Should adjuvant anthracyclines always be part of the chemo-regimen in early stage luminal breast cancer?

NO !! NOT IN ALL !!
WE HAVE OPTIONS !!

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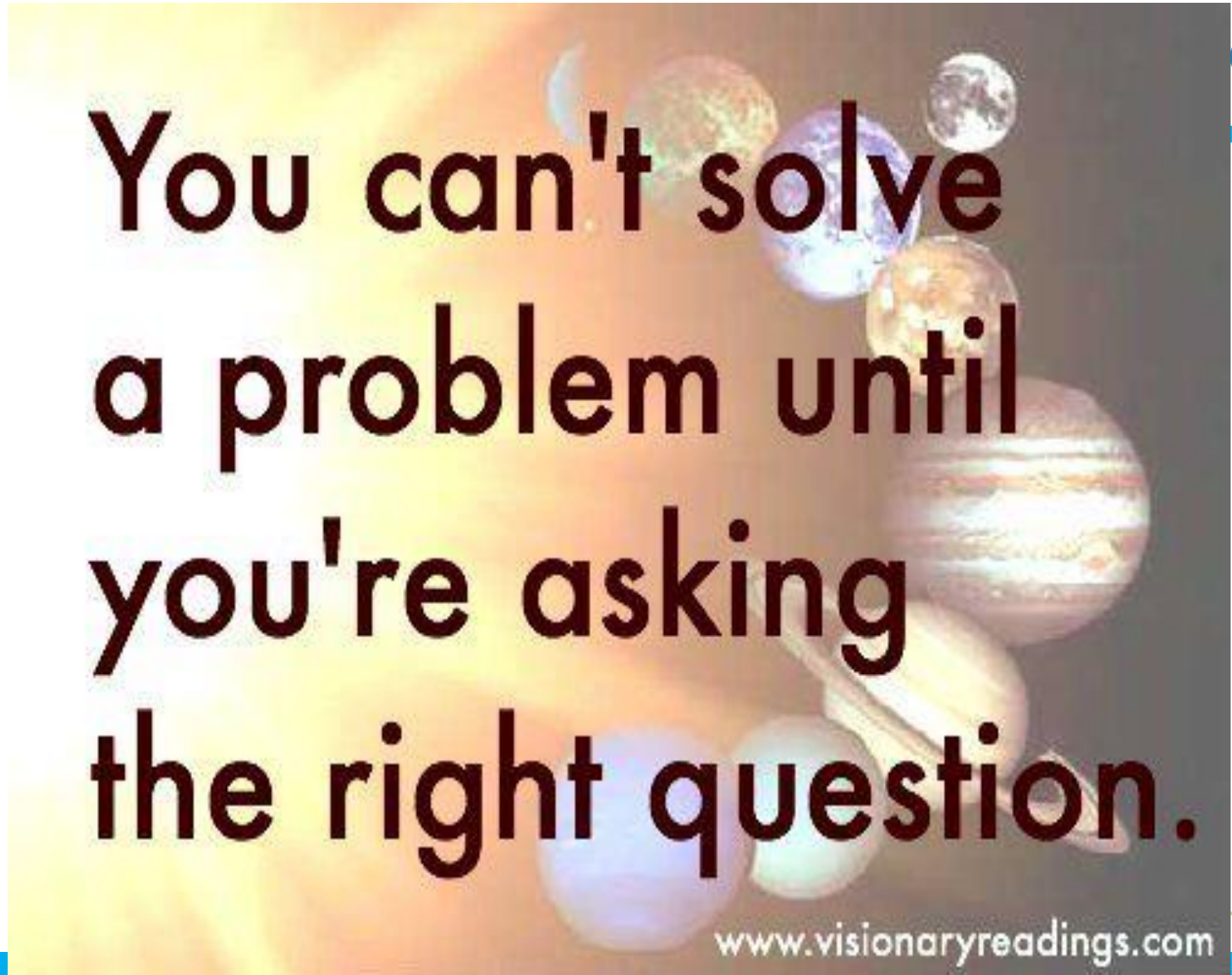
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Right Question for this debate ?

