Is the idea of R&D still relevant?

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DISCLOSURES

• Research grants from Pentax, Boston Scientific, ERBE
• Consultant/Advisory Board member for Boston Scientific and Pendopharm.
• Speaker Boston Scientific, Pendopharm, ERBE
Is the idea of R&D still relevant?
Is the idea of R&D still relevant?

YES! More than ever!
Increasing ADR and PDR (of diminutive polyps)

• CADe, 5 randomized controlled trials (4354 patients).
• Pooled ADR was significantly higher in the CADe group than in the control group 36.6% vs 25.2%
• APC was higher for ≤5-mm (RR, 1.69; 95% CI, 1.48-1.84), 6- to 9-mm (RR, 1.44; 95% CI, 1.19-1.75), and ≥10-mm adenomas (RR, 1.46; 95% CI, 1.04-2.06)
• CADe resulted in a higher sessile serrated lesion per colonoscopy (RR, 1.52; 95% CI, 1.14-2.02)
Increasing ADR and PDR (of diminutive polyps)

• ADR benchmarks/ expectations will likely continue to go up and we will likely detect many diminutive HPs with CADe or other technical improvements (High definition, Endocuff, water immersion)

• Increasing ADR/ PDR in context of many screening programs using FIT before colonoscopy
Management of Diminutive and Small Polyps

PREVALENCE of colorectal polyps

- Diminutive polyps (≤5 mm): 70-80%
- Small polyps (6-9 mm): 10-15%
- Large polyps (10-19 mm): 5-10%
- Very large (≥20 mm): ~1%

- Advanced adenoma prevalence of diminutive polyps = 0.1%-3.4%
- Cancer prevalence of diminutive polyps is = 0%-0.08%
- Percentage of adenomatous histology of diminutive polyps
  - Rectum: 6-14%
  - Sigmoid: 28%-30%.
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**Routine practice:**
Resect and histopathology examination

**Challenges:**
Higher cost; limited clinical impact on cancer prevention; delay in recommending surveillance intervals

**OPTICAL DIAGNOSIS**
"Resect & Discard"

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- Cancer prevalence of diminutive polyps = 0%-0.08%
- Percentage of adenomatous histology of diminutive polyps
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**Optical Real-time Polyp Diagnosis**

**RESECT & DISCARD**, if surveillance agreement ≥90% with pathology outcomes

**DIAGNOSE AND LEAVE**, if NPV of optical diagnosis ≥90% for rectosigmoid polyps
“Classical” Optical Polyp Diagnosis – Challenges

- >90% surveillance interval agreement only met in the academic or research settings
- Credentialing & Monitoring
- Increased documentation
- Increased procedure times / Reimbursement
- Polyp classification systems
- COMPLEXITY
  - ~50% of endoscopists reported that Diagnosing & Leaving diminutive polyps in place might increase cancer risk
  - >80% of endoscopists do not use the Resect & Discard strategy in their practice.
- Barriers of implementation:
  - Afraid of wrong optical diagnosis (45%)
  - Afraid of wrong surveillance intervals (58%)
  - Medico-legal concerns (54%)

Solutions to the « optical Dx » problems

1. AI based optical Diagnosis
   - Harmonize optical Dx skills and transfer responsibility to AI/CADx

1. Non-optical resect and discard strategies
   - Location-based resect and discard (LBRD) strategy
   - Polyp-based resect and discard (PBRD) strategy

2. Defining best cut-off size for optical diagnosis and resect & discard
   - 1-3 mm?
   - 1-5 mm?
   - 1-10 mm?
Alternative Resect-and-Discard Strategies (Location based)

<table>
<thead>
<tr>
<th>A) Non-optical</th>
<th>Rectosigmoid dim. polyps = hyperplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Location based”</td>
<td>Proximal dim. polyp = neoplastic</td>
</tr>
</tbody>
</table>

| B) Optical       | Current resect and discard approach     |
• demonstrated high (97%) surveillance interval agreement (USMFT 2020);

• significantly outperformed optical diagnosis (~90%) (using NICE and Sano classifications);

• could provide 76.7% of patients with an immediate surveillance interval recommendation (significantly higher than optical diagnosis);

• Could avoid 69.7% of pathology examination (significantly higher than optical diagnosis);
### Alternative Resect-and-Discard Strategies (Polyp based)

