YOUNG ONSET RECTAL CANCER…. MANAGEMENT CONSIDERATIONS

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INTRODUCTION AND DEFINITIONS

- Colorectal cancer (CRC) is the third most common cancer worldwide and the second most common cause of cancer death, accounting for an estimated 1.8 million new cancer diagnoses and >880,000 deaths in 2018.

Malvezzi, M. et al. European cancer mortality predictions for the year 2018 with focus on colorectal cancer. *Ann. Oncol.* **29**, 1016–1022 (2018).

INTRODUCTION AND DEFINITIONS

- While CRC incidence has stabilized in high-income countries in individuals ≥50 years of age, it has increased rapidly in individuals <50 years of age, which has been defined as **young-onset CRC (YO-CRC)**

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Akimoto, N. et al. Rising incidence of early-onset colorectal cancer – a call to action. *Nat. Rev. Clin. Oncol.* **18**, 230–243 (2021).

INTRODUCTION AND DEFINITIONS

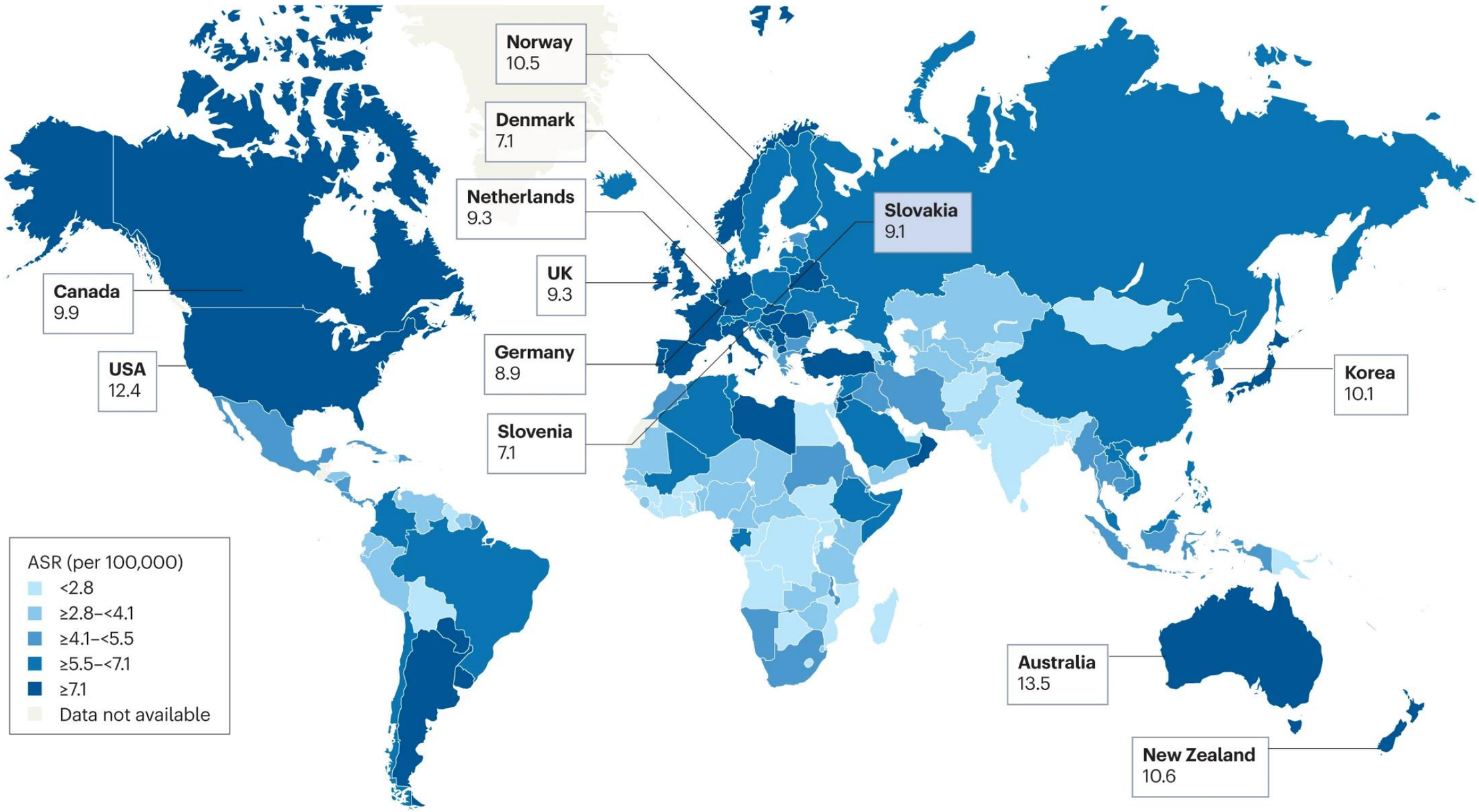
- The threshold of 50 years of age for the definition of young-onset could be reconsidered. For example, in a study from Europe the largest increase in YO-CRC incidence rate was observed within the age group 20–39 years[..]