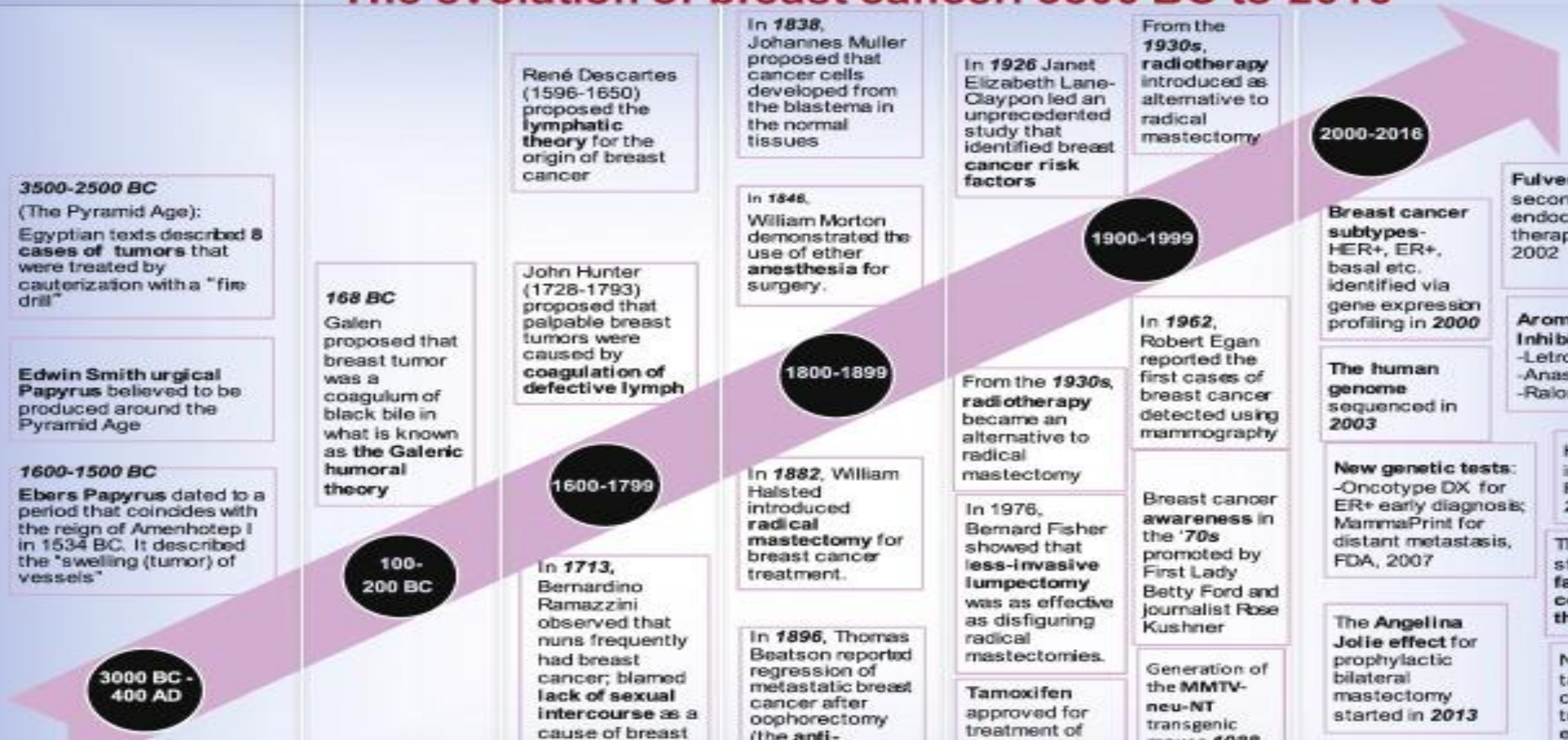
- **Is adjuvant chemotherapy omissible in women with T1–2 stage, node-positive, luminal A type breast cancer?**
  - **Not the topic/subject of debate now**
- **In which patient is chemotherapy required ?**
  - **Not the topic !!**
- **If chemotherapy is essential, which is the choice ?**
  - A Anthracycline based ? ***For all ?***
  - B. Non-Anthracycline based ?
  - My choice (in debate) is : B

Anthracycline based regime is not for all

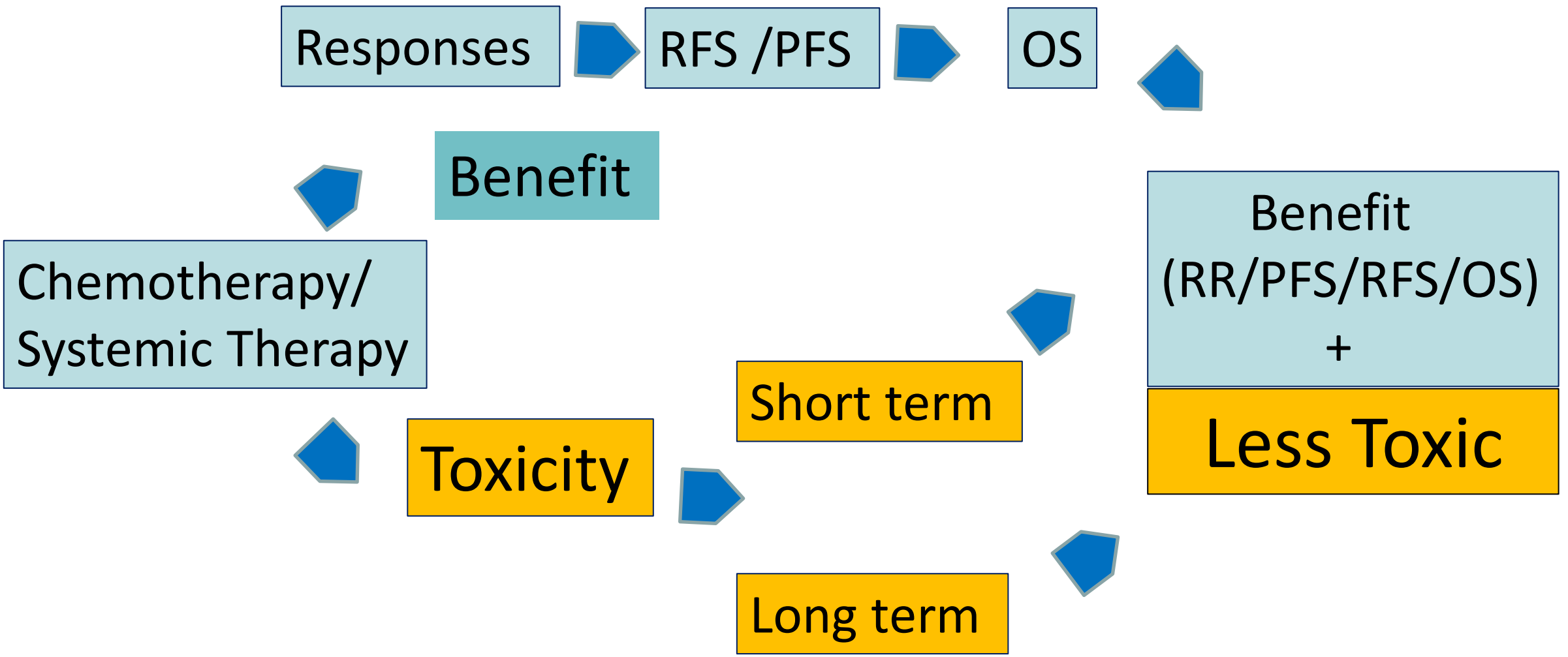
How am I going to convince you?

