La chemio-radioterapia nel trattamento del carcinoma del retto.

Dott. Francesco Fiorica

Dott. Giampaolo Zini

U.O. Radioterapia Oncologica, Ferrara

Ferrara 16/04/2011

Local Recurrence

- Usually seen within 2 years, seldom cured
- Factors influencing local recurrence include:
  - TNM Stage
  - Surgical experience/technique and completeness of resection (spillage)
  - Use of adjuvant therapy
  - Tumor differentiation and macroscopic appearance (circumferential, ulceration)
  - LVI, NVI

Stage	5 year, no adjuvant XRT
T1	10%
T2	15-35%
T3	20-45%
T4	>50%
N+	40-65%

McCall J, et al. Int J Colorectal Dis **1995** 10. 126-132
Bokey EL, et al. BJS **1999;** 86:1164.
Shirouzu et al., Am J. Surg **1993**; 165:233

RADIOTERAPIA: migliorare i risultati della chirurgia

RADIOTERAPIA POSTOPERATORIA
da sola o in associazione a chemioterapia

RADIOTERAPIA
PREOPERATORIA

RCTs

Clinical practice

Selected	Patient population	All comers
No	Comorbidity	Very frequent
Very high	Compliance	Variable
Experts	Providers	Usual caregivers
Often undetected	Adverse drug reactions	Usual setting of detection
Limited	Generalizability	Broad

Typical exclusion criteria in registrative RCTs

- Age < 18 yrs
- Age > 65 yrs
- Normal ALT levels
- Low hemoglobin (<12 g/dl)
- Low WBC count (<3,000/mm^3)
- Neutropenia (<1,500/mm^3)
- Thrombocytopenia (< 100,000/mm^3)
- Decompensated liver disease
- Bilirubin >2.0 mg/dL
- Albumin <3.5 g/dL
- Protime >2 sec prolonged
- Creatinine >1.5 mg/dL
- Alphafetoprotein >50 mg/dL
- HBsAg+
- Any other known liver disease

- Depression
- Psychiatric disease
- Coronary artery disease
- Cerebral vascular disease
- Neurologic illness
- Seizure disorders
- Alcohol abuse
- IV drug use
- Methadone treatment
- Hemophilia
- Hemoglobinopathy
- Autoimmunity
- Thyroid diseases
- Mental retardation
- Institutionalization
- Children

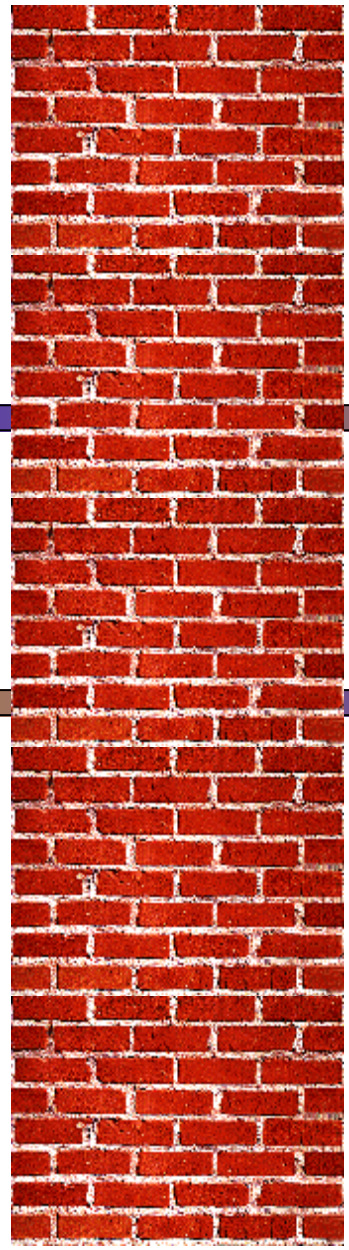
EVIDENCE BASED MEDICINE

EFFECTIVENESS

è il risultato che lo stesso intervento produce in condizioni di reale pratica assistenziale, al di fuori del contesto sperimentale

EFFICACY

è l'efficacia di un intervento sanitario in condizioni sperimentali



CLINICAL PRACTICE

RCTs MA

Bassa External validity

Alta Internal validity

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Preoperative Radiotherapy With or Without Concurrent Fluorouracil and Leucovorin in T3-4 Rectal Cancers: Results of FFCD 9203

Jean-Pierre Gérard, Thierry Conroy, Franck Bonnetain, Olivier Bouché, Olivier Chapet, Marie-Thérèse Closon-Dejardin, Michel Untereiner, Bernard Leduc, Éric Francois, Jean Maurel, Jean-François Seitz, Bruno Buecher, Rémy Mackiewicz, Michel Ducreux, and Laurent Bedenne

From the Centre Antoine Lacassagne, Nice; Centre Alexis Vautrin, Vandoeuvre-lès-Nancy; Fédération Francophone de Cancérologie Digestive; Centre Hospitalier Universitaire de Dijon, Dijon; Centre Hospitalier Universitaire de Reims, Reims; Centre Hospitalier Universitaire de Lyon "Pierre Bénite," Lyon; Clinique Claude Bernard, Metz; Centre Hospitalier de Brive, Brive; Centre Hospitalier Universitaire Côte de Nacre, Caen; Centre Hospitalier Universitaire La Timone, Marseille; Centre Hospitalier Universitaire Hôtel Dieu Nantes, Nantes; Clinique Générale, Valence; Institut Gustave Roussy, Villejuif, France; and France University Hospital, Liège, Belgium.

Submitted March 30, 2006; accepted May 23, 2006.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/06/2428-4620/$20.00

DOI: 10.1200/JCO.2006.06.7629

A B S T R A C T

Purpose
In 1992, preoperative radiot
cancers. The present rand

Patients and Methods
Patients were eligible if
accessible to digital rectal
5 weeks was delivered. C
together with leucovorin,
Surgery was planned 3 t
adjuvant chemotherapy w
the trial was overall surv

Results
A total of 733 patients
chemoradiotherapy (14.6
Complete sterilization of
(11.4% *v* 3.6%; *P* < .05).
therapy (8.1% *v* 16.5%;

Conclusion
Preoperative chemoradiot
overall survival significan
adenocarcinoma of the m

J Clin Oncol 24:4620-462

PATIENTS AND METHODS

Eligibility Criteria and Randomization

Patients were eligible if they presented with a histologically confirmed, previously untreated rectal adenocarcinoma accessible to digital rectal examination; T3 or resectable T4 tumor with no evidence of distant metastases; age younger than 75 years; and WHO performance status of 0 or 1. All patients provided written informed consent and ethical committee permission was obtained. Eligible patients were randomly allocated to either preoperative RT alone or concurrent CT-RT.

INTRODUC

In the early 1990s, after ran
operative radiotherapy (R
most European countries
for T3-4 rectal cancers, wh
ment with the National Institutes of Health recommendations.[5] The evaluation of concurrent chemotherapy and radiotherapy (CT-RT) was an attractive field of research. Pilot studies were conducted by European Organisation for Research and Treatment of Cancer (EORTC) to determine the recommended dose of bolus fluorouracil (FU) modulated with leucovorin (LV).[6] The aim of this study was to evaluate if concurrent CT-RT in a neoadjuvant schedule could increase overall survival (OS) when compared with RT alone. The Fédération Francophone de Cancérologie Diges-

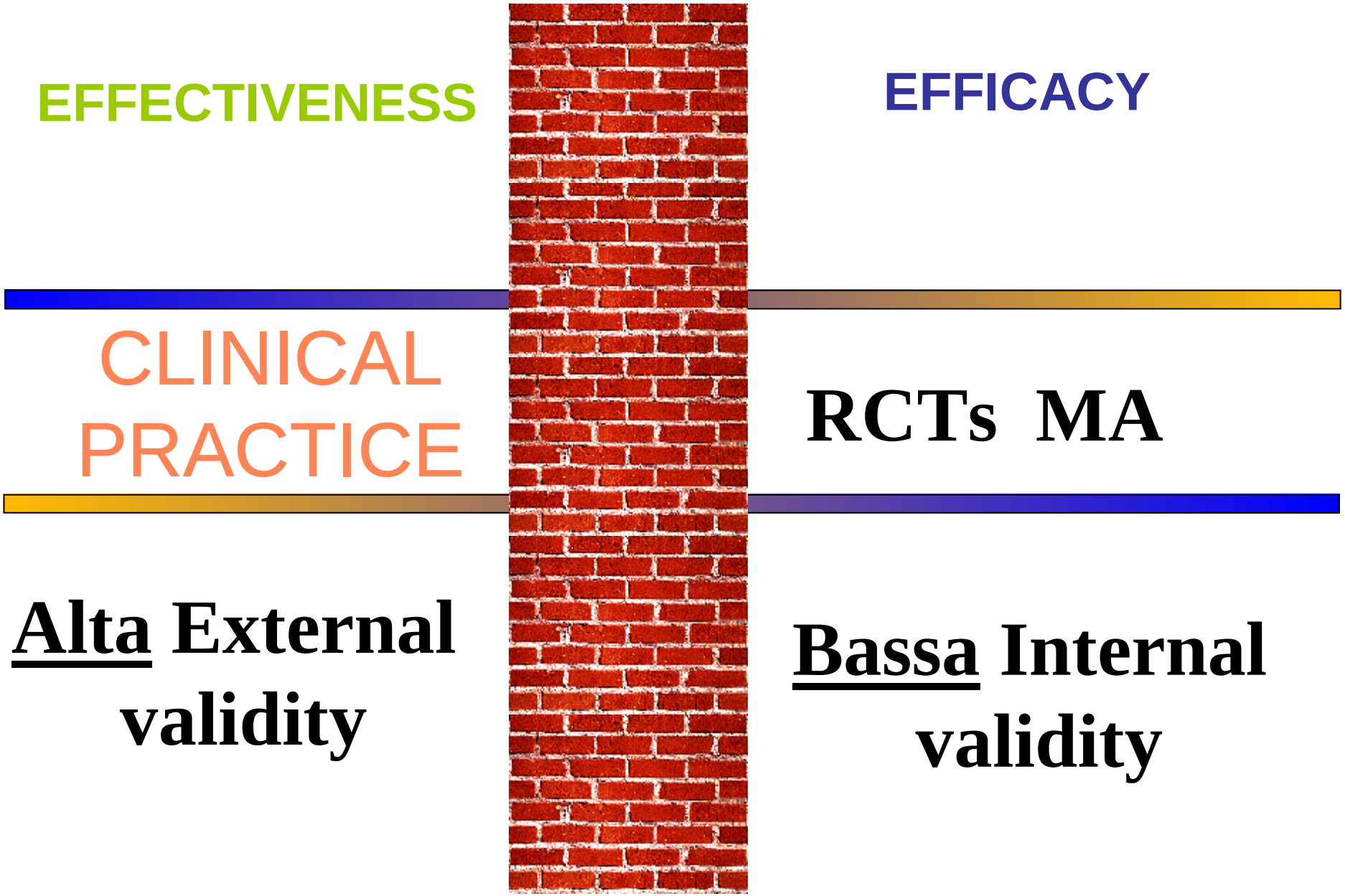
Eligibility Criteria and Randomization

Patients were eligible if they presented with a histologically confirmed, previously untreated rectal adenocarcinoma accessible to digital rectal examination; T3 or resectable T4 tumor with no evidence of distant metastases; age younger than 75 years; and WHO performance status of 0 or 1. All patients provided written informed consent and ethical committee permission was obtained. Eligible patients were randomly allocated to either preoperative RT alone or concurrent CT-RT.

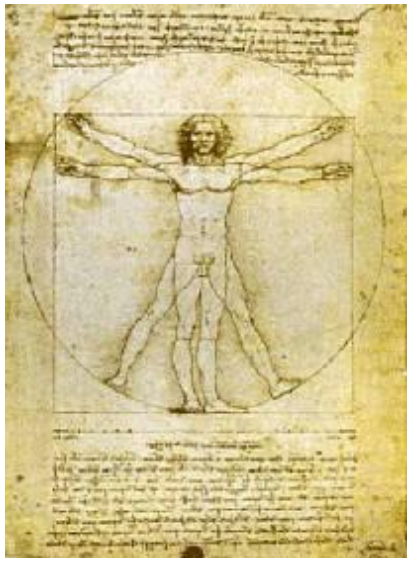
Work-Up

Before random assignment, patients underwent direct rigid proctoscopy. The distance from the lower pole of

EVIDENCE BASED RADIOTHERAPY



STATISTICAL



oggettivo

preciso e misurabile

definibile

standardizzabile

VERSUS

CLINICAL

soggettivo

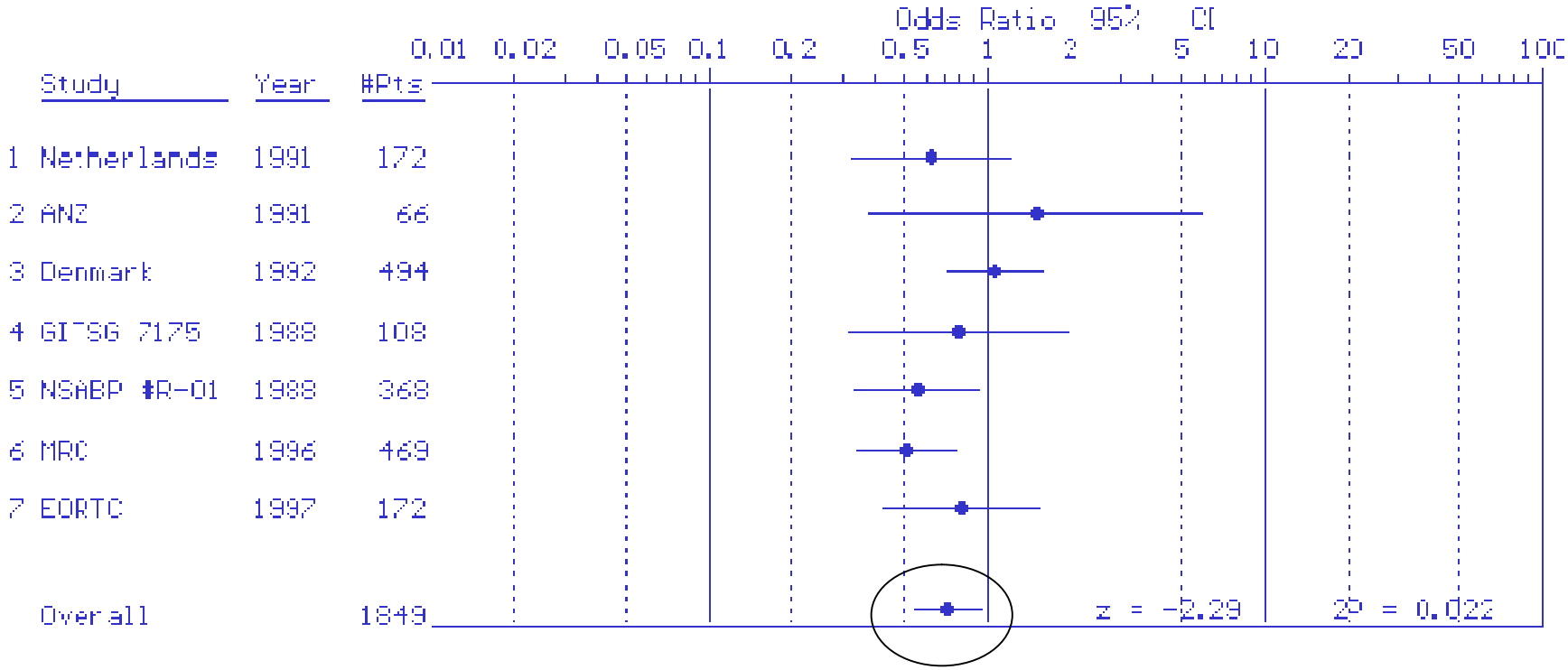
impreciso e non quantificabile

difficilmente definibile

non standardizzabile

RADIOTERAPIA POSTOPERATORIA

Meta-analysis of RCTs of Radiotherapy versus Observation
Local Failure Odds Ratio (Random Effects Model)

