 50%,
P = 0.147



Surgery = 11.8% vs CRT = 47.4%,
P =0.061

A similar trend in the 5y survival for **cancer-related deaths** was also observed surgery = 33.9% and CRT = 47.2% (P = 0.241)

The 5-year **DFS** also showed a trend to significance favoring CRT (P = 0.068), particularly for patients suffering from node-positive disease (P = 0.017).

Teoh 2013

ChemioRadioterapia Definitiva, quale Chemioterapia?

A comparison of carboplatin and paclitaxel with cisplatinum and 5-fluorouracil in definitive chemoradiation in esophageal cancer patients

Northeast Netherlands
from 1996 till 2008

Multicenter **comparative** study , 102 patients:
47 = cisplatinum/5-FU (75 mg/m2 and 1 g/m2)
55 = carboplatin/paclitaxel (AUC2 and 50 mg/m2).

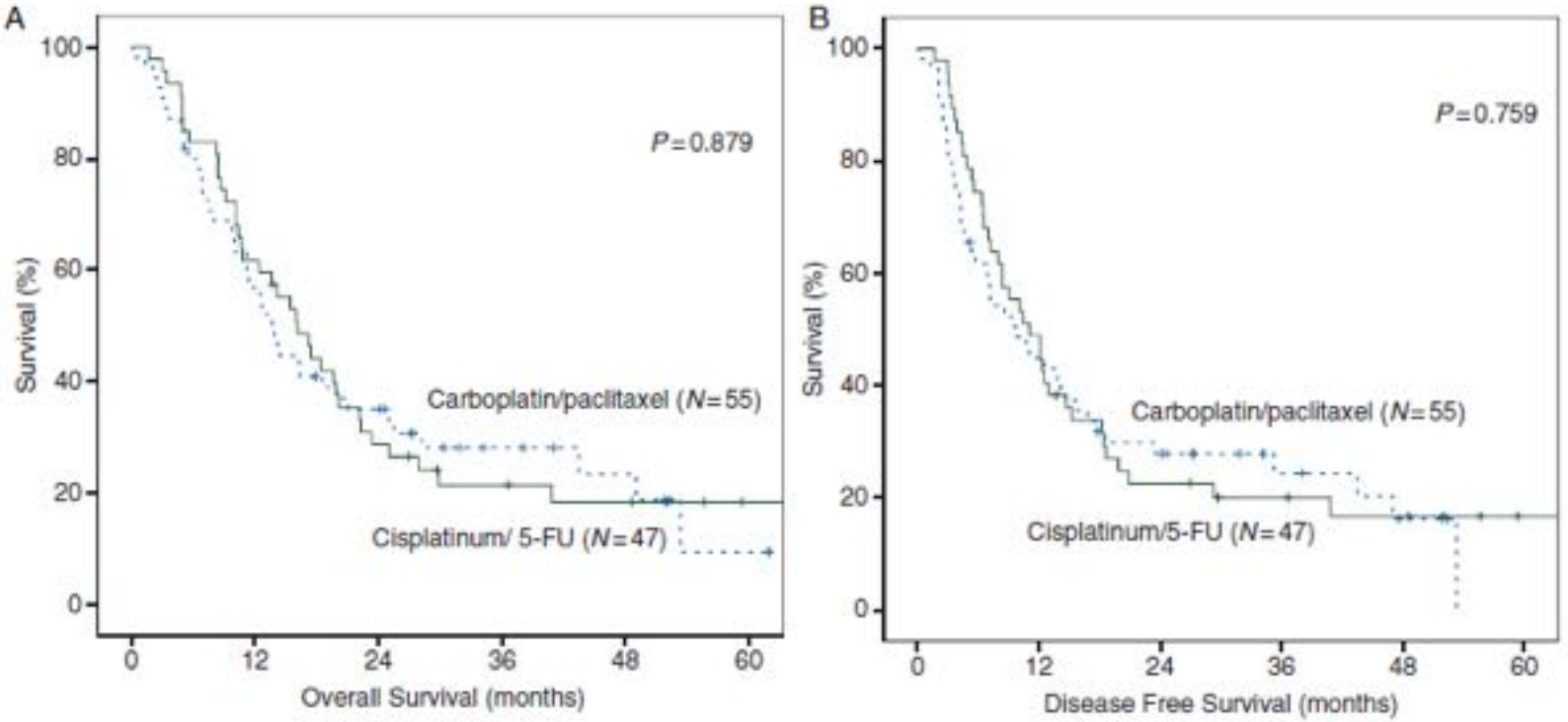


Figure 1. Kaplan–Meier survivals estimation of the overall survival (A) and disease-free survival (B) for dCRT with cisplatinum/5-FU ($N = 47$) or carboplatin /paclitaxel ($N = 55$).

Honing J 2014

ChemioRadioterapia Definitiva, quale Chemioterapia?

