

Margins:

- Impact on Local control
- Treatment options

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- “the lack of consensus regarding what constitutes an adequate margin results in the performance of mastectomies that may not be necessary ... multiple trips to the OR ... unnecessarily wide resections ...”



Morrow et al

- **Population based study**
 - 2030 women 2005 to 2006
 - Mastectomy rate : 38%
 - 9% chose mastectomy
 - 13% Pt preferred BCT but lumpectomy deemed “unsuccessful” so mastectomy



Margin Definitions

■ North America

- Negative :
 - 46% - “not at ink”
 - 29% - “> 2 mm from ink”
 - 15% - > 5 mm from ink

■ Europe

- Negative :
 - 28% - “not at ink”
 - 9% - “> 2 mm from ink”
 - 45% - > 5 mm from ink



Margin Definitions

■ Survey US surgeons

- What margin width is good enough to avoid a re-excision?
 - 13% - “not at ink”
 - 25% - “> 2 mm from ink”
 - 52% - “> 5 mm from ink”



Outline

- **Goals of Breast conservation therapy**
- **Risk Factors for Local recurrence**
- **BCT evidence**
- **Review of Relapse rate with close and positive margins**
- **Agency policy regarding margins**



Questions

- **If margins are positive should we re-excise or first do post lumpectomy mammograms to assess for extent of residual calcifications? (Should this be a standard?)**
- **How should close margins and young age determine extent of surgery (mastectomy vs breast conserving surgery and radiation)?**



Questions

- **Should we aim for bigger margins or give boost radiation? (What is the benefit of re-excision?)**
- **Is there any evidence for re-excision of skin (Anterior margins) or fascia (posterior margins)?**



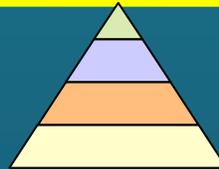
Priorities

Cure/ Survival

Local Control

Cosmetic outcome

Breast Preservation



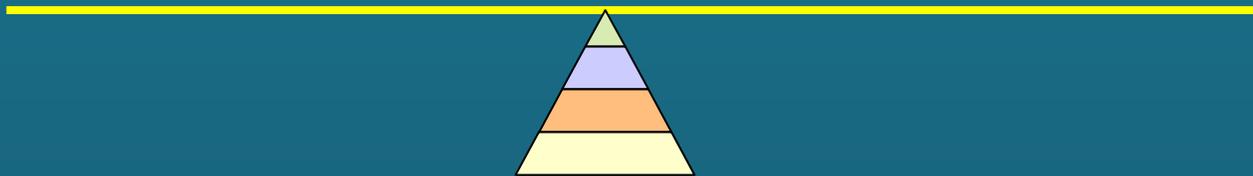
Decision making

Certainty

Patient preference

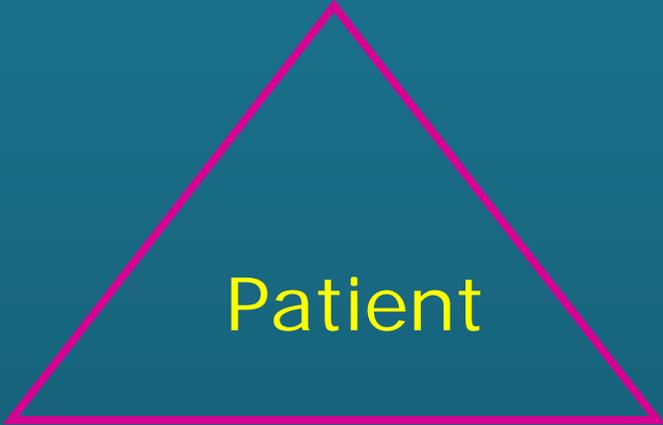
Level of evidence

Pragmatism



What to optimize?

