PICCOLI TUMORI

GLI ASPETTI DI ANATOMIA PATOLOGICA

Isabella Castellano
Dipartimento di Scienza Mediche
Università di Torino
Città della Salute e della Scienza, Torino

PROGNOSI

Biologia del tumore
(Aggressività)

- Hormone receptors (ER, PgR)
- Grading (differentiation)
- HER2
- Ki67 (proliferation)
- Vascular invasion
- Gene expression tests (molecular finger print)

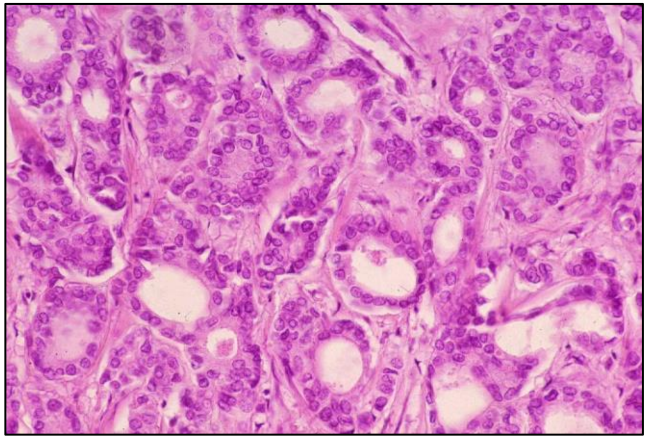
  (2009, St Gallen)

Carico tumorale
(dimensioni e disseminazione)

- Tumor size
- Number of involved lymph nodes
- Distant metastasis

?

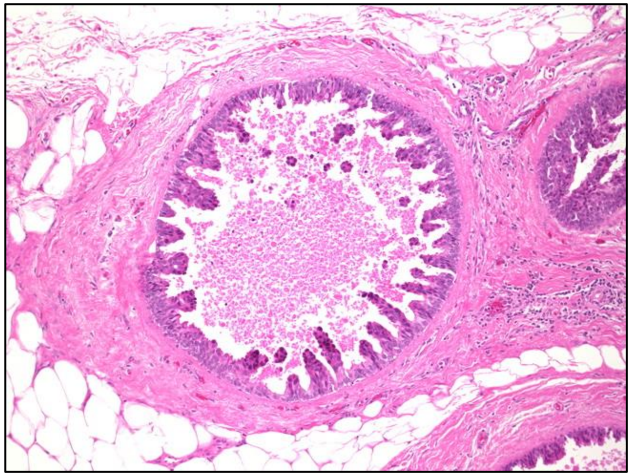
PICCOLI TUMORI



- Definizione
- Biologia
- Trattamento

CARCINOMI INVASIVI

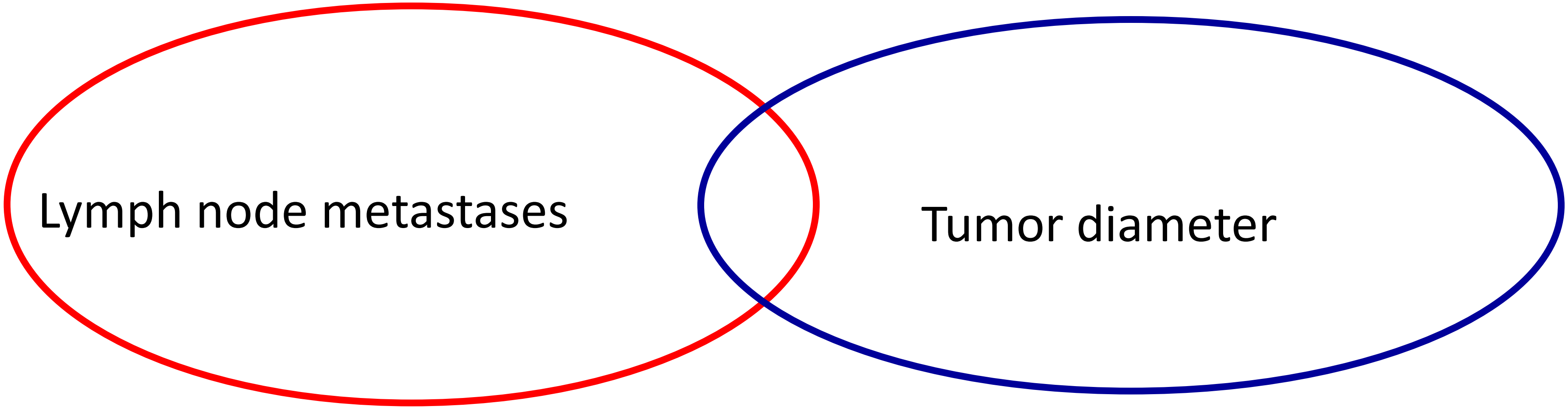
CARCINOMI IN-SITU



The Effect of Tumor Size and Lymph Node Status on Breast Carcinoma Lethality

Cancer 2003;98:2133–43.

For women with
equivalent lymph node status,
tumor size was associated with increased lethality, such that each millimeter of tumor diameter was associated with an additional 1% chance of death.



Diametro del tumore e stato linfonodale sono fattori prognostici indipendenti

J Clin Pathol 53:846-850, 2000
J Clin Oncol 8:2040-2046, 1990

Diametro del tumore e stato linfonodale sono strettamente correlati : più grosso è il tumore, più ha avuto tempo di metastatizzare ai linfonodi

Cancer 24:1071-1080, 1969
Cancer 63:181-187, 1989

Probabilità di avere metastasi nei linfonodi ascellari

T1	0-50%
T2	20-50%,
T3	50-80%

Ann Surg 1997; 226: 271–8.
Arch Surg 2001; 136: 688–92.
Ann Surg Oncol 2003; 10: 1140–51.
Breast Cancer Res Treat 2005; 91: 113

Definizione

TNM: pT1 ($\leq$2 cm)

2009 2007 2001-3

Table ... -Negative Breast

	Relative indications for chemoendocrine therapy	Factors not useful for decision	Relative indications for endocrine therapy alone
Clinicopathological features			
ER and PgR	Lower ER and PgR level		Higher ER and PgR level
Histological grade	Grade 3	Grade 2	Grade 1
Proliferation	High[a]	Intermediate[a]	Low[a]
Nodes	Node positive (four or more involved nodes)	Node positive (one to three involved nodes)	Node negative
PVI	Presence of extensive PVI		Absence of extensive PVI
pT size	>5 cm	2.1–5 cm	≤2 cm
Patient preference	Use all available treatments		Avoid chemotherapy-related side-effects
Multigene assays			
Gene signature[b]	High score	Intermediate score	Low score

ER and PgR absent, OR
HER2/*neu* gene overexpressed or amplified[d]
Node positive (4 or more involved nodes)

Definizione

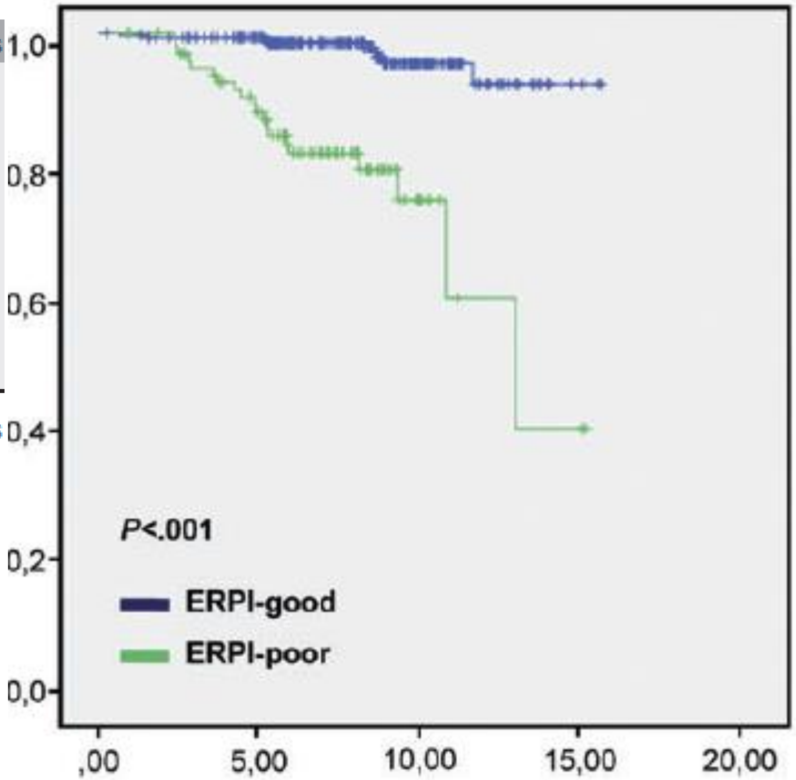
TNM: pT1 (≤2 cm)