A comparison of carboplatin and paclitaxel with cisplatinum and 5-fluorouracil in definitive chemoradiation in esophageal cancer patients

Northeast Netherlands
from 1996 till 2008

	Cisplatinum/ 5-FU (N = 47)	Carboplatin/ paclitaxel (N = 55)	P value
Completed chemotherapy	27 (57%)	44 (82%)	*0.010*
Toxities (CTCAE 4.0)			
Overall toxicity (≥grade 3)	26 (55%)[a]	12 (22%)	*0.001*
Hematological ≥grade 3	9 (19%)	2 (4%)	*0.021*
Nonhematological ≥grade 3	18 (38%)	10 (18%)	*0.028*
Grade 3	18 (38%)	8 (15%)	*0.011*
Grade 4	7 (15%)	3 (6%)	0.180
Mortality	2 (4%)	1 (2%)	0.594
Hematologic[b]			
Febrile leucopenia	6 (13%)	2 (4%)	0.139
Trombocytopenia	1 (2%)	2 (4%)	1.000
Bleeding	1 (2%)	0 (0%)	0.461
Anemia	3 (6%)	3 (6%)	1.000
Nonhematologic[b]			
Nauseau/vomiting	2 (4%)	0 (0%)	0.210
Fatigue	1 (2%)	0 (0%)	0.461
Diarrhea	0 (0%)	1 (2%)	1.000
Mucositis	2 (4%)	2 (4%)	1.000
Other	14 (30%)	7 (13%)	0.049

A higher percentage of patients completed the carboplatin/paclitaxel regimen (82% versus 57%, P = 0.010).

Hematological and nonhematological toxicity (≥grade 3) in the carboplatin/ paclitaxel group (4% and 18%) was significantly lower than in the cisplatinum/5-FU (19% and 38%, P = 0.001).

Honing J 2014

ChemioRadioterapia Definitiva, CT di induzione?

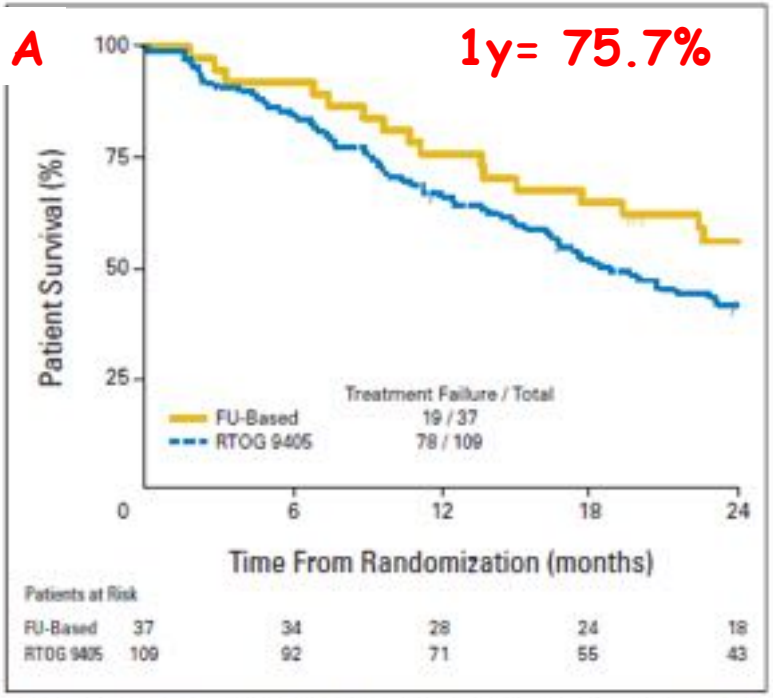
Unresectable disease

RTOG 0113: multi-institutional cooperative group setting
84 patients randomly assigned toreceive either:

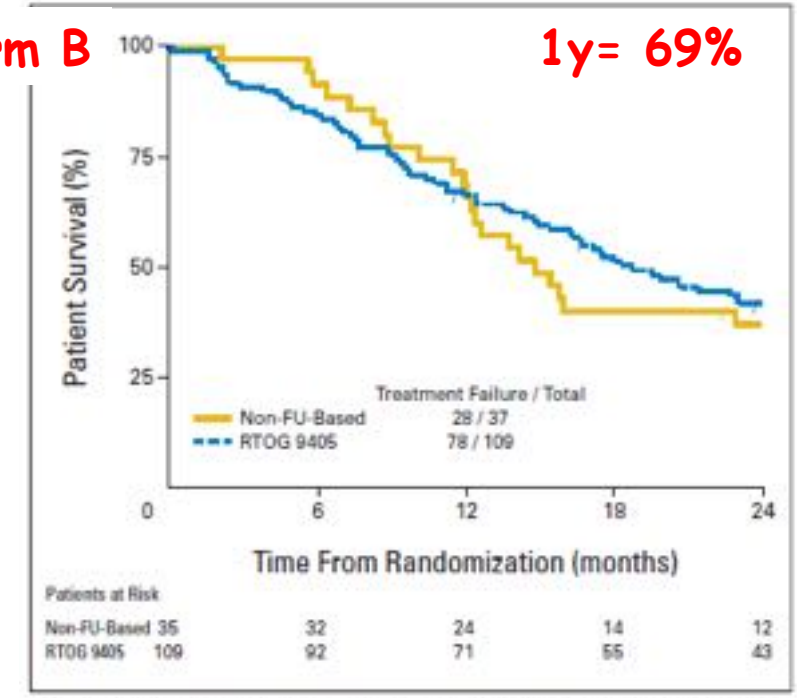
Iduction with 5FU, cisplatin, and paclitaxel and then 5FU + paclitaxel with RT 50.4 Gy (arm A)

or induction with paclitaxel plus cisplatin and then 5FU + paclitaxel with RT 50.4 Gy(arm B).

arm A **1y= 75.7%**



arm B **1y= 69%**



The primary end point was to assess whether any approach would achieve a ≥ 77.5% 1-year survival rate, surpassing the historical 66% rate from the RTOG 9405 study.

