RADIOTHERAPY AND CHEMOTHERAPY IN THE TREATMENT OF THE CANCER

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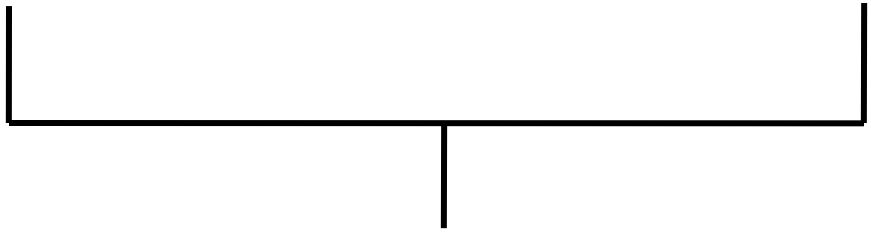
RADIOTHERAPY

Use of the **IONIZING RADIATION** to destroy the carcinogenic cells

CHEMOTHERAPY

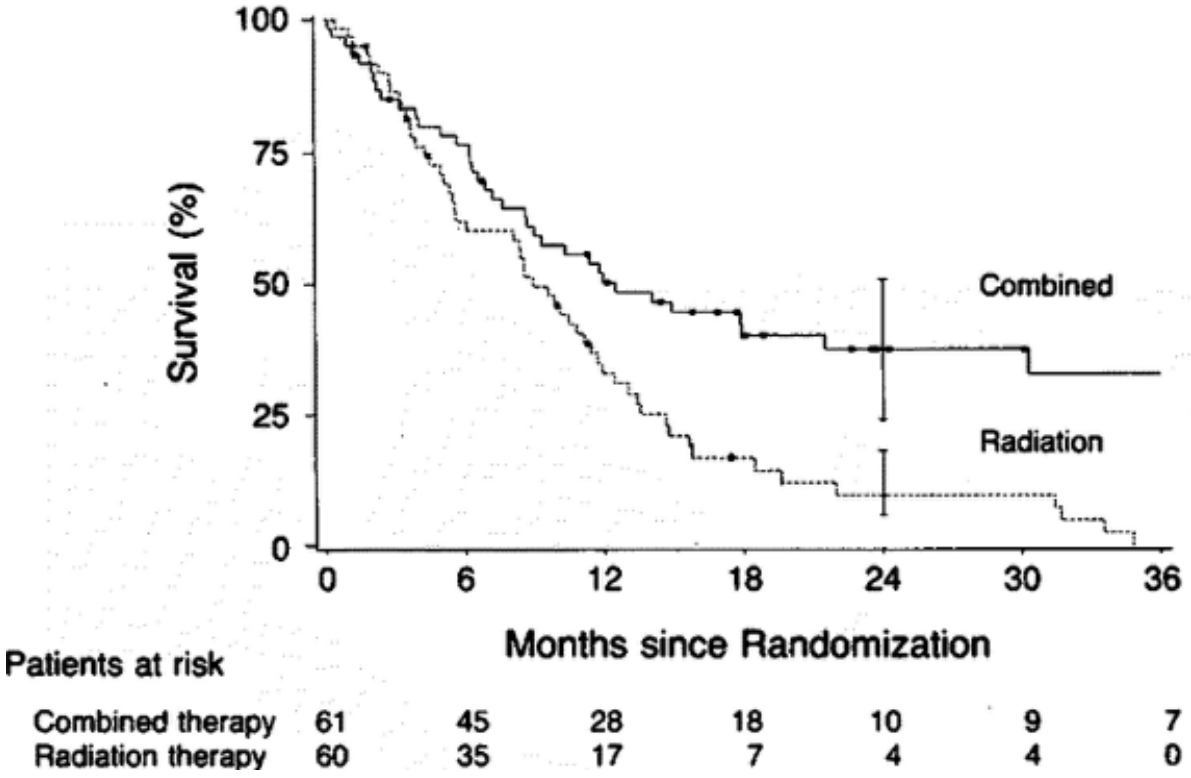
Use of **DRUGS** to destroy the carcinogenic cells



DOES ITS COMBINATION IMPROVE THE RESULTS?

