XVII CONVEGNO REGIONALE
AIRO Piemonte-Valle d'Aosta

(Presidente: dr. E. Russi)

PROBLEMATICHE EMERGENTI NEI TRATTAMENTI INTEGRATI

PROBLEMATICHE EMERGENTI NELL'IRRADIAZIONE MAMMARIA ASSOCIATA A TRATTAMENTI SISTEMICI

P. Rovea

Radioterapia 2

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Asti, 18 ottobre 2008

1) RT e nuovi regimi CHT: TIMING?

- Durata CHT, ritardo inizio RT e rischio di incremento riprese locali
- Trattamenti sistemici: impatto su recidiva locale inferiore rispetto a RT

Sequenza ottimale: sempre CHT → RT?

2) RT e I. Aromatasi: TIMING?

- TAM e RT: qualche rischio per i trattamenti concomitanti?
  (in studi in vitro: arresto delle cellule in G0-G1, relativamente rxresistenti)

Analogo rischio per Inibitori Aromatasi + RT concomitante?

3) Trattam. sistemici + RT: TOX POLMONARE?

- RT mammaria – ascella – sovraclaveare:
  - Tox polmonare lieve (polmonite e fibrosi G1 30-40%; G2 <3-4%)
  - Correlazione statistic. significativa del danno con:
    - età > 60 aa (NTCP del 50%: 40 Gy vs 27)
    - MLD, D25%, V20, frazionamento, volumi
    - CHT

- Terapie sistemiche:
  - Taxani e trastuzumab + RT: possibile effetto rxsensibilizzante (polmoniti 8%)

4) RT-CHT: ulteriore incremento rischio II tumori?

- Risultati di recenti reviews su pz affette da ca. mammario trattate fino al 2002:
  - Rischio II tumori -esclusa mamm controlat- modestamente incrementato (SIR 1.04-1.25)
  - Lieve aumento rischio per T in sedi correlate RT e CHT (SIR 1.34-2,19), cioè: rischio > in paz trattate RT e CHT (>> età giovane) rispetto alle non trattate
  - A 20 e 30 aa il rischio tende a incrementarsi leggermente
  - Altri II tumori (retto, LNH) sono invece incrementati >> in paz non RT e CHT trattate

Number of second primary cancers with standardized incidence ratios among 1-year survivors of breast cancer in Denmark 1977–2001 specified for second cancer site and for administered postoperative adjuvant radiotherapy, tamoxifen and chemotherapy.