- Demonstrate the toxicity of Anthracyclines
- Discuss the equally effective Non Anthracycline based regime
  - ABC trial, WSG Plan B trial, MINDACT trial
  - Metanalysis
- And Less toxic
- Conclude
- Judgment is yours !!

The evolution of breast cancer: 3500 BC to 2016



Evolution of Systemic Therapy



Anthracyclines for breast cancer

- Anthracyclines have been a mainstay of breast cancer therapy for decades and continues to be so.
- Strong evidence of their impact on breast cancer survival.
- Concerns regarding rare but serious long-term toxicities including
  - cardiotoxicity : could be fatal, or high morbidity
  - hematologic malignancies : Lethal
- Look for alternative adjuvant therapy options with more favourable toxicity profiles.

Toxicity of Anthracyclines

- Cardio-toxicity
- Hematological malignancy

- Others
  - Neutropenia
  - Gi Toxicity

Cardiotoxicity

- Anthracyclines can damage the myocardium and cause a variety of cardiac effects including a
  - dilated cardiomyopathy,
  - supraventricular tachycardia,
  - myopericarditis,
  - electrocardiogram changes,
  - Sudden death
- The cardiomyopathy can run the spectrum from severe congestive heart failure (CHF) to subclinical, subtle echocardiographic changes.

Cardiotoxicity

- The risk for cardiotoxicity with anthracyclines is
  - dose-dependent and
  - Cumulative
    - increases dramatically at doses higher than doxorubicin 400mg/m2 or Epirubicin 800 mg/m2
- However, when all degrees of cardiotoxicity are considered in patients receiving AC followed by paclitaxel (AC→T),
- ***there is about a 10% incidence of post-treatment cardiotoxicity and decline in LVEF.***

Risk factors for cardiotoxicity

- age (>65 years),
- higher cumulative anthracycline dose,
- mediastinal radiation,
- pre-existing cardiac disorders,
- other cardiac risk factors (i.e., hypertension)
- Additional treatment
  - Radiation therapy and trastuzumab can have additive
- or synergistic cardiotoxic effects with anthracyclines

Age and Dose dependent Cardiotoxicity

New Insight Into Epirubicin Cardiac Toxicity:
Competing Risks Analysis of 1097 Breast Cancer Patients
Marianne Ryberg et al,