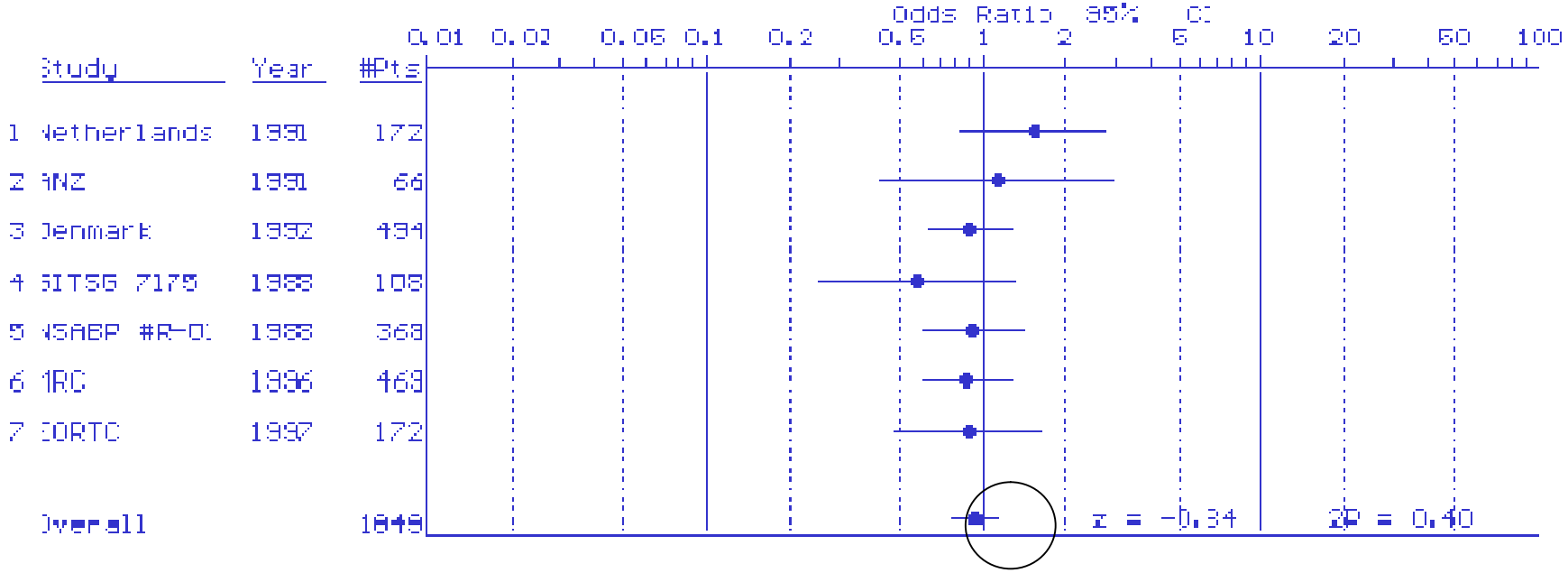


favours radiotherapy ← → favours observation

Odds Ratio = 0.73 (95% CI, 0.55 to 0.96; p=0.022)

RADIOTERAPIA POSTOPERATORIA

Meta-analysis of RCTs of Radiotherapy versus Observation
Mortality Odds Ratio (Random Effects Model)

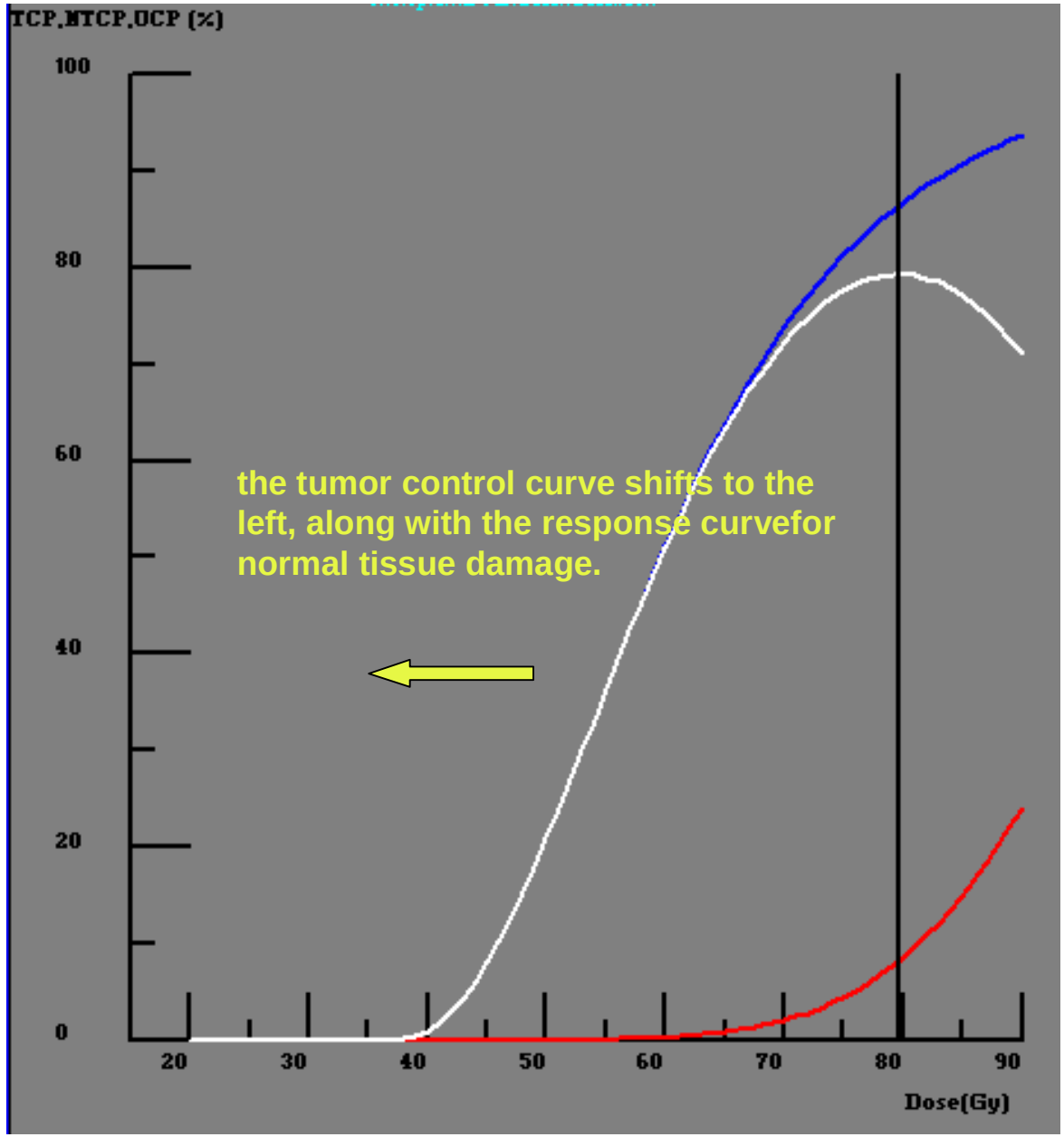


favours radiotherapy ← → favours observation

Odds Ratio = 0.92 (95% CI, 0.77 to 1.11; p=0.40)

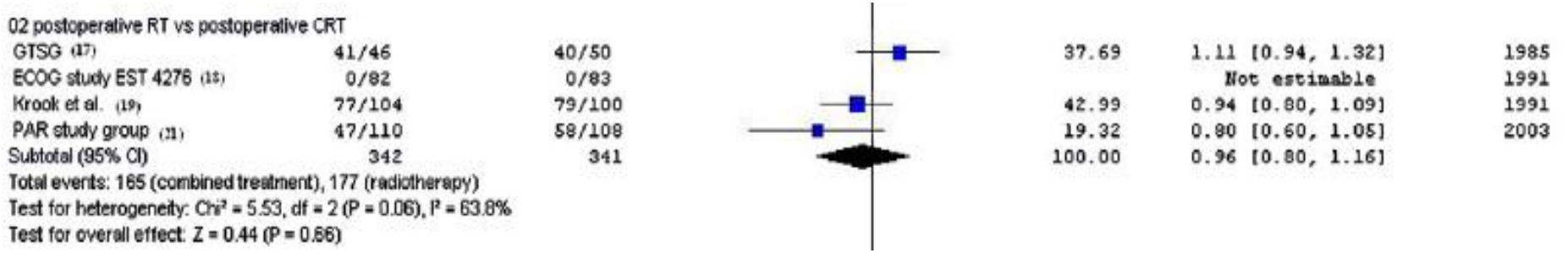
When CT is combined with RT:

The goal is to **obtain a positive therapeutic ratio**, and thus to **enhance the antitumor effect** while **minimizing toxicity** to critical normal tissues.

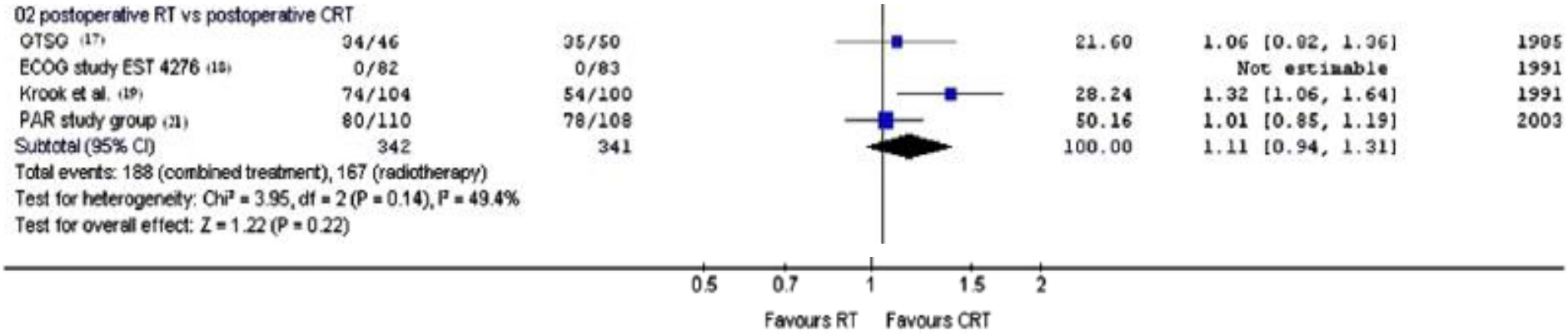


RADIOTERAPIA POSTOPERATORIA + CHEMIOTERAPIA

5 yrs local recurrence



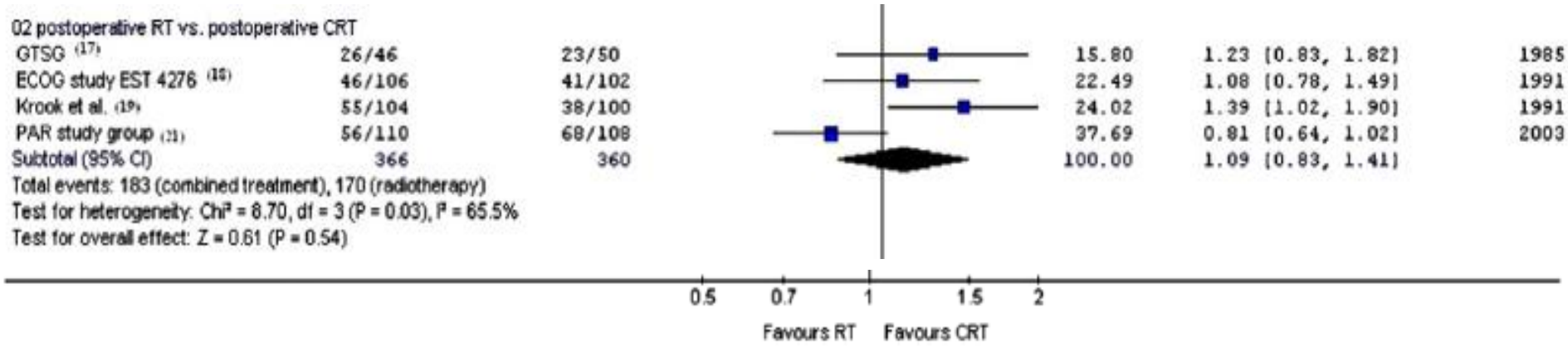
5 yrs distant metastases



Fiorica, Cancer Treat Rev. 2010

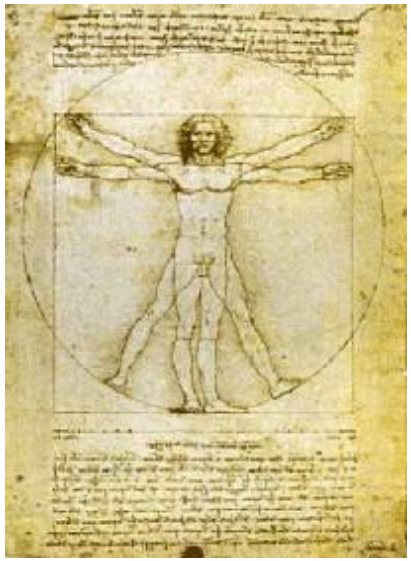
RADIOTERAPIA POSTOPERATORIA + CHEMIOTERAPIA

5 yrs overall survival



Fiorica, Cancer Treat Rev. 2010

STATISTICAL



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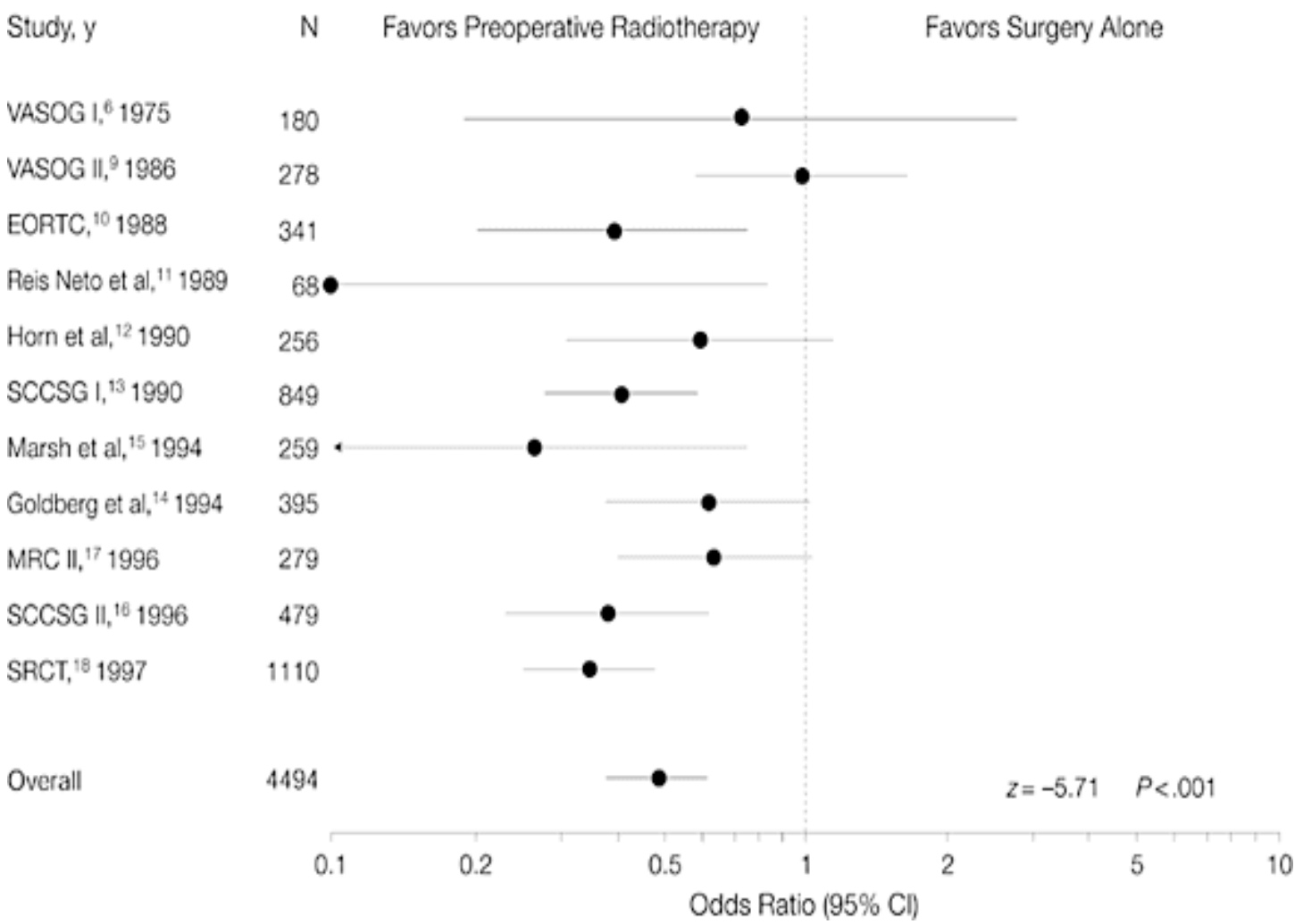
RADIOTERAPIA: migliorare i risultati della chirurgia

