Il trattamento delle stazioni linfonodali in relazione allo status del linfonodo sentinella

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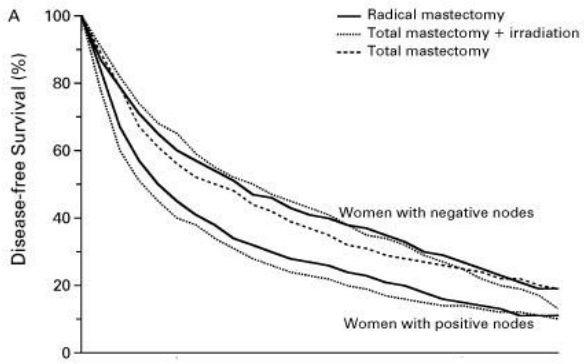
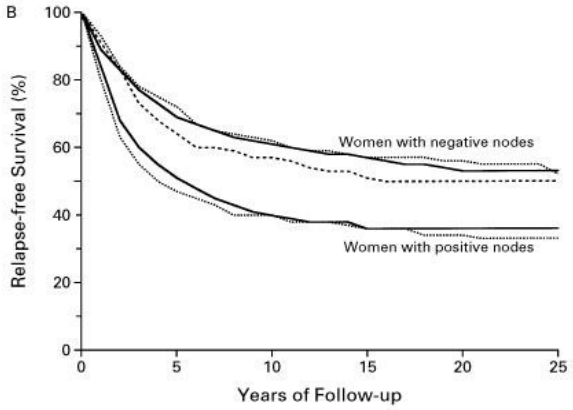
Does Axillary dissection provide a survival benefit? (1)

DFS



RFS



- NSBP-04 trial
- 1665 women enrolled
- 25 years of follow-up

No significant differences between N0 and N+ regardless of received treatment

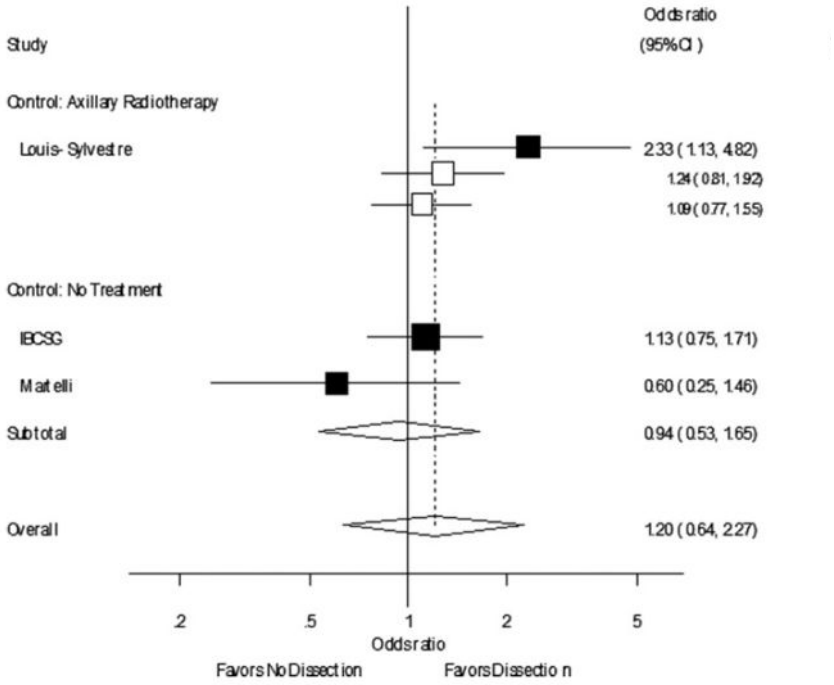
Fisher B et al. N Engl J Med 2002

NSABP B-04: Results

- XRT achieved similar local control as surgery in clinically negative axilla while it was inferior to surgery in clinically positive axilla.
- 35% of the patients randomized to the total mastectomy arm had limited axillary dissection.
- Patients who had 6 or more nodes removed did not have axillary recurrence.
- No difference in survival with respect to treatment in either arm.

