What is Comparative Effectiveness Research?

James S. Goodwin, MD
George and Cynthia Mitchell Distinguished Chair in Geriatric Medicine
Director, Sealy Center on Aging
University of Texas Medical Branch

Types of CER

- **Systematic reviews of the literature**
  - **Meta Analysis (two types)**
- **Analyses of large databases such as electronic medical records or national Medicare data**
- **Large randomized controlled trials that are representative of the population of real patients**

Effectiveness research: strengths and weaknesses of two major approaches

Type of Study	Internal validity	External validity
RCT	great	questionable
Observational	Questionable	Can be great

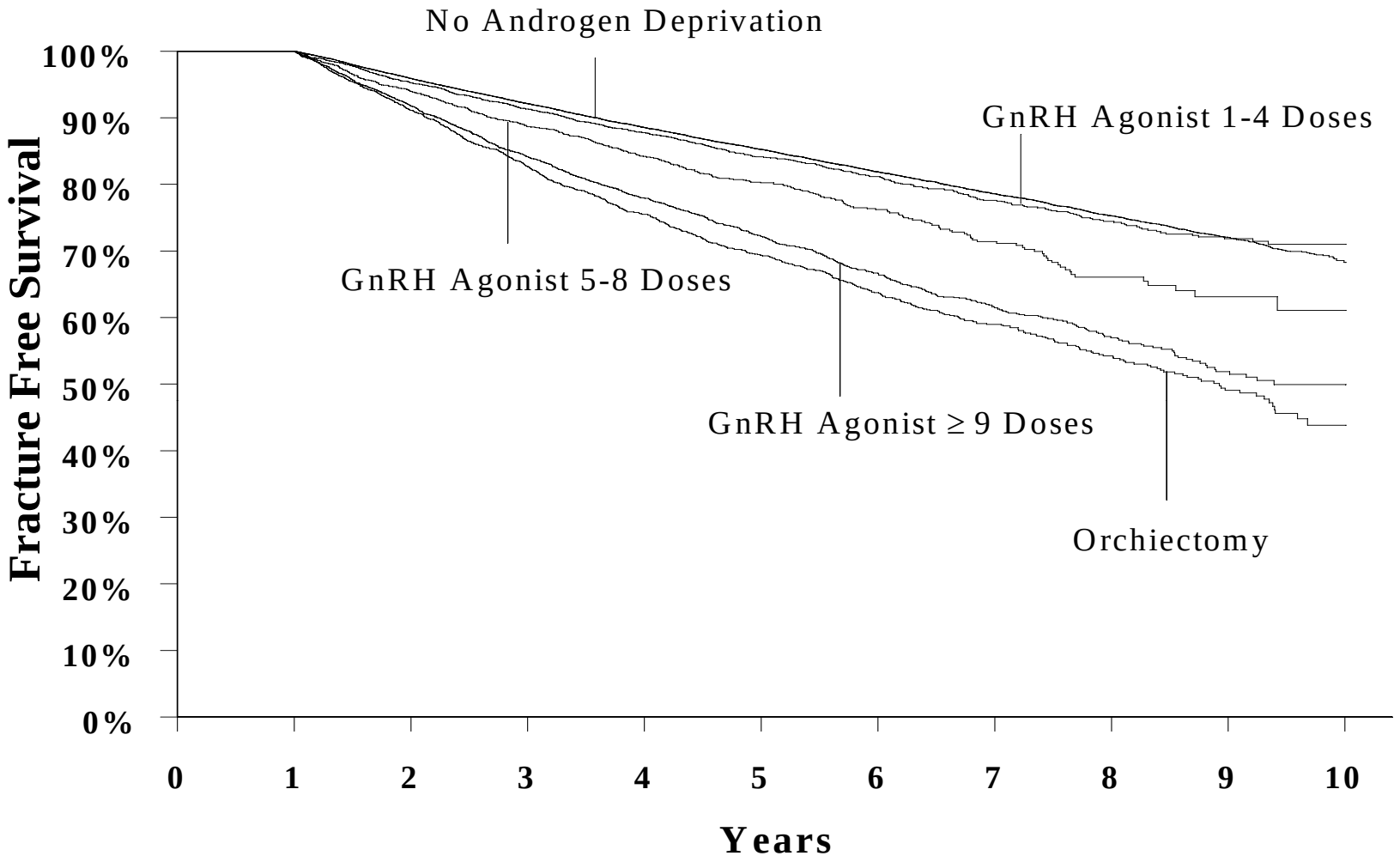
Assessing Toxicities of Therapies Using Observational Data