Ajani 2008

Unresectable disease

RTOG 0113: multi-institutional cooperative group setting

Table 3. Chemotherapy and Acute Radiotherapy Toxicity

	Fluorouracil-Based Arm (n = 37) Grade (No. of patients)					Non–Fluorouracil-Based Arm (n = 35) Grade (No. of patients)				
Toxicity	1	2	3	4	5	1	2	3	4	5
Allergy/immunology	0	0	1	0	0	0	0	0	0	0
Auditory/hearing	1	0	0	0	0	2	1	0	0	0
Blood/bone marrow	4	17	5	9	0	5	5	14	10	0
Cardiovascular, arrhythmia	0	1	1	0	0	1	0	1	0	0
Cardiovascular, general	2	3	4	2	0	4	3	2	1	0
Constitutional symptoms	10	12	9	0	0	6	16	6	3	0
Dermatology/skin	9	17	1	0	0	5	14	0	0	0
GI	5	12	18	2	0	4	8	15	6	0
Hemorrhage	1	0	1	0	1	5	0	0	0	0
Hepatic	8	1	2	0	0	5	5	0	1	0
Infection/febrile neutropenia	0	1	8	0	0	2	4	5	0	1
Lymphatics	0	0	0	0	0	1	0	0	0	0
Metabolic/laboratory	8	7	5	2	0	5	2	8	1	0
Musculoskeletal	0	0	0	0	0	1	0	1	0	0
Neurology	7	4	4	0	0	10	4	4	0	0
Ocular/visual	2	0	0	0	0	2	0	0	0	0
Pain	12	6	1	0	0	5	8	4	0	0
Pulmonary	4	6	1	0	0	2	3	1	0	0
Renal/genitourinary	5	2	0	0	0	4	3	0	0	0
Worst nonhematologic	1	6	25	4	1	1	8	17	8	1
% of patients	3	16	68	11	3	3	23	49	23	3
Worst overall	0	6	20	10	1	0	5	15	14	1
% of patients	0	16	54	27	3	0	14	43	40	3

Grade 3 toxicity = 54% in arm A and 40% in arm B.
Grade 4 toxicity = 27% in arm A and 40% in arm B.
GI grade 3 or 4 toxicities were similar in both arms
(arm A 54% and arm B 60%).