Fisher B et al. N Engl J Med 2002

Does Axillary dissection provide a survival benefit? (2)



- Meta-analysis of 4 RCTs
- More than 2000 patients
- Time-frame : 2000-2007
- No difference in OS, DM and LR associated with axillary treatment

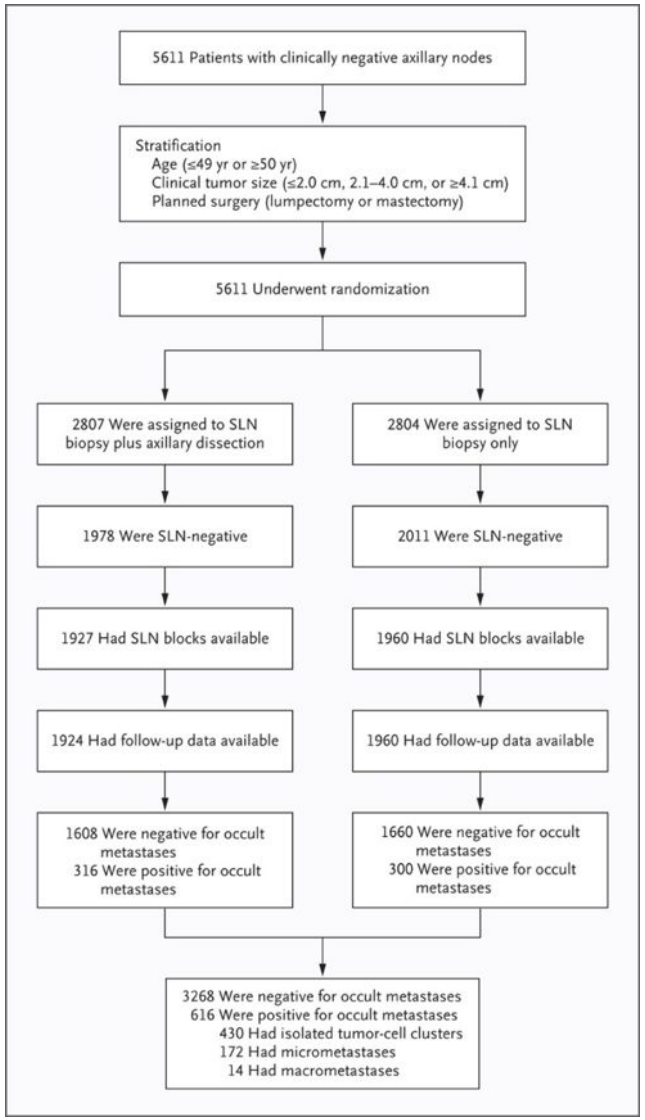
Widespread use of adjuvant chemotherapy likely responsable of the observed effect on clinical outcome

Sanghani M et al. Cancer 2009

Source	Year	Patients	T1 (%)	Breast-conserving therapy (%)	Chemo/ hormone therapy (%)	Adjuvant RT axilla (%)	Follow-up (mo), median	Axillary recurrence, *n*(%)
Yi et al	2010	1,473	69	79	NR	NM	50	3 (0.2 %)
Giuliano et al.	2010	199	70	100	60/48	NM	76	2 (0.9 %)
Takei et al.	2010	32	30	92	19/77	52	58	0
Yegiyants et al.	2010	14	66	100	92/76	0	79	1 (7.1 %)
Bilimoria et al.	2009	1,458	63	81	71/74	NM	64	18 (1.2 %)
Zakaria et al.	2008	17	62	60	53/87	19	30	0
Hwang et al.	2007	39	72	69	56/27	58	30	0
Schulze et al.	2006	1	100	74	3/68	NM	49	0
Haid et al.	2006	2	77	87	32/93	NM	47	0
Swenson et al.	2005	4	82	75	42/58	NM	33	0
Schrenk et al.	2005	4	61	29	NR	0	48	0
Fan et al.	2005	11	71	NM	NR	63	31	0
Chagpar et al.	2005	1	89	86	33	NM	40	0
Carlo et al.	2005	2	84	92	100	NM	60	0
Guenther et al.	2003	7	67	NM	100	2	32	0
Fant et al.	2003	4	81	NM	100	3	30	0

Total number of axillary recurrence in patients with macrometastatic SLN: 24/3268 **(0.7%)**

