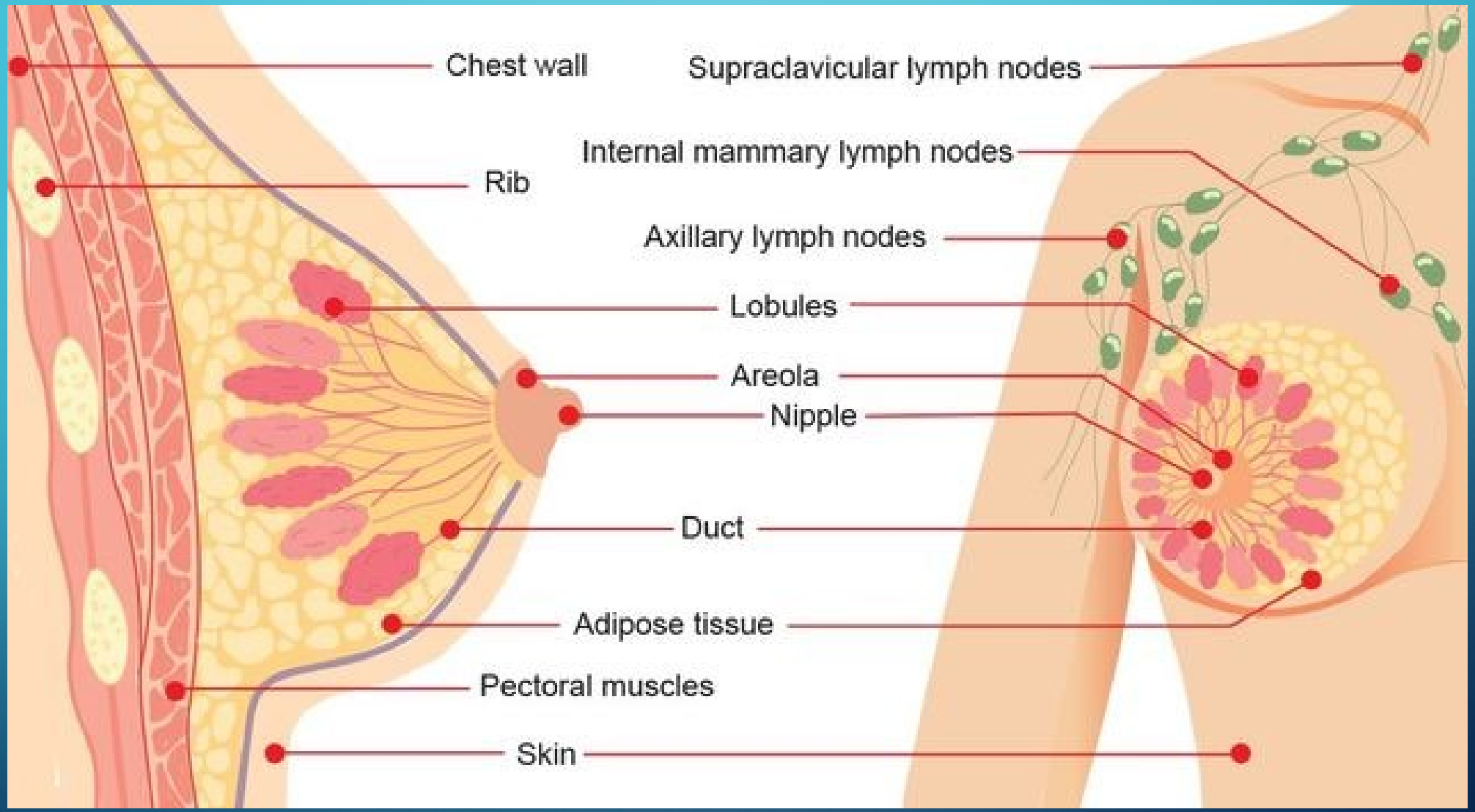
RECURRENCE RISK IN BREAST CANCER TREATMENT AND THE ROLE OF MOLECULAR SUBTYPES AND CLINICOPATHOLOGIC RISK FACTORS

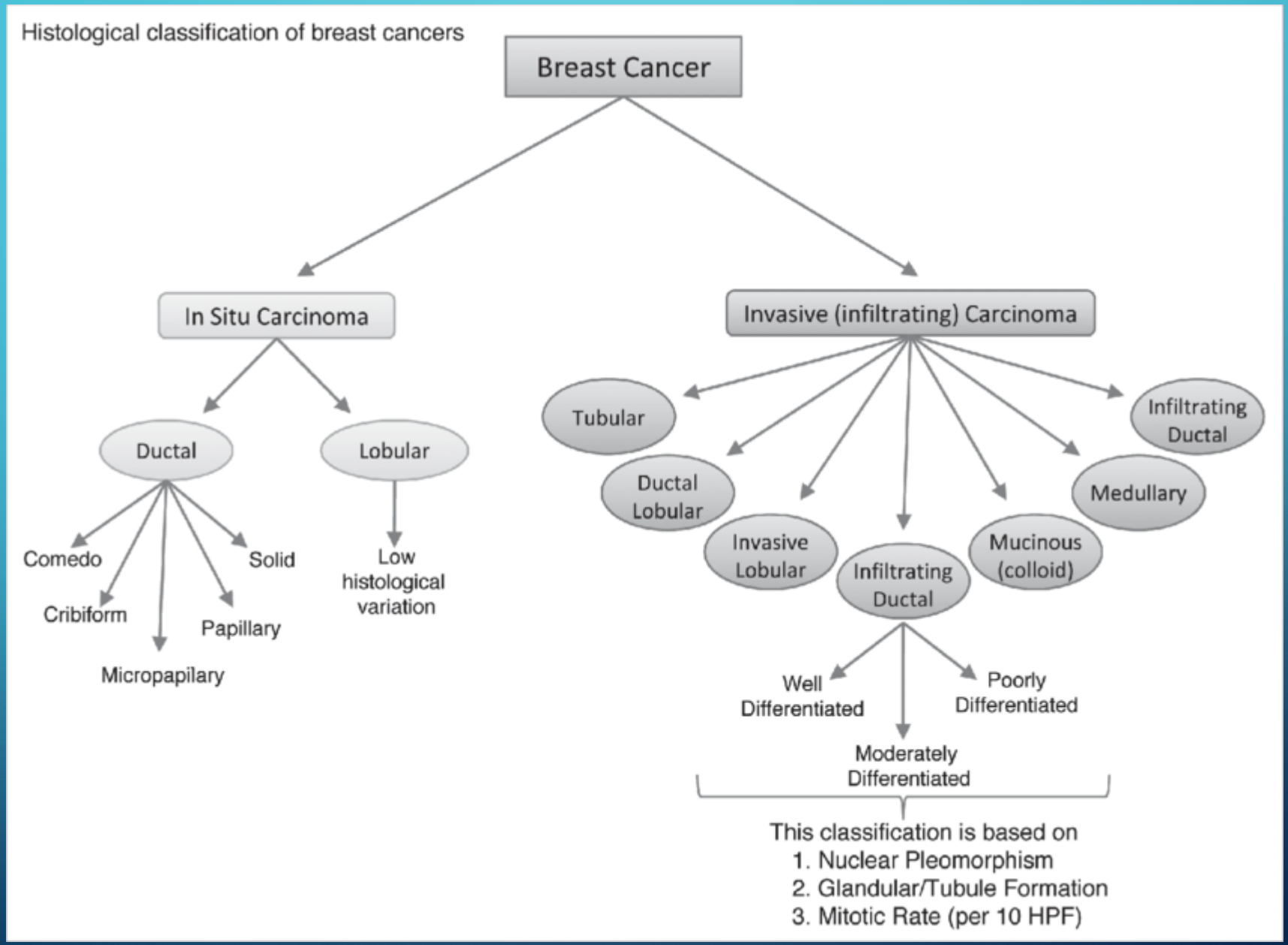
JULIE A. MARGENTHALER, MD FACS

NOVEMBER 7, 2024

BACKGROUND

- Breast Anatomy and Histopathologic Subtypes of Breast Cancer
- Historical Landmark Trials of Overall Survival and Locoregional Recurrence
- Breast Cancer Molecular Subtypes
- Locoregional Recurrence Versus Distant Recurrence
- Locoregional Recurrence Risks According to Patient and Tumor Factors

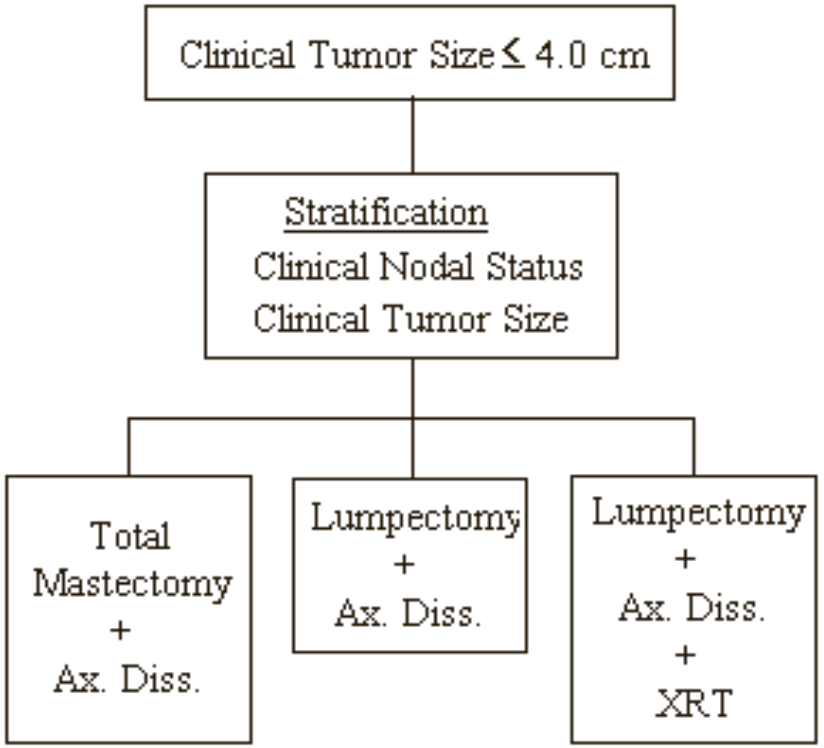

Chest wall
Rib
Lobules
Areola
Nipple
Duct
Adipose tissue
Pectoral muscles
Skin
Supraclavicular lymph nodes
Internal mammary lymph nodes
Axillary lymph nodes