1.5 cm Tabar   Città della Salute, Torino

	Status	Points
Number of metastatic lymph nodes	0	0
	1–3	1
	>3	2
Tumor size	<15 mm	0
	>15 mm	2
Androgen receptor	0%	2
	≥1%	0

Algorithm: (tumor size score value) + (number of metastatic lymph nodes score value) + (AR score value).

Annals of Oncology 2013



Definizione

TNM: pT1 ($\leq$2 cm)

1.5 cm

1 cm

Outcome of Small Invasive Breast Cancer with No Axillary Lymph Node Involvement

Table 2. Description of Treatments

Treatment	Number (%)
Local surgery:	
Mastectomy	46 (19)
Conservative	192 (81)
Axillary surgery:	
Lymphadenectomy	149 (63)
Sentinel node	89 (37)
Radiotherapy:	

Table 4. Univariate Analysis of Disease-Free Survival and Clinicopathological Characteristics

Variables	Total	DFS (%)	p-value
Age:			
>40	222	95.5	0.47
<40	16	100	
Size:			

Table 3. Characteristics of the Patients with Relapsing Disease

Age	pT	Histology	G	Hormone receptors	HER-2	Adjuvant therapy	Event
57	mic	Ductal	G3	+	–	No	Local
49	1b	Ductal	G2	+	+	No	Systemic
44	1a	Tubular	G2	+	–	No	Local
60	1b	Ductal	G3	+	–	No	Local
44	mic	Ductal	G3	+	+	No	Systemic
65	mic	Ductal	NK	+	–	TMX	Local/systemic
65	1b	Ductal	G2	+	–	TMX	Local
54	1b	Ductal	G2	+	+	No	Local
63	1b	Ductal	G2	ER– PgR+	–	No	Local
52	1b	Ductal	G1	+	–	TMX	Systemic

The Breast Journal, Volume 17 Number 1, 2011 32–38

Biologia

St Gallen 2011, 2013, 2015

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

Minimal and small size invasive breast cancer with no axillary lymph node involvement: the need for tailored adjuvant therapies

M. Colleoni[1]*, N. Rotmensz[2], G. Peruzzotti[1], P. Maisonneuve[2], G. Viale[3], G. Renne[3], C. Casadio[3], P. Veronesi[4], M. Intra[4], R. Torrisi[1] & A. Goldhirsch[1]

Annals of Oncology 15: 1633–1639, 2004

425 patients classified as having node-negative pT1mic, pT1a or pT1b after surgery

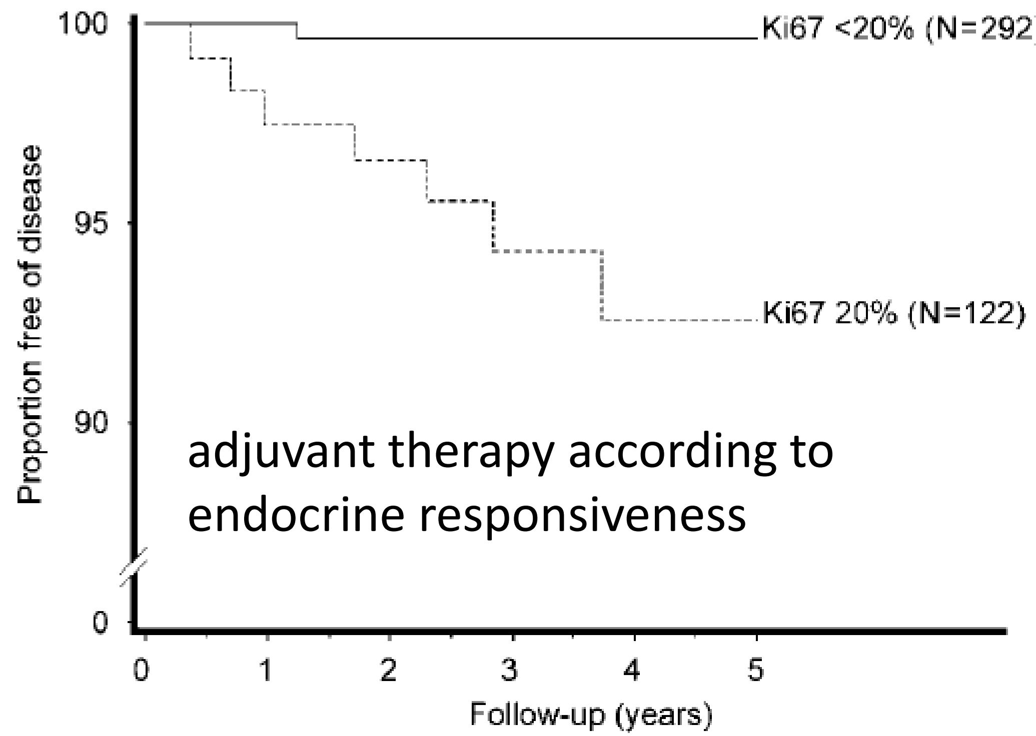
Annals of Oncology 15: 1633–1639, 2004

Table 6. Multivariate analysis in 390 patients with pT1a/ pT1b tumors

Variables	HR (95% CI)[a]	*P*
PgR (absent versus present)	2.36 (0.55–10.1)	0.247
Ki-67 (≥20% versus <20%)	12.9 (1.49–112.0)	0.020
Age (<35 versus 35+)	4.76 (0.93–24.3)	0.061

pT1a/pT1b

Proliferative activity
Ki67



adjuvant therapy according to endocrine responsiveness

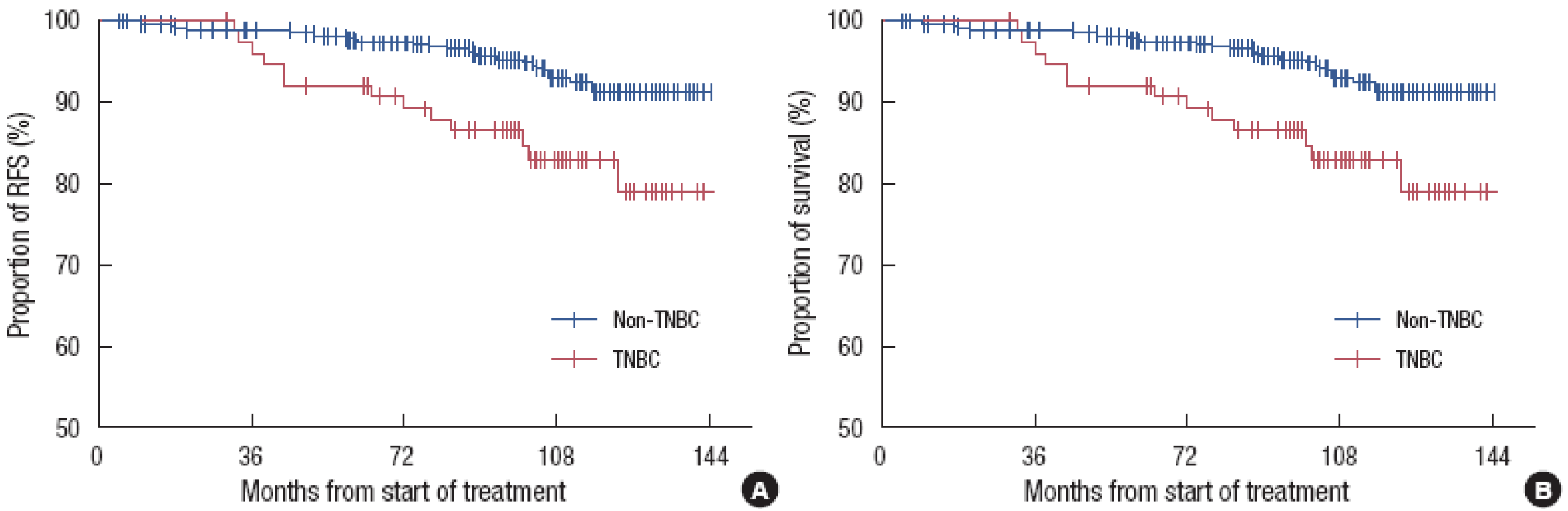
Although most patients with TNBC present with advanced stage tumors at diagnosis, about 10% present with stage I

Cancer 2007;109:1721-8.

