Role of Chemotherapy in Breast Cancer

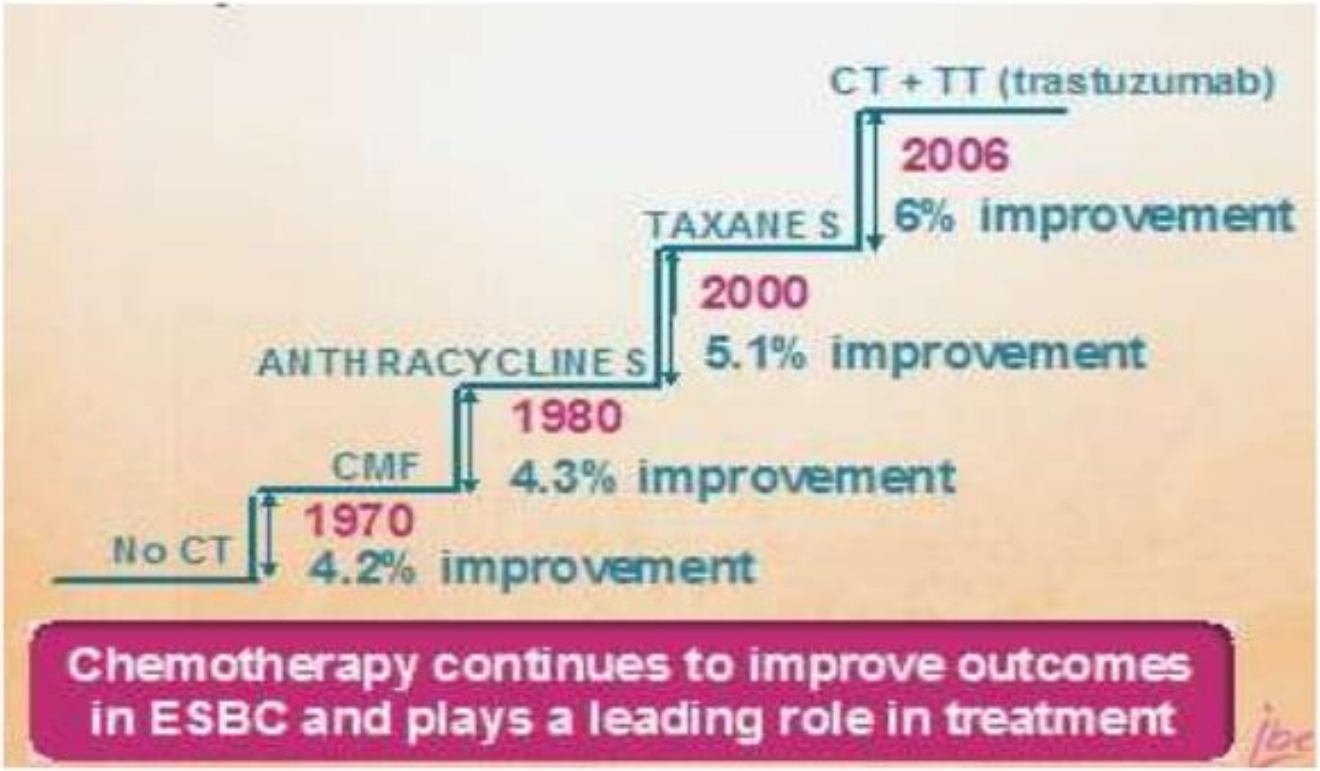
Dr Jyotirup Goswami

Consultant Radiation Oncologist

Narayana Superspeciality Hospital, Howrah

How important in systemic therapy ?

Adjuvant treatment and survival improvement
over the past 40 years



Settings

- Adjuvant
- Neo-adjuvant
- Palliative

Adjuvant Chemotherapy

Indications for adjuvant chemotherapy

Factors influencing decision are:

- N-stage (pN+)
- T-stage (pT>1cm)
- Grade (2-3)
- Presence of LVE/PNI
- Age (<35-40 years)
- ER /PR/HER-2 status (HR- & HER2+ tumors)

Adjuvant chemotherapy regimens-HER2 negative [NCCN 2019]

- **Preferred**:
- ddAC-->Paclitaxel q 2wk
- ddAC-->Paclitaxel wkly
- TC

- **Useful in selected cases**:
- ddAC
- AC
- CMF
- AC--> Paclitaxel wkly

- **Other recommended**:
- TAC
- EC
- AC-->Docetaxel 3-wkly

Adjuvant chemotherapy regimens-HER2 positive [NCCN 2019]

- **Preferred**:
- AC-->Paclitaxel + Trastuzumab (various schedules)
- AC-->Paclitaxel + Trastuzumab + Pertuzumab(various schedules)
- Paclitaxel + Trastuzumab
- Docetaxel + Carboplatin+ Trastuzumab

- **Useful in selected cases**:
- Docetaxel + Cyclophosphamide + Trastuzumab

- **Other recommended**:
- AC-->Docetaxel + Trastuzumab
- AC-->Docetaxel + Trastuzumab+ Pertuzumab

Bonadonna regimen (CMF)

Table 1 CMF studies carried out at the Istituto Nazionale Tumori in Milan

Enrolment period	Study design	Eligible patients	Intervention	No of patients
June 1973 to September 1975	Randomised controlled trial	Node positive, premenopausal, and postmenopausal	Surgery *v* CMF for 12 cycles	179 *v* 207
September 1975 to May 1978	Randomised controlled trial	Node positive, premenopausal	CMF for 12 cycles *v* CMF for 6 cycles	160 *v* 164
May 1978 to October 1980	Observational study	Node positive, premenopausal	CMF for 12 cycles	220
December 1980 to October 1985	Randomised controlled trial	Node negative and oestrogen receptor negative, premenopausal, and postmenopausal	Surgery *v* intravenous CMF for 12 cycles	45 *v* 45

- Cohort Study from Italy (3 RCTs & 1 observational study)
- 1973-1980
- Median FU 28.5 years
- CMF regimen significantly reduces the relative risk of relapse & death
- 6 cycles of CMF were equivalent to 12

BMJ. 2005;330(7485):217

EBCTCG Benefits of adjuvant chemotherapy

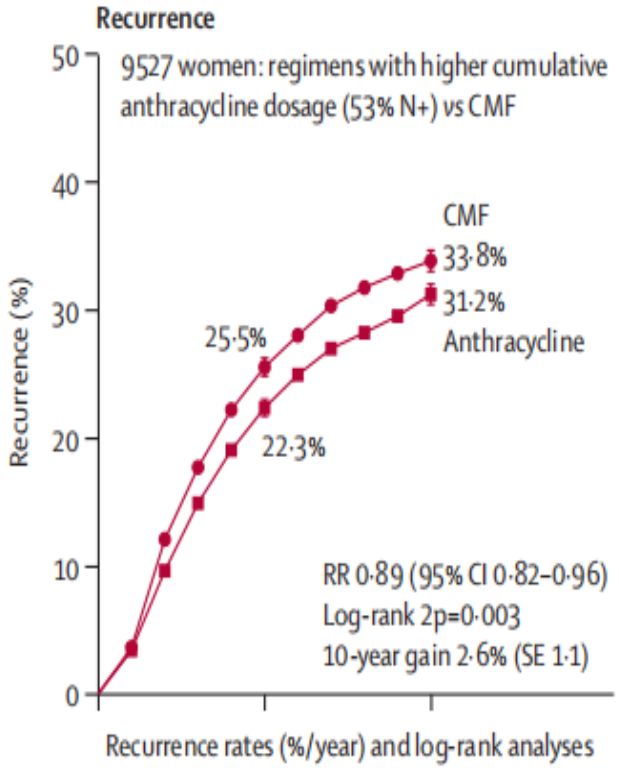
IPD meta-analyses:

- Polychemotherapy vs no chemotherapy (n=32000)
- Anthracycline chemotehrapy vs CMF (n=18000)
- Different anthracycline -based chemotherapy protocols (7000)
- Taxane + Anthracycline-based chemotherapy vs Non-taxane based chemotherapy (n=44000)

