Evidence Generation for New Technologies in Cancer Treatment

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Overview

Aims of this presentation

- **Identify challenges in evidence generation in the advanced technology radiation oncology and surgery setting**

- **Describe study designs and design innovations that may be applied to evidence generation**

- **Describe ongoing efforts to conduct clinical trials in the National Clinical Trials Network (NCTN) and elsewhere**

Obtaining Evidence

- **Assumptions:**
  - **New technologies, like all new therapeutic maneuvers, should be evaluated, tested against standards**
  - **Any therapy with broad utility is amenable to testing**
  - **Level I (randomized trial) evidence should be sought whenever possible, even if difficult**

There are new and unique challenges, but frequently the difficulties resemble those previously encountered

RCTs in Cancer Surgery- Breast Conserving

- **NSABP B-06 – Lumpectomy +/- XRT (BCS) vs. Total Mastectomy (1976)**
  - **This trial and precursor (B-04: radical vs. total mastectomy – w/intra-operative randomization) met with strong opposition from surgeons**
  - **B-06 accrual initially poor, pre-randomization method applied**
  - **After 10-year accrual period, study completed, led to 1990 NIH consensus recommendation, use variations in BCS now considered an important care quality factor**

Ref: Fisher et al. *NEJM* 2002 347:1233-41 *(and refs therein to earlier reports, history)*

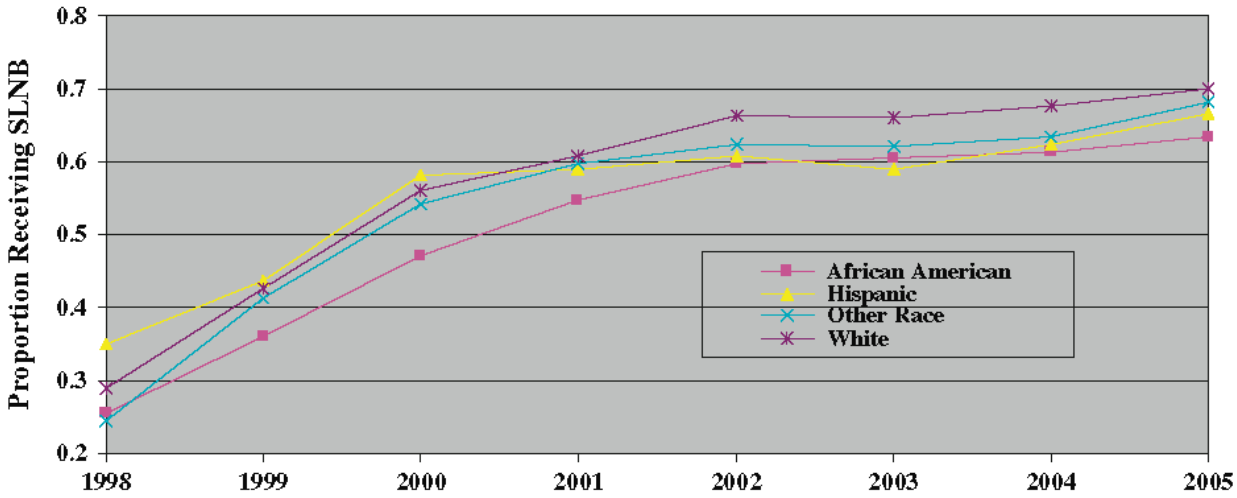
History of RCTs in Cancer Surgery

- **Revisiting Breast Surgery ~1999-2011: Sentinel Node Biopsy (SNB) trials**
  - **Similar accrual challenges for trials depending on specific question**
    - **NSABP – randomize SNB-*negative* to standard (axillary dissection) or no further surgery**
    - **ACOSOG – randomize SNB-*positive* to same - harder**
  - **Trials explicitly evaluated non-inferiority - Big N needed, ACOSOG trial did not meet accrual goal**
  - **Training/credentialing for technique needed**