Breast J 2009;15:454-60.

J Breast Cancer 2012 June; 15(2): 197-202

Impact of Triple-Negative Breast Cancer Phenotype on Prognosis in Patients with Stage I Breast Cancer



VOLUME 27 · NUMBER 34 · DECEMBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

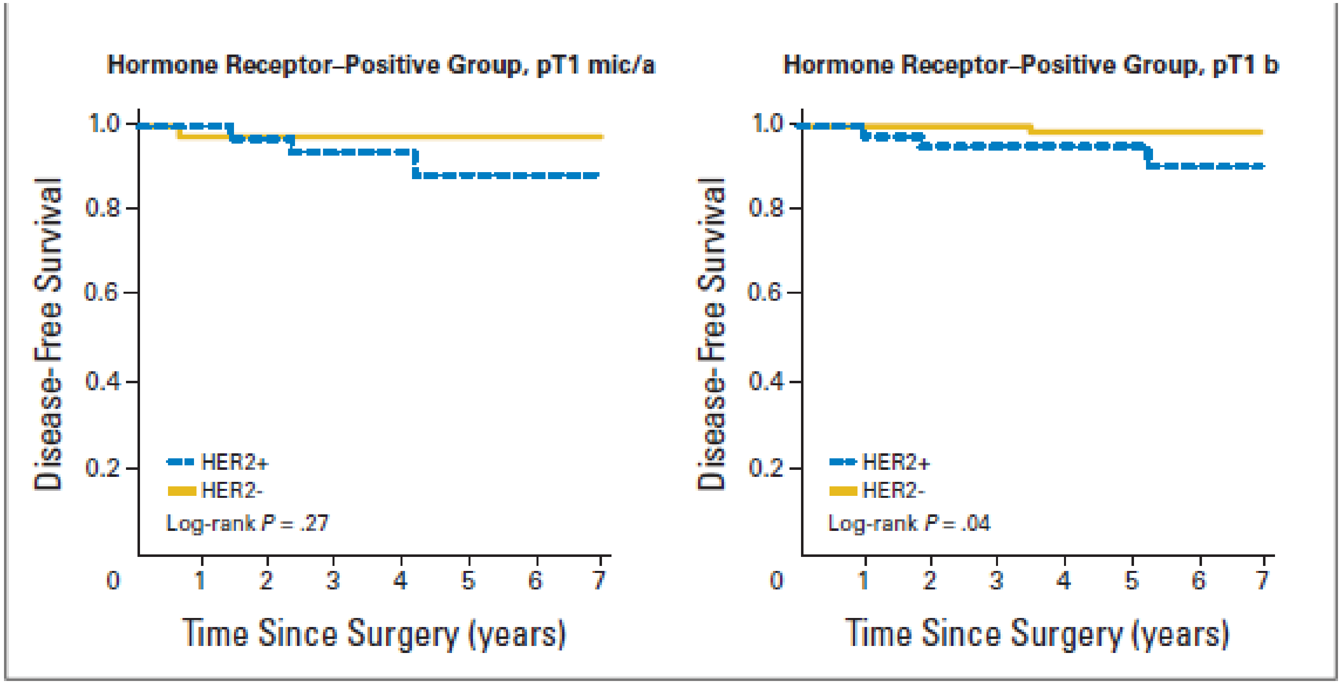
ORIGINAL REPORT

Clinical Relevance of *HER2* Overexpression/Amplification in Patients With Small Tumor Size and Node-Negative Breast Cancer

Giuseppe Curigliano, Giuseppe Viale, Vincenzo Bagnardi, Luca Fumagalli, Marzia Locatelli, Nicole Rotmensz, Raffaella Ghisini, Marco Colleoni, Elisabetta Munzone, Paolo Veronesi, Stefano Zurrida, Franco Nolè, and Aron Goldhirsch

150 pazienti HER2 positive

pT1a-b, pN0, M0 non sottoposte a trastuzumab



VOLUME 29 · NUMBER 19 · JULY 1 2011

JOURNAL OF CLINICAL ONCOLOGY

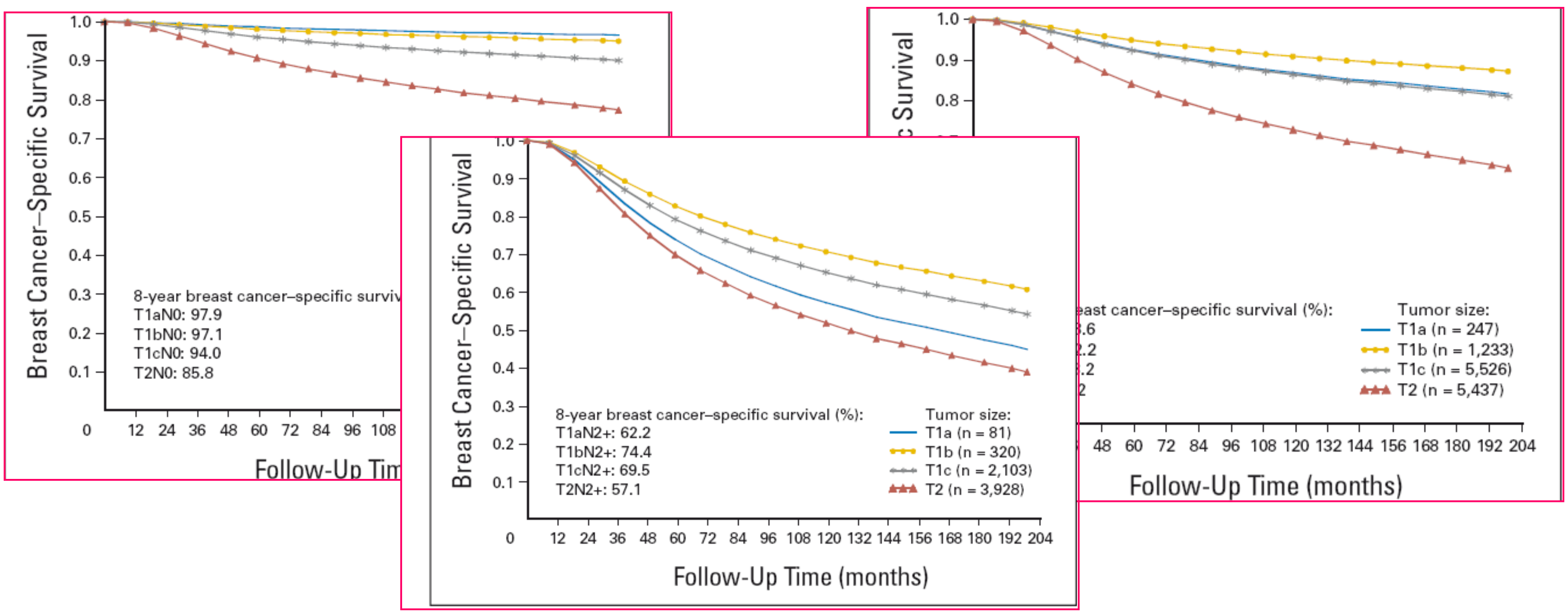
ORIGINAL REPORT

Effect of Very Small Tumor Size on Cancer-Specific Mortality in Node-Positive Breast Cancer

Jennifer Y. Wo, Kun Chen, Bridget A. Neville, Nancy U. Lin, and Rinaa S. Punglia

Conclusion

Very small tumors with four positive LNs may predict for higher BCSM compared with larger tumors. In extensive node-positive disease, very small tumor size may be a surrogate for biologically aggressive disease.