- However, majority of YO-CRC studies utilize that age threshold of 50 years as the inflexion point for the age-dependent change in CRC incidence and also the age at which most countries initiate CRC screening for the average-risk population.

Vuik, F. E. et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. *Gut* **68**, 1820–1826 (2019)

AGE-STANDARDIZED INCIDENCE RATE (ASR) OF YOUNG-ONSET COLORECTAL CANCER (YO-CRC; AGE 20–49 YEARS) IN BOTH SEXES WORLDWIDE FOR THE YEAR 2020.

SIEGEL, R. L. ET AL. GLOBAL PATTERNS AND TRENDS IN COLORECTAL CANCER INCIDENCE IN YOUNG ADULTS. *GUT* **68**, 2179–2185 (2019).



EPIDEMIOLOGY AND RISK FACTORS

- The 2 main mechanisms of the YO-CRC are either sporadic cases or genetic predisposition,
- Sporadic cases have increased as part of the general increase of the incidence of CRC in general which has many risk factors.

O'Connell, J. B. et al. Rates of colon and rectal cancers are increasing in young adults. *Am. Surg.* **69**, 866–872 (2003).

EPIDEMIOLOGY AND RISK FACTORS

- **Risk factors include:**

1- Sex:

There are notable differences in the risk of YO-CRC between men and women. SEER-based studies covering the period 2004–2015 showed an increased mortality risk for YO-CRC among men compared with women (OR 1.09, 95% CI 1.08–1.11). Studies of US-based electronic health records reached similar conclusions, with men more likely than women to develop YO-CRC (OR 1.44, 95% CI 1.11–1.87).

McClelland, P. H., Liu, T. & Ozuner, G. Early-onset colorectal cancer in patients under 50 years of age: demographics, disease characteristics, and survival. *Clin. Colorectal Cancer* **21**, e135–e144 (2022).

Gausman, V. et al. Risk factors associated with early-onset colorectal cancer. *Clin. Gastroenterol. Hepatol.* **18**, 2752–2759.e2 (2020).

EPIDEMIOLOGY AND RISK FACTORS

2- Lifestyle and diet:

Consumption of ultra-processed, high-fat foods — such as fast food — are associated with a tenfold increased risk of developing CRC, and high-fat diets increase the risk of YO-CRC by almost twofold (OR 1.98, 95% CI 1.13–3.49.

3- Obesity and diabetes:

Also, Obesity, type 2 DM and sedentary life-style were found to increase the risk of YO-CRC.

Carroll, K. L., Fruge, A. D., Heslin, M. J., Lipke, E. A. & Greene, M. W. Diet as a risk factor for early-onset colorectal adenoma and carcinoma: a systematic review. *Front. Nutr.* **9**, 896330 (2022).

EPIDEMIOLOGY AND RISK FACTORS

- **Genetic risk factors**

An inherited component is thought to be present in up to 30% of all patients with CRC, mainly owing to a first-degree relative with CRC, whereas a germline mutation is present in around 5% of all patients with CRC , However this incidence increase to 20% of patients with YO-CRC.

Patel, S. G., Karlitz, J. J., Yen, T., Lieu, C. H. & Boland, C. R. The rising tide of early-onset colorectal cancer: a comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection. *Lancet Gastroenterol. Hepatol.* **7**, 262–274 (2022)

EPIDEMIOLOGY AND RISK FACTORS

- Germline mutations which are associated with YO-CRC include 2 main diseases:

a) Hereditary nonpolyposis colorectal cancer (HNPCC) …… Lynch syndrome.

