Margins in Breast Conservative Surgery (BCS)

The surgeon's point of view

The pathologist's point of view

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SURVIVAL IN BCS

Survival of early breast cancer patients after breast-conserving surgery and radiotherapy is equivalent to survival after mastectomy

Fisher B et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. ***N Engl J Med*** *2002; 347: 1233–1241*

Veronesi U et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. ***N Engl J Med*** *2002; 347: 1227–1232*

MAIN ISSUES IN BCS

1)How much free margin is enough?

2) Does the surgical margin influence the result of BCS?

3) What does “local recurrence” mean?

4)What is the prognosis after local recurrence?

5) Are there other risk factors for local recurrence?

6) Positive or close margins: how the risk can be reduced?

7) Positive/close margin: what to do?

HOW MUCH FREE MARGIN IS ENOUGH?

NO CONSENSUS !

Greater than 1 mm ?

Gage I. Cancer 1996
Anscher MS. Ann Surg 1993
Park CC. J Clin Oncol 2000

Greater than 2 mm ?

Freedman G. Int J Radiat Oncol Biol Phys 1999
Smitt MC. Cancer 1995

Greater than 3 mm ?

Pittinger TP, Surgery 1994

Greater than 5 mm ?

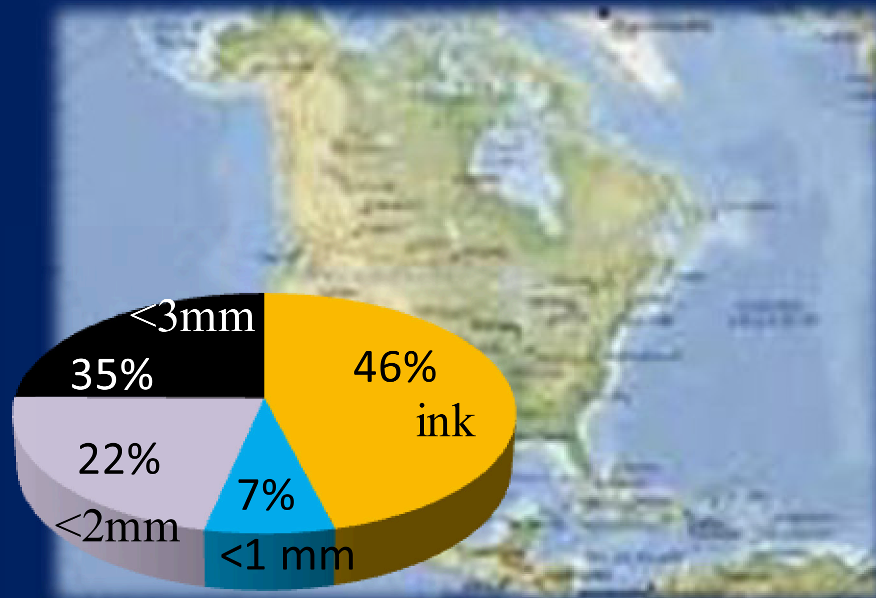
Vicini FA, J Surg Oncol 2001

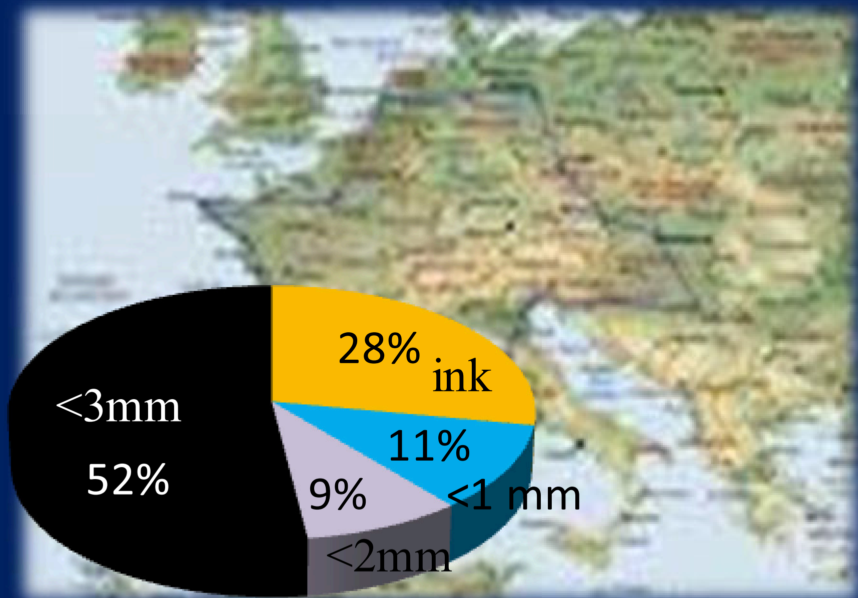
PERCEPTION ABOUT SURGICAL MARGIN STATUS AFTER BCS

Mail questionnaire

702 members of American Society of Therapeutic Radiology and Oncology

431 members of European Society of Therapeutic Radiology and Oncology





$p<0.001$

Taghian A. Ann Surg, 2005

DOES THE SURGICAL MARGIN INFLUENCE THE RESULT OF BCS?

LOCAL RECURRENCE

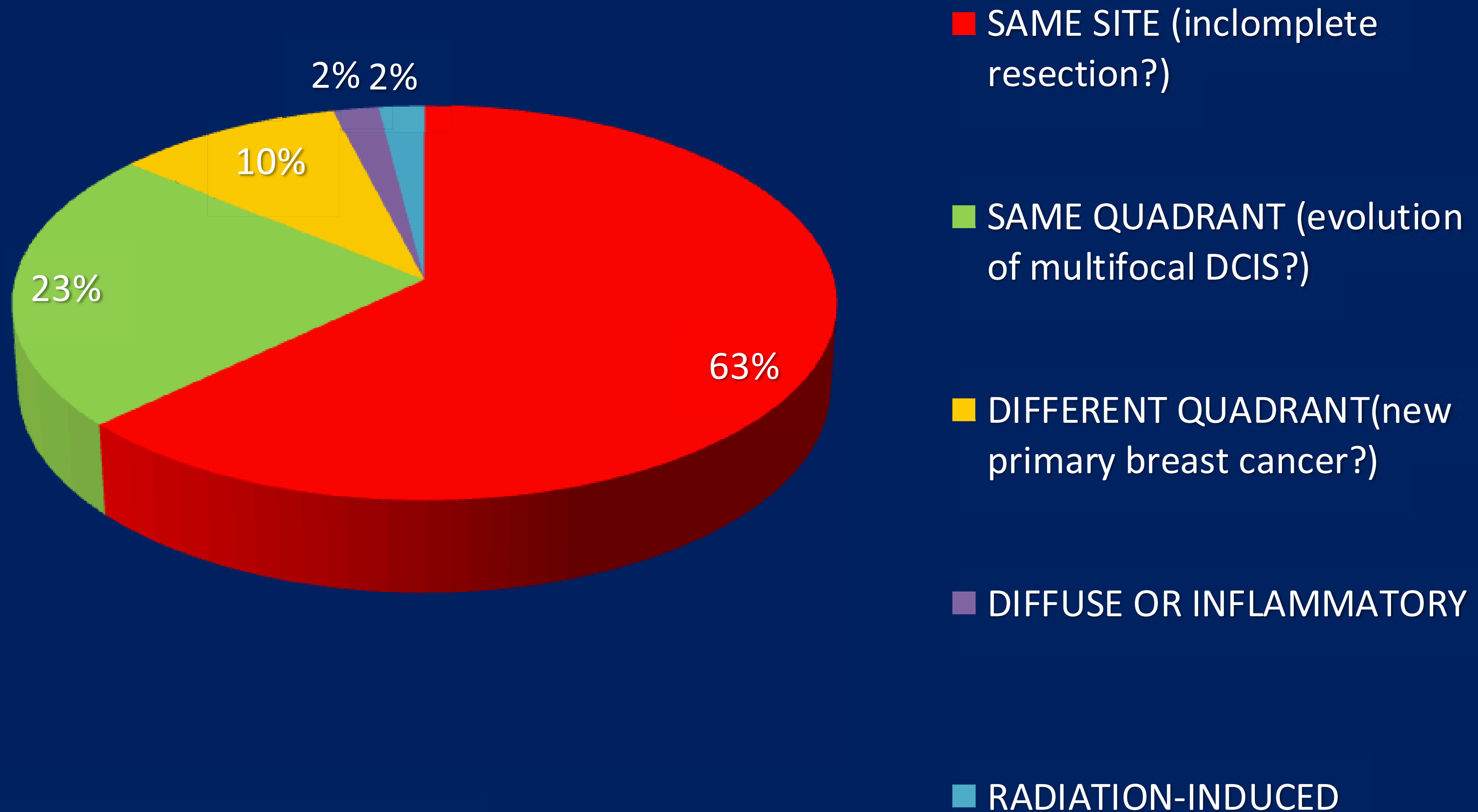
	NEGATIVE MARGIN (> cut-off)	POSITIVE /CLOSE MARGIN (<cut-off)
CUT OFF 1 mm *(Gage 1996; Park 2000; Auscher 1993; Tafra 1993)*	1.5 – 5%	2 – 22%
CUT OFF 2 mm *(Smitt 1995; Freadman 1999; Park 2000; Peterson 1999)*	1 – 7%	2 – 17%

DOES THE SURGICAL MARGIN INFLUENCE THE RESULT OF BCS?

YES!

Most of the published studies show that the margin status does influence the risk of recurrence, but the impact on overall survival has not been clearly demonstrated

WHAT DOES "LOCAL RECURRENCE" MEAN?



(Huston TL. Am J Surg, 2005)

WHAT IS THE PROGNOSIS AFTER LOCAL RECURRENCE?

Usually local recurrence after BCS is not associated with distant metastasis, in contrast to chest wall recurrence after mastectomy, in which metastasis rate is 25-50%

(Huston TL. Am J Surg, 2005)

More recent studies pointed out that local has a borderline significant impact on the occurrence of distant metastases or death, with an HR of 2.2 (95% CI 1.1-5.8) (p=0.066)

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(Botteri E. Ann Oncol ,2010)

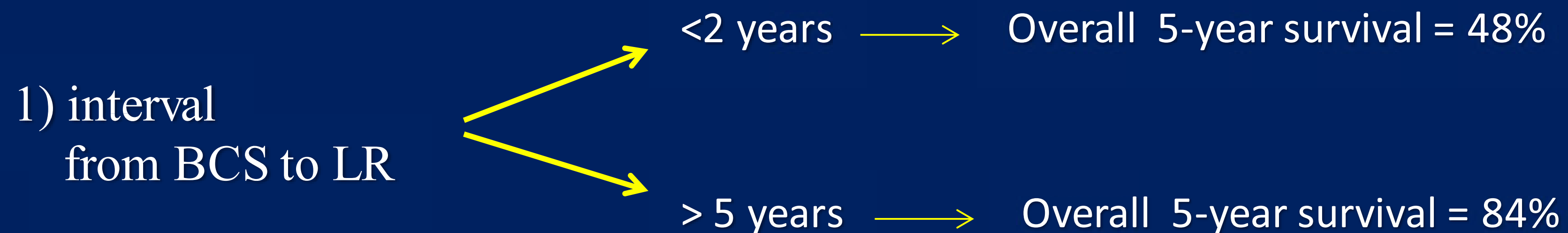
WHAT IS THE PROGNOSIS AFTER LOCAL RECURRENCE (LR)?

- Overall 5-year survival = 48 – 92%
- Median survival time = 103 months
- Median time to second relapse = 97 months

Solin LJ. Int J Radiat Oncol Biol Phys, 1994
Osborne MP. Surg Gynecol Obstet, 1992
Abner AL. J Clin Oncol ,1993
Curtz JM. Cancer, 1990

WHAT IS THE PROGNOSIS AFTER LOCAL RECURRENCE?

it depends on:



2) histologic type of LR

3) site and stage of LR

4) methods of detection

5) status of axillary lymph nodes

(Huston TL. Am J Surg, 2005)

ARE THERE OTHER RISK FACTORS FOR LOCAL RECURRENCE?

1) Pathologic margins status

2) Age < 50 years

3) Grading and comedo-subtype

4) Large tumor size

5) Positive lymph nodes

6) No postoperative RT

7) No postoperative chemotherapy or endocrine therapy

POSITIVE/CLOSE MARGINS: HOW CAN THE SURGEON AND THE PATHOLOGIST REDUCE THE RISK?

1) precise assessment of tumor localization
2) very wide excision (?)
3) intraoperative pathological margin examination (?)
4) re-resection for sampling of residual cavity (shaving)

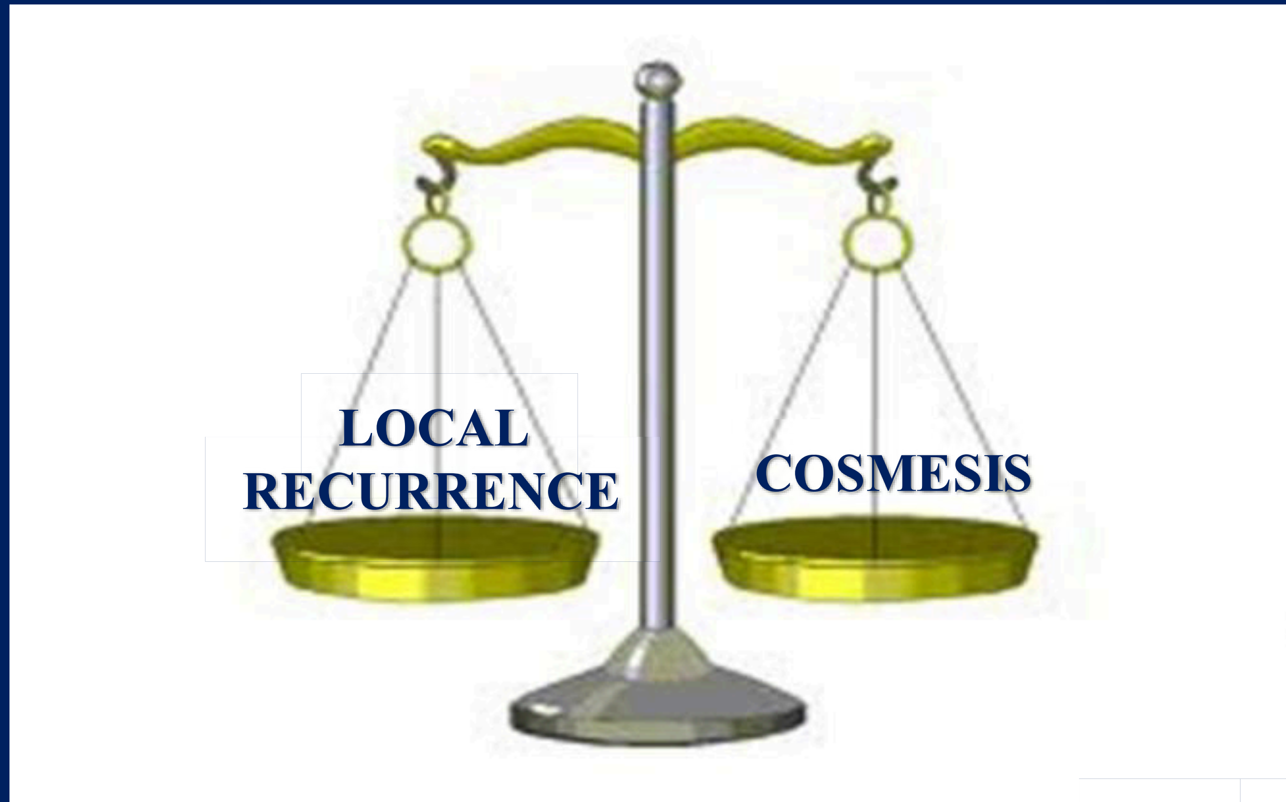
POSITIVE/CLOSE MARGINS: HOW CAN THE SURGEON AND THE PATHOLOGIST REDUCE THE RISK?

