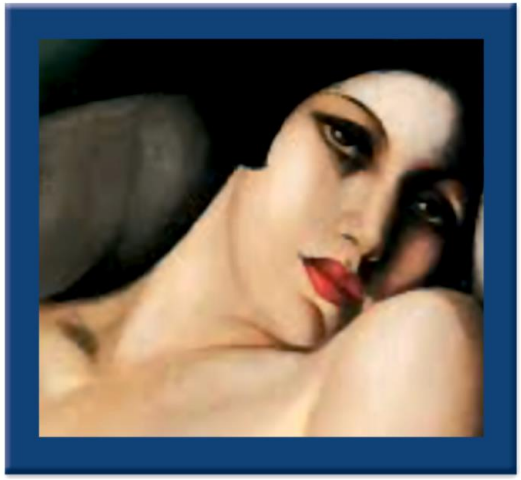
gisma
gruppoitalianoscreening
mammografico

CONVEGNO NAZIONALE
GISMA 2015

Lo Screening mammografico in Italia:
i dati, gli strumenti, la ricerca
ed i compagni di strada



Reggio Emilia
7-8 maggio 2015
UNIVERSITÀ
DEGLI STUDI
DI REGGIO EMILIA

Il futuro influenza il presente tanto quanto il passato
(F.W. Nietzsche)

PERCORSO DI
DIAGNOSI E CURA
DEI TUMORI DELLA MAMMELLA

Breast
Centres
Certification
ITALCERT scheme in partnership with BCCERT

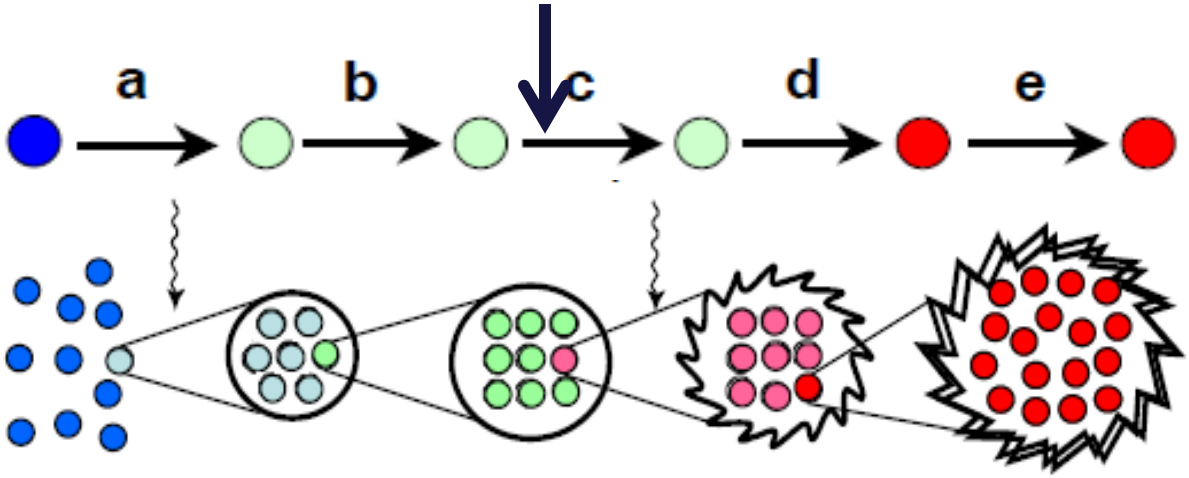
PICCOLI TUMORI CRESCONO: Gli aspetti di anatomia/patologica

Donatella Santini
US Patologia della Mammella e delle Ghiandole Endocrine
Anatomia Patologica Dir. Univeristaria
Azienda Ospedaliera Universitaria S. Orsola-Malpighi
Bologna

•donatella.santini@aosp.bo.it

PICCOLI TUMORI CRESCONO

Screening:
punto in cui il ca mammella può essere rilevato



Screening = identificazione tumori in stadio precoce
…..piccoli…pT1mic pT1a-b…….

PICCOLI TUMORI CRESCONO

Screening:
punto in cui il ca mammella può essere rilevato

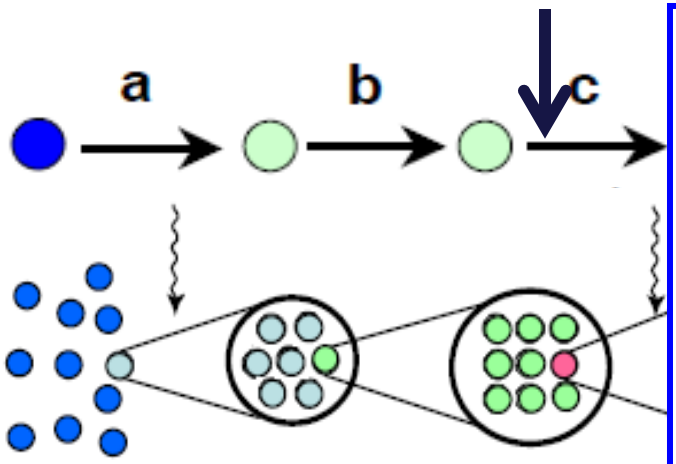


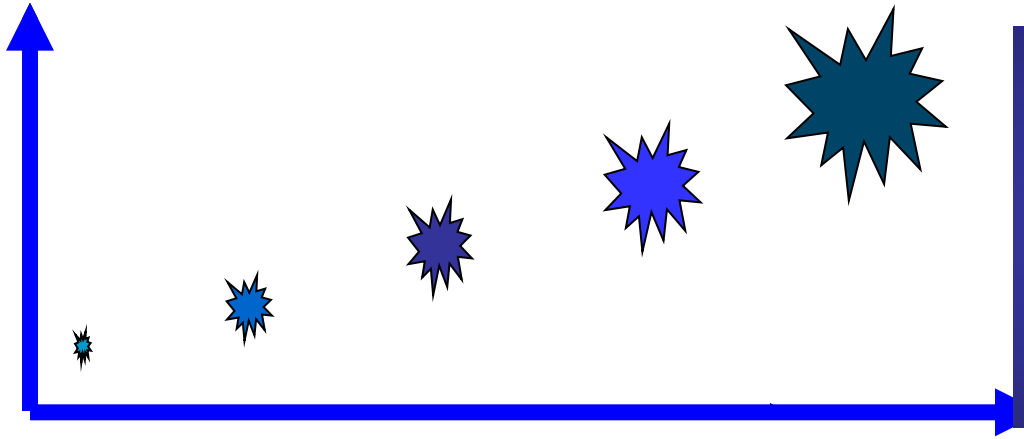
Table 1. Distribution of cancer stages (American Joint Committee on Cancer) in screened and never-screened women

Stage	Screened (%)	Unscreened (%)
I	62	39
II	30	46
III	8	8
IV	0.3	7

Adapted by permission from Macmillan Publishers Ltd on behalf of Cancer Research UK: British Journal of Cancer, advance online publication, 3 Dec 2013 (doi: 10.1038/bjc.2013.732) [11].

Downstaging nel gruppo screening è evidente

PICCOLI TUMORI CRESCONO



screening — intervallo di screening — screening

ca.intervallo → ca. intervallo asintomatici — tumori screen detected in stadio avanzato

(individuati in corso di esami opportunistici)

ca. intervallo sintomatici

fattori di ordine sociale e/o psicologico

Insorge Visibile Rx Diagnosi preclinica Palpabile Outcome

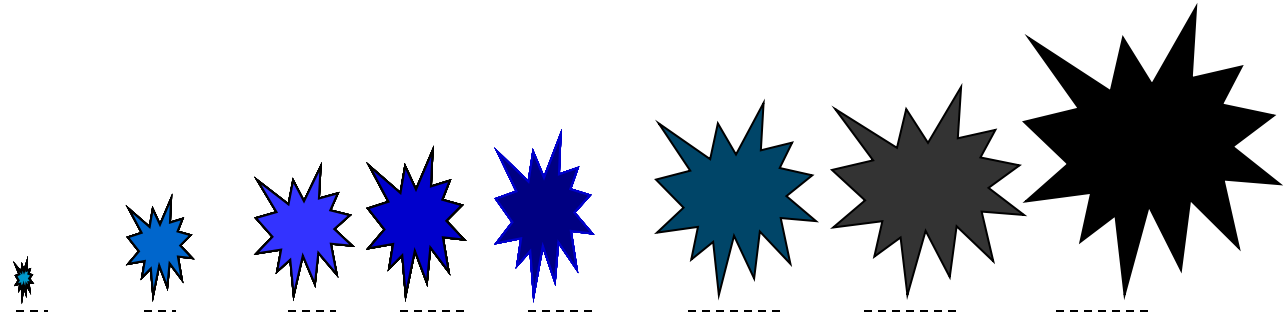
Tempo fase preclinica = Velocità di crescita

Lo screening, (mammografia biennale) non.. è perfetto?

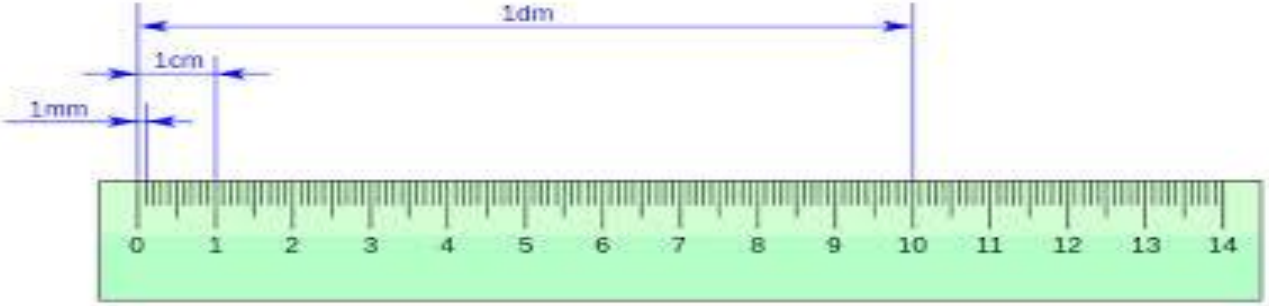
CA INTERVALLO e T2+ screen detected

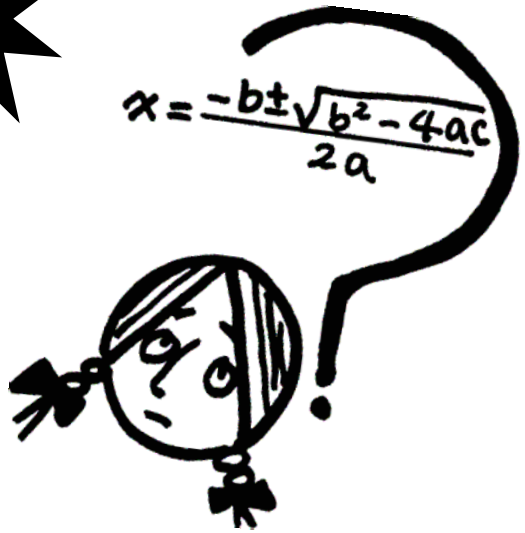
PICCOLI TUMORI CRESCONO

- Carcinoma Duttale In Situ pTis
- Carcinoma MICROINVASIVO pTmic
- Carcinoma INVASIVO pT1a-b-c
- Carcinoma INVASIVO pT2-3-4



<≤1mm 2mm 3mm 4mm 5mm 1cm 2cm 3cm





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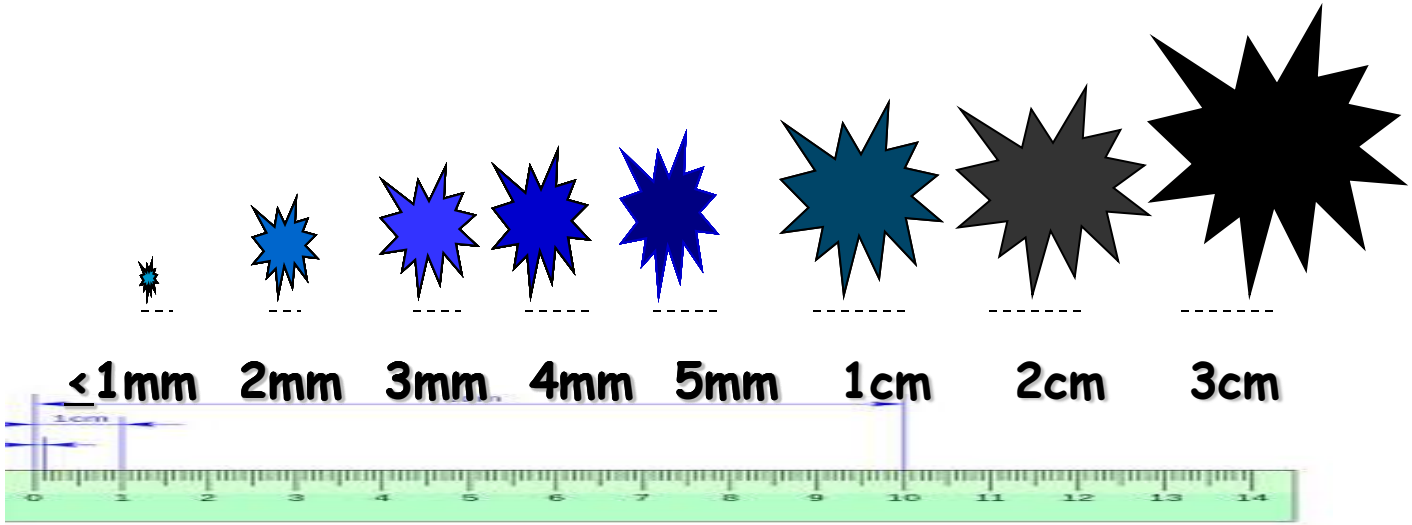
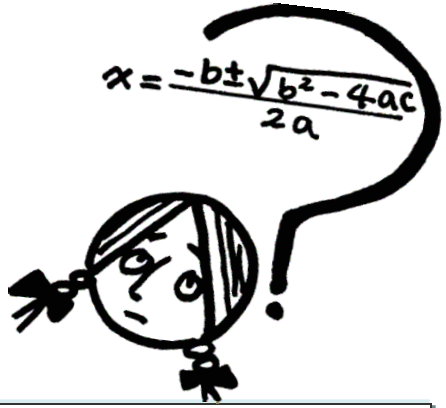
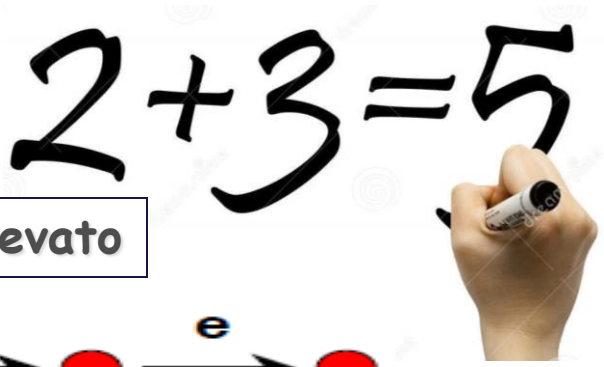




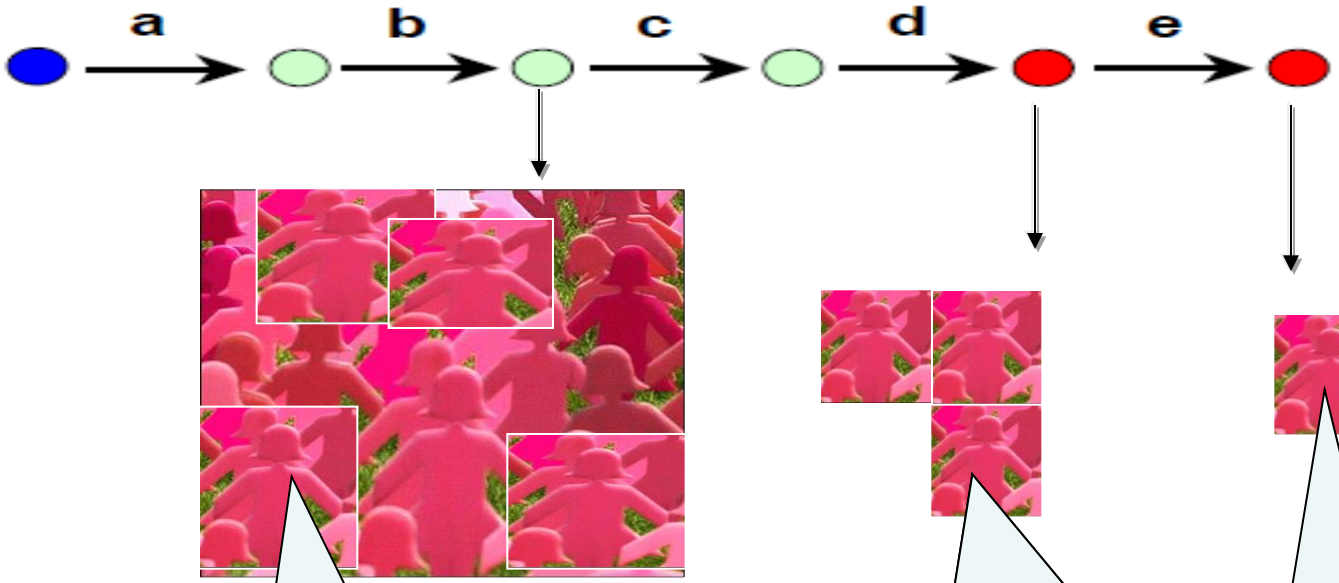
pT

Cosa ci dice la biologia?

PICCOLI TUMORI CRESCONO



Punto in cui il ca mammella può essere rilevato



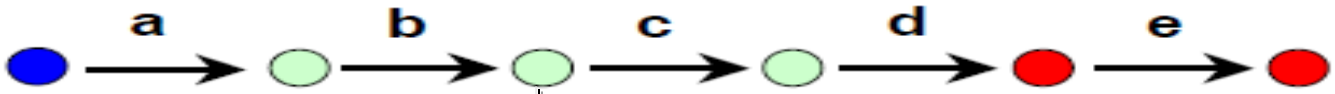
pT1N0
ER 100%
Pgr 100%
Ki67 7%
HER2 negativo

pT2N0
ER 100%
Pgr 100%
Ki67 7%
HER2 negativo

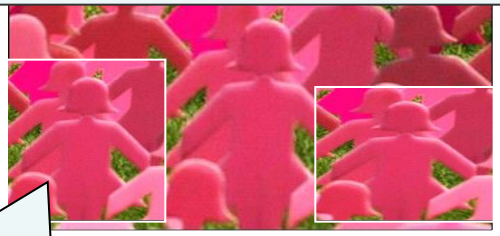
pT3N0
ER 100%
Pgr 100%
Ki67 7%
HER2 negativo

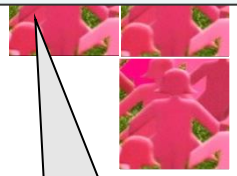
PICCOLI TUMORI CRESCONO

Screening:
punto in cui il ca mammella
può essere rilevato



.....tuttavia, tutti gli altri fattori NON sono costanti





T1N0
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Ki67 7%
HER2 negativo

T1N0
ER 40%
Pgr 20%
Ki67 37%
HER2 +++

T1N0
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Pgr 0%
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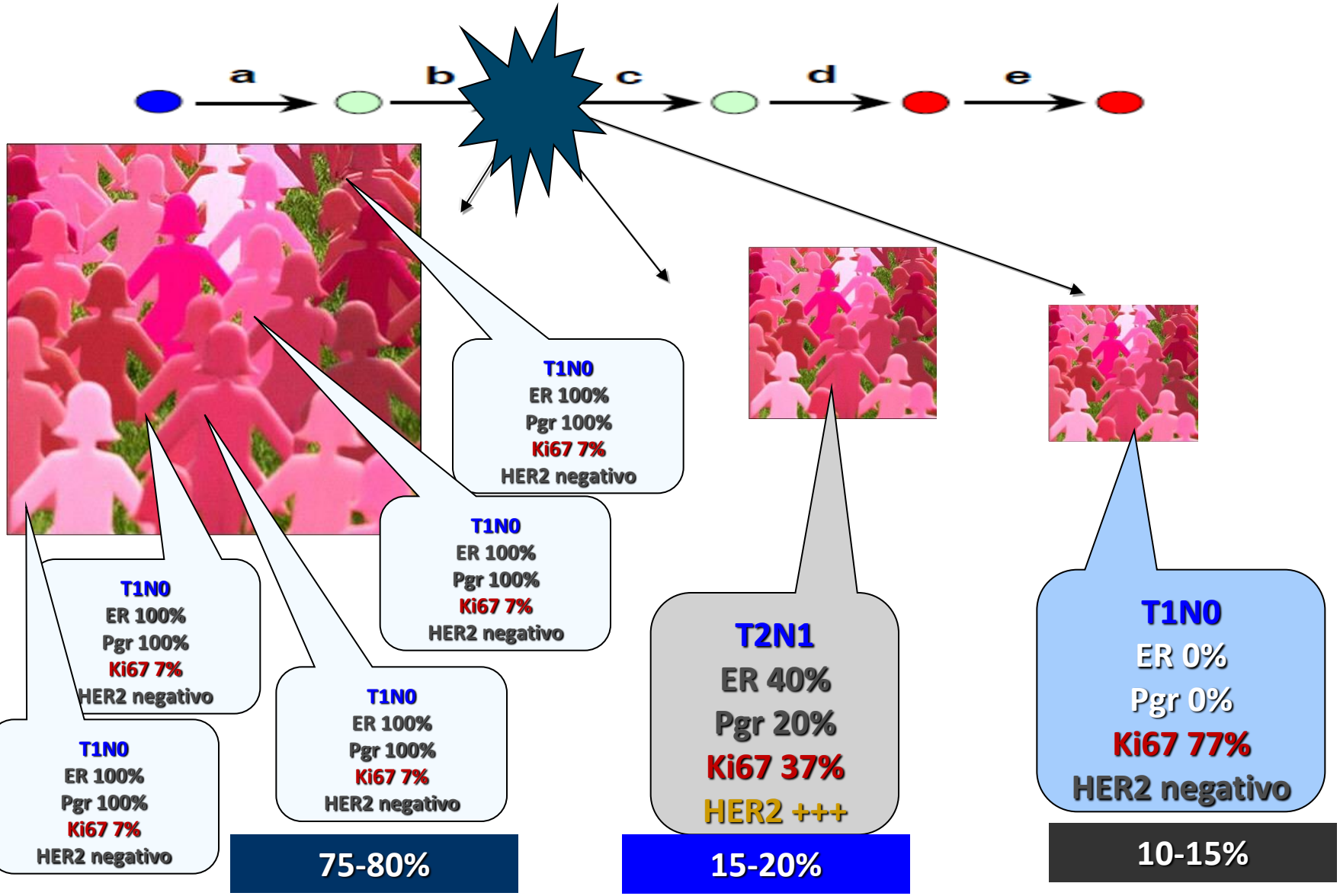
PICCOLI TUMORI CRESCONO



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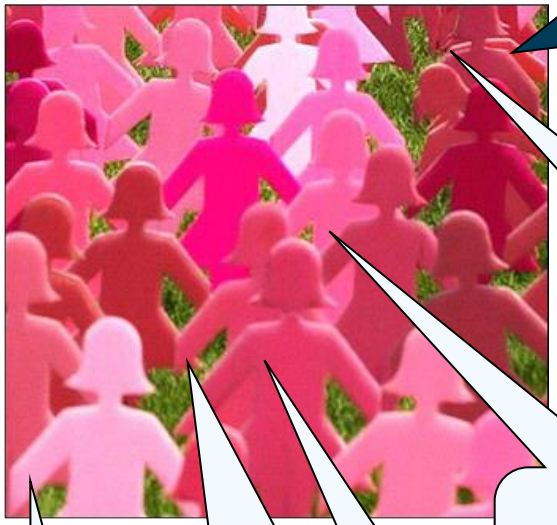
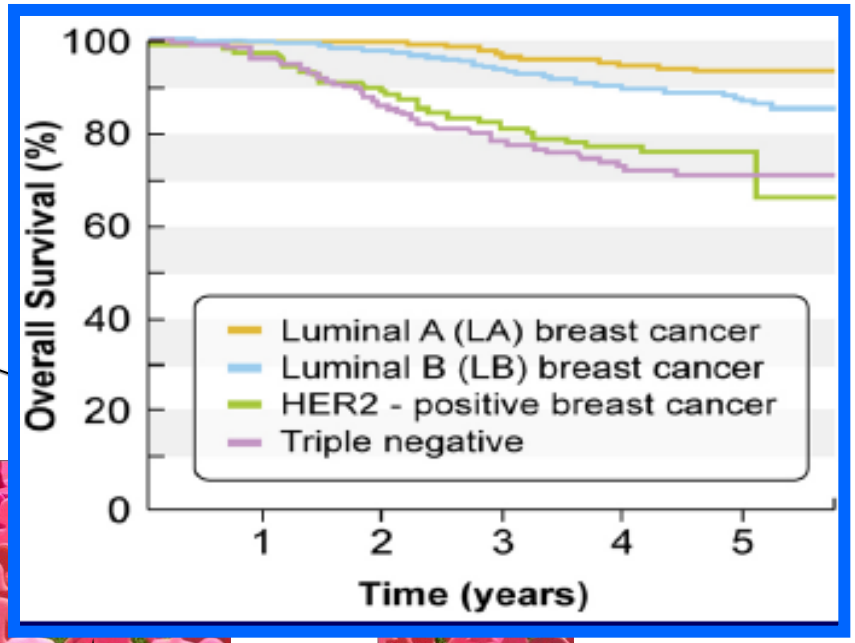


a

b

OUTCOME



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Pgr 100%
Ki67 7%
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T1N0
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Pgr 100%
Ki67 7%
HER2 negativo