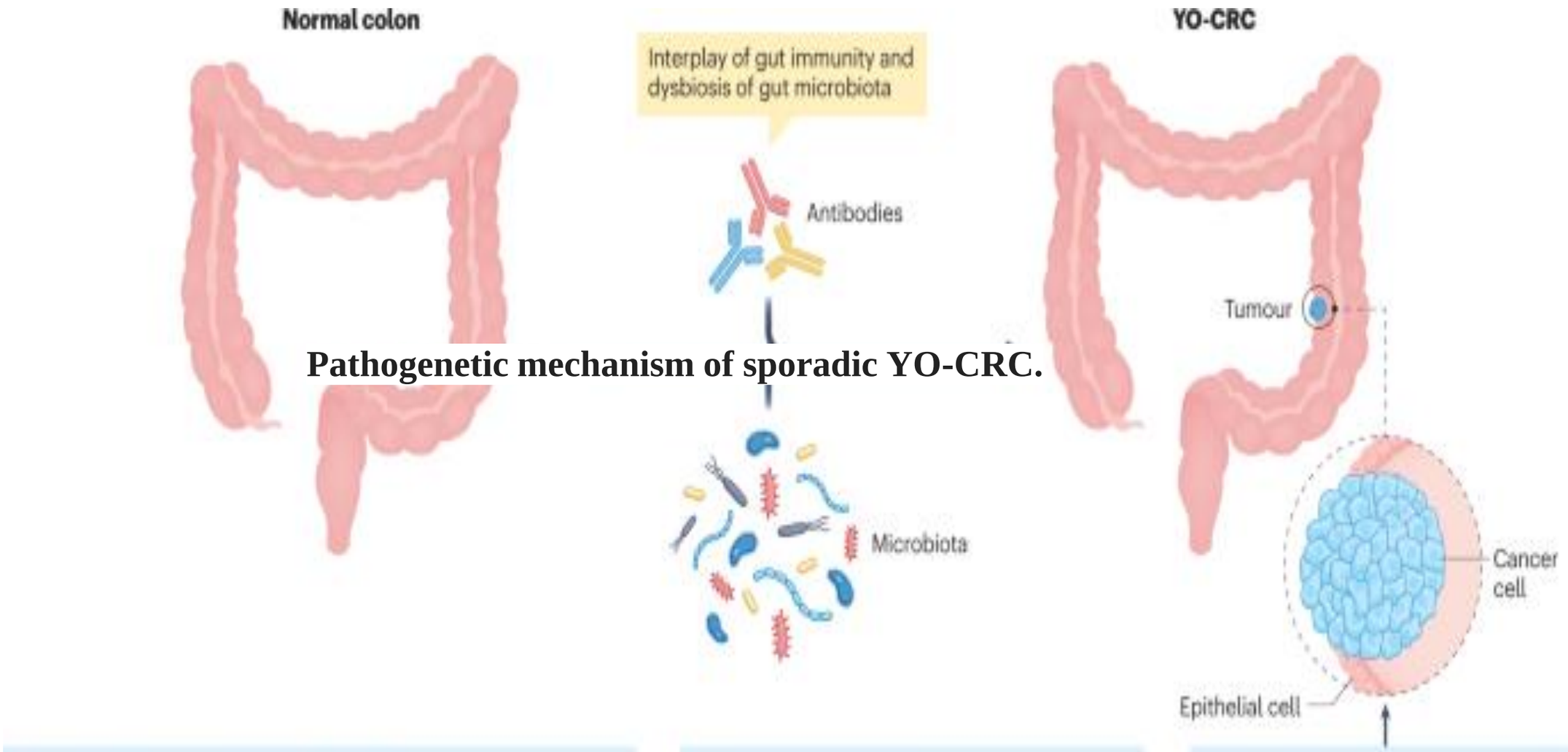
b) Polyposis colorectal cancer such as Familial adenomatous polyposis (FAP) and MUTYH-associated polyposis (MAP).