RADIOTERAPIA POSTOPERATORIA
da sola o in associazione a chemioterapia

RADIOTERAPIA
PREOPERATORIA

RADIOTERAPIA PREOPERATORIA

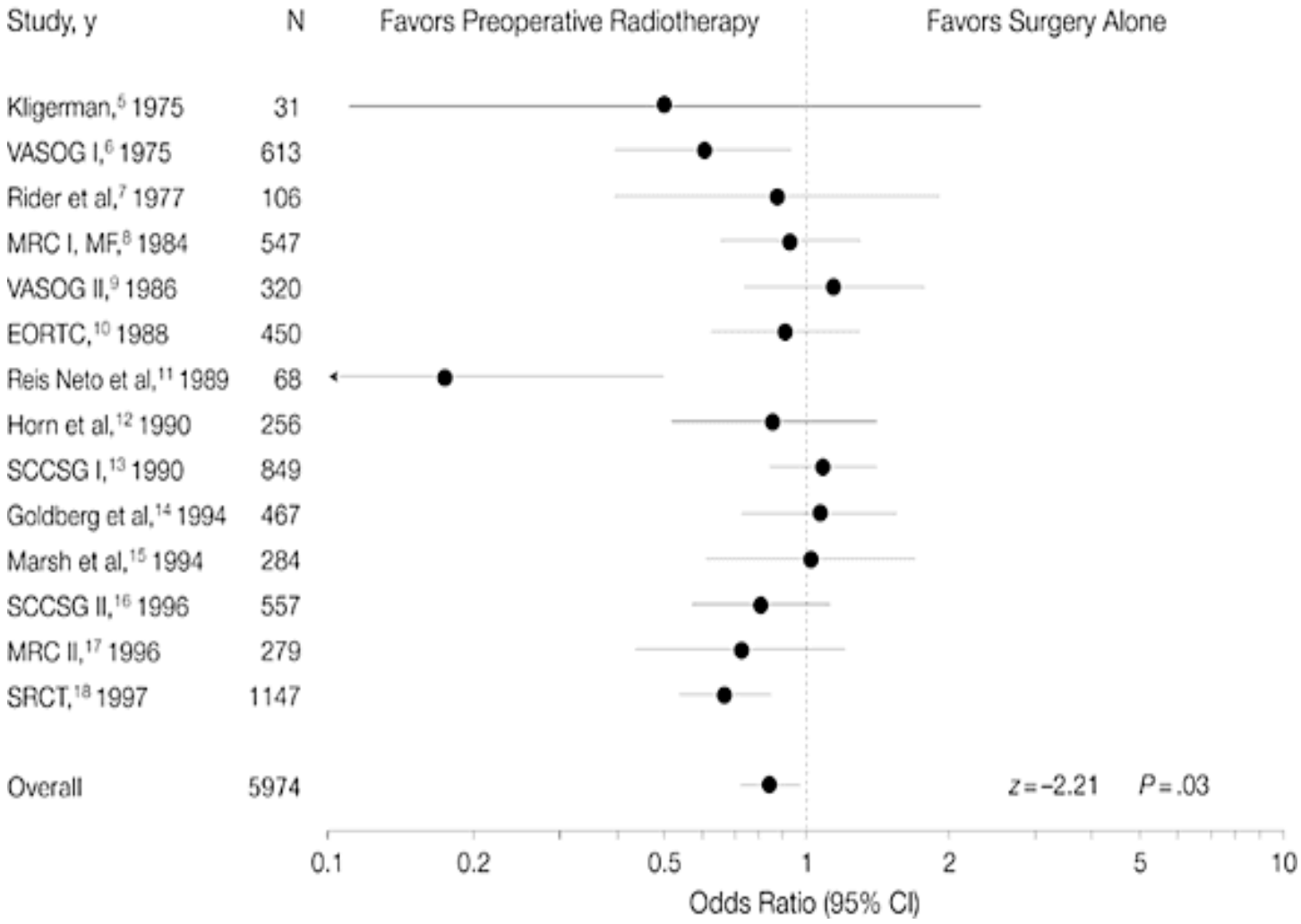
5 yrs local recurrence



Cammà, Fiorica JAMA 2000

RADIOTERAPIA PREOPERATORIA

5 yrs overall survival

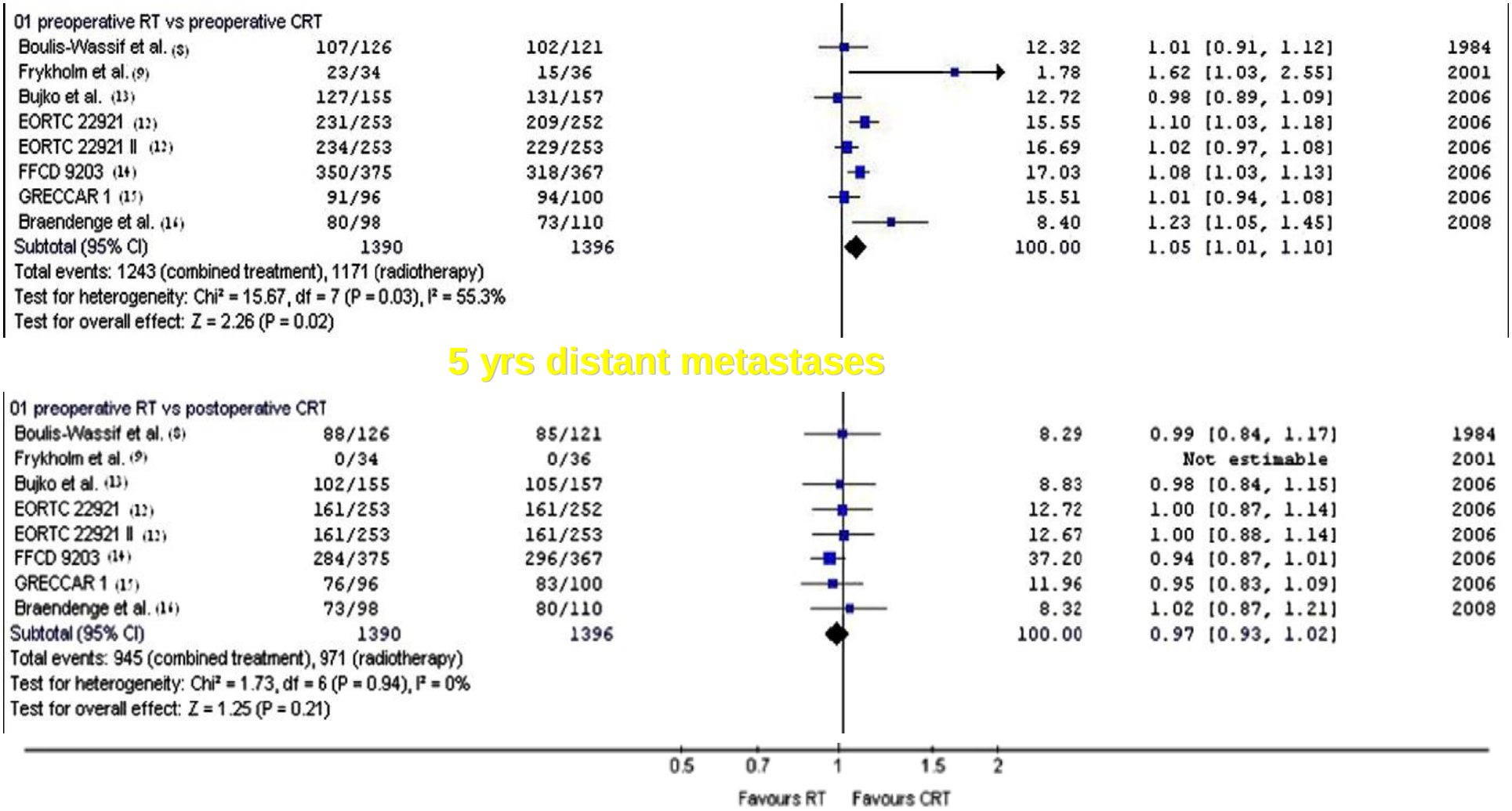


Cammà, Fiorica JAMA 2000

Introduzione della chemioterapia nei regimi pre-operatori

RADIOTERAPIA PREOPERATORIA + CHEMIOTERAPIA

5 yrs local recurrence

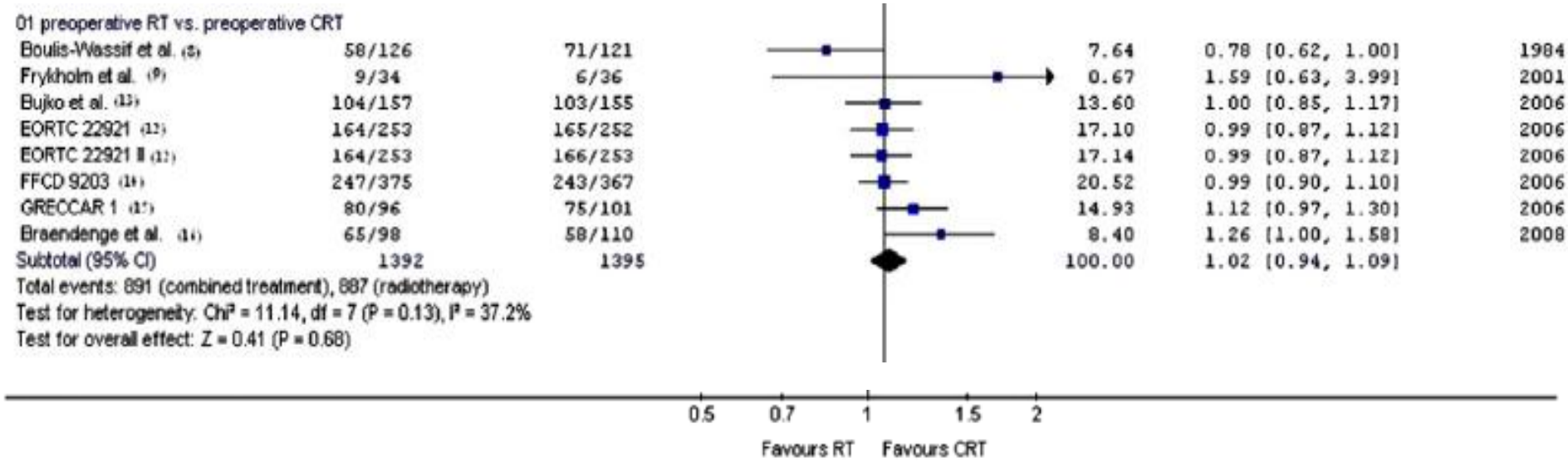


5 yrs distant metastases

Fiorica, Cancer Treat Rev. 2010

RADIOTERAPIA PREOPERATORIA + CHEMIOTERAPIA

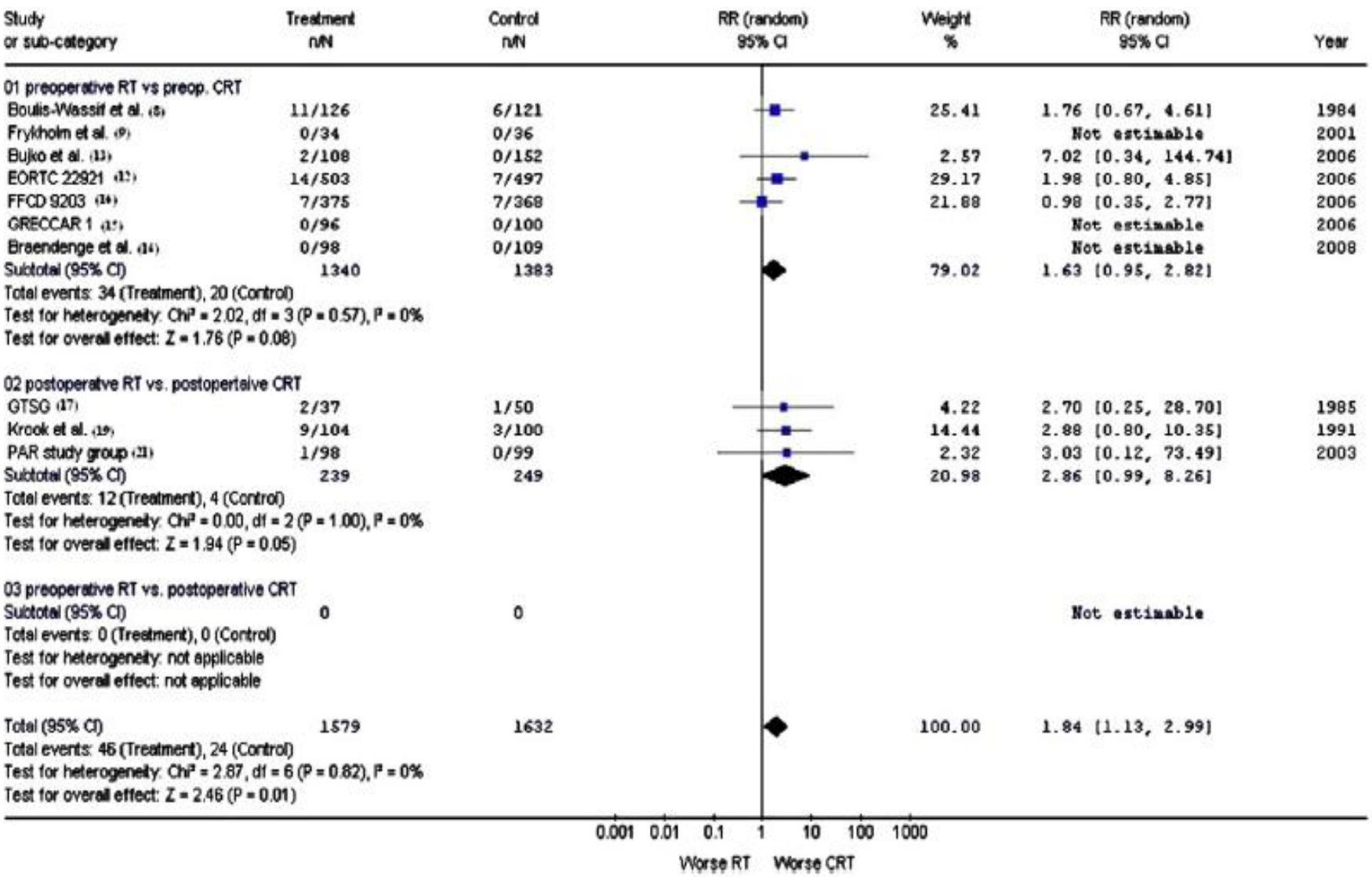
5 yrs overall survival



Fiorica, Cancer Treat Rev. 2010

RADIOTERAPIA PREOPERATORIA + CHEMIOTERAPIA

Mortalità da eventi tossici

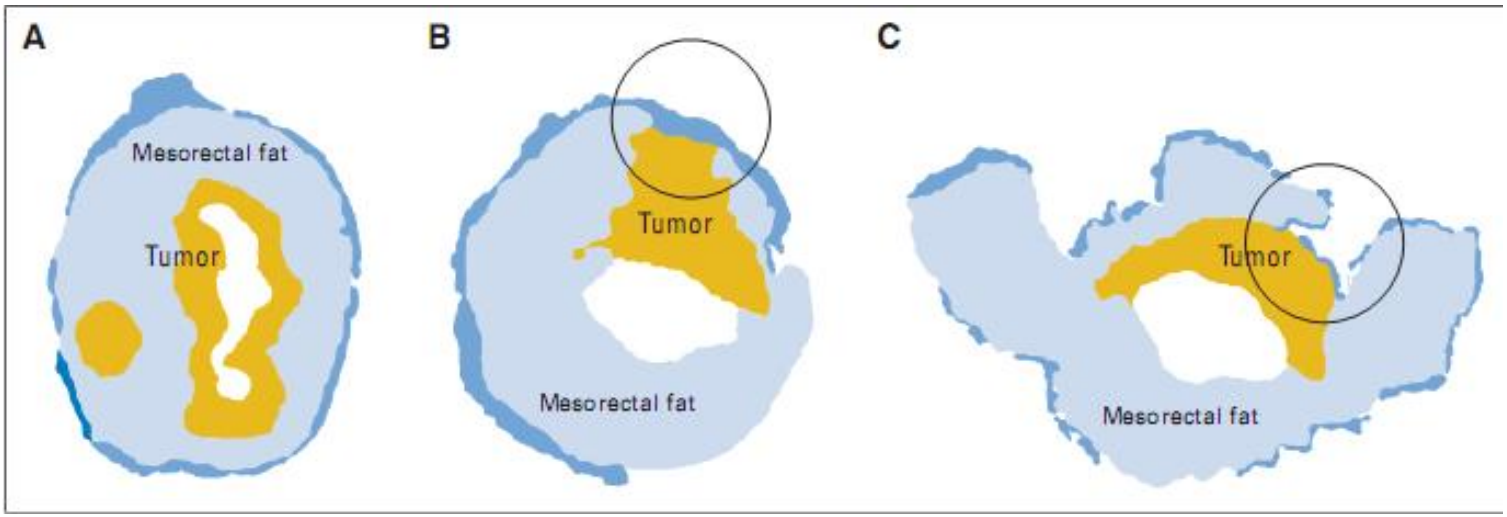


Fiorica, Cancer Treat Rev. 2010

HA UN RUOLO LA RADIOTERAPIA NELL' ERA TME?

