Randomised vs observational evidence re breast conservation

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US NIH consensus development conference 1990

Breast conservation therapy is an appropriate method of primary therapy in the majority of women with stage I and II breast cancer and is preferable because it provides survival equivalent to total mastectomy and axillary dissection while preserving the breast.

(Median follow-up 6.5 years in 6 major trials)

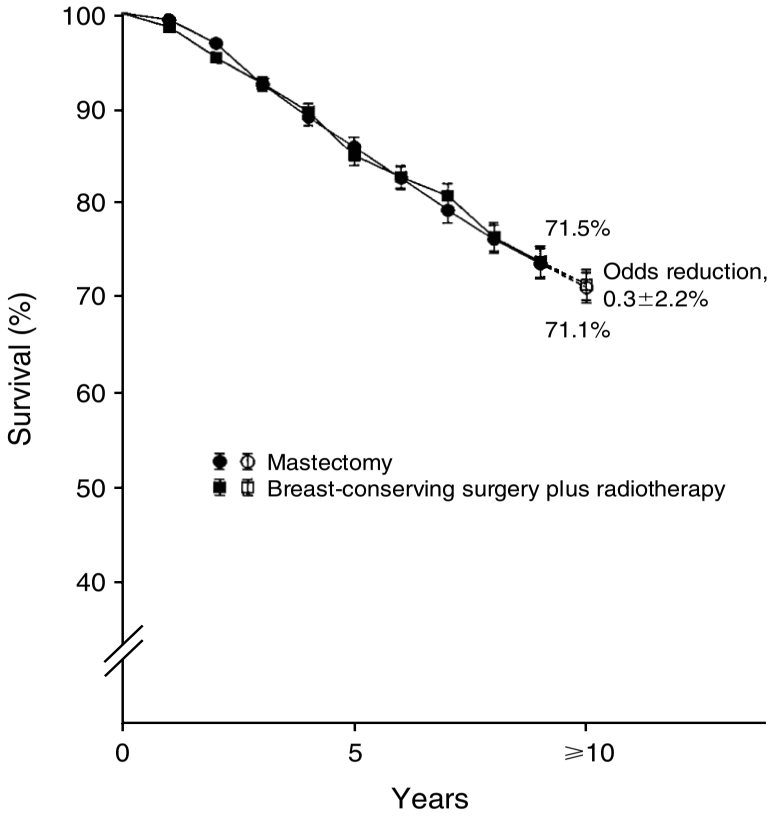


Figure 5. Ten-Year Survival among Approximately 3100 Women in Seven Randomized Trials Comparing Mastectomy with Breast-Conserving Surgery plus Radiotherapy.

EBCTCG; NEJM 1995 based on 6 major trials + 3 smaller

The randomised studies: mortality

TABLE 1. Mortality (Number of Deaths/Number Randomized)

Trial	Breast-conserving Therapy	Mastectomy	Odds Ratio (95% Confidence Interval)	Weight
NSABP-06	317/628	299/589	0.989 (0.790–1.238)	0.046
WHO (Milan)	156/352	152/349	1.032 (0.766–1.390)	0.080
NCI-USA	52/121	46/116	1.146 (0.684–1.920)	0.241
IGR (Paris)	24/88	33/91	0.662 (0.354–1.240)	0.355
EORTC 10801	208/448	165/420	1.338 (1.023–1.750)	0.065
Danish	36/430	35/429	1.029 (0.633–1.671)	0.213
Pooled			1.070 (0.935–1.224)	1

Jatoi et al; Am J Clin Oncol 2005; Median follow-up 14.7 years

The randomised studies: Local recurrence

TABLE 2. Locorgional Recurrence (Number of Patients With Locoregional Recurrence/Number Randomized)

Trial	Breast-conserving Therapy	Mastectomy	Odds Ratio (95% Confidence Interval)	Weight
NSABP-06	129/628	87/589	1.484 (1.106–1.992)	0.041
WHO (Milan)	30/352	8/349	3.365 (1.751–6.468)	0.202
NCI–USA	31/121	11/116	3.010 (1.547–5.857)	0.209
IGR (Paris)	12/88	15/91	0.802 (0.354–1.814)	0.315
EORTC 10801	76/448	45/420	1.683 (1.146–2.471)	0.070
Danish	20/430	27/429	0.728 (0.405–1.311)	0.163
Pooled			1.561 (1.289–1.890)	1

Jatoi et al; Am J Clin Oncol 2005; Median follow-up 14.7 years

Remarks

- Studies are statistically homogenous re mortality
- …but heterogenous re local recurrence (lumpectomy → quadrantectomy)
- Results not sensitive to exclusion of any of the trials
- 1990 statement, 1995 and 2005 findings consistent
- Compatible with the EBCTCG overviews of lesser vs more surgery
- Compares breast conserving surgery **+ RT** with mastectomy **+ RT when indicated**

