I NUOVI AGENTI ORMONOTERAPICI IN ASSOCIAZIONE ALLA RADIOTERAPIA: COOPERAZIONE SPAZIALE O RADIOSENSIBILIZZAZIONE TUMORALE?

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Radioterapia Oncologica
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INTRODUCTION

New hormonal drugs and radiation therapy??

Review

Concurrent hormone and radiation therapy in patients with breast cancer: what is the rationale?

Cyrus Chargari, Robert Alain Toillon, Dhara MacDermed, Pierre Castadot, Nicolas Magné

Lancet Oncol 2009; 10: 53-60

INTRODUCTION

The identification of oestrogen's central role in mammary carcinogenesis has led to investigation of **oestrogen pathways** as major **targets** for breast-cancer therapy.

The biological effects of oestrogen are mainly mediated through binding to oestrogen **receptors alpha and beta**; ligand-dependent transcription factors that determine **growth**, **survival**, and **differentiation** of breast-cancer cells.

Adjuvant **tamoxifen**, an oestrogen antagonist, reduces the risk of **distant metastases**, **local recurrence**, and **contralateral** breast cancer incidence in women with tumours that express hormone receptors.

INTRODUCTION

The **sequencing** of chemotherapy, radiation, and hormone therapy is a **challenge** for the oncologist when selecting the best treatment approach for breast cancer, and an important clinical question is whether to **combine endocrine therapy** and postoperative **radiotherapy**.

Given the widespread application of adjuvant endocrine therapy, it is important to assess the **safety and efficacy** of cancer treatments relative to their sequence of administration.

INTERACTION BETWEEN OESTROGEN AND IONISING RADIATION

INTERACTION BETWEEN OESTROGEN AND IONISING RADIATION - 1

The **cross-talk** between oestrogen receptors and growth factor signal cascades, including **MAP-kinase** and **PI3-kinase** pathways, might alter effect of ionising radiation

The effect of 17-beta oestradiol on **radiosensitivity** could be related to **inactivation of p53** which maintains genomic integrity and protects cells against radiation-induced damage

Schmidberger, Endocrine Related Cancer 2003

INTERACTION BETWEEN OESTROGEN AND IONISING RADIATION - 2

17beta-oestradiol might induce *CCND1 and* ***MYC*** expression, allowing cell-cycle-progression via **cyclin**-CDK activation and subsequent **G1/S and G2/M transitions**.

Antiestrogens cause an accumulation of cells in **G1 phase**. Estrogens reverse this block with a syncronous cohort of cells progressing through the cell cycle.

It's well known that **G1 phase** is a relative **radioresistant** phase of cell cycle

Schmidberger, Endocrine Related Cancer 2003

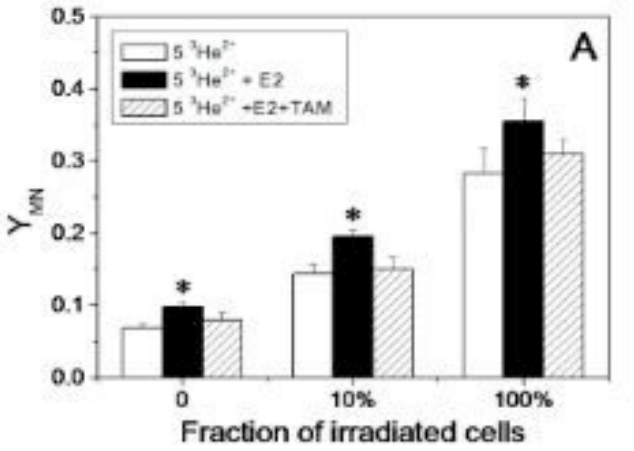
INTERACTION BETWEEN OESTROGEN AND IONISING RADIATION – IN VITRO EXPERIENCES

Comparison between **radiation ind**
bystander responses in es
positive or negati

diol
tivity and bystander
cancer cells, and the effect
nished by antiestrogen tamoxifen

Shao et al, BMC Cancer, 2008

E2 induction of **ROS** are ER dependent.
Several types of ROS mediated DNA damage can be **induced by estrogens** and their metabolites



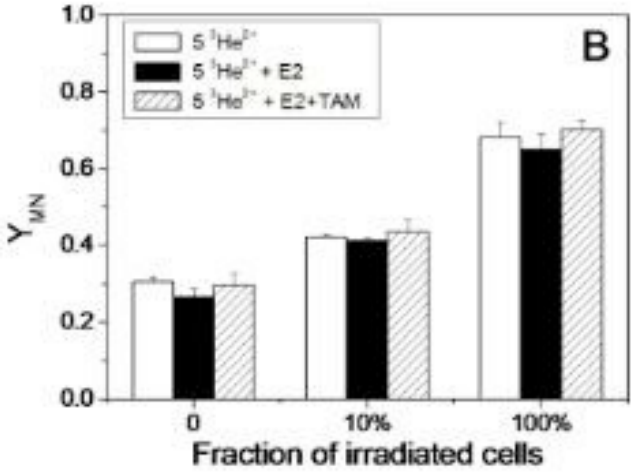


Figure 2
Influence of E2 and TAM on radiation-induced MN formation. A fraction of MCF-7 (**A**) or MDA-MB-231 (**B**) cells were individually irradiated with 5 $^3He^{2+}$ particles without or with pre-treatment with E2 or E2+TAM (*, $P < 0.05$ compared to the MN yield without E2 treatment).

