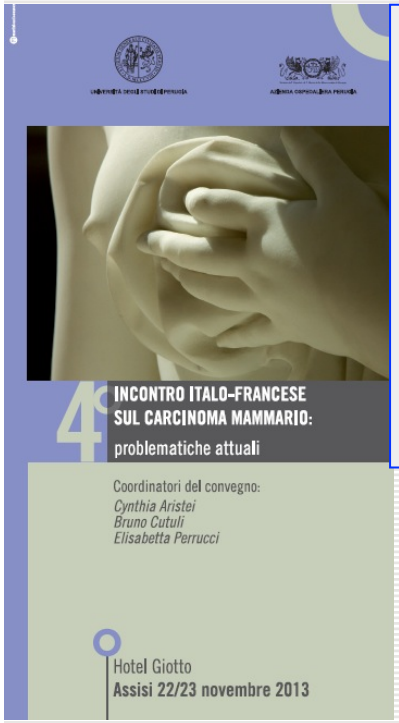


"Diagnosi intraoperatoria o preoperatoria del linfonodo sentinella? Problematiche anatomo-patologiche"

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

SNL: path

PATHOLOGICAL ASSESSMENT:

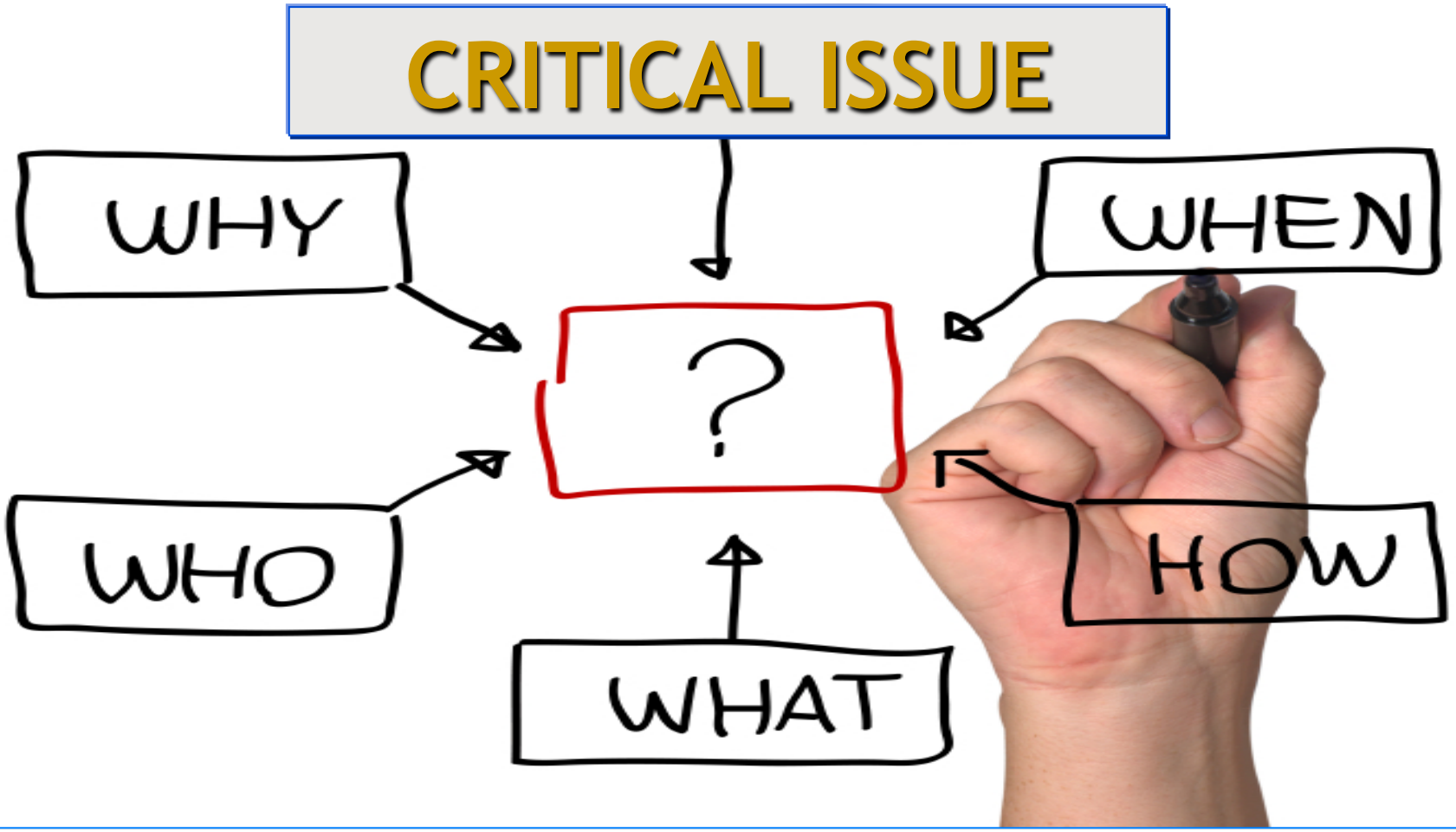
CRITICAL ISSUE

a)Pathological PROTOCOLS
b)Histological evaluation: macrometastases, micrometastases,ITC
c)Team approach
d)Impact on Pathology Dept

SNL: path

…1999……2013…

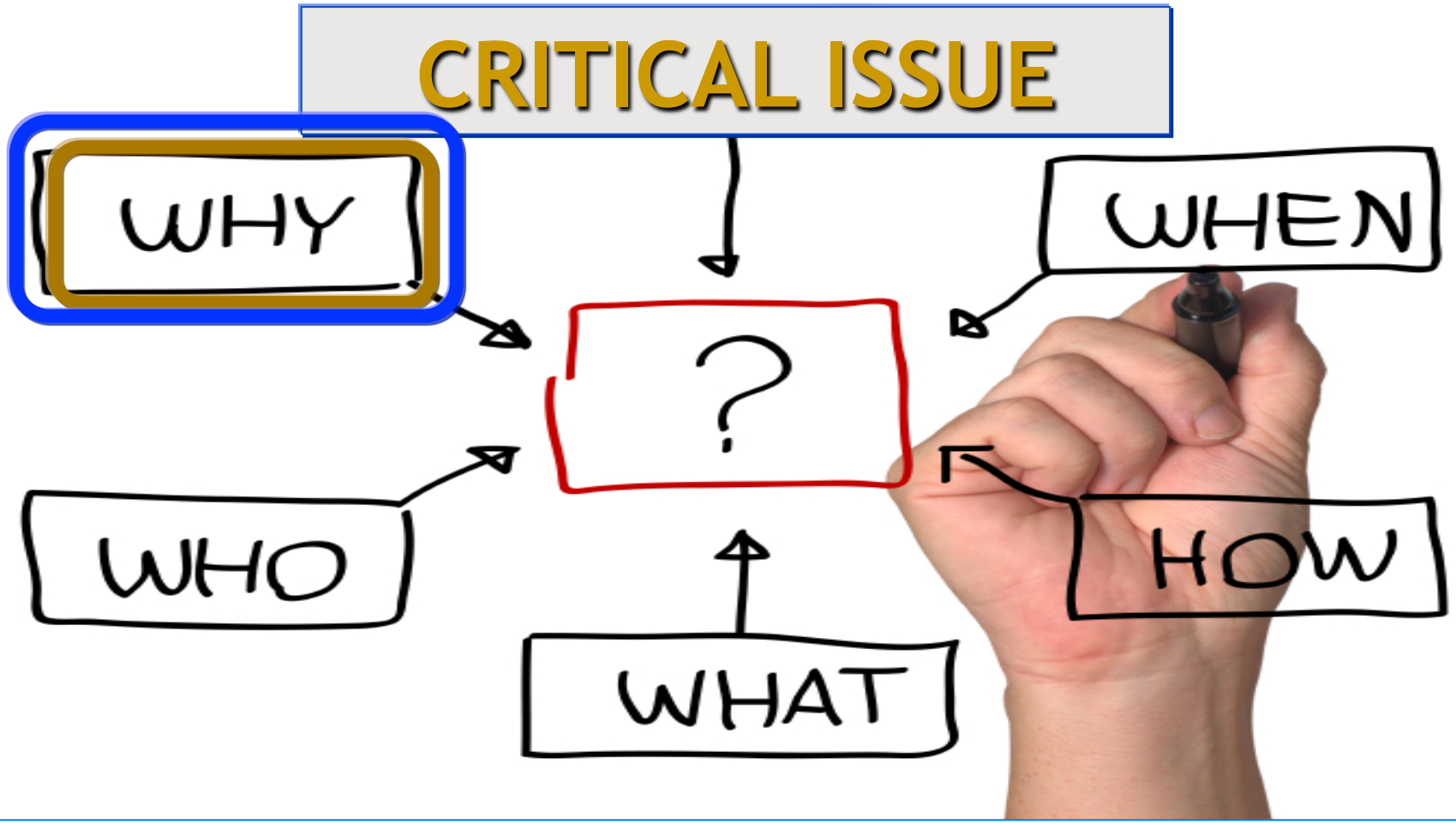
PATHOLOGICAL ASSESSMENT:



SNL: path

…1999……2013…

PATHOLOGICAL ASSESSMENT:



.. HOW.. AND WHAT...

PATHOLOGICAL ASSESSMENT:

a) PATHOLOGICAL PROTOCOLS

CRITICAL ISSUE

b) Histological evaluation:
macrometastases, micrometastases, ITC

c) Team approach

d) Impact on pathology dept

SNL: path

...1999.....2013...

- NO STANDARDIZED PROTOCOLS
- MARKED DIFFERENCES IN THE PROCESSING

SNL: path

Survey of 240 European Labs: 123 different Pathologic Protocols

Cserni G The Breast Journal 12 Suppl. 2: S152-S156, 2006

⩾SNL: path

.. HOW.. handling...