Ajani 2008

Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial

Unresectable disease

RT: 50 Gy/ 25 fx

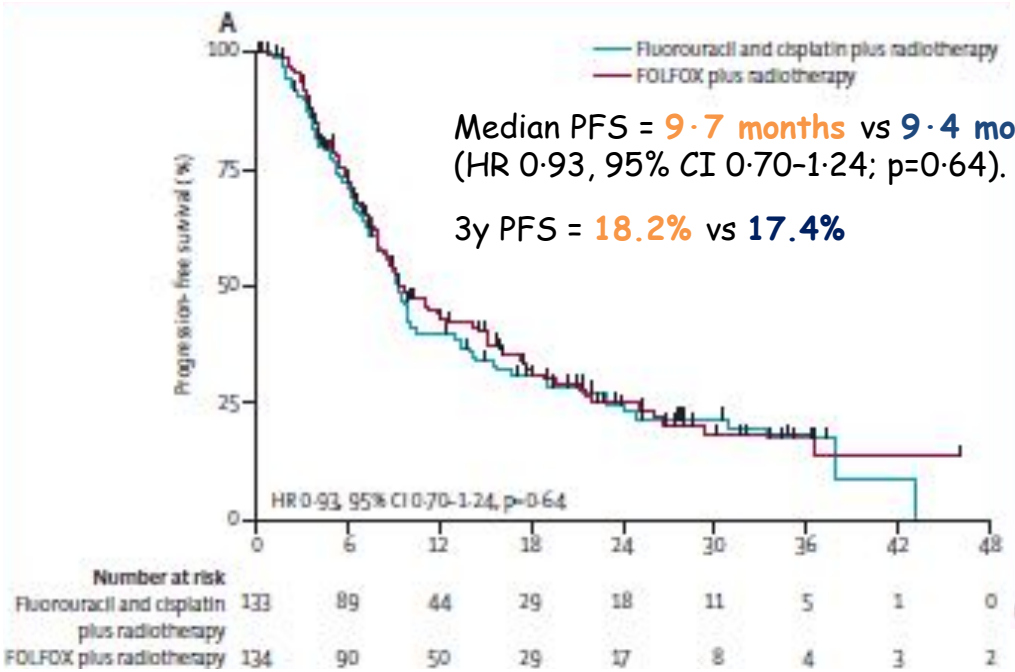
THE LANCET Oncology

Thierry Conroy, Marie-Pierre Galais, Jean-Luc Raoul, Olivier Bouché, Sophie Gourgou-Bourgade, Jean-Yves Douillard, Pierre-Luc Etienne, Valérie Boige, Isabelle Martel-Lafay, Pierre Michel, Carmen Llacer-Moscardo, Eric François, Gilles Créhange, Meher Ben Abdelghani, Beata Juzyna, Laurent Bedenne, Antoine Adenis, for the Fédération Francophone de Cancérologie Digestive and UNICANCER-GI Group

Histology:
SCC=86%
AD=14%

Primary endpoint = PFS

Median follow-up = 25.3 months

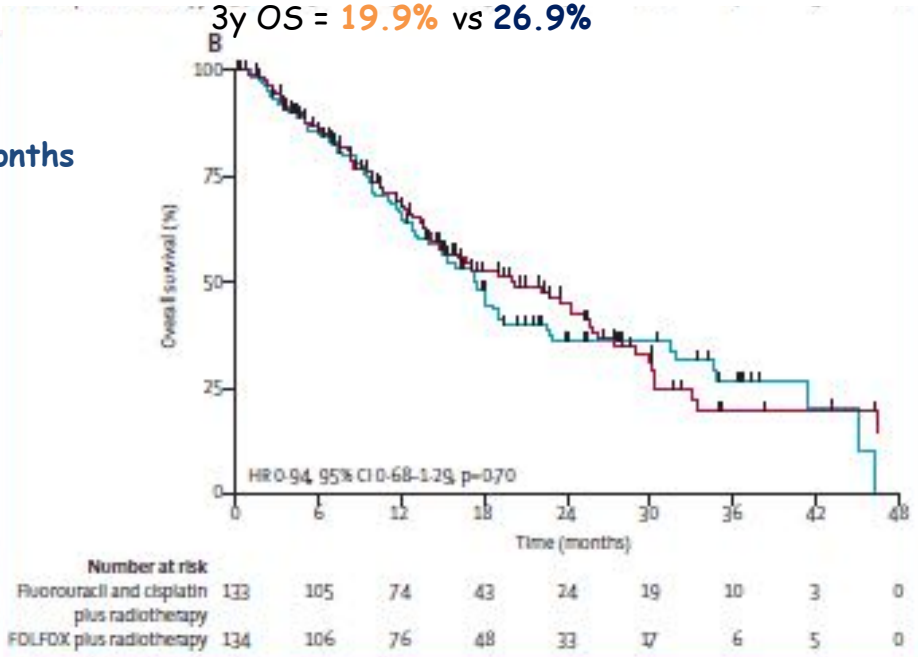


Median PFS = **9·7 months** vs **9·4 months**
(HR 0·93, 95% CI 0·70–1·24; p=0·64).

3y PFS = **18.2%** vs **17.4%**

Median OS = **20·2 months** vs **17·5 months**
(HR 0·94, 95% CI 0·68–1·29; p=0·70)

3y OS = **19.9%** vs **26.9%**



Conroy T. 2014

No significant differences were recorded in the rates of most frequent grade 3 or 4 adverse events between the treatment groups.

	FOLFOX group (n=131)			Fluorouracil and cisplatin group (n=128)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Haematological						
Neutropenia	30 (23%)	29 (22%)	9 (7%)	32 (25%)	26 (20%)	11 (9%)
Febrile neutropenia	0	5 (4%)	2 (2%)	1 (1%)	6 (5%)	3 (2%)
Neutropenia and infection	1 (1%)	2 (2%)	0	0	1 (1%)	2 (2%)
Lymphopenia	4 (3%)	14 (11%)	7 (5%)	4 (3%)	11 (9%)	11 (9%)
Leucopenia	38 (29%)	25 (19%)	3 (2%)	41 (32%)	20 (16%)	11 (9%)
Anaemia	68 (52%)	6 (5%)	1 (1%)	69 (54%)	12 (9%)	2 (2%)
Thrombocytopenia	52 (40%)	6 (5%)	3 (2%)	53 (41%)	2 (2%)	8 (6%)
Hyponatraemia	14 (11%)	3 (2%)	0	22 (17%)	5 (4%)	0
Hyperkalaemia	11 (8%)	1 (1%)	0	20 (16%)	1 (1%)	0
Hypocalcaemia	14 (11%)	0	0	13 (10%)	1 (1%)	0
Non-haematological						
Aphagia/dysphagia	16 (12%)	32 (24%)	6 (5%)	12 (9%)	31 (24%)	0
Asthenia	47 (36%)	23 (18%)	0	47 (37%)	12 (9%)	1 (1%)
Oesophagitis	19 (15%)	8 (6%)	1 (1%)	18 (14%)	11 (9%)	0
Erythema/epidermitis	9 (7%)	0	1 (1%)	17 (13%)	1 (1%)	0
Weight loss	42 (32%)	5 (4%)	0	40 (31%)	5 (4%)	0
Anorexia	25 (19%)	6 (5%)	0	19 (15%)	4 (3%)	0
Mucositis	20 (15%)	6 (5%)	1 (1%)	30 (23%)	2 (2%)	0
Vomiting	28 (21%)	4 (3%)	1 (1%)	39 (31%)	3 (2%)	0
Nausea	62 (47%)	3 (2%)	0	74 (58%)	4 (3%)	0
Odynophagia	17 (13%)	2 (2%)	0	8 (6%)	3 (2%)	0
Denutrition	0	2 (2%)	0	0	2 (2%)	0

