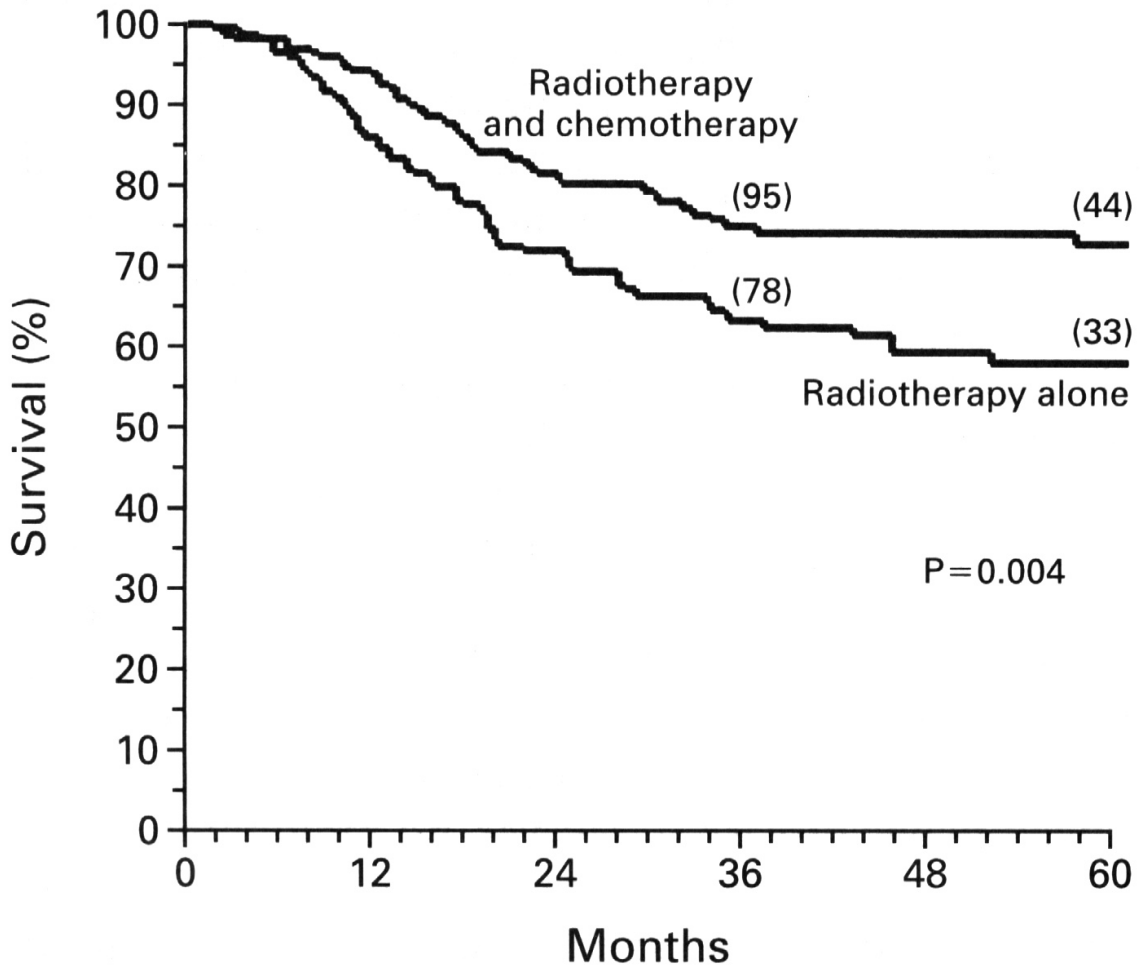
# Combining Radiation and Chemotherapy

**Drew Hope**

# Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer.




M. Morris et al, NEJM, 340:1137-1143, 1999

# Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer

| | RT (n = 193) | RT + Chemo (n = 193) |
|---|---|---|
| 5 yr OS | 58% | 73%* |
| L/R Recurrence | 35% | 19%* |
| Distant Recurrence | 33% | 14%* |

RT: 45 Gy + brachytherapy (total dose ≥ 85 Gy)
Chemo: cddp (75mg/$m^2$, d1), 5Fu (1g/$m^2$/d, d1-4), x3

M. Morris et al, NEJM, 340:1137-1143, 1999

# Ways to combine radiation and chemotherapy

- Spatial co-operation
  - e.g. breast carcinoma, SCLC
- Independent cell kill
  - e.g. Hodgkin's disease
- Non-overlapping toxicity
  - e.g. Hodgkin's disease
- Interaction
  - e.g. H&N, cervix, NSCLC

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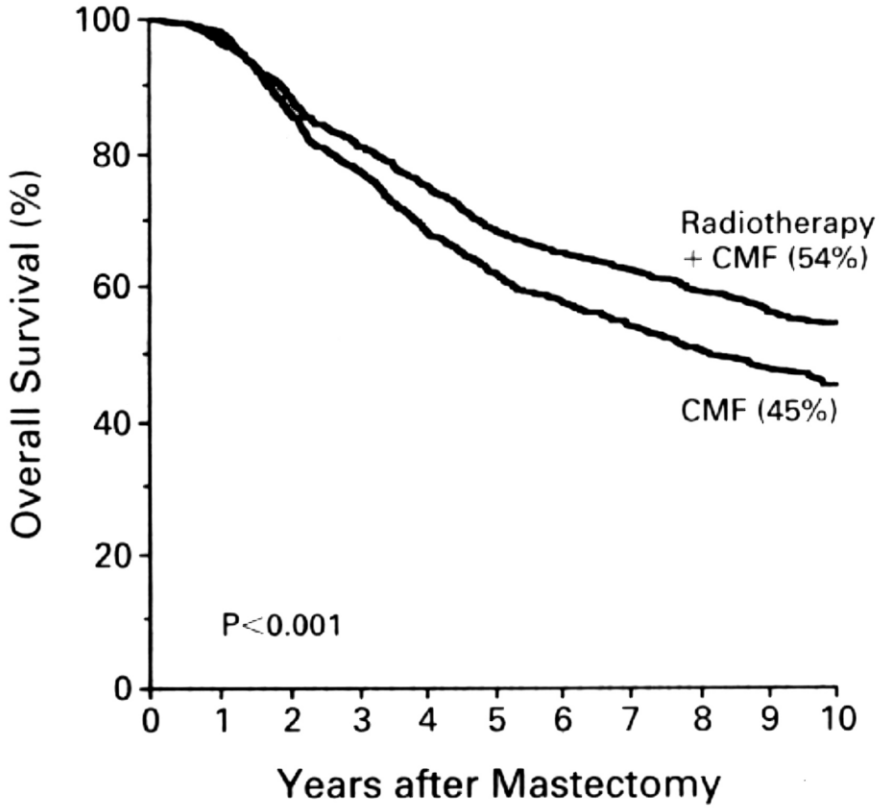
# Spatial Co-operation

- Radiotherapy for local disease; chemotherapy for systemic disease

- Radiotherapy delivered to “protected” sites
  - Prophylactic cranial irradiation for small cell lung cancer
  - CNS irradiation following chemotherapy for leukemia