J Natl Cancer Inst 2008;100: 1058 – 1067

MORE WITH

↑ AGE
↑ CUM DOSE

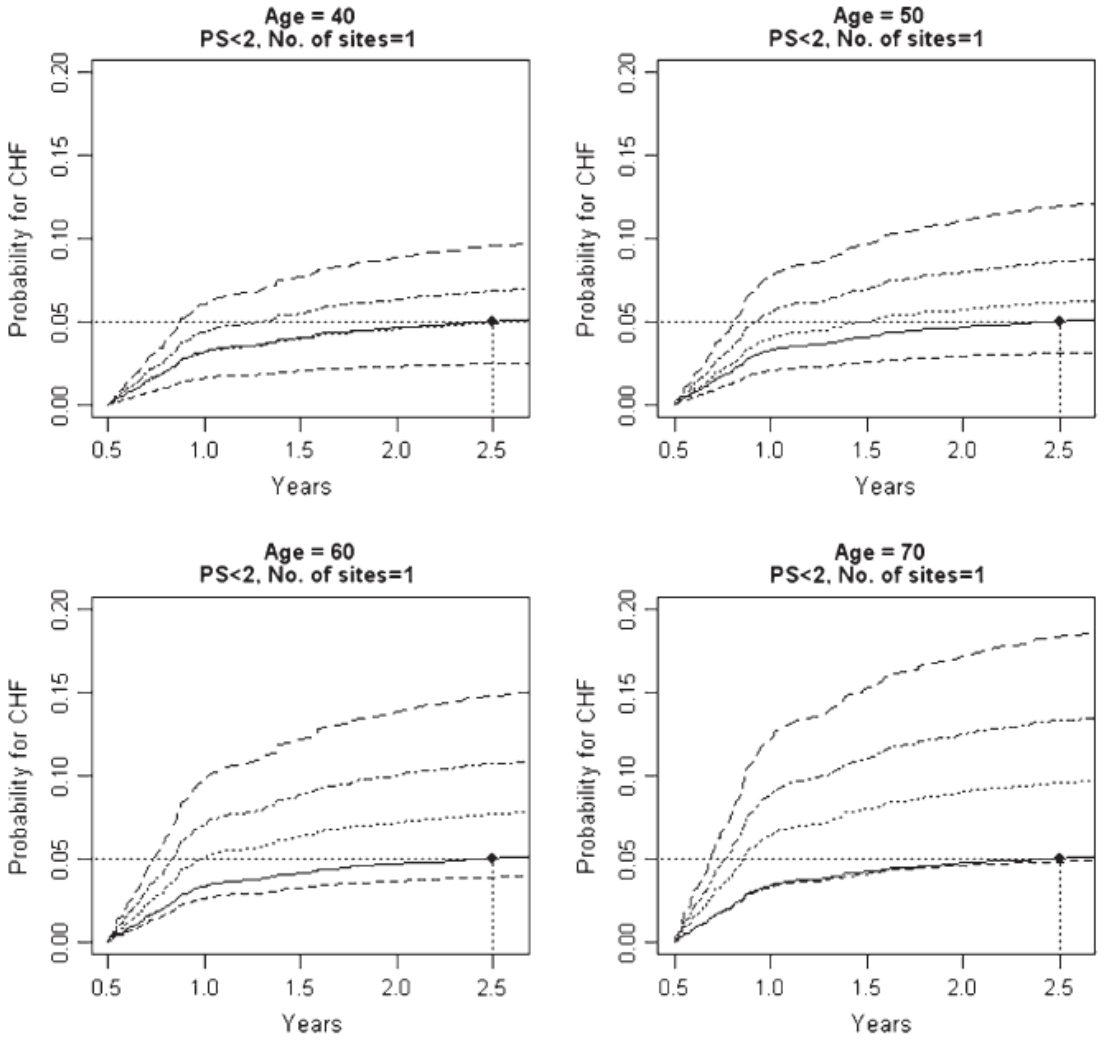


Figure 2. Risk of developing congestive heart failure (CHF) over 2.5 years from the start of epirubicin treatment for breast cancer patients aged 40, 50, 60, and 70 years, with one metastatic site and performance status (PS) less than 2 (group A in Table 3). Risks of CHF for the following maximal cumulative doses of epirubicin are plotted as follows: **dashed curve**: 600 mg/m²; **dotted curve**: 800 mg/m²; **dash-dotted curve**: 900 mg/m²; **long-dashed curve**: 1000 mg/m². The **solid curve** represents the risk of CHF corresponding to the recommended maximum cumulative dose; the point on this curve indicates the 5% probability level reached at 2.5 years (**vertical dotted lines**).

ANTHRACYCLINE INDUCED LEUKMIAS

- Anthracyclines are topoisomerase II inhibitors and thought to cause
  - secondary leukemia and
  - myelodysplastic syndrome (marrow neoplasms)
- by interfering with ligation after single and double strand breaks.
- The 5-year rate of acute leukemia after adjuvant breast cancer therapy ranged from 0% to 1.4%
- An analysis of over 20,000 patients with stage I–III breast cancer treated through the NCCN showed the RR of a marrow neoplasm with adjuvant chemotherapy was 6.8.
- The incidence was 0.46 per 1,000 patient years compared with 0.16 per 1,000 patient years in the surgery alone group.

LEUKEMIAS : OUTCOME

- Importantly, the risk continued to rise beyond 5 years, with the incidence at 10 years about double that at 5 years
- therapy-related marrow neoplasms (i.e., radiation, growth factors, alkylating agents) that present an additive or synergistic risk
- therapy-related neoplasms are more likely to have adverse features:
- Patients often have
  - increased toxicities given prior therapies, and
  - patients are more likely to have poor outcomes
  - independent of other established prognostic factors .

WHAT ARE THE ALTERNATIVES ?

- ***NO CHEMOTHERAPY***
- ***NON ANTHRACYCLINE CHEMOTEHRAPY***

Table 1. Important randomized trials comparing anthracycline and nonanthracycline adjuvant regimens in early breast cancer

Study name	Study details	Patient characteristics	Nonanthracycline regimen	Anthracycline regimen	Follow-up	DFS	OS	Bottom line
U.S. Oncology 9735	1,016 patients stage I–III	pN0 48% pN1 41% pN2-3 11% HR+ 71% Her2+ 27%[a]	TC × 4 cycles	AC × 4 cycles	7 years	81% vs. 75%	87% vs. 82%	TC is a viable nonanthracycline alternative in low-risk breast cancer
CALGB 40101	3,871 patients, N0 or N1	pN0 89% pN1 11% pN2-3 0% HR+ 68% HER2+ 15%[a]	Paclitaxel × 4–6 cycles	AC × 4–6 cycles	6.1 years	88% vs. 91%	94% vs. 95%	Paclitaxel is less toxic but has inferior efficacy to AC
BCIRG 006	3,222 patients, HER2+, N0 high-risk or N+	pN0 29% pN1 38% pN2-3 33% HR+ 54% HER2+ 100%	TCH	AC → docetaxel, AC → docetaxel+H	5 years	81% vs. 75%, 84%	91% vs. 87%, 92%	TCH is a reasonable nonanthracycline alternative in HER2+ breast cancer
ABC Trial: USOR 06-090	1,286 patients		TC × 6 cycles	TAC	6.3 years			TC is not noninferior to TaxAC in HER2-negative node-positive or high-risk node-negative patients, although the absolute difference is small.
ABC Trial: B-46-I/07132	1,051 patients		TC × 6 cycles	TAC	4.8 years			HR-positive, node-negative tumors favor TC;
ABC Trial: B-49	1,819 patients		TC × 6 cycles	Investigator choice of anthracycline and taxane containing standard regimen	2.2 years			TN tumors and HR-positive tumors with >4 lymph nodes favor TaxAC
ABC Trials	4,242 patients, HER2-neg N0 high-risk or N+	pN0 41% pN1 44% pN2-3 16% HR+ 69% HER2+ 0%	TC × 6 cycles	Taxane-anthracycline regimen as above	3.3 years	4-year IDFS 88.2% vs. 90.7%	4-year OS 94.7% vs. 95%	
WSG PlanB	2,449 patients; HER2-neg, HR-neg N0 high-risk or N1; or HR-pos and RS >11	pN0 59% pN1 33% pN2-3 8% HR+ 82% HER2+ 0%	TC × 6 cycles	EC ×4 → docetaxel × 4	5 years	90.2% vs. 89.9%	94.6% vs. 94.7%	TC × 6 cycles is an effective option in HER2-negative early breast cancer
MINDACT	1,302 patients; T1-3, N0-1, clinically and/or genomic high risk	pN0 70% pN1 30% pN2-3 0.3% HR+/HER2- 69% TNBC 21% HER2+ 10%	DC	N0: anthracycline regimen without taxane N+: anthracycline-taxane regimen	5 years	90.7% vs. 88.8%	96.2% vs. 96.3%	DC did not improve outcomes over an anthracycline-based regimen

[a]HER2 not assessed on all patients.

