#WDHD2019

29 May 2019

World Digestive Health Day

WGO Handbook on

Early Diagnosis and Treatment of GI Cancer

edited by

Drs. Ernst Kuipers and Joseph Sung

Early Diagnosis and Treatment of GI Cancer

World Gastroenterology Organisation (WGO)

The WGO Foundation (WGOF)

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Message from the Chair, World Digestive Health Day 2019
Early Diagnosis and Treatment of GI Cancer

Dear Colleagues,

Globally, cancer is the second leading cause of death[1] with an estimated 18 million cancer cases around the world. Of those cases, 4 of the 7 top most common cancers are from the digestive system.[2] It is because of this world health burden that the World Gastroenterology Organisation and The WGO Foundation have selected the Early Diagnosis and Treatment of GI Cancer as the focus of the 2019 World Digestive Health Day campaign.

Modifying or avoiding key risk factors, early detection, screenings, and treatment can reduce the number of deaths caused by cancer.[1] By increasing awareness worldwide, and in particular among low- and middle-income countries where 70% of cancer deaths occur,[1] the WGO global network of WGO member societies, partners, and sponsors can raise the level awareness.

WGO will seek to raise awareness of the Early Diagnosis and Treatment of GI Cancer through its annual public advocacy and awareness campaign, World Digestive Health Day. WDHD is celebrated each year on 29th May with associated events, activities, and initiatives continuing throughout and beyond the campaign year. WDHD will provide gastroenterologists, hepatologist, their patients, and the lay public with an understanding of the latest basic and clinical research in the screening, diagnosis, and treatment of GI cancers. This campaign will endeavor to inform physicians, pharmacists, allied health professionals, healthcare payers, and the public of the prevalence, risk factors, and causes of GI cancer. Most especially, we want to ensure that we present an evidence-based and patient-centered approach to the diagnosis and treatment of GI cancer.

WGO's task is supported by a Steering Committee with a global perspective. The Steering Committee provides expertise on the Early Diagnosis and Treatment of GI Cancer, guides the course of the campaign, and develops educational and training materials. In collaboration with WGO Member Societies, WGO Training Centers and Regional Affiliate Associations, the Steering Committee defines this global initiative and provides the resources to sustain the effort throughout the year.

Through a multi-faceted campaign, WGO will provide simple messages for the general public in order to assist them in understanding how the modification and reduction of risk factors, early diagnosis, screening, and treatment of GI cancers affects one's life and health. Secondly, WGO will develop information for healthcare professionals with an emphasis on healthcare professionals in low-resource, developing regions. Multiple informational pieces are planned and will be distributed worldwide, for patients and healthcare professionals. Through the WDHD 2019 campaign WGO looks forward to providing a better understanding and recognition of the Early Diagnosis and Treatment of GI Cancer. Your participation, through educating the public about the diseases, encouraging participation in screening programs, and promoting healthy lifestyle, is crucial for the success of this campaign.

Sincerely,

Joseph Sung MD, PhD
The Chinese University of Hong Kong

References

1: *"Cancer." World Health Organization, 12 Sept. 2018, www.who.int/en/news-room/fact-sheets/detail/cancer.*

2: *"Worldwide Cancer Data." World Cancer Research Fund, 2018, www.wcrf.org/dietandcancer/cancer-trends/worldwide-cancer-data.*

World Digestive Health Day 2019 Steering Committee

World Digestive Health Day (WDHD) 2019 is led by the following individuals representing a global view and expertise. The Steering Committee guides the course of the WDHD campaign, leading in the development of tools and activities, including this WGO handbook on the early diagnosis and treatment of GI cancer.

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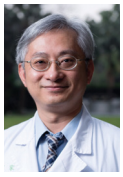

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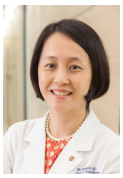

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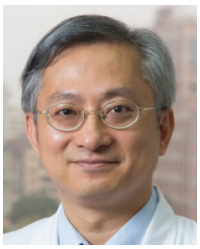
Meet Our World Digestive Health Day (WDHD) 2019 Partners

The World Gastroenterology Organisation (WGO) and the WGO Foundation (WGOF) acknowledge and thank the following WDHD 2019 partners for their contributions to the WDHD 2019 campaign, "*Early Diagnosis and Treatment of GI Cancer.*" WGO is extremely grateful for our partners' efforts to advocate, promote and raise awareness for Early Diagnosis and Treatment of GI Cancer worldwide.

Gastric Cancer Screening: Who, When, and How?



Yi-Chia Lee, MD, PhD
Professor of Internal Medicine, College of Medicine, National Taiwan University, and Graduate Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

Considerations of gastric cancer screening

Even though the incidence rate of gastric cancer is declining, it remains the fifth most frequently diagnosed cancer and the third leading cause of cancer death.[1] Gastric cancer, when diagnosed at the symptomatic stage, is associated with poor prognosis despite aggressive treatment and the only way to improve this is through early diagnosis which requires active screening. Gastric cancer screening involves morphological examination of the stomach and risk stratification. Upper endoscopy is the most reliable tool by which to reach both goals, which not only identifies subjects with early-stage neoplasms so that curative treatment can be begun, but theoretically also evaluates the severity of gastritis and quantifies the patient's future risk of gastric cancer. Nonetheless, endoscopic examination requires training, is costly and not completely safe. To utilize resources most efficiently, priorities must be set by considering which patients to screen, when is the best time to screen, and how to increase the diagnostic yield. Ultimately, screening involves examination of the stomach but because of the large population, there may be a role for non-invasive screening to choose. Also, screening must incorporate the treatment of *Helicobacter pylori* infection along with endoscopic examination, to maximize the benefit derived from both strategies.

Who to screen?

Patients with alarming symptoms, such as epigastric pain, dysphagia, body weight loss, anemia, abdominal mass, etc., undoubtedly are candidates for endoscopic examination. However, the purpose of screening is to detect a cancer before its associated symptoms appear (*i.e.*, early-stage gastric cancer); therefore, identification of the risk factors is the first priority to justify the necessity of screening for asymptomatic neoplasia. Risk factors for gastric cancer depend on whether it arises from the cardiac (the reader is referred to the separate section that addresses the Barrett's esophagus) or non-cardiac region. Our main target for screening is non-cardiac cancer, due to its much higher prevalence, especially in East Asia, Eastern Europe, and Central and South America. Risk factors of gastric cancer may include advanced age, male sex, smoking, *H. pylori* infection, dietary risk factors, such as high intake of salt (including salty and preserved foods) and lower intake of vegetables and fruit, and positive family history. Rare hereditary diseases are also associated with higher gastric cancer risk, such as familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, Peutz-Jeghers syndrome, and juvenile polyposis syndrome. Previous endoscopic observation or histological examination of the gastric mucosae can help clarify the individual risk for gastric cancer; for example, in patients with atrophic gastritis, intestinal metaplasia, mild-to-moderate dysplasia, and severe dysplasia at baseline, the subsequent risk of developing gastric cancer have been observed as 0.1%, 0.25%, 0.6%, and 6% per year, respectively.[2] The detection of hereditary genetic disorders is relatively complicated, which involves the responding to the young index cases and/or family aggregation of cancers,