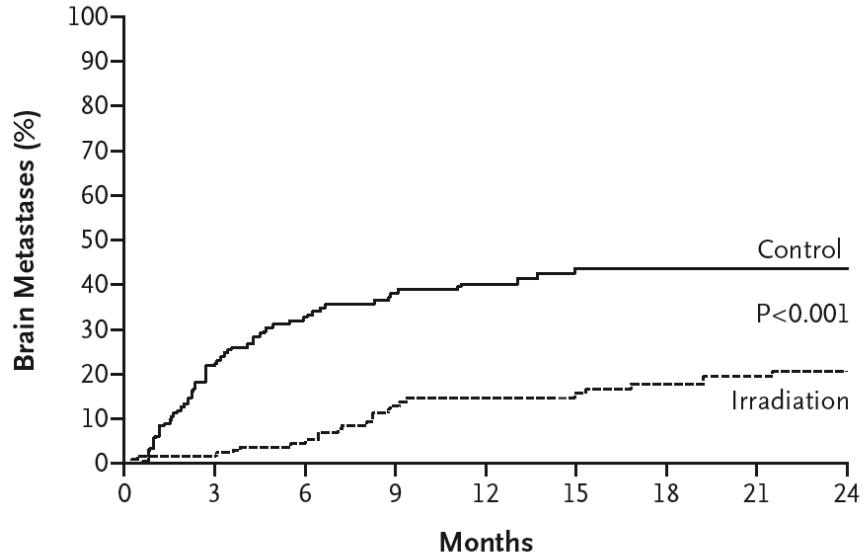
# Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy.
(Danish Breast Cancer Cooperative Group 82b Trial)




| | | | | | | |
|---|---|---|---|---|---|---|
| Radiotherapy + CMF | 852 | 755 | 641 | 555 | 392 | 188 |
| CMF | 856 | 738 | 587 | 494 | 329 | 163 |

M. Overgaard et al., N. Engl. J. Med., 337: 949-955, 1997

# Prophylactic Cranial Irradiation in Extensive Small-Cell Lung Cancer




**No. at Risk**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Control | 143 | 94 | 48 | 29 | 11 | 2 | 1 | 1 |
| Irradiation | 143 | 119 | 66 | 38 | 24 | 16 | 10 | 5 |

**Figure 1. Cumulative Incidence of Symptomatic Brain Metastases.**

The difference in the cumulative incidence of brain metastases between the irradiation group and the control group was significant (P<0.001, by Gray's method).

Slotman, B. et al., N. Engl. J. Med., 2007;357:664-72

# Prophylactic Cranial Irradiation in Extensive Small-Cell Lung Cancer

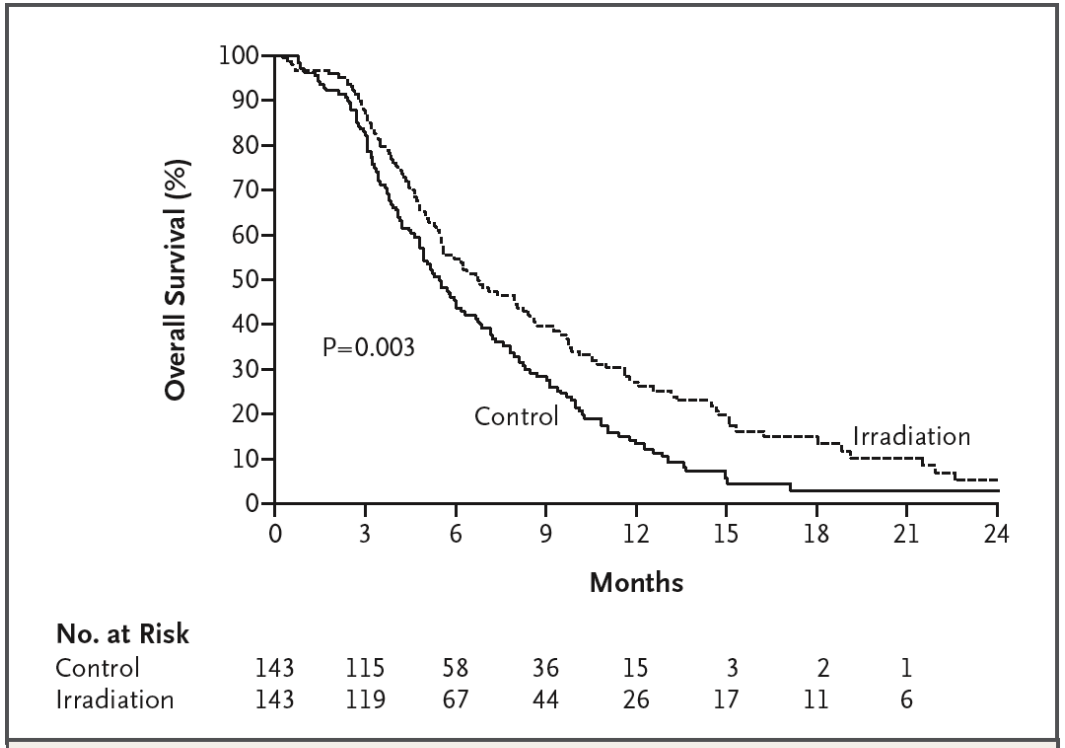



**Figure 3. Overall Survival.**

Patients in the irradiation group had a longer median overall survival (6.7 months) than did those in the control group (5.4 months) (P=0.003; hazard ratio, 0.68; 95% CI, 0.52 to 0.88).