Sensory neuropathy: 24 [18%] vs 1 [1%], p<0·0001,
increases in AST concentrations (14 [11%] vs 2 [2%], p=0·002),
increases in ALTconcentrations (11 [8%] vs 2 [2%], p=0·012)

Oesophageal/epigastric pain	16 (12%)	4 (3%)	0	13 (10%)	2 (%)	0	
Paraesthesia	61 (47%)	0	0	2 (2%)	1 (1%)	0	**p<0·0001**

Alopecia: 2 [2%] vs 12 [9%], p=0·005

Renal insufficiency	1 (1%)	0	0	4 (3%)	1 (1%)	1 (1%)	**p=0·011**

Data are n (%). FOLFOX=fluorouracil, leucovorin, and oxaliplatin.

Conroy T. 2014

Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial

THE LANCET Oncology

258 patients, randomised to receive definitive CT-RT with or without cetuximab

primary endpoint: proportion of patients who were treatment failure free at week 24 for the phase 2 trial and overall survival for the phase 3 trial

Fewer patients were treatment failure free at 24 weeks in the CRT plus cetuximab group (66·4%) than in the CRT only group (76·9%).

Failure free at 24 weeks	79 (66%)	93 (77%)
Alive and without progression at last follow-up	49 (62%)	58 (62%)
Progressed at last follow-up	17 (22%)	23 (25%)
Local	7 (41%)	10 (43%)
Metastatic	2 (12%)	6 (26%)
Both	8 (47%)	7 (30%)

The CRT plus cetuximab group also had shorter median overall survival (22·1 *vs 25·4 months,* p=0·035).

Crosby 2013

Patients who received CRT plus cetuximab had more non-haematological grade 3 or 4 toxicities (79% vs 63%; p=0·004).

The most common grade 3 or 4 toxicities were low white blood cell count (11% in the CRT plus cetuximab group vs 16%in the CRT only group), low absolute neutrophil count (12% vs 19%), fatigue (20% vs 19%), and dysphagia (27% vs 37 29%).

Interpretation

Cetuximab should not be given in addition to chemoradiation in an unselected patient population. The results of our study do, however, support the use of chemoradiation alone as a standard of care in patients with non-metastatic squamous-cell carcinoma of the oesophagus and in patients with non-metastatic adenocarcinoma who are not suitable for surgery. Indeed, the outcomes of this study would support the increased use of this treatment in patients who have a higher risk of failure of surgical treatment, either due to the existence of comorbidities or where surgical excision is likely to be incomplete. A randomised trial to compare surgical and radiotherapy-based treatments in patients with oesophageal cancer with a better outlook is warranted.

Crosby 2013

Home » Meeting Library » Virtual Meeting » 2014 Gastrointestinal Cancers Symposium

The initial report of RTOG 0436: A phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer treated without surgery.

Mohan Suntharalingam MD

Oral Abstract Session: Cancers of the Esophagus and Stomach (eQ&A)

RTOG 0436 randomized Phase III trial
weekly concurrent Cisplatin (50mg/m2), Paclitaxel (25mg/m2) and daily RT 50.4Gy/1.8Gy fx + weekly Cetuximab (400mg/m2 day 1 then weekly 250 mg/m2).

primary endpoint = overall survival
secondary objective = local control evaluation

328 eligible pts
Incidence of **grade 3/4/5** treatment related AEs was 45%, 22%,4% in Arm1 (Cetuximab) and 49%, 17%,1%inArm2 (no Cetuximab).

A **cCR** rate of 56% was observed in Arm 1 vs 59% in Arm 2 [p = 0.72].

Median follow-up for all pts is 16.3mos.
The 12 and 24mo **LF** (95%CI) forArm1 was 35% and 45% vs 42% and 49% for Arm2 [p=0.41].

The 12 and 24 mo **OS rates** for cCR pts were 79% and 60% vs 52% and 30%for those with residual disease [p<0.0001].

The 12 and 24 mo **OS** for Arm 1 is 64% and 45% vs 65% and 42% for Arm 2 [p=0.59].

Suntharalingam M, J Clin Oncol 2014;32:abstr LBA6.

