Adoption of New Technologies in Breast Radiotherapy

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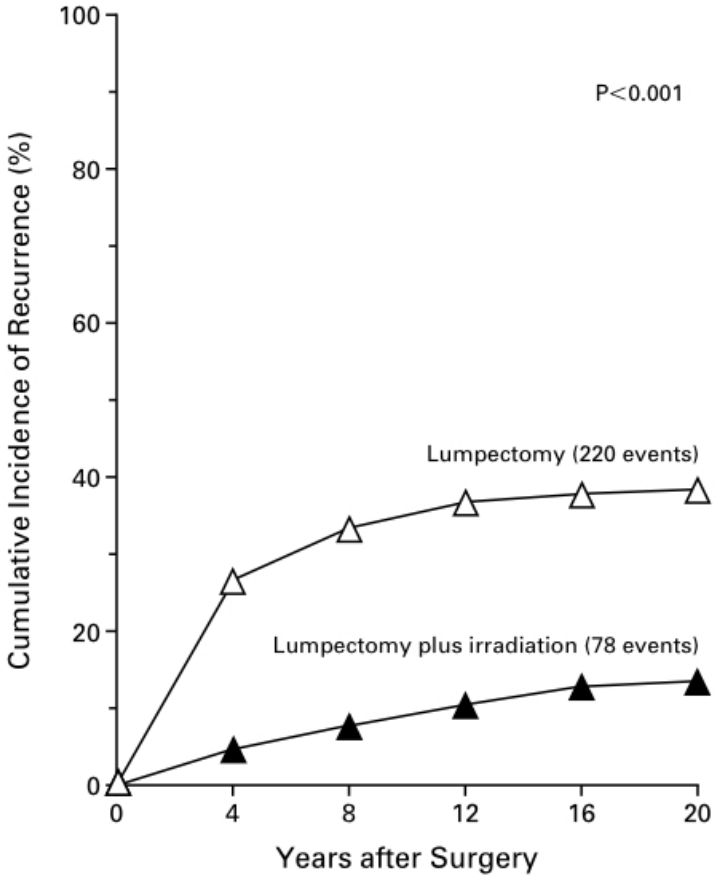
Background

- Role of RT in breast conservation firmly established by trials demonstrating significant reduction in locoregional recurrence

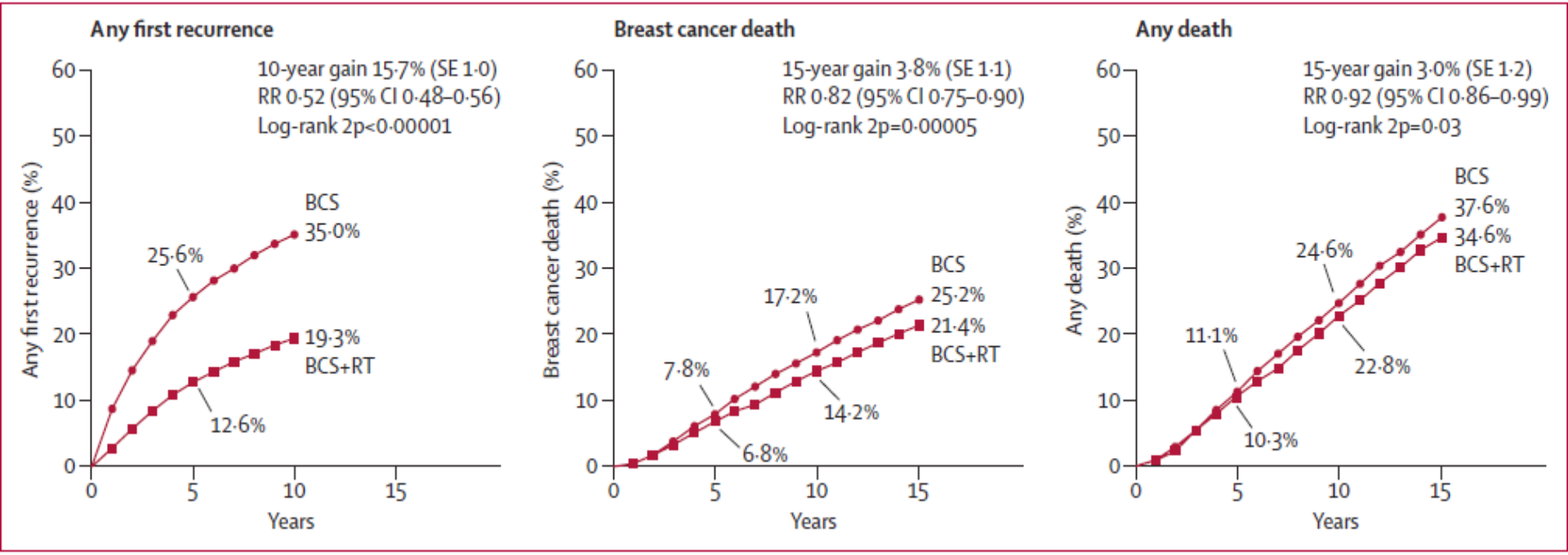


TWENTY-YEAR FOLLOW-UP OF A RANDOMIZED TRIAL COMPARING TOTAL MASTECTOMY, LUMPECTOMY, AND LUMPECTOMY PLUS IRRADIATION FOR THE TREATMENT OF INVASIVE BREAST CANCER

BERNARD FISHER, M.D., STEWART ANDERSON, PH.D., JOHN BRYANT, PH.D., RICHARD G. MARGOLESE, M.D., MELVIN DEUTSCH, M.D., EDWIN R. FISHER, M.D., JONG-HYEON JEONG, PH.D., AND NORMAN WOLMARK, M.D.

Background

- Subsequent meta-analysis also established a modest survival benefit from RT



Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Lancet 2011;378:1707-16.

How Could We Do Better?