Histological classification of breast cancers
Breast Cancer
In Situ Carcinoma
Invasive (infiltrating) Carcinoma
Ductal
Lobular
Comedo
Cribiform
Micropapilary
Papillary
Solid
Low histological variation
Tubular
Ductal Lobular
Invasive Lobular
Infiltrating Ductal
Mucinous (colloid)
Medullary
Infiltrating Ductal
Well Differentiated
Moderately Differentiated
Poorly Differentiated
This classification is based on
1. Nuclear Pleomorphism
2. Glandular/Tubule Formation
3. Mitotic Rate (per 10 HPF)

LANDMARK TRIALS

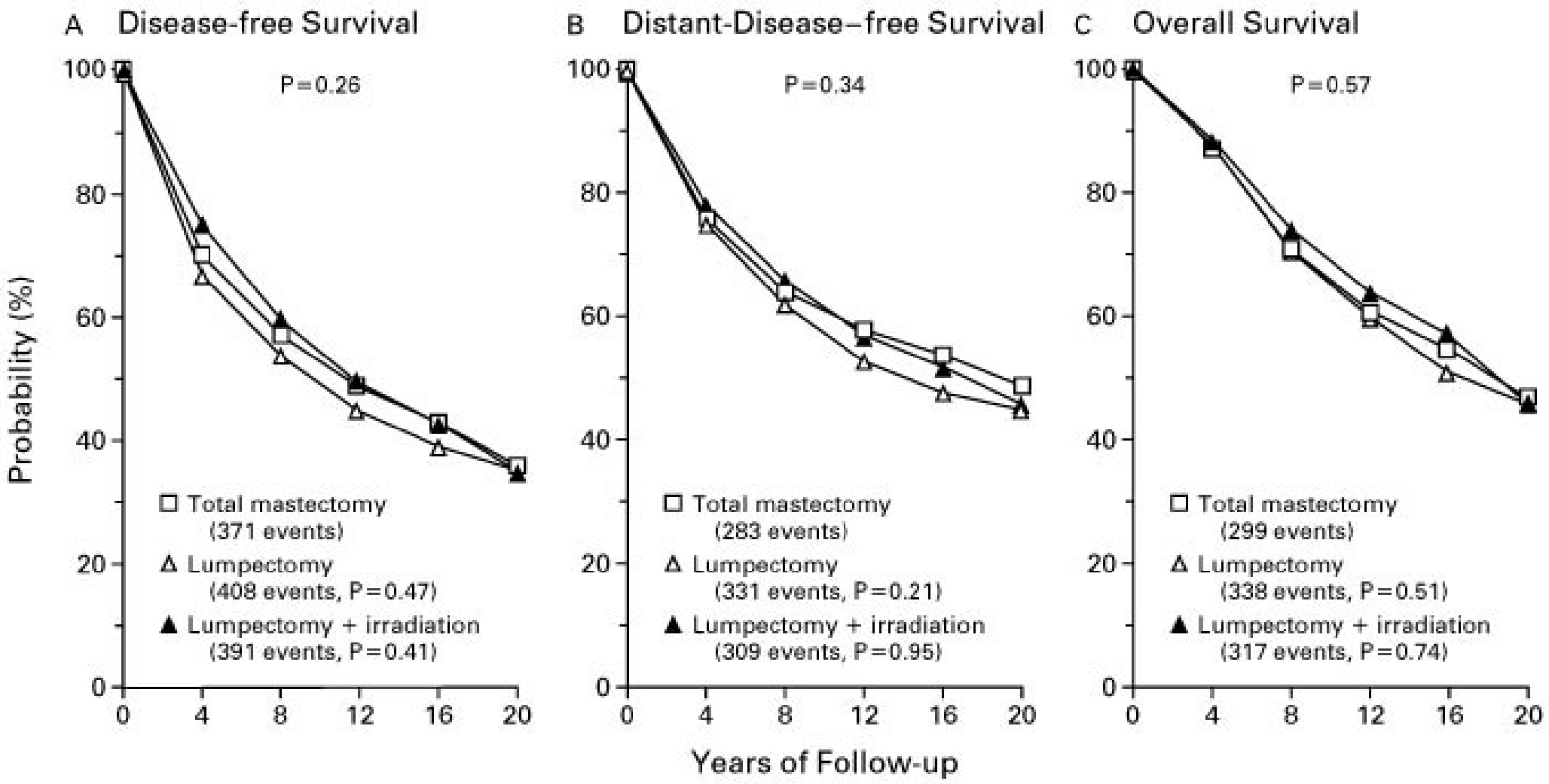
- Randomized controlled trials
  - Causal relationships can be confirmed (compared to observational data alone)
  - Control for confounding variables (co-morbidity, extent of radiation, etc.)
  - Negate selection bias (retrospective data regardless of propensity matching or other sophisticated statistical manipulation cannot)
- 6 Landmark Trials of BCT
  - Primary aim was to compare BCT to mastectomy with regard to disease-free survival and overall survival
  - Secondary endpoints can be obtained – primarily locoregional recurrence rates with long-term follow-up

NSABP B-06 (N=1851)



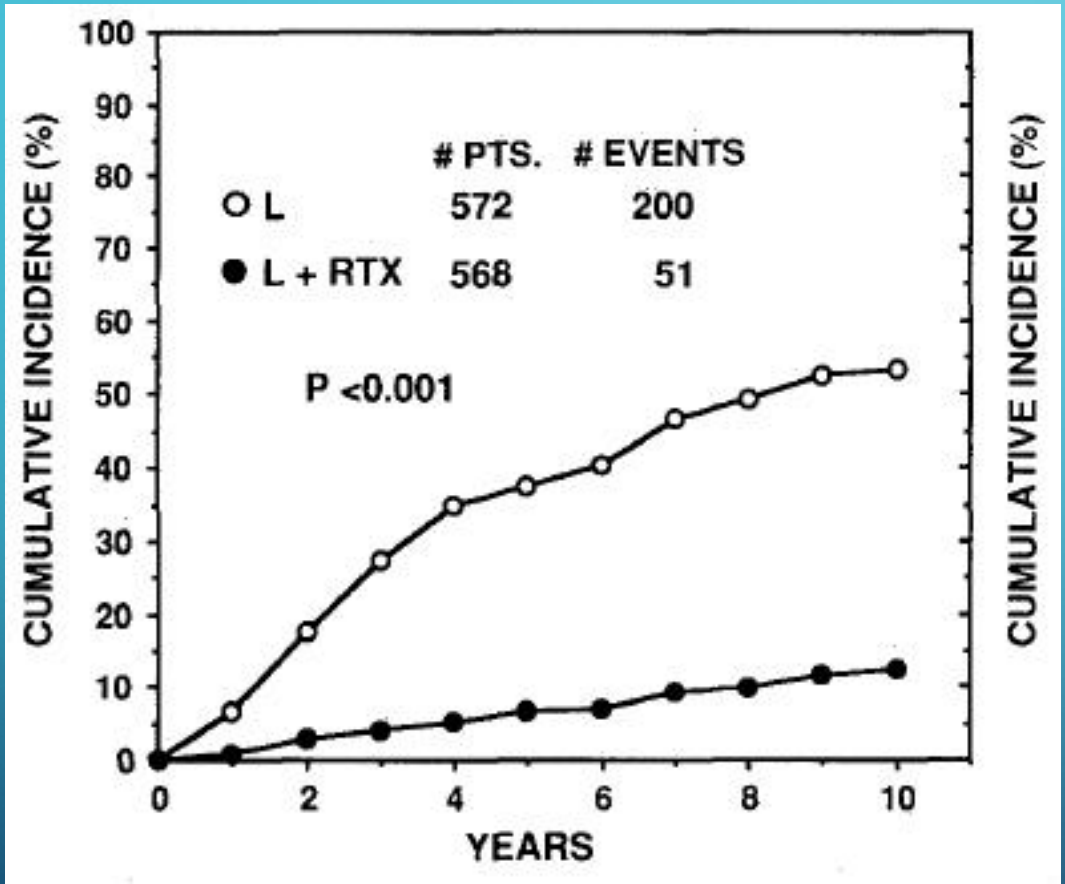
All patients with histologically positive axillary nodes receive L-PAM + 5 FU.

Total mastectomy performed in event of ipsilateral breast tumor recurrence.



Fisher B, et al. N Eng J Med 2002;347

NSABP B-06



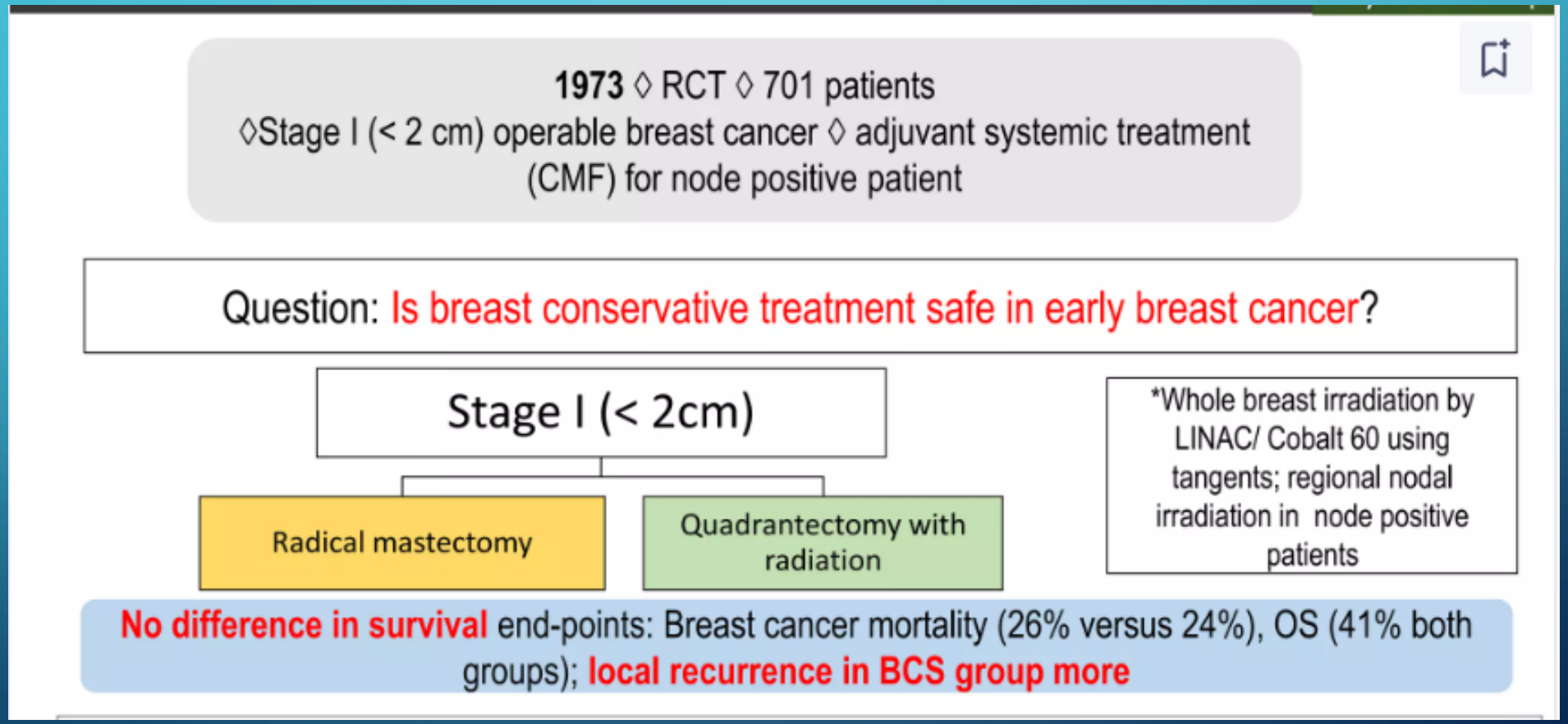
- 12% recurrence for lumpectomy + XRT
- 53% recurrence for lumpectomy alone

