Endoscopic Approaches to Reduce the Incidence of Interval Colon Cancer

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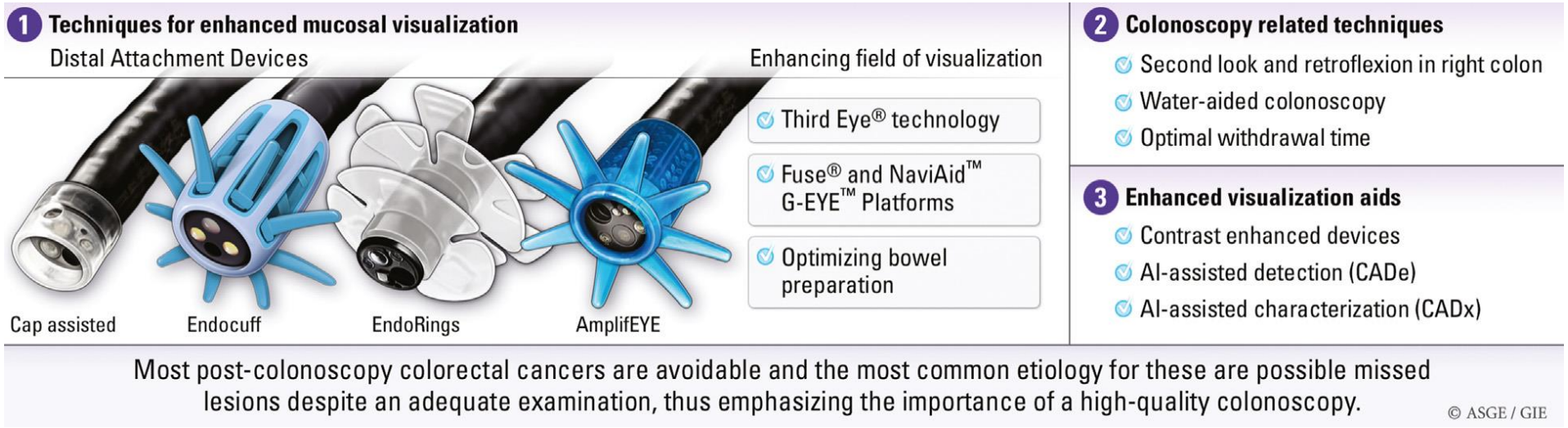

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Background and Definition

Why PCCRC matters

Background

Colorectal cancer remains the 3rd most commonly diagnosed cancer in males and the 2nd in females worldwide. By 2040, the global burden is projected to reach 3.2 million new cases and 1.6 million deaths.

Colonoscopy prevents CRC by detecting early-stage cancer and removing premalignant polyps.

Definition

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

WEO recommends the broader term **PCCRC (post-colonoscopy colorectal cancer)**.
PCCRC includes interval cancers and non-interval cancers.

WEO classification

- **Interval cancer**: detected before the next recommended screening/surveillance exam
- **Non-interval cancer**: detected at or after the recommended interval, or when no repeat interval was recommended, up to 10 years after colonoscopy

PCCRC: Epidemiology and Etiology

Key Data

Dutch FIT-based screening program: **3-year PCCRC rate 2.7%**; **53.5%** were **interval CRCs**.

Most common etiology for interval PCCRC: **possible missed lesion** despite an adequate examination (**73.6%**).

Systematic review/meta-analysis: **pooled prevalence of interval CRC 3.7%** (95% CI, 2.8%–4.9%).

Interval CRCs were **2.4 times** more likely to arise in the **proximal colon** than in the distal colon.

Associated patient factors: older age, higher comorbidity burden, and diverticular disease.

Association Between Colonoscopy Quality Metrics and PCCRC

Quality Metrics

ADR (Adenoma detection rate) is the most established surrogate marker of meticulous colon examination.

Higher ADR is associated with lower risk of PCCRC, advanced-stage interval cancer, and fatal interval cancer.

A single target ADR that guarantees lower PCCRC has not been established.

APC (Adenomas per colocoscopy) may better stratify high detectors from low detectors and may be inversely related to PCCRC risk.