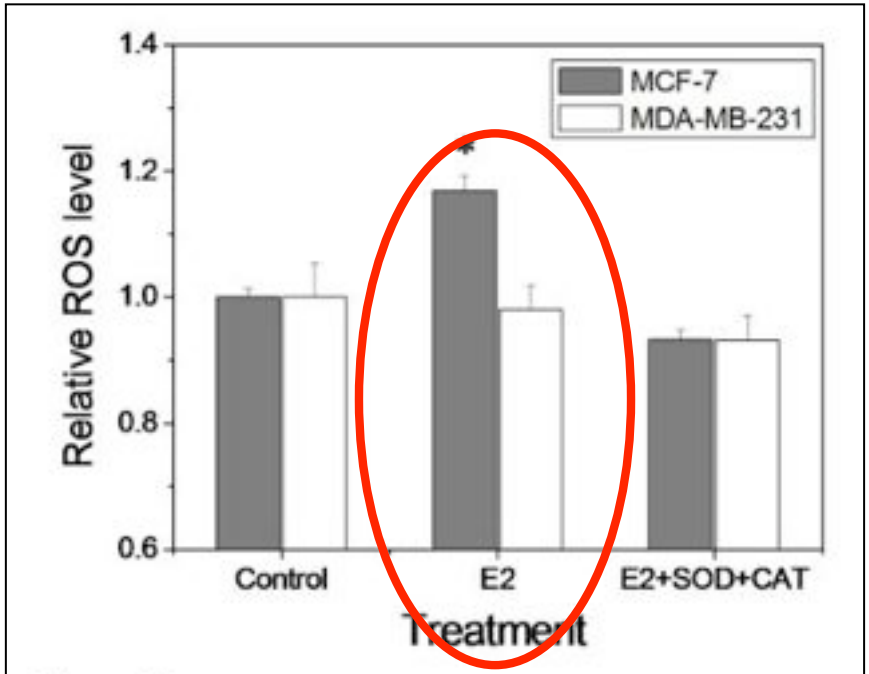


Figure 3
Relative ROS levels. MCF-7 cells and MDA-MB-231 cells were treated with E2 or the mixture of E2 and SOD plus CAT (*, $P < 0.01$ compared to the control without E2 treatment).

Shao et al, BMC Cancer, 2008

INTERACTION BETWEEN OESTROGEN AND IONISING RADIATION – IN VITRO EXPERIENCES

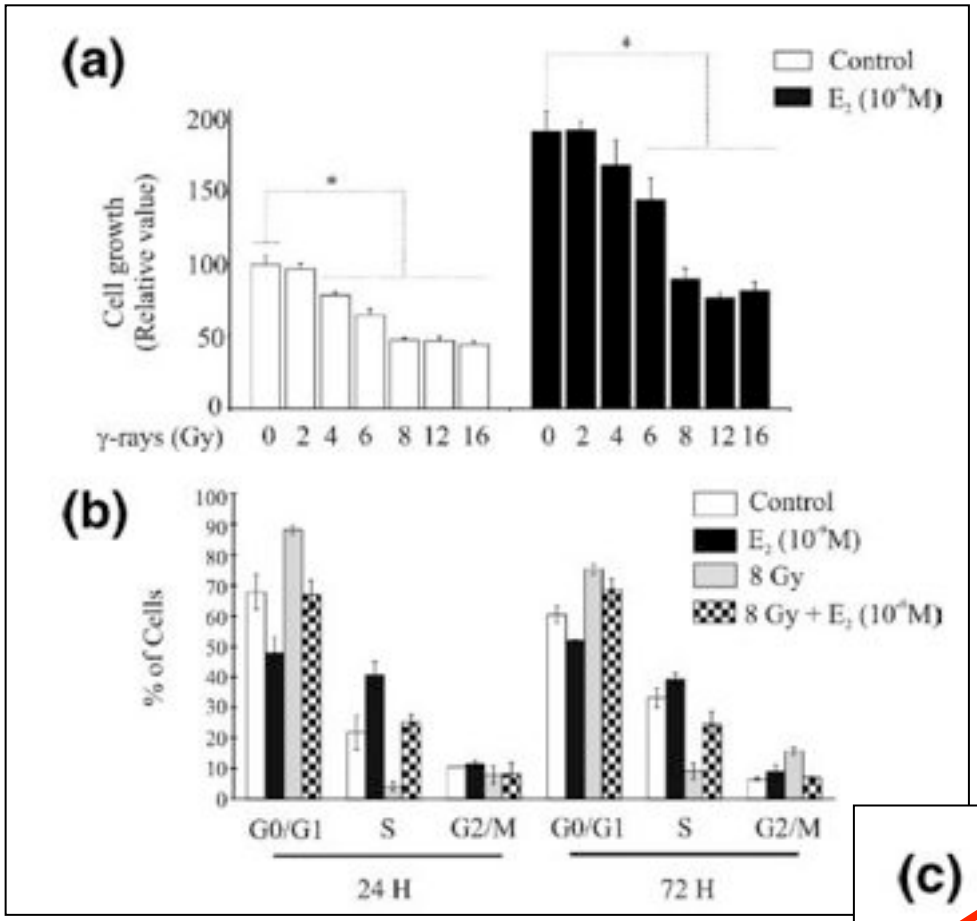
8 Gy dose of radiation diminished synthesis of oestrogen-receptor-alpha but cell[illegible]ivity to anti-oestrogenic agents w[illegible]

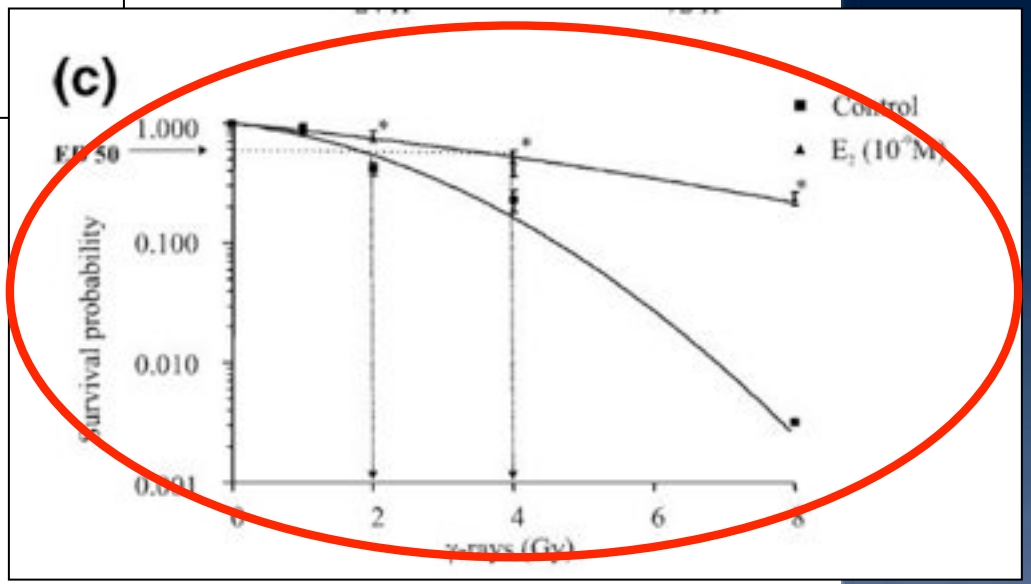
No modifi[illegible]ed.