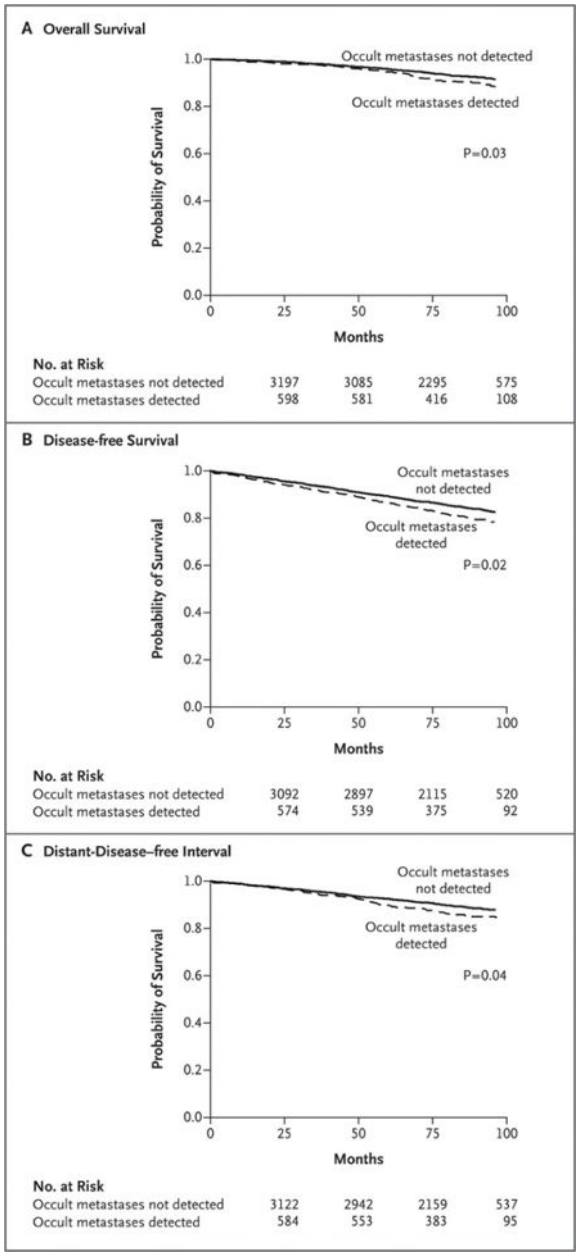
Occult nodal metastases and their clinical significance



- Women randomly assigned to sentinel-lymph-node biopsy with immediate axillary dissection or to sentinel-lymph-node biopsy alone

- Patients stratified according to **age** (≤49 years or ≥50 years), **clinical tumor size** (≤2.0 cm, 2.1 to 4.0 cm, or ≥4.1 cm in the greatest dimension), and **planned surgical treatment** (lumpectomy or mastectomy)

Weaver DL et al. N Engl J Med 2011



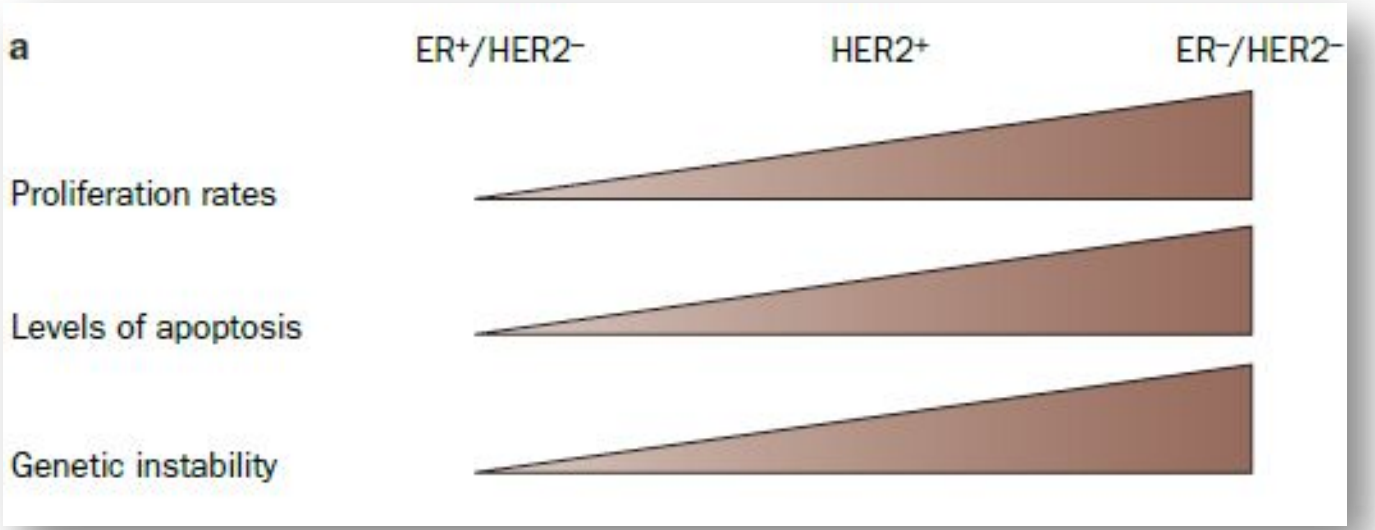
- Occult metastases were an independent prognostic variable in patients with sentinel nodes that were negative on initial examination

- The magnitude of the difference in outcome at 5 years was small (1.2 percentage points)

- These data do not indicate a clinical benefit of additional evaluation, including immunohistochemical analysis, of initially negative sentinel nodes in patients with breast cancer