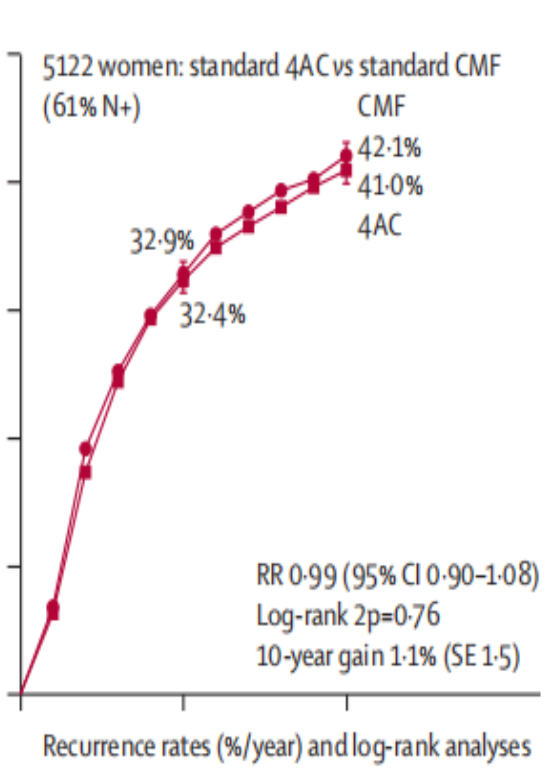
Lancet 2012; 379: 432–44

Effect on breast cancer recurrence & mortality

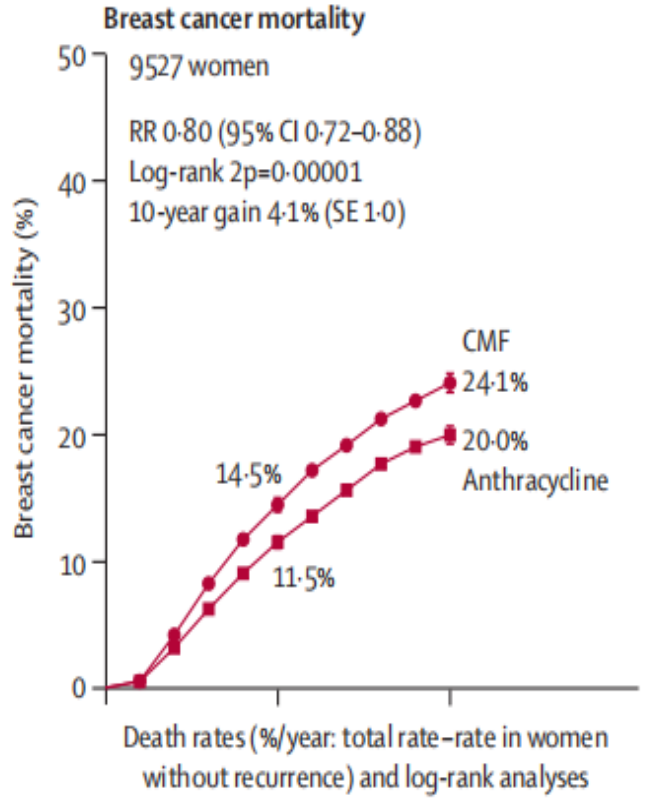
- Standard 4AC and standard CMF are equivalent
- CAF/ CEF (where anthracycline dose is higher than 4AC) are superior to standard CMF & 4AC
- 4AC f/b taxane was superior to 4AC
- 4AC f/b non-taxane was equivalent to 4AC



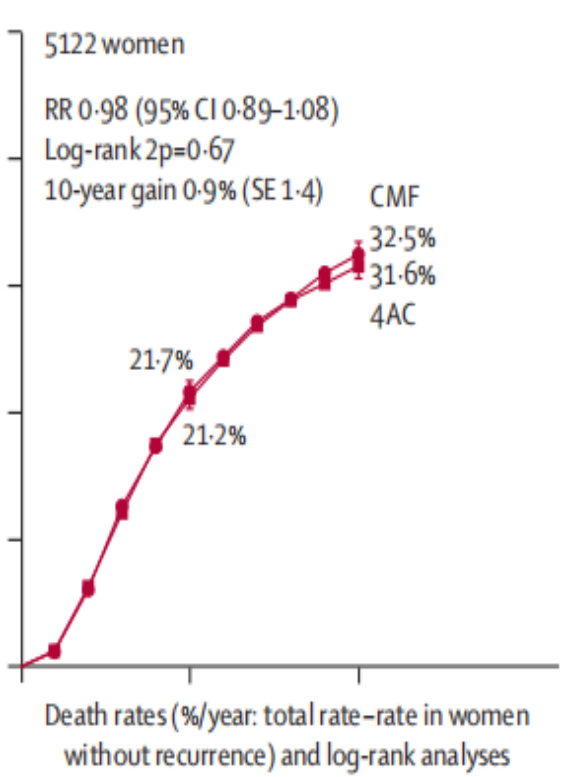
Allocation	Years 0–4	Years 5–9	Year 10+
Anth	5·05 (989/19 575)	2·45 (238/9723)	1·64 (65/3973)
CMF	6·01 (1104/18 377)	2·57 (237/9236)	1·35 (54/4007)
Rate ratio	0·85 SE 0·04	1·00 SE 0·10	1·12 SE 0·21
(O–E)/V	−74·9/457·0	0·1/106·9	2·9/26·4



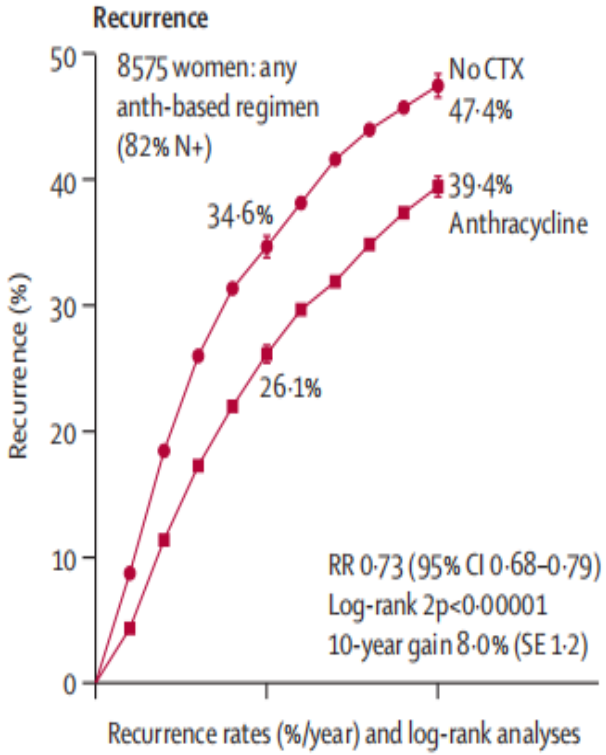
	Years 0–4	Years 5–9	Year 10+
	7·97 (820/10 292)	2·86 (194/6795)	2·36 (100/4237)
	8·21 (830/10 108)	2·99 (199/6658)	1·87 (76/4054)
	0·98 SE 0·05	0·91 SE 0·10	1·28 SE 0·17
	−8·7/355·5	−8·5/92·1	10·4/42·3

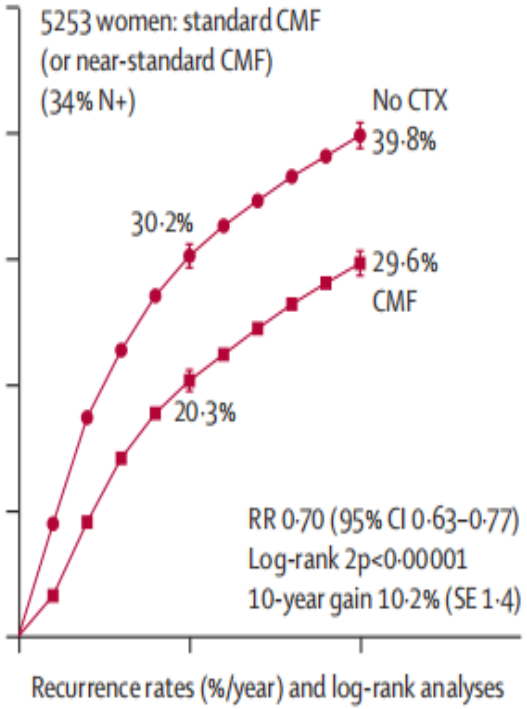


Allocation	Years 0–4	Years 5–9	Year 10+
Anth	2·39 SE 0·11	2·08 SE 0·14	0·91 SE 0·14
CMF	3·06 SE 0·12	2·50 SE 0·15	1·11 SE 0·16
Rate ratio	0·78 SE 0·06	0·84 SE 0·09	0·84 SE 0·20
(O–E)/V	−62·9/248·9	−19·3/111·5	−3·5/20·8



	Years 0–4	Years 5–9	Year 10+
	4·65 SE 0·20	2·94 SE 0·19	2·06 SE 0·20
	4·81 SE 0·21	3·04 SE 0·20	1·96 SE 0·20
	0·97 SE 0·06	0·97 SE 0·09	1·03 SE 0·15
	−6·3/245·2	−3·7/111·6	1·5/48·9