	Radiotherapy						Tamoxifen						Chemotherapy					
	yes			no			yes			no			yes			no		
	N[1]	SIR[2]	(95% CI)[3]	N	SIR	(95% CI)	N	SIR	(95% CI)	N	SIR	(95% CI)	N	SIR	(95% CI)	N	SIR	(95% CI)
Lip	2	1.6	(0.0–3.9)	1	0.3	(0.0–1.0)	0	0.0	(0.0–0.0)	3	1.0	(0.0–2.0)	1	1.9	(0.0–5.6)	2	0.6	(0.0–1.3)
Tongue	1	0.5	(0.0–1.6)	7	1.6	(0.4–2.8)	3	2.2	(0.0–4.6)	5	1.0	(0.1–1.9)	2	2.1	(0.0–4.9)	6	1.1	(0.2–2.1)
Salivary glands	1	0.9	(0.0–2.6)	1	0.4	(0.0–1.1)	0	0.0	(0.0–0.0)	2	0.7	(0.0–1.6)	0	0.0	(0.0–0.0)	2	0.6	(0.0–1.5)
Mouth	4	1.0	(0.0–2.0)	18	1.9	(1.0–2.8)	6	2.0	(0.4–3.5)	16	1.6	(0.8–2.3)	4	2.1	(0.0–4.1)	18	1.6	(0.8–2.3)
Pharynx	7	2.0	(0.5–3.6)	7	0.9	(0.2–1.6)	2	0.8	(0.0–2.0)	12	1.4	(0.6–2.2)	2	1.0	(0.0–2.4)	12	1.3	(0.6–2.1)
Oesophagus	9	1.6	(0.6–2.7)	11	0.8	(0.3–1.3)	4	0.9	(0.0–1.7)	16	1.1	(0.6–1.6)	6	2.5	(0.5–4.5)	14	0.8	(0.4–1.3)*
Stomach	19	1.4	(0.8–2.0)	38	1.2	(0.8–1.6)	19	1.8	(1.0–2.6)	38	1.1	(0.8–1.5)	12	2.4	(1.0–3.8)	45	1.1	(0.8–1.4)*
Small intestine	0	0.0	(0.0–0.0)	5	1.2	(0.2–2.3)	1	0.7	(0.0–2.2)	4	0.9	(0.0–1.8)	2	2.8	(0.0–6.6)	3	0.6	(0.0–1.3)
Colon	85	1.3	(1.0–1.6)	148	0.9	(0.8–1.1)*[4]	53	1.0	(0.7–1.2)	180	1.1	(0.9–1.2)	25	1.0	(0.6–1.4)	208	1.0	(0.9–1.2)
Rectum	39	1.0	(0.7–1.4)	105	1.2	(1.0–1.4)	30	1.0	(0.6–1.4)	114	1.2	(1.0–1.4)	22	1.4	(0.8–2.0)	122	1.1	(0.9–1.3)
Liver	1	0.2	(0.0–0.5)	5	0.3	(0.0–0.6)	0	0.0	(0.0–0.0)	6	0.4	(0.1–0.7)	0	0.0	(0.0–0.0)	6	0.3	(0.1–0.6)
Gallbladder	4	0.6	(0.0–1.1)	17	1.0	(0.5–1.5)	5	0.8	(0.1–1.6)	16	0.9	(0.5–1.3)	2	0.9	(0.0–2.1)	19	0.9	(0.5–1.3)
Pancreas	24	1.1	(0.6–1.5)	58	1.1	(0.8–1.4)	17	0.9	(0.5–1.3)	65	1.1	(0.9–1.4)	10	1.2	(0.4–1.9)	72	1.1	(0.8–1.3)
Nose, sinuses	0	0.0	(0.0–0.0)	2	0.5	(0.0–1.3)	0	0.0	(0.0–0.0)	2	0.5	(0.0–1.2)	0	0.0	(0.0–0.0)	2	0.4	(0.0–1.1)
Larynx	6	1.8	(0.4–3.3)	4	0.5	(0.0–1.1)	2	0.8	(0.0–2.0)	8	1.0	(0.3–1.6)	3	1.7	(0.0–3.6)	7	0.8	(0.2–1.4)
Lung	110	1.2	(1.0–1.4)	213	0.9	(0.8–1.1)	63	0.8	(0.6–1.0)	260	1.1	(0.9–1.2)*	54	1.2	(0.9–1.5)	269	1.0	(0.9–1.1)
Pleura	2	1.9	(0.0–4.6)	3	1.2	(0.0–2.6)	0	0.0	(0.0–0.0)	5	1.9	(0.2–3.5)	2	4.7	(0.0–11.3)	3	1.0	(0.0–2.1)
Cervix uteri	23	1.0	(0.6–1.4)	27	0.6	(0.3–0.8)	12	0.8	(0.4–1.3)	38	0.7	(0.4–0.9)	15	1.0	(0.5–1.6)	35	0.6	(0.4–0.8)
Corpus uteri	55	1.2	(0.9–1.6)	128	1.2	(1.0–1.4)	65	1.8	(1.4–2.3)	118	1.0	(0.9–1.2)*	23	1.1	(0.6–1.5)	160	1.3	(1.1–1.4)
Uterus, other	4	2.0	(0.0–3.9)	5	1.1	(0.1–2.0)	4	2.6	(0.1–5.2)	5	1.0	(0.1–1.8)	0	0.0	(0.0–0.0)	9	1.6	(0.5–2.6)
Ovary, uterine adnexa	65	1.6	(1.2–2.0)	116	1.3	(1.1–1.5)	27	0.9	(0.6–1.3)	154	1.5	(1.3–1.8)*	45	2.2	(1.5–2.8)	135	1.2	(1.0–1.5)*
Other female genital org	9	1.3	(0.4–2.1)	16	1.0	(0.5–1.5)	2	0.4	(0.0–0.9)	23	1.3	(0.8–1.9)*	3	1.1	(0.0–2.2)	22	1.1	(0.6–1.6)
Kidney	18	1.3	(0.7–1.9)	26	0.8	(0.5–1.1)	14	1.2	(0.6–1.9)	30	0.8	(0.5–1.2)	7	1.2	(0.3–2.1)	37	0.9	(0.6–1.2)
Bladder etc.	37	1.2	(0.8–1.6)	72	1.0	(0.8–1.2)	25	1.0	(0.6–1.4)	84	1.1	(0.9–1.3)	23	1.8	(1.1–2.6)	86	1.0	(0.8–1.2)*
Melanoma of skin	24	1.0	(0.6–1.3)	52	1.0	(0.7–1.2)	20	1.3	(0.7–1.8)	56	0.9	(0.7–1.1)	5	0.4	(0.1–0.7)	70	1.1	(0.9–1.4)*
Eye	2	1.0	(0.0–2.5)	6	1.4	(0.3–2.5)	1	0.7	(0.0–2.1)	7	1.4	(0.4–2.5)	1	1.0	(0.0–2.9)	7	1.3	(0.3–2.3)
Brain, nervous system	25	1.0	(0.6–1.4)	44	0.8	(0.6–1.0)	16	0.9	(0.5–1.4)	53	0.8	(0.6–1.1)	7	0.5	(0.1–0.9)	62	0.9	(0.7–1.2)
Thyroid	5	1.2	(0.2–2.3)	6	0.7	(0.1–1.3)	0	0.0	(0.0–0.0)	11	1.1	(0.4–1.7)	4	1.7	(0.0–3.3)	7	0.7	(0.2–1.2)
Bone	1	1.3	(0.0–3.9)	1	0.6	(0.0–1.8)	0	0.0	(0.0–0.0)	2	1.1	(0.0–2.5)	1	2.4	(0.0–7.2)	1	0.5	(0.0–1.5)
Soft tissues	12	3.9	(1.7–6.0)	11	1.5	(0.6–2.5)*	7	3.0	(0.8–5.2)	16	2.0	(1.0–3.0)	5	3.9	(0.8–7.0)	17	2.0	(1.0–2.9)
Non-Hodgkins lymphoma	17	0.9	(0.5–1.3)	59	1.3	(1.0–1.6)	15	1.0	(0.5–1.5)	61	1.2	(0.9–1.5)	8	0.8	(0.3–1.4)	68	1.2	(0.9–1.5)
Hodgkins disease	2	1.3	(0.0–3.1)	3	0.9	(0.0–1.9)	0	0.0	(0.0–0.0)	5	1.3	(0.2–2.5)	1	1.2	(0.0–3.5)	4	1.0	(0.0–2.0)
Multiple myeloma	1	0.1	(0.0–0.4)	25	1.3	(0.8–1.8)*	3	0.4	(0.0–1.0)	23	1.1	(0.7–1.6)	2	0.6	(0.0–1.5)	24	1.0	(0.6–1.4)
Acute leukaemia	15	2.4	(1.2–3.6)	27	1.9	(1.2–2.6)	9	1.8	(0.6–3.1)	33	2.1	(1.4–2.8)	9	3.2	(1.1–5.3)	33	1.8	(1.2–2.5)
Other leukaemia	8	0.8	(0.3–1.4)	26	1.1	(0.7–1.5)	12	1.5	(0.6–2.3)	22	0.9	(0.5–1.2)	7	1.8	(0.5–3.2)	27	0.9	(0.6–1.3)
RT-related sites[5]	174	1.3	(1.1–1.6)	311	1.0	(0.9–1.1)*	102	1.0	(0.8–1.2)	383	1.2	(1.0–1.3)	94	1.5	(1.2–1.8)	391	1.0	(0.9–1.1)*
All sites	661	1.2	(1.1–1.2)	1332	1.0	(0.9–1.0)*	454	1.0	(0.9–1.1)	1,539	1.0	(1.0–1.1)	329	1.2	(1.1–1.4)	1664	1.0	(1.0–1.1)*

1. Observed number.
2. Standardised incidence ratio.
3. 95% confidence interval.
4. * significant test for heterogeneity.
5. Salivary glands, oesophagus, stomach, lung, pleura, thyroid, bone, soft tissue and acute leukaemia.

[redacted] Risk of second primary cancer of lung, corpus uteri and ovary in 5-year survivors of breast cancer in Denmark 1977–2001 in relation to time since diagnosis of breast cancer, age at diagnosis and adjuvant treatment. The adjusted relative risk is normalized to the category with most observations and given with 95% confidence intervals.

	Lung	Corpus uteri	Ovary
	p <0.01	p =0.30	p =0.14
Time since diagnosis, years			
5–9	1	1	1
10–14	1.47 (1.08–2.00)	0.74 (0.48–1.13)	0.76 (0.48–1.19)
15–19	1.53 (1.04–2.24)	0.75 (0.41–1.37)	0.55 (0.28–1.08)
20–25	2.99 (1.83–4.90)		
	p =0.33	p =0.84	p <0.01
Age at diagnosis			
<50	1.29 (0.91–1.82)	1.15 (0.68–1.96)	1.62 (1.02–2.57)
50–59	1	1	1
60–69	1.07 (0.77–1.48)	0.93 (0.60–1.43)	0.48 (0.26–0.87)
70–79	0.70 (0.32–1.54)	1.19 (0.57–2.46)	0.30 (0.07–1.26)
	p =0.05	p =0.78	p =0.23
Radiotherapy			
Yes	1.33 (1.00–1.77)	0.94 (0.63–1.41)	1.31 (0.85–2.01)
No	1	1	1
	p =0.57	p =0.04	p =0.43
Tamoxifen			
Yes	0.90 (0.63–1.29)	1.57 (1.02–2.40)	0.78 (0.41–1.47)
No	1	1	1
	p =0.58	p =0.57	p =0.33
Chemotherapy			
Yes	1.11 (0.77–1.58)	0.85 (0.50–1.47)	1.28 (0.79–2.07)
No	1	1	1

4) RT-CHT: ulteriore incremento rischio II tumori?