Slotman, B. et al., N. Engl. J. Med., 2007;357:664-72

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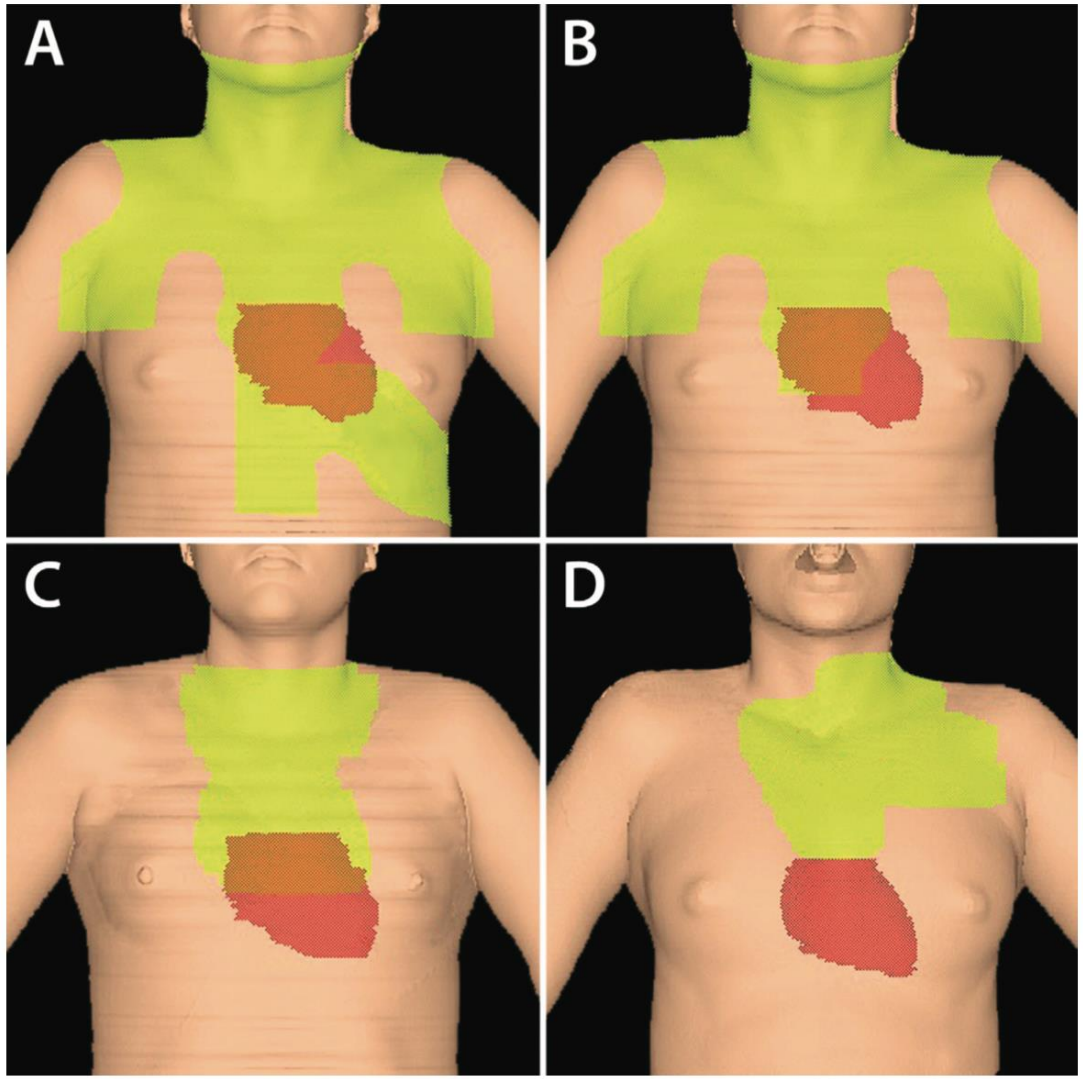
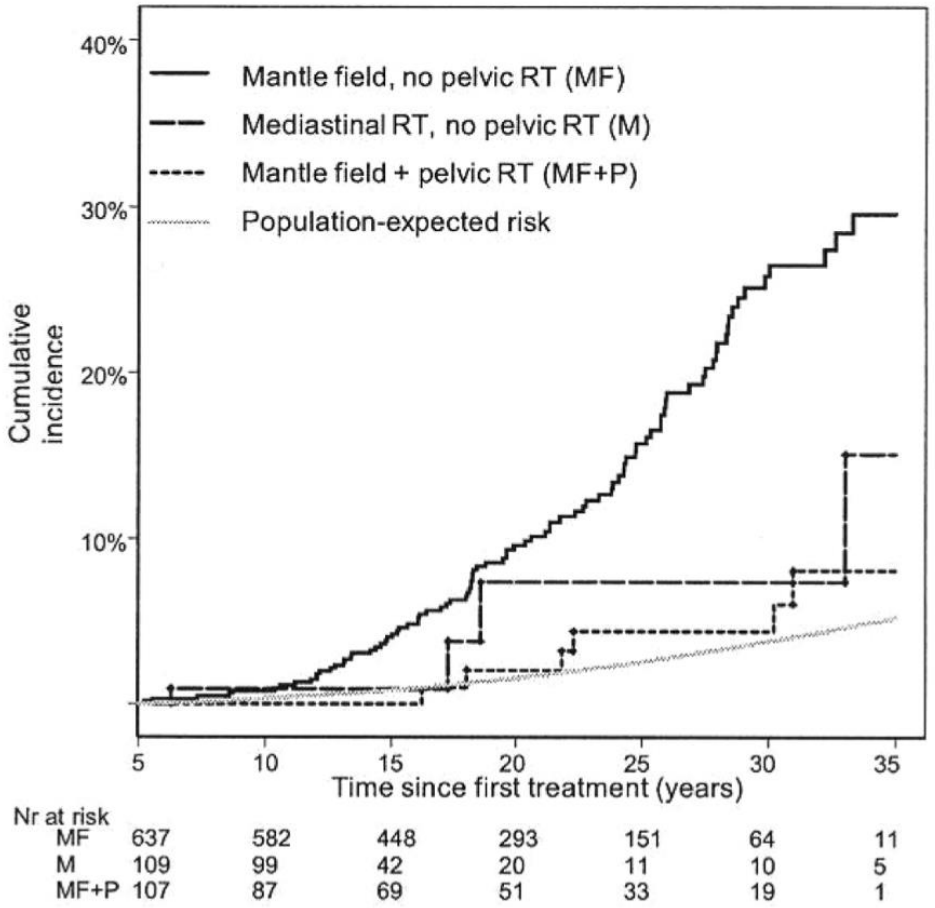
# Stage I and II Hodgkin disease (very favorable and favorable categories)

| | RT (EF, 40 Gy) | CH (MOPP/ABVD) | CH + RT (IF, ≤ 40 Gy) |
|---|---|---|---|
| 10Y OS | 80-90% | 80-90% | ~90% |
| Complications (RR) | | | |
| leukemia | 11.0 | 70.0 | reduced |
| lymphoma | 21.0 | 22.0 | reduced |
| solid tumor | 2.8 | 1.1 | reduced |
| cardiac | 2.2-3.1 | ≈1.0 | reduced |




Hodgson, Hematology 2011

# Cumulative incidence of invasive breast cancer after RT for Hodgkin disease

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Contents lists available at ScienceDirect

Radiotherapy and Oncology

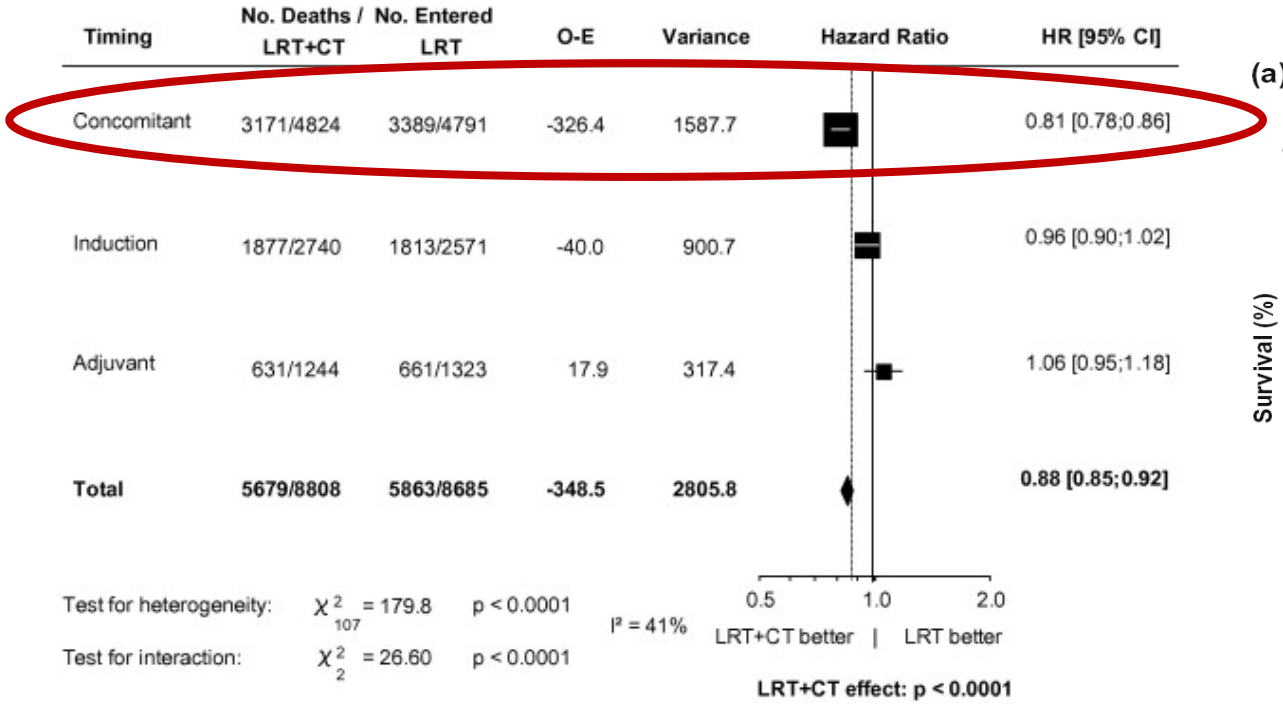
journal homepage: www.thegreenjournal.com

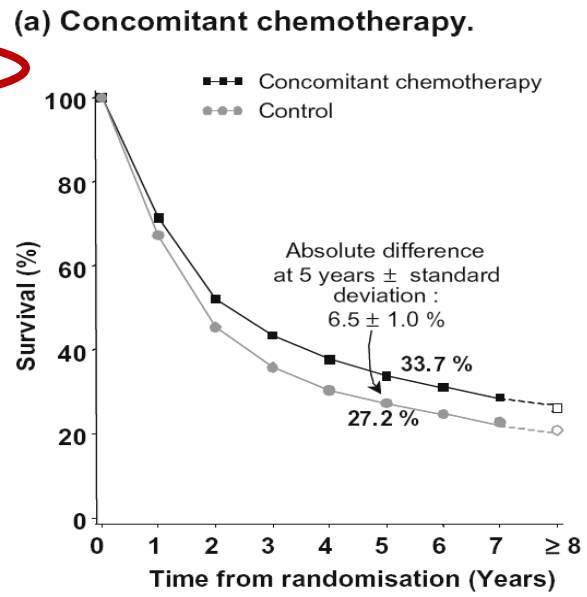
Meta analysis

# Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients

Jean-Pierre Pignon [a,*], Aurélie le Maître [a], Emilie Maillard [a], Jean Bourhis [b], on behalf of the MACH-NC Collaborative Group [1]

