The Case for Overdiagnosis and Overtreatment: Breast Cancer

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CANCER IS A COLLECTION OF HETEROGENEOUS DISEASES

Our understanding of "cancer" has evolved over time:

Old Paradigm: *inexorable progression*

Esserman et al
*Lancet Oncology* May 2014
New Paradigm: variable progression

INDOLENT or REGRESS
Normal Cell
Atypical Cell/CIS
Stage 1 Cancer

SLOW PROGRESSION
Normal Cell
Atypical Cell/CIS
Stage 1 Cancer

RAPID PROGRESSION
Normal Cell
Stage 1-3 Cancer
Detectable Metastasis
Cancer death

Idle tumors: Indolent lesions of epithelial origin

Early Detection Will Not Impact Mortality
Early Detection Can Reduce Mortality
Systemic Therapy Key to Reducing Mortality

“Cancer”
Dictionary.com Definition

cancer
noun
1. Pathology
a. a malignant and invasive growth or tumor, especially one originating in epithelium, tending to recur after excision and to metastasize to other sites.
b. any disease characterized by such growths.
2. any evil condition or thing that spreads destructively; blight.

March 2012

• Workshop convened around overdiagnosis
• Subgroup to compile recommendations to NCI
  – Signal the physician community
  – Signal the patient community
  – Generate shift in philosophy, enable improvement
  – Explain previous approach and motivate change
    • contentious debate → exploration of new concepts
• Findings summarized
  – JAMA 2013
  – Lancet Oncology May 2014

Patients assume that cancer, left untreated, will kill you
Physicians too
Recommendations to the NCI

1. Recognize that over-diagnosis occurs and is common

2. Embrace the development of new terminology to replace the word “cancer” where appropriate; use companion diagnostics to support this process

3. Create observational registries for IDLE conditions with low or uncertain risk of progression to cancer

4. Mitigate over-diagnosis by testing strategies that lower the chance of detecting unimportant lesions

5. Embrace new concepts for how to approach cancer progression and prevention

Recommendations Working Group

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- Ian M Thompson, UTHSC, San Antonio
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- Peter Nelson, M.D., Fred Hutchinson CRC
- David F. Ransohoff, M.D., UNC, Chapel Hill
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- Shelley Hwang, M.D., Duke University
- Donald A. Berry, Ph.D., UT MD Anderson Cancer Center
- Kenneth W. Kinzler, Ph.D., Johns Hopkins University
- William C Black, M.D., Dartmouth
- Howard Parnes, NCI
- Mina Bissell, LBL Berkeley
- Sudhir Srivastava, NCI, EDRN

Esserman et al. Lancet Oncology May 2014
OVERDIAGNOSIS REPRESENTS OUR ABILITY TO DETECT THE ENTIRE SPECTRUM OF CANCERS THAT ARISE

Chance Increases with Screening

- Lung:
  - Screening of general population increases incidence without changing mortality: Focus on HIGHEST RISK pts
    - 20% decrease in lung ca death
    - Incidence of stage 1 CA >> reduction in stage 2-4 cancers
    - Nodules <1cm on CT: 1.5% chance of cancer
  - Autopsy and screening: overdiagnosis 20-25%

- Thyroid
  - In office screening of thyroid nodules has become routine
  - SEER data: incidence has tripled, death rate constant

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence</th>
<th>Death rate</th>
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</thead>
<tbody>
<tr>
<td>1975</td>
<td>4.9</td>
<td>0.56</td>
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<tr>
<td>2009</td>
<td>14.3</td>
<td>0.52</td>
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</tbody>
</table>

Non-invasive Cancer

- Barrett’s Esophagus
  - Common with gastric reflux
  - Considered high risk for esophageal cancer
  - Barrett’s patients are screened with biopsy

- Longitudinal studies
  - The vast majority will never develop Ca
  - Barrett’s is an adaptation to reflux

*And yet, endoscopic screening continues...*
A TUMOR WITH LITTLE POTENTIAL FOR METASTASIS AND NONE FOR DEATH

WHAT IS THE MAGNITUDE?

