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Appropriate Margins for Breast-conserving Surgery in Patients With Early Stage Breast Cancer: A Meta-analysis

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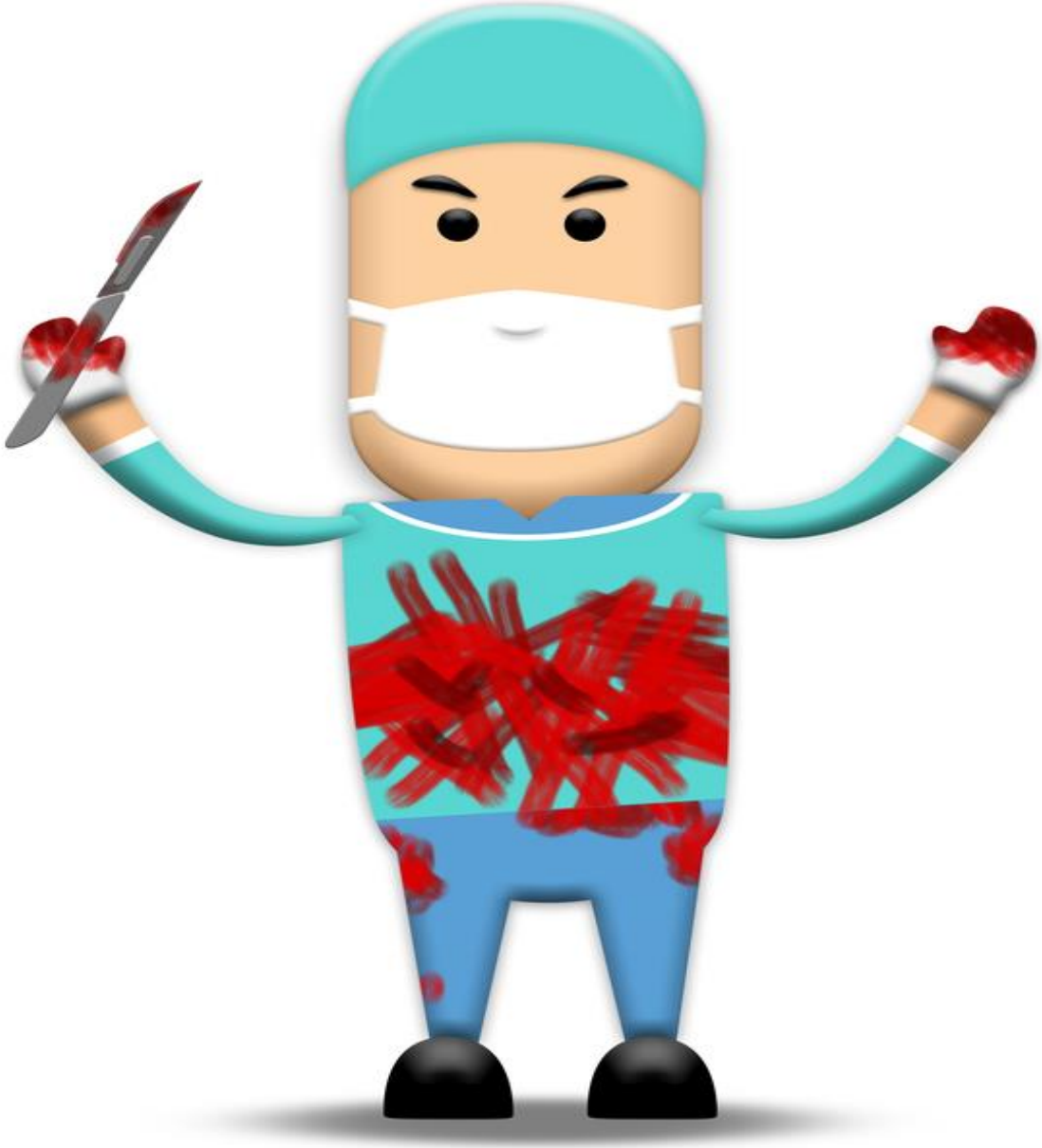
Mastology

