CARCINOMA LOBULARE INFILTRANTE: PARTICOLARITA DIAGNOSTICHE E PROGNOSTICHE

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INSTITUT DU CANCER COURLANCY - REIMS

4ème INCONTRO ITALO-FRANCESE SUL CARCINOMA MAMMARIO

ASSISI 23-24 NOVEMBRE 2013

RIASSUNTO:

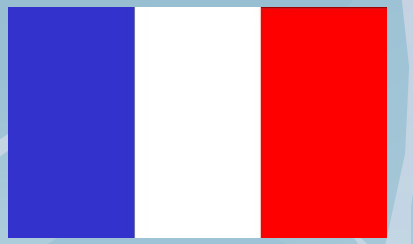
- Incidenza
- Diagnosi
- Paragoni CLI / CDI
  - Istopatologia
  - Trattamenti
  - Prognosi
- Invasione linfonodale
- Grado SBR / Recettori
- Trattamento conservativo
- Chemioterapia neoadiuvante
- Metastasi
- Conclusioni

INCIDENCE

- Infiltrating lobular carcinoma (ILC) accounts for 7-15% of all BC
- In western countries ILC incidence increased after 1980 especially in women using HRT

ARPINO G, Breast Cancer Research 2004, 6: R194-156
PAUMIER A, J Gyn Obs Biol Reprod 2003, 32 : 539-534
BIGLIA N, EJSO 2013, 39: 455-460

ILC INCIDENCE : FRENCH STUDIES



	N	%
NANTES (1985-99)[1]	2372	9.2
NANCY (1990-01)[2]	4165	9.3 3.9 [ILC+IDC]
Observatoire National (2001-02)[3]	1159	11.6 3.3 [ILC+IDC]

1 : PAUMIER JGOBR 2003, 32 : 529-34

2 : MALLOL REV. EP. SPUB. 2006, 54 : 313-325

3 : CUTULI BCRT 2006, 95 : 55-64

ILC INCIDENCE ACCORDING TO TIME NANCY EXPERIENCE (%)

	1990-93 (1137)	1994-97 (1454)	1995-01 (1574)
CCI	76,3	77,9	74,1
CLI	8,7	8,9	10
CCI+CLI	2,2	2,8	6,3
AUTRES	12,8	10,4	9,6

Réf: MALLOL Rev. Ep. Santé Pub. 2006, 54:313-325

ILC INCIDENCE : ITALIAN STUDIES

	N	%
TORINO UNIVERSITY[1]	1650	14.7
ROMA SAN GIOVANNI[2]	1182	14.5

1 : BIGLIA N, EJSO 2013, 39: 455-460

2 : FORTUNATO L, ANN SURG ONC 2012, 19: 1107-1114

ILC INCIDENCE : INTERNATIONAL STUDIES

	N	%	
BERLIN / MUNICH	2058	20	
SEOUL	3726	2.5	
ST LOUIS	4336	11	
		6 [ILC+IDC]	

HRT INFLUENCE ON HISTOLOGICAL BREAST CANCER SUBTYPES

Results of National French Survey:

1159 patients (2001-2002)

	HRT + (%) (1)	HRT - (%)
IDC	77.3	84.3
ILC	14.3	10.7
IDC+ILC	4.9	1.9
OTHERS	3.5	3.1

(1) : HRT+: 38% of the patients (287/750)

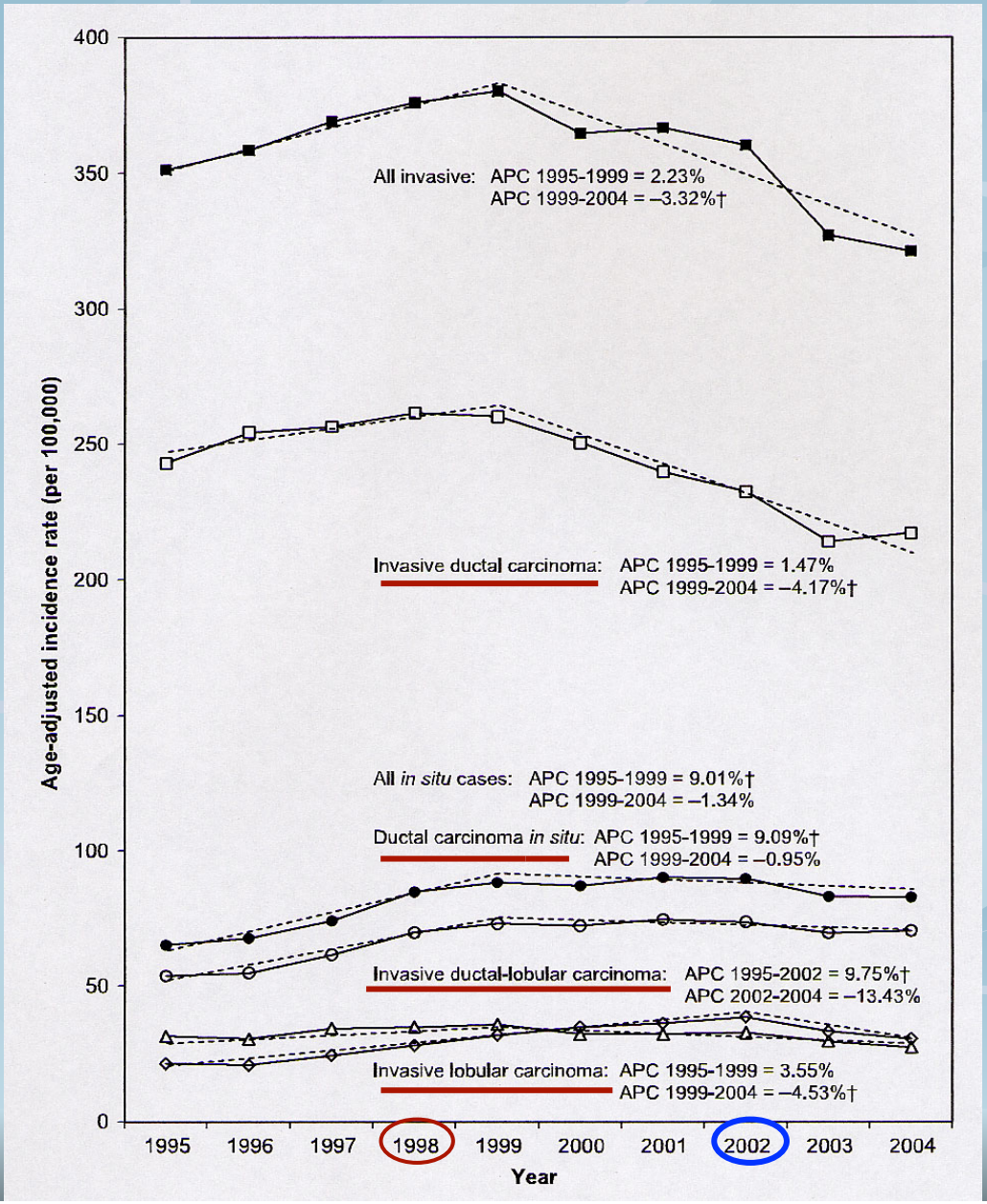
CUTULI et al BCRT 2006, 95 : 55-64

CHANGES IN BREAST CANCER INCIDENCE RATES IN THE UNITED STATES BY HISTOLOGICAL SUBTYPE AND RACE/ ETHNICITY 1995 TO 2004

- **Analysis of data from 13 registers (SEER base), with annual rates evaluation from 1995 to 2004**

LI C, Cancer Epidem Biom Prev 2007, 16 : 2773-2780

AGE-ADJUSTED BREAST CANCER INCIDENCE RATES FOR WOMEN 50 TO 79 YEARS OF AGE, 1995 TO 2004



APC : ANNUAL PERCENT CHANGE

LI, CEBP 2007, 16 : 1773

… IDC and ILC incidence rates fell steadly from 1998 to 2004, with APC -3% and APC -3.2%, and before 2002 when the Women's Health Initiative trial results were published.

Thus, the abrupt decline in HRT use starting in 2002 is unlikely to be primary responsible for the recent decline in BC rates…

ILC DIAGNOSIS (I)

- ILC often correspond to a vague area of thickening or induration without definable margins.

Discrete skin abnormalities could be associated

- Mammographic findings may be equally subtle, with areas of asymetric density, or architectural distortion
- In fact, the extent of the tumor may be subtantially underestimated by both physical examination and mammography

ILC DIAGNOSIS (II)

- Frequent occurrence in dense breasts
- 8-19% rate of false negative
- Increased ILC rate among « interval cancers »
- Interest of comparisons with US and MRI

ILC: RADIOLOGICAL FEATURES (%)

	OPACITY(1)	ARCHIT. DISTORSION	MICROCAL.	ASYMETRY	NS
HILLEREN (1991)	60	16	7	4	6
BERTRAND (1995)	67	19	10	-	7
LE GAL (1992)	54	16	24	20	8
KRECKE (1993)	68	25	10	-	-

INVASIVE LOBULAR CARCINOMA OF THE BREAST : MAMMOGRAPHIC CHARACTERISTICS AND COMPUTER AIDED DETECTION

evans w. et AL RADIOLOGY 2002, 225 182-189

- features analysis of 94 ILC detected by screening with CAD help

Resultats : RADIOLOGICAL FEATURES

- 56 (60%) masses (70% irregular / spiculated)
- 20 (21%) architectural distortion
- 18 (20%) asymetric densities / calcifications
- CAD sensitivity : 86 / 94 (91%)

NB : 31/40 prior available mammograms showed retrospectively visible findings… (24 / 31 identified by CAD)

MRI COMPARED TO CONVENTIONAL DIAGNOSTIC WORK-UP IN THE DETECTION AND EVALUATION OF ILC OF THE BREAST : A REVIEW OF EXISTING LITERATURE

MANN R, BCRT 2008, 107 : 1-14

Endpoints :

- What is the sensitivity of MRI for ILC ?
- What are the visual characteristics of ILC on MRI ?
- Are the findings of MRI equal to the findings at pathology ?
- What is the impact of MRI on surgical management of ILC ?

Results (I)

- Sensitivity ranges from 83% to 100% (average : 93%)
- Morphologic apperance is highly heterogenous and probably heavily influenced by interreader variability

Results (Ii)

- Correlation with pathology ranges from 0.81 to 0.97
- Overestimation of lesion size occurs but is rare
- In 32% of patients, additional ipsilateral lesions are detected and in 7% contralateral lesions are only detected by MRI
- MRI induces change in surgical management in 28% of cases

CLINICO-PATHOLOGICAL COMPATIVE CHARACTERISTICS BETWEEN IDC AND ILC NANTES EXPERIENCE [I]

	IDC (n=2155)	ILC (n=217)	p
AGE	56	55	NS
MENOPAUSE (%)	61	56	NS
T (%)			
T0	11	13	
T1	34	30	
T2	36	33	NS
T3-T4	13	16	
NP	6	9	
RE+ (%)	75	93	0.0001
RP+ (%)	61	71	0.025

	IDC (n=2155)	ILC (n=217)	p
SBR (%)			
I	20	7	0.001
II	56	82	
III	24	4	
NP	0	7	
MULTIFOCALITY (%)	22	39	< 0.001
pT1a-b (%)	15	16	NS
pT1c	37	31	NS
pT2 (20-30 mm)	19	20	NS
pT2 (> 30 mm)	20	28	0.001
pTx	9	5	
pN+ (%)	48	47	NS
pN ≥ 3 (%)	22	16	0.04