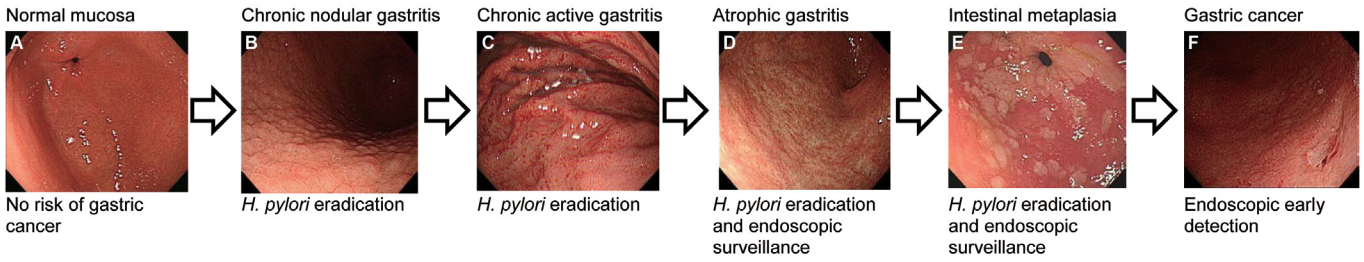


Figure 1. *The multistage progression of gastric cancer carcinogenesis and the strategy for screening or prevention. Gastric cancer does not arise from a normal mucosa (A). For the initial stages of chronic gastritis (B, C), inflammation can be effectively ameliorated by H. pylori eradication to reduce the risk of gastric cancer, while at the later stages of atrophic gastritis or intestinal metaplasia (D, E), irreversible damage on the molecular level may have occurred and endoscopic surveillance is needed to identify early-stage gastric cancer (F).*

and the identification of changes in gene loci potentially associated with gastric cancer.

When to screen?

Gastric cancer is an inflammation-related cancer and the incidence rate increases with the time of exposure to risk factors that triggers the intra-gastric inflammatory response from the host. Histologically, gastric cancer develops following a multistage process from chronic active gastritis to atrophic gastritis, metaplastic epithelia, intraepithelial neoplasia, and finally to invasive carcinoma (the so-called updated Correa cascade) (Figure 1). The carcinogenic process starts from a long latent period that typically takes decades from childhood to young adulthood, followed by an exponential increase in risk during middle age, and finally reaches a plateau in older adults, when most gastric cancers are diagnosed due to the presence of clinical symptoms and death related to gastric cancer is most likely to occur.[3] Differences in exposure to risk factors and in the host inflammatory response may affect the speed of the histological progression, leading to differences in the recommended age at which to start screening. For example, in those who live in or come from high-incidence areas, the starting age is generally recommended at around 50 years, when the endoscopic yield rate for premalignant gastric lesions and gastric cancers increases to a level that is considered cost-effective. By contrast, for residents from low-incidence areas, the diagnostic yield is very low, so that the age-based approach is neither effective nor cost-effective. In these patients, selective screening is more practical; physicians will need to evaluate the magnitude of risk factors on an individual basis.

How to screen?

To screen for gastric cancer, two direct modalities are available: upper endoscopy and contrast photofluorography. Population screening can also be done by a third method, *i.e.*, non-invasive screening by means of *H. pylori* serology and the measurements of serum pepsinogens, which will be discussed later in this manuscript.

Either the upper endoscopy or contrast photofluorography can identify a gastric cancer at the advanced stage; however, such detection does not guarantee a better survival rate (the so-called lead-time bias). By contrast, a gastric cancer diagnosed at the early stage can dramatically increase the five-year survival rate up to >90%. To reach this goal, upper

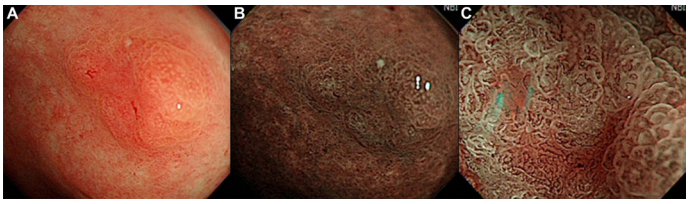


Figure 2. *Endoscopic detection with the white-light image (A), narrow-band imaging (B), and magnification (C) to identify a gastric lesion. The irregular surface and vascular patterns suggest the possibility of an early-stage gastric cancer.*

endoscopy is greatly superior to contrast photofluorography due to the higher sensitivity and specificity in the ability to detect superficial neoplastic foci of the high-definition imaging system and dye-based or digital chromoendoscopy (Figure 2). Endoscopic magnification and imaging-enhanced modalities can also allow prediction of cancer invasiveness, because they enable observation of the minute surface and vascular patterns. These minimally invasive treatments, such as endoscopic mucosectomy and submucosal dissection, can be carried out for neoplasms limited to the mucosa or submucosa.

Upper endoscopy has the additional benefit of allowing risk stratification through the evaluation of the non-neoplastic background gastric mucosae, using either the endoscopic or the histological classification system.[4] The former has the advantage of being convenient and rapid; for example, using the Kimura-Takemoto classification system, gastric mucosae can be classified into six grades according to the extension of atrophic gastritis, including the closed type (C-I, C-II, and C-III) and open type (O-I, O-II, and O-III); overall severity can be categorized into three grades as mild (C-1 and C-2), moderate (C-3 and O-1), and severe (O-2 and O-3). In patients with moderate or severe atrophic gastritis, the risk of gastric cancer is substantially increased, so endoscopic examination should be performed more cautiously and a follow-up schedule should be designed. The endoscopic classification system is, however, subject to the expertise of endoscopists and the endoscopic techniques being used, indicating the need for training and standardization to maintain a good inter-observer reliability.