Overall Survival



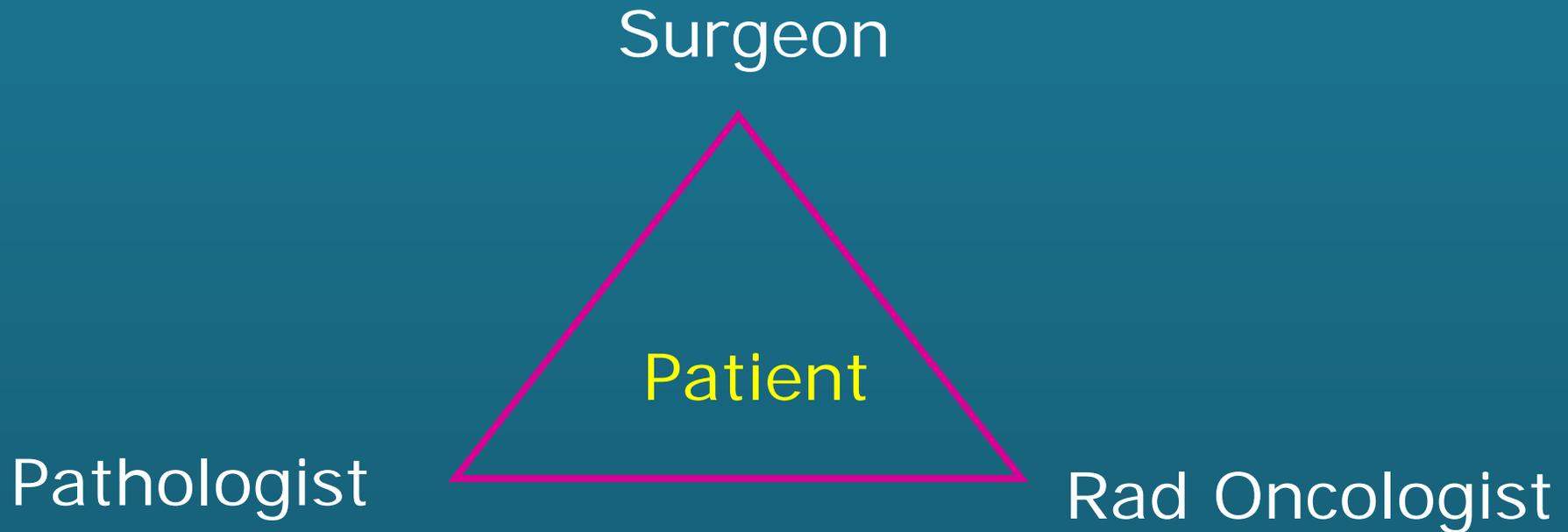
Patient

Breast
Conservation

Cosmesis



Who makes the decision? Multidisciplinary



Factors to consider when deciding to re-excise a close or positive margin

Local control

- 1) Patient Factors
 - Age
 - Young age <35 increase risk relapse
 - Inherited Susceptibility
 - BRCA increases risk relapse after BCT
 - Comorbidity
 - Contraindication to systemic therapy
 - Contraindication to radiotherapy
 - SLE, scleroderma, restricted ROM
- 2) Tumour Factors
 - Tumour size
 - Grade
 - LVI
 - Perineural invasion
 - EIC
 - Residual calcifications
 - Nodal status
 - Margin status
 - positive vs negative
 - Close vs negative ?
 - Tumour or a treatment factor
- 3) Treatment factors
 - Margins
 - Extensive positive, limited positive, close, negative
 - Extent of surgery
 - Mastectomy vs breast conservation
 - Lumpectomy vs quadrantectomy
 - Number of nodes dissected
 - Radiation dose
 - Boost: dose and technique
 - Radiation volume
 - Systemic therapy

Cosmesis

- 1) Patient and Tumour
 - Tumour/ breast ratio
 - Body mass index
 - Breast size (“separation”)
 - Tumour size/ extent of surgery
 - Infection
 - Comorbidity
 - Collagen vascular disease, HTN, DM
 - Smoking
- 2) Surgical
 - Skin excision
 - Separate breast and axilla incisions
 - Volume of breast removed
 - Orientation & length of incision
 - Infection
 - Re-excision
 - Closure of lumpectomy cavity
 - Quadrantectomy vs lumpectomy
 - Mastectomy vs breast conservation
- 3) RT
 - Whole breast dose
 - Boost dose
 - Boost technique (electrons> implant)
 - RT dose distribution/ photon energy
 - Use of bolus (skin dose)
 - Duration of therapy/ fractionation



Evidence for BCT

- 1) Does BCT with RT provide an equivalent survival to Mastectomy?
 - Yes
 - 6 RCT show equivalent OS for BCT & mastectomy
- 2) What local control is needed to achieve equivalent survival?
 - 10% at 10 years
- 3) What is the significance of a relapse in BCT?
 - Decreased survival