Dato il sempre > utilizzo di CHT e RT,

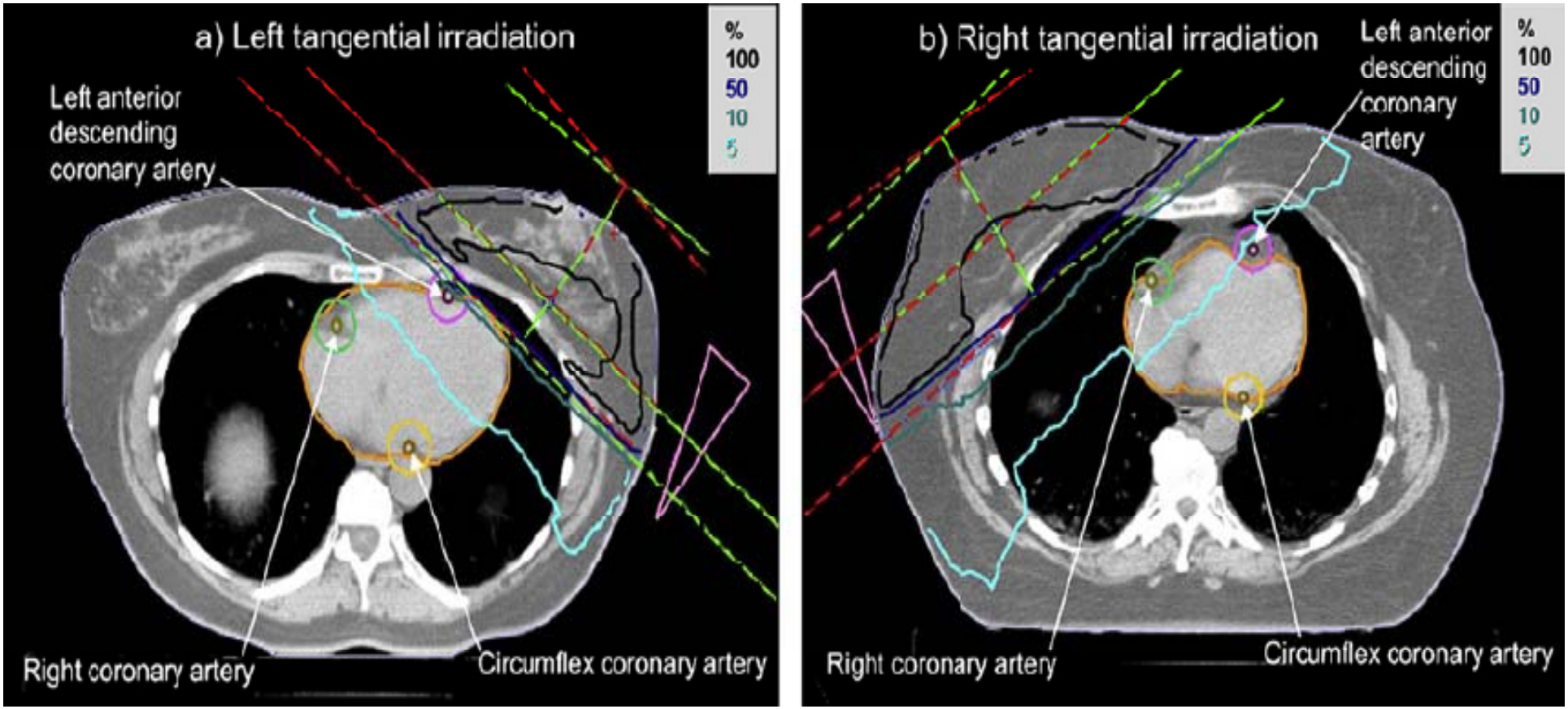
massima attenzione:

- alle indicazioni CHT e RT (soprattutto in paz giovani con T a basso rischio)
- tecnica RT (massimo risparmio dei tessuti circostanti, >> polmonari)

5) TOX CARDIACA DA TRATTAM SISTEMICI + RT

a) RISCHIO CARDIACO da **RT MAMMARIA**

- Standard attuali:
  - Ampia quota di paz riceve >50% dose prescritta al 10-20% vol cardiaco
  - Circa 50% delle paz con RT a sn riceve dose =/> 20Gy a piccola parte di vol. cardiaco anter. (LAD)
  - Curva dose-risposta x danno cardiaco ripida oltre 30-40 Gy
  - Dosi medie al cuore e coronarie:



Mean and maximum doses to the heart and three main coronary arteries from tangential pair radiotherapy

	Heart	LAD coronary artery	Right coronary artery	Circumflex coronary artery
Average mean dose (SD)* (Gy)				
Left-sided irradiation	2.3 (0.7)†	7.6 (4.5)†	2.0 (0.3)	1.8 (0.3)
Right-sided irradiation	1.5 (0.2)	1.6 (0.2)	2.0 (0.3)	1.2 (0.1)
Average maximum dose (SD)* (Gy)				
Left-sided irradiation	30.7 (10.8)†	35.2 (8.8)†	2.5 (0.3)	2.4 (0.4)
Right-sided irradiation	2.6 (0.3)	1.9 (0.2)	2.5 (0.4)	1.5 (0.2)

Abbreviation: LAD = left anterior descending.

* The mean or maximum organ dose averaged over all patients (50 or 5) for whom the assessment was carried out.

† These values were based on 50 patients, whereas all others were based on 5 patients.