- **Advantages:**
  - **Large representative sample allows estimation of toxicities in subgroups (e.g. very old, those with multiple comorbidities)**
  - **Ability to assess toxicity in "real world" rather than in setting of clinical trial with motivated patients, excellent monitoring, etc.**
  - **Ability to assess for rare toxicities and late toxicities.**

- **Disadvantages:**
  - **Selection bias**
  - **Under reporting of outcomes and covariates**
  - **Possible contamination by publicity (e.g. silicone breast implants)**

Late toxicity: the example of anti-androgens for prostate cancer

- GnRH agonists were overused in the 1990's and early 2000's in men with prostate cancer
- Androgens promote bone integrity
- Does GnRH agonist use lead to increased fractures?



(from Shahinian et al., New Engl J Med 2005; 352:154-64)

Table 4. Estimated Number Needed to Harm for the Occurrence of Any Fracture within 12 to 60 Months after Diagnosis According to Age and Extent of Androgen Deprivation.*

Age	Gonadotropin-Releasing Hormone Agonist			Orchiectomy
	1-4 doses	5-8 doses	≥9 doses	
		no. needed to harm (95%CI)		
66-69 yr	74 (50-146)	42 (29-73)	18 (16-24)	15 (13-18)
70-74 yr	69 (46-146)	39 (27-71)	17 (15-20)	14 (12-17)
75-79 yr	61 (41-125)	34 (24-61)	15 (14-17)	13 (11-15)
≥80 yr	46 (32-91)	26 (19-45)	12 (11-13)	10 (9-11)

* Estimates were calculated on the basis of adjusted rates of fracture five years after diagnosis from a Cox model with any fracture as the outcome. Doses of a gonadotropin-releasing hormone agonist were grouped according to the number of doses received within the 12 months after diagnosis. CI denotes confidence interval.

(from Shahinian et al, New Engl J Med 2005; 352:154-64)

Has Risk from Radiation Changed over Time as methods have improved?

Methods

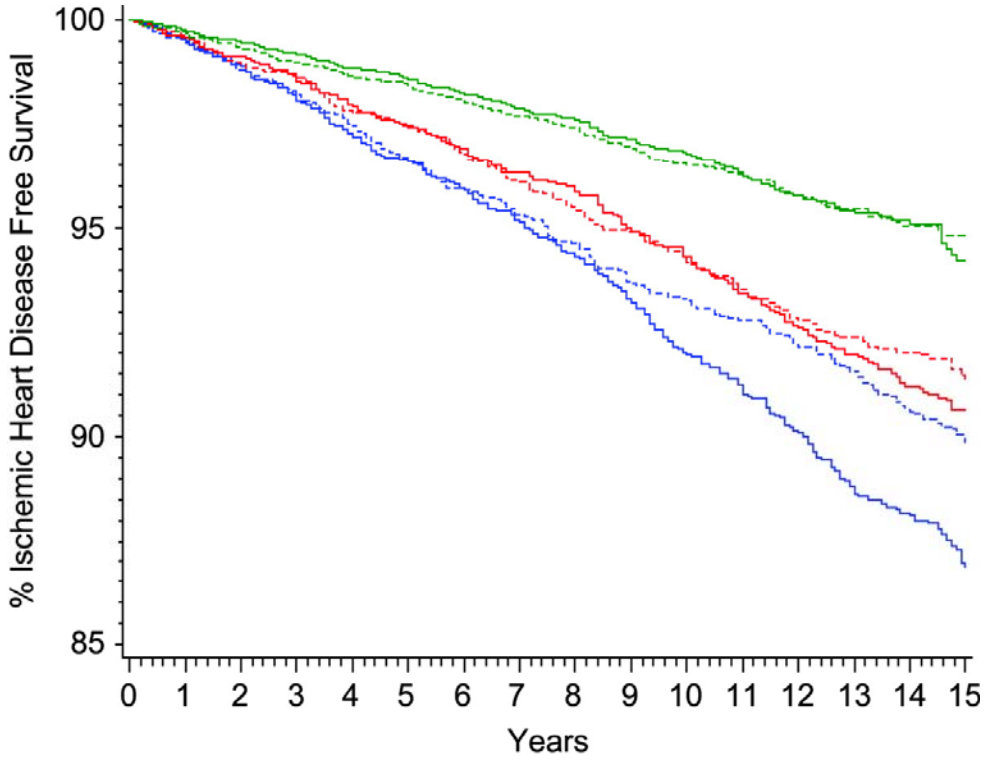
- Compared women with left versus right-sided breast cancer over time