COMBINED RADIOTHERAPY AND CHEMOTHERAPY (I)

OESOPHAGUS CARCINOMA



Wong and Malthaner, 2006

Survival

RT

1 year --- 33%

2 years --- 10 %

RT + CHEMO (Combined)

1 year --- 50%

2 years --- 38%

COMBINED RADIOTHERAPY AND CHEMOTHERAPY (II)

RECTUM CANCER

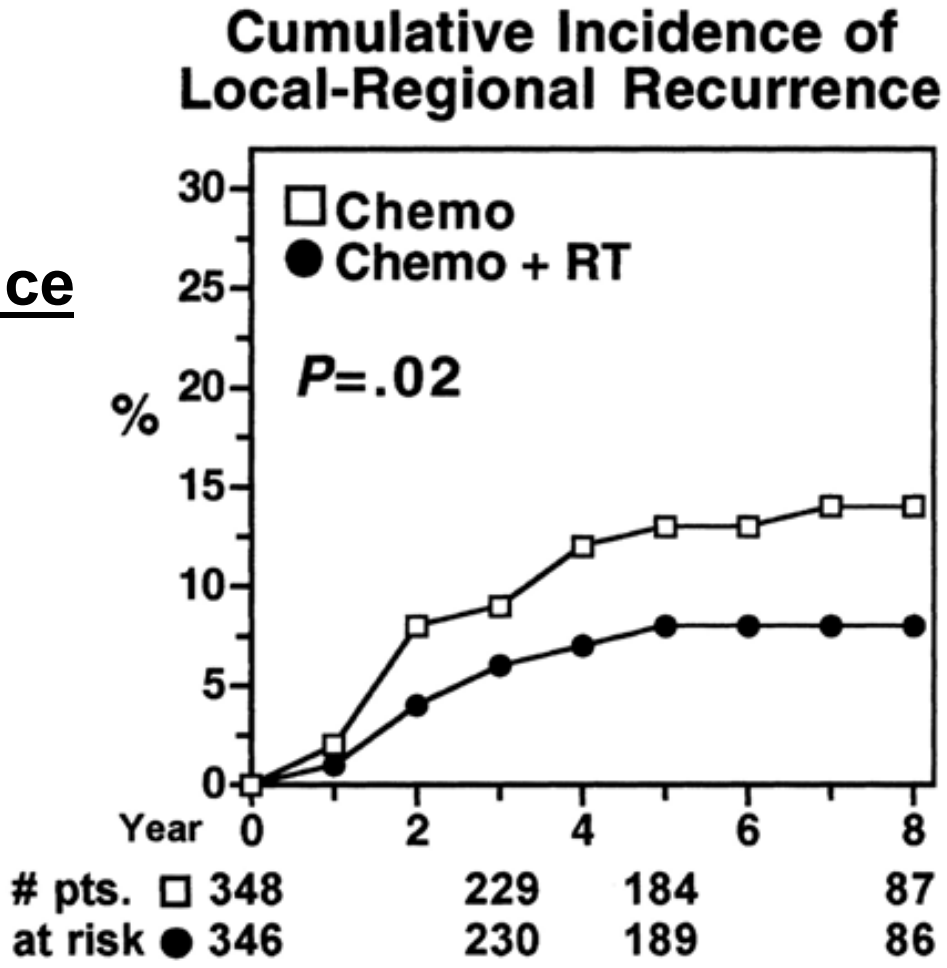
Local-regional recurrence

CHEMO

5 years --- 13%

CHEMO + RT (Combined)

5 years --- 8%



Wolmark N et al. JNCI J Natl Cancer Inst 2000;92:388-396

INTERACTION BETWEEN CHEMO AND RT

HYPOTHESIS

- **1 - DNA DAMAGE?**
  - Chemo would increase the hurt induced by the radiotherapy :
    - Free radicals.
    - Inhibition of DNA repair.
    - Increase of double strand breaks.

- **2 - ALTERATIONS IN THE CELL-CYCLE?**
  - Chemo in his interaction with the cellular cycle might go and synchronize to the tumour cells in a radiosensitive phase (e.g. G2)

- **3 - APOPTOSIS?**
  - Additive or synergistic effect in the apoptosis.

- **4 - RE-OXYGENATION?**
  - Chemo would reduce of tumour size increasing tumour oxygenation and this would increase tumour radiosensitivity.

- **5 – INHIBITION OF CELL PROLIFERATION?**
  - Brake of the cellular proliferation for the QT after RT's cycle would reduce the multiplication of carcinogenic cells.

Summary of the preclinical data regarding the mechanisms of interaction between ionizing radiation and chemotherapeutic agents

	DNA damage Induction	Repair	Chromosome aberration	Cell cycle	Apoptosis	Re-oxygenation
Antimetabolites						
5-Fluorouracil	–	±	–	+	?	?
Methotrexate	?	?	?	?	?	?
Hydroxyurea	?	±	+	+	?	?
Gemcitabine	–	–	+	+	–	?
Fludarabine	–	–	+	+	–	?
Plant derivatives						
Vinca alkaloids	?	–	?	+	?	?
Etoposide	?	+?	–	+	+	?
Camptothecin	?	?	–	±	±	?
Taxanes	?	–	+	+	+	+
Antibiotics						
Doxorubicin	–	±	±	+	?	?
Mitomycin-C	?	?	–	?	?	?
Bleomycin	?	–	±	+	?	?
Actinomycin-D	?	+?	?	?	–	–
Alkylating agents						
Cisplatin	+?	+	?	–	?	?
BCNU	?	+	–	?	?	?
Cyclophosphamide	?	?	–	?	?	?