75-80%

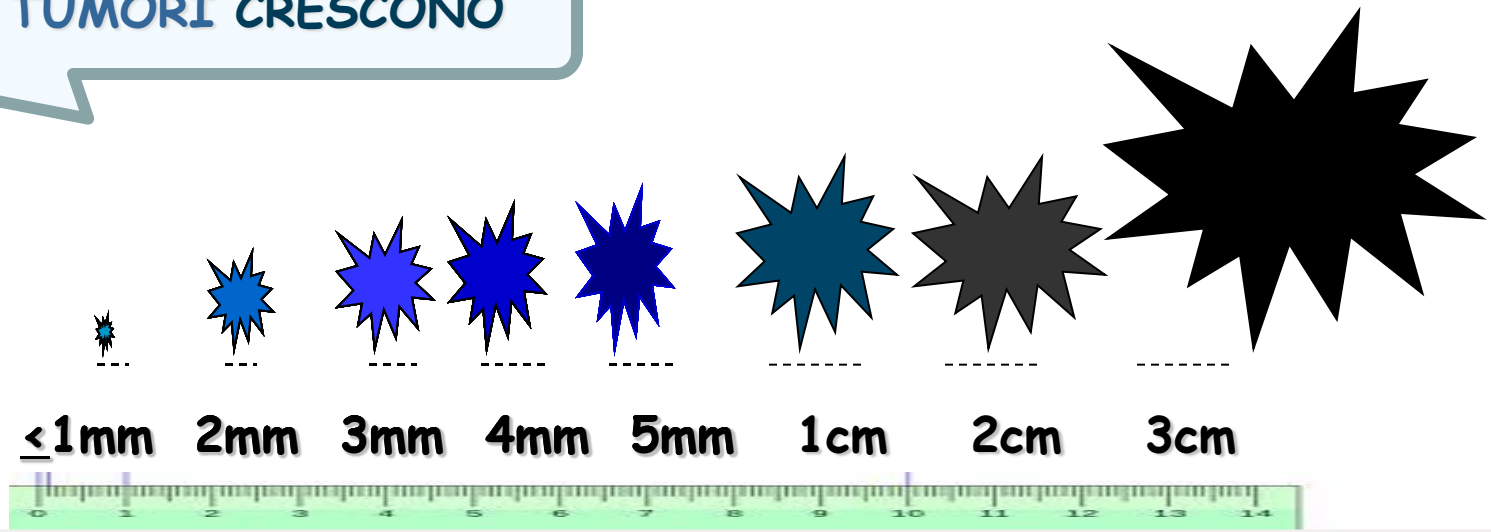
T2N1
ER 40%
Pgr 20%
Ki67 37%
HER2 +++

15-20%

T1N0
ER 0%
Pgr 0%
Ki67 77%
HER2 negativo

10-15%

PICCOLI TUMORI CRESCONO



Otto parametri (pT, pN,istotipo,Grading, ER/PgR,Ki-67, LVI. Vasc.,HER2) e >200 combinazioni

T2N2
ER 100%
Pgr 100%
Ki67 7%
HER2 negativo

T2N1
ER 40%
Pgr 20%
Ki67 37%
HER2 +++

T1N0
ER 0%
Pgr 0%
Ki67 77%
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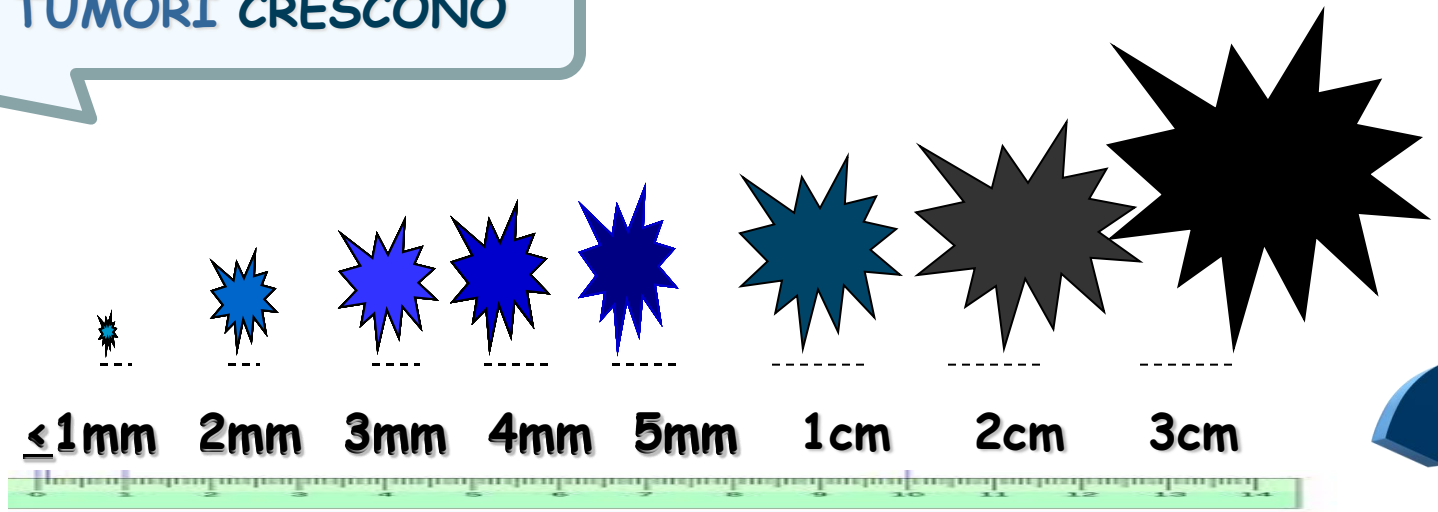
PICCOLI TUMORI CRESCONO



E' molto probabile che ogni classe molecolare abbia il suo tipo di carcinogenesi e nesso di causalità

T2N2
ER 100%
Pgr 100%
Ki67 7%
HER2 negativo

T2N1
ER 40%
Pgr 20%
Ki67 37%
HER2 +++

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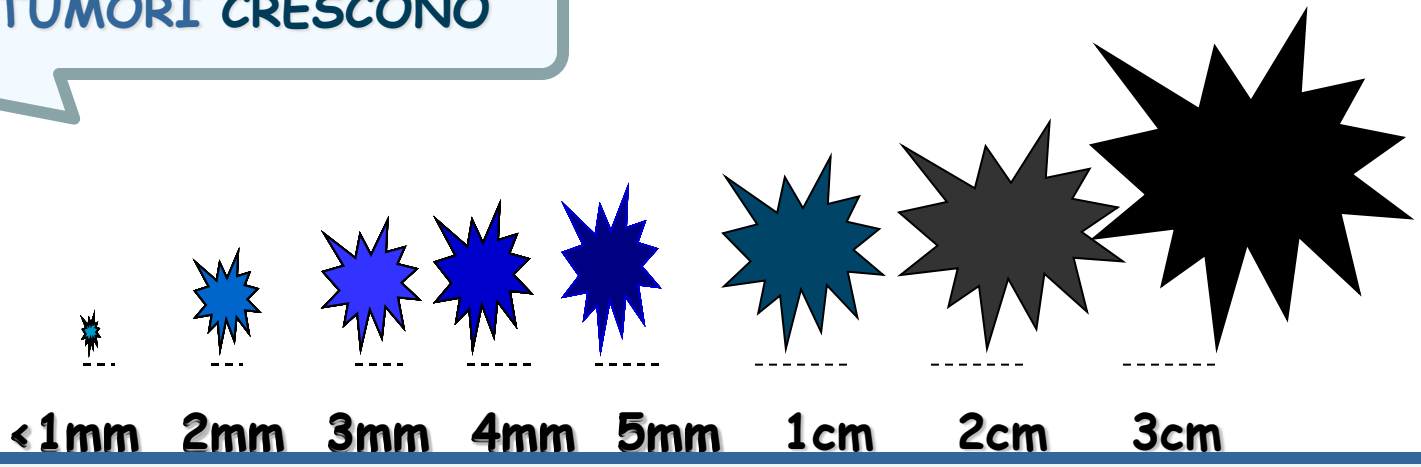
PICCOLI TUMORI CRESCONO



1. Relazione tra lesione precancerose, DCIS, Ca Microinvasivo e carcinoma invasivo ancora poco chiara

2. NON solo progressione LINEARE

T2N2
ER 100%
Pgr 100%
Ki67 7%
HER2 negativo

T2N1
ER 40%
Pgr 20%
Ki67 37%
HER2 +++

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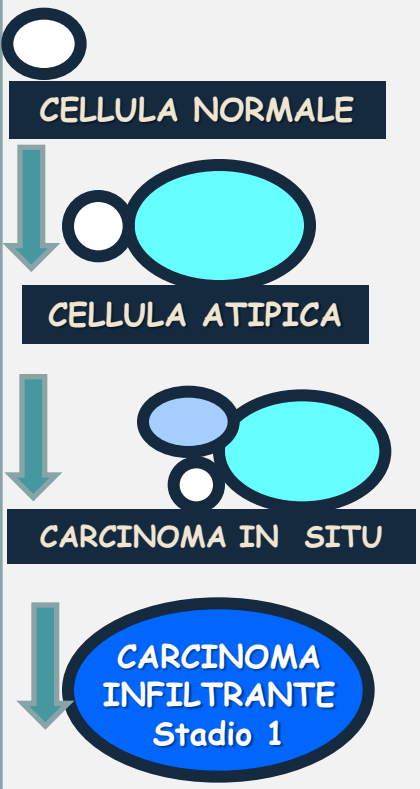
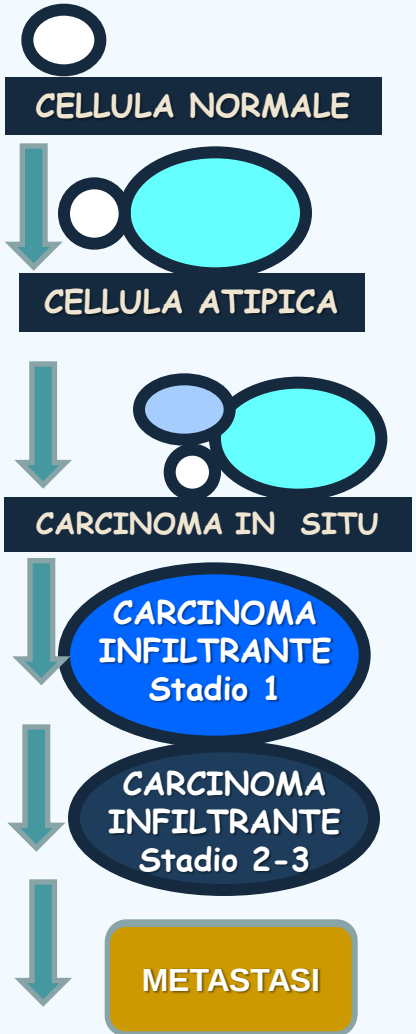
PICCOLI TUMORI CRESCONO

NUOVO PARADIGMA: VARIABILE progressione

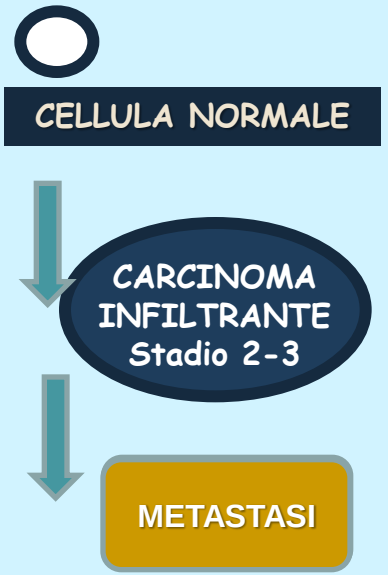
INDOLENTE vs REGRESSIONE



LENTA PROGRESSIONE



RAPIDA PROGRESSIONE



PICCOLI TUMORI CRESCONO

NUOVO PARADIGMA: VARIABILE progressione

INDOLENTE vs REGRESSIONE

DIAGNOSI PRECOCE NO EFFETTO MORTALITA'

CELLULA ATIPICA

CARCINOMA IN SITU

CARCINOMA INFILTRANTE Stadio 1

LENTA PROGRESSIONE

DIAGNOSI PRECOCE PUO' AVERE EFFETTO MORTALITA'

CELLULA ATIPICA

CARCINOMA IN SITU

CARCINOMA INFILTRANTE Stadio 1

CARCINOMA INFILTRANTE Stadio 2-3

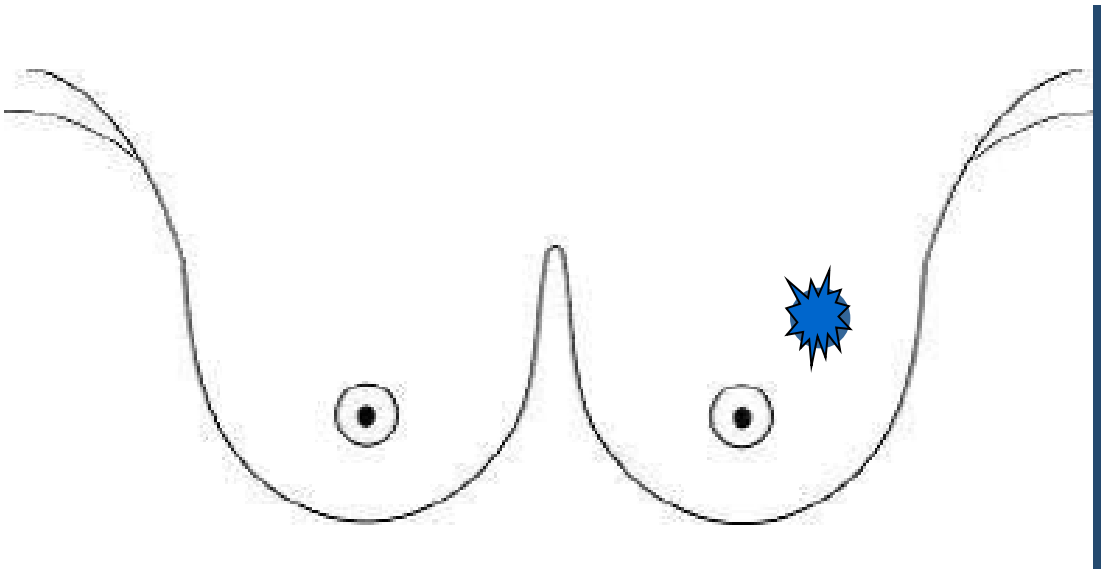
METASTASI

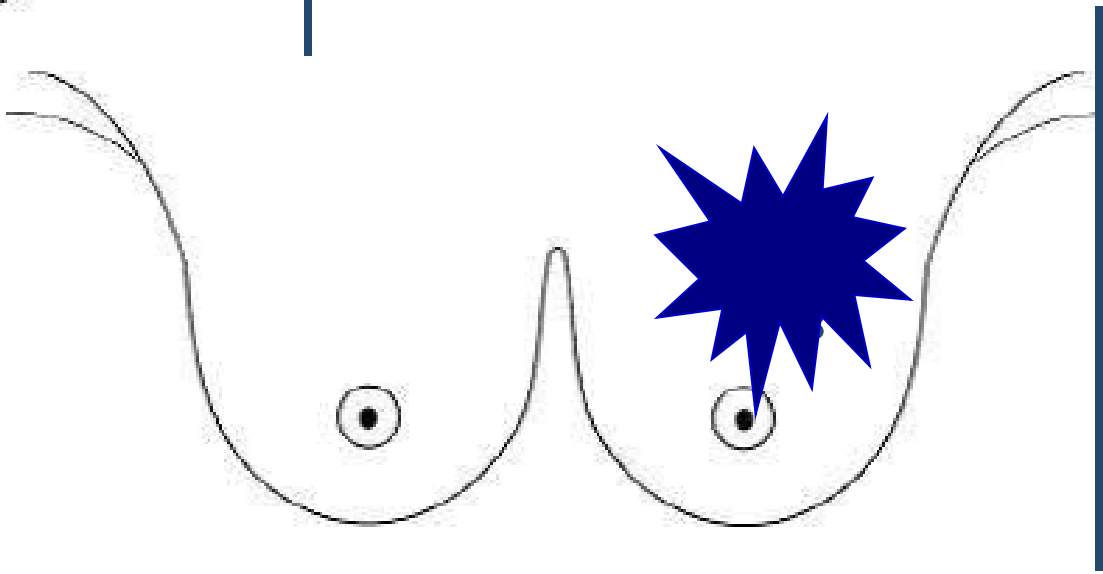
RAPIDA PROGRESSIONE

DIAGNOSI PRECOCE + TERAPIA SISTEMICA PUO' AVERE EFFETTO MORTALITA'

METASTASI

PICCOLI TUMORI CRESCONO





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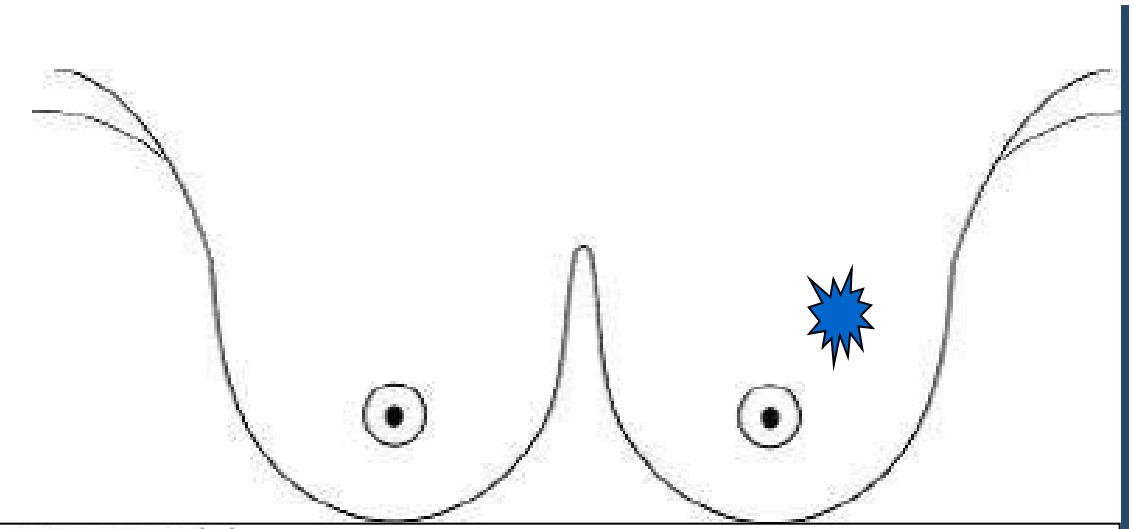

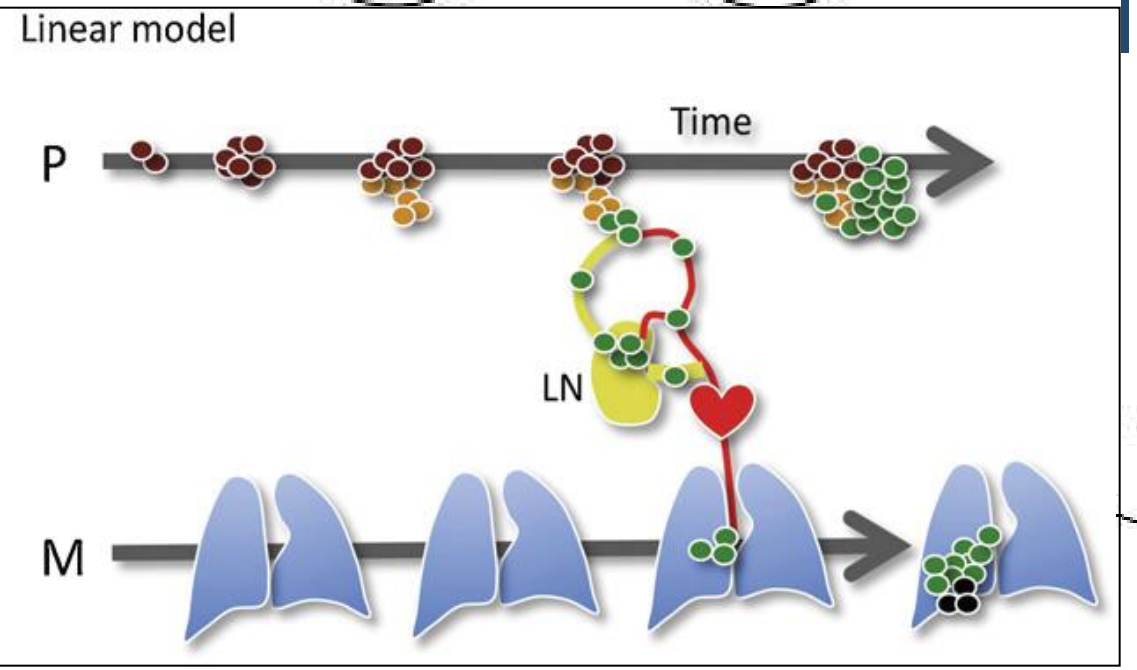

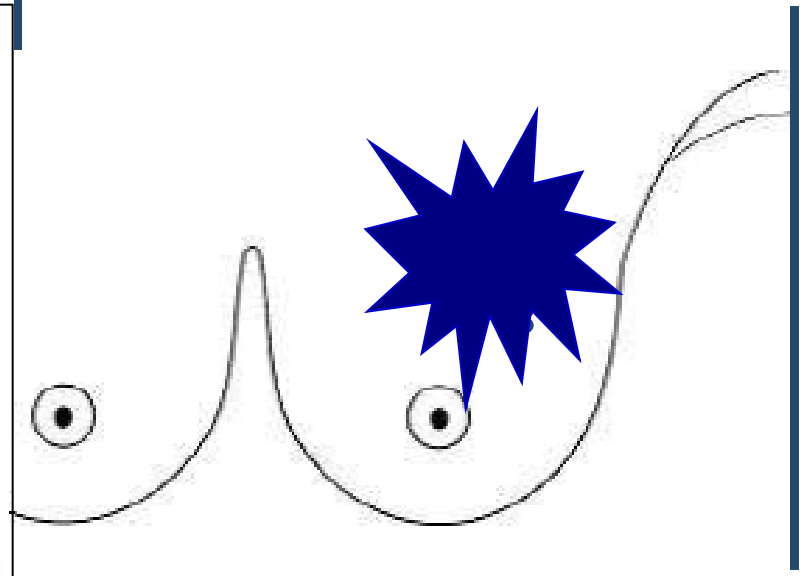

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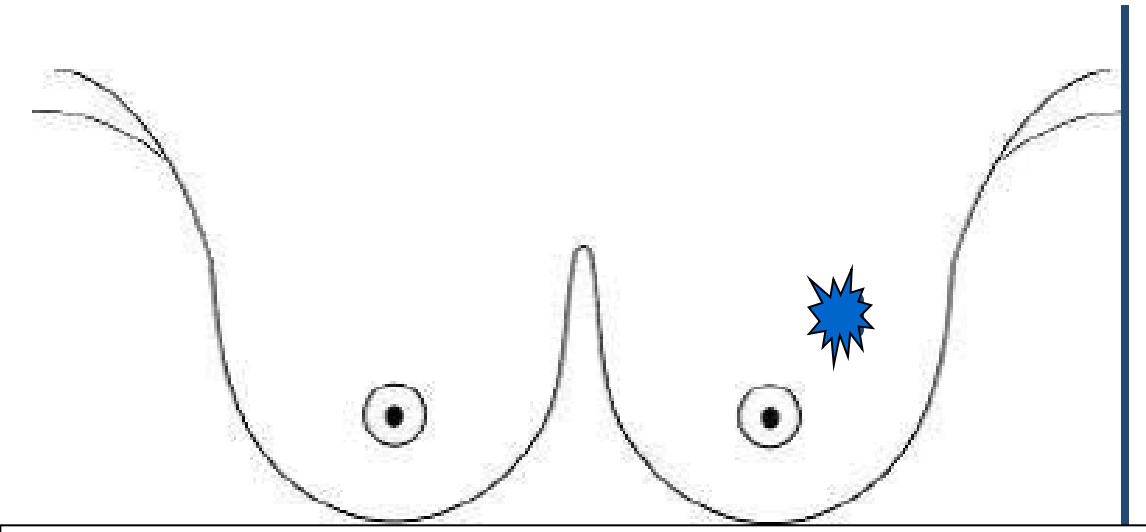