[a] Department of Biostatistics and Epidemiology, Institut Gustave-Roussy, Villejuif, France
[b] Department of Radiotherapy, Institut Gustave-Roussy, Villejuif, France




Pignon et al, Radioth Oncol 2009: 92; 4-14

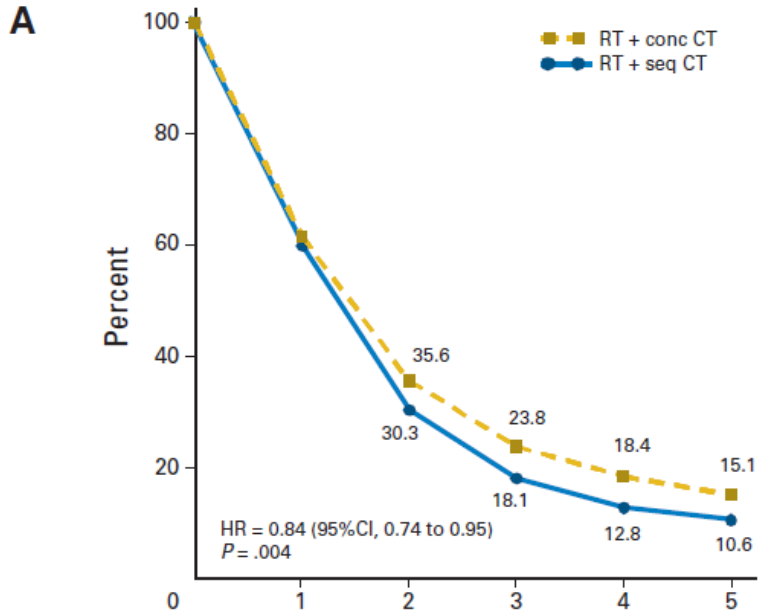
VOLUME 28 · NUMBER 13 · MAY 1 2010

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

From the Unit of Biostatistics and Epidemiology and Radiation Oncology, Institut Gustave-Roussy, Villejuif; Institut de Cancérologie de la Loire, Department of Medical Oncology, Saint Etienne; Institut Universitaire de Recherche Clinique, Université Montpellier I – Statistical Unit, Montpellier; University of Paris-South, Paris, France; Bodine Center, Department of Radiation Oncology; Department of Radiation Therapy Oncology Group Statistics, American College of Radiology, Philadel-

# Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non–Small-Cell Lung Cancer

*Anne Aupérin, Cecile Le Péchoux, Estelle Rolland, Walter J. Curran, Kiyoyuki Furuse, Pierre Fournel, Jose Belderbos, Gerald Clamon, Hakki Cuneyt Ulutin, Rebecca Paulus, Takeharu Yamanaka, Marie-Cecile Bozonnat, Apollonia Uitterhoeve, Xiaofei Wang, Lesley Stewart, Rodrigo Arriagada, Sarah Burdett, and Jean-Pierre Pignon*




| | Deaths/Person-Years by Period | | | | |
|---|---|---|---|---|---|
| | 0y–1y | 1y–2y | 2y–3y | 3y–4y | > 4y |
| RT+ conc CT (n = 603) | 240/498 | 147/276 | 67/171 | 30/116 | 37/186 |
| RT+ seq CT (n = 602) | 253/491 | 171/242 | 70/129 | 30/ 83 | 23/126 |

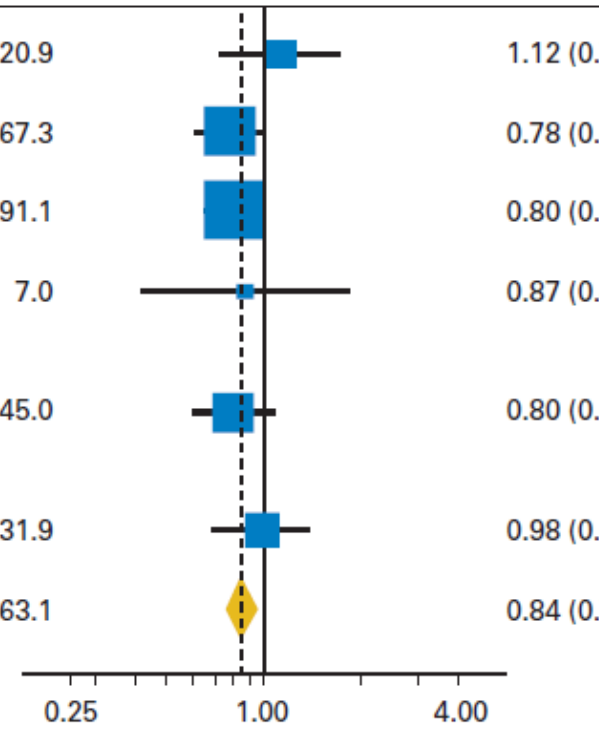
Auperin et al., *J Clin Oncol 28:2181-2190.* 2010

# Overall Survival

**A**

| Trial | No. Deaths / No. Entered RT + Conc CT | RT + Seq CT | O-E | Variance | HR (95% CI) |
|---|---|---|---|---|---|
| CALGB 8831 | 45/46 | 39/45 | 2.4 | 20.9 | 1.12 (0.73 to 1.72) |
| WJLCG | 131/156 | 142/158 | -16.8 | 67.3 | 0.78 (0.61 to 0.99) |
| RTOG 9410 | 180/204 | 189/203 | -20.5 | 91.1 | 0.80 (0.65 to 0.98) |
| GMMA Ankara 95 | 15/15 | 15/15 | -1.0 | 7.0 | 0.87 (0.41 to 1.82) |
| GLOT-GFPC NPC | 87/102 | 96/103 | -9.9 | 45.0 | 0.80 (0.60 to 1.07) |
| EORTC 08972 | 63/80 | 66/78 | -0.5 | 31.9 | 0.98 (0.69 to 1.39) |
| Total | 521/603 | 547/602 | -46.4 | 263.1 | 0.84 (0.74 to 0.95) |