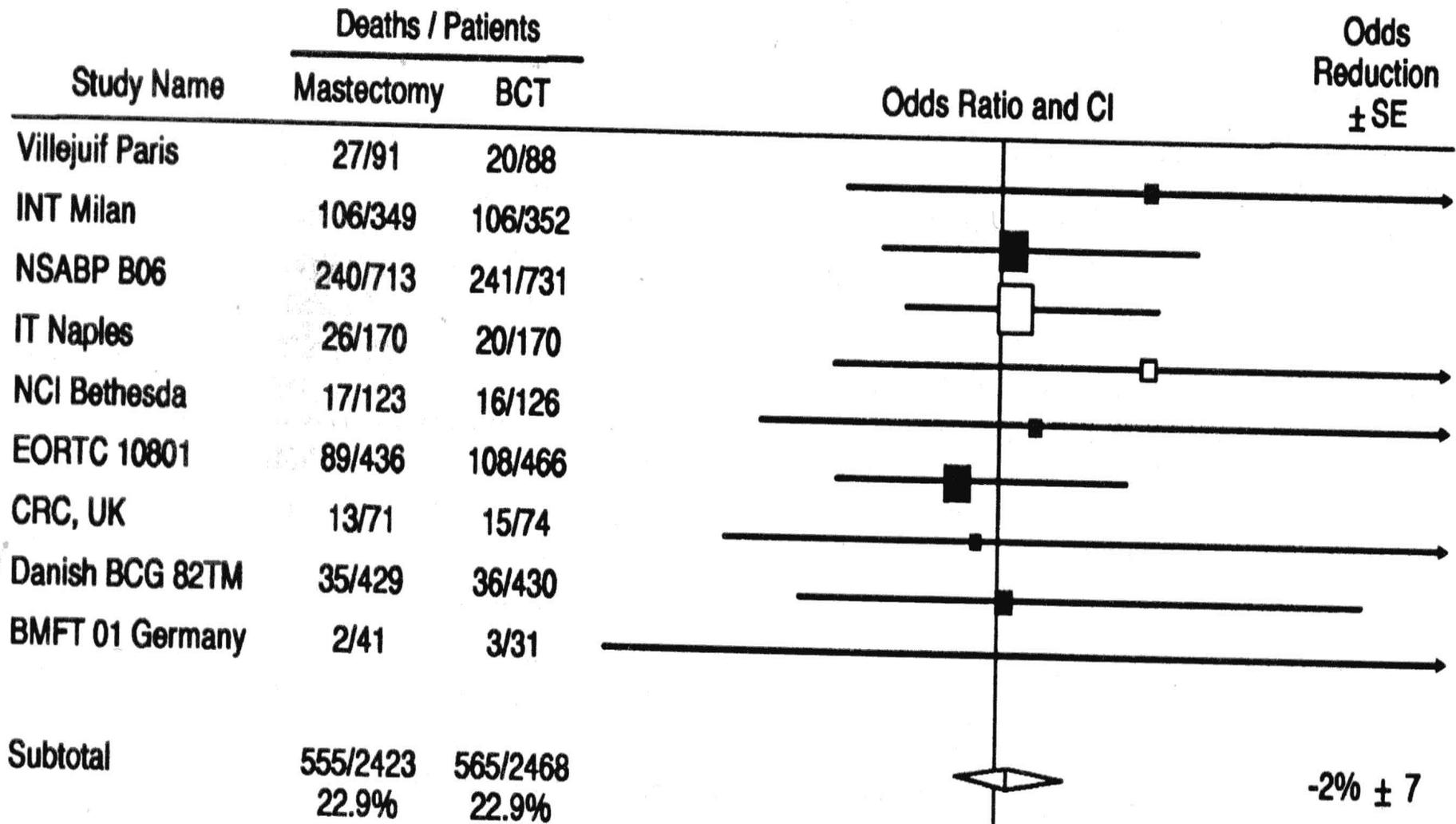


Mastectomy vs BCT Studies

Centre	Surgery/Margins	Radiation
NCI –US	Gross resection/ micro + ok	boost to 65Gy
IGR	Complete resection by 2 cm	Boost to 60 Gy
NSABP B06	Micro negative (not at ink)	No boost, 50 Gy
Milan 1	Quadrantectomy	Boost to 60 GY
Danish	Gross resection/ micro + ok If peripheral: includes skin and fascia	-: boost to 60Gy
		+: boost to 75Gy
EORTC	Gross resection with 1 cm	Boost to 75Gy



Metanalysis: OS BCT vs Mastectomy



Mast vs BCT Studies: Relapse in BCT arms

Centre	Number	10 yr Local Relapse	Annual relapse rate
NCI –US	237	15%	1.5%
IGR	179	5%	0.5%
NSABP B06	1851	14% @ 20 years	0.7%
Milan 1	701	8.8% @ 20 years	0.45%
Danish	905	2.4% @ 6 years	0.4%
EORTC	903	<2 cm: 8% @ 8 yr	1%
		2-5cm: 17% @8yr	2%



Outcome after local relapse after BCT

- 1) Disease free survival after salvage mastectomy for isolated in breast relapse
 - 60-75%
- 2) Overall survival after salvage mastectomy
 - 70-85%
 - le 1/4 to 1/5 patients with in breast relapse die of breast cancer
 - Increased risk if : young <40 years, LVI +, large primary at diagnosis (40% DFS at 5 yrs)



Conclusion

- 1) Acceptable local relapse rate, for equivalent OS:
 - 1%/yr,
 - or 10% at 10 yrs





What is the risk of relapse with positive or close margins?



Recurrence Rates For + Margins

TABLE 3. *Recurrence rates (%) by margin status*

Author (institution)	No. of patients (median F/U)	End point	Negative	Close	Positive
Borger et al. ⁸¹ (Netherlands)	1,026 (6.5 yr)	5-yr actuarial	2	6	16
Dewar et al. ⁸² (Gustave-Roussy)	757 (9 yr)	10-yr actuarial	6	—	14
Freedman et al. ⁸³ (Fox Chase)	1,262 (6.3 yr)	5-yr actuarial 10-yr actuarial	4 7	7 14	5 12
Park et al. ⁸⁴ (JCRT)	340 (10.8 yr)	8-yr crude rate	7	7	14 ^a /27 ^b
Anscher et al. ⁸⁵ (Duke)	259 (3.8 yr)	5-yr actuarial	2	—	10
Smitt et al. ⁸⁶ (Stanford)	289 (6 yr)	10-yr actuarial	2	16	0 ^a /9 ^b
Peterson et al. ⁸⁷ (U. Penn.)	1,021 (6.1 yr)	8-yr actuarial	8	17	10
Wazer et al. ⁸⁸ (Tufts)	498 (6 yr)	10-yr actuarial	2	2	15
Pittinger et al. ⁸⁹ (U. Rochester)	211 (4.5 yr)	Crude rate (F/U 54 mo)	3	2.9	25
Cowen et al. ⁹⁰ (Marseilles)	152 (6 yr)	5-yr actuarial	—	—	20

10 Year Recurrence Rates by Margins

Centre	Number	Negative	Close	Positive
IGR	757	6%	NA	14%
FCCC	1262	7%	14%	12%
Stanford	289	2%	16%	
Tufts	498	2%	2%	15%
Curie* *large tumors	257	17%	32%	24%
Dutch	1753	6.9%		12.2%
Dutch <40y		8.4%		36.9%
Dutch >40y		2.6%		2.2%



Can radiotherapy deal with a positive margin just as well as a re-excision?