17bet[illegible]**he growth inhibi[illegible]ionising radiation** in MCF-7 [illegible]cancer cells.

The hormone **lowered the radiosensitivity of these** cells

Toillon et al, IJROBP, 2007





Toillon et al, IJROBP 2007

COMBINING TAMOXIFEN WITH RADIOTHERAPY

VOLUME 23 · NUMBER 1 · JANUARY 1 2005

JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Radiation Therapy and Tamoxifen: Concurrent or Sequential? That Is the Question

Timothy Whelan and Mark Levine, *Departments of Medicine and Clinical Epidemiology and Biostatistics, McMaster University, and the Juravinski Cancer Centre, Hamilton, Ontario, Canada*

PRECLINICAL DATA-
IN VITRO EXPERIENCES

- Sutherland 1982, Osborne 1983: dose-dependent increase in the percentage of cells accumulating in G0/ G1

- Wazer 1989, Ichikawa 200[illegible] tumour effect of tamoxifen on MCF[illegible] expression of cyclin-depende[illegible], especially P21/34, that would norm[illegible]gulated by the activity of wildtype P53, wit[illegible] a mechanism similar to that of ionising radiation

- Paulsen 1996: hormone therapy might alter radiation sensitivity, even in cells negative for oestrogen receptors, with increased radiation resistance in cell lines

Contra

PRECLINICAL DATA – IN VITRO EXPERIENCES

- Sarkaria 1994: growth of MCF-7 cells was inhibited by 4-hydroxytamoxifen but no substantial change in radiation sensitivity of 17beta-oestradiol-stimulated

- Spom 1986, Bord 1995, Yoo 2008: non-hormon ets of tamoxifen include induction of cell secretion of TGF-ß, a potent inhibitor of epithelial cell proliferation and a a prometastatic signal in some tumour cells but also important in the pathogenesis of fibrosis