PRECISE ASSESSMENT OF TUMOR LOCALIZATION

1) intraoperative ultrasound-guided localization
2) wire-guide localization
3) radioguided occult lesion localization (ROLL)
4) intraoperative specimen radiography

POSITIVE/CLOSE MARGINS: HOW CAN THE SURGEON AND THE PATHOLOGIST REDUCE THE RISK?

VERY WIDE EXCISION (?)



Holland R, Cancer, 1985
Veronesi U, Eur J Cancer, 1990

POSITIVE/CLOSE MARGINS: HOW CAN THE SURGEON AND THE PATHOLOGIST REDUCE THE RISK?

INTRAOPERATIVE PATHOLOGICAL MARGIN EXAMINATION (?)

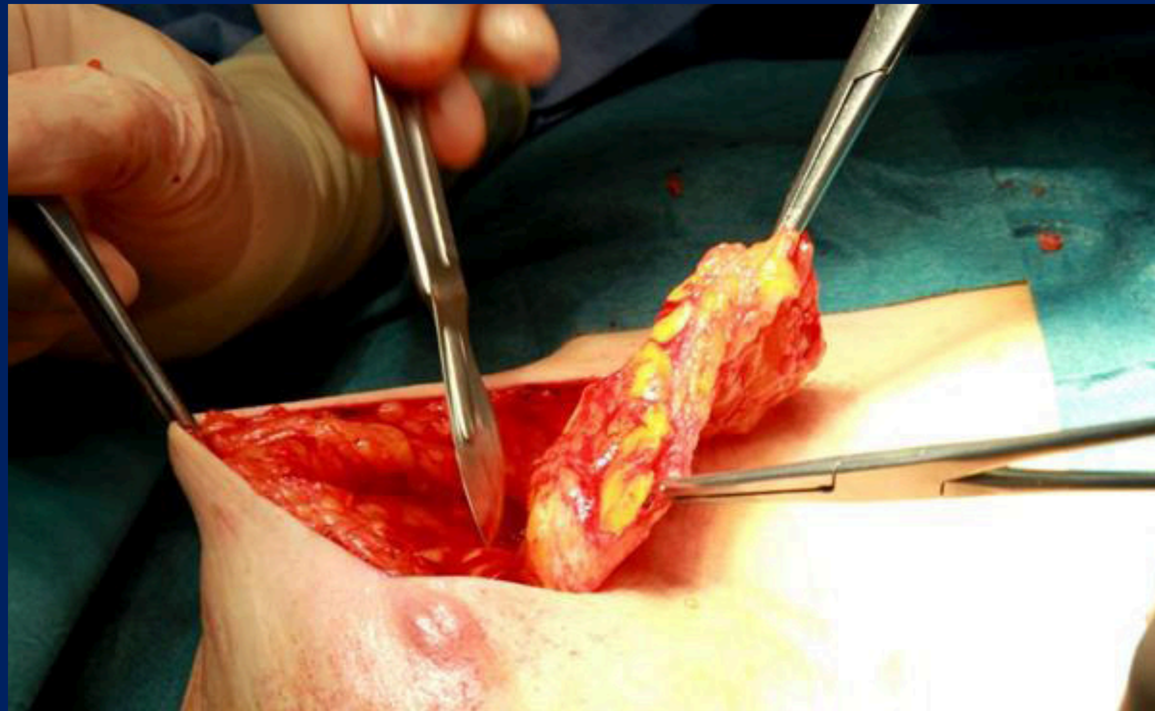
Impossible serial sampling of specimen margins: possible failure in detecting small tumors or DCIS (specificity nearly 100% but sensitivity nearly 65-78%)

Prolonged operation time (about 30 minutes)

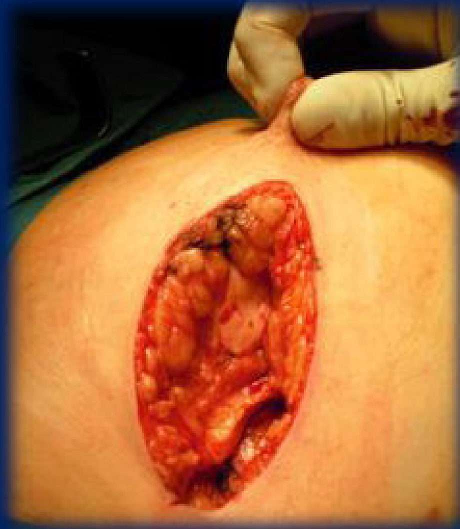
Pleijhuis RG, Ann Surg Oncol 2009
Cendan JC, J Am Coll Surg, 2005
Olson TP, Surg Oncol 2007

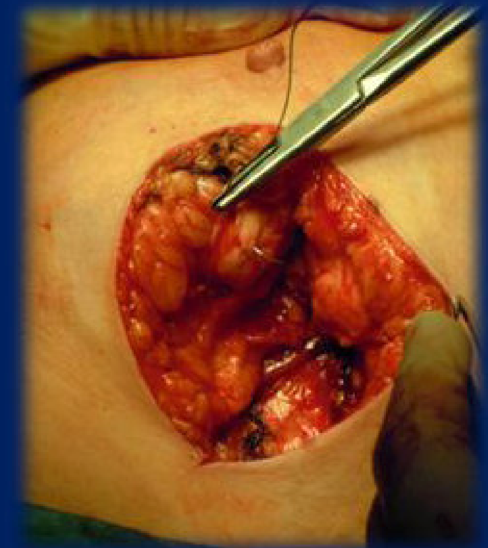
POSITIVE/CLOSE MARGINS: HOW CAN THE SURGEON AND THE PATHOLOGIST REDUCE THE RISK?

RE-RESECTION FOR SAMPLING OF RESIDUAL CAVITY (SHAVING)



RE-RESECTION FOR SAMPLING OF RESIDUAL CAVITY (SHAVING)



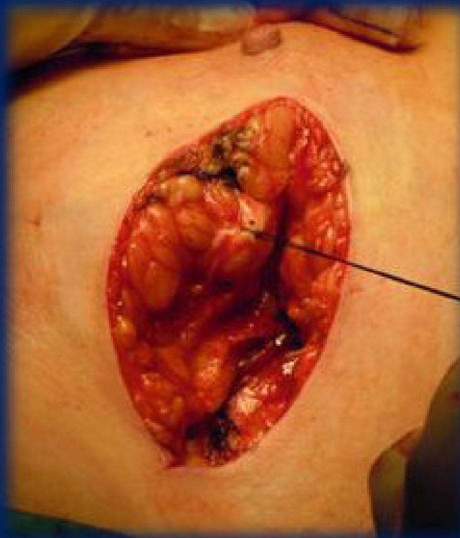


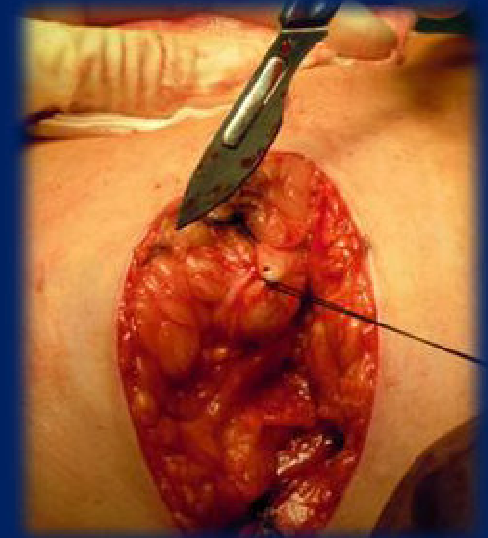
PROS

- Accuracy in margins assessment
- Higher rate of negative resection margins
- Lower re-operation rate
- Costs

CONTRAS

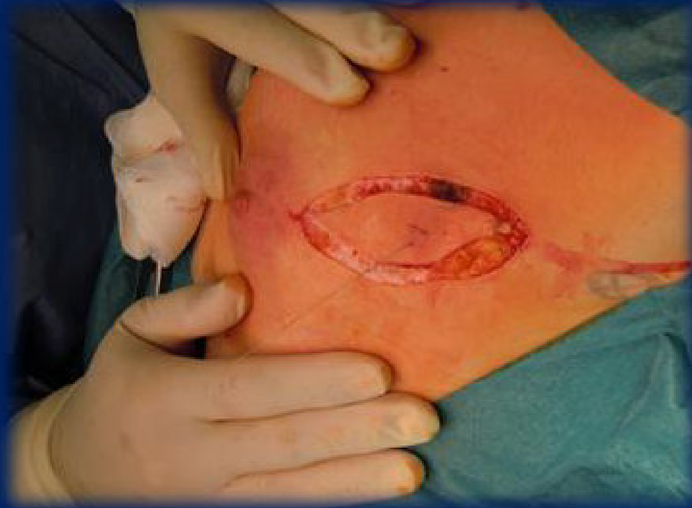
- Resection volume and cosmetic outcome (?) ⟶ **NO!**

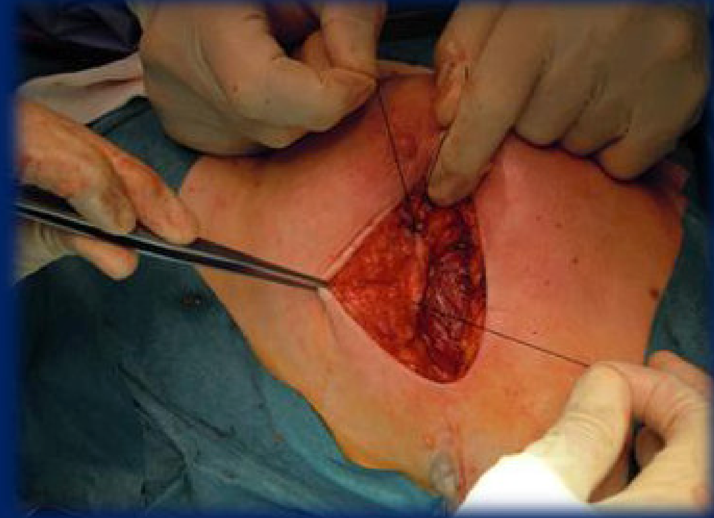


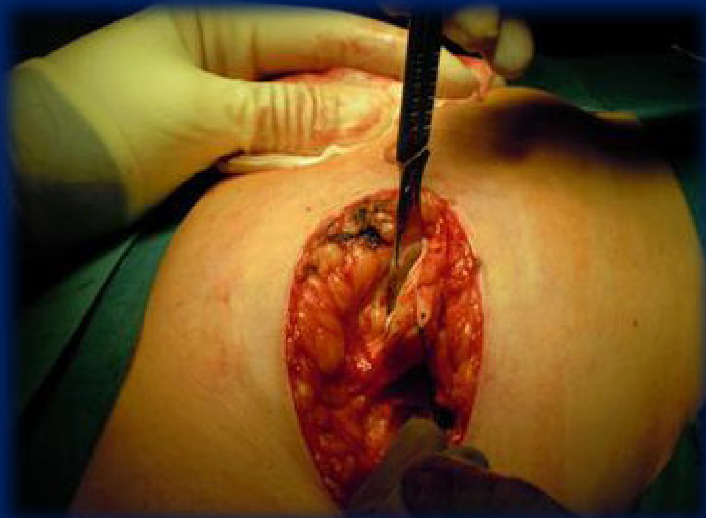


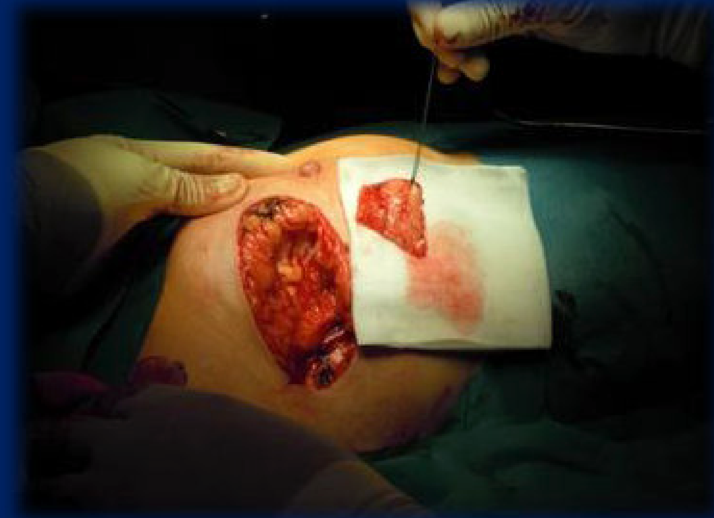
Rizzo M. Ann Surg Oncol 2010

RE-RESECTION FOR SAMPLING OF RESIDUAL CAVITY (SHAVING)



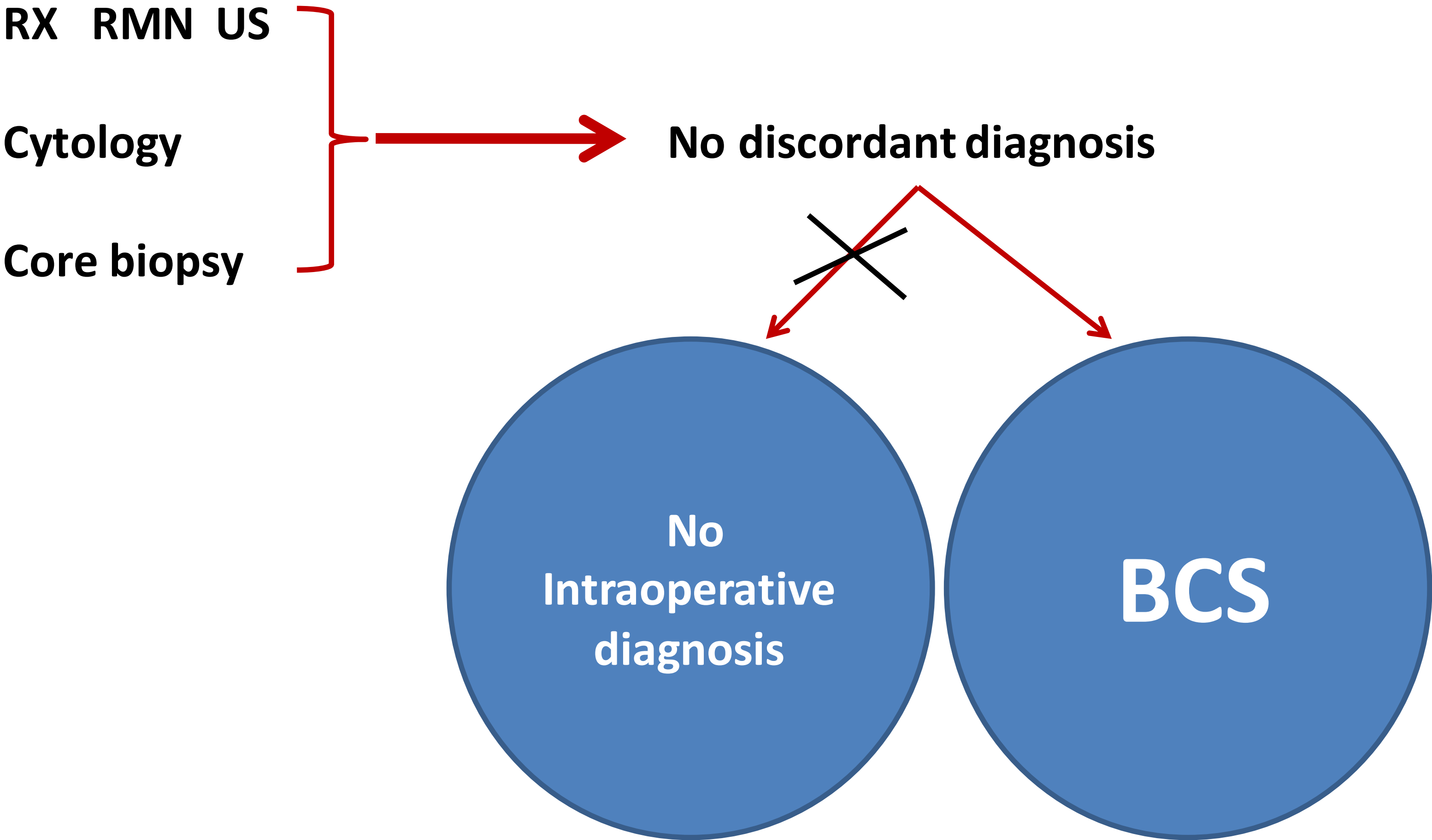






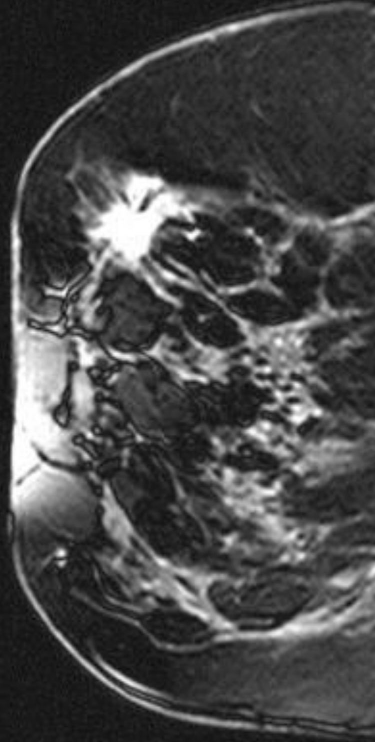
BCS and Surgical Margins:
The role of pathology