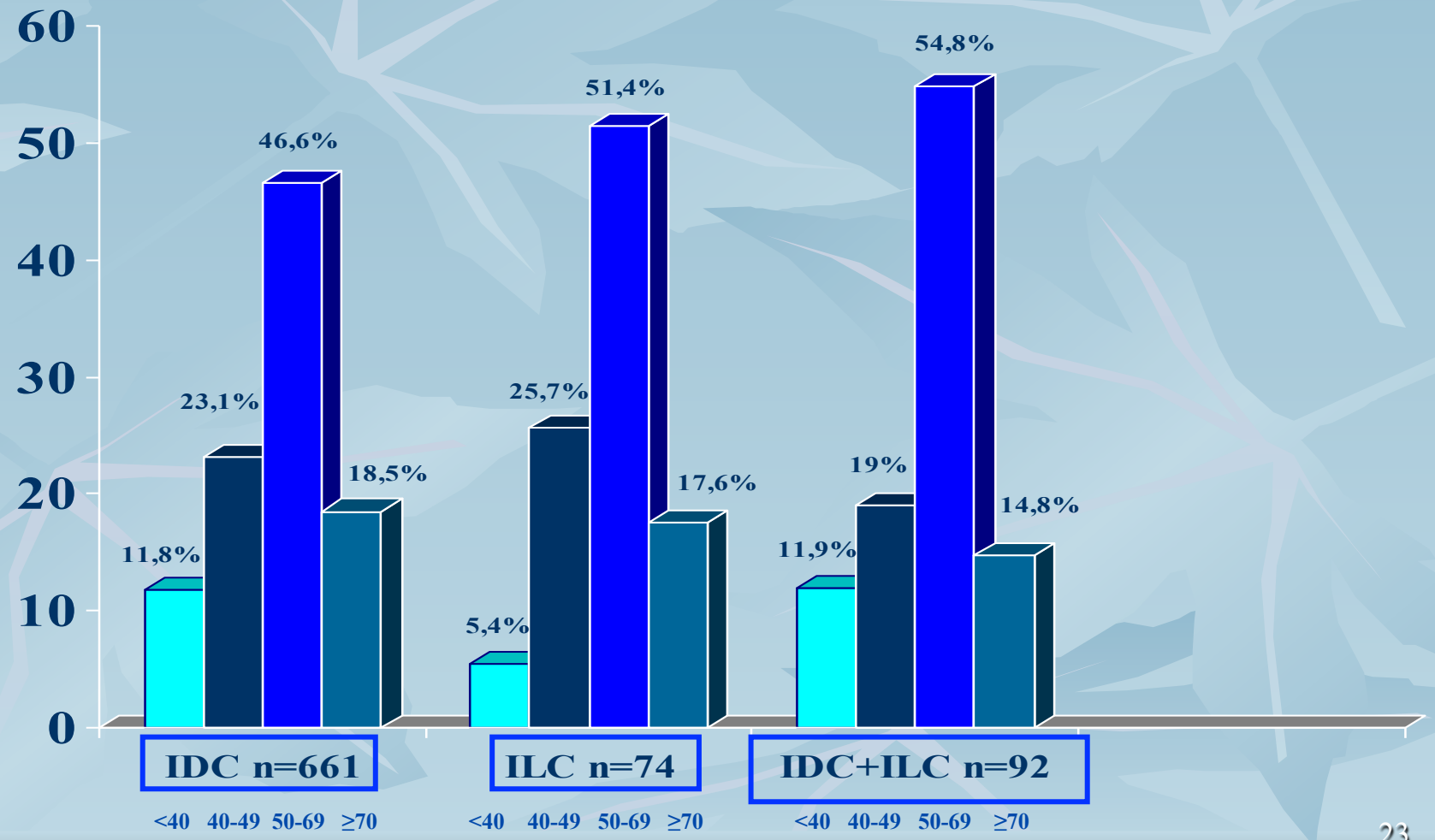
COMPARATIVE ANALYSIS BETWEEN ILC, IDC and mixed forms

yeatman t, ANN SURGERY 1995, 222 : 549-561

- Analysis of 777 cases treated in TAMPA :

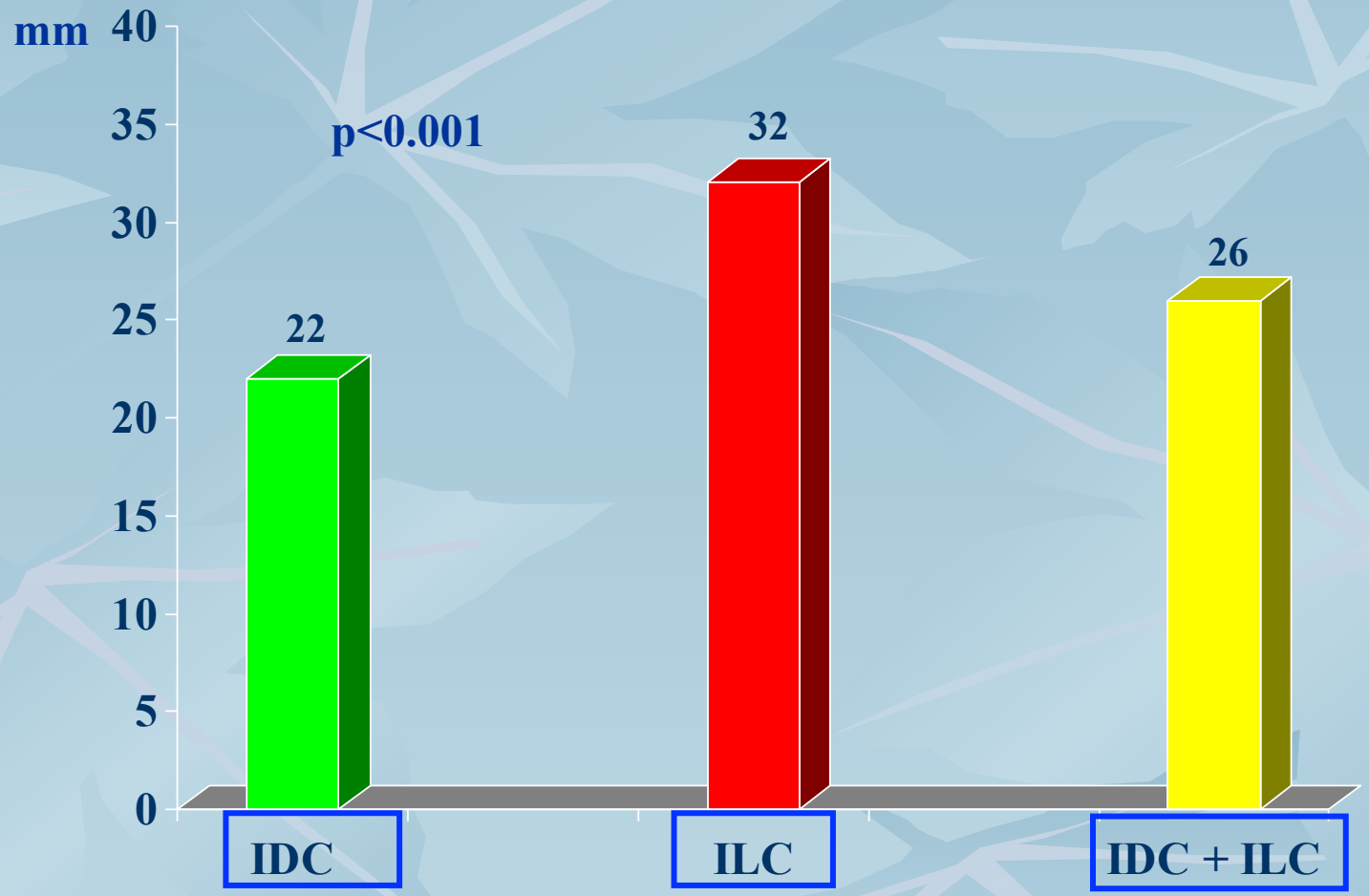
- 661 IDC (85%)
- 74 ILC (9.5%)
- 42 IDC + ILC (5.5%)

SUBTYPE DISTRIBUTION ACCORDING TO AGE



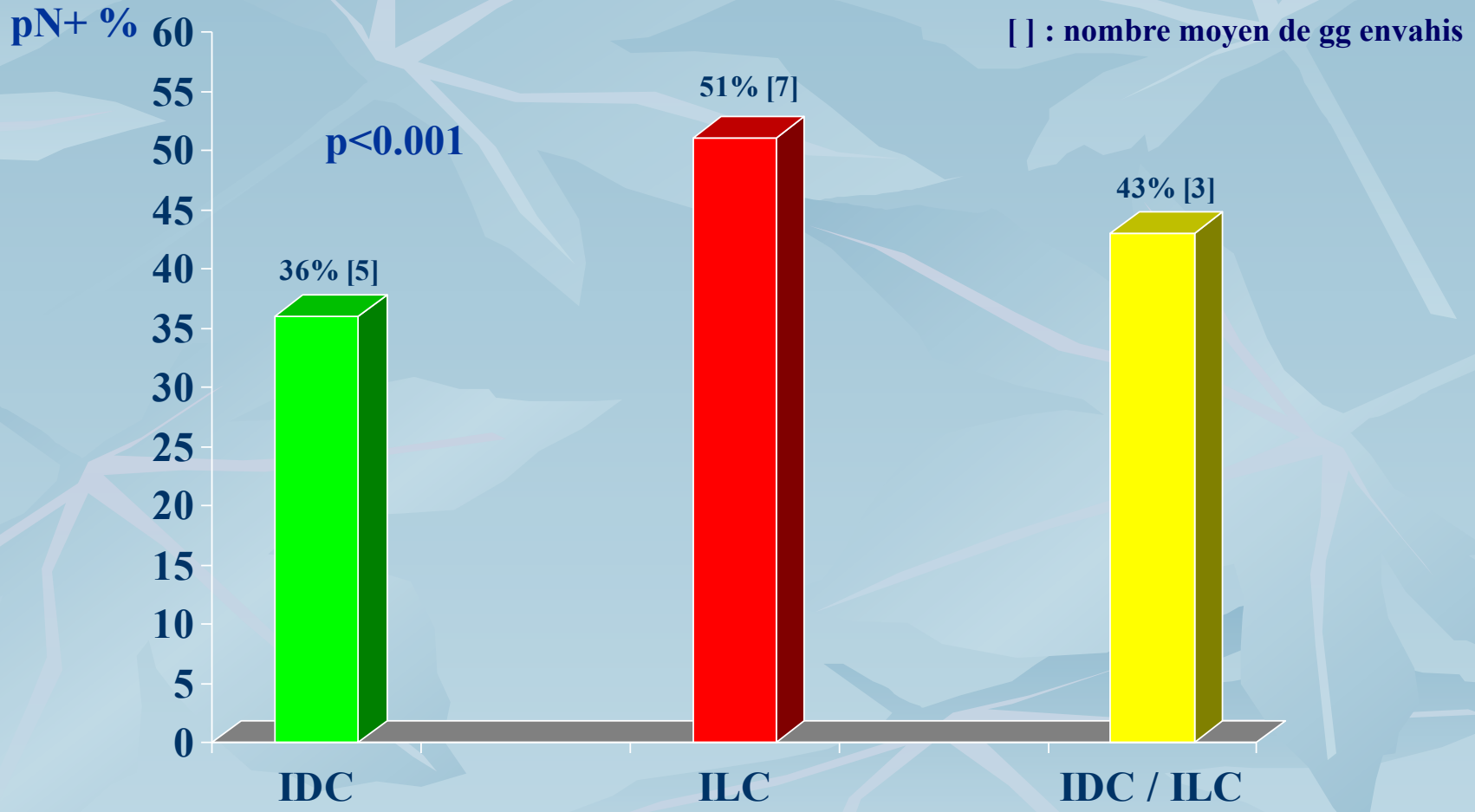
YEATMAN 1995

MEDIAN SIZE ACCORDING TO HISTOLOGICAL SUBTYPE



YEATMAN 1995

AXILLARY NODAL INVOLVEMENT ACCORDING TO HISTOLOGICAL SUBTYPE



AXILLARY NODAL INVOLVEMENT (ANI) ACCORDING TO HISTOLOGICAL SUBTYPE FOR TUMORS T0 T1 T2 ≤ 4 cm

MARTIN C, CUTULI B, Cancer 2002, 94 : 314-322

- Analysis of 795 unselected patients treated from 1980 to 1997 by breast conserving surgery and