TME is sub-optimal in more than 40% of patients where positive circumferential margin was detected.

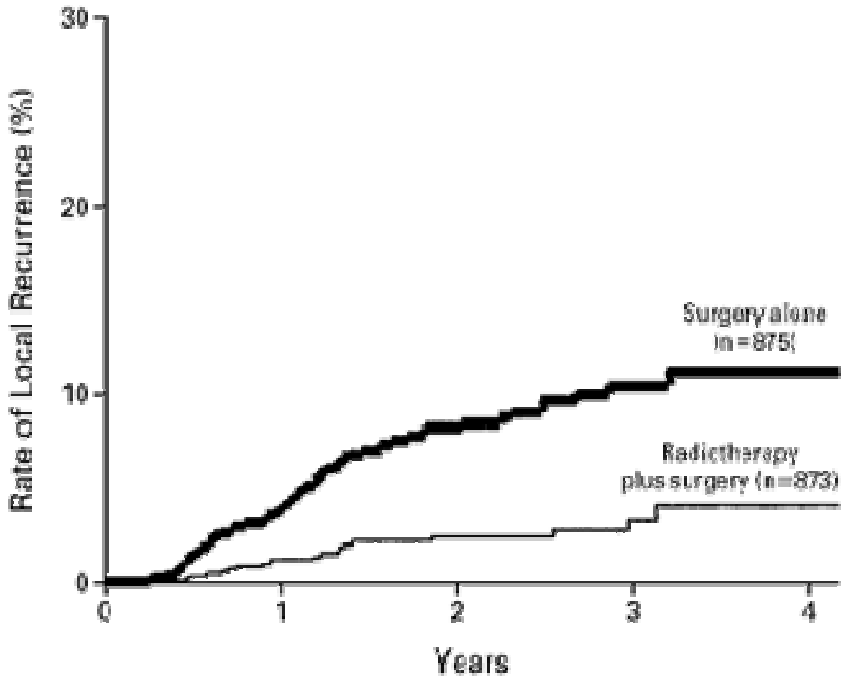
Nagtegaal, JCO 2008



Positive circumferential margin is associated with a 51% increase in the likelihood of local Recurrence

Nagtegaal, JCO 2008

RADIOTERAPIA PREOPERATORIA E TME

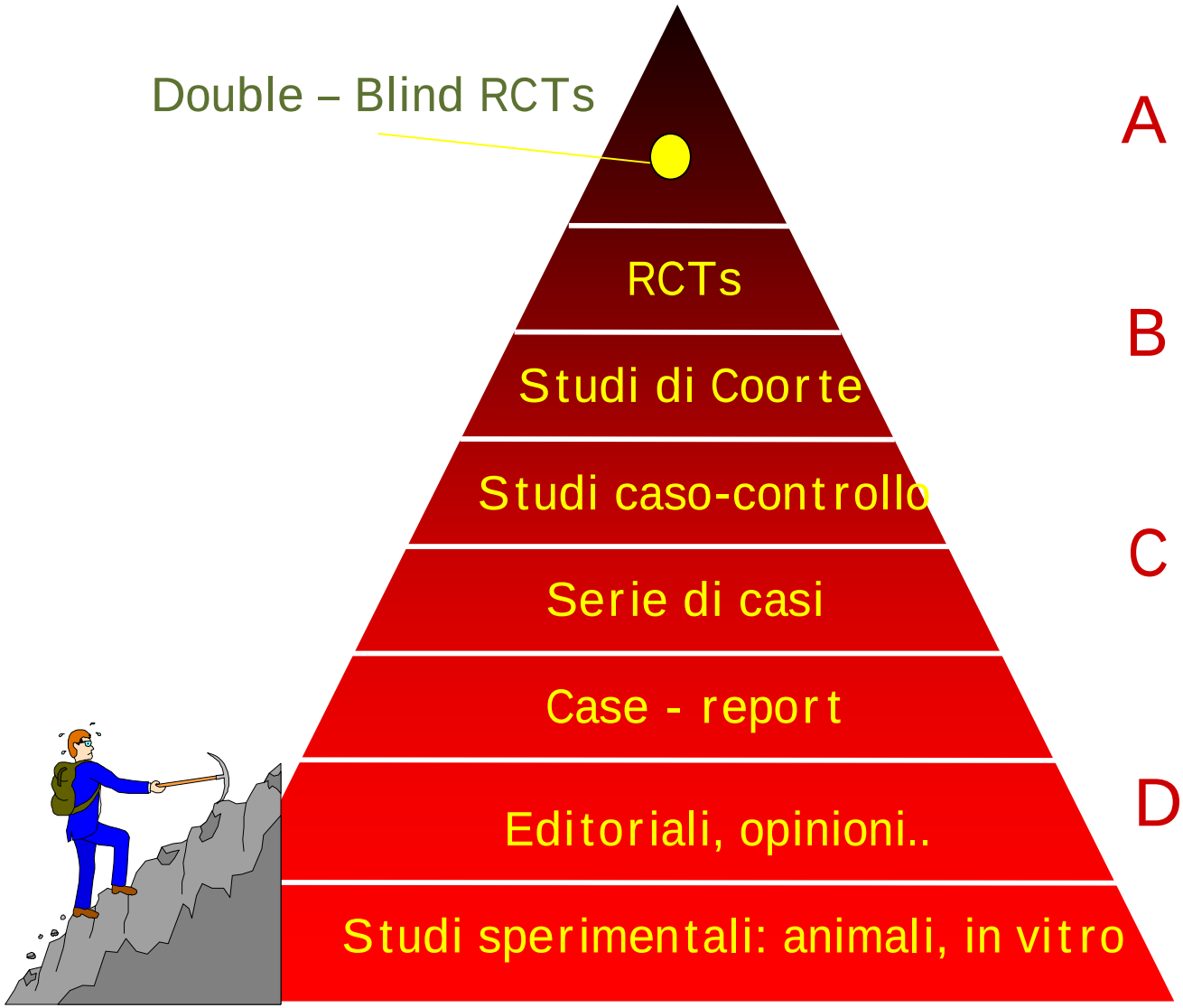


No. at Risk					
Radiotherapy plus surgery	873	691	407	179	30
Surgery alone	875	688	406	173	37

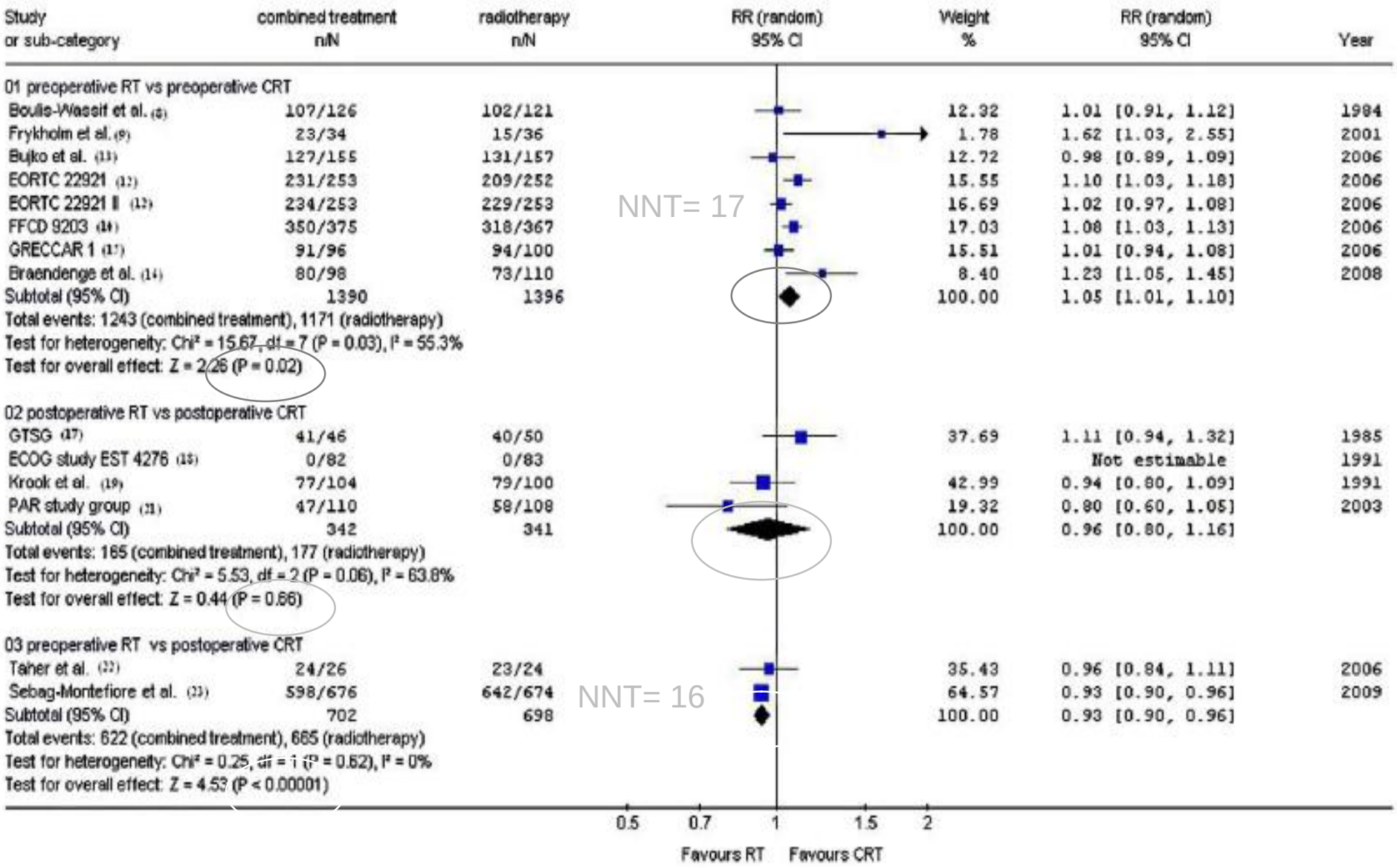
Kapiteijn, NEJM 2001

Exclusion of trials with ⩽ 50% TME				
5-yr local control	⩾50% TME (1459)	13,14,15,16	1.05 (0.98–1.13)	0.15
5-yr overall survival	⩾50% TME (1459)	13,14,15,16	1.06 (0.97–1.16)	0.22

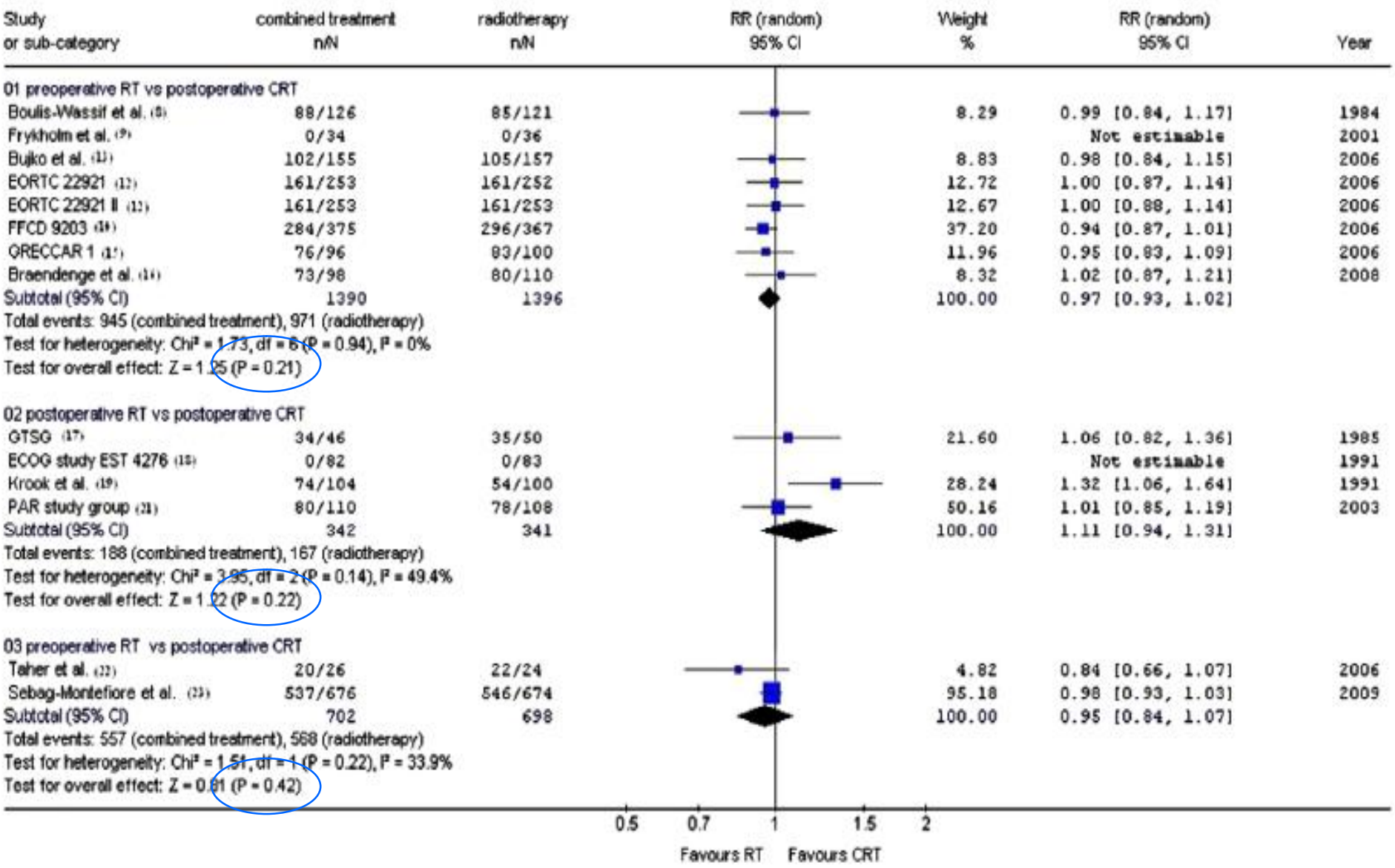
Fiorica, Cancer Treat Rev. 2010


Double – Blind RCTs
RCTs
Studi di Coorte
Studi caso-controllo
Serie di casi
Case - report
Editoriali, opinioni..
Studi sperimentali: animali, in vitro
A
B
C
D