1. Imprint cytology
2. Frozen sections
3. Permanent formalin fixed paraffin embedded

4. US-guided needle biopsy

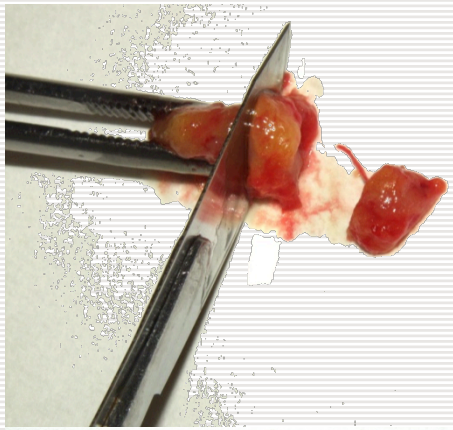
5. EE vs IHC
6. Molecular Methods

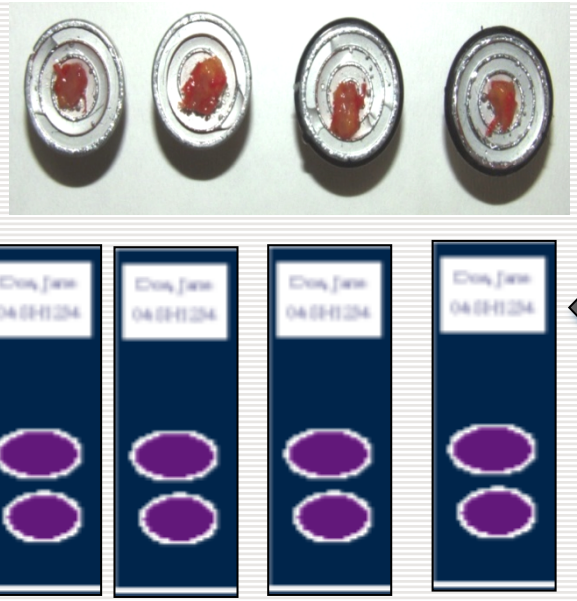
SNL: path

.. HOW.. handling...

PROTOCOL requirements:

1. A **SENSITIVE** but **PRACTICAL METHOD** of examination
2. Criteria to determine which metastases are meaningful





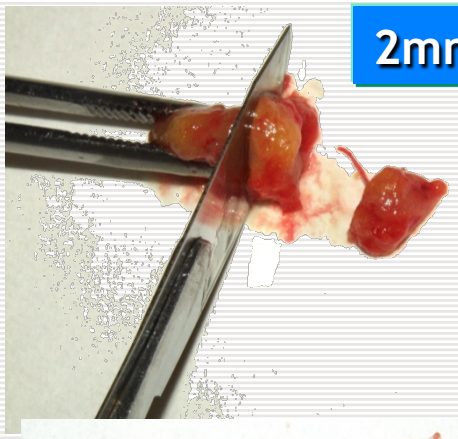
SNL: path

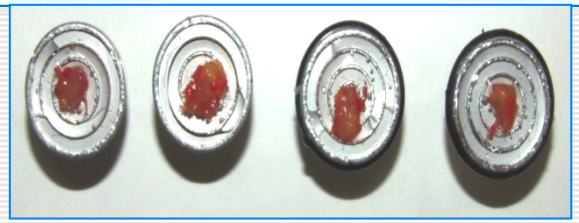
HOW..handling..WHAT...search

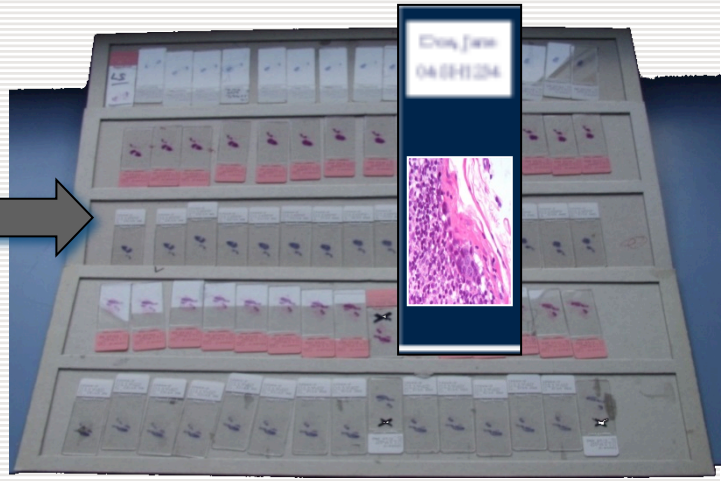
PROTOCOL requirements:

1. A sensitive but PRACTICAL METHOD of examination

2. CRITERIA to determine which METASTASES ARE MEANINGFUL



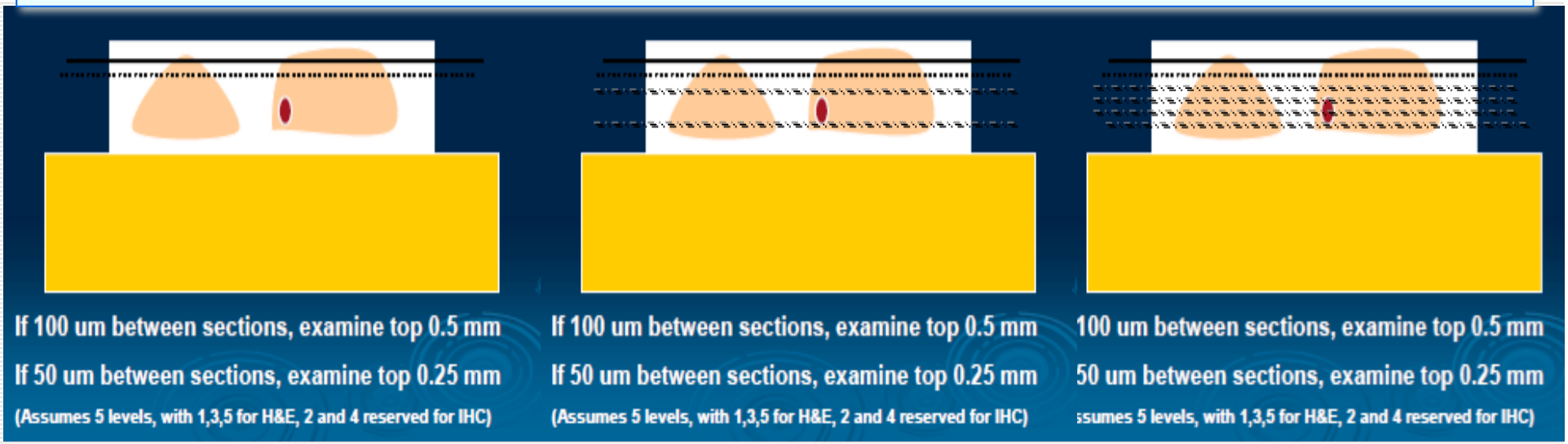




SNL: path

- **MARKED DIFFERENCES IN THE PROCESSING**

1. number of sections examined
2. cutting intervals
3. use of IHC



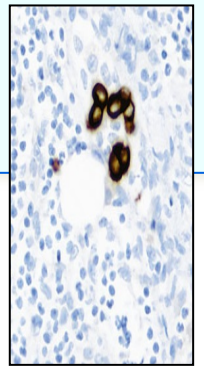
SNL: path

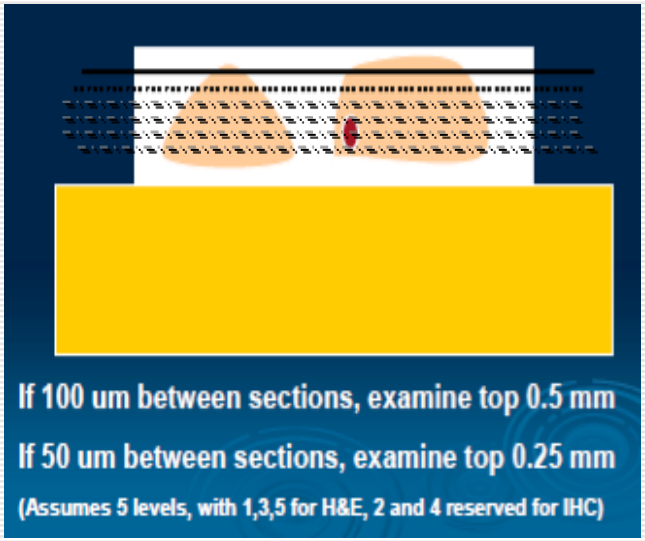
…1999……2013…

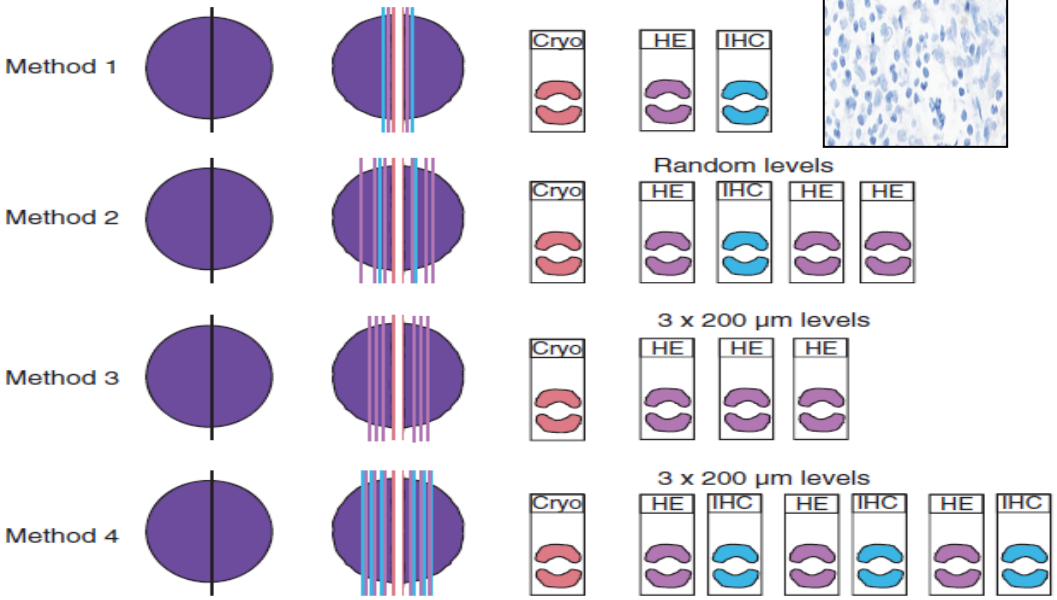
…WHAT ..learned…

- **MARKED DIFFERENCES IN THE PROCESSING**

1. number of sections examined
2. cutting intervals
3. use of IHC







SNL: path

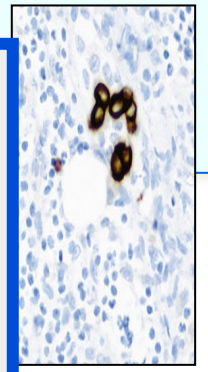
…1999……2013…

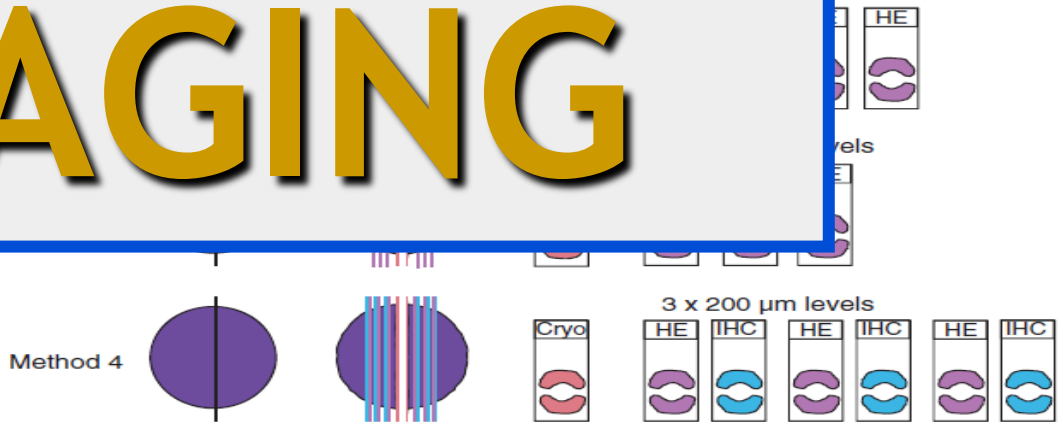
…WHAT ..learned…

- **MARKED DIFFERENCES IN THE PROCESSING**

1. number of sections examined
2. cutting intervals

DRAMATIC UPSTAGING





If 50 um between sections, examine top 0.25 mm

(Assumes 5 levels, with 1,3,5 for H&E, 2 and 4 reserved for IHC)

SNL: path

- **NODAL UPSTAGING RATE:**
  9%-47% due to more scrutiny given to the SLNs.

- **Wide range in UPSTAGING has been attributed to differences in pathology protocols, which lack standardisation, despite guidelines created with this aim.**

SNL: path

PATHOLOGICAL ASSESSMENT:

a) Pathological protocols
b) **Histological evaluation**: macrometastases, micrometastases, ITC

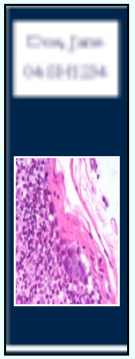
c) Team approach
d) Impact on pathology dept

….. HOW….reading…

PATHOLOGICAL ASSESSMENT:

a) Pathological protocols

b) **Histological evaluation:** r CRITICAL ISSUE s,
micrometastases, ITC



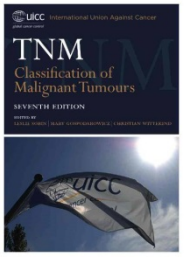
c) Team approach

d) Impact on pathology dept

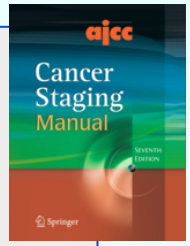
SNL: path

CRITICAL ISSUE

DEFINITION: ITC vs MICROMTS



Different criteria interepretation



- SIZE
-QUALITATIVE FEATURES
-LOCALIZATION

SNL: path

- UICC and AJCC definitions: imprecise
- Both systems use size of the largest metastatic cluster…but UICC also considers some qualitative features (ie, proliferation and extravasation)
- No generally accepted definition for a cluster, which complicates size measurement in case of multiple clusters

Cancer 103:358-367,2005
Breast 15:347-354, 2006
J Clin Oncol 26:258-263, 2008
Am J Surg 186:324-329 2003
Cancer 112:1672-1678, 200

SNL: path

- SUBOPTIMAL REPRODUCIBILITY
- No perfect "concordance" between AJCC and UICC

Cancer 103:358-367,2005 ; Breast 15:347-354, 2006
J Clin Oncol 26:258-263, 2008; Am J Surg 186:324-329 2003
Cancer 112:1672-1678, 200

SNL: path

- **SUBOPTIMAL REPRODUCIBILITY**
- **No perfect "concordance" between AJCC and UICC**

To improve reproducibility

- **EWGBSP offered some refinements of the current nodal staging definitions**

Cancer 103:358-367,2005 ; Breast 15:347-354, 2006
J Clin Oncol 26:258-263, 2008; Am J Surg 186:324-329 2003
Cancer 112:1672-1678, 200

EWGBSP

CRITICAL ISSUE

- Not consider lesions purely outside the lymph node as evidence of nodal involvement
- **More importantly, clusters, if located within the parenchyma of the lymph node irrespective of their size, are considered as micrometastasis.**

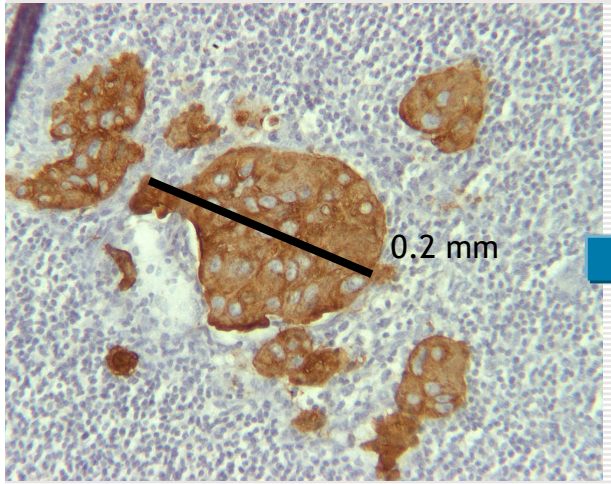
SNL: path

CRITICAL ISSUE

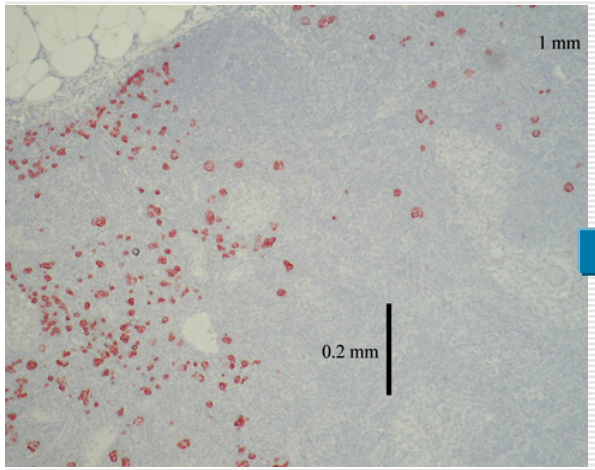
These variations in the definition led to

24% discordance

Illustrative cases



- **EWGBSP**: **micrometastasis** on the basis of location
- **AJCC**:**ITC**, largest cluster not larger than 0.2 mm
- **TNM 7**: **ITC**



- **EWGBSP**: **micrometastasis** on the basis of location
- **AJCC**: **ITC**
- **TNM 7**: >200 cells **micrometastasis**

SNL: path

...WHEN.....?

PATHOLOGICAL ASSESSMENT:

a) **Pathological protocols** CRITICAL ISSUE

b) **Histological evaluation:** CRITICAL ISSUE

macrometastases, micrometastases, ITC

a) Team approach

b) Impact on pathology dept

SNL: path

...WHEN.....

- Intra-operatively
- Pre-operatively
- Post-operatively

SNL: path

...WHEN...HOW.. WHAT...search

- Intraoperatively
- Preoperatively
- Postoperatively

...WHY...?.....Clinical QUESTION

SNL: path

...WHEN...HOW.. AND WHAT...search

- **Intra**operatively
- Preoperatively
- Postoperatively

...WHY...?

.....Clinical **QUESTION**

SNL: path

...WHEN.....HOW..

Intraoperative evaluation can be performed using

1. Imprint cytology
2. Frozen sections
3. Molecular Methods

Pathologic intraoperative Evaluation

Imprint cytology

- **SUCCESS RATE HIGH: varying according to the institutions.**

- Meta-analysis (Tew et al.):
  -63% sensitivity
  -sensitivity for MIC vs MAC (22% vs. 81%).

- Lorand et al :
  -sensitivity significantly lower for: oldest patients, small (T1a-b) tumors, lobular subtype.

Pathologic intraoperative Evaluation

Frozen sections

- ROUTINE AT MOST INSTITUTIONS
- NO SPECIFIC GUIDELINES

a) Some examine only 1 single slice of the node.

b) Number sections examined variable (most 2-3 levels)

c) SOME ENTIRE BLOCK sectioned to generate hundreds of sections,resulting in no tissue left for permanent sectioning.

SNL: path

Pathologic intraoperative Evaluation

Frozen sections:

CRITICAL ISSUE

- FSs SUBOPTIMAL QUALITY
- Incomplete sections MAY EXCLUDE the subcapsular sinus
- DIFFICULT to obtain satisfactory sections from LN usually replaced by adipose tissue

Pathologic intraoperative Evaluation

Frozen sections: CRITICAL ISSUE

- FSs SUBOPTIMAL QUALITY

- Tendency of FSs:
  - to fold and tear during preparation
  - to loosen from the slides during staining

SNL: path

Pathologic intraoperative Evaluation

- DISADVANTAGES
- ADVANTAGES

Pathologic intraoperative Evaluation

DISADVANTAGES

Advantages	Disadvantages
Frozen sections	
Tissue diagnosis (nodal architecture)	Freezing artifacts
Usually specific, less deferred diagnoses	Requires more time
Enables differentiation of macrometastases and micrometastases	Some tissue is lost
Histologists are more familiar with the method	More expensive
Can be complemented by rapid IHC	Sampling errors may occur
Imprint cytology	
Simple	Fewer cells assessed
Cheap	More indeterminate and deferred diagnoses
Rapid	Cannot differentiate between micrometastases and macrometastases
May give excellent cytological details	Sampling errors may occur
Requires cytology training	
Can be complemented by rapid IHC	