GPM
GRUPO DE PESQUISAS EM MASTOLOGIA

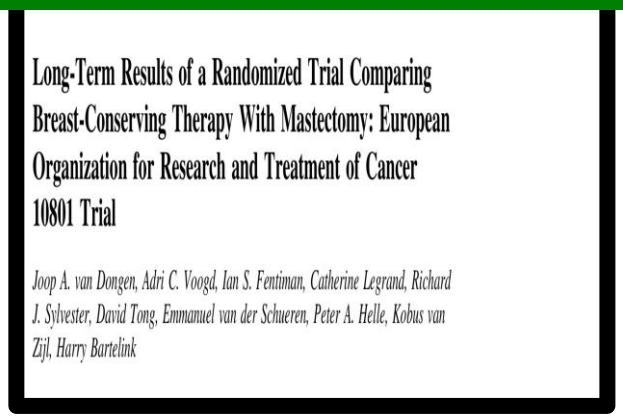
HGF HOSPITAL GERAL DE FORTALEZA

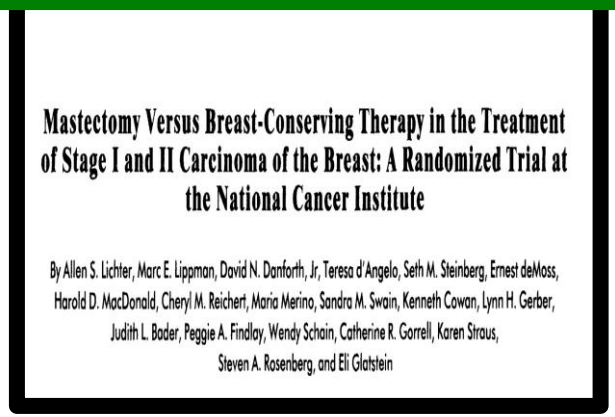


TOTAL MASTECTOMY VERSUS LUMPECTOMY

TWENTY-YEAR FOLLOW-UP OF A RANDOMIZED TRIAL COMPARING TOTAL MASTECTOMY, LUMPECTOMY, AND LUMPECTOMY PLUS IRRADIATION FOR THE TREATMENT OF INVASIVE BREAST CANCER

Similar Survival





Margins

Recurrences	Re-operations
>10%	

Local Recurrence (LR)

LR < 5%:

1- Better Radiology

2- Better Pathology

3- Systemic Therapy

Systemic Therapy and Local Recurrence

NSABP B-14	NSABP B-13
• RL 10 Years	• RL 10 anos years
• Positive RH Tumors	• Negative RH Tumors
• TAM Vs Placebo	• QT vs Placebo
• 14.7 ➡ 4.3%	• 13.4% ➡ 2.6%

Margins Definition: No ink on Tumor

Margins

Recurrences	Re-operations
>10%	20-25%

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation: Breast Cancer

Society of Surgical Oncology—American Society for Radiation Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Stages I and II Invasive Breast Cancer

Meena S. Moran, MD,* Stuart J. Schnitt, MD,† Armando E. Giuliano, MD,‡ Jay R. Harris, MD,§ Seema A. Khan, MD,‖ Janet Horton, MD,¶ Suzanne Klimberg, MD,# Mariana Chavez-MacGregor, MD,** Gary Freedman, MD,†† Nehmat Houssami, MD, PhD,‡‡ Peggy L. Johnson,§§ and Monica Morrow, MD‖‖

28.162 patients in 33 estudies (1506 local recurrences – 5.3%)

Positive margins: OR 1.96 (CI 1.72-2.24)

Model 1

Bigger margins was not associated with better local control (1, 2 and 5mm)

Model 2

Appropriate margins for breast-conserving surgery in patients with early stage breast cancer: A meta-analysis

Frank Vicini, Vivek Verma, Harlan Sayles, Abram Recht, Chirag Shah

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Cleveland Clinic Taussig Cancer Institute
Beth Israel Deaconess Medical Center, Harvard Medical School, UCLA Medical School, Radiation Oncology

Methods

- Systematic literature review (1995-2016)
- Inclusion criteria:
  - Minimum follow-up: 50 months
  - Explicit pathologic definition of margin status
  - Local recurrence reported in relation to margin status
- 38 studies with 55,302 patients identified, including 31 of the 33 studies from the previous meta-analysis (>***20,000 additional patients***)
    - 1 updated study
    - 1 follow-up <50 months (eliminated)
- Median follow up 7.2 years

Methods

- Margin definitions similar to previous analysis
- "Positive" = invasive cancer or DCIS at the surgical margin
- "Negative" = no tumor within specified distance from margin
- "Close" = no tumor on ink but there was tumor less than specified distance from the margin
- Series of models developed based on cut-point desired