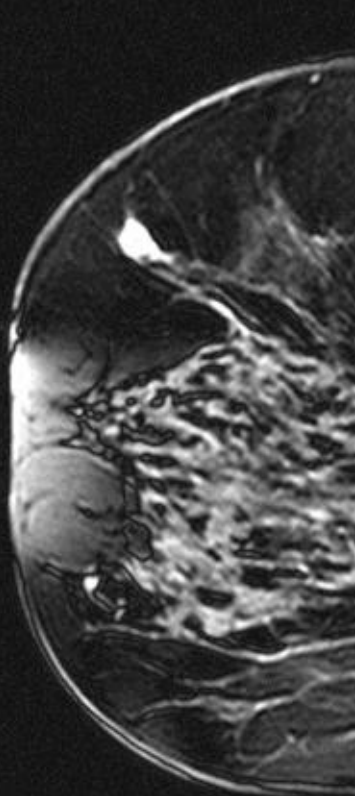
Preoperative diagnosis:

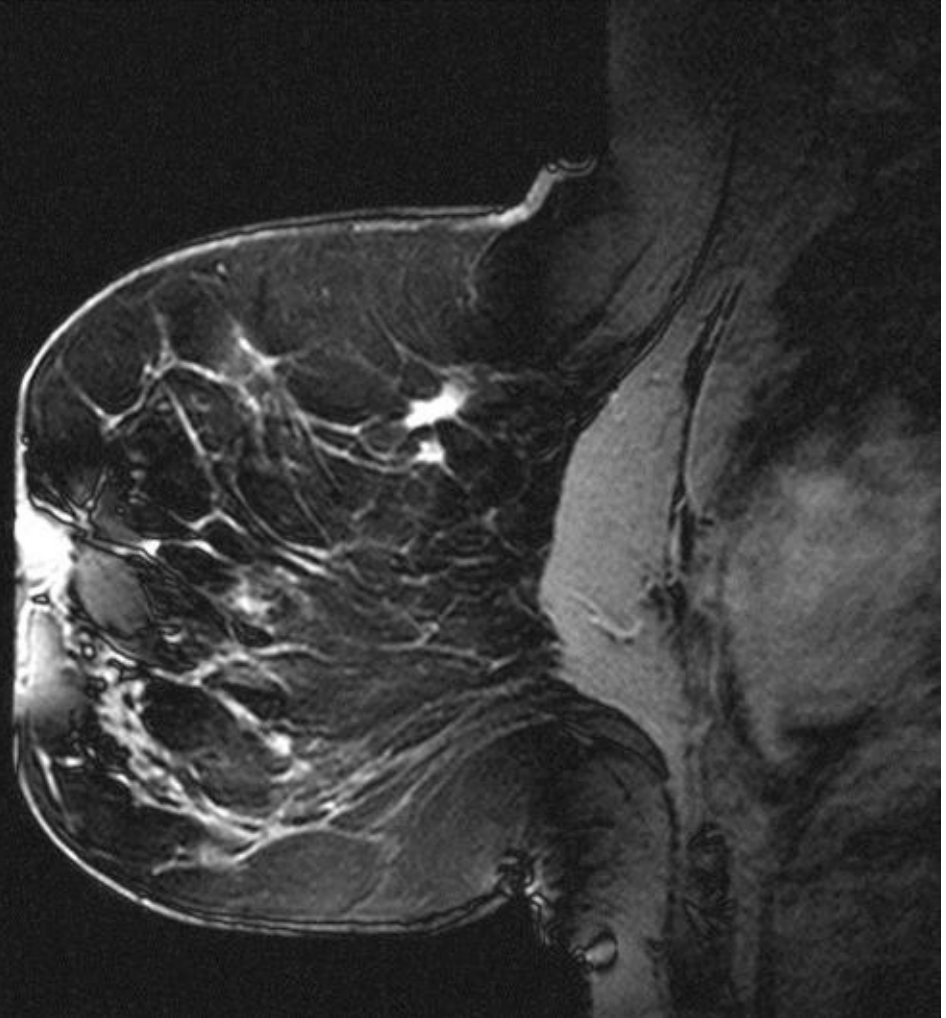


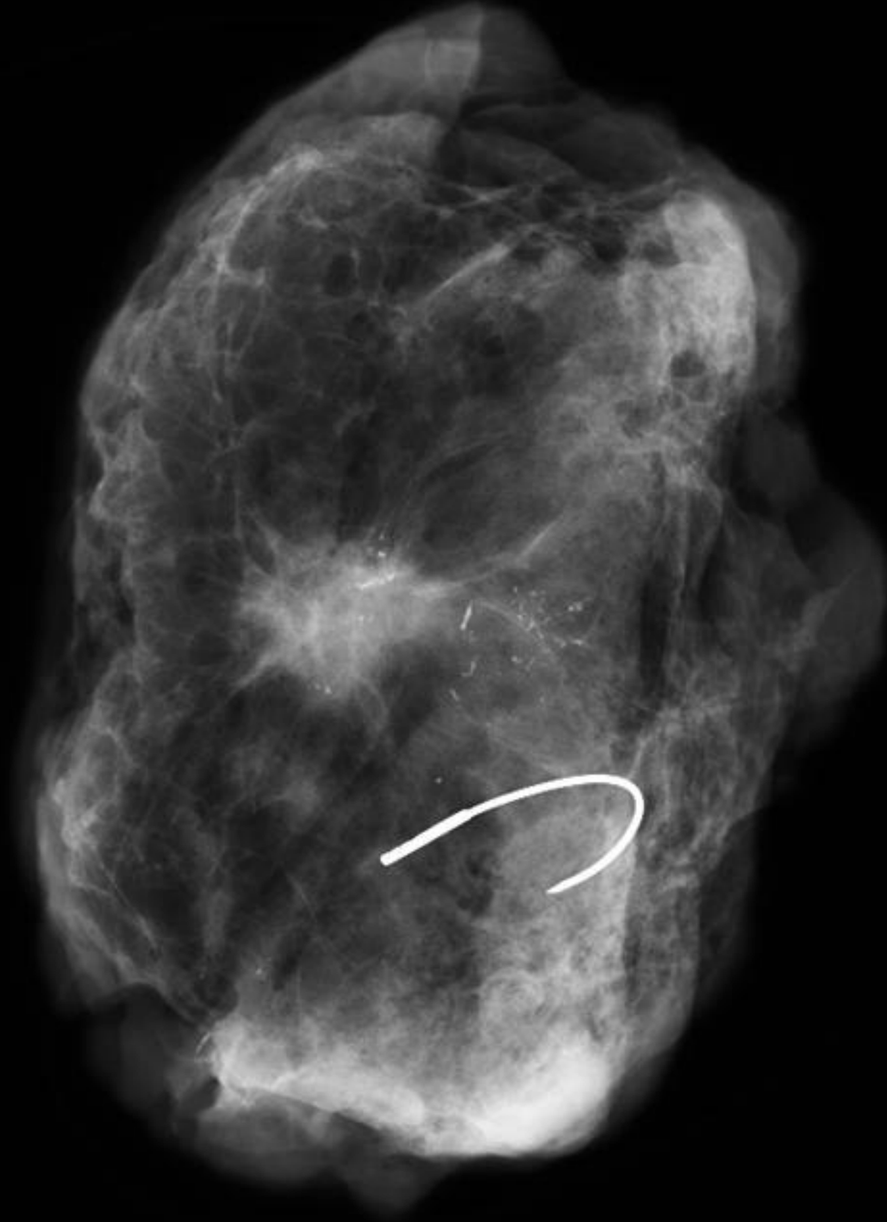
Guided macroscopic sampling: use of specimen radiography for assesment of surgical margins