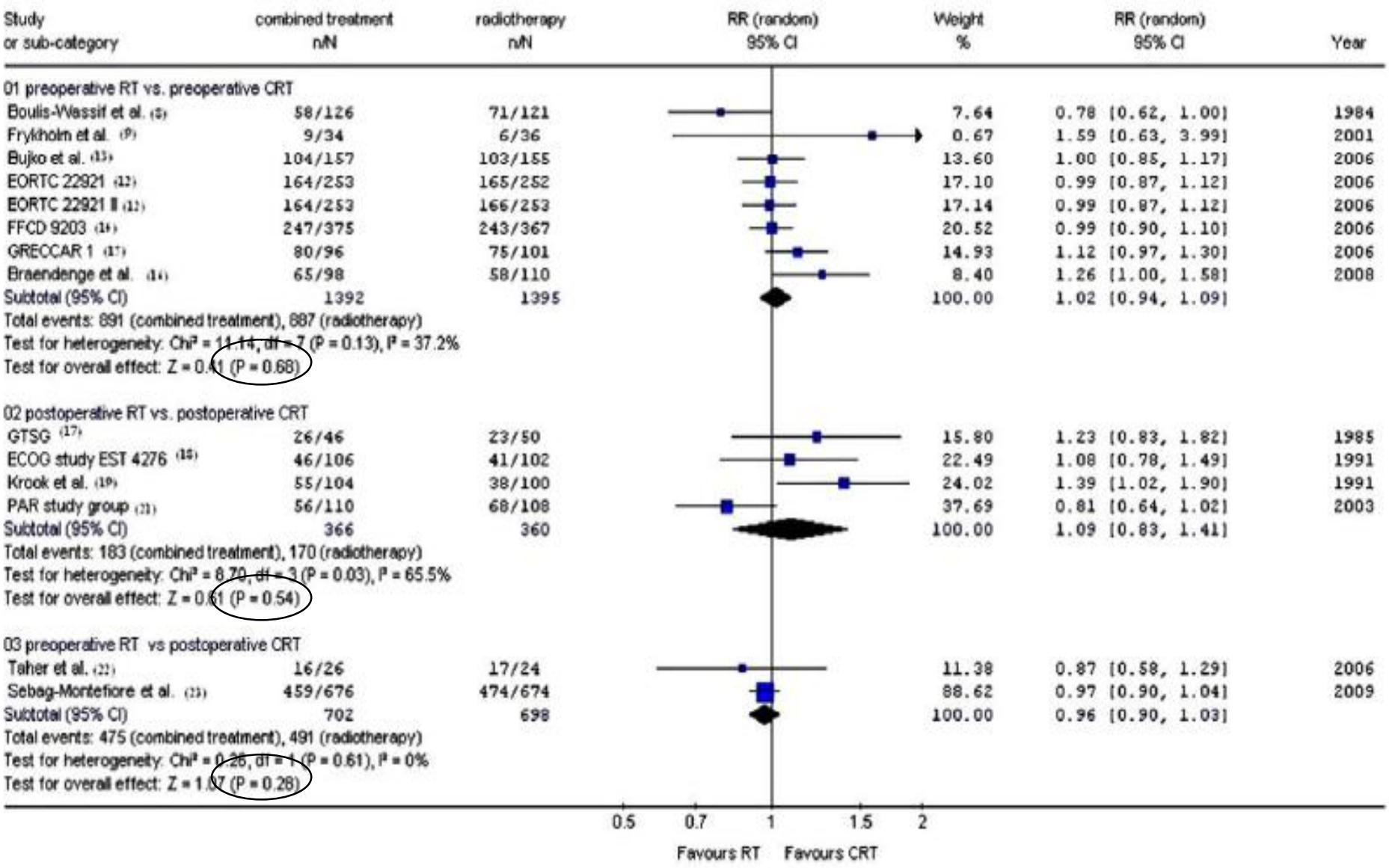
5-year local control



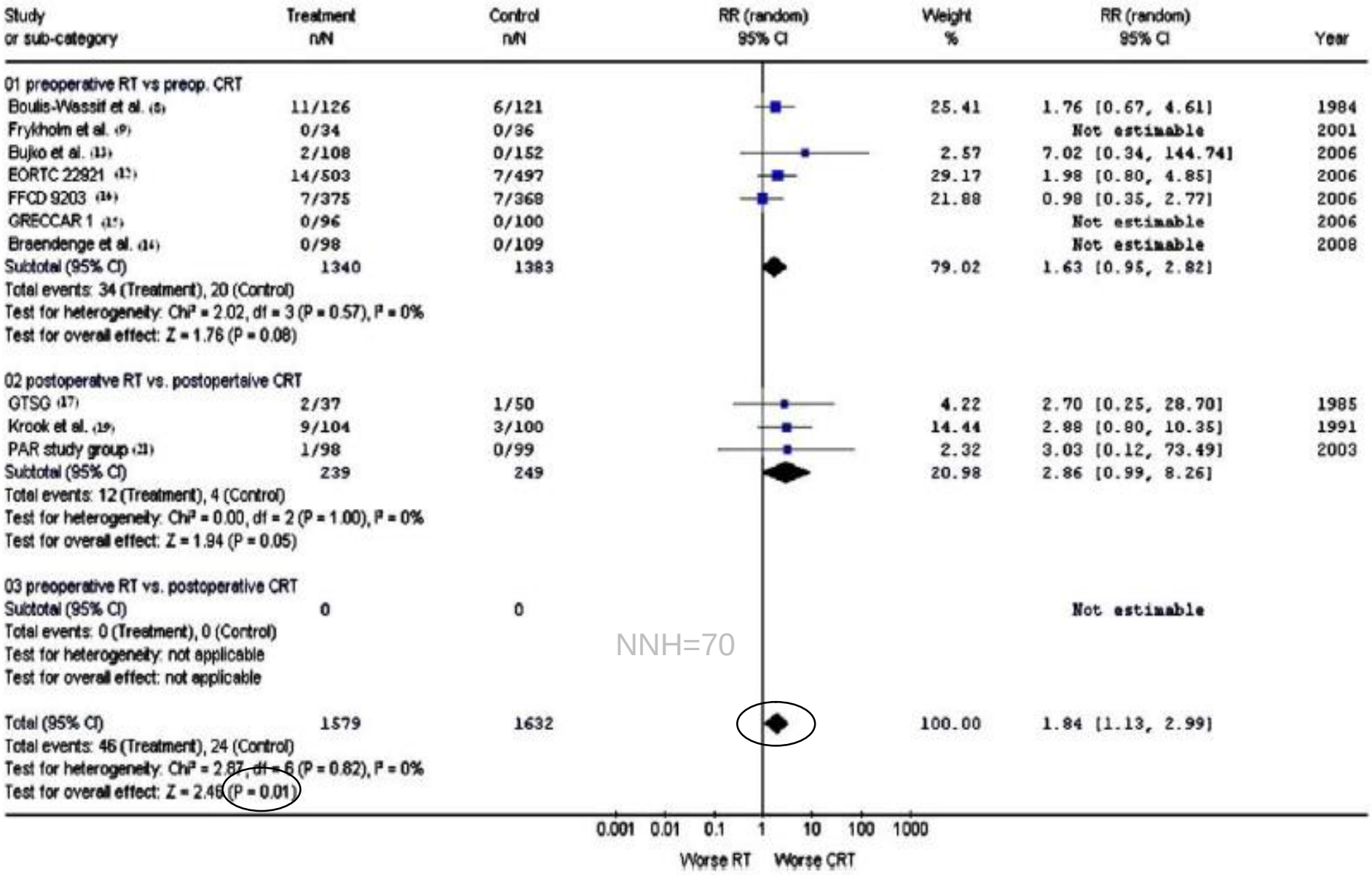
5-year distant metastases control



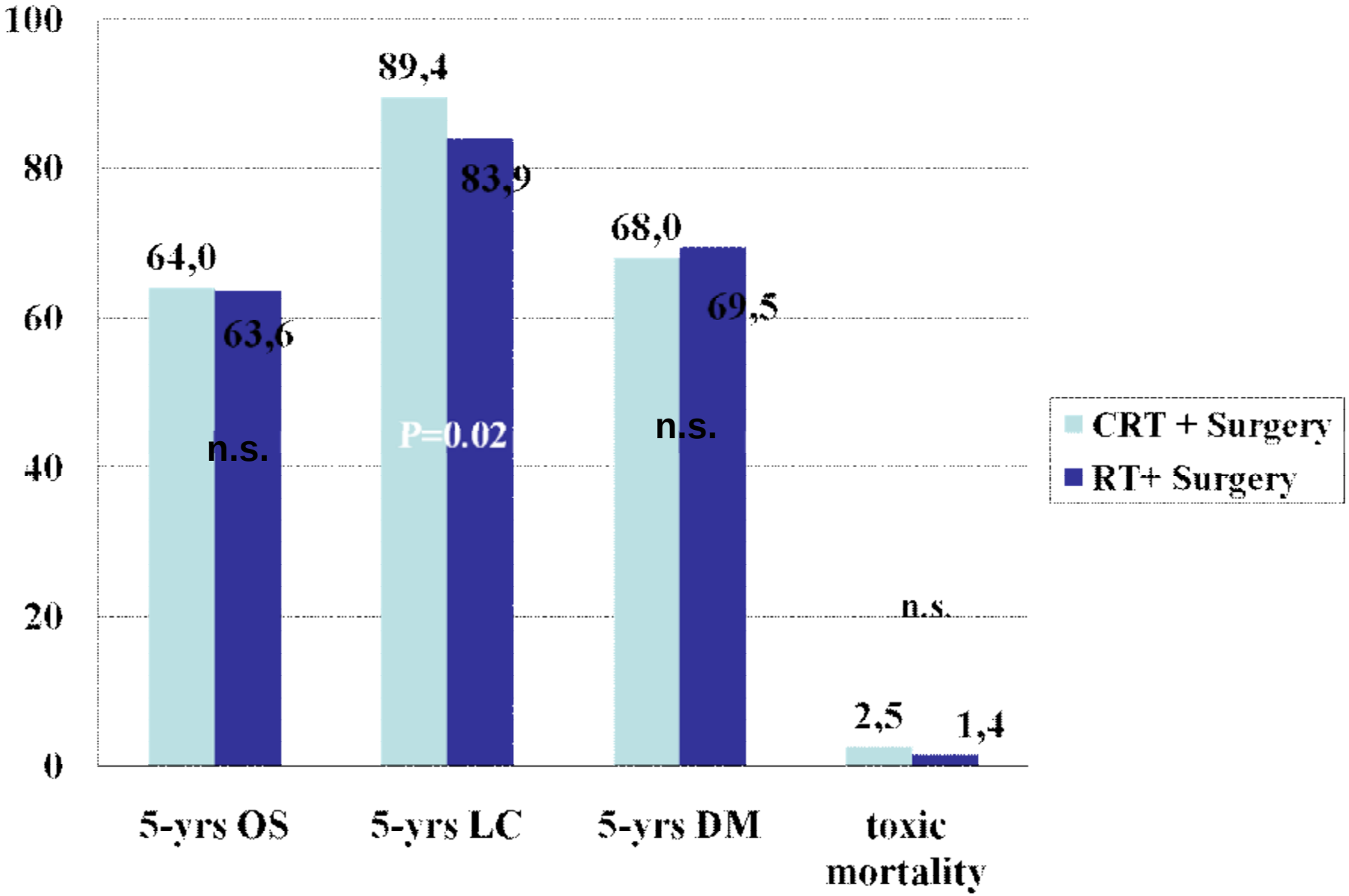
5-year overall survival



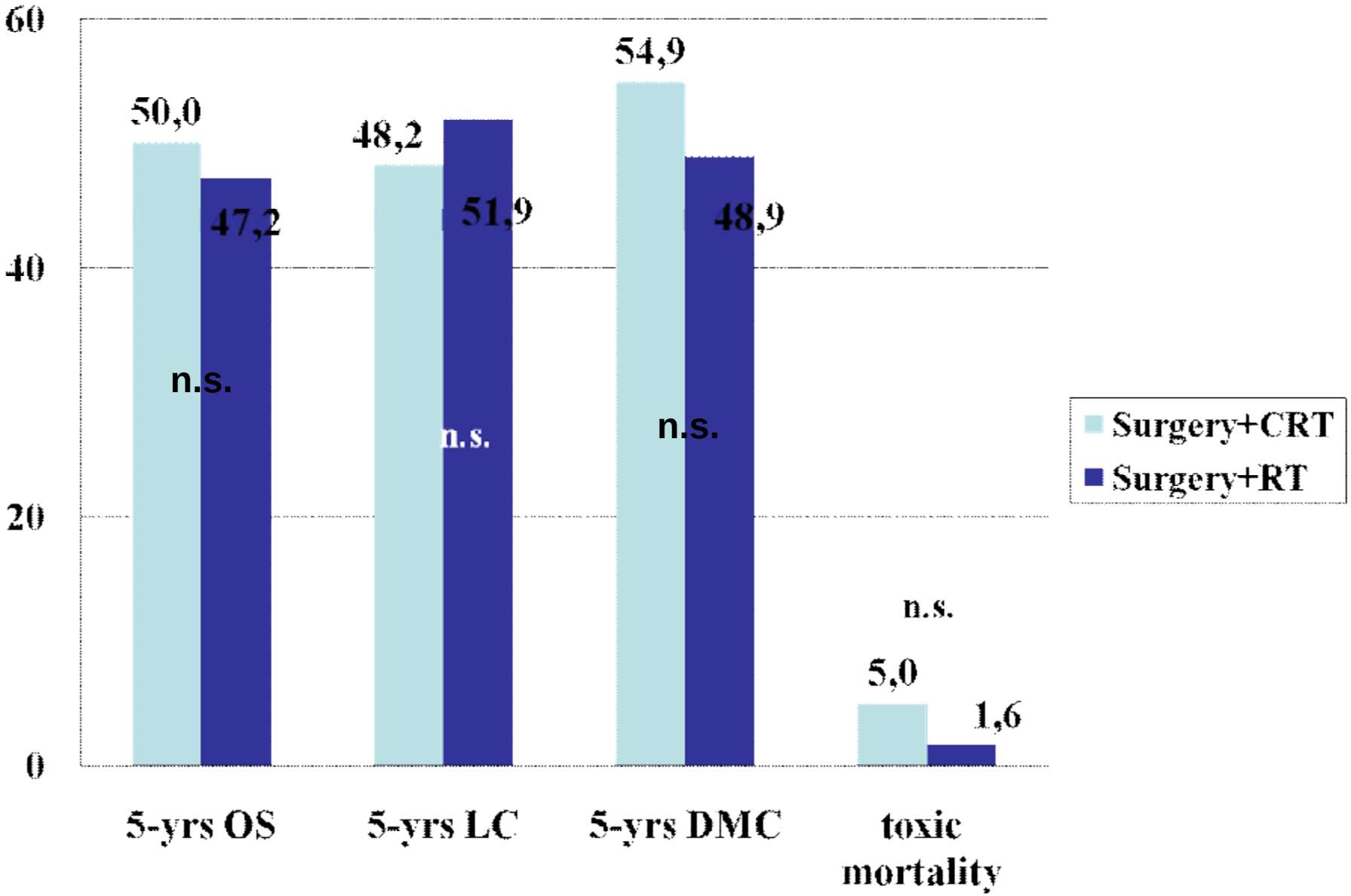
mortality related to toxic events mortality related to toxic events