Abbreviations: AC, doxorubicin, cyclophosphamide; DC, docetaxel, capecitabine; DFS, disease-free survival; EC, epirubicin, cyclophosphamide; IDFS, invasive disease-free survival; neg, negative; OS, overall survival; pos, positive; TAC, docetaxel, doxorubicin, cyclophosphamide; TC, taxane, cyclophosphamide; TCH, docetaxel, carboplatin, trastuzumab.

The ABC study

- Joint analysis of three adjuvant breast cancer trials
  - comparing TC X 6 vs TaxAC
- 4,242 patients with LN positive or high-risk N0 HER2-negative breast cancer
- Patients were stratified by
  - HR status,
  - nodal involvement,
  - and parent trial.

Patients

- 69% of patients had HR positive disease.
- Most patients had limited nodal involvement:
  - 41% were lymph node negative,
  - 44% had one to three lymph nodes,
  - only 16% had four or more lymph nodes involved

Planned interim analysis

- TC was statistically inferior to TaxAC in IDFS
  - when 334 IDFS events have occurred (over half of an anticipated 668), the hazard ratio exceeded the 1.18 prespecified hazard ratio cutoff and
- ***There was no significant difference in overall survival***
  - (hazard ratio 1.08, 95% CI 0.82–1.41, p = .60).
- At the cutoff time, the hazard ratio was 1.23 (95% CI 1.01–1.50), which translated into an absolute difference in 4-year IDFS of 2.5%
  - **TC 88.2% and TaxAC 90.7%**
- Toxicities were consistent with those previously described with each regimen.
- In the TaxAC arm,
  - five patients developed leukemia,
  - none in the TC arm.
- ***TC is as effective and less toxic***

Exploratory Analysis

- TaxAC was favored in the studies with longer follow-up, although this did not meet statistical significance
  - (hazard ratio 1.31, 95% CI 0.97–1.78 and
  - B46/07132 hazard ratio 1.34, 95% CI 0.94–1.91).
- TC is better in HR + N0 disease
- HR-positive, lymph node-negative breast cancer favored TC
  - (hazard ratio 0.69, 95% CI 0.39–1.19), with an absolute 4-year IDFS difference of 2.7%.)

HR + N0 Disease

Table 2. Exploratory analysis from the anthracycline in early breast cancer trials

	HR positive		HR negative	
	TaxAC vs. TC difference in 4-year IDFS	Hazard ratio (95% CI)	TaxAC vs. TC difference in 4-year IDFS	Hazard ratio (95% CI)
Lymph node negative	−2.7%	0.69 (0.39–1.19)	2.5%	1.31 (0.86–1.99)
1–3 lymph nodes	2.0%	1.14 (0.77–1.69)	10.9%	1.58 (0.90–2.79)
4+ lymph nodes	5.8%	1.46 (0.95–2.26)	11.0%	1.34 (0.62–2.91)

Abbreviations: CI, confidence interval; HR, hazard ratio; IDFS, invasive disease-free survival; TaxAC, taxane- and anthracycline-containing regimen; TC, taxane, cyclophosphamide.

WSG Plan B trial - a phase III trial

- HER-2-negative lymph node-positive and high-risk lymph node-negative (T2-4, G2-3, <35 years, *or high uPA/PAI-1*) breast cancer.
- The trial was designed with a noninferiority margin of 4.4% for the non-anthracycline compared with the anthracycline regimen.
- Over 2,400 patients with high-risk disease were randomized
  - to TCx6 or ECx4→Tx4