–, Not demonstrated; +, demonstrated; ±, conflicting data; ?, unknown.

Joiner M, van der Kogel A. Basic Clinical Radiobiology: fourth edition. Great Britain: Hodder Arnoldin; 2009.

ANALYSIS OF RESULTS

- **1** – DNA DAMAGE→ Chemo increases the damage induced by radiotherapy.

  PROBLEM → **Chemo haven't got selective anti-tumour effect.**

- **2** - ALTERATIONS IN THE CELL-CYCLE?

  PROBLEM → **The synchronization between chemo an RT is difficult**

- **3** - APOPTOSIS

  EFFECT →**Chemo + RT: only an additive effect.**

- **4** - RE-OXIGENACIÓN

  PROBLEM → **More studies are needed with more chemotherapy drugs.**

- **5** - **INHIBITION OF CELL PROLIFERATION**

  RESULTS → **More studies are needed.**

TOXICITY OF CONCOMITANT CHEMORADIATION

EARLY TOXICITY

Gastrointestinal
Skin
Bone marrow

INCREASE

LATE TOXICITY

Lung
CNS
Heart
Skin
Kidney
Bladder

INCREASE

DEPENDS ON THE SPECIFIC DRUG TOXICITY

Summary of the preclinical data regarding the toxicity of concomitant chemoradiation

	Early effects	Late effects
Antimetabolites		
5-Fluorouracil	+ (GI, skin)	?
Methotrexate	+ (GI)	?
Hydroxyurea	+ (GI)	?
Gemcitabine	+ (GI)	± (lung)
Fludarabine	+ (GI)	± (CNS)
Plant derivatives		
Vinca alkaloids	− (GI, BM)	?
Etoposide	?	?
Taxanes	+ (GI)	?
Antibiotics		
Doxorubicin	+ (GI, skin)	+ (heart, lung)
Mitomycin-C	+ (GI, BM)	+ (lung)
Bleomycin	+ (GI, skin)	+ (skin, lung)
Actinomycin-D	+ (GI, BM, skin)	+ (lung)
Alkylating agents		
Cisplatin	+ (GI)	+ (kidney)
BCNU	+ (GI)	+ (lung)
Cyclophosphamide	+ (GI, skin)	+ (lung, bladder, CNS)

BCNU, β-chloro-nitrosourea; BM, bone marrow; CNS, central nervous system; GI, gastrointestinal.
−, Not demonstrated; +, demonstrated; ±, conflicting data; ?, unknown.

Joiner M, van der Kogel A. Basic Clinical Radiobiology: fourth edition. Great Britain: Hodder Arnoldin; 2009.

Gregoire et al, 1997.

BENEFIT OF A COMBINED MODALITY TREATMENT

Therapeutic ratio (TR) → **TR > 1 → More effective**

TR < 1 → More toxic than beneficial

Comparison of efficacy and side-effects after concomitant chemoradiotherapy for locally advanced squamous cell carcinoma of the cervix

	Radiotherapy alone[1] (%)	Chemoradiotherapy[2] (%)	Therapeutic ratio
Recurrence rate at 5 years	35	19	–
Early effects (grades 3–5)	5	45	0.2
Early effects (excluding haematological toxicity) (grades 3–5)	2	10	0.4
Late effects (grades 3–5)	11	12	1.7

[1]External pelvic radiotherapy up to 45 Gy in 4.5 weeks followed by a brachytherapy implant with a total dose equal to or greater than 85 Gy; $n = 193$.

[2]Cisplatin (75 mg/m^2, day 1) + 5-fluorouracil (1g/m^2 per day, days 1–4) × 3, every 3 weeks; $n = 195$.

Joiner M, van der Kogel A. Basic Clinical Radiobiology: fourth edition. Great Britain: Hodder Arnoldin; 2009.

Morris et al, 1999.

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1. *Wong and Malthaner, 2006 (Carcinoma esofágico)*
   - *http://www.nejm.org/doi/full/10.1056/NEJM199206113262403*

2. *Wolmark N et al. JNCI J Natl Cancer Inst 2000;92:388-396 (Carcinoma de recto)*
   - *http://jnci.oxfordjournals.org/content/92/5/388.long*

3. *Joiner M, van der Kogel A. Basic Clinical Radiobiology: fourth edition. Great Britain: Hodder Arnoldin; 2009.*