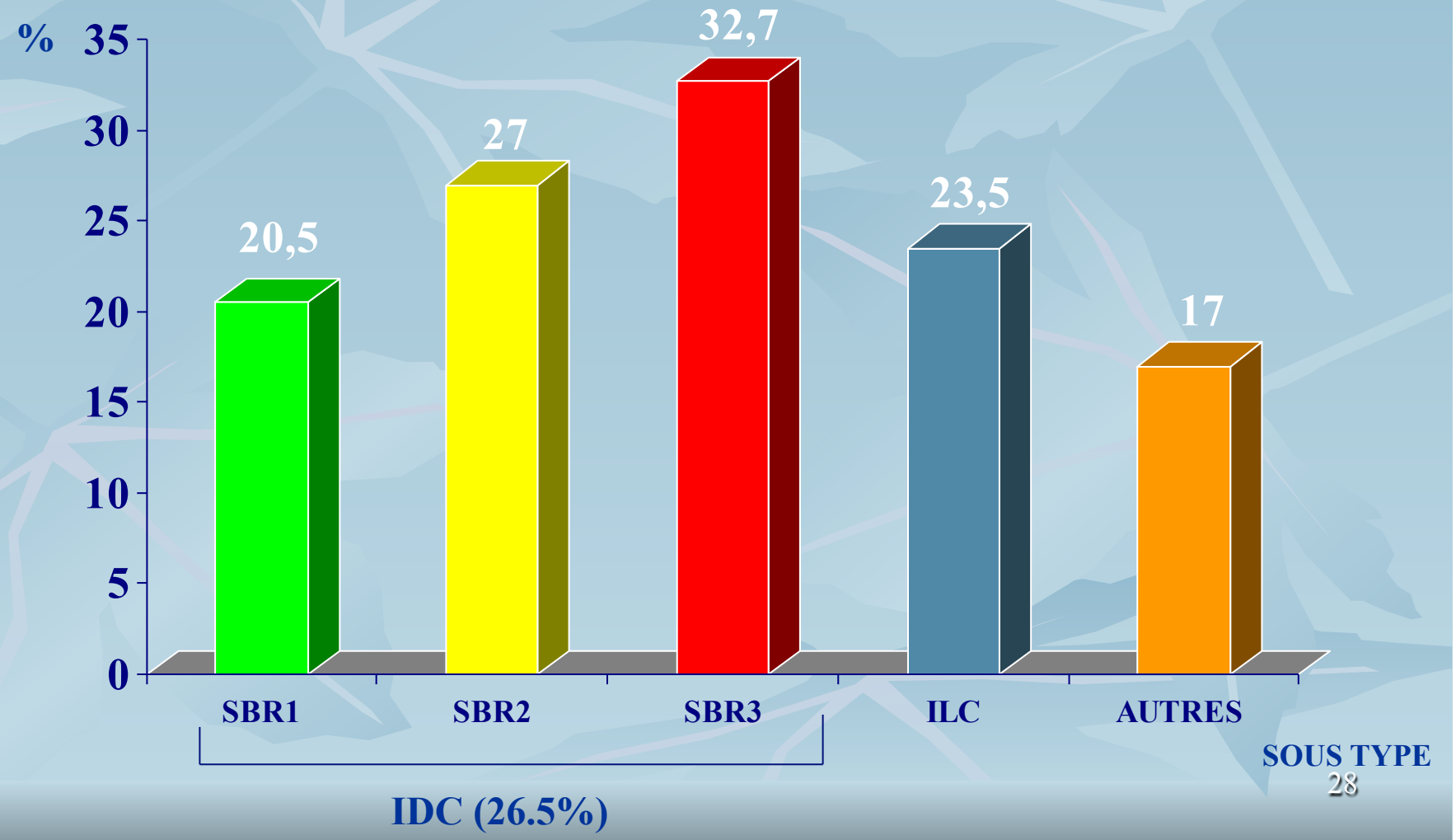
RT ± CT ± HT, with an axillary dissection and > 10 sampled lymph nodes

- Overall ANI rate: 25.7%

POPULATION CHARACTERISTICS

SIZE	
T0	22%
T1	45%
T2 ≤ 4 cm	33%
TOPOGRAPHY	
Inner	27%
Median	17%
Outer	56%
SUBTYPE	
IDC (663)	83%
SBR I	23%
SBR II	40%
SBR III	20%
ILC (85)	11%
OTHERS (45)	6%

AXILLARY NODAL INVOLVEMENT ACCORDING TO HISTOPATHOLOGICAL SUBTYPE



ALNI ACCORDING TO HISTOLOGICAL SUBTYPE AND GRADE

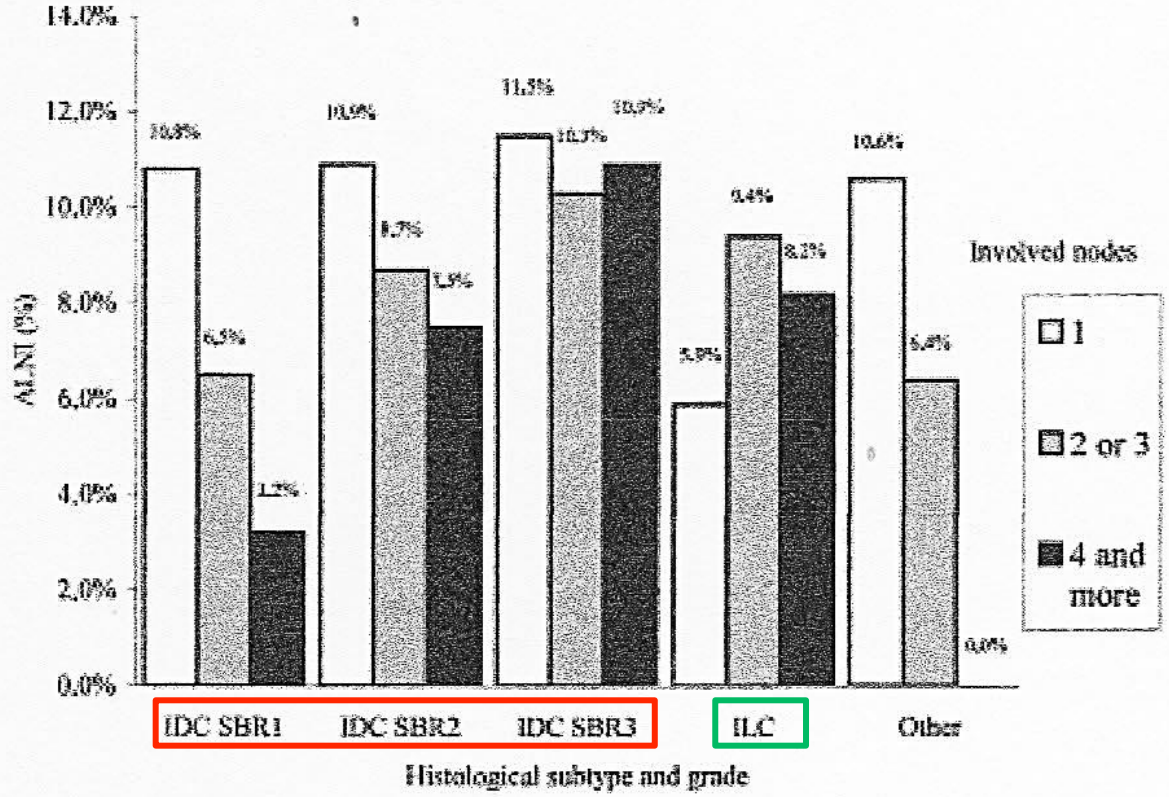
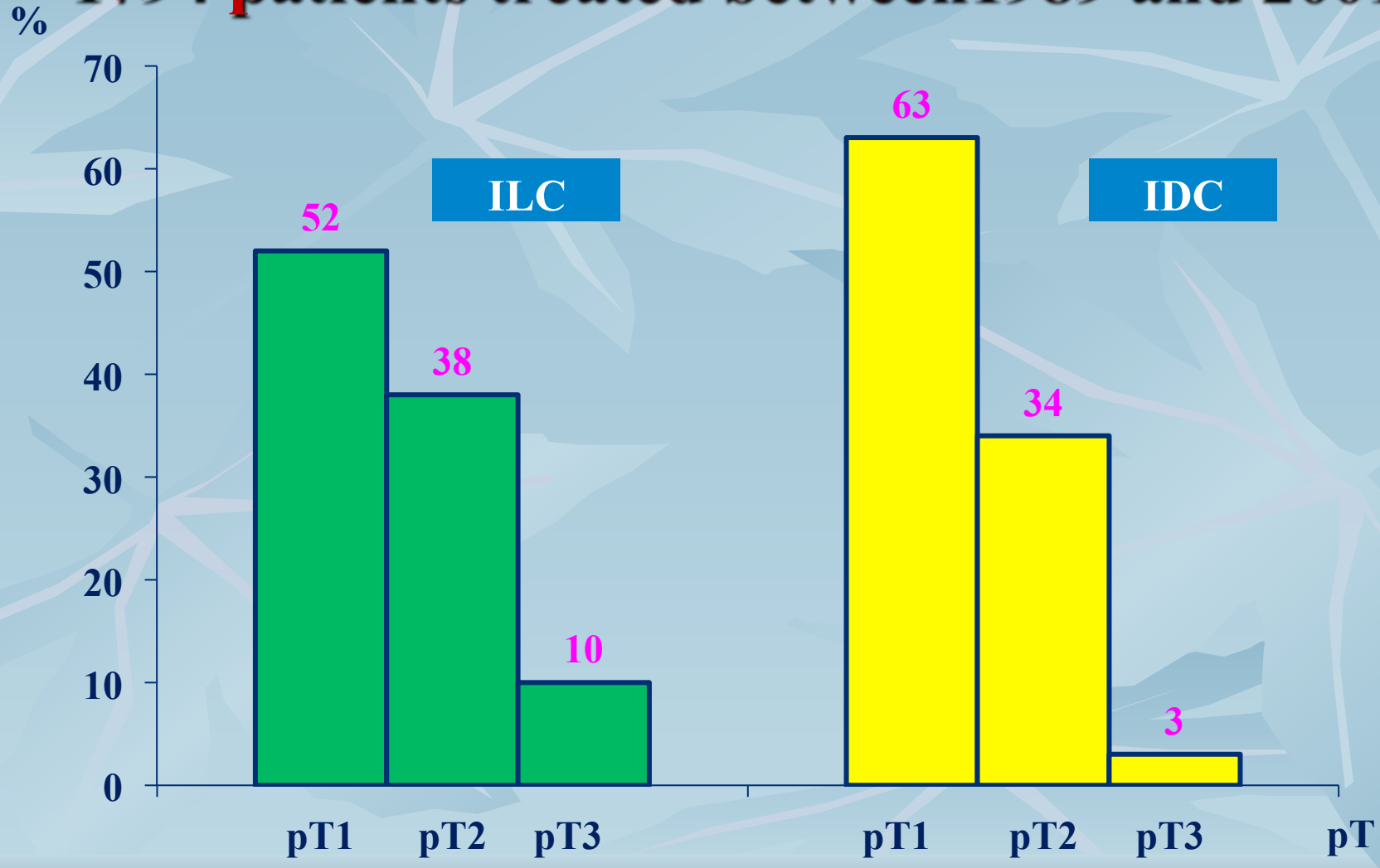


FIGURE 3. Axillary lymph node involvement (ALNI)categories according to histologic subtype and grade. IDC: infiltrating ductal carcinoma; ILC: infiltrating lobular carcinoma; SBR: Scarff–Bloom–Richardson.

ILC/IDC COMPARATIVE FEATURES AUSTRALIAN EXPERIENCE

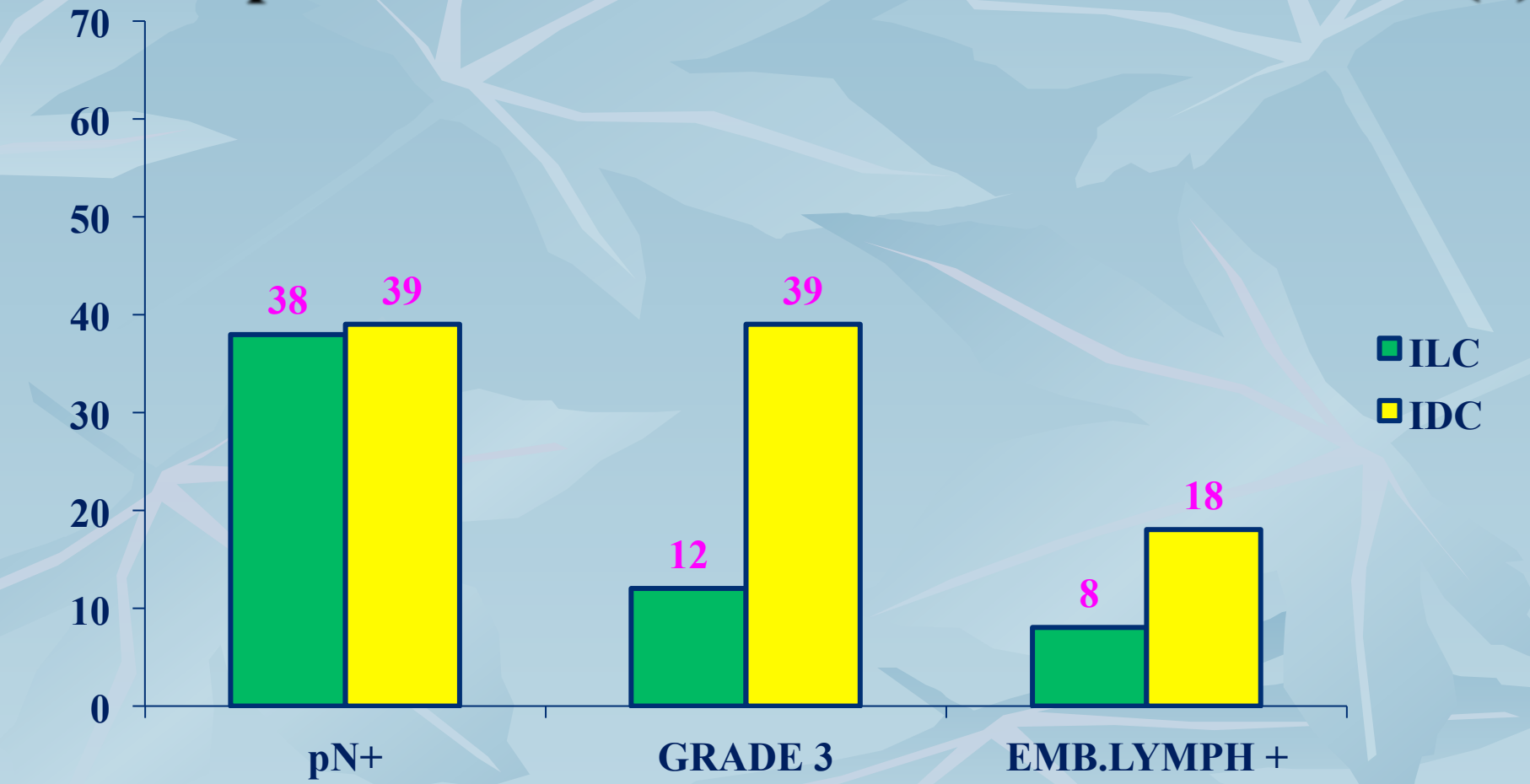
1794 patients treated between1989 and 2001 (1)