MECHANISM AND PATHOPHYSIOLOGY

Sporadic YO-CRC

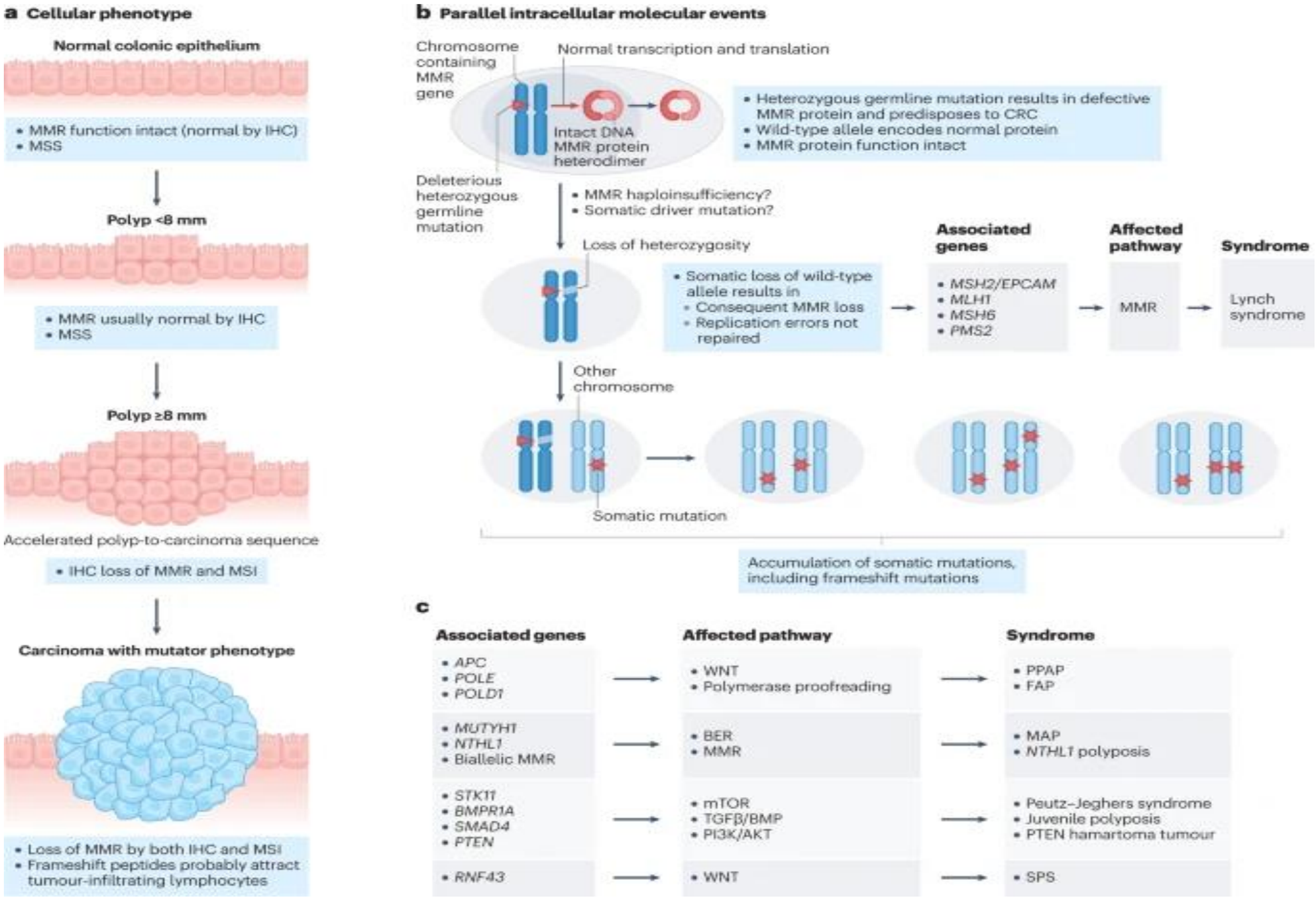
- Risk factors during the life-course that may be involved in the development of young-onset colorectal cancer (YO-CRC), including environmental exposures, medication use and diet. All of these factors influence the gut microbiota, creating a susceptible environment for CRC by inducing inflammation, suppressing immunity and promoting tumour growth.