Fisher B, et al. N Eng J Med 2002;347

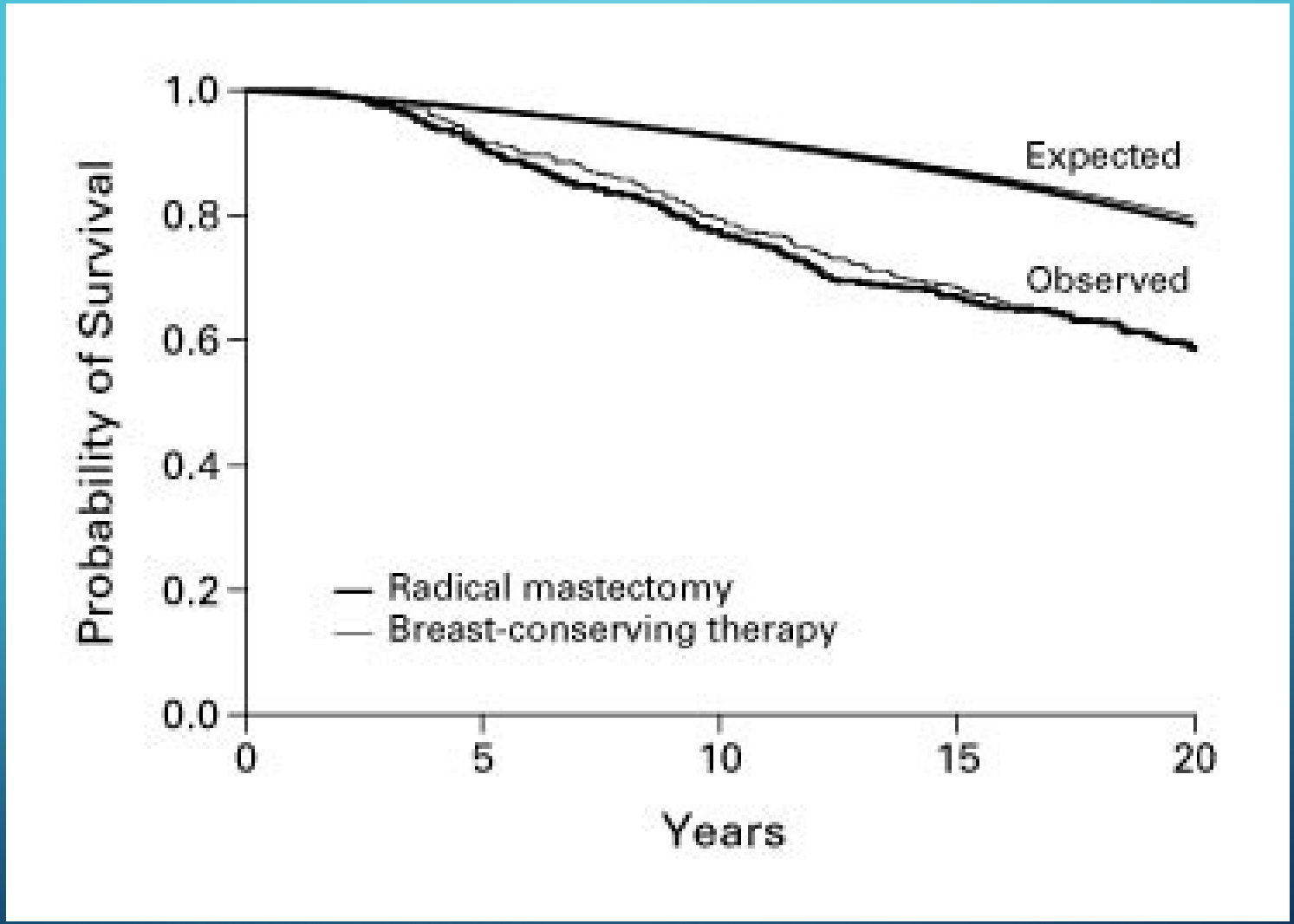
NSABP B-06

- No significant difference in overall survival based on method of locoregional treatment
- Adjuvant XRT is key in patient undergoing BCT to minimize locoregional recurrence
- Risk of distant failures in patients suffering an IBTR was 3.4X higher than those without IBTR
- 86% of IBTRs occur in the lumpectomy bed or in same quadrant

MILAN CANCER INSTITUTE TRIAL



MILAN CANCER INSTITUTE TRIAL

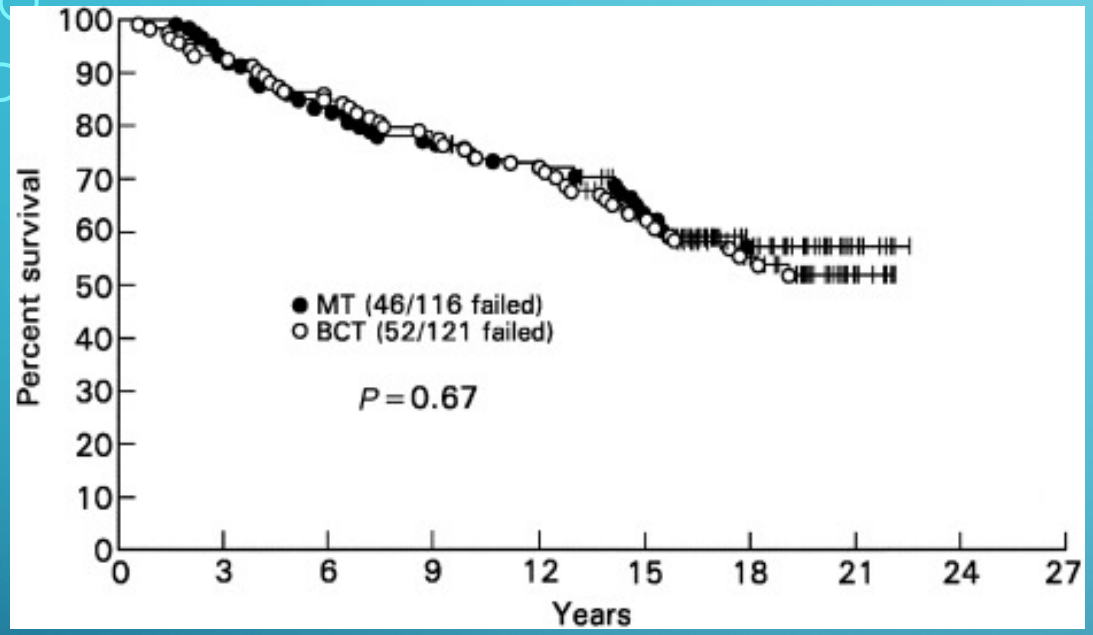


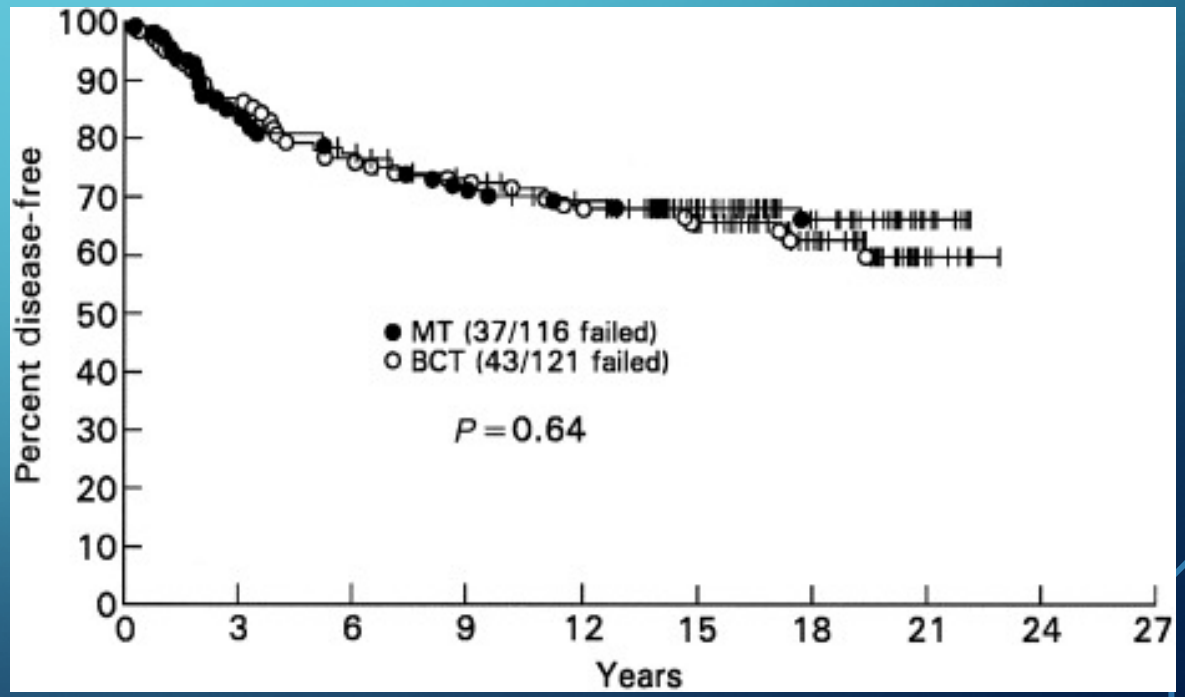
Veronesi U, et al. N Eng J Med 2002;347(16)

MILAN CANCER INSTITUTE TRIAL

- N=352 underwent breast-conserving surgery
- At 12 years of follow-up, 14 of 352 (4%) suffered an IBTR

NCI TRIAL





Poggi MM et al. Cancer 2003;98(4)

NCI TRIAL

	Mastectomy (*n* = 116)	BCT (*n* = 121)
Site		
Local (isolated chest wall or in-breast)	0	27
Regional only	3	0
Local and regional/distant	8	4
Distant only	27	30
Contralateral breast tumors	7	5
Nonbreast histology tumors	10	10

BCT: breast conservation therapy.