RT Only

- **Leuven, Belgium**
 - 221 patients, 15 year follow-up
 - Biopsy only followed by RT
 - Tis, T1-T3
 - RT to 60-110Gy
 - Relapse rates:
 - range from 3%/yr for 5 years,
 - then 1%/yr for next 10 years

(Eur J Cancer 26(6): 674-679, 1990)



Are there RCT Boost vs Re-excision?

No, but ...

- **MILAN II: QUART vs TART RCT,**
- **1985-1987, 705 pts**
- **TART:**
 - **Tumourectomy : 1 cm margin, does not skin and fascia, no re-excision of margins**
 - **RT: 45 Gy/25# whole breast + 15Gy iridium boost**
- **QUART:**
 - **Quadrantectomy : 3 cm margin, include skin and fascia**
 - **RT: 50 Gy/25# whole breast + 10 Gy/5# e- boost**



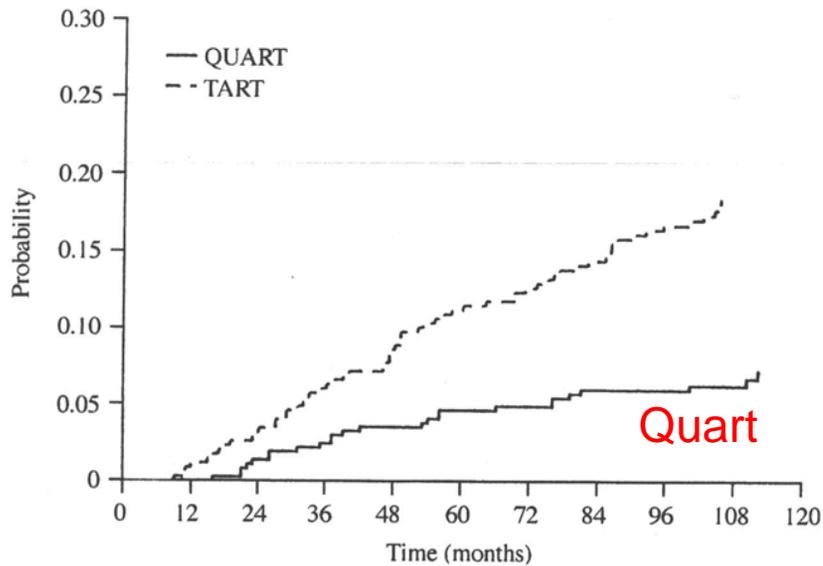


Figure 3. Crude cumulative IBTR incidence curves in the two treatment arms.

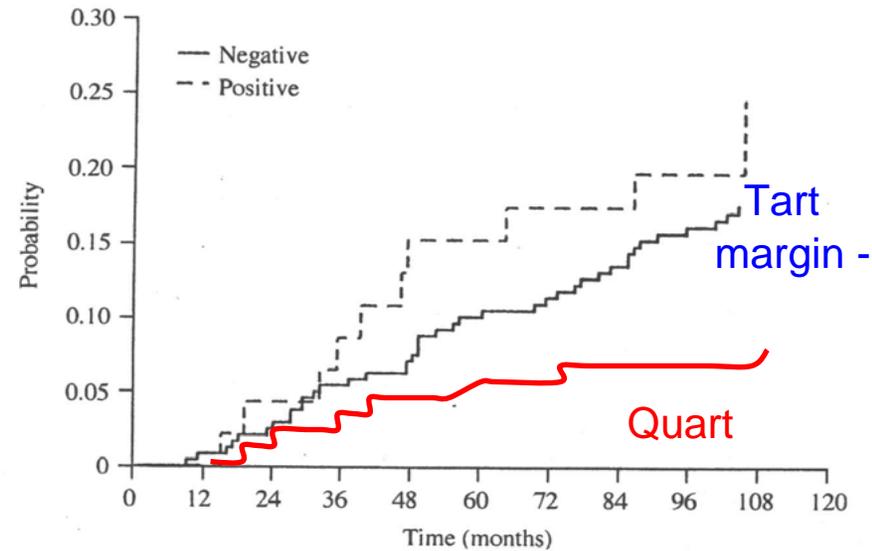


Figure 4. Crude cumulative IBTR incidence curves in the TART treatment arm according to surgical resection margins.

RCT of Margin Positive Patients

- EORTC 22881 positive margin trial
 - RCT of 10Gy vs 25Gy boost after Lump and WBRT
 - Closed early due to poor accrual
 - 251 margin + pts, 11 year follow-up



