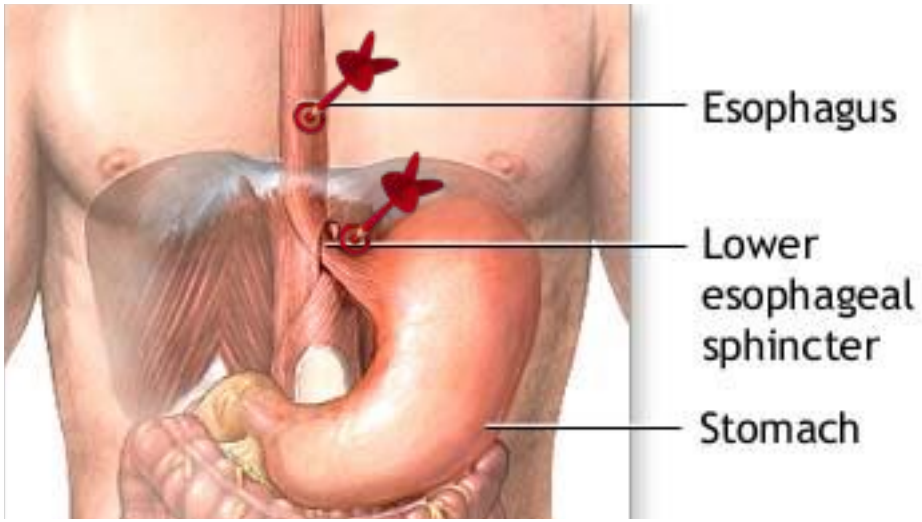
SESSIONE III

Distretto addominale: il trattamento multimodale delle neoplasie dell'esofago e della giunzione gastroesofagea

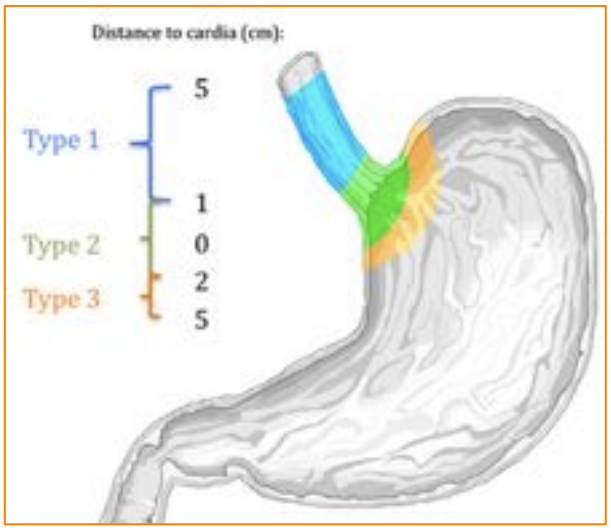
Trattamento Trimodale: indicazioni e risultati

Francesco Cellini

Esophageal + Geastroesophageal Junction (GEJ) Lesions



The 7th International Union Against Cancer (UICC) TNM Classification GEJ tumors (i.e. the Siewert type I-II-III) are grouped as a subsite of esophageal cancer



- Esophageal and GEJ lesions present similar behaviors
- Change incidence patterns localization
- In developed countries, the incidence of gastric cancer originating from the cardia follows that of the esophageal cancer
- Similar LN spread for distal esophagus and GEJ lesions
- AdenoCa more frequent for GEJ (90%)

Leers *et al*; J Thor Card Surg 2004

Crew *et al*; Sem Onc 2004

Blot *et al*; JAMA 1991

Sobin *et al*; TNM classification 2009

- Until ‘80 RT mainly involved in treatment of pts no suitable for surgery

- Mostly oriented to the treatment of SCC (intrinsic AdenoCa radioresistance)

From ‘80 to ‘90:

- Introduction of Chemosensibilization (↑ efficacy)
- Multimodal Integration with Surgery (TMT)

} Inclusion of AdenoCa

- Phase III Trials preoperative RTCT + Surg vs Surg alone

✓ Walsh *et al*; N Engl J Med - 1996

✓ Urba *et al*; JCO - 2001

✓ Burmeister *et al*; Lancet Oncol - 2005

✓ Tepper *et al*; JCO - 2008

✓ van Hagen *et al*; N Engl J Med - 2012

Phase III Trial Chir ± Preop RTCT (TMT)

The New England Journal of Medicine

A COMPARISON OF MULTIMODAL THERAPY AND SURGERY FOR ESOPHAGEAL ADENOCARCINOMA

THOMAS N. WALSH, M.D., NOIRIN NOONAN, M.B., DONAL HOLLYWOOD, PH.D., ALAN KELLY, PH.D., C.STAT.,

TABLE 1. CHARACTERISTICS OF THE TWO TREATMENT GROUPS AT BASE LINE.

CHARACTERISTIC	SURGERY ALONE (N=55)	MULTIMODAL THERAPY (N=58)
Age (yr)		
Median	65	65
Range	37–75	47–75
	no. of patients	
Sex		
Male	44	39
Female	11	19
Tumor site		
Middle third of esophagus	5	11
Lower third of esophagus	27	31
Cardia	23	16

- Accrual 1990-1995
- 113 pt (100% AdenoCa*)
- RTCT (3DCRT): 40 Gy (2.7 Gy fx) + 5Fu/CDDP
- 3yySVV 32% RTCT+Surg vs 6% Surg*

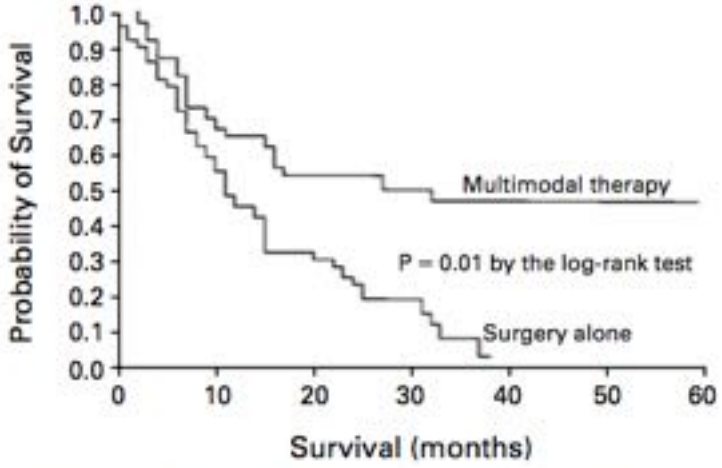


Figure 1. Kaplan–Meier Plot of Survival of Patients with Esophageal Adenocarcinoma, According to the Intention-to-Treat Analysis.

Preoperative Tumor Staging

The extent of the tumor was evaluated in each patient by physical examination, chest radiography, abdominal ultrasonography, and upper gastrointestinal endoscopy. Bronchoscopy was performed when indicated by symptoms, the location of the tumor, or chest radiography. Computed tomography was performed in selected patients with equivocal findings on chest radiographs or liver ultrasonograms. Isotope bone scans were occasionally performed if indicated.

Walsh *et al*; N Engl J Med 1996

Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial

Bryan H Burmeister, B Mark Smithers, Val Gebski, Lara Fitzgerald, R John Simes, Peter Devitt, Stephen Ackland, David C Gotley, David Joseph,

	Chemoradiotherapy and surgery (n=128)	Surgery alone (n=128)
Age (years)		
Median (range)	61 (41–80)	62 (28–83)
Sex		
Women	22 (17%)	28 (22%)
Men	106 (83%)	100 (78%)
Performance status		
0	40 (31%)	44 (34%)
1	88 (69%)	84 (66%)
Tumour histology		
Squamous-cell carcinoma	45 (35%)	50 (39%)
Adenocarcinoma	80 (63%)	78 (61%)
Mixed or other	3 (2%)	0
Tumour location		
Lower third	99 (77%)	104 (81%)
Middle or upper third	29 (23%)	24 (19%)
Regional nodes involved on CT		
Yes	20 (16%)	19 (15%)
No	108 (84%)	109 (85%)

- Accrual 1994-2000
- 256 pt (60% AdenoCa)
- RTCT (Simulator): 35 Gy (2.4 Gy fx) + 5Fu/CDDP
- 3yySVV 42% RTCT+Surg vs 36% Surg

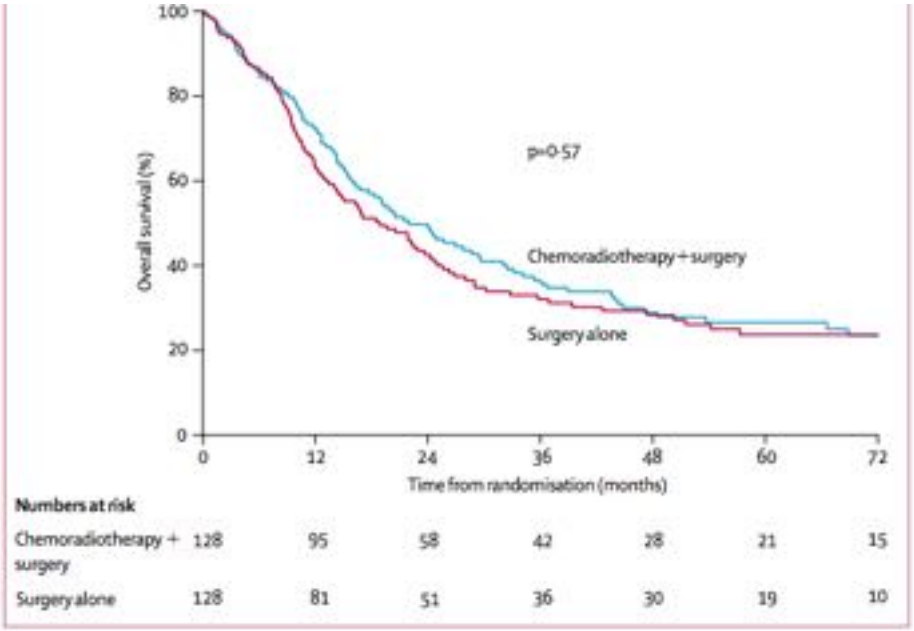


Figure 2: Survival by treatment group

Burmeister *et al*; Lancet Oncol 2005

Phase III Trial Chir ± Preop RTCT (TMT)