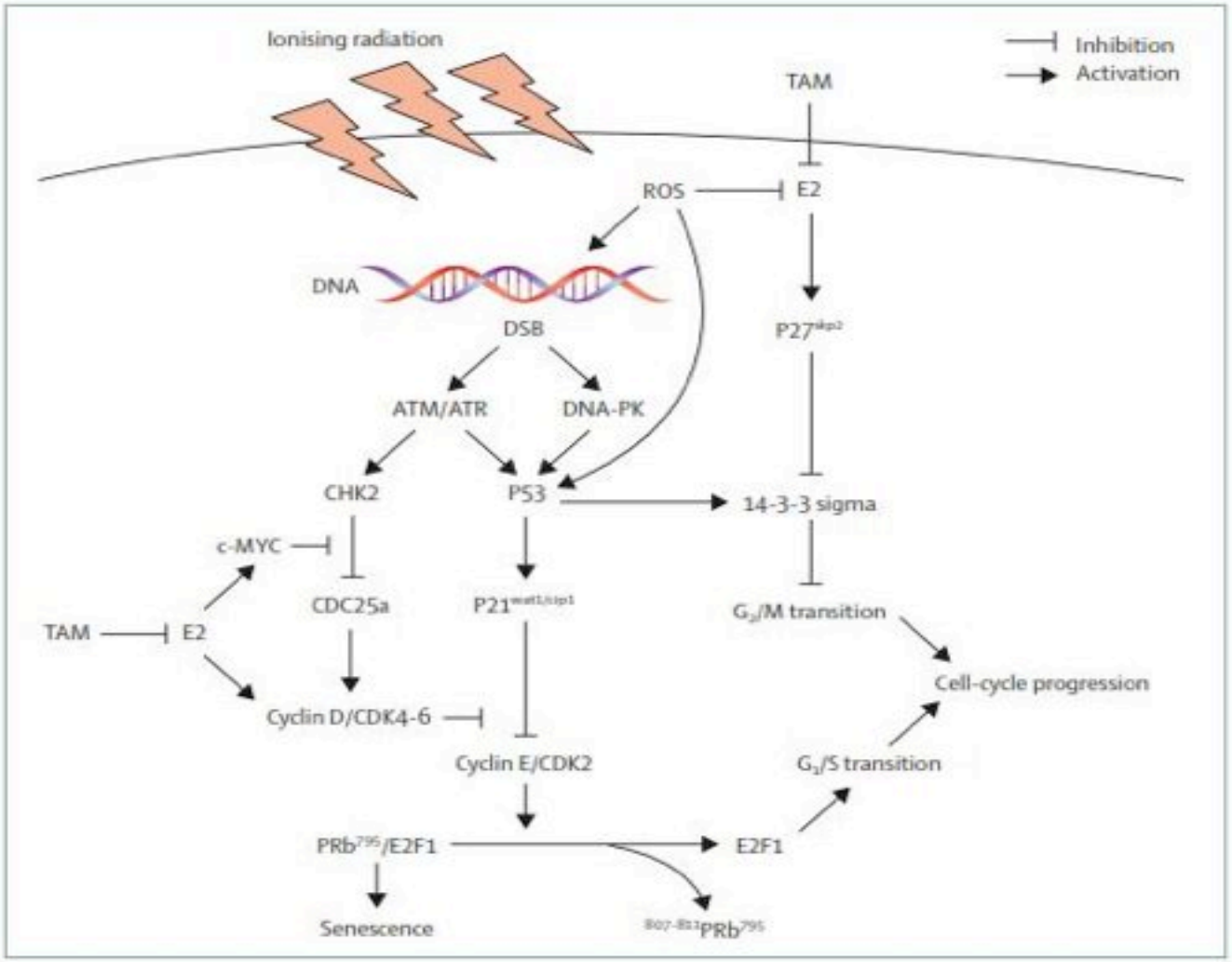
Pros

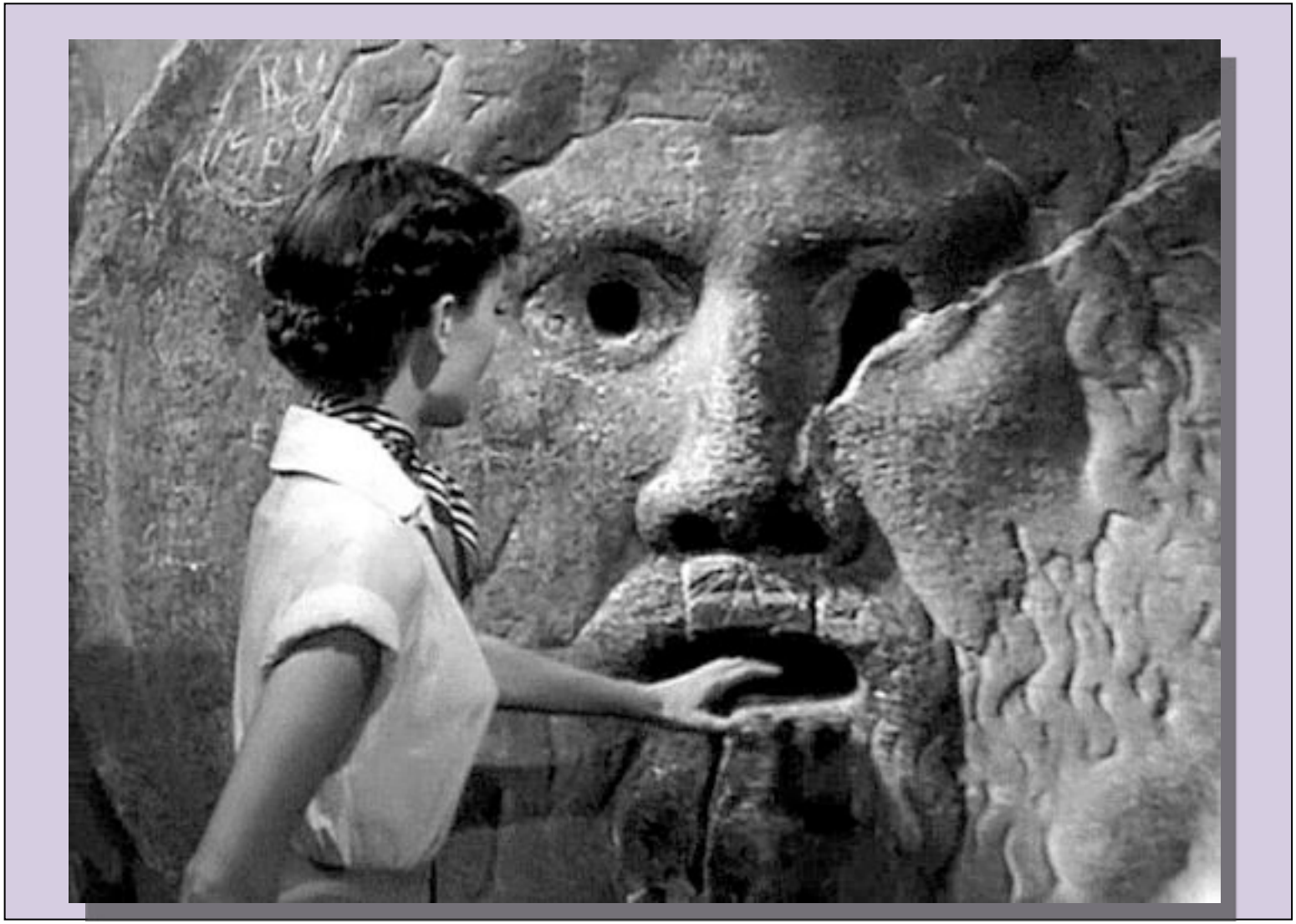
PRECLINICAL DATA – IN VIVO EXPERIENCES

- *Kantorowitz 1993*: Combined **tamoxifen and radiation** resulted in **significant reduction** in tumour **volumes** and suppressed additional tumour growth compared with radiation alone.

- *Sarkaria 1995*: reduction in cell proliferation rate induced by **17β oestradiol deprivation** in MCF-7 human breast xenografts during **fractionated** radiotherapy.

POTENTIAL DIRECT GENOMIC EFFECT OF ESTRADIOL, TAMOXIFEN, AND IONISING RADIATION ON INHIBITION OF CELL CYCLE PROGRESSION





CLINICAL EXPERIENCES

CLINICAL EXPERIENCE

Cancer Treatment Reviews 35 (2009) 409–416

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

ANTI-TUMOUR TREATMENT

Combining systemic therapies with radiation in breast cancer

Krzysztof Adamowicz *, Małgorzata Marczewska, Jacek Jassem

Medical University of Gdansk, Department of Oncology and Radiotherapy, ul. Debinki 7, 80-211 Gdansk, Poland

Retrospective studies comparing various sequences of tamoxifen and radiotherapy in adjuvant treatment of breast cancer.