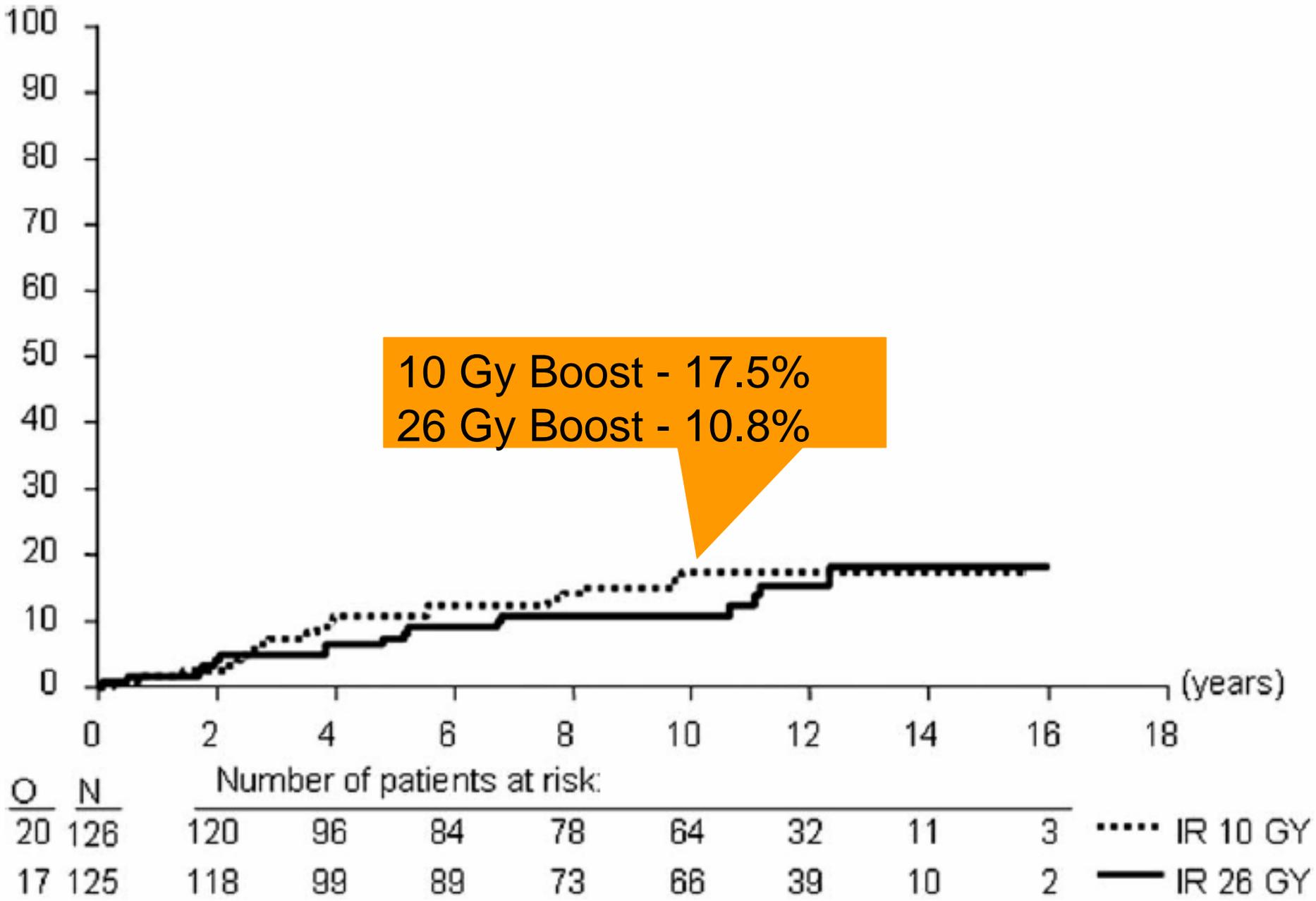
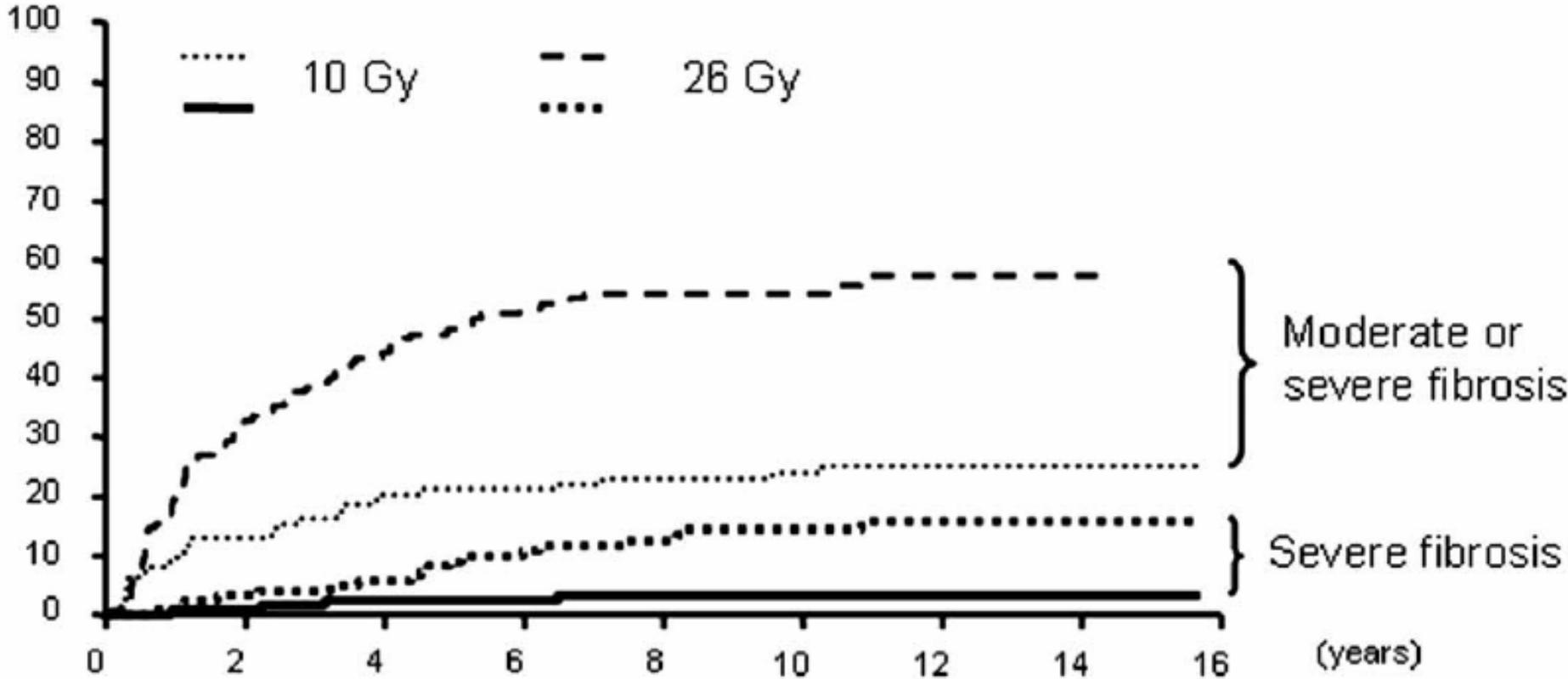