PATHOGENETIC MECHANISM OF SPORADIC YO-CRC.



Pathogenetic mechanism of sporadic YO-CRC.

PATHOGENETIC MECHANISMS IN HEREDITARY YO-CRC.



DIAGNOSIS

- The lack of screening in younger patients, more aggressive tumor features, and patients and clinicians ignoring or misinterpreting symptoms lead to a higher percentage (85%) of patients with YO-CRC presenting symptomatically at diagnosis and, therefore, with later stage cancers than among patients with CRC overall (50%), of which many cases are detected by screening.

- The most common presenting symptoms in YO-CRC are abdominal pain (46%) and rectal bleeding (47%), while weight loss is the least common symptom (8%). Other common symptoms at diagnosis include abdominal distension, change in bowel habits and fatigue.

Willauer, A. N. et al. Clinical and molecular characterization of early-onset colorectal cancer. *Cancer* **125**, 2002–2010 (2019).

Vajravelu, R. K., Mehta, S. J. & Lewis, J. D., Early-age Onset Colorectal Cancer Testing, Epidemiology, Diagnosis, and Symptoms Study Group. Understanding characteristics of who undergoes testing is crucial for the development of diagnostic strategies to identify individuals at risk for early-age onset colorectal cancer. *Gastroenterology* **160**, 993–998 (2021)

DIAGNOSIS

- If a patient presents with CRC-related symptoms, a colonoscopy with biopsy of the malignant tumor is indicated, except when an endoscopically respectable tumor is expected during colonoscopy, in which case the biopsy should be omitted because it might hinder radical removal of the malignant tumor.

- Other radiological investigations (such as MRI rectum, PET CT for metastatic work up) and laboratory investigations (such as routine blood tests and tumor markers) should be same as CRC.

Di Leo, M. et al. Risk factors and clinical characteristics of early-onset colorectal cancer vs. late-onset colorectal cancer: a case-case study. *Eur. J. Gastroenterol. Hepatol.* **33**, 1153–1160 (2021).

SCREENING

- There is a strong evidence that screening reduces the incidence and mortality of CRC. Screening may be **non-imaging screening (that is, stool-based),** predominantly performed by immunochemical testing for occult blood in the feces, as well as **imaging-based screening, predominantly performed by endoscopy**. CRC screening has been implemented in many countries, with most organized population screening programs focusing on individuals 50–75 years of age.

- However, most screening programs usually misses the YO-CRC which is -by definition- developing of CRC before the age of 50, hence the importance of early and personalized screening in certain families.

Kuipers, E. J. et al. Colorectal cancer. *Nat. Rev. Dis. Primers* **1**, 15065 (2015).

World Health Organization. *Colorectal Cancer Screening*. *IARC Handbooks of Cancer Prevention* Vol. 17 (IARC, 2019).

SCREENING (LYNCH)

Amsterdam Minimum Criteria (1990)

1. At least 3 cases of colorectal cancer in relatives (verified pathologically)
2. One is a first degree relative of the other two
3. At least two successive generations should be affected
4. One case of colorectal cancer diagnosed before the age of 50 years old
5. FAP should be excluded

Revised Amsterdam Criteria II (1998)

1. At least 3 relatives with an HNPCC-associated cancer (cancer of the colorectum, endometrium, small bowel, ureter or renal pelvis)

2-5. As for the minimum criteria

SCREENING (FAP)

Surveillance in patients with classic FAP

- The cumulative risk of CRC development in patients with classic FAP can approach **100%.** The standard of care for classic FAP includes **endoscopic screening combined with prophylactic surgery when the polyp burden is no longer endoscopically manageable**. Diagnosis of CRC before the age of 20 years is unusual, so colonoscopic screening is generally recommended **every 1 to 2 years beginning at age 10–12 years**.. After colectomy, annual surveillance by flexible sigmoidoscopy of the remaining rectal mucosa or ileal pouch is recommended every 6–12 months.