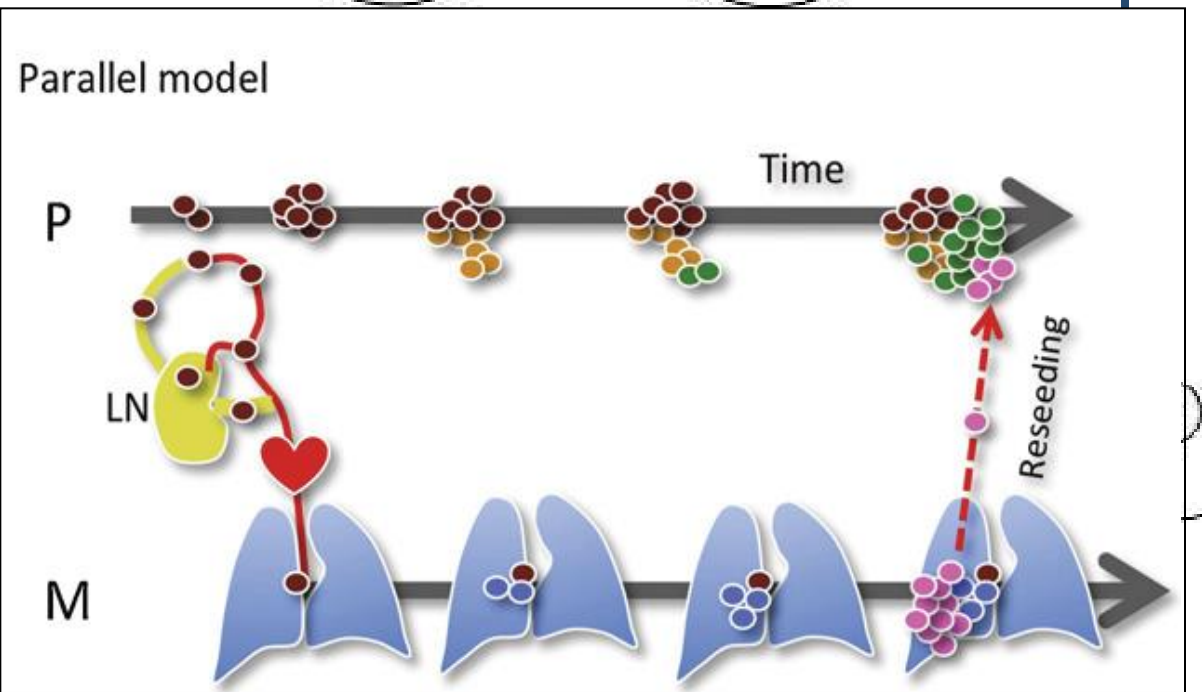

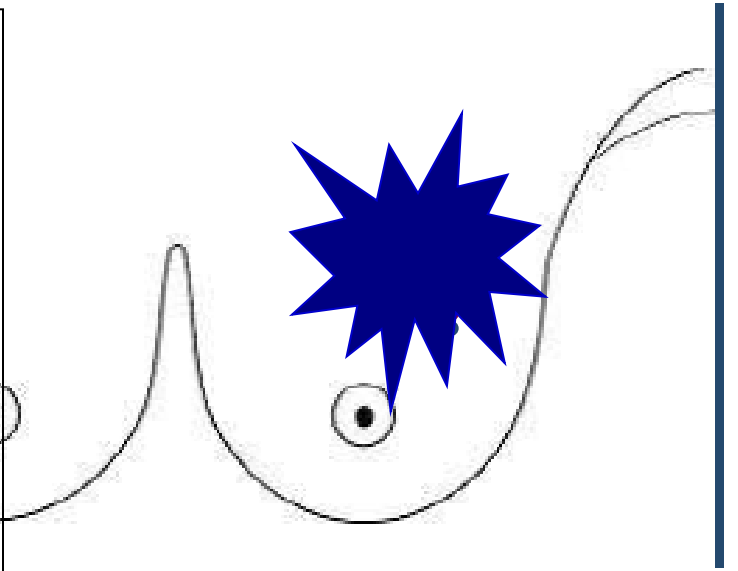

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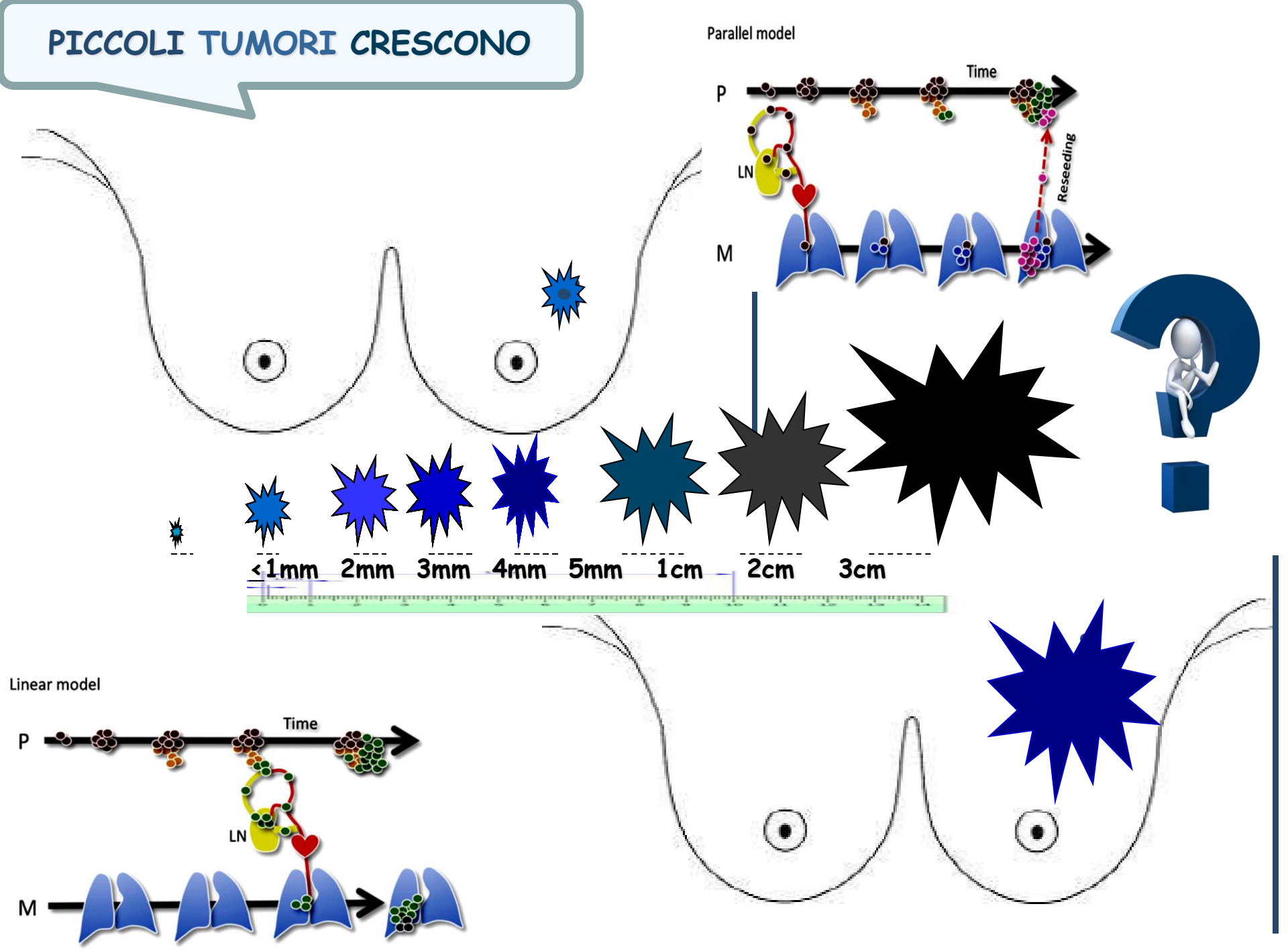

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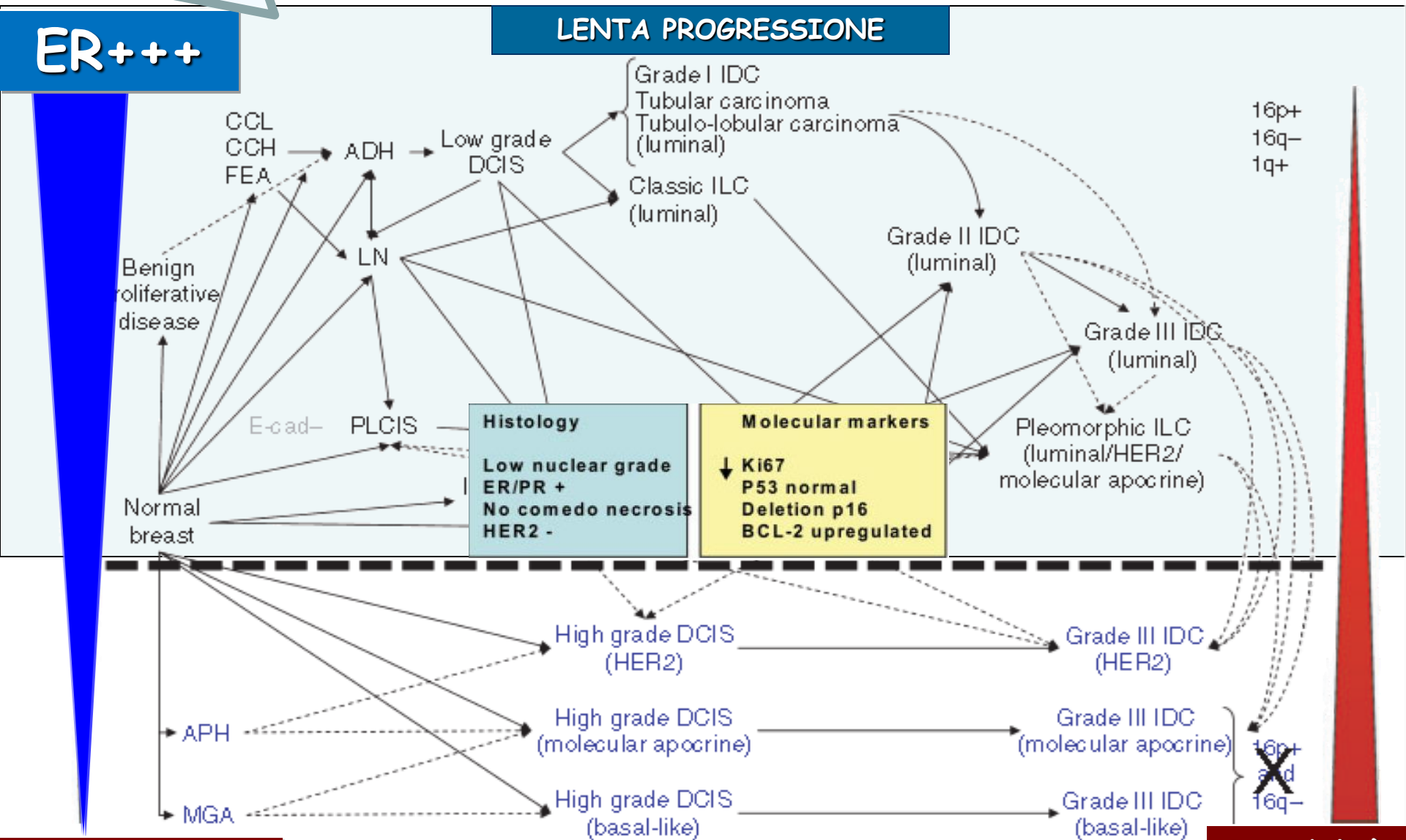

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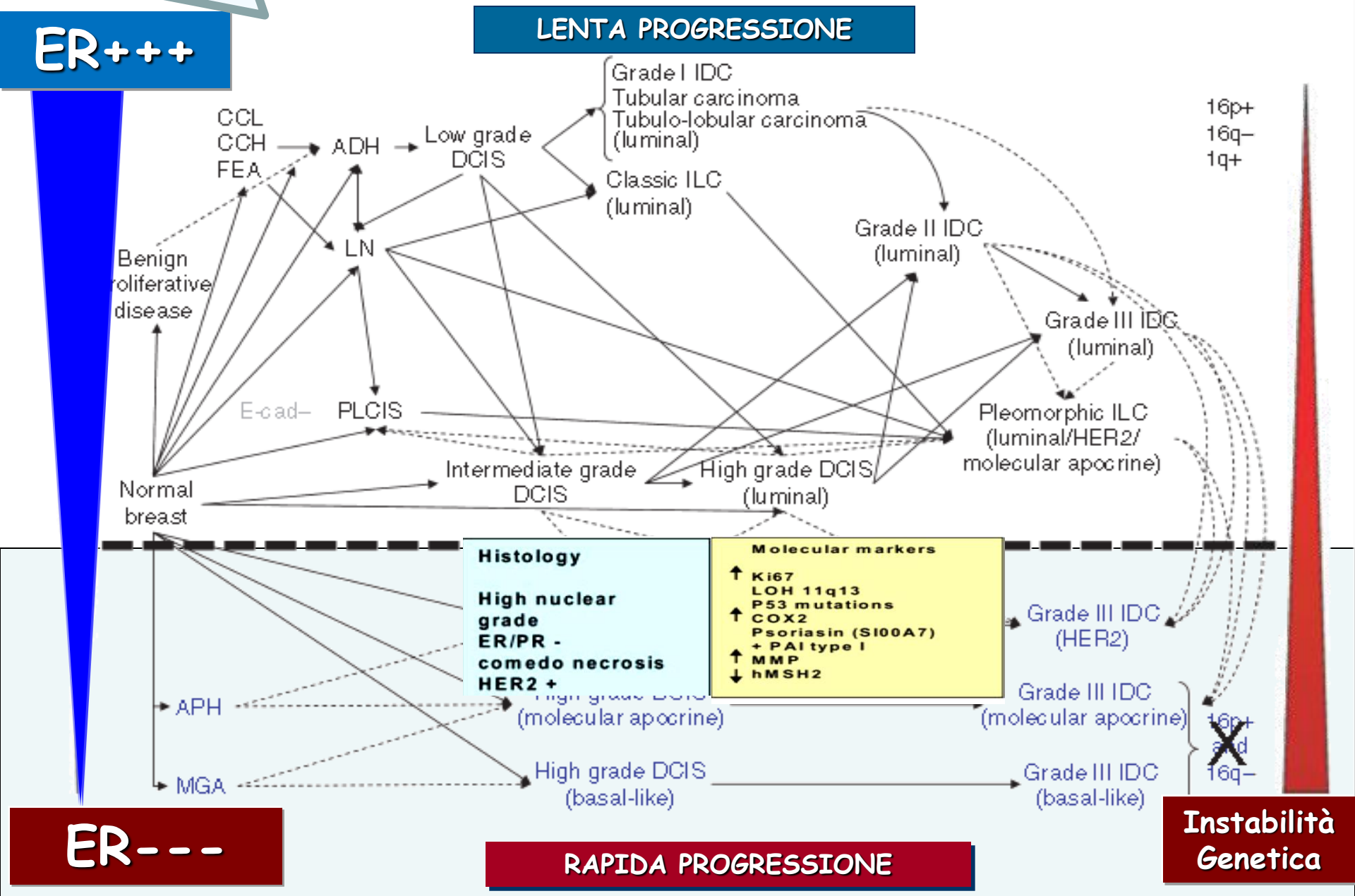

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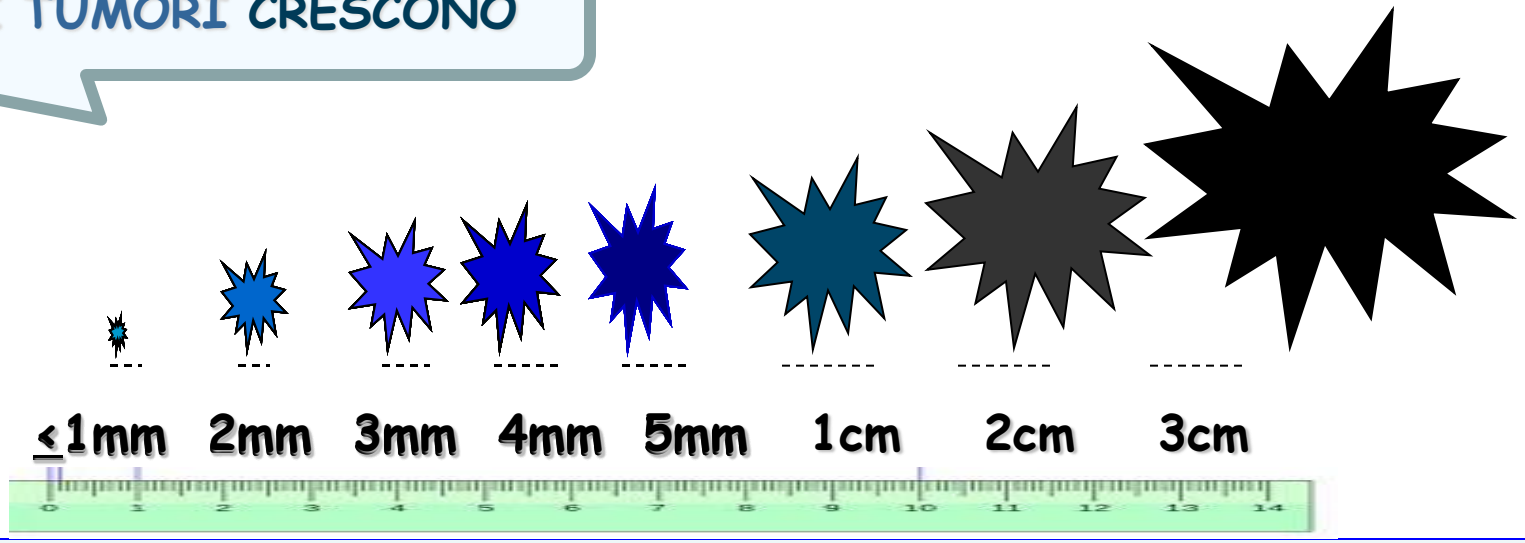
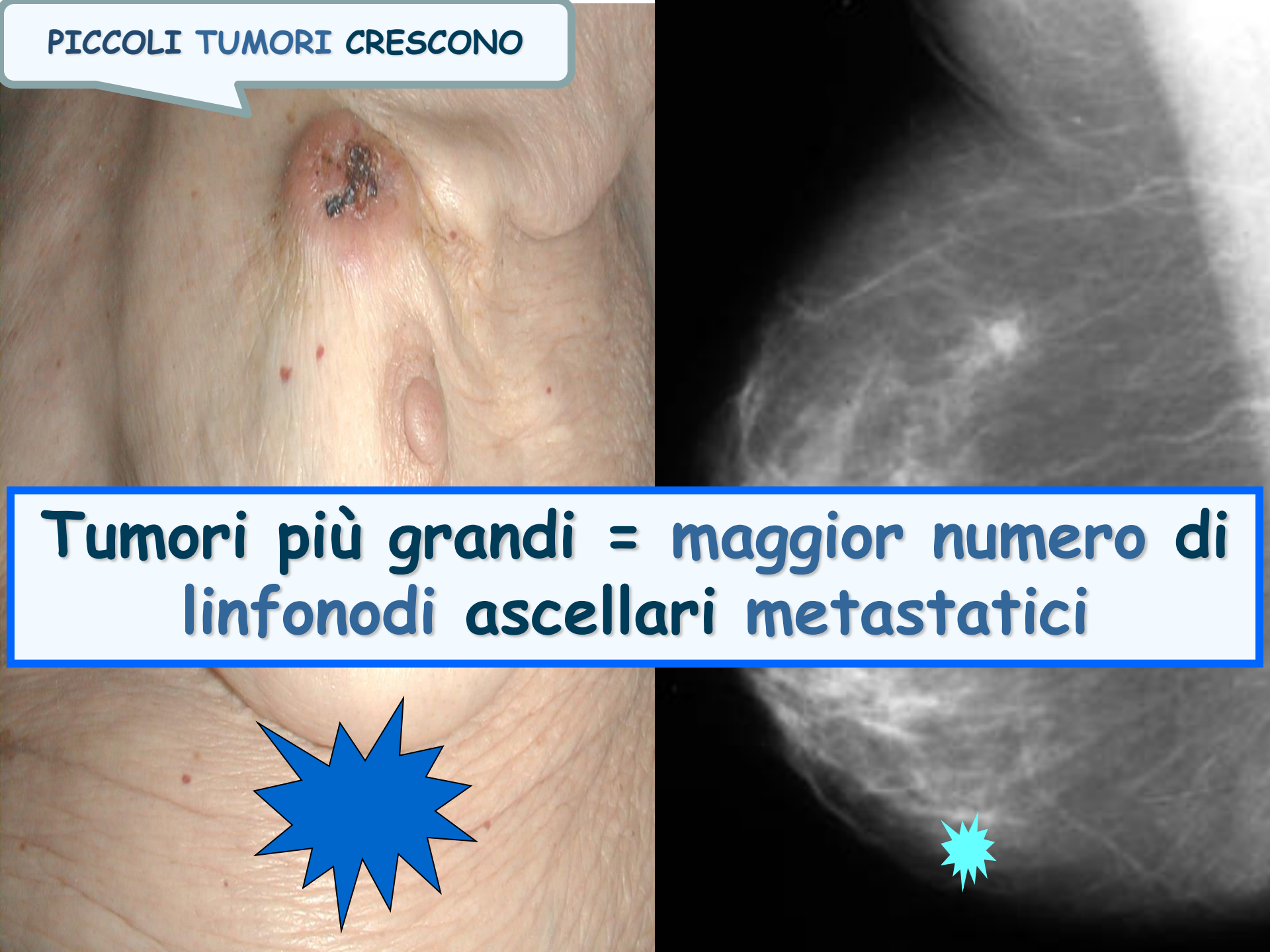


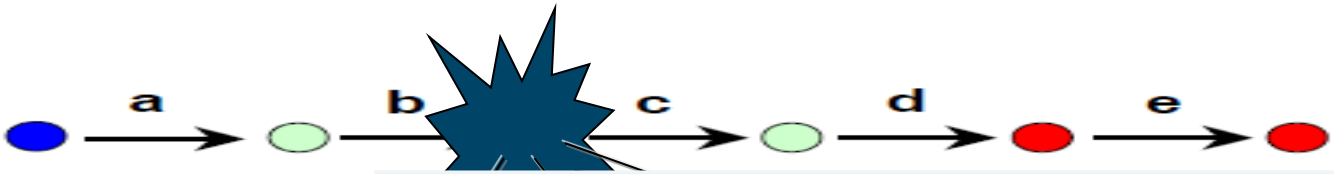
...quali certezze?..

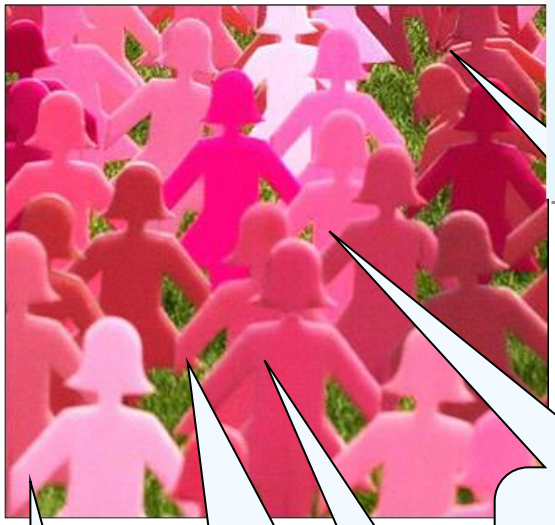
PICCOLI TUMORI CRESCONO



Tumori più grandi = maggior numero di linfonodi ascellari metastatici

PICCOLI TUMORI CRESCONO





... REGOLA !

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Pgr 100%
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HER2 negativo

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Ki67 77%
HER2 negativo

10-15%

PICCOLI TUMORI CRESCONO

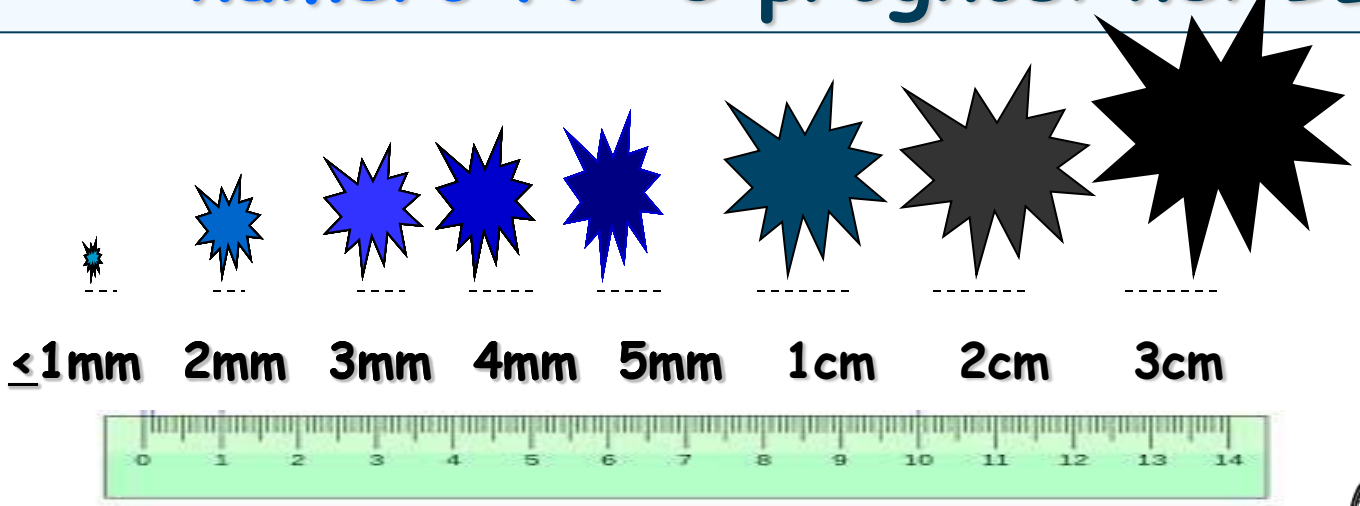
- T non BLBC/TN (aggiustati per G) correlazione fortemente positiva tra aumento delle dimensioni e aumento numero N+ (P per trend < .001)
- OVS peggiore con aumento dimensioni tumore

- T BLBC/TN NO ASSOCIAZIONI per N+ e OVS (p per trend = 0.58)

Foulkes WD Breast Cancer Res Treat 2009

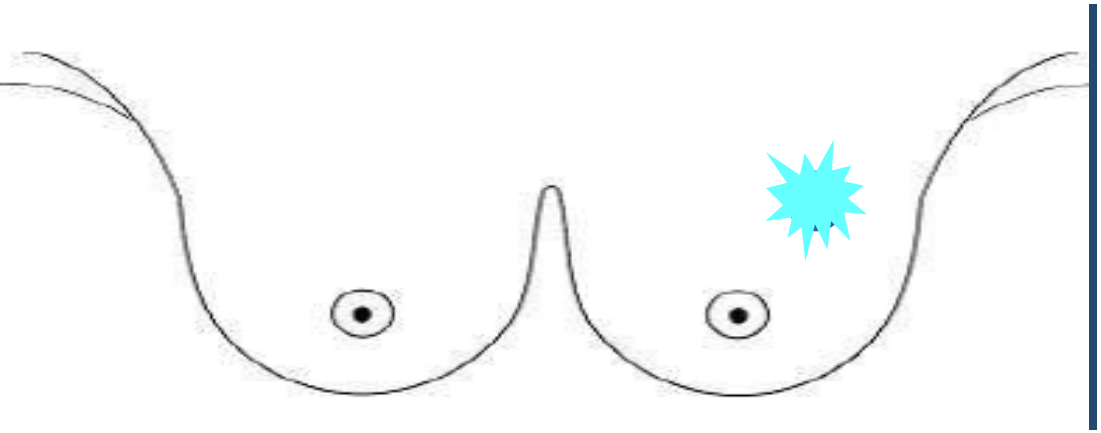
PICCOLI TUMORI CRESCONO

DIMENSIONI tumore non è indicatore di numero N+ e prognosi nei BLBC/TN…..