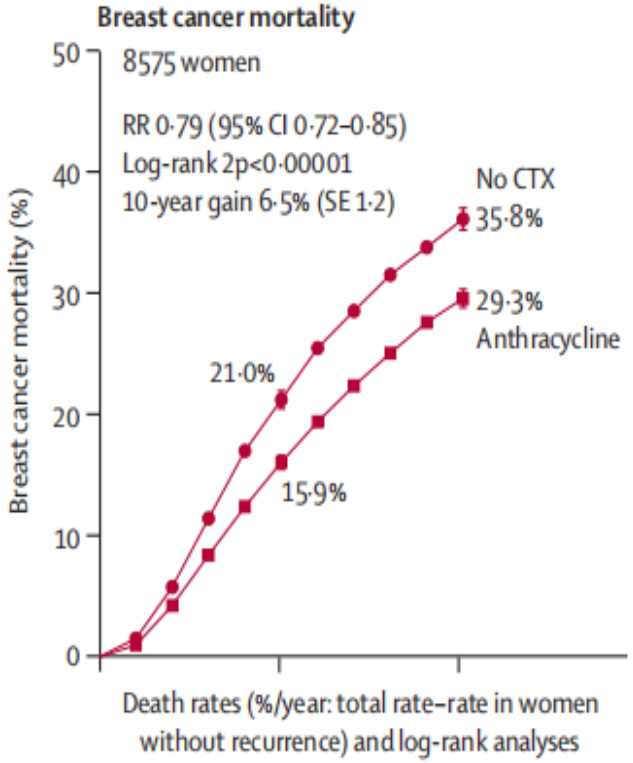


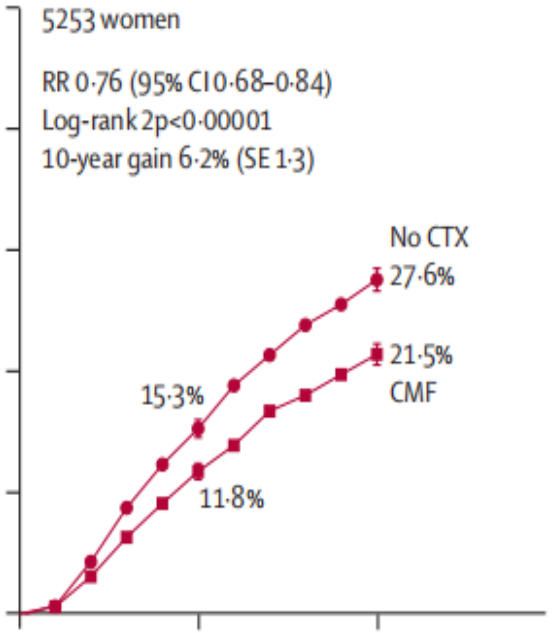
Recurrence rates (%/year) and log-rank analyses

Allocation	Years 0–4	Years 5–9	Year 10+
CTX	6·14 (1179/19 190)	4·06 (487/11 981)	2·91 (161/5530)
No CTX	9·06 (1259/13 899)	4·56 (365/8011)	3·87 (159/4104)
Rate ratio	0·69 SE 0·04	0·89 SE 0·07	0·72 SE 0·11
(O–E)/V	–185·2/489·8	–20·0/174·7	–21·2/65·5

Recurrence rates (%/year) and log-rank analyses

Years 0–4	Years 5–9	Year 10+
4·83 (549/11 357)	2·58 (207/8038)	1·88 (116/6155)
7·20 (748/10 385)	2·93 (210/7158)	1·90 (100/5260)
0·61 SE 0·05	0·84 SE 0·09	0·99 SE 0·14
–135·5/277·0	–16·9/95·9	–0·7/48·7



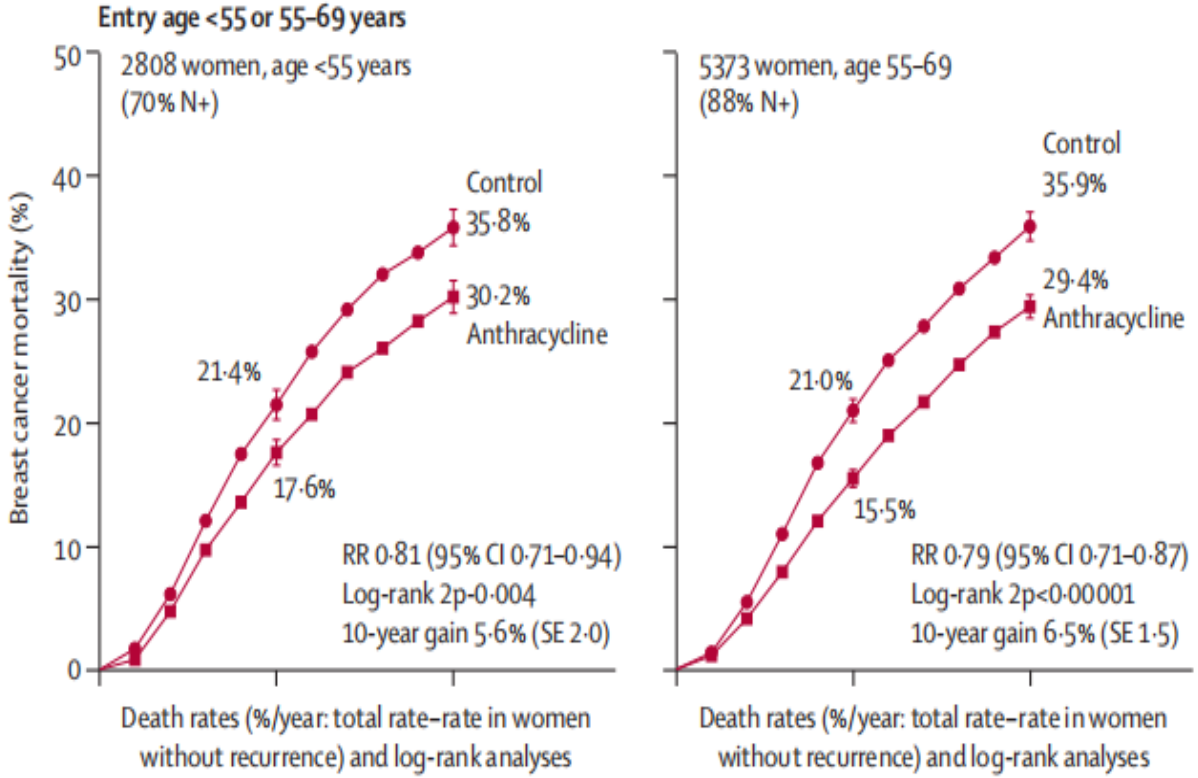


Death rates (%/year: total rate–rate in women without recurrence) and log-rank analyses

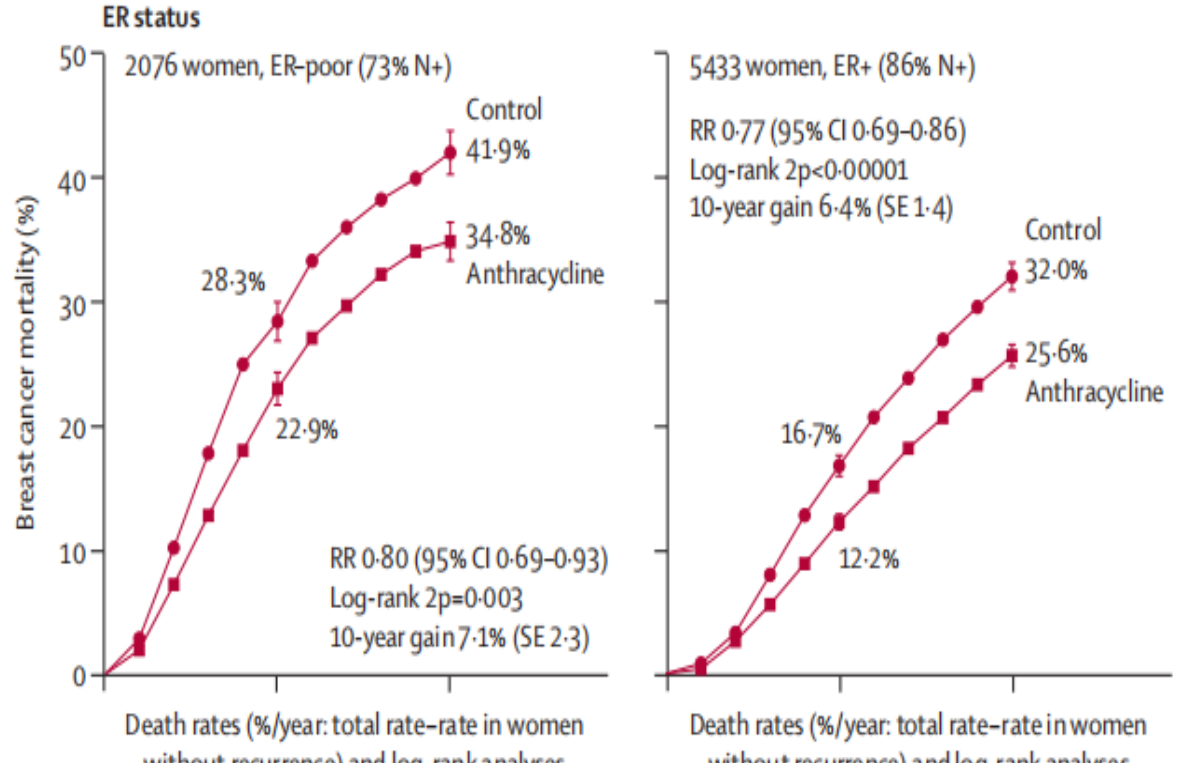
Allocation	Years 0–4	Years 5–9	Year 10+
CTX	3·38 SE 0·13	3·57 SE 0·16	2·83 SE 0·19
No CTX	4·77 SE 0·17	4·31 SE 0·21	2·98 SE 0·22
Rate ratio	0·73 SE 0·05	0·83 SE 0·07	0·92 SE 0·11
(O–E)/V	–97·5/307·0	–35·9/193·2	–6·7/81·0