Population

	# of studies	Median	(Range)
Number of subjects	38	826	48-11900
Follow-up (years)	38	7.15	4.2-13.3
Age (years)	33	55	40-63
T1 T2+ Other	31 31 31	74.1% 23.5% 0.0%	43.4-100.0% 0.0-56.6% 0.0-5.5%
N0 N+/Unknown	30 30	71.7% 28.3%	58.2-100.0% 0.0-41.8%
Re-excision rate	19	41.6%	6.1-68.4%
WBI Dose (Gy)	37	47.7	40-60
Boost Dose (Gy)	33	13	0-21.25
Endocrine Therapy	30	39.1%	0.0-79.7%
Chemotherapy	29	24.4%	0.0-100.0%

Covariate	Follow-up time adjusted model p-values- Model 1			
	Margin = 0	Margin = 1	Margin = 2	Margin = 5
Median study year	0.193	0.246	0.130	**0.002**
Median patient age	**0.048**	**0.040**	0.051	0.086
Median follow-up	N/A	N/A	N/A	N/A
100% stage 1/2+	0.898	0.973	0.638	0.413
Negative Nodes	0.386	0.365	0.405	0.930
Re-excision rate	0.099	0.575	0.301	0.078
WBI median dose	0.769	0.914	0.912	0.998
Median boost dose	0.361	0.335	0.295	0.129
Endocrine Therapy	**0.001**	**0.002**	**<0.001**	**<0.001**
Chemotherapy	0.989	0.655	0.829	0.651

Methods

- 3 Models in Present Analysis:
  - Model 1: similar to previous analysis (Model 1) of negative vs. close/positive
  - Model 2: performed to assess impact of margin width range rather than a set margin width
    - 0-2 mm, 2-5 mm, >5 mm
    - Not included in previous analysis
  - Model 3: similar to previous meta-analysis of negative, close, positive margins (1, 2 e 5mm)

Results- Model 1

Odds ratios for local recurrence for negative vs. close/positive margins

- >0 mm: 0.46 (0.40-0.53, p<0.001)
- >1 mm: 0.43 (0.36-0.51, p<0.001)
- >2 mm: 0.49 (0.42-0.55 p<0.001)
- >5 mm: 0.53 (0.43-0.66, p<0.001)

- Best odds ratio for 1 mm margin, as compared to close/positive margin
- Similar results to previous meta-analysis
- Odds ratios are very similar: unable to say what's the optimal margin

Results- Model 3

When modeling as negative, close, or positive margins, reduced rates seen with negative margins with lowest rates seen at 2 and 5 mm

MVA confirmed margin status and width as factors associated with local recurrence. Last two bullet points below are the difference from previous work

- Negative/Close/Positive Margins
  - 1 mm: 8.0%/13.0%/14.0%
  - 2 mm: 3.6%/5.5%/9.5%
  - 5 mm: 2.9%/4.1%/12.8%
- Odds Ratio for Local Recurrence by Margin Status
  - Close vs. Negative: 1.58 (1.32-1.89)
  - Positive vs. Negative: 2.49 (2.10—2.96)
  - **2 mm vs. 1 mm: 0.50 (0.42-0.59)**
  - **5 mm vs. 1 mm: 0.40 (0.33-0.48)**

Model 2

- All patients within a given margin range were compared against all patients within other margin ranges
- 4 groups included 66% of all cases

Range	Margin range classifications
≤ 0mm	≤ 0
0-2 mm	0-1, 1-2, 0-2
2-5 mm	2-5
>5 mm	>5