Barrow, P., Khan, M., Lalloo, F., Evans, D. G. & Hill, J. Systematic review of the impact of registration and screening on colorectal cancer incidence and mortality in familial adenomatous polyposis and Lynch syndrome. *Br. J. Surg.* **100**, 1719–1731 (2013).

SCREENING (AFAP, MAP)

- In AFAP, the development of adenoma and CRC is **delayed by 10–20 years compared with classic FAP**. For patients with AFAP or MAP, CRC screening follows the same principle as for classic FAP: as a more proximal colonic polyp distribution can be present, colonoscopy every 1–2 years from the age of 18 years to the mid-20s is the CRC screening approach. Prophylactic surgery is indicated when the polyp burden becomes no longer endoscopically manageable.

Burt, R. W. et al. Genetic testing and phenotype in a large kindred with attenuated familial adenomatous polyposis. *Gastroenterology* **127**, 444–451 (2004).

SCREENING

- **Cascade testing**

The discovery of a pathogenic variant in an affected proband provides an opportunity for at-risk relatives to pursue genetic testing, known as cascade testing, which can lead to personalized cancer risk management and risk reduction.

PREVENTION.

- In a third to a half of all patients, CRC, including YO-CRC, is attributable to modifiable risk factors, such as obesity, smoking, lack of physical exercise, and an unhealthy diet, which can be addressed through primary prevention measures. Emerging evidence shows that adherence to a **Mediterranean diet** and its related micronutrients, **long-term aspirin use**, and **physical exercise** are inversely associated with CRC risk.

LoConte, N. K. et al. Lifestyle modifications and policy implications for primary and secondary cancer prevention: diet, exercise, sun safety, and alcohol reduction. *Am. Soc. Clin. Oncol. Educ. Book.* **38**, 88–100 (2018)

Farinetti, A., Zurlo, V., Manenti, A., Coppi, F. & Mattioli, A. V. Mediterranean diet and colorectal cancer: a systematic review. *Nutrition* **43-44**, 83–88 (2017)/Cao, Y. et al. Population-wide impact of long-term use of aspirin and the risk for cancer. *JAMA Oncol.* **2**, 762–769 (2016)./Oruc, Z. & Kaplan, M. A. Effect of exercise on colorectal cancer prevention and treatment. *World J. Gastrointest. Oncol.* **11**, 348–366 (2019).

