AIFA-UNICRI- OPBG-NIMR
Training Course
"Good Clinical Practices (GCP) in developing settings: the promotion of international harmonization for the respect of ethical principles, human rights and justice"

11-14 June 2012
The National Institute for Medical Research (NIMR) Campus
Isamilo Road, Mwanza
Tanzania

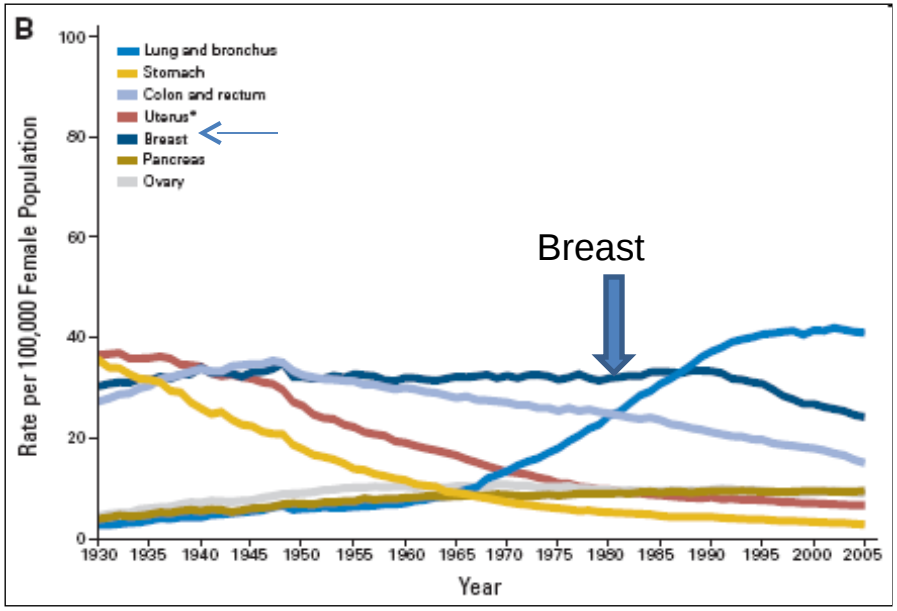
"The natural history of tumors as a basis for controlled clinical trials: breast and cervical tumors and specific methodological aspects of clinical trials"

Dino Amadori
Scientific Director IRCCS - IRST

BREAST CANCER EPIDEMIOLOGY

***Clinical Cancer Advances**: major research advances in cancer treatment, prevention, and screening*

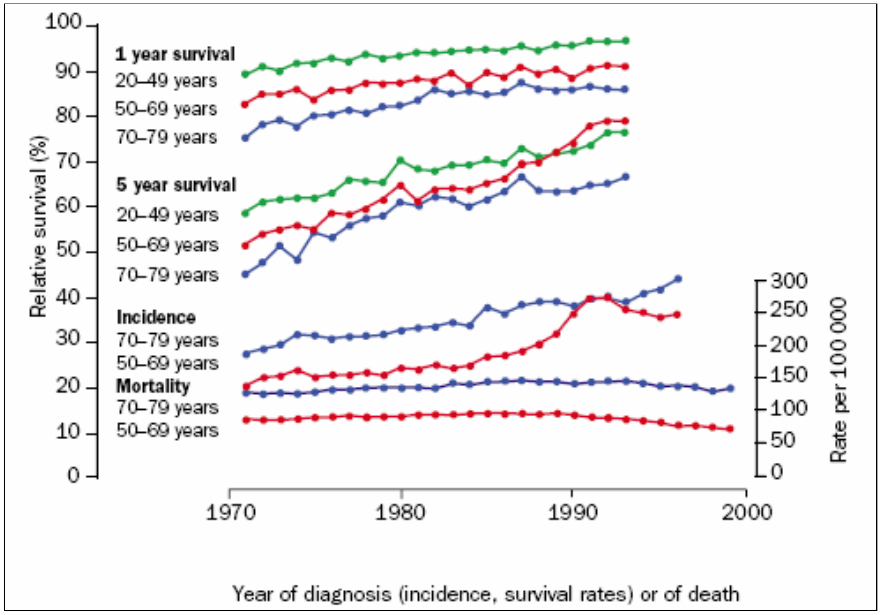
*Since 1990, **american** cancer **mortality rates have declined** by 15%*



*Age-adjusted cancer death rates by site in the **United States** from 1930 to 2005 for women*

Petrelli NJ, Winer EP, JCO 2009

*The **continuing fall** in breast **cancer mortality** in **England and Wales***



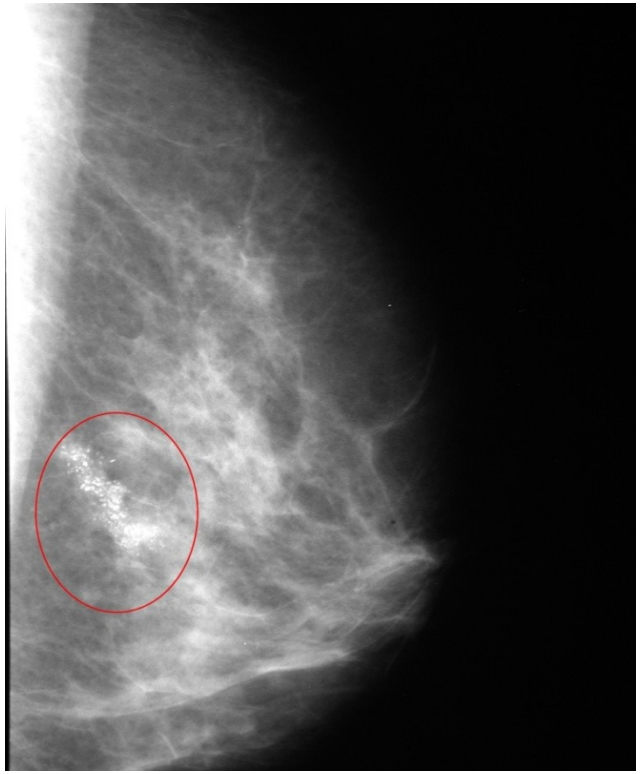
Survival rates for women diagnosed with breast cancer in England and Wales aged 20–49 years, 50–69 years, and 70–79 years during 1971–93

Peto. The Lancet 2000

BREAST CANCER SCREENING

Breast cancer meets all criteria for screening

1. *Breast cancer is an important public health problem*
2. *Smaller tumor size at diagnosis conveys greater likelihood of cure*
3. *There are treatments available that alter the natural history of the disease*
4. *Screening test is easy to administer, safe and relative inexpensive*



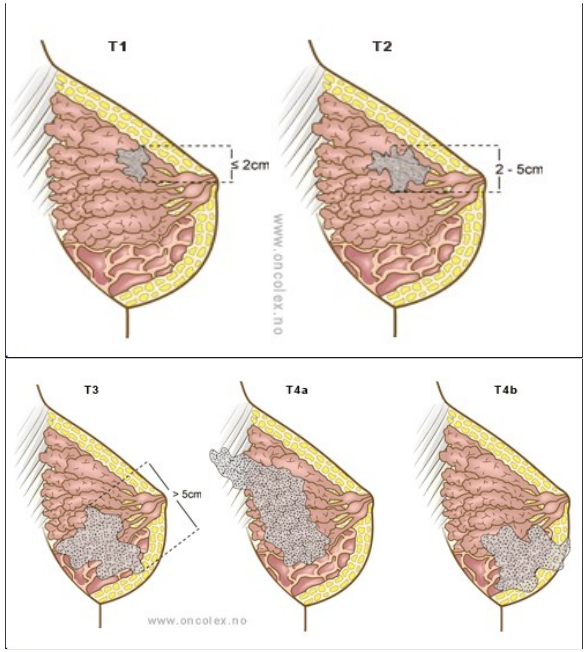
Mammography *is the screening test*

Mammographic screening for breast cancer demonstrably lowers mortality in women ***aged 50 years and older and in women aged from 40 to 49 years***

BREAST CANCER STAGING

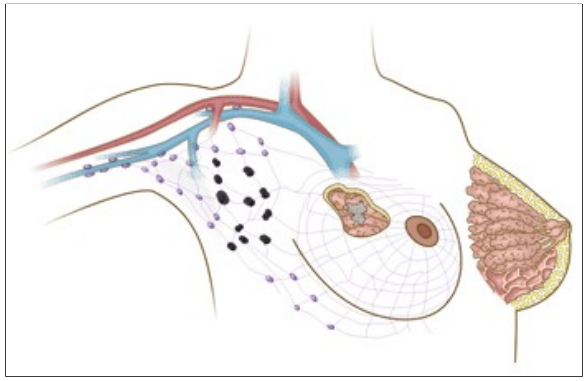
T: Tumor Size

- ***TX**: Tumor cannot be assessed*
- ***T0**: No evidence of a tumor*
- ***Tis**: Cancer in situ (LCIS, DCIS or Paget's disease)*
- ***T1**: Tumor is ≤ 2 cm*
- ***T2**: Tumor is > 2 and < 5 cm*
- ***T3**: Tumor is > 5 cm*
- ***T4**: Tumor is any size, has attached itself to the chest wall and spread to the pectoral (chest) lymph nodes*



N: Palpable Nodes

- ***NX**: lymph nodes cannot be assessed (lymph nodes were previously removed, etc.)*
- ***N0**: cancer has not spread to lymph nodes*
- ***pN1mi**: micrometastasis (> 0.2 mm, but < 2 mm)*
- ***N1**: metastasis in 1-3 ipsilateral axillary lymph node(s)*
- ***N2**: metastasis in 4-9 ipsilateral axillary lymph nodes*
- ***N3**: metastasis in 10 or more ipsilateral axillary lymph nodes*



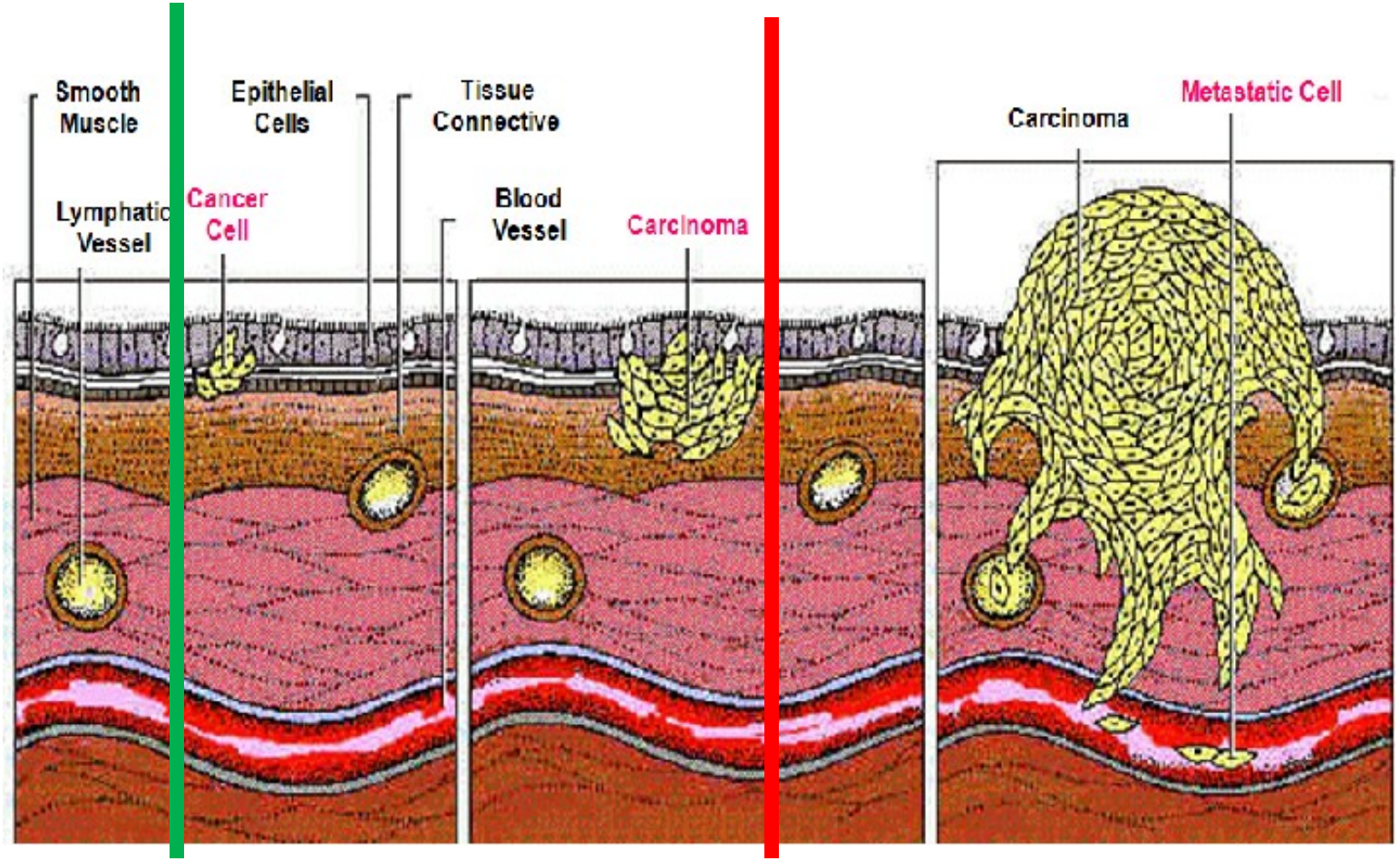
M: Metastasis

- ***MX**: metastatis cannot be assessed*
- ***M0**: no distant metastasis to other organs*
- ***M1**: distant metastatis to other organs*

CARCINOGENESIS…

Primary Prevention
Chemoprevention

Early Diagnosy:
Secondary prevention



Systemic treatment of breast cancer has 4 main objectives a function of phase of disease

*1.To reduce risk of incidence of cancer in subpopulation at high risk (**CHEMOPREVENTION TREATMENT**)*

*2.To reduce risk of relapse after surgical remuval of breast cancer (**ADJUVANT TREATMENT**)*

*3.To reduce the volume of cancer mass before surgical remuval (**NEOADJUVANT OR PRIMATY TREATMENT**)*

*4.To control advanced disease improving survival (**TREATMENTE OF ADVANCED DISEASE** with first, second, third lines of treatment)*

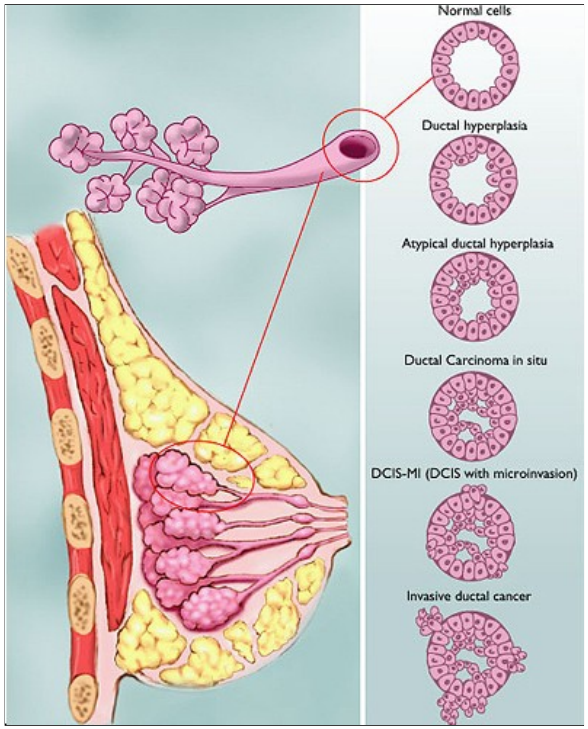
*5.To reduce disease related symptoms improving quality of life (**PALLIATIVE TREATMENT**)*

PREMALIGNANT AND IN SITU BREAST DISEASE

- *atypical ductal hyperplasia (ADH),*
- *atypical lobular hyperplasia (ALH),*

- *lobular carcinoma in situ (LCIS):*
  - *LIN1,*
  - *LIN2.*

- *Ductal carcinoma in situ (DCIS) →preinvasive malignant lesion:*
  - *DIN1b,*
  - *DIN2,*
  - *DIN3.*

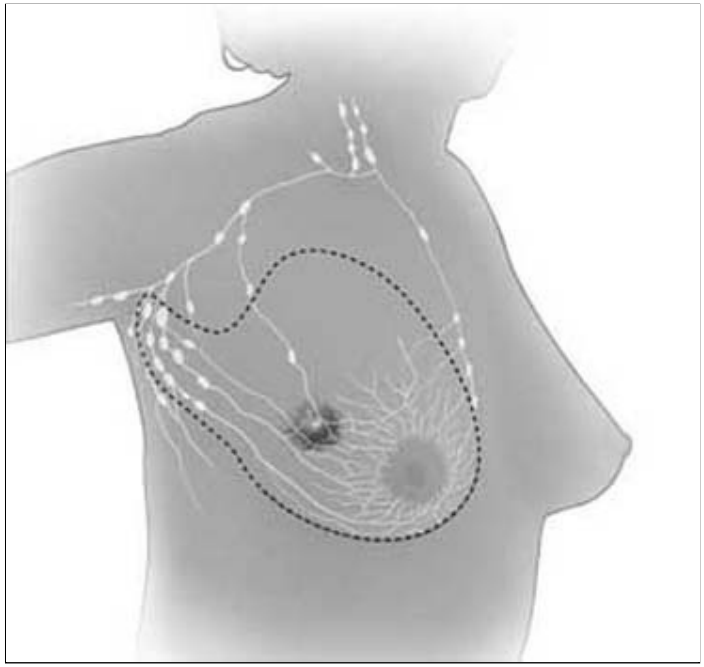


*An **increased risk is assigned for progressing to a malignant lesion without a treatment***

↕ ***CHEMOPREVENTION TREATMENT***

What kind of treatment for premalignant lesions is recommended?