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Bryan H Burm

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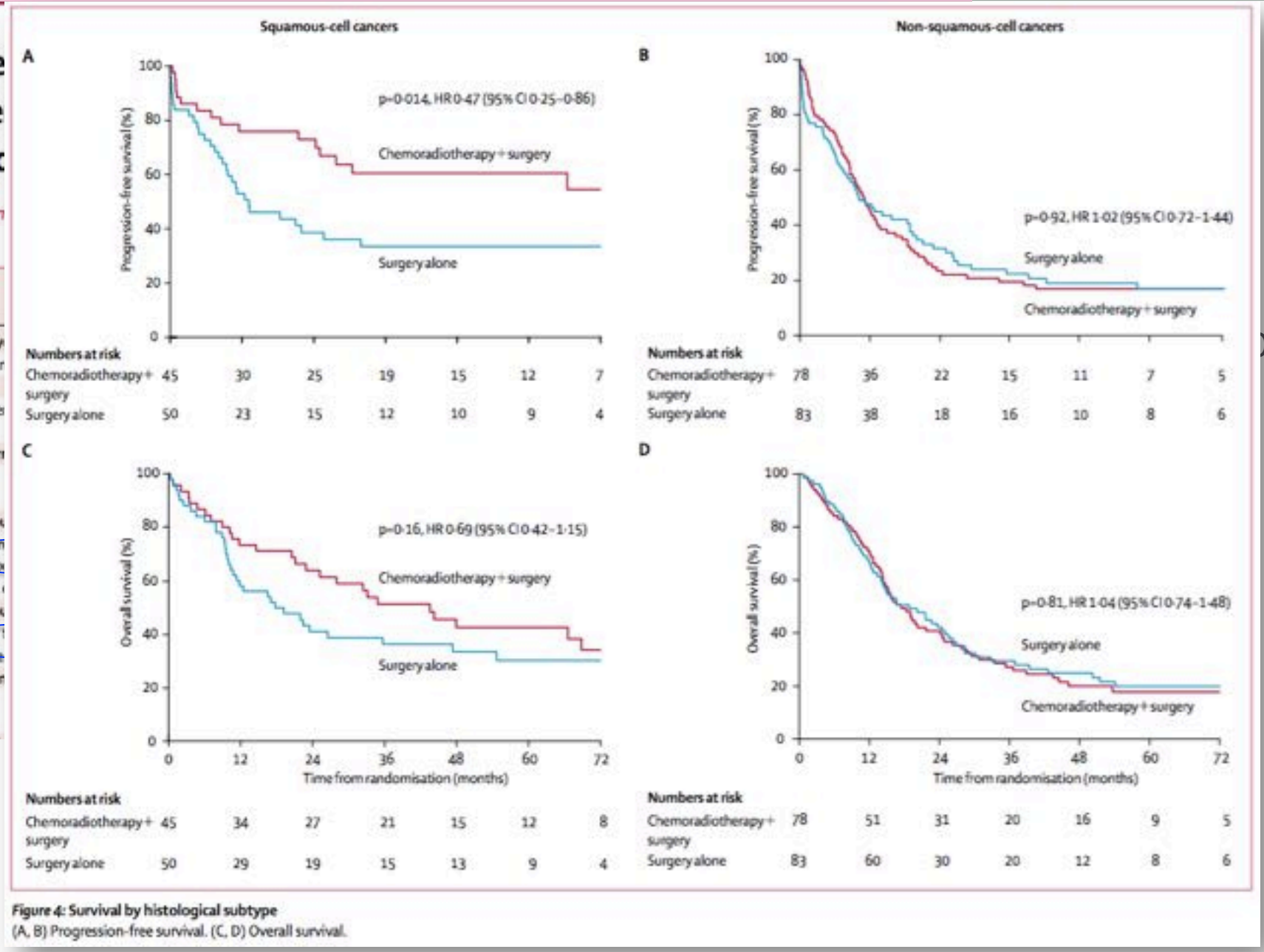


Figure 4: Survival by histological subtype
(A, B) Progression-free survival. (C, D) Overall survival.

DDP

Burmeister *et al*; Lancet Oncol 2005

Phase III Trial Chir ± Preop RTCT (TMT)

The NEW ENGLAND JOURNAL of MEDICINE

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,

Table 1. Characteristics of Patients with Resectable Esophageal or Esophagogastric-Junction Cancer, According to Treatment Group.*

Characteristic	Chemoradiotherapy and Surgery (N=178)	Surgery Alone (N=188)
Age — yr		
Median	60	60
Range	36–79	36–73
Male sex — no. (%)	134 (75)	152 (81)
Tumor type — no. (%)		
Adenocarcinoma	134 (75)	141 (75)
Squamous-cell carcinoma	41 (23)	43 (23)
Other	3 (2)	4 (2)
Tumor length — cm†		
Median	4	4
Interquartile range	3–6	3–6
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)

van Hagen *et al*; N Engl J Med 2012

Phase III Trial Chir ± Preop RTCT (TMT)

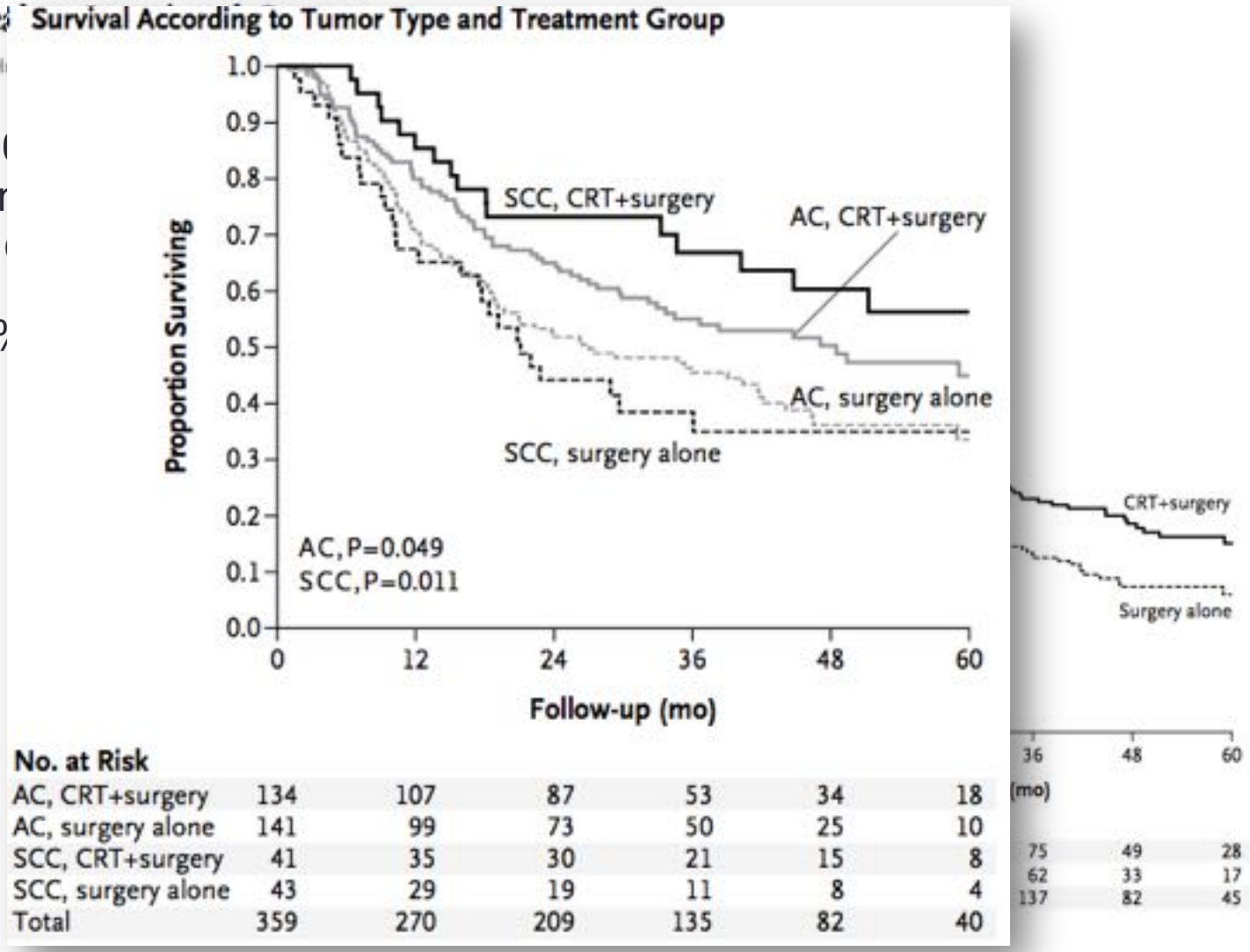
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Preoperative Chemoradiotherapy for Esophage