Fig. 1. Cumulative incidence of local failure (as first event).



Toxicity – 10 year Incidence Fibrosis

	Severe	Moderate or severe
High Dose	14%	68%
Low Dose	3%	27%



Can radiotherapy deal with a close margin just as well as a re-excision?



How close, and how much

- 1) Definitions (vary):
 - Negative: > 2 mm
 - Close: not at ink but within 2 mm
 - Positive: at ink
 - Limited positive: vary ++
 - < 3 Low power fields
 - Single inked surface
 - <3 inked surfaces
 - A single shave margin
 - Extensive positive: not limited



Close margins

- 1) Fox Chase (IJROBP 4(5):1005-)
 - Retrospective. 1262 patients (T1-T2)
 - All path reviewed, 59% had re-excisions
 - RT: 46Gy + boost
 - Definitions:
 - Positive: at ink: boost 20 Gy
 - Close: < 2mm: boost 18Gy
 - Negative: > 2mm: boost 14 Gy



Close margins

- Fox Chase (IJROBP 4(5):1005-)

■ local relapse	5yrs	10 yrs:
■ Negative	4%	7%
■ Close	7%	14%
■ Positive	5%	12%

-No diff for DCIS or invasive at margins

-Systemic therapy delayed but didn't prevent relapse

- If close or + margin:

-> 1%/yr relapse even with boost & systemic therapy

- If < 2 mm margin: re-excise



Focal positive margins

- 2) Schnitt (Cancer 74:1746-)
 - Retrospective, 885 pts, Stage I and II,
 - RT: all > 60 Gy to tumour bed
 - local relapse 5yrs
 - Negative 0%
 - Close 4%
 - Positive Focally = 5%, extensive = 21%



RT Boosts with negative margins

■ EORTC trial

- 5318 patients, 5 yr F-up
- Lumpectomy with negative (not at ink) margins & Ax ND & 50Gy whole breast
- Randomized:
 - No boost vs 16Gy boost
- At 5 yrs

	no boost		Boost
■ local relapse:	7.3%	vs	4.3 % (p<0.001)
■ cosmesis:	86%	vs	71%

(NEJM 2001; 345: 1378-1387)



Table 4. Univariate Analysis for Local Relapse in Patients With 0 or 16 Gy Boost

Contrast by Factor	P	Hazard Ratio	95% CI
Age > 50, yes v no	< .0001	0.40	0.28 to 0.57
N+ according to local pathology, N+ v N-	.2585	0.77	0.48 to 1.22
Systemic treatment (chemotherapy or tamoxifen), yes v no	.0089	0.57	0.38 to 0.87
Volume of excision biopsy specimen, cm ³	.1068	1.00	1.00 to 1.00
Treatment, no boost v boost 16 Gy	.0008	1.86	1.29 to 2.68
Vascular invasion, yes v no	.9715	0.99	0.65 to 1.50
Extensive intraductal component, yes v no	.8975	1.04	0.57 to 1.90
Histology			
Lobular v ductal	.4451	0.72	0.32 to 1.68
Mixed pattern v ductal	.3184	0.72	0.37 to 1.38
Other v ductal	.6439	0.88	0.50 to 1.54
Histologic grade			
Intermediate v high	.0320	0.60	0.37 to 0.96
Low v high	.0003	0.46	0.31 to 0.70
Ductal component involved, yes v no	.5254	1.17	0.72 to 1.89
Lobular component involved, yes v no	.2482	0.73	0.43 to 1.24
Mitotic activity index, < 10 v > 10	.0267	0.66	0.45 to 0.95
Margin involved of DCIS, not involved v involved	.3710	0.82	0.53 to 1.27
Margin involved of DCIS/invasive tumor, not involved v involved	.6779	0.92	0.64 to 1.34
Margin involved of invasive tumor, not involved v involved	.4127	1.20	0.78 to 1.84
Margin of DCIS			
No DCIS v positive	.4862	0.78	0.38 to 1.58
Close v positive	.9276	0.97	0.46 to 2.03
Negative v positive	.8362	0.93	0.48 to 1.81
Grade of DCIS			
No DCIS v high grade	.9640	1.02	0.51 to 2.03
Low v high	.1826	1.57	0.81 to 3.06
Moderate v high	.7457	1.12	0.59 to 2.16
Margin of invasive tumor			
Negative v close	.6589	1.11	0.71 to 1.73
Incomplete v close	.2191	0.46	0.11 to 2.03
Estrogen positive, yes v no	.0330	0.63	0.41 to 0.96
Progesterone positive, yes v no	.4286	0.84	0.54 to 1.30

Abbreviation: DCIS, ductal carcinoma in situ.