Higher **proximal serrated polyp detection rate** is associated with lower PCCRC mortality.

Modifiable risk factors

Incomplete colonoscopy

Low polypectomy rate

Low annual colonoscopy volume

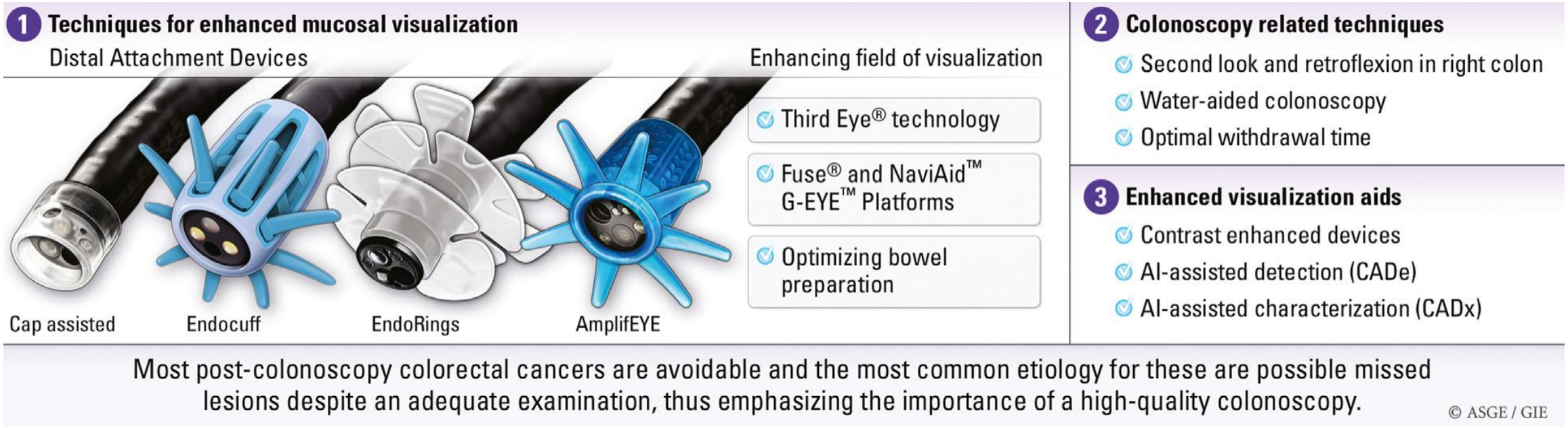
Incomplete resection, especially for lesions >10 mm

Missed lesions, particularly in the right colon

Failure to adhere to appropriate surveillance intervals

Graphical Abstract

Roadmap of the review article



Techniques for Enhanced Mucosal Visualization (1)

Distal attachment devices

Lesions behind flexures, haustral folds, and tight angulations may be missed on forward view.

Distal attachments: Transparent cap, Reveal Cap, AmplifEYE, EndoCuff, EndoCuff Vision, EndoRings, G-Eye

Field-of-view expansion: Third Eye Retroscope / Panoramic, FUSE, extrawide-angle-view colonoscope, NaviAid G-EYE

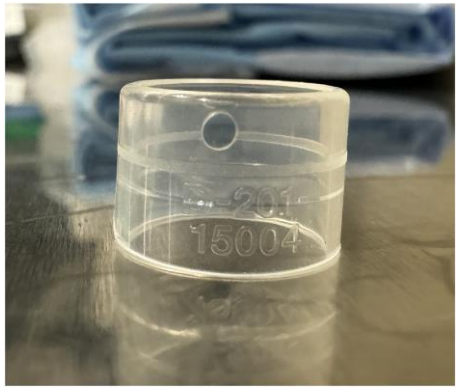


Figure 1. Distal attachment cap

Figure 2. EndoCuff Vision

Distal Attachment Devices (1)

Transparent cap and EndoCuff / EndoCuff Vision

Transparent cap

Presses and hooks colonic folds, exposes proximal fold surfaces, and helps reveal blind spots.