PICCOLI TUMORI CRESCONO

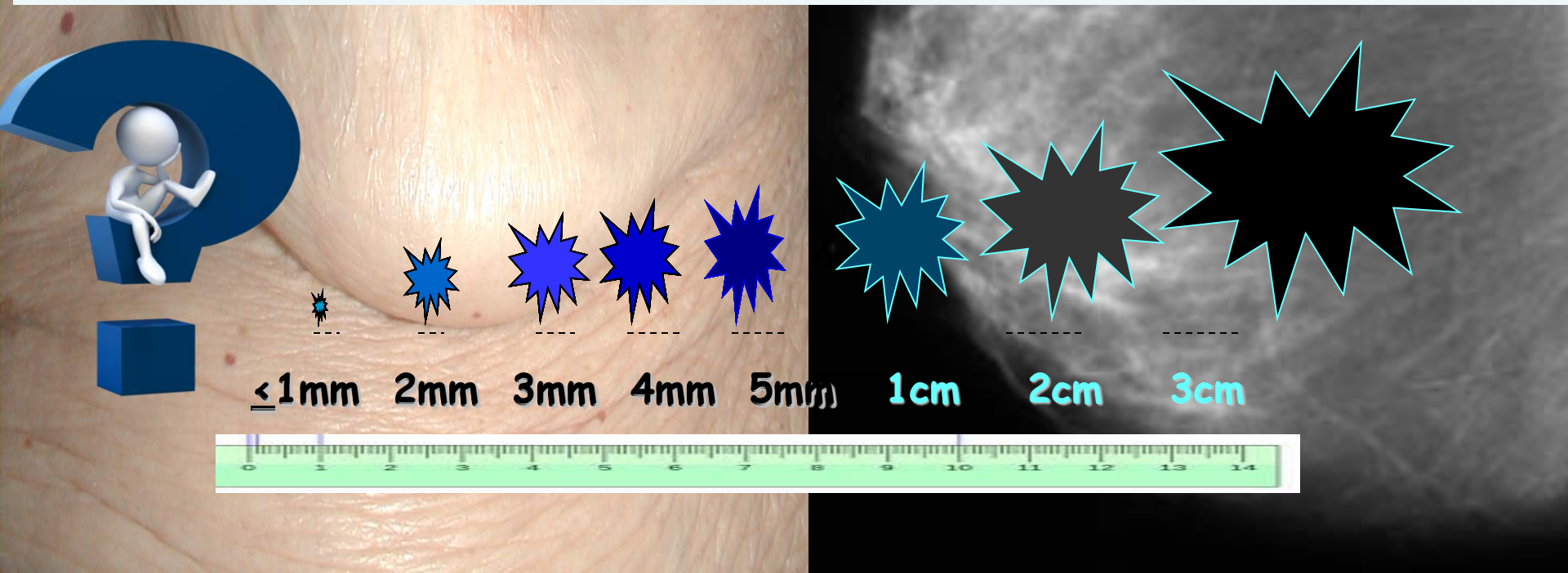
…perché.. sono intrinsecamente aggressivi e rischiano di metastatizzare precocemente.



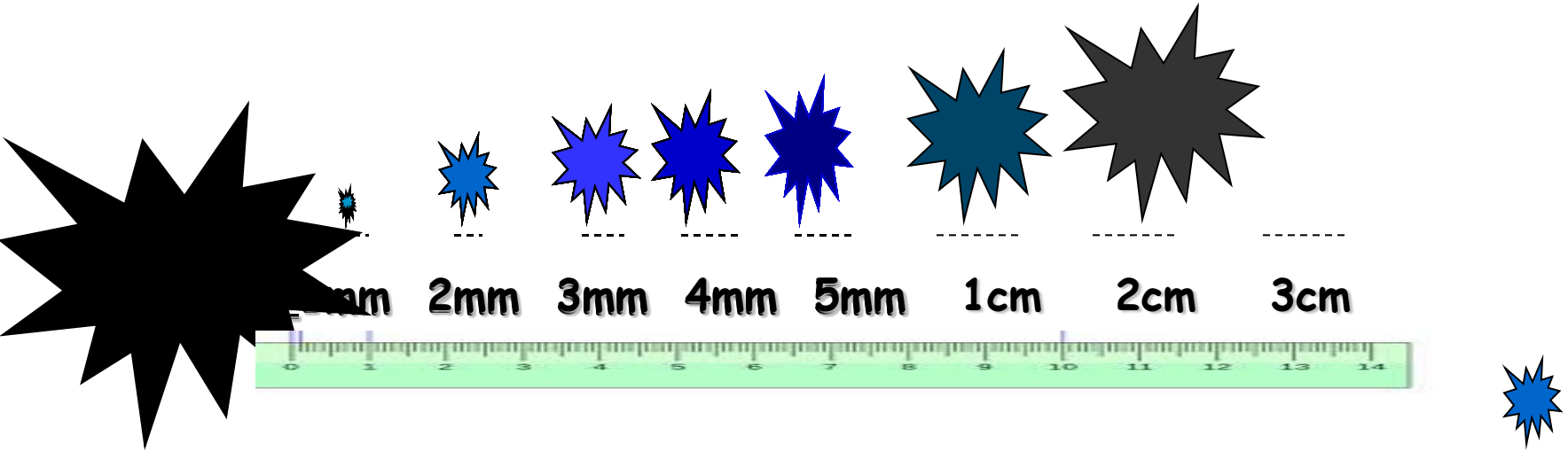
Foulkes WD1 Nat Rev Clin Oncol. 2010

PICCOLI TUMORI CRESCONO

IL PARADOSSO DELLA BIOLOGIA



PICCOLI TUMORI CRESCONO



LENTA PROGRESSIONE

G1

ER+PgR+

Ki-67 basso

HER2 neg

RAPIDA PROGRESSIONE

G3

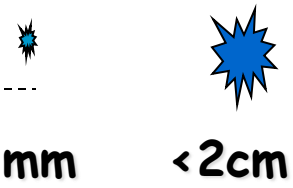
ER+/- PgR+/-

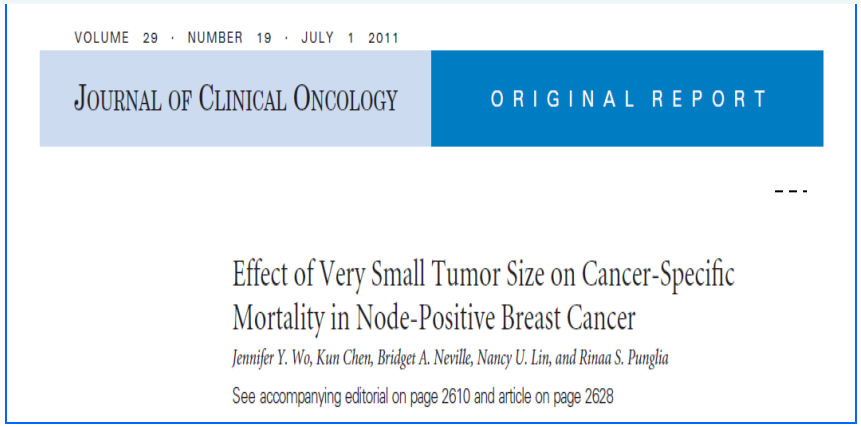
Ki-67 alto

HER2 pos+++

PICCOLI TUMORI CRESCONO

IL PARADOSSO DELLA BIOLOGIA





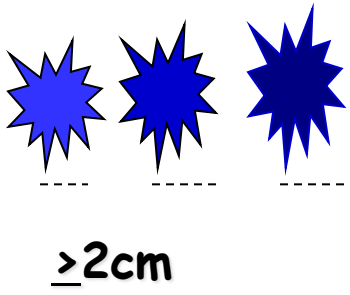
VOLUME 29 · NUMBER 19 · JULY 1 2011

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

See accompanying editorial on page 2610 and article on page 2628



→Carcinoma INVASIVO pT1N2

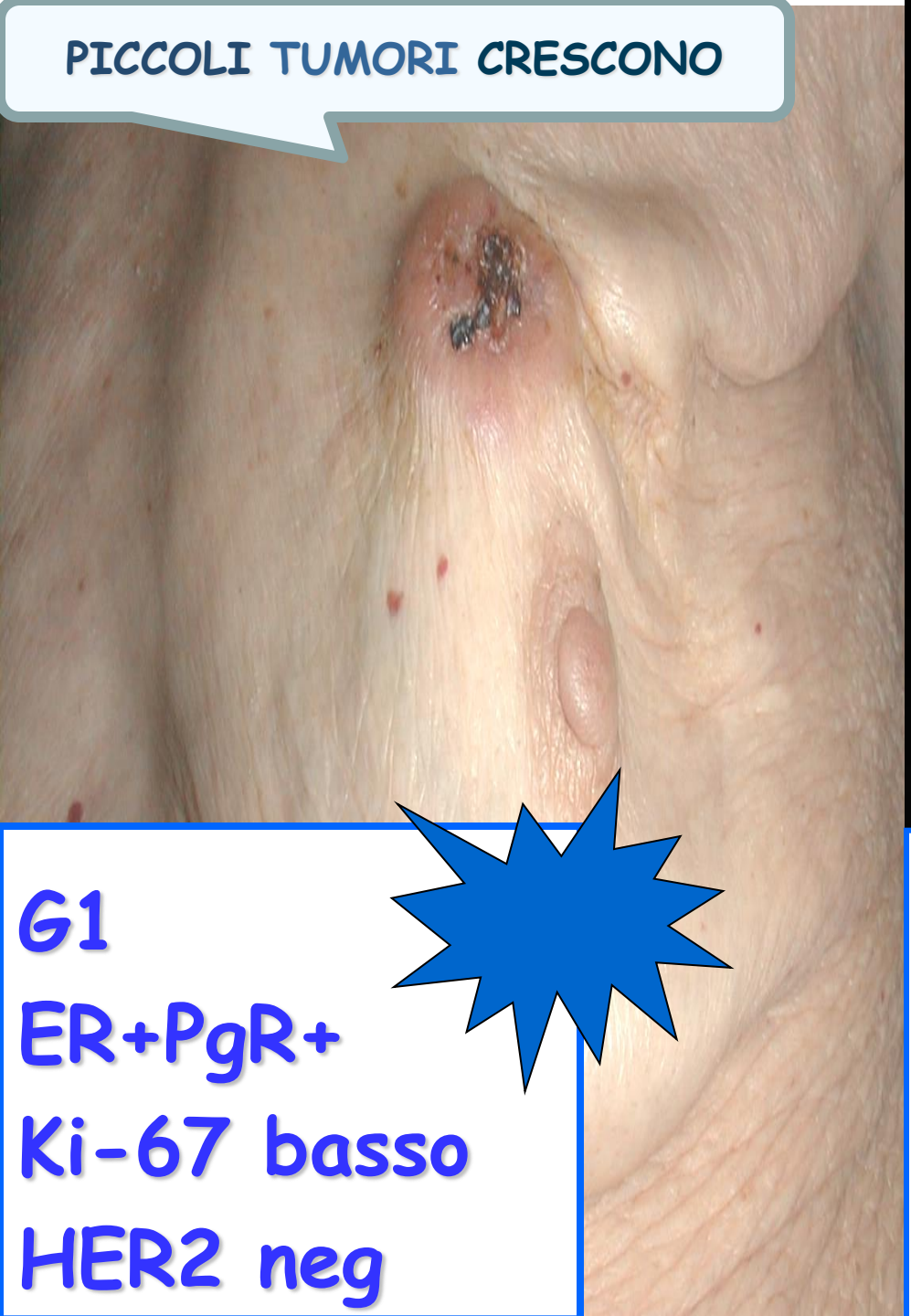
→Carcinoma INVASIVO pT2N2

pT1N2 (4N+) maggiore probabilità "Breast Cancer Specific Mortality" rispetto ai pT2N2 (4N+)

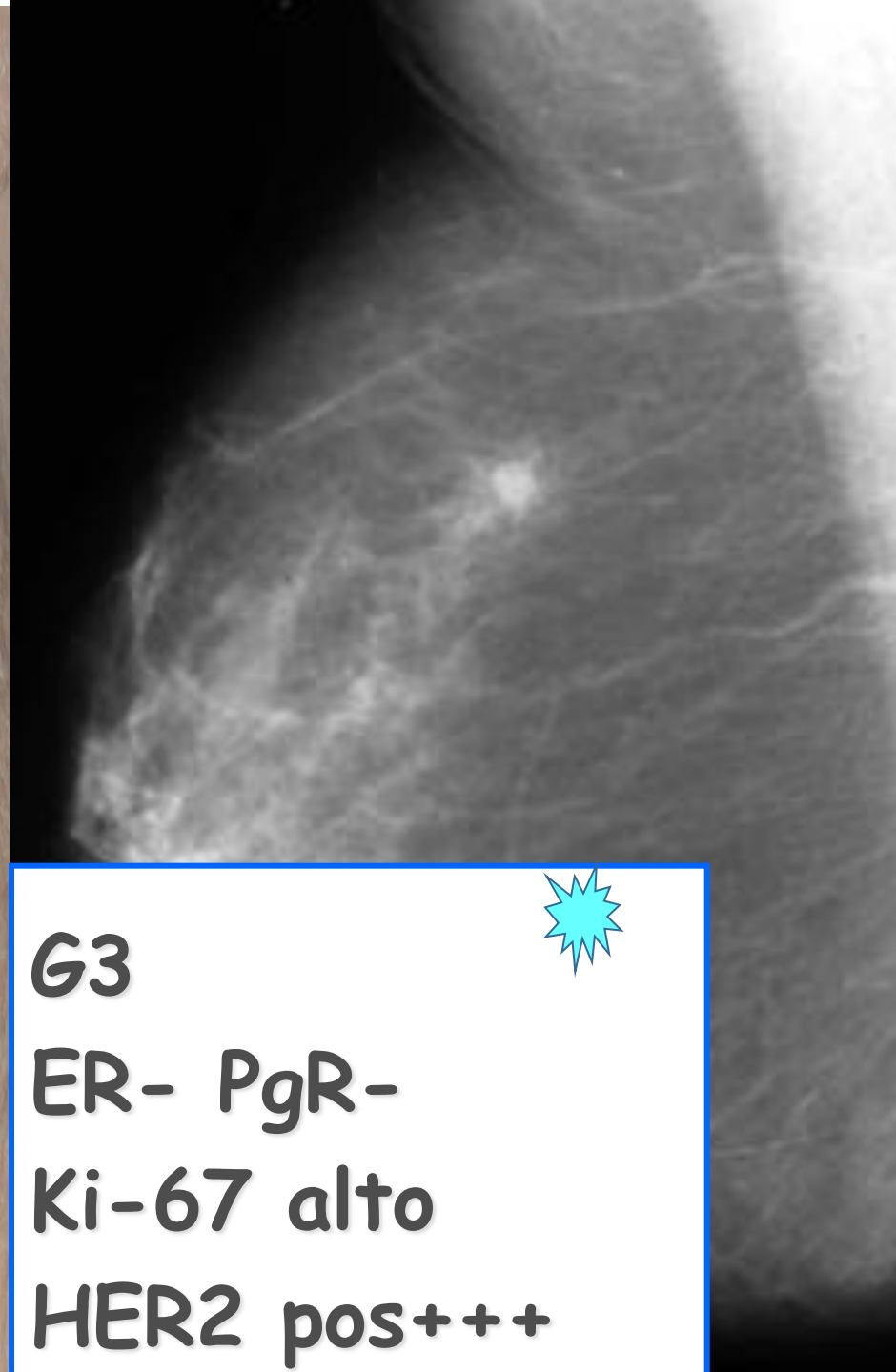
(*P* .001)

.. In questo stadio piccole dimensioni del tumore surrogato per malattia biologicamente più aggressiva ….

PICCOLI TUMORI CRESCONO

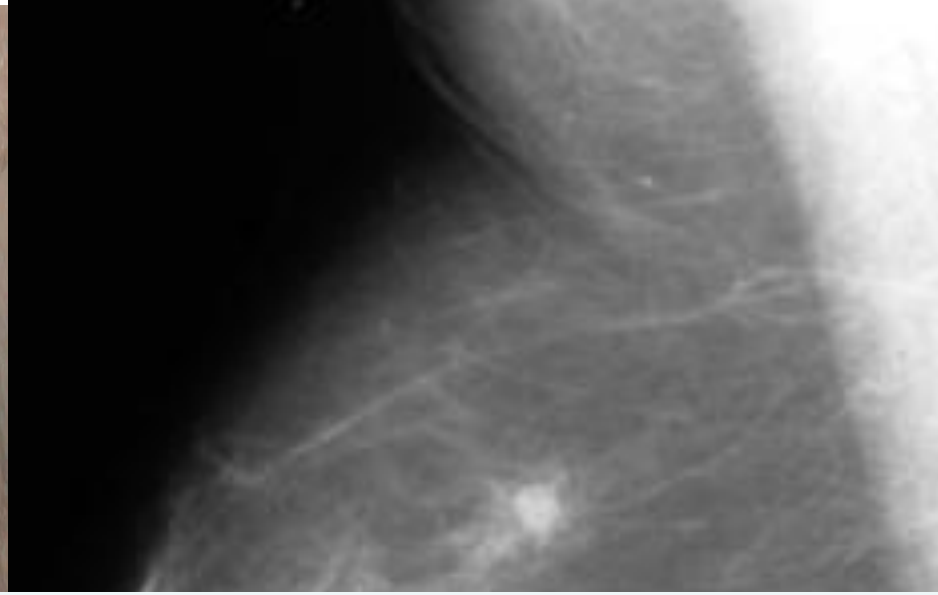


G1
ER+PgR+
Ki-67 basso
HER2 neg



G3
ER- PgR-
Ki-67 alto
HER2 pos+++

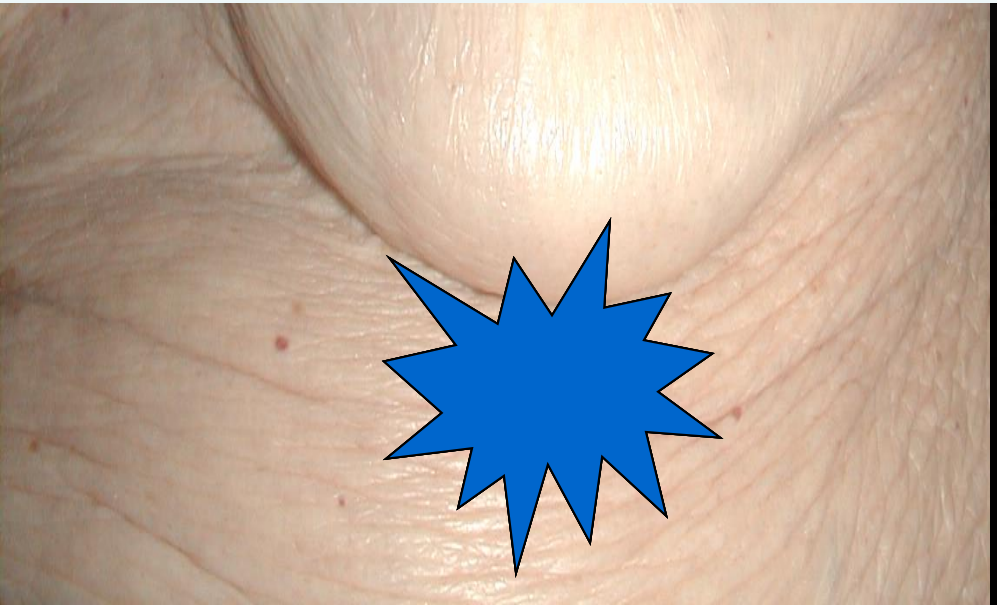
PICCOLI TUMORI CRESCONO

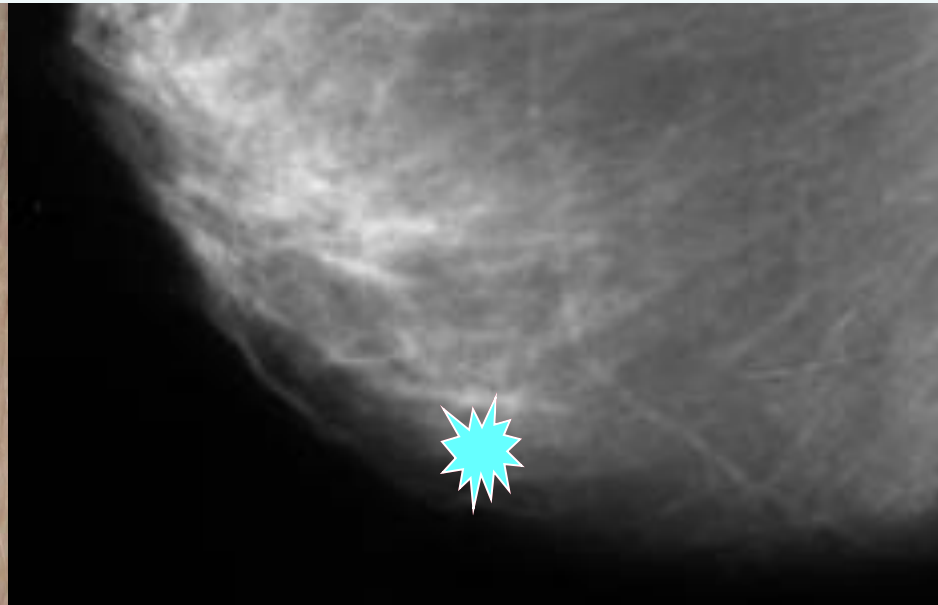


IL PARADOSSO DELLA BIOLOGIA

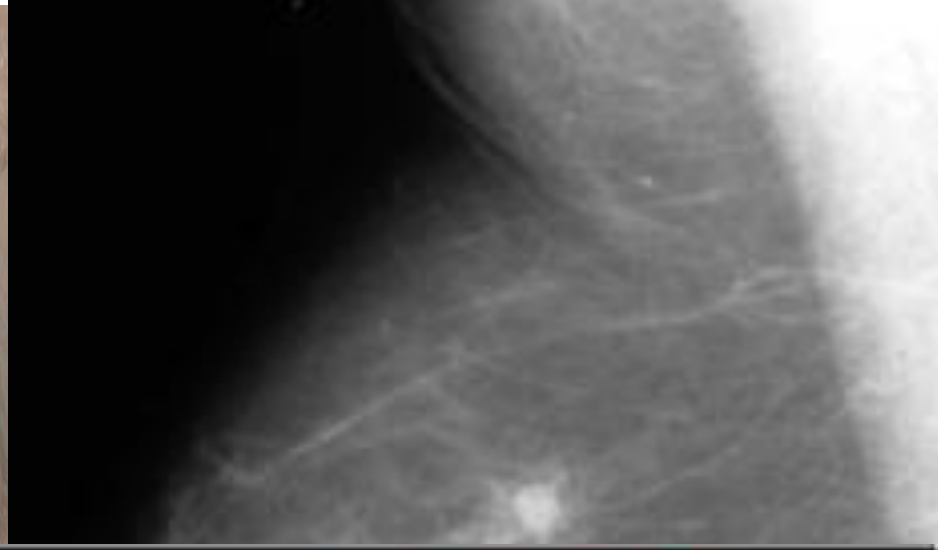
GRANDE BUONO

PICCOLO CATTIVO



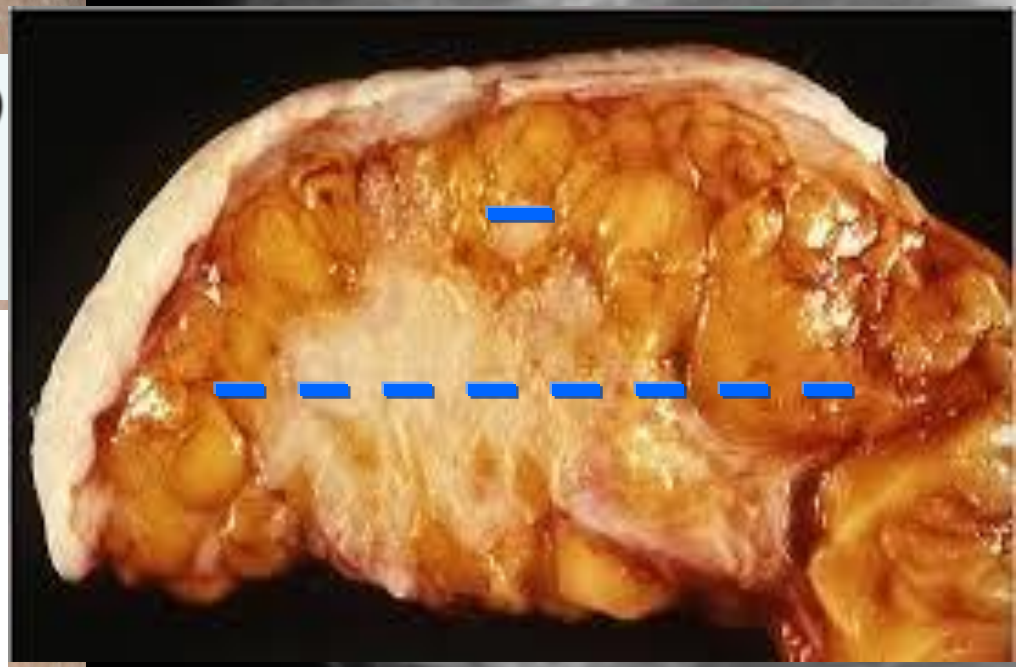


PICCOLI TUMORI CRESCONO



IL PARADOSSO

GRANDE BUONO



Dossus and Benusiglio *Breast Cancer Research* (2015) 17:37
DOI 10.1186/s13058-015-0546-7

Breast Cancer RESEARCH

REVIEW

Lobular breast cancer: incidence and genetic and non-genetic risk factors

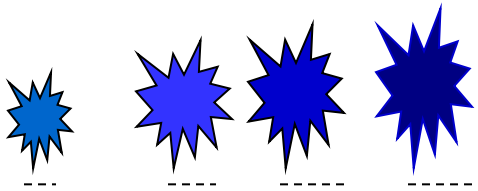
Laure Dossus[1,2] and Patrick R Benusiglio[3,4*]