Weaver DL et al. N Engl J Med 2011

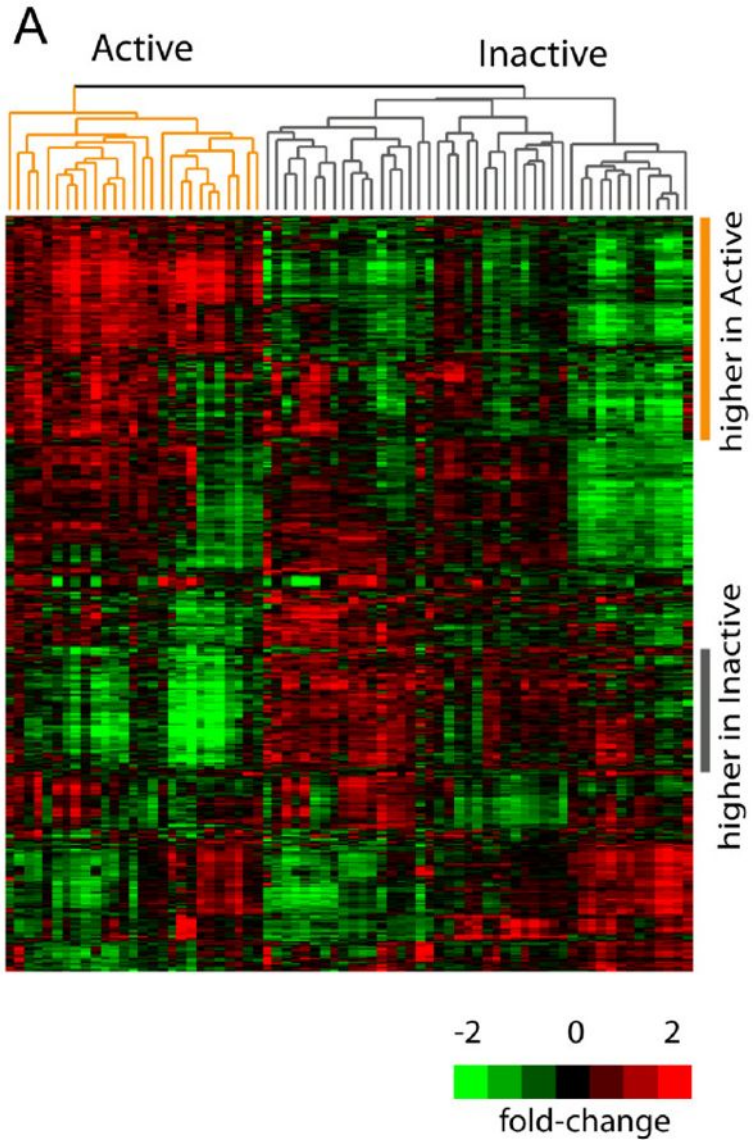
Heterogeneity of breast cancer

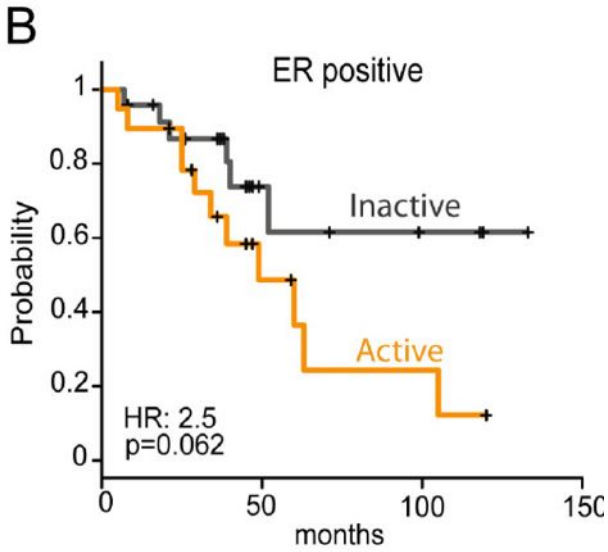


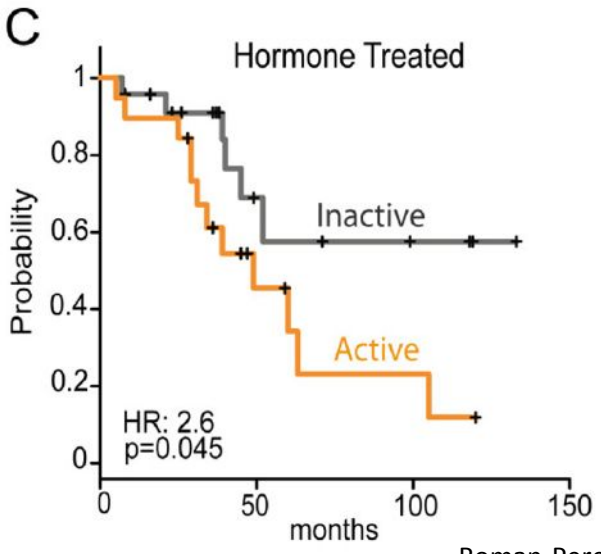
- Profound differences exist between different types of breast cancer
- For the more aggressive tumours nodal status cannot be as sufficient prognostic factor