Death rates (%/year: total rate–rate in women without recurrence) and log-rank analyses

Years 0–4	Years 5–9	Year 10+
2·51 SE 0·14	2·42 SE 0·16	1·80 SE 0·16
3·23 SE 0·17	3·14 SE 0·19	2·10 SE 0·18
0·75 SE 0·07	0·74 SE 0·08	0·82 SE 0·12
–43·5/151·3	–33·7/109·6	–11·9/59·1



Allocation	Years 0–4	Years 5–9	Year 10+	Years 0–4	Years 5–9	Year 10+
Anth	3·81 SE 0·24	3·53 SE 0·28	1·85 SE 0·25	3·26 SE 0·16	3·63 SE 0·20	3·43 SE 0·28
Control	4·77 SE 0·29	4·11 SE 0·34	2·01 SE 0·28	4·79 SE 0·22	4·40 SE 0·27	3·65 SE 0·33
Rate ratio	0·79 SE 0·09	0·81 SE 0·11	0·96 SE 0·21	0·71 SE 0·06	0·86 SE 0·08	0·94 SE 0·13
(O–E)/V	−25·5/108·4	−13·5/63·4	−0·9/21·0	−65·9/193·2	−19·2/125·4	−3·5/58·3



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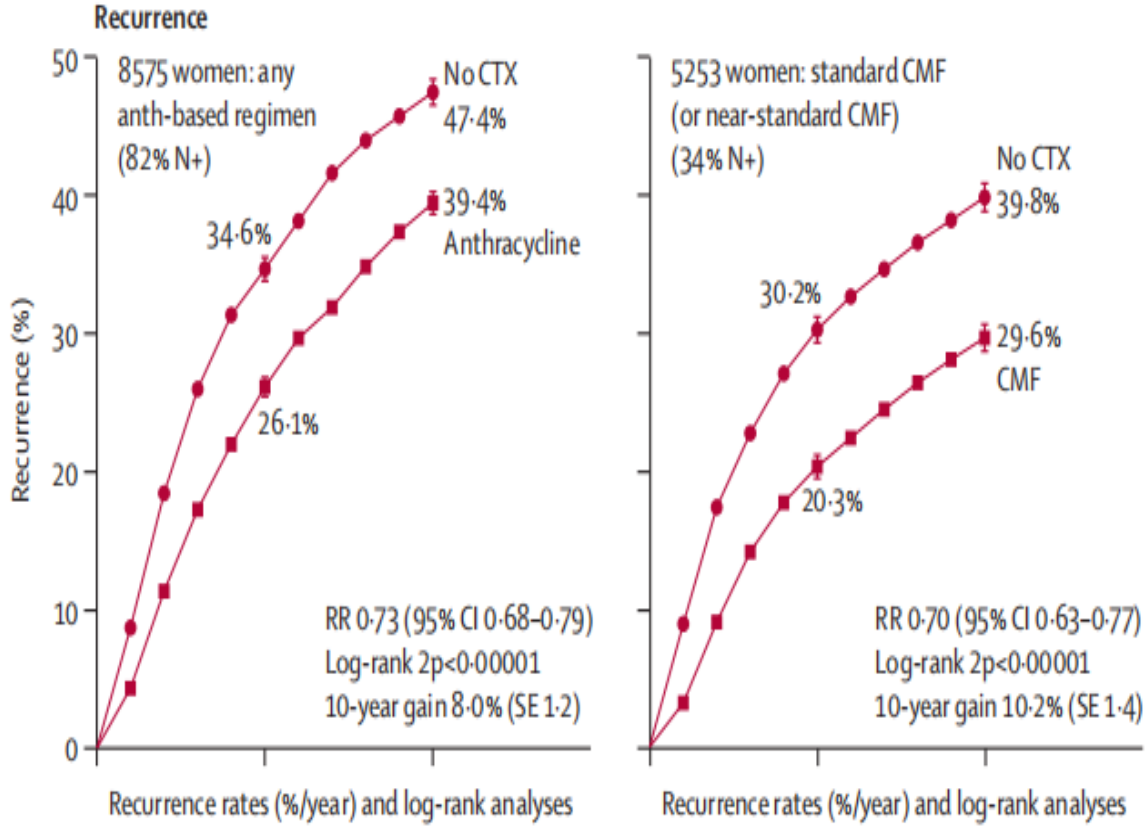
Anth	4·96 SE 0·32	3·50 SE 0·33	2·64 SE 0·36	2·60 SE 0·14	3·40 SE 0·19	3·09 SE 0·26
Control	6·84 SE 0·41	4·47 SE 0·42	2·92 SE 0·41	3·63 SE 0·19	4·17 SE 0·25	3·14 SE 0·30
Rate ratio	0·76 SE 0·08	0·80 SE 0·13	0·98 SE 0·20	0·71 SE 0·07	0·81 SE 0·08	0·92 SE 0·14
(O–E)/V	−29·2/107·7	−10·8/48·7	−0·5/24·1	−54·3/156·2	−26·4/123·3	−4·0/48·9



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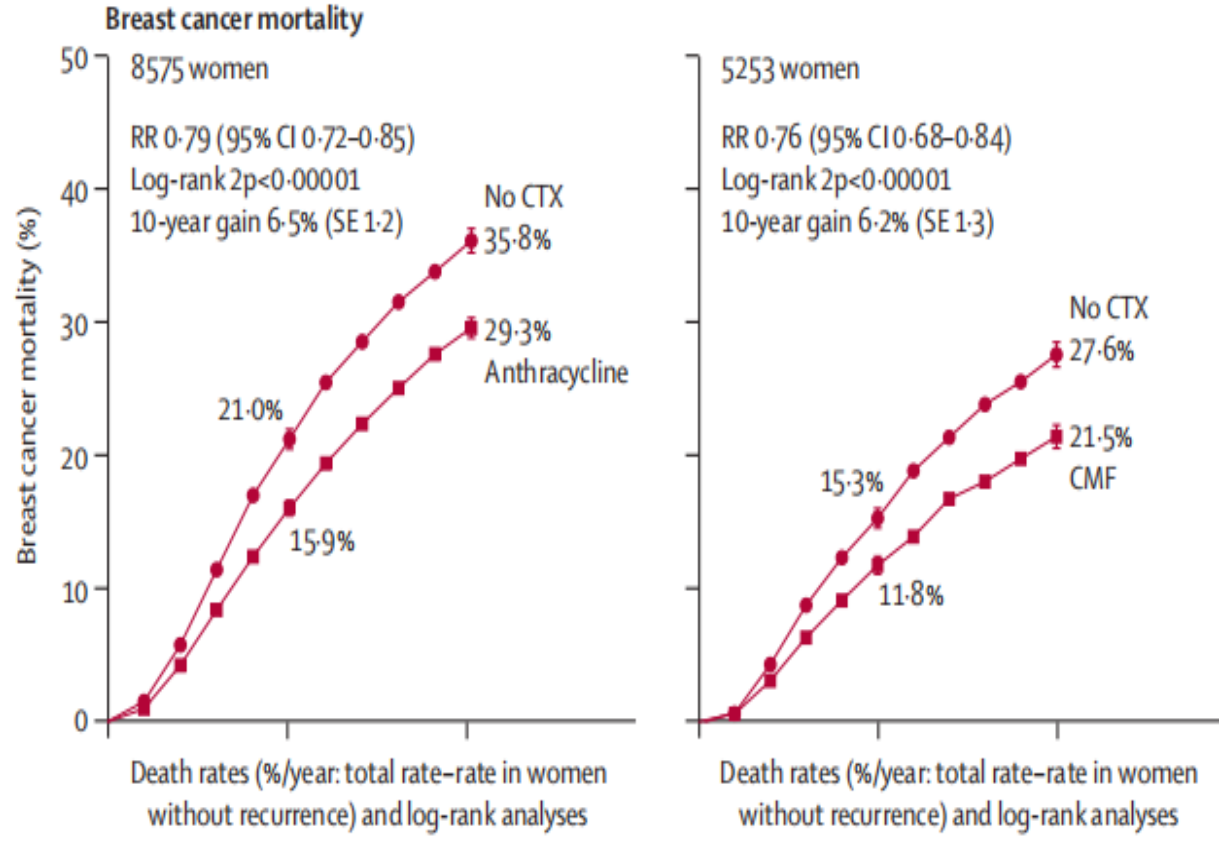