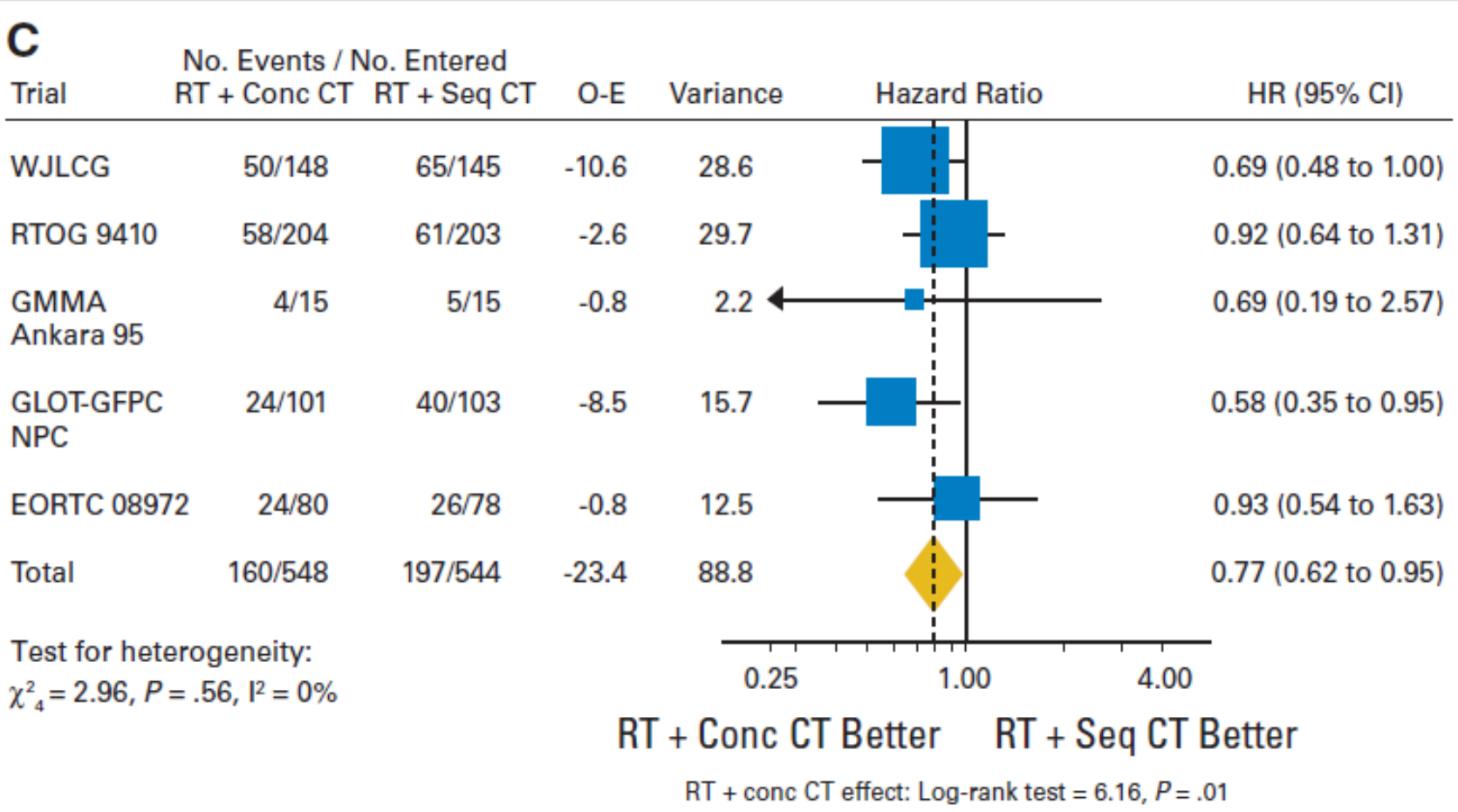
Test for heterogeneity:
$\chi^2_5 = 3.24$, $P = .66$, $I^2 = 0\%$




RT + conc CT effect: Log-rank test = 8.19, $P = .004$

Auperin et al., *J Clin Oncol 28:2181-2190.* 2010

# Local Control



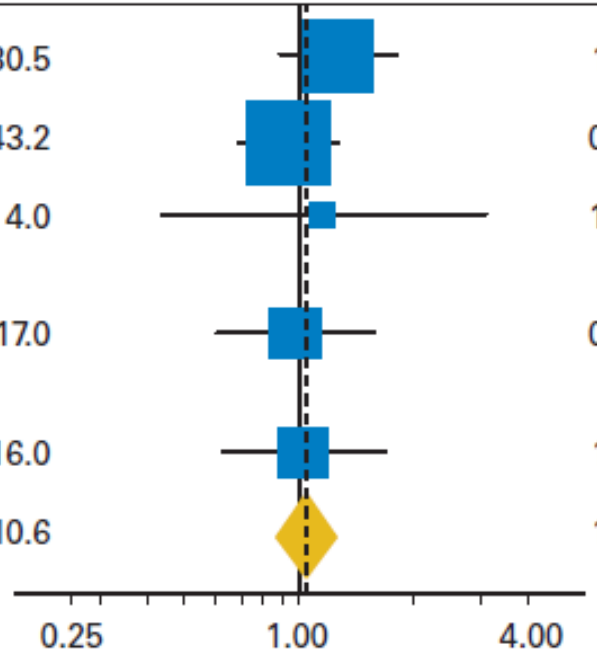

Auperin et al., *J Clin Oncol 28:2181-2190.* 2010

# Distant Control

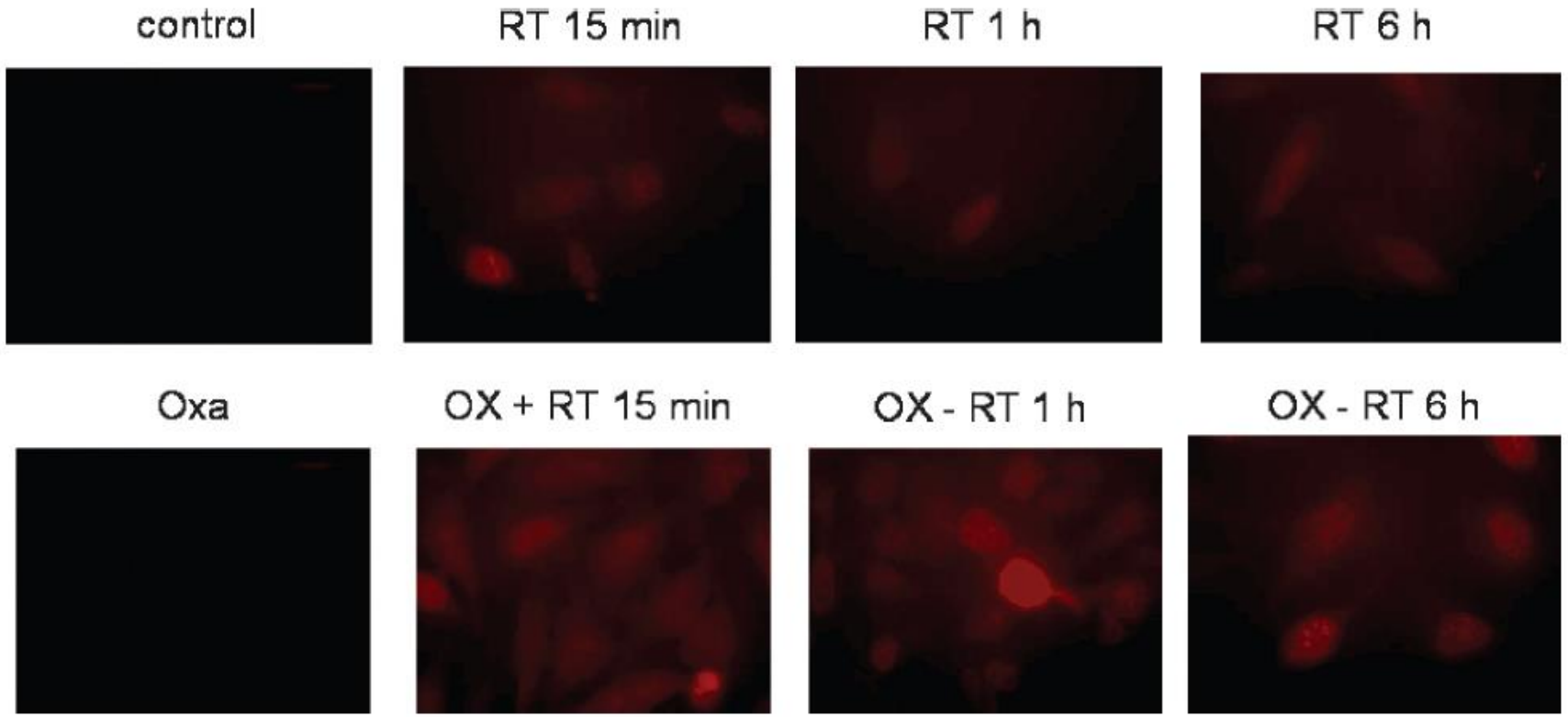
**D**

| Trial | No. Events / No. Entered RT + Conc CT | RT + Seq CT | O-E | Variance | HR (95% CI) |
|---|---|---|---|---|---|
| WJLCG | 67/148 | 55/145 | 7.0 | 30.5 | 1.26 (0.88 to 1.79) |
| RTOG 9410 | 85/204 | 88/203 | -3.1 | 43.2 | 0.93 (0.69 to 1.25) |
| GMMA Ankara 95 | 8/14 | 8/14 | 0.5 | 4.0 | 1.15 (0.43 to 3.08) |
| GLOT-GFPC NPC | 34/101 | 36/103 | -0.5 | 17.0 | 0.97 (0.60 to 1.56) |
| EORTC 08972 | 32/80 | 32/78 | 0.3 | 16.0 | 1.02 (0.63 to 1.67) |
| Total | 226/547 | 219/543 | 4.2 | 110.6 | 1.04 (0.86 to 1.25) |