Post Hoc Path Review

-1616 pts initially negative margins

-Median F-up = 10 years

-On review:

1137 negative, 306 close, 52 +

•Significant On MVA for Local Relapse

- Age
- RT boost
- Grade

•Margin status Not Significant Neither close nor positive

What about close Ant or Post margins

- Fox Chase Cancer Center
 - 200 pts between 1974 and 2001
 - “accepted for RT after BCS despite close or positive margins”



Who Doesn't need a Re-Excision

- FCCC – Reasons for no Re-excision
 - 47% either Anterior or posterior margin
 - 35% refused further surgery
 - 13% focal involvement
 - 7% older or poor comorbidity
 - 5% No EIC

American Journal of Clinical Oncology • Volume 30, Number 2, April 2007



What about close Ant or Post margins

- Fox Chase Cancer Center
 - Median F-up = 7 years
 - 10 Year Actuarial LR 5%



Conclusions

- 1) Margins should be assessed
 - Orient and ink specimen
 - Different ink for different sides of specimen
 - Re-excision specimens should be oriented and inked
 - OR report should describe if:
 - Deep margin included pectoral fascia
 - Anterior margin left only skin anteriorly
 - Orientation of any re-excision



Conclusions

- 2) Principles
 - Balance survival/ conservation/ cosmesis
 - Incorporate patient preference
 - Where cosmesis will be significantly worse a patient may tolerate a slightly higher recurrence risk



Conclusions

- **3) Principles**
 - **Take as little breast tissue to optimize control and cosmesis.**
 - **Don't take skin if possible**
 - **Fewer cancer cells left, better local control with RT**
 - **Boost improves control but compromises cosmesis**
 - **Larger Excision: improves control but worse cosmesis**
 - **Especially is skin taken**



Conclusions

- 4) Grossly positive margins
 - In general: should be excised.
 - Would not have been included in most RCT
- 5) Focally positive margins
 - A unifocal margin on 3 LPF (eg a few mm at on one slide): controversial.
 - Anterior or posterior margin – unlikely gross residual
 - If little impact on cosmesis, and young:
 - generally should re-excise
 - If older, high systemic risk, ant or post:
 - No re-excision just RT Boost.
 - If < 40 yrs and EIC, definitely re-excise.



Conclusions

- **6) Close margins (< 2 mm)**
 - Controversial
 - If young (<40 yrs & EIC), should re-excise
 - Other factors should be considered
 - Benefit of re-excision uncertain, but probably best

- **7) Negative margins (> 2 mm)**
 - Do not need re-excision
 - Do not need boost, unless young (< 50 y or grade 3)
 - < 50 year old: offered RT boost for better local control, but worse cosmesis



BCCA Management Manual:

Guidelines for Re-excision and Boost

- 1) For patients with invasive disease:
 - Invasive and dcis are treated equally
- 2) A negative margin is $> 2\text{mm}$
- 3) A positive margin is touching ink
- 4) A close margin is anything in between
- 5) Re-excision to negative margins is generally recommended for positive or close margins
- 6) if re-excision is $< 2\text{ mm}$ and re-excision is declined or inappropriate: Boost with RT



BCCA Management Manual:

Guidelines for Re-excision and Boost

- **7) Re-excision more strongly recommended if:**
 - **Margins positive or < 2 mm and:**
 - **Age < 40 yrs**
 - **Extensive DCIS (EIC)**
 - **Lobular histology**
 - **LVI**
 - **No systemic therapy**
 - **Multiple margins involved**
 - **Margin status unknown**
 - **Low systemic risk**





Simple Take home message

- What is appropriate management of close or positive margin?
 - Re-excision



Subtle take home message

- What is appropriate management of close or positive margin?
 - Individualize!



Questions

- **Should we aim for bigger margins or give boost radiation? (What is the benefit of re-excision?)**
- **Not necessarily, bigger volumes worse cosmesis, aim for a negative margin,**
- **Re-excision likely a benefit for some patients,**
 - **LR : 7%, OS: 1-2% if positive**
 - **Similar but less certain if close**



TABLE 1. Five-year Actuarial Rate of Recurrence of the Tumor in the Breast in Relation to the Extent of Breast Resection and the Presence of EIC

Tumor Size	No. of Patients	Extent of Breast Resection*			Probability Value†	
		Smallest	Intermediate	Largest		
EIC ⁺	T ₁	83	29%	22%	10%	0.07
	T ₂	78	36%	26%	9%	0.04
EIC ⁻	T ₁	182	9%	2%	0%	0.02
	T ₂	164	6%	2%	3%	NS

* For patients with T₁ tumors, the volume of breast resected corresponds to <13 cm³, 13–48 cm³, and >48 cm³ for smallest, intermediate, and largest resections, respectively.

For patients with T₂ tumors, the volume of breast resected corresponds to <35 cm³, 35–74 cm³, and >74 cm³ for smallest, intermediate, and largest resections, respectively.