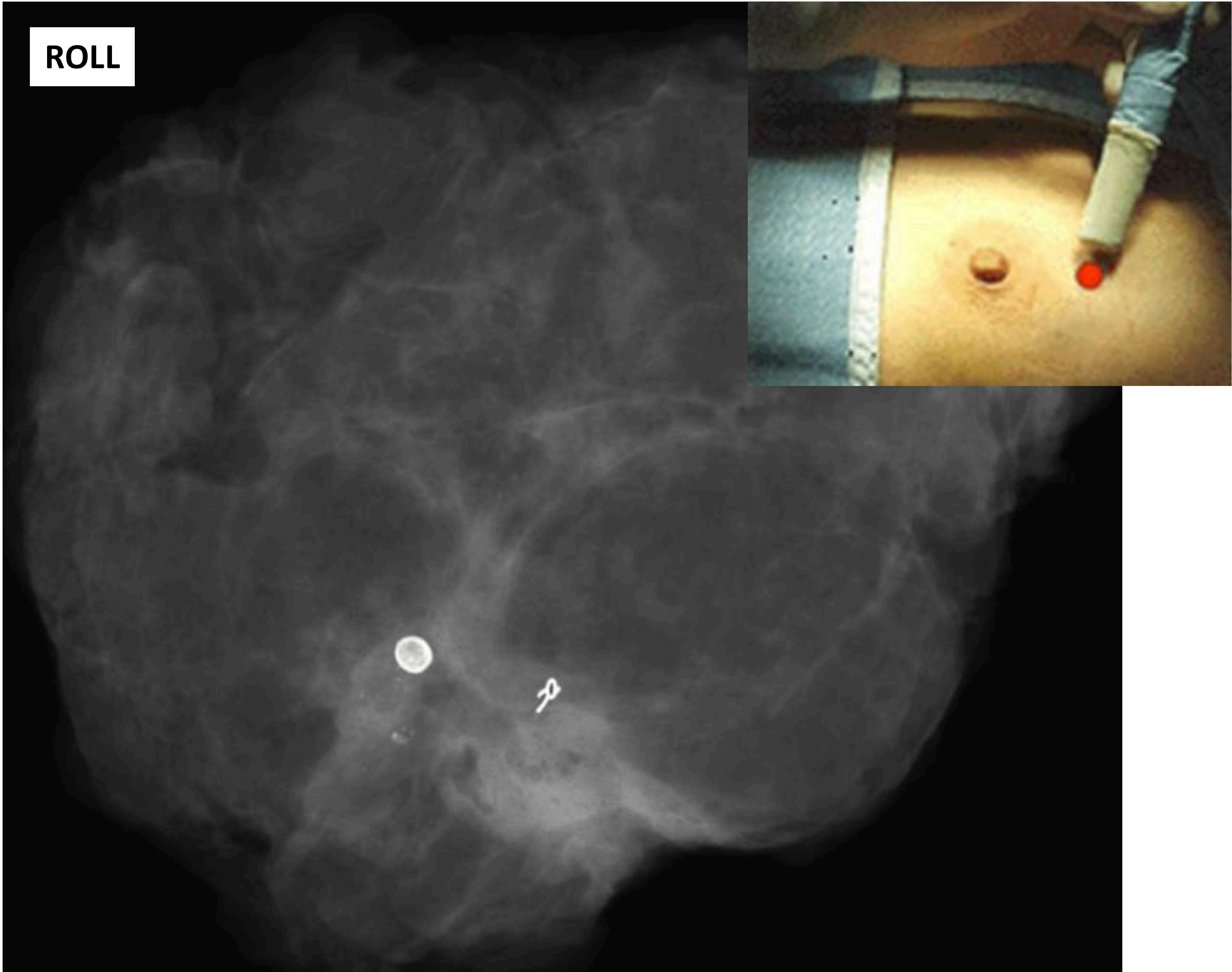
RMN



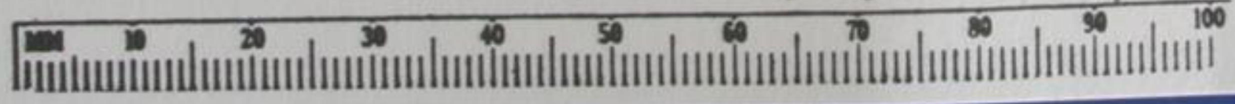


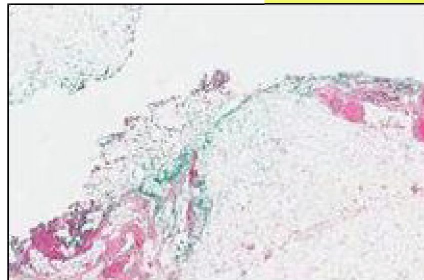



Compression–free specimen mammography

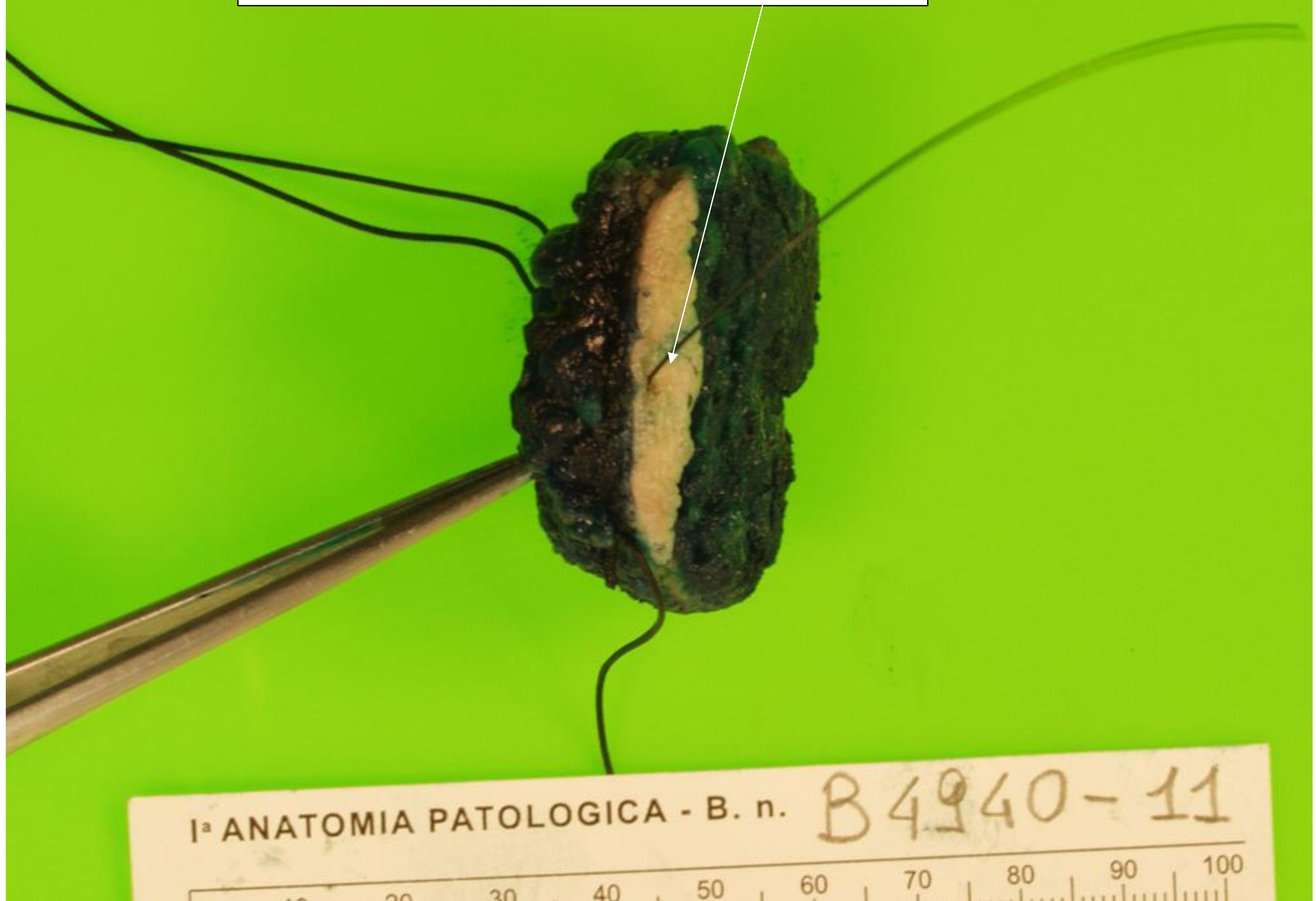

ROLL

Typical example of breast-conserving surgery
Black silk sutures for specimen orientation
(short suture for nearest margin)

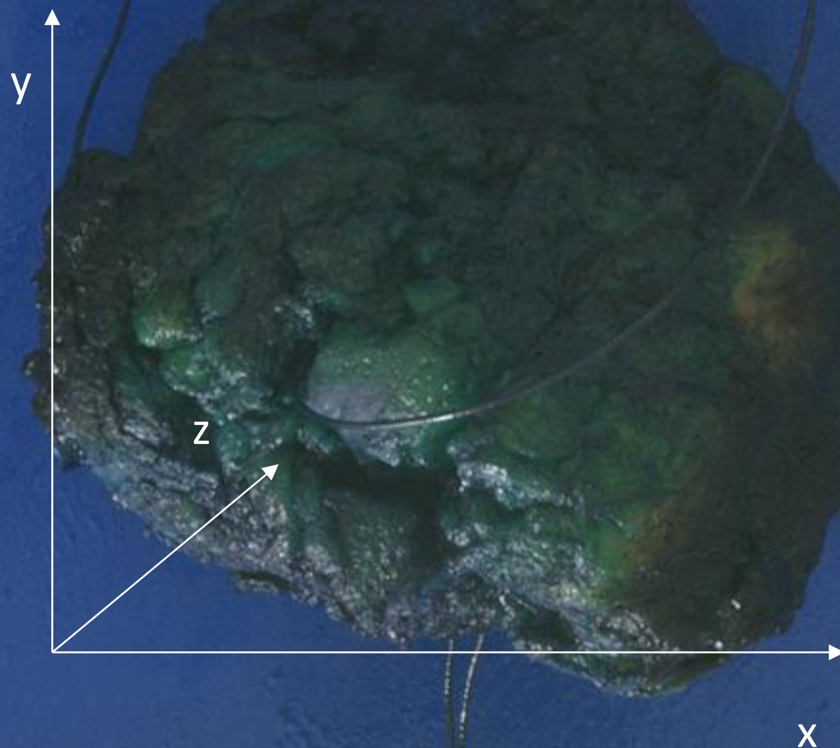

Iª ANATOMIA PATOLOGICA - B. n. B4534-11
MM 10 20 30 40 50 60 70 80 90 100



Multiple colored inks to designate superior, inferior and deep posterior surfaces


Lesion orientation : a needle wire localization
Iª ANATOMIA PATOLOGICA - B. n. B 4940 - 11
10
20
30
40
50
60
70
80
90
100

Three dimensional measure



1

2

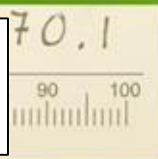
3

black

green

blue

n



Specimen is serially sectioned approximately every 3 mm, along the entire long axis lenght

1
1AP 11 06670
1 A4 MAM 1
1AP 11 06670
1 A3 MAM 1
1AP 11 06670
1 A2 MAM 1

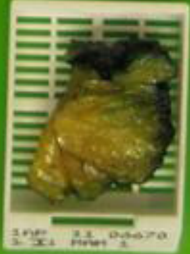
2
1AP 11 06670
1 B2 MAM 1
1AP 11 06670
1 B1 MAM 1

3
1AP 11 06670
1 C2 MAM 1
1AP 11 06670
1 C1 MAM 1

1AP 11 06670
1 D3 MAM 1
1AP 11 06670
1 D2 MAM 1
1AP 11 06670
1 D1 MAM 1

1AP 11 06670
1 E4 MAM 1
1AP 11 06670
1 E3 MAM 1
1AP 11 06670
1 E2 MAM 1
1AP 11 06670
1 E1 MAM 1

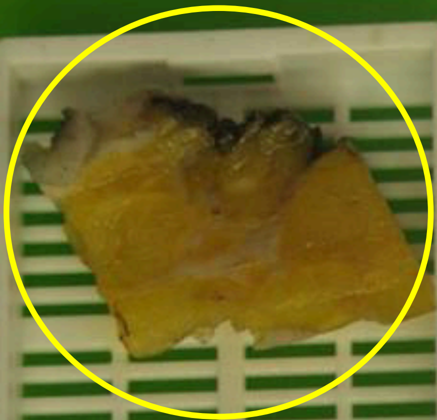
1AP 11 06670
1 F3 MAM 1
1AP 11 06670
1 F2 MAM 1
1AP 11 06670
1 F1 MAM 1



1AP 11 06670
1 L3 MAM 1
1AP 11 06670
1 L2 MAM 1

n

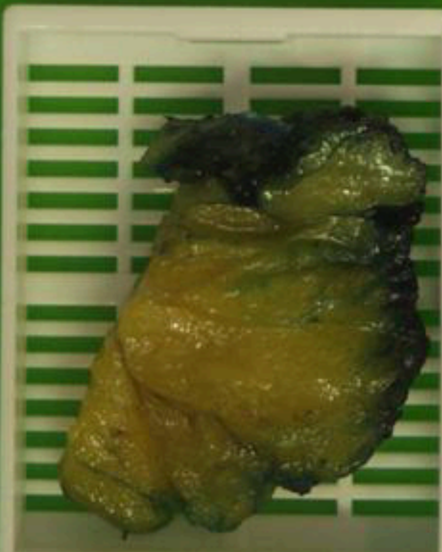
1 A1 MAM 1

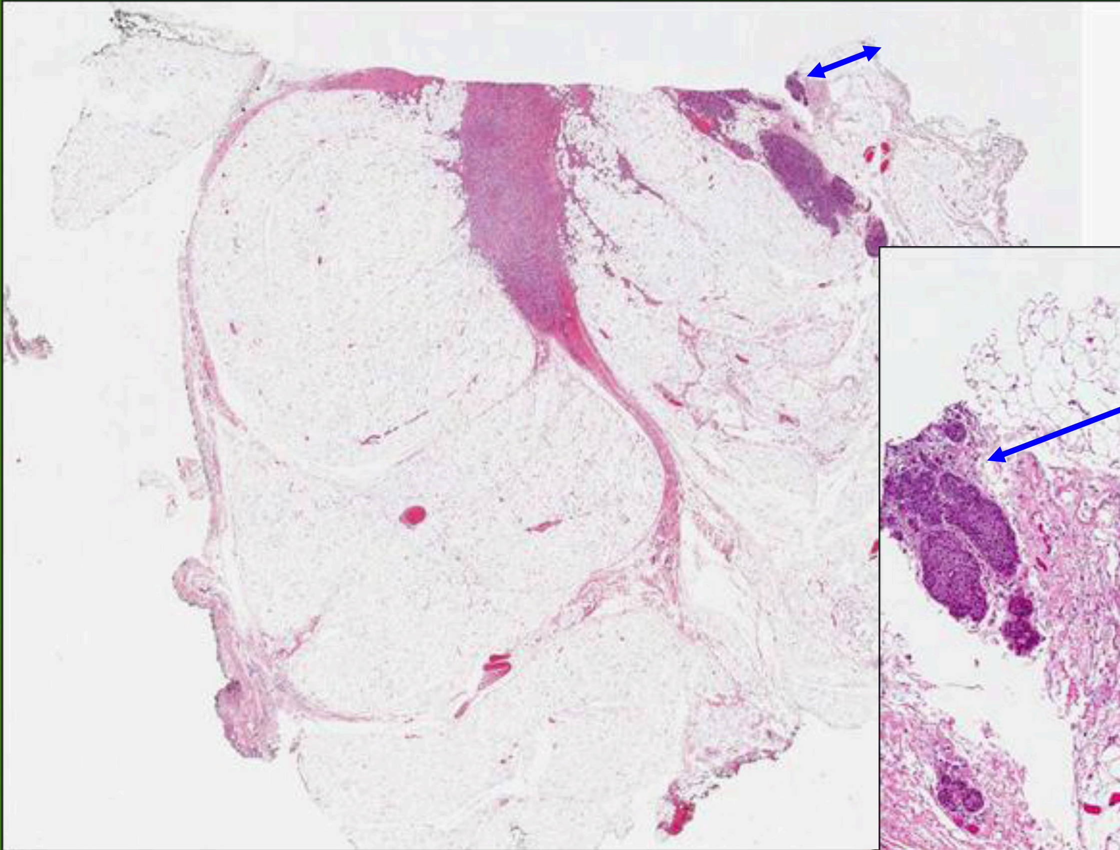
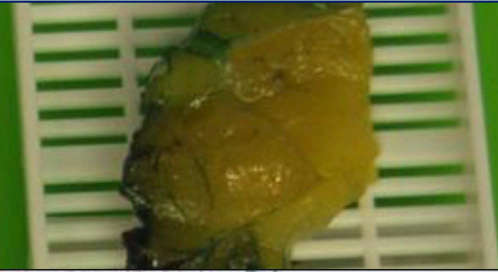
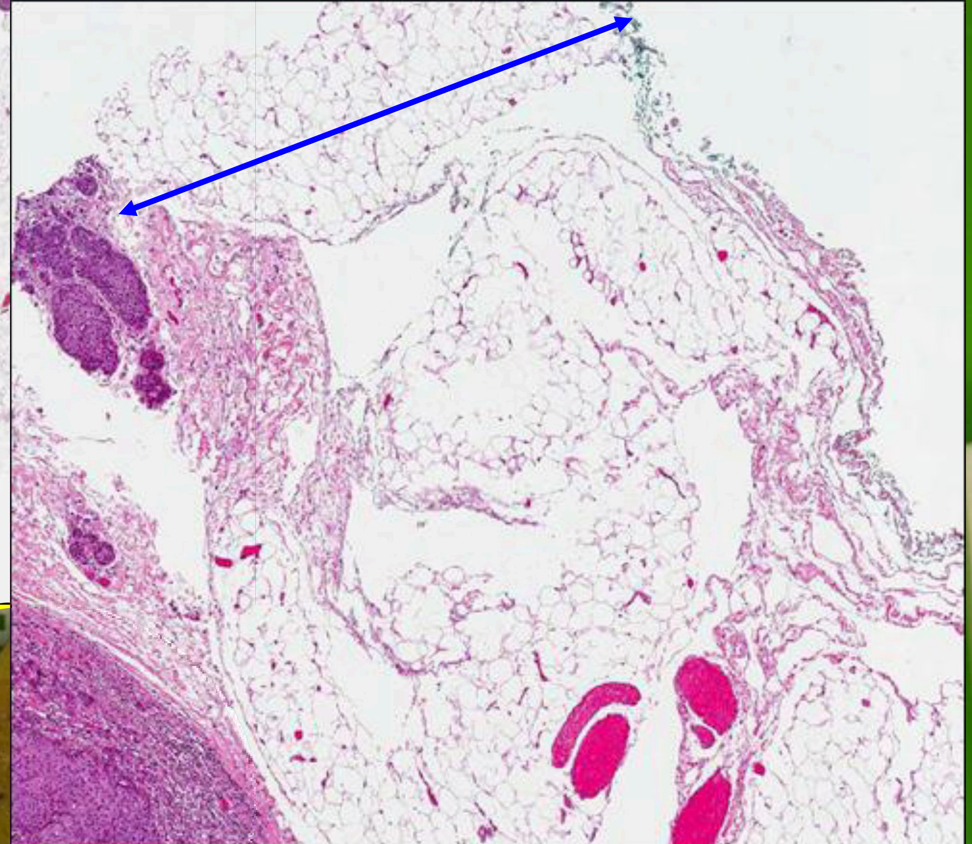
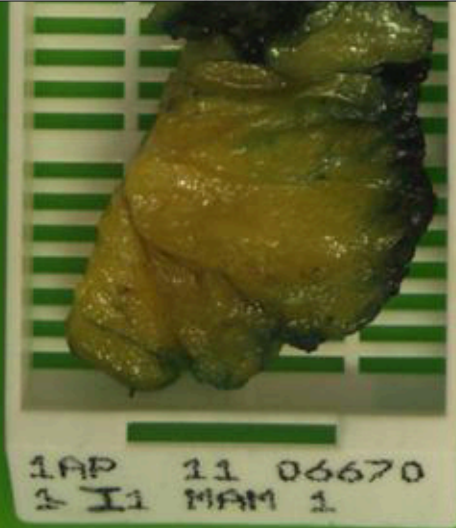