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Benefit of chemo-endocrine therapy

- 194 trials
- 6 combined meta-analyses relating to chemo-endocrine therapy
- Anthracycline-containing regimens are significantly more effective than CMF for breast cancer recurrence & mortality
- 6-months of anthracycline-based chemotherapy reduced the annual breast cancer death rate by 38% in age <50 years & by 20% in age 50-69 years, largely irrespective of ER status & endocrine therapy
- For ER+ patients, there is a further reduction of 31% with 5 years of Tamoxifen, irrespective of age & PR status.
- Thus for middle aged ER+ patients, 6 months anthracycline & 5 years of Tamoxifen provide for final mortality reductions of 57% and 45% respectively for age <50 years & 50-69 years.
- OS would be comparably improved

Lancet 2005; 365: 1687–1717

A-->T vs more A: NSABP B-28

- Phase III RCT
- N=3060 (at least one LN +)
- All patients received 4 cycles AC
- Randomised to 4 cycles of Taxane vs 4 more cycles of AC
- Taxane used was Paclitaxel 225mg/m^2 3-weekly
- (Endocrine therapy & post-BCS radiotherapy as indicated)

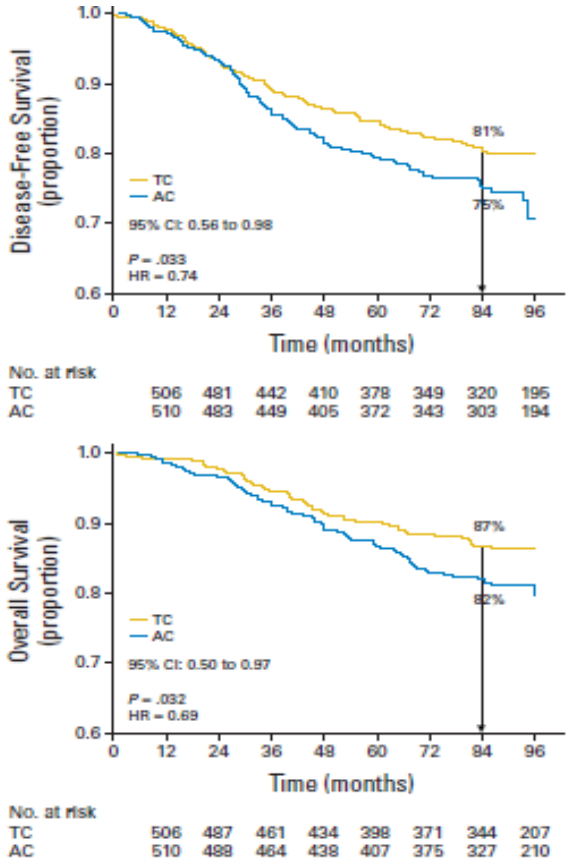
- Paclitaxel significantly improved DFS (76% +/-2% vs 72% +/-2%)
- OS was also improved but not significantly so (85%+/-2%)
- Toxicity acceptable
- No difference in outcomes based on HR status & Tamoxifen use
- Thus A->T is more effective than more A

J Clin Oncol 2005; 23:3686-3696

Should AC still be a standard of care?

- US Oncology Research Trial 9735
- Phase III RCT
- Stage I-III BC
- N=1017
- Arm A: 4 x AC (60/600 mg/m^2 3-weekly) [n=510]
- Arm B: 4 x TC (75/600 mg/m^2 3 weekly) [n=506]

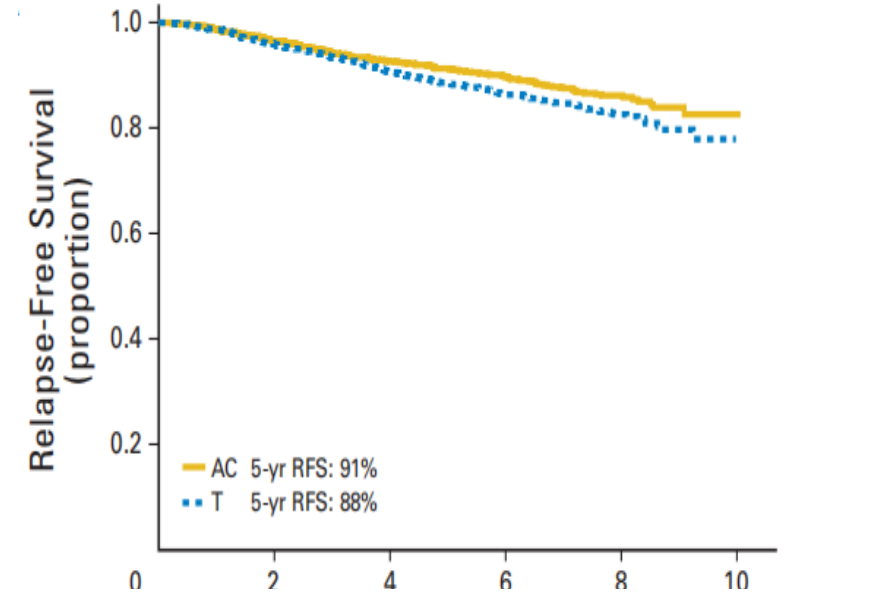
- TC was associated with significant improvement of DFS (81 % vs 73%, p=0.033)
- TC was also associated with significant improvement of OS (87% vs 82%, p=0.032)
- TC was superior irrespective of age, HR status , HER-2 status or treatment
- Older women experienced more FN with TC & more anemia with AC

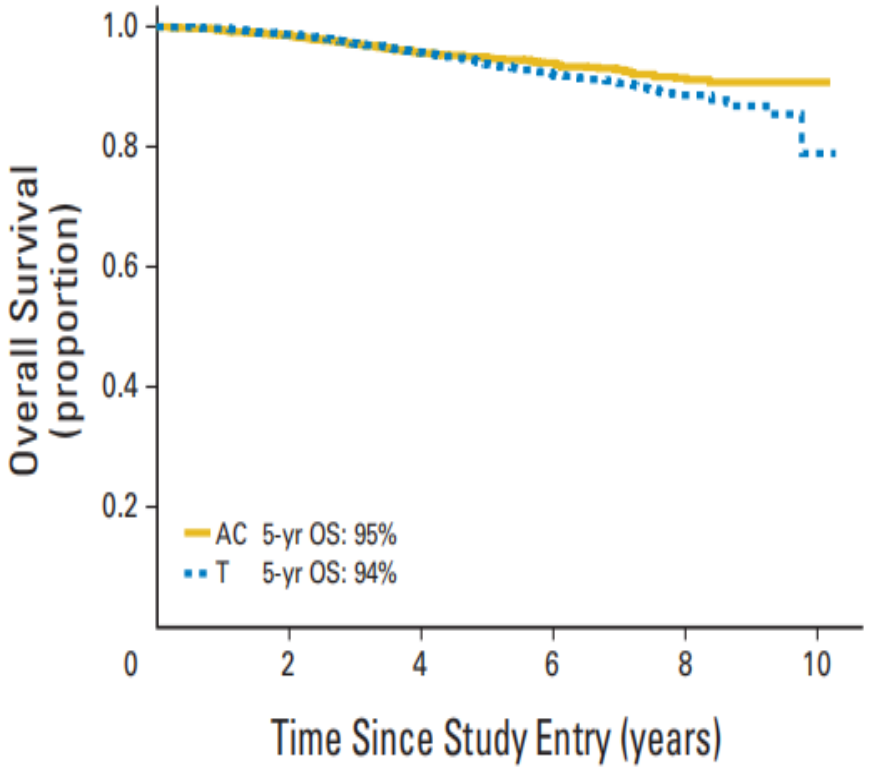


JCO 27 (2009)

AC vs T

- Taxane was not shown to be non-inferior to AC
- Estimated absolute advantage at 5 years for AC was 3% for RFS and 1% for OS
- Hematologic toxicity was more common for AC
- Neuropathy was more common for T





J Clin Oncol 2014;32:2311-17

TAC vs FAC

- Phase III RCT
- N=1060
- Node negative BC with at least one risk factor (pT>2cm, gr 2-3, ER-, age <35)
- Randomised to FAC or TAC every 3 weeks for 6 cycles after surgery

- DFS was significantly superior for TAC (90.1%) vs FAC (85.3%) (p=0.03)
- OS was not significantly different
- TAC was associated with significantly more grade 3-4 toxicity

N Engl J Med 2010;363:2200-10.