Meta-analysis summary for preoperative approach

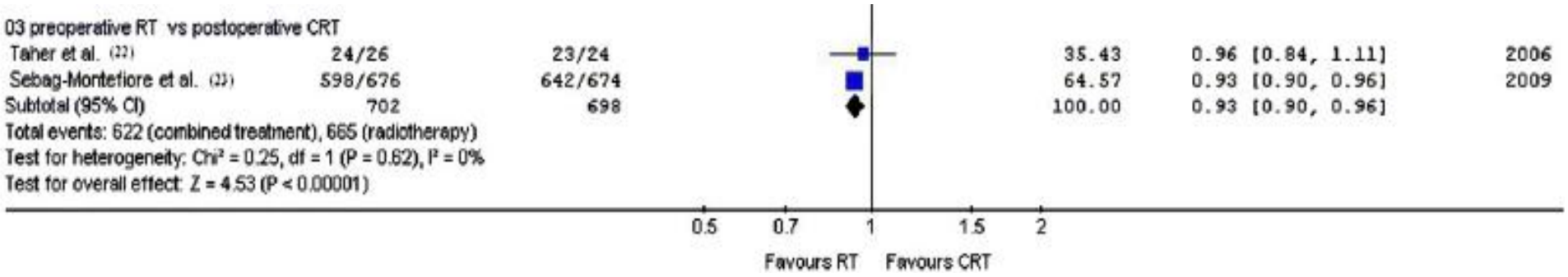


Meta-analysis summary for postoperative approach

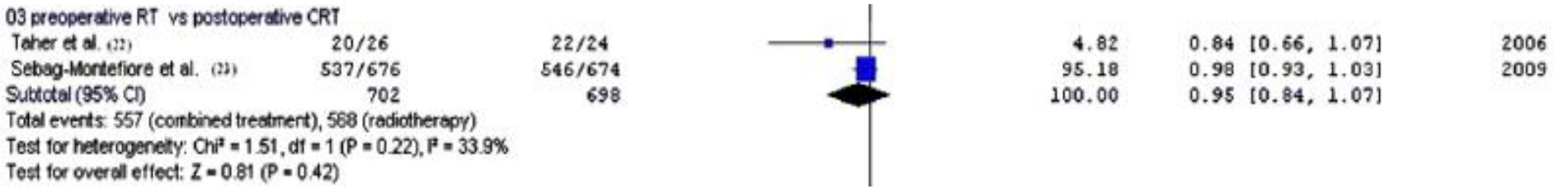


CRT PREOPERATORIA VS. CRT POSTOPERATORIA

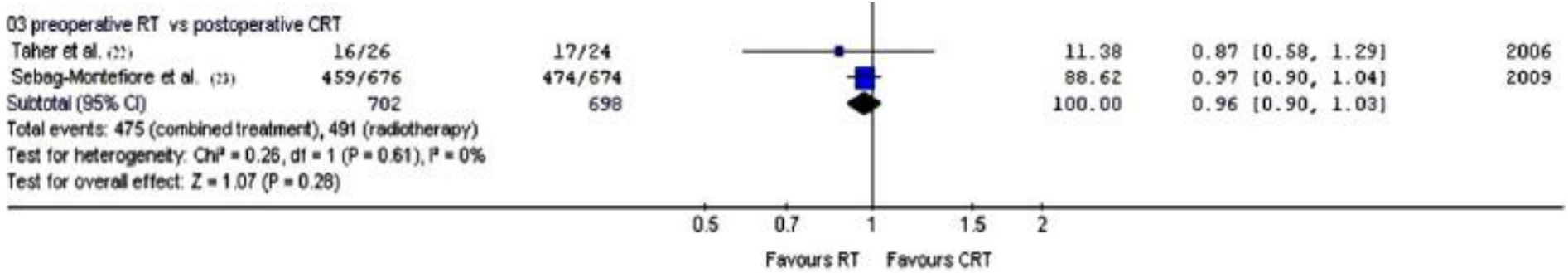
5 yrs local recurrence



5 yrs distant metastases

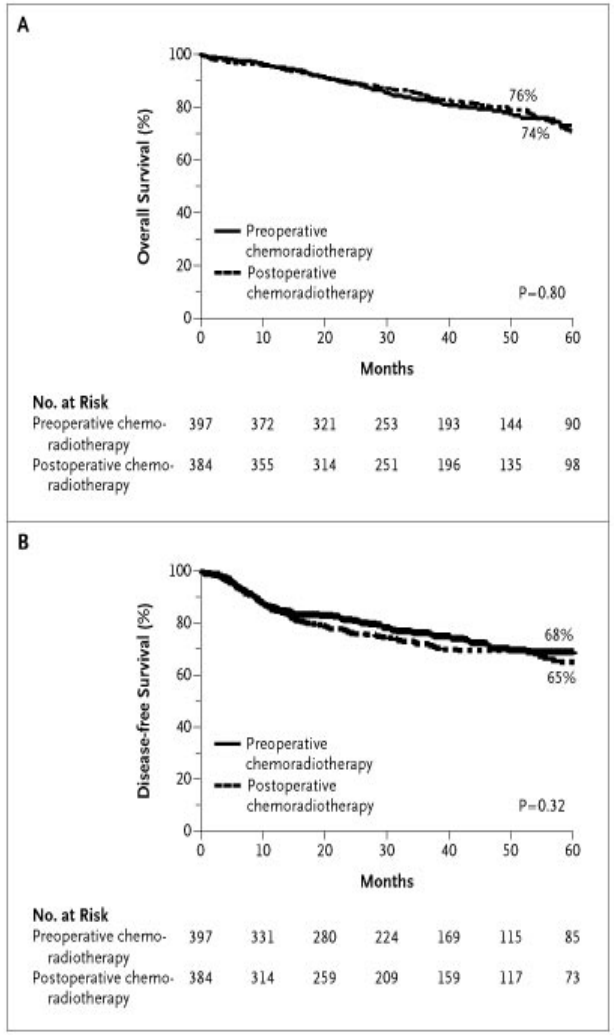


5 yrs overall survival

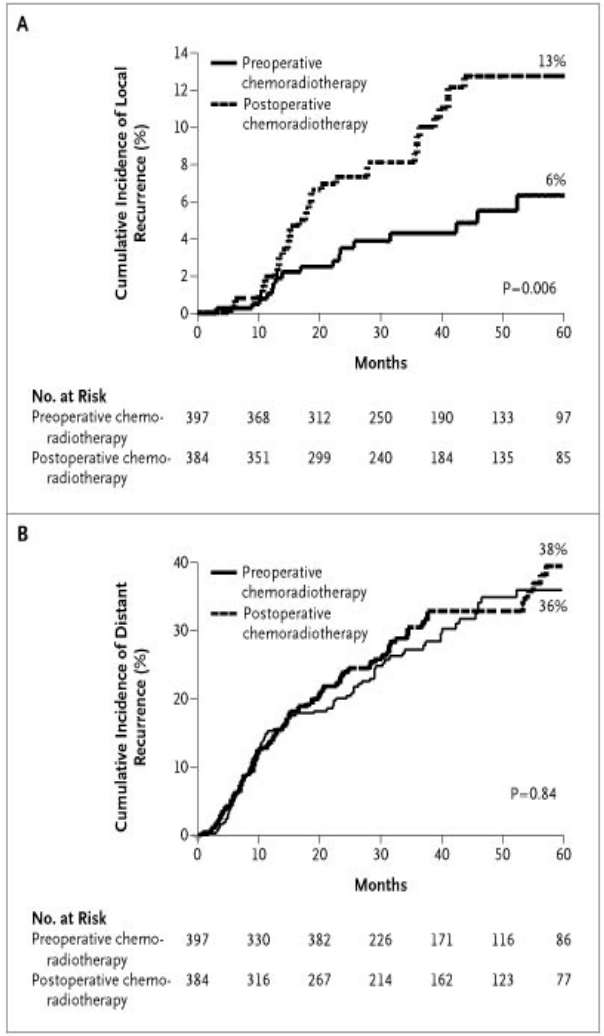


Fiorica, Cancer Treat Rev. 2010

CRT PREOPERATORIA VS. CRT POSTOPERATORIA

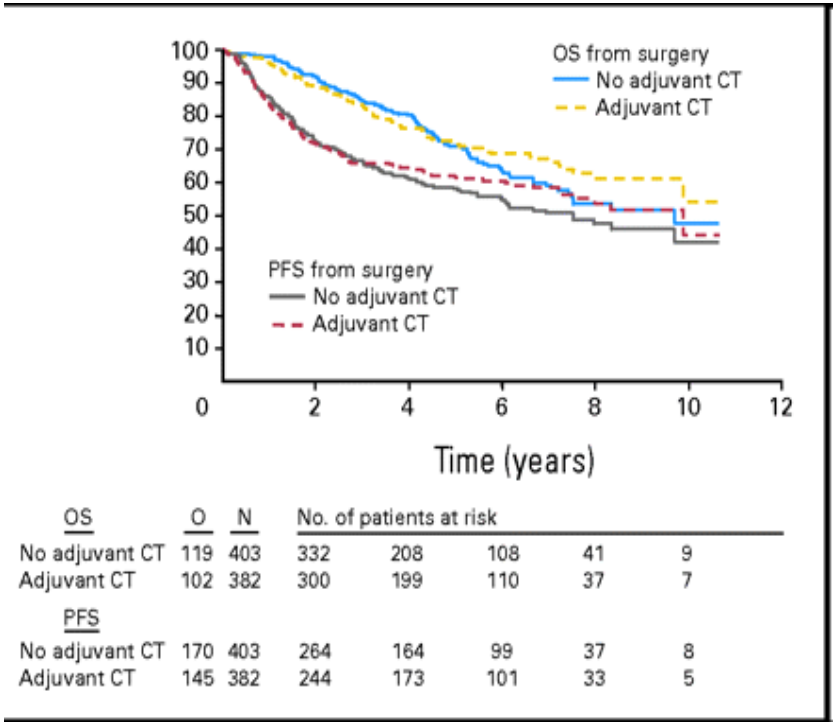


Overall survival and DFS



Local recurrence and DM

Sauer, NEJM,2004



OS	O	N	No. of patients at risk				
No adjuvant CT	119	403	332	208	108	41	9
Adjuvant CT	102	382	300	199	110	37	7
PFS							
No adjuvant CT	170	403	264	164	99	37	8
Adjuvant CT	145	382	244	173	101	33	5

Bosset, JCO 2010

Exclusion of trials with no adjuvant CT				
5-yr local control	Adjuvant CT (1961)	12,14,,16	1.08 (1.02–1.14)	0.005
5-yr overall survival	Adjuvant CT (1961)	12,14,16	1.02 (0.94–1.10)	0.69

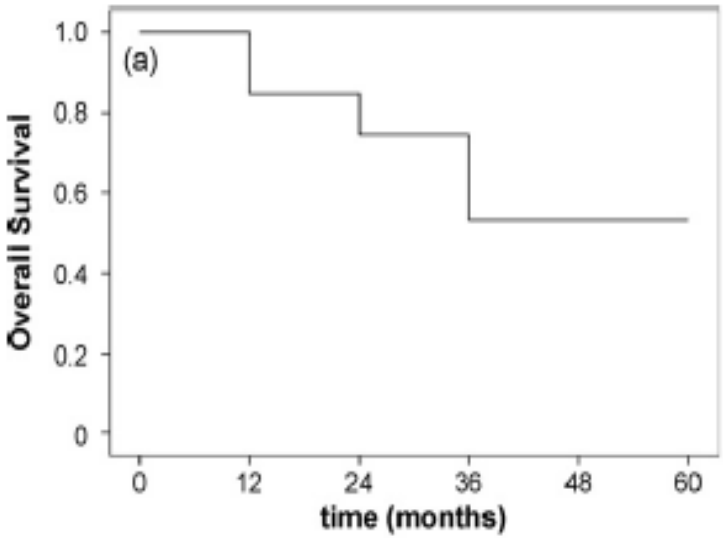
Fiorica, Cancer Treat Rev. 2010

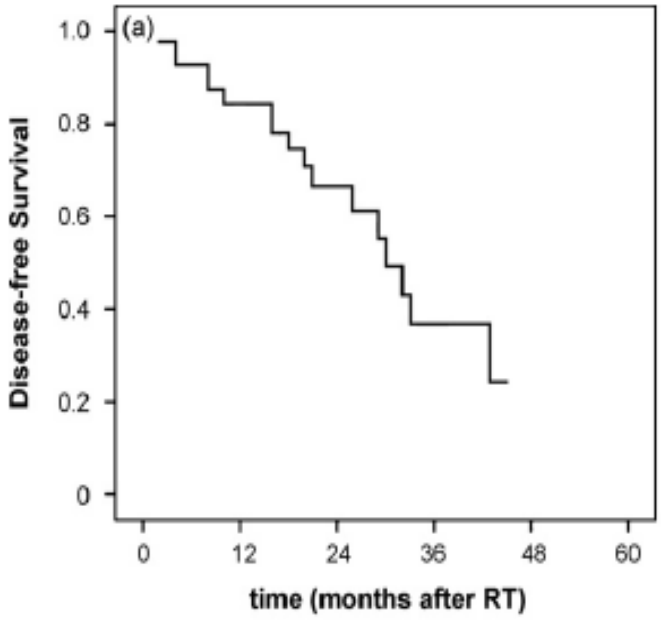
Conclusions 1

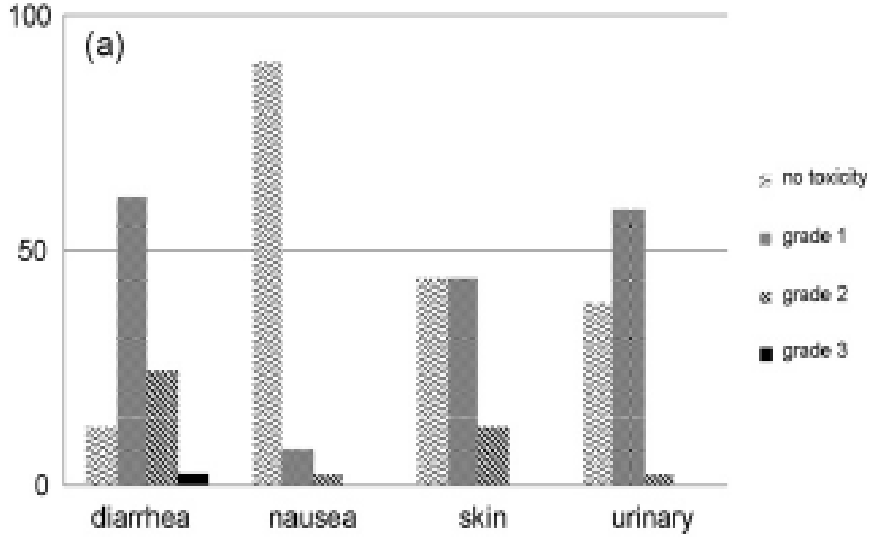
In patients with resectable rectal cancer, CRT does not increase overall survival, despite the fact that preoperative CRT significantly reduces the risk of the local recurrence.