TUMORE PICCOLO?

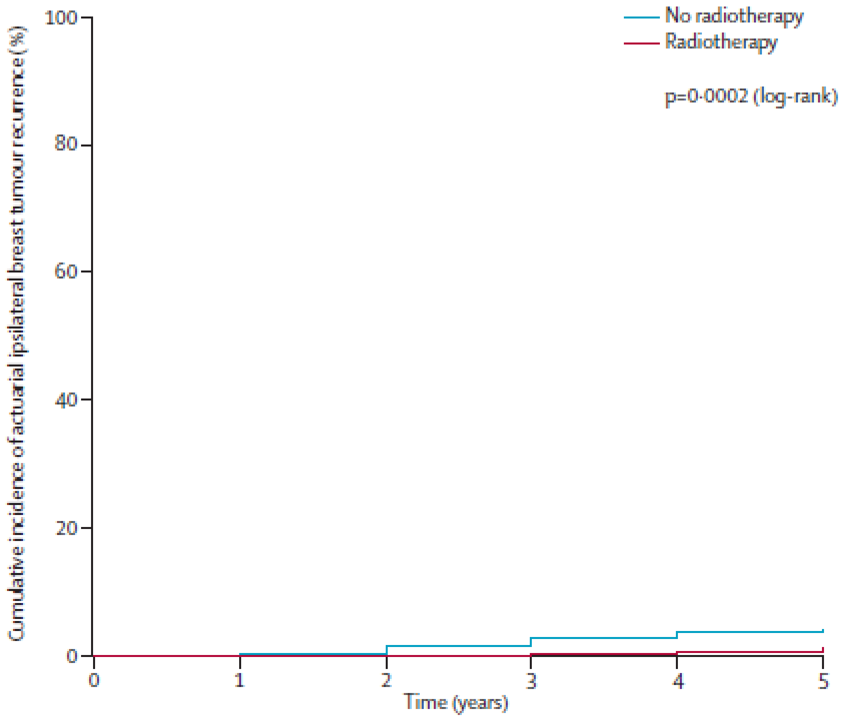
KI67?
STATO ORMONALE?
STATO DI *HER2*
STATO LINFONODALE?

TERAPIA

Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial

Ian H Kunkler, Linda J Williams, Wilma J L Jack, David A Cameron, J Michael Dixon, on behalf of the PRIME II investigators

Lancet Oncol 2015; 16: 266–73



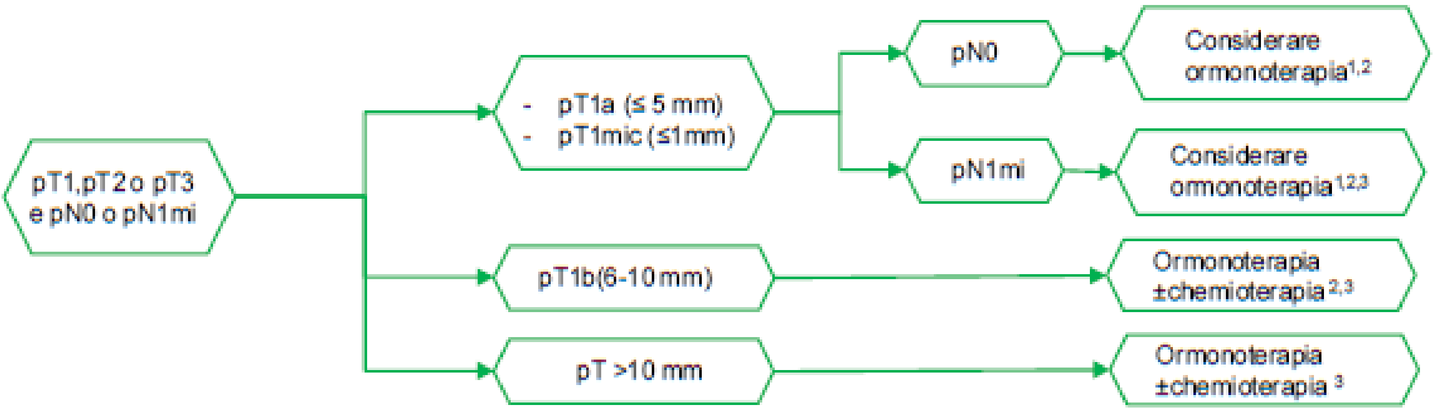
Number at risk

		0	1	2	3	4	5
No radiotherapy	Entering interval	668	643	607	560	464	311
	Events	1	9	6	5	2	(3)
Radiotherapy	Entering interval	658	631	597	551	472	324
	Events	0	0	1	2	2	(0)

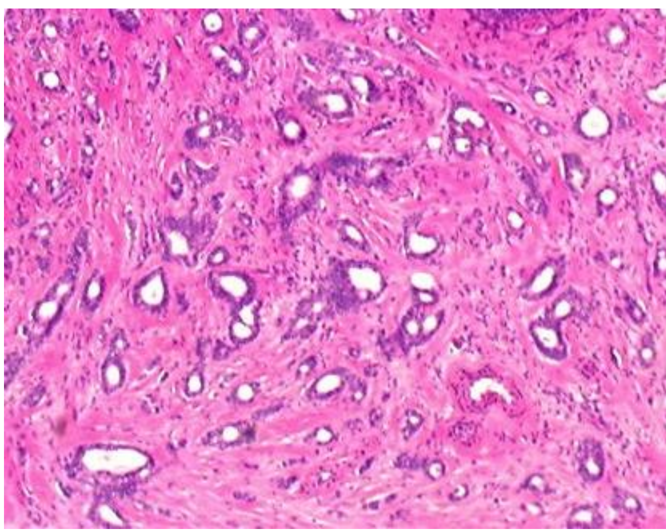
In ogni caso la percentuale di recidive locali a 5 anni è molto bassa (4%)

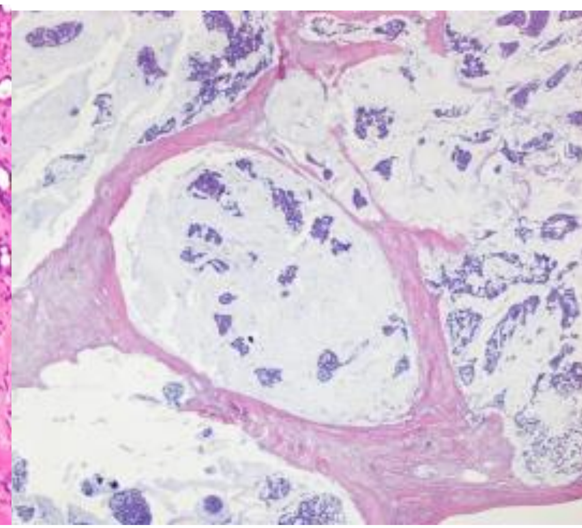
Figura 5 – CARCINOMA MAMMARIO INFILTRANTE **Aiom, 2014**