Meta-analysis of Taxanes as adjuvant in EBC

- 13 RCTs
- N=22093
- Pooled estimate of DFS was 0.83 ($p<0.00001$)
- Pooled estimate of OS was 0.85 ($p<0.00001$)
- Absolute 5-yr risk reduction for DFS was 5% and for OS was 3%.
- Benefit was seen for sequential rather than combination taxanes with anthracyclines

Benefit of taxane is independent of:

- Type of taxane used
- Age
- Menopausal status
- HR status
- No of axillary LN involved

JCO 2008;26:44-53

Taxanes in EBC-Cochrane Meta-analysis (2010)

- 12 studies
- N=18304
- No of deaths=2483
- HR for both OS & DFS was 0.81 ($p<0.00001$) favouring taxane regimens
- Did not identify a subgroup of patients where taxanes were more or less effective
- Choice of taxane, dosage & scheduling were not seen to have any significant difference

Optimal scheduling of Taxane chemotherapy

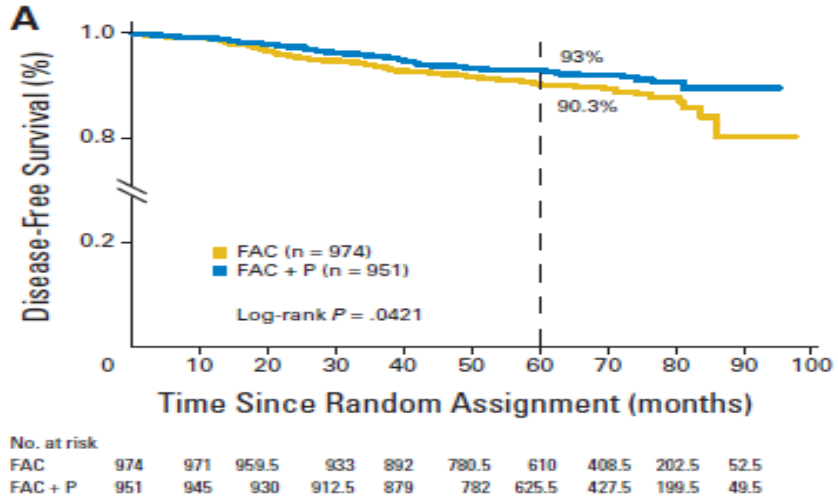
- Although earlier studies have used Taxanes in traditional 3-weekly regimen, the standard of care today is weekly Paclitaxel or 3-weekly Docetaxel
- Based on the ECOG study
- N=4950
- High risk BC (T2-T3,N0 or T1-T3,N+) post-BCS/MRM
- All patients received 4 cycles of standard AC (60/600 mg/m^2 3-weekly) [+ radiotherapy + endocrine therapy (as indicated)]
- Randomised to : weekly Paclitaxel 80 mg/m^2 x12, 3-weekly Paclitaxel 175 mg/m^2 x 4, weekly Docetaxel 35 mg/m^2 x 12 or 3-weekly Docetaxel 100 mg/m^2 x4
- Primary endpoint was DFS

N Engl J Med 2008;358:1663-71.

- Weekly Paclitaxel was associated with significantly improved OS over 3-weekly Paclitaxel
- Weekly Paclitaxel was associated with similar improvement of DFS irrespective of HR status in HER2-ve patients
- No such improvement of DFS with weekly Docetaxel was seen
- Weekly Paclitaxel & 3-weekly Docetaxel were associated with significantly improved DFS over 3-weekly Paclitaxel
- Weekly Paclitaxel was associated with significantly worse gr 2 or more neuropathy
- Overall no difference in OS between the weekly & 3-weekly arms or between Paclitaxel & Docetaxel arms

Is there any difference with Taxane scheduling after FAC?

- GEICAM/2003-02 Study
- T1-T3N0 BC
- N=1925
- Randomised to FAC x6 vs FACx4→Tx8 (weekly Paclitaxel)



- Adjuvant FAC –wP has a small but significant DFS benefit (93% vs 90% at 5 years, p =.04)
- More fatigue & peripheral neuropathy
- Less febrile neutropenia

J Clin Oncol 2013;31:2593-99

Sequential vs Concurrent Taxanes: BIG 02-98

- N=2887
- 4-arms:
- Ax4-->CMF [sequential control]
- ACx4-->CMF [concurrent control]
- Ax3-->Tx3-->CMF [sequential taxane]
- ATx4-->CMF [concurrent taxane]

- Significant DFS & OS benefit of sequential T (Docetaxel) vs others
- HRs favoured sequential T in all subtypes except Luminal A, which have the best prognosis

Nab Paclitaxel vs Solvent based Paclitaxel-EBC

- Gepar-Septo GBG 69
- Phase III RCT
- N=1229
- Randomised to Paclitaxel x12 f/b EC x 4 versus Nab-Paclitaxel x 12 f/b EC x 4
- Paclitaxel 80mg/m^2 weekly; Nab-Paclitaxel 150 mg/m^2 weekly (later modified to 125 mg/m^2 weekly)
- HER2+ patients also received anti-HER2 therapy

- Pathological Complete Response was significantly more common with Nab-Paclitaxel
- Grade 3-4 anemia & sensory neuropathy were more with Nab-Paclitaxel

Lancet Oncol 2016

Do all patients need 6 cycles of adjuvant chemotherapy?

- CALGB 40101
- N=3171; study duration 2002-2008
- Operable BC with 0-3 positive LN
- Randomised to 4 or 6 cycles of chemotherapy (AC or single agent T) [After 2003, chemotherapy given as dose-dense regimen; RT/ endocrine therapy/ Trastuzumab used as per indication]
- 4-year RFS for 6 vs 4 cycles was 90.9% vs 91.8% (p=NS)
- 4-year OS for 6 vs 4 cycles was 95.3% vs 96.3% (p=NS)
- No interaction between treatment duration & chemotherapy regimen, HR/HER-2 status

JCO 2012

Dose dense vs conventionally scheduled chemotherapy

- CALGB 9741
- N=2005

(I) sequential A x 4 --> T x 4 --> C x4 with doses every 3 weeks

(II) sequential A x 4--> Tx 4--> Cx 4

with doses every weeks with filgrastim

(III) concurrent ACx4--> Tx4 every 3 weeks

(IV) concurrent ACx 4--> Tx 4 every 2 weeks with filgrastim.

- Dose-dense regimens significantly improved DFS and OS
- No difference between DFS and OS of sequential vs concurrent schedules
- No interaction between dose density and sequence
- Severe neutropenia was less frequent in DD arms

J Clin Oncol 2003;21:1431-39.

Should older patients receive standard chemotherapy? CALGB 49907

- Stage I-IIIB BC, age >=65 years
- Bayesian statistical design (N=600-1800)
- Discontinued after 600 patients enrolled due to clear futility
- Randomised to standard chemotherapy vs Capecitabine
- Standard chemotherapy was CMF or AC
- RFS at 3-years 85% vs 68% [standard vs Cap]
- OS at 3- years 91% vs 86% [standard vs Cap]
- Conclusion: Standard chemotherapy superior for elderly patients of BC over Capecitabine

N Engl J Med 2009;360:2055-65

Predicting the benefit of Chemotherapy

Predicting the benefit of chemotherapy- Genomic

- Mammaprint (70 gene assay)
- Oncotype DX (21 gene assay)

- Oncotype DX
- 21 gene assay
- Was assessed in a German study involving 15 centres; N=366
- Offered to patients with operable EBC
- pT1-T3,pN0-N1
- Physicians had to complete a pre & post-test questionnaire
- Oncotype DX RS score resulted in a change of physician decision in 33% cases (25% resulted in addition of chemotherapy to endocrine therapy & 38% resulted in omission)
- Using the test was cost-effective versus standard clinical practice

Annals of Oncology 2013;24:618-24

MINDACT

- Phase III RCT
- EBC
- N=6693
- Genomic risk (using Mammaprint) & Clinical risk (using Adjuvant!Online) were determined
- High clinical & genetic risk patients received chemotherapy, whereas those with low risk did not
- For discordant results, patients were randomised to chemotherapy or no chemotherapy

- 1550 patients were at high clinical & low genomic risk
- Survival without DM in this group for patients who did not receive chemotherapy vs those who did was 1.5 % lower (95.9% vs 94.4% at 5 years)
- Thus, around 46% of patients who are at high clinical (but low genomic risk) can safely be spared chemotherapy
- There was no advantage of chemotheapy for patients with low clinical but high genomic risk
- DVS & OS were not different in the chemotherapy vs no chemotherapy groups

N Engl J Med 2016;375:717-29.