1AP 11 06670
1 G2 MAM 1

1AP 11 06670
1 G1 MAM 1

1AP 11 06670
1 I2 MAM 1


1AP 11 06670
1 I1 MAM 1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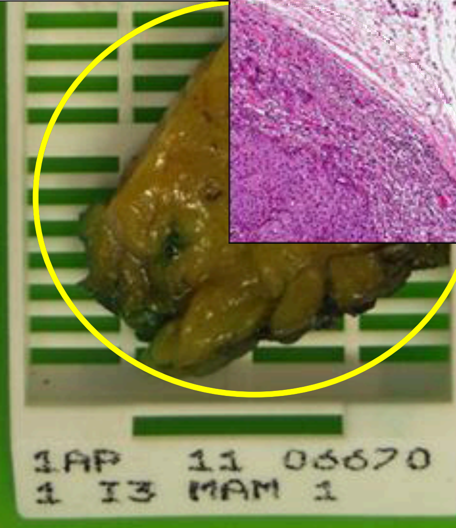
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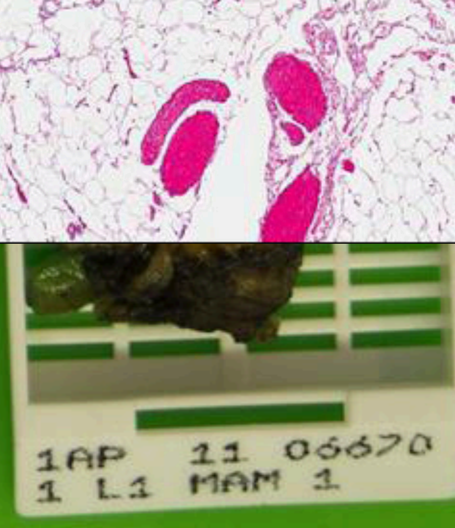
1 I3 MAM 1

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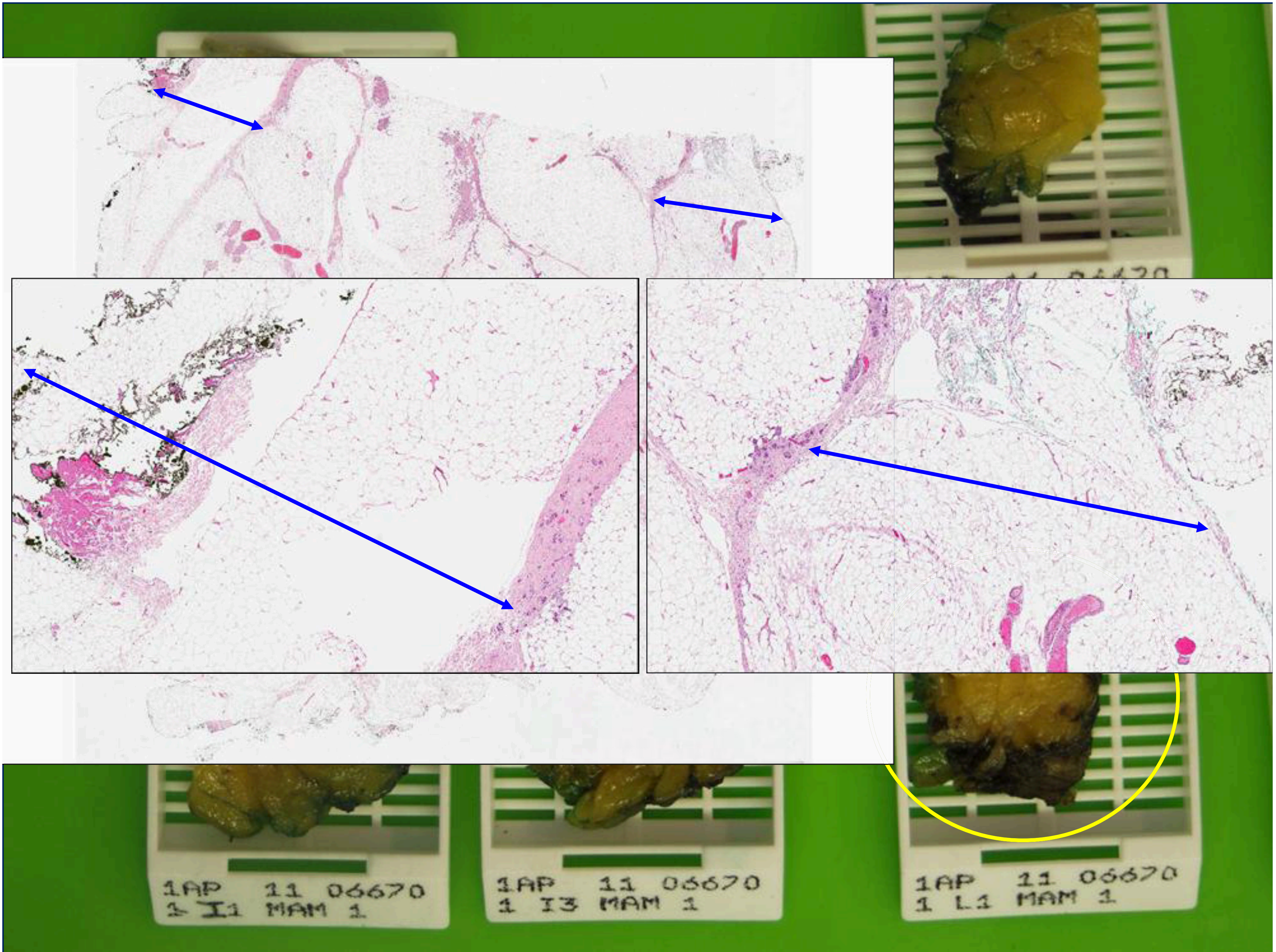
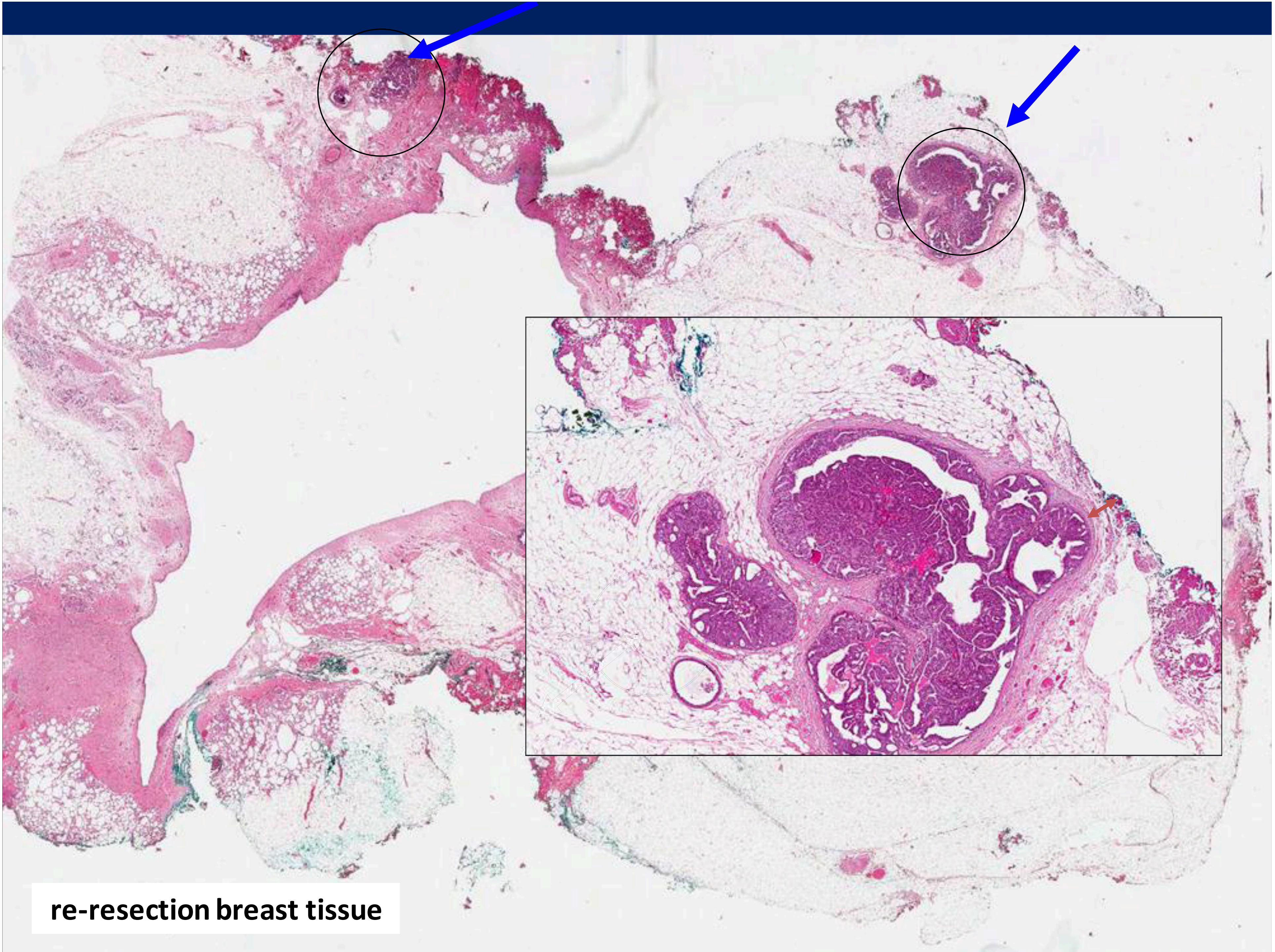
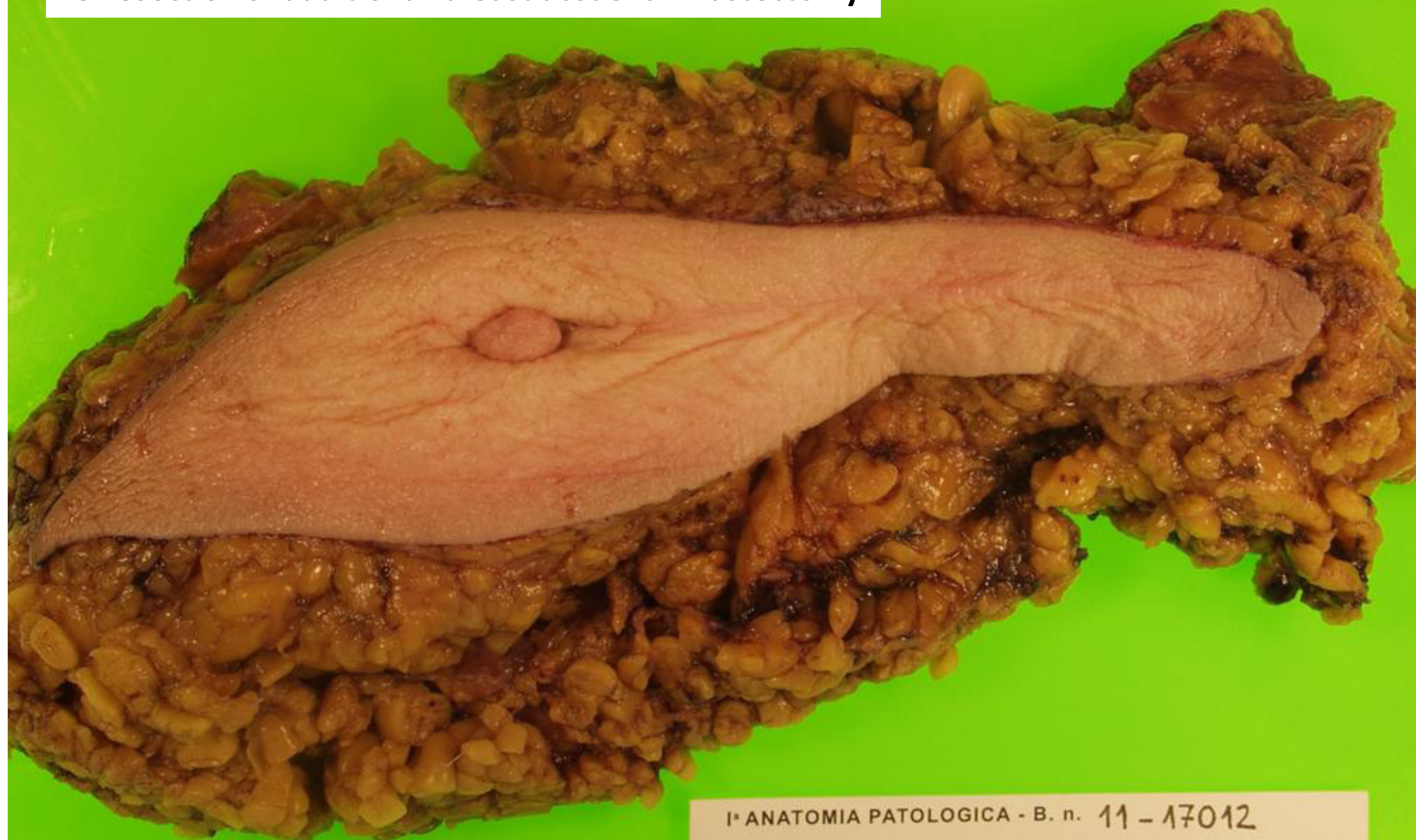

1AP 11 06670
1 I1 MAM 1
1AP 11 06670
1 I3 MAM 1
1AP 11 06670
1 L1 MAM 1

BCS resection bed cavity

BCS resection bed cavity, ink to designate definitive margins,
sutures toward tumor


re-resection breast tissue


re-resection of additional breast tissue or mastectomy
Iª ANATOMIA PATOLOGICA - B. n. 11 - 17012
mm 10 20 30 40 50 60 70 80 90 100

Tumor at edge defined as:

2000 Park, 2005 Dooley, 2007 Wright, 2009 Povoski:**≤1 mm** from edge

2002 Swanson, 2003 Mai, 2005 Nadeem,2008 Schiller, 2009 Hewes **:<1 mm** from edge

2005 Cao, 2006 Mendez, 2007 Cabioglu, 2008 Jacobson 2009 Sabel **≤2 mm** from edge

2004 Keskek, 2005 Balch, 2006 Huston **<2 mm** from edge

2009 Tengher-Barna **≤3 mm** from edge

2004 Fleming, 2006 Dillon, 2006 Janes, **<5 mm** from edge

2001 Gibson, Jenkinson, Moore, 2004 Miller, 2006 Aziz, 2007 Kotwall,Smitt,
2008 Soucy, Lovrics: **at edge**

Extreme Variability

(Used for definitive BCS procedure and for only diagnostic surgical excisional biopsy)

(Popovski et al. , BMC Cancer 2009, 9: 254)

Macroscopical Evaluation of Margins

- European guidelines for quality assurance in breast cancer screening and diagnosis (2009)
- Rosai and Ackerman’s surgical Pathology (2011)

Histological Evaluation of Margins

- Protocol for the examination of specimens from patients with invasive carcinoma of the breast (based on AJCC/UICC TNM, 7th edition, 2009; approved by the College of American Pathologists)

1. To determine the appropriateness of the extent of resection
2. To determine if BCS is not sufficient, but re-resection or mastectomy is required
3. To limit the volume of re-resection

Brescia Department of Pathology Report

Margin involved

- The tumor is present on the resection margin
- The exact site/s and the extension (focal, moderate, extensive) of involvement are specified