22% IBTR in the BCT group at 18 years median follow-up

Poggi MM et al. Cancer 2003;98(4)

INSTITUT-GUSTAVE ROUSSY (IGR) TRIAL

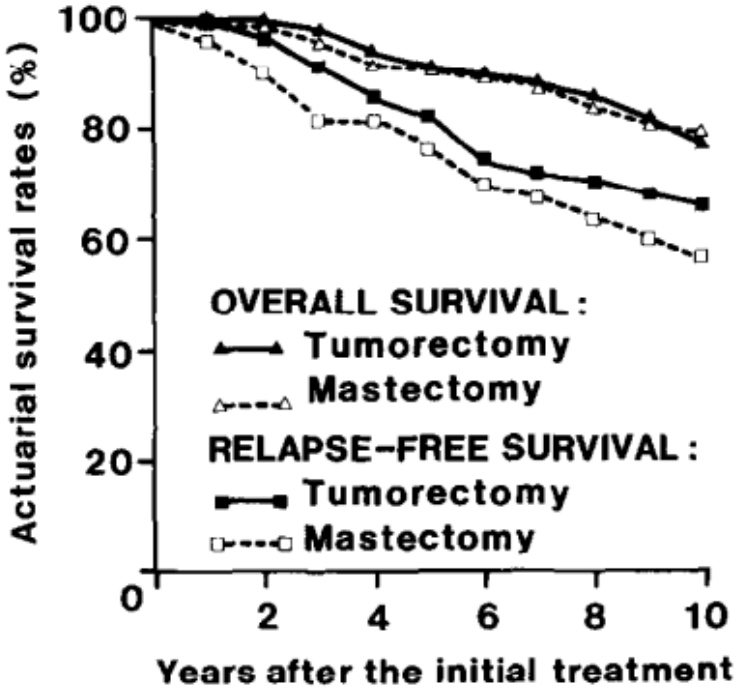


Fig. 1. Survival and relapse-free survival curves in the two treatment groups.

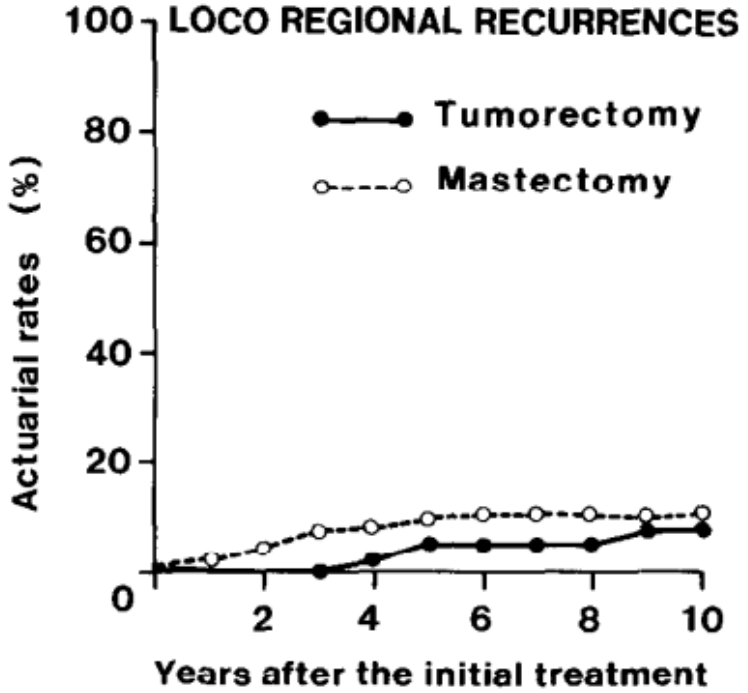
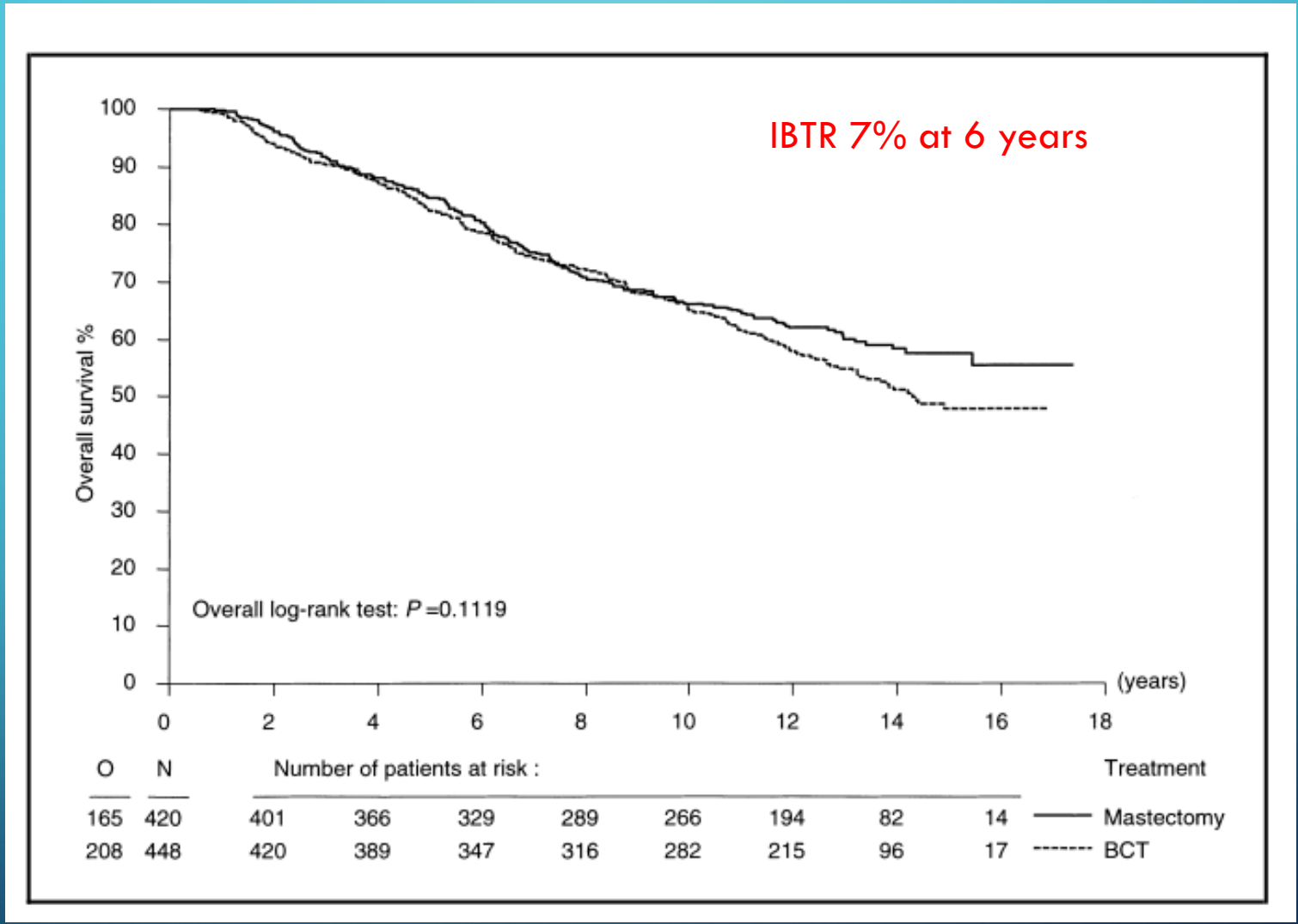


Fig. 3. Locoregional recurrences occurred after conservative treatment and mastectomy.

Sarrazin D et al. Radiotherapy and Oncology 1989; 14

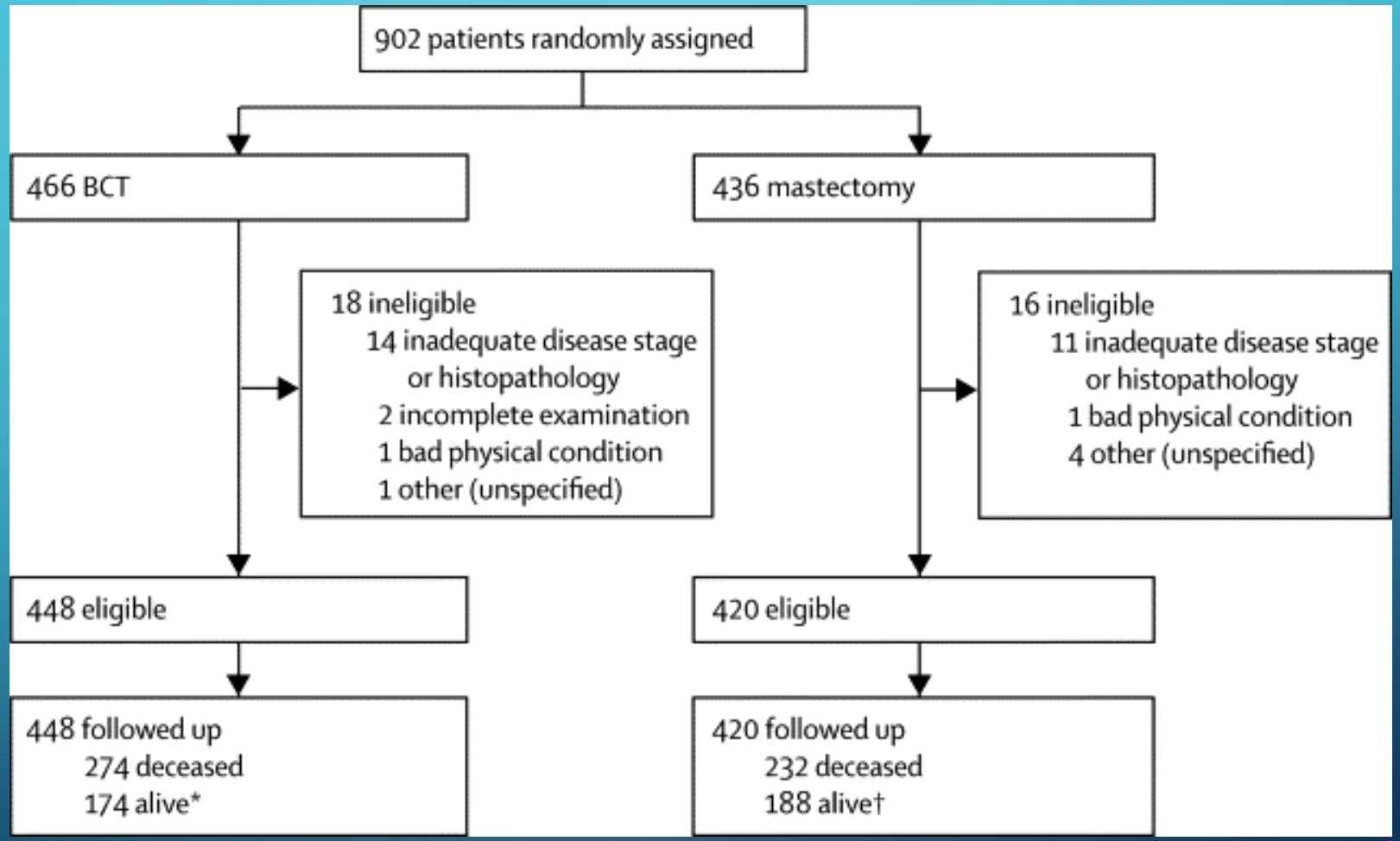
5% of BCT patients had a IBTR at 10 years