P. van Hagen, M.C.C.M. H

- Accrual 200
- 366 pt (Ader
- RTCT: 41.2
- 5yySVV 58%



van Hagen *et al*; N Engl J Med 2012

Phase III Trial Chir ± Preop RTCT (TMT)

	N° Pts	Accrual	Rate adeno	Tumor site	Dose/Fx (Gy)	Concurrent CT	3 yy OS % [RTCT+ surg vs. surg alone]	5 yy OS % [RTCT+ surg vs surg alone]	Median SVV (mth) [RTCT+ surg vs surg alone]	Median fup (mth)
Walsh [43]	113	1990-1995	100%	Middle+ Lower Esophagus + Cardias	40/2.7	CDDP + 5Fu	32 vs. 6 (p=0.01)	-	16 vs 11	10 (0.1-59)
Urba [46]	100	1989-1994	75%	Proximal+ Middle + Lower Esophagus + GEJ	45/1.5 (twice daily)	CDDP+ 5Fu+ Vimblastine	30 vs. 16 (p=0.15)	-	16.9 vs 17.6	98.4 (72-118.8)
Burmeister [48]	256	1994-2000	62%	Proximal +Middle+ Lower Esophagus	35/2.4	CDDP + 5Fu	42 vs. 36 (p=0.57)	21 vs. 19	22.2 vs. 19.3	65 (0.4-120)
Tepper [49]	56	1997-2000	75%	Toracic Esophagus (below 20 cm)+ GEJ <2cm distal spread in cardia	50.4/1.8	CDDP + 5Fu	-	39 vs. 16 (p=0.002)	53.8 vs. 21.5	72 (NR)
Van Hagen [50]	366	2004-2008	75%	Proximal +Middle+ Lower Esophagus + GEJ	41.2/1.8	Carboplatin + Paclitaxel	58 vs. 44 (p=0.003)	47 vs. 34	49.4 vs. 24	45.4 (25.5-80.9)

Cellini *et al*; Radiat Oncol 2014

- Meta-analyses:
  - Potential Gain: better investigating outcome (significant results)
  - Potential Limits:
    - Variability/biases by different features of included patients over different trials
    - Reduced efficacy in secondary objectives evaluation

Meta-analyses

Author	Trials	Period	pts	SVV Benefit for TMT	Notes
Urschel 2003 [Am J Surg]	9	1992-2002	1116	1-2-3 yy SVV	3 yy SVV benefit higher for concomitant vs sequential RTCT
Fiorica 2004 [GUT]	6	1992-2001	764	3 yy SVV	↑ postoperative mortality
Arnott 2005 [IJROBP]	5	1981-1992	1147	Non significant trend at 2 and 5 yy	SCC 86%
Greer 2005 [Surgery]	6	1992-2001	738	Small non significant trend	Same trial selection Fiorica
Gebski 2007* [Lancet Oncol]	10 (18)	1982-2006	1209 (2933 Tot)	2 yy SVV	Smaller significant benefit also for NACT
Jin 2009 [World J Gastr]	11	1992-2008	1308	1-3-5 yy SVV	
Sjoquist 2011* [Lancet Oncol]	14 (24)	1983-2004	2048 (4188 Tot)	2 yy SVV	CROSS reported as Abstract
Wang 2012 [Dig Dis Sci]	12	1992-2009	1529	1-3-5 yy SVV	- SVV benefit only for concomitant RTCT - SVV benefit only for SCC
Deng 2014 [Diagn Pathol]	13	2001-2013	1930	Significant: ↓ Postop ✚ ↓ Loc Recs ↓ M+ Rates	- “postoperative efficacy” - Potential bias - CROSS Included

Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis

Katrin M Sjoquist, Bryan H Burmeister, B Mark Smithers, John R Zalcberg, R John Simes, Andrew Barbour, Val Gebski, for the Australasian Gastro-Intestinal Trials Group

2yy SVV Benefit

- RTCT+Surg vs Surg alone= 8.7% (HR 0.78; CI95% 0.70-0.88; p<0.0001)
- CT+Surg vs Surg alone= 5.1% (HR 0.87; CI95% 0.79-0.96; p=0.005)

8·7% and a number needed to treat of 11. There was no evidence of significant heterogeneity between the trials or between pooled results by tumour histology. The survival benefits for neoadjuvant chemoradiotherapy were similar in the tumour type subgroups: squamous-cell carcinoma (HR 0·80, 95% CI 0·68–0·93; p=0·004) and adenocarcinoma (0·75, 0·59–0·95; p=0·02).

included updated data on previously published studies nts and about evious meta- ngthened the uvant therapy resent meta- neoadjuvant herapy before e of chemo- radiotherapy is not only stronger than previously reported but is also clear for both squamous-cell carcinoma and adenocarcinoma histologies. Neoadjuvant chemotherapy also seemed to be associated with improvements in each histological subtype compared with surgery alone, although the treatment effects were not as large as for chemoradiotherapy. Both treatment strategies cause toxicities that are well known and that potentially increase the risk of surgical morbidity.

There is evidence that neoadjuvant chemoradiotherapy increases the rate of complete resection,[15,47] particularly for patients with locally advanced disease, although this increase has not always translated into a survival benefit in individual studies. The two most recent trials that assessed neoadjuvant chemoradiotherapy have been reported as abstracts only.[15,42] In the larger Dutch trial,[42] there was a survival benefit for patients who had neoadjuvant chemoradiotherapy with paclitaxel and carboplatin weekly for 5 weeks with 41·4 Gy radiotherapy compared with those who had surgery alone. In the French trial,[11] in which patients received the typical

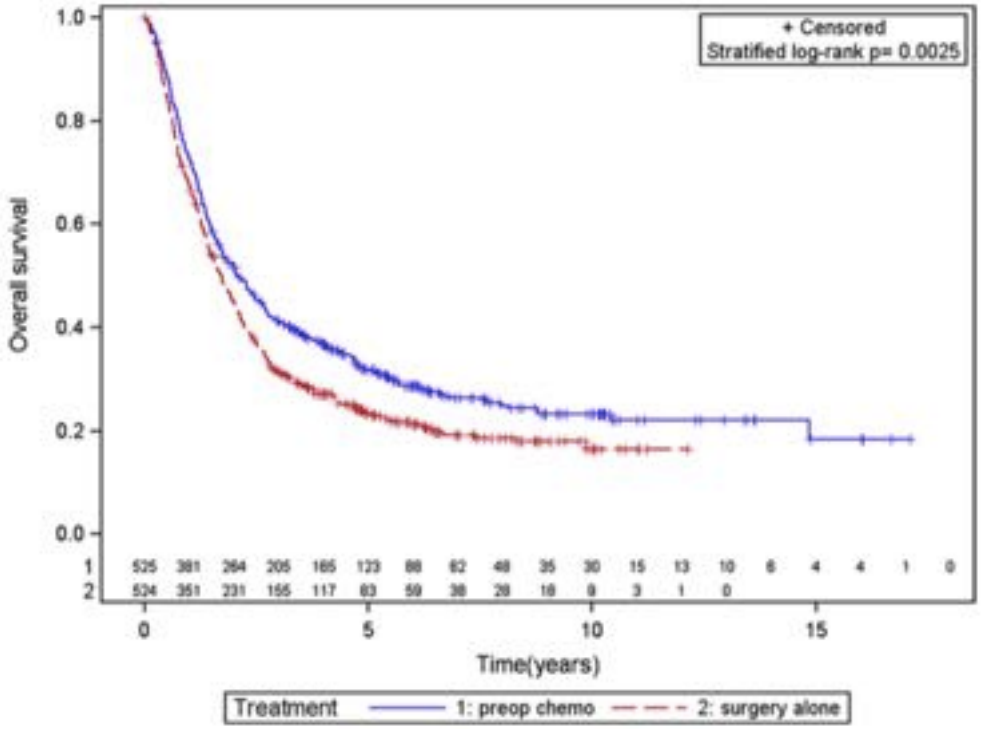
radiotherapy. The inclusion of chemoradiotherapy arms in future trials of neoadjuvant treatments is supported by the results of this meta-analysis. Treatment decisions for

Sjoquist *et al*; Lancet Oncol - 2011

Available at www.sciencedirect.com
SciVerse ScienceDirect
journal homepage: www.ejcancer.com
EJC
ELSEVIER

Preoperative chemo(radio)therapy versus primary surgery for gastroesophageal adenocarcinoma: Systematic review with meta-analysis combining individual patient and aggregate data ☆

Ulrich Ronellenfitsch [a,*], Matthias Schwarzbach [b], Ralf Hofheinz [c], Peter Kienle [a], Meinhard Kieser [d], Tracy E. Slanger [e], Bryan Burmeister [f], David Kelsen [g], Donna Niedzwiecki [h], Christoph Schuhmacher [i], Susan Urba [j], Cornelis van de Velde [k], Thomas N. Walsh [l], Marc Ychou [m], Katrin Jensen [d]