By contrast, the histological classification system, which is based on the microscopic evaluations of biopsied samples from the antrum, angle, and the body, can be more objective and reliable but is more time-consuming. For example, the

use of Operative Link for Gastritis Assessment of Atrophic Gastritis (OLGA) and Operative Link for Gastritis Assessment of Intestinal Metaplasia (OLGIM), in which the antral and corpus mucosae are scored according to the presence and severity of atrophic gastritis and intestinal metaplasia, respectively, results in a four-tiered scale that allows stratification of the global severity of premalignant gastric lesions into grades 0 to IV. Subsequent gastric cancers predominantly occur in those diagnosed with extensive premalignant conditions, defined as OLGA or OLGIM grade III-IV gastritis.[5]

The endoscopic and histological methods can be moderately correlated in clinical practice. They are complementary and the choice is dependent on the local conditions and available resources. Knowing that the mean sojourn time of gastric cancers is estimated at about 2 years when they stay in the mucosa or submucosa allows the clinician to determine the surveillance interval. For example, in high-risk areas, the strategies of stopping surveillance, surveillance every 5 years, surveillance every 2 years, and an annual schedule have been recommended for subjects diagnosed with OLGA or OLGIM stage I, II, III, and IV gastritis, respectively.[6] For subjects with extensive premalignant lesions in low- or intermediate-risk areas, repeat endoscopic screening at an interval of about 3 years has been suggested.[7, 8]

How to increase the diagnostic yield?

Although risk assessments based on age, race, *H. pylori* infection, and family history are simple and convenient, their ability to rule in or rule out subjects from endoscopic screening remains imprecise. To predict the intra-gastric histopathological findings, non-invasive serological tests are commercially available. These have the potential to increase the diagnostic yield of endoscopy through the selective use of advanced imaging technologies. Measurements of tumor markers that are generated from the tumor itself are intuitive; these may include the cancer antigen 72-4 (Ca 72-4), gastric carcinoma-associated antigen (MG7-Ag), inter-alpha-trypsin inhibitor heavy chain 3 (ITIH3), carbohydrate antigen 19-9 (Ca 19-9), carcinoembryonic antigen (CEA), serum trefoil factor 3 (TFF3), microRNAs, and others. However, early-stage gastric cancers tend to be superficial so they are unlikely to shed detectable amount of tumor markers into the systematic circulation.

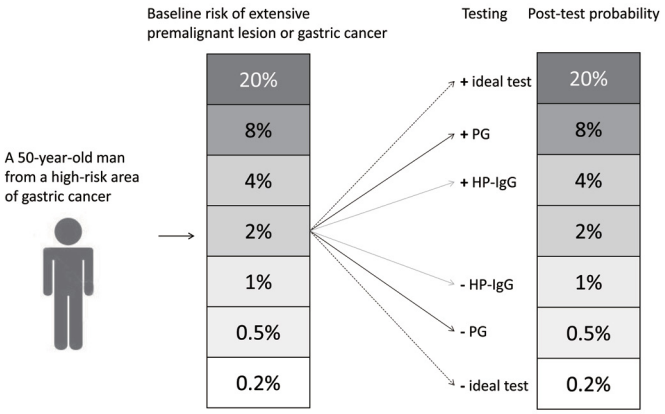


Figure 3. *Calculation of the post-test probability by multiplying the baseline risk of an individual with the likelihood ratio of a positive or negative screening test result. We assume that the positive/negative likelihood ratios of the anti-H. pylori IgG test (HP-IgG), serum pepsinogen test (PG), and an ideal test are 2/0.5, 4/0.25, and 10/0.1, respectively.*

Currently, the most reliable and applicable method of early serological detection is the measurement of serum pepsinogen, which focuses on risk stratification instead of direct tumor detection. Pepsinogen is the inactive precursor of pepsin secreted by the gastric glands and about 1% of intra-gastric pepsinogen will diffuse into the bloodstream and become reliably measurable. In the presence of atrophic gastritis, serum levels of pepsinogen-I, which are secreted by the chief and mucous neck cells in the fundic glands, will decline, and those of pepsinogen-II, which are secreted by cells in the pyloric and Brunner glands, tend to be constant or higher, such that the pepsinogen-I/II ratio will decrease. Pooled analyses have indicated that the positive and negative likelihood ratios of the pepsinogen test are about 4 and 0.25, respectively, so this approach has two benefits: first, to rule in the high-risk subjects for endoscopic examination, and second, to rule out the low-risk subjects from screening such that resource allocation can be more efficient.

The application of such a screening test is demonstrated in Figure 3, where the post-test probability can be estimated by using the baseline risk of an individual and the positive or negative result of a screening test. In subjects from a high-risk area, for example, one may expect a prevalence rate of 2% for extensive premalignant lesions or gastric cancer; given a positive result of pepsinogen testing, the post-test probability can be increased to 8% (2% × positive likelihood

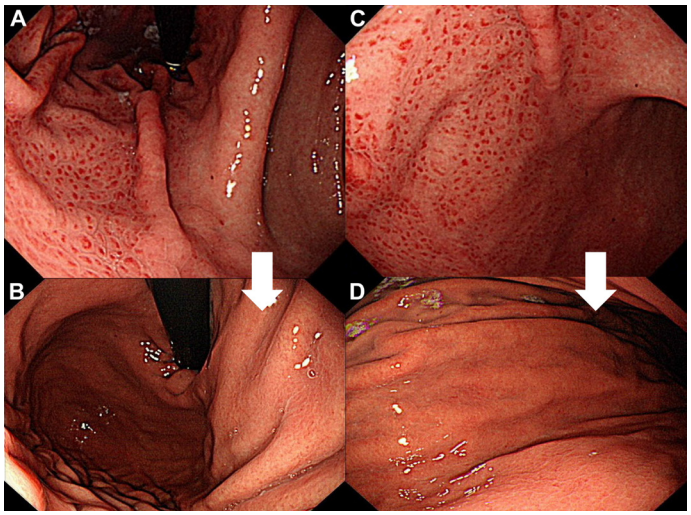


Figure 4. *Changes in intragastric mucosal inflammation before (A, C, upper) and after (B, D, lower) H. pylori eradication.*

ratio of 4). Therefore, endoscopic screening is recommended and the procedure should be performed judiciously. By contrast, in subjects from a low-risk area, where the prevalence rate is expected at 0.2%, the post-test probability can be lowered as far as to 0.05% (0.2% × negative likelihood ratio of 0.25) given a negative result of pepsinogen testing, which suggests that such patients are unlikely to benefit from endoscopic screening.

How to combine H. pylori eradication with endoscopic screening?

Although endoscopic screening is accurate for both cancer detection and risk prediction, it cannot arrest the natural disease course. To stop the progression of carcinogenesis and reduce the occurrence of new gastric cancers, the modifiable risk factors must be eliminated. In addition to lifestyle modifications (including abstinence from excessive salt intake, cigarette smoking, and excessive alcohol use, and the encouragement of fresh fruit and vegetable intake), screening and treating *H. pylori* infection, which accounts for about 90% of non-cardiac gastric cancers, are the most effective means by which to heal the mucosal inflammation, halt the histological progression, and thus reduce the gastric cancer risk (Figure 4). Non-invasive tests for *H. pylori* may include the immunoglobulin (IgG) serological test, C13-urea breath test, and stool antigen test. The screening choice depends on the prevalence rate of *H. pylori* infection and the resources available for a specific population.