Authors	Study arms	OS (10 years)	DFS	Distant recurrence (10 years)	Local recurrence (10 years)
Ahn et al.[83]	RT + TAM	84%	NR	18%	10%
	RT → TAM	82%	NR	22%	14%
Harris et al.[84]	RT + TAM	81%	85%	NR	3%
	RT → TAM	86%	76%	NR	7%
Pierce et al.[85]	RT + TAM	88%	83%	NR	7%
	RT → TAM	90%	83%	NR	5%

CLINICAL EXPERIENCE

Pierce et al, JCO 2005

- 107 pts SEQ RT-TAM
- 202 pts CONC RT-TAM
- Median F-up 10.3 years

NO differences in

- 10-year **DFS** *(P 0.76 adjusted for patient characteristics)*

- 10-year **OS** *(adjusted P 0.65)*

- *breast **recurrence** (P 0.54)*

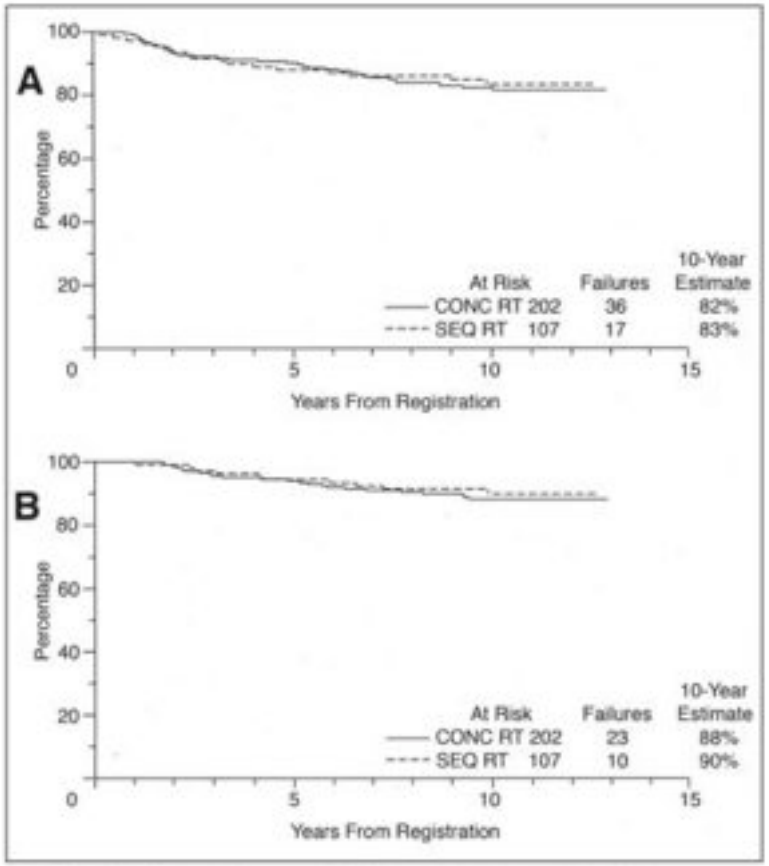


Fig 2. (A) Disease-free survival for patients treated with concurrent tamoxifen (TAM) and radiotherapy (CONC RT) versus sequential TAM and RT (SEQ RT). (B) Overall survival for patients treated with CONC RT versus SEQ RT.

CLINICAL EXPERIENCE

Harris et al, JCO 2005

Table 2. Outcomes According to Tamoxifen Sequence

Outcome	Concurrent Tamoxifen %	Concurrent Tamoxifen 95% CI (%)	Sequential Tamoxifen %	Sequential Tamoxifen 95% CI (%)	P
Local recurrence, years					
5	2	1 to 6	2	1 to 8	.52
10	3	1 to 8	7	3 to 18	
Relapse-free survival, years					
5	92	87 to 96	89	83 to 95	.35
10	85	77 to 90	76	64 to 85	
Overall survival, years					
5	94	88 to 97			
10	81	73 to 90			

- 104 pts SEQ RT-TAM
- 174 pts CONC RT-TAM
- Median F-up 8.6 years

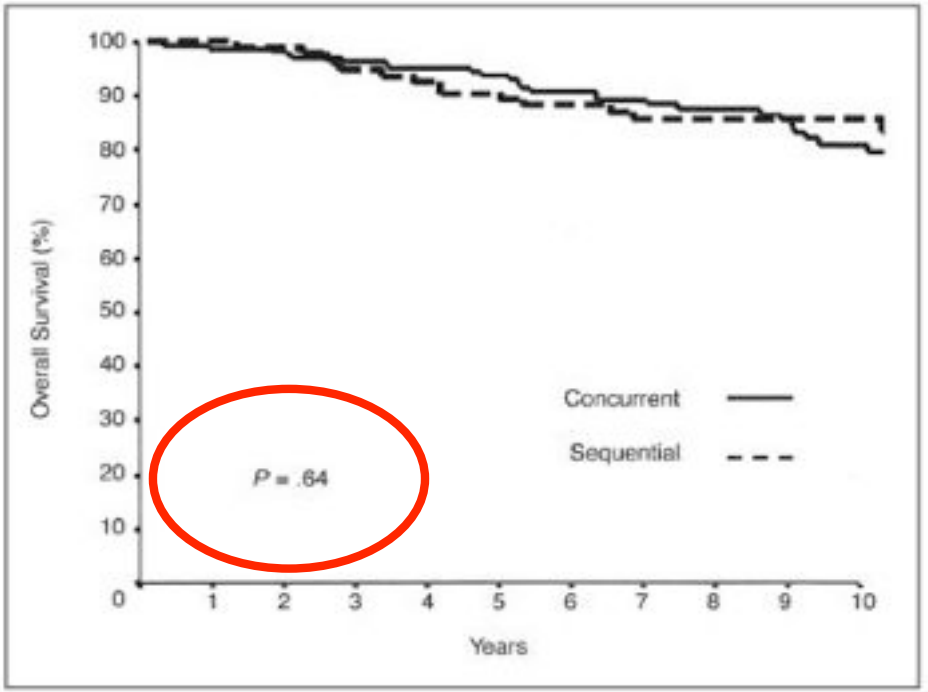


Fig 1. Overall survival according to tamoxifen sequence.

CLINICAL EXPERIENCE

Ahn et al, JCO 2005

Table 2. Outcome Measures Based on Sequence of Tamoxifen Relative to RT

Outcome	CON-TAM	SEQ-TAM	*P*
Breast recurrence			
No	241	227	.73
Yes	13	14	
Nodal recurrence			
No	252	237	.37
Yes	2	4	
Distant metastasis			
No	233	222	.16
Yes	21	29	
Secondary malignancy			
No	210	203	.61
Yes	44	38	

Abbreviations: RT, radiation therapy; CON-TAM, concurrent tamoxifen; SEQ-TAM, sequential tamoxifen.

