Stemma dell'Ospedale di S. Maria della Misericordia di Perugia

Stato dell'arte nei trattamenti integrati dei tumori esofagei

Marco Lupattelli
SC Radioterapia Oncologica - Perugia

I SESSIONE
APPROPRIATEZZA DELL'IMAGING NEI TUMORI DELL'ESOFAGO
Moderatori:
Luca Brunese - Renzo Corvo'
Felice Mucilli

Neoplasia Esofago e GEG

- Riunificazione sec. TNM 2010
- Chirurgia: standard …. ma R0 nel T3 nel 30% casi
- Recidive locoregionali: 30-40%
- 5yOS: <35% (<20% se localmente avanzata)

Razionale terapie multimodali

TERAPIA MULTIMODALE

- PRE-OPERATORIA
- POST-OPERATORIA

RADIOTERAPIA PRE-OPERATORIA

STUDI di FASE III

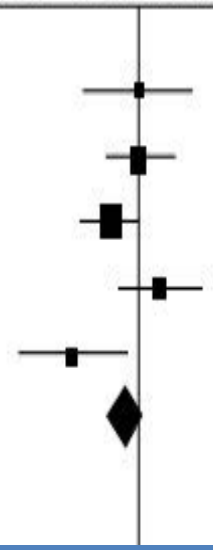
Ref.	Study period	Treatment	No. of patients	Histology	Complete resection	Local recurrence rate	Operative mortality	5-yr OS	Conclusion
Launois *et al*[5], 1981	1973-1976	40 Gy RT + Surgery	67	SCC	74%	NA	22.6%	9.5%	No significant benefit of pre-op RT
		Surgery	57	SCC	78%	NA	23.4%	11.5%	
Gignoux *et al*[8], 1987	1976-1982	33 Gy RT + Surgery	NA	SCC	43%	46%	NA	11%	No significant benefit of pre-op RT
		Surgery	NA	SCC	55%	67%	NA	10%	
Wang *et al*[7], 1989	1977-1985	40 Gy RT + Surgery	104	SCC	74%	41%	5%	5%	Higher pre-op RT dose or post-op RT required
		Surgery	102	SCC	65%	34%	6%	30%	
Arnott *et al*[4], 1993	1979-1983	20 Gy RT + Surgery	90	SCC/AC	76%	NA	NA	9%	No benefit of low dose RT
		Surgery	86	SCC/AC	72%	NA	NA	17%	
Nygaard *et al*[6], 1992	1983-1988	35 Gy RT + Surgery	NA	SCC	34%	NA	NA	21%	Beneficial effect of pre-op RT
		Surgery	NA	SCC	32%	NA	NA	9%	

RADIOTERAPIA PRE-OPERATORIA

Study or subgroup	Preoperative RT Events	Total	No preoperative RT Events	Total	O-E	Variance	Weight	Hazard ratio Exp [(O-E)/V], fixed, 95%CI
1.1.1 Preoperative RT only trials								
Launois 1981	56	61	40	46	0.22	22.60	9.3%	1.01 (0.67, 1.53)
Gignoux 1988	108	116	108	113	1.02	53.72	22.2%	1.02 (0.78, 1.33)
Wang 1989	131	195	165	223	-16.67	78.83	32.6%	0.81 (0.65, 1.01)
Arnott 1992	87	90	75	86	6.82	40.02	16.5%	1.91 (0.87, 1.62)
Nygaard 1992 (a)	52	58	50	50	-11.58	22.92	9.5%	0.60 (0.40, 0.19)
Subtotal (95%CI)		520		518			90.1%	0.91 (0.80, 1.04)
Total events	434		438					

Heterogeneity: $\chi^2 = 8.69$, df = 4 ($P = 0.07$); $I^2 = 54\%$

Test for overall effect: $Z = 1.37$ ($P = 0.17$)



HR 0.89

Evidenza: RT preoperatoria non migliora OS nelle neoplasie esofago potenzialmente resecabili.
Limite: dose e tecnica RT. EBM: I, A

