Prevention of Interval Colorectal Cancers: What Do We Need to Know?

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Japan Polyp Study Workgroup
Background

“Only option” that allows **visualization** and **removal** of lesions throughout the entire colon in a single test.

✓ Previous colonoscopy was associated with 60% reduction in CRC mortality\(^1\)) and 70% reduction in the incidence of late-stage CRCs\(^2\)).


“**Why does colonoscopy not prevent more CRCs?**”
CASE, 70 yrs Male

8 August, 2011

Retroflex View  Straight View

M/D adenocarcinoma,
Type2, T3N0M0, A/Colon
5 adenomas (< 10 mm, LGD) were removed during 4 times TCS (in 2004, 2005, 2006, 2008)

M/D adenocarcinoma: pSS, n=0/33
Terminology and Definition of “Interval CRC”

Rabeneck L et al. proposed using the term “Postcolonoscopy CRC” for any CRC found after a colonoscopy. Rabeneck L, et al. Frontline Gastroenterol 2010

Large retrospective studies have used the percentage of CRCs that occur “6 to 36 months after colonoscopy” as a proxy for interval CRCs. Singh H, et al. Am J Gastroenterol 2010

WEO CRC Screening Meeting
Expert Working Group “Right-sided lesions & Interval CRCs”

CRC diagnosed after a screening test or examination in which no cancer is detected and before the date of the next recommended examination.

## Incidence and Risk Factors of Interval CRC

<table>
<thead>
<tr>
<th>Retrospective Studies</th>
<th>Incidence of ICRCs:</th>
<th>Risk Factors:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baxter et al.</td>
<td>6.8% (distal colon) vs 12.4% (proximal colon)</td>
<td>Endoscopist's specialty, non-hospital-based setting</td>
</tr>
<tr>
<td>Singh et al.</td>
<td>2.1% (distal colon) vs 5.9% (proximal colon)</td>
<td>Older age, diverticular disease, proximal location, endoscopist's specialty</td>
</tr>
</tbody>
</table>

Interval CRC; Frequency

- **Proximal Colon:** 5.9-14.4%
- **Distal Colon:** 2.1-6.8%

**“These data suggest that interval CRCs are related, in large part, to the quality of the index exam”**

Farrar et al. 2006 (Clin Gastroenterol Hepatol)

- 27% of ICRCs developed at previous polypectomy segments

Sanduleanu S, et al. Nat Rev Gastroenterol Hepatol 2012 (modified)
## Molecular Characteristics of Interval CRCs

<table>
<thead>
<tr>
<th>Study (Population)</th>
<th>Results &amp; Conclusion</th>
</tr>
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<tbody>
<tr>
<td><strong>Interval CRC vs Non-Interval CRC</strong></td>
<td></td>
</tr>
<tr>
<td>MSI: 29.0-30.4% vs 10.3-11.0% <em>(P&lt;0.01)</em></td>
<td></td>
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<tr>
<td><strong>KRAS mutation</strong>: 12.9% vs 28.9% <em>(P=0.03)</em></td>
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<tr>
<td>CIMP-high: 57% vs 33% <em>(P=0.004)</em></td>
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</tr>
<tr>
<td><strong>BRAF mutation</strong>: 28% vs 19% <em>(P=0.18)</em></td>
<td></td>
</tr>
<tr>
<td><strong>KRAS mutation is inversely associated with ICRCs and with MSI. BRAF mutation is not associated with ICRCs</strong></td>
<td></td>
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</table>

*Sanduleanu S, et al. Nat Rev Gastroenterol Hepatol 2012*

Etiology of Interval CRCs

3 Plausible Reasons

1. Missed lesions
2. Rapid progression
3. Incomplete polypectomy

“These data suggest that interval CRCs are could be reduced substantially by high-quality colonoscopy”

- 50% to 75% of interval CRCs were likely the result of missed or incompletely resected lesions and less than 30% were rapidly progressing lesions.

- Most interval CRCs likely resulted from missed rather than new lesions (by using mathematic model).