IDLE conditions?

IDLE tumors

- Evidence suggests ultralow cancers exist
  - Pre-screening: 10-20% of all cancers
  - Post Screening Era: 25-50% of all cancers
    • Possibly up to 50% of non-palpable cancers (BMJ 2014)
    • Based on trials, cohort studies
  - A problem if not recognized and treated accordingly

- Opportunity to improve our approach to prevention and treatment

- Opportunity to improve screening
  - Learn who is at risk for what type of cancer
  - What should be a target for call back/biopsy?

Canadian RCT: 25 years of followup
Women 40-69, conducted during the Tamoxifen Era

With Mammograms

- 44,925 women received mammograms and breast exams
- 3,250 women had a diagnosis of breast cancer
- 500 women died from breast cancer

Without Mammograms

- 44,910 women received breast exams
- 3,133 women had a diagnosis of breast cancer
- 505 women died from breast cancer

1 in 424 women were diagnosed with and treated for cancers that would never come to clinical attention

Miller et al BMJ Feb 2014
IDLE tumors

- Excess of 106 cancers/
- Estimate: 1/424 women screened
- 22% of all cancers
- 50% of non-palpable cancers

Finding cancer at the earliest possible point—may not be optimal under all conditions

IF WE CANNOT RECOGNIZE AND TREAT ACCORDINGLY

What Can Be Done?

- Invest in better biomarkers of extremely low metastatic potential
- Recognize that non-palpable mammographically detected breast cancers have a high chance of being IDLE
  - AVOID OVERTREATMENT
- Don’t overscreen
  - Minimize detection of IDLE conditions
  - Don’t make low grade DCIS a target of early detection

Defining “IDLE” Tumors

70 gene Prognosis Signature: “Ultra-low Threshold”

70 significant prognosis genes

van’t Veer et al., Nature 2002

Effect of screening on the detection of good and poor prognosis breast cancers

Laura Esserman, Yiwey Shieh, Laura Van’t Veer

Dan Moore, Emiel JT Rutgers, Michael Knauer, Valesca Retel, Stella Mook, Sabine Linn, Flora E van Leeuwen, Annuska Glas

Early Detection Research Network,
UCSF Dean’s Summer Research Fellowship
Study Design

• Large database of 862 patients with known 70-gene prognosis signature outcomes from previous European trials. Selected node-negative cases only.


  • Cohort 2: Screening era: pts diagnosed 2004-6 in 17 community-based hospitals (RASTER) in the Netherlands, where screening uptake is approx 80%.
    • subset of screen-detected cancers

• Analyzed 2 age groups separately:
  • Age 49-60: screened in cohort 2 but not cohort 1 (TEST)
  • <40 years: not screened in either cohort (CONTROL)

Findings

• As age increases, the proportion of
  – grade 1 tumors increases
  – MammaPrint low (good risk) tumors increase
  – Hormone receptor positive tumors increase

• Distribution of good/poor risk tumors with screening
  – Does not shift in women under the age of 40
    • 25-30% good risk
  – Substantially shifts in women aged 49-60
    • Cohort 1: 40% good risk (no screening)
    • Cohort 2: 58% good risk (“screening”)
      – 67% good risk in screen detected cancers

Shieh Esserman, van’t Veer ASCO 2010
Esserman, Shieh, van’t Veer Br Ca Research and Treatment 2011

HR+HER2- ultra-low risk patients:
Tamoxifen (TAM) vs. Untreated
Preliminary Results: Stockholm 1 Randomized Trial

STO trial long-term survival in Mammaprint Ultra-low risk by treatment arm

Only 106 patients in total. Not significantly differential survival by treatment.