Cserni G et al European Journal of Cancer 39 (2003) 1654-1667

SNL: path

Pathologic intraoperative Evaluation

- Imprint overall sensitivity: 63%
- Frozen overall sensitivity: 78%

SNL: path

Pathologic intraoperative Evaluation

- **DISADVANTAGES:**

a) False Negative 15%-20%

b) False Positive

- ADVANTAGES

SNL: path

Pathologic intraoperative Evaluation

- **DISADVANTAGES:**

a) False Negative 15%-20%

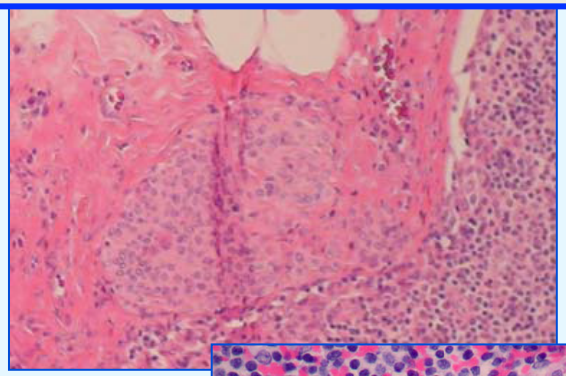
b) False Positive

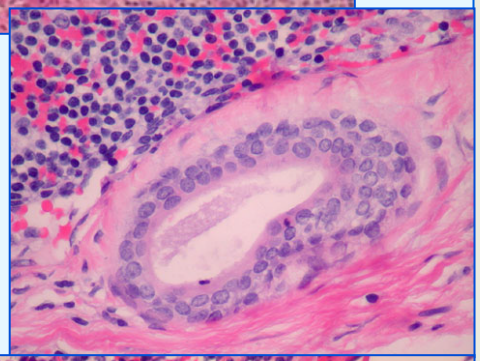
- ADVANTAGES

SNL: path

Pathologic intraoperative Evaluation

FP: potential for false positives



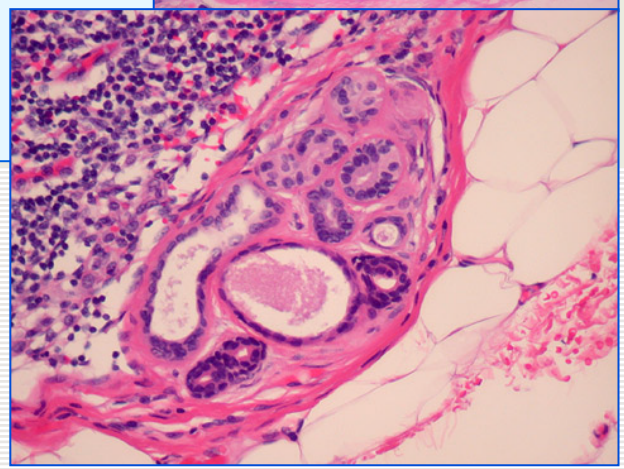


BENIGN INCLUSIONS

- Axilla - benign breast tissue, nodal nevi

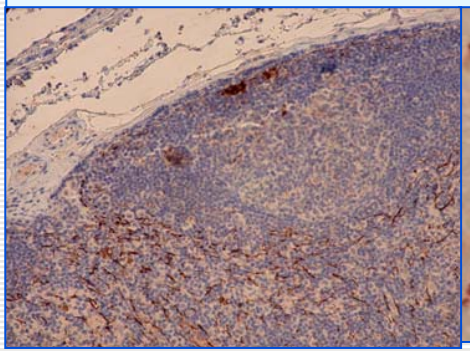
MECHANICAL TRANSPORT OF BENIGN EPITHELIUM

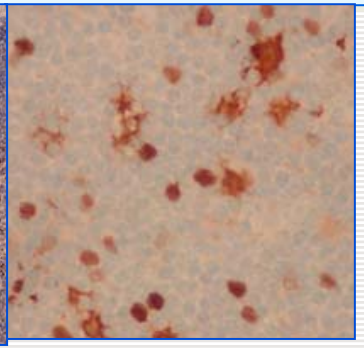
- Breast tissue from biopsy or injection site massage



IMMUNOHISTOCHEMISTRY

- Non specific staining
- Cross reactivity - especially dendritic cells





SNL: path

Pathologic intraoperative Evaluation

Imprint

accuracy 77%-99% sensitivity 30%-96%

FN RATE 6%-70% (mean 31.1%)

Frozen

accuracy 82%-98% sensitivity 55%-91%

FN RATE 9%-45% (mean 22.7%)

Cserni G et al European Journal of Cancer 39 (2003) 1654-1667

≥SNL: path

Pathologic intraoperative Evaluation

FN

Table 6
Studies on the intra-operative assessment of SNs

A	B	LEVELS/	STAINS	F	TP	TN	FP	FN	ACC (%)	SENS (%)	SPEC (%)	PPV (%)	NPV (%)	FNR (%)	FRR (%)
FS	[97]	28	1 (2)	HE	IHC	6	17	0	5	82	55	100	100	77	45	23
FS	[98]	47[a]	NI	HE	HE	10	36	0	1	98	91	100	100	97	9	3
FS	[99]	54	2	HE	Mult. HE + IHC	21	31	0	2	96	91	100	100	94	9	6
		74[a]	2	HE	Mult. HE + IHC	27	43	0	4	95	87	100	100	91	13	9
FS	[100]	62	⩾1	HE	HE + IHC same level	19	34	0	9	85	68	100	100	79	32	21
FS	[13]	96	3 (both sides)	HE	HE	24	68	0	4	96	86	100	100	94	14	6
FS	[101]	107	3 consec	HE	3 HE	32	57	0	18	83	64	100	100	76	36	24
FS	[102]	157	NI	HE	Mult. HE + IHC	41	116	0	18	90	69	100	100	87	31	13
FS	[103]	165[a]	NI	HE	Mult. HE at 2–3 mm	19	141	2	3	97	86	99	90	98	14	2
FS	[104]	203	2	HE	Mult. HE at 2 mm + IHC	53	132	1	17	91	76	99	98	89	24	11
IC + FS	[100]	38	⩾1	MG + IHC/HE	HE + IHC same level	3	25	0	10	92	77	100	100	89	23	11
IC + FS	[105]	278	1	DQ	HE same level	53	206	0	19	93	74	100	100	92	26	8
		278	1	DQ	Mult. HE + IHC	53	167	0	58	79	48	100	100	74	52	26
IC	[106]	25	1	RAL	NI	4	19	0	2	92	66	100	100	90	33	10
IC	[100]	38	1	MG + IHC	HE + IHC same level	6	25	0	7	82	46	100	100	78	54	22
IC	[99]	45	⩾2	DQ	Mult. HE + IHC	14	23	0	8	82	64	100	100	74	36	26
		59[a]	⩾2	DQ	Mult. HE + IHC	16	33	0	10	83	62	100	100	77	38	23
IC	[107]	55	=2	HE	HE same level	14	40	0	1	98	93	100	100	98	7	2
IC	[108]	60	=2	HE	Mult. HE + IHC	19	28	0	13	78	59	100	100	68	41	32
IC	[109]	65	⩾2 (1/slice)	P or DQ	Mult. HE + IHC	17	33	1[c]	14	77	55	97	94	70	45	30
IC	[110]	101	⩾2 (1/slice)	P	HE + IHC same level	30	67	1[c]	3	96	91	99	97	96	9	4
IC	[111]	109	2–6	Giemsa	Mult. HE + IHC	32	63	0	14	87	70	100	100	82	30	18
IC	[112]	124[a]	1	HE	HE same level	22	101	0	1	99	96	100	100	99	5	1
IC	[113]	148	=2	Giemsa and P	3-level HE + IHC	40	86	2	20	85	67	98	95	81	33	19
IC	[114]	150	1	HE	3-level HE, IHC in some	20	113	0	17	89	54	100	100	87	46	13
IC	[115]	161[b]	2	IHC	Mult. HE + IHC	30	126	0	5	97	86	100	100	96	14	4
IC	[116]	381[b]	2	DQ	Mult. HE + IHC	15	254	1	35	88	30	100	94	88	70	12
IC	[103]	479[a]	>1	HE	Mult. HE at 2–3 mm	65	409	1	4	99	94	100	98	99	6	1

A, Method; B: reference; C: number of patients; D: number of levels studied intraoperatively; E: stains used intraoperatively; F: final histopathology details: SN,

Ultrarapid cytokeratin ICC/IHC enhances the intraoperative detection of SN micrometastases and metastases of invasive lobular carcinoma

Cserni G et al European Journal of Cancer 39 (2003) 1654-1667

SNL: path

Pathologic intraoperative Evaluation

ORIGINAL ARTICLE

Effectiveness of Sentinel Lymph Node Intraoperative Examination in 753 Women With Breast Cancer

Are We Overtreating Patients?

Mario Taffurelli, MD, Isacco Montroni, MD,* Donatella Santini, MD,† Monica Fiacchi, MD,* Simone Zanotti, MD,* Giampaolo Ugolini, MD, PhD,* Margherita Serra, MD,* and Giancarlo Rosati, MD, PhD**

(*Ann Surg* 2012;255:976–980)

- Overall 54% sensitivity and 100% specificity in detecting Ma/Mi/ITCs

- Sensitivity :

89% if only Mas were considered

64% if Mas and Mis were counted together

SNL: path

Pathologic intraoperative Evaluation

ADVANTAGES:

one-step surgical procedure about 25% pts

DISADVANTAGES:

a) False Negative 15%-20%

b) False Positive

SNL: path

...WHEN...HOW.. AND WHAT...search

ADVANTAGES:

one-step surgical procedure about 25% pts

DISADVANTAGES:

a) False Negative 15%-20%

b) False Positive

...WHY...? nical QUESTION

SNL: path

…WHEN……

- Intraoperatively
- **Pre**operatively
- **Post**operatively

Permanent Sections

……Clinical **QUESTION**

SNL: path

...WHEN.....

- Intraoperatively
- **Preoperatively**
- Postoperatively

.....Clinical **QUESTION**

SNL: path

Pathologic pre-operatively Evaluation

1. FNA Cytology

SNL: path

Pathologic PREoperative Evaluation

Role ultrasound-guided FNC

- Sensitivity: 58.6%
- Specificity: 100%
- FNAC identifies 59% of N+ cases/26% of study cases

Axillary lymph node cytology can save SLN procedures and is recommended as routine practice.
Routine axillary ultrasonography, with cytology of sonographically visible lymph nodes,followed by immediate axillary dissection only in case of positive cytology proved to be the best approach in terms of cost-benefit ratio.