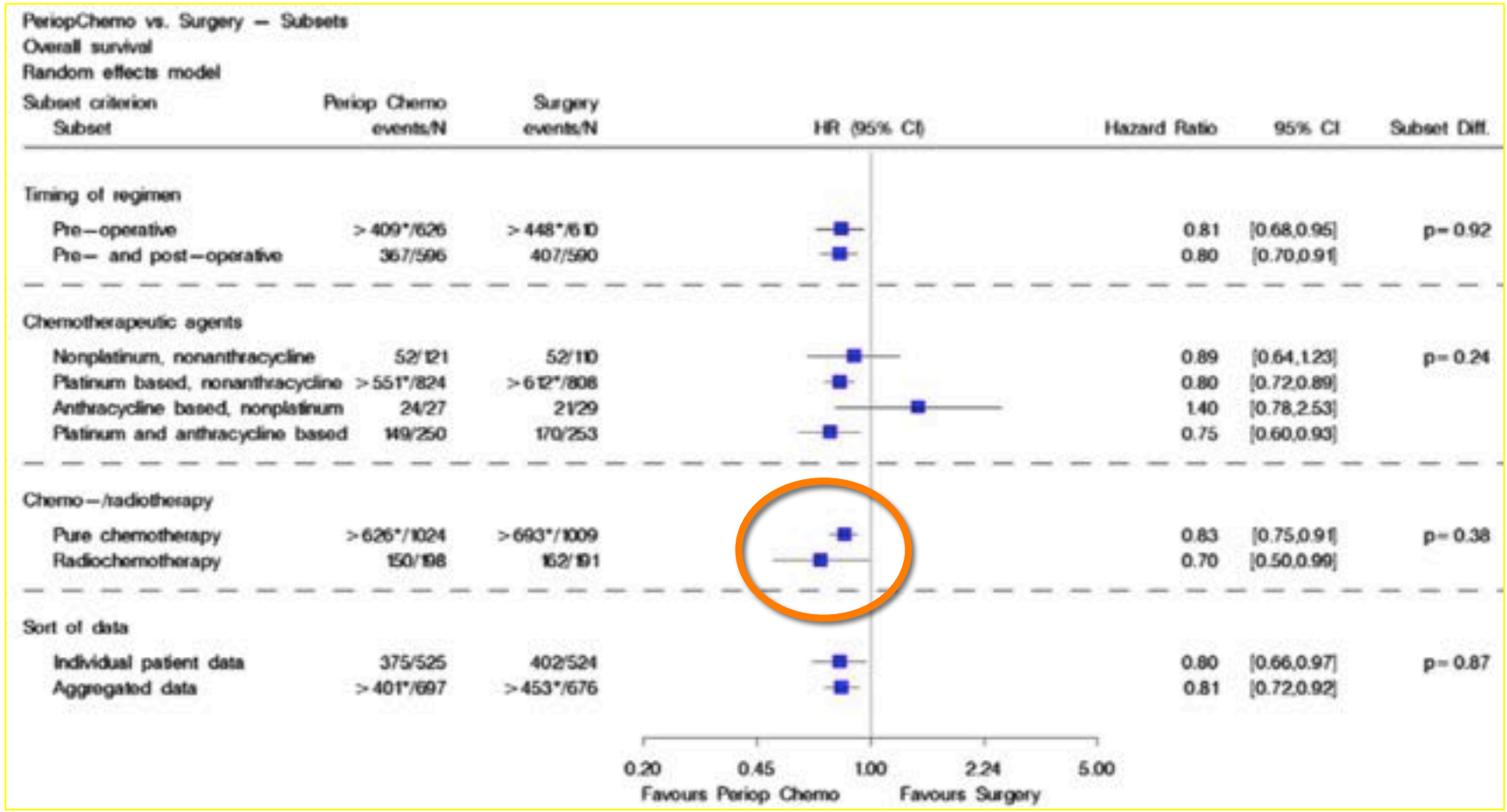


- ✓ Comparing CT ± RT
- ✓ Aggregate and individual pt data (IPD)
- ✓ Adenocarcinomas only,
- ✓ All sites included: esophagus; GEJ; Stomach
- ✓ No M+
- ✓ 14 Randomized trials (2422 pts)
- ✓ CROSS not included

CT(±RT) provides an absolute survival increase of 9% at 5 yy (23%→32% alive)

Ronellenfitsch *et al*; Eur J Cancer - 2013

"…the wider CI of the HR was due to the lower number of patients in this subset, exclusively comprised of oesophageal and gastroesophageal junction tumours…"



Ronellenfitsch *et al*; Eur J Cancer - 2013

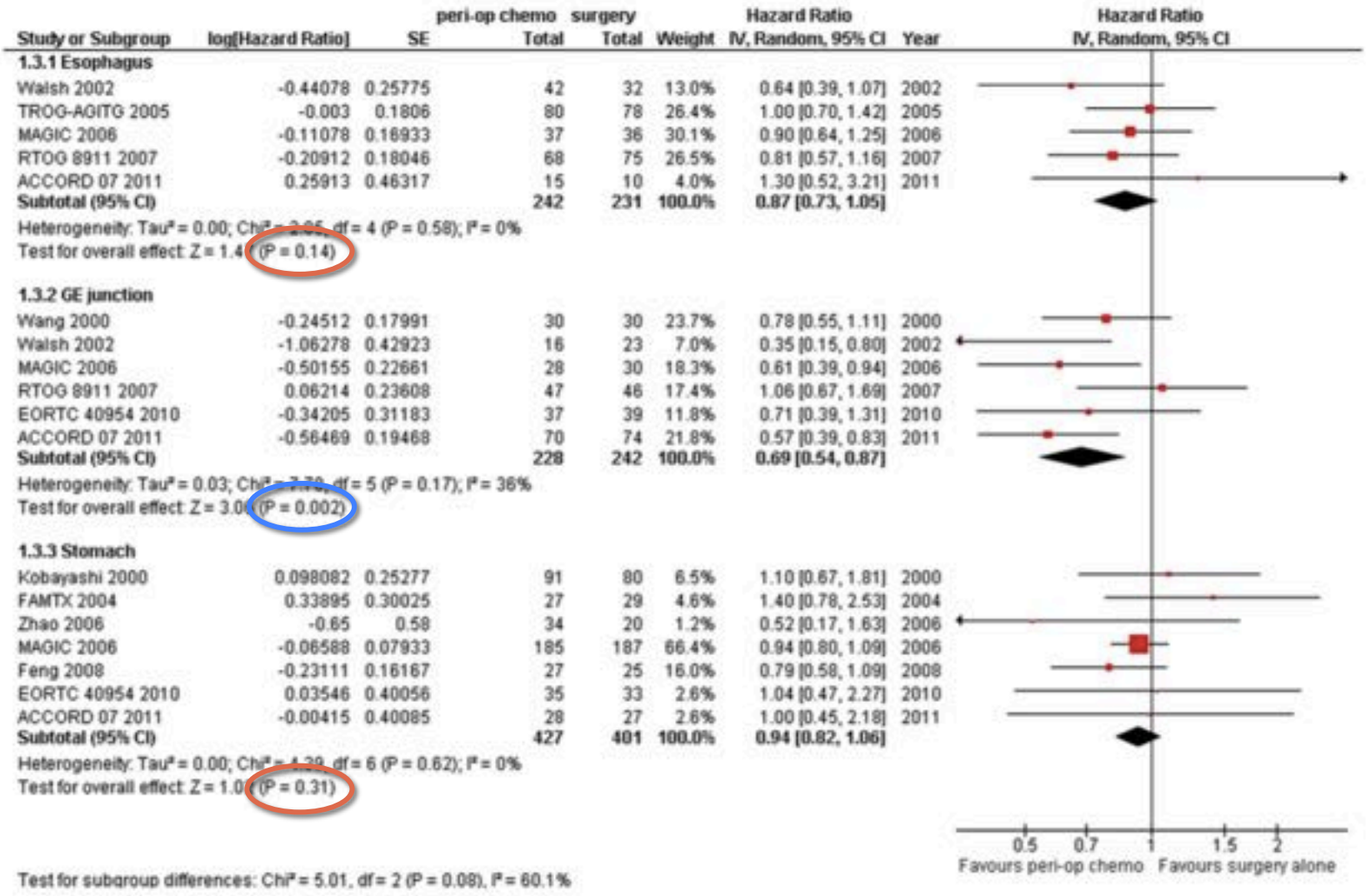
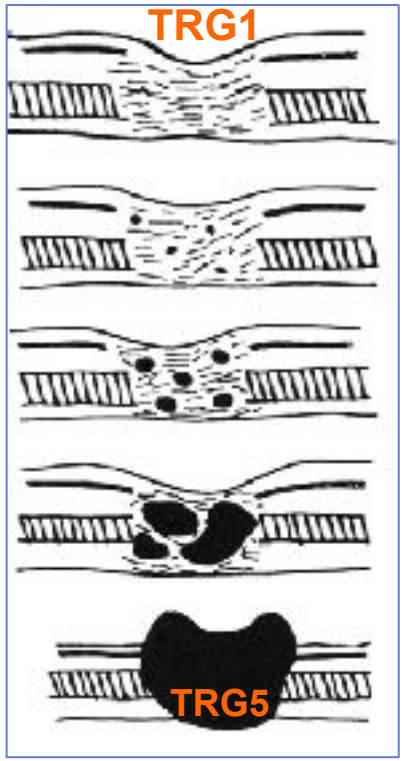


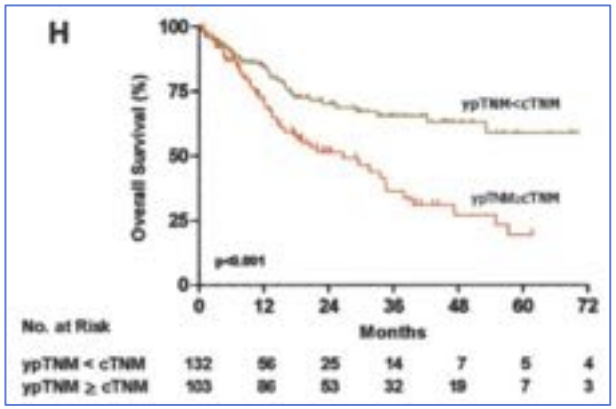
Fig. 5. Forest plot for overall survival by tumour site (calculated using random-effects models).