SURGICAL OPTIONS



Treatment of the Breast

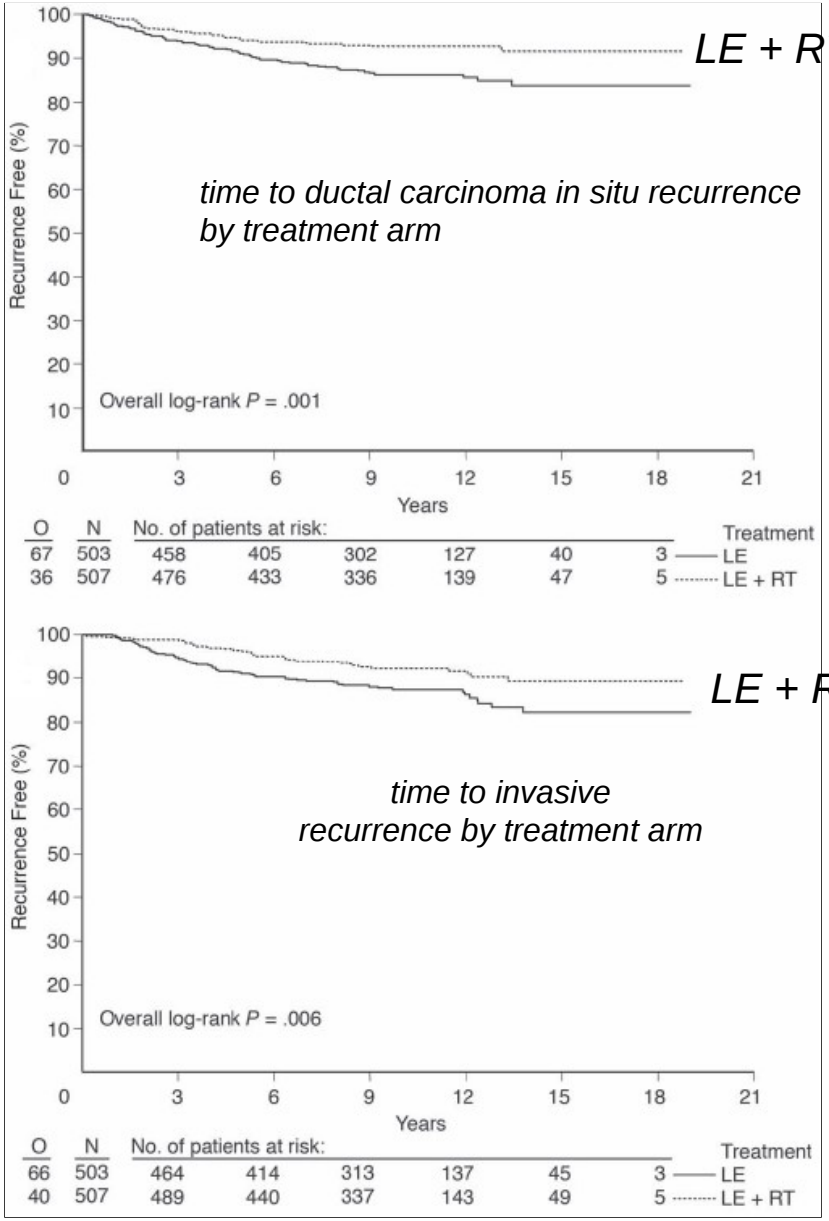
Mastectomy *is recommended for multicentric DCIS when there are diffuse malignant calcifications and when negative margins cannot be obtained.* ***Breast-conserving surgery with radiation*** *is recommended for those with localized DCIS excised to clear margins.*

Treatment of axilla

In the early 1980s, axillary dissection was the standard procedure, but metastases were rarely detected using conventional histology (<1%).

At today ***axillary dissection and BLS are not performed*** *because* ***risk of isolated axillary recurrence with no axillary surgery is less than 0.1%, regardless of whether RT and tamoxifen are administered***

RADIOTHERAPY



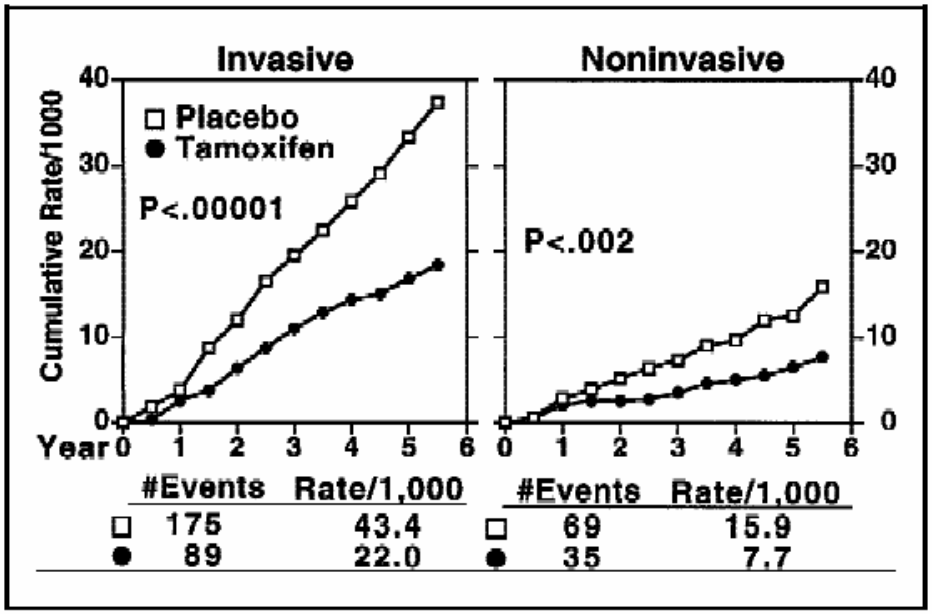
Breast-Conserving Treatment With or Without Radiotherapy in Ductal Carcinoma-In-Situ

With long-term follow-up, RT after local excision (LE) for DCIS continued to reduce the risk of local recurrence (in situ or invasive), with a 47% reduction at 10 years.

Nina Bijker, JCO 2006

CHEMOPREVENTION with tamoxifen

LCIS ***is typically positive for ER and PR staining by IHC*** *and negative for HER-2/neu so there is a rationale for endocrine chemoprevention*

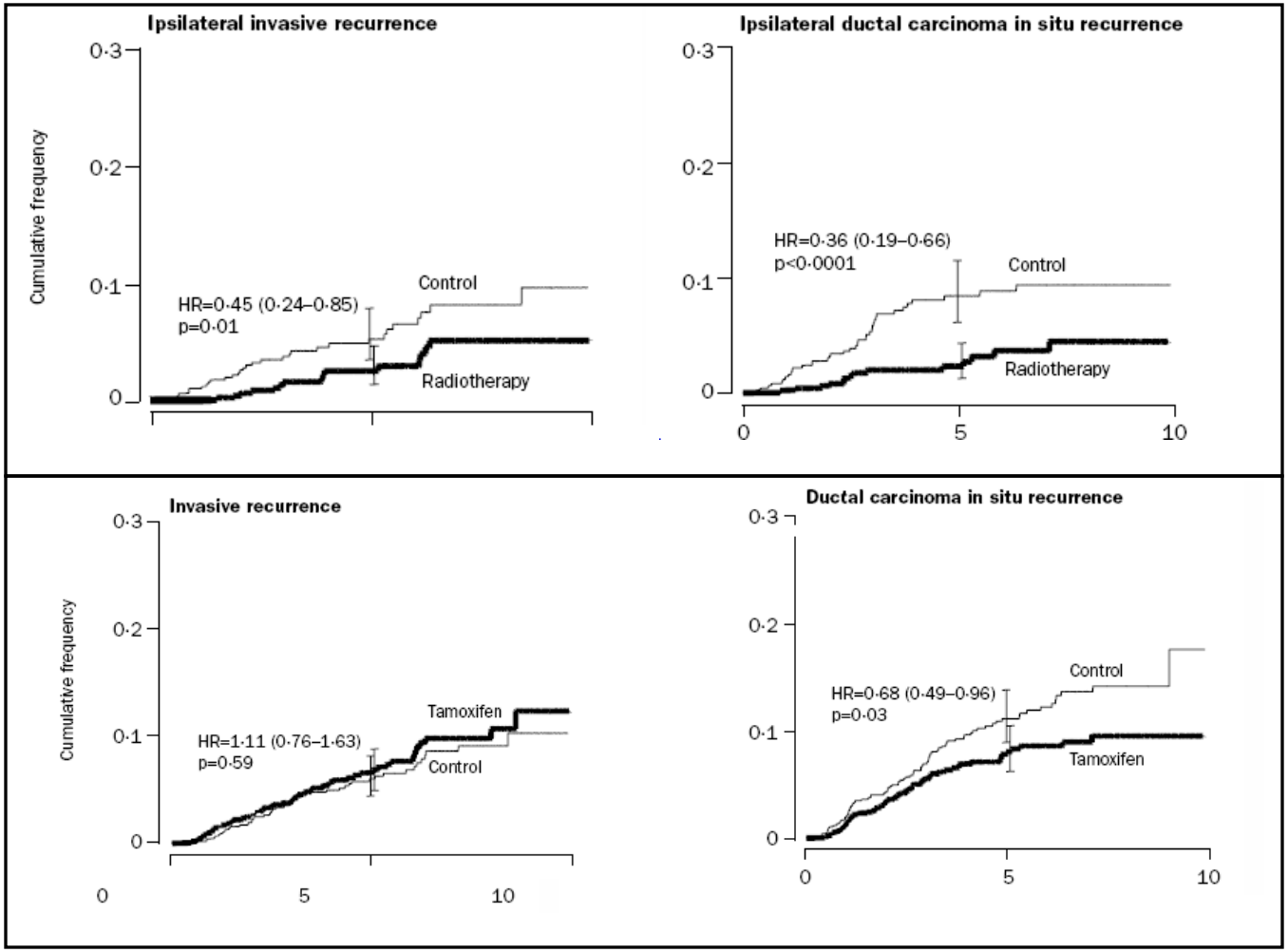


Tamoxifen *decreases the incidence of invasive (49%) and noninvasive (50%) breast cancer*

Fisher B, J Natl Cancer Inst. 1998 : NSABP P1 study

RADIOTHERAPY and CHEMOPREVENTION

Radiotherapy and tamoxifen in women with completely excised DCIS

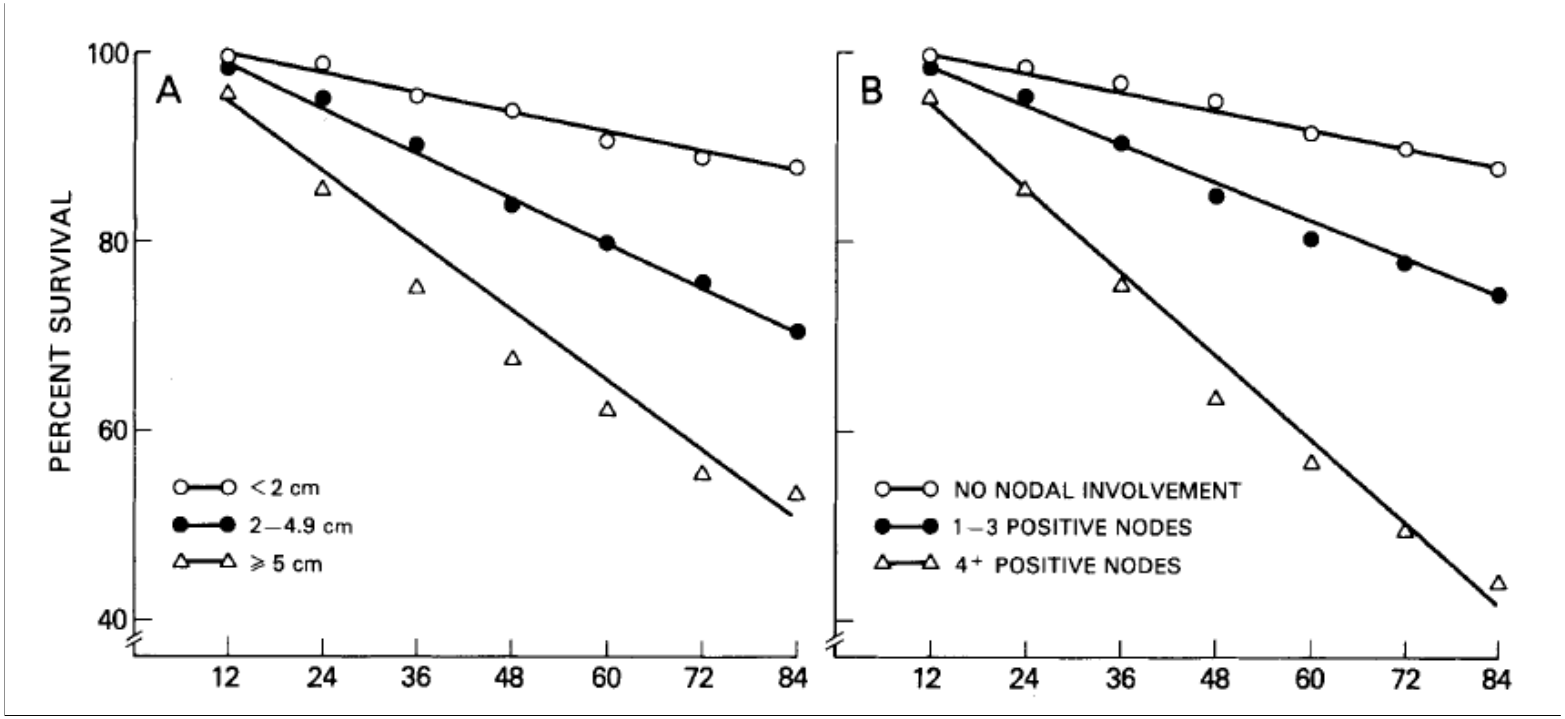


Radiotherapy can be recommended for patients with DCIS treated by complete local excision; however, there is little evidence for the use of tamoxifen in these women

Houghton J, Lancet 2003

BREAST CANCER PROGNOSIS

*Relation of **Tumor Size**, **Lymph Node Status** and survival in breast cancer*