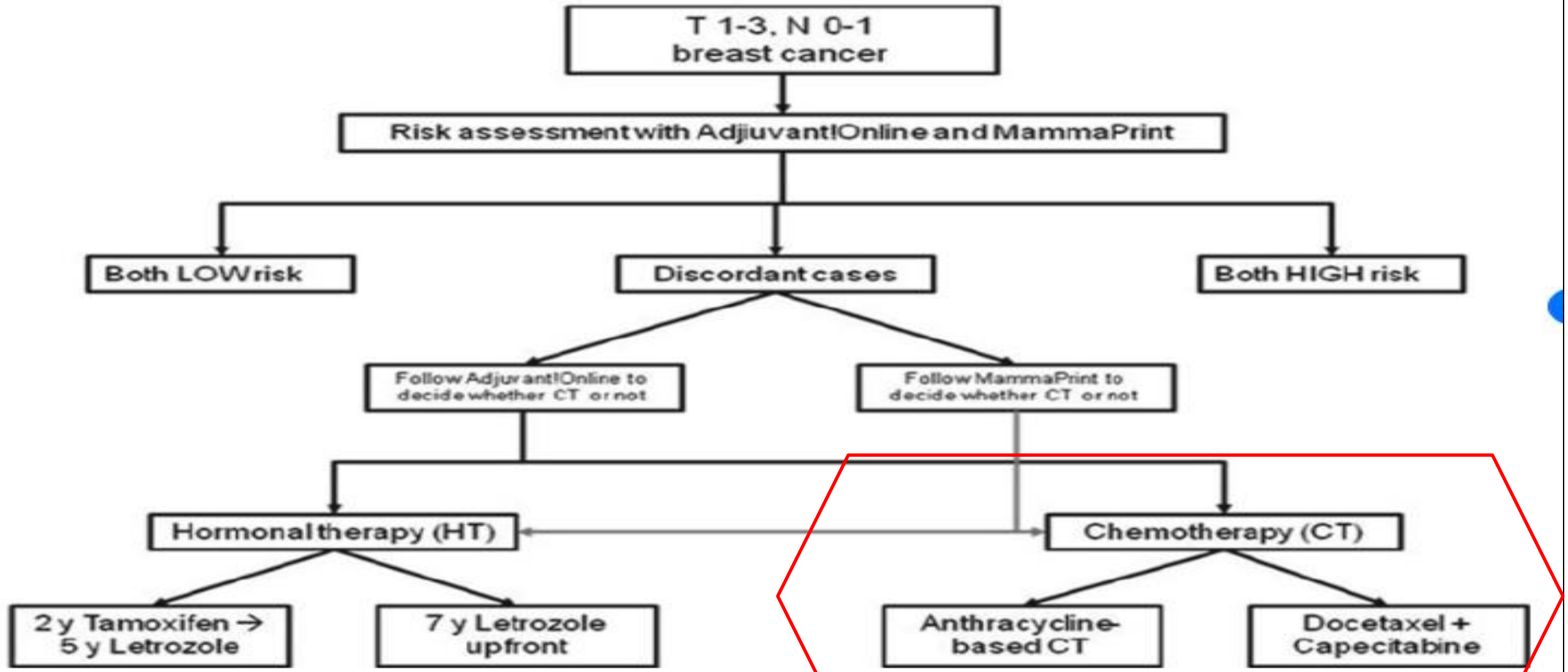
Results

- Patients
  - 41 % percent of patients had LN + disease,
  - 82% were HR positive,
  - 42% had grade 3 tumors.
- Survival
  - 5 year DFS (90.2% vs. 89.9%) : NS
  - 5-year OS (94.7% vs. 94.6%).: NS
- Pts with the highest recurrence scores (RS > 25),
  - the 5-year DFS was 86% versus 85%.

Results

- Slightly more treatment-related deaths in the TCx6 arm
  - (0.4 vs. 0.1%)
- More serious adverse events in the anthracycline-containing arm (397 vs 358 events).
- ***TCx6 is noninferior to ECx4→Tx4 and***
- ***patients are "sufficiently treated" with TC x6***.
- ***21-gene recurrence score was not predictive*** of efficacy of anthracycline therapy

MINDACT TRIAL



1 MINDACT trial design

RESULTS

- At a median of 5 years follow-up,
  - ***DC was not superior to the anthracycline regimens***,
  - ***with a DFS of 90.7% versus 88.8%.***
  - For patients with both clinical and genomic high-risk disease,
  - the DFS was not statistically different (86.1% vs. 88.1%).

Effectiveness of an Adjuvant Chemotherapy Regimen for Early-Stage Breast Cancer: A Systematic Review and Network Meta-analysis

JAMA Oncol. 2015 December ; 1(9): 1311–1318

Wu Ding,MDa, Zhian Li, MDa, Caiyun Wang, MDb, Jiangfeng Dai, MDa, GuoDong Ruan, MDa, Chuanjian Tu, MDa
.

STUDY OF 24 trials.

The TC and platinum-containing regimens had OS benefit similar to that of sequential AC-T

(TC hazard ratio [HR], 0.93; 95%CI, 0.62–1.40; and platinum HR, 0.93; 95%CI, 0.66–1.31).

Patients treated with CMF or AC had significantly worse OS than those treated with sequential AC-T (CMF HR, 1.56; 95%CI, 1.32–1.85; and AC HR, 1.22; 95%CI, 1.10–1.37).

Platinum-containing regimens tended to be more toxic than sequential AC-T.

The toxicity of TC was similar to or less than that of sequential AC-T.

Meta-regression analysis showed that hormone receptor status did not impact the HRs for OS for any regimen.

PARAS HOSPITALS
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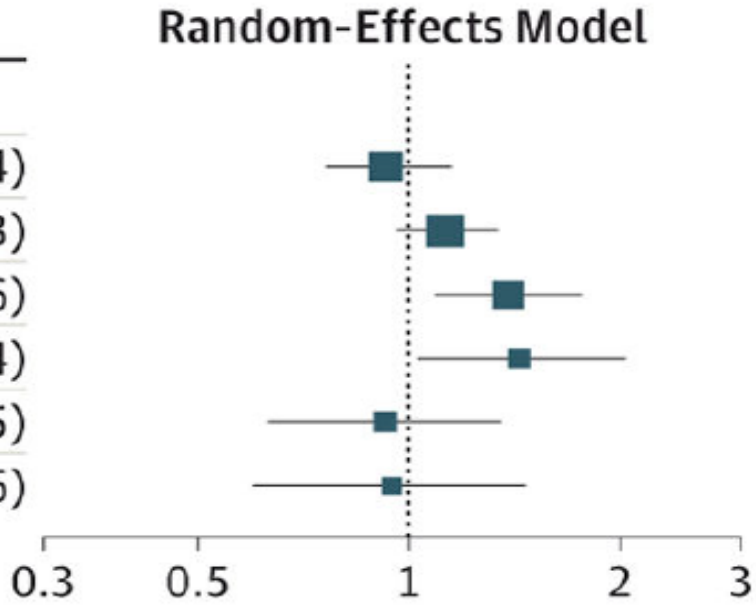
A Overall survival