Patient Inclusion (N=27,283)

- Women in SEER (1973-2000 dataset)
- In situ, localized, or regional breast cancer
- Diagnosed between 1973 and 1989
- Known disease laterality
- Treated with primary surgical therapy followed by adjuvant radiation

(from Giordano et al., J Natl Cancer Inst 2005; 97:419-424)

Mortality from heart disease in women receiving radiation, by breast cancer laterality and year of diagnosis



1985-1989

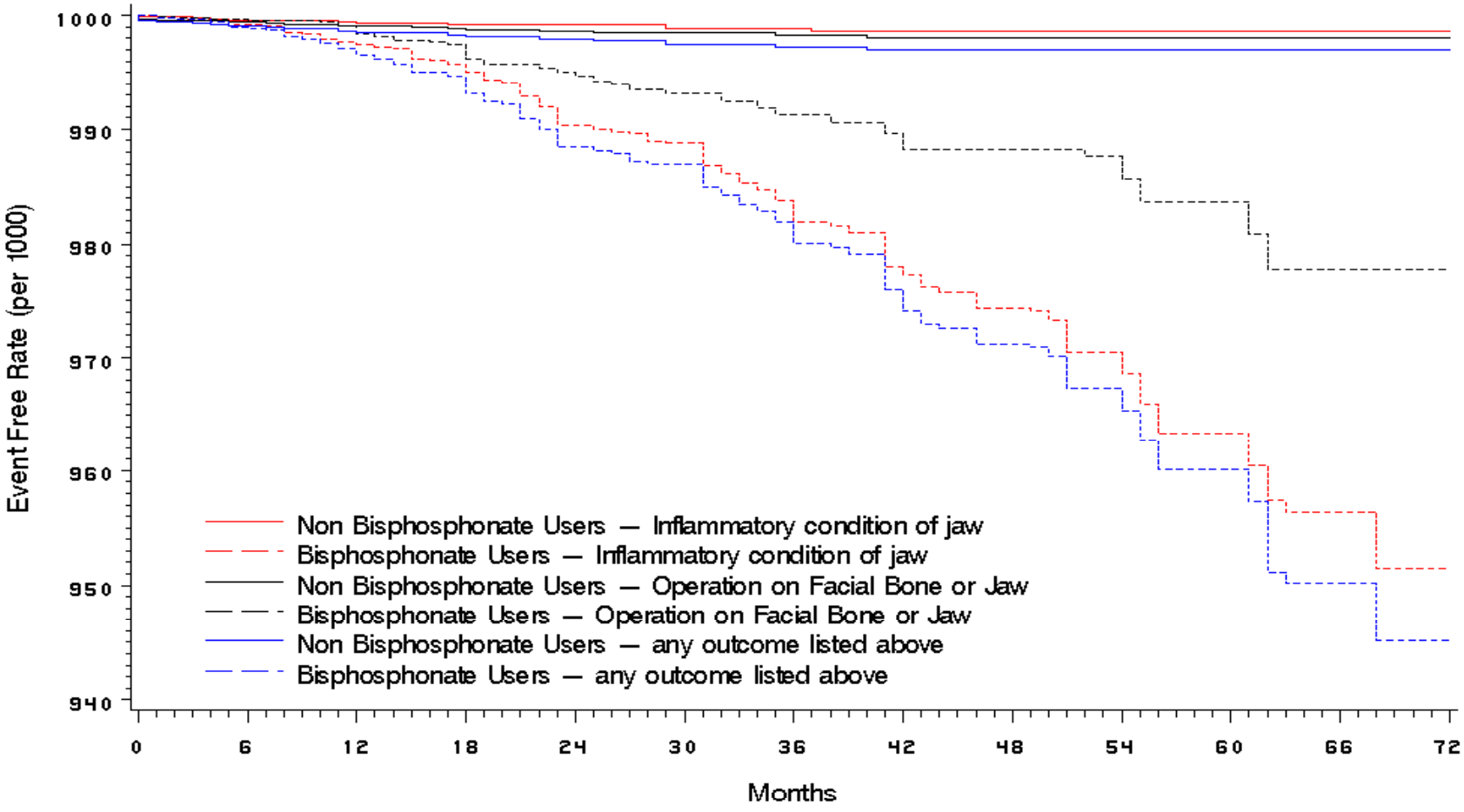
1980-1984

1973-1979

No. of patients at risk		0 year	3 year	6 year	9 year	12 year	15 year
1973-1979	Right	4201	3113	2241	1761	1453	1214
	Left	4451	3305	2384	1885	1523	1272
1980-1984	Right	3131	2539	2044	1676	1425	1232
	Left	3364	2748	2159	1788	1512	1287
1985-1989	Right	5953	5266	4553	4014	2770	507
	Left	6183	5457	4780	4194	2868	533