PICCOLI TUMORI CRESCONO

IL PARADOSSO DELLA BIOLOGIA

→Carcinoma MICROINVASIVO pTmic

≤1mm



2mm 3mm 4mm 5mm

→Carcinoma INVASIVO pT1a

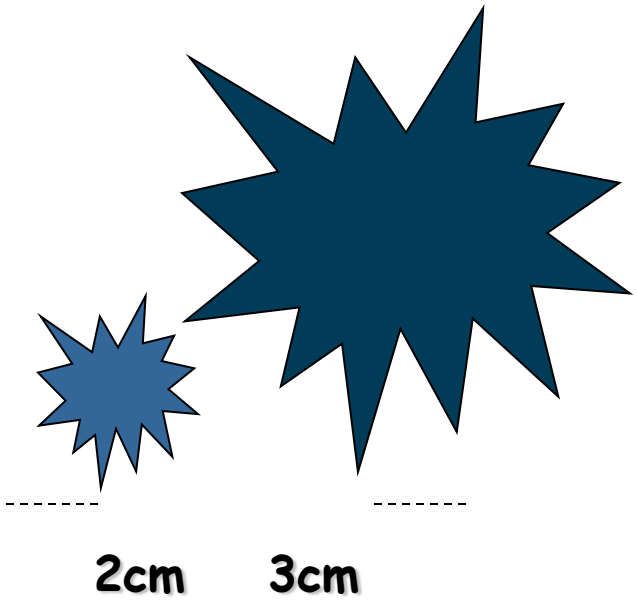
RO neg e HER2+++ più frequenti nei pT1mic

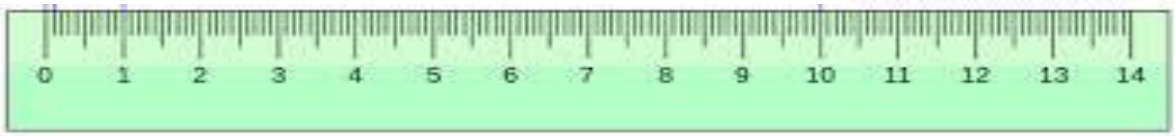
RO pos e HER2--- più frequenti nei pT1a

Mori M et al 2013 ; Yang P el al 2003

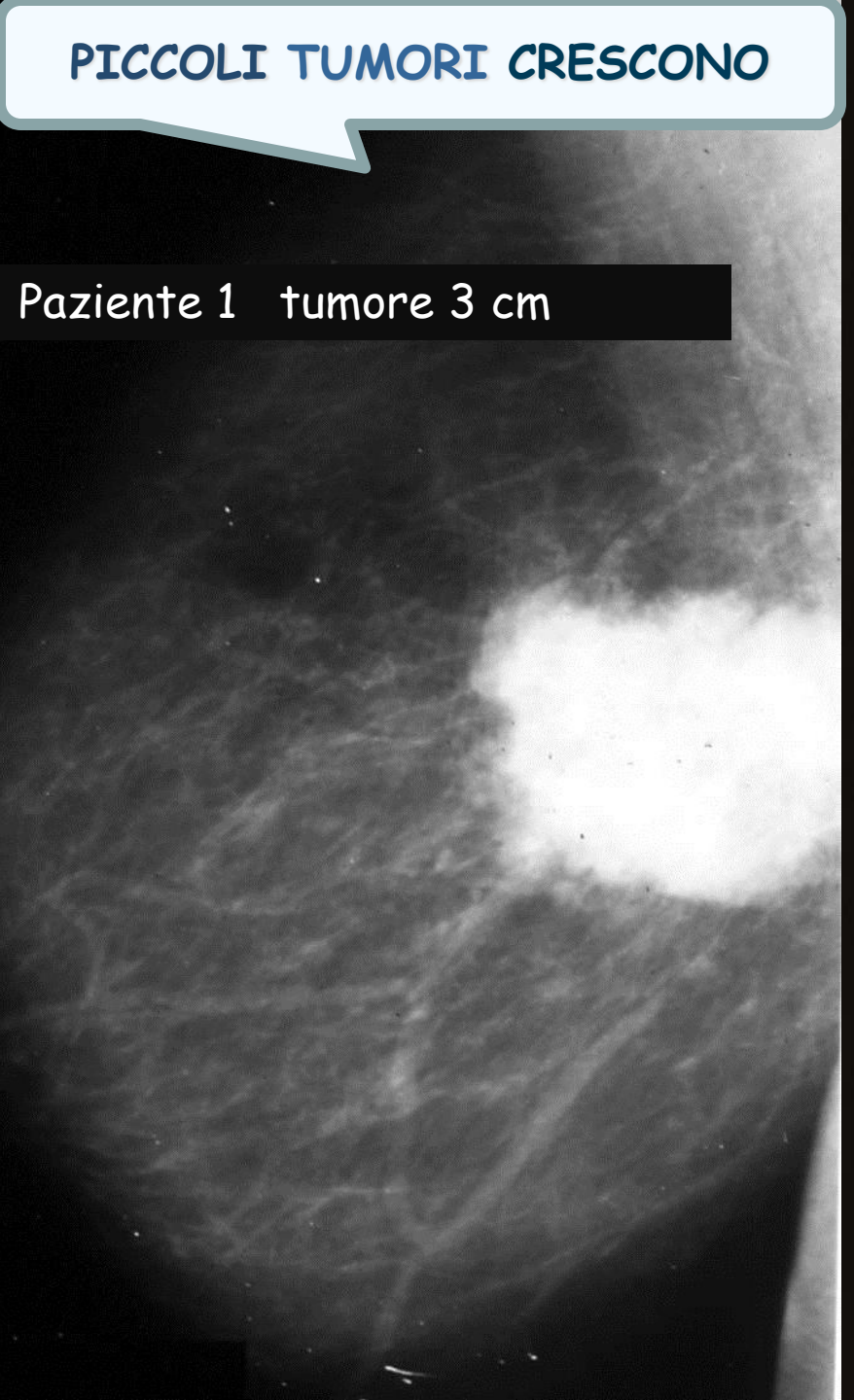
PICCOLI TUMORI CRESCONO

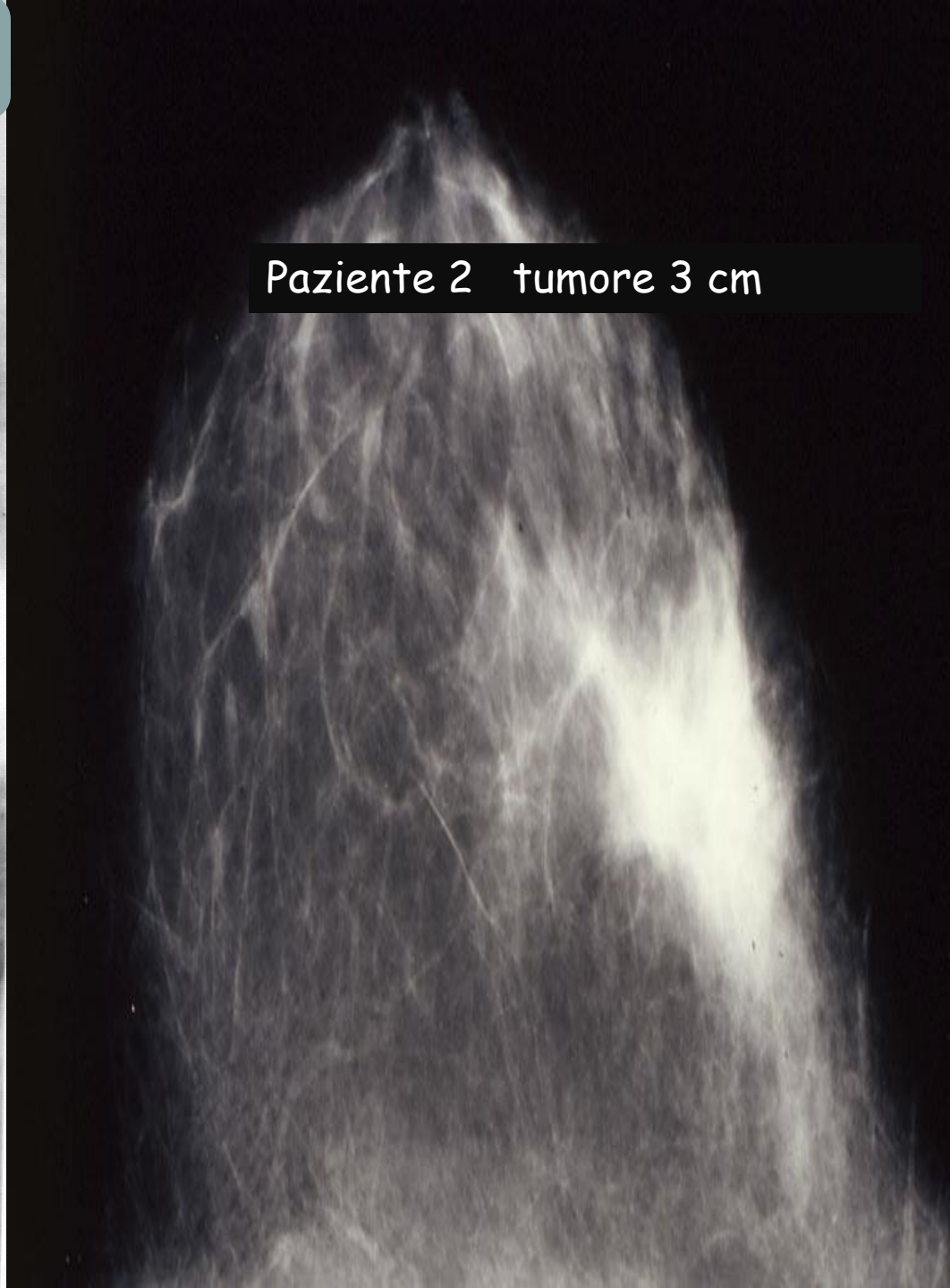
Carcinoma INVASIVO pT2-3-4





PICCOLI TUMORI CRESCONO

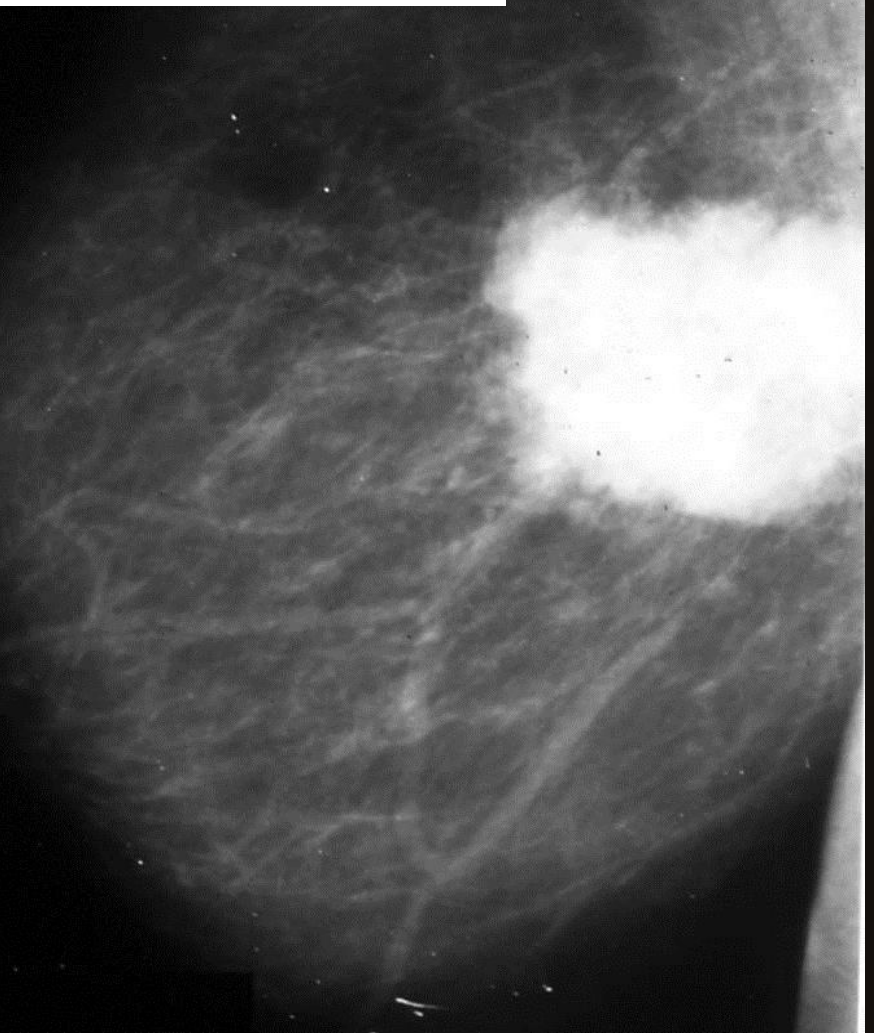




PICCOLI TUMORI CRESCONO

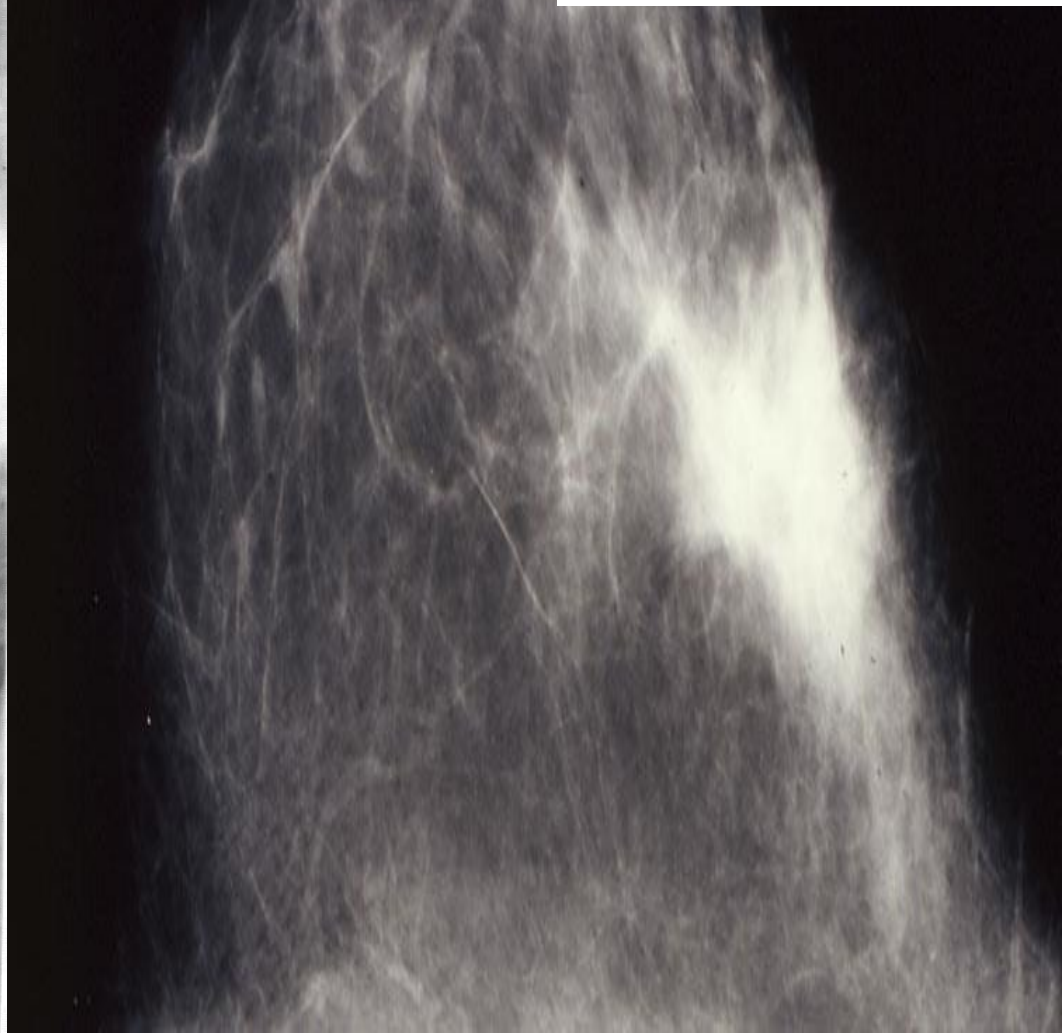
Paziente 1 tumore 3 cm

Pre CHEMIO



Paziente 2 tumore 3 cm

Pre CHEMIO



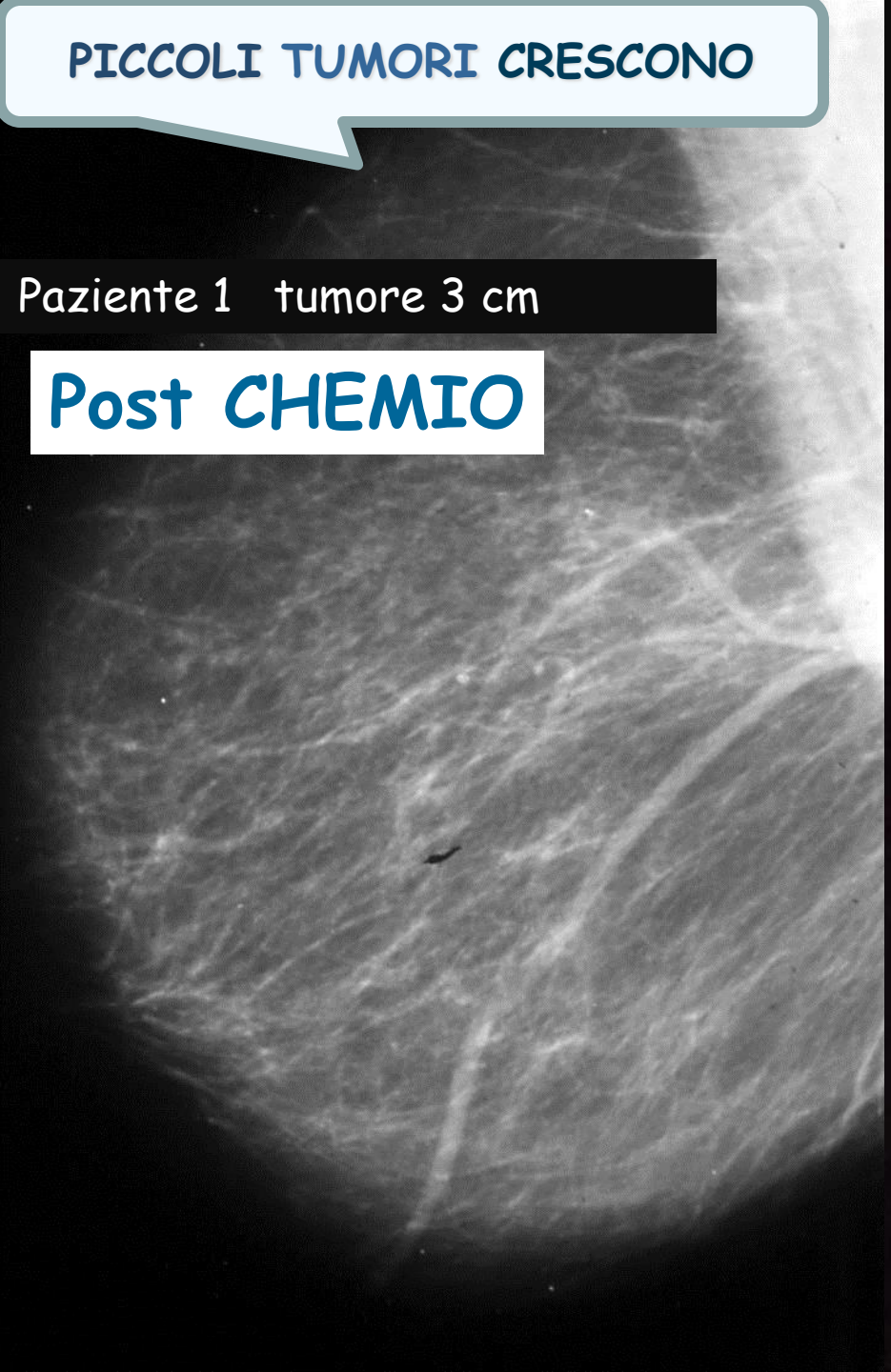
PICCOLI TUMORI CRESCONO

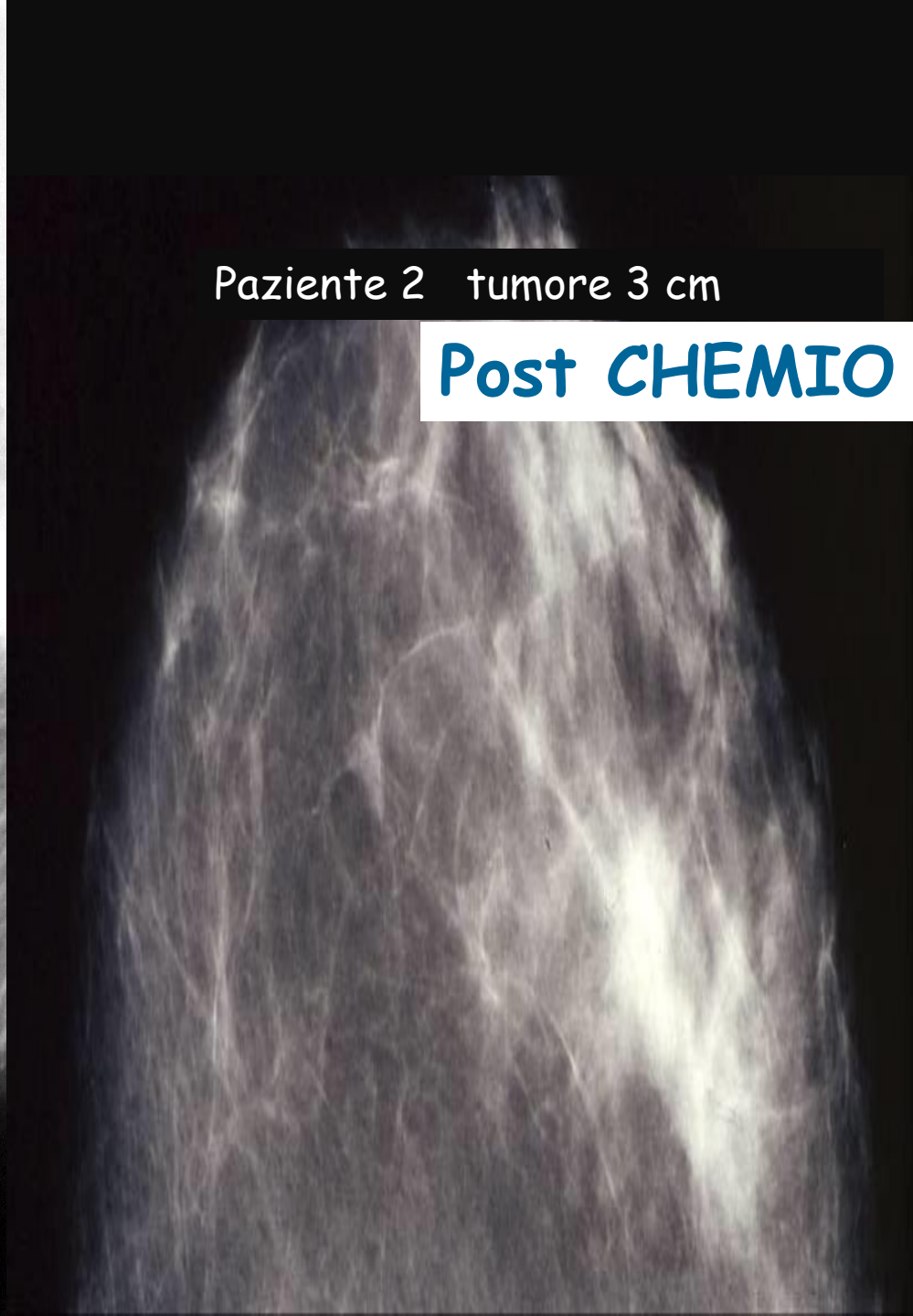
- Terapia neoadiuvante
- Standard di cura per i tumori localmente avanzati
- Pz stadio I-IIIA:

- Aumenta% di chirurgia conservativa
- Non influenza sopravvivenza libera da malattia o sopravvivenza globale

In grado di valutare la risposta clinica e patologica al trattamento

PICCOLI TUMORI CRESCONO





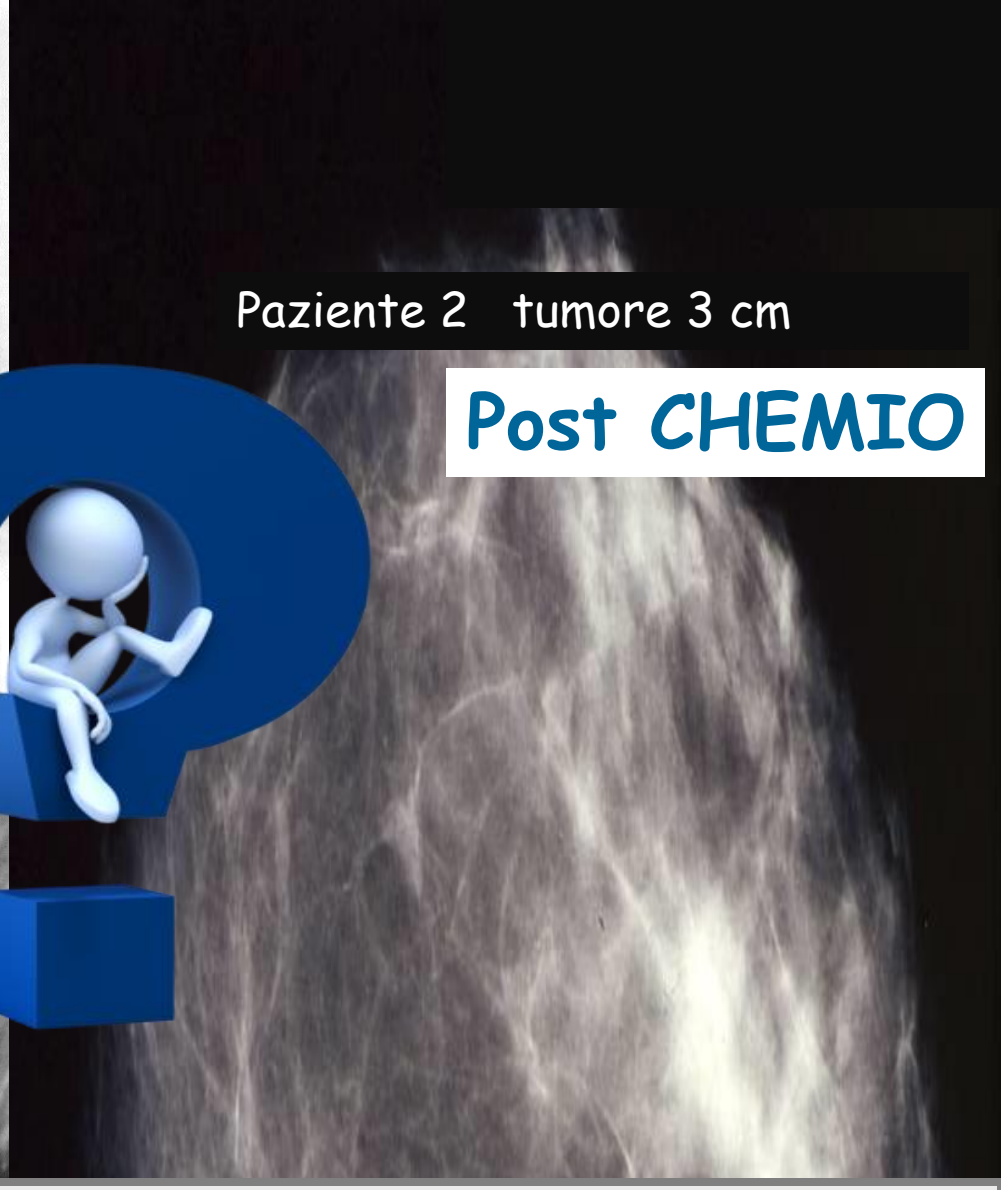
PICCOLI TUMORI CRESCONO

Paziente 1 tumore 3 cm

Post CHEMIO

Paziente 2 tumore 3 cm

Post CHEMIO



IL PROBEMA:

PATOLOGICO

BIOLOGICO

PICCOLI TUMORI CRESCONO

Efficacia terapia sistemica può essere valutata in vivo:

RISPOSTA PATOLOGICA

Informazioni relative alla risposta patologica possono essere utilizzate per modificare o cambiare la terapia

- ☺ Pazienti che ottengono una buona risposta clinica miglioramento DFS e OVS
- ☺ **Pazienti che attengono una riposta patologica completa (pCR) hanno prognosi eccellente**

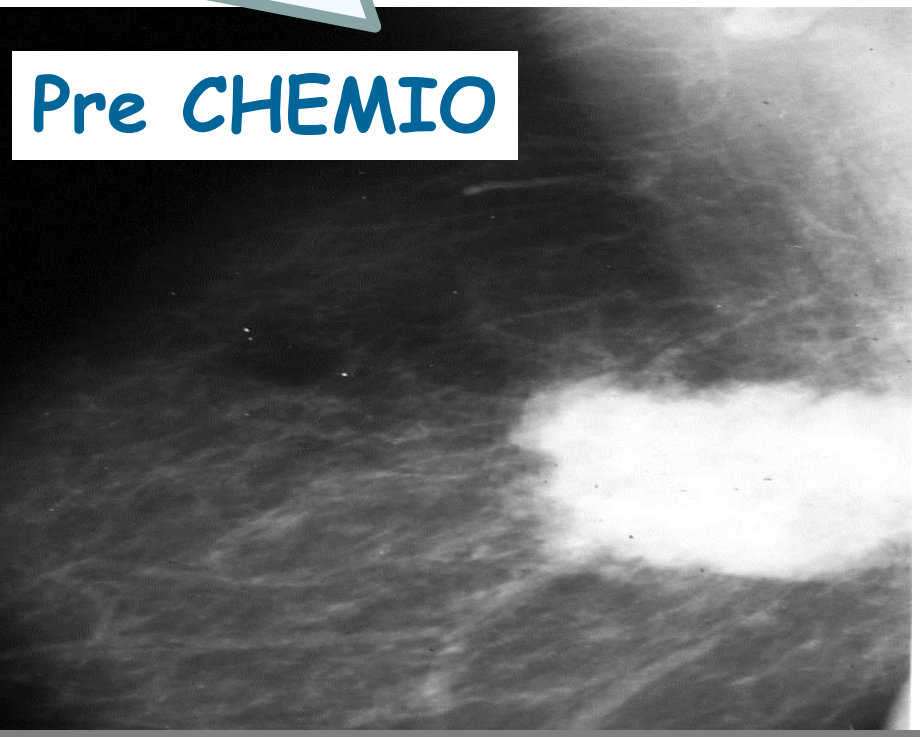
J Clin Oncol 17:460–467, 1999
Breast 12:320–327, 2003
Breast Cancer Res Treat 94:255–263, 2005
J Natl Cancer Inst 97:1137–1142, 2005
J Clin Oncol. 23:8331–8339, 2005
J Clin Oncol. 23:9304–9311, 2005
J Clin Oncol. 25:4414–4422, 2007

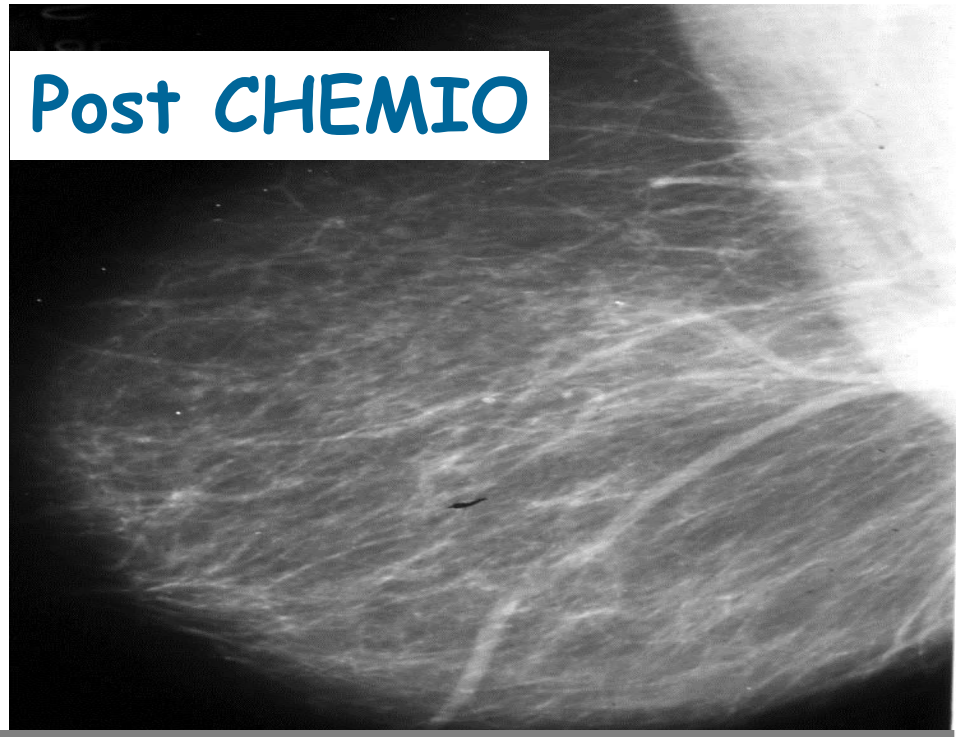
PICCOLI TUMORI CRESCONO

- DIVERSE MODALITA' DI RISPOSTA

- DIVERSA CELLULARITA' TUMORALE RESIDUA

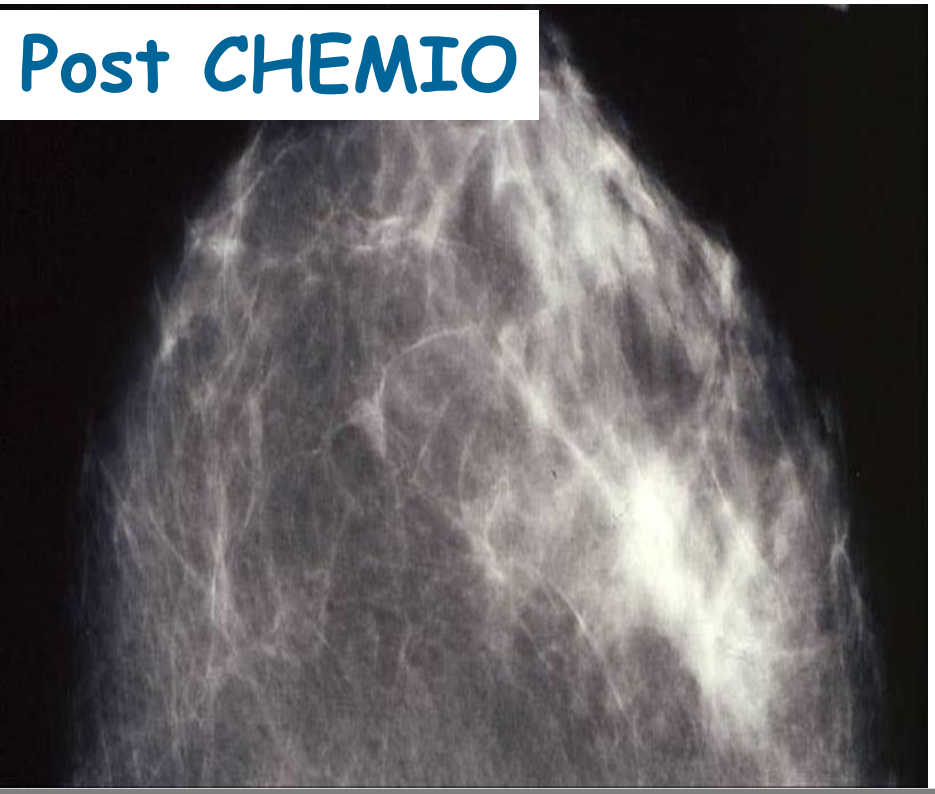
PICCOLI TUMORI CRESCONO

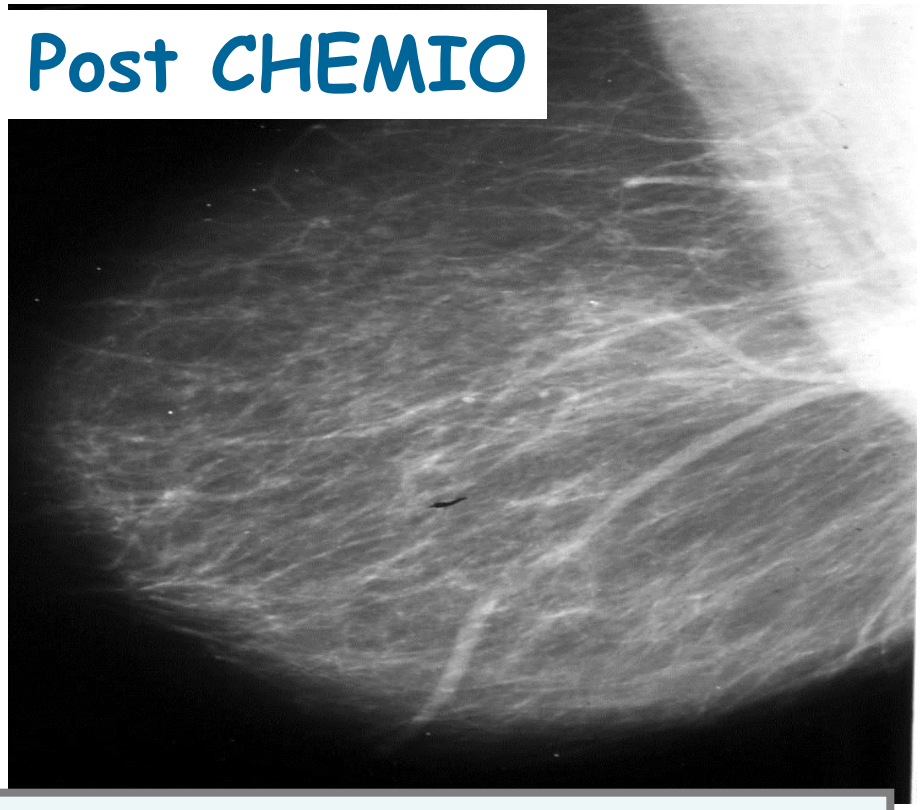




CELLULARITA' RESIDUA NON CORRELATA CON DIMENSIONI MACROSCOPICHE pre e/o post

PICCOLI TUMORI CRESCONO

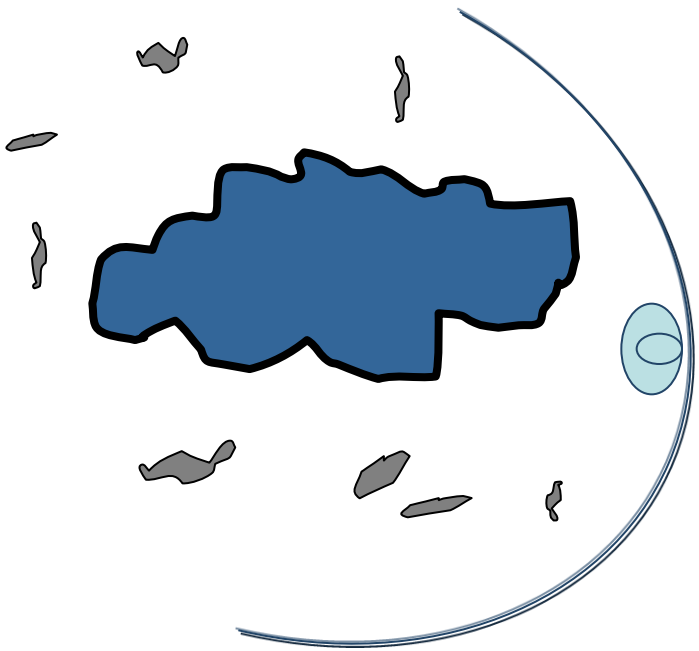


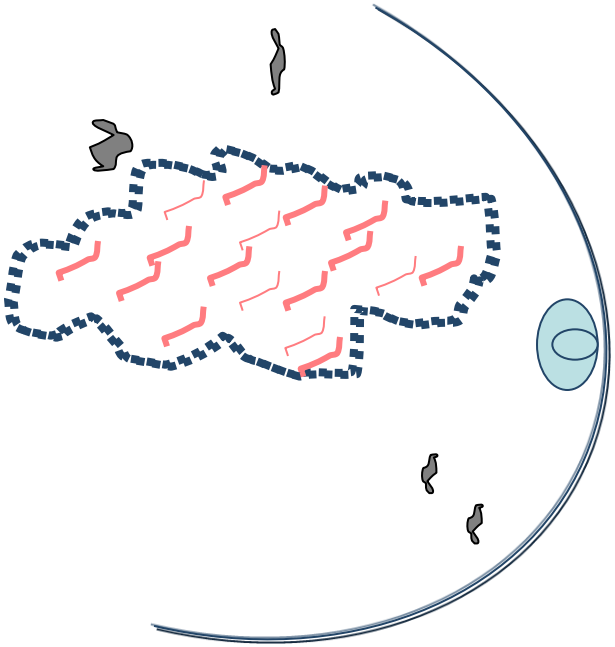


Minima cellularità residua non è necessariamente associata con un decremento massimo del tumore

PICCOLI TUMORI CRESCONO

p Risposta Completa



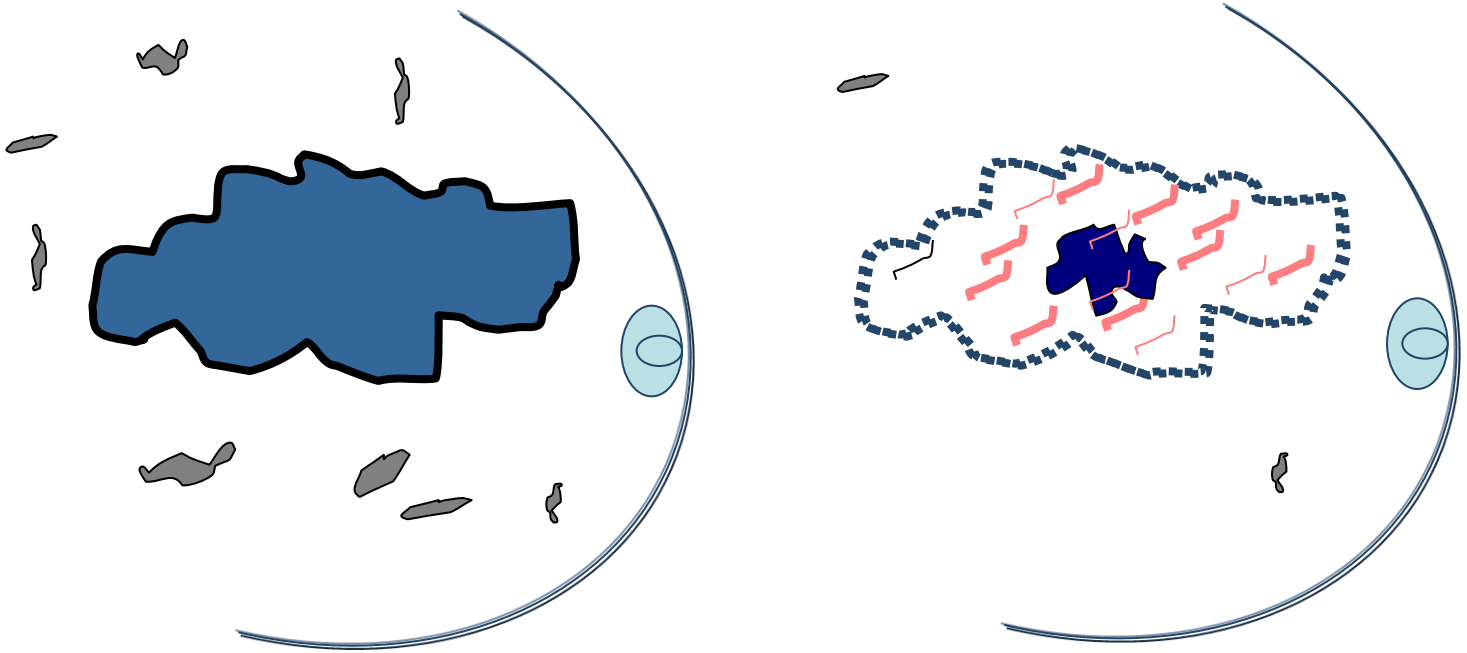


Solo fibrosi e flogosi

→ DIVERSE MODALITA' DI RISPOSTA

PICCOLI TUMORI CRESCONO

pRisposta Parziale

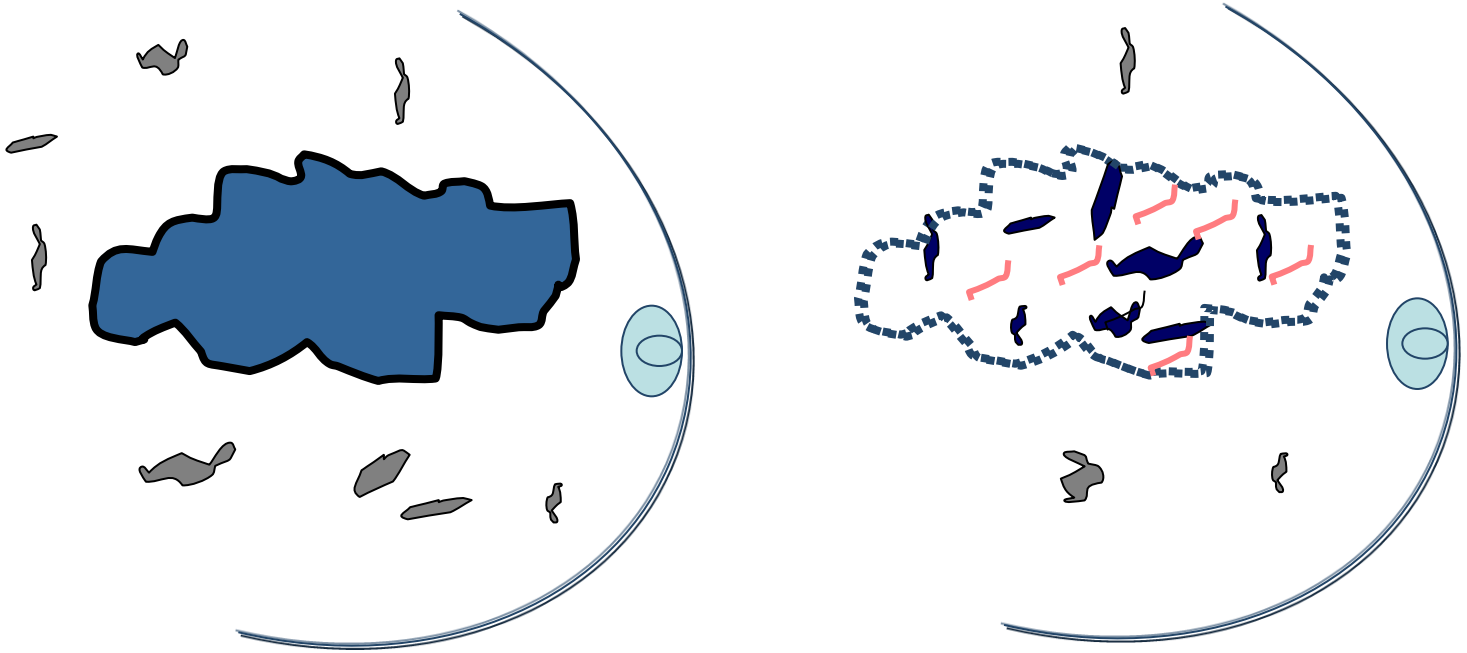


Singola area nodulare di ca invasivo

→ DIVERSE MODALITA' DI RISPOSTA

PICCOLI TUMORI CRESCONO

pRisposta Parziale

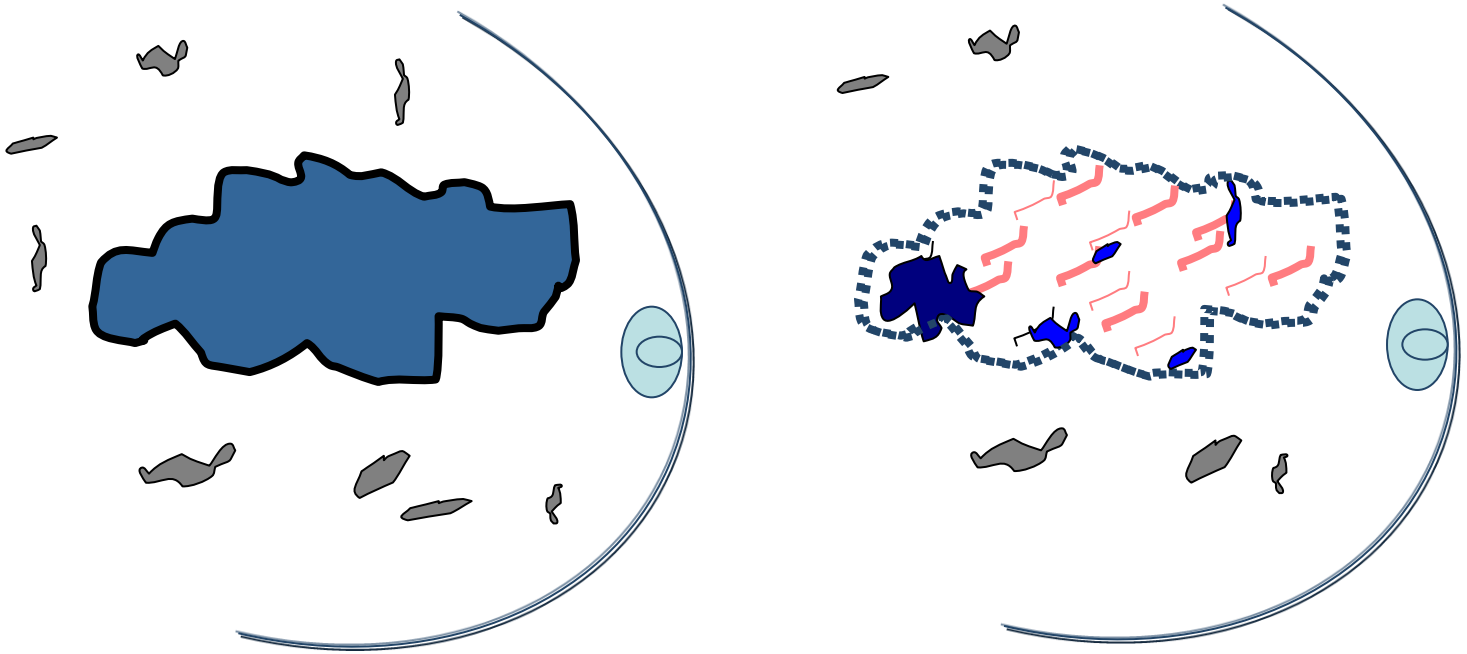


Gruppi di singole cellule sparse e diffuse

→ DIVERSE MODALITA' DI RISPOSTA

PICCOLI TUMORI CRESCONO

pRisposta Parziale



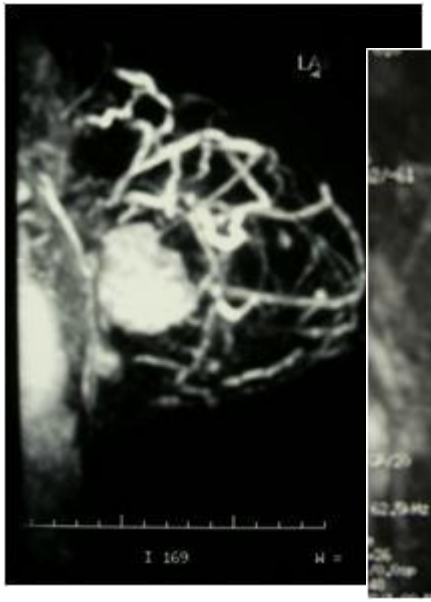
Area nodulare maggiore e piccoli nidi sparsi