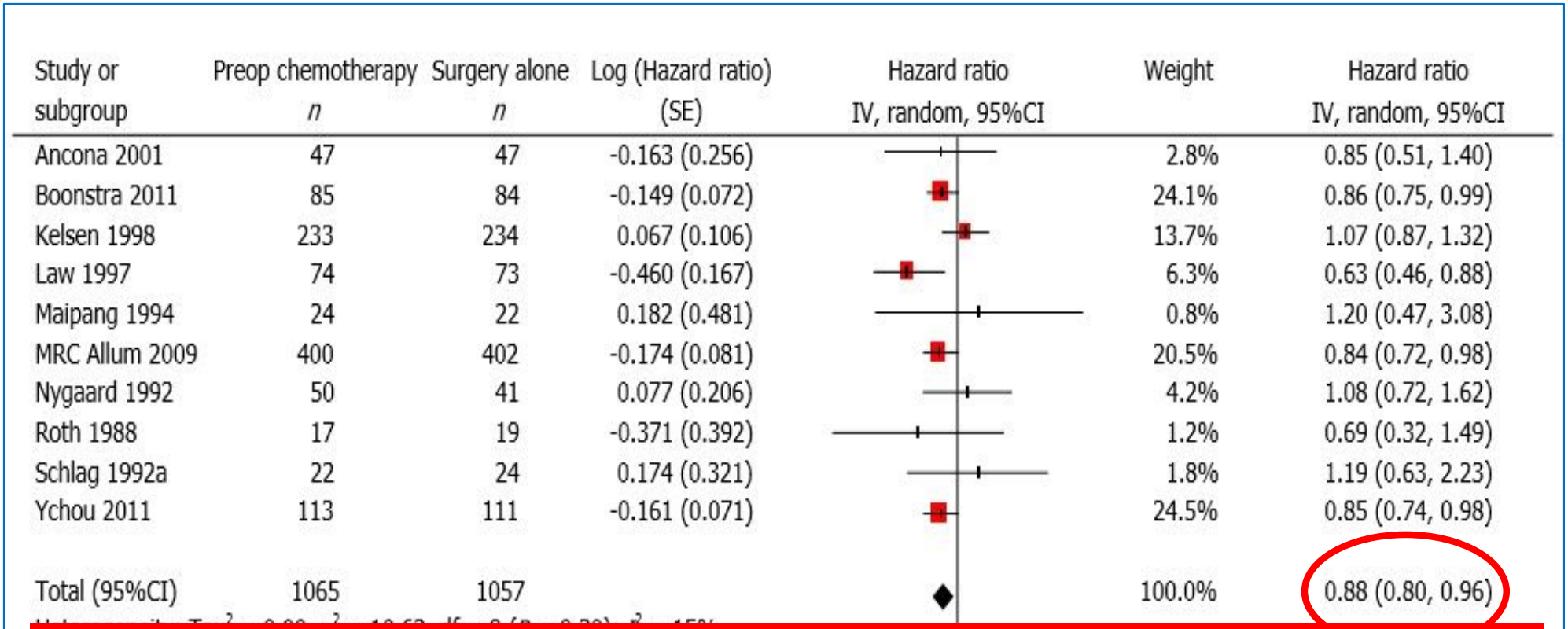
CHEMIOTERAPIA PRE-OPERATORIA

STUDI di FASE III

Studio	N. Pz	Istologia	Sede neoplasia	Tipo CT	pRC	5aa-OS	Note
RTOG-8911 Anno 2007	440	SCC/ ADC >50%	Esofago/ GEG	DDP-FU	2.5%	ND	ND radicalità chirurgica
MRC-OE02 Anno 2009	802	SCC/ ADC 66%	Esofago/ GEG	DDP-FU-	3%	23 vs 17%	
MAGIC Anno 2006	503	SCC ADC 62%	GEG 25%	ECF	NR	36 vs 23%	Compliance 41%
FNCLCC-FFCD Anno 2011	113	SCC/ADC	Esofago/ GEG 75%	DDP-FU	40%	38vs 24%	↑ radicalità chirurgica; compliance 50%

Intervallo RT-chirurgia: 2-6 settimane

Chemioterapia preoperatoria



Study or subgroup	Preop chemotherapy *n*	Surgery alone *n*	Log (Hazard ratio) (SE)	Hazard ratio IV, random, 95%CI	Weight	Hazard ratio IV, random, 95%CI
Ancona 2001	47	47	-0.163 (0.256)		2.8%	0.85 (0.51, 1.40)
Boonstra 2011	85	84	-0.149 (0.072)		24.1%	0.86 (0.75, 0.99)
Kelsen 1998	233	234	0.067 (0.106)		13.7%	1.07 (0.87, 1.32)
Law 1997	74	73	-0.460 (0.167)		6.3%	0.63 (0.46, 0.88)
Maipang 1994	24	22	0.182 (0.481)		0.8%	1.20 (0.47, 3.08)
MRC Allum 2009	400	402	-0.174 (0.081)		20.5%	0.84 (0.72, 0.98)
Nygaard 1992	50	41	0.077 (0.206)		4.2%	1.08 (0.72, 1.62)
Roth 1988	17	19	-0.371 (0.392)		1.2%	0.69 (0.32, 1.49)
Schlag 1992a	22	24	0.174 (0.321)		1.8%	1.19 (0.63, 2.23)
Ychou 2011	113	111	-0.161 (0.071)		24.5%	0.85 (0.74, 0.98)
Total (95%CI)	1065	1057			100.0%	0.88 (0.80, 0.96)

<u>Evidenza</u>: CT preoperatoria migliora OS nelle neoplasie esofago (1/3 inferiore) e GEG.

Limite: “compliance” al trattamento. EBM I, A.

CHEMIO-RADIOTERAPIA PRE-OPERATORIA

STUDI di FASE III

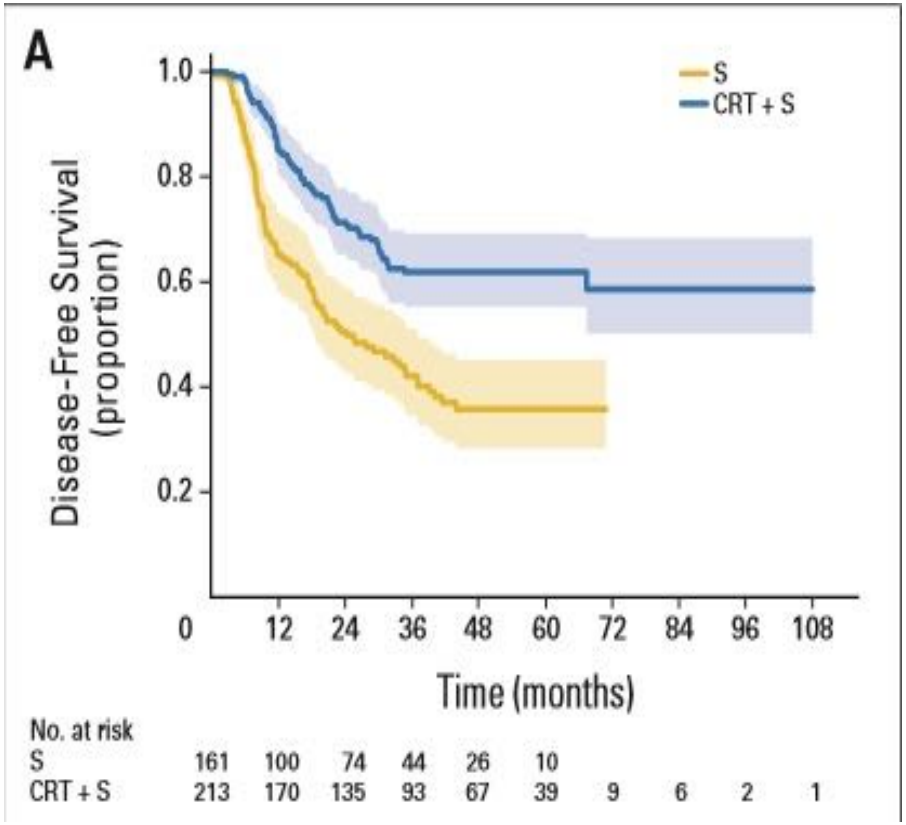
Autori	N. Pz	Istologia	Tipo RT	Tipo CT	pRC	OS	Note
Walsh 1996	176	ADC	40Gy/15	DDP-FU	25%	3aa: 6 vs 32%	N+ 42 vs 82%
Urba 2001	100	SCC/ ADC 75%	45Gy/30	DDP-FU-VBL	28%	3aa: 16 vs 30%	
Burmeister 2005	256	SCC 35% ADC 62%	35Gy/15	DDP-FU	12.5%	ND 36 vs 42%	↓ N+ e ↑R0 / SCC
Tepper 2008	56	SCC/ADC	50Gy/28	DDP-FU	40%	5aa: 16 vs 39%	
van Hagen 2012	366	SCC 23% ADC 75%	41.4Gy/23	CBDCA-Tax	29%	5aa: 34 vs 47%	↑ R0 (92 vs 69%)
Marlette 2014	195	SCC 70% ADC 29%	45Gy/25	DDP-FU	33.3%	ND	↑ mortalità post-op