ChemioRadioterapia Definitiva, Adenocarcinoma

UK cancer centre
between 1995 and 2009

Retrospective analysis of 266 pts, 53% AD

2 cycles of neoadjuvant CT and two cycles of concurrent CT with cisplatin 60 mg/m2 3weekly and continuous infusion of 5-FU 300 mg/m2/day, given concurrently with 50 Gy EBRT.

median survival of 20.6 months

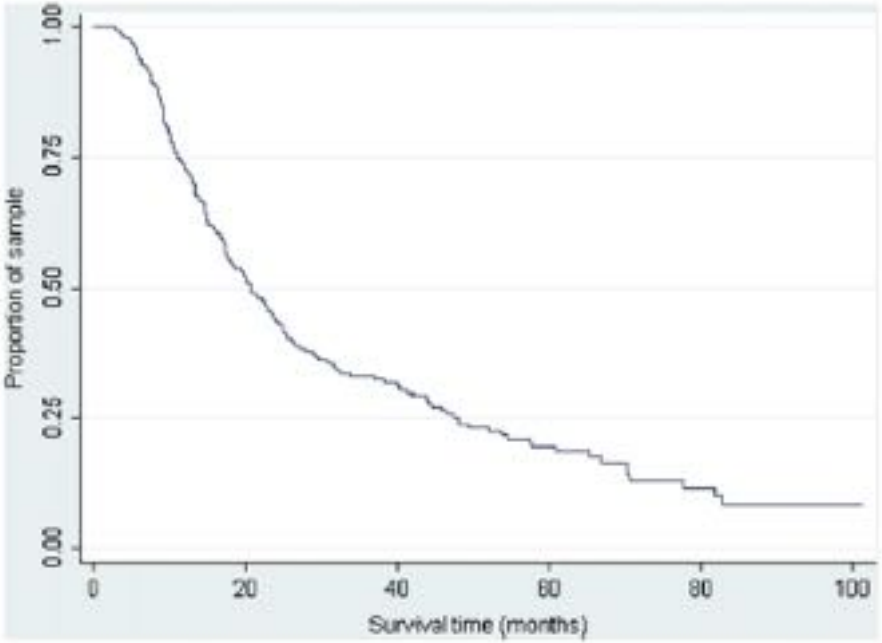


Fig. 1. Kaplan–Meier curve for the 266 patients undergoing chemoradiotherapy.

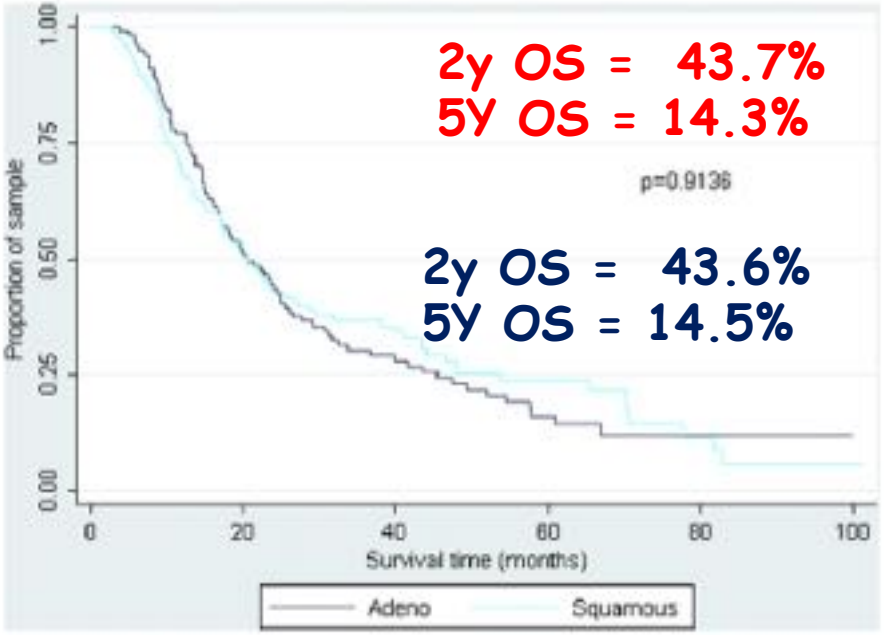


Fig. 3. Kaplan–Meier curves according to histology.

Gwynne 2011

ChemioRadioterapia Definitiva, pazienti anziani

109 pts >70 y

Table I Patient characteristics

	n = 109
Age (s.d., min–max)	74.4 ± 3.7 (70–88)
Sex ratio (men/women)	90/19
WHO performance status (*n*, %)	
0	24 (22.0)
1	63 (57.8)
2	22 (20.2)
WHO <2	87 (79.8)
Atkinson dysphagia score (*n*, %)	
0	5 (4.6)
1	27 (24.8)
2	55 (50.4)
3	15 (13.8)
4	7 (6.4)
Dysphagia stage ⩾2	77 (70.6)
Initial BMI ($kg.m^{-2}$, s.d.)	24.9 ± 6.8
Initial weight loss (%, s.d.)	7.7 ± 6.6
Initial weight loss ⩾ 10% (*n*, %)	36 (33.0)
Initial albumin ($g.l^{-1}$, s.d.)	37.7 ± 5.1
Creatinine clearance ($ml.min^{-1}$, s.d.)	73.2 ± 22.3
Charlson score[a]	
Median (min–max)	1 (0–6)
Charlson score ⩾2	27 (30.7%)

BMI = body mass index; *n* = number of patients; s.d. = standard deviation. [a]Available for 88 patients.