5) TOX CARDIACA DA TRATTAM SISTEMICI + RT

a) RISCHIO CARDIACO da **RT MAMMARIA**

- Meccanismi di danno:
  - Micro- e macrovascolare
  - → lesione miocardica (disfunzione >> diastolica; aritmie)
  - → lesione coronarica (peggiorata dall'iperlipemia)
  - → lesione pericardica e valvolare
- Clinica (f up minimo: 10 aa):
  - malattia coronarica (IMA silente)
  - cardiomiopatia (favorita da precedenti terapie cardiotox) → insuff card congestizia e disturbi conduzione

5) TOX CARDIACA DA TRATTAM SISTEMICI + RT

a) RISCHIO CARDIACO da RT MAMMARIA

- Fattori di rischio:
  - Volume cardiaco irradiato, dosi, frazionam
  - Tradizionali fattori di rischio (fumo, obesità, ipertens…)
  - Uso di TAM (TGF beta), antracicline, altri CHT, trastuzumab
- Epidemiologia:
  - Spartiacque: metà aa '80 (la % media del vol cardiaco che riceve 5 Gy BED passa da 87% a 41% dopo 1985)

Studies assessing cardiovascular morbidity and mortality of breast cancer radiotherapy

Study	*N*	Years of treatment	Follow-up	Type of study	Type of comparison	Irradiated volume/ treatment setting	Beam quality/ radiotherapy technique	Outcome
Cuzick et al.[6]	7941	1949–1979	>12 years	Metaanalysis (RCT, ID)	RT vs. no RT	Postmastectomy	Various	↑ Cardiac mortality
Clarke et al.[61]	51,300	Up to 1995	ND	Metaanalysis (RCT, ID)	RT vs. no RT	BCT and postmastectomy	Various	↑ Cardiac mortality
Jones and Ribeiro[60]	1461	1949–1955	34 years	RCT	RT vs. no RT	Postmastectomy	Orthovoltage	↑ Overall mortality (attributed mostly to cardiovascular disease)
Host et al.[58]	1115	1964–1972	11–20 years	RCT	RT vs. no RT	Postmastectomy	Orthovoltage or ^{60}Co/ direct fields including IMN	↑ MI deaths in stage I patients treated with ^{60}Co
Nixon et al.[14]	745	1968–1986	⩾12 years	Institutional	L vs. R	BCT	Megavoltage photons, tangential/wide tangents	NS (cardiac mortality)
Haybittle et al.[59]	2800	1970–1975	158–216 months	RCT	RT vs. no RT	Postmastectomy	Orthovoltage or megavoltage	↑ Cardiac mortality (most pronounced in L-sided tumours treated with orthovoltage)
Hooning et al.[25]	6490	1970–1986	Median 13.8 years	Bi-institutional	RT vs. no RT	BCT and postmastectomy	Various	Postmastectomy: ↑ CV deaths BCT: NS
Darby et al.[18]	89,407	1970–1996	ND	Population-based (Swedish Cancer Registry)	L vs. R	BCT and postmastectomy	ND (unknown percentage of irradiated patients)	↑ Cardiac mortality >10 years after RT
Rutqvist et al.[35]	960	1971–1976	Median 16 years	RCT	RT vs. no RT	Pre- or postmastectomy	Preoperative: tangential ^{60}Co, postoperative: electrons	↑ Cardiac mortality in patients treated with ^{60}Co to L breast
Giordano et al.[11]	27,283	1973–1989	Median 111 months	Population-based (SEER)	L vs. R	BCT and postmastectomy	ND	↑ Cardiac mortality for women treated in 1973–1979 NS for years 1980–1984 and 1985–1989
Darby et al.[17]	115,165	1973–2001	ND	Population-based (SEER)	L vs. R	BCT and postmastectomy	ND	↑ Cardiac mortality >10 years after RT
Fisher et al.[73]	1851	1976–1984	Median >20 years	RCT	RT vs. no RT	BCT	Megavoltage photons/ tangential	NS ↑ Non-breast cancer deaths (HR 1.23)
Rutqvist et al.[13]	684	1976–1987	Median 9 years	Institutional	RT vs. no RT	BCT	Megavoltage photons tangential	NS (MI morbidity and mortality)
Harris et al.[74]	961	1977–1994	Median 12 years	Institutional	L vs. R	BCT	Megavoltage photons/ tangential	OS – NS (3.5% vs. 2%) ↑ CAD and MI ↑ Cardiac deaths in 2nd decade
Paszat et al.[16]	3006	1982–1987	Median 106 months	Population-based (Ontario Cancer Registry)	L vs. R	BCT	Not stated	↑ Risk of fatal MI
Vallis et al.[9]	2128	1982–1988	Median 10.2 years	Institutional	L vs. R	BCT	Megavoltage photons/ tangential	NS (cardiac morbidity and mortality)
Hojris et al.[8]	3083	1982–1990	Median 10 years	RCT	RT vs. no RT	Postmastectomy	Electrons	NS (cardiac morbidity and mortality)
Patt et al.[12]	16,270	1986–1993	Median 9.5 years	Population-based (SEER)	L vs. R	BCT and postmastectomy	ND	NS (cardiac morbidity)

Abbreviations: BCT, breast conserving therapy; CAD, coronary artery disease; CV, cardiovascular; EBCTCG, Early Breast Cancer Trialists Cooperative Group; ID, individual data; IMN, internal mammary nodes; L, left; MI, myocardial infarction; *N*, number of patients; ND, no data; NS, non-significant difference; R, right; RCT, randomized controlled trials; RT, radiotherapy; SEER, Surveillance, Epidemiology and End-Results.

5) TOX CARDIACA DA TRATTAM SISTEMICI + RT

a) RISCHIO CARDIACO da **RT MAMMARIA**

Situazione attuale:

- SEER data-base: 2-10%, che aumenta col f up
- Recenti acquisizioni.
  - Possibile danno cardiaco da basse dosi (scattered dose: 1-3 Gy) da sostanze pro-infiammatorie→ aterosclerosi; immunità T-cell alterata; >instabilità genomica placca aterosclerotica.
  - Malattia cardiaca asintomatica.
  - Possibilità di complicanze vascol non cardiache (>> RT sovraclav, mamm interna): danno micro- e macrovasc (art sottoclav, ascell, carotide comune…) → rischio TIA, dolori, parestesie, faticabilità, Raynaud-like, cianosi, les cutanee ischemiche…

5) TOX CARDIACA DA TRATTAM SISTEMICI + RT

b) RISCHIO CARDIACO da

TRATTAMENTI SISTEMICI

Cancer-Drug Associated Cardiac Diseases 2007

Drug	Toxic dose range	Comments	Incidence
Chemotherapeutics			
Anthracyclines - Doxorubicin - Epirubicin	 >450 mg/m^2 (total dose) >720 mg/m^2	Congestive heart failure (CHF) cardiomyopathy, arrhythmias	 2-12% 4-15%
Paclitaxel	Conventional dose	Bradycardia, CHF in combination	
Cyclophosphamide	>100-120 mg/kg	CHF, hemorrhagic myocarditis/pericarditis	
5-Fluorouracil Capecitabine	Conventional dose	Angina/myocardial infarction	2-3%
Cisplatin	Conventional dose	Acute myocardial ischemia	5%
New cancer drugs			
Trastuzumab (Herceptin®)	Conventional dose	CHF, cardiomyopathy	3-28%
Lapatinib (Tykerb/Tycerb®)	Conventional dose	CHF, cardiomyopathy	2-4%
Imatinib (Gleevec®)	Conventional dose	CHF	5%
Bevacizumab (Avastin ®)	Conventional dose	HTN, thrombosis, cardiomyopathy	5-20%
Sunitinib (Sutent®)	Conventional dose	HTN, thrombosis, cardiomyopathy	10-30%
Sorafenib (Nexavar®)	Conventional dose	HTN, thrombosis, cardiomyopathy	3-17%