In populations with a low prevalence rate of gastric cancer, most *H. pylori* carriers will remain in the stages of chronic gastritis upon screening (Figure 1: left side). Testing and treating *H. pylori* infection is sufficient, followed by a retest to confirm successful eradication. However, in high-risk populations, although *H. pylori* eradication can reduce the risk, it cannot reset the biologic clock to zero because a great proportion of subjects already harbor premalignant lesions (Figure 1: right side) and, in some of them, the genetic or epigenetic damage has become irreversible so that they still carry gastric cancer risk. Therefore, the treatment of *H. pylori* infection should be provided as early as possible and the risk stratification and endoscopic screening need to be integrated in a stepwise manner. For example, based on information from *H. pylori* and pepsinogen tests, the population can be stratified into four groups: low-risk: *H. pylori* (-) and pepsinogen (-); average-risk: *H. pylori* (+) and pepsinogen (-); high-risk: *H. pylori* (+) and pepsinogen (+); and very high-risk: *H. pylori* (-) and pepsinogen (+). *H. pylori* carriers should actively receive treatment while those categorized as being in higher-risk groups are candidates for endoscopic screening. This approach, the so-called ABCD method, has been confirmed effective on the population level.[9] However, since *H. pylori* eradication can reverse the severity of atrophic gastritis but the molecular damage may persist, application of the ABCD method in the post-eradication period needs to be cautious. For this unmet need, direct measurement of the molecular damage in the gastric mucosae is a potential solution to identify those who retain the risk and benefit from long-term screening after eradication.[10]

Conclusions

To eliminate the threat from gastric cancer, both *H. pylori* eradication (primary prevention) and endoscopic screening (secondary prevention) are needed to, respectively, reduce the incidence rate of gastric cancer by ameliorating mucosal inflammation and improve the mortality rate through the detection of early-stage neoplasms. The connection between the two strategies involves careful risk stratification based on the population risk, family history and/or pepsinogen tests, so as to maximize the use of the available resources.

Gastric Cancer Screening: Who, When, and How?, continued

References:

1. *Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.*
2. *de Vries AC, van Grieken NC, Looman CW, Casparie MK, de Vries E, Meijer GA, Kuipers EJ. Gastric cancer risk in patients with premalignant gastric lesions: a nationwide cohort study in the Netherlands. Gastroenterology. 2008;134:945-52.*
3. *Wu JY, Lee YC, Graham DY. The eradication of Helicobacter pylori to prevent gastric cancer: a critical appraisal. Expert Rev Gastroenterol Hepatol. 2019;13:17-24.*
4. *Tan MC, Graham DY. Gastric cancer risk stratification and surveillance after Helicobacter pylori eradication: 2020. Gastrointest Endosc. 2019;90:457-60.*
5. *Graham DY, Rugge M, Genta RM. Diagnosis: gastric intestinal metaplasia: what to do next? Curr Opin Gastroenterol. 2019;35:535-43.*
6. *Graham DY, Asaka M. Eradication of gastric cancer and more efficient gastric cancer surveillance in Japan: two peas in a pod. J Gastroenterol. 2010;45:1-8.*
7. *Pimentel-Nunes P, Libânio D, Marcos-Pinto R, et al. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. Endoscopy. 2019;51:365-88.*
8. *Kim GH, Liang PS, Bang SJ, Hwang JH. Screening and surveillance for gastric cancer in the United States: Is it needed? Gastrointest Endosc. 2016;84:18-28.*
9. *Sugano K. Screening of gastric cancer in Asia. Best Pract Res Clin Gastroenterol. 2015;29:895-905.*
10. *Takeshima H, Ushijima T. Accumulation of genetic and epigenetic alterations in normal cells and cancer risk. NPJ Precis Oncol 2019;3:7.*

Gastric cancer prevention in Japan: Is a national program justified?

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Introduction

Fifty thousand people die of gastric cancer every year in Japan, and it ranks second highest among all causes of cancer death[1]. It used to be thought that gastric cancer was caused by high salt intake, smoking tobacco, and consumption of burnt fish or meat, as well as genetic factors. However, it was subsequently clarified that around 98% of gastric cancer in Japan is caused by infection with *Helicobacter pylori* (*H. pylori*)[2]. In other words, gastric cancer is nearly always due to *H. pylori* infection.

In 1982, *H. pylori* was first identified in the gastric mucosa by Warren and Marshall in Australia[3]. After their discovery, researchers all over the world became interested in the relationship between this bacterium and gastric diseases, and numerous investigations were performed. At the World Gastroenterology Organisation meeting in 1990, *H. pylori* was recognized as a very likely cause of gastritis. In 1994, the consensus report by the National Institute of Health (NIH) of the U.S. recognized it as a cause of gastric/duodenal ulcer, and H. pylori eradication therapy was recommended for the prevention of recurrence. In the same year, the cancer research organization of the World Health Organization (IARC) identified *H. pylori* as a definite carcinogen for gastric cancer[4]. In 2001, it was confirmed that gastric cancer will not occur unless a person is infected with *H. pylori*[5]. In 2005, the Nobel Prize in Physiology or Medicine was awarded to Warren and Marshall for their great contribution to the prevention and treatment of gastric diseases through discovery of *H. pylori* and elucidating its relationship with gastritis.

The usefulness of *H. pylori* eradication therapy for preventing gastric cancer was verified after clarification of the relationship between *H. pylori* and this cancer. However, it was also shown that eradication of *H. pylori* cannot completely suppress the occurrence of gastric cancer, which means that periodic checking after eradication is necessary to eliminate gastric cancer in Japan[6]. The Ministry of Health, Labour and Welfare approved expansion of insurance coverage for *H. pylori* eradication therapy to prevent gastritis (chronic active gastritis) from February 2013, which was the first time in the world.

Prevention of Gastric Cancer

Since it has been clarified that gastric cancer is caused by *H. pylori* infection rather than lifestyle factors in most patients, it is necessary to change our strategy for this cancer. If a cancer is suspected to be caused by infection, taking aggressive preventive measures will greatly decrease its occurrence and result in a dramatic decrease in the number of deaths. In Japan, various measures have been taken against hepatitis virus infection, mainly to prevent liver cancer, and the number of deaths from liver cancer has been decreasing[7]. However, the number of deaths from gastric cancer has shown little change and has remained around 50,000 per year for several decades, so current preventive measures can hardly be considered successful. While the cause is viral infection in one case and bacterial infection in the other, the actions taken against cancer caused by infection should not differ between liver cancer and gastric cancer. Thus, the basic preventive strategy for gastric cancer should be switched from conventional screening examination (mainly by barium studies) to primary prevention by eradication of *H. pylori*.