Table 1. Calculations of harm versus benefit of QUART versus TART

Treatment	No local recurrence	Local recurrence	Re-excision	Mastectomy	Deaths/10 years
TART (100 cases)	72 enjoy good cosmesis	18 suffer the distress of LR	10 suffer poor cosmesis	8	21
QUART (100 cases)	93 suffer the distress of poor cosmesis	7 suffer the distress of LR	2 suffer even poorer cosmesis	5	21

Cochrane RA, Valasiadou P, Wilson AR, et al. Cosmesis and satisfaction after breast-conserving surgery correlates with the percentage of breast volume excised.

Br J Surg. 2003;90:1505–1509.

Questions

- Is there any evidence for re-excision of skin (Anterior margins) or fascia (posterior margins)?
- Yes, ant and post margins likely of less significance than other margins, Boost OK, less need to re-excise if: only skin anteriorly and only fascia posteriorly.



Questions

- If margins are positive should we re-excise or first do post lumpectomy mammograms to assess for extent of residual calcifications? (Should this be a standard?)
- post op mammo are useful, especially if extensive Ca+. If extensive Ca, consider bracketing wires.
- If unknown margin and no Ca+ on mammo. More comfortable with RT boost



Questions

- **How should close margins and young age determine extent of surgery (mastectomy vs breast conserving surgery and radiation)?**
- If all 3 of EIC, young age (< 40) and close margins it is very bad news, definitely do re-excision, if margins still close - mastectomy





Other Guidelines

- **Scottish:**
 - For BCT: “lateral margins should be 1 mm or more clear of disease”
- **American College of Radiology:**
 - “in general if margins are microscopically involved, a re-excision should be done”.
 - “This may not be necessary on patients who have only focal margin involvement and in whom there is no extensive intraductal component”
 - “patients with EIC-positive tumour and a positive margin should undergo a re-excision”



Other Guidelines

- **COIN (Royal College UK)**
 - For BCT: relapse in breast should be less than 10% at 5 years
- **National Cancer Institute (USA):**
 - “there is a debate as to whether completely clear microscopic margins are necessary”.
 - “patients with positive, close or unknown margins after an excisional biopsy, larger tumours (T2), positive axillary nodes, EIC, and lobular histology correlate with a higher likelihood of persistent disease on re-excision ”



Other Guidelines

- **Cancer Care Ontario**

- “There is controversy about further management when ... involvement of margins of resection”
- “these patients are at increased risk for a local recurrence and re-excision or total mastectomy should be seriously considered. The patients should be informed that the margins are positive. The efficacy of a radiation boost to the tumour site is unclear”



Other Guidelines

- **Canadian Consensus Guidelines**
 - “mastectomy should be considered: .. Failure to obtain tumour-free margins”
 - “to obtain optimal clinical control ... tumour-involved margins should be revised by opening the original incision”
 - “ exceptions may be considered when involvement is microscopic and when such intervention would cause significantly poorer cosmesis. Of course the patient must fully understand that local recurrence may be more likely”



General conclusions

- No consensus on what constitutes clear margins
- Most evidence suggests increased risk of local relapse
- No definite evidence of decreased survival
- No consensus of definitive data on ideal approach to managing close margins



General conclusions

- LR rate at 5 years may be premature to assess impact of close margins, especially in presence of systemic Tx
- Patients with negative final margins after re-excision have same low risk of relapse as those with initially negative margins (Freedman)
- Margins on DCIS depend on RT use. In general, same rules as Invasive if using RT.



General conclusions

- Close margins more of a worry if accompanied by:
 - Young age (< 40 - 50)
 - High grade
 - Lobular
 - EIC
 - Multiple, or broadly, close margins



Subclassifications

- **Positive margins**
 - **Focal, (30% have residual on re-exc'n)**
 - **Minimal, (45% have residual on re-exc'n)**
 - **Moderate, (70% have residual on re-exc'n)**
 - **Extensive, (85% have residual on re-exc'n)**

Neuschatz, Cancer, 2002



Predictors of negative margins

- Confirmed diagnosis
- Palpable mass
- Small tumour size
- Ductal histology (vs lobular)
- Unifocality
- Absence of LVI
- Tumour cavity excision
- Large excision volumes
- *Absence of EIC,*
- *low Grade,*
- *absence of specimen orientation*



What factors increase risk of relapse with positive or close margins?

- 1) Age (< 40, < 50) (JCO 10:474-)
- 2) EIC (JCO 10:474-)
- 3) Lobular carcinoma (JCO 10:474-)
- 4) Margin proximity (< 1, 2, 3 mm)
- 5) Margin extent (focal vs extensive)
- 6) Margin location (anterior/posterior/lateral)
- 6) Lymphatic invasion (JCO 10:474-)
- 7) Systemic therapy (JCO 10:474-)
 - May just delay relapse
- 8) Systemic risk
 - Local control less important with high systemic risk



What about Patient Preferences?

- **1) Mastectomy vs Conservation**
 - 69% of informed eligible women prefer BCT to mastectomy (Fallowfield)
- **2) Survival**
 - No arbitrary cutoff for survival, each patient should be presented risk and benefits.
 - 50% of premenopausal women accept chemotherapy for a 1% survival benefit.
 - (Lancet 2001: 2: 691-697)
- **3) Boost vs Re-excision**
 - No preference data
 - No RCT on control or cosmesis