Prospective studies suggested improved small-polyp detection without longer cecal intubation time or total procedure time.

Tandem RCT: all-adenoma miss rate was lower with cap-fitted colonoscopy: 21% vs 33%, P = .04.

Large multicenter RCT in 1,203 patients: HD-WL vs EndoCuff Vision vs Reveal Cap.
ADR: **57.3% vs 59.1% vs 55.7% (P = .6)**; APC: 1.4±1.9 vs 1.6±2.4 vs 1.4±2.0 (P = .3).
No significant differences in advanced adenoma detection, sessile serrated lesions, or right-colon ADR.

EndoCuff / EndoCuff Vision

Initial studies showed improved ADR, but later larger RCTs were mixed.

12-RCT cumulative analysis (8,638 patients): ECV did not significantly improve ADR vs HD colonoscopy, RR 1.12 (95% CI 0.99–1.27).

Greater benefit was reported in **endoscopists with ADR <30%**, with ADR improvement around 9.4%.

- Mucosal abrasions and patient discomfort were reported.
- Passage through the sigmoid colon may be difficult in severe angulation, low-BMI females, or diverticular disease.

distal attachment cap (Figure 1) and EndoCuff Vision (Figure 2)

Distal Attachment Devices (2)

AmplifEYE and EndoRings

AmplifEYE

Similar to EndoCuff Vision, with a single row of fingers that are 1 mm longer.

Pilot RCT: ADR was not statistically significant: 47.1% vs 40.9%, P = .253.
However, **PDR** was higher: 68.2% vs 54.3%, P = .009.
Serrated polyp detection rate was higher: 37.6% vs 20.1%, P < .001.

Noninferiority RCT found AmplifEYE noninferior to ECV for adenoma detection.

EndoRings

A silicone-rubber device consisting of 2 layers of flexible circular rings.

Initial tandem RCT showed a **33% reduction** in **adenoma miss rate**.

Later trials did not reproduce a clear ADR advantage.

ADR RR 1.10 (95% CI 0.95–1.28)
Advanced adenoma detection RR 1.16 (95% CI 0.88–1.51)

Adenomas per patient: 1.9±1.3 vs 2.1±1.5;
Advanced adenomas per patient: 1.0±1.2 vs 1.0±1.2

Enhancing the Field of Visualization (1)

Third Eye Retroscope and Third Eye Panoramic

Third Eye Retroscope

Auxiliary through-the-scope retrograde imaging device designed to detect lesions on proximal folds and flexures.

A miniaturized camera at the tip provides a continuous retrograde image during withdrawal.

Ex vivo and small clinical studies **improved detection of simulated polyps**; later trials reported **increased polyp and adenoma detection**.

Withdrawal time and total procedure time may increase.

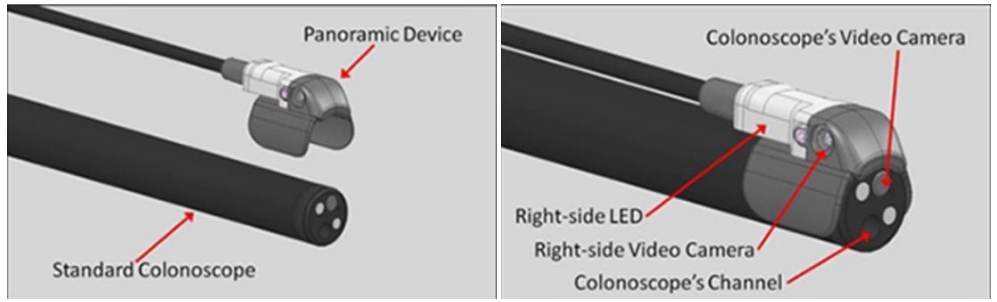
Third Eye® Retroscope®. Source: Gralnek IM. *Digestive Endoscopy*. 2015;27:223–231.

Third Eye Panoramic

Introduced to address learning curve and disposable-cost issues.

Initial data: **overall ADR 44%**, mean withdrawal time 10.15±5.56 min, mean total procedure time 20.31±5.14 min.