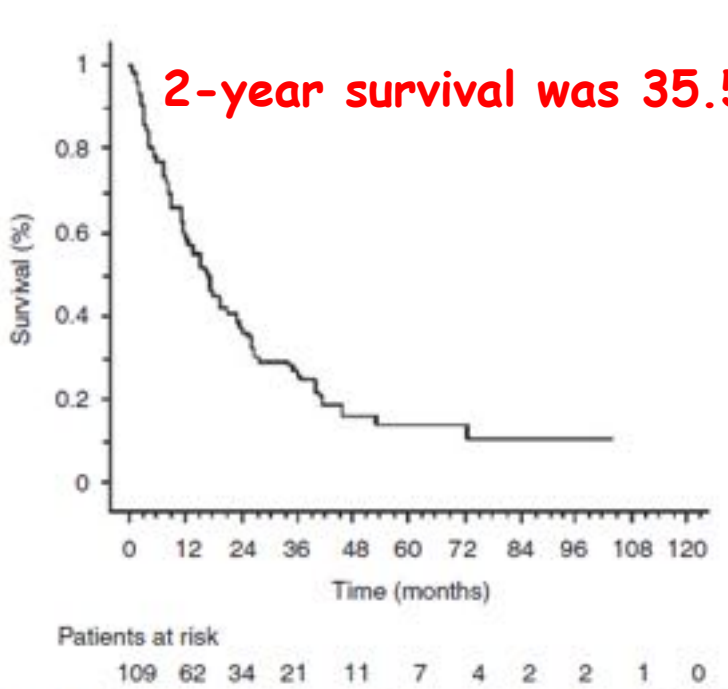


Figure 1 Overall survival. The median overall survival was 15.2 ± 2.8 months.

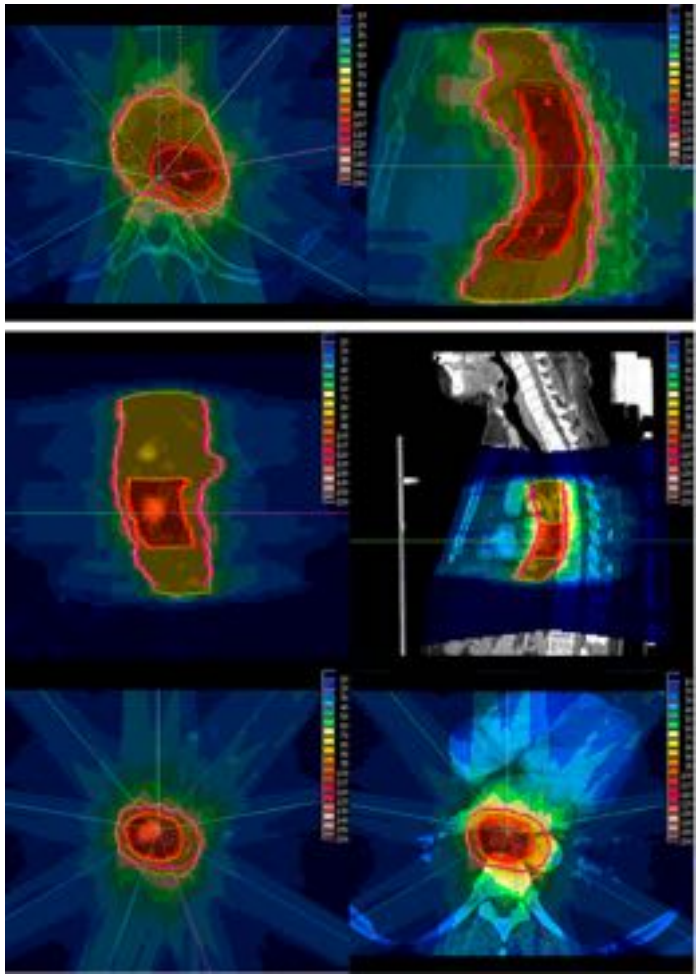
Patients with adverse effects ⩾grade 2 (*n*, %)	62 (56.9)
Patients with treatment delay more than 1 week (*n*, %)	45 (41.3)
Patients with treatment discontinuation (*n*, %)	17 (15.6)
Patients with chemotherapy dose reduction (*n*, %)	58 (53.2)
Due to adverse events	33 (30.3)
Due to age	25 (22.9)
Patients with treatment toxicity ⩾grade 2 (*n*, %)	
Neutropaenia	27 (24.8)
Vomiting	16 (14.7)
Mucitis	15 (13.8)
Infection	13 (11.9)
Diarrhoea	8 (7.3)
Renal insufficiency[a]	6 (5.5)

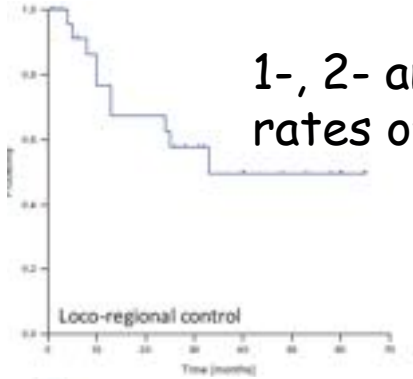
CCR was observed in 63 patients (57.8%)