HTN = Hypertension

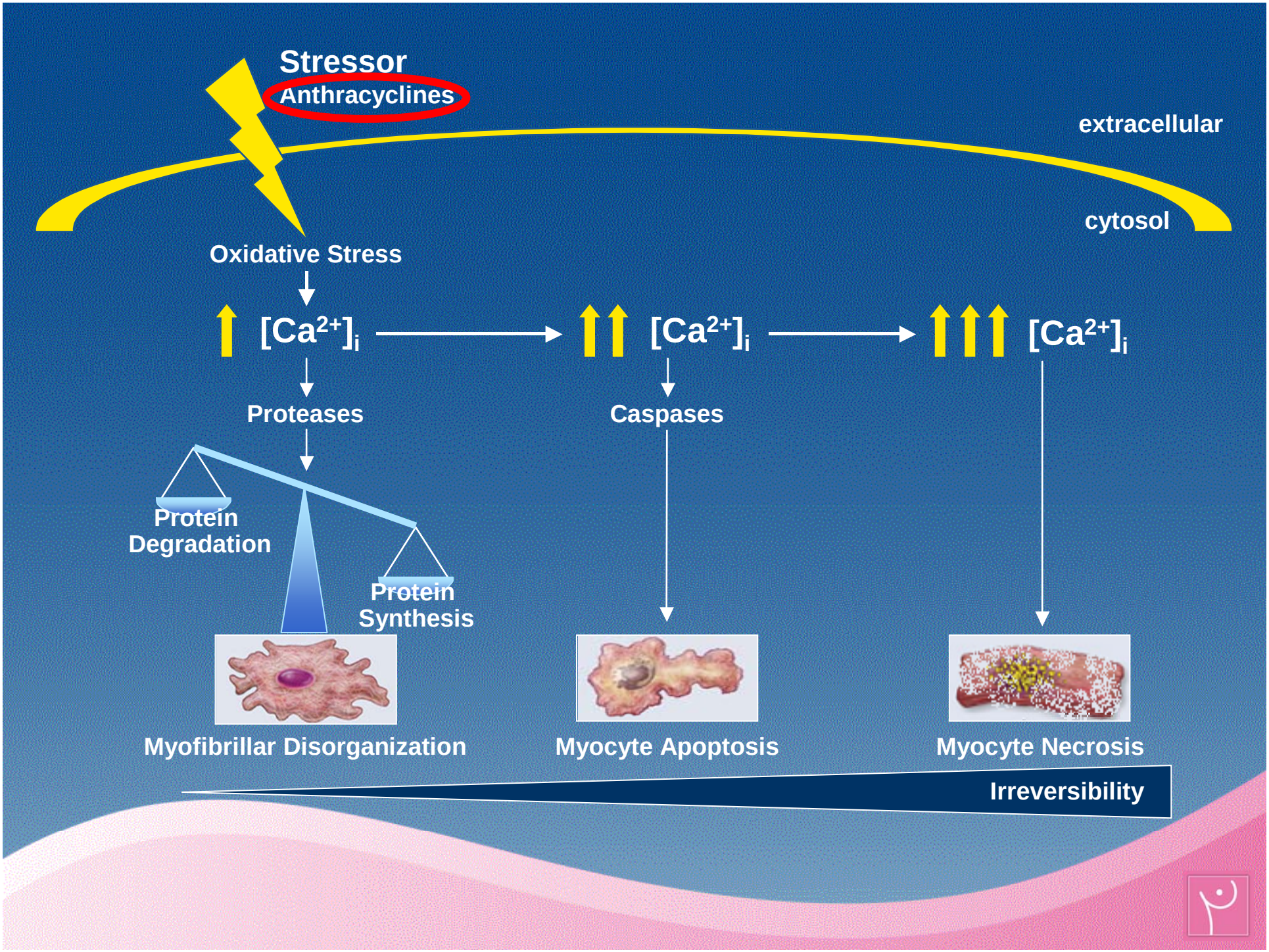
Jones LW et al. J Am Coll Cardiol. 2007;50:1435-1441
Zuppinger C et al. Cardiovasc Toxicol. 2007;7:61-66

5) TOX CARDIACA DA TRATTAM SISTEMICI + RT

b) RISCHIO CARDIACO da **ANTRACICLINE**

- Danno:
  - Alterazioni funzionalità cardiaca e scompenso 0-2% (2-4% se associaz Trastuzumab)
- Meccanismo:
  - Danno tipo I: "injury", stress ossidativi intracell, morte miociti (visibile biopsia) e danno a fibroblasti e cell endoteliali→ miocardite, pericardite, disfunz ventricolare >> sistolica