<table>
<thead>
<tr>
<th>SCENARIO</th>
<th>RULE</th>
<th>FOLLOW-UP INTERVALS FOR COLONOSCOPY (YEARS)</th>
<th>IF FAMILY HISTORY OF CRC (1ST DEGREE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No polyp</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>1-2 diminutive polyps (≤ 5 mm)</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>1-3 small polyps (≤ 9 mm)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>≥ 4 polyps, any size</td>
<td>Follow-up histology results</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>≥ 1 polyp ≥ 10 mm</td>
<td>Follow-up histology results</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Insufficient or inadequate bowel prep.</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

1) Polyp-based post-hoc  
2) Polyp-based by endoscopist immediately post procedure
### Immediate surveillance recommendations

- Pathology based: 46%
- Optical diagnosis: 78%
- Polyp-based (post-hoc): 85%
- Polyp-based (endoscopist): 85%

### Surveillance interval agreements

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Optical (NICE)</th>
<th>Polyp-Based (post hoc)</th>
<th>Polyp-Based (Endoscopists)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agreement, n (%)</td>
<td>91% (95% CI: 89-94)</td>
<td>90% (95% CI: 87-92)</td>
<td>73% (95% CI: 69-76)</td>
</tr>
<tr>
<td>Shorter surveillance, n (%)</td>
<td>4%</td>
<td>6%</td>
<td>19%</td>
</tr>
<tr>
<td>Longer surveillance, n (%)</td>
<td>4%</td>
<td>4%</td>
<td>8%</td>
</tr>
</tbody>
</table>
### Surveillance interval agreements

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Agreement, % (95% CI)</th>
<th>Shorter surveillance, % (95% CI)</th>
<th>Longer surveillance, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optical diagnosis (vs reference standard based on 2012 guideline)</td>
<td>95.8 (0.94–0.97)</td>
<td>1.4 (0.007–0.02)</td>
<td>2.8 (0.02–0.04)</td>
</tr>
<tr>
<td>PBRD (post-hoc vs reference standard based on 2012 guideline)</td>
<td>90.7 (0.89–0.92)</td>
<td>5.8 (0.04–0.07)</td>
<td>3.5 (0.02–0.05)</td>
</tr>
<tr>
<td>PBRD (by endoscopist vs reference standard based on 2012 guideline)</td>
<td>76.4 (0.74–0.79)</td>
<td>15.4 (0.13–0.18)</td>
<td>8.3 (0.07–0.10)</td>
</tr>
<tr>
<td>PBRD (post-hoc vs reference standard based on 2020 guideline)</td>
<td>98.0 (0.97–0.99)</td>
<td>0.1 (0–0.006)</td>
<td>1.9 (0.01–0.03)</td>
</tr>
</tbody>
</table>

### Clinical benefits of PBRD

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Immediate surveillance interval recommendations, %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathology based</td>
<td>50.6</td>
<td>0.47–0.54</td>
</tr>
<tr>
<td>Optical diagnosis</td>
<td>76.1</td>
<td>0.73–0.79</td>
</tr>
<tr>
<td>PBRD</td>
<td>93.7</td>
<td>0.92–0.95</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Pathology examinations required, %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathology based</td>
<td>REFERENCE</td>
<td>REFERENCE</td>
</tr>
<tr>
<td>Optical diagnosis</td>
<td>29.4</td>
<td>0.26–0.32</td>
</tr>
<tr>
<td>PBRD</td>
<td>12.2</td>
<td>0.10–0.15</td>
</tr>
</tbody>
</table>
PBRD Main Findings

• Reached 98.0% agreement of surveillance intervals compared with pathology (higher than that for optical diagnosis, USMFT 2020);

• If used in real time by endoscopists, the adherence to guideline recommendations is lower;

• Could avoid 87.8% of pathology examination (significantly higher than optical diagnosis, when used for up to 10mm polyps);

• is a feasible resect and discard alternative that can be used without specialized equipment, training, or optical diagnosis skills.

• Reduction in pathology exams means also reduction in follow up of results and documenting/communicating results results after colonoscopy = reduced workload for endoscopist
R&D Size cut off study

➢ **Aim:** to evaluate which cut-off levels (1–3 mm, 1–5 mm, 1–10 mm) would affect the safety and efficacy of optical polyp diagnosis.

➢ No distinction between LGD, HGD, SSL sub-entities yet within optical Dx/ R&D

➢ **Hypothesis:** a lower polyp size cut-off for optical diagnosis (e.g., 1–3 mm) is associated with a lower risk of misclassifying advanced colorectal neoplasia when using optical polyp diagnosis.
Method

➢ A post-hoc analysis of data from 3 prospective single-center studies

• N patients (colonoscopies) = 3374;
• N polyps = 1-3 mm: 3278/7655 (42.8); 1-5 mm: 5906/7655 (77.1); 1-10 mm: 7291/7655 (95.2)

• **Inclusion criteria:** aged 45–80 years, indication of a screening, surveillance, or diagnostic colonoscopy.