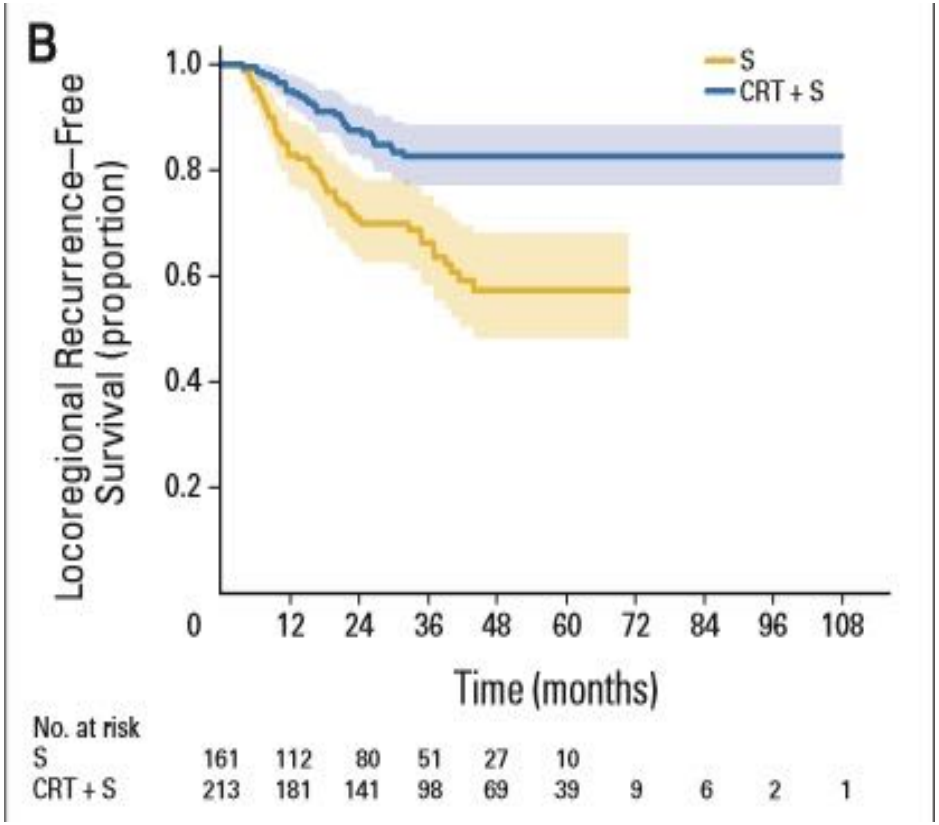
Intervallo RT-chirurgia: 3-8 settimane

Patterns of Recurrence After Surgery Alone Versus Preoperative Chemoradiotherapy and Surgery in the CROSS Trials