In the plan for promoting cancer prevention in Japan (revised in 2012), it is stated that "human papilloma virus is related to cervical cancer, hepatitis virus to hepatocellular carcinoma, human T-cell leukemia virus 1 to adult T cell leukemia (ATL), and *H. pylori* to gastric cancer." It was also stated that "the usefulness of *H. pylori* eradication therapy should be reviewed on the basis of findings obtained inside and outside Japan." This mention of taking action against *H. pylori* in Japan's basic cancer policy is epoch-making, and may result in a fundamental change to the conventional policy of gastric cancer screening by barium studies that has been employed for several decades.

When devising a plan to eliminate gastric cancer in Japan, it is important to create separate measures for young and elderly people. This is because 100% prevention of gastric cancer can be achieved by performing *H. pylori* eradication therapy in young persons, but the occurrence rate of gastric cancer after eradication tends to increase over time (Figure1)[1]. Different approaches are required accordingly.

Gastric cancer prevention in Japan: Is a national program justified?, continued

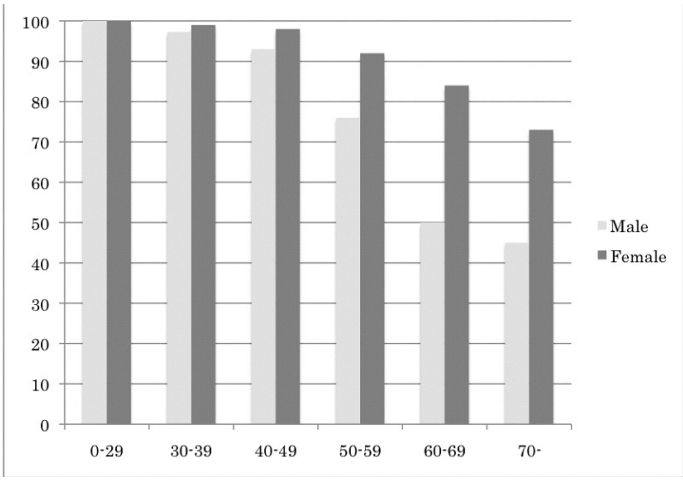

Figure 1. *Possible rate of gastric cancer prevention by eradication of Helicobacter pylori*

For young persons, it is recommended to test for *H. pylori* infection between commencement of junior high school and graduation from university, and immediately perform *H. pylori* eradication therapy if the result is positive, even when the person has no symptoms. Eradication at this stage will prevent nearly 100% of gastric cancer, as well as other diseases related to *H. pylori* such as gastric ulcer and gastric polyp[8].

The new national health insurance coverage of *H. pylori* eradication therapy to prevent gastric cancer makes it possible for us to go directly to a medical institution for diagnosis and treatment of gastric cancer due to *H. pylori* infection. Initial diagnosis of gastritis by endoscopy is required, and chronic gastritis seems to be detected in most persons. Obligatory endoscopy may reveal gastric cancer in many elderly persons. This situation corresponds to endoscopic examination under national health insurance. All persons in whom gastritis is diagnosed should receive *H. pylori* eradication therapy. Periodic endoscopic review once every year or two after eradication of *H. pylori* is desirable for persons with obvious atrophic gastritis. On the other hand, persons with mild/no gastritis or negative for *H. pylori* should have optional examinations such as a complete medical checkup. Suppressing the occurrence of atrophic gastritis, a precancerous condition, is important for eliminating gastric cancer in Japan. Accordingly, gastritis due to infection with *H. pylori* should be eliminated from Japan by *H. pylori* eradication therapy, and the awareness of the general public concerning *H. pylori* and gastritis should be raised.

To prevent death from gastric cancer, the first step is to attend a medical center, even if you have no symptoms, and undergo testing for gastritis due to *H. pylori* infection. Gastritis should be documented endoscopically before receiving *H. pylori* eradication therapy under the national health insurance scheme. The examination of *H. pylori* could be approved when gastritis is diagnosed endoscopically. Usually a test for *H. pylori* antibody or a urea breath test is carried out. Eradication therapy is provided when you are positive for *H. pylori* infection, involving three different oral medications that are taken for a week. The therapy only needs to be taken for one week, so you should be careful not to forget any of the doses of medication, since the eradication rate decreases if 2 or 3 doses are missed. The effect of H. pylori eradication therapy is judged at one month or longer after its completion. Assessment of the effect of the therapy is compulsory because gastric cancer cannot be prevented unless eradication of *H. pylori* is confirmed. Even if eradication is "successful", follow-up endoscopy should be done once a year if atrophic gastritis has been diagnosed, since gastric cancer often occurs within 1 to 3 years after eradication in persons with atrophic gastritis.

Because gastric cancer arises from gastritis due to *H. pylori* infection, it is very likely to be prevented by thorough treatment of gastritis. Now that the baby-boomers who account for a large proportion of the Japanese population are reaching the age of 65 years, which is the high-risk cancer age, deaths from gastric cancer were expected to increase and reach 60,000 in the year 2020. However, nearly 6 million persons received *H. pylori* eradication therapy in the 6 years after it became available under the national health insurance scheme, and deaths from gastric cancer have been decreasing (48,632 in 2013, 47,903 in 2014, 46,659 in 2015, and 45,509 in 2016, 44189 in 2018). In short, the number of deaths from gastric cancer has decreased by nearly 12% (Figure 2)[9]. While almost 50,000 people used to die of gastric cancer every year, the number of deaths has been decreasing since the initiation of national health insurance coverage and 16,000 lives have been saved over 6 years. Thus, a public subsidy from national health insurance has dramatically increased the number of persons receiving *H. pylori* eradication therapy and has decreased deaths from gastric cancer. It is a phenomenal outcome, not only unprecedented in Japan but also in medical systems worldwide.

Gastric cancer prevention in Japan: Is a national program justified?, continued

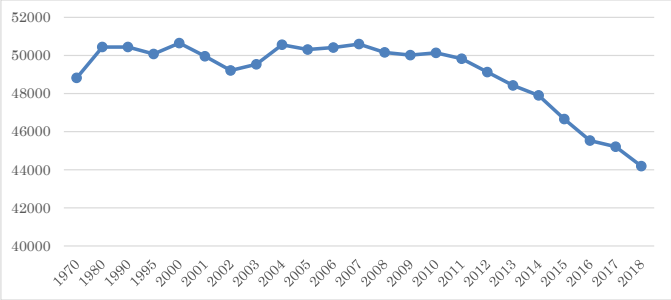

Figure 2. *Changes of gastric cancer deaths in Japan, partially modified ref 9*

However, 35 to 50 million persons in Japan are thought to be infected with *H. pylori*, so this is only the beginning and much more effort is needed to eliminate gastric cancer.