Brancato B et al Radiol Med 108: 345-355, 2004

Pretreatment axillary ultrasonography and core biopsy in patients with suspected breast cancer: Diagnostic accuracy and impact on management☆

Maria Jose Garcia-Ortega[a,*], Marina Alvarez Benito[a,1], Elena Fuentes Vahamonde[b,2], Pilar Rioja Torres[c,3], Ana Benitez Velasco[d,4], Maria Martínez Paredes[e,5]

[a] Breast Imaging Center, Radiology Department, Hospital Universitario Reina Sofia, Avda. Menendez Pidal s/n, 14004 Cordoba, Spain
[b] Pathology Department, Hospital Universitario Reina Sofia, Avda. Menendez Pidal s/n, 14004 Cordoba, Spain
[c] Clinical Management Unit, Department of General and Digestive Surgery, Hospital Universitario Reina Sofia, Avda. Menendez Pidal s/n, 14004 Cordoba, Spain
[d] Nuclear Medicine Department, Hospital Universitario Reina Sofia, Avda. Menendez Pidal s/n, 14004 Cordoba, Spain
[e] Radiology and Physical Medicine Area, University of Cordoba Medical School, Avda. Menendez Pidal s/n, 14004 Cordoba, Spain

Ultrasonography and axillary core biopsy enable adequate pretreatment staging in patients with breast cancer and has a positive impact in their management

- Sensitivity 69.1%
- Specificity 100%

SNL: path

Pathologic PREoperative Evaluation

Role ultrasound-guided FNC

- Sensitivity: 58.6%
- Specificity: 100%
- FNAC identifies 59% of N+ cases/26% of study cases

Axillary lymph node cytology can save SLN procedures and is recommended as routine practice.
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Brancato B et al Radiol Med 108: 345-355, 2004

SN biopsy was avoided in 33% of pts triaged directely to ALND

SNL: path

…WHEN……

- Intraoperatively
- **Pre**operatively
- **Post**operatively

Permanent Sections

……Clinical **QUESTION**

SNL: path

...WHEN...HOW.. AND WHAT...search

1.PARAFFIN-EMBEDDED

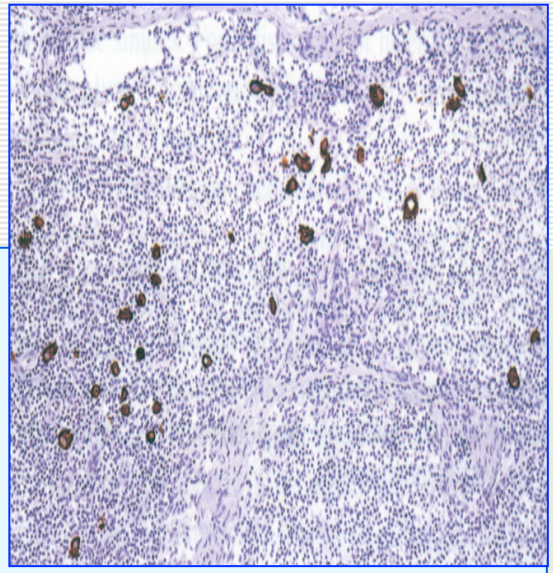
Permanent Sections

Pathologic PRE-POSToperative Evaluation

Permanent Sections

- Standard: MULTILEVEL ASSESSMENT
- This increases the likelihood of finding MIC
- Range:2-5 levels /100-200 µm intervals.
- Distance between levels NOT STANDARDIZED and ranges from 10 to 500 µm

Role of Immunostains



- Performed to increase the likelihood of detection of MIC
- Abs: cytokeratin (CK) -AE1/AE3, MNF116,CAM5.2, CK19
- Commonly suggested for evaluation of nodes from a patient with LOBULAR CARCINOMA.

Role of Immunostains

CRITICAL ISSUE

1. When H&E sections are negative ?
2. Only in dubious cases ?
3. Which antibody?

- CAM 5.2 sensitivity 100%
- AE1/AE3 pool of cytocheratins
- MNF116
- EMA
- MUC 1 low sensitivity and low specificity

≥SNL: path

Role of Immunostains

..WHY YES?

a) More accurate staging

b) Reduce FALSE NEGATIVE

c) Easier identification of MIC and ITC

Cserni G et al BJC 2004

Role of Immunostains

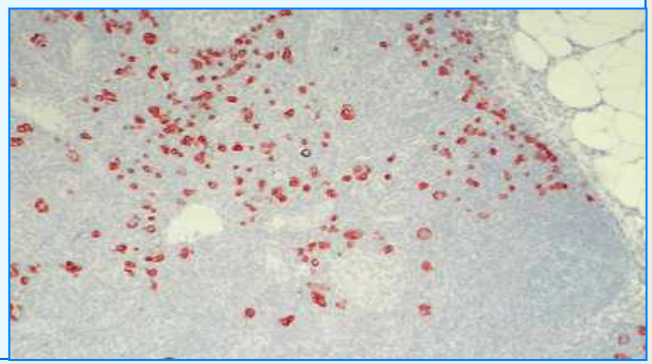
WHY NOT?

Intensive routine use of IHC is not without controversy and is not uniformly recommended

1. Increased cost
2. These methods detect ITCs.
3. Poor significance and NO practical relevance of these cells

Role of Immunostains

- IHC is more commonly performed for evaluation of nodes from a patient with lobular carcinoma.



PATHOLOGICAL ASSESSMENT

CRITICAL ISSUE

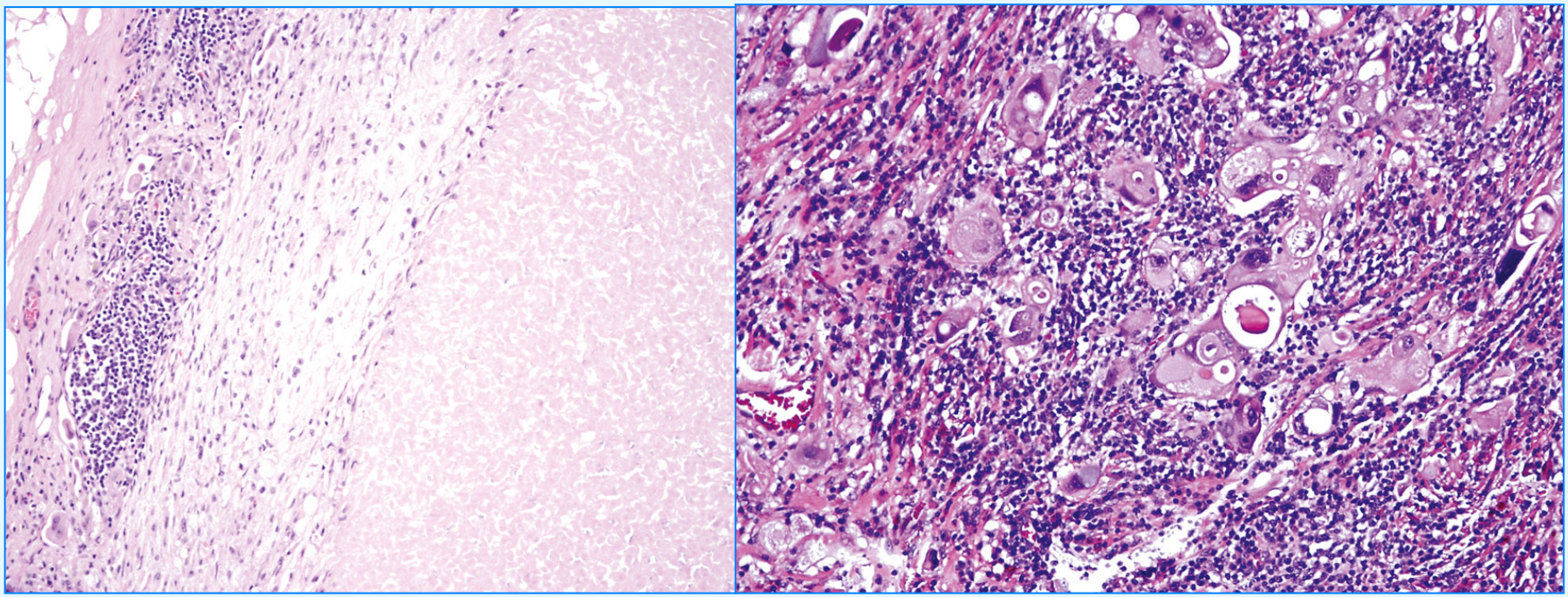
Extranodal Invasion

- **Associated with increased likelihood of non-SLN involvement.**
- **Classified into minimal (if < 1 mm beyond the capsule) or prominent (if > 1 mm).**
- Documentation of extranodal fat involvement is easier on the capsular surface but is often difficult in hilo

PATHOLOGICAL ASSESSMENT:

CRITICAL ISSUE

Pathological assessement post Primary CTh



SNL: path

...WHEN.....

Classic nodal staging scenario includes

- **Intraoperative pathological** assessment of the SLN (frozen sections, touch imprints, scrapes or a combination of these, or molecular)

- **Pre-Postoperative Formalin** Fixed-Paraffin embedding of the remaining tissues or all SNL and PERMANENT SECTIONS used for a final pathological diagnosis of the nodes

≥SNL: path

...1999.....2013...

PATHOLOGICAL ASSESSMENT:

a)PATHOLOGICAL PROTOCOLS
b)Histological evaluation: macrometastases, micrometastases,ITC

c)Team approach CRITICAL ISSUE
d)Impact on pathology dept

SNL: path

Pathologic Evaluation

CRITICAL ISSUE

- Time consuming for lab personnel
- Dramatic increase in workload
- Full protocol cannot be performed quickly, inexpensively

SNL: path

…1999……2013…

…WHAT ..learned..

PATHOLOGICAL ASSESSMENT:

- Predictive value is "TEAM SPECIFIC
- Predictive value is "METHOD SPECIFIC”

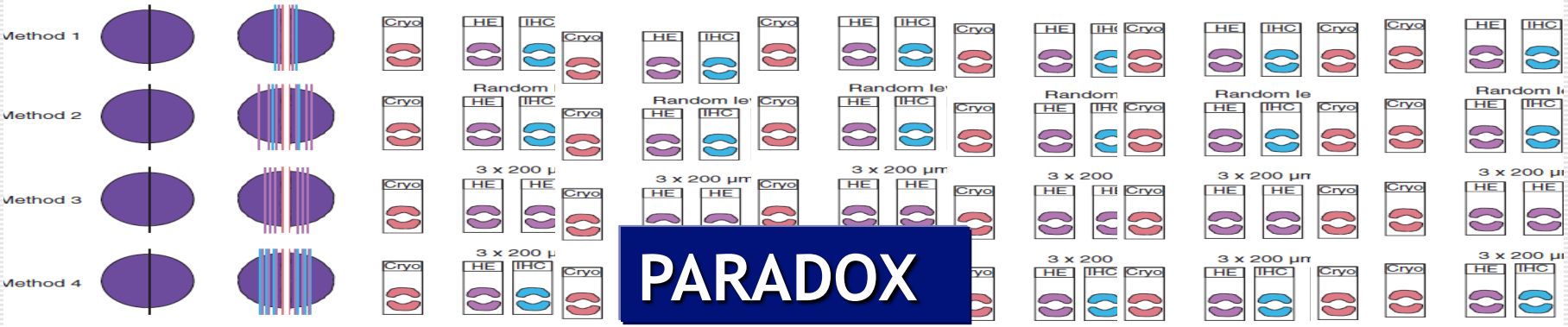
- Sensitivity vs acceptable work-load

SNL: path

…1999……2013…

…WHAT ..learned..