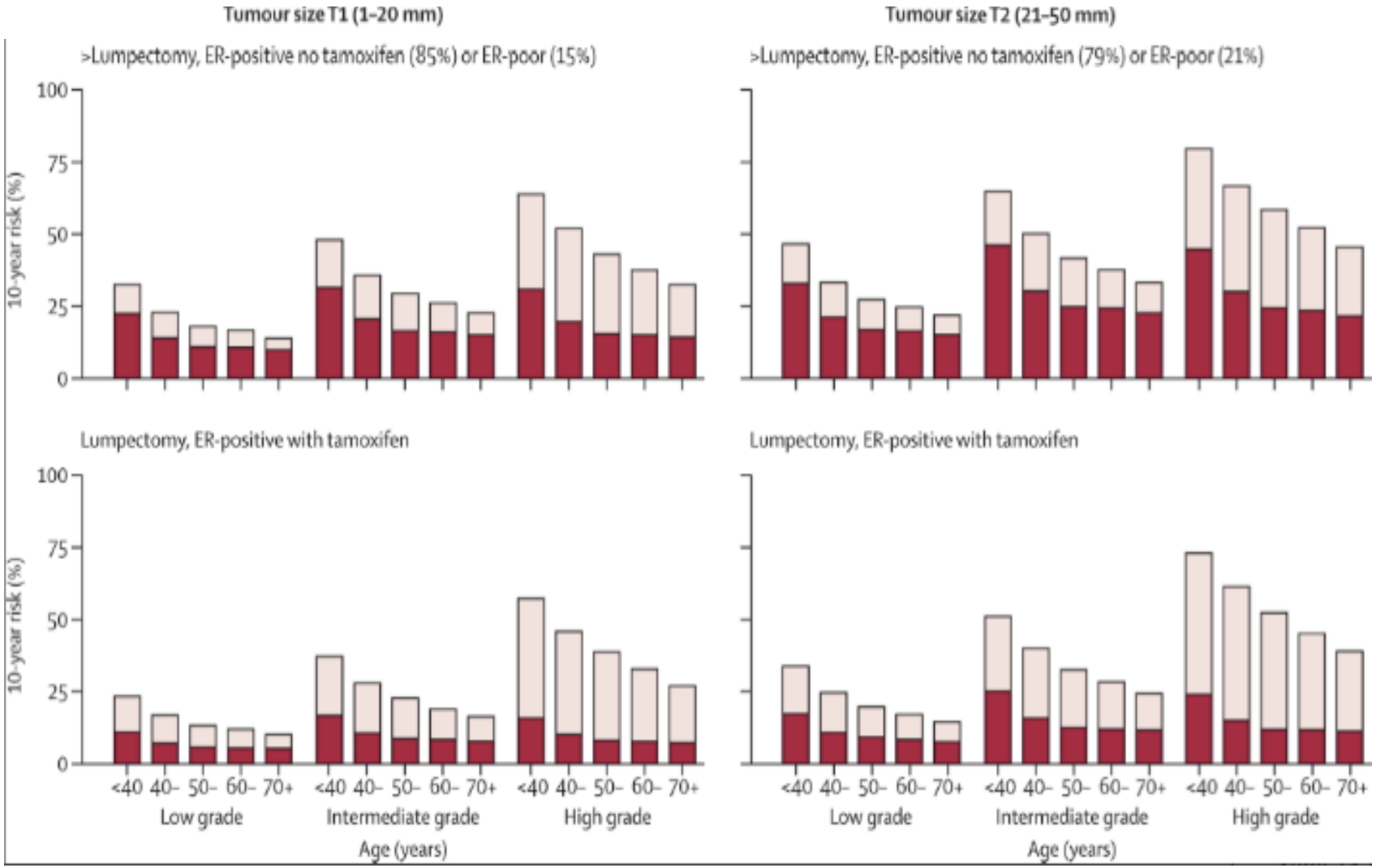
- RT is associated with toxicity, burden, and expense
  - Conventional regimens involve 6 weeks of daily treatments
  - This may compromise access to breast conservation
- Ideally, we would identify patients in whom we could safely omit RT altogether
- And for those likely to benefit from RT, we would identify ways to administer it more quickly, with equal (or better) efficacy and equal (or less) toxicity

What We Will Discuss Today

- 3 Approaches, 3 Levels of Technological Sophistication
  - Low tech: selective omission of RT
  - Middle ground: whole breast hypofractionation
  - High tech: accelerated partial breast irradiation

- Goal: to compare and contrast the level of evidence supporting each approach and to evaluate patterns of uptake

The Rationale for Selective Omission of RT: Not All Patients Gain the Same Absolute Benefit



Selective Omission: The Evidence

- CALGB 9343
  - 636 women, age 70+
  - Clinical stage I, ER+
- Randomization
  - Tamoxifen +/- RT
- 10-yr LRR 10% vs 2% (favoring +RT)
- No significant difference in distant metastases, breast cancer-specific mortality, or all-cause mortality

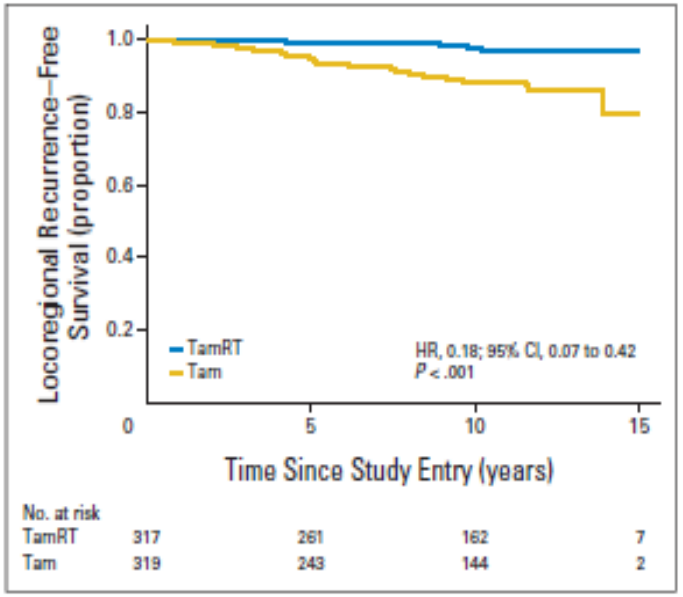


Fig 2. Time to local or regional recurrence. HR, hazard ratio; Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.