Because of long procedure times and practical limitations, the device has fallen out of favor in clinical practice.



Rubin M et al. *World J Gastroenterol*. 2015;21:10683–10687.

Enhancing the Field of Visualization (2)

FUSE, extrawide-angle-view colonoscope, and NaviAid G-EYE

FUSE / extrawide-angle

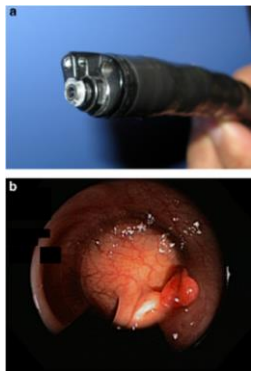
Developed to expand the visual field and lower AMR.
Initial **FUSE** studies were favorable.

In a large randomized trial among high-level detectors with a baseline screening ADR of about 40%, forward-viewing HD instruments outperformed FUSE.

For high-performing endoscopists, image resolution may trump angle of view.

The **extrawide-angle-view colonoscope** also failed to show an incremental increase in ADR over standard colonoscopy.

Dik VK, et al. *World J Gastroenterol*. 2014;20:2200–2211.



Moriyama, T., Uraoka, T., Esaki, M. and Matsumoto, T. (2015), Recent advances in colonoscopy. Digestive Endoscopy, 27: 40-44.

NaviAid G-EYE

Among the field-expansion platforms, NaviAid G-EYE is presented more favorably in the review.

It **increased ADR**, **lowered AMR**, and showed comparable time to cecum and cecal intubation rates compared with standard colonoscopy.

Gralnek IM. *Emerging technological advancements in colonoscopy*. **Digestive Endoscopy.** 2015;27:223–231.

Enhancing the Field of Visualization (3)

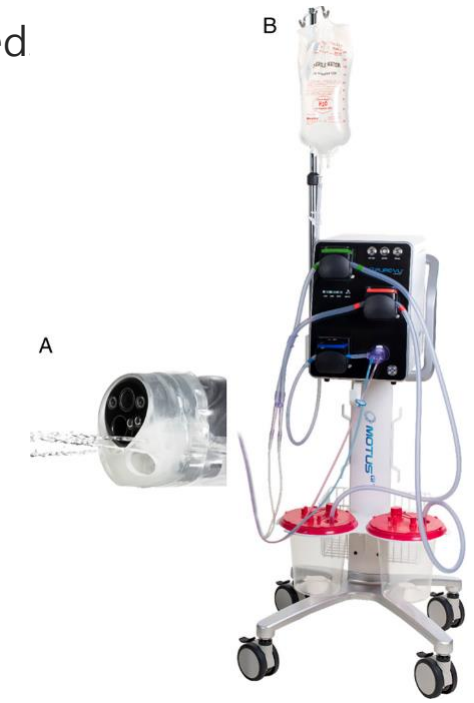
Optimizing bowel preparation

Bowel preparation

Inadequate bowel preparation occurs in **up to 20%** of colonoscopies and **lowers detection** while **increasing miss rates**.

Guidelines recommend **split-dose preparation**: the remainder should be taken **4–6 hours before colonoscopy**.
Multimedia-based patient education improves bowel preparation adequacy and ADR.
A low-residue diet or **full liquids** until the evening before colonoscopy is recommended.

The intraprocedural **Pure-Vu EVS system** is promising, but real-world data are still needed



Source: Motus GI Holdings, Inc. Pure-Vu® EVS System.

Colonoscopy-Related Techniques (1)

Second look and retroflexion in the right colon

Rationale

Standard colonoscopy provides limited protection from **right-sided colon cancers**.

Differences in tumor biology and the morphology of proximal lesions are contributing factors.

Many experts advocate a second examination of the right colon: either a **second forward view** or **retroflexion**.

Evidence

Both **proximal retroflexion** and **second-look examination** have been associated with higher ADR and lower AMR.

Meta-analysis of 3,901 patients: **second forward view** improved **right-colon ADR** (RR 1.39; 95% CI, 1.22–1.58).
Right-colon PDR also improved (RR 1.47; 95% CI, 1.30–1.65).