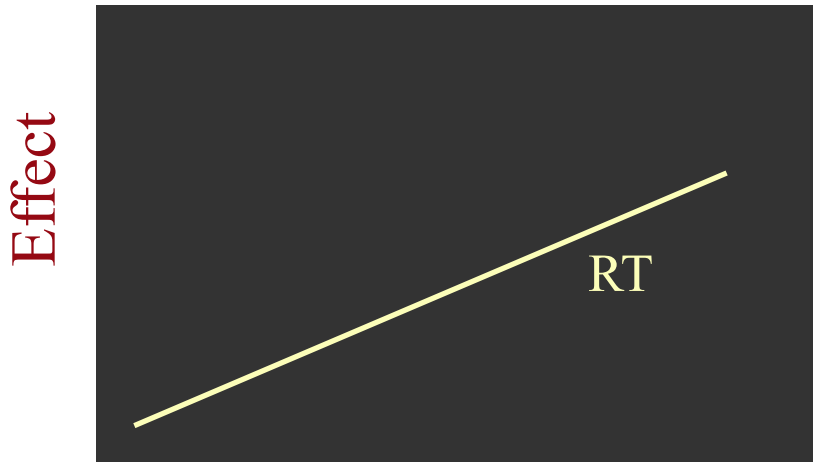
Test for heterogeneity:
$\chi^2_4 = 1.76$, $P = .78$, $I^2 = 0\%$