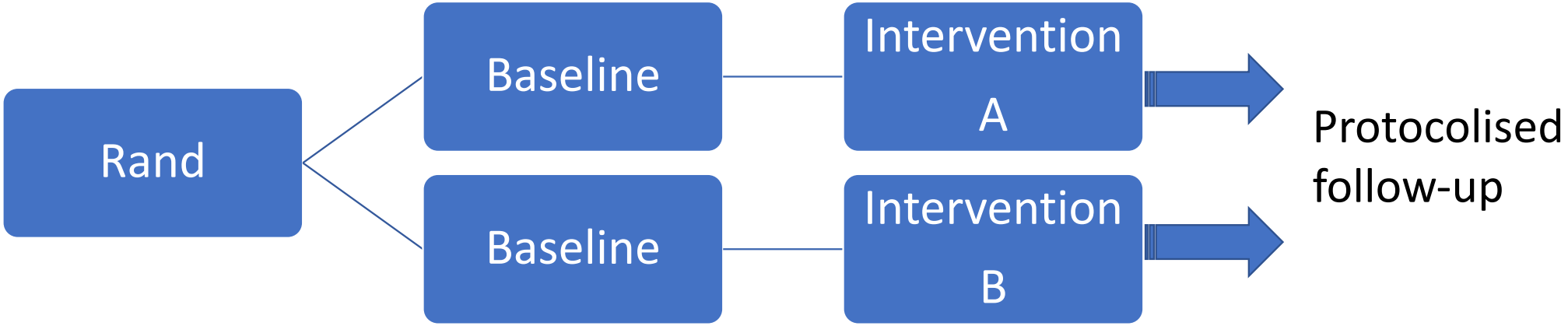
Clinical panorama after the trials

- At average less advanced disease
- Much wider indications for adjuvant systemic therapy
- Guidelines generally prescribe microscopically free margins
- Considerably better diagnostic procedures to confirm multifocality
- A much larger proportion of women having screen-detected disease

The three last points have a larger impact in the BCT group:
A stage drift of a larger proportion of severe cases in the MT group follows.
Lead time is added at a larger quantity to the BCT group.

Today's practices also invokes a situation where in observational studies there are few patients who have MT in reality could have been offered BCT on sound medical grounds.

A proper randomisation creates two groups very similar at baseline before any intervention: Avoids **selection bias**, the major threat in clinical studies. ITT possible.

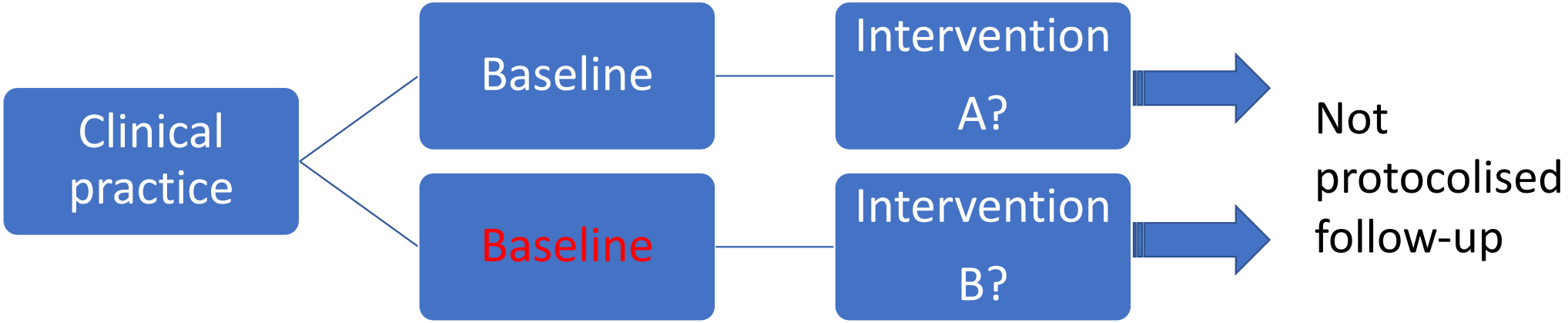


Well-defined interventions dictates indications for add-on therapies: avoids **confounding.**

Well-defined and recorded follow-up: avoids **information bias**

Confounding and information bias not ”automatically” removed by randomisation

Selection: many factors of the process not recorded at all and many others are recorded crudely or with misclassification. Few MT patients today not even suitable for BCT.



Interventions not well defined and e.g. information on add-on therapies may be completely missing.

Follow-up not protocolised and similar for groups: may not be large problem for mortality.

Essentially a PP analysis

Methods to mimic RCT in observational data

- No consensus
- *Propensity scoring* only accounts for known and measured disturbing factors
- *Instrumental variable analysis* can account for unknown and unmeasured factors, but require stronger assumptions
- Both methods are only valid for those patients who might have been offered both treatments: may be a very small group today
- **All modelling** require advanced assumptions – most often not verifiable
- Further difficulties if ITT should be mimicked

Most often Obs and RCT agree, but…

Observational Studies Analyzed Like Randomized Experiments

An Application to Postmenopausal Hormone Therapy and Coronary Heart Disease

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Background: The Women's Health Initiative randomized trial found greater coronary heart disease (CHD) risk in women assigned to estrogen/progestin therapy than in those assigned to placebo. Observational studies had previously suggested reduced CHD risk in hormone users.

Methods: Using data from the observational Nurses' Health Study, we emulated the design and intention-to-treat (ITT) analysis of the randomized trial. The observational study was conceptualized as a sequence of "trials," in which eligible women were classified as initiators or noninitiators of estrogen/progestin therapy. We also present comparisons between these estimates and previously reported Nurses' Health Study estimates.

Conclusions: Our findings suggest that the discrepancies between the Women's Health Initiative and Nurses' Health Study ITT estimates could be largely explained by differences in the distribution of time since menopause and length of follow-up.

(*Epidemiology* 2008;19: 766–779)

Epidemiology 2008;19:766-79

Another notable example of discrepancy observational studies and RCT:

HRT after a breast cancer diagnosis. A carefully done case/control study (and weaker cohort studies) had contrary results to two RCT:s.

We will not know if an observational study lives up
to our present demands on causal inference in clinical studies
until we have done the confirming RCT.

In today's clinical practice, however, a new trial of BCT vs
MT may not be a high priority.