DANISH BREAST CANCER COOPERATIVE GROUP



Blichert-Toft M, et al. J Natl Cancer Inst Monogr 1992; 11

EORTC 10801



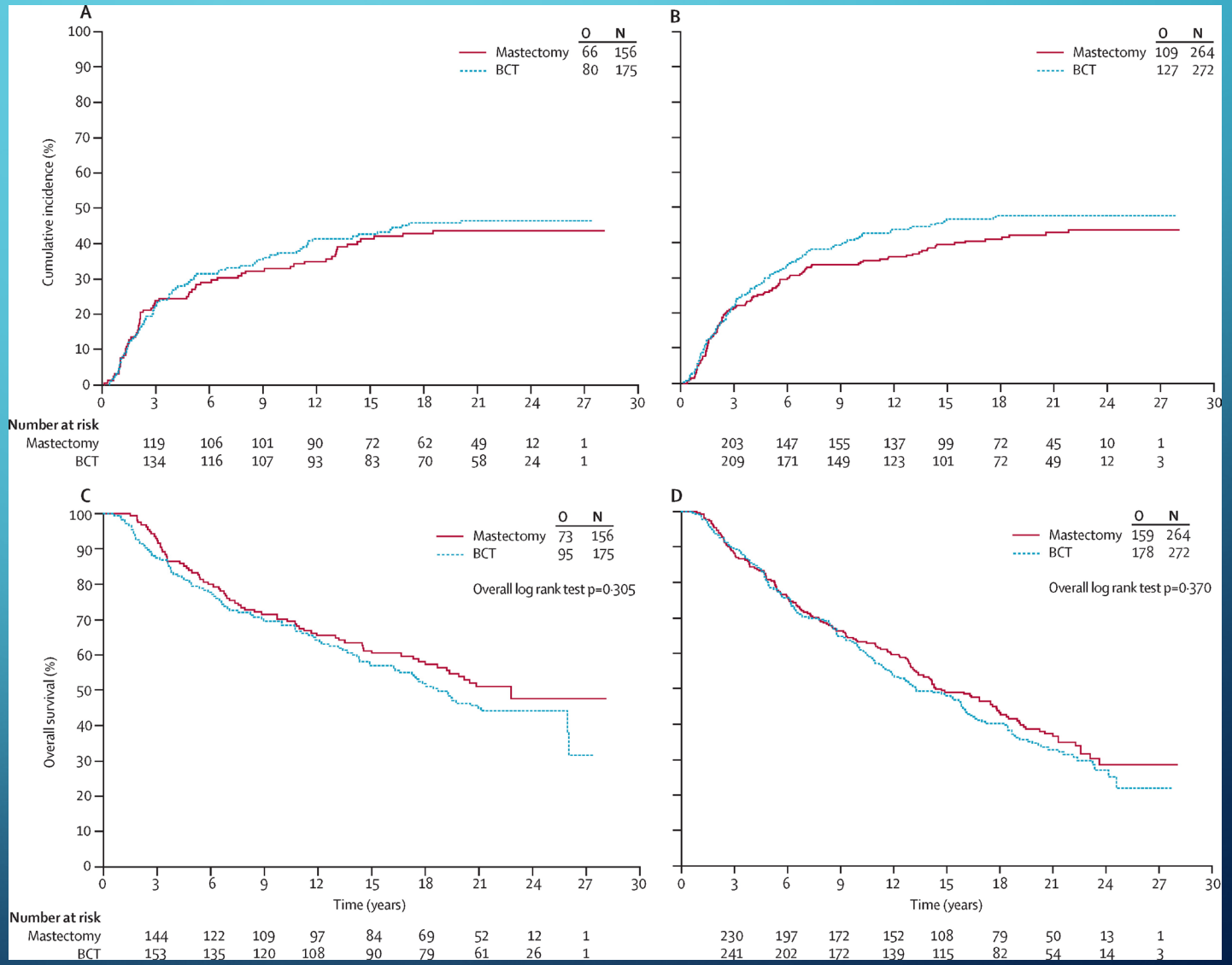
Litiere S, et al. Lancet 2012;13

EORTC 10801

27 of 292 (9.2%) had a local recurrence at 8 years

16% for tumors 2-5 cm

7% for tumors ≤2 cm



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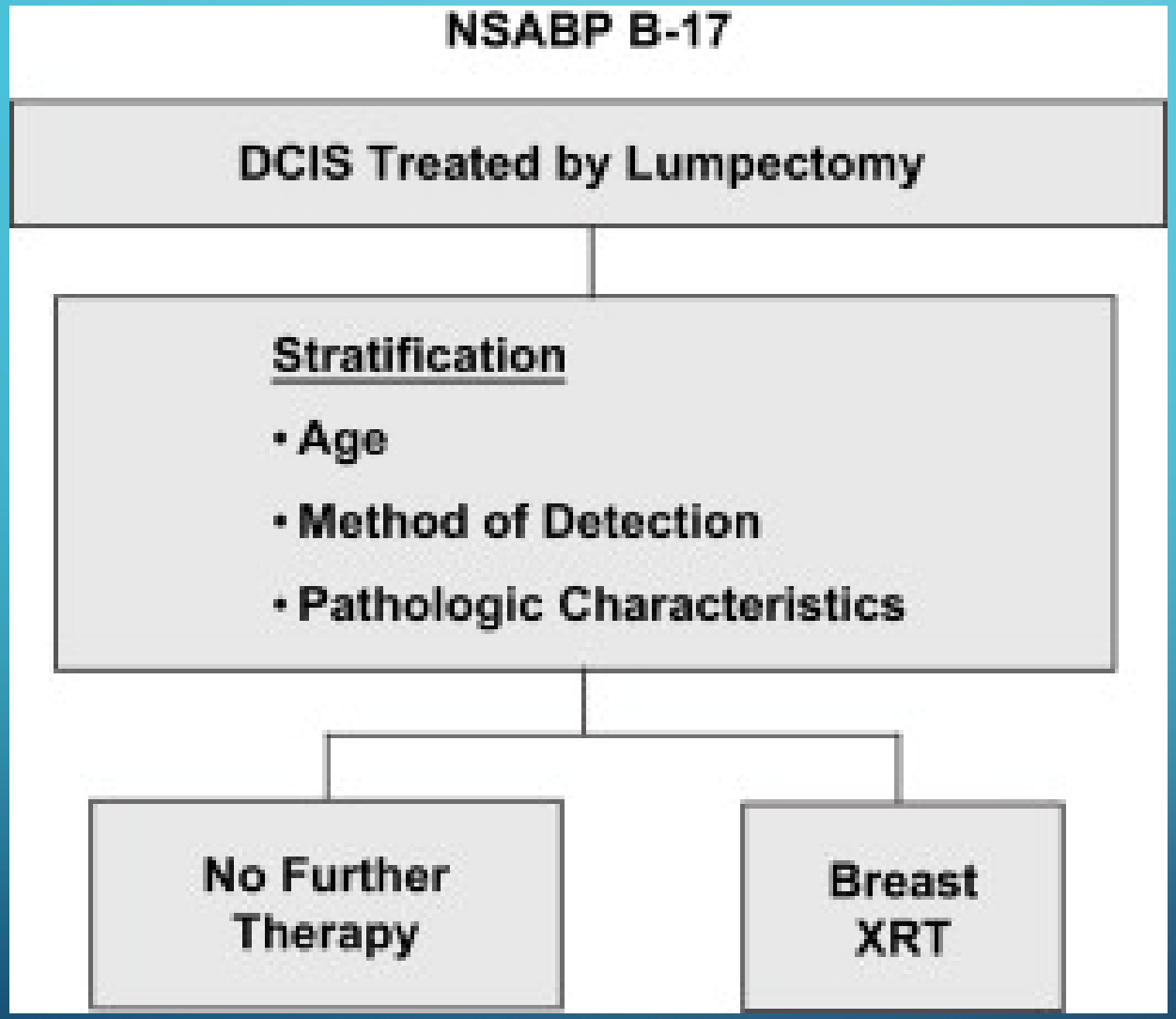
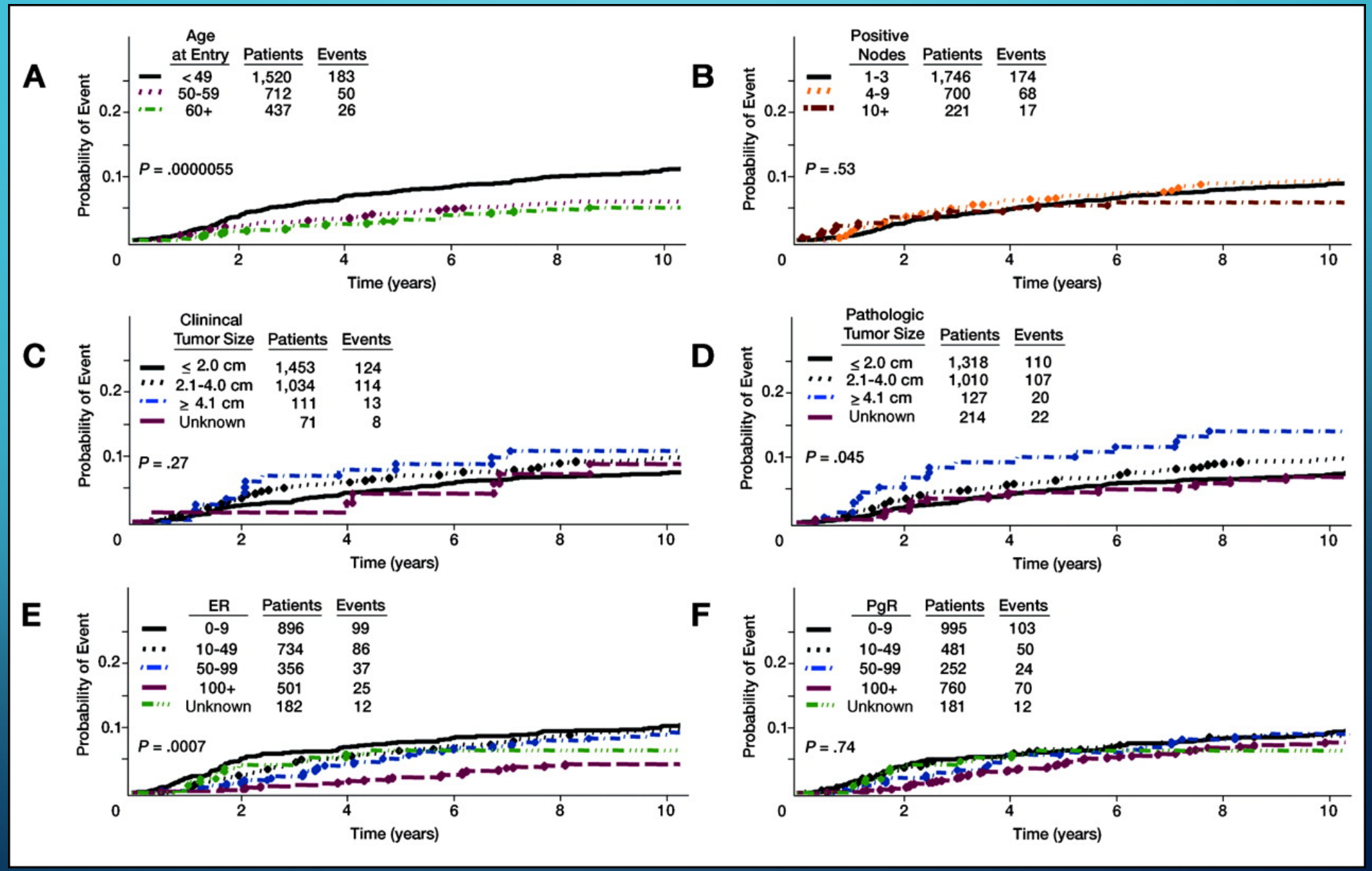