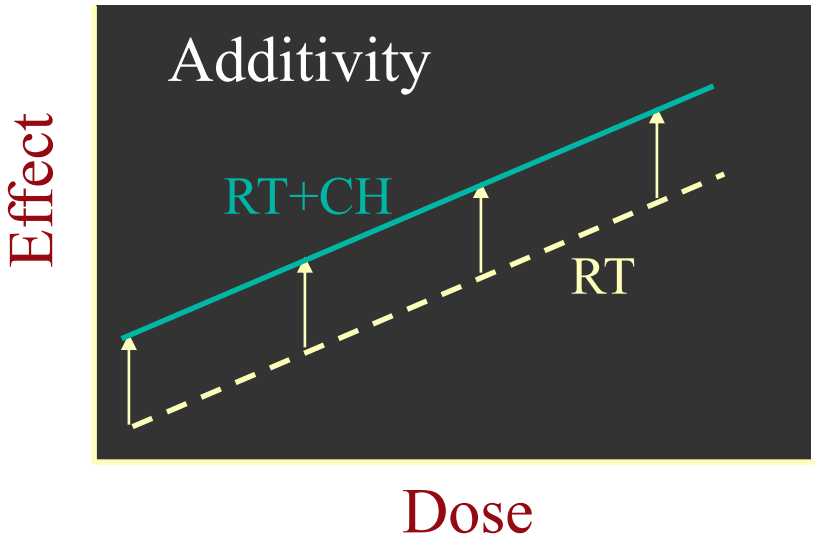


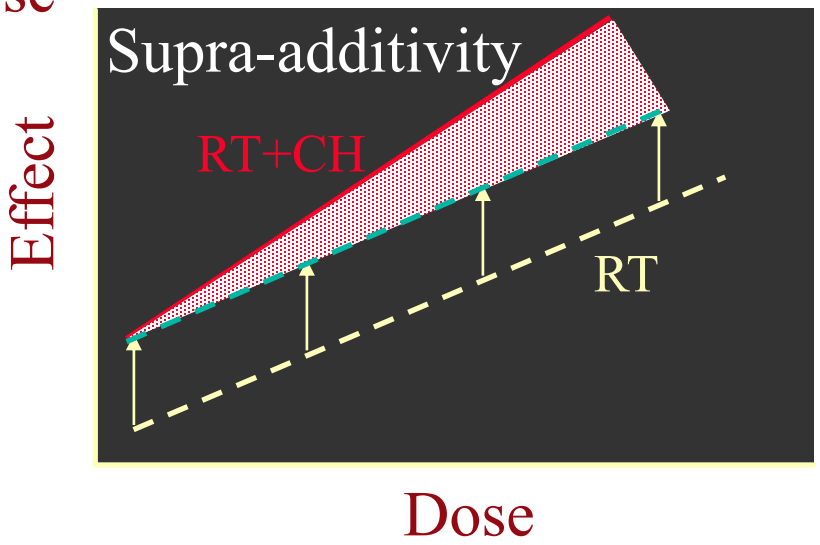

RT + conc CT effect: Log-rank test = 0.16, $P = .69$


control
RT 15 min
RT 1 h
RT 6 h
Oxa
OX + RT 15 min
OX - RT 1 h
OX - RT 6 h

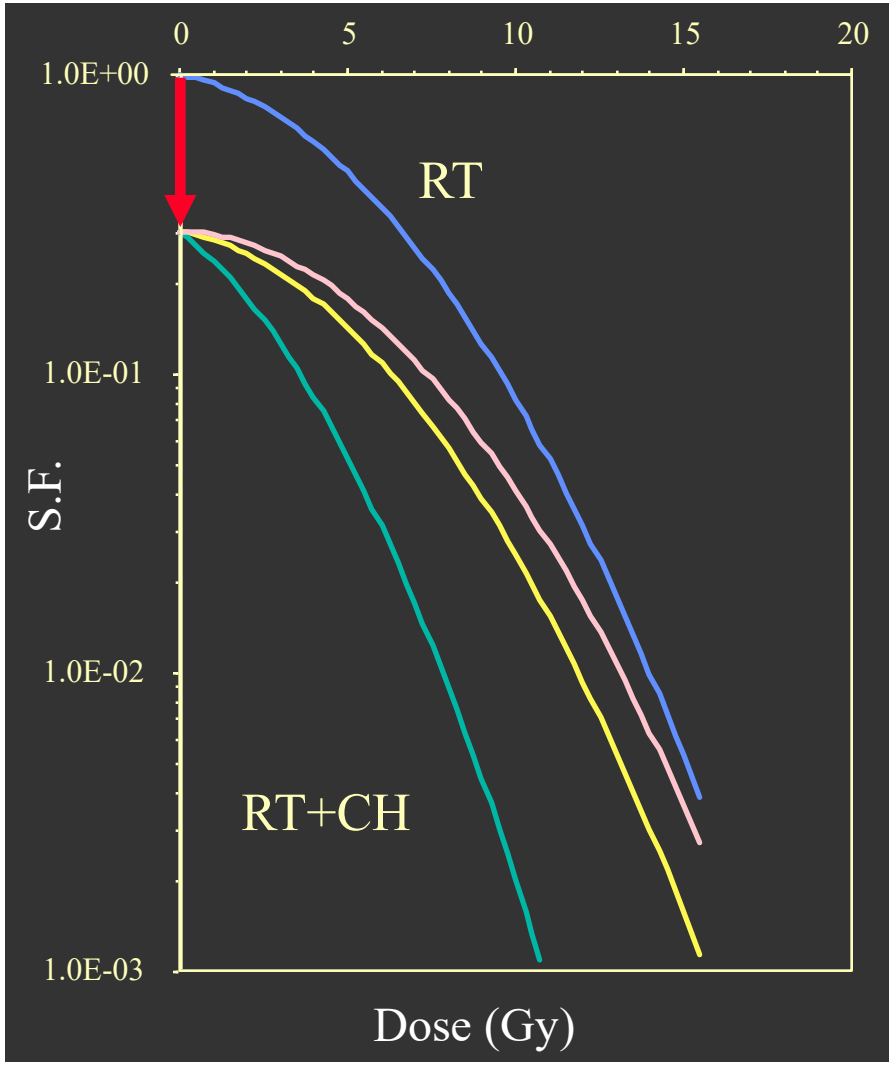
# Combined chemo- and radiotherapy



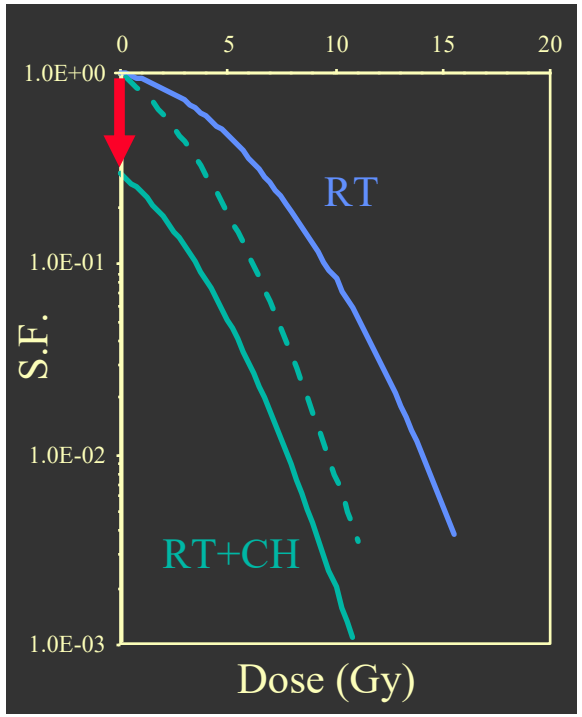



# Combined chemo- and radiotherapy

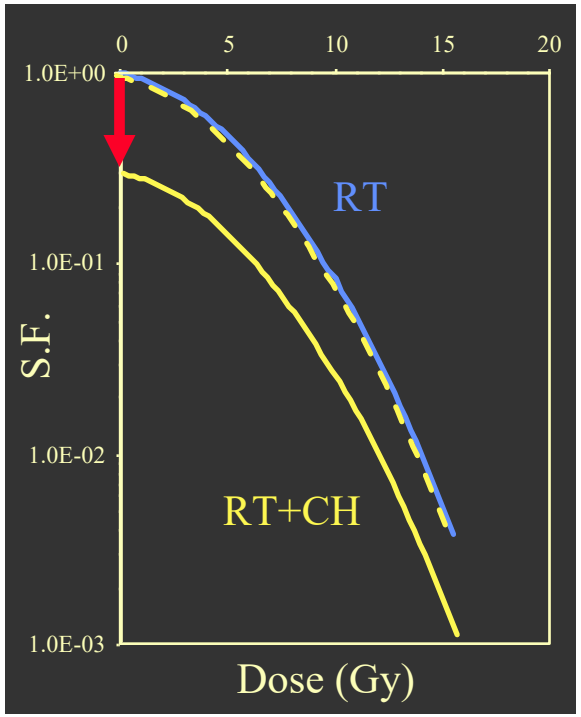


# Combined chemo- and radiotherapy

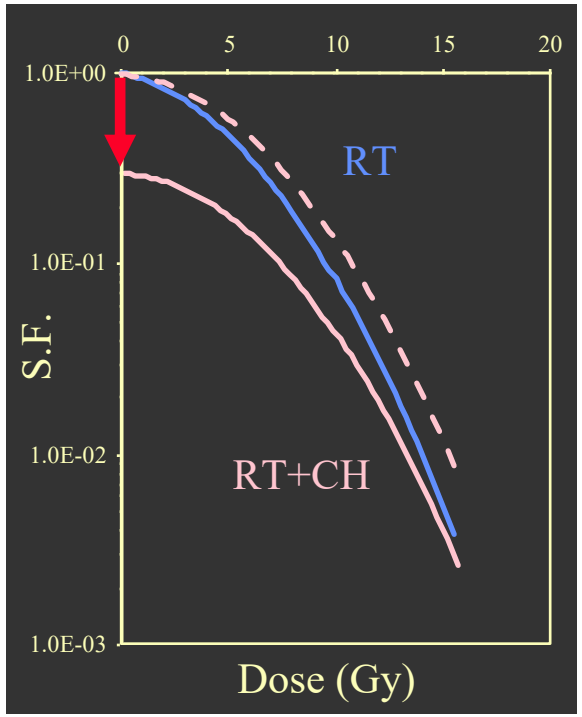
Enhancement




Non-interaction




Inhibition



# Rationale for combining chemotherapeutic agents and ionizing radiation

- modulation of DNA/chromosome repair
- regulation of tumor cell proliferation
- increased tumor cell loss
- increased tumor cell re-oxygenation

# Combined chemo- and radiotherapy treatment: Cellular / molecular interaction

## Antimetabolites

| | DNA damage induction | DNA damage repair | Chromosome aberration | Cell Cycle | Apoptosis |
|---|---|---|---|---|---|
| 5-Fu | - | -/+ | - | + | ? |
| MTX | ? | ? | ? | ? | ? |
| HU | ? | -/+ | + | + | ? |
| dFdC | - | - | + | + | - |
| F-ara-A | - | - | + | + | -? |

# Combined chemo- and radiotherapy treatment: Cellular / molecular interaction

## Plant derivatives

| | DNA damage induction | DNA damage repair | Chromosome aberration | Cell Cycle | Apoptosis |
|---|---|---|---|---|---|
| Vinca-alkaloids | ? | - | ? | + | ? |
| Etoposide | ? | +? | - | + | + |
| Camptothecine | ? | ? | - | -/+ | -/+ |
| Taxanes | ? | - | + | + | + |

