


OMED COLORECTAL CANCER SCREENING COMMITTEE MEETING

Saturday, May 17, DDW San Diego, 2008

Presenter: T. Church




World Organisation of Digestive Endoscopy

Trial Design in Mass Screening for Cancer

Tim Church
University of Minnesota


Introduction: History, Impact

- History
 - HIP study of BrCa screening
 - Subsequent trials of breast, colorectal, lung, prostate, ovarian cancer screening
- Impact
 - Breast & colorectum screening widely recommended
 - Downside: PrCa also widely screened, sometimes recommended



Why randomized?

- Lead time
 - Distorts survival time
- Length bias & overdiagnosis
 - Distorts case comparisons
- Self-selection
 - Healthy screenees
 - Higher risk: symptoms or family or personal history



OMED COLORECTAL CANCER SCREENING COMMITTEE MEETING

Saturday, May 17, DDW San Diego, 2008

Presenter: T. Church

Specific Issues

- Not necessarily unique to screening
- Special emphasis in screening
- Larger impact
- More prevalent



Intention to treat dilutes efficacy estimates

- Contamination
 - Perceived desirability of screening by subjects
 - May be why they volunteered
 - Commonly recommended by health care providers
- Compliance
 - Unpleasantness of procedures
 - Fear of consequences
 - Avoidance of diagnostic procedures



Sample selection

- Volunteers
 - Required by law/custom in some areas
 - Represents likely compliers, not whole population
- Whole population
 - Representative of population characteristics
 - Could over-estimate non-compliance in practice



OMED COLORECTAL CANCER SCREENING COMMITTEE MEETING

Saturday, May 17, DDW San Diego, 2008

Presenter: T. Church

Size & complexity

- Low rates of cause-specific death \Rightarrow large sample sizes
- Single-site studies require massive recruitment from single geography
- Multi-site studies require complexity in design, management, and analysis of trial
 - Training, remote randomization, data QA
 - Stratification, site-specific effects, compliance adjustment



Outcomes

- Cause-specific
 - Manageable study size
 - Directed at target disease
 - Unintended consequences (e.g., procedure deaths)
- Total mortality
 - Summarizes all effects leading to death
 - Requires huge sample size (example)



Protocol specificity

- Screen-only
 - Positives are referred to “the community” for follow-up (e.g., PLCO, NLST)
- Comprehensive diagnostic protocol
 - Requires funding for follow-up procedures
 - Requires specifying a diagnostic approach
 - Acceptable?
 - Justifiable?



OMED COLORECTAL CANCER SCREENING COMMITTEE MEETING

Saturday, May 17, DDW San Diego, 2008

Presenter: T. Church

Mechanism of effect

- Some screening (e.g., CRC) has two effects
- Early detection
 - Primary aim of most cancer screening
 - Treatment more effective earlier
- Prevention
 - Decreased morbidity? Over-diagnosis
 - Decrease incidence \Rightarrow decrease mortality?



Age- & sex-specific effects

- Studies designed with fixed age range
- Do not address starting at younger or older ages than eligible
- Men and women often have different rates
 - E.g., breast, colorectal
- Broad age ranges
- Adequate sample size for sex-specific estimates?



Changing technologies: during trial

- Enhancements can be included
- Dilute the effect of new technology if old less effective, or vice versa
- Sample size can be increased to compensate, allow separate estimation of new & old effect



OMED COLORECTAL CANCER SCREENING COMMITTEE MEETING

Saturday, May 17, DDW San Diego, 2008

Presenter: T. Church

Changing technologies: after trial

- New trial?
 - New mechanism: stool test vs. endoscopy? Endoscopy vs. radiography?
 - Different disease spectrum: polyp detection vs. early CRC detection?
- Head-to-head?
 - Same sensitivity & specificity \neq same effect
 - Missed cancers might have different prognosis by detection method: e.g., size vs. genetic abnormality



Classes of screening tests (so far)

- Fecal tests
 - Fecal occult blood test (FOBT)
 - Guaiac-based FOBT
 - Immunochemical FOBT (FIT)
 - Genetic/epigenetic-based fecal test (GFT)
- Endoscopic tests
 - Flexible sigmoidoscopy (FSG)
 - Colonoscopy (COLO)
- Radiography
 - Barium-enema xray (BEX)
 - CT colonography or virtual COLO (VC)
- Blood-based genetic/epigenetic test (GBT)



Example: FOBT/FIT vs. GFT or GBT

- Suppose genetic test better at finding incurable cancers & less important polyps vs. FOBT/FIT
- But genetic test worse at finding curable cancers and important polyps
- Improved sensitivity, but poorer mortality & incidence effect
- Numerical example



OMED COLORECTAL CANCER SCREENING COMMITTEE MEETING

Saturday, May 17, DDW San Diego, 2008

Presenter: T. Church

Hypothetical comparison of FIT and GFT

- Suppose FIT sensitivity (SE) for all lesions is the same and equals 80%
- For GFT, suppose the SE for
 - Curable cancers (75% of all) is 75%
 - Incurable cancers (25% of total) is 95%
 - Overall sensitivity is 80%
- Mortality effect of GFT will only be 93.75% that of FIT
- Head-to-head give wrong answer



VC vs. COLO

- Matching lesions depends upon proper classification of lesion size, but $\pm 50\%$ error allowed (e.g., see Pickhardt et al. 2003 NEJM)
- Error in classification not considered in estimation
- Unknown effects of not removing 6-9mm lesions
- Effect of radiation on long-term risks of cancer & mortality



FOBT/FIT vs. COLO

- Can assume COLO effect is bigger, since higher sensitivity & specificity dominates FOBT/FIT
 - i.e., can't find it on COLO, won't find it on FOBT/FIT
- No direct data on COLO incidence effect
 - observational estimates on polyp removal effect range from 0% (Robertson et al.) to 95% (Winawer et al.)
- No direct data on COLO mortality effect
 - case-control studies on FSG show wide range depending upon how bias is controlled (Selby et al., Newcomb et al., Church)
- No direct data on COLO costs vs. no COLO



OMED COLORECTAL CANCER SCREENING COMMITTEE MEETING

Saturday, May 17, DDW San Diego, 2008

Presenter: T. Church

Summary & discussion

- Trials have large impact on practice, address more obvious biases
- Unique challenges for screening trials in size, complexity, endpoints, protocols
- Replication important to acceptance
- Need to establish clear criteria for new trials vs. head-to-head comparisons