Tougeron 2008

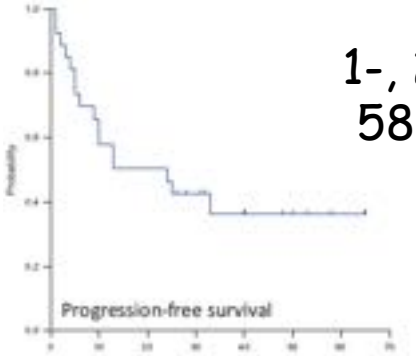
ChemioRadioterapia Definitiva & IMRT, VMAT, IGRT

27 consecutive patients,
CT + IMRT-SIB with total doses of 56-60 Gy (single dose 2-2.14 Gy),
while regional nodal regions received 50.4 Gy (single dose 1.8 Gy) in 28 fractions.

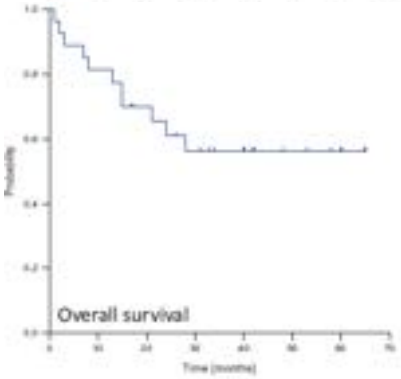




1-, 2- and 3-year-locoregional control rates of 77%, 65% and 48%.



1-, 2- and 3-year-DFS rates were 58%, 48% and 36%,



1-, 2- and 3-year-OS rates were 82%, 61% and 56%.

Roeder 2014, Nguyen 2014, Yang 2009

In Summary:

La possibilità di escludere la chirurgia è da considerare in pazienti con carcinoma del **tratto cervicale** responsivi a CT/RT, ove l'intervento di laringoesofagectomia potrebbe essere evitato e riconsiderato solo in caso di recidiva locale o di sicura persistenza di malattia e in pazienti selezionati con recidiva locale.

Riguardo le localizzazioni toraciche, sia nello studio tedesco che in quello francese, che includevano prevalentemente SCC, **non sono state evidenziate differenze statisticamente significative in termini di sopravvivenza** nei bracci di trattamento che hanno comparato CT/RT seguita da chirurgia vs CT/RT esclusiva.

Nello studio tedesco, inoltre, **la risposta clinica alla CT di induzione** prima del trattamento combinato CT/RT seguito o meno dalla chirurgia, è risultato essere **un fattore prognostico indipendente per la sopravvivenz**a.

Stahl 2005, Bedenne 2007

Un **incremento nella dose di RT** nello studio RTOG 94-05 (64.8Gy vs 50.4Gy) **non** ha comportato un miglioramento in sopravvivenza e in tasso di controllo locale

Minsky 2004

In Summary:

Schemi di chemioterapia a base di **platino e di fluoropirimidine** si sono di mostrati ben tollerati ed efficaci e rappresentano al momento il trattamento più utilizzato.

Il trattamento CT/RT con **carboplatino e paclitaxel** ha mostrato un buon profilo di tollerabilità e di efficacia.

Ajani 2008

Lo schema **FOLFOX-4** rispetto a CRT con fluorouracile e cisplatino è risultato **equiattivo e ben tollerato**, sebbene non mostri vantaggi significativi in sopravvivenza libera da progressione e sopravvivenza globale.

Conroy T. 2014

Cetuximab non dovrebbe essere somministrato in aggiunta ai comuni schemi di chemioterapia concomitante se non in popolazioni selezionate di pazienti.

Crosby 2013

In Summary:

Riguardo la **popolazione anziana**, i dati relativi all'impiego del trattamento combinato CT/RT esclusivo sono limitati; infatti, nello studio tedesco venivano esclusi dall'arruolamento tutti i pazienti di età >70 anni e nello studio francese non è stata eseguita alcuna stratificazione per età.
Alcune esperienze sono state condotte e risulta come l'età non sembri rappresentare di per sé una controindicazione oltre che per la chirurgia anche per il trattamento CT/RT esclusivo che potrebbe essere proposto a pazienti anziani attentamente selezionati e dopo adeguata Valutazione Geriatrica Multidisciplinare.

Tougeron 2008

Nella scelta di un trattamento nel **subset di pazienti localmente avanzati, inoperabili**, considerata la sopravvivenza quale endpoint primario, devono essere adeguatamente valutati i costi/benefici, con particolare attenzione agli effetti tossici tardivi dei trattamenti stessi.

Ishikura 2003

3D-CRT è considerata **la terapia standard** permettendo precisa e affidabile distribuzione di dose ai volumi bersaglio con buon risparmio di tessuti sani circostanti.

NCCN guidelines 2015

ASLCagliari
SISTEMA SANITARIO DELLA SARDEGNA

Thanks for your the attention

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