✓ We previously reported two complete colonoscopies using high-definition endoscope may lengthen the follow-up interval after polypectomy based on the results of the Japan Polyp Study (JPS).

We detected “FIVE interval cancers” during 4 years’ surveillance period after baseline colonoscopy in our JPS...
Objectives

✓ To clarify clinicopathological characteristics of “Interval CRCs/Interval index lesions (ILs)*” and “Risk factors.

✓ To provide insight on the etiology of interval CRCs/Interval ILs.

* ILs: LGD ≥ 10 mm, HGD, Invasive cancer
Eligible patient (40-69 yrs)

Start

Interval 1 year

Initial colonoscopy (1\textsuperscript{st} CS)

Confirmation colonoscopy (2\textsuperscript{nd} CS)

Randomization

2\textsuperscript{nd} follow-up colonoscopy

2\textsuperscript{nd} follow-up colonoscopy

Interval 1 year

1\textsuperscript{st} follow-up colonoscopy

Pure NAD [Adenoma (-)]

Internal control group

Clean Colon

2757

1087

1079

591

Interval Cancer (Case 1: 64 yrs, Male)

Initial colonoscopy (1st CS)

Confirmation colonoscopy (2nd CS)

10 months

T3N0M0
Borr. Type 2

Start

R

12m

24m
(1y)

1st follow-up colonoscopy

48m
(3y)

2nd follow-up colonoscopy

Interval Cancer (Case 1: 64 yrs, Male)

Initial colonoscopy (1st CS)

Confirmation colonoscopy (2nd CS)

10 months

T3N0M0
Borr. Type 2

Start

R

12m

24m
(1y)

1st follow-up colonoscopy

48m
(3y)

2nd follow-up colonoscopy
Interval Cancers
(Case 2: 56 y, Female, Case 3: 58 y, Male, Case 4: 59 y, Female)

Confirmation colonoscopy (2nd CS)

A/Colon: T1 (SM) 0-Ils

D/Colon: T1 (SM) 0-IIa+IIc

S/Colon: T1 (SM) 0-Ils(IIc)

Initial colonoscopy (1st CS)

Start

12m

24m (1y)

1st follow-up colonoscopy

48m (3y)

2nd follow-up colonoscopy

Confirmation colonoscopy (2nd CS)
Interval Cancer (Case 5: 62 yrs, Male)

Confirmation colonoscopy (2nd CS)

Initial colonoscopy (1st CS)

1st follow-up colonoscopy

2nd follow-up colonoscopy

Rectum: T2N0M0
Borr. Type 2

22 months
Introduction and informed consent sought by investigators

Eligible patient (40-69yrs)

Randomization

Initial colonoscopy (1st CS)

Confirmation colonoscopy (2nd CS)

Interval 1 year

Start 12m

2041 First time CS

2nd follow-up colonoscopy

2-Exam group

1-Exam group

1st follow-up colonoscopy

48m (3y)

Pure NAD [Adenoma (-)]

Internal control group

Clean Colon
We attempted to remove all neoplastic polyps.

We can evaluate the risk for "Index lesions (ILs)" one year after initial "clean colon".

* ILs: LGD ≥ 10 mm, HGD, Invasive cancer
Clinicopathological Characteristics of “Interval Index Lesions” at the 2nd CS

“Index lesions” after 1 year

56 lesions in 54 pts/ 2041 pts (2.6%)

[Interval cancer: 4 pts (0.2%)]

- Invasive Ca: 4
- Intra-mucosal Ca (HGD): 34
- LGD ≥ 10 mm: 18

T1 (SM)
Ca: 1

T3 Ca: 1

T1 (SM)
Ca: 2

• Proximal colon: 32 (57%)
  (mean size, SD: 11.2 ± 8.3 mm)
• Distal: 24 (43%)
  (mean size, SD: 8.9 ± 4.0 mm)
Clinicopathological Characteristics of “Interval Index Lesions” at the 2\textsuperscript{nd} CS

“Index lesions” after 1 year

56 lesions in 54 pts/ 2041 pts (2.6%)
[Interval cancer: 4 pts (0.2%)]