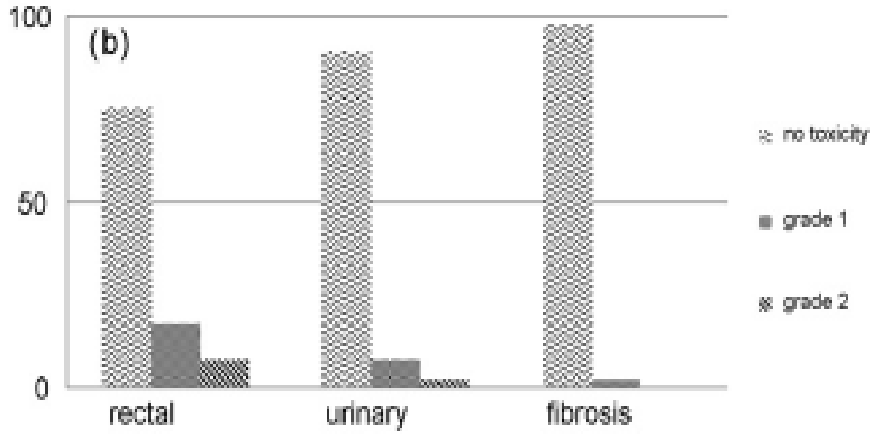
No reduction in the distant metastases rate was found.

Toxicity-related mortality is significantly increased by the concomitant approach, emphasizing the need for safer treatment combinations.









Fiorica, Arch Gerontol Geriatr. 2009

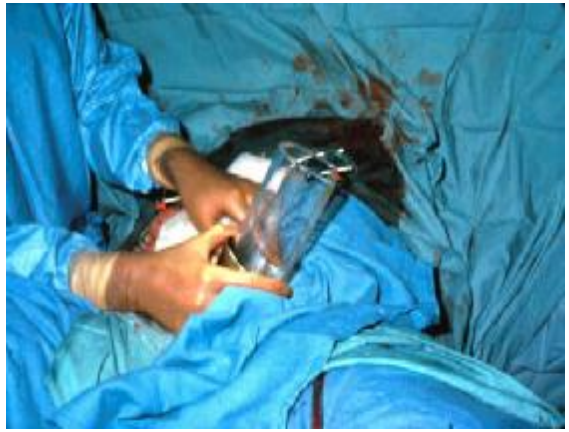
Conclusions 2

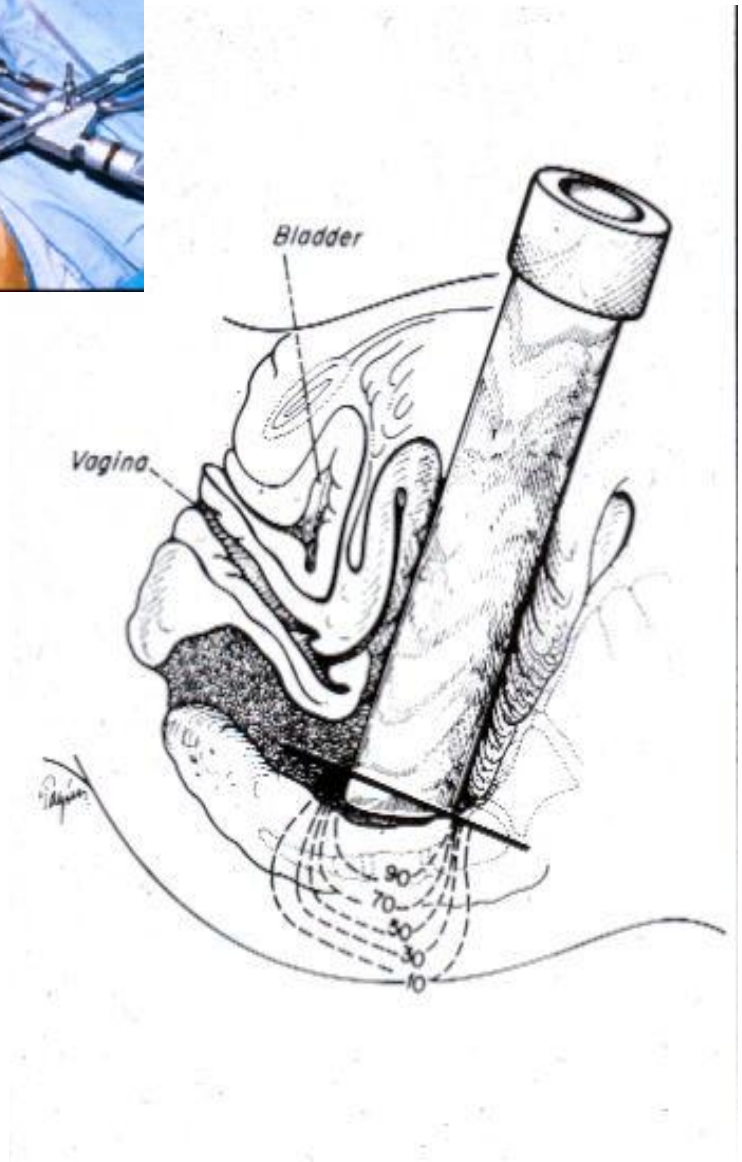
In elderly patients

compliance with radiotherapy is good and rate of toxicity is acceptable

patients with no or mild co-morbidities have a significantly better survival

Increasing severity of co-morbidity may sufficiently shorten remaining life expectancy to cancel gains with adjuvant radiotherapy.




Bladder
Vagina
90
70
50
30
10

Conclusions 3

The addition of IORT to conventional treatment methods has improved local control as well as survival in recatal cancer in both the primary and locally recurrent disease settings

Use of of Novel and Molecular –targeted chemo-therapies combined to RT

Capecitabina

Oxaliplatino

Cetuximab

Bevacizumab

RT

Use of of Novel and Molecular –targeted chemo-therapies combined to RT

Capecitabine

RCT: XELODA vs 5FU + RT (50.40 Gy)

An higher rates of pathological T and N downstaging … but these differences did not reach statistical significance.

Hofheinz, JCO 2009

A n ongoing trial NSABP R-04 trial

Use of of Novel and Molecular –targeted chemo-therapies combined to RT

Oxaliplatin

RCT: Studio Terapia Adiuvante Retto (STAR-01)

RT + 5FU with or without Oxaliplatin weekly

No statistical differences in outcome, only an increase of toxicities in Oxaliplatin group (24%vs 8%).

Aschele, JCO 2009

RCT: ACCORD 12/0405-Prodige 2

RT + Xeloda with or without Oxaliplatin weekly

An higher rate of complete response, but an increase of toxicity

Gerard, JCO 2010

Use of of Novel and Molecular –targeted chemo-therapies combined to RT

Cetuximab

Glynne-Jones reviewed a series of phase 1 and 2 studies with cetuximab incorporated in neoadjuvant chemoradiotherapy.

-Increase of diarrhea
-Complete response rate 9.1%

Glynne-Jones, Acta Oncol 2010

Ongoing XERXES study

Use of of Novel and Molecular –targeted chemo-therapies combined to RT

Bevacizumab

Willet et al. : RT +5FU + Bevacizumab

High rate of pathological downstaging

Willet JCO 2009

Crane et al. 32% of pathologic complete response

Crane , IJROBP 2010

ECOG 3204: phase 2

Pathological response 33%

Landry IJROBP 2009

Biomarkers for Response to Neoadjuvant Chemoradiation for Rectal Cancer

p53

The majority of studies revealed no correlation between p53 and treatment outcome. Four of 21 studies claimed a positive correlation; one claimed that p53 staining (mutation) predicted good response, whereas the other three claimed that p53 staining was a predictor of poor response. These data suggest that p53 is unlikely to serve as a predictor of response to neoadjuvant CRT

EGFR

Only one study revealed an association between positive/negative EGFR staining and treatment outcome. It may be more valuable to quantitatively measure EGFR expression rather than assessing whether biopsies stain positive or negative for EGFR. Two of the four studies, involving 87 and 183 patients, that evaluated.

Kuremsky JG IJROBP 2009

Biomarkers for Response to Neoadjuvant Chemoradiation for Rectal Cancer

TYMS

Four of five studies evaluating TYMS expression revealed significant associations with clinical endpoints. Three studies revealed better outcome with low or absent pretreatment TYMS expression, whereas one study revealed better outcome with high TYMS expression. The study that found a correlation between low TYMS expression and downstaging failed to reveal a correlation with local recurrence or survival. The single study that found a correlation between high pretreatment TYMS expression and improved response involved only 19 patients who received both 5-FU and oxaliplatin. The extremely small number of patients and addition of oxaliplatin may have confounded this study's results. The two remaining studies supporting TYMS expression levels with outcome included small patient numbers. If there is an effect of TYMS on outcome, it could be due to enhancing 5-FU's effect. There is not enough evidence to support the use of TYMS protein quantification as a predictor of treatment response in rectal cancer. However, TYMS DNA may have value as a predictive biomarker, and its clinical utility should be evaluated as an adjunct in larger trials involving neoadjuvant CRT for rectal cancer.

Kuremsky JG IJROBP 2009

Biomarkers for Response to Neoadjuvant Chemoradiation for Rectal Cancer

Ki-67

On the basis of the literature, it seems unlikely that Ki-67 has any utility in predicting outcome to treatment for rectal cance

p21

Two studies revealed improved outcomes with low or negative p21 expression, whereas two different studies showed improved outcomes in tumors with high or positive p21 expression . On the basis of *in vitro* studies, it would be predicted that tumors with low or absent p21 expression would be more radio- and/or chemosensitive, leading to better outcomes. The two studies that found a correlation between decreased or absent p21 staining and poor outcome involved treatments in addition to 5-FU and external-beam radiotherapy. The additional treatments may have confounded the results.

Larger, prospective clinical trials should be conducted to determine the ability of low p21 expression to predict better outcome.

Kuremsky JG IJROBP 2009

Biomarkers for Response to Neoadjuvant Chemoradiation for Rectal Cancer

bax/bcl-2

More studies evaluating bax as a predictive biomarker are needed owing to the limited data available for bax. Because only one of 12 studies showed a significant correlation between bcl-2 expression and treatment outcome, it is unlikely that bcl-2 is a useful clinical marker.

Microarray

Both studies and reported the ability to accurately determine responders and nonresponders on the basis of microarray-determined gene expression profiles. Between the 54 genes differentially expressed in the Ghadimi study and the 43 genes differentially expressed in the Rumkus study, there was no concordance with even one gene between the two studies. Although gene array expression data generate interesting results that may lead to the further exploration of candidate genes, the complexity and magnitude makes the results difficult to interpret. Two studies with a small number of patients are not enough to validate the use of microarray-determined gene expression profiles to predict response to neoadjuvant CRT in rectal cancer.

Kuremsky JG IJROBP 2009

Biomarkers for Response to Neoadjuvant Chemoradiation for Rectal Cancer

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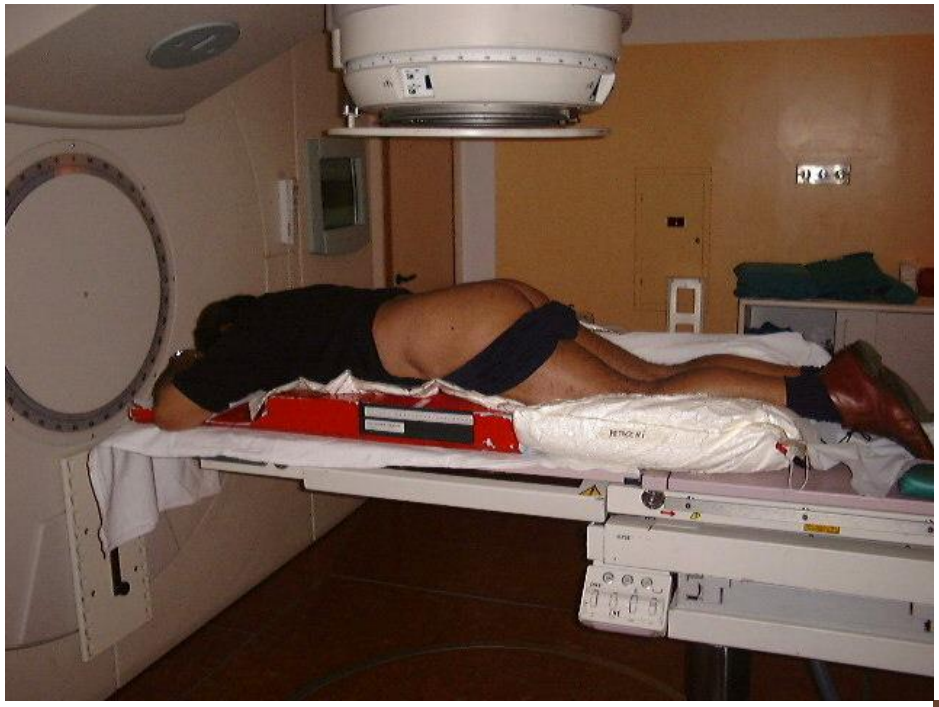
Kuremsky JG IJROBP 2009


PHILIPS

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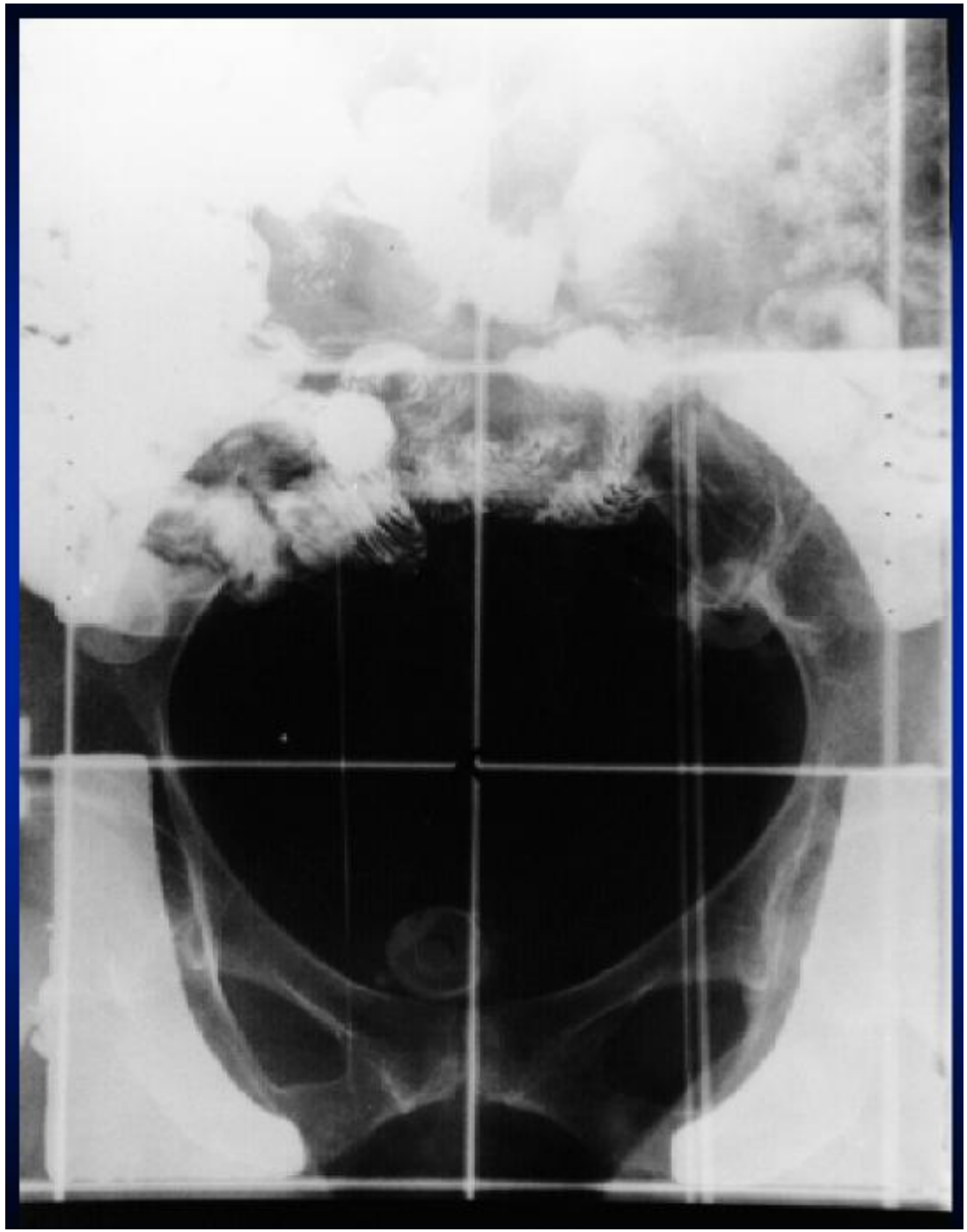