Breast cancer survival is a function of primary tumor diameter and nodal status

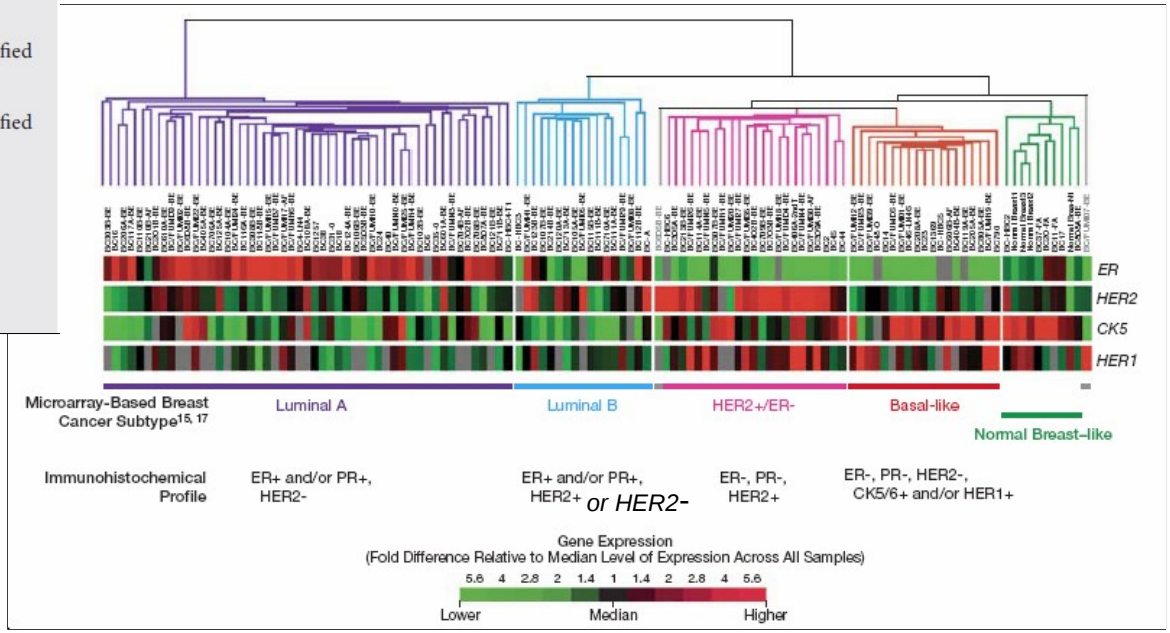
L. Carter, Cancer 1989

Breast cancer IS NOT a single disease

We can identify different subtypes defined by genetic array testing or by immunohistochemistry

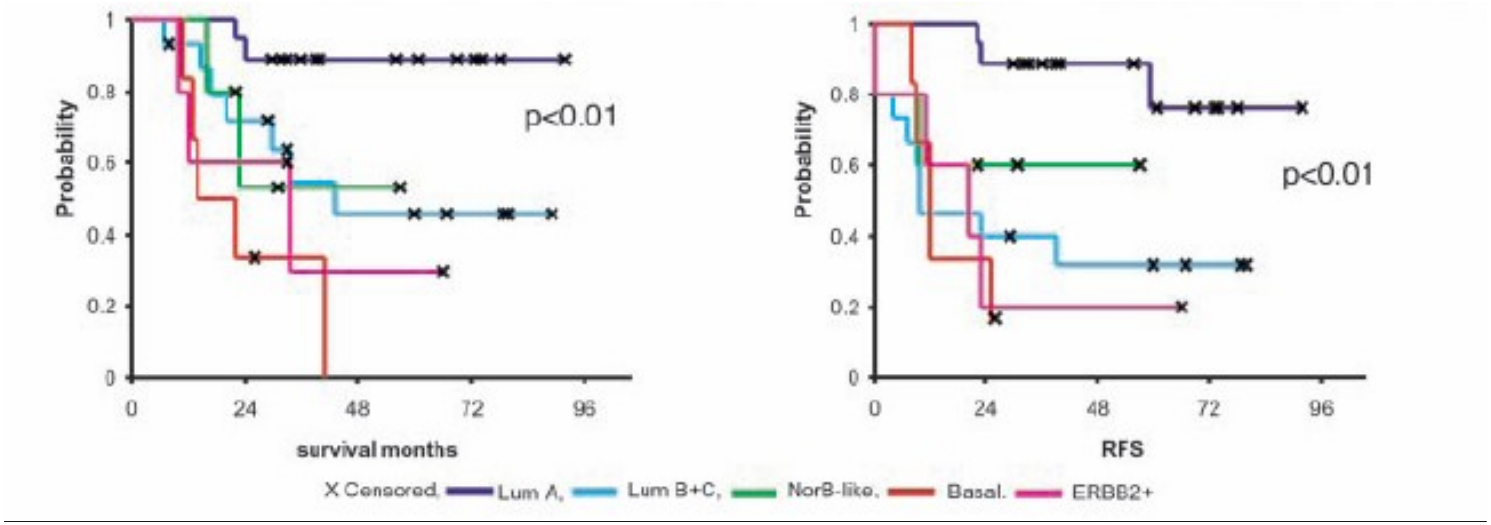
Intrinsic Subtype (1)	Clinico-pathologic definition
Luminal A	**'Luminal A'** ER and/or PgR positive(76) HER2 negative (77) Ki-67 low (<14%)*
Luminal B**	**'Luminal B (HER2 negative)'** ER and/or PgR positive HER2 negative Ki-67 high **'Luminal B (HER2 positive)'** ER and/or PgR positive Any Ki-67 HER2 over-expressed or amplified
Erb-B2 overexpression	**'HER2 positive (non luminal)'** HER2 over-expressed or amplified ER and PgR absent
'Basal-like'	**'Triple negative (ductal)'** ER and PgR absent HER2 negative

St Gallen meeting, 2011



Adapted from Lisa Carey. JAMA 2006

Different tumor subclasses have clinical implications



Survival analyses on a subcohort of patients with locally advanced breast cancer ***uniformly treated*** *in a prospective study*

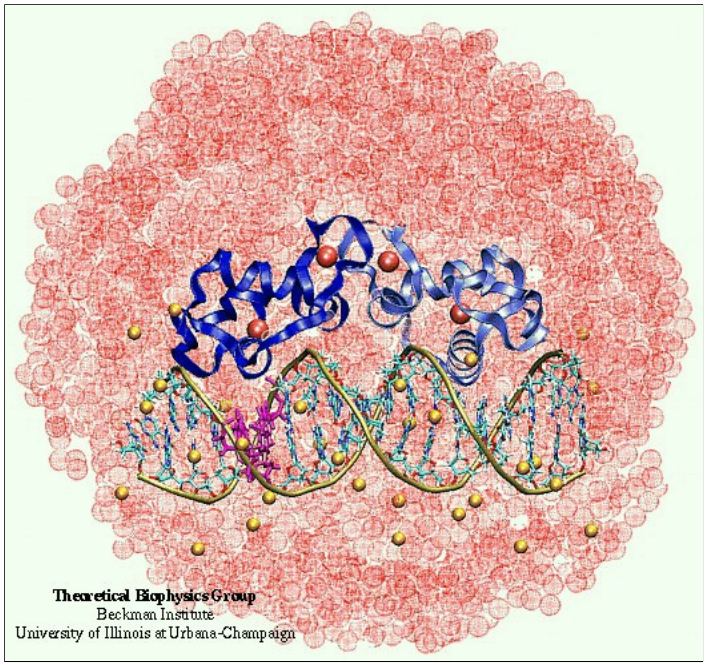
There is ***significantly different outcomes for the patients belonging to the various groups.***

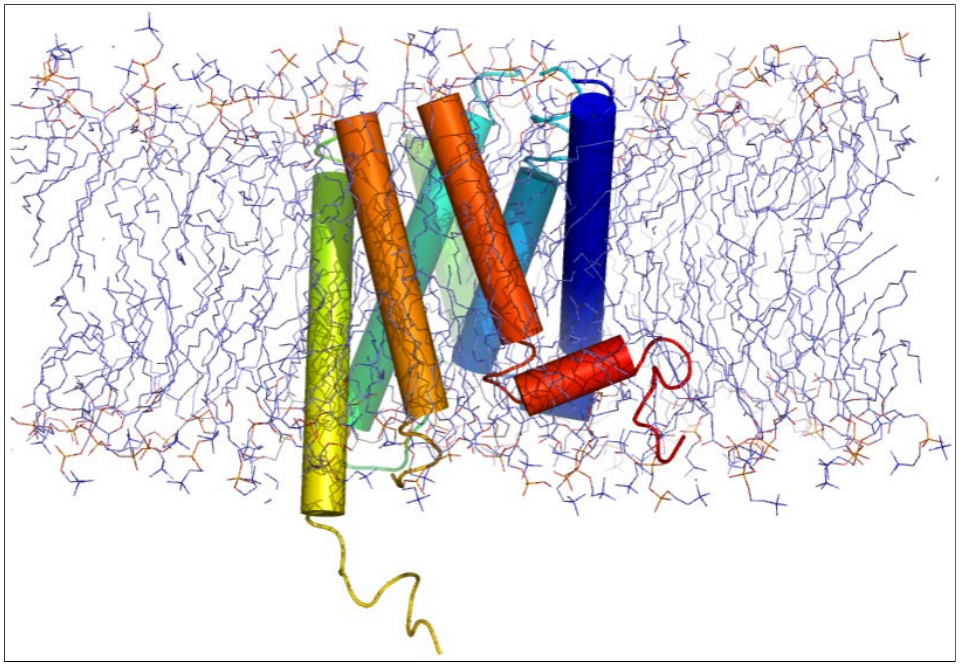
We can observe a ***poor prognosis for the basal-like subtype and HER2/ ER− subtype*** *and a significant difference in outcome for the two estrogen receptor-positive groups.*

Sørlie. PNAS 2001

*The **identification** of estrogen receptor **(ER)** and Human Epidermal Growth Factor Receptor 2 **(HER2)** and the discovery of their role in breast cancer proliferation was a milestone in the breast cancer story.*

*It allowed the development of specific **drug able to target and to block** these receptors obtaining cancer cells death: **antiestrogen agents** and **trastuzumab***



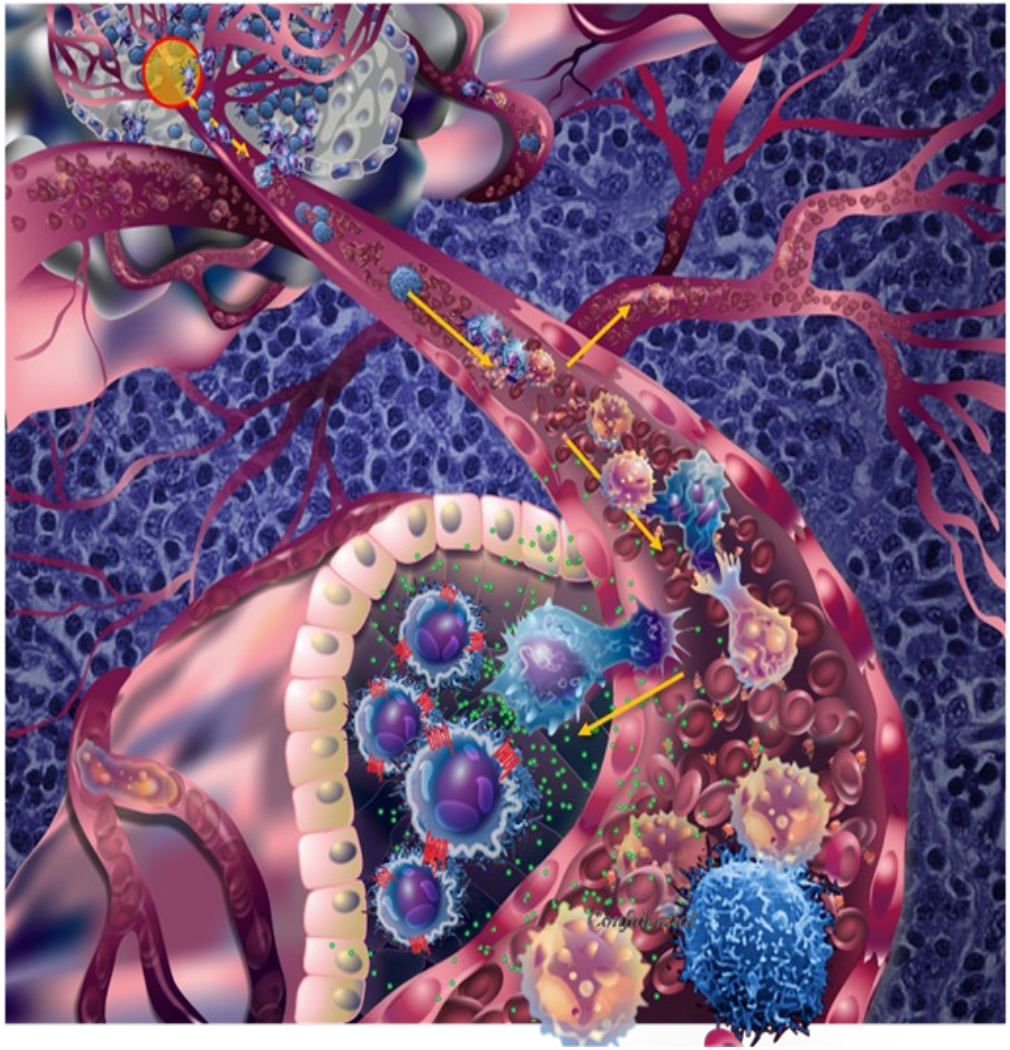


Nuclear ER ← **antiestrogen agents**

Transmembrana HER2 ← **trastuzumab**

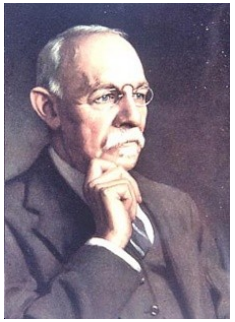
ADJUVANT SYSTEMIC TREATMENT

is the treatment administered after surgical treatment



The objective is to ***eradicate micrometastatic deposits of tumor that are present at the time of diagnosis in order to avoid relapse of disease***

Double Helix of Breast Cancer Therapy: Intertwining the Halsted and Fisher Hypotheses



William Stewart Halsted

Bernard Fisher

Halsted hypothesis

paradigm of the preceding for the surgeon

Breast cancer as a disease spreading in an orderly and typically contiguous manner*: from breast to lymph nodes and only then to distant metastatic sites.*

Fisher hypothesis

The systemic hypothesis of breast cancer

Breast cancer is considered a systemic disease at time of diagnosis*, a condition requiring treatment of the entire patient rather than just the source organ.*

We have the ***necessarily double-stranded approach*** *to* ***prevent relapses of disease*** ***improving patient's outcome in terms of disease free survival (DFS) and overall survival (OS)***

Rabinovitch and Kavanagh. JCO 2009

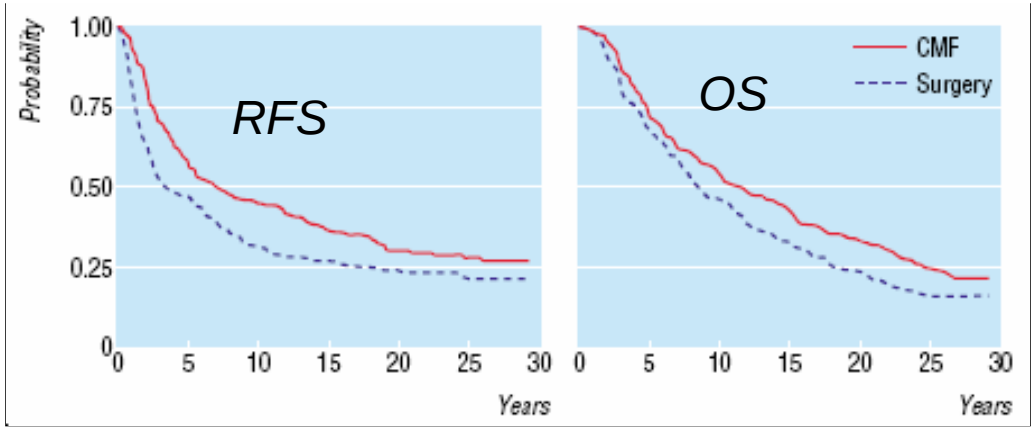
Type of treatment for different subtipes

'Subtype'	Type of therapy	Notes on therapy
'Luminal A'	Endocrine therapy alone	Few require cytotoxics (e.g. high nodal status or other indicator of risk: see text).
'Luminal B (HER2 negative)'	Endocrine ± cytotoxic therapy	Inclusion and type of cytotoxics may depend on level of endocrine receptor expression, perceived risk and patient preference.
'Luminal B (HER2 positive)'	Cytotoxics + anti-HER2 + endocrine therapy	No data are available to support the omission of cytotoxics in this group.
'HER2 positive (non luminal)'	Cytotoxics + anti-HER2	Patients at very low risk (e.g. pT1a and node negative) may be observed without systemic adjuvant treatment.
'Triple negative (ductal)'	Cytotoxics	
'Special histological types'*		
A. Endocrine responsive	Endocrine therapy	
B. Endocrine nonresponsive	Cytotoxics	Medullary and adenoid cystic carcinomas may not require any adjuvant cytotoxics (if node negative).