- Invasive Ca: 4
- Intra-mucosal Ca (HGD): 34
- LGD ≥ 10 mm: 18

- T1 (SM) Ca: 1
- T3 Ca: 1
- T1 (SM) Ca: 2

- Proximal colon: 32 (57%)
  (Non-polypoid; 19/32: 59%)
- Distal: 24 (43%)
  (Polypoid; 18/24: 75%)
“Interval” Index Lesions

T/Colon: 12 mm, IIa+IIc (LST-NG)

During the 2\textsuperscript{nd} colonoscopy, we detected many flat lesions

\% NP-CRN\textsl{s}/ All Index Lesions
25/56 (45%)
Proximal: 19/32 (59%)
Distal: 6/24 (25%)

T/Colon: 12 mm, IIa (LST-NG)
## Risk Factors of the Interval Index Lesions - Univariate Analysis -

<table>
<thead>
<tr>
<th></th>
<th>IL (+) (n=54)</th>
<th>IL (-) (N=1987)</th>
<th>Risk Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Gender (Male/ Female)</td>
<td>41/13</td>
<td>1206/781</td>
<td>1.25 (1.07-1.46)</td>
</tr>
<tr>
<td>Age (≥ 60/&lt; 60)</td>
<td>31/23</td>
<td>874/1113</td>
<td>1.31 (1.03-1.65)</td>
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<tr>
<td>CRC family history* (+/-)</td>
<td>5/49</td>
<td>279/1708</td>
<td>0.66 (0.28-1.53)</td>
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### 1st CS Findings

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<th>IL (+)</th>
<th>IL (-)</th>
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<tr>
<td>Bowel Preparation (Fair/ Good, Excellent)</td>
<td>1/53</td>
<td>100/1887</td>
<td>0.37 (0.05-2.59)</td>
</tr>
<tr>
<td>Index lesion (+/-)</td>
<td>21/33</td>
<td>483/1504</td>
<td>1.60 (1.14-2.26)</td>
</tr>
<tr>
<td>Polyp size** (≥ 6mm/≤ 5mm)</td>
<td>34/20</td>
<td>872/1115</td>
<td>1.43 (1.16-1.77)</td>
</tr>
<tr>
<td>No. of polyp** (≥ 3/1-2/0)</td>
<td>24/19/11</td>
<td>469/871/647</td>
<td>1.88 (1.38-2.56)🗀</td>
</tr>
</tbody>
</table>

* First Degree Relative  ** Maximum size/ Number of adenoma during the 1st TCS
🗀 Polyp number (≥ 3 vs 1-2/0)
# Risk Factors of the Interval Index Lesions

- **Multivariate Analysis** -

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<td>Gender (Male/ Female)</td>
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<td>1.68 (0.90-3.12)</td>
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<td>Age (≥ 60/&lt; 60)</td>
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<td>1.55 (0.90-2.68)</td>
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<tr>
<td>CRC family history* (+/-)</td>
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<td>279/1708</td>
<td>0.64 (0.26-1.59)</td>
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<td>1st CS Findings</td>
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<td>Bowel Preparation (Fair/ Good, Excellent)</td>
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<tr>
<td>Index lesion (+/-)</td>
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<td>483/1504</td>
<td>1.21 (0.63-2.30)</td>
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<tr>
<td>Polyp size** (≥ 6mm/≤ 5mm)</td>
<td>34/20</td>
<td>872/1115</td>
<td>1.40 (0.69-2.84)</td>
</tr>
<tr>
<td>No. of polyp** (≥ 3/ 1-2/ 0)</td>
<td>24/19/11</td>
<td>469/871/647</td>
<td>1.73 (0.96-3.13)†</td>
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* First Degree Relative  ** Maximum size / Number of adenoma during the 1st TCS
† Polyp number (≥ 3 vs 1-2/ 0)
Conclusion

Uncertain Issues

1. Relationship between serrated lesions (SSA/P) and interval CRCs
2. Objective measurements of “high-quality colonoscopy” ... ADR? FDR? SDR?
3. Endoscopist training; how to train young endoscopists?
Thank you for your kind attention