- 241pts SEQ RT-TAM
- 254 pts CONC RT-TAM
- Median F-up 10 years

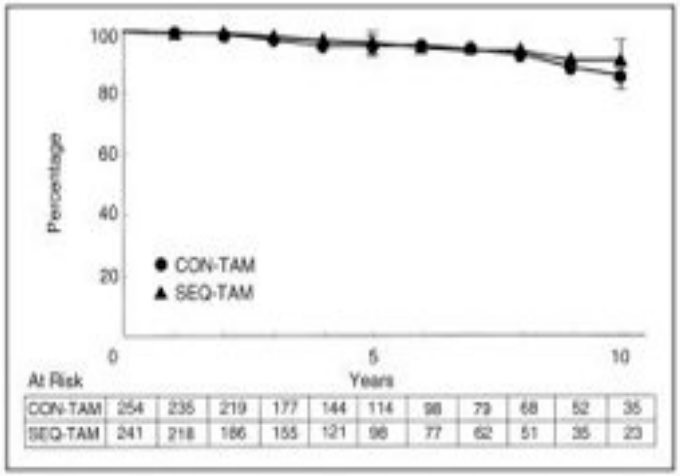


Fig 2. Ipsilateral breast-relapse–free survival by tamoxifen sequencing. CON-TAM, concurrent tamoxifen; SEQ-TAM, sequential tamoxifen.

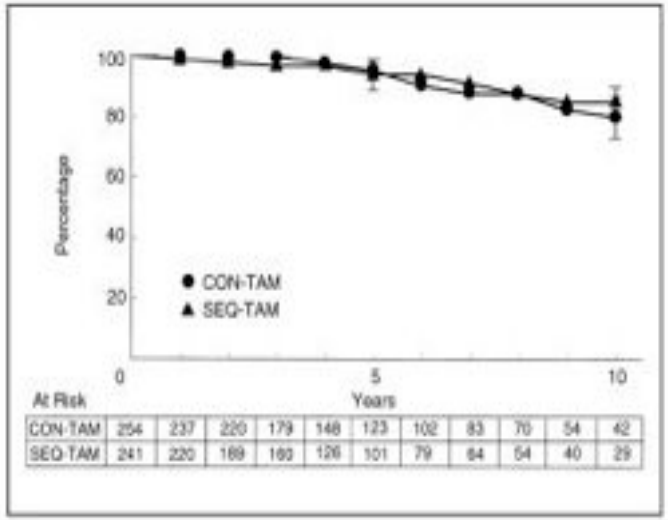


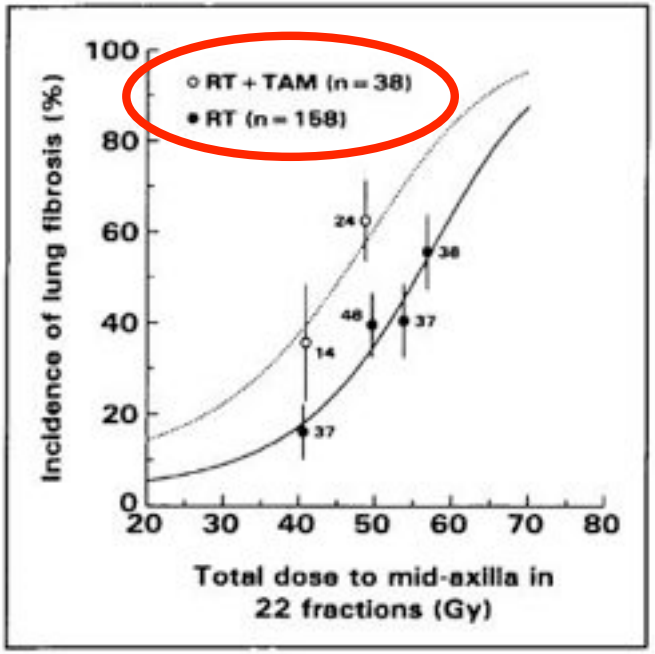
Fig 1. Overall survival by tamoxifen sequencing. CON-TAM, concurrent tamoxifen; SEQ-TAM, sequential tamoxifen.

WHAT ABOUT TOXICITY?

