Interval Cancers: What is Next?

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Defining the mission

Mercury project: human in orbit/outer space

- 1958-1963
- $277 million in 1965 dollars
- Team of 2 million people
- 26 flights (seven human)
Colorectal cancer mission: getting towards zero deaths

• Three methods for getting there:

  *Prevention and early detection key for interval cancers*

Prevention (polyp and cancer)

Overlap: polyp removal, chemoprevention, etc.

Screening/Early Detection

Treatment

GI/PCP
Public health
Pathologists
Health systems
Insurance

Public health
Nutrition
Pharmacy

Oncology
Health systems
Insurance
Screening Mission: Minimize preventable cancers/deaths

- Prevention (polyp and cancer)
- Screening/Early Detection
- Treatment
Trends differ for men and women, but both impacted by screening.

ACS, 2018

Cancer mortality: women

Cancer mortality: men

Similar 1950
There are many CRC deaths even with effective screening.
Screening test criteria can guide ways of decreasing interval cancers

- **Detectable** preclinical disease: polyps & early CAs
- **Treatment** of preclinical disease improves outcomes: polyp removal & early CA treatment
- **Most feasible, proven tests** (Béatrice Lauby-Secretan, IARC, NEJM, 2018)
  - FIT
  - Sigmoidoscopy
  - Colonoscopy
  - Others likely helpful (CT, stool DNA) though uncertain intervals, less favorable cost structures
Several tests, none perfect: how to optimize?

<table>
<thead>
<tr>
<th>Screening Technique</th>
<th>Strength of Evidence Regarding Colorectal Cancer Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reduction in Incidence</td>
</tr>
<tr>
<td><strong>Stool-based tests</strong></td>
<td></td>
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<tr>
<td>Screening every 2 yr with guaiac test</td>
<td>Suggestive of a lack of effect</td>
</tr>
<tr>
<td>without rehydration</td>
<td></td>
</tr>
<tr>
<td>Screening every 1 or 2 yr with higher-</td>
<td>Limited</td>
</tr>
<tr>
<td>sensitivity guaiac test (with rehydration)</td>
<td></td>
</tr>
<tr>
<td>Screening every 2 yr with FIT</td>
<td>Limited</td>
</tr>
<tr>
<td><strong>Endoscopic techniques</strong></td>
<td></td>
</tr>
<tr>
<td>Single screening with sigmoidoscopy</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Single screening with colonoscopy</td>
<td>Sufficient</td>
</tr>
<tr>
<td><strong>CT colonography</strong></td>
<td></td>
</tr>
<tr>
<td>Single screening with CT colonography</td>
<td>Limited§</td>
</tr>
</tbody>
</table>

(Béatrice Lauby-Secretan, IARC, NEJM, 2018)
Developing a consistent process can decrease interval cancers

Define outcomes

Identify modifiable problems that impact outcomes

Develop interventions
Define outcomes

• Post-colonoscopy colorectal cancers is outcome
  – Interval cancers (before next recommended screening or surveillance)
  – Non-interval cancers
    • At next screening (type A)
    • At next surveillance (type B)
    • No future screening/surveillance recommended (type C)

World Endoscopy Organization Consensus Statements on Post-Colonoscopy and Post-Imaging Colorectal Cancer, Matthew Rutter, Iosif Beintaris et.al. Gastro, 2018
Identify modifiable problems

• Looking at patients with the outcome
  – Formal process to identify PCCRC patients
  – Root cause analysis of PCCRC patients identified
    • Probable missed (adequate exam)
    • Probable missed (inadequate exam)
    • Detected, no resected
    • Likely incomplete resection
    • Likely new CRC (partially preventable=polyps)

World Endoscopy Organization Consensus Statements on Post-Colonoscopy and Post-Imaging Colorectal Cancer, Matthew Rutter, Iosif Beintaris et.al. Gastro, 2018
Adequate documentation: some influence re-screening

- Date of colonoscopy
- *Patient age
- Patient sex
- *Procedure indication (screening, surveillance, symptomatic)
- *Predisposing risk factors for CRC (e.g. high-risk cohort such as Ulcerative or Crohn’s colitis or hereditary forms of CRC such as Lynch syndrome and familial adenomatous polyposis)
- *Quality of bowel preparation (using a validated score)
- *Extent of exam (including photo-documentation of 2 of 3 cecal hallmarks: appendiceal orifice, ileocecal valve, terminal ileum)
- Location of all visualized polyps
- *Estimated size of all visualized polyps
- Paris classification of all visualized polyps by segment of colon
- Type of endoscopic resection (cold snare, cold biopsy, hot biopsy, hot snare, EMR, ESD)
- *Completeness of polyp resection and if en-bloc or piecemeal fashion.
- *Completeness of polyp resection, as judged by the histopathologist
- Other colonic pathology (such as diverticulosis or inflammatory bowel disease)
- Post-procedure management plan