• **Exclusion criteria:** known inflammatory bowel disease, active colitis, coagulopathy, familial polyposis syndrome, poor general health (American Society of Anesthesiologists class >3), an indication for emergency colonoscopy due to an active upper or lower gastrointestinal bleed or intensive care unit admission, and missing or unclear data on demographic or colonoscopy characteristics.
Study Outcomes

➢ **Primary outcome:** the probability that a polyp with advanced histology undergoing optical diagnosis was misdiagnosed, resulting in an inappropriate delayed follow-up of either 2 or 7 years for the patient.

➢ **Secondary outcomes:**

- the agreement between surveillance intervals based on optical diagnosis of polyps of 1–3 mm, 1–5 mm, and 1–10 mm and the pathology-based recommendations.
- the diagnostic properties of optical prediction for neoplastic rectosigmoid polyps.
- The proportion of the reduction in histopathology examinations and the proportion of patients who could have received an immediate surveillance recommendation
Number of Patients with Surveillance Delays for 79 Patients with Advanced Histology

<table>
<thead>
<tr>
<th>Polyp size cut-off</th>
<th>2-year delay, n (%)</th>
<th>7-year delay, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3 mm</td>
<td>0 (0)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>1–5 mm</td>
<td>1 (1.3)</td>
<td>9 (11.4)</td>
</tr>
<tr>
<td>1–10 mm</td>
<td>3 (3.8)</td>
<td>17 (21.5)</td>
</tr>
</tbody>
</table>
Surveillance Interval Agreement

In patients that optical diagnosis can change their recommended surveillance interval (%)

<table>
<thead>
<tr>
<th>Surveillance Interval</th>
<th>Correct</th>
<th>Shorter</th>
<th>Longer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 mm</td>
<td>97,2</td>
<td>1,8</td>
<td>0,9</td>
</tr>
<tr>
<td>1-5 mm</td>
<td>95,5</td>
<td>3,0</td>
<td>1,5</td>
</tr>
<tr>
<td>1-10 mm</td>
<td>94,2</td>
<td>3,7</td>
<td>2,0</td>
</tr>
</tbody>
</table>

Whole cohort

1-3 mm 1-5 mm 1-10 mm
## Benefits of Optical Diagnosis

<table>
<thead>
<tr>
<th>Reference standard and polyp optical diagnosis</th>
<th>Immediate surveillance interval recommendations</th>
<th>Total reduction in needed pathology examinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate surveillance interval recommendations</td>
<td>24,4</td>
<td>0,0</td>
</tr>
<tr>
<td>Total reduction in needed pathology examinations</td>
<td>41,0</td>
<td>33,5</td>
</tr>
<tr>
<td></td>
<td>58,2</td>
<td>62,3</td>
</tr>
<tr>
<td></td>
<td>73,3</td>
<td>78,2</td>
</tr>
</tbody>
</table>

The proportion of patients that could have been communicated with surveillance intervals immediately and the reduction in histopathology examinations (%).
Summary of Findings

• Limiting optical diagnosis to polyps of 1–3 mm reduced the risk of mismanagement and delayed surveillance intervals for patients with small advanced neoplasia.

• Optical diagnosis for polyps 1–3 mm, 1–5 mm, and 1–10 mm resulted in >90% agreement of the assigned surveillance intervals compared with pathology.

• Starting optical diagnosis at the low threshold of 1–3 mm is a cost-effective, safe, and feasible approach to implementing a “resect and discard” strategy in routine clinical practice.
Pathology should not be viewed as the criterion standard for diagnosing colorectal lesions ≤3 mm.

• Shahidi et al. (2020)
  • 458 (71.1%) polyps had a concordant pathologic diagnosis with optical decision on pathology.
  • 577 (89.6%) polyps had a concordant pathologic diagnosis with AI-assisted optical decision on pathology.
  • 168 (90.3%) polyps had a concordant AI-assisted endoscopy with optical decision on pathology.
Conclusion

• Resect and Discard is more relevant than ever because of increasing ADR/PDR (including increased detection diminutive polyps/HPs)

• PDR seems to go above 80% in newer studies and increasing percentage of small/diminutive polyps (95% in size cut off study)

• Different approaches are meanwhile available to overcome the problems that made widespread implementation of R&D not feasible in the past:
  • AI assisted optical diagnosis
  • Non-optical approaches such as location based or polyp based
  • Limiting polyp size for Resect and discard

We need Society endorsement for implementation