    → POSSIBILE SCOMPENSO

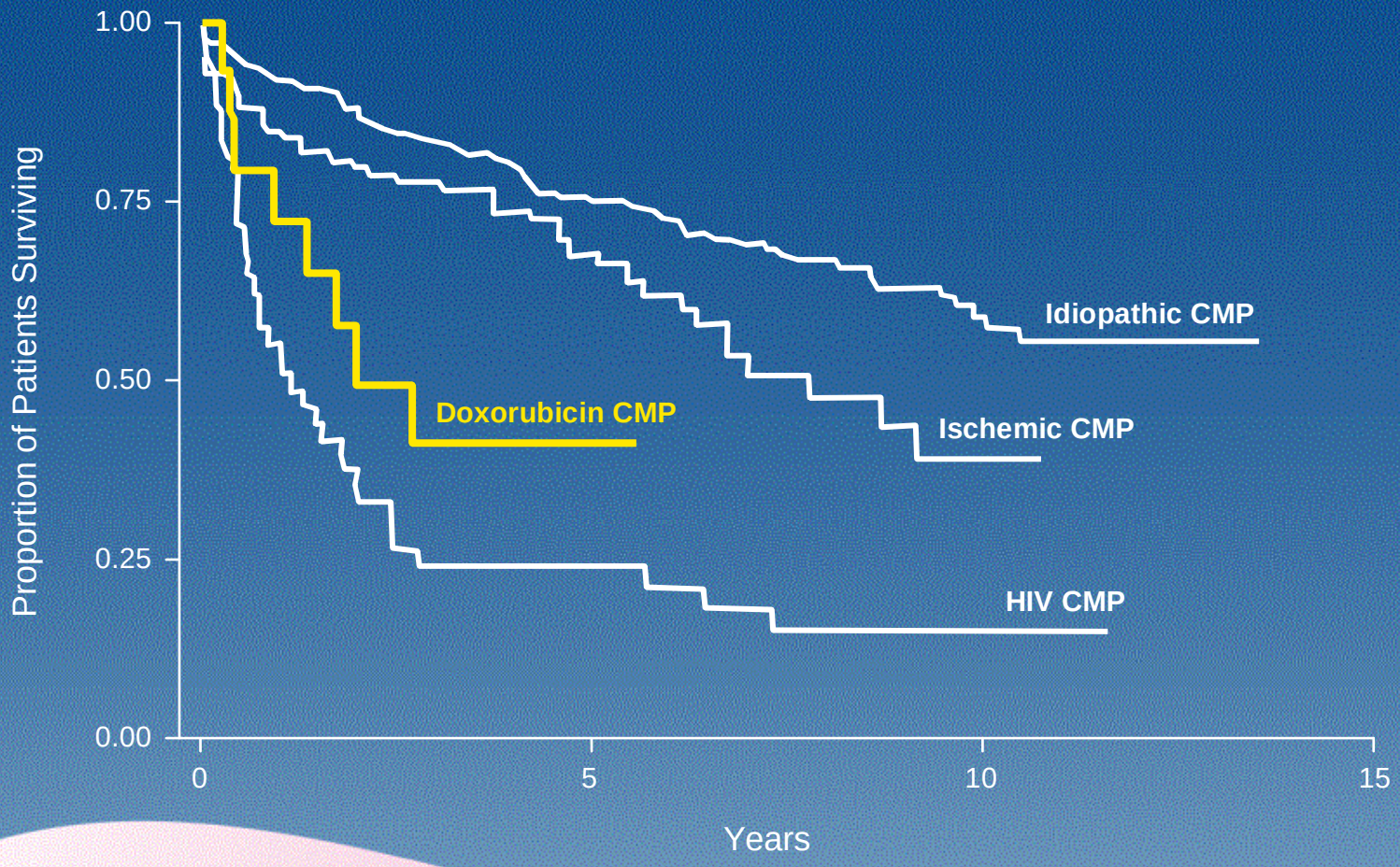

Stressor
Anthracyclines
extracellular
cytosol
Oxidative Stress
[Ca2+]i
[Ca2+]i
[Ca2+]i
Proteases
Caspases
Protein Degradation
Protein Synthesis
Myofibrillar Disorganization
Myocyte Apoptosis
Myocyte Necrosis
Irreversibility

5) TOX CARDIACA DA TRATTAM SISTEMICI + RT

b) RISCHIO CARDIACO da **ANTRACICLINE**

- Caratteristiche del danno:
  - Possibile latenza; spesso irreversibile, dose dipendente, incrementato da: **concomitanza CHT (Paclitaxel) o trastuzumab, RT sequenz o concomit**, patol cardiache e/o ipertensione preesistenti, età > 65-70 aa.
  - Prognosi peggiore rispetto a cardiomiopatie da altra causa

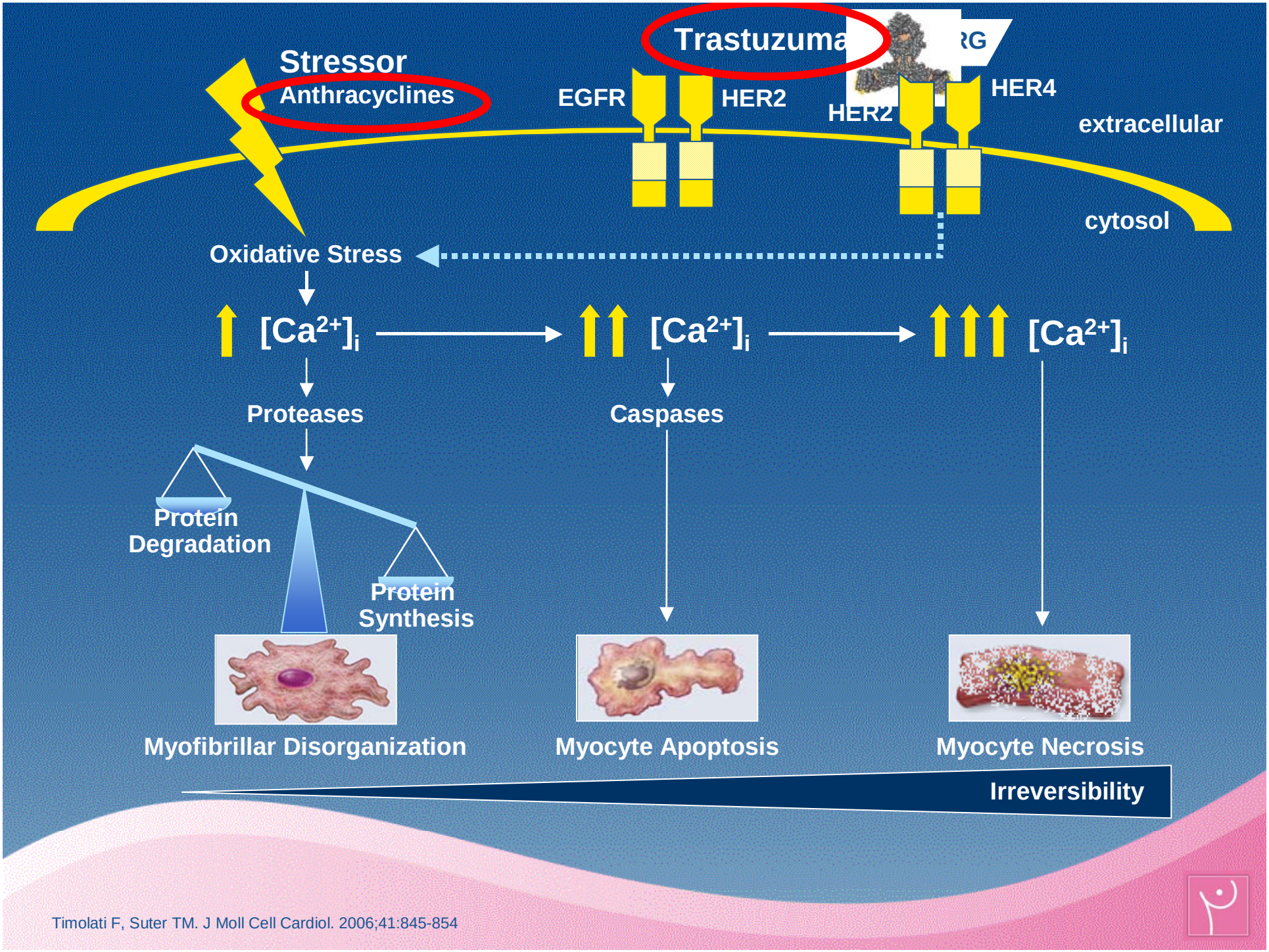
Anthracycline-Associated Heart Failure



5) TOX CARDIACA DA TRATTAM SISTEMICI + RT

c) RISCHIO CARDIACO da **TRASTUZUMAB**

- Meccanismo del danno:
  - (Esatto meccanismo: non chiaro). I recettori target sono espressi anche nel cuore; blocco sistema erb B2 (che modula anche la tox da antracicline)