*BOLD indicates factors particularly likely to change post-procedure management plan

World Endoscopy Organization Consensus Statements on Post-Colonoscopy and Post-Imaging Colorectal Cancer, Matthew Rutter, Iosif Beintaris et.al. Gastro, 2018
Measure quality related to outcomes

- **Endoscopist ADR**
- **Facility PCCRC rate**
  - Unadj PCCRC = PCCRCs/(PCCRCs + detected CRCs)
    - Biased by follow-up time
  - Denote follow-up time (e.g. PCCRC-3) for all persons followed 5 years, to allow comparisons
    - Mainly detects missed cancers, not missed polyps

World Endoscopy Organization Consensus Statements on Post-Colonoscopy and Post-Imaging Colorectal Cancer, Matthew Rutter, Iosif Beintaris et.al. Gastro, 2018
Adenoma Detection Rate in 10 minutes or less

• Why it matters overall
• Increasing ADR for all patients
• Improving ADR for individual MDs
Why it matters overall: differences in ADR are associated with future cancer risk

Adjusted* HR (95% CI)

Quintile
HR (95% CI) = 0.97 (0.96, 0.98)

Quintile 1: HR = 1.00 (CRCs = 186)  
Quintile 2: HR = 0.93 (0.70, 1.23, CRCs = 144)  
Quintile 3: HR = 0.85 (0.68, 1.06, CRCs = 139)  
Quintile 4: HR = 0.70 (0.54, 0.91, CRCs = 167)  
Quintile 5: HR = 0.52 (0.39, 0.69, CRCs = 76)

Corley, NEJM 2014
The net effect is that improving quality may extend life and decrease costs.
How can we improve?

• Want something
  – Proven to work
  – Preferably not just by being observed
  – An overall advantage: improves ADR without markedly increased time, difficulty, expense
Improving ADRs for all patients

- Split bowel preps
- Water immersion and water exchange
  - Hsieh (GIE 2017, RCT), Hafner (Cochrane, 2015); Leung (GIE 2012, syst review)
- Chromoendoscopy (Omata, Scand J G 2014 meta-analysis of chromo, cap, etc.)
- Endoscopic devices
  - Endocuff (Tsiamoullos, GIE 2017; van Doorn Gut 2017)
  - Cap assisted (Desai, GIE 2017)
    - Right sided: standard 17% vs. cap assisted 23%
    - No difference other studies (Pohl, Endo 2015), variable by endoscopist
  - Special scopes, “third eye”
Many RCTs demonstrate improvement

• Dynamic position changes (Lee AJG, 2016)
  – ADR 33 vs. 42.4 % in left lateral vs. changing position
  – But not in another study, ?from higher ADRs (Ou GIE 2014)

• Jet water vs. syringe irrigation (Hoffman, WJG 2015)

• L-menthol “relaxer” 42.6% vs. 60.2% (Inoue, Endoscopy 2014)

• Leadership training (Kaminski Gut, 2016)
  – GI leader, hands on/assess/feedback vs. feedback only
  – 3.9% absolute ADR increase (p=0.017)
Improving ADRs for individual endoscopists improved outcomes

• Polish colonoscopy CRC program
• Quality interventions
  – Feedback on ADR, cecal intubation
  – 1.5% mean improvement per year in ADR
• Evaluated 294 MD-level ADRs and pt outcomes
• ADR categories: ≤ 11.2%, 11.2-15.1%, 15.1-19.2%, 19.2-24.6% and >24.6%

Kaminski, Gastro 2017
Moving up ADR categories = lower CRC risk

<table>
<thead>
<tr>
<th>Category</th>
<th>Adjusted Hazard Ratio</th>
<th>95% CI</th>
<th>No. of cancers/100,000 p-yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No improvement</td>
<td>1.00</td>
<td>(0.48, 1.51)</td>
<td>22.26</td>
</tr>
<tr>
<td>Improvement from 1 to 2</td>
<td>0.85</td>
<td>(0.59, 1.49)</td>
<td>19.06</td>
</tr>
<tr>
<td>Improvement from 1 or 2 to 3</td>
<td>0.94</td>
<td>(0.44, 1.30)</td>
<td>21.13</td>
</tr>
<tr>
<td>Improvement from 1-3 to 4</td>
<td>0.76</td>
<td>(0.14, 0.71)</td>
<td>16.97</td>
</tr>
<tr>
<td>Improvement from 1-4 to 5</td>
<td>0.31</td>
<td>(0.06, 0.60)</td>
<td>7.09</td>
</tr>
<tr>
<td>Remain in 5th</td>
<td>0.19</td>
<td></td>
<td>4.32</td>
</tr>
</tbody>
</table>
Other MD-level interventions fall into four main areas

Seven articles, 10 abstracts; largest 43 MDs (Shaukat)

• Increase withdrawal time alone (2)
• Increase withdrawal time plus feedback (2)
• Segmental withdrawal time plus enhanced inspection training (1)*
• Multiple interventions (2)
  – Training, mentoring, feedback, financial penalty

Gastrointest Endosc. 2011 Can we improve adenoma detection rates? A systematic review of intervention studies. Corley DA, Jensen CD, Marks AR.
But efforts to increase withdrawal time alone don’t reliably improve adenoma detection rates.