JCO 2014

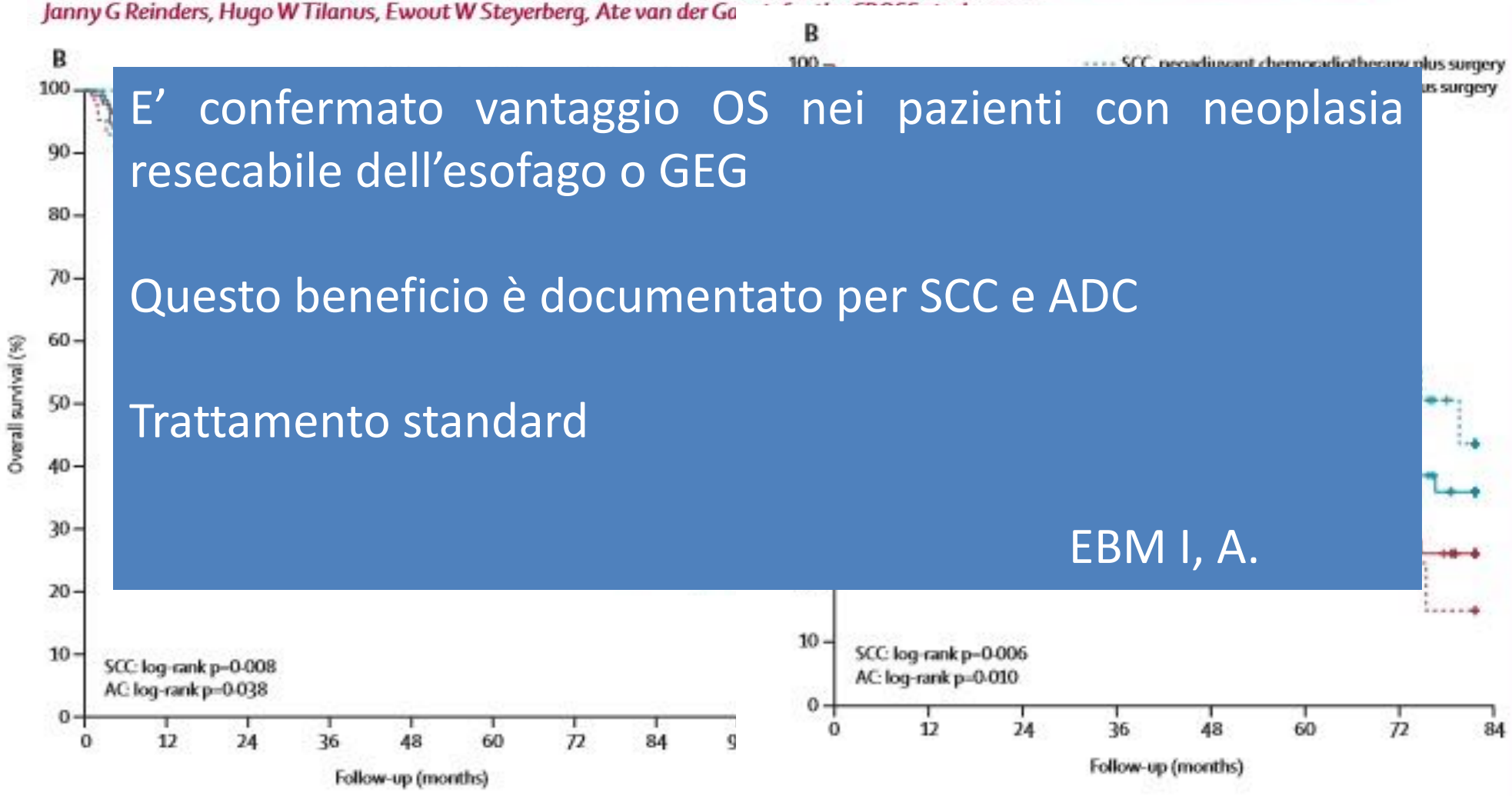
Vera Oppedijk, Ate van der Gaast, Jan J.B. van Lanschot, Pieter van Hagen, Rob van Os, Caroline M. van Rij, Maurice J. van der Sangen, Jannet C. Beukema, Heidi Rütten, Patty H. Spruit, Janny G. Reinders, Dick J. Richel, Mark I. van Berge Henegouwen, and Maarten C.C.M. Hulshof





Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial

Joel Shapiro, J Jan B van Lanschot, Maarten C C M Hulshof, Pieter van Hagen, Mark I van Berge Henegouwen, Bas P L Wijnhoven, Hanneke W M van Laarhoven, Grard A P Nieuwenhuijzen, Geke A P Hospers, Johannes J Bonenkamp, Miguel A Cuesta, Reinoud J B Blaisse, Olivier R C Busch, Fiebo J W ten Kate, Geert-Jan M Creemers, Cornelis J A Punt, John Th M Plukker, Henk M W Verheul, Ernst J Spillenaar Bilgen, Herman van Dekken, Maurice J C van der Sangen, Tom Rozema, Katharina Biermann, Jannet C Beukema, Anna H M Piet, Caroline M van Rij, Janny G Reinders, Hugo W Tilanus, Ewout W Steyerberg, Ate van der Ga



E’ confermato vantaggio OS nei pazienti con neoplasia resecabile dell’esofago o GEG

Questo beneficio è documentato per SCC e ADC

Trattamento standard

EBM I, A.

Confronto CROSS vs FFCD 9901

Autore	PS WHO	Sede neoplasia	Stadio	Istologia	Tipo CT	Tipo RT
CROSS	0 (85%) 1 (15%)	Esofago inf. 60% GGE 25%	II-III; T3 80% N1 65%	SCC 23% ADC 75%	CBDCA-Tax	41.4Gy/23 fr
FFCD 9901	0 (75%) 1 (25%)	Esofago toracico medio-inf 90%	I (20%)-IIA-B T3 18% N1 28%	SCC 70% ADC 29%	DDP-FU	45Gy/25 fr

Autore	Tecnica RT	Tox ≥ 3	NO CHIR	pRC	pRC per istotipo	Mortalità	CHIR. R0 braccio chirurgia
CROSS	3DC 4 campi	17%	6%	29%	SCC 49% ADC 23%	4%	69%
FFCD 9901	AP/PA	30%	14%	33%	NR	11%	92%

Confronto CROSS vs FFCD 9901

- Differenze in sede, istotipo e stadio di malattia
- Differenze RT: tecnica e volumi
- Casistica: limitata nell'FFCD con ↓ potere statistico studio, lento reclutamento, basso carico lavoro per centro con ↑ potenziale tox

- Stadio II-III: efficacia terapia trimodale
- Limiti studio Francese con conclusioni criticabili
- Stadio I ("early disease"): dubbio ruolo terapia preoperatoria. Chirurgia: opzione standard

Role of neoadjuvant treatment in clinical T2NoMo oesophageal cancer: results from a retrospective multi-center European study

Eur J Cancer 2016

Sheraz R. Markar, Caroline Gronnier, Arnaud Pasquer, Alain Duhamel, Hélène Beal, Jérémie Théreaux, Johan Gagnière, Gil Lebreton, Cécile Brigand, Bernard Meunier, Denis Collet, Christophe Mariette on behalf of the FREGAT working group – FRENCH – AFC[1]

[1] See Appendix B .

Methods. Data were collected from 30 European centres from 2000 to 2010. Among 2944 included patients, 355 patients (12.1%) had cT2N0 disease

Results. No si of in hospital morbidity and the time of surgery, with cant tumour downstaging a is effect was further enha apy had no significant eff ere were no significant differences between neoadjuvant chemotherapy and chemoradiotherapy in short- or long-term outcomes.

Chirurgia terapia standard se stadiazione adeguata

EBM II, B

Conclusion. Surgery alone treatment approach should be recommended as the primary treatment approach for cT2N0 oesophageal cancer despite 50% of patients having nodal disease at the time of surgery.