Foulkes WD et al. Nat Rev Clin Oncol 2010

Tumor microenviroment influence clinical outcome

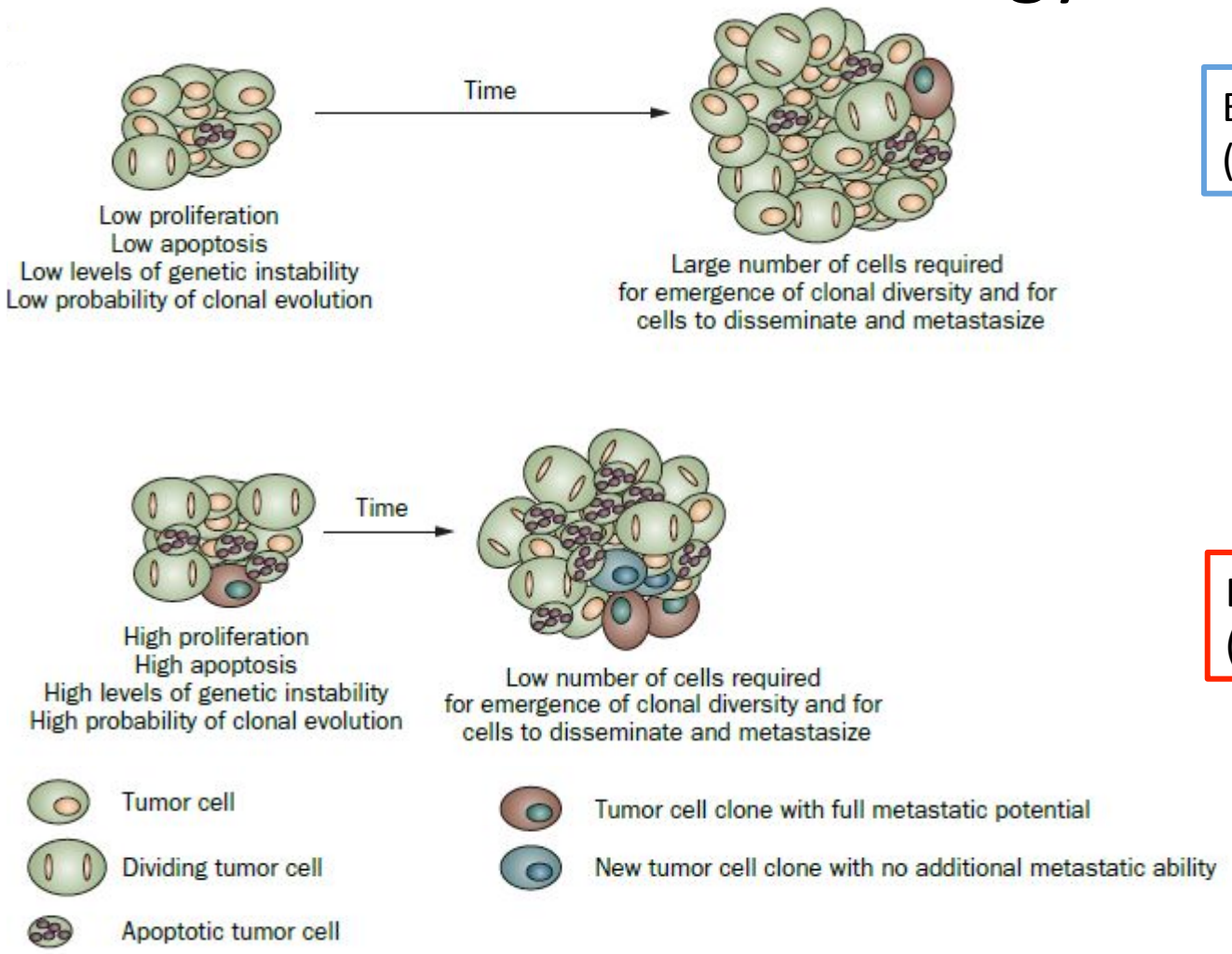






Roman-Perez E et al Breast Cancer Res 2012

Size does (not) always matter: considering tumour biology

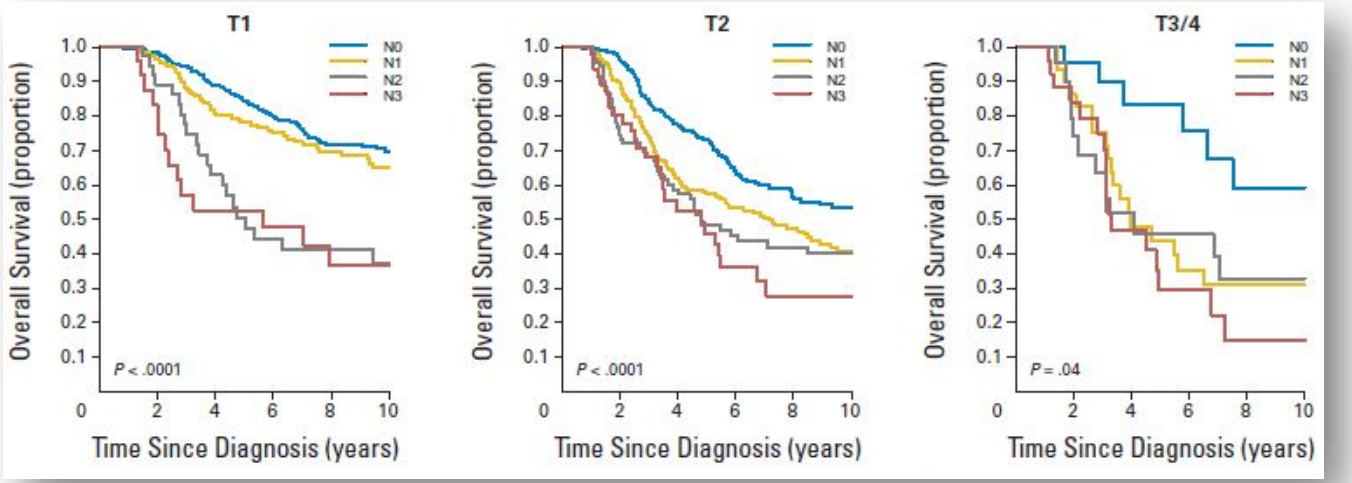