UPSTAGING OF PATIENTS



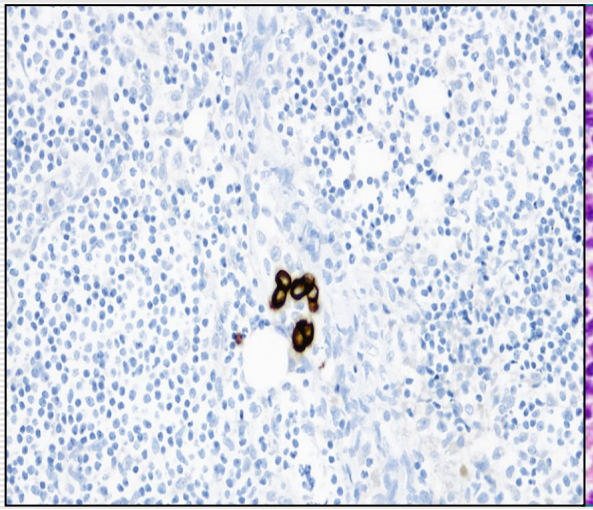
PARADOX

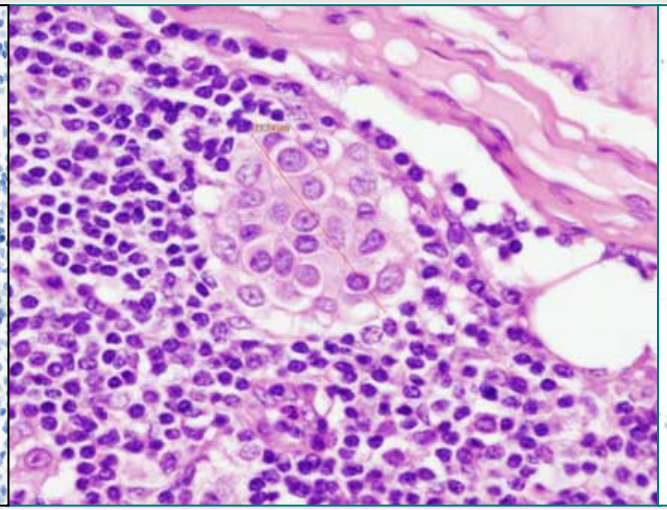
Increase and improvement in
'IDENTIFICATION OF A MINIMAL TUMOR VOLUME"
in SLN led to progressive **'SLIP'** of the traditional concept and significance of
lymph node STAGING

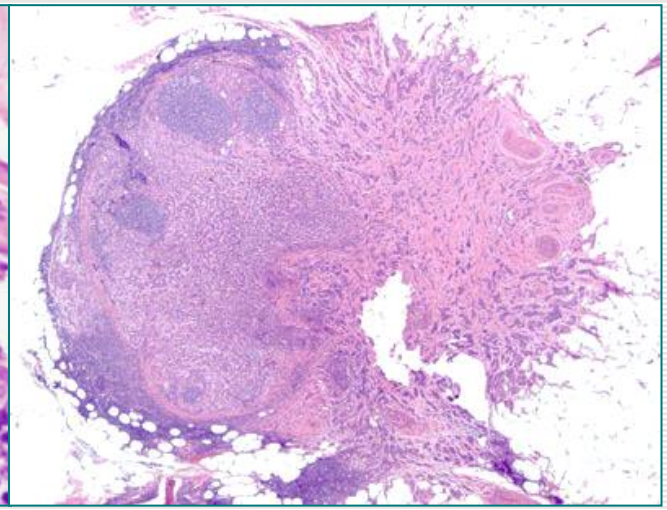
SNL: path

..2013

Goal: Identify clinically Significant metastatic deposits





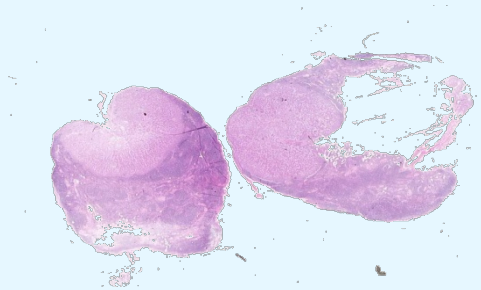


SNL: path

...WHAT ..learned..

Although **HISTORICALLAY lymph node status** is has been considered the **most relevant single prognostic factor of breast cancer**, there are **NOW LIMITATIONS** in establishing its **real prognostic information**

STAGING - pTNM



pN -

pN +

SNL: path

Anni 70-80

+/-NIENTE
+/- TAM
+/- Chemioterapia (CMF, AC)

Anni 90

+/- NIENTE
+/- TAM
+/-LHRH analoghi
+/-Inibitori aromatasi
+/- Chemioterapia (FEC; antracicline-CMF)

Fine anni 90- anni 2000

+/- inibitori aromatasi
+/- TAM
+/- LHRH analoghi
+/- Chemioterapia (antra/taxani)
+/- Trastuzumab
..... **Trial RCT**.....

..2013

SNL: path

Anni 70-80

+/-NIENTE

Most patients receive systemic adjuvant treatment, and prognostic marker reflects the effect of that factor

..... Trial RCT.....

..2013

≥SNL: path

Anni 70-80

+/-NIENTE

+

+

Currently, lymph node status has decreased in importance both in terms of prognosis and treatment planning

..... Trial RCT.....

..2013

SNL: path

Although some data suggests that MIC are of prognostic importance, there has also been a major evidence suggesting that MIC detected in SLN do not have the same bearing on prognosis as MICs from older series

..2013

1. MIRROR TRIAL
2. ACOSOG Z0010 Trial
3. NSABP B-32 trial (5611 pts)
4. ACOSOG Z0011 trial
5. Trial 23-01 of the International Breast Cancer Study Group (IBCSG)

≥SNL: path

...WHEN...HOW..WHAT...search

..... it seems that MIC should not be looked for in SLN samples, and the general recommendation of identifying possibly all MACROMETASTASES would be further supported.....

..2013

SNL: path

…WHEN…HOW..WHAT…search

- Intra-operatively
- Pre-operatively
- Post-operatively

SNL: path

...WHEN...HOW.. AND WHAT...search

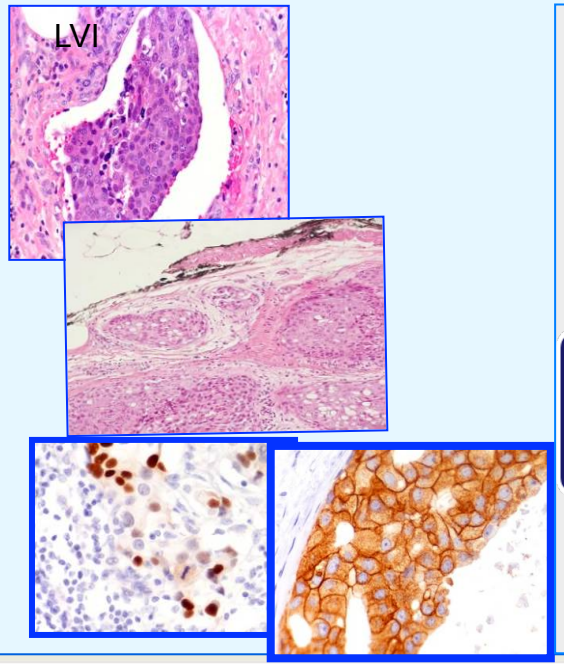
..... MACROMETASTASES
on FROZEN SECTION
and
STANDARD HISTOPATHOLOGY
result in a
HIGH acceptable sensitivity.....

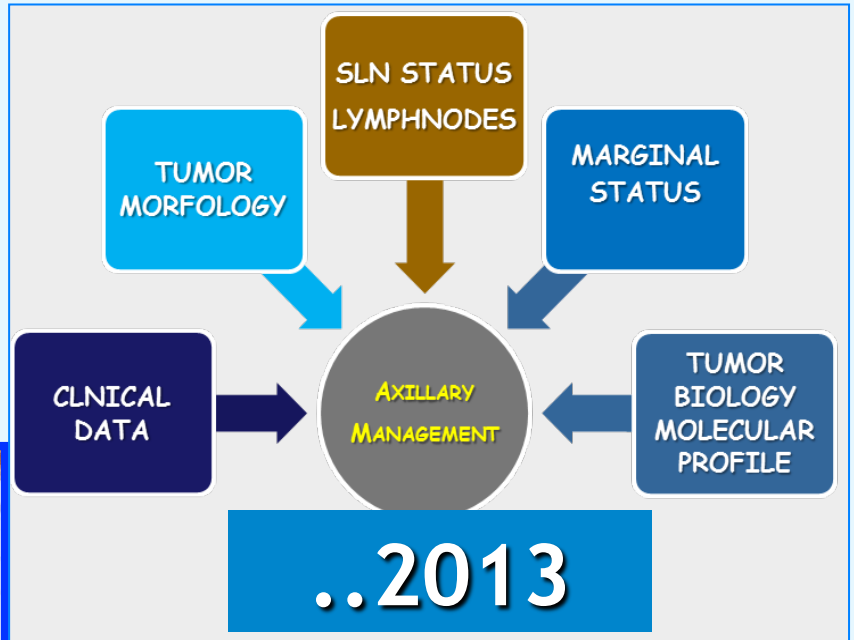
SNL: path

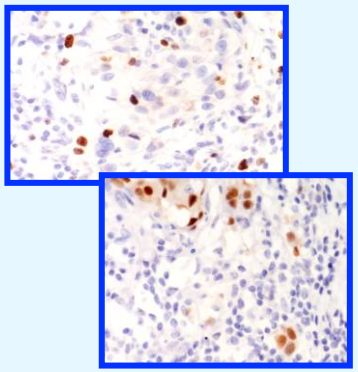
CRITICAL ISSUE

Intra-operatively

....final decision based on more complex and complete information .....