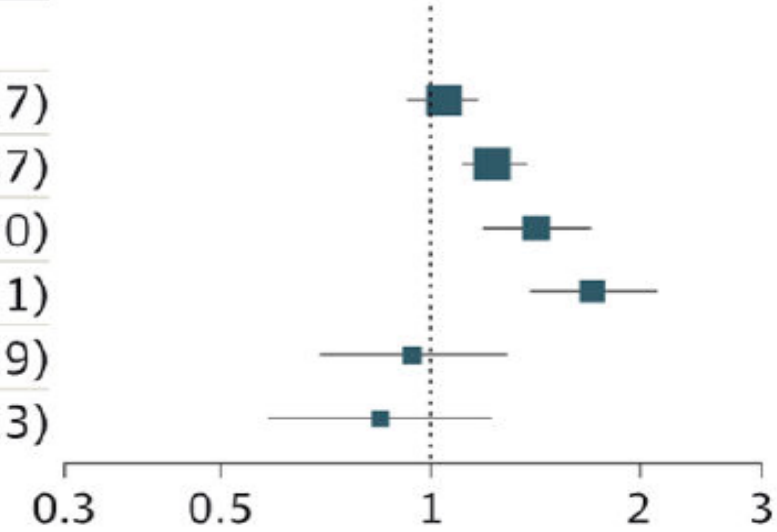
Regimen	HR (95% CI)
AC-T	1.00
ACT	0.93 (0.77-1.14)
Anthracycline alone	1.13 (0.97-1.33)
CMF	1.39 (1.10-1.76)
No adjuvant chemotherapy	1.45 (1.03-2.04)
Platinum-containing regimens	0.93 (0.63-1.35)
TC	0.95 (0.60-1.46)



B Event-free survival

Regimen	HR (95% CI)
AC-T	1.00
ACT	1.05 (0.94-1.17)
Anthracycline alone	1.24 (1.12-1.37)
CMF	1.43 (1.20-1.70)
No adjuvant chemotherapy	1.71 (1.40-2.11)
Platinum-containing regimens	0.95 (0.70-1.29)
TC	0.86 (0.59-1.23)

Figure3



A Overall unacceptable AEs

Regimen	OR (95% CI)
AC-T	1.00
ACT	1.95 (0.97-
Anthracycline alone	0.73 (0.41-1.32)
CMF	0.18 (0.07-0.48)
Platinum-containing regimens	3.55 (0.80-15.71)
TC	0.56 (0.13-2.35)

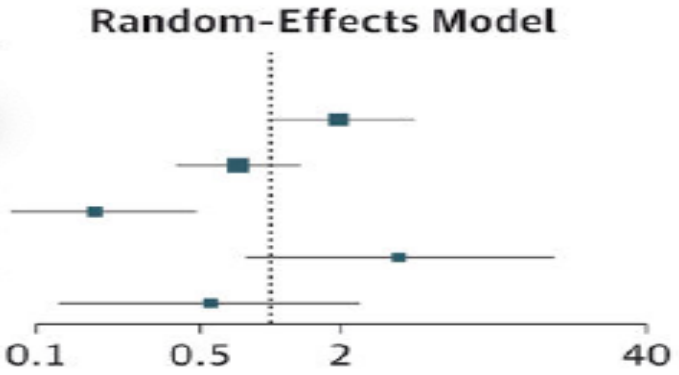
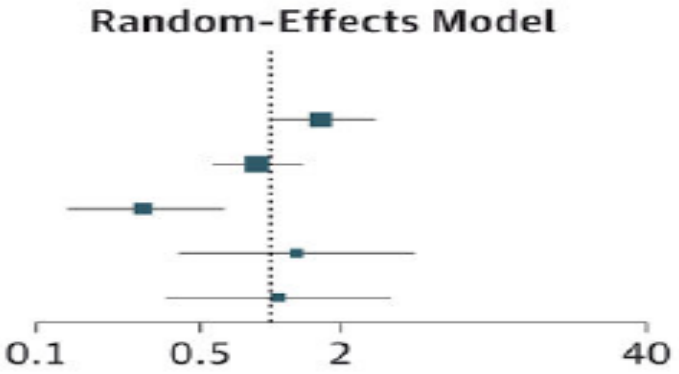


Figure4

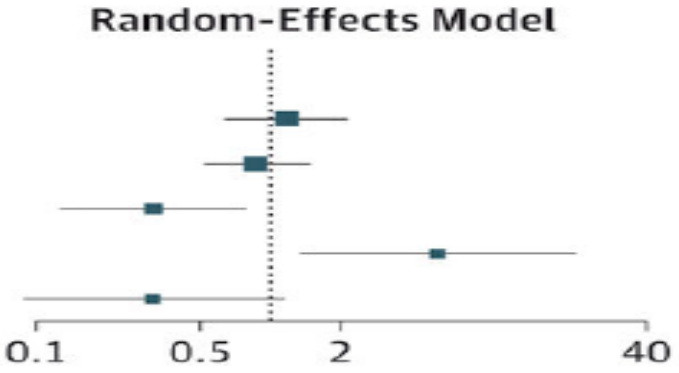
B Hematologic unacceptable AEs

Regimen	OR (95% CI)
AC-T	1.00
ACT	1.65 (0.99-2.74)
Anthracycline alone	0.88 (0.57-1.35)
CMF	0.29 (0.14-0.63)
Platinum-containing regimens	1.30 (0.42-4.07)
TC	1.08 (0.37-3.17)



C Nonhematologic unacceptable AEs

Regimen	OR (95% CI)
AC-T	1.00
ACT	1.17 (0.65-2.10)
Anthracycline alone	0.88 (0.53-1.46)
CMF	0.32 (0.13-0.78)
Platinum-containing regimens	5.17 (1.36-19.67)
TC	0.32 (0.09-1.12)



RESULTS

- First, sequential AC-T should still be the first choice for chemotherapy in the general population of patients with early-stage breast cancer on the basis of OS and risk of unacceptable AEs. .
- Second, ***TC was similar to sequential AC-T in terms of treatment effect and unacceptable AEs and might be considered as a first choice treatment for patients with high risk of cardiotoxic effects.***
- Third, although platinum-containing regimens have recently been considered for breast cancer treatment, they are not superior to sequential AC-T in terms of OS and tend to be more toxic.