ER+/Her-
(Luminal A)

ER-/Her-
(basal-like)

Foulkes WD et al. Nat Rev Clin Oncol 2010

Nodal status and clinical outcome in basal-like breast cancer



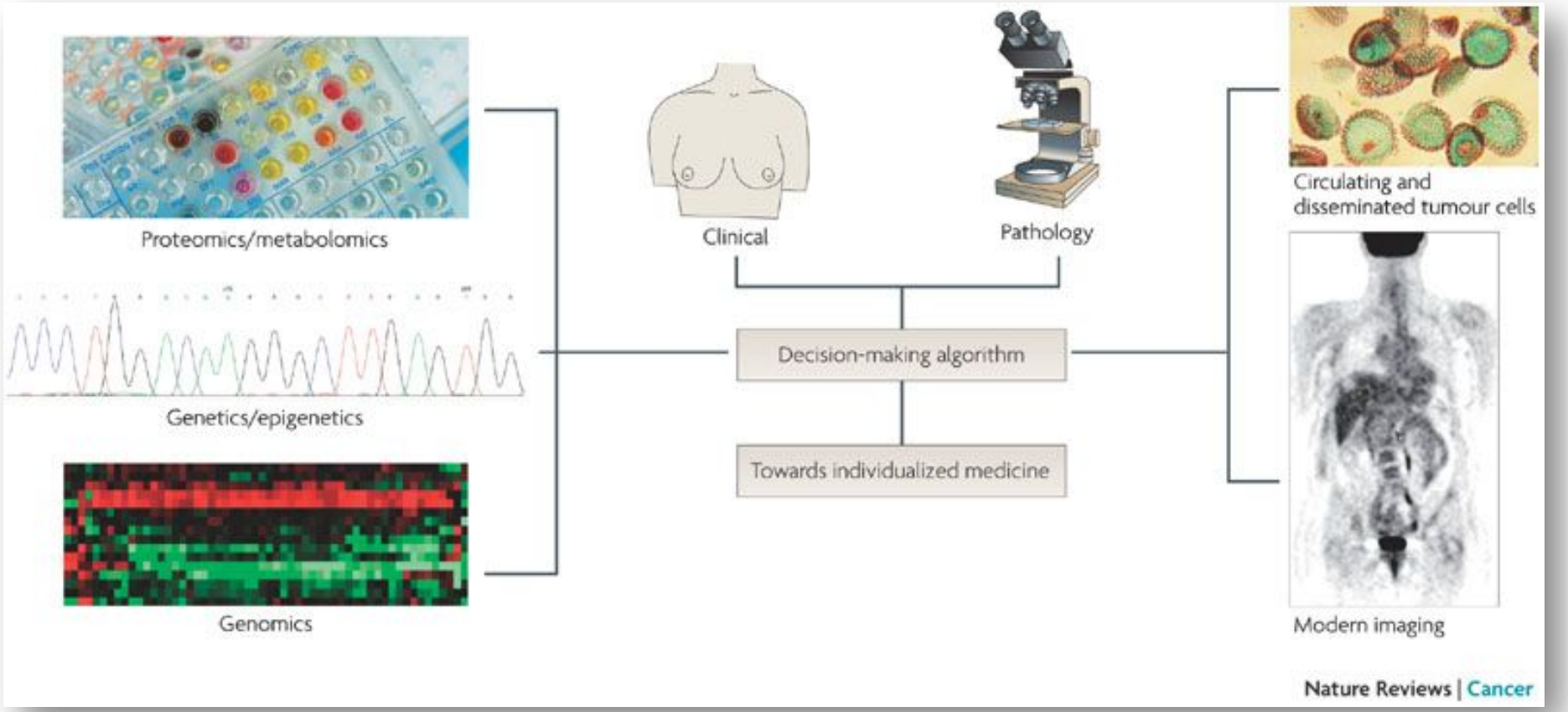
- 1171 patients diagnosed with triple-negative BC between 1980 and 2009