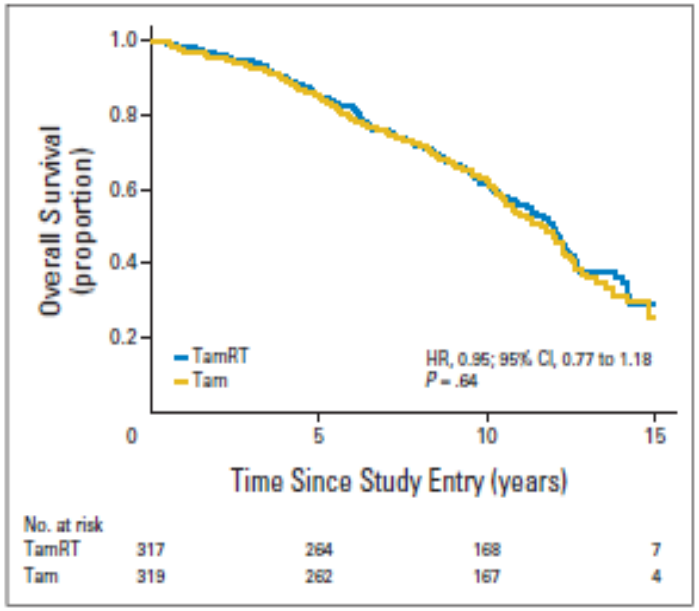
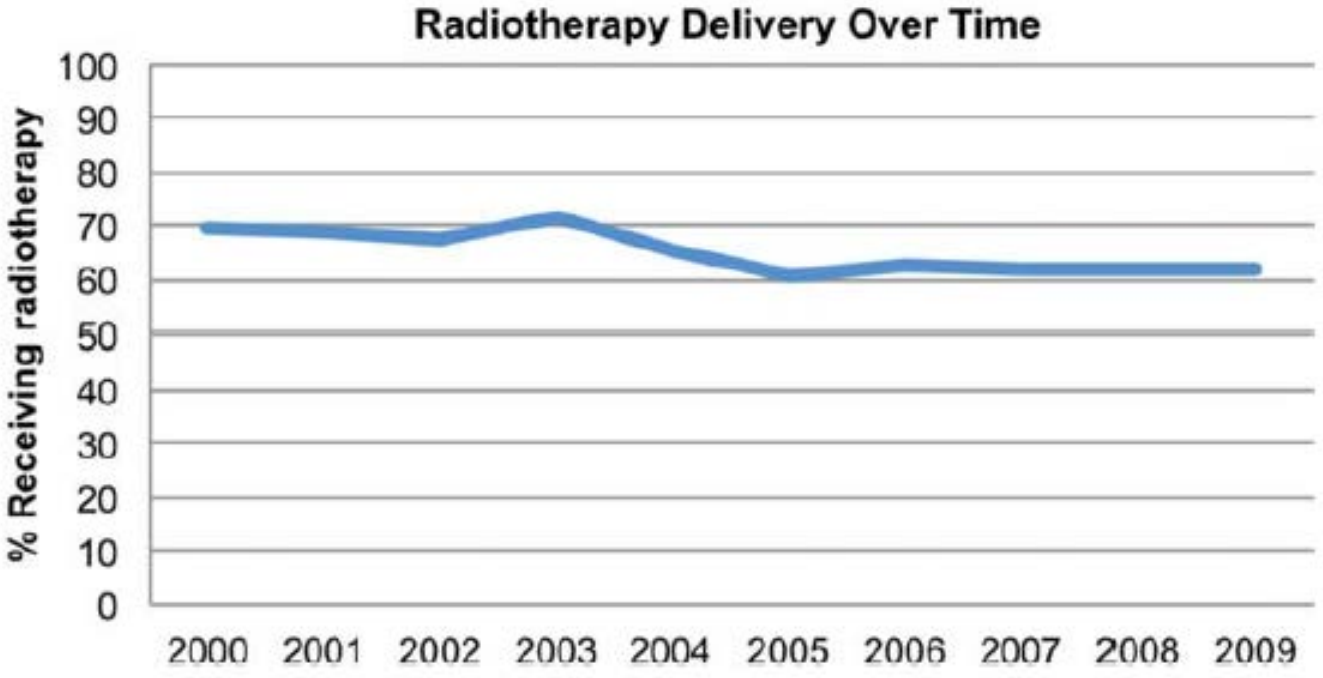


Fig 5. Overall survival. HR, hazard ratio; Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.

Hughes KS et al. J Clin Oncol 2013;31:2382-7.

Uptake of RT Omission in Elderly Patients



SEER data: among women aged ≥70 treated with breast conserving surgery, 68.4% in 2000-2004 and 61.7% treated 2005-2009 received adjuvant RT

Palta M et al. Cancer 2015; 121:188-93.

Uptake of RT Omission in Elderly Patients

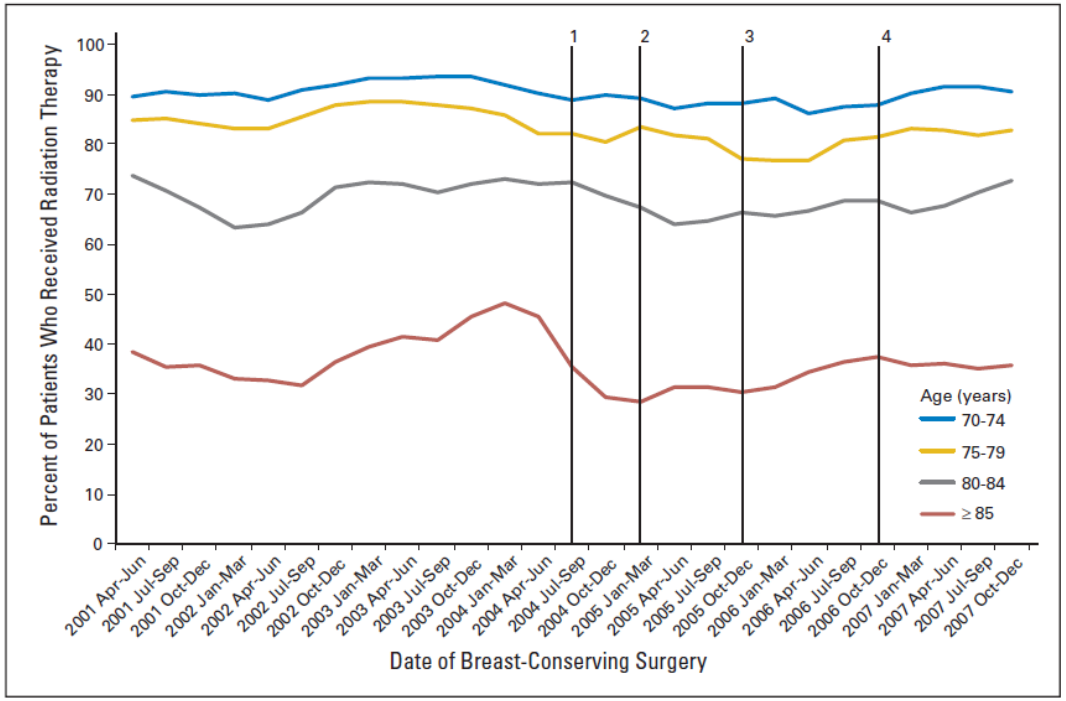


Fig 1. Temporal trend in the use of radiation therapy by age category. 1: September 2004, Cancer and Leukemia Group B (CALGB) C9343 study was published; 2: March 2005, revised National Comprehensive Cancer Network (NCCN) guidelines were announced; 3: November 2005, revised NCCN guidelines were published; 4: December 2006, C9343 update with 8-year follow-up was published.

SEER-Medicare data: 79% of women received RT prior to study publication compared to 75% after; among patients with life expectancy less than 5 years, RT use decreased by 3.7%, from 44% prepublication to 41% afterwards

Soulos P et al. J Clin Oncol 2012;30:1601-07.

Reflections

- Hard to convince patients and physicians alike to omit treatments
- Both groups tend to be risk averse and focus on anticipatory regret
- Physicians also face strong financial disincentives to omitting therapy altogether in a fee-for-service system
- But we really haven't succeeded in identifying any patients who truly receive no benefit from RT
- So can we at least make RT delivery more efficient?