Conclusion

Gastric cancer is a malignancy that has claimed many lives in Japan. Over the past 40 years alone, about 50,000 people have died of this cancer every year, for a total of around 2 million deaths. Attempts to control gastric cancer were started by targeting early diagnosis and treatment. The concept of early gastric cancer was developed in Japan, and diagnostic techniques for this cancer were refined. Later, *H. pylori* was identified as the main cause of gastric cancer and various preventive measures were initiated. The universal healthcare system in this country is unique in the world, and the endoscopic techniques of physicians for diagnosing gastric cancer are the most advanced. *H. pylori* eradication therapy for the prevention of gastric cancer was approved by the national health insurance scheme in 2013 for the first time in the world. The movement to eliminate gastric cancer is gathering speed and we are entering a new era in which dying of gastric cancer is no longer necessary.

References

1. *Asaka M. A new approach for elimination of gastric cancer deaths in Japan. Int J Cancer. 2013 15;132:1272-6.*
2. *Matsuo T et al. Low prevalence of Helicobacter pylori-negative gastric cancer among Japanese. Helicobacter. 2011 16:415-9.*
3. *Warren JR & Marshall BJ. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1983 I:1273-5.*
4. *Schistosomes, liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June 1994. IARC Monogr Eval Carcinog Risks Hum. 1994;61:1-241.*
5. *Uemura N et al. Helicobacter pylori infection and the development of gastric cancer. N Engl J Med 2001 345:784-9.*
6. *Fukase K et al. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. Lancet. 2008 372:392-7.*
7. *Oza N et al. Current activities and future directions of comprehensive hepatitis control measures in Japan: The supportive role of the Hepatitis Information Center in building a solid foundation. Hepatol Res 2017 47:487-496.*
8. *Asaka M et al. Roadmap to eliminate gastric cancer with Helicobacter pylori eradication and consecutive surveillance in Japan. J Gastroenterol. 2014 49:1-8.*
9. *Tsuda M et al. Effect on Helicobacter pylori eradication therapy against gastric cancer in Japan. Helicobacter 2017 22: doi: 10.1111/hel. 12415*

Helicobacter pylori and gastric cancer

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Introduction to gastric cancer and *Helicobacter pylori*

Until the mid-twentieth century gastric cancer was the most common cause of cancer deaths in countries where such records are kept. It still remains the third most common cause of cancer deaths with the majority of these deaths occurring in Asia. In the late 19th century the tight link between atrophic gastritis, hypochlorhydria-achlorhydria and gastric cancer was first established. However, it was not until the mid-1980s and following the discovery of *H. pylori* that the story came together. *H. pylori* infections proven to be the most common cause of gastritis and gastric atrophy allowing all of the different links and pieces of evidence to come together into a complete story. *H. pylori* is a gram negative bacterium for whom humans are the natural host. The organism is trophic for gastric epithelium and highly adapted to survive in the hostile acid environment of the stomach. Attachment of the bacterium to the gastric mucosa results in a brisk inflammatory response. This rapidly involves into chronic destructive gastritis characterized by both acute and chronic inflammation thus was named acute-on-chronic inflammation. The histologic damage is initially largely restricted to the non-acid producing portions of the stomach and produces an antral predominant gastritis. Over time the infection/inflammation extends proximally and may eventually involve and damage the entire stomach to become pan-gastritis. Further progression produces progressive atrophy that may finally result in achlorhydria and even result in loss of the infection because of loss of a gastric epithelium to which the organisms attach.

Prolonged inflammation can result in development of gastric cancer which is classified as an inflammation-associated malignancy. The risk of developing gastric cancer among those with *H. pylori* infections is multi-factorial related in part to the ability of the organism to produce inflammation, to the response of the host to inflammation, and to the diet which also modulates the host response and tissue damage. This is

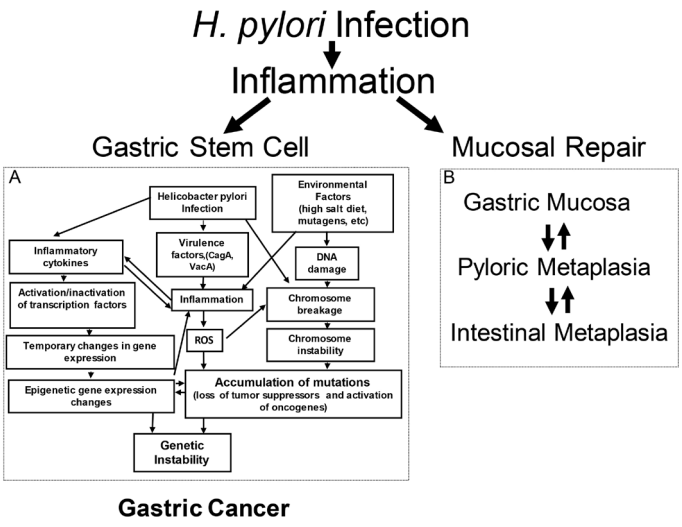

Figure 1. *Schematic showing the inter-related factors thought to play a role in H. pylori-related gastric carcinogenesis.*

expressed as bacterial, host, and environmental factors any one of which can assume a dominant role (Figure 1).

H pylori virulence, host, and environmental factors

H. pylori vary widely in terms of virulence which reflects the strain's ability to elicit inflammation (virulence). Virulence is reflected in bacterial biomarkers such as the presence and expression of the cytotoxin-associated gene, *cagA* and the vacuolating toxin gene, *vacA*. There are also biomarkers for host factors which relate to the extent of host's inflammatory response such as the up or down regulation of the inflammatory response related to polymorphisms of specific interleukin genes such as IL-Iß. Diet is one of the most important of the environmental factors as diets high in salt and low in fresh fruits and vegetable are associated with enhanced inflammation and an increase risk of gastric cancer. Rapid changes in diet and food preservation occurred in the late 19th through the 20th century when refrigeration replace salt in food preservation and improved transportation changed the diet from seasonal to one in which fresh fruits and vegetables were available year around. This was coupled with improvements in housing, sanitation and water supplies which ultimately resulted in a reduction of transmission of *H. pylori* especially to children. Together these events results in a prolonged and marked fall in the prev-

alence of gastric cancer which was initially replaced by an increase in *H. pylori*-associated peptic, particular duodenal ulcers but eventually was expressed as a decline in all *H. pylori*-associated diseases. Nonetheless, worldwide *H. pylori* remains an important human pathogen with between 40 and 50% of the world's population being currently infected.