In the choice and delivery of cancer care we have to consider the following ***risk factors****:*

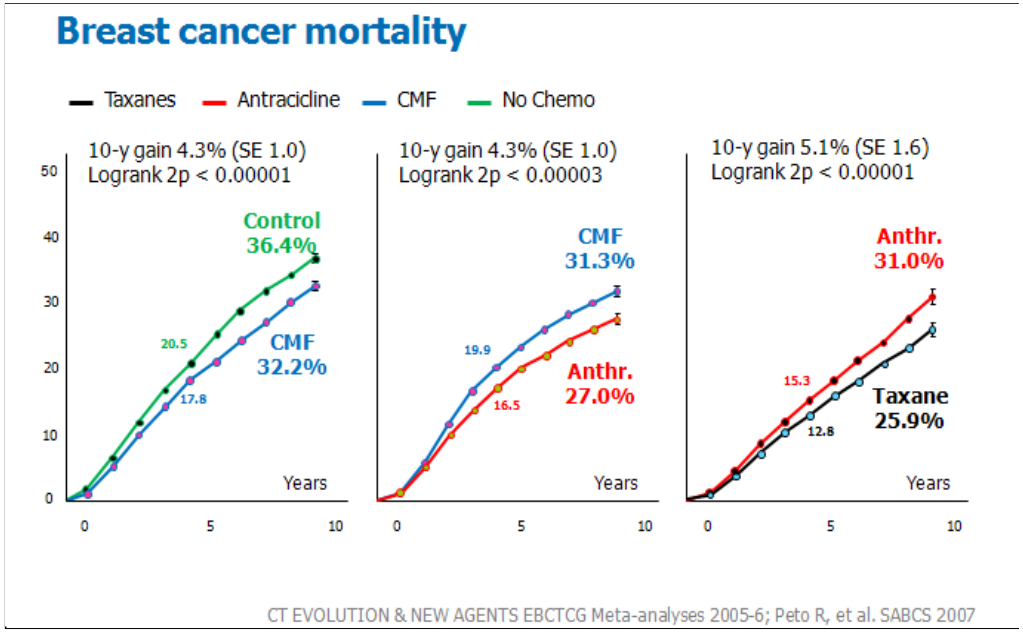
1.histological grade
2.proliferation index
3.hormone receptor status
4.HER2 status
5.disease extent (node positivity per se is NOT an indication for use of chemotherapy, though a strong majority would use it if more than three lymph nodes were involved)

CHEMOTHERAPY allows improvement in DFS and OS



CMF regimen
(cyclophosphamide, methotrexate, fluorouracil)
benefits patients at risk of relapse of distant disease without evidence of detrimental effects

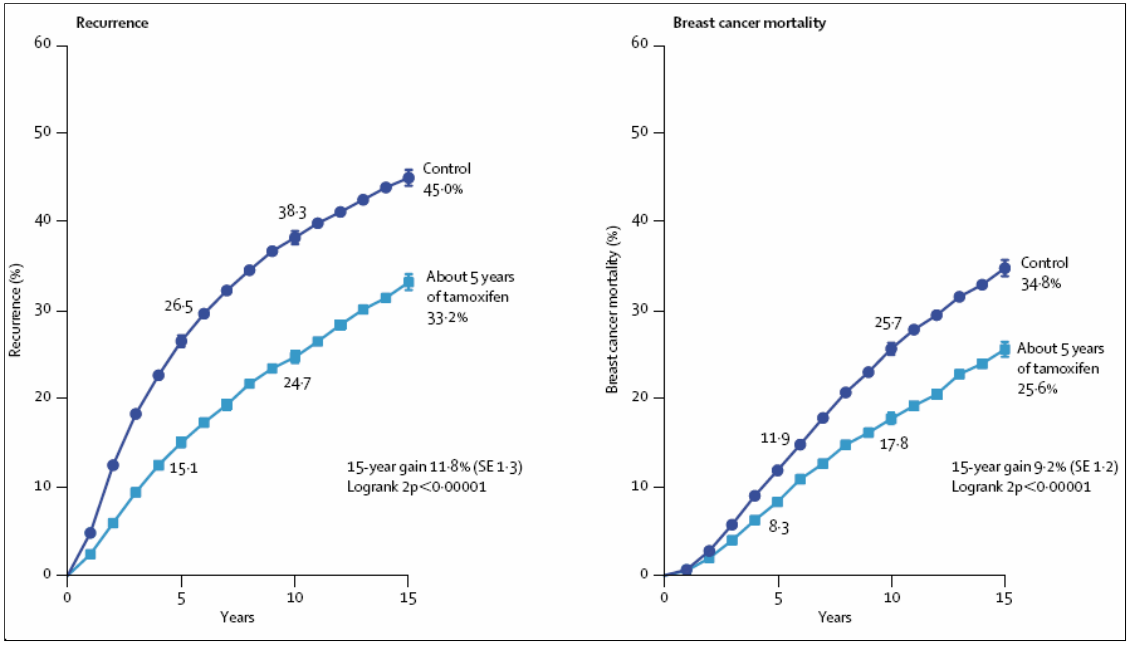
Bonadonna. BMJ, 2005



The most benefit in adjuvant treatment is achieved with ***sequential regimens with anthracyclines and taxanes***

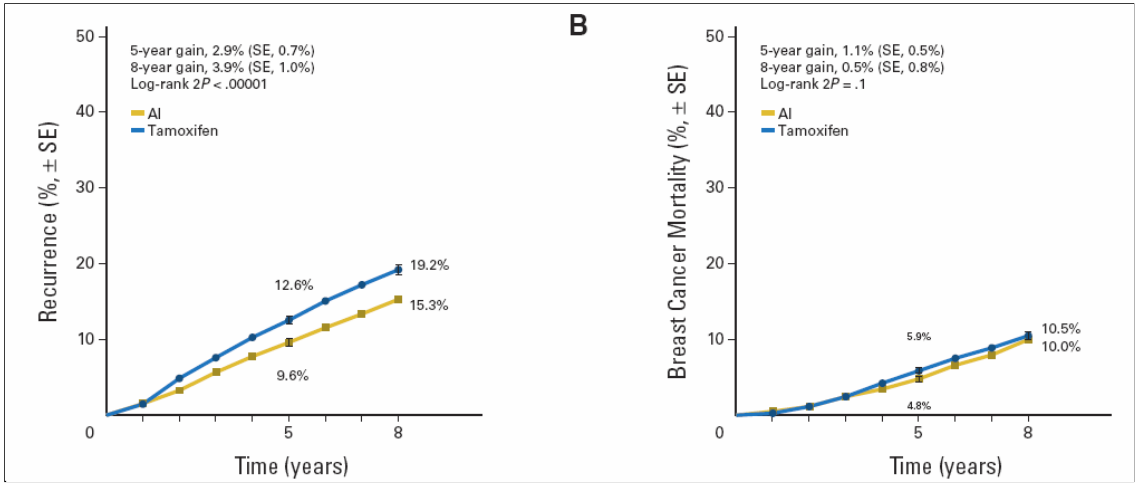
Peto. SABS 2007

ENDOCRINE TREATMENT allows improvement in DFS and OS



Tamoxifen *administrated for a duration of 5 years results in a* ***reduction of recurrence and mortality***

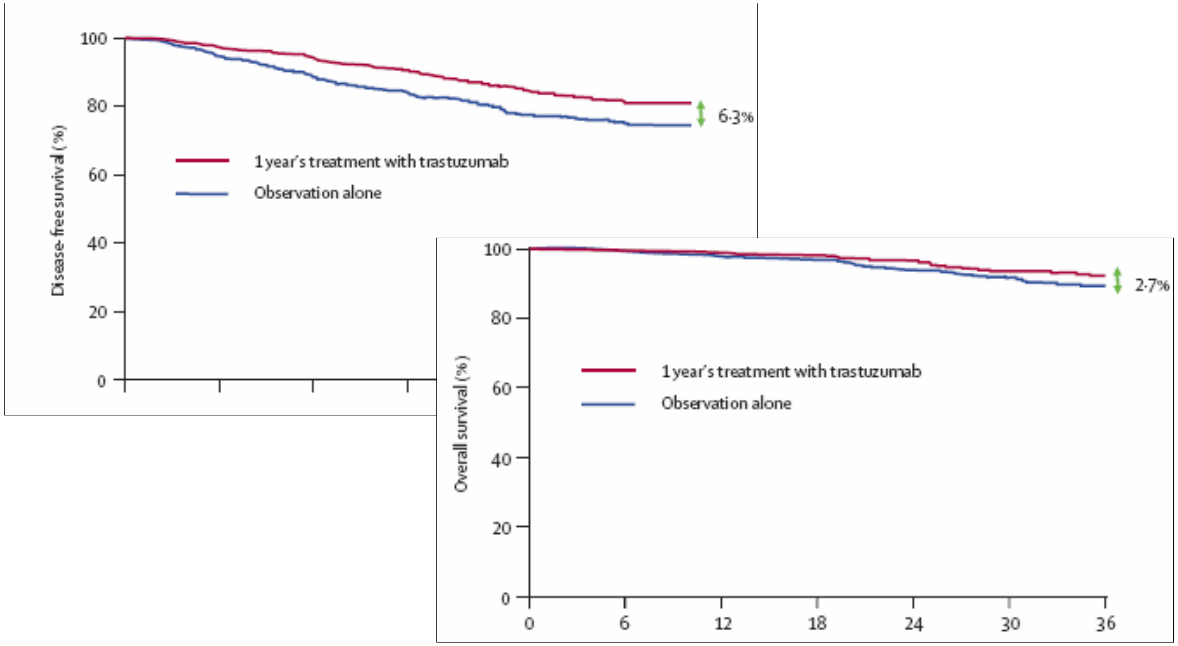
EBCTCG overview, Lancet 2005



Third-generation ***aromatase inhibitors*** *(AIs) produce significantly* ***lower recurrence rates*** *compared with tamoxifen, either as initial monotherapy or after 2 to 3 years of tamoxifen*.

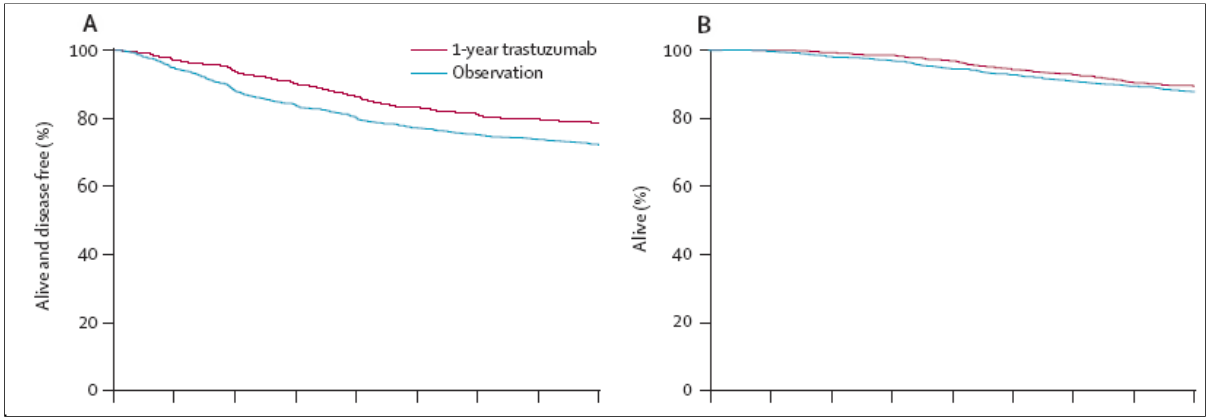
Dowsett. JCO 2010

Anti-HER2 treatment allows significant clinical benefit at 4-year median follow-up (HERA trial).



After median follow-up of 2 years
1 year of treatment with trastuzumab after adjuvant chemotherapy *has a significant DFS and* ***OS benefit***

Smith. Lancet 2007

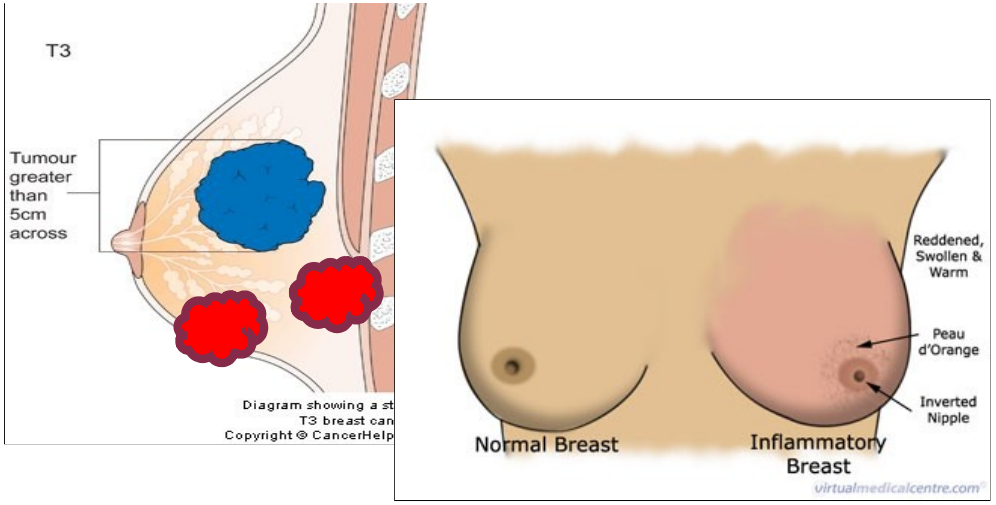


At 4-year median follow-up treatment with ***adjuvant trastuzumab for 1 year after chemotherapy*** *is associated with significant* ***DFS benefit***

L. Gianni Lancet 2012

NEOADJUVANT/PRIMARY TREATMENT

is the treatment given before surgical resection



Neoadjuvant treatment converts many patients with PRIMARY INOPERABLE BREAST CANCER (inflammatory breast cancer or local advanced disease) into candidates for surgical resection

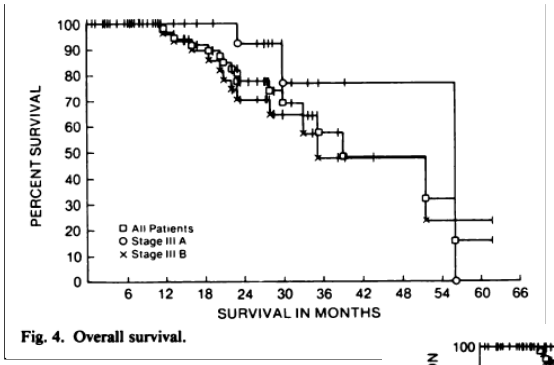


Fig. 4. Overall survival.