Rationale for Whole Breast Hypofractionation

- Traditional RT schedules (multiple small "fractions" of dose) sought to exploit differences in DNA repair capability of tumor cells and normal tissues
  - Complicated models derived from preclinical data
- More recently, some preclinical models have suggested that shorter courses of RT (in bigger "fractions") to slightly lower total doses might be equally effective and might not lead to excessive late toxicity in the treatment of breast cancer

Time-dose factors in radiotherapy: a review of the human data

H. D. Thames [1], S. M. Bentzen [2], I. Turesson [3], M. Overgaard [2] and W. Van den Bogaert [4]

[1] *Department of Biomathematics, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, U.S.A.,* [2] *Radiophysics Laboratory, Radiumstationen, Aarhus Kommunehospital, Aarhus C, Denmark,* [3] *Department of Oncology, The University of Gothenburg, Gothenburg, Sweden, and* [4] *Department of Radiotherapy, Academisch Ziekenhuis St. Rafael, Leuven, Belgium*

(Received 12 June 1989, revision received 26 April 1990, accepted 10 May 1990)

Recovery capacity of human tissues and tumors.

Tissue/tumor	α/β (Gy)
Early reactions	
Skin (erythema)	8.8 (6.9, 11.6)
	12.3 (2, 23)
(desquamation) ($t \leq 29$ days)	11.2 (8.5, 17.6)
($t > 29$ days)	18–35
Lung (acute)	>8.8
Late reactions	
Supraglottic larynx (late sequela)	3.8 (0.8, 14)
Larynx (cartilage necrosis)	~3.4
	<4.4
	<4.2
Oropharynx (late sequelae)	~4.5
Skin (Telangiectasia)	3.9 (2.7, 4.8)
Skin	3.7 (0.2, 47)
Skin (subcutaneous fibrosis)	1.9 (0.8, 3)
Shoulder (impaired movement)	3.5 (0.7, 6.2)
Lung	3.3 ± 1.5
Lung (pneumonitis)	<3.8
Cord (myelopathy)	<3.3
Brachial plexus (plexopathy)	<5.3
Bowel (stricture/perforation)	$2.2 < \alpha/\beta < 8$
Tumors	
Vocal cord	>9.9
Oral cavity/oropharynx	>6.5, 10.3
	>7
Lung (squamous cell, large cell, adenoca.)	~50–90
Cervix	>13.9
Skin	8.5 (4.5, 11.3)
Melanoma	0.6 (−1.1, 2.5)
Liposarcoma	0.4 (−1.4, 5.4)

Whole Breast Hypofractionation: The Evidence

- Multiple RCTs have established this approach to be equally safe and effective in many patients treated with breast conserving surgery
  - 2002: Canadian trial early outcomes
  - 2005, 2006, 2008: UK trial results
  - 2010: Long-term Canadian trial results
  - 2011: ASTRO Consensus Guideline
  - 2013: ASTRO Choosing Wisely Top Five
  - 2013: Long-term START trial results

Uptake of Whole Breast Hypofractionation vs IMRT

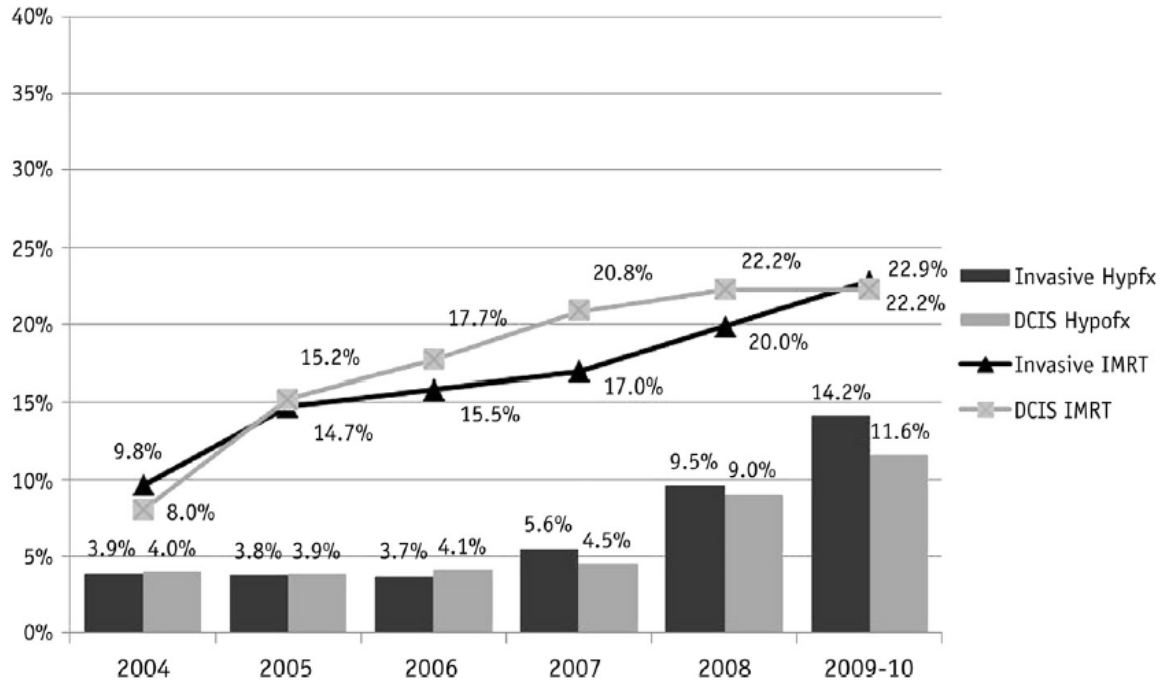
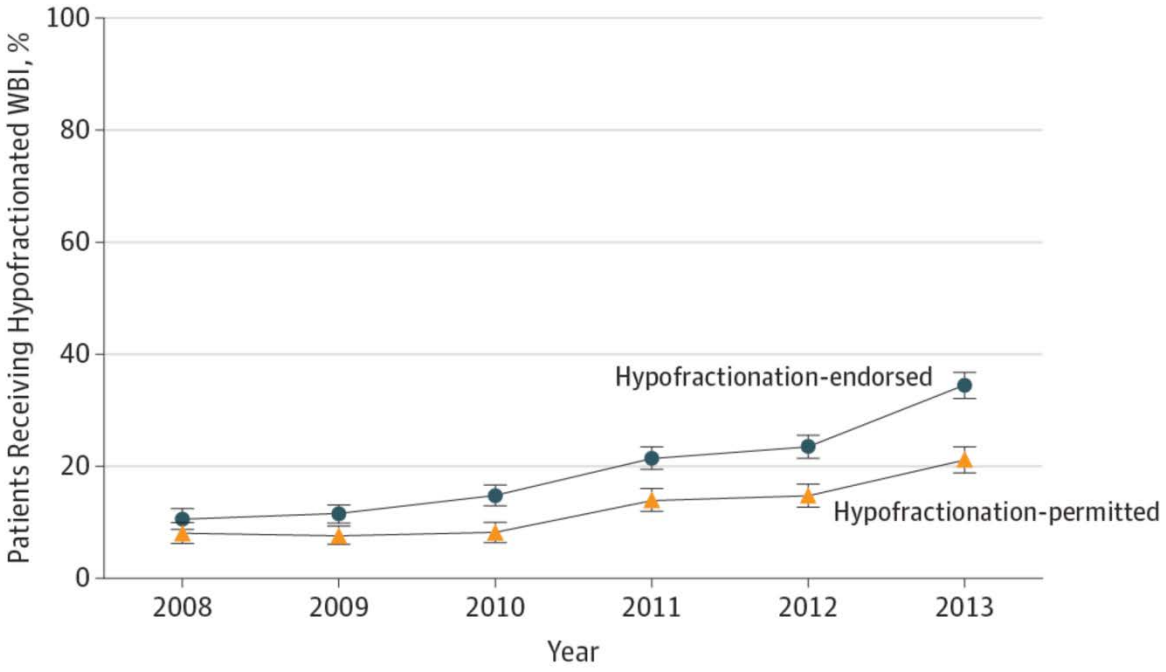


Fig. 1. Rates of hypofractionated radiation therapy and IMRT use over time. DCIS = ductal carcinoma in situ; IMRT = intensity modulated radiation therapy.