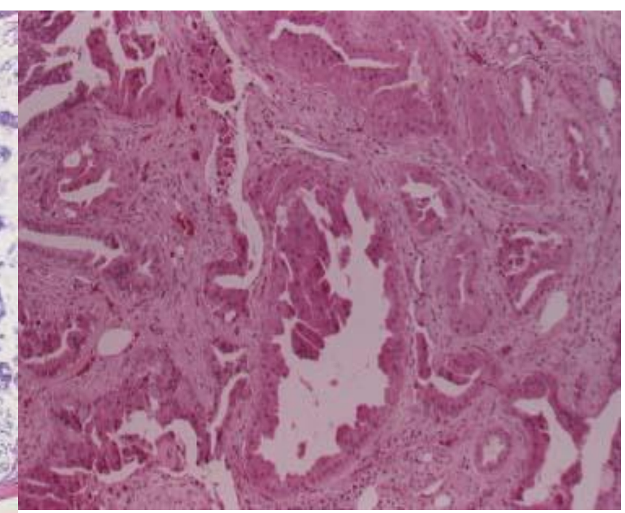
Terapia sistemica adiuvante: ER positivi e/o PgR positivi; HER2-negativo



TUBULARI, MUCINOSI E PAPILLARI
SE <1cm e SENZA INTERESSAMENTO LINFONODALE**:**
POSSIBILE ASTENERSI DAL TRATTAMENTO







Aiom, 2014

Figura 6- CARCINOMA MAMMARIO INFILTRANTE

Terapia sistemica adiuvante: ER positivi e/o PgR positivi; HER2-positivo

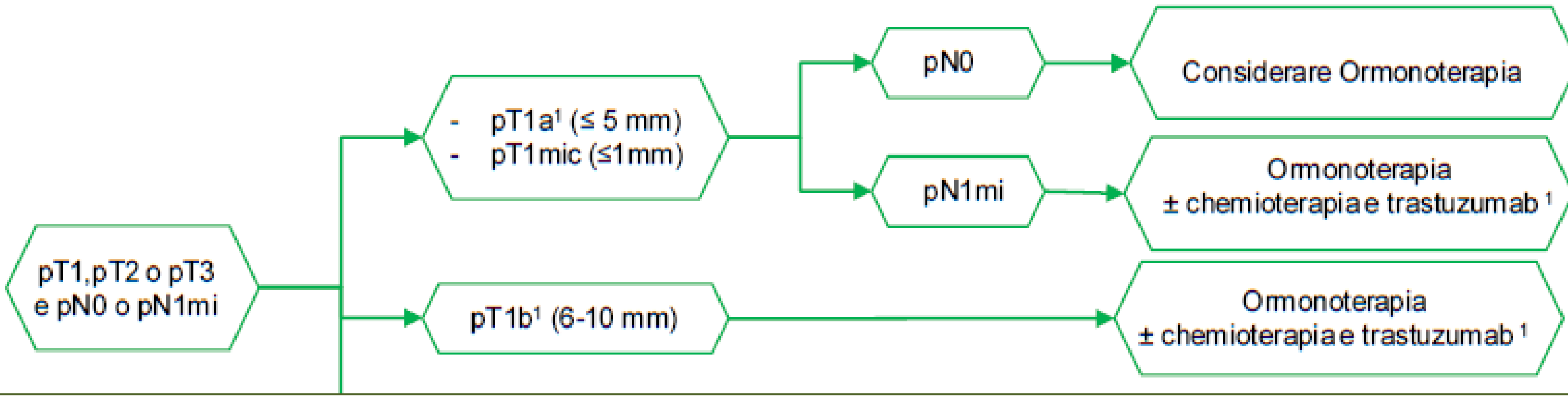
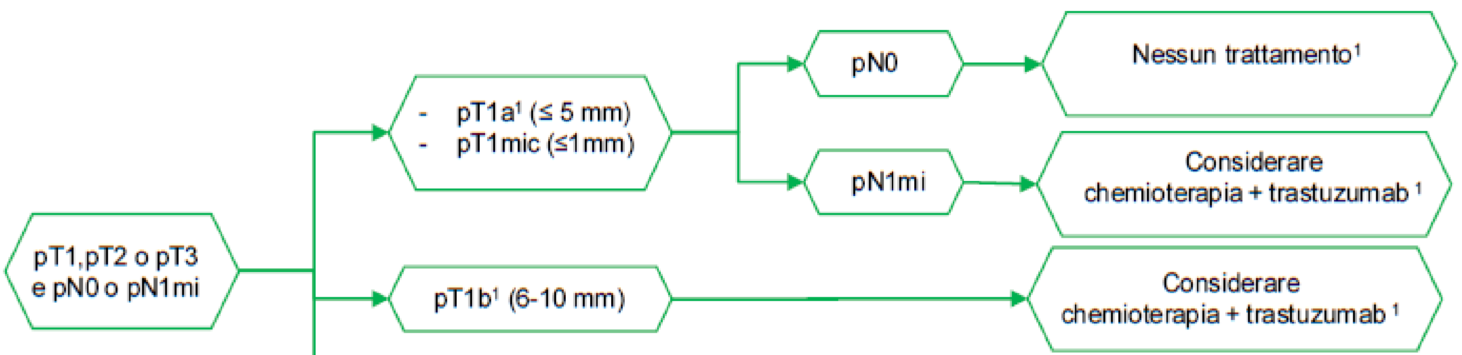
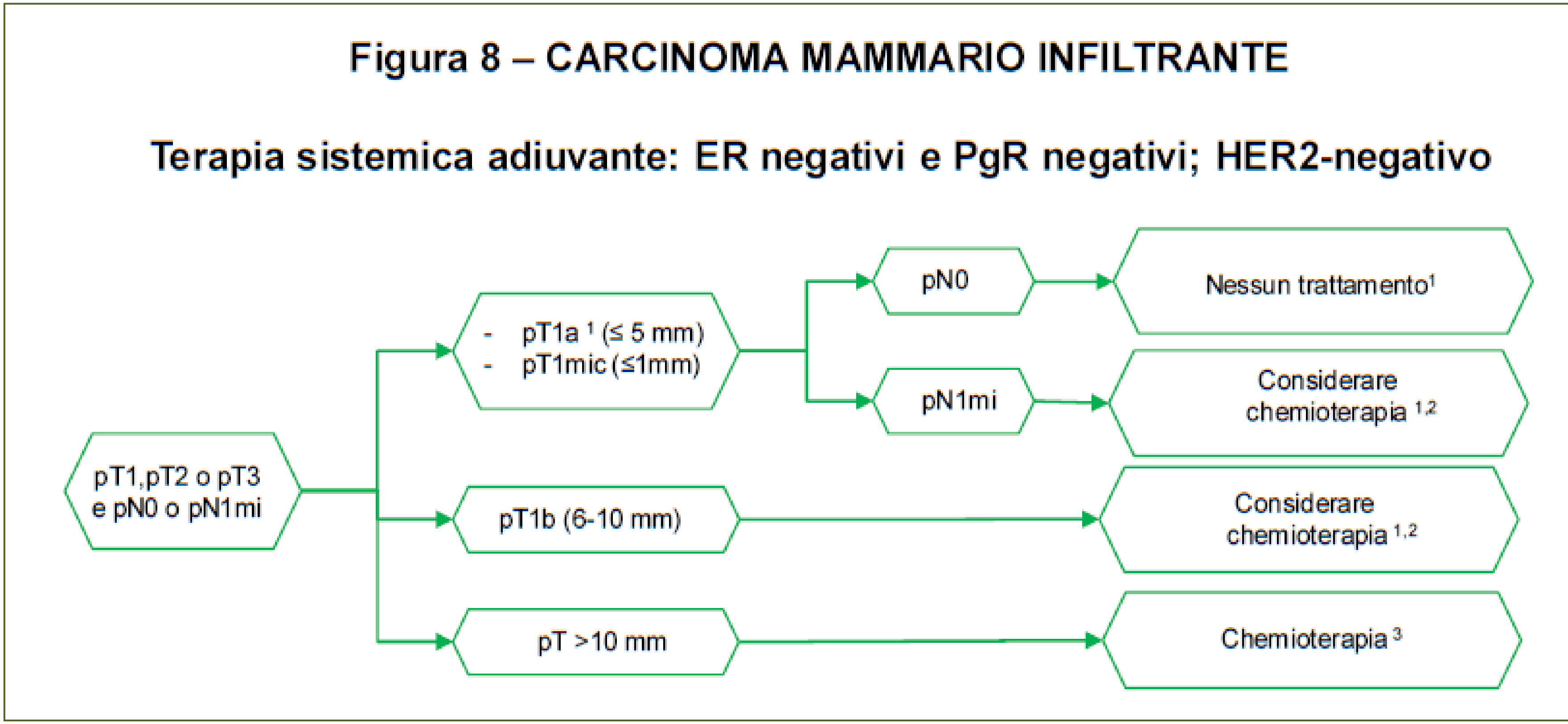