Timolati F, Suter TM. J Moll Cell Cardiol. 2006;41:845-854

5) TOX CARDIACA DA TRATTAM SISTEMICI + RT

c) RISCHIO CARDIACO da **TRASTUZUMAB**

- Tipologia del danno:
  - Danno tipo II, "insult", disfunzione miocardica (senza necrosi miociti), senza alterazioni alla biopsia, non dose dipendente, reversibile

Treatment-Related Cardiac Dysfunction: Differentiation

	Type I (Myocardial damage)	Type II (Myocardial dysfunction)
Typical agent	Doxorubicin	Trastuzumab
Mechanism	Free radical formation, oxidative stress/damage	Blocked ErbB2 signaling
Cardiac tissue	Ultrastructural abnormalities (eg, vacuoles, necrosis)	No ultrastructural abnormalities
Clinical course/response to therapy	Underlying damage permanent and irreversible; may stabilize	Typically reversible; high likelihood of recovery in 2-4 mo
Dose effects	Cumulative, dose related	Not dose related

5) TOX CARDIACA DA TRATTAM SISTEMICI + RT

c) RISCHIO CARDIACO da **TRASTUZUMAB**

- Fattori di rischio:
  - Pregresso/concomitante uso antracicline (tox NYHA III – IV: 3-4%) per inibizione riparaz. danno cardiaco
  - Concomitante uso di paclitaxel (docetaxel: meno tox; effetto sinergico sul T)
  - Preesistente patologia cardiaca, obesità, iperlipemia, ipertensione, età > 50 aa
  - RT concomitante?

Trastuzumab Cardiotoxicity: Risk Factors

Anthracyclines Type I cardiotoxicity (myocardial damage)	**Trastuzumab** Type II cardiotoxicity (myocardial dysfunction)
Combination chemotherapy	Prior/concomitant anthracyclines
Prior/concomitant mediastinal radiotherapy	
Age >70	Age >50 years
Previous cardiac disease	Previous cardiac disease
Hypertension	Hyperlipidemia

5) TOX CARDIACA DA TRATTAM SISTEMICI + RT

c) RISCHIO CARDIACO da **TRASTUZUMAB**

- Incidenza del danno:
  - I linea: 0-5%; II – III linea: 8-10%; con antracicl concomitanti: 15-30% (III-IV NYHA). Valutazioni su paz non cardiopatici!
  - Non nota la tox a lungo termine; per ora il vantaggio su DFS e OS sembra > del rischio cardiaco.

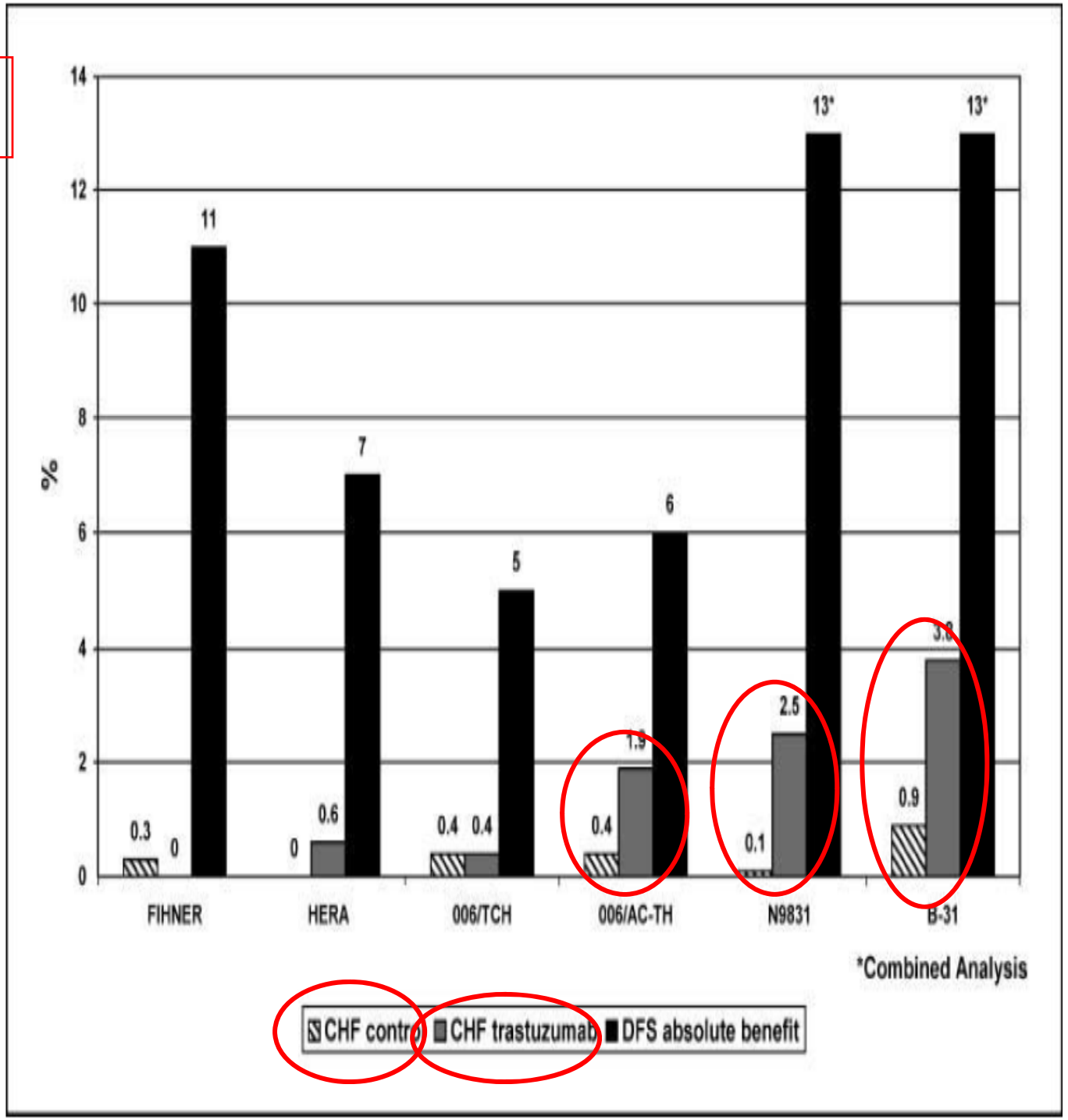
Table 7. Randomized Controlled Trials of Trastuzumab