(from Giordano et al., J Natl Cancer Inst, 2005; 97:419-424)

Survival free of jaw toxicity after IV bisphosphonates in 14,349 users vs 28,698 matched controls



(from Wilkinson et al, J. Natl. Cancer Inst, 2007;Jul 4; 99(13):1016-24)

Comparing outcomes of different treatments with observational data: fraught with difficulty

- **This is a major goal of the CER initiative**
- **Many, many papers published comparing the results of alternative treatments based on observational data, for example, different treatments for cancer or different treatments for ischemic heart disease**
- **There is growing concern that such analyses cannot provide valid information because of selection bias.**

Selection Bias

- **Treatments in observational studies are not randomly assigned. They are chosen by patients and physicians, based on many different factors.**
- **Those factors may not all be measurable in the available data, yet they may influence the treatment outcome.**
- **The example of self-rated health.**
- **A variety of statistical techniques have been proposed to account for selection bias, but it is unclear if they accomplish that.**

Using SEER Medicare data to examine the power of selection bias

- SEER/Medicare allows us to look at effect of various treatments for cancer on mortality
- SEER provides data on cause of death, which can serve as an internal control on selection bias
- In other words, an effective treatment for a given condition should only improve mortality from that condition, not from other conditions

The direction and effect of potential selection biases in observational studies comparing outcomes of different treatments

Treatments compared	Potential for selection bias		Effect of bias on hazard of death		
	Healthier patients	Worse cancer	Cancer-specific mortality	Mortality from other causes	All-cause mortality
Adjuvant Chemotherapy vs. none	↑↑	↑↑↑	↑↑	↓↓↓	↑ or ↓
Adjuvant radiotherapy vs. none	↑↑	↑↑↑	↑	↓↓↓	↓↓
Surgery vs. Radiotherapy	↑↑↑	↓↓	↓↓	↓↓↓	↓↓↓
Any treatment vs. no treatment	↑↑↑	↑↑ or ↓↓*	↑ or ↓	↓↓↓	↑ or ↓

*** Two types of patients might be likely to receive no treatment: those with less aggressive tumors, such as men who choose "watchful waiting" with low grade prostate cancers; and those diagnosed with highly aggressive metastatic cancers, such as multifocal glioblastoma**

(from Giordano et al. Cancer, 2008; 112(11):2456-66)

An example of a bad idea:

"Survival associated with treatment vs.. observation of localized prostate cancer in elderly men" **(Wong et al, JAMA 2006; 296:2683-93)**

- **SEER Medicare study of 44,630 men diagnosed with prostate cancer in 1991-99**
- **Stratification by propensity to adjust for confounders**
- **Treated patients had significantly better all-cause survival than untreated men (HR=0.69; 95% CI=0.60, 0.72).**

Thinking about Survival after treatment for prostate cancer: a re-examination of the data

- We used identical methods, but examined effect of prostate cancer treatment on mortality for specific causes of death.

Cause of Death	HR (95% CI) Associated with treatment vs. non-treatment
All causes	0.67 (0.64; 0.70)
Prostate cancer	0.71 (0.59; 0.85)
All non cancer death	0.60 (0.50; 0.65)
Heart disease	0.63 (0.50; 0.69)
Diabetes	0.48 (0.32; 0.72)

(from Giordano et al., Cancer, 2008; 112 (11):2456-66)

Survival after a diagnosis of prostate cancer according to treatment and also compared to age-matched men without cancer

	Hazard of death	
	HR	(95% CI)
Non Cancer	1.00	
With Radical Prostatectomy	0.60	(0.54; 0.66)
With Radiation	0.90	(0.85; 0.96)
Watchful waiting	1.27	(1.19; 1.36)

*Adjusted for age at diagnosis, SEER region, year of diagnosis, and comorbidity

(from Giordano et al. Cancer, 2008; 112(11):2454-66)

Conclusion

Comparative Effectiveness Research is a term used to describe a broad range of activities that aim to assess which individual patients might benefit from a given treatment. This is a very important goal. Some of the techniques are relatively untested and may not survive detailed scrutiny.