Margin not involved

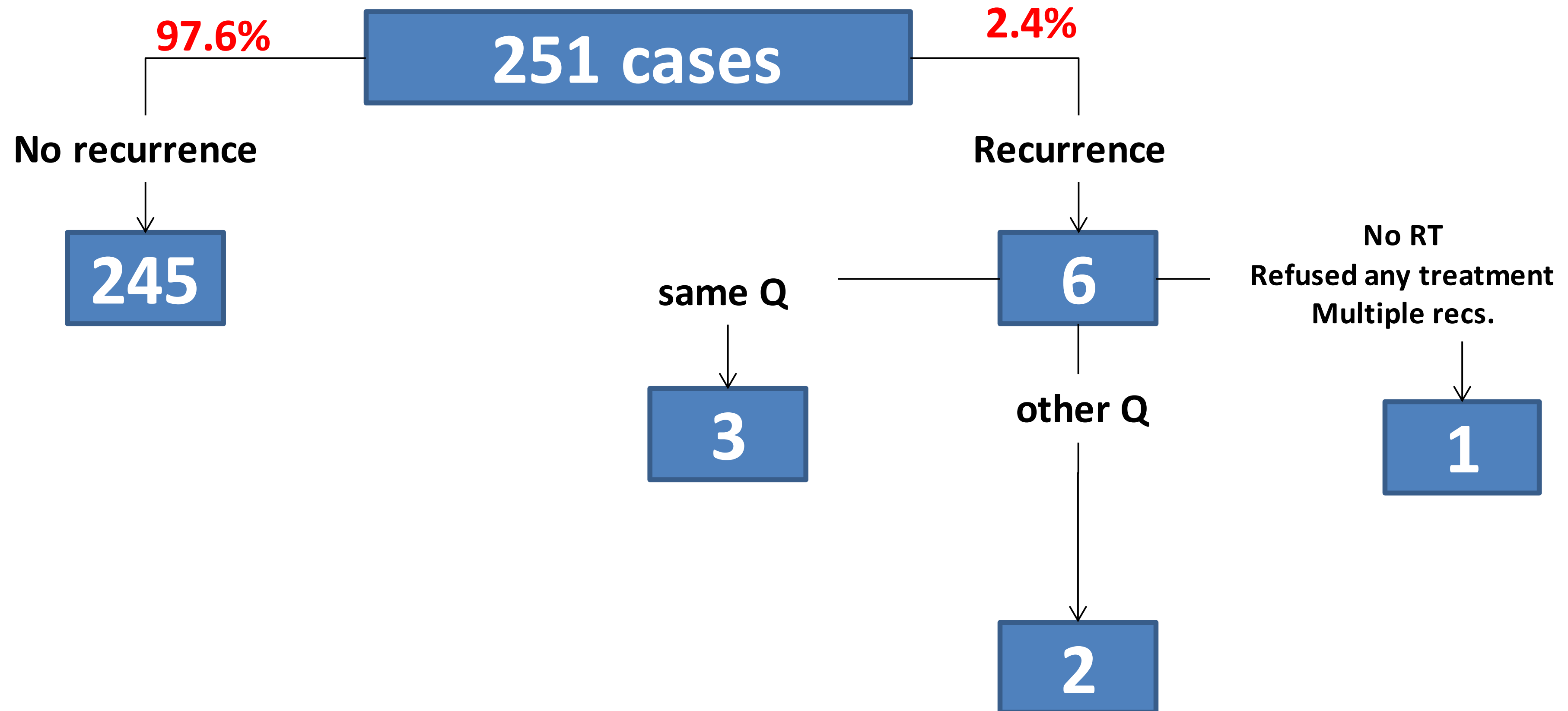
- The tumor is absent on the resection margin
- The exact distance is specified, based on macroscopy or microscopy evaluation, with indication of site(s)

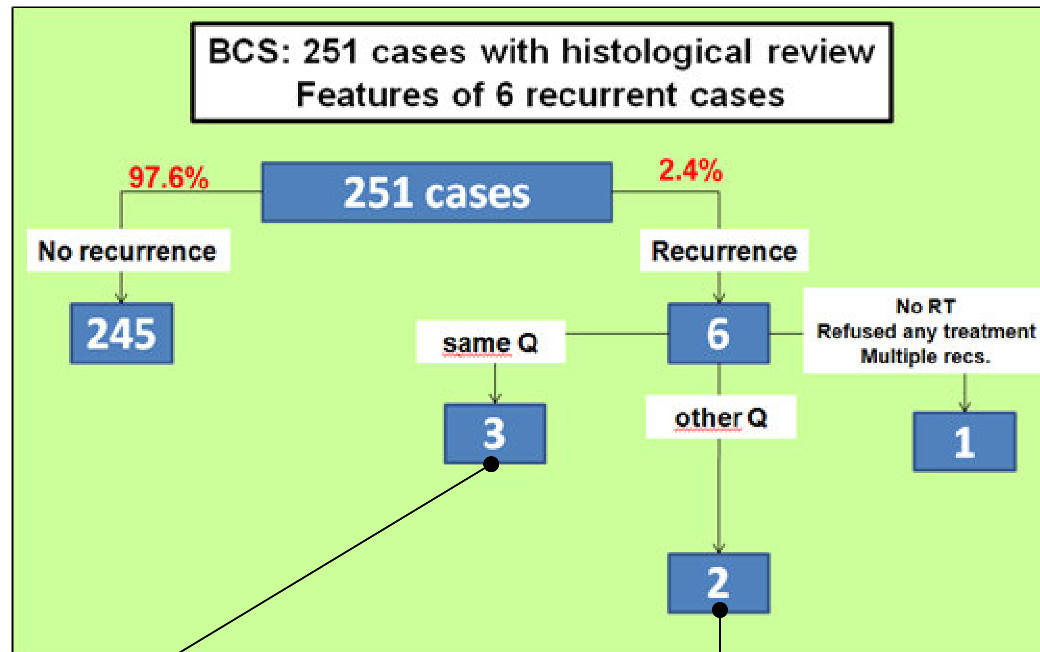
NOTE

•Distinct evaluations for invasive and in situ carcinoma (if associated)

•The specification of site margin(s) is not required by C.P.A., but "*may be clinically important, but are not yet validated or regularly used in patient management*"

BCS: 251 cases with histological review
Features of 6 recurrent cases





- All IDC
  - a) **pT2N0G3**
  - b) **pT1bN1mi(SN)G1**
  - c) **pT1miN0G2**

MARGINS

- Positive: 0
- Minimal distance:
  - 5 mm
  - 1 cm
  - >1 cm

- All IDC
  - a) **pTisN0G3**
  - b) **pT1cN0G2**

MARGINS

- Positive: 0
- Minimal distance:
  - 5 mm
  - >1 cm

OUR EXPERIENCE

II Division of General Surgery; Az. Spedali Civili - Brescia

Breast conservative surgery (BCS+RT) 2000-2005

PATIENTS' FEATURES

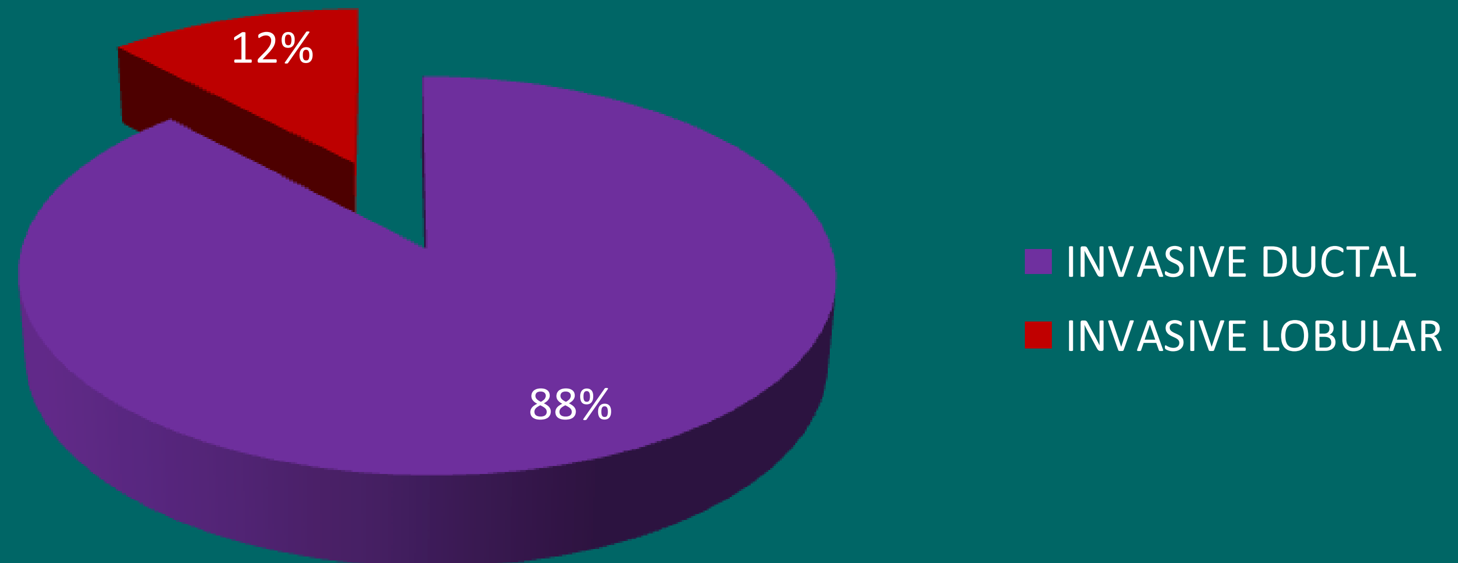
- Total number: 470 cases unifocal T1N0
- Median age: 60 years (range 26-78 ; IQR 60-75)
- Median Follow-Up: 6.9 years (range: 5-11)

Definition of surgical margins (our policy)

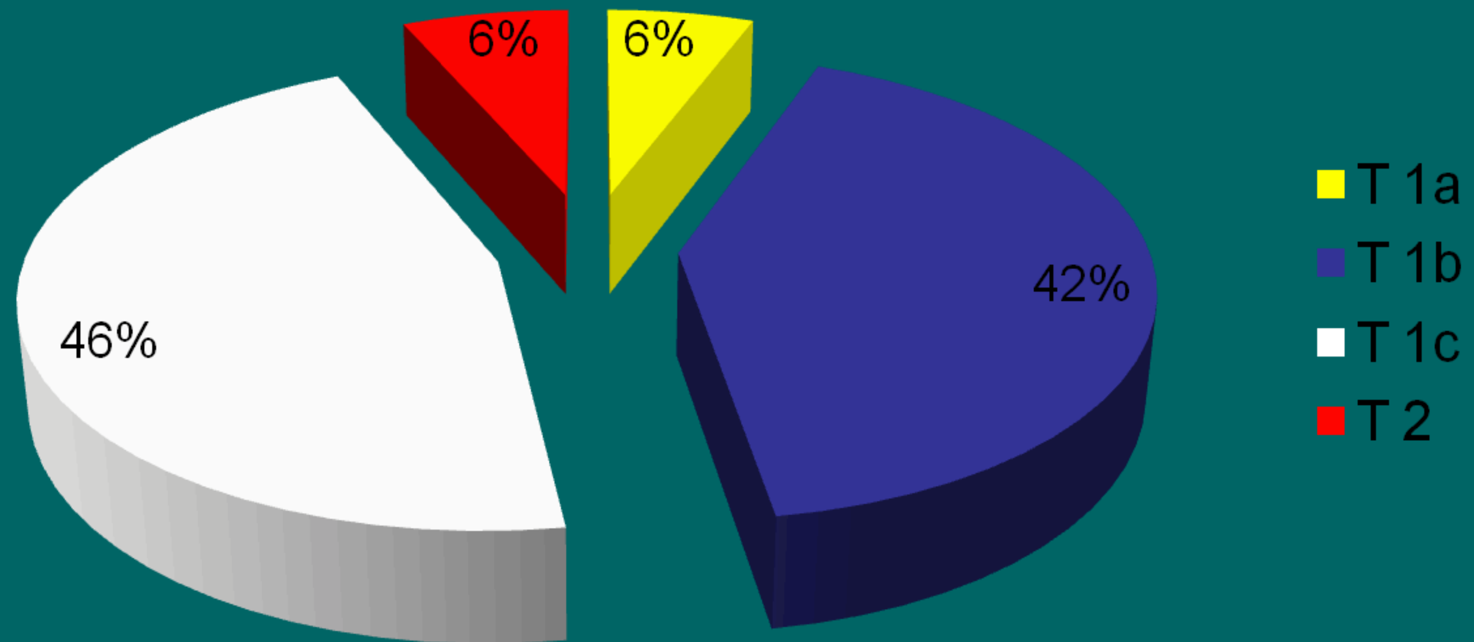
- **Positive:** tumor cells (invasive or DCIS) at the inked edge of specimen
- **Close:** tumors cells at 1 mm or less at the inked edge of specimen
- **Negative:** no tumor cells within 1 mm of the inked edge of specimen