COMBINED DATA

- the data in total suggest the
  - absolute benefit of an anthracycline- and taxane-containing regimen compared with a non-anthracycline adjuvant regimen is at best small
  - likely limited to the higher-risk patients.
  - Long term Toxicity is less

  - There is an effective and less toxic Non Anthracycline regime alternative to Anthracycline based CT

CONCLUSIONS

- Treatment with a potentially cardiotoxic drug
  - may often be inevitable to extend survival for a cancer patient.
  - it is essential to be aware of the risk of cardiotoxicity, not
- only because cardiotoxicity can progress to a potentially fatal outcome- ***AVOIDABLE LOSS OF LIFE / QUALITY OF LIFE***

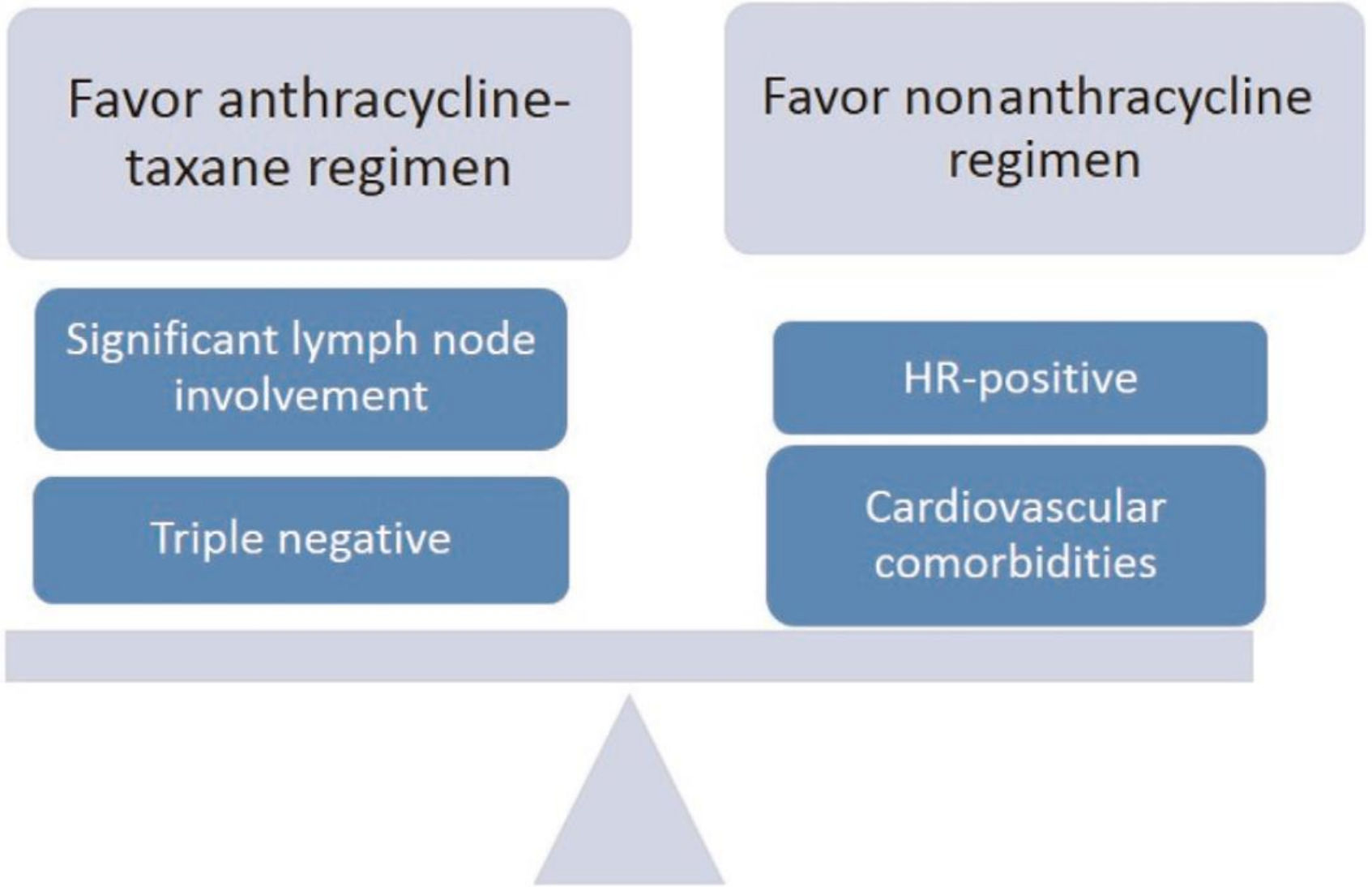


Figure 1. Factors influencing decisions regarding anthracycline

Should adjuvant anthracyclines always be part of the chemo-regimen in early stage luminal breast cancer?

NO !! NOT IN ALL !!
WE HAVE OPTIONS

ANTHRACYCLINE BASED CT HAS TOXICITY PROBLEM

THERE ARE OTHER EQUALLY EFFECTIVE OPTIONS

AND LESS TOXIC.

TC IS A GOOD OPTION