Réf: MOLLAND J THE BREAST 2004, 13: 389-396

ILC/IDC COMPARATIVE FEATURES AUSTRALIAN EXPERIENCE

1794 patients treated between1989 and 2001 (2)



Réf: MOLLAND J THE BREAST 2004, 13: 389-396

COMPARISON IDC-ILC: histopathological features and treatments

Expérience de l'université de TURIN

BIGLIA N et al EJSO 2013, 39: 455-460

Analysis of 1650 patients treated between 1999 and 2009:

- **1407 IDC (85,3%)**
- **243 ILC (14,7%)**

COMPARISONS IDC-ILC (%) [I]

	IDC (1407)	ILC (243)	p
Median age	58	60	NS
Median size (mm)	19	20	NS
pN+	47	43	NS

COMPARISONS IDC-ILC (%) [II]

	IDC (1407)	ILC (243)	p
MULTIFOCALITY	17	34	< 0.001
GRADE			
G1	12	12	
G2	39	57	< 0.001
G3	49	31	
RE+	84	98	< 0.001
RP+	80	89	
Her2 (2+/3+)	34	22	< 0.001
KI 67 > 20%	62	45	< 0.001

ILC: special histopathological and prognostic features

HOUSTON Expérience

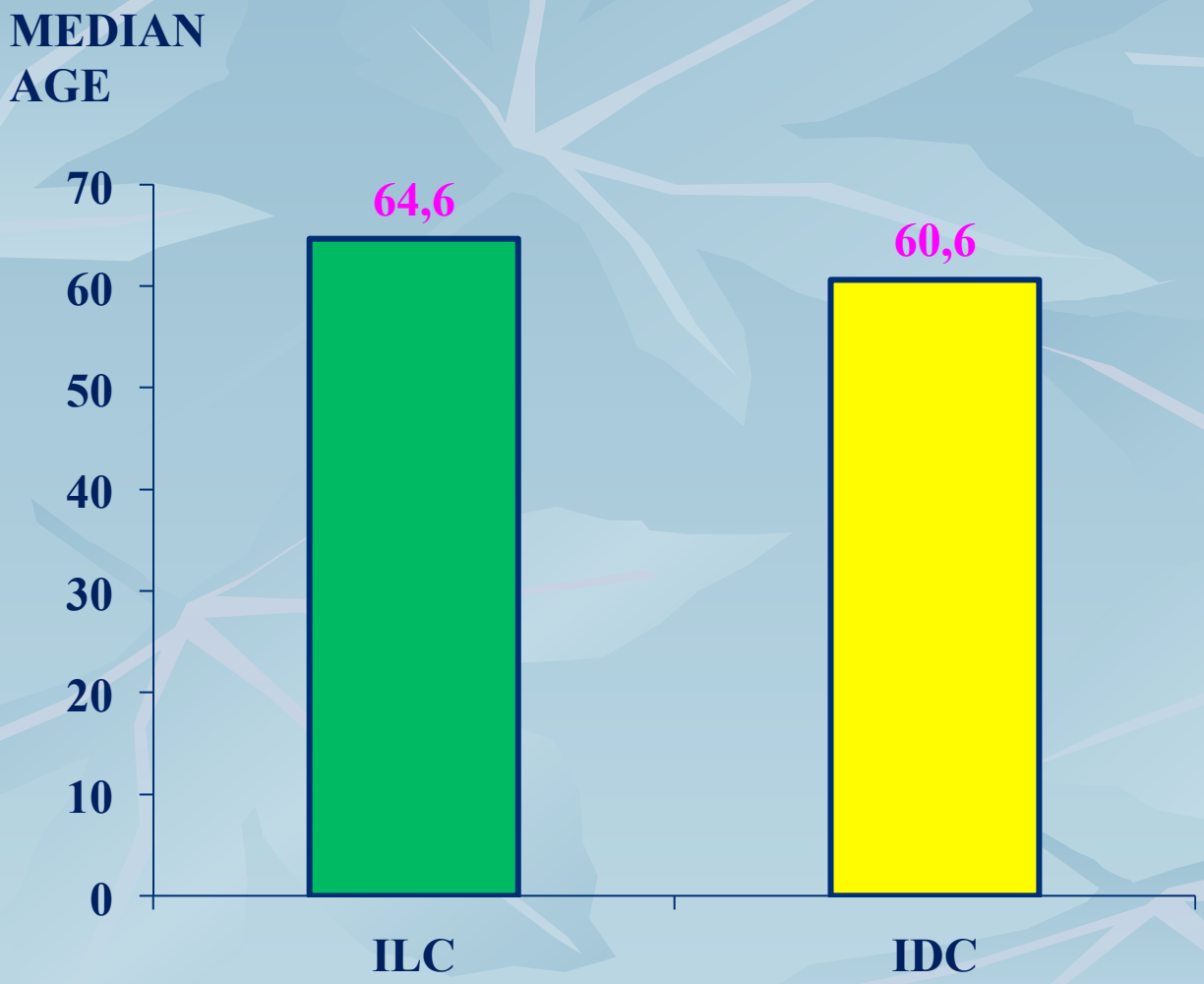
G.ARPINO et al BREAST CANCER RES 2004, 6: R1 149-156