Figura 7- CARCINOMA MAMMARIO INFILTRANTE

Terapia sistemica adiuvante: ER negativi e PgR negativi; HER2-positivo



pT1a: non esistono dati prospettici riguardo all'utilizzo della CT+trastuzumab



pT1a: la CT può essere presa in considerazione se G3 o KI67 elevato

Adenoideo cistico se inferiore a 1 cm non necessita di trattamento

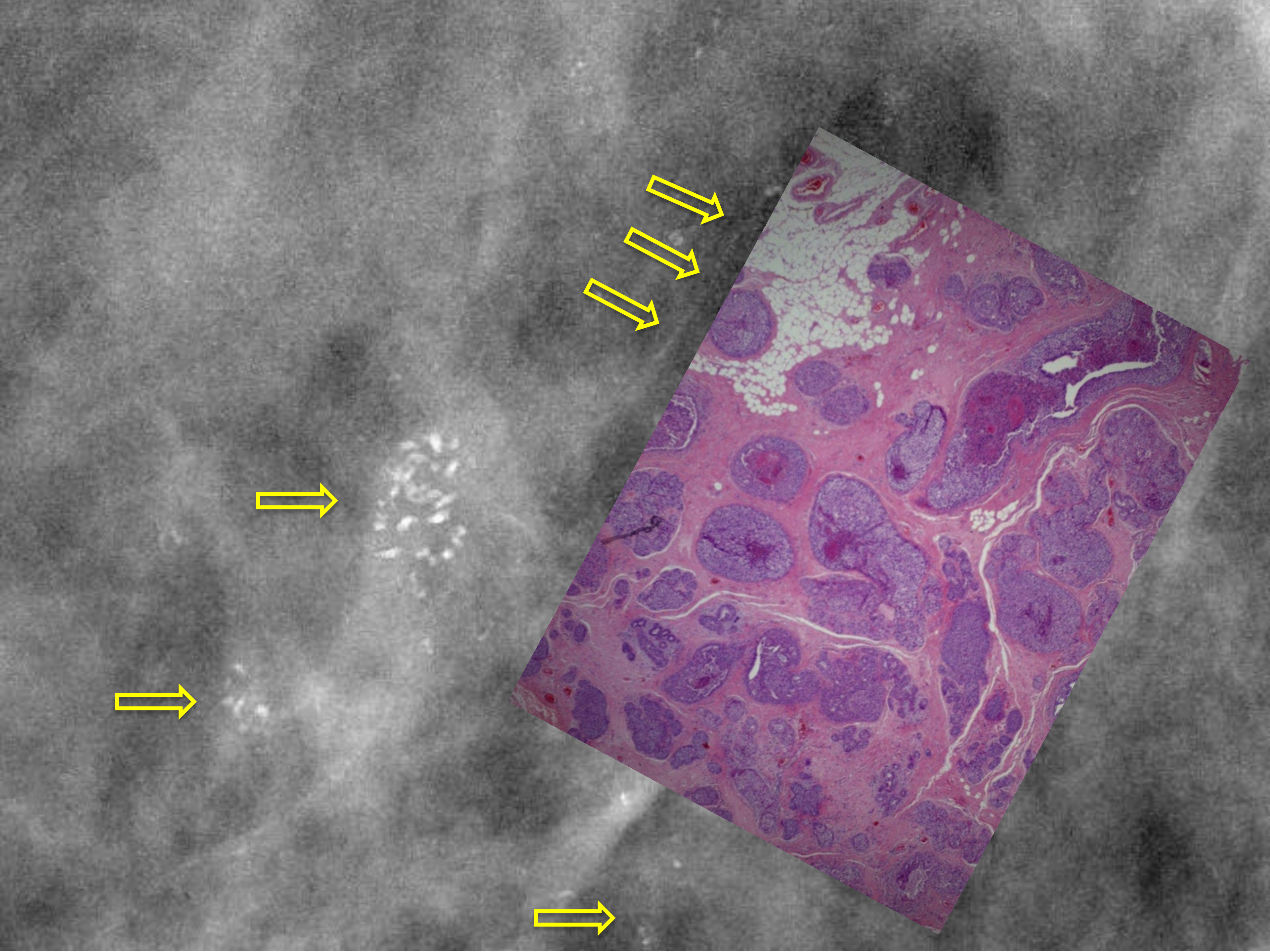
CARCINOMA MICROINVASIVO

Solin LJ1, Fowble BL, Yeh IT, Kowalyshyn MJ, Schultz DJ, Weiss MC, Goodman RL.
Microinvasive ductal carcinoma of the breast treated with breast-conserving surgery and definitive irradiation.
Int J Radiat Oncol Biol Phys. 1992;23(5):961-8.

Prognosi eccellente

In considerazione della bassa numerosità delle casistiche di carcinoma microinvasivo, non si dispone di studi clinici che indirizzino le decisioni terapeutiche. AIOM 2014

Ma c’è MICROINVASIVO E MICROINVASIVO….



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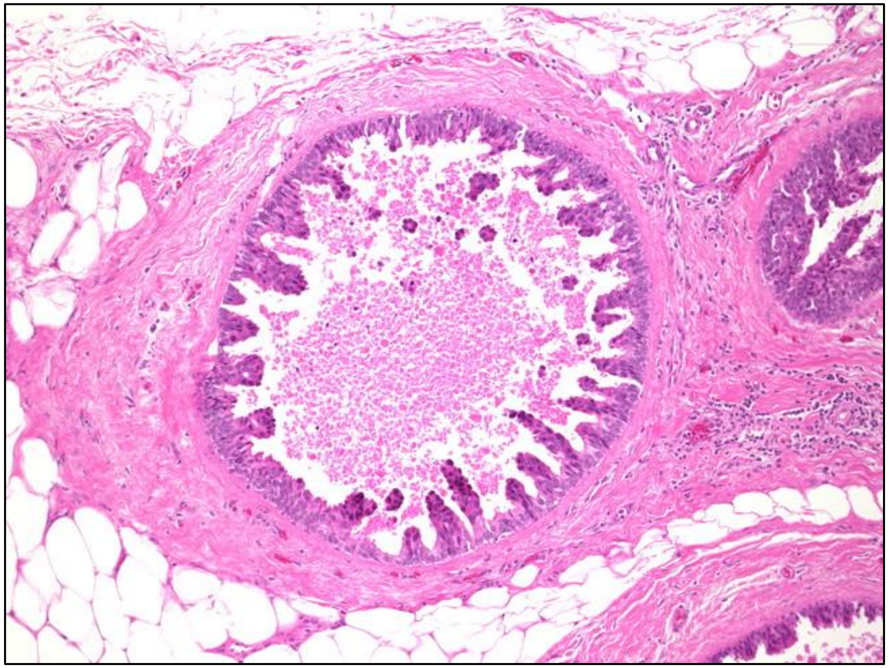
CARCINOMI DUTTALI IN SITU