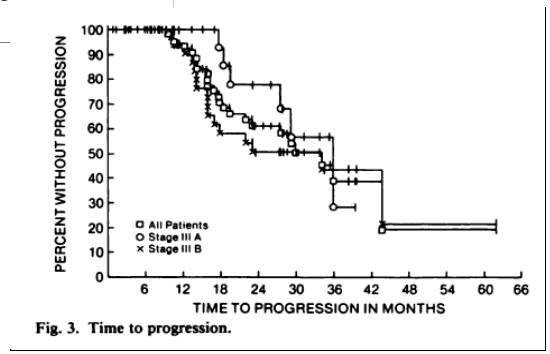
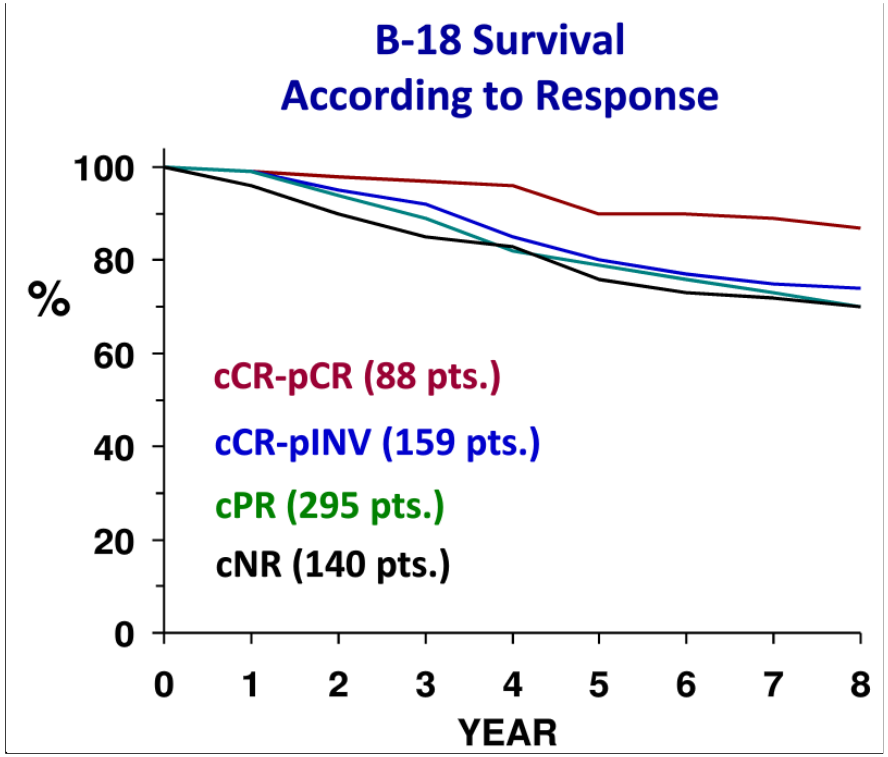


Fig. 3. Time to progression.

Neoadjuvant treatment offers good results on systemic disease control

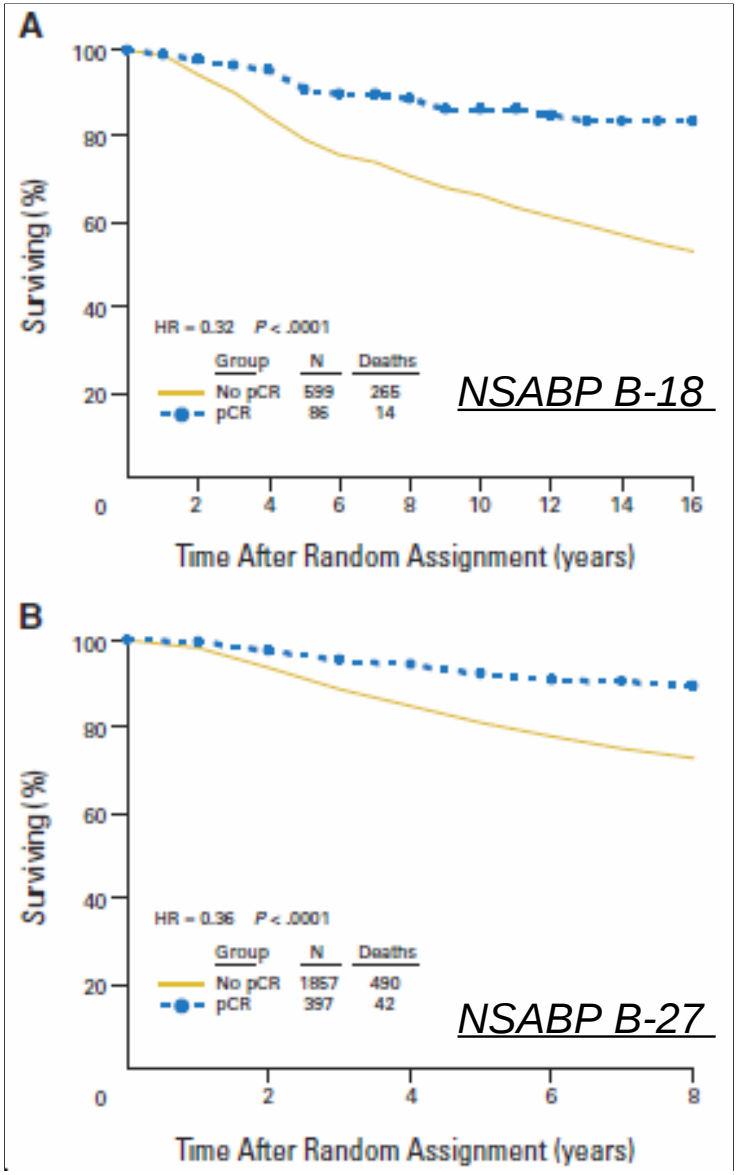
Swain SM. Cancer Res 1987

The end point of neoadjuvant treatment is pathologic complete response (pCR)



pCR *seems to* ***identify a subset of patients with a more favorable prognosis*** *associated with neoadjuvant treatments*

Treatment with CHEMOTHERAPY allows achievement of pCR



Multiple trials *(including NSABP B-18 and NSABP B-27) have demonstrated* ***superior survival outcomes in individuals achieving a pCR***
response at the time of definitive surgery

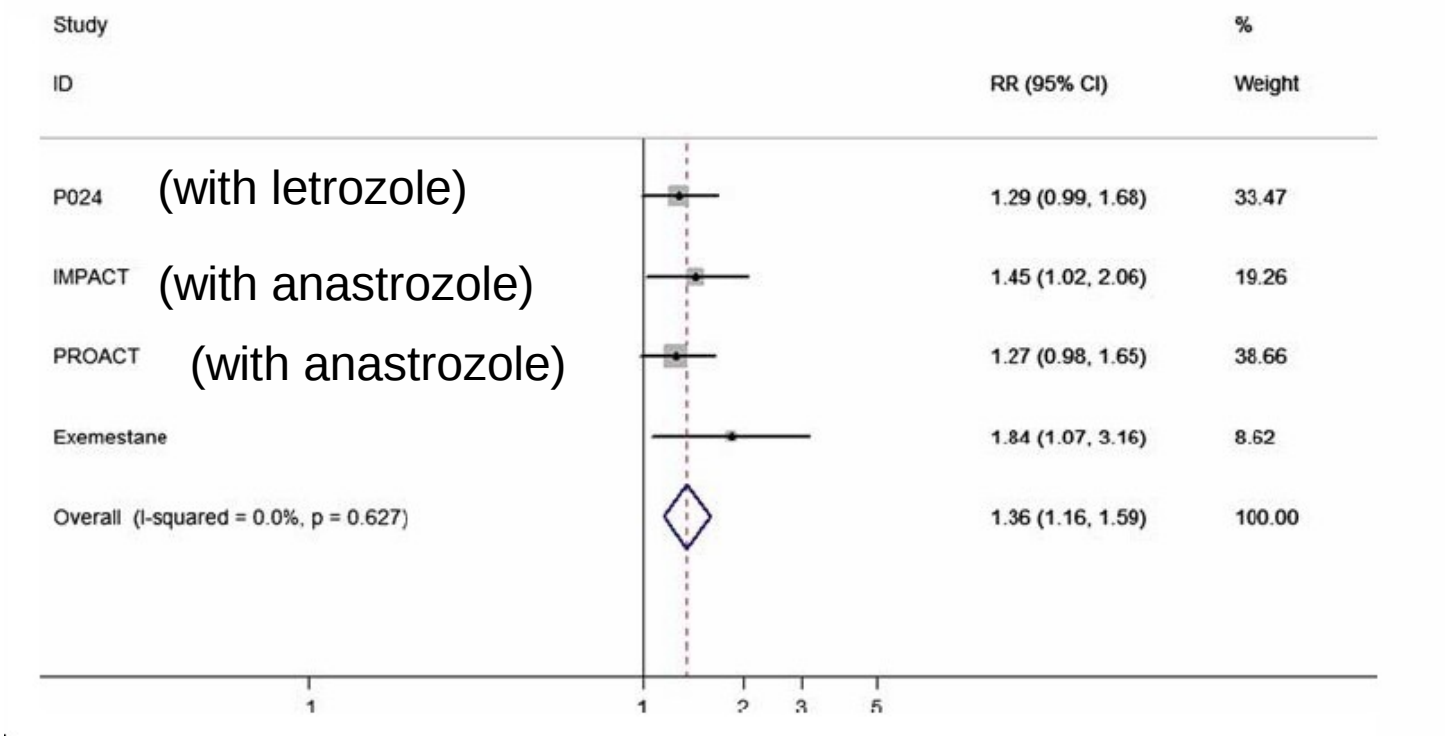
Rastogi P. JCO 2008

NSABP B-18: preoperative AC
NSABP B-27: preoperative AC and docetaxel

ENDOCRINE TREATMENT allows breast conservation

Since 1980 treatment with ***tamoxifen*** *as primary approach has showed* ***clinical response and a good rate of breast conservation***

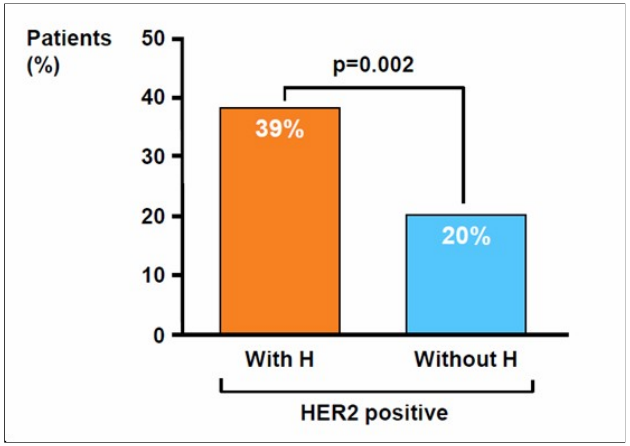
Meta-analysis evaluating the ***breast conserving surgery rate*** *of pre-operative* ***aromatase inhibitors*** *compared to pre-operative tamoxifen in postmenopausal women with hormone showed* ***more effectiveness of AI***



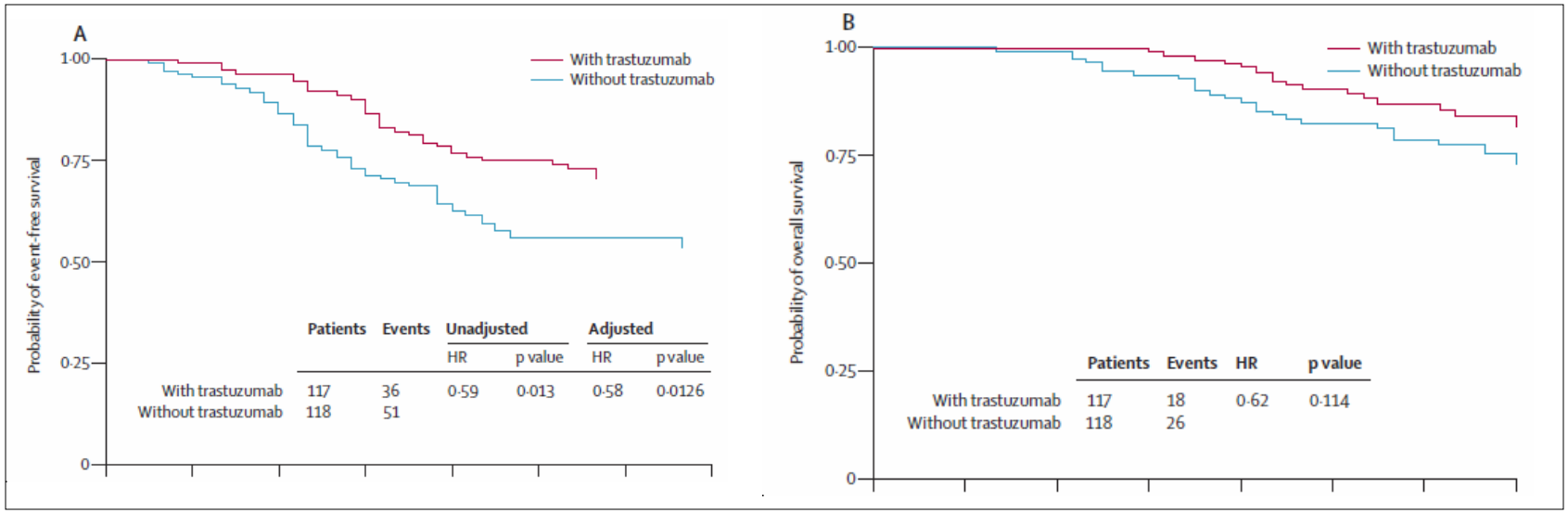
Seo. Cancer Chemother Pharmacol. 2009

Anti-HER2 treatment allows improved pCR and improved outcome

NOHA study: *neoadjuvant CT with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant CT in HER2+ early breast cancer*



Pathological complete response: improved pCR rate using trastuzumab

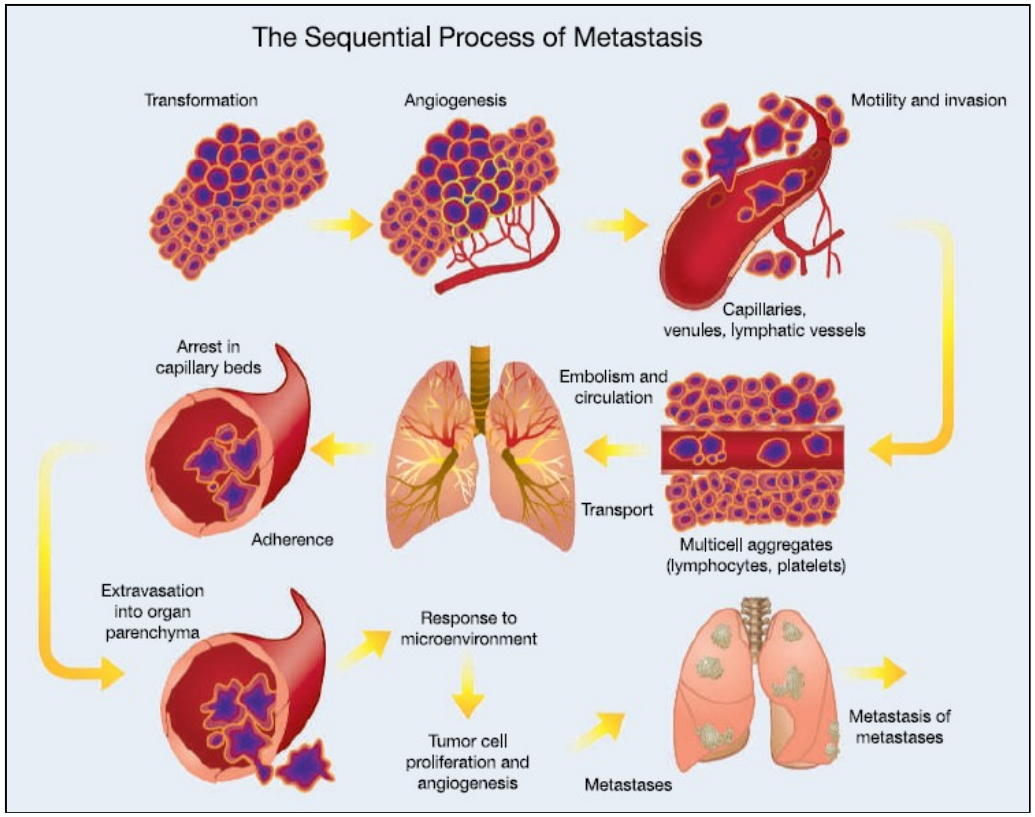


There is an ***improvement in DFS and OS using trastuzumb***

Gianni L, Lancet 2010

TREATMENT OF ADVANCED DISEASE

In 1900 the surgeon ***Stephen Paget*** *initially identified the role of host-tumor interactions on the basis of a review of autopsy records. His* ***"seed and soil" hypothesis*** *was substantiated a century later*.