Side effects of chemotherapy

- Nausea-vomiting
- Alopecia/ nail bed changes
- Malaise/ fatigue
- Diarrhoea/constipation
- Peripheral neuropathy
- Bone marrow depression & failure
- Immunosuppression
- Congestive heart failure
- Ischemic heart disease
- Infertility
- Gonadal failure
- Tissue damage due to drug extravasation
- Second malignancy

Alternatives to genomic selection

- IHC4 (ER, PR, HER-2 & Ki-67)

- Similar prognostic information
- Some concern about false +ve & false -ves on IHC

Predicting the benefit of chemotherapy- Clinical

- Genetic testing may be difficult/ expensive
- Good clinical surrogates can help drive decision making
- PREDICT 2.0/ Adjuvant!Online

- Considers age at presentation, mode of presentation, T-size, number of LN involved, grade, ER status, Ki-67 status
- Older patients with smaller tumors & pN0 disease & ER positivity may get only marginal benefit with chemotherapy plus endocrine therapy vs endocrine therapy alone

Neoadjuvant chemotherapy

Principles of neoadjuvant chemotherapy

- In general, survival is similar for neoadjuvant vs adjuvant chemotherapy

Advantages :

- Facilitate BCS (eg where large tumor in small breast)
- Convert inoperable tumors to operable (T4/ bulky N2/N3)
- Allow time for genetic testing
- Allow time for breast reconstruction in patients planned for mastectomy

Disadvantages with neoadjuvant chemotherapy

- Possible overtreatment (as exact pathological stage is unknown)
- Possible undertreatment (especially in case of good response!, especially after BCS in LABC)
- Possible disease progression, as main locoregional therapy is delayed
- Contra-indication: wherever disease extent cannot be accurately measured

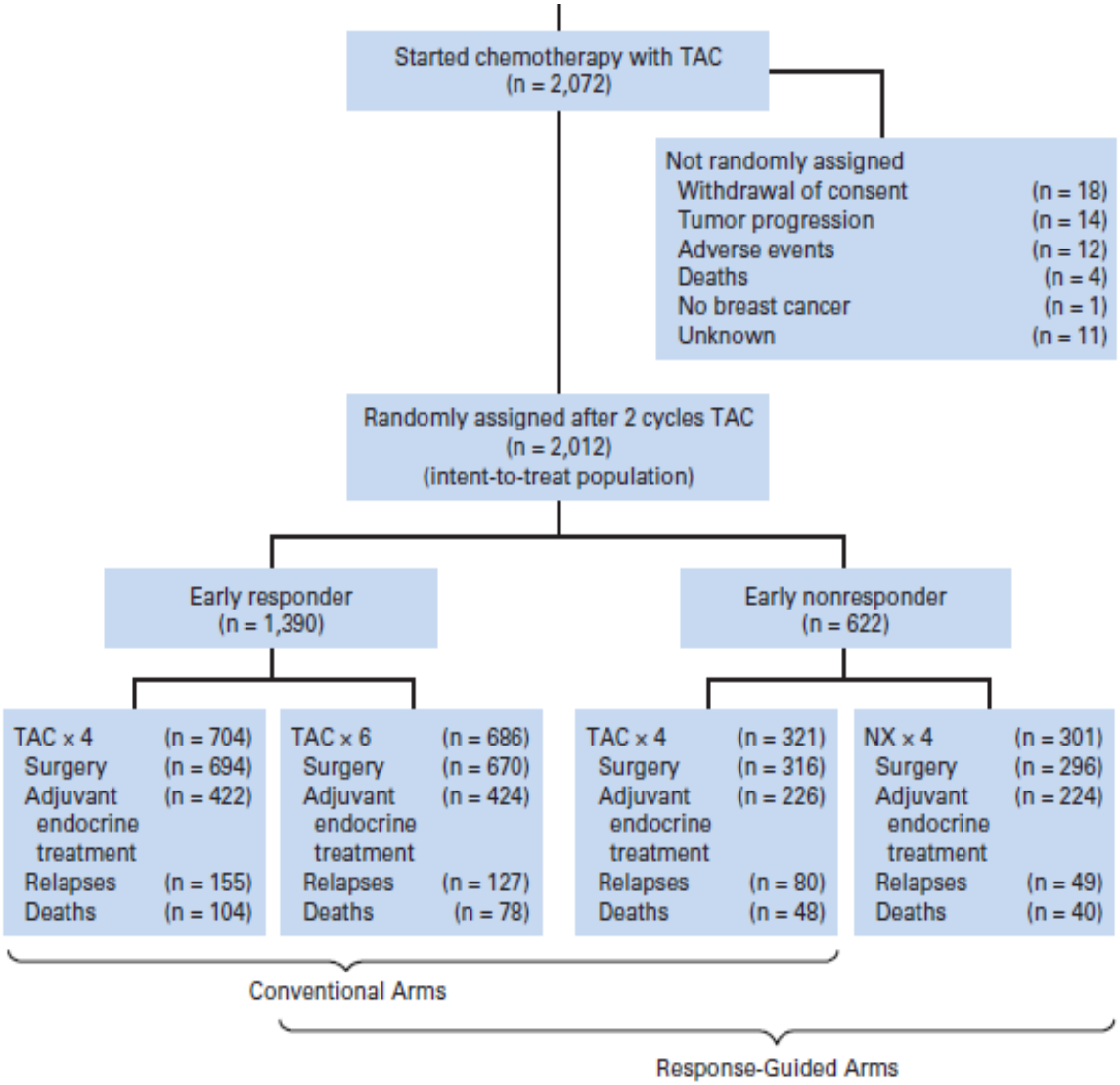
Adjuvant vs Neoadjuvant chemotherapy EBCTCG 2018

- 10 trials (1983-2002)
- N=4576
- NACT in EBC
- 69% of patients had CR/PR
- Patients allocated NACT were more likely to have BCS (65% vs 49%)
- Patients allocated NACT had significantly more local recurrence (at 15 years, 21.4% vs 15.9%, p=0.0001). However, all these were older trials using regimens which are not standard for modern practice (no anti-HER2 therapy as well)
- There were no differences in distant recurrence, breast cancer mortality or death from any cause

Lancet Oncol 2018; 19: 27–39

- Effect of NACT was more in larger tumors (2-4cm) & less significant for smaller tumors (<2cm)
- Proportional increase in LR did not vary significantly by tumor size or chemotherapy regimen

Can response to NACT help to tailor further chemotherapy?



- GeparTrio study
- N=2072

- DFS & OS were superior after response-guided chemotherapy
- DFS was superior for HR+ tumors but not HR-tumors
- pCR predicted for superior DFS in HR- tumors.

J Clin Oncol 2013;31:3623-30

How important is pCR after NACT?

- pCR defined as no infiltrative or insitu residual in breast or nodes
- N=6377
- Patient data from 7 RCTs using NACT
- DFS for patients achieving pCR was significantly superior
- pCR was associated with improved DFS in case of luminal type B-HER2 negative, HER2 positive non-luminal & triple negative BC [aggressive subtypes]
- pCR did not correlate with improved DFS for luminal type A and type B-HER2 positive [slowly proliferating subtypes]

J Clin Oncol 2012;30

NACT vs NAHT

- Meta-analysis
- 20 studies
- N=3490
- NAHT with AI had a similar clinical & radiologic response rate & BCS rate
- NAHT had lower toxicity

- NAHT with AI was superior to Tam for RR & BCS rate
- NAHT with AI+TKI had superior radiologic but not clinical RR