How *H. pylori* causes cancer

Initial research focused on putative *H. pylori* virulence factors such as CagA as possibly having special roles in gastric carcinogenesis. However, even infection with even most avirulent *H. pylori* (as assessed by presence or absence of putative virulence factors) is associated with gastric cancer. Importantly, in regions where gastric cancer and the most virulent *H. pylori* are both prevalent, changes in diet resulted in a dramatic decline in the both the rate of development and prevalence of both atrophic changes and gastric cancer. Currently, the bulk of evidence is consistent with the notion that *H. pylori*-induced inflammation rather than any putative *H. pylori* carcinogen is most likely the key variable. This is also consistent with knowledge that persisting inflammation of any organ is associated with an increased risk of cancer. *H. pylori* causes both persisting acute and chronic inflammation resulting in the presence of reactive oxygen and nitrogen species that can result in progressive genetic changes (Figure 2). The presence of genetic damage is reflected in both epigenetic markers (eg, methylation) as well as by progressive genetic instability and accumulation of irreversible genetic damage including loss of tumor-suppressor genes.

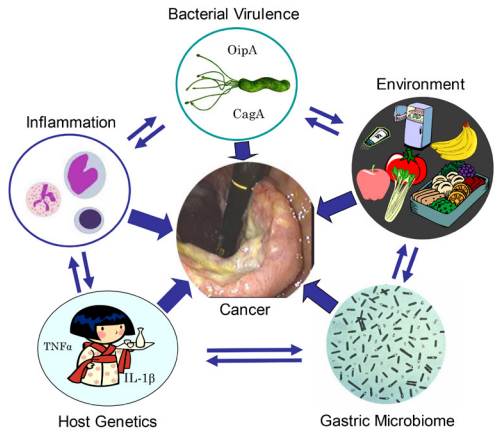

Figure 2. Representation of the pathogenesis of *H. pylori*-induced gastric mucosal damage resulting in changes associated with inflammation-*H. pylori*-induced carcinogenesis (panel A) and mucosal repair (Panel B). Pyloric or pseudopyloric metaplasia and intestinal metaplasia are potential reversible biomarkers of past or ongoing gastric mucosal injury. The extent and severity of metaplastic mucosa correlates with gastric cancer risk in those with *H. pylori* gastritis. Gastric cancer arises from injury from gastric stem cells rather then from intestinal metaplasia. Adapted from

The presence of genetic alterations are also reflected by histologic changes as the progression of chronic active gastritis to atrophic gastritis and the presence of potentially reversible metaplastic epithelia (pseudopyloric and metaplastic). Intestinal metaplasia is no longer thought to progress directly to cancer, rather it is a biomarkers of the presence of the genetic instability that may promote progression of gastric stem cells to gastric cancer stem cells, intraepithelial neoplasia, and finally to invasive carcinoma (Figure 2). *H. pylori* itself may also play a role in carcinogenesis as the organism can result in breakage of double-stranded DNA and impair DNA repair (Figure 2). Because *H. pylori* infection is the main factor initiating and perpetuating this process, eradication of *H. pylori* should prevent most gastric cancers.

Does *H. pylori* infection have redeeming features?

When it was recognized that *H. pylori,* like hepatitis B, had been associated with humans and human migration for ten's of thousands of years, it was asked whether *H. pylori,* in addition to being a pathogen, might also play an important positive role. A number of possibilities were raised such as preventing obesity, childhood asthma, etc. This issue as since largely been resolved with the bulk of evidence coming down on the side of *H. pylori* being a pathogen and one, like hepatitis B, we would be better off without. Early man was host to many parasites and pathogens; *H. pylori* is one of the few remaining. While the concerns such as protection against childhood asthma, obesity, etc have been disproved, the loss of *H. pylori* does have ramifications in that the damage it causes (atrophic gastritis - the precursor lesion for gastric cancer) also had a potentially relevant side effect in that the resulting reduction in acid secretion also reduces the frequency of symptomatic gastroesophageal reflux disease and the risk of Barrett's esophagus. Esophageal adenocarcinoma is a rare disease arising from Barrett's

Helicobacter pylori and gastric cancer, *continued*

esophagus that requires a healthy stomach. In contrast to Barrett's esophagus, gastric cancer affects all races and sexes whereas esophageal adenocarcinoma associated with Barrett's is a rare disease with an incidence approximately equivalent to small intestinal cancer, that occurs predominantly in white men. The trade-off includes elimination of the most common cause of cancer deaths as well as of the numerous *H. pylori* associated diseases such as peptic ulcer which, until recently, affected approximately 10% of the population and was a major cause of morbidity and gastrointestinal hemorrhage.

Whom to test and how to detect *H. pylori*?

All consensus conferences held since the landmark Kyoto consensus on *H. pylori* in 2015 have agreed that a) *H. pylori* is, and should be treated as, an undesirable infectious disease, and that b) whenever recognized, *H. pylori* infections should be cured. The recommendations were primarily aimed at developed countries and those areas and groups where reinfection rates are low. The ultimate goal is to eradicate the infection world wide and thus eliminate gastric cancer as an important cause of mortality (see below).

H. pylori infections are relatively easy to diagnose as there are a number of reliable tests for *H. pylori* detection including urea breath tests, stool antigen tests, culture, histologic examination of gastric biopsies, serologic tests for *H. pylori* antibody and an increasing number of molecular tests based on identifying *H. pylori* genes. The best approach for a particular region or person will vary depending on availability, cost, and what is planned to do with the information (eg, epidemiology vs. individual patient care).

H. pylori therapy

The reader is referred to the separate section dedicated to *H. pylori* therapy. Suffice it to say, that *H. pylori* was only recently recognized as an infectious disease such that the principles and practices involved in the treatment of infectious diseases including antimicrobial stewardship are only now becoming recognized as important to *H. pylori* and have yet to be fully implemented. We are now in the transition period from antibiotic regimens based on trial and error that overall produced relatively poor cure rates to a traditional susceptibility-based approach using the principles of antibiotic stewardship. Antibiotic stewardship encompasses identification of the optimum antimicrobial regimen for a region or population including the drugs, doses, dosing intervals, duration, etc. Only proven highly effective regimens should be given empirically and this should include monitoring of results and antimicrobial susceptibility. If, or when, effectiveness falters due to increasing resistance, previously effective empiric regimen should only continued to be used based on patient specific susceptibility results. A new effective empiric regimen will then be developed as a replacement as an optimized susceptibility-based regimen. Until the transition to new approaches using the principles of antimicrobial therapy is completed using quality measures for assessment of infectious disease therapy and current experience or opinion-based regimens are discarded .we will not be able to universally offer reliable cure rates.