- 65% detection rate with 7-minute withdrawal
- 100% detection rate with 10-minute withdrawal

Sawhney Gastro 2008
More time alone doesn’t work

- Careful inspection
- Longer exam times
- Higher ADRs
Recent other MD-level RCTs no clear impact

9 sites, 22K colos

1 hour didactic
Review ADR
Review low performers
1:1 proctoring on request
EQUIP posters
Phone calls 2-4 weeks

All sites started recording ADR

Some devices may help
Endocuff increased ADRs in RCT

- 500 pts, 4 endo units in Germany
- ADR 20.7% vs. 35.4% (p<0.001)
- Another trial: more effect sigmoid & cecum (Blecker J Clin Gastro 2015)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.029</td>
<td>1.010-1.047</td>
<td>0.002</td>
</tr>
<tr>
<td>Endocuff</td>
<td>2.090</td>
<td>1.335-3.273</td>
<td>0.001</td>
</tr>
<tr>
<td>Withdrawal time</td>
<td>1.164</td>
<td>1.047-1.295</td>
<td>0.005</td>
</tr>
<tr>
<td>Procedure time</td>
<td>1.069</td>
<td>1.036-1.103</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.740</td>
<td>1.110-2.728</td>
<td>0.016</td>
</tr>
<tr>
<td>Colon cleanliness</td>
<td>0.603</td>
<td>0.385-0.944</td>
<td>0.027</td>
</tr>
</tbody>
</table>

Floer Plos One 2014
Increased ADR and total # adenomas for pre: during but not during: post
The graph shows the change in NCWT (number correct words typed) over different time periods.

- **Pre**: Time period before any intervention, indicating NCWT improvement of 3 mins 30 secs ($P < .001$).
- **Cuff**: Time period after a cuff intervention, indicating NCWT improvement of 2 mins 15 secs ($P = .05$).
- **Post**: Time period after the intervention, showing the increased time spent on NCWT.
Training pathologists increases adenoma detection

• Review of hyperplastic polyps >=6mm in RCT
  – 263 polyps reviewed
  – 33 (12.5%) reclassified
    • 32 sessile serrated adenoma
    • 1 traditional serrated adenoma
  – More common in right colon

Racho RG, ...Wallace MB, Dig Dis Sci 2017
Improving ADR

• Get a good field of view
  – Split prep, good compliance
  – Wash and clean

• Devices may help
  – May be partially by increasing focus on quality
  – May be more helpful in low detectors

• Training, focus, leadership may help

• Pathologist training to identify serrated adenomas

• Need proven MD-level interventions
  – Durability unclear
  – Effective interventions likely multi-faceted, should be straightforward to replicate and disseminate
Next steps: implementing quality processes and developing reproducible interventions

Define outcomes

PCCRCs: new, clear definition
- Interval (mostly missed)
- Next screening (new and missed polyps)
- PCCRC-3 and PCCRC-5 to compare centers

Identify modifiable problems that impact outcomes

Quality: Implement systems for monitoring
- Exam completion
- Complete resection
- ADR
- Review of interval cancers

Develop interventions

Need randomized trials of standardized, reproducible methods
- Leadership
- MD or unit-level ADR training
- Some devices or techniques likely help
Need for systems-level interventions

• Aligning of incentives for quality/outcomes
  – Volume rewarded
    • Fast, large numbers
  – Quality not largely recognized
    • ADR, complete resection = fewer repeat exams, lower cancer rates

• Recognition of public health measures
  – Stop smoking, healthy diet both prevent cancer deaths and many other deaths
  – Concern regarding healthy screenee effect
Thank You!
Higher ADRs had improved outcomes

• Increased ADR associated with
  – HR = 0.63 (0.45–0.88) for CRC
  – HR = 0.50 (0.27–0.95) CRC death

• Compared with no increase in ADR, reaching or maintaining ADR > 24.6%
  – Reach this ADR: HR = 0.27 (0.12–0.63) for CRC
  – Maintain this ADR (high-detector) 0.18 (0.06–0.56)