Trial	Design/Treatment	No. of Patients	Median Follow-Up (months)	Key Findings
Metastatic				
Slamon[74]	Open-label	469		TTP, 7.4 *v* 4.6 months; $P < .001$; OS, 25 *v* 20; $P = .05$
	AC ± trastuzumab	281		TTP 7.8 *v* 6.1; $P < .001$; OS 27 *v* 21; $P = .16$; NYHA III, IV 16% *v* 3%
	Paclitaxel ± trastuzumab	188		TTP, 6.9 *v* 3.0; $P < .001$; OS, 22 *v* 18; $P = .17$; NYHA III, IV 2% *v* 1%
Adjuvant				
HERA[76]	Open-label	3,387	12	DFS HR, 0.54; 95% CI, 0.43 to 0.67; $P < .0001$
	Trastuzumab: 1 year *v* observation after adjuvant chemotherapy that included anthracyclines (94%); taxanes (26%); and radiation (76%)			Distant DFS HR, 0.49; 95% CI, 0.38 to 0.63; $P < .0001$
				OS HR, 0.76; 95% CI, 0.47 to 1.23; $P = .26$
				Symptomatic CHF 1.7% *v* 0.06%; $P < .001$
				NYHA III, IV CHF 0.5% *v* 0%, $P = .002$
Romond[75]	Open label	3,351	24	DFS HR, 0.48; 95% CI, 0.39 to 0.59; $P < .0001$; distant DFS HR, 0.47; 95% CI, 0.37 to 0.61; $P < .001$; OS HR, 0.67; 95% CI, 0.48 to 0.93; $P = .015$; NYHA III, IV: CHF, 4.1% *v* 0.8%; NSABPB B-31, 2.9% *v* N9831, 0%
	AC followed by paclitaxel ± trastuzumab (1 year)			
Slamon[77]	Open label	3,222	23	
	AC followed docetaxel ± trastuzumab (AC-DH) (1 year)			DFS AC plus docetaxel *v* AC-DH: HR, 0.49; $P = .00000005$; SCE, 1.2% *v* 2.3%; $P = .05$
	Docetaxel/carboplatin trastuzumab (DCH) (1 year)			DFS AC plus docetaxel *v* DCH: HR, 0.61; $P = .0002$; SCE, 1.2% *v* 1.2%; $P = 1.00$
Joensuu[79]	Open-label	232	36	DFS docetaxel or vinorelbine + trastuzumab HR, 0.42; 95% CI, 0.21 to 0.83; $P = .01$; OS HR, 0.41; 95% CI, 0.16 to 1.08; $P = .07$; SCE, 0% *v* 3%
	Docetaxel or vinorelbine ± trastuzumab (9 weeks) followed by FEC			

Abbreviations: AC, doxorubicin and cyclophosphamide; TTP, time to progression; OS, overall survival; NYHA III, IV, New York Heart Association; HERA, Herceptin Adjuvant Trial; DFS, disease-free survival; HR, hazard ratio; CHF, congestive heart failure; NSABP, National Surgical Breast and Bowel Project; SCE, symptomatic cardiac events; FEC, fluorouracil, epirubicin, and cyclophosphamide.

Chronic heart failure

Fig. 1. The incidence of CHF from the Finnish Herceptin Study (*FINHER*), Herceptin Adjuvant trial (*HERA*), Breast Cancer International Collaborative Group trial 006 (*006*) with TCH and AC-TH analyzed separately, the North Central Cancer Treatment Group trial 9831 (*N9831*), and NSABP B-31 (*B-31*). *CHF control*, percentage of the incidence of NYHA grades 3 and 4 CHF in the nontrastuzumab arm; *CHF-T*, percentage of the incidence of NYHA grades 3 and 4 CHF in trastuzumab arm; *DFS*, disease-free survival at the time of the last follow up. *FINHER*, 3 y (64); *HERA*, 2 y (69), *006*, 23 mo (70), *N9831*, 4 y (67), and *B-31*, 4 y (66).



5) TOX CARDIACA DA TRATTAM SISTEMICI + RT

c) RISCHIO CARDIACO da **TRASTUZUMAB**

- Integrazione con RT:
  - Concomitante? Sequenziale? Dati attuali non sufficienti.
  - Utilizzo immediato (concomitante) è migliore.
  - Radiosensibilizzante sulle cell HER2+? Rischio tox cutanea, esofagea, polmonare (→polmoniti!), cardiaca >> se RT mamm interna e (??) se RT mamm sn.

5) TOX CARDIACA DA TRATTAM SISTEMICI + RT

d) RISCHIO CARDIACO da **TAXANI**

- Paclitaxel: bradicardia asintomatica e/o ipotensione (30%); aritmie, IMA, tachicardie ventricol 0.1-05%; potenzia cardiotox da antracicline e trastuzumab
- Nuove formulazioni: < impatto sul danno da antracicline

5) TOX CARDIACA DA TRATTAM SISTEMICI + RT

e) RISCHIO CARDIACO da **INIBITORI AROMATASICI**

- Studi TAM vs I.A.: trend (ai limiti della significatività) per impatto negativo cardiaco.
  - Per riduzione estradiolo circolante?
  - Alterazioni metabolismo lipidico?
  - Cardioprotezione da TAM?

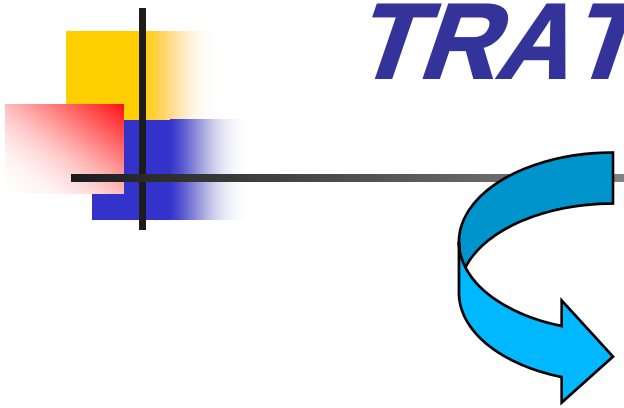
5) TOX CARDIACA DA TRATTAM SISTEMICI + RT

f) RISCHIO CARDIACO da **NUOVI FARMACI**

- Bevacizumab:
  - incremento eventi cardiaci (> 2-3%); peggiora cardiotox da antracicline
- Lapatinib:
  - Disfunzione contrattile, peggiora cardiotox da CHT (forse meno del trastuzumab)

→Interferenza con i meccanismi di salvataggio del cuore già danneggiato da altri farmaci. Poco f up. Necessità di studi.

5) TOX CARDIACA DA TRATTAM SISTEMICI + RT



CONCLUSIONI

- "Consapevolezza" delle molteplici possibilità di danno cardiaco
- **RT**: utilizzo progressivo delle tecniche migliori; attenzione a paz con allargamento cardiaco e/o obesi; valutare bene RT mamm interna. PBI?
- **CHT**: tecniche di somministrazione antracicline più sicure; sottogruppi di paz non necessitanti di antracicline? Uso sequenziale del trastuzumab(?)
- **In generale**: attenzione ai precedenti cardiaci; paz anziane; interventi precoci sugli stili di vita; ricerca della patologia cardiaca in fase pre clinica

Grazie per l'attenzione!