Results –Model 2

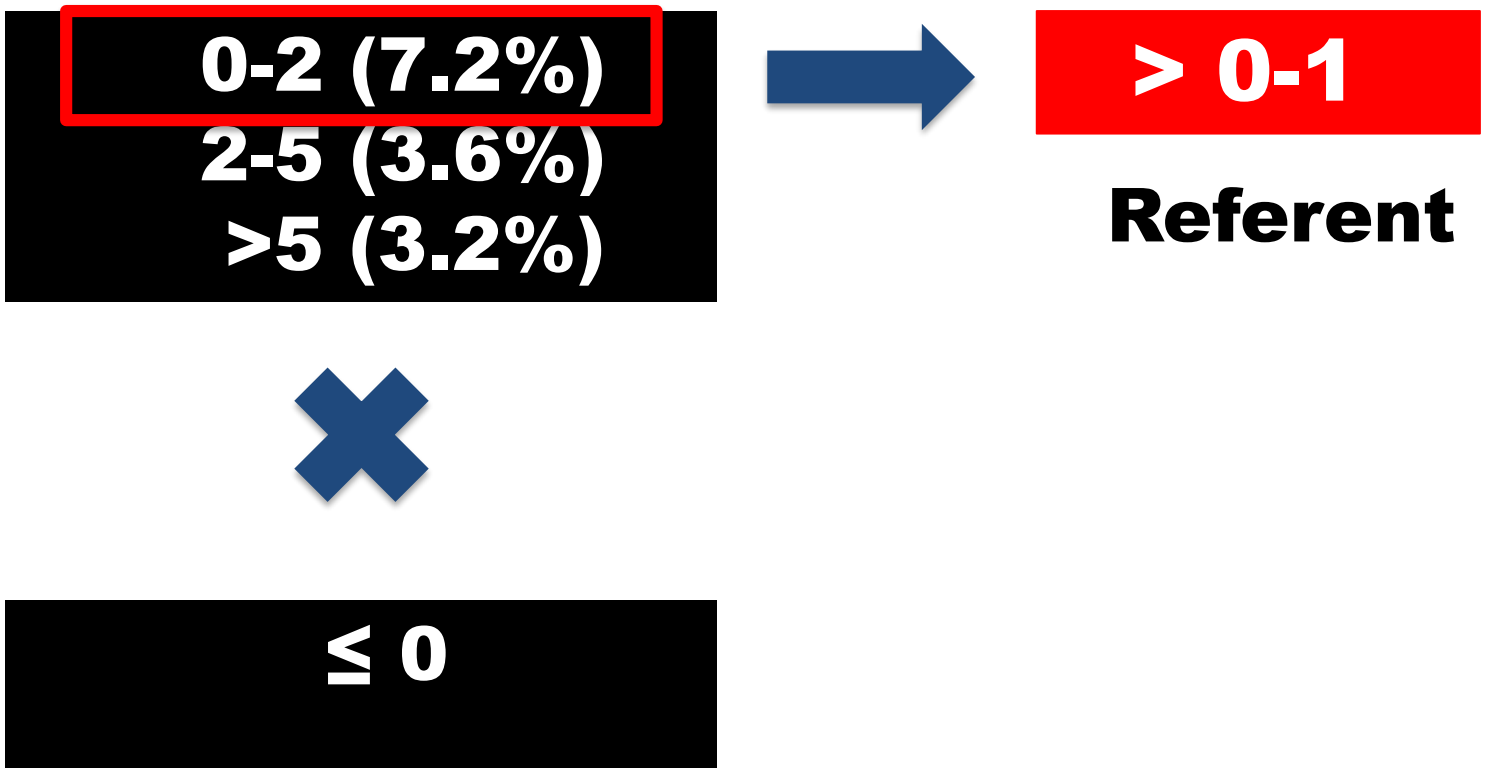
- Looking at range of margins, a wider margin further reduced local recurrence and was validated on MVA
- Margin range (negative/close) vs. Positive Margin
  - >0-2 mm: 7.2%, OR: 0.56 (0.49-0.63, p<0.001)
  - 2-5 mm: 3.6%, OR: 0.44 (0.35-0.56, p<0.001)
  - >5 mm: 3.2%, OR: 0.32 (0.26-0.41, p<0.001)
- Multivariate Analysis: margin width only significant variable (larger margin, lower recurrence)

Conclusions

- Limitations of meta-analysis preclude definitive conclusion regarding appropriate margins
- However: data suggest having a margin width beyond no tumor on ink may further reduce rates of local recurrence
  - Consistent with DCIS margin analysis: 2 mm
- Further prospective studies required to validate appropriate margin width
- Question- Should we achieve a 1-2 mm margin (as compared to no tumor on ink)?
  - Potential local control benefit vs. morbidity, time, cost?
  - Which patients with 'no tumor on ink' need more surgery?

?