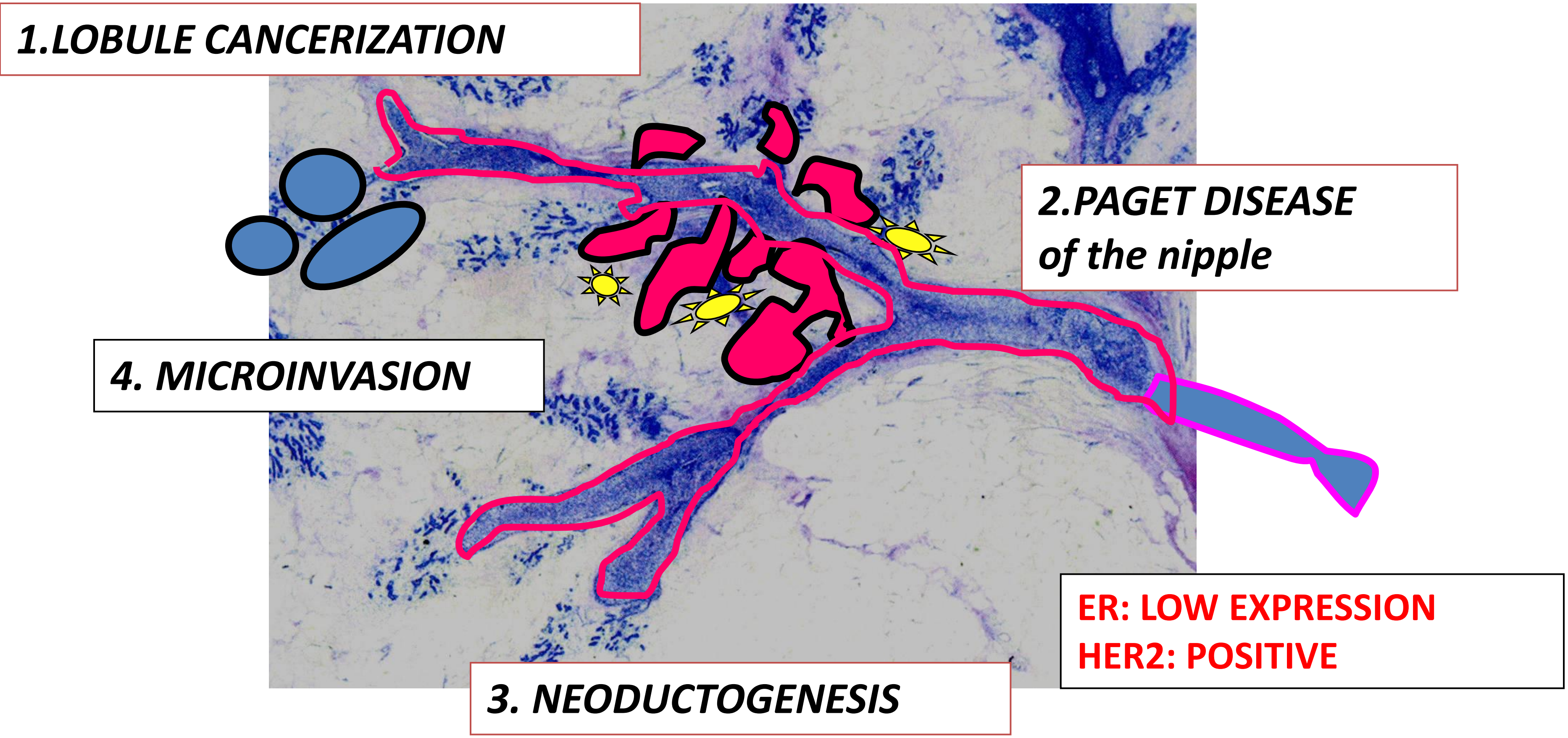
MARCATORI PROGNOSTICI

ESTENSIONE
GRADO NUCLEARE
STATO DEI MARGINI DI RESEZ
MYCROPAPILLARY TYPE

ER low expression
HER2 overexpression

DIN3/high grade DCIS

Tot T. kind permission



Tot Tibor Virchows Arch (2005) 447: 1–8

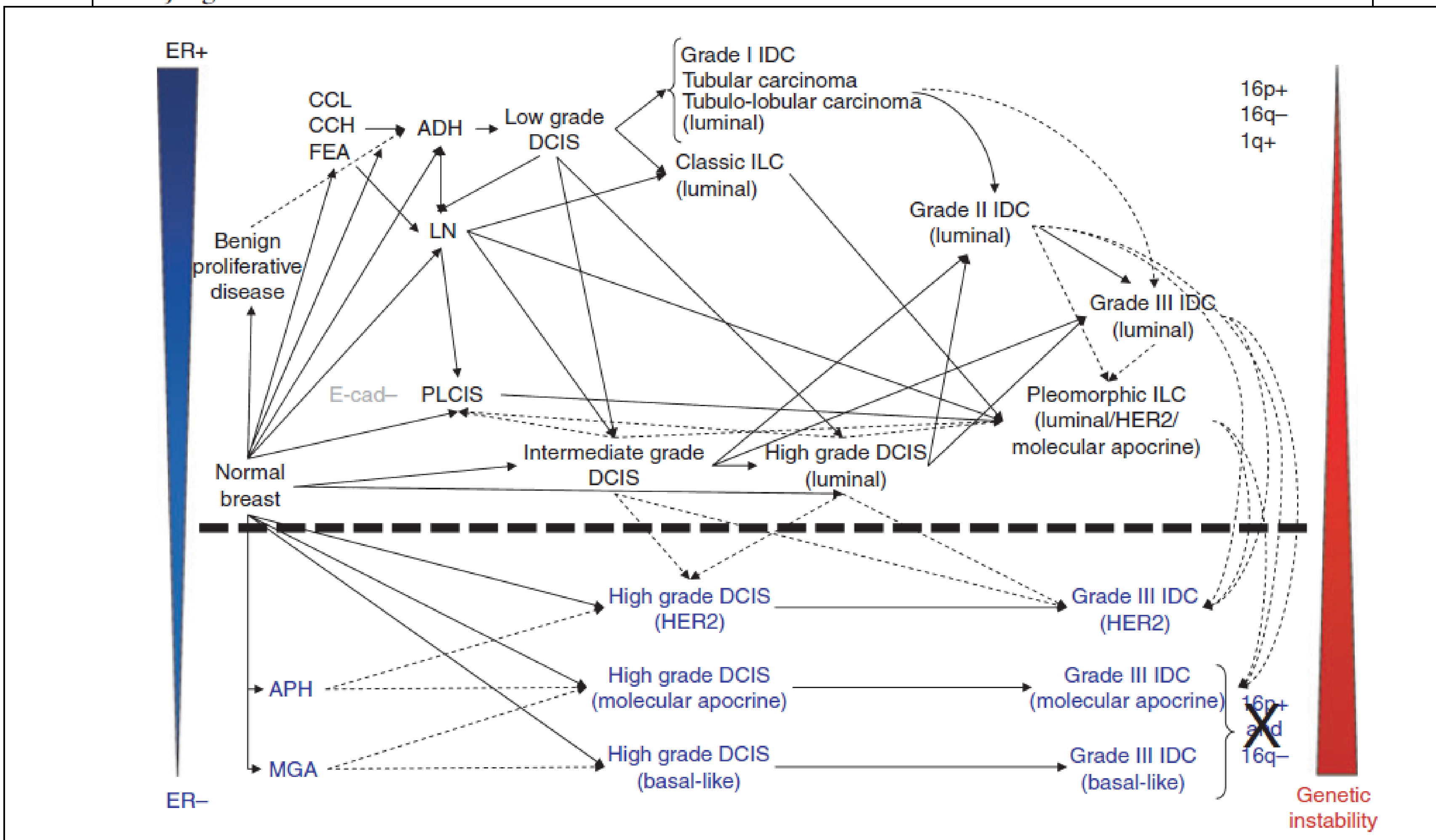
Laszlo Tabar, et al *Cancer* 2004;101: 1745–59

Histopathology 2010, **57**, 171–192.