Chemioterapia pre-operatoria vs chemio-radioterapia pre-operatoria

Chemioterapia preoperatoria vs chemio-radioterapia preoperatoria

Autore	Sede	Istologia	Tipo CT	Tipo CT-RT	pRC	Stato LN	CHIR. R1	3aa-OS
Stahl **Anno 2009**	**Esofago GGE**	**ADC**	**DDP-FU-LV**	**30Gy/15fr DDP-VP16**	**2 vs 16%**	**38 vs 64%**	**3 vs 13%**	**28 vs 47% p 0.07**
Burmeisteir **Anno 2011**	**Esofago GGE**	**ADC**	**DDP-FU**	**35Gy/15 fr DDP-FU**	**0 vs 13%**	**31 vs 56%**	**0 vs 11%**	**ND**

Criticità: numerosità campione (126 e 75 pazienti arruolati)

A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction

Ann Oncol 2016

F. Klevebro[1*], G. Alexandersson von Döbeln[2], N. Wang[3], G. Johnsen[4], A.-B. Jacobsen[5], S. Friesland[2], I. Hatlevoll[6], N. I. Glenjen[7], P. Lind[8], J. A. Tsai[1], L. Lundell[1] & M. Nilsson[1]

Patients and methods: Recruited 181 patients with carcinoma of the oesophagus or the gastro-oesophageal junction……. The primary end point was pCR after neoadjuvant treatment. Three cycles of DDP/5FU were administered in both arms, whereas 40 Gy of concomitant radiotherapy was added in the nCRTarm.

Results: pCR being achieved in 28% after nCRT versus 9% after nCT (p=0.002). Lymph-node metastases were observed in 62% in the nCT group versus 35% in the nCRT group (p=0.001). The R0 resection rate was 87% after nCRT and 74% after nCT (p=0.04). There was no difference in OS. Per-protocol analyses OS stratified by histological tumour type indicated similar numbers with lower survival in patients with AC after nCRT and slightly improved survival for patients with SCC after nCRT.

A limitation of the study is that it was designed to distinguish a difference in complete histological response and is hence underpowered for the survival analyses. No difference between the treatment arms in the frequency of postoperative complications.

Chemioterapia preoperatoria vs chemio-radioterapia preoperatoria

- ↑radicalità chirurgica (R0)
- ↑ pRC nel trattamento combinato preop
- ↓ recidive locoregionali nel trattamento combinato preop
- ↓ metastasi LN

Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis

Val Gebski, Bryan Burmeister, B Mark Smithers, Kerwyn Foo, John Zalcberg, John Simes, for the Australasian Gastro-Intestinal Trials Group

Beneficio su OS di CT-RT preoperatoria (8.7% a 2aa) o CT (5.1% a 2 aa) rispetto chirurgia da sola in pazienti con neoplasia esofagea localmente avanzata cT3-4N1-3.

EBM I, A

I dati di letteratura non consentono di definire un chiaro vantaggio della terapia trimodale (CT-RT-CHIR) su quella bimodale (CT-CHIR).

Necessità di studi clinici prospettici di confronto tra terapia tri- vs bi-modale

ORIGINAL ARTICLE

Pathol Oncol Res 2016

Meta-Analysis for the Therapeutic Effect of Neoadjuvant Therapy in Resectable Esophageal Cancer

Yusen Zhu[1] · Min Liu[2] · Xiaojing Yun[1] · Dongmei Wang[1] · Yuhuan Bai[1] · Guizhi Zhang[1] · Bei Ji[1] · Changchun Jing[1]

24 articoli per un totale di 4718 casi.

Obiettivi primari: chirurgia radicale (R0), mortalità perioperatoria, recidiva, DFS, OS e/o 1-, 2- o 5-y OS.

Differenza significativa in 5y OS tra NCT e chirurgia.
Differenza statisticamente significativa obiettivi primari tra NCRT e chirurgia.
Differenza significativa in 3yOS tra NCRT e NCT .

NCRT e NCT superiori alla chirurgia, vantaggio NCRT rispetto a NCT.
Limite: dimensioni casistiche studi

Eur J Cardio-Th Surg 2016

Neoadjuvant chemoradiotherapy or chemotherapy? A comprehensive systematic review and meta-analysis of the options for neoadjuvant therapy for treating oesophageal cancer

Han-Yu Deng[a,b], Wen-Ping Wang[a], Yun-Cang Wang[a,b], Wei-Peng Hu[a,b], Peng-Zhi Ni[a,b], Yi-Dan Lin[a] and