50 Gy standard dose
9% received a boost

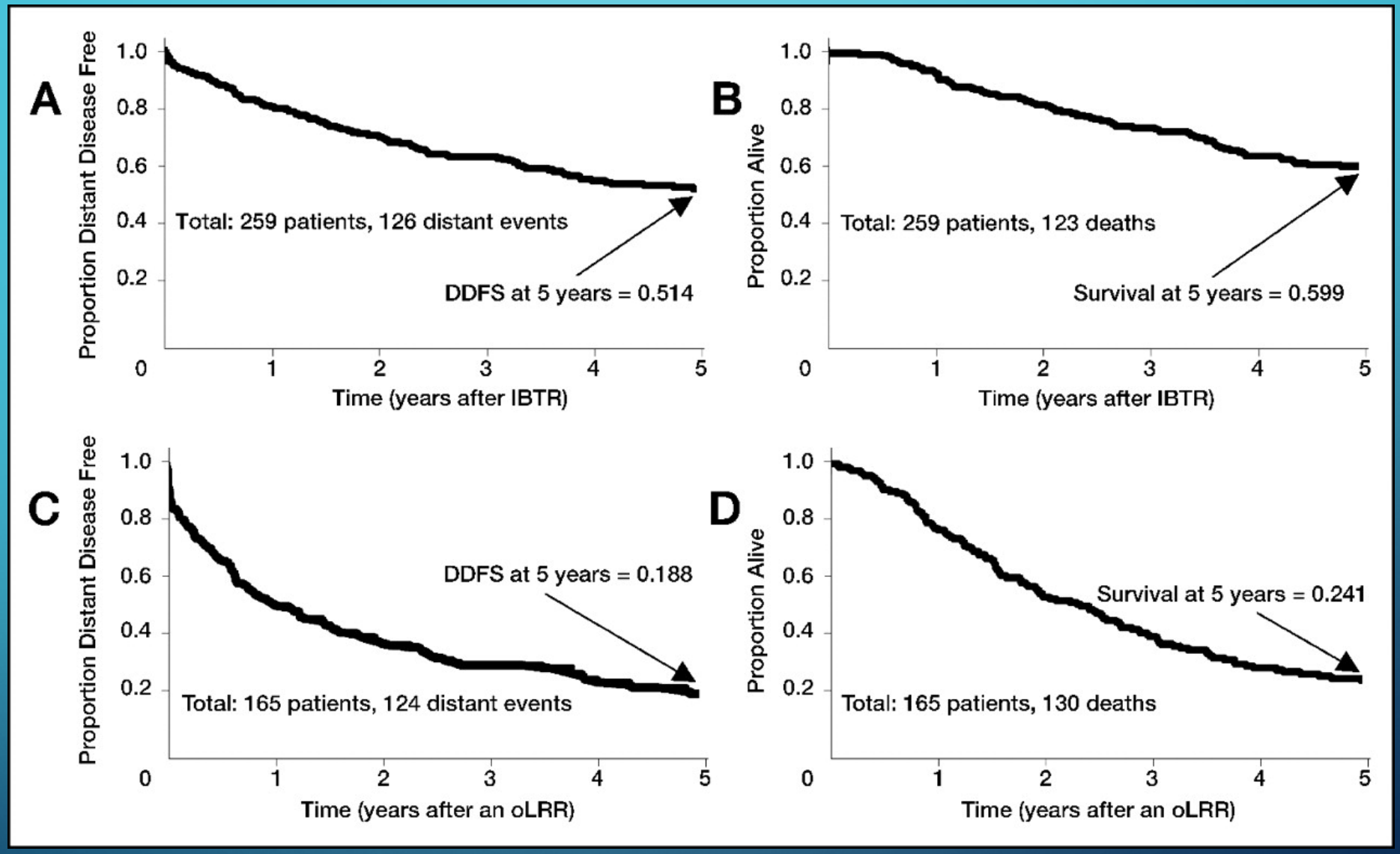
NSABP B-17

	Lump Alone	Lump+XRT
Non-invasive IBTR	14.6%	8.0%
Invasive IBTR	16.8%	7.7%
Overall Survival	86%	87%
Contralateral breast cancer	3%	5%

*at 8 years



Wapnir IL et al., JCO 2006; 24(13)



Wapnir IL et al., JCO 2006; 24(13)

Locoregional recurrence after breast-conserving therapy remains an independent prognostic factor even after an event free interval of 10 years in early stage breast cancer

E. Tanis [a], C.J.H. van de Velde [b], H. Bartelink [c], M.J. van de Vijver [d], H. Putter [e], J.A. van der Hage [a,*]

- 7751 patients
- 10.9 years median f/u

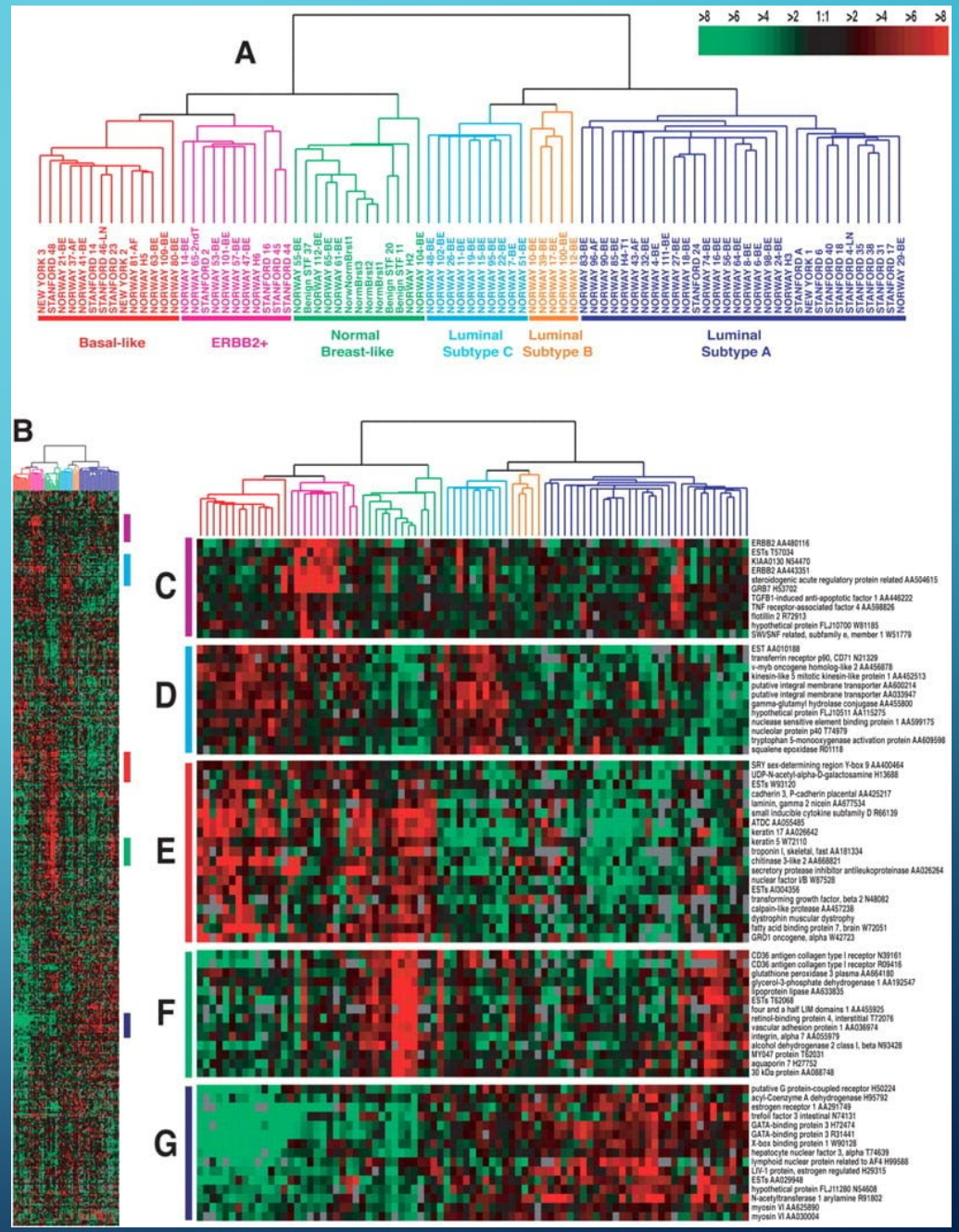
Table 1
Demography.