CRITICAL ISSUE

..2013

PATHOLOGICAL ASSESSMENT:

1. Prognostic value of 'low-volume' nodal disease: is its diagnosis necessary?
2. Are all small-volume metastases similar or do they behave similarly?
3. Is size the only variable that defines therapeutic options?
4. How adequate are classical variables in the TNM staging system?

⩾SNL: path

CRITICAL ISSUE

..2013

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CRITICAL ISSUE

..2013

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SNL: path

CRITICAL ISSUE

..2013

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SNL: path

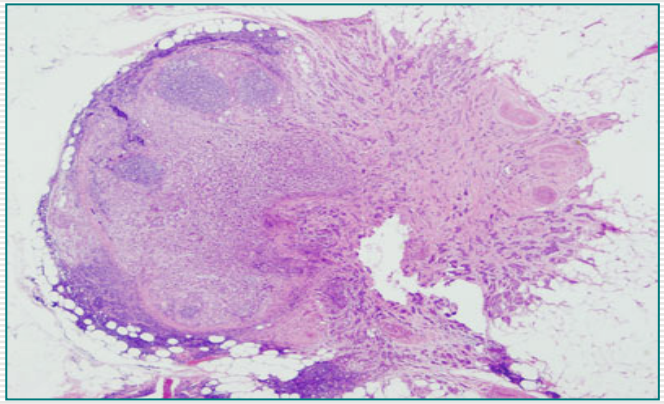
CRITICAL ISSUE

..2013

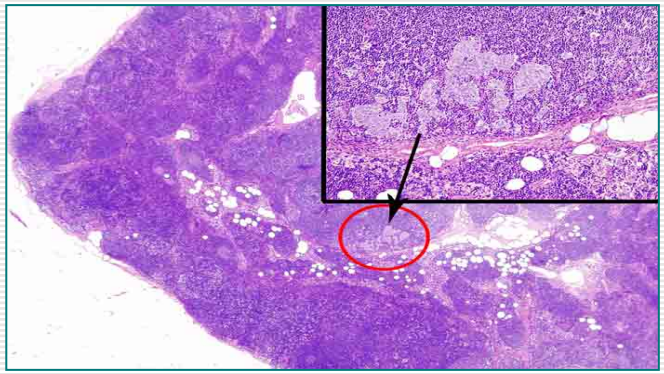
CLINICALLY SIGNIFICANT TUMOR BURDEN

Goal: CLINICALLY SIGNIFICANT TUMOR BURDEN

Macrometastasi



Micrometastasi



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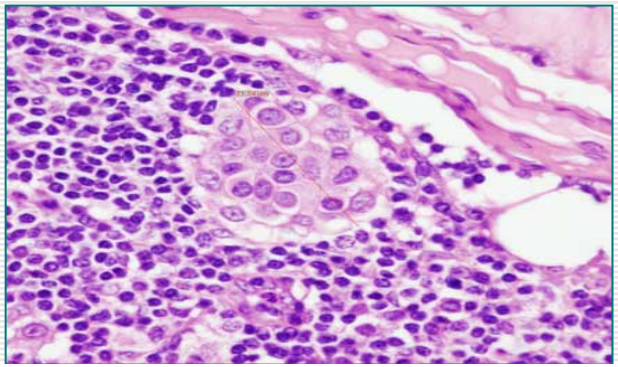
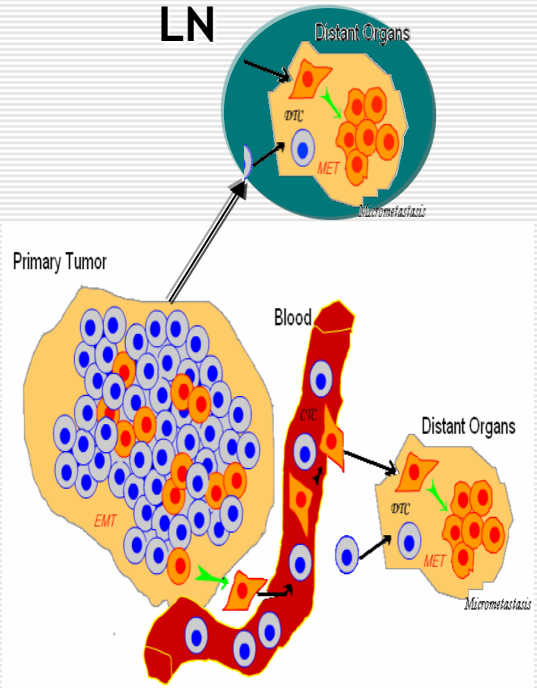
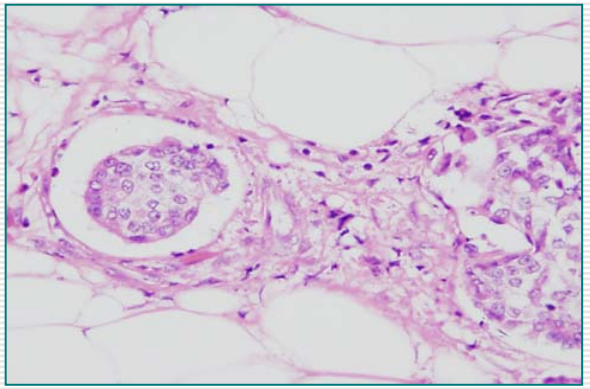


LN



LVI



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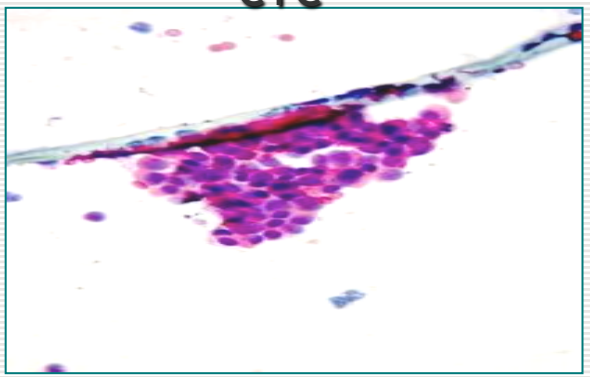

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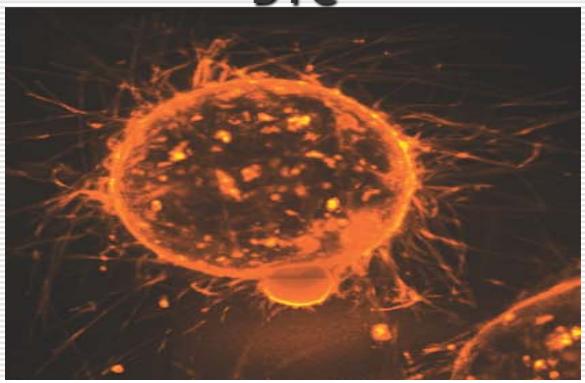
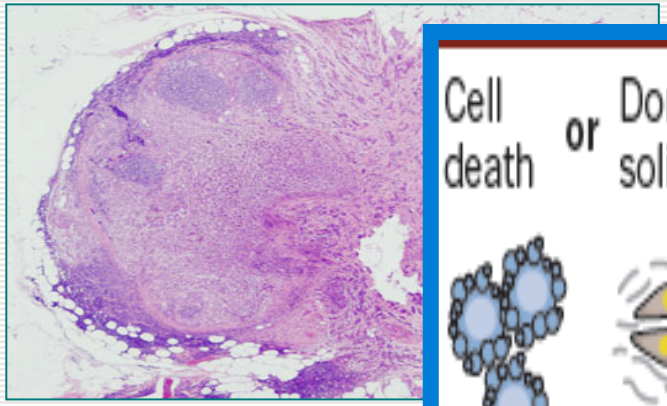


≥Goal: CLINICALLY SIGNIFICANT TUMOR BURDEN

Macrometastasi



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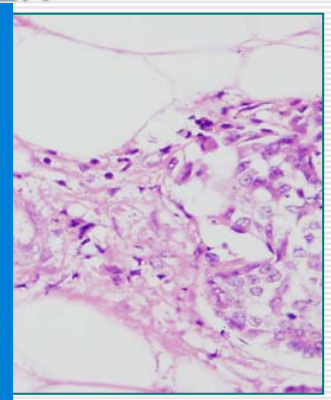
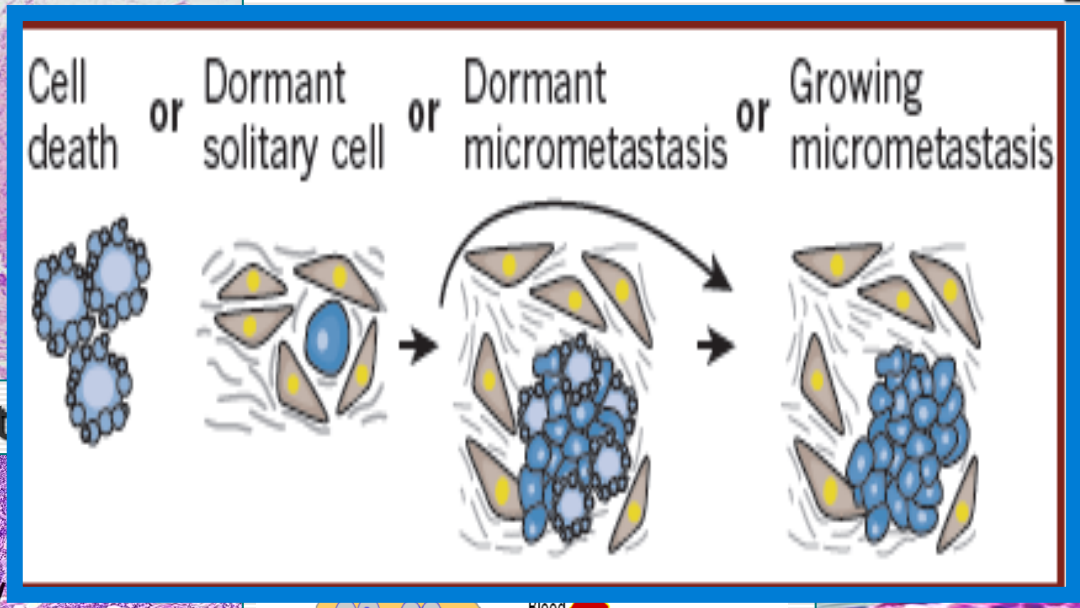
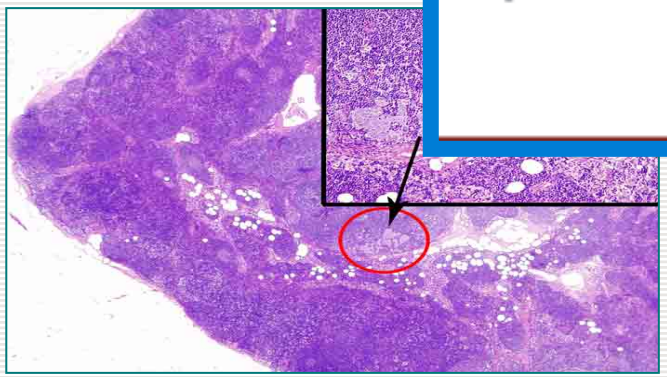