TOXICITY

Radiotherapy-Related Lung Fibrosis Enhanced by Tamoxifen

*Søren M. Bentzen, Jerzy Z. Skoczylas, Marie Overgaard, Jens Overgaard**



Journal of the National Cancer Institute, Vol. 88, No. 13, July 3, 1996

- 46 pts SEQ RT-TAM
- 38 pts CONC RT-TAM

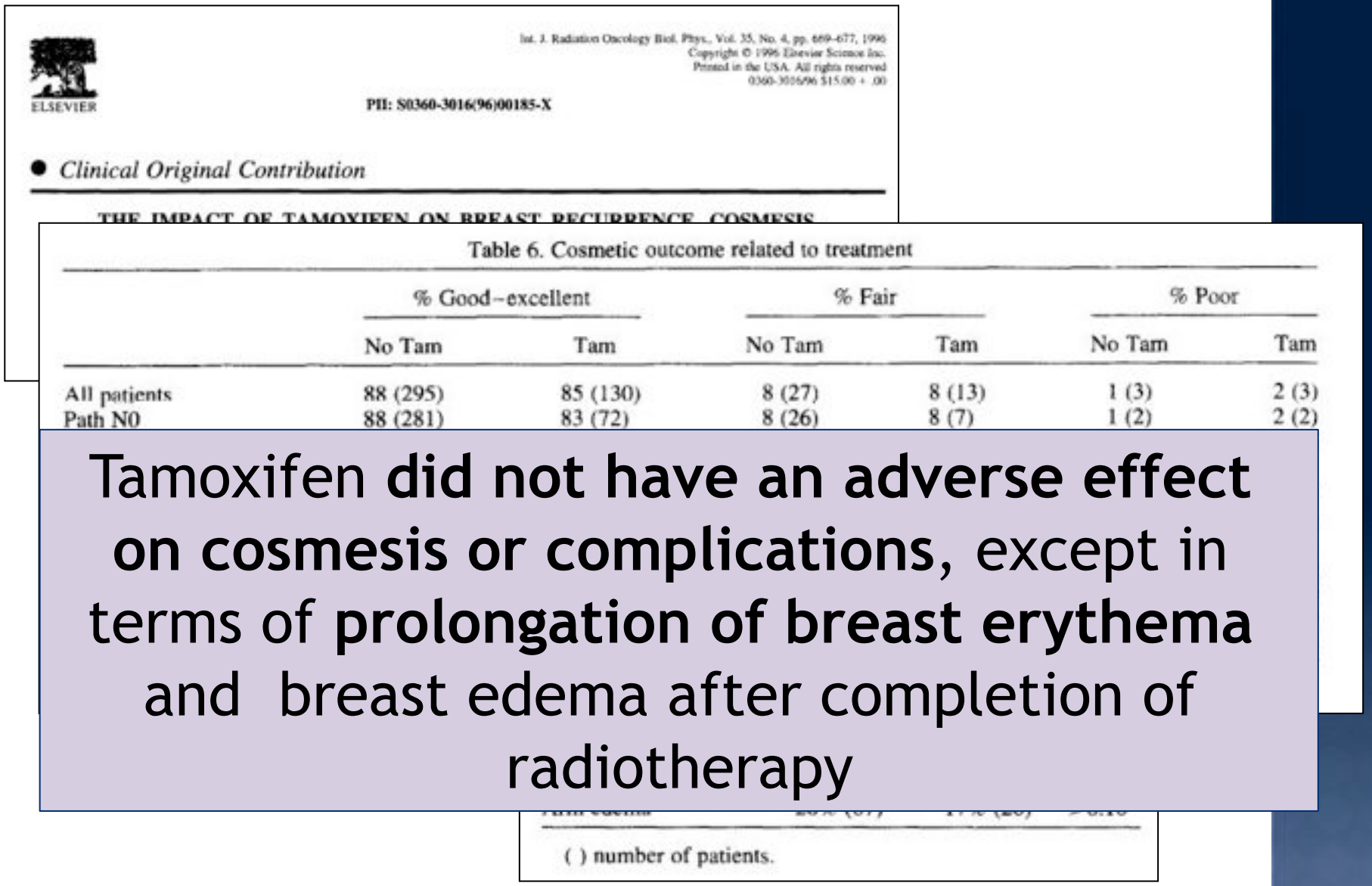
- **Significant association between tamoxifen and incidence of marked lung fibrosis (*P*=.01).**

- **Significant relationship between incidence of lung fibrosis and total radiation dose (*P*=.0005).**

- **Increased risk of marked lung fibrosis for patients CONCOMITANT RT-TAM (*P*=.007).**

- **Patient age and menopausal status did not significantly influence the results.**

TOXICITY



Int. J. Radiation Oncology Biol. Phys., Vol. 35, No. 4, pp. 669–677, 1996
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PII: S0360-3016(96)00185-X

● *Clinical Original Contribution*

THE IMPACT OF TAMOXIFEN ON BREAST RECURRENCE, COSMESIS

Table 6. Cosmetic outcome related to treatment

	% Good–excellent		% Fair		% Poor	
	No Tam	Tam	No Tam	Tam	No Tam	Tam
All patients	88 (295)	85 (130)	8 (27)	8 (13)	1 (3)	2 (3)
Path N0	88 (281)	83 (72)	8 (26)	8 (7)	1 (2)	2 (2)

( ) number of patients.

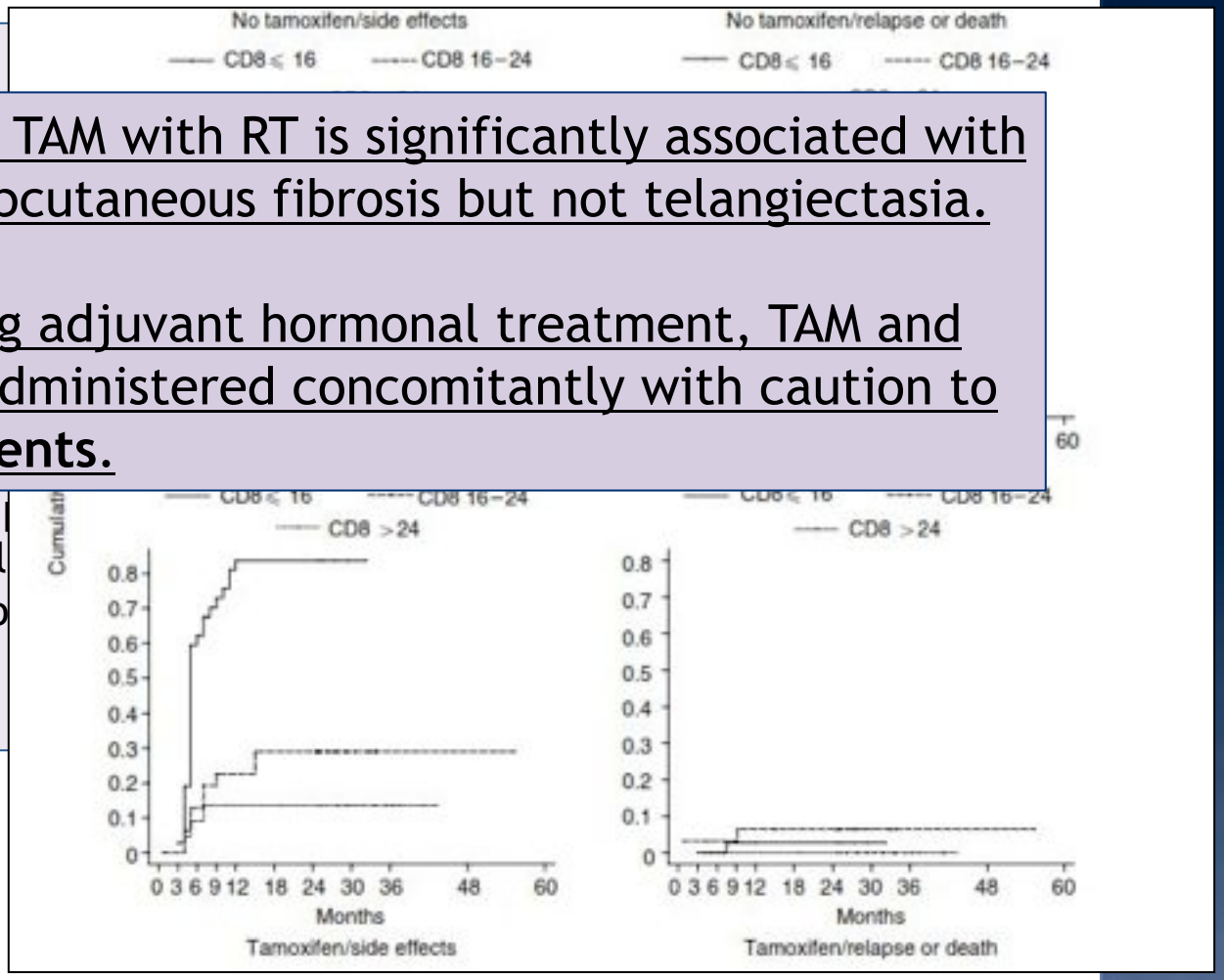
Tamoxifen **did not have an adverse effect on cosmesis or complications**, except in terms of **prolongation of breast erythema** and breast edema after completion of radiotherapy