X axis starts at 50%

Proportion of Node-Negative Patients Classified as Low Risk by RS and RSPC:
At least 50%

Pathology-Clinical; RS, Recurrence Score

Ca Cancer Registry/ SEER:
Women >50 with stage 1 NO grade 1 comprise 50% of all breast cancer
Review of Adjuvant Therapy to Reduce Local Recurrence

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Accrual dates</th>
<th>N</th>
<th>Study arms</th>
<th>5 year LRR</th>
<th>10 year LRR</th>
<th>12.6 year LRR</th>
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<tr>
<td>TARGET-A</td>
<td>2000 – 2012</td>
<td>2232</td>
<td>IORT</td>
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<td>EBRT</td>
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<td>STUDIES COMPARING XRT vs. NO XRT</td>
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<td>CALGB C9343 Hughes et al 2000</td>
<td>1994 – 1999</td>
<td>606</td>
<td>Tam</td>
<td>4%</td>
<td>7%</td>
<td>10%</td>
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<td></td>
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<td>Tam+RT</td>
<td>1%</td>
<td>1%</td>
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<td>FYles et al 2011</td>
<td>1992-2000</td>
<td>611</td>
<td>Tam</td>
<td>5.5%</td>
<td>13.8%</td>
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<td>Tam+RT</td>
<td>0.4%</td>
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<td>(subset of G1/2, lum A patients)</td>
<td>Tam</td>
<td>2%</td>
<td>4.9%</td>
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<td>STUDIES COMPARING HYPOFRACTIONATED 3-WEEK EBRT vs. 5-WEEK EBRT</td>
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<td>Whelan et al 2010</td>
<td>1993-1996</td>
<td>1234</td>
<td>3 week EBRT</td>
<td>2.33%</td>
<td>6.2%</td>
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<td>5 week EBRT</td>
<td>2.17%</td>
<td>6.7%</td>
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<td>START-B 2008</td>
<td>1999-2001</td>
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<td>5 week EBRT</td>
<td>3.3%</td>
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What is the magnitude of the problem in screening?

- The focus of screening shifted
  - Invasive cancers $\rightarrow$ DCIS $\rightarrow$ Any calcifications
  - 500,000-1 million biopsies a year in the US

- No established benefit to the shift
  - Should we be afraid to “observe” low risk calcifications?
  - Is someone’s life threatened by not knowing?

- Aggregate cost of screening (Thorsen et al Annals of Int Med Feb 2014)
  - 65% of population (age 40+ annually): $7.8 billion
  - 85% of population (age 40+ annually): $10 billion
  - 85% of population (USPSTF biennially): $3.5 billion
    - Biopsy rates are half (Kerlikowski Annals Int med 2011)
    - No significant increase in the rates of locally advanced cancers

*It is time to step up as a community and call for a change*
Embracing Learning and Change Going Forward

Look less hard when screening:

- Many biopsies are performed for calcifications with a low risk of being low grade DCIS
  - Most often benign, incidental DCIS
  - Should these be a target for screening?
  - Urgency to diagnose?

- Targeting more appropriate lesions for detection will reduce the number of biopsies
  - Target >50% risk DCIS or >10% Invasive Ca

Ways to Find Less DCIS

- Raise Thresholds for biopsy

- Consider Biennial screening for lower risk women
  - Reduces biopsy rates substantially without significantly increasing late stage presentation

- Future: risk based screening
  - Tailor screening frequency to risk/ models
    - Family history, gene mutations and variations, breast density, exposures
  - Context of underlying risk could be an important predictor of “consequential” disease

Indolent Disease

- Is part of the spectrum of changes in tissues
  - Reservoir of discoverable “disease”

- More likely to be found with screening
  - Especially if biopsy rates are high or ability to sample a large fraction of the target organ
    - Prostate is perfect example

- Found for many organ types when screening is introduced
  - Breast, Prostate, Lung, Thyroid, Barrett’s

- Risk based screening is being tested as a strategy to improve the problem
  - Lung cancer is an excellent example
  - Focus on individuals with greater risk for development of cancer
    - The case for prevention therefore becomes more compelling
    - Does the context of overall risk matter? Is it perhaps the most important?