History of RCTs in Cancer Surgery

Sentinel Node Biopsy

Meanwhile, SNB has moved into wide use, with studies noting unequal access (?):



Annual adjusted rates with 95% confidence intervals

	White (referent)	African American	Hispanic	Other non-white
1998	0.29 (referent)	0.26 (0.24, 0.27)	0.35 (0.32, 0.38)	0.25 (0.22, 0.27)
1999	0.43 (referent)	0.36 (0.35, 0.38)	0.44 (0.411 0.46)	0.41 (0.39, 0.44)
2000	0.56 (referent)	0.47 (0.46, 0.49)	0.58 (0.44, 0.49)	0.54 (0.40, 0.45)
2001	0.61 (referent)	0.55 (0.53, 0.56)	0.59 (0.57, 0.61)	0.60 (0.57, 0.62)
2002	0.66 (referent)	0.60 (0.58, 0.61)	0.61 (0.59, 0.63)	0.63 (0.60, 0.65)
2003	0.66 (referent)	0.60 (0.59, 0.62)	0.59 (0.57, 0.61)	0.62 (0.60, 0.64)
2004	0.68 (referent)	0.61 (0.60, 0.63)	0.62 (0.60, 0.64)	0.64 (0.61, 0.66)
2005	0.70 (referent)	0.64 (0.62, 0.65)	0.67 (0.64, 0.69)	0.68 (0.66, 0.70)

Ref: Chen et al. *J Natl Cancer Inst* 2008 100:462-474

History of RCTs in Surgery: Sentinel Node Biopsy

Trials completed/published 2003-2011

- First published results reported comparisons of recurrence, much debate over this as appropriately rigorous endpoint
- Trials showing acceptably similar *survival* (8-yr abs. deficit ~1.5% for SNB in NSABP trial) did not appear until 2010

Refs: Veronesi *N Engl J Med* 2003;349:546–53**,** Krag *Lancet Oncol*. 2010;11: 927–33, Guilano *JAMA*. 2011;305:569-75

Why Are Technology Trials Difficult?

- **Regulatory**
  - Requirements for devices different (lower) relative to drugs
  - Surgical (formal) regulatory control absent (unless device involved)

- **Cultural**
  - Randomization less accepted in surgical setting – by patients also
  - Surgery effects immediate, localized – focus is often on secondary effects more than primary efficacy
  - Effects often incremental, logical extension of existing treatment – fewer unexpected effects

Why Are Technology Trials Difficult?