JAMA Oncol 2016

Chemotherapy for Locoregional Recurrence

Chemotherapy in Isolated Locoregional Recurrence

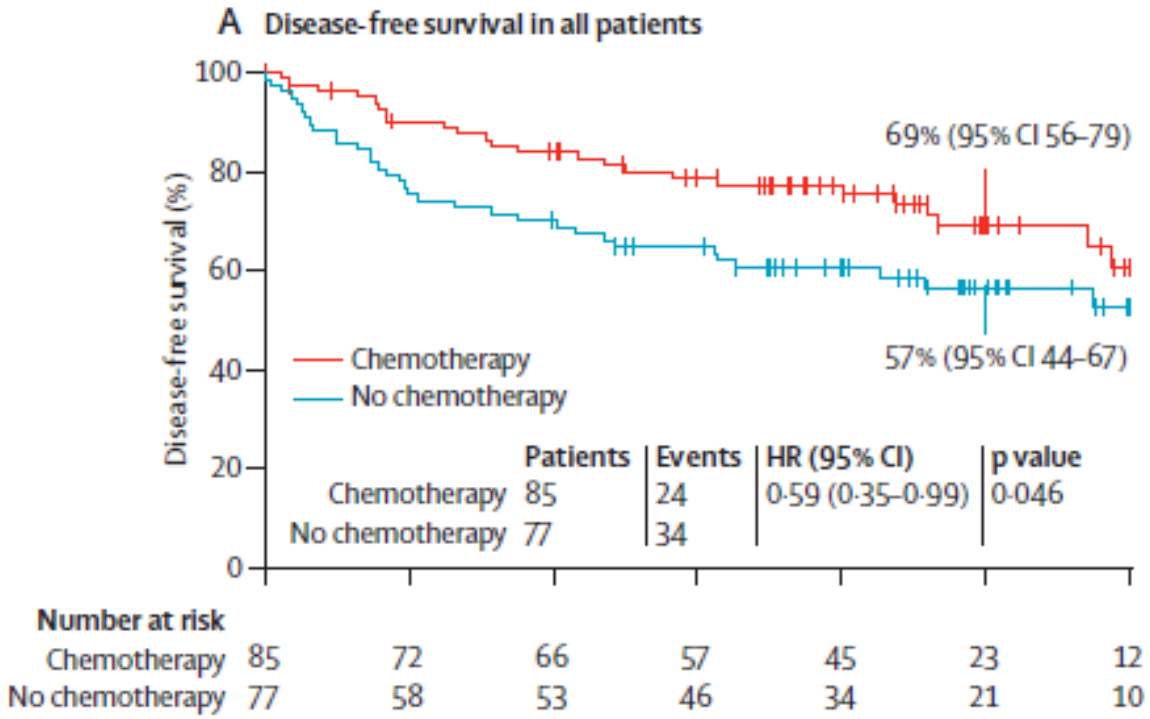
- Controversial area
- Surgery is a must for ILRR; most cases would receive adjuvant radiotherapy as well
- The CALOR trial is the first randomised study to show benefit of adjuvant chemotherapy in ILRR

CALOR trial

- Multicentric phase III randomised controlled trial
- Expected improvement of 5-yr DFS with adjuvant chemotherapy =10% (from 50% to 60%)
- N=162
- Surgery + RT (N=77) vs Surgery + RT + chemotherapy (N=85)
- RT was recommended in all margin +cases
- Endocrine therapy for ER+
- Anti-HER therapy optional
- No definite chemotherapy protocol but multidrug & 4 doses mandatory

Lancet Oncol 2014; 15: 156–63

- 5-yr DFS with chemotherapy vs without was 69% vs 57% (p=0.046)
- The benefit was more with ER- patients (though not statistically significant)
- Interpretation: Adjuvant chemotherapy should be recommended in patients of completely resected ILRR of breast cancer, especially where the ILRR is ER negative



Chemotherapy for Metastatic Disease

Indications for chemotherapy in Metastatic disease

- HR negative tumors
- HR positive tumors with symptomatic visceral metastases
- HR positive tumors with progression/ unacceptable toxicity after 3 lines of endocrine therapy

Principles of chemotherapy in Metastatic disease

- Little compelling evidence that multiagent chemotherapy is superior to single agent chemotherapy in terms of response rate
- Multiagent chemotherapy is also more toxic
- In general, chemotherapy would be continued till progression/ death/ unacceptable toxicity
- Increasing role of locoregional treatment even in M1 disease

MBC chemotherapy regimens-HER2 negative [NCCN 2019]

Preferred:

- Doxorubicine
- Liposomal Doxorubicin
- Paclitaxel
- Gemcitabine
- Capecitabine
- Vinorelbine
- Eribulin
- PARP inhibitors (BRCA mut)
- Platinums (TNBC + BRCA mut)
- Atezolizumab (TNBC with PD-L1 +)

Useful in selected cases:

- AC
- EC
- CMF
- Paclitaxel + Bevacizumab
- Docetaxel + Capecitabine
- Gemcitabine +Paclitaxel
- Gemcitabine + Carboplatin

Other recommended:

- Cyclophosophamide
- Docetaxel
- Ixabepilone
- Epirubicin
- Nab-Paclitaxel

MBC chemotherapy regimens-HER2 positive [NCCN 2019]

Preferred:

- Pertuzumab + Trastuzumab + Docetaxel
- Pertuzumab + Trastuzumab + Paclitaxel

Other recommended:

- T-DM1
- Trastuzumab +Docetaxel
- Trastuzumab + Paclitaxel +/- Carboplatin
- Trastuzumab + Capecitabine
- Trastuzumab + Vinorelbine
- Trastuzumab + Lapatinib
- Lapatinib + Capecitabine
- Docetaxel
- Ixabepilone
- Epirubicin
- Nab-Paclitaxel

Taxanes vs Anthracyclines as 1st line in MBC

- IPD from 8 RCTs
- N=3034
- Single agent trials: similar RR & OS. For PFS, Taxanes have significantly worse HR (p=0.011)

- (Data in favour of Anthracycline single agent is driven by a single trial using 3-weekly Paclitaxel as as a comparator)

- Combination trials: similar OS, but significantly better RR (p<0.01)and PFS (p=0.031) with Taxanes

JCO 2008;26:1980-86

Which is the best Taxane in MBC?

- Phase III RCT
- N=449
- Randomised to 3-weekly Paclitaxel 175 mg/m^2 or Docetaxel 80 mg/m^2
- Till progression or unacceptable toxicity

- Docetaxel was associated with significantly better DFS & TTP
- Docetaxel also had higher RR (though not significant)
- Both hematologic & non-hematologic toxicities were more with Docetaxel
- However, global QoL scores were not different between the 2 arms

J Clin Oncol 2005;23:5542-51

Nab Paclitaxel vs Solvent based Paclitaxel-MBC

- ABI-007
- Phase III RCT
- N=460
- Randomised to Paclitaxel x 3 versus Nab-Paclitaxel x 3
- Paclitaxel 175mg/m^2 3-weekly; Nab-Paclitaxel 260 mg/m^2 3-weekly
- HER2+ patients also received anti-HER2 therapy

- Response Rate & Time to Tumor Progression were significantly more common with Nab-Paclitaxel
- Grade 3-4 anemia & febrile neutropenia were less common with Nab-Paclitaxel
- Grade 3-4 sensory neuropathy was more with Nab-Paclitaxel

J Clin Oncol 2005;23:7794-7803

Gemcitabine in MBC

- Phase III RCT
- Locally recurrent or metastatic BC
- Prior anthracycline (but not taxane) chemotherapy
- Gem+ Paclitaxel vs Paclitaxel
- Gem given as D1,D8
- Paclitaxel given 3 weekly

- Median survival for GT was 18.6 months vs 15.8months for T (p=0.0489)
- RR was 41.4% vs 26.2%(P=0.0002)
- TTP was 6.14 months vs 3.89 months(p=0.0002)
- Registration trial for FDA approval of GT for Breast Cancer

J Clin Oncol 2008;26:3950-57

Is more chemotherapy better?

- Meta-analysis of 11 RCTs
- N=2269
- Longer first-line chemotherapy duration resulted in significantly better DFS & OS
- No differences based on number of cycles or concomitant endocrine therapy

J Clin Oncol 2011;29:2144-2149

Take Home Messages

Early Breast Cancer

- Polychemotherapy is standard of care
- Anthracycline-containing regimens are superior to CMF
- Taxane-containing regimens are generally superior to regimens based only on anthracyclines
- Sequential taxanes are preferable
- If using Paclitaxel, weekly administration preferred

- It is possible to combine clinical & genomic data to determine the group of patients most benefited by chemotherapy
- Neoadjuvant chemotherapy followed by BCS may lead to worse locoregional control
- It is possible to tailor adjuvant chemotherapy based on response to neoadjuvant chemotherapy
- pCR is a robust predictor of outcome

Advanced Breast Cancer

- Chemotherapy after local treatment provides benefit in isolated locoregional recurrence
- In MBC, endocrine therapy remains standard of care for HR+ patients without visceral crisis
- Chemotherapy in MBC is indicated in patients with HR- disease & in HR+ after 3 lines of endocrine therapy or in case of visceral crisis, where urgent response is required
- Both single & multi-agent chemotherapy regimens available
- Anthracycline-naïve patients should receive Anthracyclines first, if using single-agent chemotherapy
- Taxane-containing regimens are superior
- Docetaxel is superior to Paclitaxel in MBC
- Novel agents like Gemcitabine, Ixabepilone & Nab-Paclitaxel are of increasing benefit
- For HER2+ MBC, there has been tremendous progress in targeted therapy , giving it a pivotal role