Micrometast



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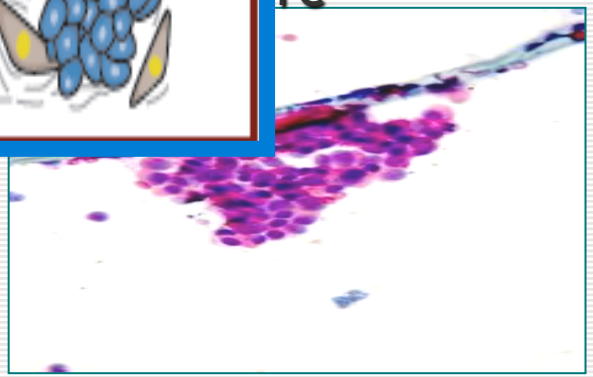

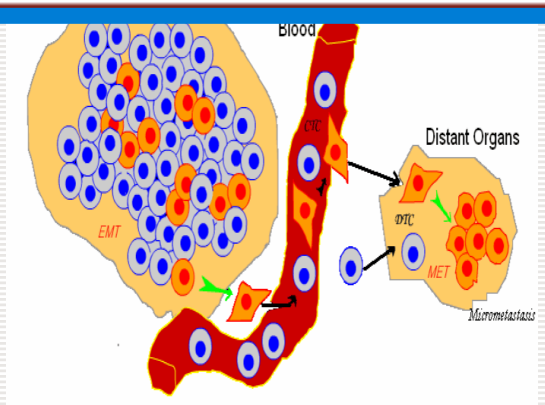

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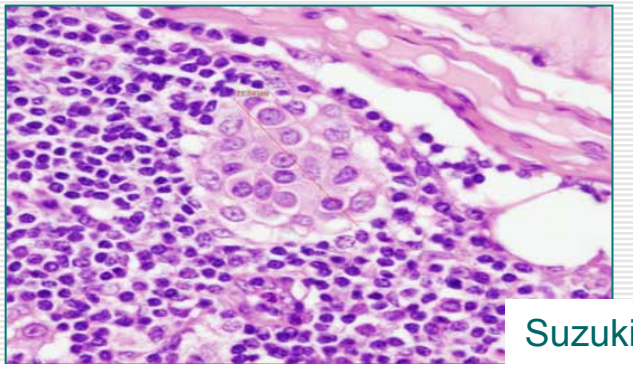

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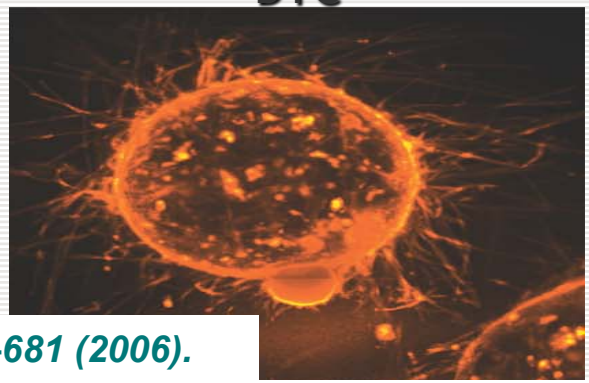
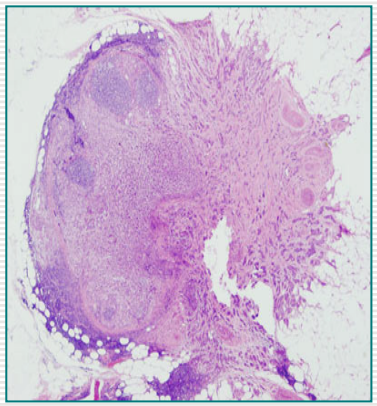


Suzuki, M. *et al. Am. J. Pathol.* ***169, 673–681 (2006).***

≥Goal: CLINICALLY SIGNIFICANT TUMOR BURDEN

Macrometastasi



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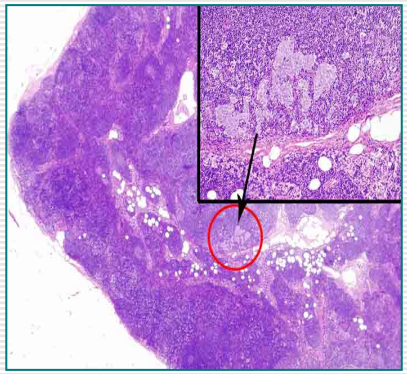

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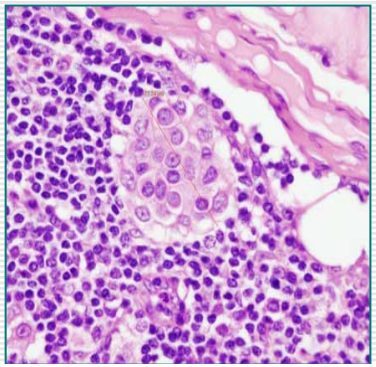
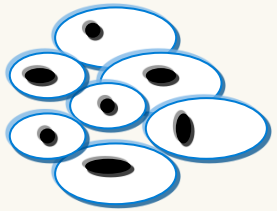
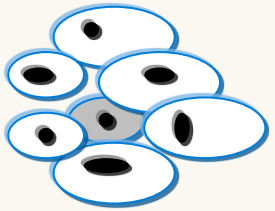


Nature 485, S55,2012



NO tumor staminal cells



Yes Tumor staminal cells

METASTASIS

The rude awakening

If detected early, most cases of breast cancer seem to be curable. But the tumour's deadly offspring could be sleeping in the body.

BY JOCELYN RICE

Ann Chambers has a series of graphs tacked up in her office at the London Regional Cancer Program in Canada, where she is an oncologist. "I stare at them all the time," she says.

These charts are assembled from more than 60 years of data gathered at the MD Anderson Cancer Center in Houston, Texas, and show how the ten-year survival curves for local and metastatic breast cancer have changed over the decades (see 'The hard facts', page S56). The picture they paint of breast cancer, Chambers says, has regions of darkness and light.

On the one hand, the overall survival rate of patients with breast cancer has vastly improved. Sixty years ago, only a quarter of patients were alive ten years after being diagnosed; now, that figure exceeds three-quarters. On the other hand, for patients whose tumour has metastasized — spread to distant sites outside the breast — at the time of diagnosis, the picture remains dismal. Even now, a patient with metastatic breast cancer has only a 22% chance of surviving more than ten years.

The graph that troubles Chambers most, however, is the one for patients with local breast cancer who show no evidence of metastasis at diagnosis. Decade after decade, the survival curves for these patient cohorts decline over time, with the current ten-year survival rate at 86%. The implication is that, despite appearing free of disease, "there are hidden tumour cells in these women", says Chambers. These cells are lurking in a state of suspended animation. It might be a rare event; however, even 25 years after diagnosis, these dormant cells can reawaken, growing into a full-blown metastasis and ultimately killing a patient who was once considered to be cured.

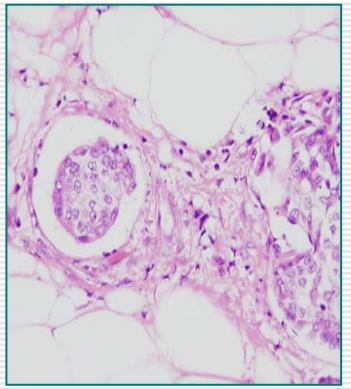
The cells that give rise to such late metastases remain mysterious. Where are they hiding? Why do they reawaken? "This is a very peculiar biology," says Klaus Pantel, an oncologist at the University Medical Center Hamburg-Eppendorf in Germany. "If we can understand what the body is doing to control this cancer for 10 or 15 years, and what stops this control and eventually leads to metastatic relapse, we can foresee completely new strategies for controlling disseminated cancer."

SEEDS AND SOIL

One thing we do know about these dormant cells is where they originally came from. In most patients who develop metastases, tumour cells have already undergone a cascade of transformations at the time of diagnosis, allowing many of them to escape from the primary lesion (see "The right trait', page S58). These cells enter the bloodstream, either directly or by way of the lymph nodes, and circulate through the body. In cancer, "dissemination is an early event", says Christoph Klein, a cancer biologist at the University of Regensburg, Germany. Indeed, research by Klein and others shows[2] that escaped tumour cells can sometimes be detected even in patients diagnosed with ductal carcinoma *in situ* (DCIS), an early-stage breast cancer in which the tumour appears to be confined to the lining of the milk ducts.

NATURE.COM
For more of the latest research on breast cancer:
go.nature.com/gypxbk

LVI



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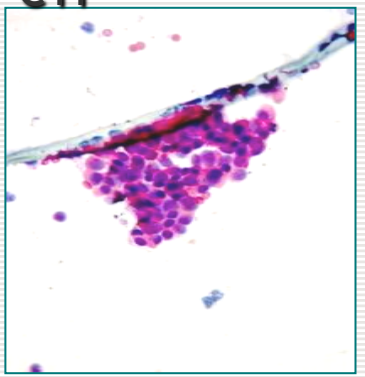

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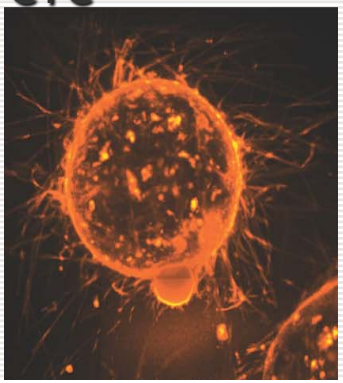

SNL: path

CRITICAL ISSUE

..2013

Traditional system of staging is still valuable in the context of the new "bio-pathological setting of 5 biomolecular classes of breast cancer and in a " pre-molecular ERA "?

SNL: path

CRITICAL ISSUE

..2013

CERTAINTY……

"Lymph node metastases are indicators and not governors of distant metastases"

Blake Cady 1984

molecular ERA "?

There are truths so clear that escape us, and the truth hidden by so hit us Xavier Wheel