No significant difference in additional ADR between second forward view and retroflexion.

Colonoscopy-Related Techniques (2)

Water-aided colonoscopy

Techniques

Water immersion: water is infused during insertion; residual water is mainly removed during withdrawal.

Water exchange: gasless insertion in clear water, minimizing distension and maximizing cleanliness during insertion.

Key trial findings

Compared with air insufflation, **water exchange** improved **overall ADR**: 49.3% vs 40.4% (P = .03).

Right-colon ADR improved: 24.0% vs 16.9% (P = .04).

Right-colon advanced ADR improved: 6.1% vs 2.5% (P = .03).

Mean adenomas per procedure and cleanliness scores were also higher.

- However, most data come from a limited number of centers, and many experts consider routine use inefficient.
- Water-based insertion may also improve patient comfort in unsedated or minimally sedated procedures.

Colonoscopy-Related Techniques (3)

Withdrawal time

Withdrawal time correlates with **ADR**.

Accumulating evidence suggests that **longer withdrawal time**, especially **≥9 minutes**, improves overall yield.

Benefits include **higher ADR**, **better advanced adenoma detection**, **higher sessile serrated lesion detection**, and **reduced PCCRC incidence**.

- USMSTF: mean withdrawal time 6–10 minutes
- ACG-ASGE (earlier): at least 6 minutes
- ACG-ASGE Task Force (2024): **average withdrawal time 8 minutes** in normal colonoscopies included in the calculation

Enhanced Visualization and Characterization Aids (1)

Contrast-enhanced devices

Devices discussed

Linked color imaging (LCI; Fujifilm)

New-generation narrow-band imaging (NBI; Olympus)

I-scan (Pentax)

Texture and color enhancement imaging (TXI; Olympus)

Main findings

Compared with high-definition standard colonoscopy, these technologies have been reported to **increase APC and ADR**.

Recent RCTs showed **TXI increased ADR and APC**, including better detection of polyps <10 mm, proximal and distal lesions, and flat/right-sided polyps.

LCI may improve detection of proximal colon lesions and sessile serrated lesions.

Most evidence comes from controlled settings; real-world data are still emerging.

Enhanced Visualization and Characterization Aids (2)

AI-assisted detection (CADe)

Potential advantages

CADe may minimize the probability of missing a polyp during colonoscopy.

Randomized studies showed **higher ADR** than standard colonoscopy, with some increase in withdrawal time.

Network meta-analysis suggested CADe **outperformed** several other interventions for **ADR improvement**.

Multiple tandem trials showed **reduced AMR** and modest **improvement in ADR and APC**.

Limitations emphasized in the review

Real-world studies have not consistently reproduced the trial benefits.

No clear increase in advanced adenoma detection. 25.8% vs 24.0% (P = .464).

More unnecessary removal of non-neoplastic polyps.

False-positive signals, distraction, and perceived prolonged procedure time.

Supportive evidence that CADe decreases PCCRC is currently lacking.

Enhanced Visualization and Characterization Aids (3)

AI-assisted characterization (CADx)

Potential advantages

CADx helps **optical characterization of colorectal polyps** and may support "**resect-and-discard**" or "**leave-in-situ**" strategies.

ASGE recommends **at least 90% negative predictive value** for optical diagnosis of rectosigmoid neoplastic polyps ≤5 mm.

Limitations emphasized in the review

A cumulative analysis of >3,500 patients found **no additional benefit or harm** for management of diminutive rectosigmoid polyps.

Another prospective trial found **no clinically relevant difference** when commercially available CADx systems were used.