- SEER-Medicare Data: Low uptake even in low-risk older patients; even in patients over age 80, only 25% received hypofractionation in 2009-10

Jagsi R et al. Int J Radiat Oncol Biol Phys 2014;90:1001-09.

Uptake of Whole Breast Hypofractionation

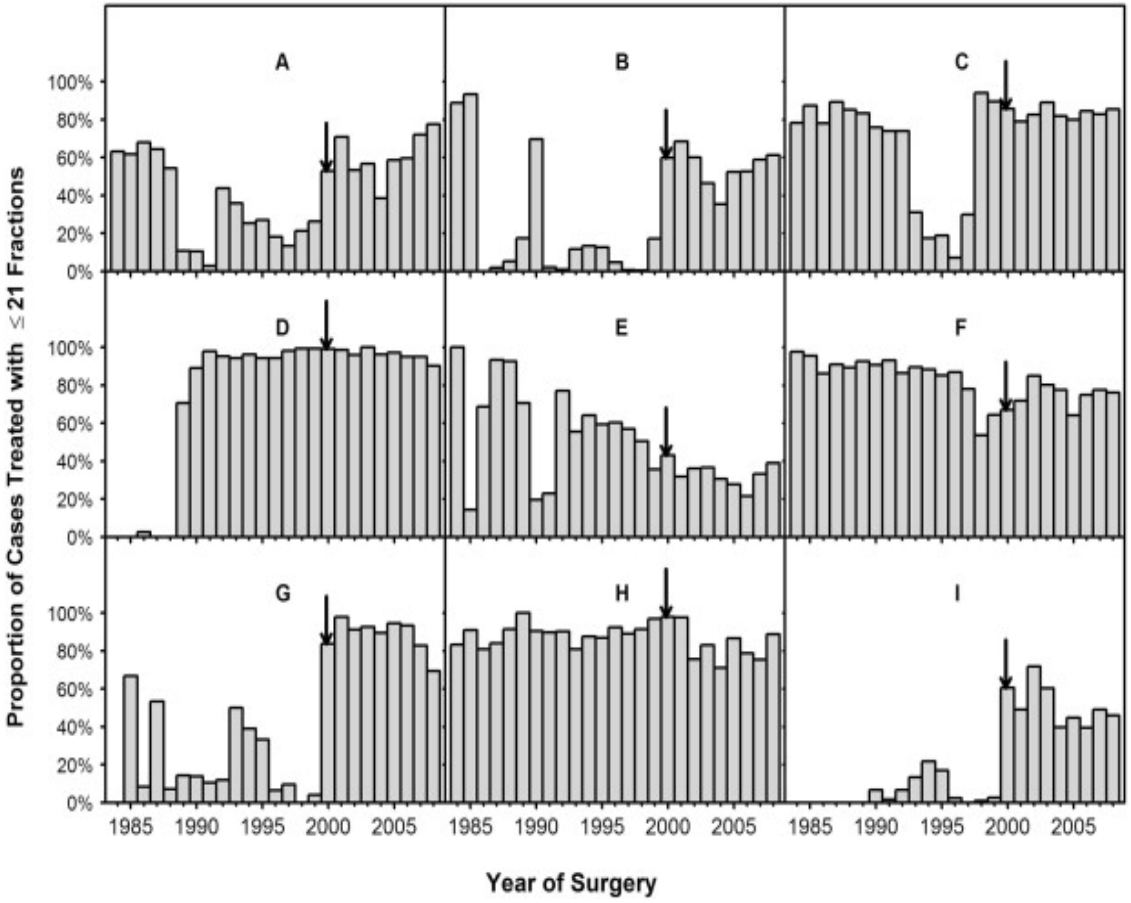


Total No. of patients						
Hypofractionation-endorsed	1091	1468	1450	1595	1695	1625
Hypofractionation-permitted	666	1221	1190	1253	1211	1178

Patients in 14 Commercial Health Insurance Plans: use of hypofractionation among guideline-endorsed patients rose from 10.6% in 2008 to 34.5% in 2013; hypofractionation was associated with 9% savings in cost

Bekelman J et al. JAMA 2014;312:2542-50.

What About Canada?

