NCCRT Small polyp workshop
Sept. 2, 2009

Beth McFarland, MD
American College Radiology
Spectrum of colorectal disease

Target lesion

LOW MORTALITY

<table>
<thead>
<tr>
<th>Diminutive</th>
<th>Small</th>
<th>Adv Adenomas</th>
<th>Adenoca (local)</th>
<th>Adenoca (invasive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5mm polyps</td>
<td>6-9 mm</td>
<td>≥ 10 mm</td>
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HIGH MORTALITY
Paradigm shift of colorectal polyp screening—
to detect polyps, but not remove

- CTC and other technologies (Aeroscope) provide high resolution to structurally detect, but do not remove polyps

- **Management** based on:
  » Size/number of polyps
  » Add clinical context of patient age, comorbidity, colorectal risks/sx’s

3D CTC of 4 mm polyp
Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008: A Joint Guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology
CA Cancer J Clin 2008;58:130-160; originally published online Mar 5, 2008;
DOI: 10.3322/CA.2007.0018

This information is current as of September 21, 2008
Overview of meeting process

- Literature review
  » Chiranjeev Dash, Idris Guessous (Emory)
- Clinical experiences
- Expert opinions

- Summary of evidence based knowledge
  » what is known vs not known
- Consensus statements
- Identify areas for research
Participants

• Chair- David A. Lieberman, MD
• ACS
• Gastroenterology
• Radiology
• Pathology
• Patient advocates
Overview of meeting agenda

• Review of prevalence/location/histology
  » C. Dash, L. Butterfly, M. O’Brien, D. Dwyer

• Biology of polyps to cancer
  » L. Burgart

• Natural history of polyps
  » C. Dash, P. Pickhardt, B. Cash, S. Winawer

• Harms/cost issues/modeling
  » C. Dash, C. Hur, A. Zauber

• Management issues/framing the issues
  » D. Rex, D. Johnson

• Summary - consensus, research
  » D. Lieberman
Prevalence/location/histology

• New data $\text{vs}$ older data
• Screening/asx $\text{vs}$ at risk cohorts
• Different definitions used
  » size or histology
Advanced Adenoma (AA)

**Definition:**
- Size $\geq$ than 1cm.
- $>25\%$ Villous
- High grade dysplasia/invasive carcinoma
  (not serrated)

**Prevalence**
- Screening Cohort 3-11%
- NPS Referral Cohort 56%

Courtesy of Michael O’Brien, pathology
Definition:  
Polyp size categories

- Diminutive  \( \leq 5\text{mm} \)
- Small  \( 6-9\text{ mm} \)
- Large  \( \geq 10\text{ mm} \)
Current polyp recommendations

• **USMSTF 2006 post polypectomy surveillance update for colonoscopy** *(Winawer et al)*
  » Small hyperplastic rectal polyps are benign - f/u 10 years
  
  » One or two < 1 cm tubular adenoma(s), with only LGD - f/u 5-10 yrs
  
  » 3 or more adenomas of any size defines increased risk / closer surveillance

• **2008 ACS recommendations for polyps at CTC** *(Lieberman et al)*
  » All patients with polyps ≥ 6 mm should be offered OC (as clinically indicated)
  
  » Management of ≤ 5 mm polyps less understood
Search Strategy
(Dash, Emory)

• MEDLINE
• Broad search strategy
• # identified: 6241 articles
• Inclusion criteria:
  » Full length reports
  » Average-risk screening population
  » Reported data on small/diminutive polyps
  » English language
• Prevalence data based on 27 articles
Prevalence of advanced adenoma $\leq 5$mm:

- Lieberman: 63 / 13,992 (0.4%) (0.3% if no SSA)
- Pickhardt: 1 / 1,233 (0.1%)
- Kim: 3 / 3,163 (0.1%)

0.1-0.3%
Prevalence of 6-9 mm polyps

0.3 to 0.5%
What % of small adenomas are tubular?

Read, 1997; Lieberman, 2000; Sung, 2003; Butterly, 2006; Strul, 2006; Regula, 2006; Lieberman, 2008;
What % of small adenomas have high grade dysplasia?