BCS: OUR EXPERIENCE

HISTOLOGY

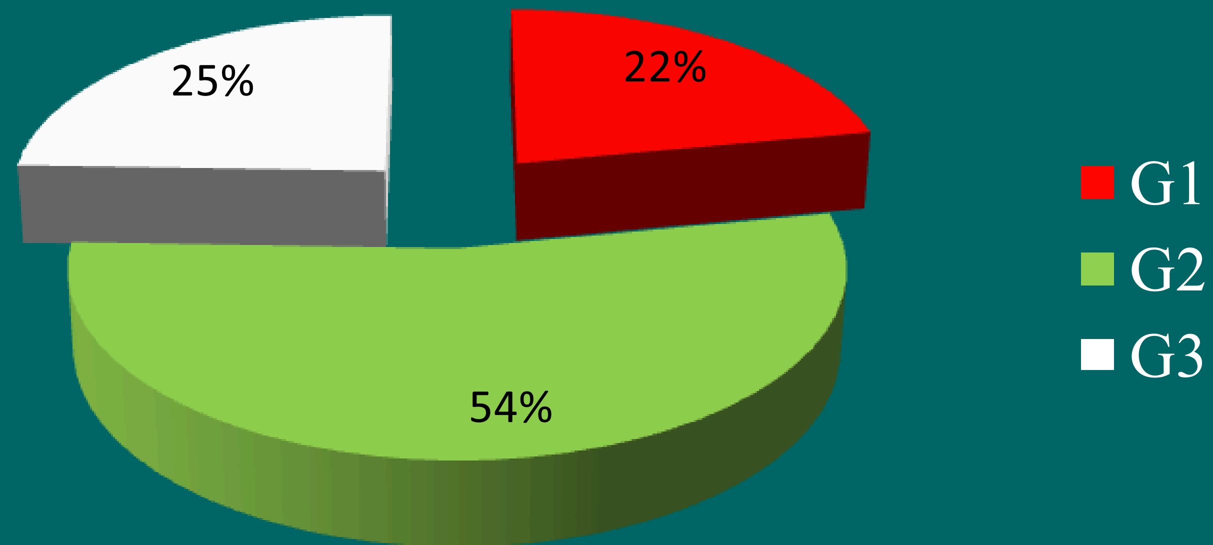


BCS: OUR EXPERIENCE



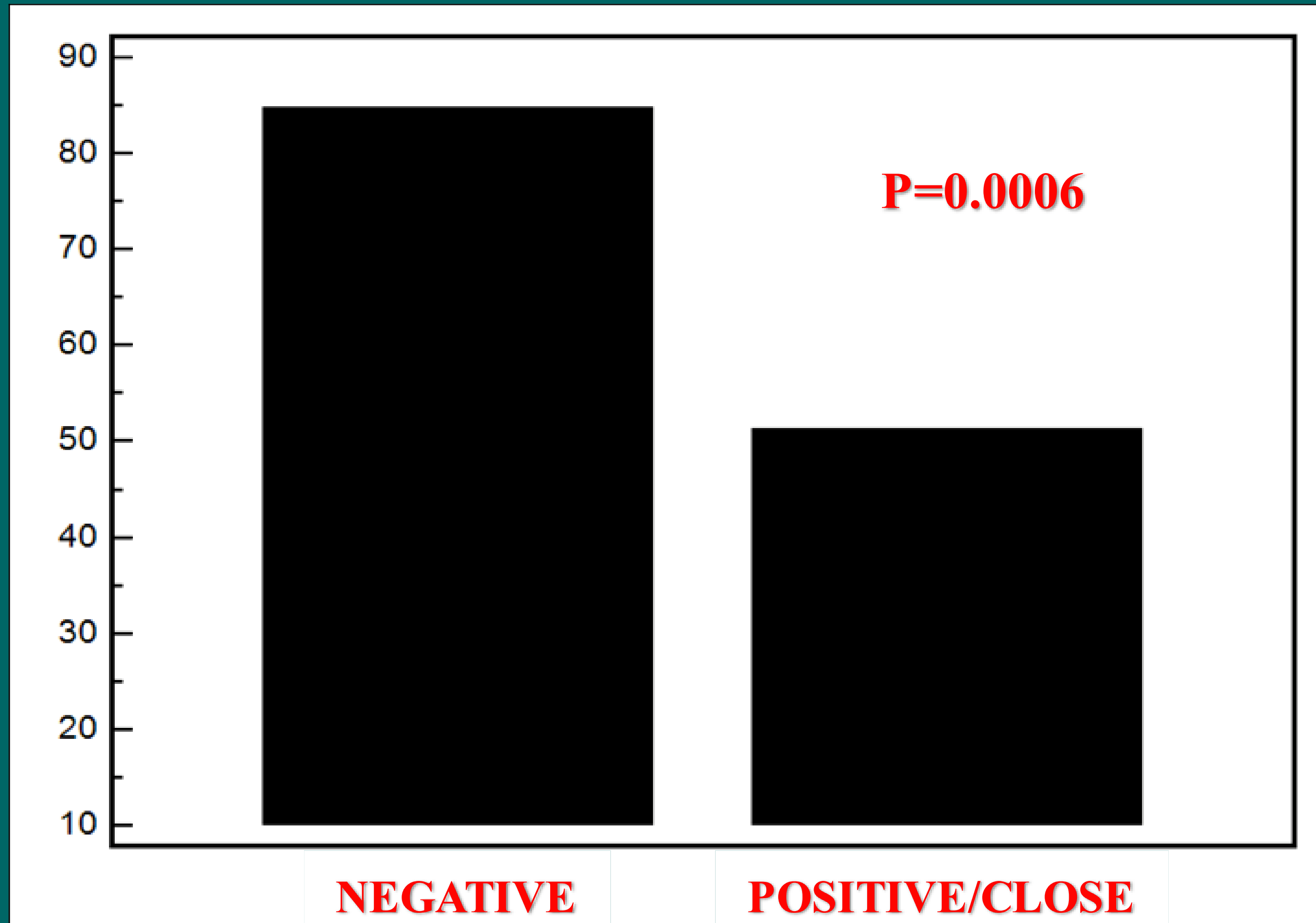
BCS: OUR EXPERIENCE

GRADING



BCS: OUR EXPERIENCE

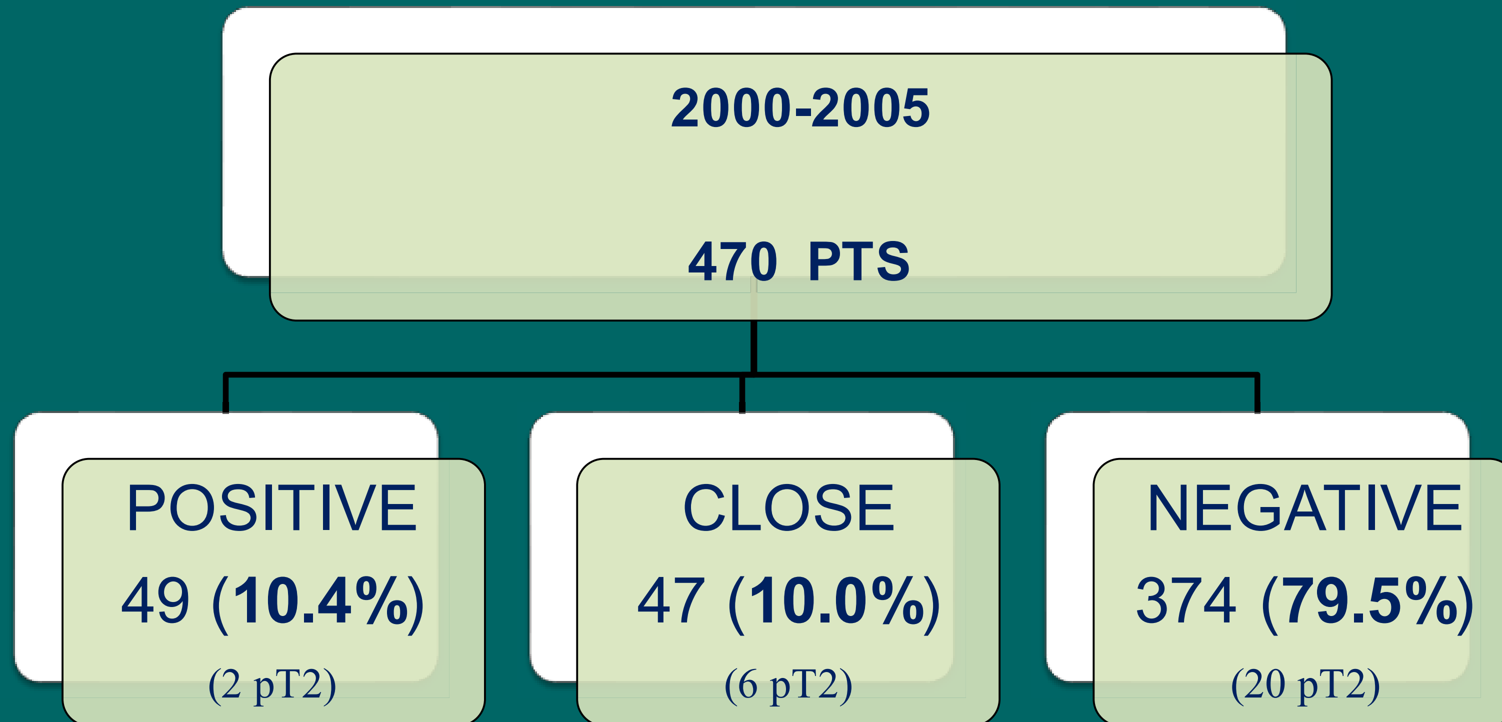
MEDIAN SPECIMEN VOLUME (cc)



MARGINS

BCS: OUR EXPERIENCE

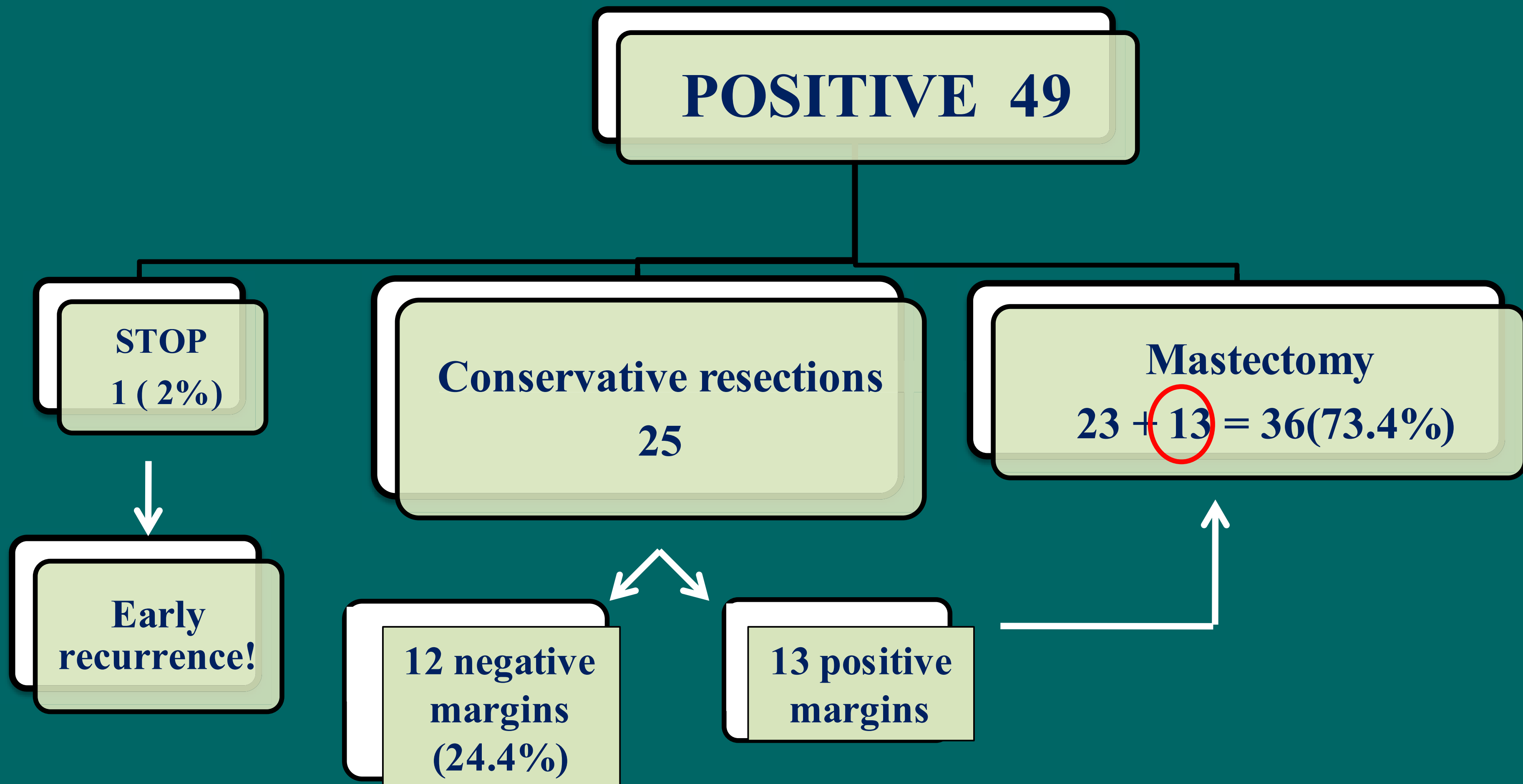
MARGINS in BCS



RE-RESECTION (SHAVING) :
28 PTS → 4 POSITIVE/CLOSE MARGINS (14.2%)