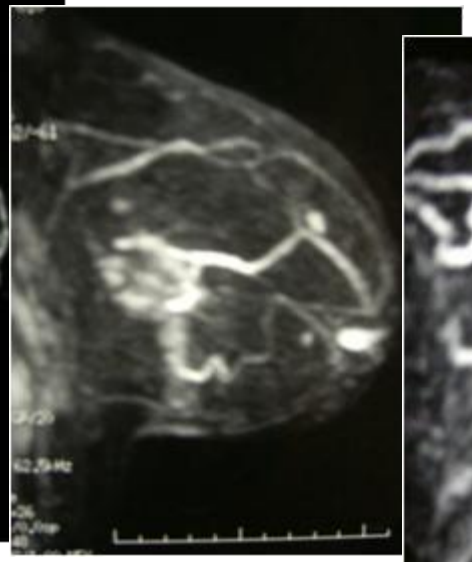
→ DIVERSE MODALITA' DI RISPOSTA

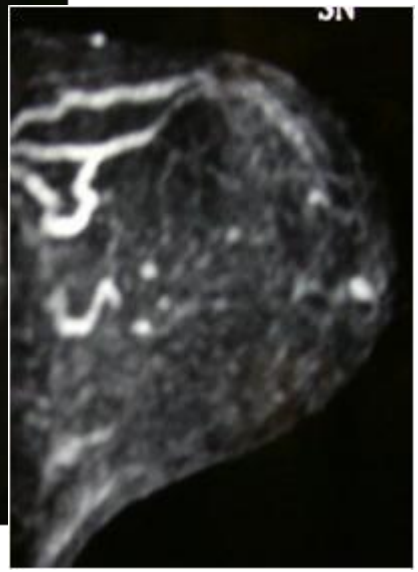
PICCOLI TUMORI CRESCONO

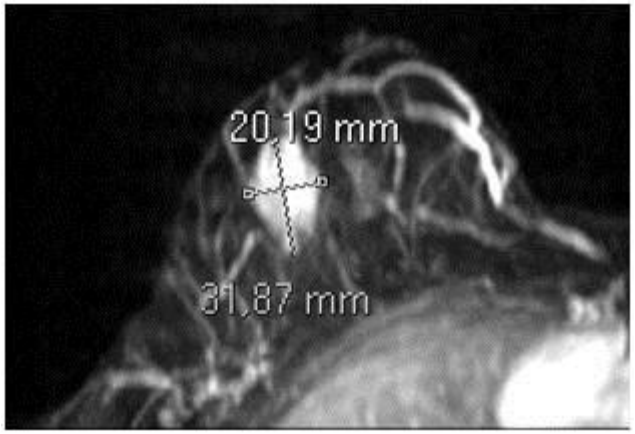
RM: RISULTATI

1. Analisi Dimensionale (criteri WHO)
2. **Analisi Morfologica (pattern di riduzione concentrico o frammentato della massa)**
3. Analisi Cinetica









PRE-NCT → IV CICLO → VI-VIII CICLO

PICCOLI TUMORI CRESCONO

G1
ER+PgR+
Ki-67 basso
HER2 neg

G3
ER- PgR-
Ki-67 alto
HER2 pos+++

Analisi Morfologica
(pattern di riduzione concentrico o frammentato della massa o scomparsa)

PICCOLI TUMORI CRESCONO

G1
ER+PgR+
Ki-67 basso
HER2 neg

G3
ER- PgR-
Ki-67 alto
HER2 pos+++

… i diversi Tipi
«BIOPATOLOGICI»
rispondono in
maniera diversa

PICCOLI TUMORI CRESCONO

G1
ER+PgR+
Ki-67 basso
HER2 neg

G3
ER- PgR-
Ki-67 alto
HER2 pos+++

pCR compreso stato LN

Boughey et al Ann Surg 260:608–616, 2014

PICCOLI TUMORI CRESCONO

G1
ER+PgR+
Ki-67 basso
HER2 neg

G3
ER- PgR-
Ki-67 alto
HER2 pos+++

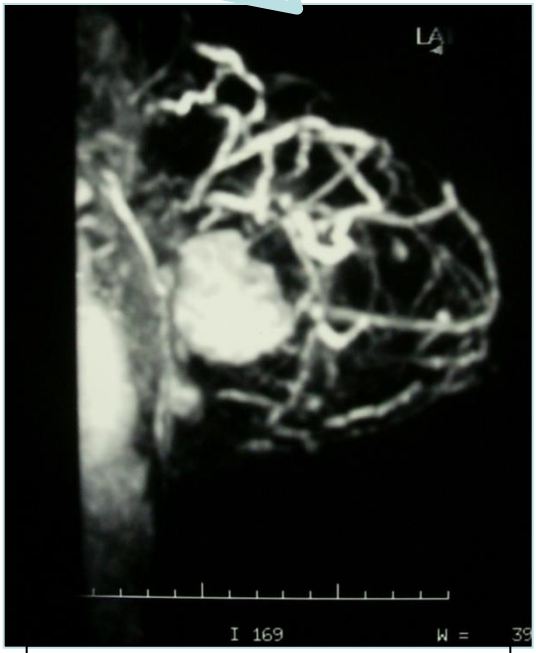
pCR compreso stato LN

RO+ e HER2-
11.4%

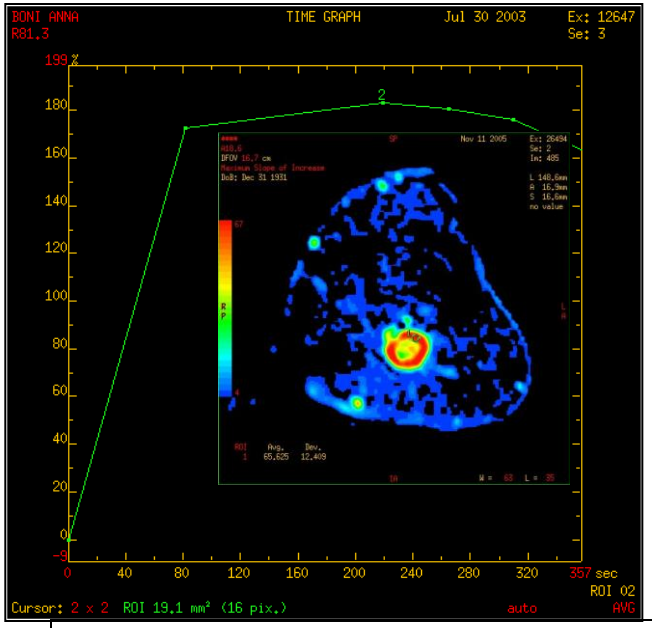
TN e HER2+
38.2% -45.4%

Boughey et al Ann Surg 260:608–616, 2014

PICCOLI TUMORI CRESCONO



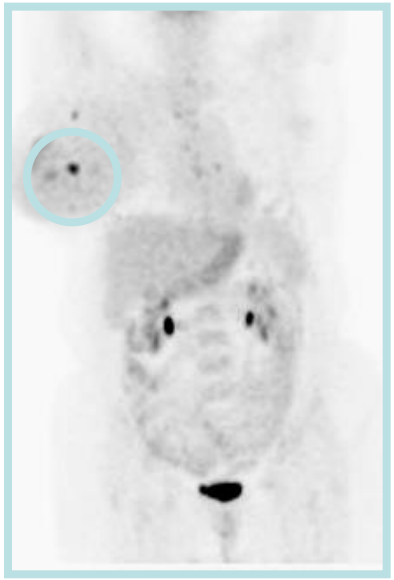
Analisi dimensionale



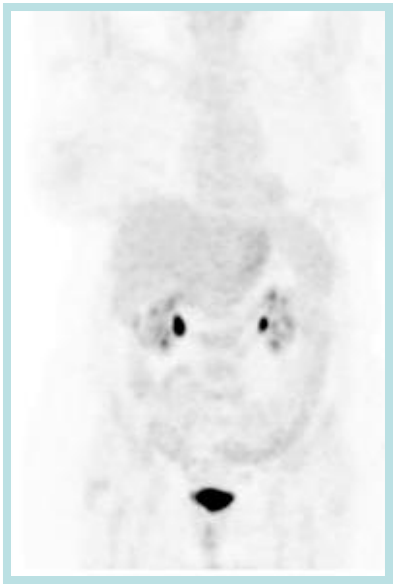
Analisi cinetica: curva tipo T/II maligna

No curva

“responder””

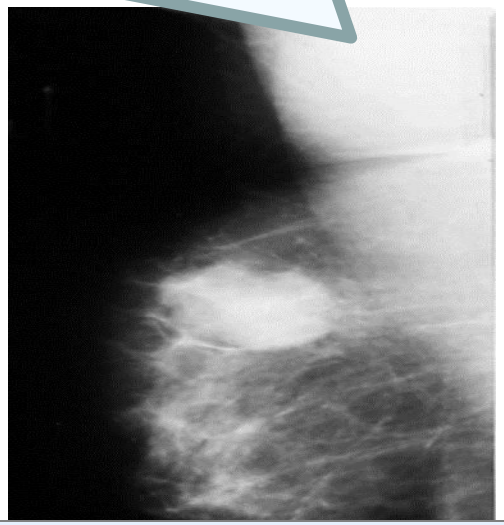


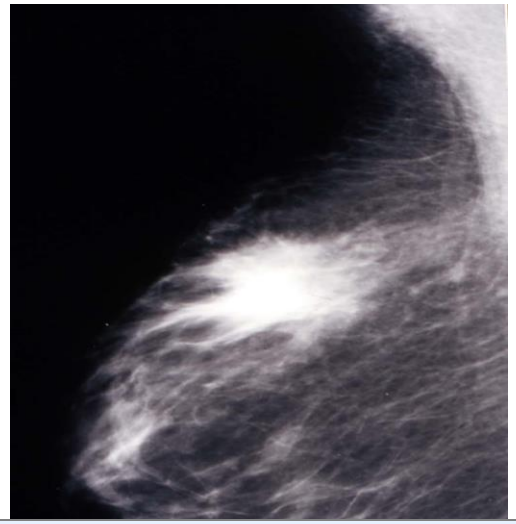
basale

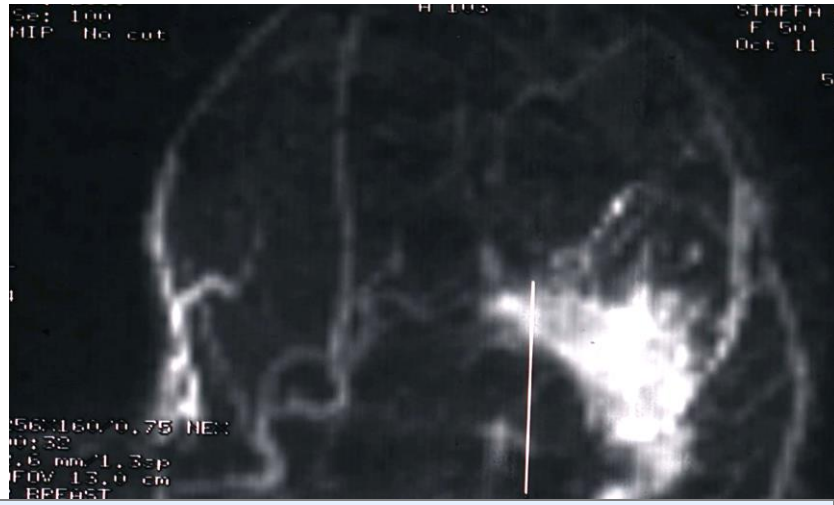


VI ciclo Pre-I

PICCOLI TUMORI CRESCONO



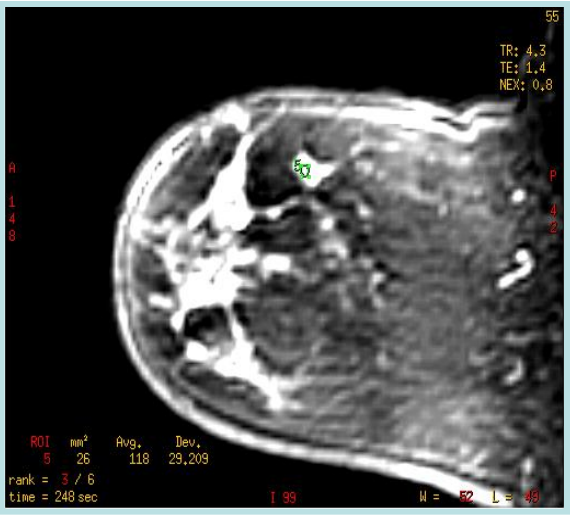




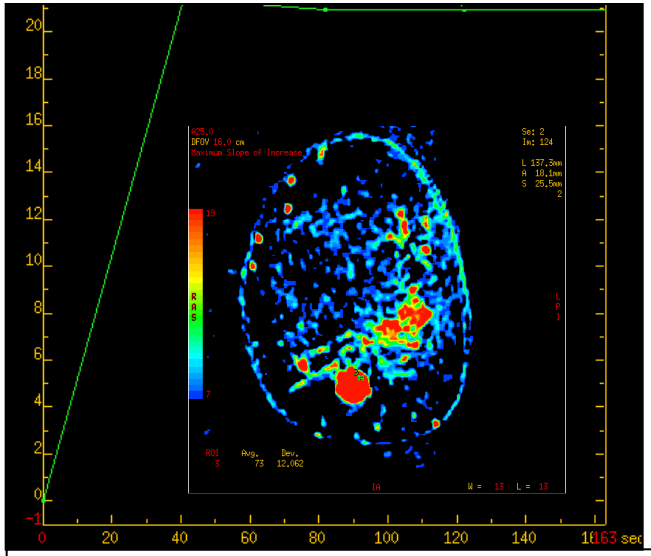
....ma..60-85% pPR

Bear HD, J Clin Oncol. 2003;21:41 4174.
von Minckwitz G,. J Clin Oncol. 200 23:2676-2685.
Toi M,. Breast Cancer Res Treat. 2 3;110:531-539.

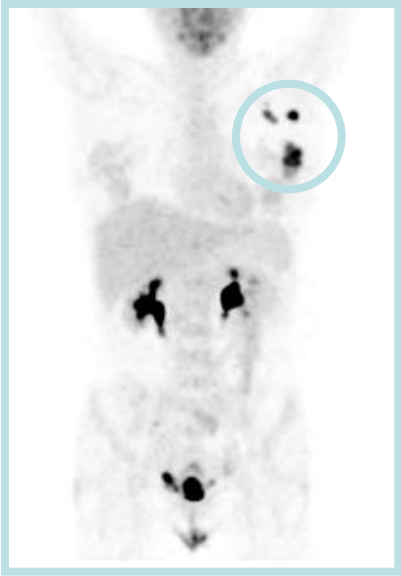
PICCOLI TUMORI CRESCONO



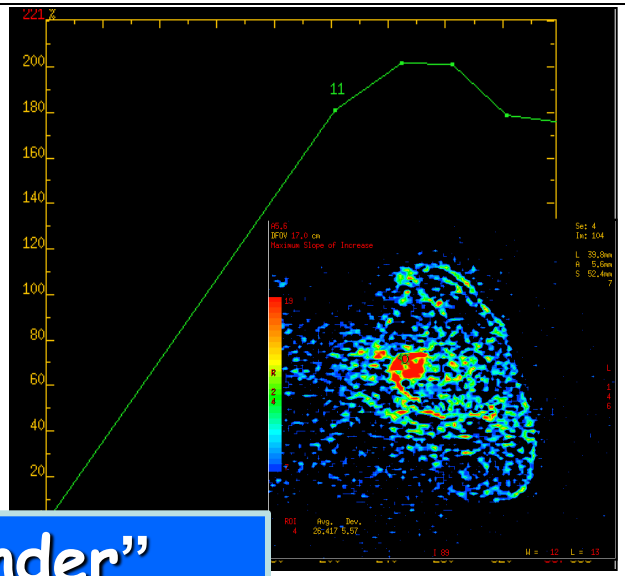
Analisi dimensionale



Analisi cinetica: curve maligne



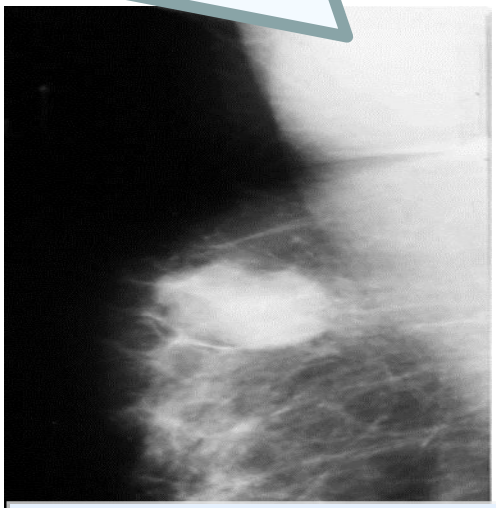
basale

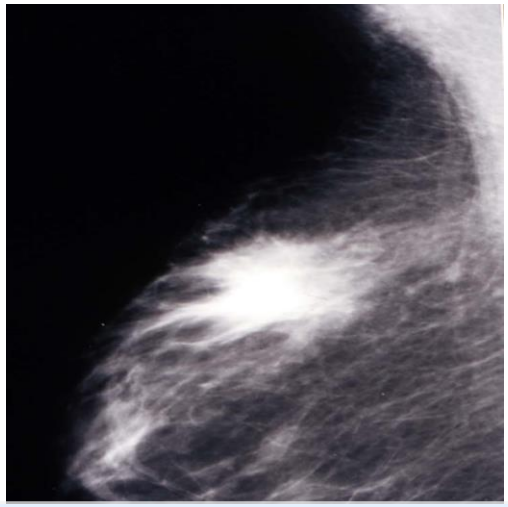


VI ciclo
Pre-I

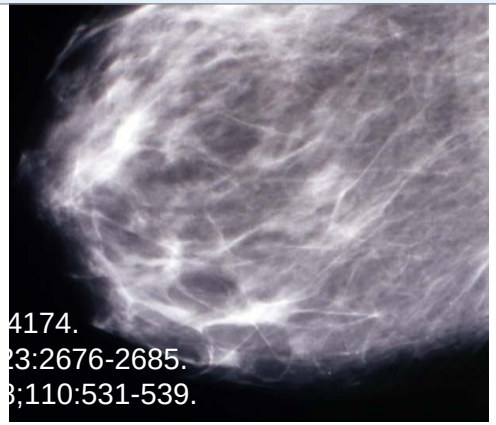
"no responder"

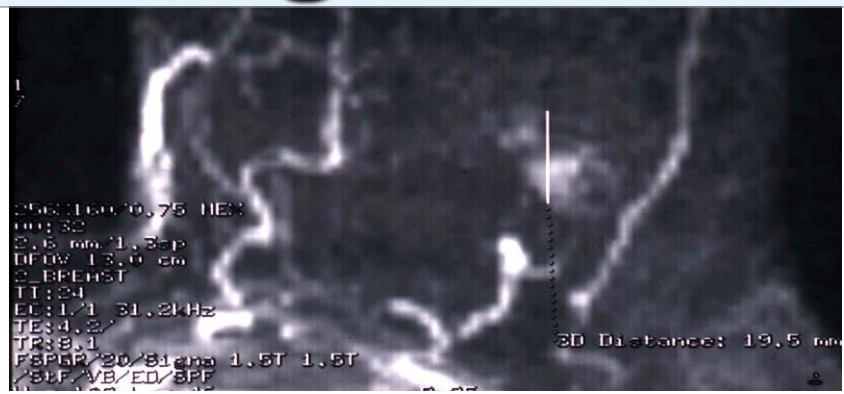
PICCOLI TUMORI CRESCONO





REGOLE???. pPR...tutti uguali...? .





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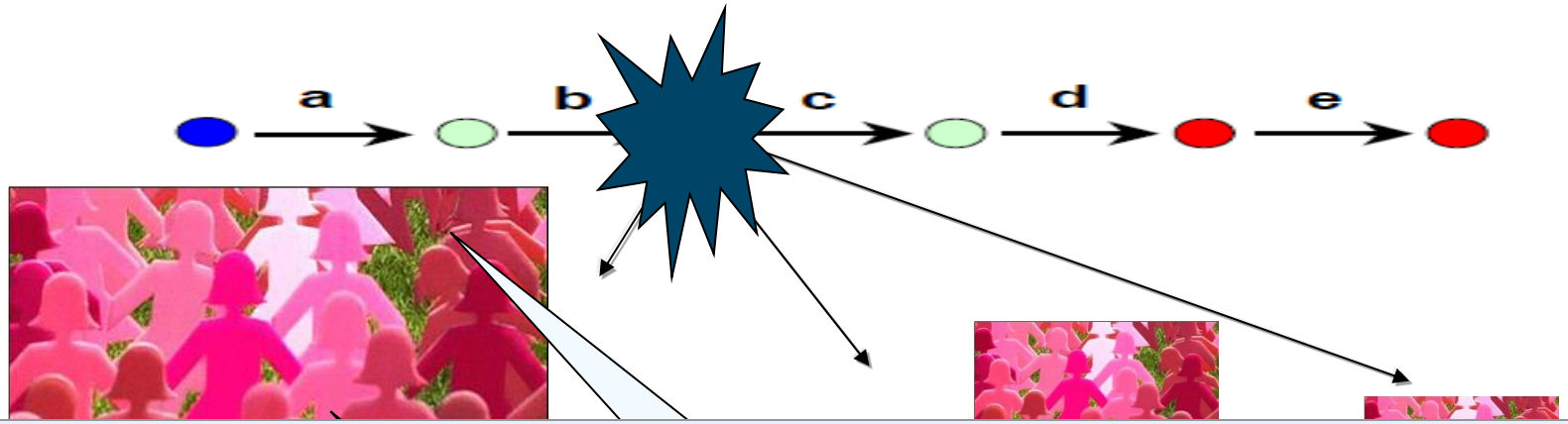
PICCOLI TUMORI CRESCONO



Tipi principali morfologici di residuo tumorale CORRELATI o CORRELABILI con ……

ER 100%
Pgr 100%
Ki67 7%
HER2 negativo

T1N0
ER 100%
Pgr 100%
Ki67 7%
HER2 negativo

HER2 negativo

T1N0
ER 100%
Pgr 100%
Ki67 7%
HER2 negativo

75-80%

T2N1
ER 40%
Pgr 20%
Ki67 37%
HER2 +++

15-20%

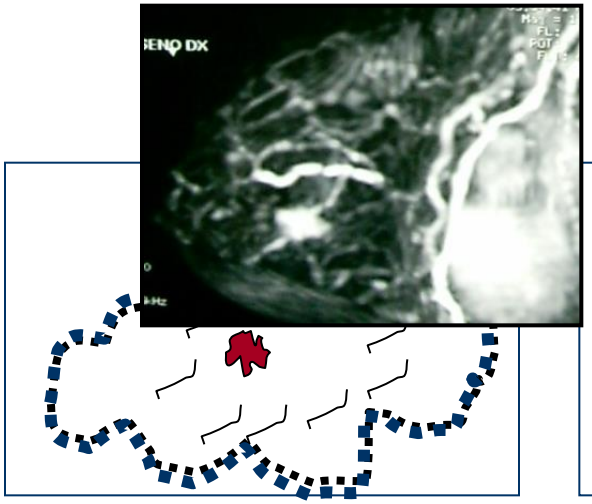
T1N0
ER 0%
Pgr 0%
Ki67 77%
HER2 negativo

10-15%

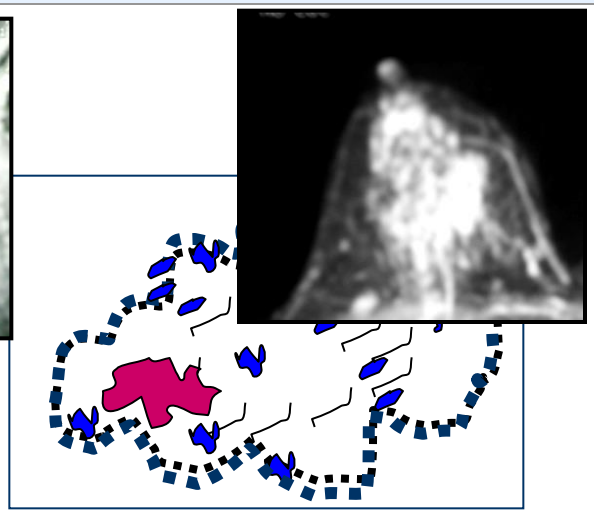
PICCOLI TUMORI CRESCONO

60-85% pPR

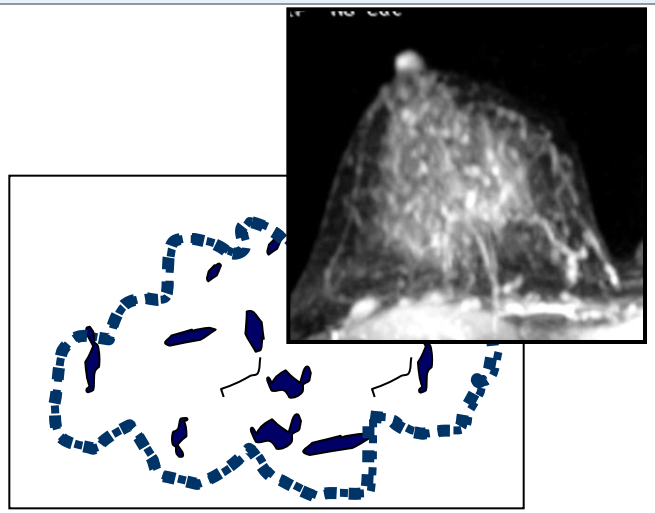
Tipi principali morfologici di residuo tumorale CORRELATI con.....IMAGIN



Singola area di ca invasivo



Area nodulare maggiore e piccoli nidi o singola area di ca invasivo

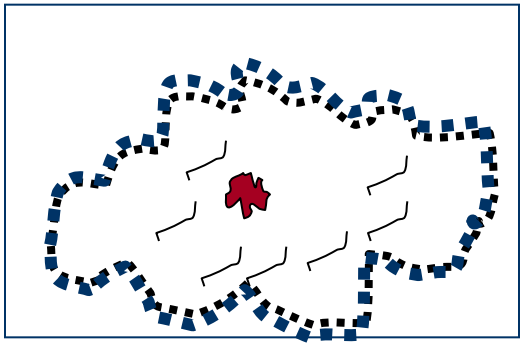


Gruppi di singole cellule sparse e diffuse

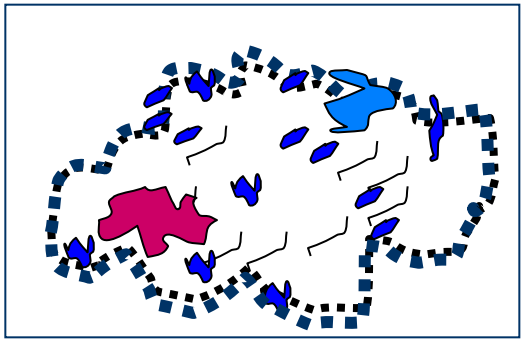
PICCOLI TUMORI CRESCONO

60-85% pPR

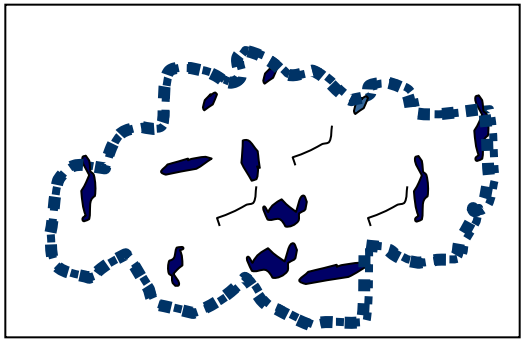
Tipi principali morfologici di residuo tumorale CORRELATI con biologia