Read, 1997; Lieberman, 2000; Butterly, 2006; Strul, 2006; Regula, 2006; Kim, 2007; Lieberman, 2008;
## Prevalence / Cancer yields (screening/ asx cohorts)

<table>
<thead>
<tr>
<th>Size (mm)</th>
<th>Prevalence AA</th>
<th>% invasive ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5 mm</td>
<td>0.1-0.3%</td>
<td>0-0.06%</td>
</tr>
<tr>
<td>6-9 mm</td>
<td>0.3-0.5%</td>
<td>0.1-0.2%</td>
</tr>
</tbody>
</table>
Management issues of diminutive polyps

• **Expert consensus (in progress):**
  » Most patients with 1-5 mm polyps can be safely f/u with CTC in 5 years.
  » If multiple 1-5 mm polyps with high confidence at CTC, are these reported (? management)

• **Research topic:**
  » Do patients with 3 or more adenomas, all \(< 5\) mm in size, have increased risk of AA, compared to patients with 1-2 diminutive adenomas?
    » NPS had too few data
    » ?Kaiser/VA other data bases to investigate
Overview of meeting agenda

• Review of prevalence/location/histology

• Biology of polyps to cancer
  » Major pathway (CIN)
  » Microsatellite instability (MSI)
    » Serrated adenoma
Brief History of Colorectal “Adenomas”
(Larry Burgart)

**Serrated Things**

- 1980’s
  - HPP

- 1990’s
  - HPP

- 2000’s
  - “Sessile serrated Adenoma” (SSA)
  - AdCA

**Adenomatous Things**

- 1980’s
  - TA
  - TVA
  - VA
  - AdCA

- 1990’s
  - TA
  - TVA
  - VA
  - AdCA

- 2000’s
  - TA
  - TVA
  - VA
  - AdCA
Major CRC pathways

- Chromosomal instability path (CIN)- 85%
  » APC, DCC, K-ras, p53

- Microsatellite instability (MSI)- 15%
  » 90% of these due to *methylation* of MLH1 gene promoter (older pts, right colon, F>M, BRAF +)
    » Sessile serrated adenomas (SSA) are CRC precursors
    » Hyperplastic polyps (HPP) are not CRC precursors
  » 10% are due to Lynch syndrome (BRAF -)
Goblet cell

HPP

Microvesicular HPP

Sessile Serrated Adenoma

CRC precursor

Courtesy of Larry Burgart
MVSP: SSA Precursor?

- Morphological Similarity
- BRAF mut frequency
- Spectrum of CpG island Methylation

Courtesy of Michael O’Brien
The Serrated Pathway to Colon CA is Now Undeniable, and the “SSA” is the precursor

Sessile
Serrated
Adenoma

Mixed polyp w/ adenoma component

AdenoCA
## Existing terminology for SSA

<table>
<thead>
<tr>
<th>Name</th>
<th>Pub Med Hits</th>
</tr>
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<tbody>
<tr>
<td>Sessile serrated adenoma*</td>
<td>26</td>
</tr>
<tr>
<td>Sessile serrated polyp</td>
<td>27</td>
</tr>
<tr>
<td>Serrated polyp with abnormal proliferation</td>
<td>6</td>
</tr>
<tr>
<td>Serrated adenoma</td>
<td>180</td>
</tr>
<tr>
<td>Colorectal polyp w/ epithelial serrated prolif.</td>
<td>4</td>
</tr>
</tbody>
</table>

*Torlakovic and Snover, AJSP January 2003

For our discussion today, we will use “sessile serrated adenoma”, but beware the difficulties if you search the literature.
SSA’s can be quite small

<table>
<thead>
<tr>
<th>SSA size</th>
<th>CA/Dysplasia Size</th>
<th># CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-10 mm</td>
<td>2-4 mm</td>
<td>6</td>
</tr>
<tr>
<td>3-14 mm</td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

Summary:
Biology of cancers

• **Consensus:** Serrated sessile adenomas (SSA) are associated with BRAF mutations and progress to malignancy

• **Research topics:**
  » What is the prevalence of SSA in small polyps?
  » Can pathological interpretation of SSA be standardized and reproduced?
Overview of meeting agenda

• Review of prevalence/location/histology

• Biology of polyps to cancer

• Natural history of polyps
  » Older data
  » On-going studies
POLYP Size changes
(over 2-5 yrs)
POLYP Size changes
(over 2-5 yrs)
• Loeve, 2004:

  » The expert MISCAN-COLON model predicted a higher cancer incidence and lower adenoma detection rates than observed in the National Polyp Study.