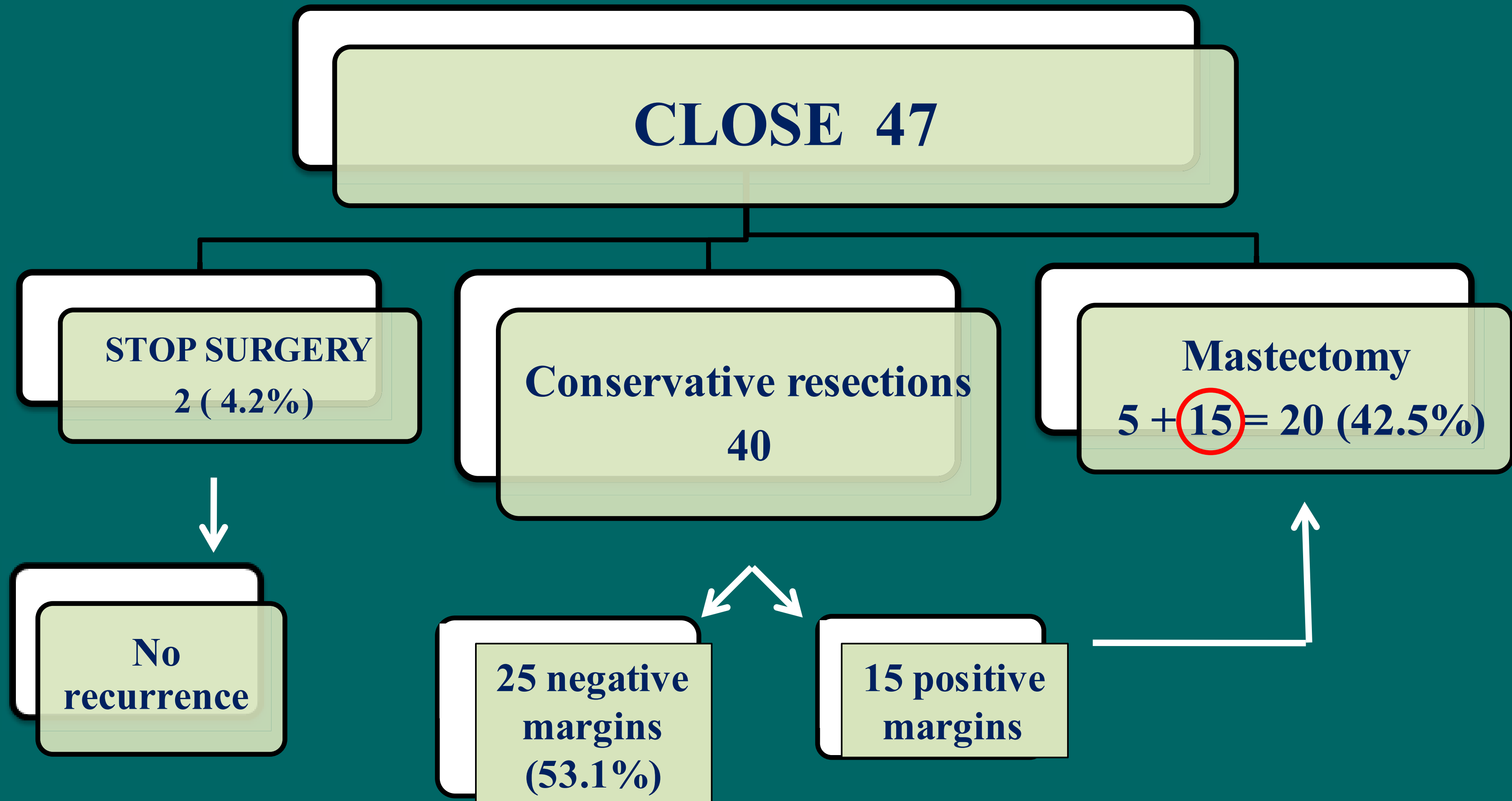
BCS: OUR EXPERIENCE

MARGINS in BCS



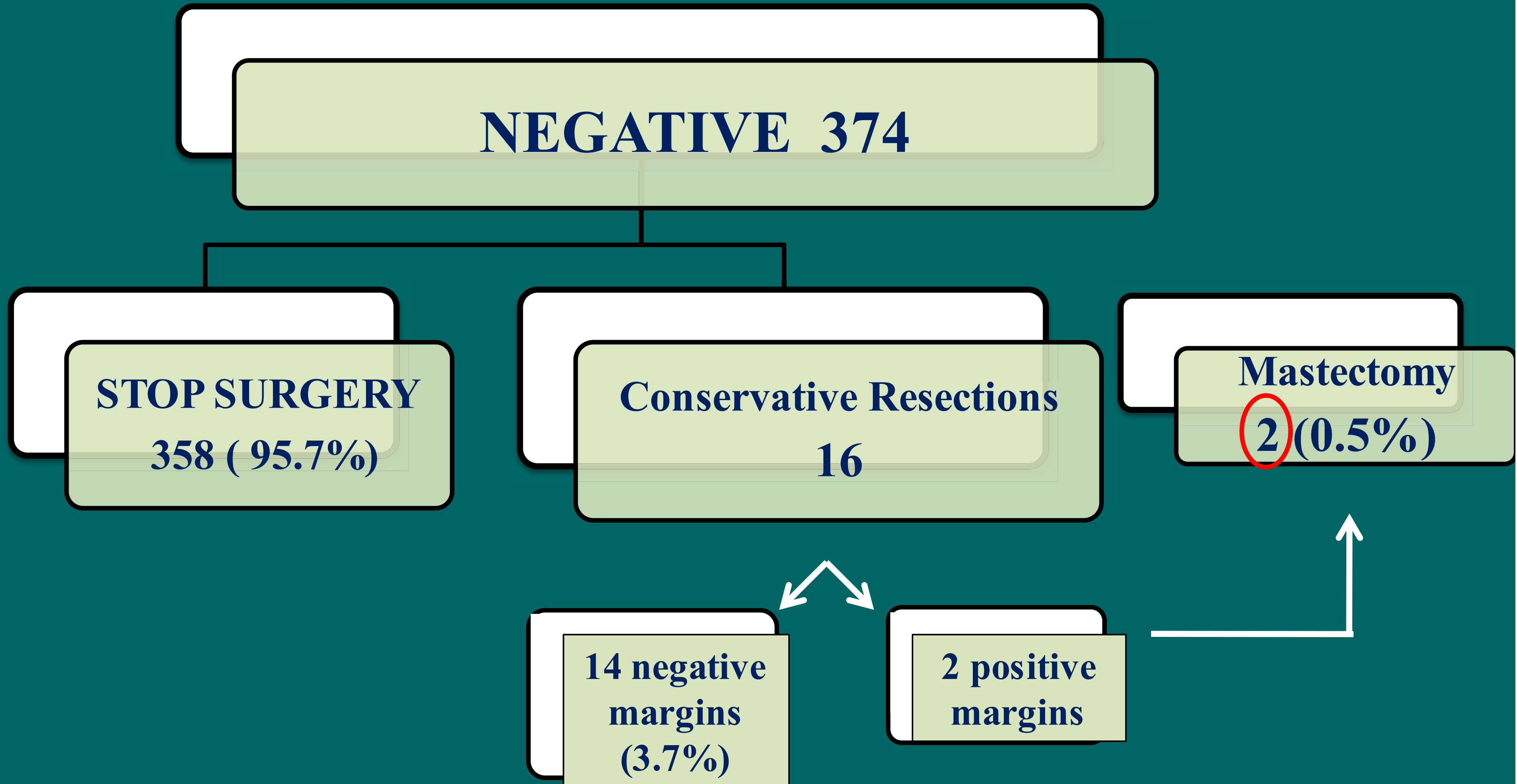
BCS: OUR EXPERIENCE

MARGINS in BCS

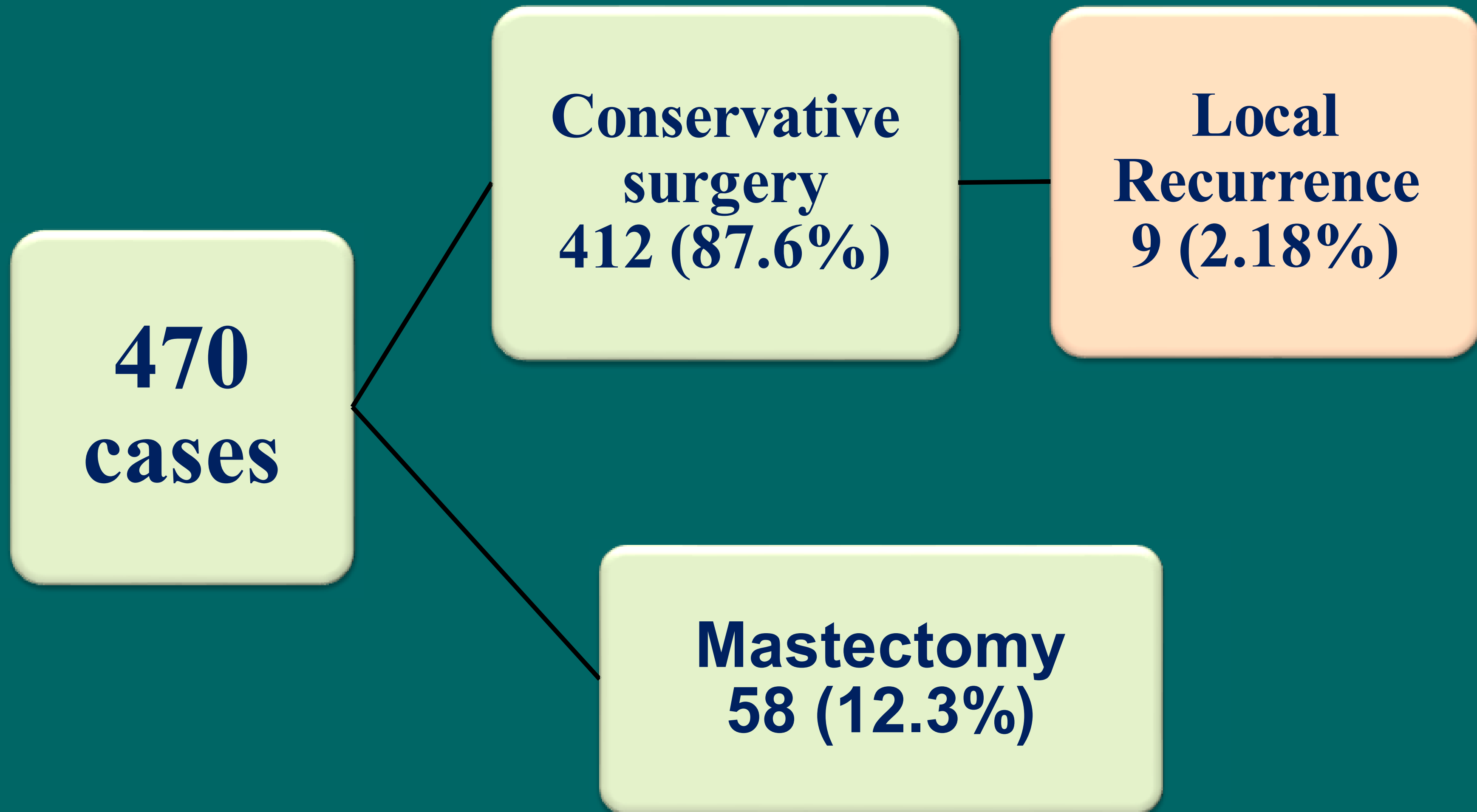


BCS: OUR EXPERIENCE

MARGINS in BCS



BCS: OUR EXPERIENCE 2000-2005



STATISTICAL ANALYSIS

- Univariate and multivariate logistic regression analyses were used to assess the impact of potential clinical and pathological features as risk factors for local recurrence, cancer-related mortality and survival with metastasis.
- Mann-Whitney U-test was use to assess the impact of specimen volume on surgical margins

FOLLOW-UP
(470 cases 2000-2005)

- LOCAL RECURRENCE (after BCS): 9/412 (2.18%)
- PATIENTS ALIVE WITH METASTATIC DISEASE: 19/470 (4%)
- CANCER-RELATED MORTALITY: 10/470 (2.12%)

VARIABLES INCLUDED INTO ANALYSIS

- Extension of *in situ* component
- Tumor dimensions
- SLN status
- Grading
- Her2/neu
- Estrogen receptors (ER)
- Progesteron receptors (PR)

- Surgical margins (mm)
- Vascular invasion
- Patient's age

RECURRENCE

VARIABLE	UNIVARIATE ANALYSIS (P-VALUE)	MULTIVARIATE ANALYSIS (P-VALUE)
Age **(continous v.)**	0.55	n.s.
Tumor size (mm) **(continous v.)**	0.37	n.s.
***In situ* neoplasia at margins** **(yes/not)**	0.29	n.s.
Margins (mm from tumor) **(continous v.)**	0.17	n.s.
Grade (G) **(continous v.)**	0.81	n.s.
Neural invasion **(yes/not)**	0.53	n.s.
Vascular invasion **(yes/not)**	0.38	n.s.
Chemotherapy **(yes/not)**	0.056	n.s.
% *in situ* neoplasia in surgical specimen **(continous v.)**	0.65	n.s.
% ER(continous v.)	0.36	n.s.
% PR(continous v.)	0.5	n.s.
Her2(continous v.)	0.35	n.s.

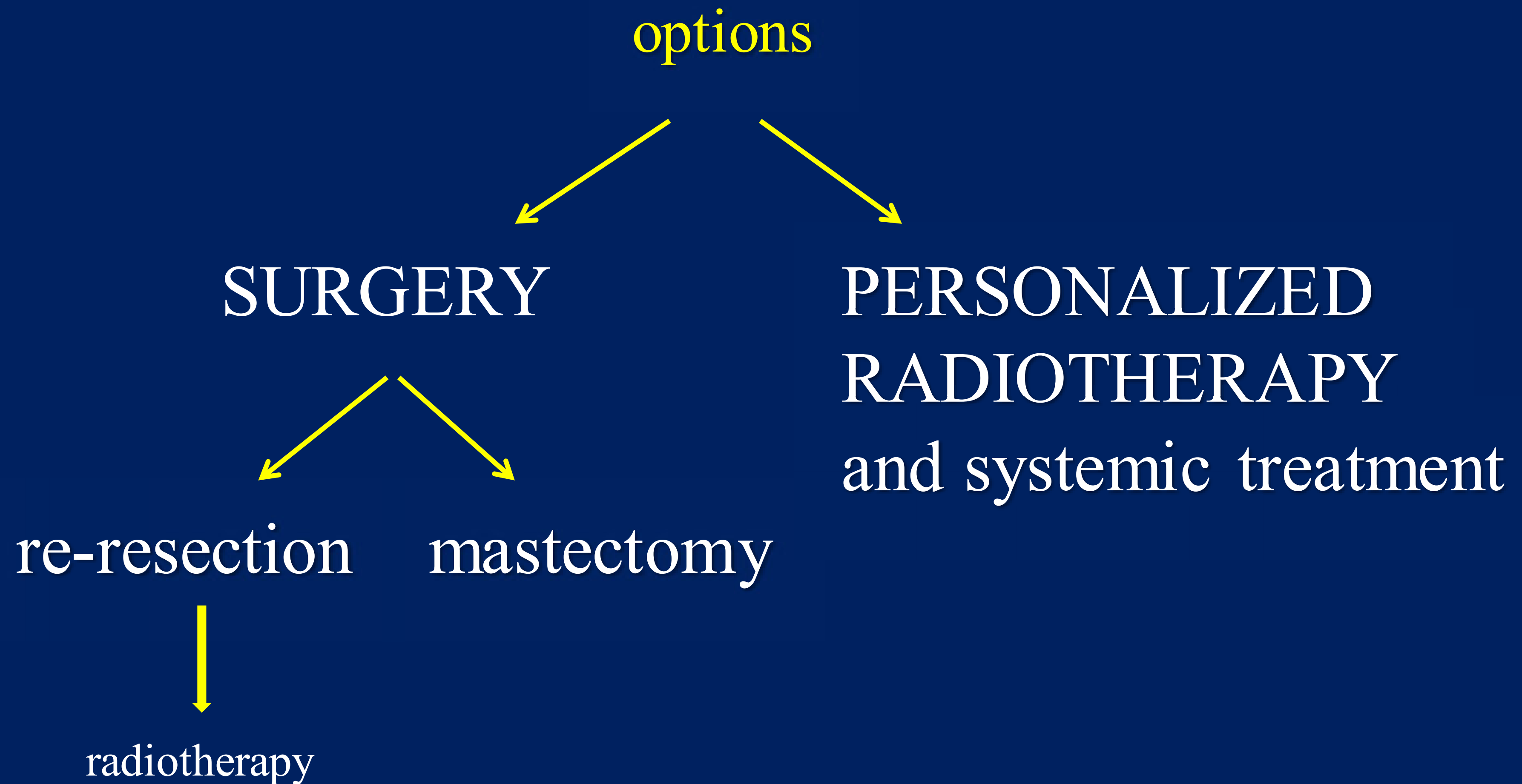
ALIVE WITH SYSTEMIC DISEASE

INDEPENDENT VARIABLE	UNIVARIATE ANALYSIS (P-VALUE)	MULTIVARIATE ANALYSIS (P-VALUE)
Age	0.28	n.s.
Tumor size (mm)	**0.0006**	**0.0022**
SLN status	**0.038**	n.s.
Axillary lymph node status	0.4	n.s.
Grade (G)	**0.0003**	n.s.
Vascular invasion	0.94	n.s.
Chemotherapy	0.31	n.s.
% ***in situ*** **neoplasia in surgical specimen**	0.85	n.s.
%ER	0.16	n.s.
%PR	0.71	n.s.
Her2	0.19	n.s.
Recurrence	0.39	n.s.

MORTALITY

INDEPENDENT VARIABLE	UNIVARIATE ANALYSIS (P-VALUE)	MULTIVARIATE ANALYSIS (P-VALUE)
Age	0.91	n.s.
Tumor size (mm)	**0.0035**	**0.0033**
SLN status	**0.032**	n.s.
Axillary lymph node status	0.5	n.s.
Grade (G)	**0.001**	n.s.
Vascular invasion	0.5	n.s.
Chemotherapy	0.7	n.s.
% *in situ* neoplasia in surgical specimen	0.98	n.s.
%ER	0.45	n.s.
%PR	0.68	n.s.
Her2	0.35	n.s.
Recurrence	0.47	n.s.

POSITIVE/CLOSE MARGIN: WHAT TO DO?



POSITIVE/CLOSE MARGIN: WHAT TO DO?

RE-RESECTION

The patients with final negative margins after re-excision have the same low risk of LR in 10 years as the patients with initially negative margins (Freedman G, J Radiat Oncol Phys, 1999)

BUT

Negative cosmetic impact
Feeling of failure of the previous treatment
Patient disappointment and anxiety
Higher costs
Risk of further positive margins

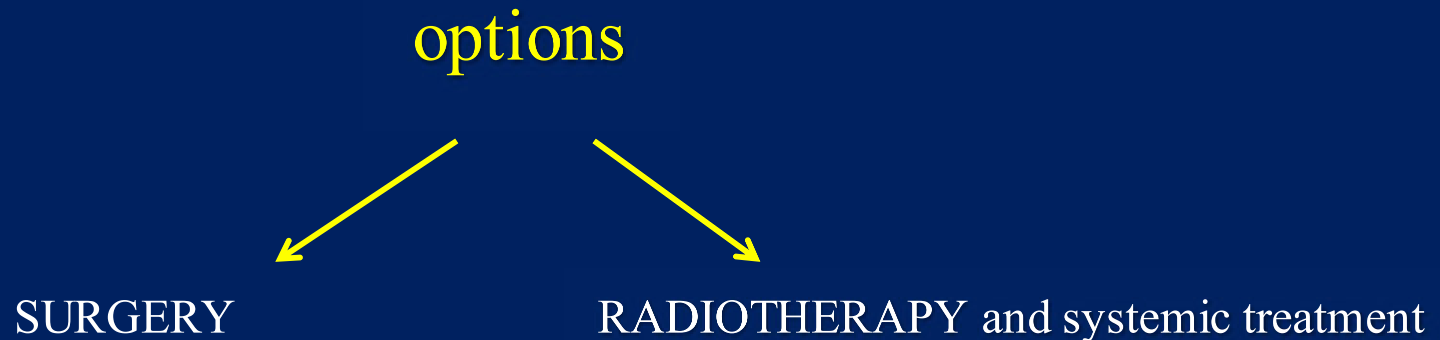
RE-RESECTION

In DCIS at margins an important factor of increased risk of residual disease at re-excision is the exstension of margin involvement

MARGINS INVOLVEMENT	RESIDUAL DISEASE IN RE-EXCISED SPECIMEN
focal	30%
minimal	46%
moderate	68%
extensive	85%

Neuschatz AC, Cancer 2002

POSITIVE/CLOSE MARGIN: WHAT TO DO?



NO RULE

Each case should be evaluated individually with multidisciplinar approach (surgeon, radiotherapist, oncologist and pathologist)