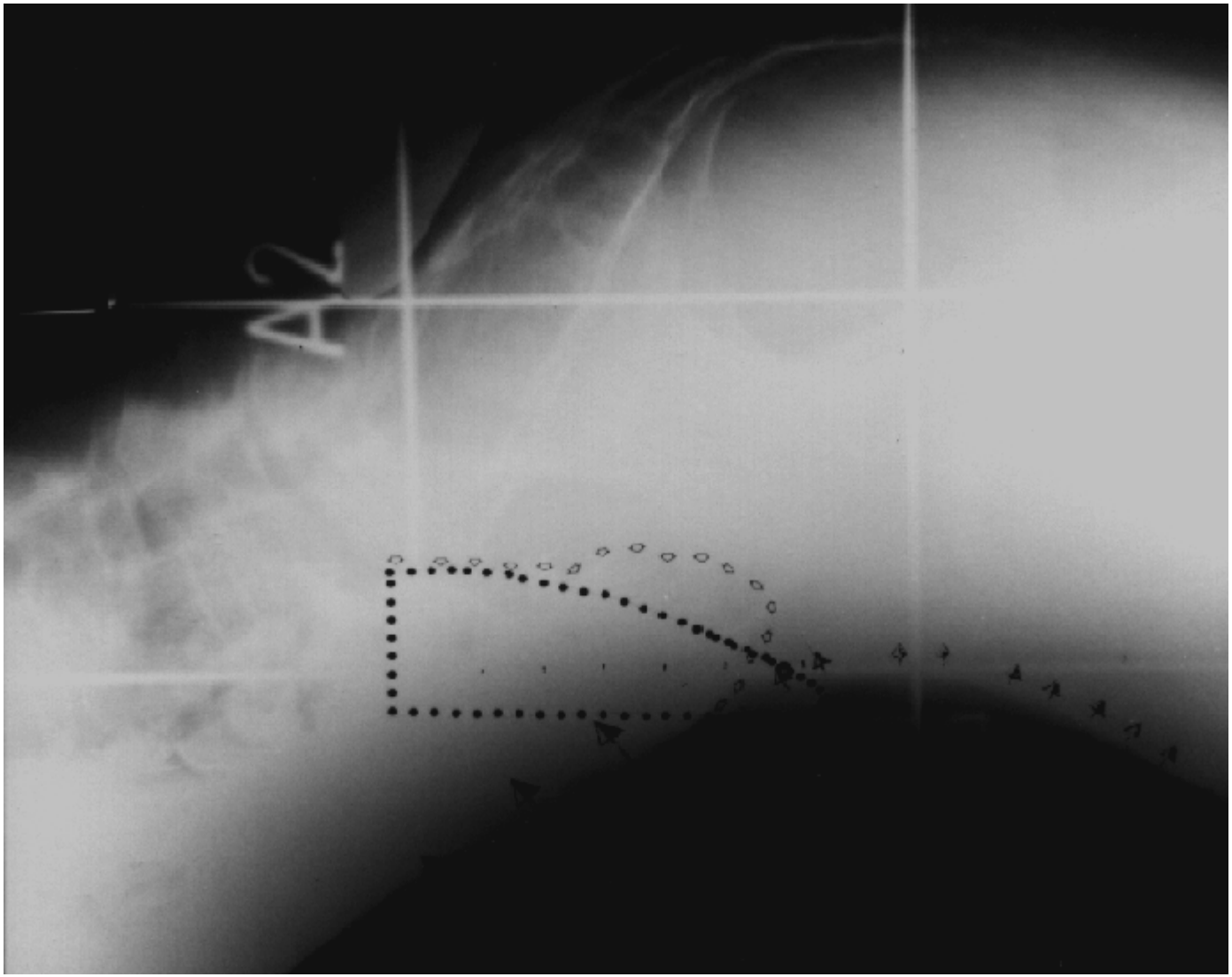
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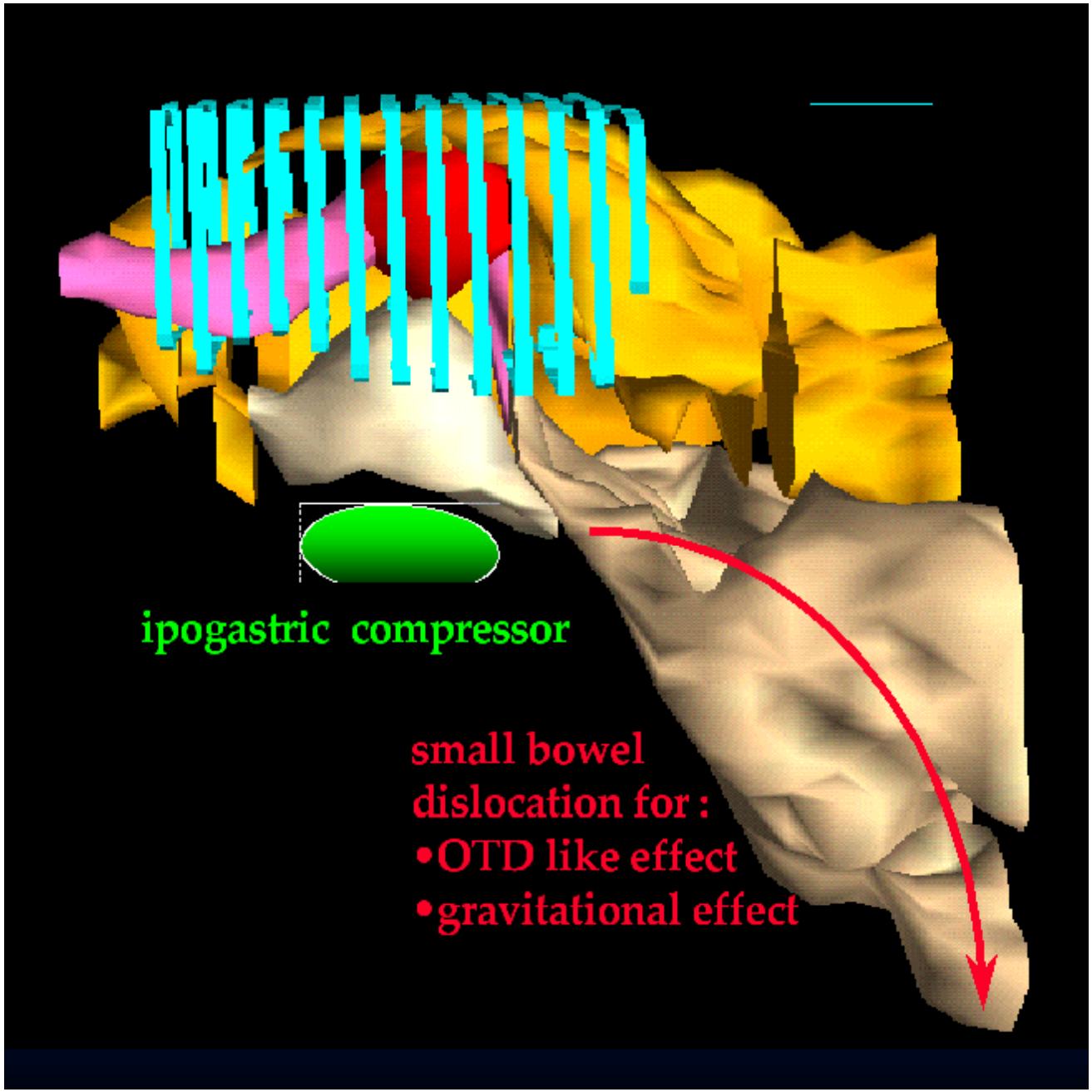
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small bowel
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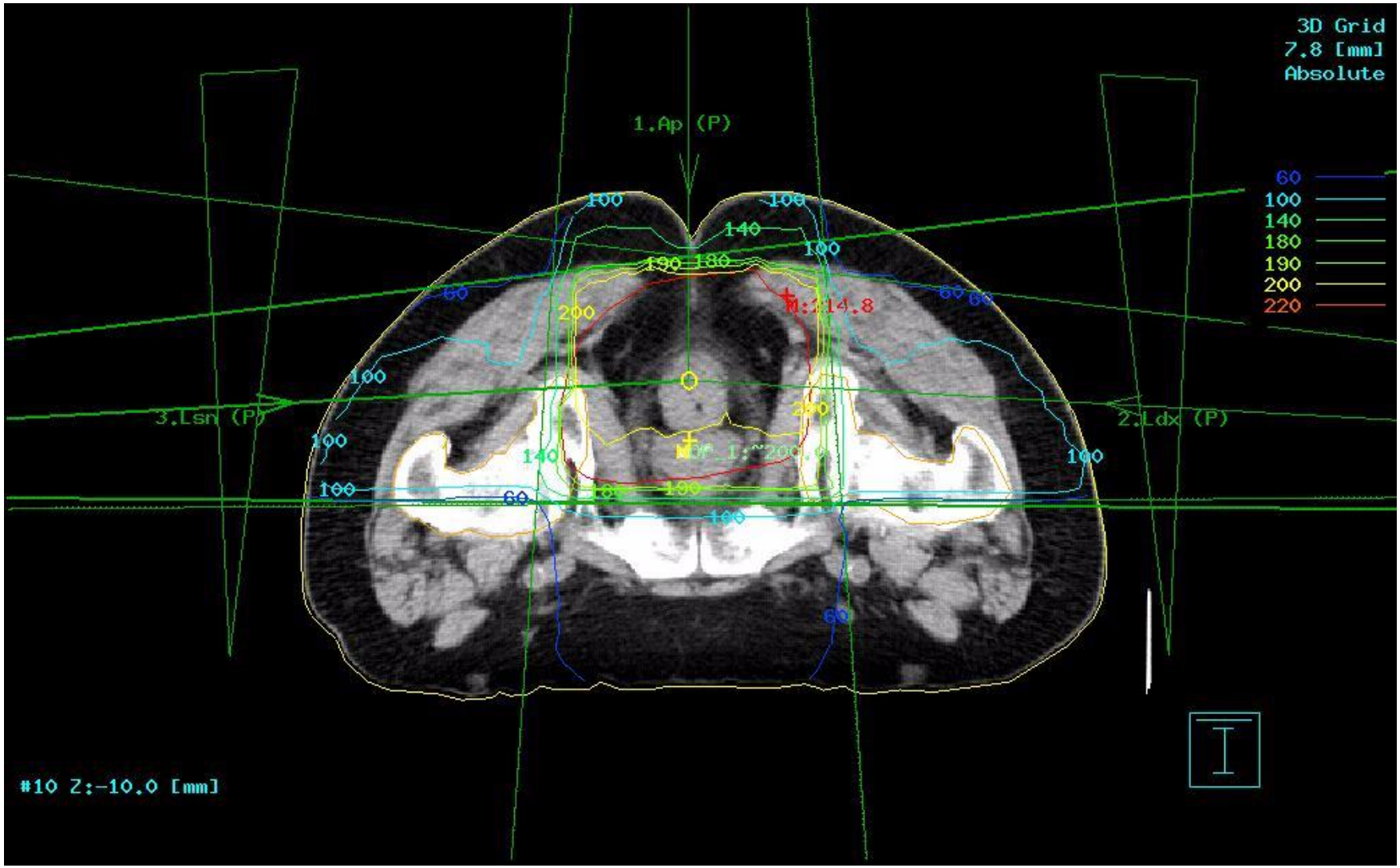
•OTD like effect
•gravitational effect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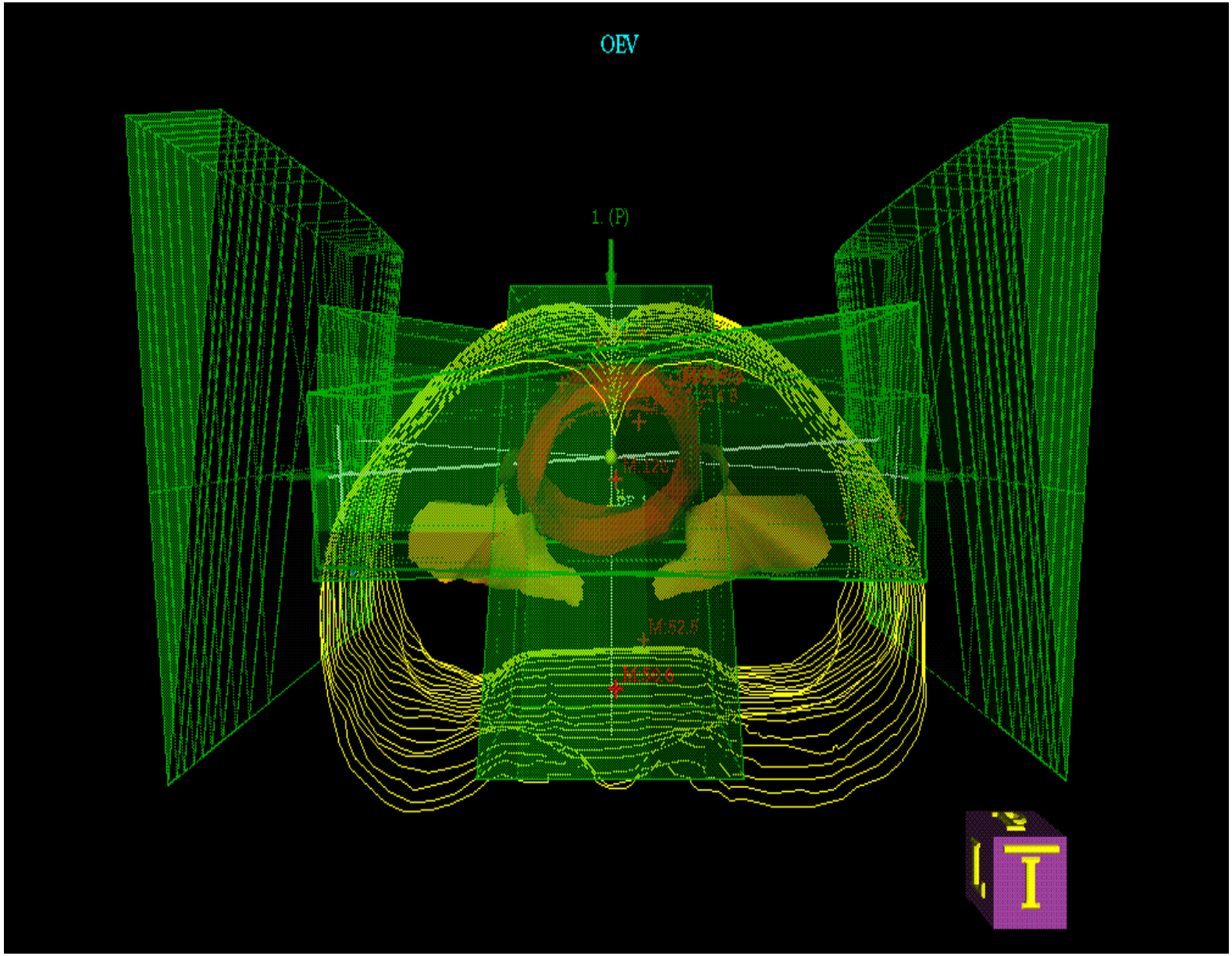
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External validity

REVIEW

Randomized Trials Stopped Early for Benefit
A Systematic Review

Victor M. Montori, MD, MSc

Context Randomized clinical trials (RCTs) that stop earlier than planned because of an-

Conclusions: RCTs stopped early for benefit are becoming more common, often fail to adequately report relevant information about the decision to stop early, and show implausibly large treatment effects.

These findings suggest clinicians should view the results of such trials with skepticism.

JAMA. 2005;294:2203-2209