  » “….. a new factor had to be introduced, i.e., adenoma regression.”

  » In summary, a high adenoma incidence combined with spontaneous regression of adenomas is the only explanation of the observed adenoma detection rate that does not increase simulated cancer incidence and even decreases the simulated cancer incidence.
Two large ON-GOING clinical research efforts

• Colon health initiative (CHI)
  » Bethesda Naval Medical Center
  » Brooks Cash, gastroenterologist

• University of Wisconsin (UW)
  » Perry Pickhardt, radiologist

• Integrated high volume clinical and research programs
Longitudinal f/u study of 6-9 mm polyps at CTC

<table>
<thead>
<tr>
<th></th>
<th>CHI</th>
<th>U of Wisconsin</th>
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<tbody>
<tr>
<td></td>
<td><em>Brooks Cash, DDW 08</em></td>
<td><em>Perry Pickhardt, SGR 08</em></td>
</tr>
<tr>
<td># polyps (pts)</td>
<td>51 (43 pts)</td>
<td>128 (100 pts)</td>
</tr>
<tr>
<td>% AA</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>Mean f/u</td>
<td>1.1 yr</td>
<td>1.4 yr</td>
</tr>
<tr>
<td>% all polyps that grew</td>
<td>19.6%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Mean growth rate of AA</td>
<td>1.3mm/yr</td>
<td>1.4 mm/yr</td>
</tr>
</tbody>
</table>
Initial Screening CTC

2-year CTC Follow-up

Linear size: 7.8 mm to 7.6 mm – Volume: 270 mm$^3$ to 230 mm$^3$

Courtesy of Pickhardt
Summary:
Natural History of small polyps

• **Consensus statement:** Natural history of small polyps is less certain, but majority appear to regress or be stable over 1-5 year intervals

• **Research topics:**
  » Can non-invasive technologies be used to determine growth rates?
  » Are there risk factors associated w/progression?
Overview of meeting agenda

- Review of prevalence/location/histology
- Biology of polyps to cancer
- Natural history of polyps
- Harms/cost issues/modeling
  - OC vs CTC - risks
  - Cost effectiveness issues
Harms and Cost Issues of Managing Small Adenomas: Microsimulation Modeling Approach

Ann G Zauber

September 2, 2009
Atlanta, Georgia
NCCRT Quality Assurance Workshop: The Management of Small Colorectal Polyps

MISCAN: Ann Zauber, Marjolein van Ballegooijen, Iris Lansdorp-Vogelaar

SimCRC: Karen Kuntz, Amy Knudsen

CRC-SPIN: Carolyn Rutter, James Savarino
Post-polypectomy bleeding (major):
Small polyps vs. large polyps

![Graph showing comparison between small and large polyps for post-polypectomy bleeding complications.](image)
CTC Radiation dose

Supine  Prone

90 mAs  12 mAs
Overview of meeting agenda

• Review of prevalence/location/histology
• Biology of polyps to cancer
• Natural history of polyps
• Harms/cost issues/modeling
• Management issues/framing the issues
  » Gastroenterologists
  » Radiologists
  » Patient care advocates
Summary

• Consensus statements
  » Evidence based
  » Expert opinion

• Research topics
Possible consensus statements

• Management of 6-9 mm polyps
• Management of $\leq 5$ mm polyps
• Adenoma prevalence rates determined at OC are operator-dependent, true rates probably higher
• Quality assurance key across modalities
• Considerable variability exists in pathological interpretation of polyps (especially for serrated adenomas)
Research topics

- Risks of 3 or more only ≤ 5mm polyps?
- Natural history studies to assess growth
- Racial differences in prevalence and histology of small polyps?
- Prevalence of SSA/ standardization of reporting
- Techniques to decrease and/or study risks at OC and CTC
Discipline of the pursuit