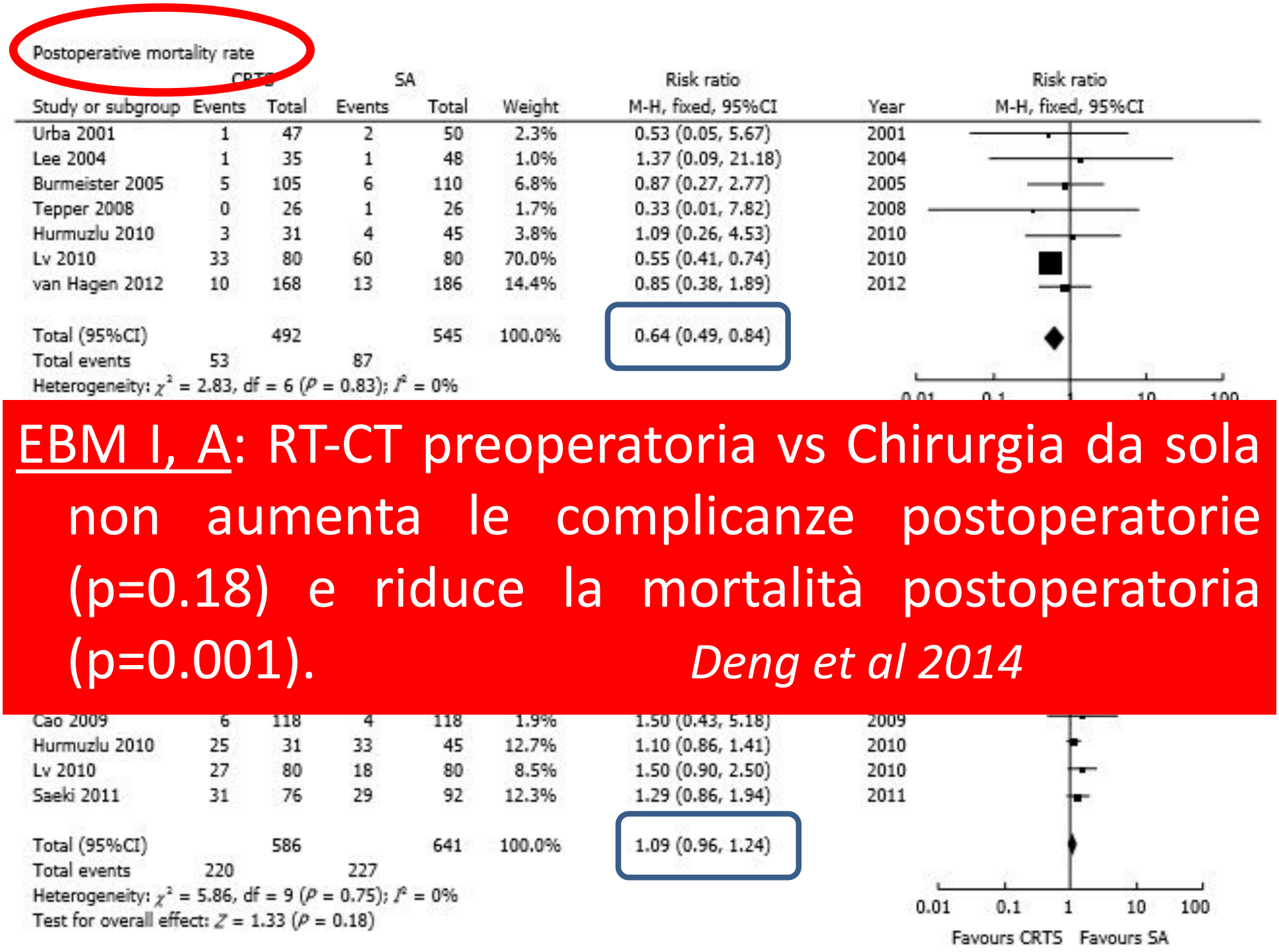
Limiti:

-Dimensione campione studiato

- qualità di alcuni studi inclusi nell'analisi

- eterogeneità analisi per sottogruppi correlata alla esiguità dei pazienti arruolati nei singoli studi

Necessità studi prospettici randomizzati



EBM I, A: RT-CT preoperatoria vs Chirurgia da sola non aumenta le complicanze postoperatorie (p=0.18) e riduce la mortalità postoperatoria (p=0.001).

Deng et al 2014

Systematic review

Meta-analysis of postoperative morbidity and perioperative mortality in patients receiving neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal and gastro-oesophageal junctional cancers

View issue TOC
Volume 101, Issue 4
March 2014
Pages 321–338

Analizzati 23 studi.

Confrontando NACT o NACTRT vs chirurgia da sola, non è stato documentato aumento morbidità/mortalità attribuibile alla terapia neoadiuvante.

Analisi NACTRT nel SCC: aumento rischio mortalità totale e correlata al trattamento rispetto sola chirurgia ($p = 0{\cdot}032$ and $p = 0{\cdot}030$).

Nessuna differenza tra NACTRT e NACT riguardo morbidità o mortalità.

CHEMIO-RADIOTERAPIA ESCLUSIVA

QUANDO?

- Neoplasia non resecabile (cT4) o con esteso coinvolgimento linfonodale (N2).
- Neoplasia esofago cervicale (EBM III, B).
- Neoplasia localmente avanzata potenzialmente resecabile (stadio II-III) che rifiutano chirurgia
- Neoplasia localmente avanzata potenzialmente resecabile (stadio II-III) non operabili per comorbidità

STUDI di FASE III

Studio	Istologia	Random	chirurgia	Risultati	Note
RTOG-8501 Anno 1999	ADC/SCC	64Gy vs DDP-FU + 50Gy	NO	5y OS 0 vs 26%	Maggiore efficacia SCC
German study Anno 2009	SCC	DDP-FU + 50Gy vs RT-CT-CHIR	SI	2y PFS 41 vs 64% a favore CHIR	ND a 5-10y
FFCD 9102 Anno 2007	SCC (90%)	DDP-FU 46Gy + CHIR vs DDP-FU + 66Gy	SI	ND in OS; ↑LC 65 vs 57%	↑ mortalità perioperatoria
Intergroup 0123 Anno 2002	SCC/ADC	DDP-FU-50.4Gy Vs DDP-FU 64.8Gy	NO	ND in 2y-LC e OS	↑ tossicità braccio dose RT maggiore

Clinical Investigation

Radiation Dose Escalation in Esophageal Cancer Revisited: A Contemporary Analysis of the National Cancer Data Base, 2004 to 2012

Jeffrey V. Brower, MD, PhD,* Shuai Chen, PhD,†
Michael F. Bassetti, MD, PhD,* Menggang Yu, PhD,†
Paul M. Harari, MD,* Mark A. Ritter, MD, PhD,*
and Andrew M. Baschnagel, MD*

IJROBP 2016

Studio retrospettivo in pazienti affetti da neoplasia esofago stadio I-III, sottoposti a RT-CT esclusiva con dose di RT ≥ 50Gy.

Inclusi nell'analisi 6854 pazienti.
Nessuna differenza in termini di OS tra 50-50.4Gy e > 50.4Gy.
Nessun beneficio per istotipo (SCC) o per tecnica RT (IMRT).
Fattori prognostici: sesso F, basso indice di Charlson, sede cervicale o 1/3 superiore, SCC, estensione T /N.