Ronellenfitsch *et al*; Eur J Cancer - 2013

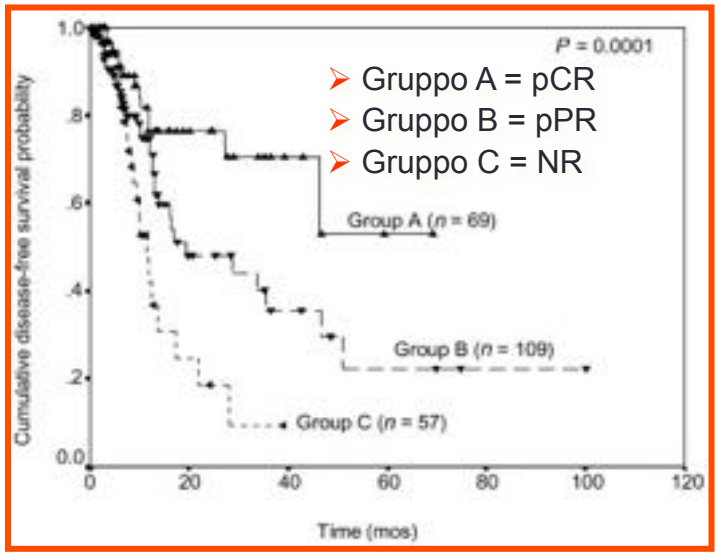


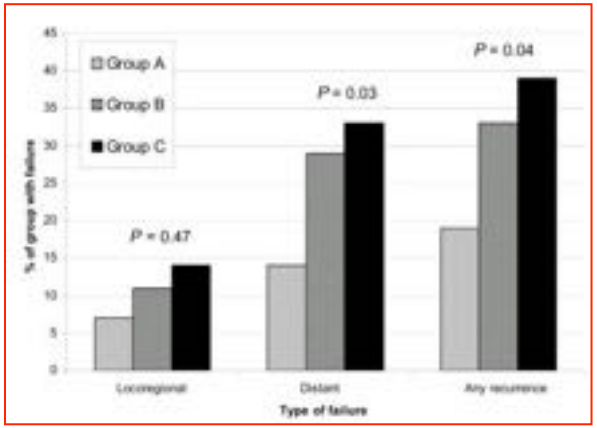
- 93 Specimens → correlation with DFS (p=0.001)

- 235 pts (clinical Stage II, III, IVA) Esophagus+ GEJ udergoing TMT
- DFS and OS independently predicted by posttherapy p-stage (p= 0.02)



- Same Patient Group





Rohatgi *et al*; Cancer 2005
Chierieac *et al*; Cancer 2005
Mandard *et al*; Cancer 1994

Pathological Complete Response - pCR

	N° Pts	Accrual	Rate adeno	Tumor site	Dose/Fx (Gy)	Concurrent CT	% pCR (N° pts RTCT arm)
Walsh [43]	113	1990-1995	100%	Middle+ Lower Esophagus + Cardias	40/2.7	CDDP + 5Fu	25% (13/52)
Urba [46]	100	1989-1994	75%	Proximal+ Middle + Lower Esophagus + GEJ	45/1.5 (twice daily)	CDDP+ 5Fu+ Vimblastine	28% (14/50)
Burmeister [48]	256	1994-2000	62%	Proximal +Middle+ Lower Esophagus	35/2.4	CDDP + 5Fu	16% (16/103)
Tepper [49]	56	1997-2000	75%	Toracic Esophagus (below 20 cm)+ GEJ <2cm distal spread in cardia	50.4/1.8	CDDP + 5Fu	40% (10/25)
Van Hagen [50]	366	2004-2008	75%	Proximal +Middle+ Lower Esophagus + GEJ	41.2/1.8	Carboplatin + Paclitaxel	29% (47/161)

Cellini *et al*; Radiat Oncol 2014

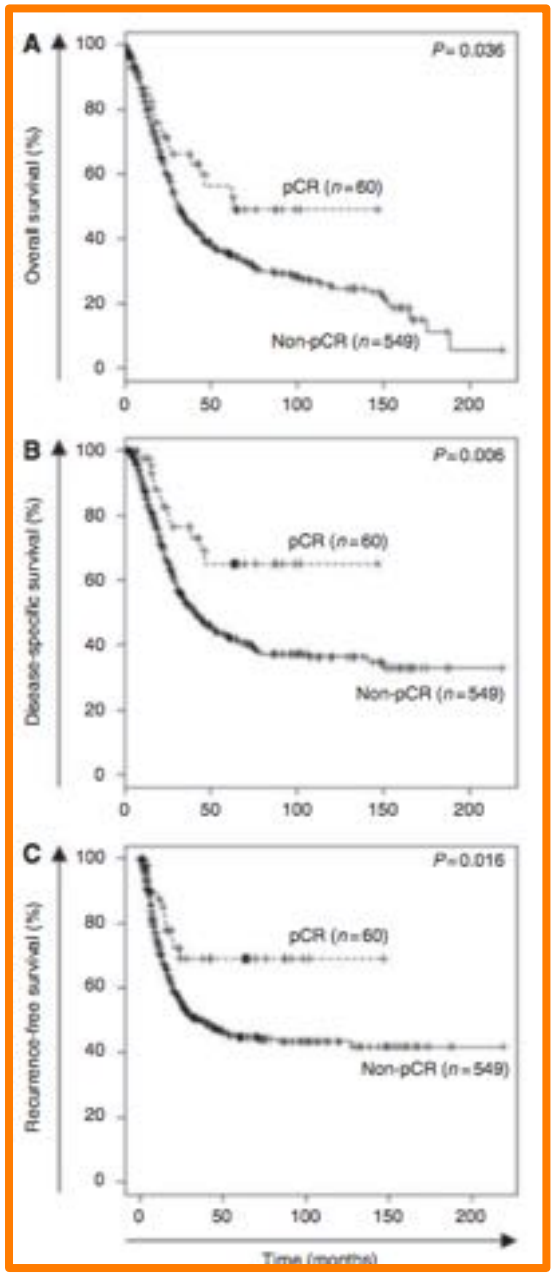
- Retrospective evaluation
- 714 pts (1985-2009) preoperative treatment CT±RT [→ what RT?]