Main Interpretation Model 2



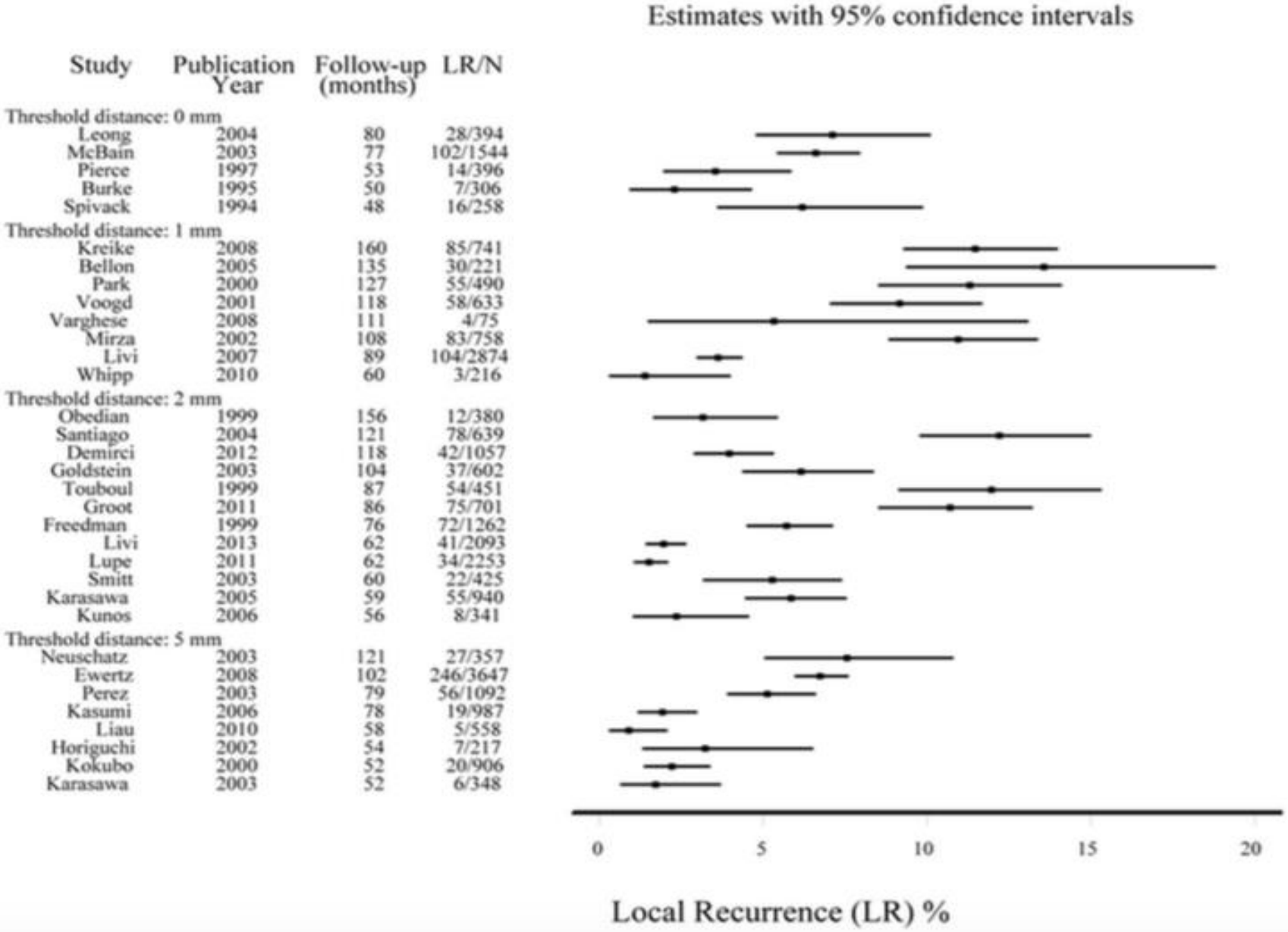
Crude Local Recurrence- Model 1

Negative vs close/positive

Margin (mm) and status	Number of studies providing data	Total number of observations	Total number	LR %
≤0	28	3	352	10.3
>0	38		1758	3.8
≤1	29	988	405	10.2
>1	27	33565	1161	3.5
≤2		5978	519	8.7
>2		31757	1053	3.3
	38	9781	659	6.7
	8	19059	604	3.2

Major Methodological Problem

to wider margins observed with greatest difference (benefit) seen at 1 mm (6.7%), but similar rates of recurrence with all negative margin definitions (3.2-3.8%)



Houssami, et al. Ann Surg Oncol, March, 2014

Probably, did not capture the full effect of improvements in systemic therapy

Systemic Therapy
24%(CT) and 39% (ET)