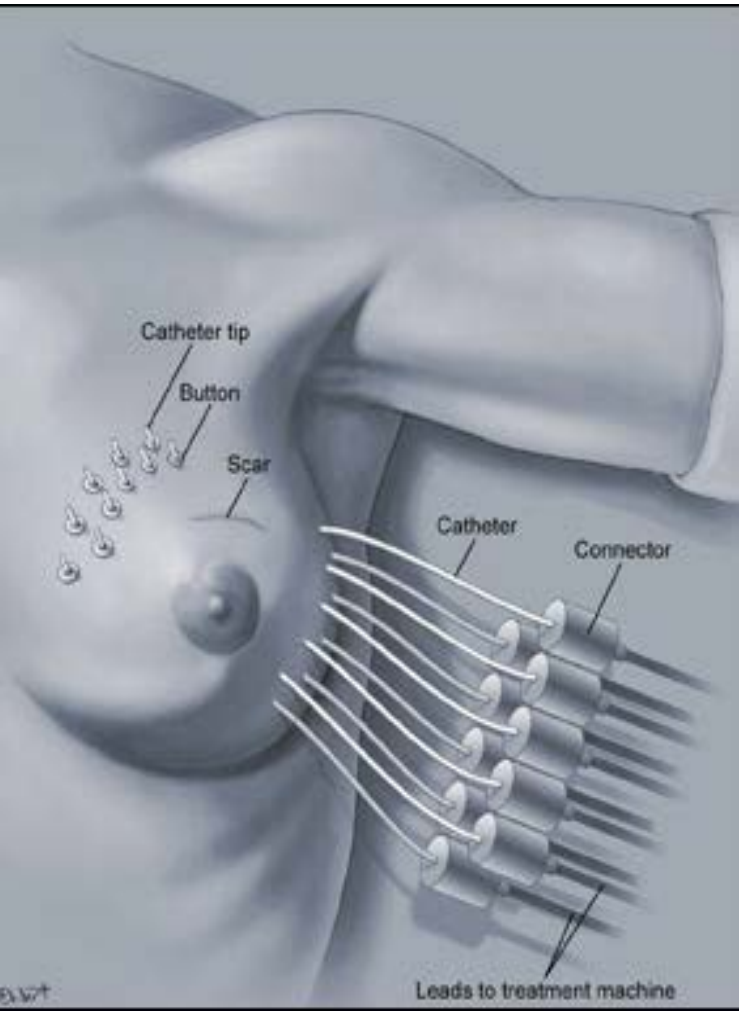


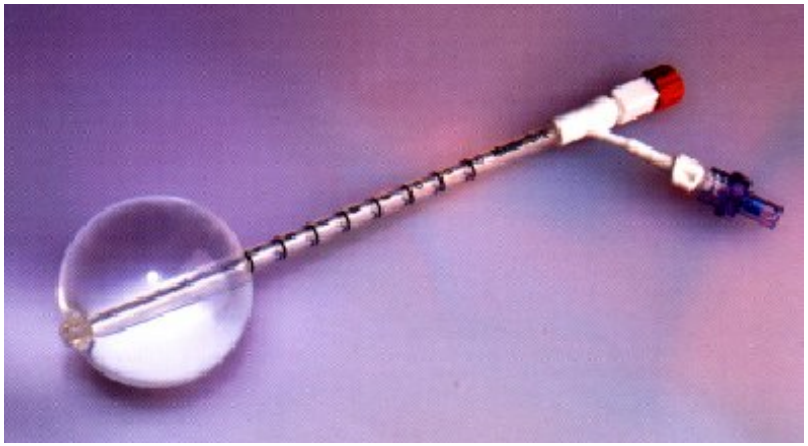
Ashworth A et al. Int J Radiat Oncol Biol Phys 2013; 86:51-7.

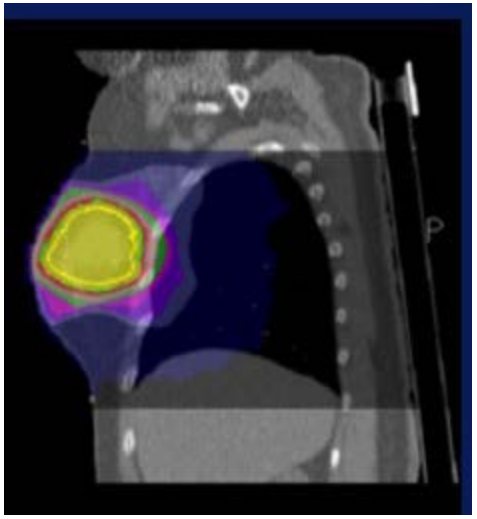
Rationale for APBI

- Patterns of failure studies suggested that most tumors recur in the immediate vicinity of the tumor bed
- If only part of the breast were targeted, one might tolerably administer much higher doses per fraction and increase the efficiency of treatment
- Depending on technique, one might also reduce dose to normal tissues and reduce toxicity
- Evidence actively being collected