- RTCT= 17% pCR / CT= 4% pCR

- Significant correlation pCR – Clinical Outcome

- No differences for recurrence features depending on RTCT/CT inducing pCR

- No differences in recurrence patterns by pCR vs non-pCR groups



Fields *et al*; British J Cancer 2011

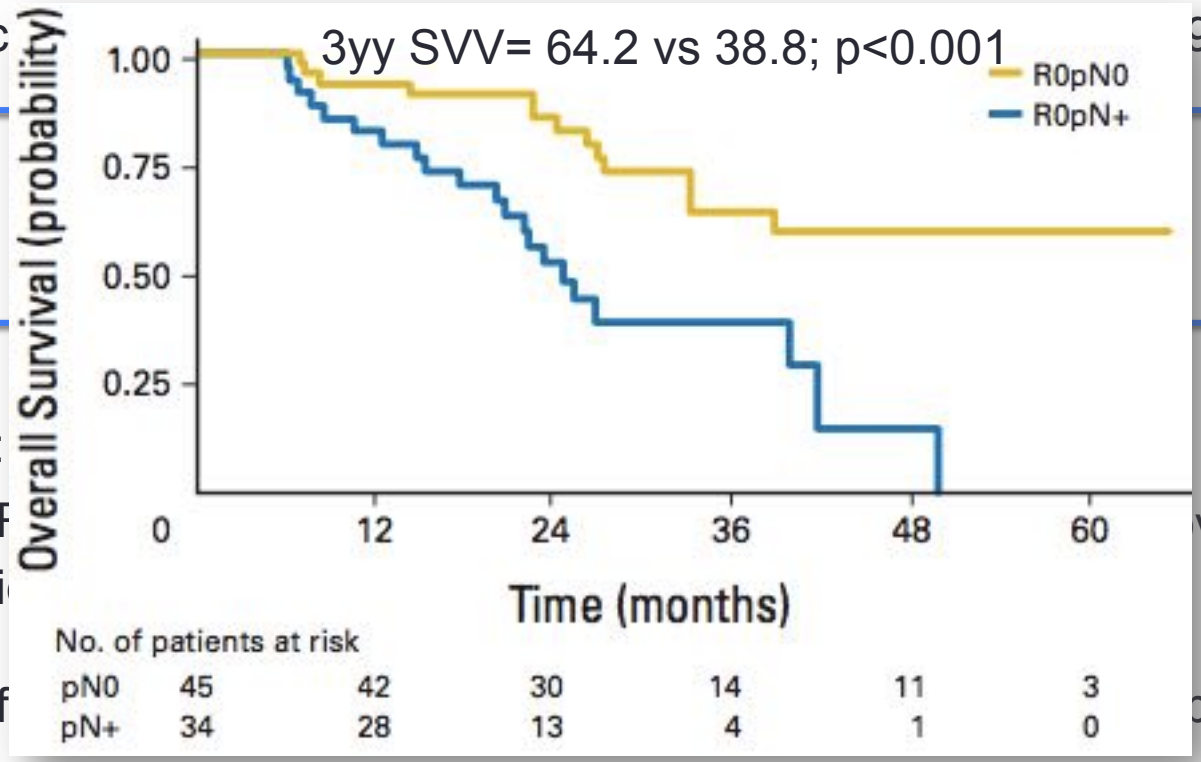
1. Burmeister 2011:
   - Phase II Randomized
   - 75 pts Esophagus + GEJ (100 pts planned)
   - CT: 5-Fu+CDDP
   - RTCT: adding 35 Gy(2.4 fx)
   - Non significant trend favoring RTCT for PFS (14vs 26 mth) + OS (29vs 32 mth)
   - Significant improvement of pCR (8 vs 31%; p=0.01)
     - and R1 rates (11vs 0%; p=0.04) for RTCT
       - Similar toxic profile

2. Stahl 2009:
   - Phase III Randomized
   - 126 pts Siewert I-III (326 pts planned)
   - CT: 15ww 5-Fu+Leucov+CDDP
   - RTCT: 12ww CT+3ww x 30 Gy(2.0 fx)
   - Non significant trend favoring RTCT for 3yySVV (47.4 vs 27.7 %; p=0.07) *
     - Significant improvement of pCR (2 vs 15.6%; p=0.03) favoring RTCT
     - Significant improvement of pN0 (36.7 vs 64.4%; p=0.03) favoring RTCT

Stahl *et al*; JCO - 2009

Burmeister *et al*; Eur J Cancer - 2011

1. Burmeister 2011:
   - Phase II Randomized
   - 75 pts Esophagus + GEJ (100 pts planned)
   - CT: 5-Fu+CDDP
   - RTCT: adding 35 Gy(2.4 fx)
   - Non signific… …9vs 32 mth)



2. Stahl 2009:
   - Phase III R… …v+CDDP
   - 126 pts Si… …x 30 Gy(2.0 fx)
   - Non signif… …p=0.07) *
     - Significant improvement of pCR (2 vs 15.6%; p=0.03) favoring RTCT
     - Significant improvement of pN0 (36.7 vs 64.4%; p=0.03) favoring RTCT

Stahl *et al*; JCO - 2009

Burmeister *et al*; Eur J Cancer - 2011

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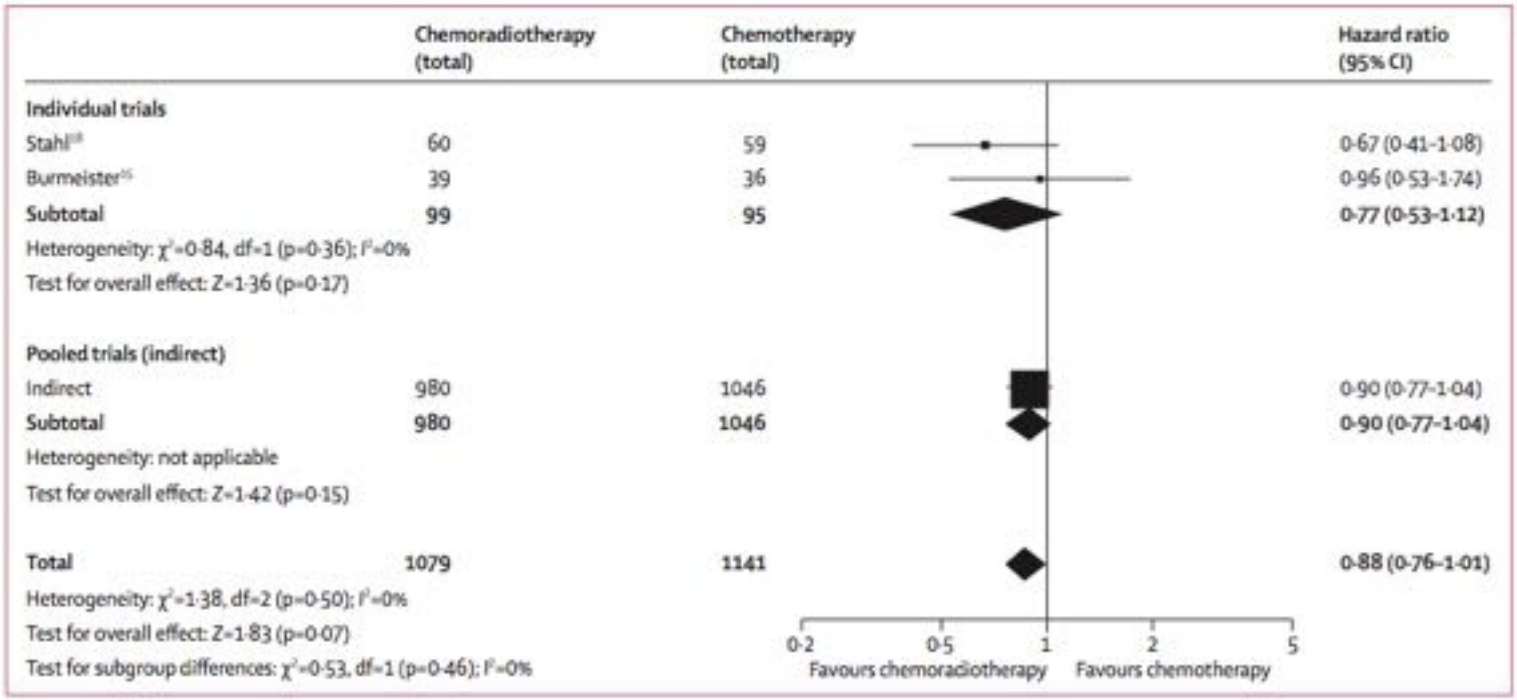


Sjoquist *et al*; Lancet Oncol - 2011

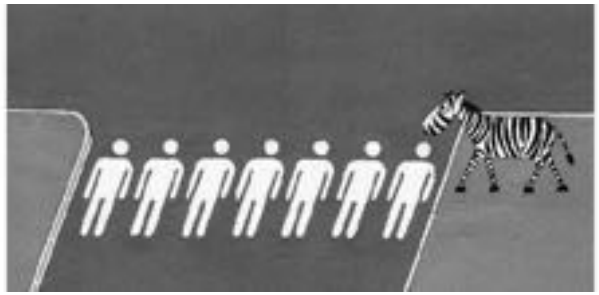
Indicazioni

NCCN National Comprehensive Cancer Network®

- ✓ NCCN
- ✓ ESMO
- ✓ AIRO
- ✓ AIOM

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Aiom



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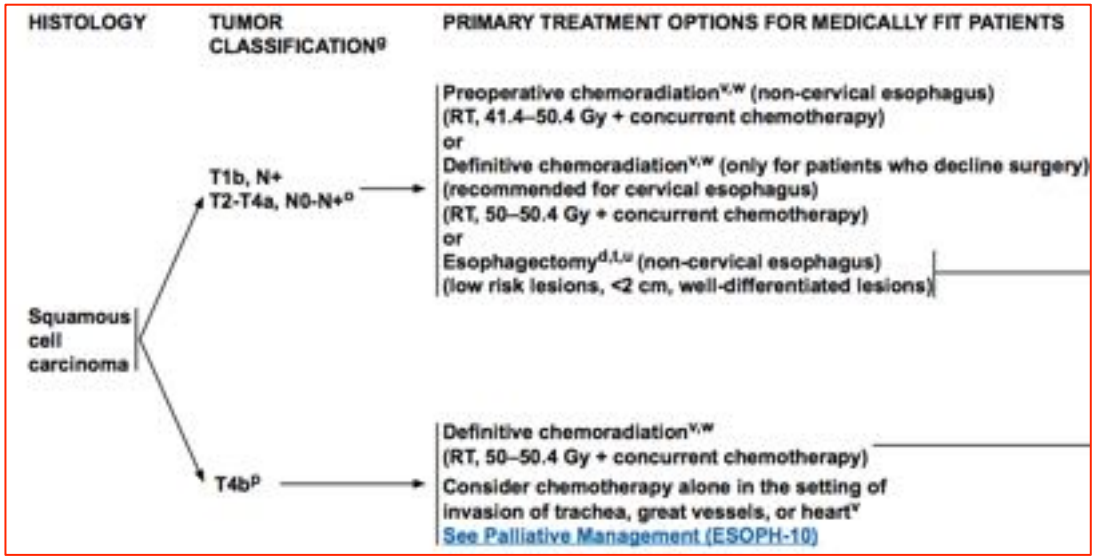