REVIEW

Breast cancer precursors revisited: molecular features and progression pathways

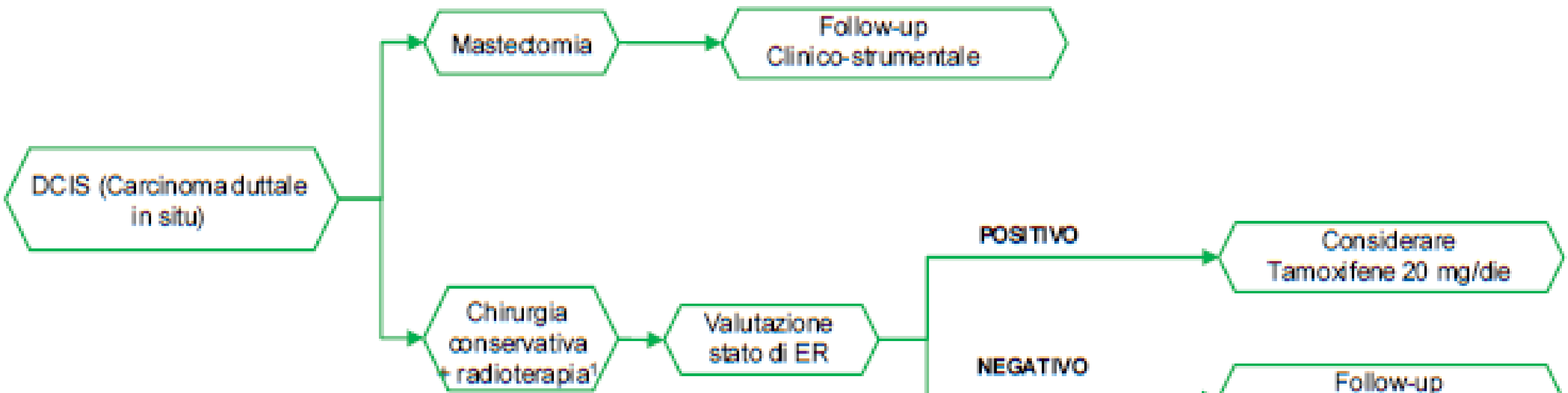
Maria A Lopez-Garcia,[1,2] Felipe C Geyer,[1] Magali Lacroix-Triki,[1,3] Caterina Marchió[4] & Jorge S Reis-Filho[1]



TRATTAMENTO

ORMONOTERAPIA

Figura 1 - CARCINOMA DUTTALE IN SITU (DCIS): trattamento



AIOM 2014

The Onco*type* DX® Breast Cancer Assay for DCIS: A Genomic Risk Stratification Tool

DCIS Score™ Result: Gene Selection

Proliferation

Ki-67
STK15
Survivin
Cyclin B1
MYBL2

Hormone Receptor Group

PR

GSTM1

Reference

Beta-actin
GAPDH
RPLPO
GUS
TFRC

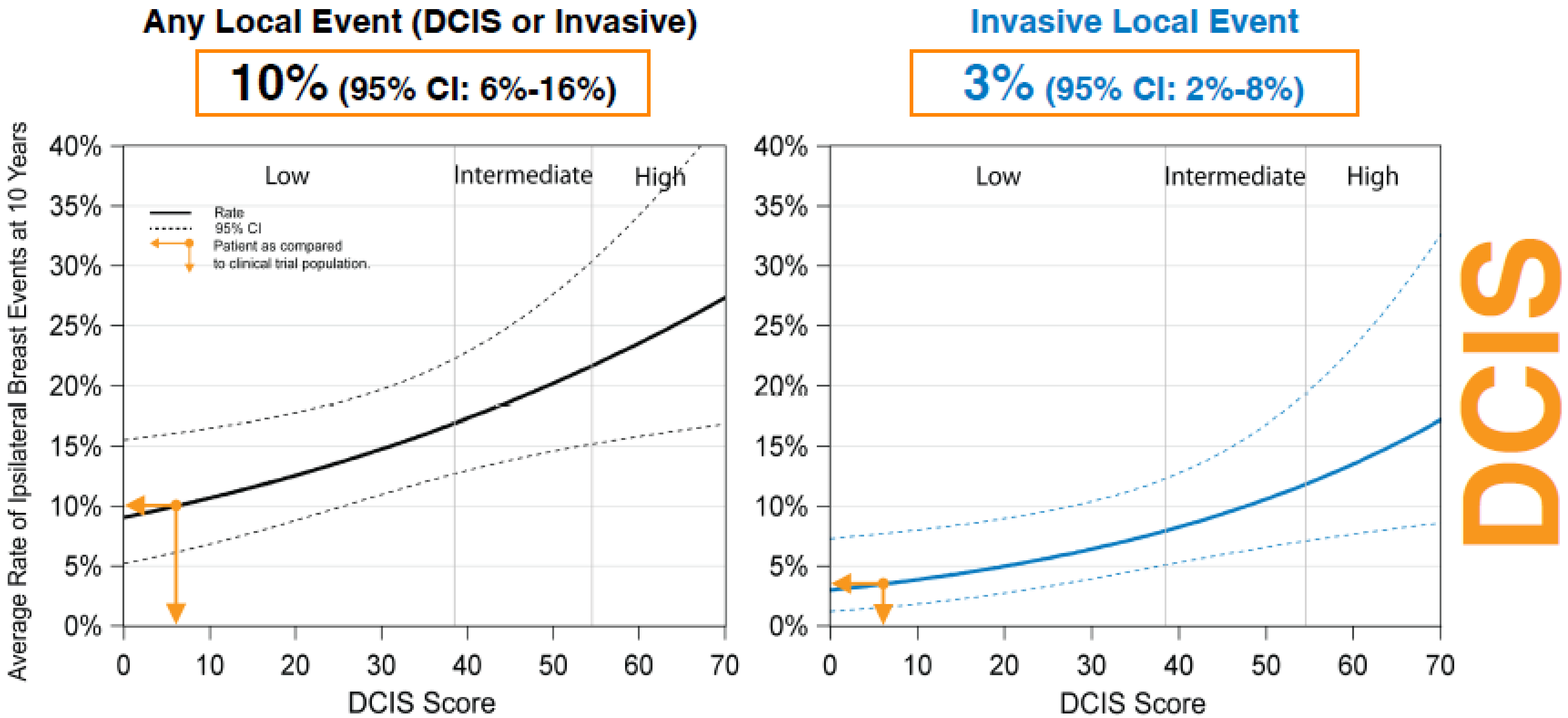
The DCIS Score result:

- **Is a continuous variable**
- **Is a quantitative risk assessment (number between 0 – 100)**
- **Reflects each individual patient's tumor biology**

Solin et al. *J Natl. Cancer Inst.* 2013.

VALIDATO IN PAZIENTI CHE HANNO EFFETTUATO SOLO CHIRURGIA E NON RADIOTERAPIA

Estensione tumorale: ≤2.5 cm
Margini ≥ 3 mm



These results are from a clinical validation study of 327 patients from the ECOG 5194 study (Solin et al. *J Natl Cancer Inst.* 2013.).

- Low < 39, Intermediate 39 – 54, High ≥ 55

CONCLUSIONI

LA DIMENSIONE DELLA LESIONE E' UN FATTORE PROGNOSTICO INDIPENDENTE DI SOPRAVVIVENZA GLOBALE E LIBERA DA MALATTIA

E' difficile definire un valore soglia al di sotto o al di sopra del quale il tumore possa essere considerato a cattiva o a buona prognosi, fatta eccezione per i tumori molto piccoli.

Anche nei tumori pT1a e pT1b la valutazione del rischio non può prescindere dal considerare gli altri parametri prognostici, quali lo stato dei linfonodi ascellari, i fattori biologici (Ki-67, stato dei recettori ormonali, stato di HER2, grading) e l'età della paziente.

Considerando questi parametri la letteratura (e anche le Linee Guida) ci suggeriscono la possibilità di omettere radio/ormonoterapia su pazienti selezionate

E' necessaria la messa a punto di nuovi studi per determinare l'influenza della componente *IN SITU* associata a tumori piccoli e dei tumori *IN SITU PICCOLI* per evitare under/over treatment

GRAZIE