50400 patients treated from 1970 to 1998

- **45070 IDC (89,6%)**
- **4140 ILC (8,2%)**
- **1190 OTHERS (2,2%)**

Median fu: 87 months

AGE COMPARISON



p < 0,0001

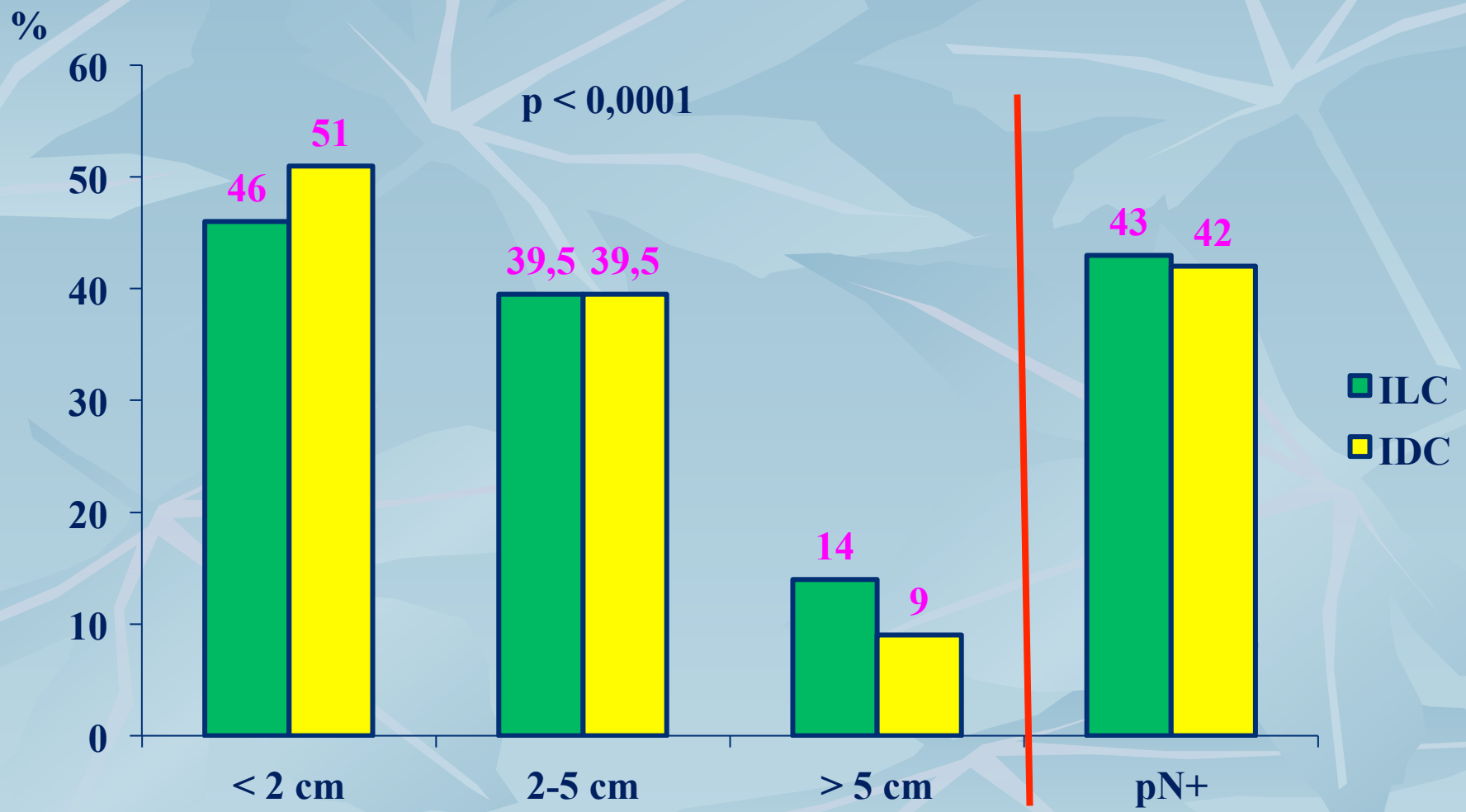
< 50 A

ILC: 19,4%

IDC: 27,8%

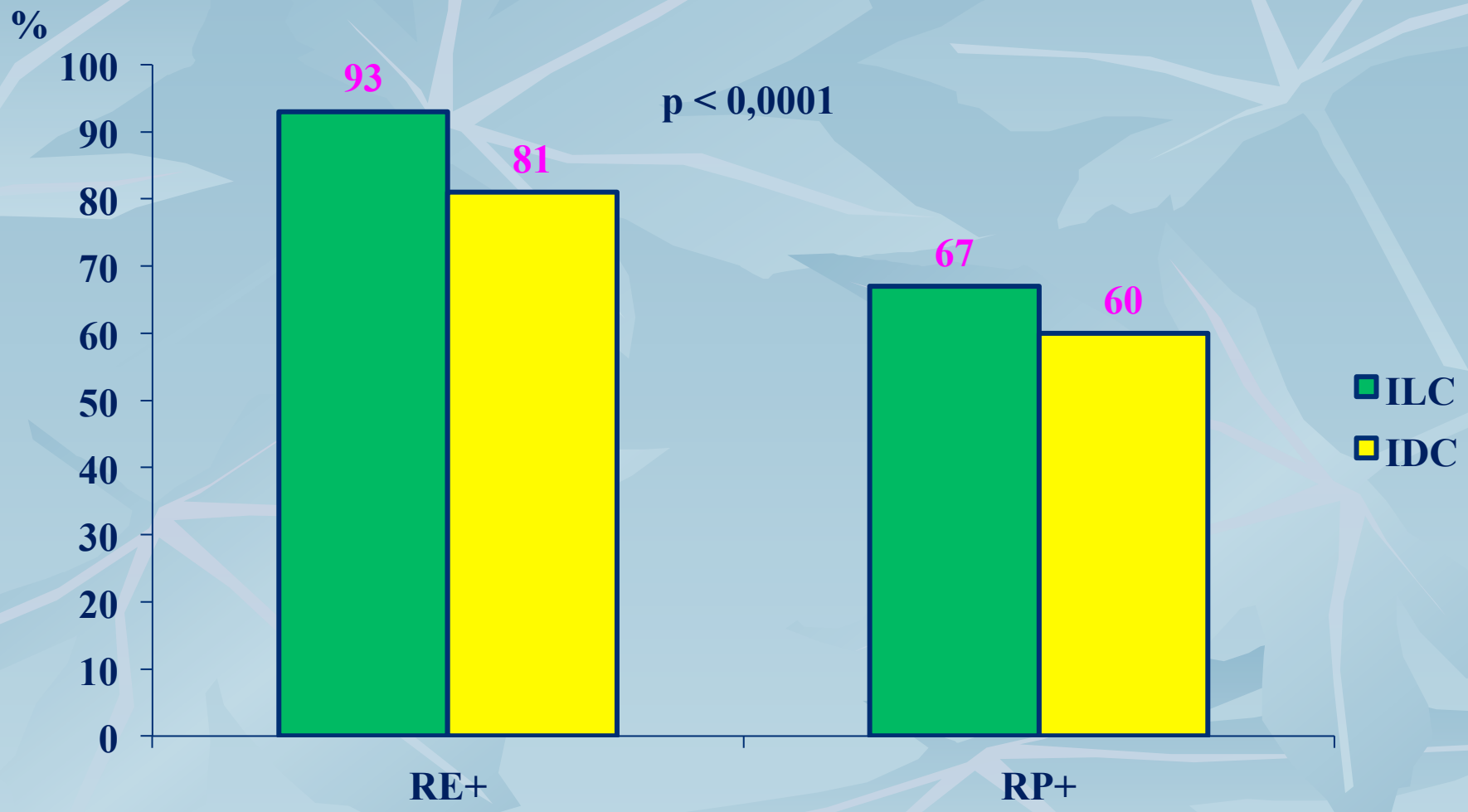
Réf: ARPINO G 2004

pT and pN COMPARISON



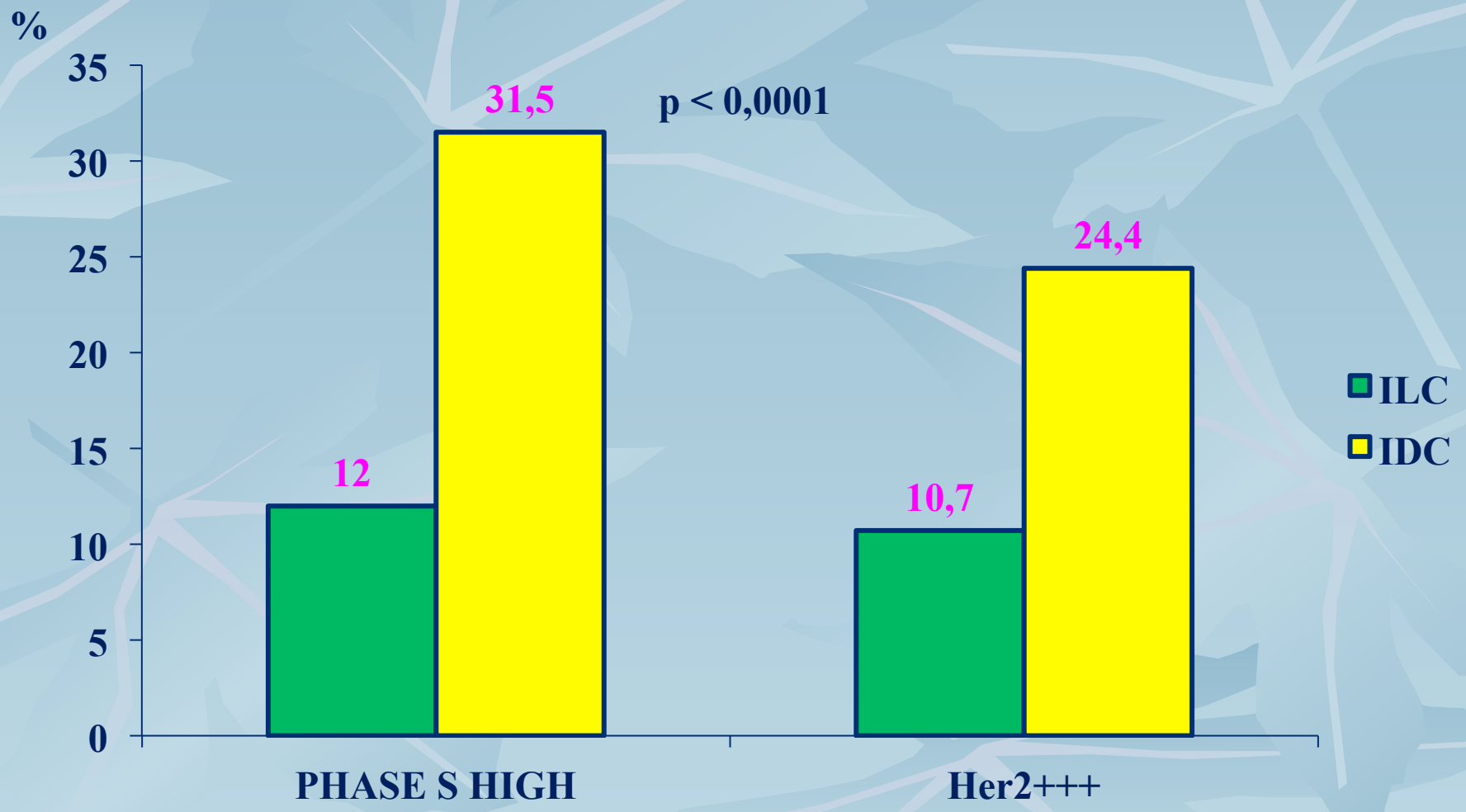
Réf: ARPINO G 2004

RE and RP COMPARISON



Réf: ARPINO G 2004

phase S et Her2 COMPARISON



Réf: ARPINO G 2004

ILC AND SENTINEL NODE BIOPSY

CLASSE JM CANCER 2004, 100: 935-41

Detection rate comparison between 208 IDC and 35 ILC treated at Nantes Cancer Center from 1999 to 2003

(T0T1T2 ≤ 3 cm, with SNB + complementary AD)

No clinico-pathological differences between IDC and ILC except for SBR grading:

(SBR2: IDC = 40% ILC = 88%)

RESULTS: (SNB)

	IDC (208)	ILC (35)
Detection rate	93.2%	94.3%
Sampled SN	2.2	2
SN+	35.6%	30.3%
SN+ (isolated)	60.5%	50%
SN+ (micromet.)	21%	6%

RESULTS: (AXILLARY DISSECTION)

	IDC (208)	ILC (35)	p
Median number of lymphnodes sampled	9,5	9,8	NS
pN+ %	40,8	31,4	NS
False negative rates	7,6%	9%	NS

CONCLUSION: ⟹ SLN is feasible in ILC as well as in IDC

COMPARISONS IDC-ILC (%)
types of surgery

	IDC (1407)	ILC (243)	p
BCS	76,4	72,8	NS
MASTECTOMY	23,6	27,2	NS

NB: taux de « seconde chirurgie » double pour les CLI (24,2% vs 9,8%)

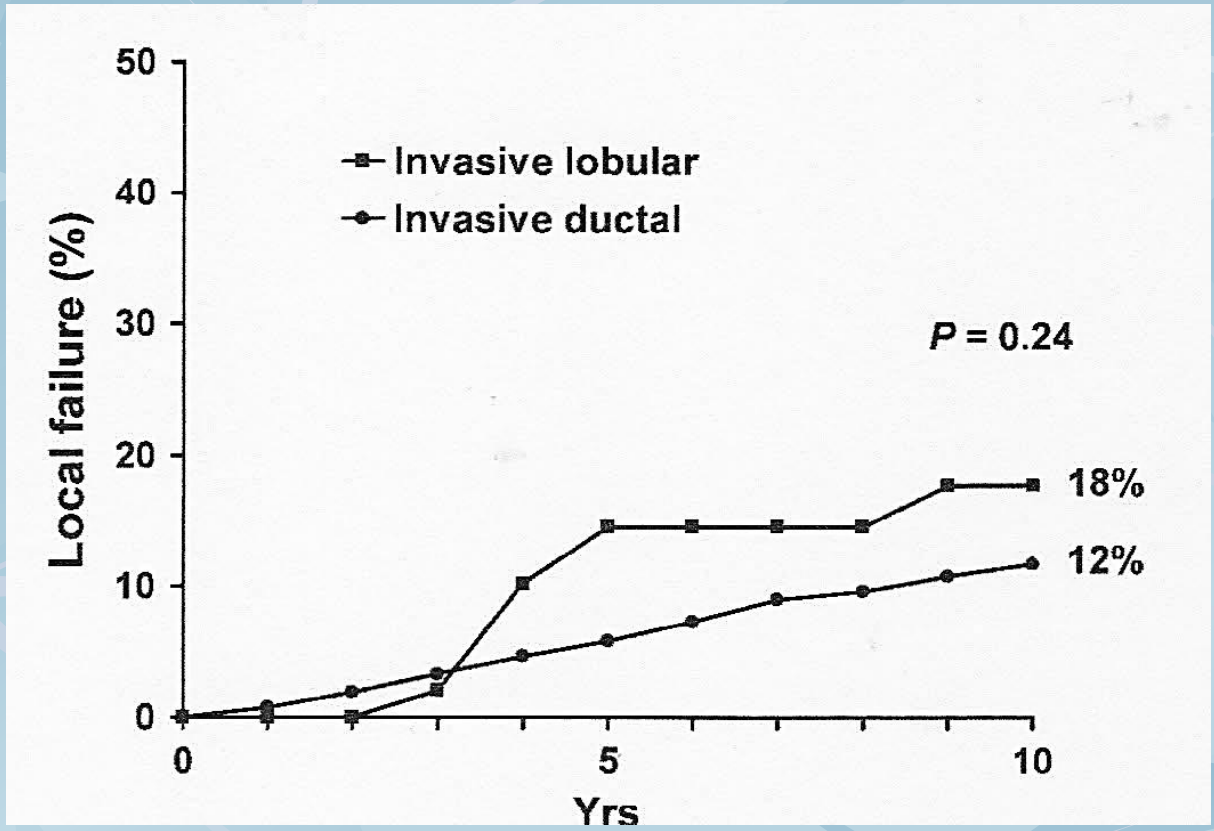
Réf: BIGLIA EJSO 2013, 39: 455-60

LOCAL RECURRENCE AFTER BREAST CONSERVING SURGERY IDC/ILC COMPARISON

AUTEUR	N	% ILC	FU	LR-IDC	LR-ILC
SALVADORI (1997)	2189	12,6	120	7	7
PEIRO (2000)	1337	8	132	13	15
VO (2006)	1210	7	120	7	9
SANTIAGO (2003)	1148	4,8	108	12	18
PAUMIER (2003)	2372	9	60	12,3	6,5

NB: aucune différence significative

LOCAL RECURRENCE AFTER BCS



Réf: SANTIAGO, Cancer 2005, 103: 2447-54

LR RISK FACTORS IN ILC AFTER BCS+RT:

Impact of margins and grade: Deutch experience

JOBSEN J, EJSO 2010, 36: 176-181

Analysis of 330 ILC treated from 1983 to 2005 (median fu: 95 months)

RESULTS: (I)

METASTASIS: 42/318 (13%)

RISK FACTORS (M): G3 vs G2 (HR 6.9 p< 0.001)
pT2 vs pT1 (HR 3.2 p<0.001)
pN+ vs pN0 (HR 7.7 p=0.001)

RESULTS: (II)

LOCAL RECURRENCES: 21/330 (6%)

RISK FACTORS :

margins + vs - (HR 3.5 p= 0.009) [1]

age > 50 vs < 50 (HR 0.25 p=0.003)

[1] especially < 50 y

BCT IN ILC VS IDC: HOUSTON EXPERIENCE

VO TN, AM J Surg 2006, 192: 552-5

1974-1999 MD ANDERSON CC DATABASE

IDC: 1126 (93%)
ILC: 84 (7%)

10-YEAR LLR: ILC: 7%
IDC: 9%

10-YEAR DSS and CBC: Same rates

DISEASE-FREE AND OVERALL SURVIVAL

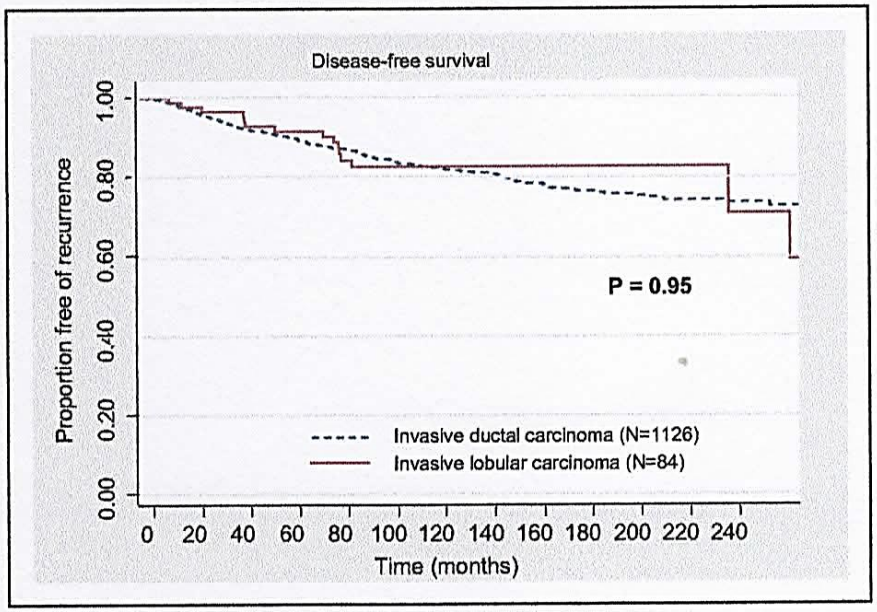


Fig. 2. Disease-free survival.