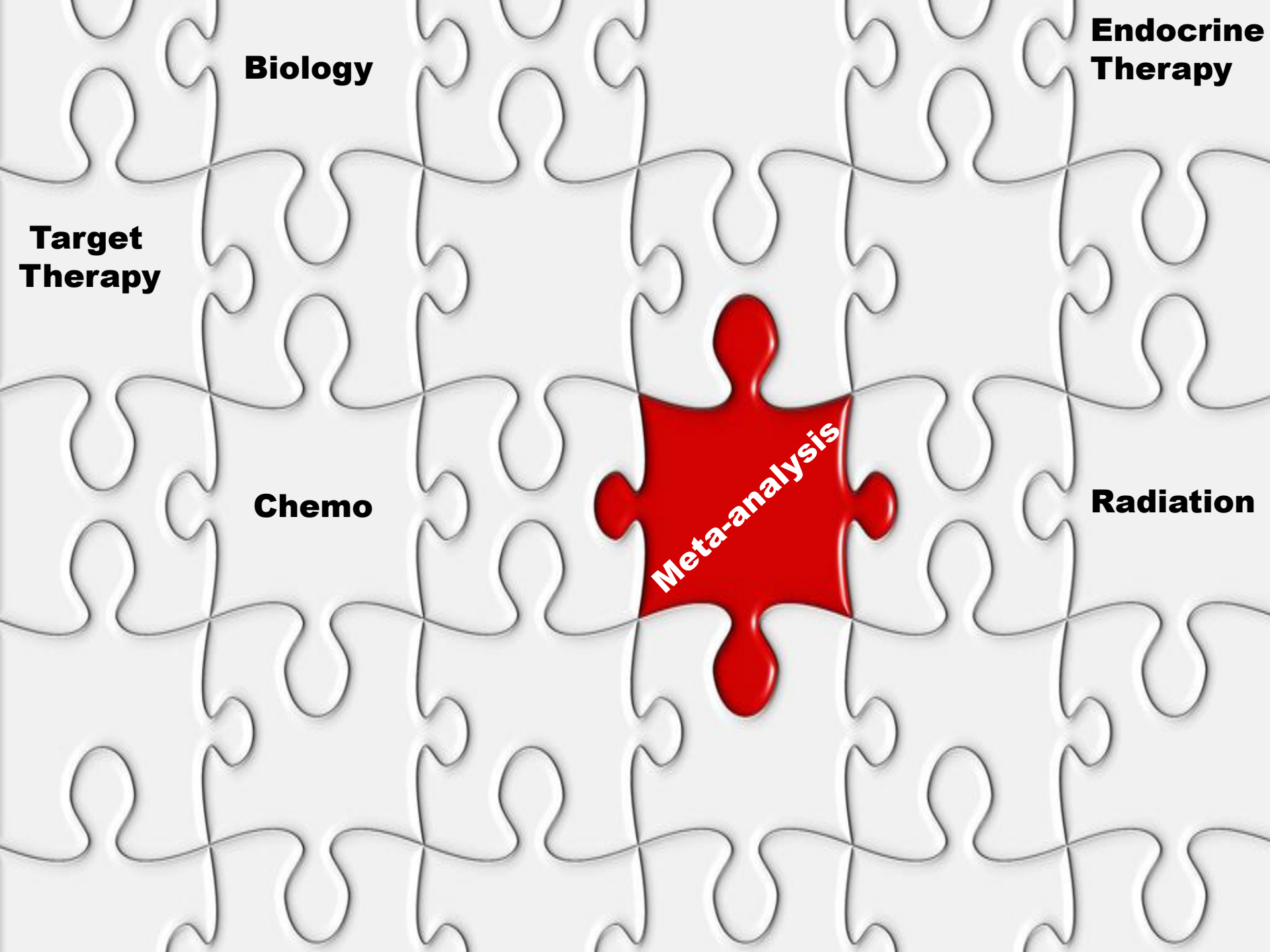
Status HER2 ?
Molecular Subtype ?

Better Systemic Therapy

Treatment	Relative risk of LRR
Tamoxifen ×5 years versus placebo	0.47
Anastrozole versus tamoxifen	0.83
Tamoxifen ×2 ⇒ anastrozole versus tamoxifen ×5	0.50
Chemotherapy versus none (<50 years)	0.63
Trastuzumab versus none	0.47

Mannino M, et al. Radiother Oncol 2009

Kiess AP, et al. Cancer 2012


Biology
Endocrine Therapy
Target Therapy
Meta-analysis
Chemo
Radiation

Thank you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