Patients with BCT included in this analysis	7751
Age ⩽40 at diagnosis	914 (11.8%)
Median age of diagnosis (range)	53.7 (22.7–85.9)
Median years of follow-up (range)	10.1 (0-16.9)
Loss of follow-up *N* (%)	19 (0.2%)
Locoregional recurrences *N* (%)	910 (11.7%)
Recurrence <5 years	547 (7.1%)
Recurrence >5 & <10 years	299 (3.9%)
Recurrence >10 years	64 (0.8%)
Median years until locoregional recurrence (range)	3.97 (0.07–14.85)
Adjuvant chemotherapy *N* (%)	1229 (15.9%)
Adjuvant radiotherapy *N* (%)	7653 (98.7%)
Clinical tumour size *N* (%)	
T1 (<2 cm)	3618 (46.7%)
T2 (2–5 cm)	4076 (52.6%)
T3 (>5 cm)	39 (0.5%)
Positive lymph node status	2064 (26.6%)
Deaths *N* (%)	1694 (21.9%)

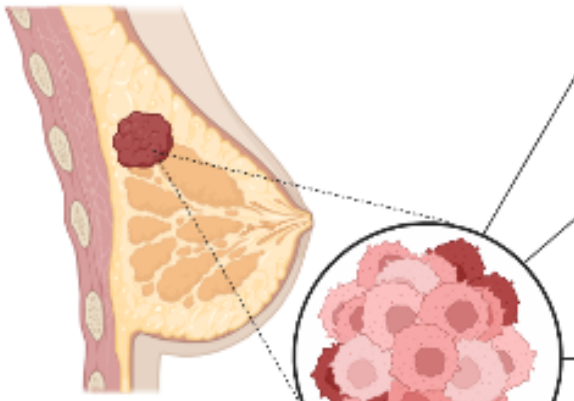
Table 2
Locoregional recurrence (LRR) versus no LRR.

	LRR+ ($n = 910$)	LRR− ($n = 6841$)
Age under 40 years	199 (21.8%)	715 (78.2%)
Clinical tumour stage		
T1	386 (10.7%)	3232 (89.3%)
T2	516(12.7%)	3560 (87.3%)
T3	5 (12.8%)	34 (87.2%)
Node positive	253 (12.3%)	1811 (87.7%)
Adjuvant chemotherapy	152 (12.4%)	1077 (87.6%)

Perou CM, et al.
Nature 2000;406(6797):747-752



5 Main Intrinsic or Molecular Subtypes of Breast Cancer



Receptors
HR: Hormone
ER: Estrogen
PR: Progesterone
HER2

Luminal A (~40%)
HR+ (ER+ and/or PR+), HER2-

- Most prevalent subtype
- Low levels of Ki-67: control cancer cell growth
- Targeted therapy: Tamoxifen

Normal-like (~2-8%)
HR+ (ER+ and/or PR+), HER2-

- Low levels of Ki-67: control cancer cell growth
- Slightly worse prognosis than Luminal A
- Targeted therapy: Tamoxifen

Luminal B (~20%)
HR+ (ER+ and/or PR+), HER2+/-

- High levels of Ki-67: fast cancer cell growth
- Targeted therapy: Tamoxifen

HER2-enriched (~10-15%)
HR- (ER-, PR-), HER2+

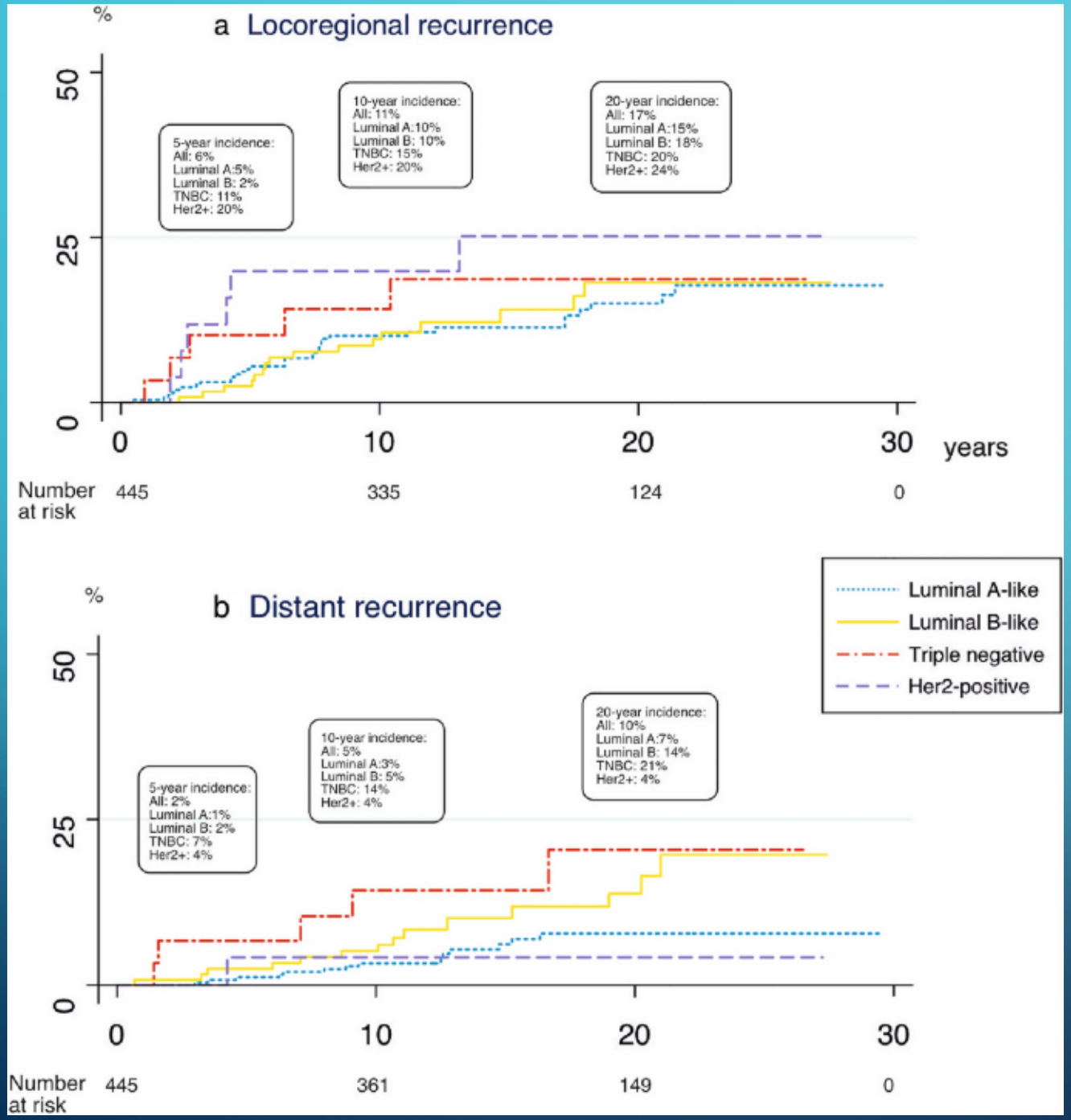
- Amplification/overexpression of receptor HER2
- Faster growth than luminal subtypes
- Targeted therapy: Herceptin

Triple Negative (~15-20%)
HR- (ER-, PR-), HER2-

- Most aggressive subtype
- Occurs more often in younger women
- Highest association to BRCA1 mutations

Best prognosis

Worst prognosis



Rask G, et al. Br Ca Res Treat 2022; 195

JAMA Surgery | Original Investigation

Locoregional Recurrence Patterns in Patients With Different Molecular Subtypes of Breast Cancer

Jong-Ho Cheun, MD, MS; Hong-Kyu Kim, MD, PhD; Hyeong-Gon Moon, MD, PhD; Wonshik Han, MD, PhD; Han-Byoel Lee, MD, PhD

Overall IBTR 2.8%

- 2.1% for Luminal A
- 3.3% for Luminal B
- 3.5% for TNBC
- 5.8% for HER2 enriched

Table 1. Demographic and Clinicopathological Characteristics of Patients (continued)