TOXICITY

Azria et al, Br J of Cancer, 2004

Concomitant use of tamoxifen with radiotherapy enhances subcutaneous breast fibrosis in hypersensitive patients

- 56 pts SEQ RT-TAM



Concomitant use of TAM with RT is significantly associated with the incidence of subcutaneous fibrosis but not telangiectasia.

In patients receiving adjuvant hormonal treatment, TAM and RT should only be administered concomitantly with caution to **radiosensitive patients.**

well as in the group of
considered as potential
radiosensitive (CD8 apo

TOXICITY

Harris et al, JCO 2005

- 104 pts SEQ RT-TAM
- 174 pts CONC RT-TAM
- Median F-up 8.6 years

Table 3. Complications and Cosmesis According to Tamoxifen Sequence

Variable	Concurrent Tamoxifen		Sequential Tamoxifen		P
	No. of Patients	%	No. of Patients	%	
Breast edema, grade					
0-2	162	95	98	95	.96
3-4	8	5	5	5	
Arm edema, grade					
0-2	168	98	101	97	.53
3-4	3	2	3	3	
Rib fracture					
Absent	174	100	103	99	.31
Present	0		1	1	
Pneumonitis					
Absent	172	99	104	100	.53
Present	2	1	0		
Cosmesis at 3 years					
Excellent or good	122	95	76	95	.92
Fair	6	5	4	5	
Cosmesis at 5 years					
Excellent or Good	87	94	51	94	.83
Fair	6	6	3	6	

COMBINING AROMATASE INHIBITORS WITH RADIOTHERAPY

PRECLINICAL DATA – IN VITRO EXPERIENCES

Aromatase inhibitors **block conversion of androgens to oestrogens**, by **inhibition of aromatase enzyme** function, leading to suppressed oestrogen synthesis.

Compared with radiotherapy alone, combined radiotherapy and letrozole produced a **significant decrease in radiation-induced G2 phase** arrest and in the number of cells in the S phase, with cell redistribution in the G1 phase.

Azria, Cancer Radiotherapie 2004
Azria, Breast Cancer Research 2005

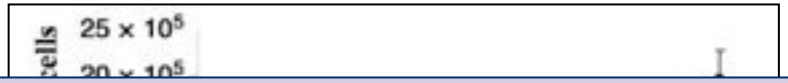
PRECLINICAL DATA – IN VITRO EXPERIENCES

Research article

Open Access

Letrozole sensitizes breast cancer cells to ionizing radiation

David Azria[1], Christel Larbouret[2], Severine Cunat[3], Mahmut Ozsahin[4], Sophie Gourgou[5], Pierre Martineau[6], Dean B Evans[7], Gilles Romieu[8], Pascal Pujol[3] and Andre Pèlegrin[2]



Treatment with letrozole results in a steeper **decline in cell survival** due both to a higher initial slope of the dose-response curve and to a major decrease of the quadratic parameter.

These results thus show possible **additive effects** for the **combined** treatment.

CLINICAL EXPERIENCE

Lancet Oncol, 2010

Concurrent or sequential adjuvant letrozole and radiotherapy after conservative surgery for early-stage breast cancer (CO-HO-RT): a phase 2 randomised trial

David Azria, Yazid Belkacemi, Gilles Romieu, Sophie Gourgou, Marian Gutowski, Khalil Zaman, Carmen Llacer Moscardo, Claire Lemanski, Michael Coelho, Barry Rosenstein, Pascal Fenoglietto, Nigel E A Crompton, Mahmut Ozsahin

Letrozole can be **safely** delivered shortly after surgery and **concomitantly** with radiotherapy.

Long-term follow-up is needed to investigate **cardiac side-effects** and cancer-specifc outcomes.

CONCLUSIONS

The **antagonistic** interaction of **tamoxifen** and **XRT** which was observed in several in vitro studies has not been confirmed in clinical or in animal studies.

Possibly the experimental endpoints of the in vitro systems have not been relevant for the in vivo situation, since important determinants of radiation-induced tumor control, such as **repopulation**, cannot be assessed in vitro.

The **mechanisms** of **interaction** between **hormones** and anti-hormones with **radiation-induced DNA damage** might be more complex in tumor cells compared with normal tissues.

CONCLUSIONS

Available clinical studies do not indicate that simultaneous application of tamoxifen and RT is **disadvantageous**.

The **tolerance of lung tissue to RT** might be slightly reduced if tamoxifen is given simultaneously; the duration of breast **edema** might be augmented.

Cosmetic results have not been impaired by a combined treatment with tamoxifen.

Randomised study are investigating the importance of combining hormonal therapy to adjuvant chemotherapy *(i.e. GIM 10)*.

Whenever indicated, **both treatment modalities should be started early after surgery.**

Acknowledgments

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