- Patients stratified by tumor size (T) and nodal status (N)

- No difference in terms of OS in N1 patients vs N2-N3 patients

Hernandez et al. JCO 2011

Paradigmatic shift in prognostic parameters



Foulkes WD et al. Nat Rev Clin Oncol 2010

New tools for breast cancer prognosis

oncotype DX®
Breast Cancer Assay

mammaprint®

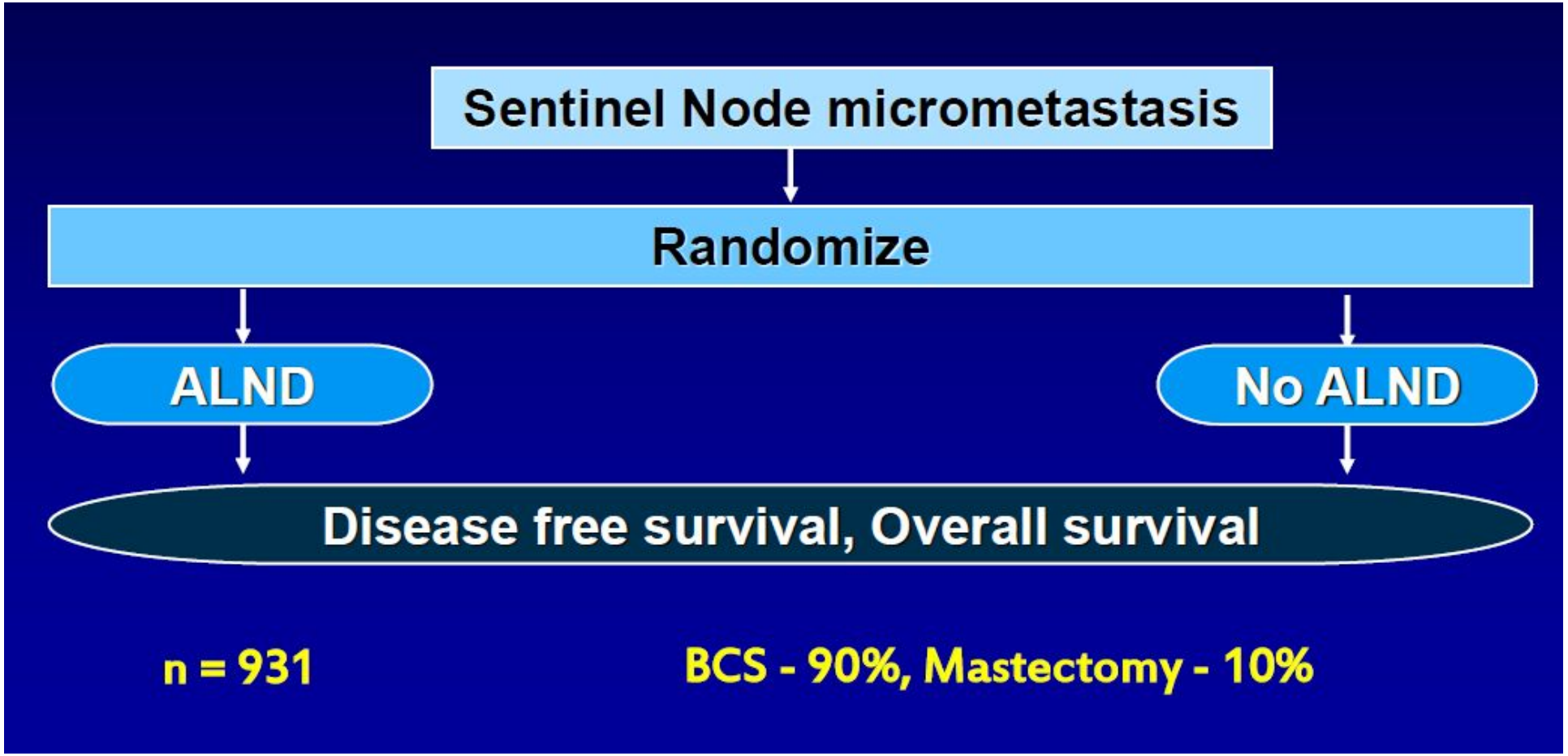
ACOSOG-Z001

	ALND (420)	SLN only (436)
cT1	67,9%	70,6%
ER+	83%	83%
Macrometastases	62,5%	55,2%
Adjuvant RT	96%	97%
Axillary recurrences	0,5% (2)	0,9% (4)

- Median Follow-up: **6,3 years**
- No significant differences in survival or locoregional recurrence between the SLND plus ALND group versus the SLND alone group.
- Recurrence rates in the ipsilateral axilla were similar between the two arms with four recurrences (0.9percent) in the SLND alone arm compared with two recurrences (0.5 percent) in the SLND plus ALND arm.

Giuliano A et al. JAMA 2011

IBCSG 23-01 study design



Galimberti V et al. Lancet Oncol 2013

IBCSG 23-01 results

Endpoints	ALND (%)	No ALND (%)	p
Primary: **DFS**	87.3	88.4	0.48
Secondary: **OS**	97.6	98	0.35

- Median follow-up: **4.75 years**
- No significant difference in DFS rate for patients treated with an ALND compared with those treated with a SLND (87 versus 92 percent).
- No significant difference in OS rate for patients treated with an ALND compared with those treated with a SLND (97.6 versus 98.0 percent).

Galimberti V et al. Lancet Oncol 2013

POSNOC trial (ongoing)

PATIENT POPULATION

Women≥18 years

T1 or T2, N0,M0 unilateral breast cancer

Node negative
(clinical, ultrasound/FNA or core biopsy)

BCS/Mastectomy + 1-2 sentinel node macrometastases
(intraoperative or postoperative SN assessment)

STRATIFICATION

Institution

Age (<50, ≥50)

BCS/Mastectomy

ER (positive, negative)

Number of positive nodes (1, 2)

→ RANDOMISATION 1:1

→ ARM 1: No Axillary Treatment

→ ARM 2: Axillary Treatment (ANC or ART)

- All patients will receive adjuvant systemic therapy (chemotherapy and/or endocrine therapy) with or without Herceptin
- All patients may receive breast/chest wall RT
- 5 years follow-up: clinic visit or telephone 6, 12, 24 and 48 months; clinic visit 36 and 60 months after randomisation