AI platforms for colonoscopy	
Computer-aided detection [CADe] systems	**Manufacturer**
GI Genius	Medtronic (Minneapolis, Minn, USA)
EndoScreener	Shanghai Wision AI Co, Ltd (Shanghai, China)
DISCOVERY	Pentax Medical (Tokyo, Japan)
Endo-AID	Olympus Medical Systems (Tokyo, Japan)
CADEYE	Fujifilm (Tokyo, Japan)
Endoangel	Wuhan Medical Technology Co Ltd (Wuhan, China)
EndoBRAIN-EYE	Cybernet Systems Corp (Tokyo, Japan)
SKOUT	Iterative Scopes (Cambridge, Mass, USA)
MAGENTIQ-COLO	Magentiq Eye (Haifa, Israel)
Eagle Eye, v. 5.1	Xiamen Innovision (Xiamen, China)
WISE VISION	NEC Co. (Tokyo, Japan)
Computer-aided diagnosis [CADx] Systems	
GI Genius Intelligent Endoscopy Module (version 3.0.0)	Medtronic
EndoBRAIN/EndoBRAIN-PLUS/EndoBRAIN-UC	Cybernet Systems Corp (Tokyo, Japan)
CADEYE	Fujifilm (Tokyo, Japan)

Table 2. AI platforms for screening colonoscopy

Summary Table from the Review

Table 1. Summary of strategies to reduce incidence of PCCRC

	Key considerations
Techniques for enhanced mucosal visualization	
Distal attachment devices	• Increase in adenoma detection • Reduced insertion times and withdrawal times • Higher sessile serrated lesion detection rates
Transparent Cap (Olympus, Tokyo, Japan)	
Reveal Cap (US Endoscopy, Mentor, Ohio, USA)	
AmplifEYE (Medivators Inc, Minneapolis, Minn, USA)	
EndoCuff (Arc Medical, Leeds, United Kingdom)	
EndoCuff Vision (Olympus, Center Valley, PA, USA)	
EndoRing (EndoAid Ltd, Caesarea, Israel)	
G-Eye (SMART Medical Systems Ltd, Ra'anana, Israel)	
Enhancing field of visualization	• Increase in adenoma detection • Longer withdrawal times • Longer total procedure times • Need for separate processors and instruments • No longer commercially available
Third Eye Retroscope (TER; Avantis Medical Systems, Sunnyvale, Calif, USA)*	
Third Eye Panoramic (TEP; Avantis Medical Systems)*	
Fuse (EndoChoice Inc, Alpharetta, Ga, USA)	
Extrawide-angle-view colonoscope (Olympus, Tokyo, Japan)*	
NaviAid G-EYE System (SMART Medical Systems Ltd)	
Optimizing bowel preparation	• Increase in adenoma detection • Real-world clinical studies lacking
Split-dose bowel preparation	
Precolonoscopy patient education	
Intraprocedural bowel cleansing system: Pure-Vu EVS System (Motus GI, Israel)†	
Colonoscopy-related techniques	• Water exchange increases insertion time, but the withdrawal time is same as other techniques • Increase in adenoma detection • Decrease in adenoma miss rate
Second look and retroflexion in the right side of the colon	
Water-aided colonoscopy	
Withdrawal time	
Enhanced visualization and characterization aids	• Increase in adenoma detection rate and adenomas per colonoscopy • Data primarily from controlled studies
Contrast-enhanced devices	
Linked color imaging (LCI, Fujifilm)	
New-generation narrow-band imaging (NBI, Olympus)	
I-scan (Pentax)	
Color enhancement imaging (TXI, Olympus)	
Artificial intelligence (AI)	• Multiple platforms available • Emerging data • Cost-effectiveness • Ongoing research on detection of polyps with confirmation of clinically relevant histopathology
AI-assisted detection (CADe)	
AI-assisted characterization (CADx)	

PCCRC, Postcolonoscopy colorectal cancer.
*Devices/platforms no longer commercially available.

Conclusion and Future Directions

Most PCCRCs are **avoidable** and are likely due to **missed lesions during an otherwise adequate examination.**

Nearly **40% of PCCRCs** were classified as likely new cancers and missed lesions in a large U.S. population-based setting.

Optimization of colonoscopy techniques, with or without adjunctive methods, remains paramount to **increase ADR** and **reduce adenoma and polyp miss rates**.

AI and image-enhancement platforms are rapidly evolving, but long-term real-world outcome data are still needed.

Quality metrics, **operator experience**, and **training** must go hand in hand with **technological advancement** to reduce PCCRC worldwide.