Dati di letteratura: 50-50.4Gy dose di riferimento

CHIRURGIA di SALVATAGGIO

Dati di letteratura

- Dopo CT-RT esclusiva nel SCC: persistenza o recidiva nel 60% casi
- Chirurgia di salvataggio: mortalità del 15-22% (Nishimura 2007; Chen 2014)
- Miglioramento tecniche chirurgiche e assistenza perioperatoria con mortalità 0-2% (Chao 2009; Yoo 2012)
- Dati recenti CT-RT esclusiva SCC stadio II-III (JCOG9906 Kato 2011) nella preservazione organo (SM 29 mesi; 3yOS 44.7% e 5yOS 36.8%)
- Problemi aperti: tipo follow-up, difficoltà monitoraggio risposta e diagnosi recidiva/persistenza
- Alternative a chirurgia: CT o CT-RT o Brachiterapia o trattamenti endoscopici (stent, laser, crioterapia, ecc)

Systematic review and meta-analysis on the significance of salvage esophagectomy for persistent or recurrent esophageal squamous cell carcinoma after definitive chemoradiotherapy

DISEASES OF THE ESOPHAGUS 2016

K. Kumagai,[1] D. Mariosa,[2] J. A. Tsai,[1] M. Nilsson,[1] W. Ye,[2] L. Lundell,[1] I. Rouvelas[1]

TRATTAMENTO INVESTIGAZIONALE

Chirurgia di salvataggio superiore in termini di OS alla CT-RT di salvataggio. Mortalità correlata alla chirurgia 10.3% ma non confrontabile con quella correlata alla CT-RT.

TERAPIA POST-OPERATORIA

CHEMIO-RADIOTERAPIA POSTOPERATORIA nel SCC

- Chirurgia “up-front” per scelta pz/ch rgo, impossibilità a ricevere terapia oria, stadiazione preoperatoria i
- Se chirurgia R0: ness ne a trattamento adiuvante per as cio OS **EBM Ia, A**

  Teniere 19 en 1995, NCCN 2015; ESMO 2016
- Se chi N+: la radio-chemioterapia adiuva brerebbe migliorare LC e OS

  Chen 2012, Hsu 2014 **EBM III, C**
- Terapia adiuvante: maggiore tossicità e ridotta compliance

NO GRAZIE

CHEMIO-RADIOTERAPIA POSTOPERATORIA nella GEG (ADC)

VOLUME 30 · NUMBER 19 · JULY 1 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Updated Analysis of SWOG-Directed Intergroup Study 0116: A Phase III Trial of Adjuvant Radiochemotherapy Versus Observation After Curative Gastric Cancer Resection

Stephen R. Smalley, Jacqueline K. Benedetti, Daniel G. Haller, Scott A. Hundahl, Norman C. Estes, Jaffer A. Ajani, Leonard L. Gunderson, Bryan Goldman, James A. Martenson, J. Milburn Jessup, Grant N. Stemmermann,† Charles D. Blanke, and John S. Macdonald

Giunzione E-G 20%

SURVIVAL AFTER ADJUVANT CHEMORADIOTHERAPY OR SURGERY ALONE IN RESECTABLE ADENOCARCINOMA AT THE GASTRO-ESOPHAGEAL JUNCTION

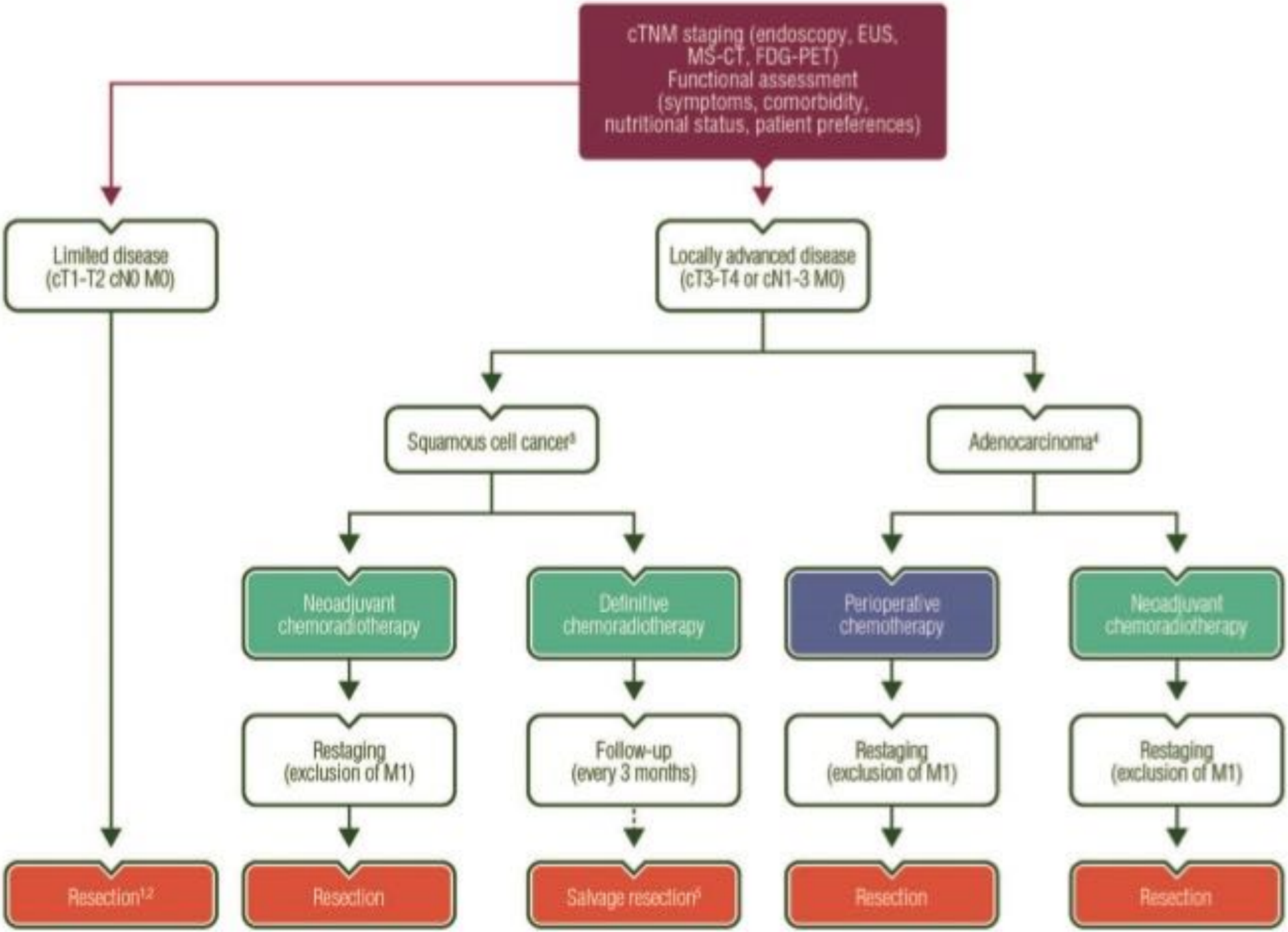
S. C. Kofoed[1], A. Muhic[2], L. Baeksgaard[2], M. I... ...en[1], J. Holm[1], L. Bardram[1], B. Brandt[3], J. Brenø[3], L. B. S...