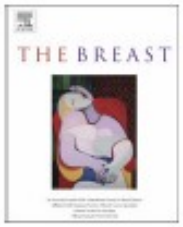
An improved ***understanding of the metastatic process*** *and the* ***attributes of the cells selected by this process*** *is critical for the treatment of patients with systemic disease.*
The goal is obtain a ***control of disease through reduction of tumor burden (response rate, RR), extention of time to progression of disease (TTP), improvement in survival***

Fatima Cardoso, The Breast 18 (2009) 271–272

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst



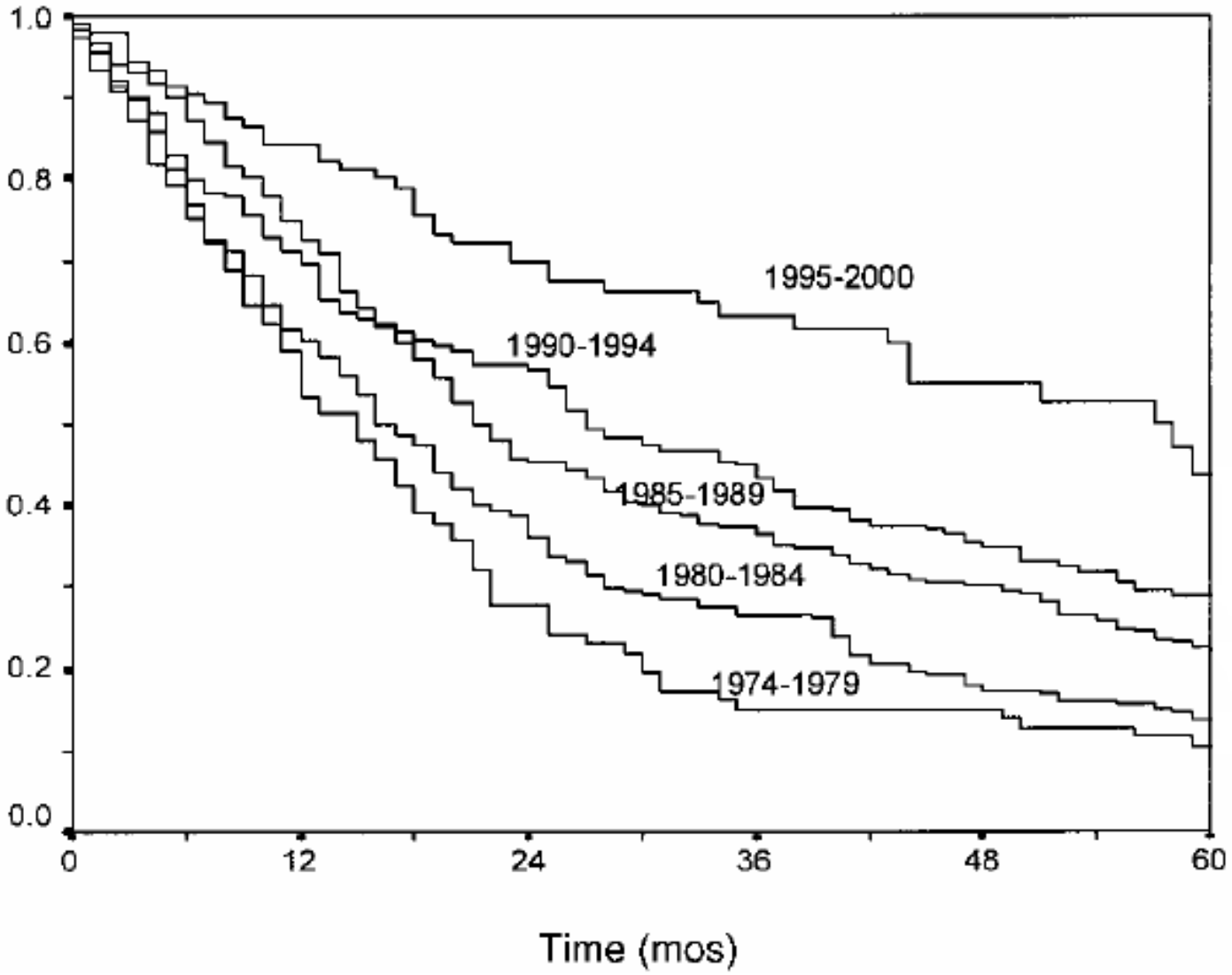
Editorial

Metastatic breast cancer patients: The forgotten heroes!

Metastatic breast cancer has, for too long, been considered a hopelessly incurable disease.

An OS improvement was shown in two recent cohorts of patients with MBC as compared with the previous 20 years.
The greatest improvement is most ***probably related to the development and widespread availability of modern systemic therapies***

The prognosis for patients with recurrent breast cancer improved between 1974 and 2000



Giordano, M. D. Anderson Cancer Center. Cancer 2004

Treatment with CHEMOTHERAPY can achieve an improvement in RR, TTP and OS

In the management of metastatic breast cancer (MBC) the indication of chemotherapy is an ***aggressive disease with related symptoms and visceral involvement***

Combination chemotherapy *is associated with an improved RR and TTP and median OS is improved with a combination regimen using a taxane backbone in patients oretreated with anthracyclines*

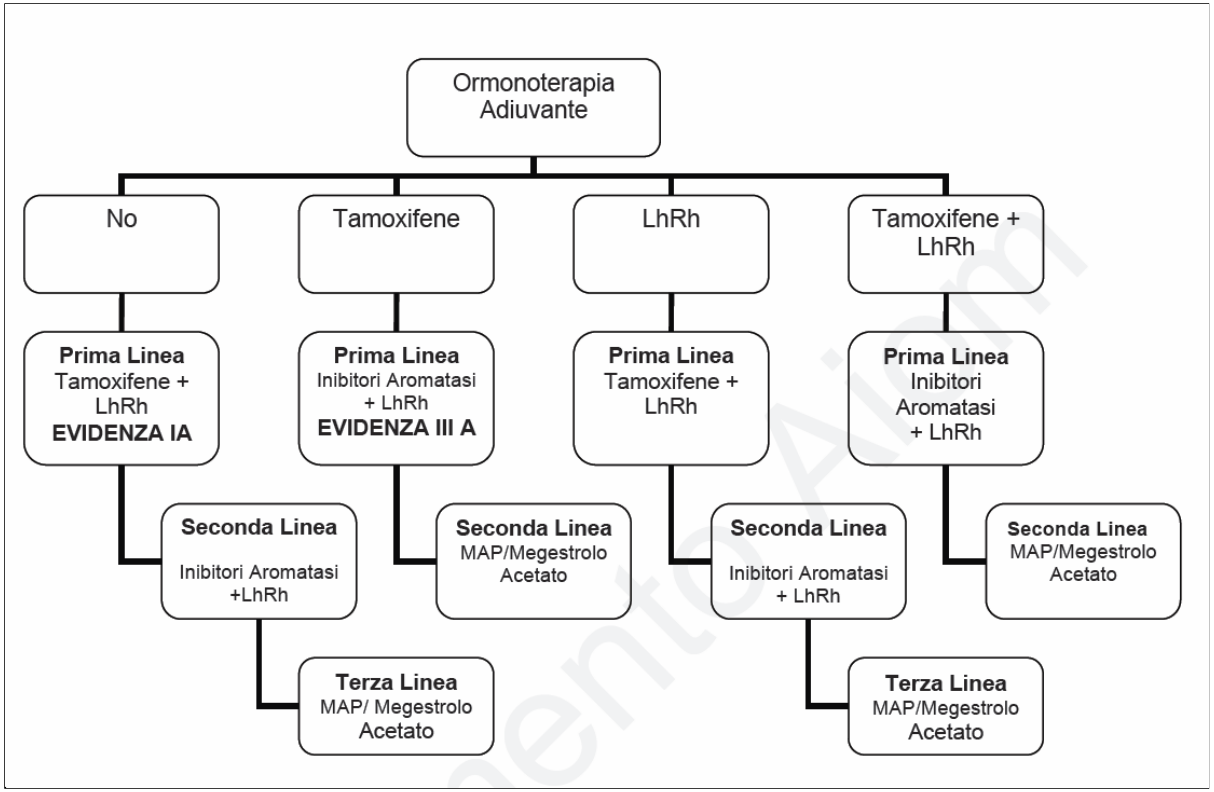
Author Year	Comparison	No. of patients	First therapy for MBC, %	Mean RR, %	Median TTP, mo	Median OS, mo	Crossover, %
Albain	Paclitaxel	529	100	26	4.0	15.8	16
2008(10)	Pac + G			41†	6.1†	18.6†	
Beslija	Docetaxel	100	100	40	7.7	19.0	74
2006(44)	Doc + X			68†	9.3†	22.0†	
O'Shaughnessy	Docetaxel	511	33	30	4.2	11.5	17
2002(12)	Doc + X			42†	6.1†	14.5†	
Soto	X → Taxane	368	78	45	8.4	31.5	64
2006(45)	X + Pac			64†	6.7	33.1	
	X + Doc			75*	8.1	28.5	
Sledge	Doxorubicin	739	85	36	5.8	18.9	58
2003(22)	Paclitaxel			34	6.0	22.2	59
	A + Pac			47†	8.0†	22.0	
Tomova	Doc → G	100	NR	28	6.7	15.9	NA
2008(48)	Doc + G			31	7.0	15.5	

Cardoso F, JNCI 2009

ENDOCRINE TREATMENT allows to improve RR, TTP

*The indication of endocrine treatment for MBC patients is a **limited, indolent, asymptomatic and without visceral involvement disease***

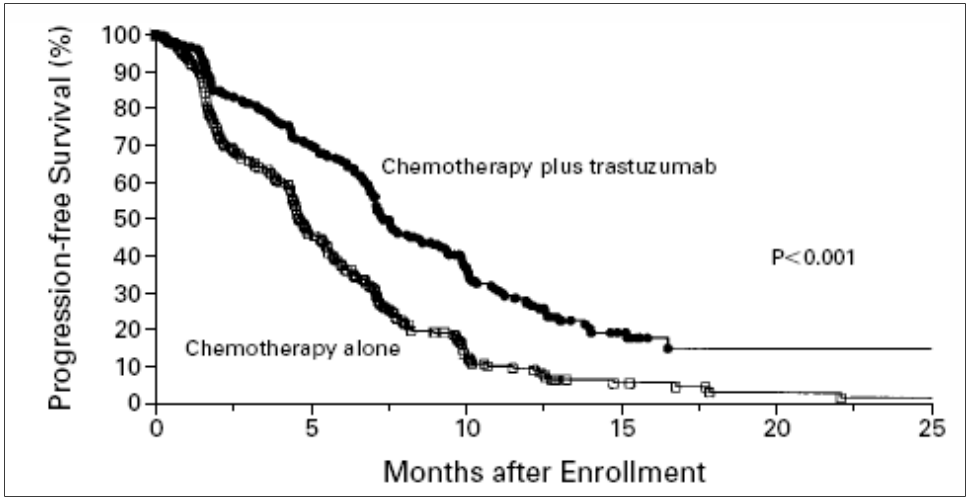
*The choice of which endocrine agent use is based on comparisons among hormonal treatments evaluating **improvement in RR and TTP.***

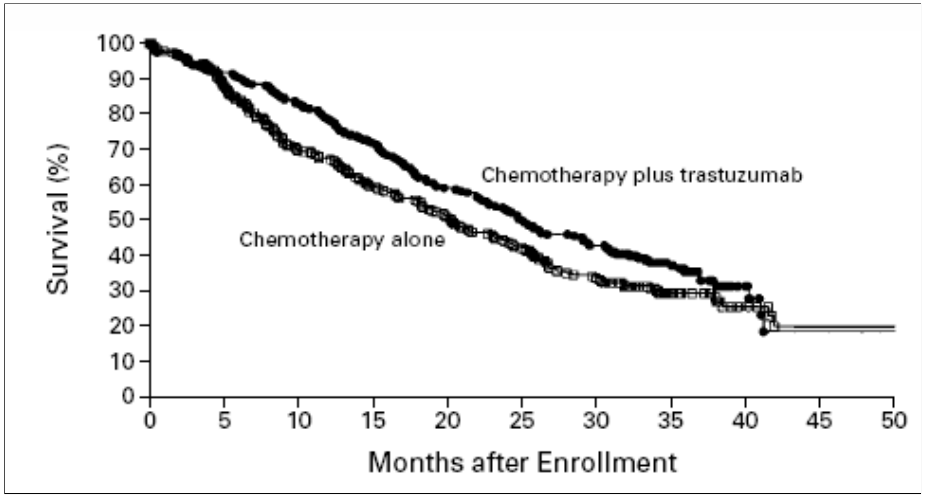


*The **different side-effect and toxicity profiles as well as the route of administration** of should be considered in the choice of endocrine treatment in the individual patient.*

Anti-HER2 treatment allows improved outcome

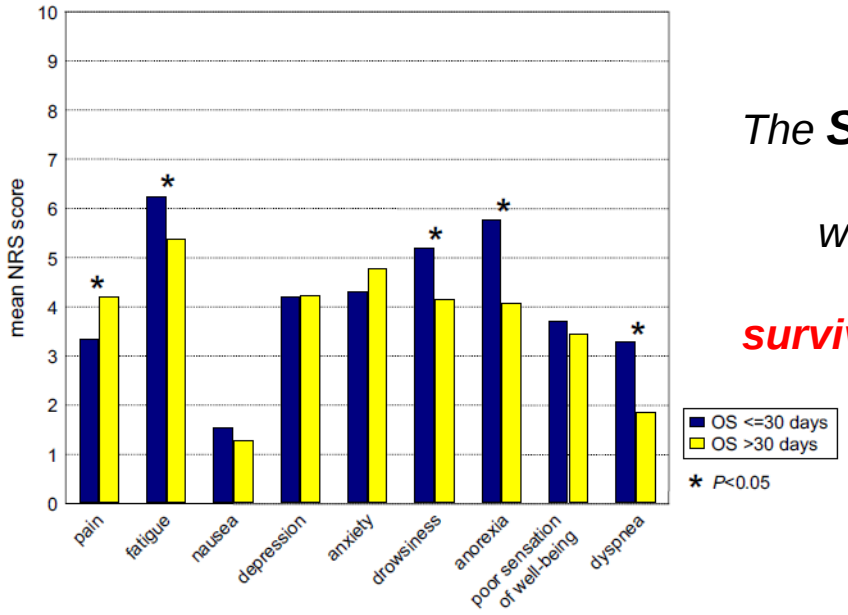
*Trastuzumab increases the clinical benefit (PFS and OS) of **first-line chemotherapy** in metastatic breast cancer that overexpresses HER2.*





Slamon. NEJM 2001

PALLIATIVE TREATMENT



*The **SDS (symptoms distress score)** at baseline was **highest for patients with the shortest survival** compared to those with a survival time of more than one month*

ESAS (Edmonton Symptom System Asessment Sysem) value at admission and relation to survival