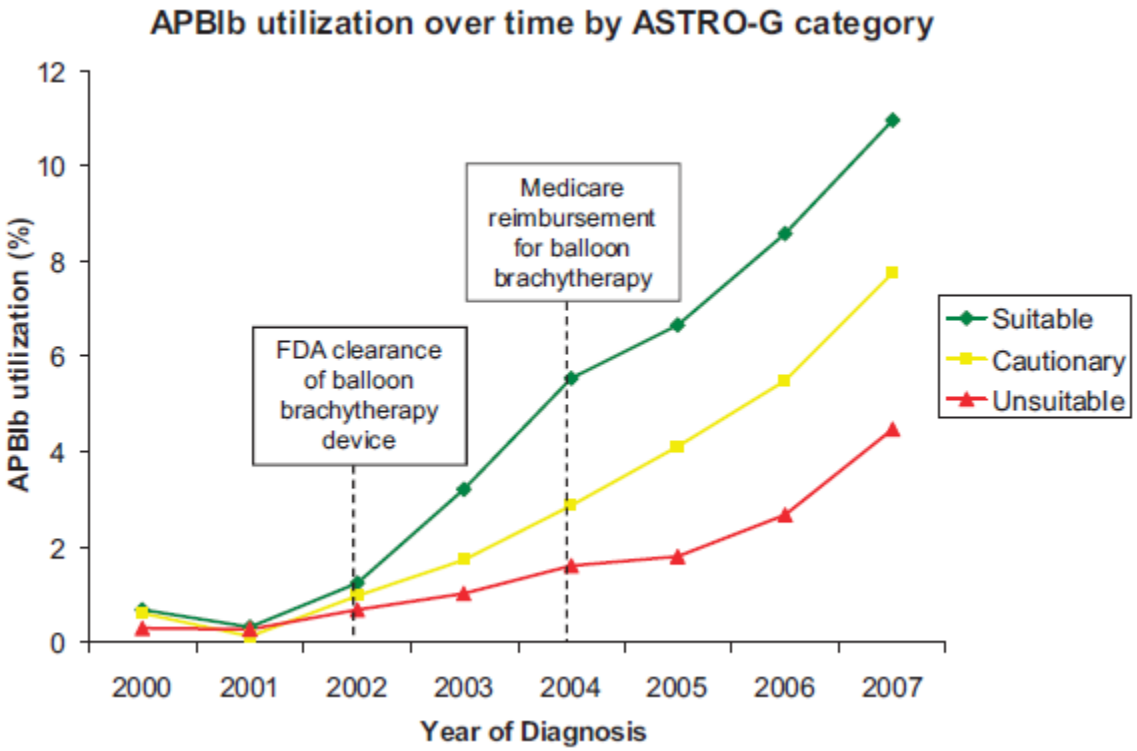
APBI Techniques





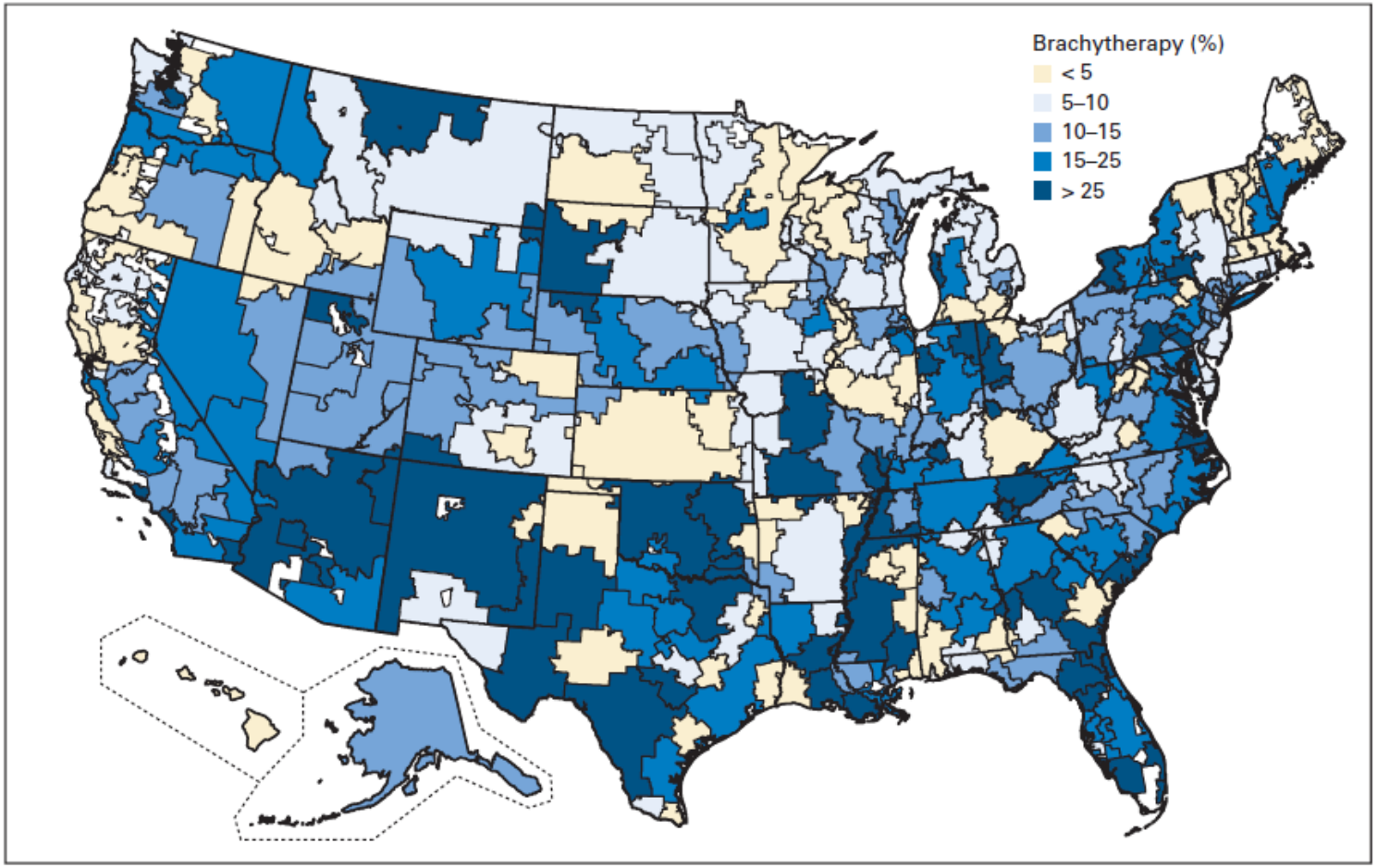


Brachytherapy Utilization



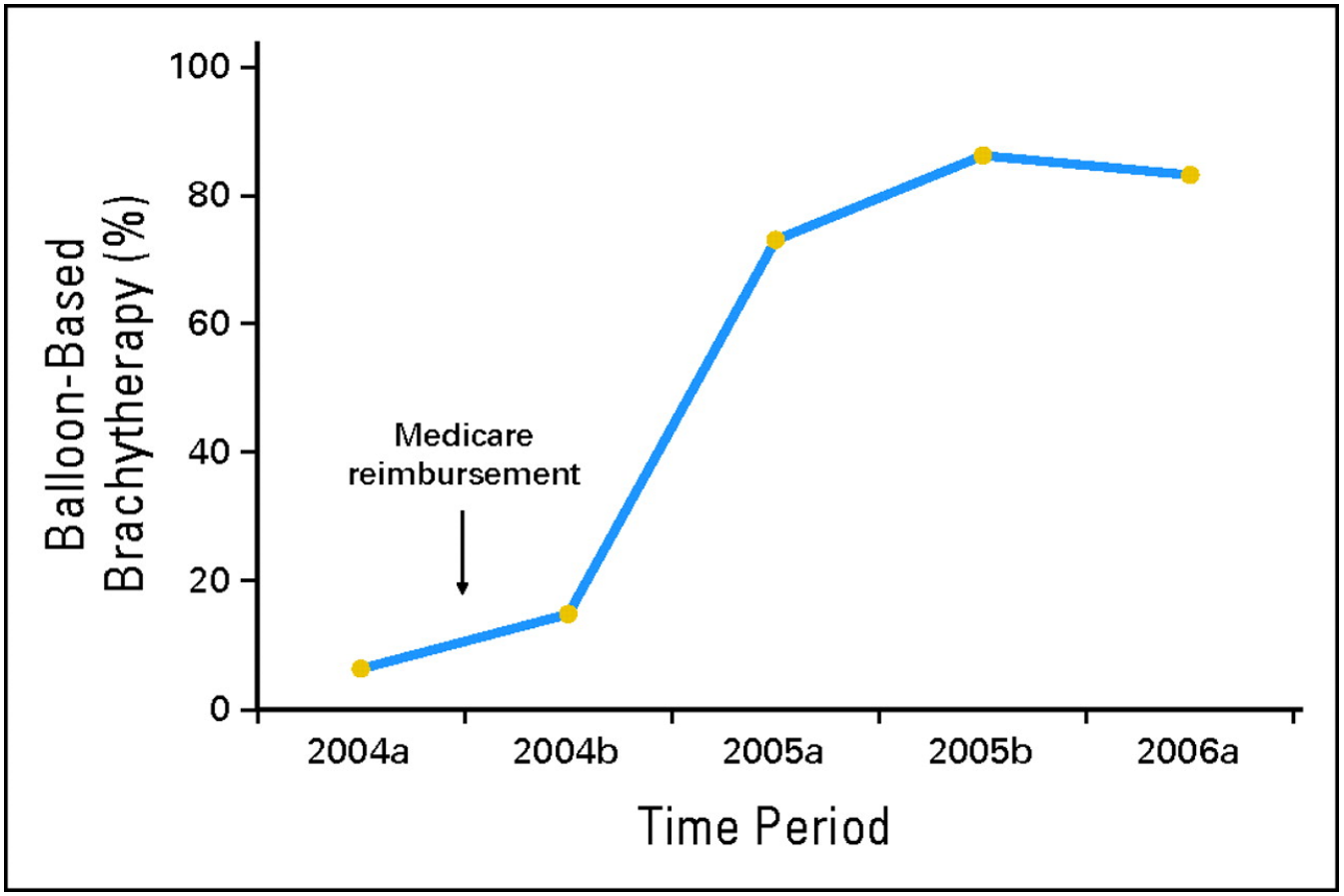
Hattangadi et al, J Natl Cancer Inst 104:29-41, 2012