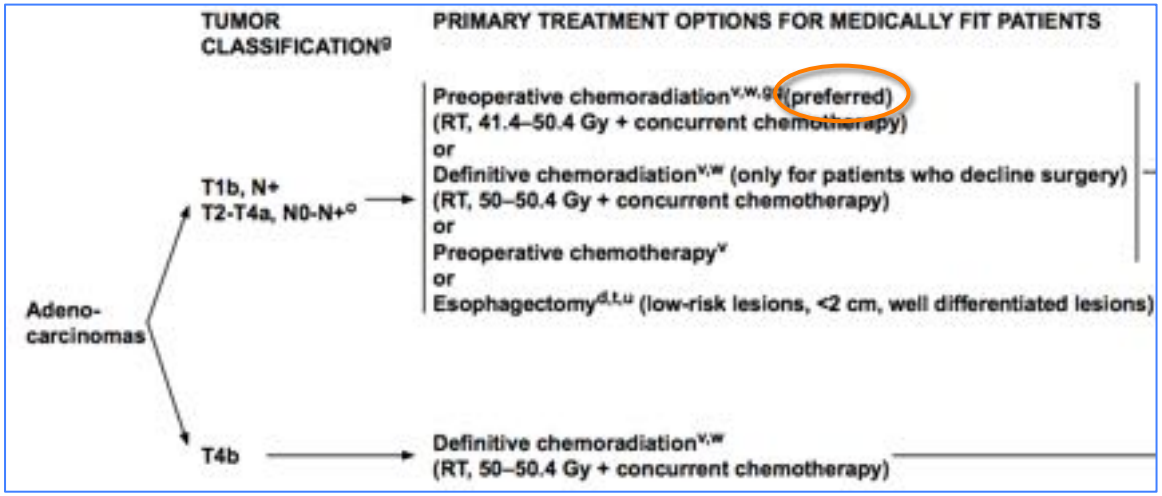

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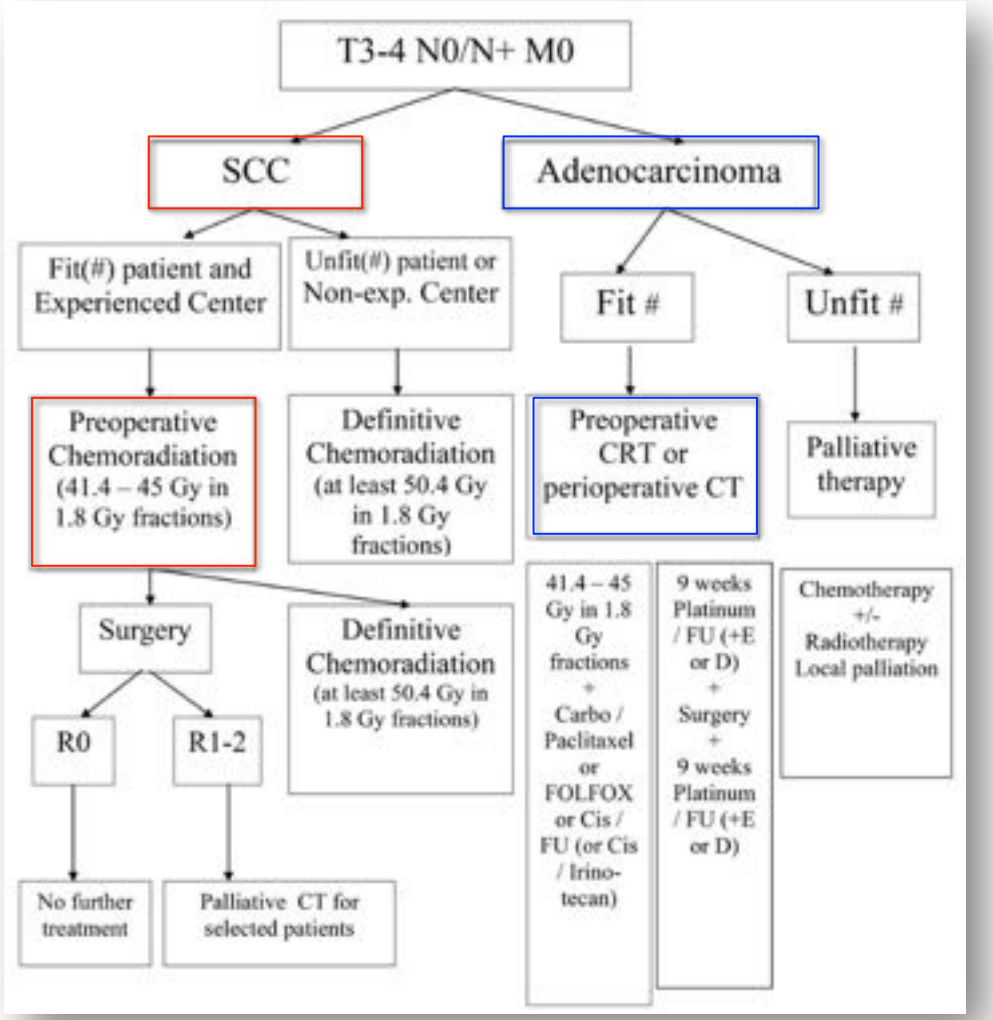
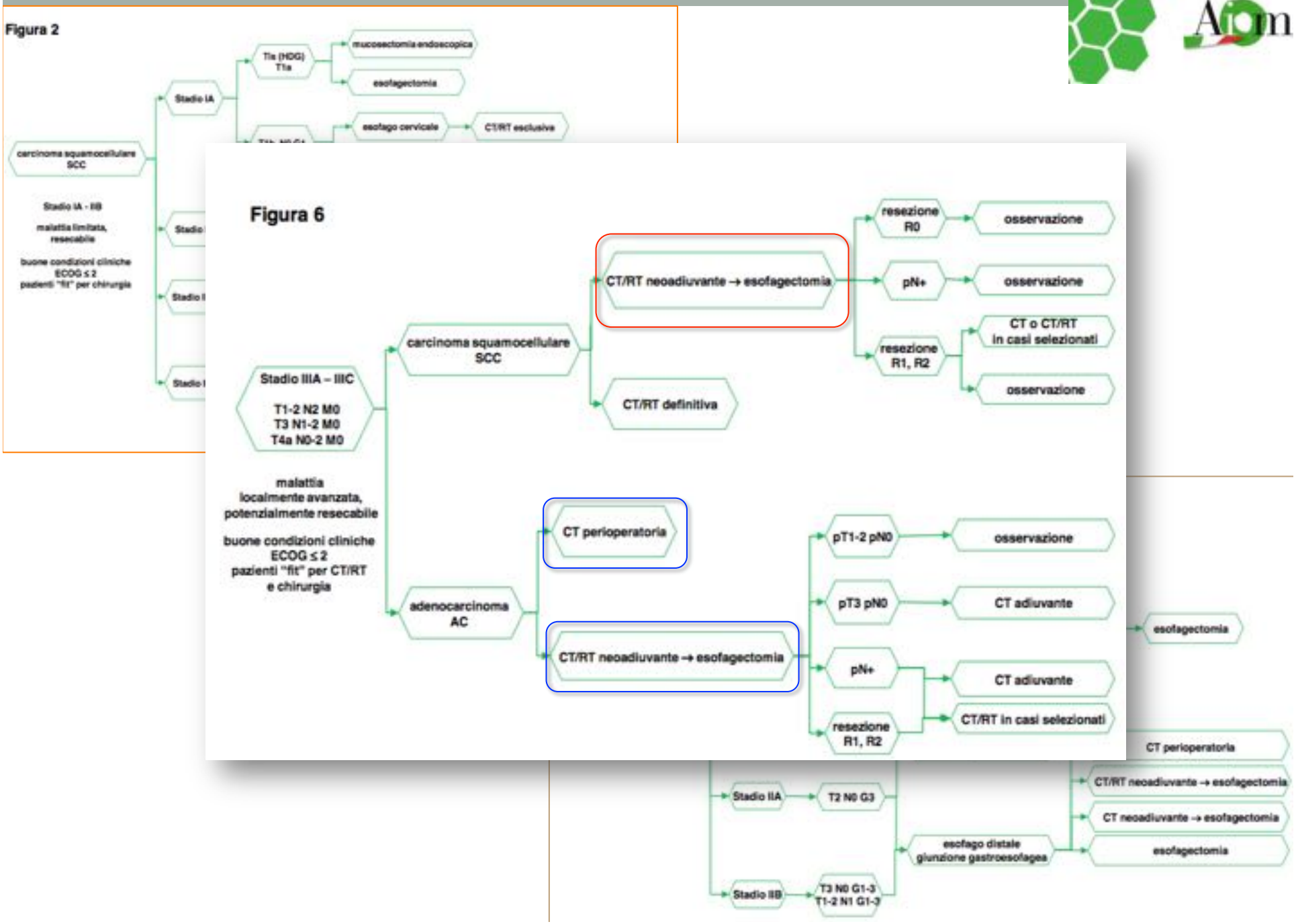