Mean Values of Symptom Intensity Over Time (162 patients)

Symptom	Day 1 (± SD)	Day 7 (± SD)	P^a
Pain	3.85 (3.42)	2.73 (2.66)	<0.0001
Fatigue	5.46 (3.15)	4.67 (3.07)	0.003
Nausea	1.57 (2.68)	0.91 (1.81)	0.001
Depression	4.17 (3.46)	3.73 (3.26)	0.082
Anxiety	4.33 (3.36)	3.73 (3.18)	0.015
Drowsiness	4.38 (3.40)	4.77 (3.11)	0.130
Anorexia	4.52 (3.63)	3.01 (3.27)	<0.0001
Well-being	3.39 (3.27)	2.82 (2.84)	0.023
Dyspnea	2.17 (3.03)	1.61 (2.49)	0.006

***A statistically significant reduction during admission** involved all but depression and drowsiness symptoms*

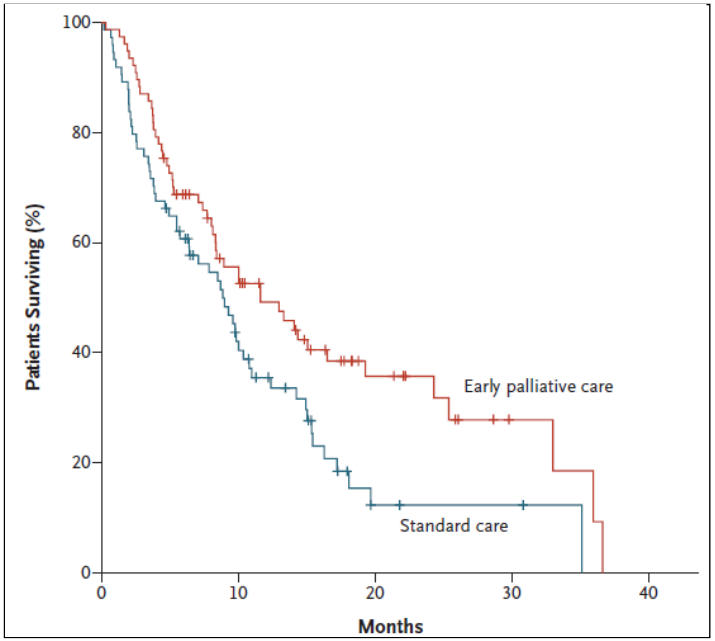
Modonesi, Journal of Pain and Symtom Management 2005

PALLIATIVE TREATMENT

Variables	Univariate		Multivariate	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Care model				
SC	1		1	
ePSC	0.69 (0.48–0.99)	0.037	0.69 (0.48–0.99)	0.045
Wards				
Oncology	1.00 (0.75–1.35)	0.98	1.02 (0.76–1.36)	0.91
Non-oncology	1		1	
Metastatic disease				
No	1.12 (0.89–1.41)	0.35	1.16 (0.92–1.46)	0.22
Yes	1		1	
Gender				
Males	0.75 (0.62–0.90)	0.002	0.76 (0.63–0.91)	0.003
Females	1		1	
Age	0.99 (0.99–1.00)	0.016	1.00 (0.99–1.00)	0.25
Analgesic therapy				
Non-opioids	1.00		1	
Weak opioids	1.19 (0.74–1.92)	0.47	1.12 (0.70–1.79)	0.64
Strong opioids	1.38 (0.88–2.17)	0.16	1.00 (0.84–2.05)	0.23

*ePSC(palliative/supportive care) integrated with primary oncologic care was an independent factor associated with a 31% **reduced** risk of suffering from **severe pain***

Bandieri, Ann Oncol 2012



***Early integration of palliative care** for patients with metastatic NSCLC has effects on **survival and quality of life** that are similar to the effects of first-line chemotherapy in such patients*

Temel, NEJM 2010

PALLIATIVE TREATMENT

Table 3. Survival in Days From Admission: Sedated Versus Nonsedated Patients

Study	Sedated Patients					Nonsedated Patients					*P*
	Mean	SE/SD	Median	Range	90%/95% CI	Mean	SE/SD	Median	Range	90%/95% CI	
Ventafridda et al[5]			25	NR				23	NR		.57
Stone et al[6]	18.6	NR				19.1	NR				> .2
Fainsinger et al[7]	9	5	8	2-16		6	7	4	1-33		.09
Chiu et al[8]	28.5	36.4				24.7	30.9				.430
Muller-Busch et al[9]	21.5	20.3	15.5	1-109		21.1	23.6	14.0	0-199		NR
Sykes et al[10]											.23
48-hour sedation	14.3		7.0	1-182	11.2 to 17.4	14.2		7.0	1-80	12.7 to 15.7	
7-day sedation	36.6		34.5	7-86	31.5 to 41.7	14.2		7.0	1-80	12.7 to 15.7	
Kohara et al[11]	28.9	25.8				39.5	43.7				.10
Vitetta et al[12]	36.5				20.4 to 52.7	17				2.2 to 31.8	.1
Rietjens et al[13]			8	0-38				7	0-38		.12
Mercadante et al[14]	6.6	4.6				3.3	2.8				.003
Maltoni et al[15]			12		10 to 14			9		8 to 10	.330

Abbreviation: NR, not reported.

Comparing survival of sedated and not sedated patients with terminal cancer, ***sedation approach was not shown to be associated with worse survival***

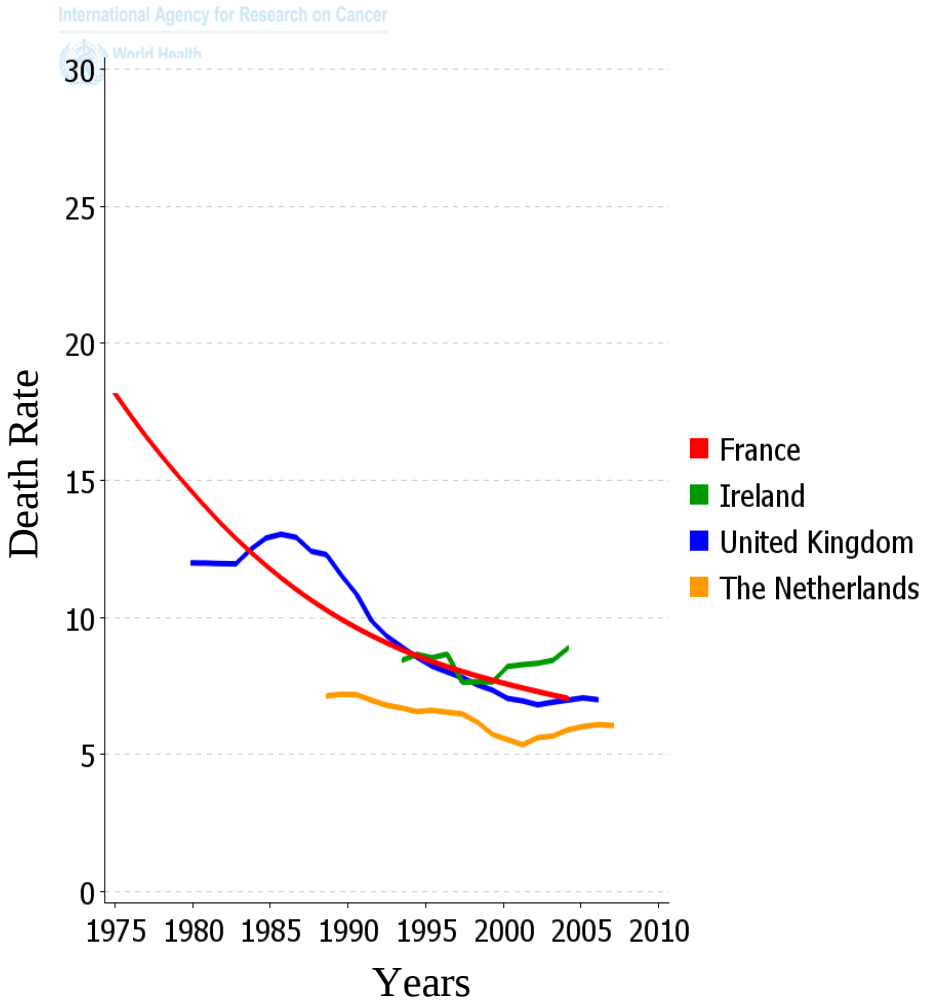
Maltoni M, JCO 2012

Conclusions

1. ***Breast cancer screening*** ***reduces*** *mortality*
2. ***Adjuvant treatment*** *avoid* ***relapse*** *of disease*
3. ***Neodjuvant treatment*** *allows* ***surgical resection of locally advanced tumors*** *and* ***absence of invasive cancer (pCR)***
4. ***Treatment of advancer disease*** *allows* ***control of disease***
5. ***Early access to palliative/supportive care*** *allows provides* ***cancer pain treatment and improve survival rate***

The natural history of tumors as a basis for controlled clinical trials: cervical tumors

EPIDEMIOLOGY IN ITALY



Incidence:

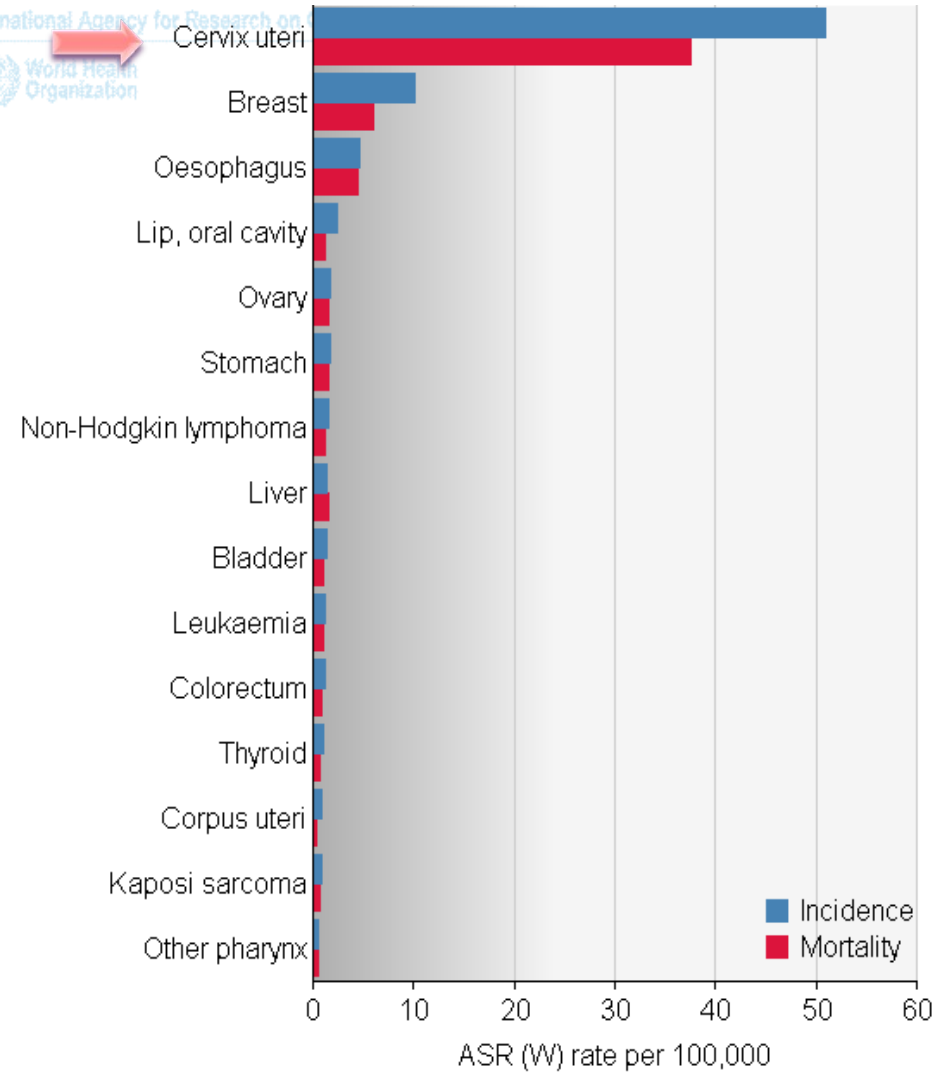
- *About 3,000 new cases/year*
- *The second most frequent cancer in young women (20-39 years)*

Mortality:

- *approximately 1.3% of all cancer deaths in women*
- *13% of deaths from gynecologic cancers*
- *for women aged 20 to 39 years, cervical cancer remains the second leading cause of deaths from cancer after breast cancer, accounting for about 10% of all cancer deaths*

Globocan2008

INCIDENCE AND MORTALITY DATA IN TANZANIA



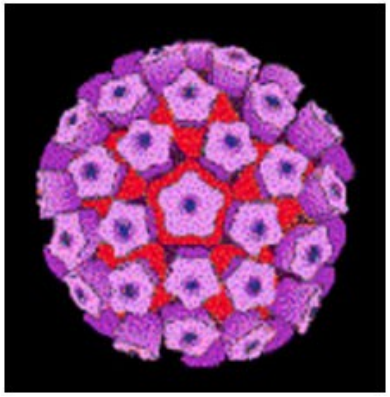
Cancer	Incidence		Mortality	
	Number	(%)	Number	(%)
Cervix uteri	6241	52.9	4355	51.2
Breast	1307	11.1	739	8.7
Oesophagus	530	4.5	509	6.0
Lip, oral cavity	296	2.5	137	1.6
Ovary	252	2.1	191	2.2
Stomach	192	1.6	181	2.1
Non-Hodgkin lymphoma	305	2.6	259	3.0
Liver	182	1.5	180	2.1
Bladder	162	1.4	118	1.4
Leukaemia	202	1.7	193	2.3
Colorectum	136	1.2	109	1.3
Thyroid	144	1.2	84	1.0
Corpus uteri	102	0.9	35	0.4
Kaposi sarcoma	157	1.3	135	1.6
All cancers	11777	99.8	8453	99.4

Globocan2008

RISK FACTORS

Human Papillomavirus (HPV):

HPV DNA is present in more than 99% of cervical carcinomas



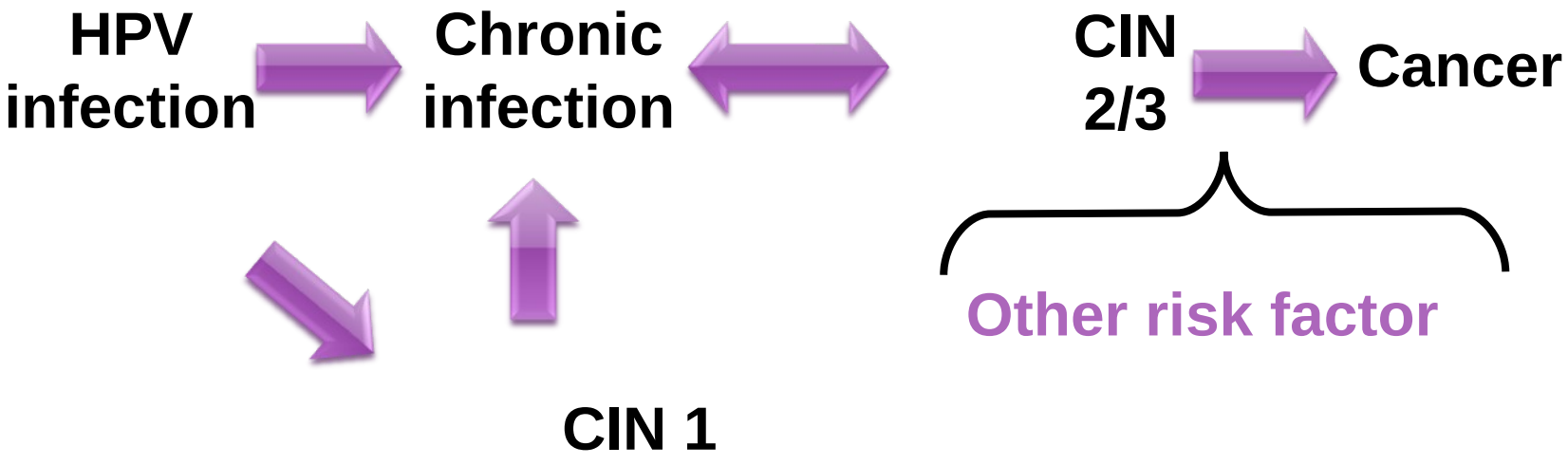
Other risk factors:

- *First coitus at a young age*
- *Multiple sexual partners*
- *Promiscuous sexual behavior*
- *Uncircumcised partner*
- *Low socio-economic status*
- *Poor hygiene*
- *HIV infection*

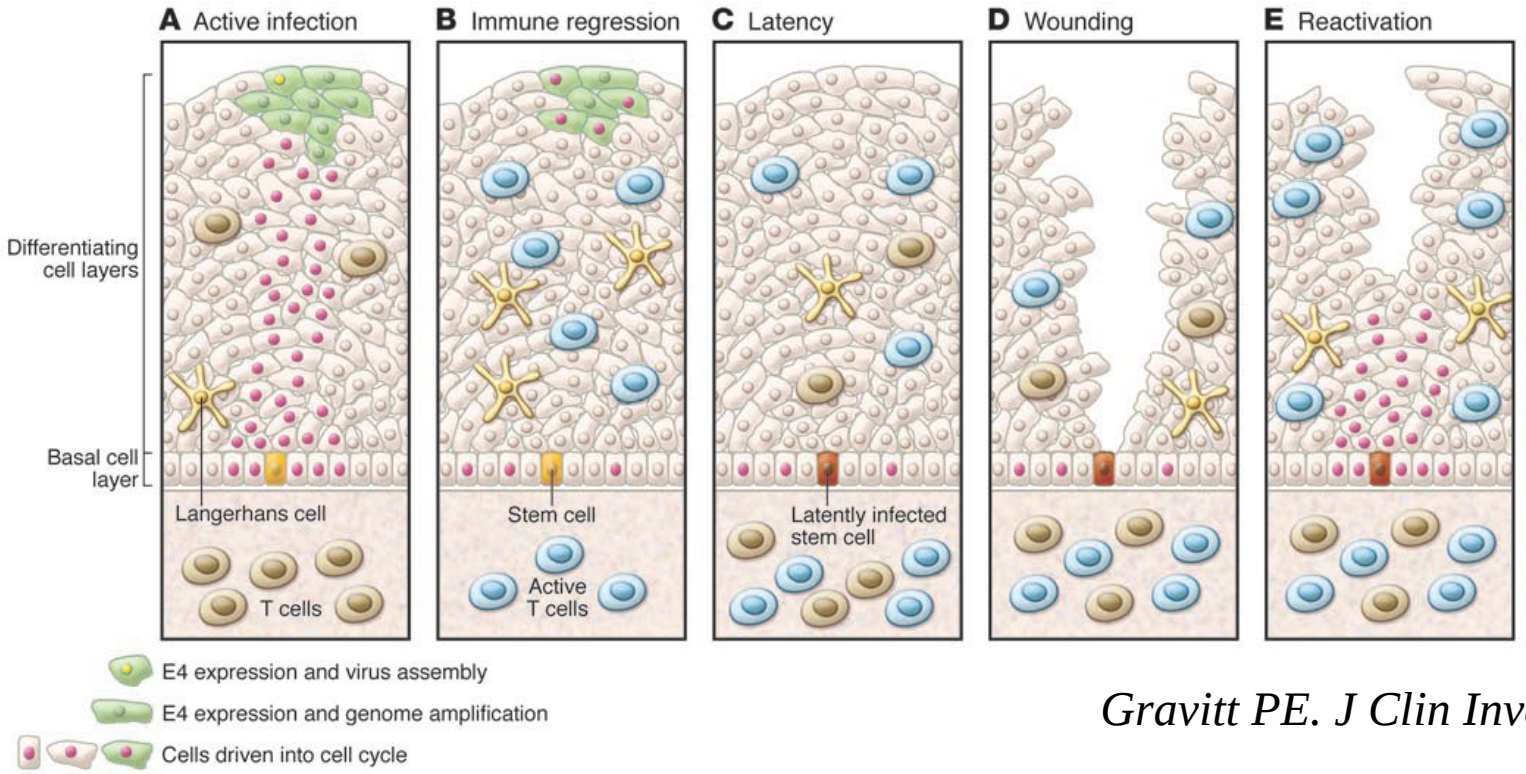
HPV INFECTION

Normally a self-limiting infection (mean: 8 months)

3-6 months 4-5 years 9-15 years



HUMAN PAPILLOMAVIRUS AND CERVICAL CANCER



Gravitt PE. J Clin Invest. 2011

A) *Active infection stimulates proliferation of basal layer, leading to genome amplification and new virion production.*

B) *Active infection triggers an effective immune response, leading to immune regression with infiltration of predominantly T cells.*

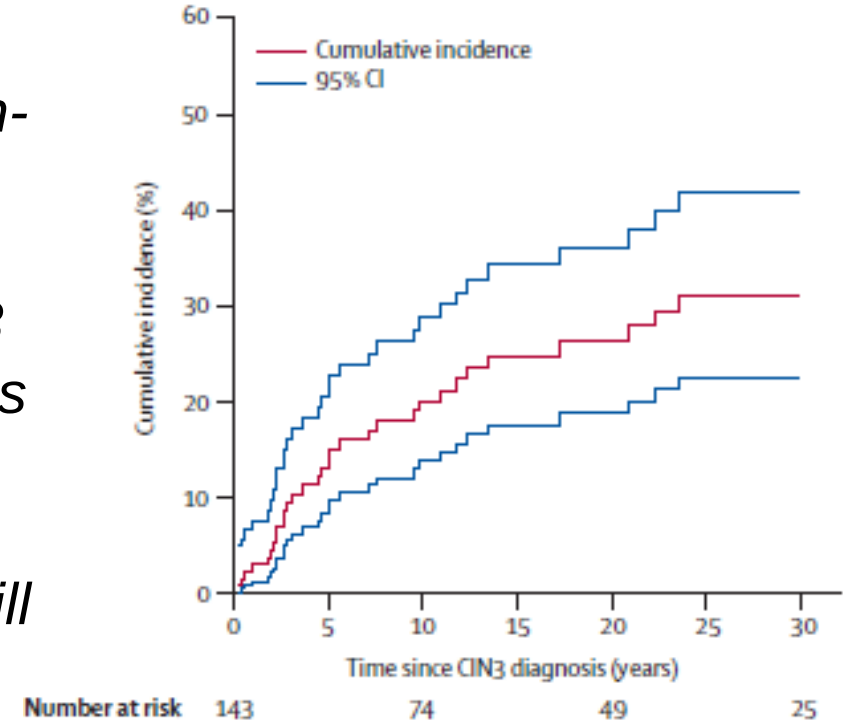
C) *Viral latency may ensue, with viral genomes restricted to stem cells in the basal layer of the epithelium.*

D and E) Wounding may stimulate latently infected basal cells to divide and trigger reactivation and stimulation of tissue-resident memory T cells.

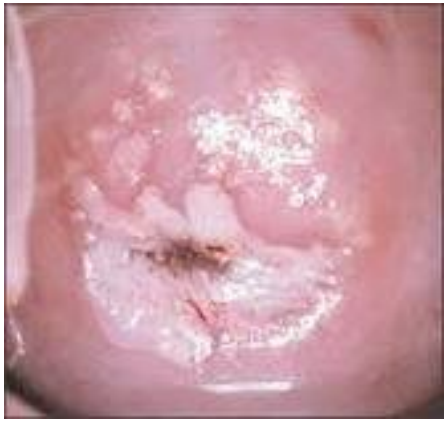
Natural History

- *HPV infections are very common; very few infections progress to high-grade cervical intraepithelial neoplasia (CIN2 or CIN3).*
- *The rate of progression from CIN3 to invasive cancer within 30 years is about 31%.*
- *Unsolved questions remain:*

1. *Which patient with HPV infection will develop pre-neoplastic lesions?*
2. *Which patient will progress from CIN1 to CIN2/3 or to invasive cancer?*
3. *What is the role of vaccine in patients with HPV infection?*



McCredie MR, et al. Lancet Oncol. 2008



THE LANCET Oncology

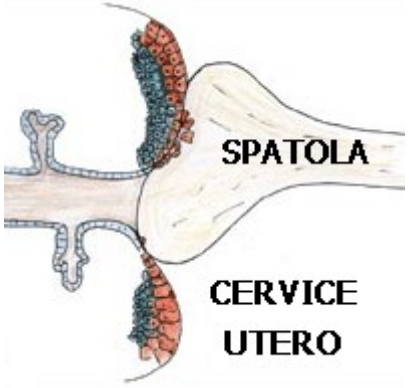
ISTITUTO SCIENTIFICO ROMAGNOLO PER LO STUDIO E LA CURA DEI TUMORI

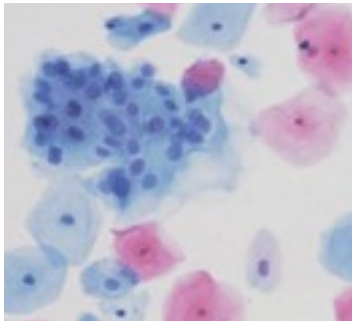
Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial

HPV-16/18 vaccine proved efficacy against CIN3 lesions (irrespective of HPV type in the lesion and including lesions with no HPV DNA detected), reducing the risk by 93.2% (95% CI 78.9—98.7).

Lehtinen M, et al. Lancet Oncol 2012

However, Papanicolaou (Pap) screening remains the standard test to evaluate metaplastic/dysplastic changes that arise at the junction between the columnar epithelium of the endocervix and the squamous epithelium of the ectocervix.





Primary Treatment

- *Concurrent chemo-radiation therapy is the treatment of choice for stage IB2-IVA disease on the basis of results from 5 RCTs*

TABLE 1. ESTIMATES OF THE RELATIVE RISK OF DEATH IN FIVE CLINICAL TRIALS OF CONCURRENT CHEMOTHERAPY AND RADIOTHERAPY.

STUDY	FIGO STAGE*	TREATMENT		RELATIVE RISK OF DEATH IN COMPARISON GROUP
		CONTROL GROUP	COMPARISON GROUP	
Keys et al.[1]	IB2	Radiotherapy	Radiotherapy plus weekly cisplatin	0.54
Rose et al.[2]	IIB–IVA	Radiotherapy plus hydroxyurea	Radiotherapy plus weekly cisplatin	0.61
			Radiotherapy plus cisplatin, fluorouracil, and hydroxyurea	0.58
Morris et al.[3]	IB2–IVA	Extended-field radiotherapy	Radiotherapy plus cisplatin and fluorouracil	0.52
Whitney et al.[5]	IIB–IVA	Radiotherapy plus hydroxyurea	Radiotherapy plus cisplatin and fluorouracil	0.72
Peters et al.[6]	IB or IIA (selected postoperatively)	Radiotherapy	Radiotherapy plus cisplatin and fluorouracil	0.5

*FIGO denotes the International Federation of Gynecology and Obstetrics.

Thomas GM. N Engl J Med 1999

- *Is there a role for neoadjuvant treatment?*
- *Which patients can benefit from such a strategy?*
- *What is the best regimen?*

Adjuvant Treatment

- *Adjuvant pelvic radiation with concurrent Cisplatin-containing chemotherapy is indicated after radical hysterectomy in cases of:*
  - ✓ *Positive pelvic nodes*
  - ✓ *Positive surgica*
  - ✓ *Large primary s*
  - ✓ *Deep stromal*
  - ✓ *Lympho-vascul*

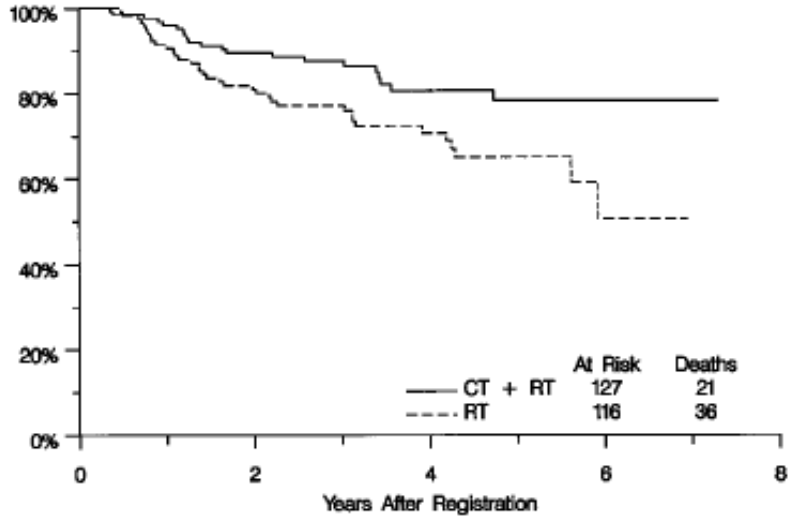


Fig 2. Overall survival for 127 patients randomized to receive CT + RT and for 116 patients randomized to receive RT alone.

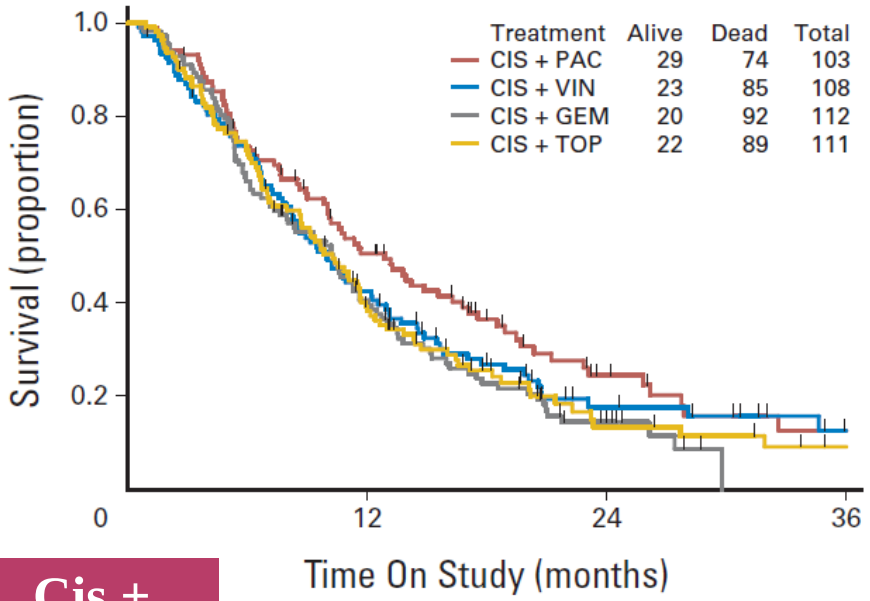
Peters WA 3rd, et al. J Clin Oncol. 2000

- *Adjuvant pelvic radiotherapy with concurrent Cisplatin and 5Fluoruracil has shown to significantly improve:*
  - ✓ ***Disease-free survival***
  - *(HR for RT alone 2.01, p = .003)*
  - ✓ ***Overall survival***
  - *(HR for RT alone 1.96, p = .007)*

- *Are there other prognostic factors to predict the probability of systemic relapse?*
- *Are there subsets of patients who could benefit from chemotherapy alone?*

Stage IVB (Metastatic) Disease

- *Cisplatin + Paclitaxel would not appear to be superior to Cisplatin-combination with Topotecan, Gemcitabine or Vinorelbine, even though there is a trend in favor of response rate, progression-free survival and overall survival.*



	Cis + Pac	Cis + Vin	Cis + Gem	Cis + Top
OR	29.1	25.9	22.3	23.4
PFS	5.82	3.98	4.70	4.57
OS	12.9	10	10.3	10.2

Monk BJ, et al. J Clin Oncol. 2009

- *Are there predictive factors of response?*
- *Are there important biological pathways involved in disease progression that could be targeted?*
- *Are there other regimens that could be more effective?*