ANC: Axillary Node Clearance

BCS: Breast Conserving Surgery

ART: Axillary Radiotherapy

SN: Sentinel Node

POSNOC trial study design

- **Randomised, multicentre, non-inferiority trial**
- Sample size - 1900
- Timeline:
  - Recruitment 45 months
  - Follow-up 60 months
- Trial results 120 months **(10 years)**

EORTC 10981-22023 (AMAROS)

Median **follow-up** was **6.1 years** for the patients with positive sentinel lymph nodes

Axillary recurrence occurred in **four** of **744** patients in the ALND group and **seven** of **681** in the axillary RT group.

5-year axillary recurrence was **0.43%** (95% CI 0·00—0·92) after ALND versus **1.19%** (0·31—2·08) after axillary RT.

The planned non-inferiority test was underpowered because of the low number of events.

ALND and axillary RT after a positive sentinel node provide **excellent and comparable** axillary control for patients with T1—2 primary breast cancer and no palpable lymphadenopathy.

Donker M et al. Lancet Oncol 2014

AMAROS trial
Is it a practice changing study?

The extremely low rate of axillary recurrence in both study arms does not allow to draw any definitive conclusions.

The trial do not take in account all the very low-risk patients (probably a not negligible rate) that could reasonably not undergo any intervention.

We have to consider the **suboptimal dose** delivered in adjuvant setting in case of presence of **residual** axillary disease, and the technical challenge of **re-irradiation** in case of recurrence in already irradiated patients.

Axillary RT could be a **valid option** in case of no indication to lymphadenectomy, and it will represent **one more tool** in the hand of the oncologist.

Conclusions

- A growing body of evidence has been published recommending that a considerable number of patients can forgo ALND
- Over the years the axillary nodal status has shifted from a prognostic to staging factor
- An increasing number of scientific evidences are changing the way breast cancer should be approached and treated
- Translational oncology is the future to understand and treat **any** cancer in the most effective way.