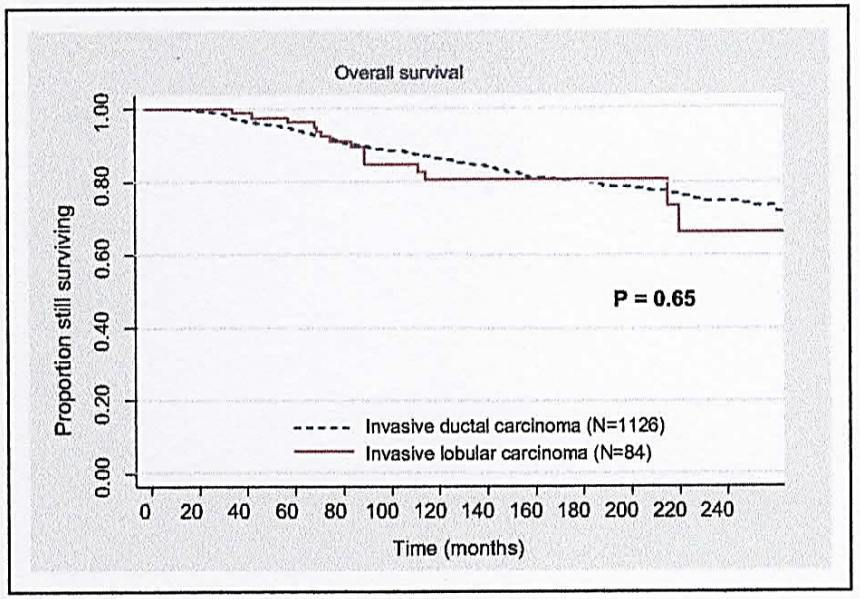


Fig. 3. Overall survival.

VO TN, Am J Surg 2006, 192: 552-5

COMPARATIVE IDC/ILC PROGNOSIS

IBCSCG Experience

(analysis of 9374 patients inclused in 15 trials between 1978 and 2002)

PESTALOZZI B JCO 2008, 26: 3006-3014

- **8607 IDC (91,8%)**
- **767 ILC (8,2%)**

FU MEDIAN: 13 YEARS

IDC/ILC COMPARISON (%)

	IDC	ILC	p
Age> 50	55	59	0,02
pN+	69	72	0,2
GRADE 3	42	12	< 0,01
pT2	51	55	< 0,01
EMB. VASCUL	37	19	< 0,01

LOCOREGIONAL TREATMENTS (%)

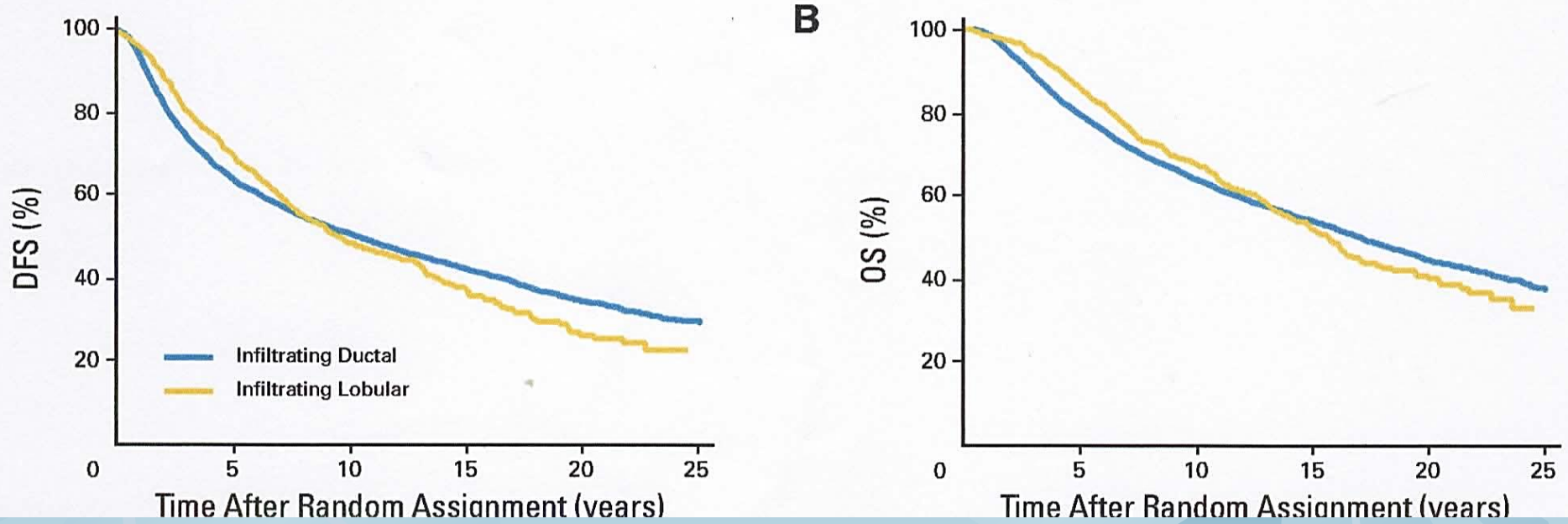
	IDC	ILC
MASTECTOMY (1)	56	72
BCS (2)	44	28

(1) 90% without RT
(2) 5% without RT

$p < 0,01$

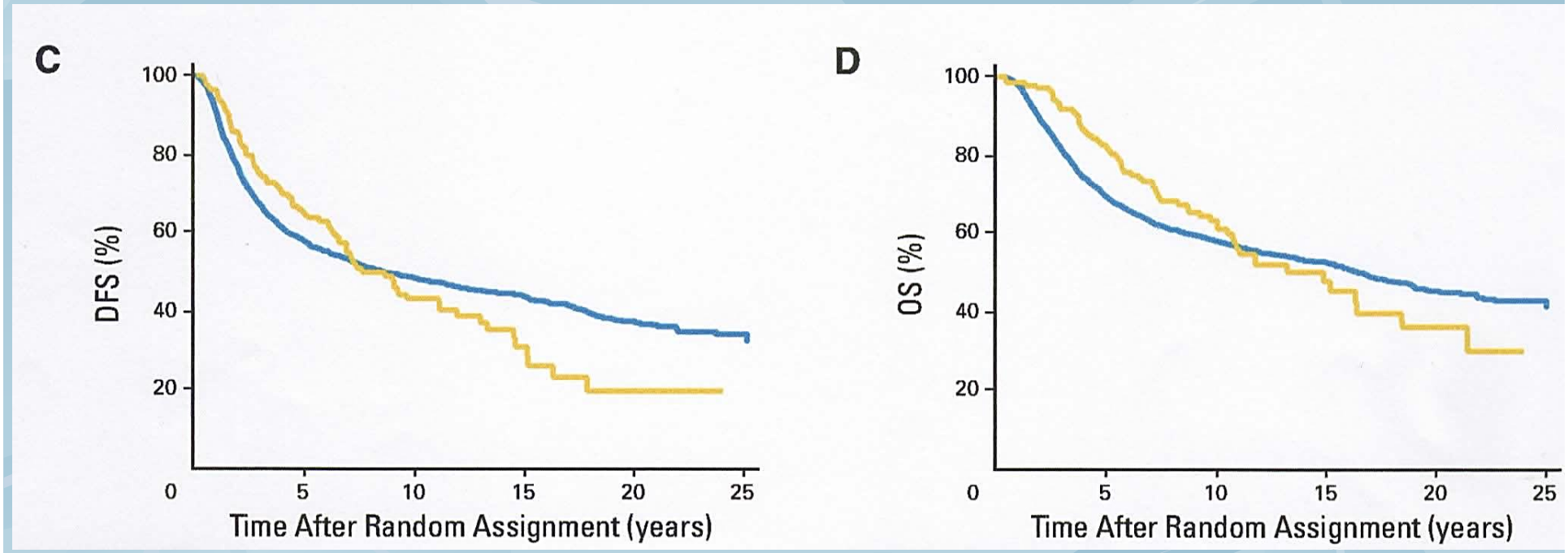
NB: CT and HT were similar: HT: 18% CT: 38% and CT+HT: 38%

DFS and OS



PESTALOZZI JCO 2008

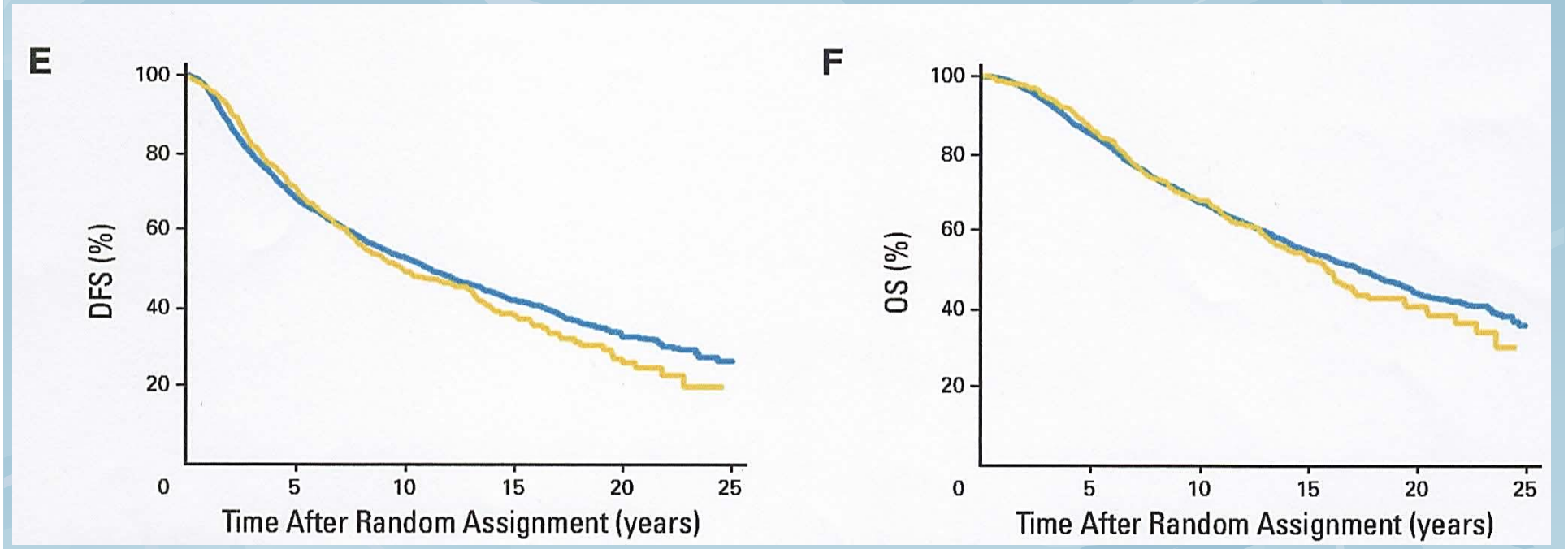
DFS and OS (RE-)



IDC ILC

PESTALOZZI JCO 2008

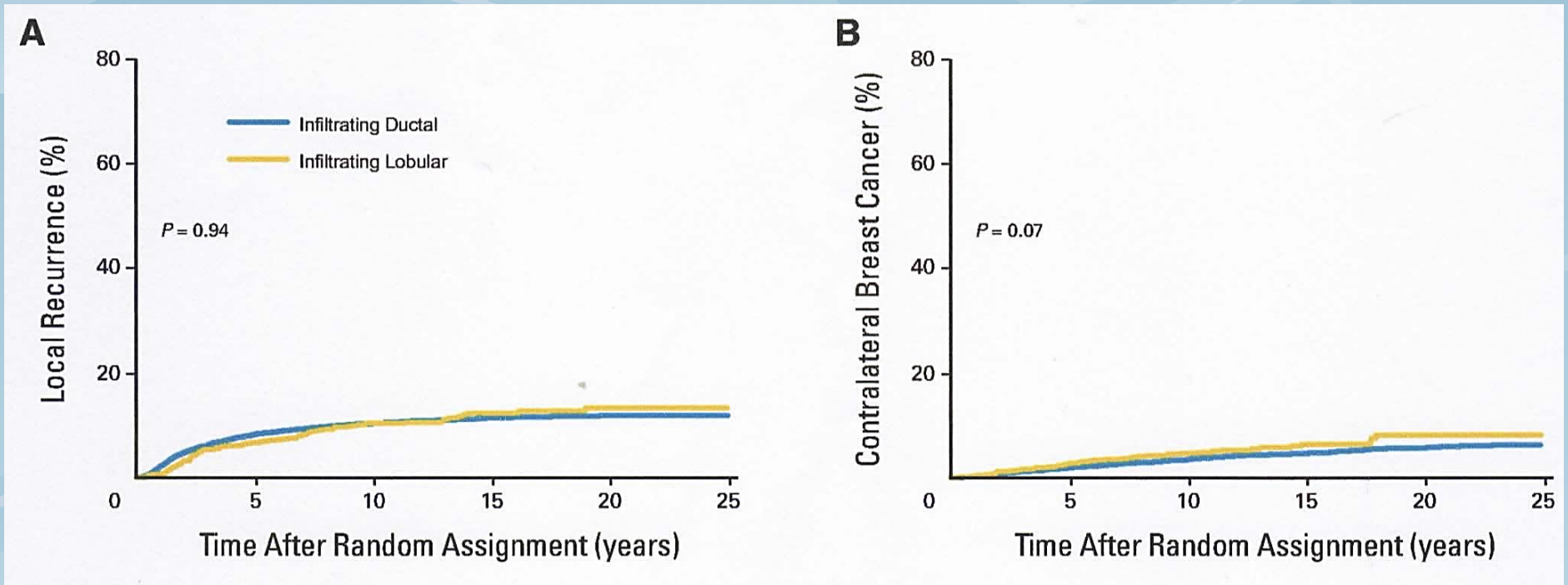
DFS and OS (RE+)