Brachytherapy Utilization



Presley et al, J Clin Oncol 2012

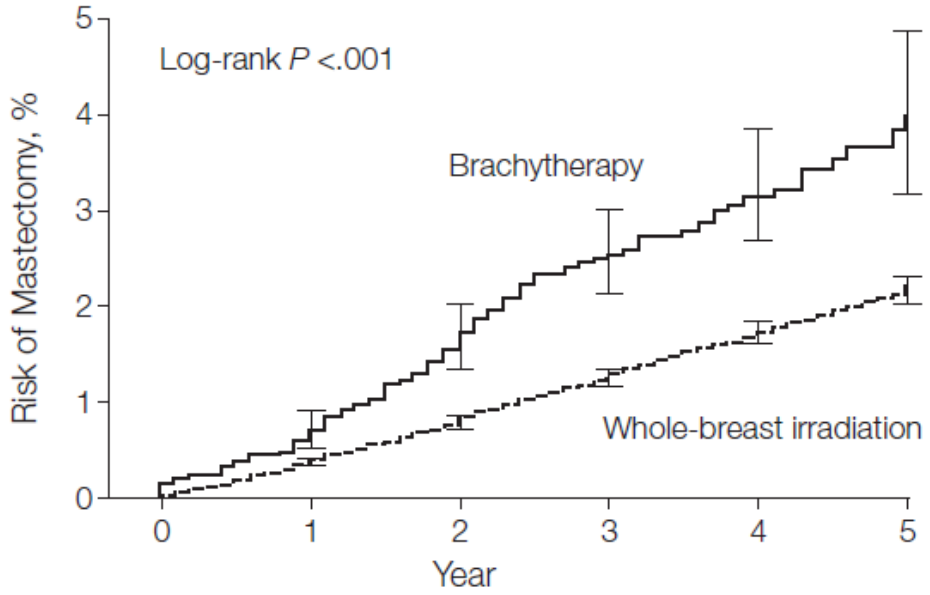
Balloon Utilization



Smith et al, J Clin Oncol 29:157-165, 2011

Kaplan-Meier Curves

Figure 2. Cumulative Incidence of Subsequent Mastectomy



No. of patients at risk						
Brachytherapy	6952	6746	4287	2419	1176	442
Whole-breast irradiation	85 783	81 651	62 268	43 704	26 991	11 735

The difference in risk was significant ($P < .001$, log-rank). Error bars indicate 95% confidence intervals.

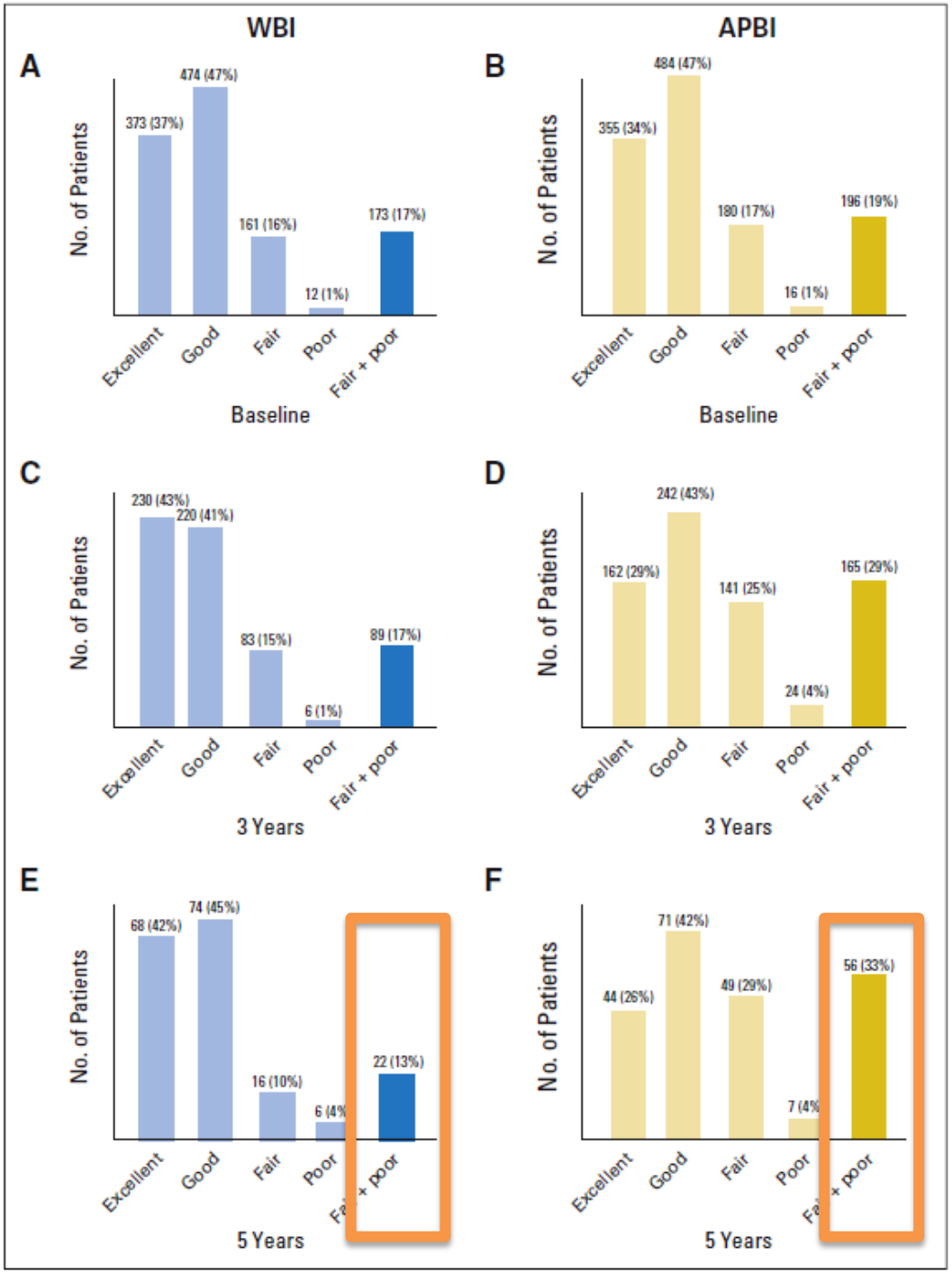
Smith et al, JAMA 2012; 307(17):1827-37

External Beam APBI:
An Alternative High-Tech Approach

- Michigan trial: adverse cosmesis observed in >20% of cases leading to early closure

Jagsi R et al. Int J Radiat Oncol Biol Phys 2010;76:71-8.

RAPID Trial



Olivotto et al., J Clin Oncol 2013; 31:4038-45.

Conclusions

- The quest to identify less burdensome approaches to breast RT is a worthy endeavor
- Lower tech approaches have been less quickly adopted than higher tech approaches in the US, even when the former more firmly grounded in evidence
  - Reimbursement mechanisms can create perverse financial incentives
  - “Gizmo idolatry” is common among physicians and patients alike
- We can learn much from the adoption of new technology in breast radiotherapy
  - New approaches require evidence-based evaluation before implementation