# Combined chemo- and radiotherapy treatment: Cellular / molecular interaction

## Antibiotics

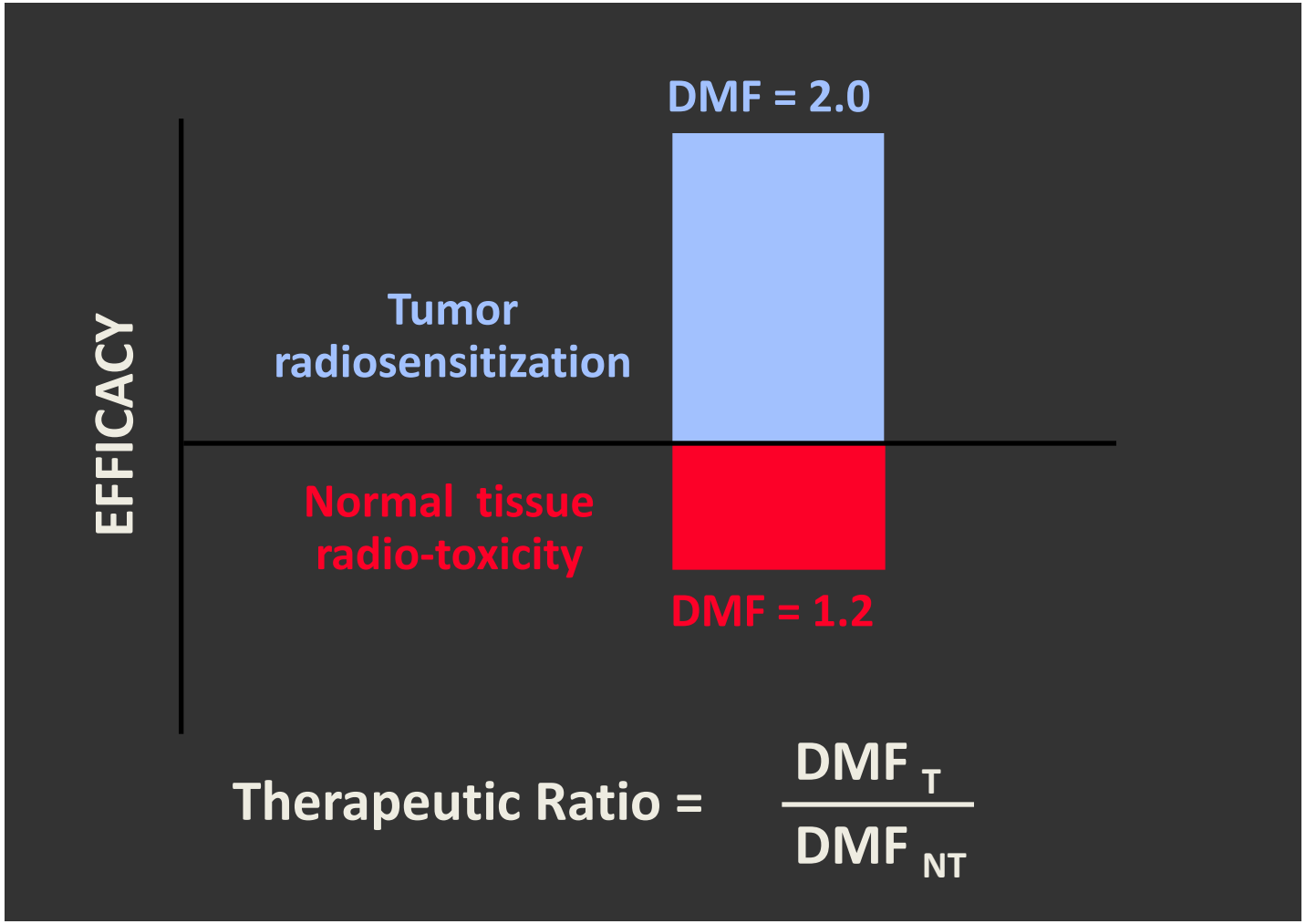
| | DNA damage induction | repair | Chromosome aberration | Cell Cycle | Apoptosis |
|---|---|---|---|---|---|
| Adriamycin | - | -/+ | -/+ | + | ? |
| Mitomycin-C | ? | ? | - | ? | ? |
| Bleomycin | ? | - | -/+ | + | ? |
| Actinomycin-D | ? | +? | ? | ? | - |

# Combined chemo- and radiotherapy treatment: Cellular / molecular interaction

## Alkylating agents

| | DNA damage induction | DNA damage repair | Chromosome aberration | Cell Cycle | Apoptosis |
|---|---|---|---|---|---|
| Cis-platinum | +? | + | ? | - | ? |
| BCNU | ? | + | - | ? | ? |
| Cyclophosphamide | ? | ? | - | ? | ? |

# Therapeutic ratio



# Combined chemo- and radiotherapy treatment:normal tissue toxicity

| | Acute effect | Late effect |
|---|---|---|
| Antimetabolites | | |
| 5-Fu | ++ (GI, skin) | |
| MTX | ++ (GI) | |
| HU | ++ (GI) | |
| dFdC | ++ (GI)± (lung) | |
| F-ara-A | ++ (GI)± (CNS) | |
| Alkylating agents | | |
| cis-platinum | ++ (GI)+ (kidney) | |
| BCNU | ++ (GI)+ (lung) | |
| cyclophosphamide | ++ (GI, skin) | + (lung, bladder, CNS) |
| Antimetabolites | | |
| adriamycine | ++ (GI, skin) | + (heart, lung) |
| mitomycin-C | ++ (GI, BM) | + (lung) |
| bleomycin | ++ (skin, GI) | + (skin, lung) |
| actinomycine-D | ++ (GI, BM, skin) | + (lung) |
| Plant derivatives | | |
| Vinca-alcaloides | - (GI, BM) | ? |
| Etoposide | ? | ? |
| Taxanes | + (GI) | ? |

# Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer.

M. Morris et al, NEJM, 340:1137-1143, 1999.

| | RT (n = 193) | RT + Chemo (n = 193) |
|---|---|---|
| Early toxicity (G3-5) | 10 (5%) | 88 (45%) |
| Early toxicity* (G3-5) | 4 (2%) | 20 (10%) |
| Late toxicity (G3-5) | 22 (11%) | 24 (12%) |

* non hematologic only

RT: 45 Gy + brachytherapy (total dose ≥ 85 Gy)
Chemo: cddp (75mg/$m^2$, d1), 5Fu (1g/$m^2$/d, d1-4), x3

Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer.

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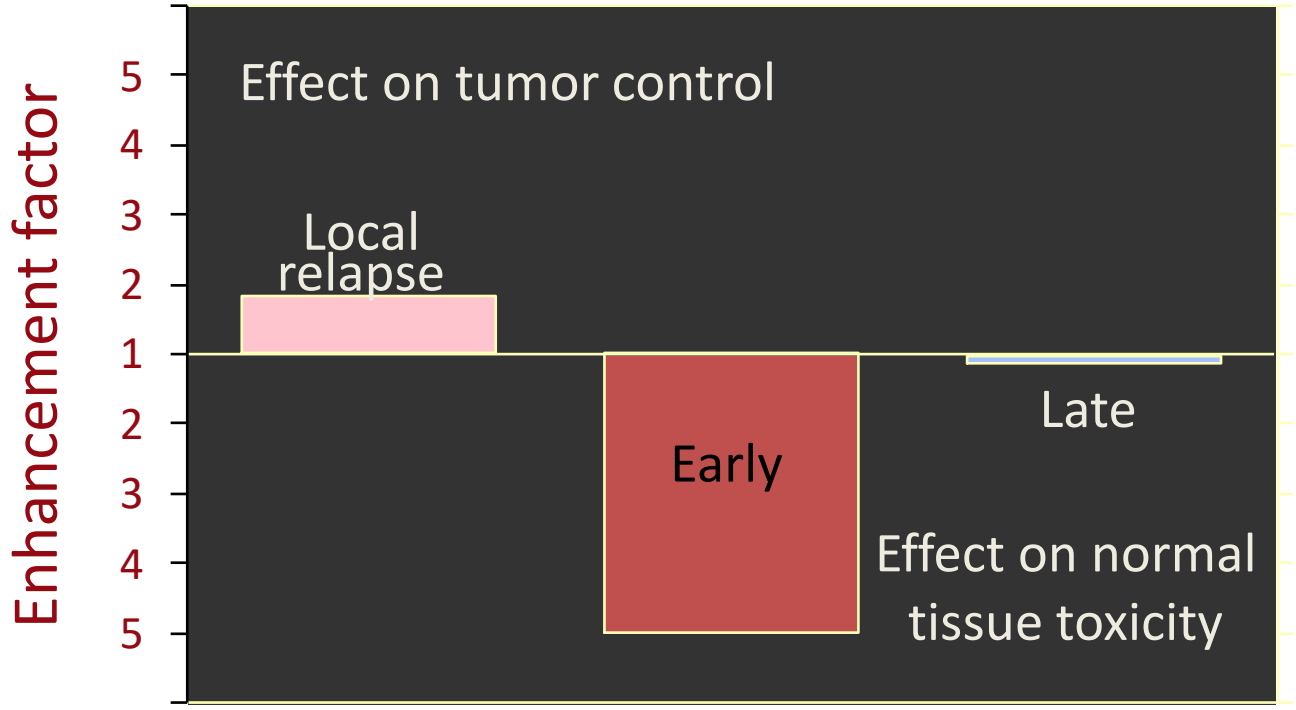

# Combined chemo- and radiotherapy treatment

- Can improve efficacy of RT alone
- Whether this widens the therapeutic ratio or not is often not evaluated rigorously in clinical trial setting
- Doses of both agents may require adjustment to maintain iso-toxicity (early vs late)
- Designs should explicitly incorporate assessment of therapeutic ratio