Singola area di ca invasivo



Area nodulare maggiore e piccoli nidi o singola area di ca invasivo

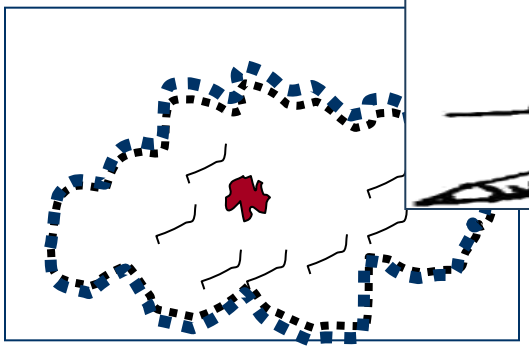


Gruppi di singole cellule sparse e diffuse

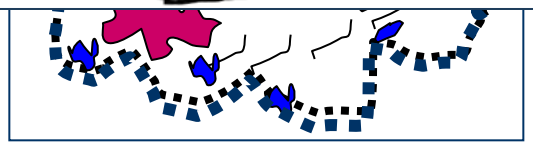
PICCOLI TUMORI CRESCONO

60-85% pPR

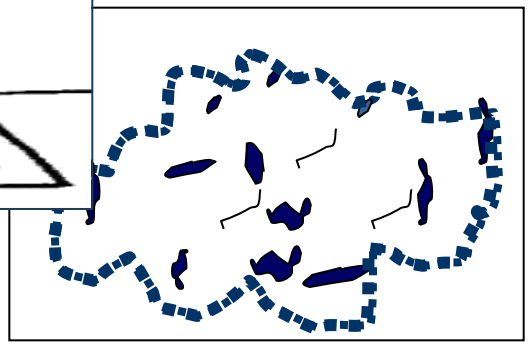
Tipi principali morfologici di residuo tumorale CORRELATI con biologia



Singola area di ca invasivo



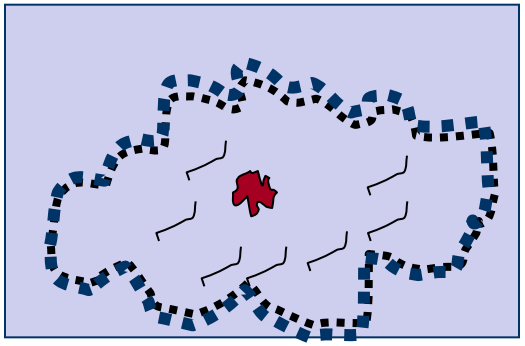
Area nodulare maggiore e piccoli nidi o singola area di ca invasivo



Gruppi di singole cellule sparse e diffuse

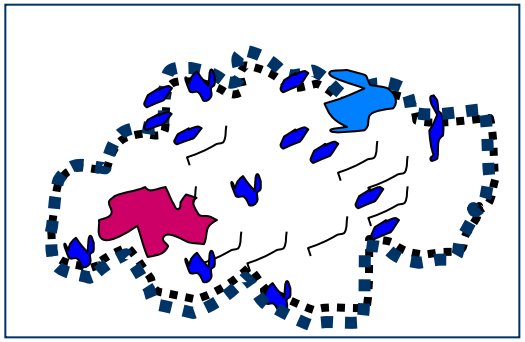
PICCOLI TUMORI CRESCONO

Riduzione concentrica
Nodulo Solitario

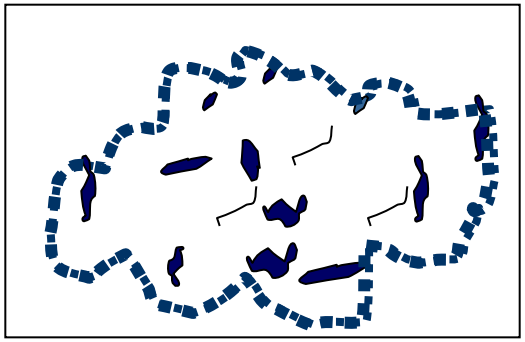


Singola area di ca invasivo

TN



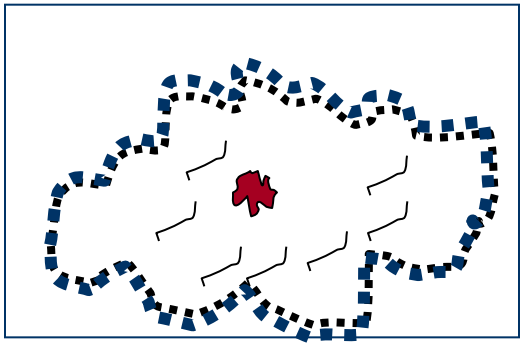
Area nodulare maggiore e piccoli nidi o singola area di ca invasivo



Gruppi di singole cellule sparse e diffuse

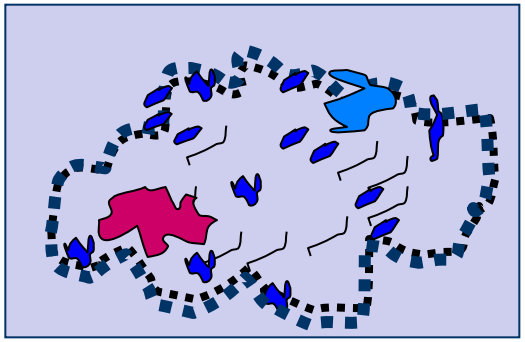
PICCOLI TUMORI CRESCONO

Riduzione con Nidi-Clusters sparsi



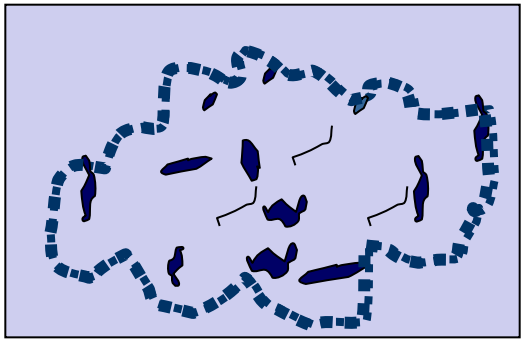
Singola area di ca invasivo

TN



Area nodulare maggiore e piccoli nidi o singola area di ca invasivo

ER+++



Gruppi di singole cellule sparse e diffuse

HER2+++

PICCOLI TUMORI CRESCONO

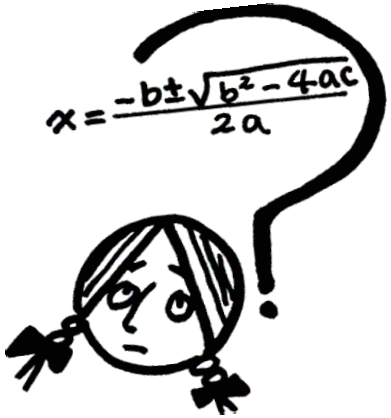
- RO-neg e HER2-positivi fattori predittivi di pCR

- RO-pos e HER2-negativi bassi tassi di pCR rispetto a altri sottogruppi.

Bear HD, J Clin Oncol. 2003;21:4165-4174.
von Minckwitz G,. J Clin Oncol. 2005;23:2676-2685.
Toi M,. Breast Cancer Res Treat. 2008;110:531-539.

PICCOLI TUMORI CRESCONO

pCR significativo minor rischio di recidiva rispetto ai pazienti con pPR



PICCOLI TUMORI CRESCONO

pCR significativo minor rischio di recidiva rispetto ai pazienti con pPR

HER2+ e TN

MAGGIORE PROBABILITA' pCR

Migliori candidati Tp Chir Conservativa

MINORE RISCHIO RIPRESA MALATTIA

PICCOLI TUMORI CRESCONO

pCR significativo minor rischio di recidiva rispetto ai pazienti con pPR

HER2+ e TN

MAGGIORE PROBABILITA' pCR

Migliori candidati Tp Chir Conservativa

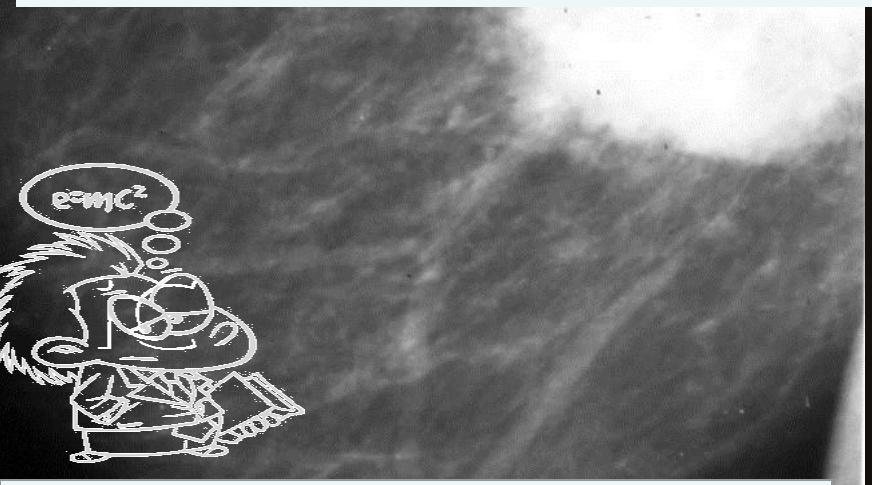
MINORE RISCHIO RIPRESA MALATTIA

PICCOLI TUMORI CRESCONO

G1
ER+PgR+
Ki-67 basso
HER2 neg

G3
ER- PgR-
Ki-67 alto
HER2 pos+++

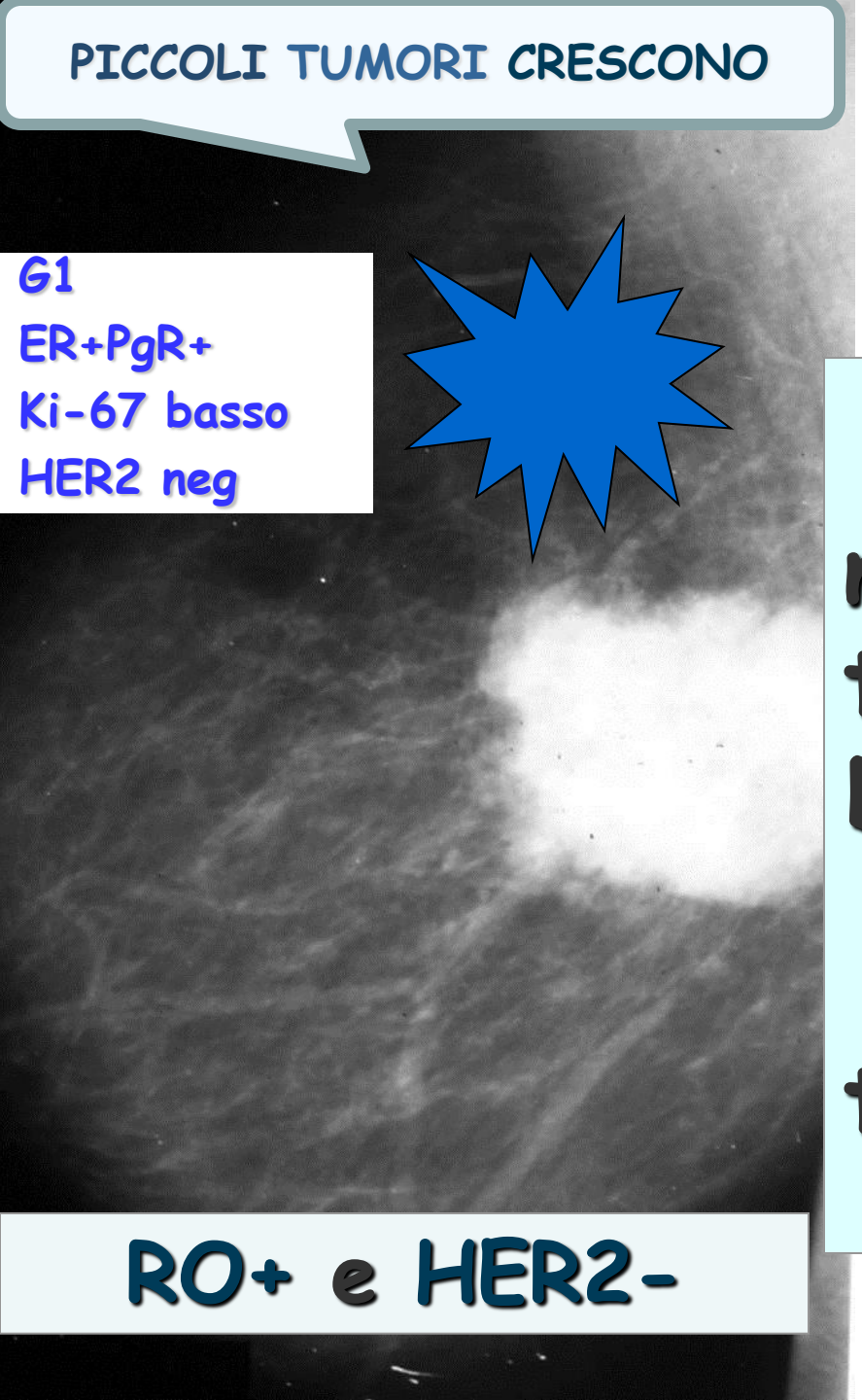
IL PARADOSSO DELLA BIOLOGIA



RO+ e HER2-

TN e HER2+

PICCOLI TUMORI CRESCONO



RO+ e HER2-

- Tumori RO+/HER2- nonostante bassi tassi di pCR migliore DFS e OVS
- RO+ ripresa tardiva (molti anni)

PICCOLI TUMORI CRESCONO

TN e HER2+ ripresa precoce (entro i primi 3 anni)

Bear HD, J Clin Oncol. 2003;21:4165-4174.
von Minckwitz G,. J Clin Oncol. 2005;23:2676-2685.
Toi M,. Breast Cancer Res Treat. 2008;110:531-539.

PICCOLI TUMORI CRESCONO

G1
ER+PgR+
Ki-67 basso
HER2 neg

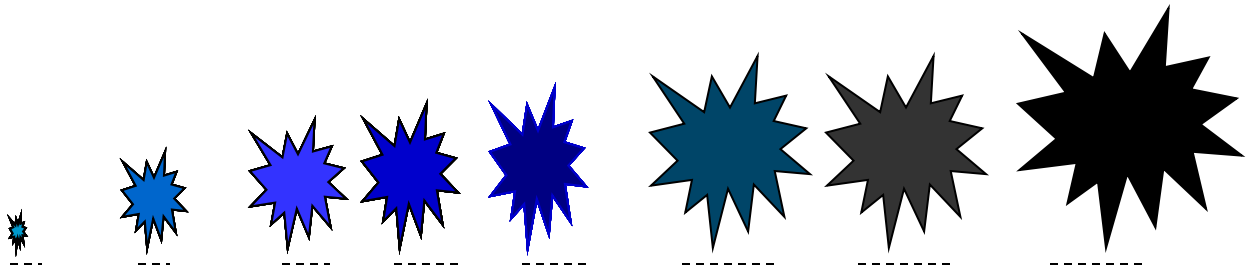
G3
ER- PgR-
Ki-67 alto
HER2 pos+++

- pPR RR 1.6 volte superiore a pCR
- N+ rischio di recidiva 2.8 volte maggiore
- SOTTOTIPO "BIOPATOLOGICO"

FATTORE PREDITTIVO INDIPENDENTE PIU' POTENTE

PICCOLI TUMORI CRESCONO

- Carcinoma Duttale In Situ pTis
- Carcinoma MICROINVASIVO pTmic
- Carcinoma INVASIVO pT1a-b-c
- Carcinoma INVASIVO pT2-3-4



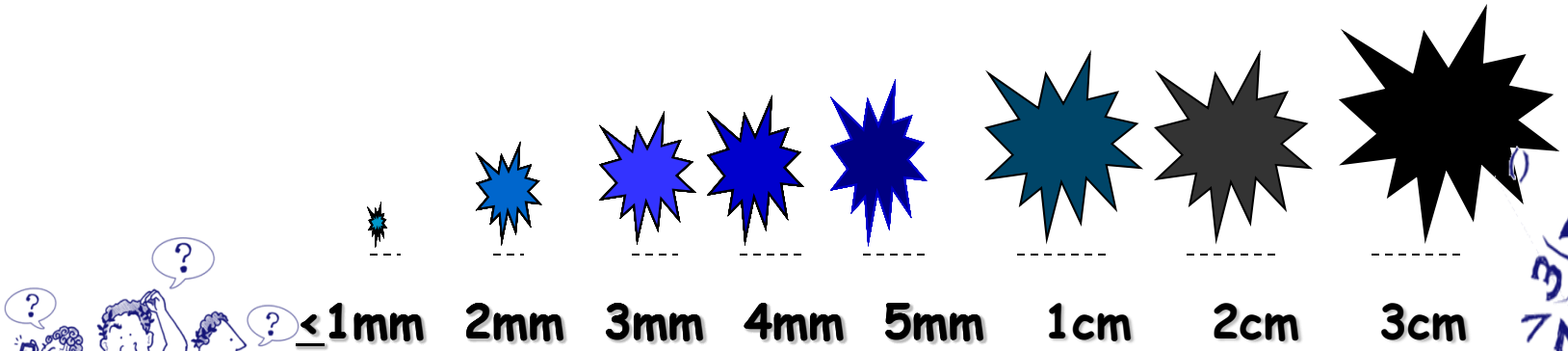
≤1mm 2mm 3mm 4mm 5mm 1cm 2cm 3cm

Cosa ci dice la biologia?

pT

PICCOLI TUMORI CRESCONO

- Carcinoma Duttale In Situ pTis
- Carcinoma MICROINVASIVO pTmic
- Carcinoma INVASIVO pT1a-b-c
- Carcinoma INVASIVO pT2-3-4



Cosa ci dice la biologia?

pT vs pBioMol

PICCOLI TUMORI CRESCONO

SI screening

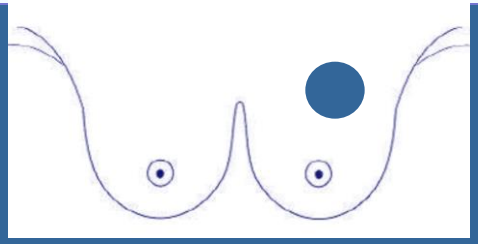
Destinate a sviluppare un cancro di 4 cm con 5 N+ nel corso dello stesso tempo

NO Screening

PICCOLI TUMORI CRESCONO

SI screening

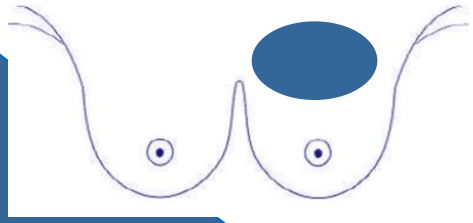
Rilevato un cancro
2cm con 5N+



Destinate a sviluppare un cancro di 4 cm con 5 N+ nel corso dello stesso tempo

NO Screening

Rilevato un cancro
4cm con 5N+



PICCOLI TUMORI CRESCONO

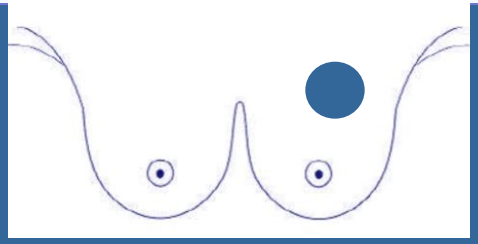
SI screening

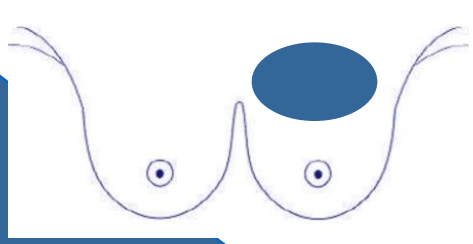
NO Screening

Destinate a sviluppare un cancro di 4 cm con 5 N+ nel corso dello stesso tempo

Rilevato un cancro 2cm con 5N+

Rilevato un cancro 4cm con 5N+





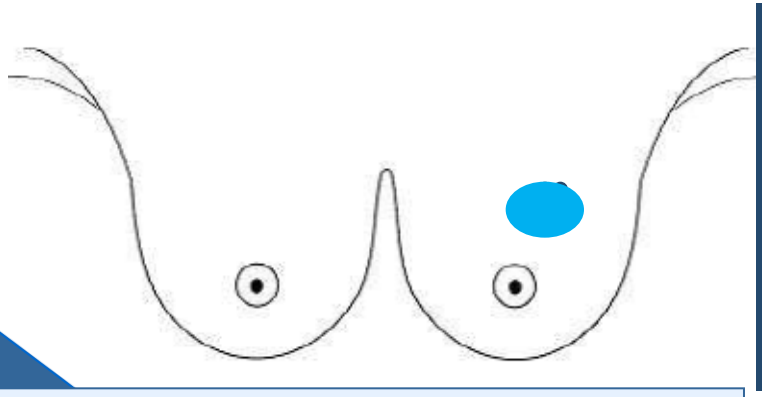
Outcome a 15 anni MIGLIORE

Outcome a 15 anni PEGGIORE

PICCOLI TUMORI CRESCONO

Ma questo scenario NON vale per tutti i sottotipi di cancro della mammella e per tutte le età

PICCOLI TUMORI CRESCONO

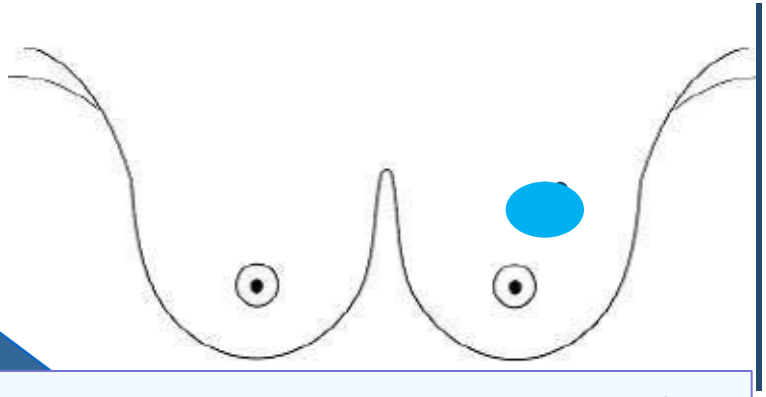


……tumori in cui il «*dado è tratto* » precocemente

sottogruppi di donne (TN-BL-HER2) precoce tendenza a sviluppare metastasi NON LN,…

…, in particolare..donne più giovani

PICCOLI TUMORI CRESCONO



….. vani gli sforzi per ridurre la mortalità individuando tumori di dimensioni sempre minori

PICCOLI TUMORI CRESCONO

Miglioramento sarà limitato ai tumori che sono RO-positivi, dove il rapporto tra le dimensioni del tumore, N+ e sopravvivenza è abbastanza costante e lineare

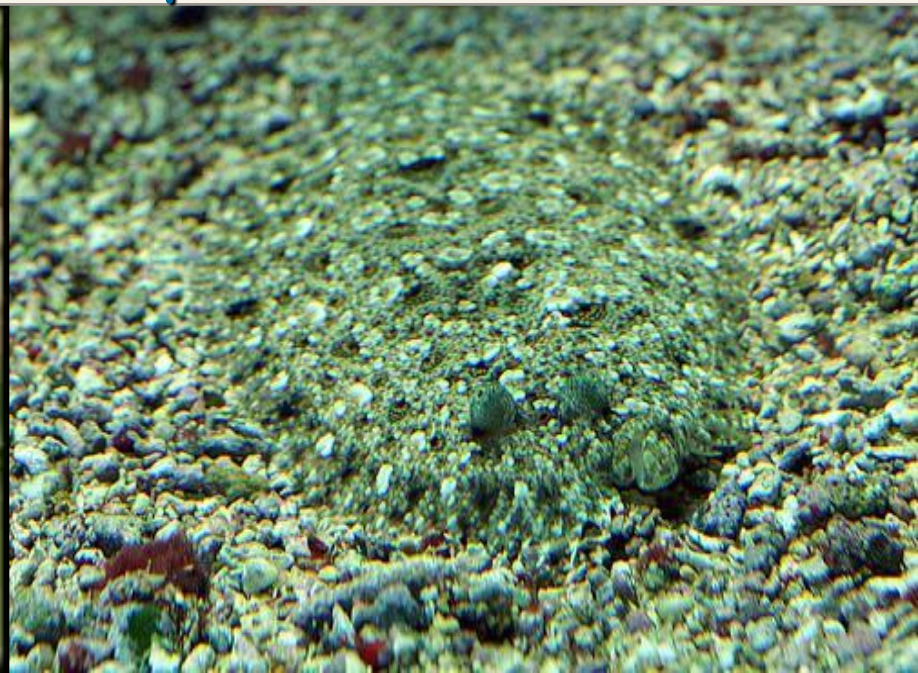
….meno per TNBC e/o HER2……giovani, mutate etc

PICCOLI TUMORI CRESCONO

… PARADOSSO ……

… i tumori che mammografia è in grado di rilevare BENE ed in modo affidabile, non sono spesso fatali, e i tumori che sono spesso mortali non possono essere rilevati in modo attendibile….

PICCOLI TUMORI CRESCONO

Un viaggio di scoperta non è cercare nuove terre ma avere nuovi occhi

Non importa quello che stai guardando ma quello che riesci a vedere…..