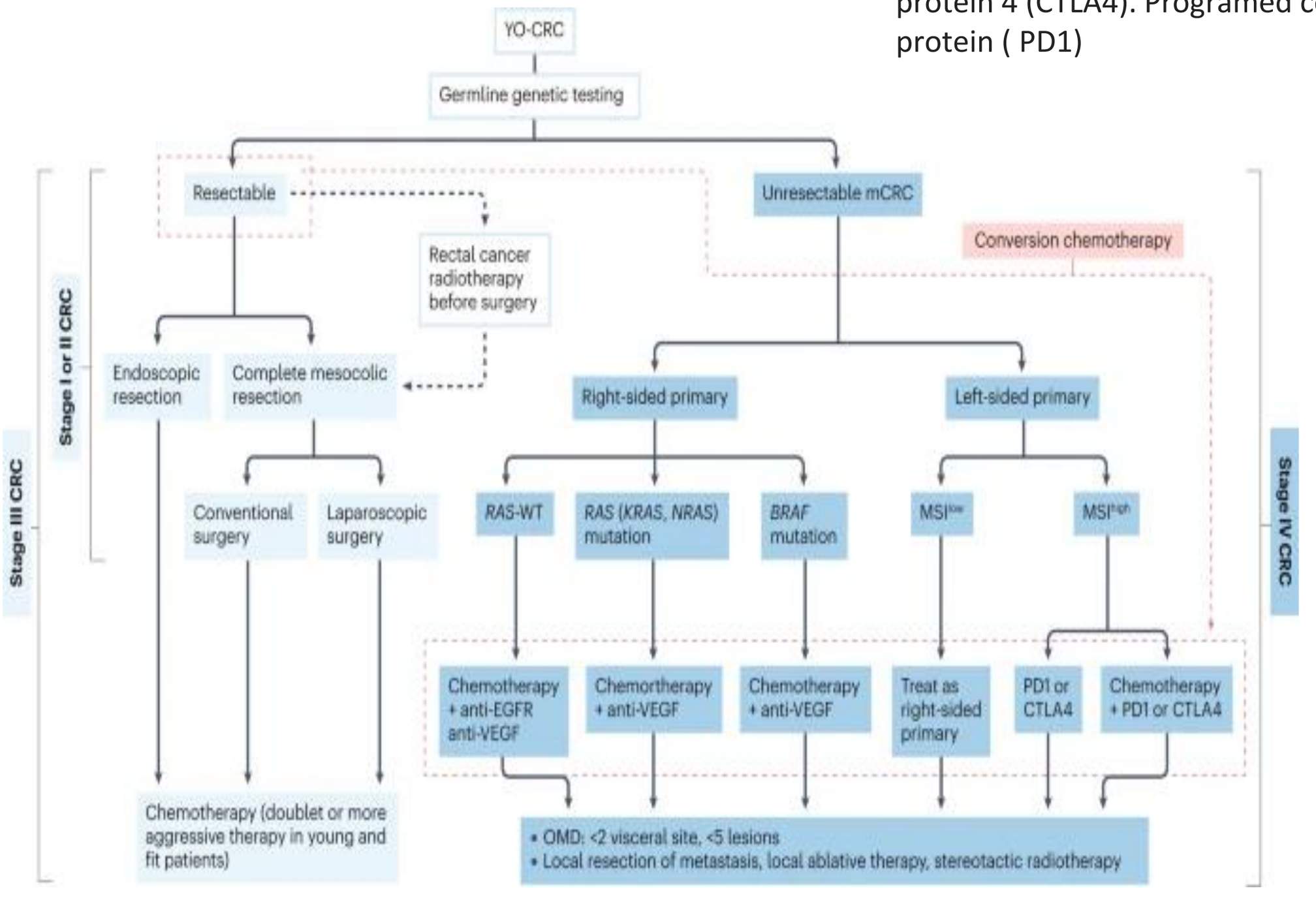
MANAGEMENT

- Treatment of young-onset colorectal cancer (YO-CRC) follows the same principles as for later-onset CRC, and the approach depends on whether the tumor is resectable and the stage and location of the primary tumor. Stages are defined by the TNM staging system. Surgical removal of tumors is followed by consolidation chemotherapy. Non-resectable tumors are treated with induction chemotherapy combined with immunotherapy.

Spaander, M.C.W., Zauber, A.G., Syngal, S. *et al.* Young-onset colorectal cancer. *Nat Rev Dis Primers* **9**, 21 (2023)

MANAGEMENT

Anti epidermal growth factor (anti EFGR). Anti vascular endothelial growth factor (anti VEGF), cytotoxic t lymphocyte associated protein 4 (CTLA4). Programed cell death protein (PD1)



MANAGEMENT

- Patients with YO-CRC tend to present with advanced-stage disease. Nevertheless, surgical treatment of YO-CRC **follows the same stage-appropriate oncological principles** as those for CRC in older patients, while often favoring minimally invasive approaches.

- For selected early-stage lesions with only mucosal invasion (Tis–T1), several advanced endoscopic resection techniques have gained popularity, with data demonstrating technical safety, earlier procedural recovery and short-term outcomes comparable to those after standard surgical resection. **Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD**) have become standard practice in the treatment of early-stage CRC.

Spaander, M.C.W., Zauber, A.G., Syngal, S. *et al.* Young-onset colorectal cancer. *Nat Rev Dis Primers* **9**, 21 (2023)

MANAGEMENT

Spaander, M.C.W., Zauber, A.G., Syngal, S. *et al.* Young-onset colorectal cancer. *Nat Rev Dis Primers* **9**, 21 (2023)

Approach	5-year survival (%)	Recurrence (%)	Mortality (%)	Complications (%)
Endoscopic resection	90–100	13.6–18.7 (5-year)	1.6–3.8 (5-year)	0–9
Laparoscopic resection	94.2	16 (3-year)	<1% (30-day)	19
Open colectomy	89.17	18 (3-year)	1 (30-day)	19
Total mesorectal excision	91.4	7.3 (5-year)	0.8 (30-day)	15–20

QUESTIONS??

THANK YOU