NO GRAZIE

Results: in N+ pa... ...year DFS after adjuvant chemoradiothera... ...rgery alone (n = 43) was 24% and 37%, respe... ...ime of survival was prolonged by 10 month in ... who received chemo-radiotherapy.

Conclusion: ...-radiotherapy according to the intergroup-0116 protocol migh... still be a reasonable option after curative resection in patients with GEJ adenocarcinomas and positive lymph node status, who did not receive neoadjuvant chemotherapy.

EBM I, C


cTNM staging (endoscopy, EUS, MS-CT, FDG-PET)
Functional assessment (symptoms, comorbidity, nutritional status, patient preferences)
Limited disease (cT1-T2 cN0 M0)
Locally advanced disease (cT3-T4 or cN1-3 M0)
Squamous cell cancer[3]
Adenocarcinoma[4]
Neoadjuvant chemoradiotherapy
Definitive chemoradiotherapy
Perioperative chemotherapy
Neoadjuvant chemoradiotherapy
Restaging (exclusion of M1)
Follow-up (every 3 months)
Restaging (exclusion of M1)
Restaging (exclusion of M1)
Resection[1,2]
Resection
Salvage resection[5]
Resection
Resection

RT: quale frazionamento?

In generale non esistono studi di confronto

- Preop: frazionamento ottimale non definito. 41.4Gy/23 fr o 45-50.4Gy/25-28 fr

- Esclusivo: 50-50.4Gy/25-28 frazioni.

  Nessun vantaggio con aggiunta brachiterapia (Gaspar et al RTOG 9207)

- Postop: 50.4/28 fr

CT preoperatoria concomitante RT: quale regime?

- Efficacia schemi contenenti taxani (CBDCA-taxolo
  CI
  20

DDP-FU o FOLFOX
vs
schema contenente taxani
(CBDCA-tax o DCF)

Stu			
Honi Ann			r ance
PRODIGE5/ACCORD17 **Conroy et al** **Lancet Oncol 2014**	PF vs FOLFOX a parità di RT	ND in termini di PFS e OS	**Nessuna differenza in tossicità; FOLFOX più conveniente rispetto PF**

Chemioterapia preoperatoria vs chemio-radioterapia preoperatoria

Trial	Country	Histology	Site	Randomization
AEGIS	Ireland	ADK	Oesophagus + GEJ	Preop concurrent RT (41.4 Gy) + CBDCA-Tax × 5 cycles (CROSS regimen) versus Periop ECF × 6 cycles (3 preop and 3 post-op; MAGIC regimen)
				+ CBDCA-Tax × 5 cycles
				p and 4 post-op)
				rent RT (45 Gy) + 5FU
				and 3 post-op; MAGIC regimen)
				+ CBDCA-Tax × 5 cycles (CROSS regimen) versus Preop DOC × 2 cycles + Preop concurrent RT (41.4 Gy) + CBDCA-Tax × 5 cycles (CROSS regimen) versus Preop DOC × 4 cycles + Preop concurrent RT (41.4 Gy) + CBDCA-Tax × 5 cycles (CROSS regimen)

JCOG 1109 – NexT study
E-GEG
CT (PF) vs CT (DCF) vs PF-RT

Table 3 Ongoing Trials Involving Systemic Approaches With Radiotherapy

Clinical Trial Identifier	Cancer Type	Regimen	Agent and Target
NCT01196390; ongoing, but no longer recruiting	HER-2 (+) esophageal ACA	Neoadjuvant paclitaxel, carboplatin, and 50.4 Gy (28 fractions) with or without trastuzumab	Trastuzumab, anti-HER-2/Neu MAB
NCT02530437; not yet recruiting	Esophageal and GEJ ACA	Paclitaxel, carboplatin, and 50.4 Gy (28 fractions) with either concurrent or preceding taladegib	Taladegib, Hedgehog inhibitor
NCT02375581; currently recruiting	Esophageal SCC and ACA	Concurrent icotinib with 50-60 Gy (25-30 fractions)	Icotinib, anti-EGFR TKI
NCT02545751; not yet recruiting	Metastatic esophageal SCC and ACA	Concurrent thymalfasin with 25 Gy (5 fractions)	Thymalfasin, stimulates immune system proliferation and differentiation
NCT02381561; not yet recruiting	Advanced UGI and lower GI cancers	Ropidoxuridine with concurrent radiotherapy (dosing dependent on cancer site)	Ropidoxuridine, prodrug for nucleoside analog idoxuridine

CONSIDERAZIONI

- pCR: circa 30% dopo neoadiuvante, principale fattore prognostico
- Criticità: eterogeneità studi per istologia, dose e tecnica RT, regime chemioterapia, tecniche chirurgiche, dimensioni casistiche, staging, spazio temporale studi (intervallo di 30-40 aa)
- Importanza multidisciplinarietà
- Studi prospettici