IDC ILC

PESTALOZZI JCO 2008

LOCAL RECURRENCE AND CONTRALATERAL BC



PESTALOZZI JCO 2008

DFS IN DC AND ILC
TURIN EXPERIENCE

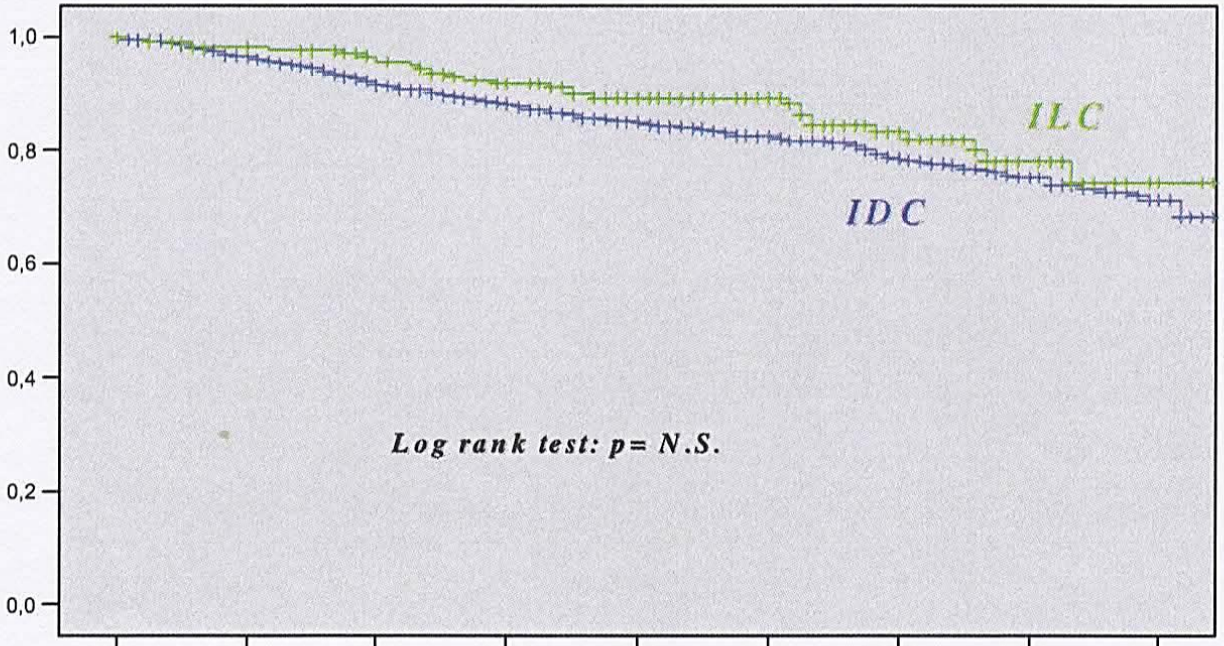
	ALL	pT1	pT2-3	pN0	pN+
IDC	79	87	76	90	75
ILC	83	89	77	92	83

NB: aucune différence n'est significative

BIGLIA N. EJSO 2013, 39: 455-460

DISEASE FREE SURVIVAL BY HISTOLOGICAL TYPE

N. Biglia et al./EJSO 39 (2013) 455–460



No at risk									
ILC	210	196	178	145	112	85	51	22	6
IDC	1158	1063	909	716	540	382	240	134	50

IDC VS ILC PROGNOSIS

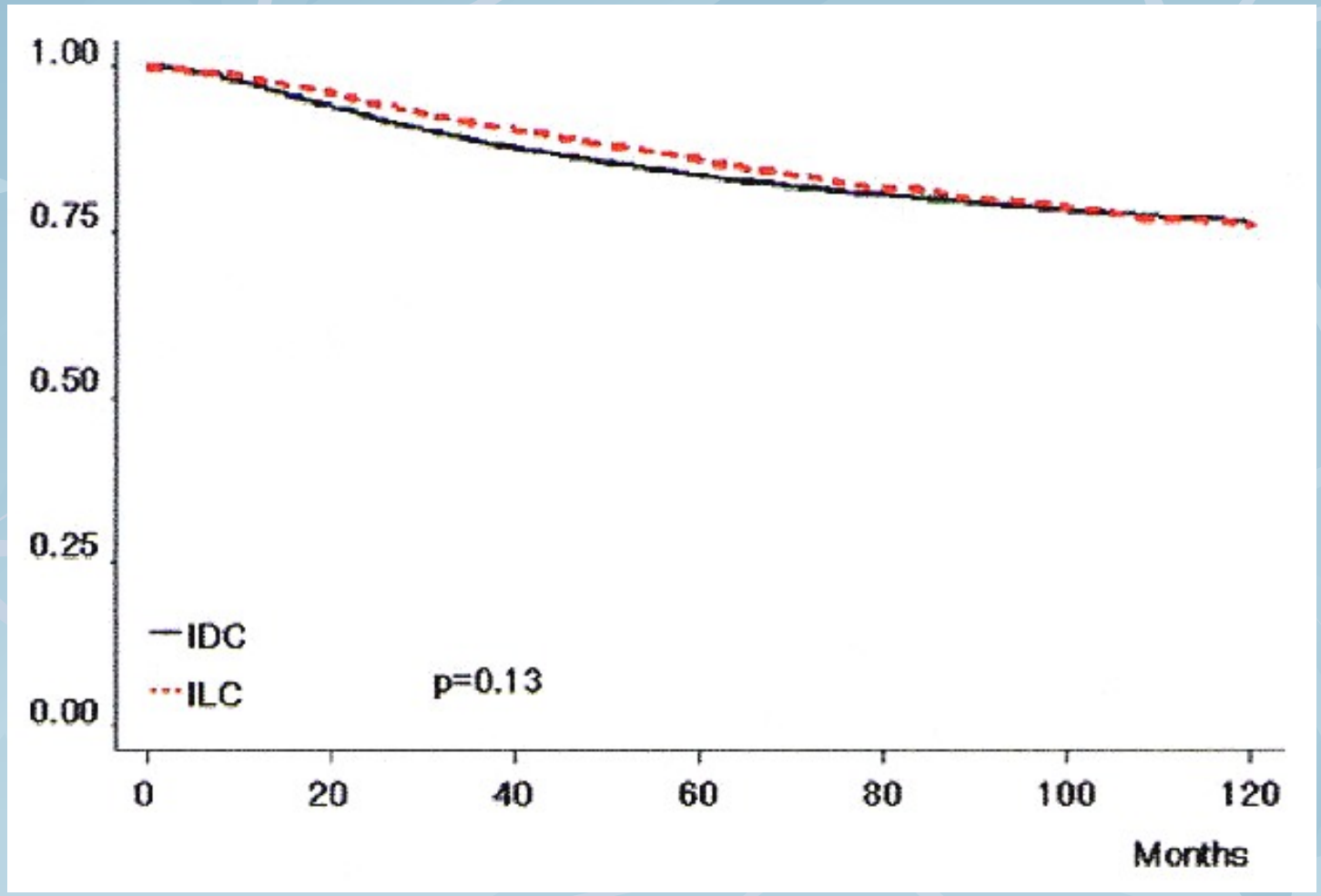
DATABASE CALIFORNIA TEXAS (1970-1998)

- IDC: 45170
- ILC: 4140 (8,25%)

IDENTICAL RATES IN DFS AND OS

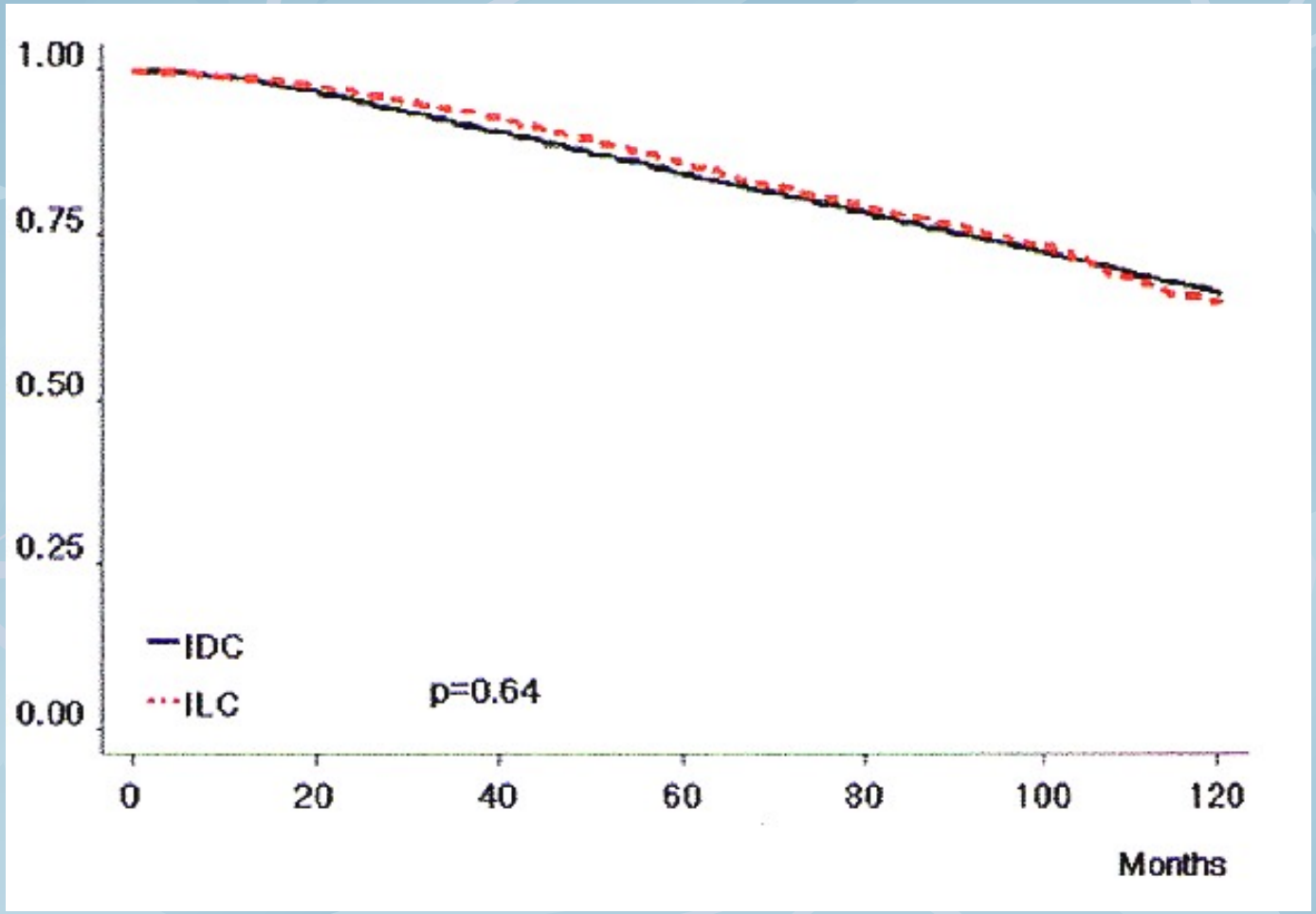
ARPINO, BREAST CANCER RESEARCH 2004

DFS AT 5 YEARS: ILC = 85.7% IDC = 83.5%



ARPINO, BREAST CANCER RESEARCH 2004

OS AT 5 YEARS : ILC = 85.6% IDC = 84.1%



ARPINO, BREAST CANCER RESEARCH 2004

INVASIVE LOBULAR VS DUCTAL BREAST CANCER: A STAGE-MATCHED COMPARISON OF OUTCOMES

WASIF N Ann Surg Oncol 2010, 17:1862-69

Analysis of SEER DATABASE:

263408 women treated from 1993 to 2003

RESULTS (%)
pN0

	ILC	IDC	p
5-y DSS (global)	90	88	< 0.001
T1 N0	98	96	<0.001
T2 N0	94	88	< 0.001
T3 N0	92	83	< 0.001

RESULTS (%)
pN+

	ILC	IDC	p
5-y DSS			
pT1 N1	89	88	NS
pT2 N1	81	73	< 0.001
pT3 N1	72	56	< 0.001

CONTRALATERAL BREAST CANCERS (CBC) ASSESSMENT DIFFICULTIES (I)

A) Synchronous CBC:

- various delay: 3-12 months

B) Metachronous CBC:

- DCIS: included or not
- previous RLR and/or metastases: inclusion or not

CONTRALATERAL BREAST CANCERS (CBC) ASSESSMENT DIFFICLTIES (II)

A) Differents populations

- Age
- Treatement (BCS/MASTECTOMY)
- case-control studies

B) Treatment heterogeneity

- Locoregional / systemic

COMPARATIVE ANALYSIS OF CBC ACCORDING TO HISTOLOGY:

	IDC	ILC	P
ARPINO (2004)	11.2%	21%	<0.0001
(TEXAS – CALIFORNIA DATABASE: 50 000 pts)			
SANTIAGO (2005)	7%	11%	0.4
(PHILADELPHIA DATABASE: 1093 BCS+RT)			

NEO-ADJUVANT CT
HOUSTON EXPERIENCE

- Analysis of 1034 patients treated by neoadjuvant CT from 1985 to2002 (T1-T3 ; N0-2 M0)

	IDC (912)	ILC (122)	p
Median age	47	53	
RE and RP – (%)	38	8	< 0.001
Nucl. Grade (%)			
I	3	32	
II	42	52	< 0.001
III	56	16	
pN (%)			
0	41	37	
1-3	59 / 33	63 / 22	0.001
≥ 4	26	41	

MD ANDERSON CC STUDY

Cristofanilli jco 2005, 23 : 41-48

- 70 months fu results

	IDC (912)	ILC (122)	p
DFS (5a)	66%	87%	0.004
OS (5a)	70%	93%	0.001

ILC: LESS RESPONSE BUT BETTER PROGNOSIS

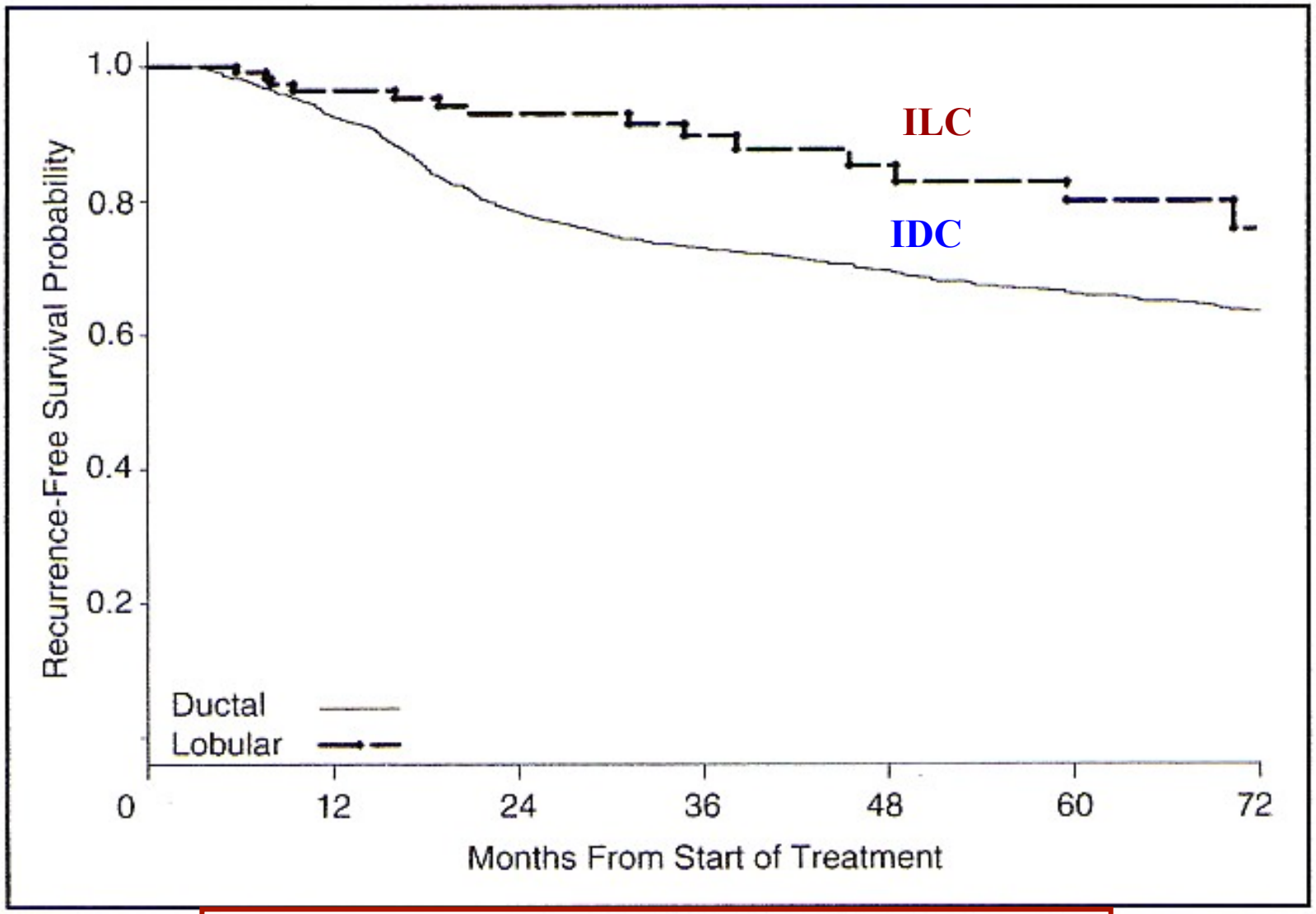


Fig 1. Recurrence-free survival by histologic type.

CRISTOFANILLI JCO 2005, 23 : 41-48

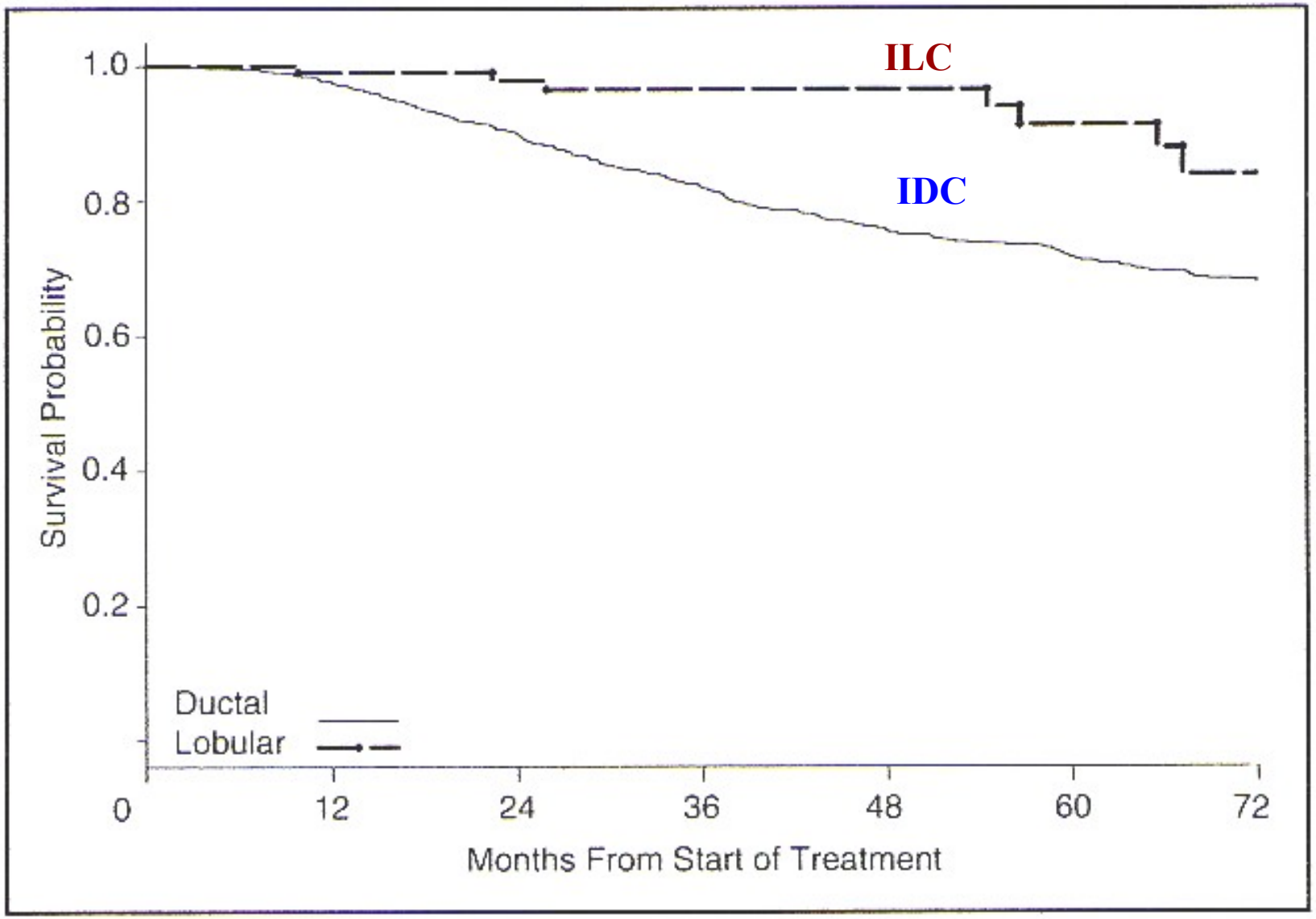


Fig 2. Overall survival by histologic type.

CRISTOFANILLI JCO 2005, 23 : 41-48

CHEMOTHERAPY IN DUCTAL COMPARED TO LOBULAR CARCINOMA OF THE BREAST: A meta-analysis of published trials including 1764 lobular bc

PETRELLI F, BARNI S BCRT 2013

Analysis of 17 studies, with a total of 14 409 cases

- **IDC: 1264.5 (87.8%)**
- **ILC: 1764 (12.2%)**

BUT… WIDE VARIATIONS:

- **Total number of cases (49 to 6205!)**
- **% of ILC (5% to 20.6%)**

Pathological COMPLETE RESPONSE (pCR)			
	VARIATIONS	POOLED	p
IDC	6-46.2%	16.7	< 0.00001
ILC	0-38.6%	5.9	< 0.00001
OVERALL CLINICAL RESPONSE RATE (ORR)			
IDC	58-85%	—	?
ILC	26-75%	—	?

COMPLETE CLINICAL RESPONSE (CCR)

IDC	8.5-34%
ILC	0-18%

BREAST CONSERVING TREATMENT (BCT)

	VARIATIONS	POOLED	p
IDC	33-82%	54%	< 0.00001
ILC	17-72%	35%	< 0.00001

ILC AND METASTASIS

SOME SPECIFIC INVOLVEMENTS:

- **GASTRO-INTESTINAL TRACT**

(stomach / duodenum / colon)

- **GENITAL TRACT**

(ovaries++ / uterus)

- **UNCOMMON SITES**

(sometimes revealing)

i.e : orbit / bladder

DETAILED COMPARED METASTASIS RATES

ARPINO STUDY (BRCT 2004)

	IDC (%)	ILC (%)	P
Bone	35	35	NS
Skin	27	32	NS
Liver	11	7	NS
Lymphnodes	22	16	0.018
Lung/pleura	18	9	0.002
CNS	5.3	1.7	0.032
Ovaries	0.7	2.2	0.0003
Gi tract	1.1	4.5	0.009

It's possible to predict ILC agressivity?

- **SOME ISTOLOGICAL SUBTYPES**

(alveolar / pleomorphic / solid)

- **HIGH NUCLEAR GRADE**
- **SOME MOLECULAR PROFILES**

(HR- / Her2+++)

Réf: RAKHA E, ELLIS I BCRT 2008, 111: 121-7
GUDLAUGSSON E BCRT 2010, 121: 35-40
GRUEL N EJC 2010, 46: 2399-2407

CONCLUSIONS (1)

- ILC represent 7-15% of BC
- Radiological diagnosis is often difficult (MRI)
- Clinical symptoms are important
- ILC often are HR++ / low grade / Her2-
- Sentinel node biopsy and BCS
- DCS+ RT give the same results than in IDC

(but with higher re-excision rate)

CONCLUSIONS (2)

- Response rate to neoadjuvant CT is less than ILC
- Metastatic sites are often unusual
- Global prognosis is comparable to IDC, and may be better in recent series

GRAZIE PER L'ATTENZIONE!