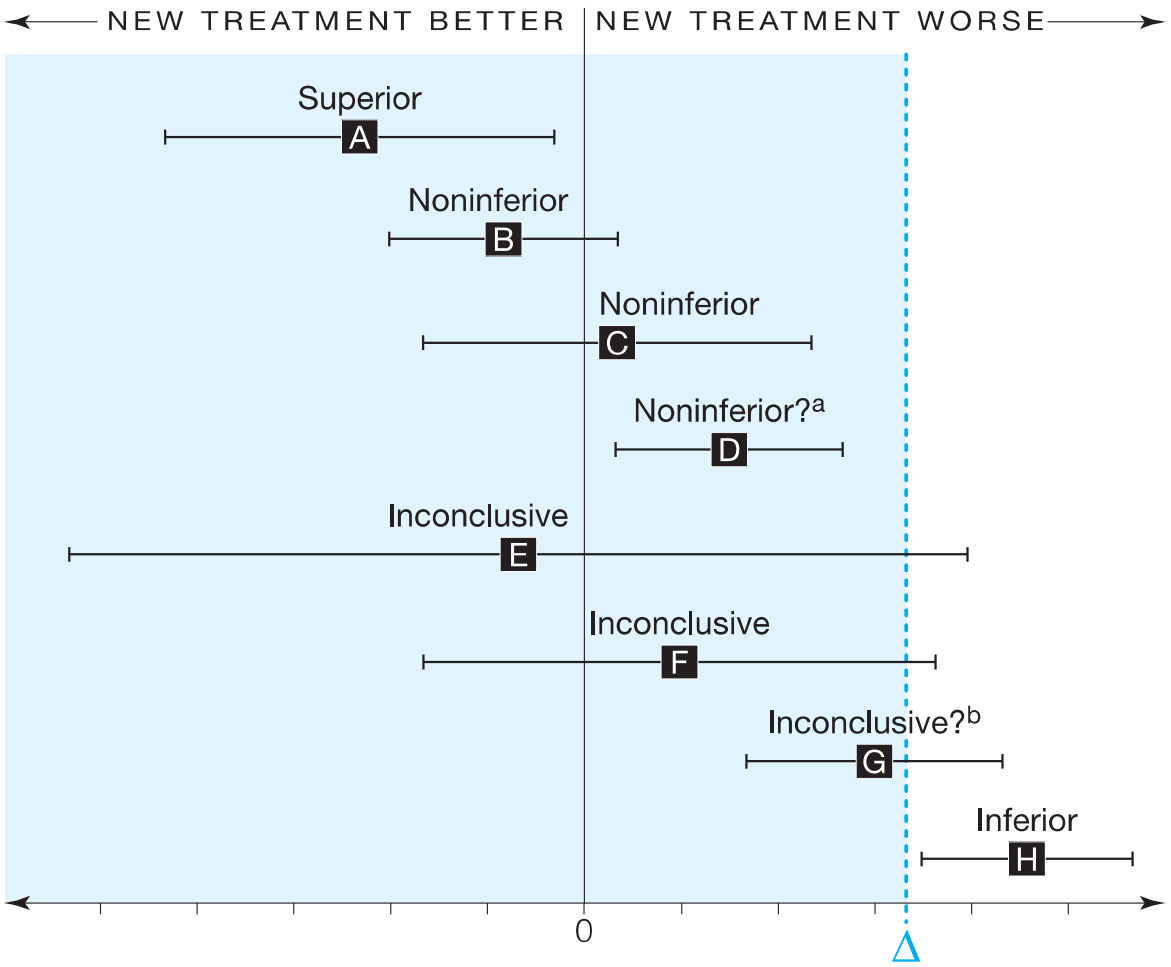
- **Logistical, Practical**
  - **Upfront investment in new technology motivates use, dissuades randomization to non-use**
  - **Many trial design elements (blinding, placebos) infeasible, impractical, or highly controversial**

Why Are Technology Trials Difficult?

- **Statistical Design Challenges**
  - Equipoise (or better) assumed, leading to slower accrual
  - The 'rarified air' of cutting-edge clinical trials – portability, reproducibility concerns may lessen impact even when trials performed
  - Appropriate endpoints in relation to time horizons in an setting of evolving technology – but *need* long-term outcomes
  - Trial goals: Superiority vs. non-inferiority, defining the acceptable margin in latter

Equal Outcomes: What We are Often Seeking to Achieve w/Technology

The Meaning(s) of Non-inferiority:



Treatment Difference for Adverse Outcome
(New Treatment Minus Reference Treatment)

Ref: Piaggio *JAMA* 2012;308:2594-

Equal Outcomes: What We are Often Seeking to Achieve w/Technology

Comments:

- **Non-inferiority def'n must be accepted by practitioners *and* patients – small margin ➔very large sample size – often must compromise**
- **'Negative' superiority trial ≠ demonstration of non-inferiority**
- **Compliance is important – Intention To Treat (analyze in assigned arm irrespective of treatment receipt) not appropriate**

Ex/ Non-Inferiority Trial

Ex/ Partial Breast Irradiation after Lumpectomy:

- **Greatly reduced treatment time vs. external beam RT**
- **NSABP B-39/RTOG 0413 - 4300 patients, to establish PBI local failure rate not worse and EBRT by more than 1.5 (estimated HR must be < 1.17)**
- **Meanwhile, PBI in use, ASTRO and others have guidelines to identify candidate patients**
- **Early conflicting studies on cosmesis, short-term results – First trial (RAPID) showed poorer cosmesis, AEs (2012). Hungarian trial (2013) showed opposite. Recent long term registry study (2015) supports efficacy and safety. Awaiting our results . . .**

Refs: Kamras *Ann Surg Onc* 2015, online 28 April

Other Study Designs

Other Randomized Trial Designs

Cluster Randomized Trial:

- In addition to typical (patient-level) randomized trials, cluster randomized trials may be useful in technology evaluation. Here, randomize institutions/centers rather than patients
  - Advantage is simplicity of implementation, logistics
  - Disadvantage is intentional confounding of center and treatment (is this ok?). Not all centers get to participate in new technology, misses key suspected difference
- Design is common in education, behavioral health, and economic 'field trial' interventions – methodology is advancing

What are the Alternatives to Randomized Trials?

Causal Inference: **As the name suggests, infer a causal relationship when observing an association**

- **Ex/ Random assignment of treatment –**
  - **Assures that observed differences between treatment groups are due solely to the intervention**
  - **Has advantage of controlling *unknown* as well as known confounders. Even controls for yet unknown confounders (i.e., new markers)**
  - **Permits higher-evidence looks for interaction effects - responsive/non-responsive subsets**

Alternatives to Randomized Trials

Causal Inference:

- How can causal inference be made in absence of randomization?
  - Adjustment for confounders – straightforward – 'model' one's way to the truth – has well-known shortcomings
  - Propensity score adjustment – model probability of treatment choice – standardize/adjust treatment groups by this factor using stratification, matching, or weighting

Alternatives to Randomized Trials

Causal Inference:

- **Approaches to support causal inference to be made in absence of randomization (cont.)**
  - **Instrumental variables analysis– identify variable(s) strongly related to treatment choice but not outcome. Standardization on this factor or instrument can concurrently control known and unknown confounders – like randomization**

Ref: see Hadley et al *J Natl Cancer Inst* 2010;102:1780-93 for both propensity score and IV illustration in cancer

Role of Registries

Registries are key to primary and secondary evidence generation:

- **Registries with features of trials (active ascertainment, well-defined inclusion criteria, auditing) are best**
- **Greater inclusiveness, novel data fields, provide real-world checks on trial results, usage patterns, costs, etc.**
- **Amenable to high quality observational methods and study designs, better at avoiding 'data mining disasters'**
- **Many great examples: MUSIC, NROR, CaPSURE/CAESAR, PROMIS, etc**

Who Should Perform Trials in the Latest Technologies?

Different Perspectives:

- **Single institutions or small networks**
  - **Pros: uniformity of implementation, nimble adaptation to technology questions**
  - **Cons: duplication of infrastructure, generalizability issues, limited catchment area**
- **NCI National Clinical Trials Network**
  - **Pros: experience/infrastructure in place, larger geographically and institutionally diverse sampling**
  - **Cons: large management structure, competing priorities**

Who Should Perform Technology Trials?

Answer: Everyone!

1) **NCTN:** Trials are ongoing (next slides)

1) **Institution-led –** MGH PARTIQOL

1) **Partnerships – two examples:**

- U19: Collaborate w/NCTN, shared development. Early (Phase I/II trials) at MGH/MDACC - later expanded to phase IIR and III in NCTN
  - Proton vs. photon trials underway several disease sites including lung, esophagus, and prostate

- PCORI: Upenn and NCTN (NRG Oncology)
  - Pragmatic trial of proton vs. photon for HRQOL, CV events, and other outcomes in locally advanced left-side breast cancer

Some Clinical Trials in the National Clinical Trials Network

NRG Oncology Trials

Proton Radiation Therapy:

- **RTOG/NRG 1308 (opened 02/14)**
  - **Photon vs. proton radiation phase III (superiority) trial in stage II-IIIb inoperable non-small cell lung cancer**
  - **16 centers credentialed so far, photon/proton 'partnering' for centers that do not have latter – so that fully randomized trial is possible in large number of centers**
  - **accrual proceeding (40/560 enrolled)**

Broadening the Randomized Trial Approach

Design Scenario:

- **NRG BN001: Proton vs. photon phase II (pilot superiority) trial in glioblastoma, where both modalities not present at all sites**

  - **Because not all centers have protons (or proton partners), how to design a trial with more centers to keep group engaged?**
  - **Here, we have confounding between center and modality, more like a cluster randomized trial, but without random modality assignment**

Broadening the Randomized Trial Approach

Approach – NRG BN001:

- Two parallel trials with two related questions:
  - Trial I (non-proton centers): Randomize to (A) Standard dose photon vs. (B) High-dose photon (hypofractionated)
  - Trial II (proton centers): Randomize to (A`) Standard dose photon vs. (C) proton
- Then, use information from comparing A vs. A`, causal inference methods - to investigate whether a robust comparison of high-dose photon (B) to proton (C) is supported. Determine phase III carry-forward.

When Trials Fail

Certain trial types seem to have high chance of failure that perhaps could have been anticipated. Other failures are unanticipated

When Trials Fail

Some recent NCTN Surgery/XRT Studies that were terminated due to insufficient accrual performance:

- **ACOSOG Z4099/RTOG 1021 Stereotactic body radiation therapy (SBRT) vs. curative surgery for stage I lung cancer**
  - **Reason: equipoise misperception, difficult to randomize between modalities**

- **RTOG 1221 – Transoral endoscopic surgery followed by tailored chemo/RT vs. Standard chemo/RT for inoperable III-IV oropharynx cancer who are p16-negative**
  - **Reason: ?**

When Trials Fail

Institution	Eligible Candidates Screened	Reason(s) Given for Lack of Accrual
Cleveland Clinic	0	No patients identified
Fox Chase Cancer Center	3	Patient did not want chemotherapy Randomization
Greater Baltimore Medical Center	2	Travel distance for RT Concerns re: randomization
Henry Ford	4	Travel distance for RT Concerns re: randomization
Mayo Clinic (MN)	3	Travel distance for RT
Stanford University	2	History of Lymphoma (5yrs) Travel distance for RT
Washington University	1	Randomization: Patient
UC-San Francisco	0	No patients identified
Total	15	

RTOG 1221 – Accrual experience

- **Zero Accrual, after 15 months**
- **Barriers to Success**
  - **Disease Too Rare**
    - **15 patients screened (informal poll of investigators)**
    - **Incidence of** HPV-negative disease in OP (Waldeyer's Ring) **<u>much lower</u> than expected**, even based on 0129 numbers—used for trial design after CTPM
  - **H&N Surgery clinical research teams stretched thin:** fatigued from launching two trials simultaneously
    - E3311 launched 1st (~44 centers est.), then RTOG1221 (16-26 centers, est.)
  - **Concerns about randomization?**
    - Too few patients screened to know for certain

Thanks to C. Holsinger (PI) for this info

Where to Focus Effort

To continue evidence generation in advanced technology treatments in cancer:

- **Insist on the primacy of high-level evidence so that trials can succeed**
- **Apply best established methods for trials, work to identify feasible yet meaningful endpoints**
- **Continue exploring variations on standard head-to-head comparative trials – how far can we go and still assure high-level evidence?**
- **Better project accrual and trial success before trial launch**
- **Use registries effectively – try hybrids - trial within enveloping registry, for example – capture non-trial entrant information**

Conclusions

- **Technology creates new as well as previously encountered clinical evidence generation challenges – not insurmountable**
- **Patients deserve same high level of evidence, attendant safety and secondary benefit/risk evaluation, as other treatment modalities**
- **In current environment, systems and payers justifiably expect the same**

Thanks for Your Attention!

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