Characteristic	Patients, by breast cancer subtype[a]				
	All (N = 16 462)	HR+/*ERBB2*− (n = 10 075)	HR+/*ERBB2*+ (n = 1846)	HR−/*ERBB2*+ (n = 1908)	HR−/*ERBB2*− (n = 2633)
Resection margin, No./total No. (%)[d]					
Clear	8412/10 313 (81.6)	5279/6618 (79.8)	812/996 (81.5)	757/918 (82.5)	1564/1781 (87.8)
Close or involved	1834/10 313 (17.8)	1301/6618 (19.7)	175/996 (17.6)	149/918 (16.2)	209/1781 (11.7)
Unknown	67/10 313 (0.6)	38/6618 (0.6)	9/996 (0.9)	12/918 (1.3)	8/1781 (0.4)
Neoadjuvant chemotherapy					
Administered	2674 (16.2)	1119 (11.1)	494 (26.8)	439 (23.0)	622 (23.6)
Not administered	13 788 (83.8)	8956 (88.9)	1352 (73.2)	1469 (77.0)	2011 (76.4)
Adjuvant chemotherapy					
Administered	6955 (42.2)	3615 (35.9)	851 (46.1)	916 (48.0)	1573 (59.7)
Not administered	8244 (50.1)	5613 (55.7)	866 (46.9)	876 (45.9)	889 (33.8)
Unknown	1263 (7.7)	847 (8.4)	129 (7.0)	116 (6.1)	171 (6.5)
Adjuvant radiotherapy					
Administered	11 093 (67.4)	6894 (68.4)	1225 (66.4)	1058 (55.5)	1916 (72.8)
Not administered	4634 (28.1)	2689 (26.7)	560 (30.3)	771 (40.4)	614 (23.3)
Unknown	735 (4.5)	492 (4.9)	61 (3.3)	79 (4.1)	103 (3.9)
Adjuvant hormonal treatment					
Administered	11 368 (69.1)	9620 (95.5)	1677 (90.8)	29 (1.5)	42 (1.6)
Not administered	5008 (30.4)	388 (3.9)	151 (8.2)	1879 (98.5)	2590 (98.4)
Unknown	86 (0.5)	67 (0.7)	18 (1.0)	0	1 (0.0)
ERBB2-targeted treatment					
Administered	1894 (11.5)	0	1001 (54.2)	893 (46.8)	0
Not administered	14 568 (88.5)	10 075 (100)	845 (45.8)	1015 (53.2)	2633 (100)
Interval of mammography, median (IQR), mo	12.0 (10.7-13.3)	12.0 (10.6-13.3)	12.1 (10.9-13.5)	12.1 (10.8-13.5)	12.0 (10.8-13.5)
Interval of clinic visits, median (IQR), mo					
≤5 y After surgery	6.0 (4.2-8.5)	5.8 (4.1-8.2)	6.2 (4.4-8.6)	6.5 (4.5-9.1)	6.3 (4.3-9.1)
>5 y After surgery	35.6 (24.0-61.2)	36.1 (24.0-61.6)	34.3 (24.0-60.0)	36.8 (24.0-61.8)	32.4 (24.0-60.0)
IBTR, No./total No. (%)[d]	286/10 313 (2.8)	137/6618 (2.1)	33/996 (3.3)	53/918 (5.8)	63/1781 (3.5)
RR	466 (2.8)	187 (1.9)	54 (2.9)	82 (4.3)	143 (5.4)
CBC	325 (2.0)	167 (1.7)	33 (1.8)	35 (1.8)	90 (3.4)
Follow-up period, median (IQR), mo	73.7 (46.3-116.2)	74.4 (48.4-114.8)	69.8 (43.3-110.1)	72.0 (43.2-116.0)	76.0 (41.1-120.0)

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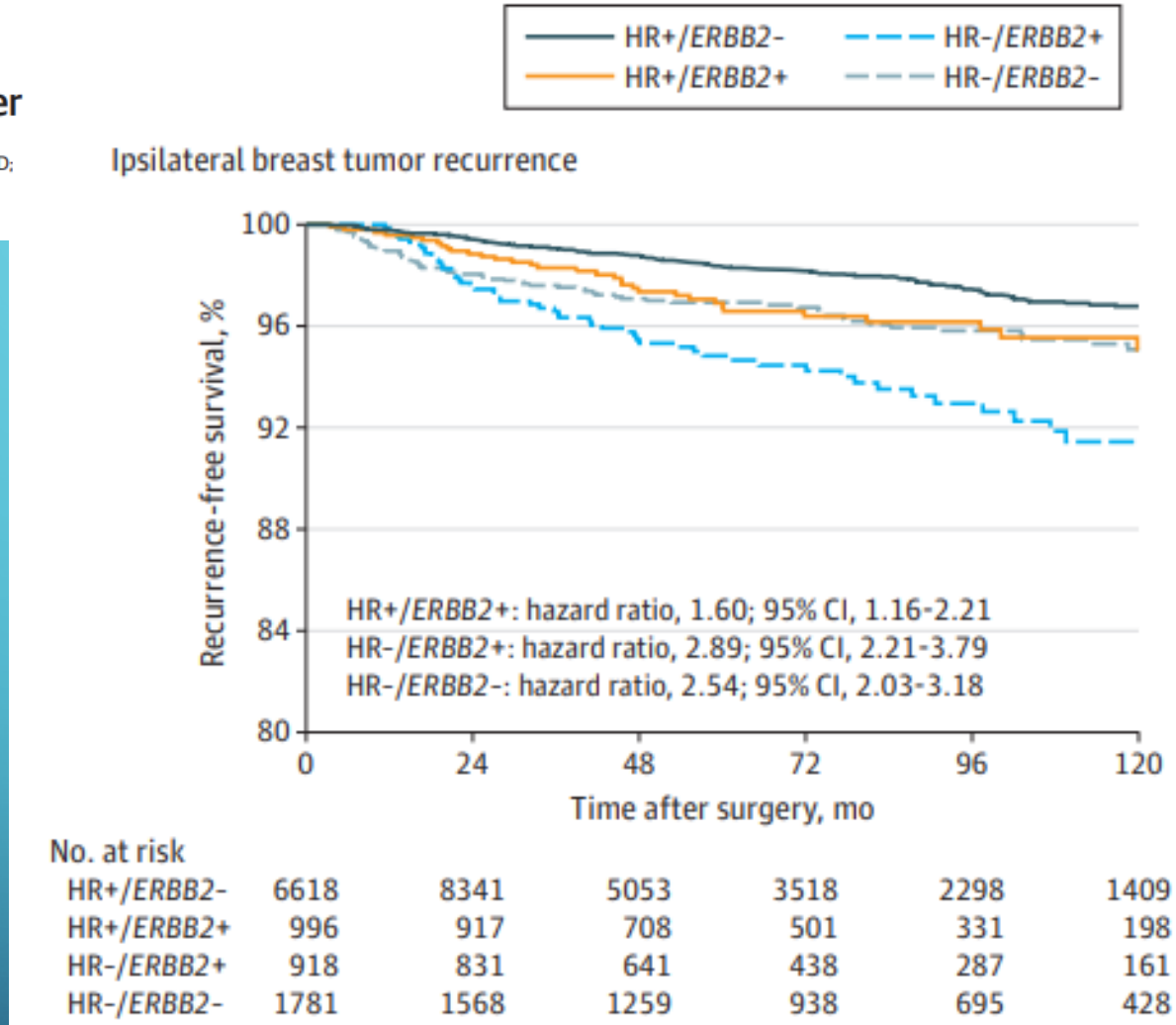

No. at risk

HR+/*ERBB2*-	6618	8341	5053	3518	2298	1409
HR+/*ERBB2*+	996	917	708	501	331	198
HR-/*ERBB2*+	918	831	641	438	287	161
HR-/*ERBB2*-	1781	1568	1259	938	695	428

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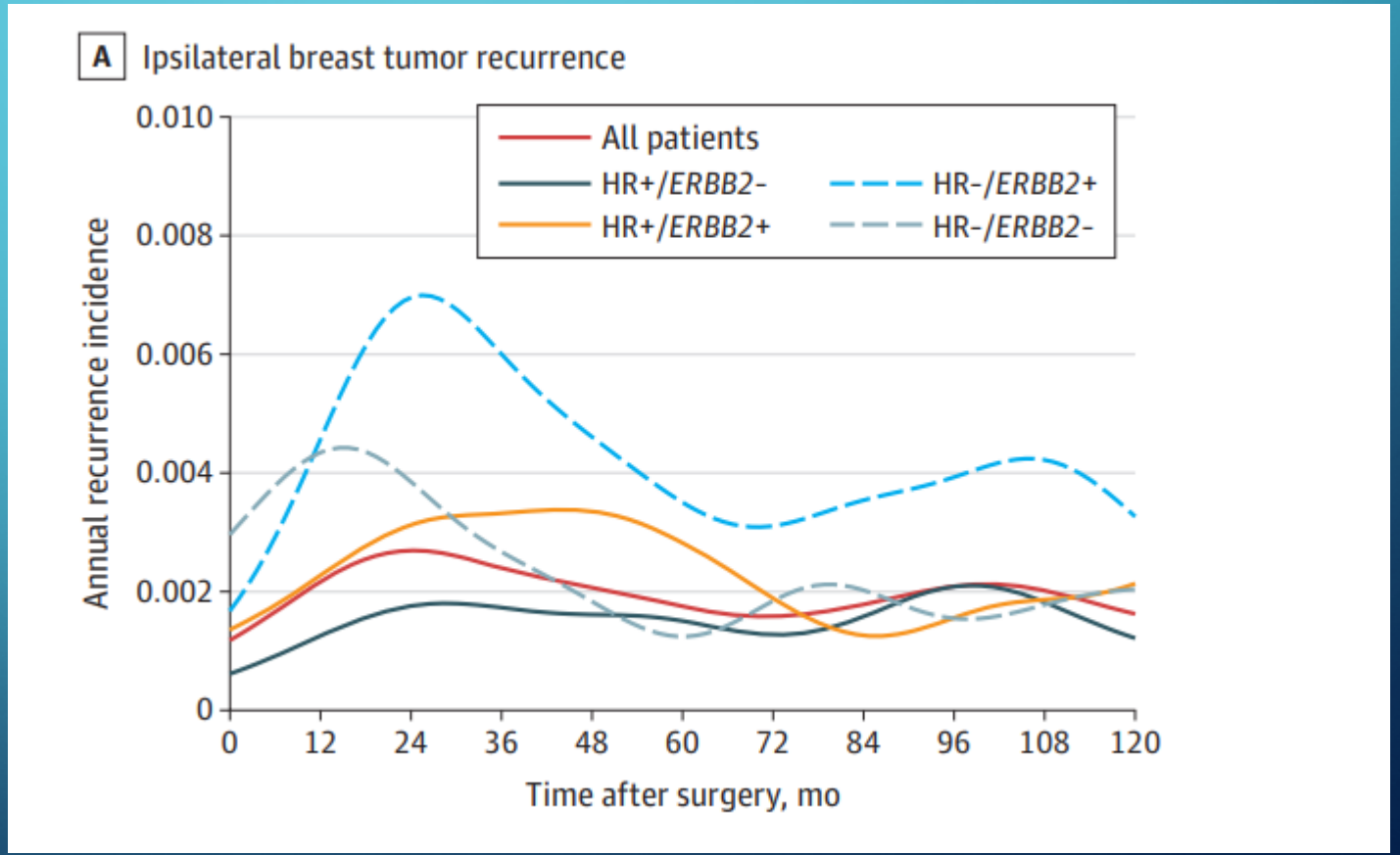

SUMMARY

- Patient and standard clinicopathologic tumor factors impact locoregional recurrence (younger age, larger T size, positive nodal status)
- Randomized clinical trial data demonstrate in-breast tumor recurrence rates ranging from 4%-22%
- Locoregional recurrence has a significant impact on overall survival that was observed in NSABP B-06 and all studies thereafter
- Molecular intrinsic subtyping of breast cancer can better predict the risk for locoregional recurrence which remain ~2-6% with modern systemic and radiation therapeutic approaches