Stahl *et al*; Ann Oncol- 2013

Indicazioni



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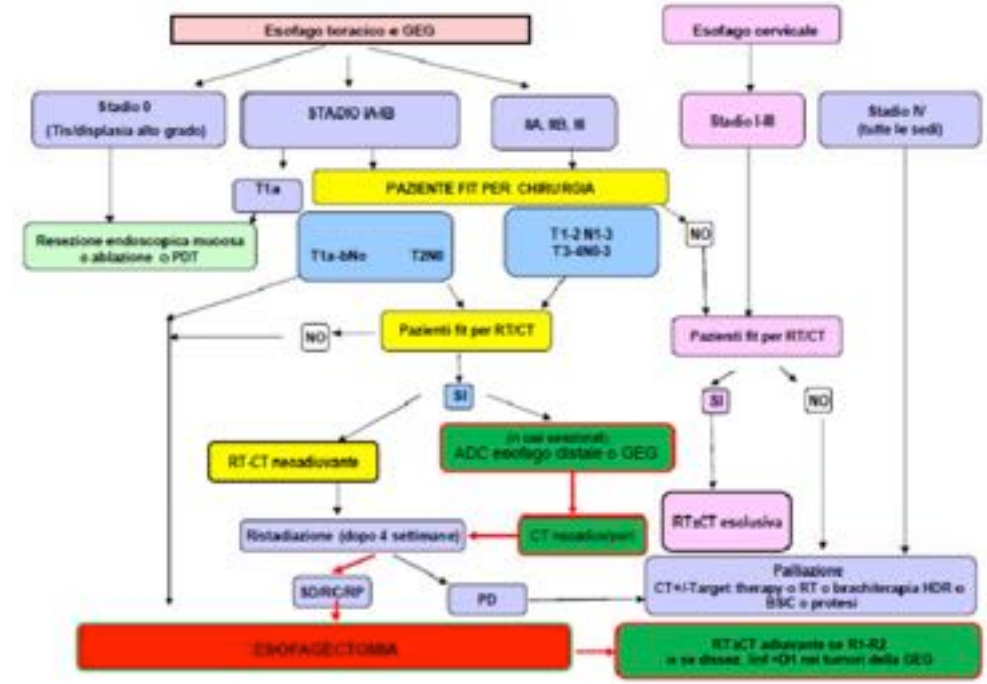
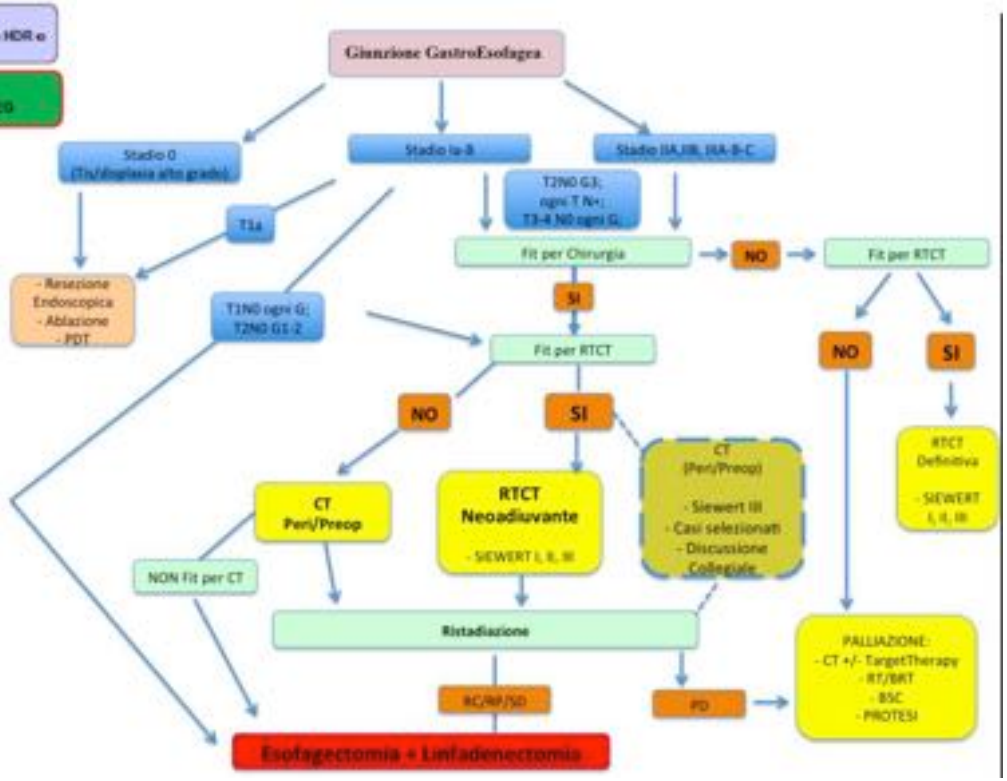




Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis

Katrin M Sjoquist, Bryan H Burmeister, R Mark Smithers, John R Zalcberg, R John Simes, Andrew Barbour, Val Gebski, for the Australasian Gastro-Intestinal Trials Group

….”the focus of future trials should be on:

1. identification of the optimum regimen of neoadjuvant therapy
    2. and should aim to minimise treatment toxicities and effect on quality of life,
        3. as well as attempt to identify and select those patients most likely to benefit from specific treatment options…..”

Sjoquist *et al*; Lancet Oncol - 2011

1. Identification Of The Optimum Regimen Of Neoadjuvant Therapy
    - Optimization fo RTCT Schedules
    - Targeted Therapies (?)

✧ Human Epidermal Growth Factor (HER) Type 2 Targeting Agents

✓ ↑Trastuzumab; ↑? T-DM1; ? Lapatinib

✧ Epidermal Growth Factor's Receptor (EGFR) Inhibitors

✓ ↓? Cetuximab; ↓ Panitumumab; ↓ Gefitinib; ↑ Erlotinib

✧ Vascular Endothelial Growth Factor (VEGF) Inhibitors

✓ ?↓ Bevacizumab; ↓ Sorafenib; ? Sunitinib; ? Crizotinib

✧ mTOR Inhibitors

✓ ? Everolimus

Cellini *et al*; CMC 2014

1. Identification Of The Optimum Regimen Of Neoadjuvant Therapy
    - Optimization fo RTCT Schedules
    - Targeted Therapies (?)

- "…National Cancer Institute's (NCI) investment in oesophageal cancer research increased from 22.3 million to 33.0 million dollars per year from 2007 to 2011…"

NCI, Office of Budget and Finance; 2013

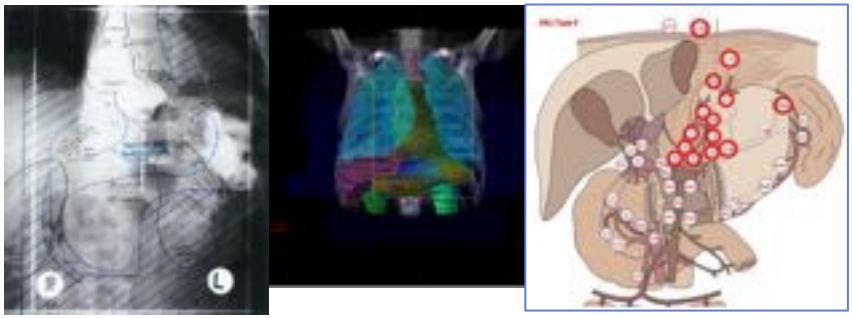
Cellini *et al*; CMC 2014

2. Minimise Treatment Toxicities

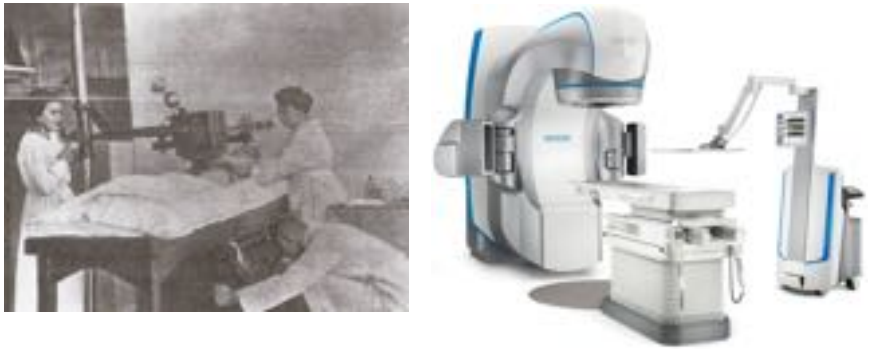
Treatment related toxicity evaluation:

- Klevebro *et al;* Eur J Surg Oncol 2015
- Deng *et al;* Diagn Pathol 2014
- Kumagai *et al;* Br J Surg 2014

Volume Definition



Advanced Technologies



Role for Elderly patients

- Rochigneux *et al;* J Visc Surg 2012
- Camerlo *et al;* Diagn Pathol 2014

3. Identify And Select Patients for Specific Treatment

- ✓ Imaging
- ✓ Molecular/Genetics features
- ✓ Modelling


That's all Folks!