How to ultimately eliminate *H. pylori and gastric cancer*

The presence of clean water, good sanitation, good household hygiene, and good housing result in breaking the chain of *H. pylori* transmission and the gradual population loss of *H. pylori* which is experienced as a birth cohort phenomenon. The natural process requires at least a century or more to accomplish and can easily be disrupted by war or other major population dislocations. Traditionally, vaccines are ideal for prevention of infectious diseases but only limited progress has been made toward finding an *H. pylori* vaccine and to date funding for vaccines remains scant to absent. Infected children are the reservoir and *H. pylori* will remain a problem unless the pattern of almost universal transmission to children in developing countries can be disrupted. Breaking transmission typically follows acquisition of good sanitation and clean water and improved housing.

Gastric cancer can be also prevented or reduced by *H. pylori* eradication before irreversible genetic changes occur in the gastric mucosa. The current maker used to identify this the point of potentially no return is development of pan-atrophic gastritis. Thus, the earlier in the progression of damage that *H. pylori* eradication is done the more likely that gastric cancer will be prevented. However, after the risk appears, the further per year increase in risk is exponential such that *H. pylori* eradication even after the development of one early gastric cancer can reduce the risk of metachronous cancers. The rule is eradication early in the course of the disease is best but any time before development of invasive cancer should produce a measurable benefit in terms of reduction in gastric cancer risk.

Helicobacter pylori and gastric cancer, *continued*

References

1. *El-Serag HB, et al. Houston Consensus Conference on testing for Helicobacter pylori infection in the United States. Clin Gastroenterol Hepatol. 2018;16:992-1002.*
2. *Graham DY. Helicobacter pylori update: Gastric cancer, reliable therapy, and possible benefits. Gastroenterology. 2015;148:719-31.*
3. *Graham DY, et al. Guilt by association: intestinal metaplasia does not progress to gastric cancer. Curr Opin Gastroenterol. 2018;34:458-64.*
4. *Graham DY. History of Helicobacter pylori, duodenal ulcer, gastric ulcer and gastric cancer. World J Gastroenterol 2014;20:5191-5204.*
5. *Hooi JKY, et al. Global prevalence of Helicobacter pylori infection: Systematic review and meta-analysis. Gastroenterology. 2017;153:420-29.*
6. *Ikuse T, et al. Inflammation, Immunity, and vaccine development for the gastric pathogen Helicobacter pylori. Curr Top Microbiol Immunol. 2019;421:1-19.*
7. *Lee YC et al. Association between Helicobacter pylori eradication and gastric cancer incidence: A systematic review and meta-analysis. Gastroenterology. 2016;150:1113-24.*
8. *Sugano K, et al. Kyoto global consensus report on Helicobacter pylori gastritis. Gut. 2015;64:1353-67.*
9. *Tan MC, et al. Gastric cancer worldwide except Japan. In: Gastric cancer with special focus on studies from Japan. In: Shiotani A, ed. Gastric cancer with special focus on studies from Japan. Singapore: Springer, 2018:17-28.*
10. *Zeng M, et al. Efficacy, safety, and immunogenicity of an oral recombinant Helicobacter pylori vaccine in children in China: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015:386:1457-67.*

Non-endoscopic Diagnosis of Early Gastric Cancer

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Introduction

Upper gastrointestinal endoscopy is still considered the gold standard for diagnosis of gastric cancer with its high accuracy and ability to obtain confirmatory histology. With the increasing use of high definition endoscopy and image enhanced endoscopy, early lesions could be easily identified and optical diagnosis of suspected gastric lesions could be achieved, which could also improve patient's outcome. However, due to the invasive nature and the discomfort associated with endoscopic examination, it may not be the preferred choice by many patients, particularly for screening purpose in asymptomatic subjects. Moreover, the cost and availability of upper endoscopy is another critical obstacle for the widespread application of this endoscopic examination.

Given the wide geographical and ethnical variations in gastric cancer incidences, the mass adoption of upper endoscopy in some low risk countries for gastric cancer screening and surveillance may not be cost-effective. Apart from endoscopy, screening by photofluorography or blood tests are generally considered to be alternatives, particularly in high-risk populations. These tests, on the other hand, may lack sensitivity or specificity for diagnosis of early gastric cancer. In this chapter, the role of non-endoscopic diagnosis for gastric cancer including radiological imaging and serological diagnosis will be discussed.

Radiological diagnosis

Radiological examination by using photofluorography or barium studies have been practiced in Japan since 1960 and subsequently adopted in the nationwide screening program in Japan. The reported sensitivities and specificities for gastric cancer screening are more than 80% in Japanese series[1]. The Japanese Guidelines for Gastric Cancer Screening, which used data from case-control and cohort studies, recommended photofluorography as both mass screening and opportunistic screening. There is however no randomized controlled trial comparing the accuracy of this method on screening for gastric cancer. As the interpretation of these images require certain level of expertise, it is seldom practiced in other countries except in Korea. Even in Japan, it is gradually replaced by endoscopy for the early detection and screening of gastric lesions.

There are however no data to support the use of other cross-sectional imaging for detection of gastric mucosal lesions, including computerized tomography and magnetic resonance imaging. The role of fluorodeoxyglucose (FDG) positron-emission tomography (PET) is also limited to staging of confirmed gastric cancer rather than early cancer development as some gastric cancer, particularly mucinous cancers consume less glucose, can be less FDG avid on PET. Transabdominal ultrasound has no role on gastric cancer detection.

Serological diagnosis

There are so far no reliable blood biomarkers for gastric cancer. Most currently available blood tests aim to identify patients at risk of gastric cancer rather than detecting early gastric lesions. Specifically, blood tests that identify the presence of gastric atrophy and *Helicobacter pylori* infection, which are both risk factors for gastric cancer development.

H. pylori serology

As most of the gastric cancers are associated with chronic *H. pylori* infection, identification of *H. pylori* infected subjects could act as the first step in selecting at-risk subjects. Detection of IgG antibody against H. pylori would detect both past and present *H. pylori* infection. The advantage of testing for IgG antibody is that the antibody would persist in the blood for a certain period even after successful eradication of the bacterium. However, the performance of different commercially available serological tests can be quite variable and local validation is generally recommended due to the presence of difference in dominant *H. pylori* strains in different geographic regions.

While not all *H. pylori* infected individuals would develop gastric cancer and the lifetime risk is generally less than 5%, the combined use of *H. pylori* serology and blood biomarkers for gastric atrophy could further help to identify the group of high-risk subjects for endoscopic examination.

Non-endoscopic Diagnosis of Early Gastric Cancer, continued

Gastrin-17

Gastrin-17 is secreted by the G-cells of the gastric antrum and would stimulate the secretion of gastric acid. As it is regulated by the normal function of the antrum as well as by the acid produced by the gastric parietal cells, the interpretation of the G-17 level can be complicated. The levels of G-17 can be low, normal or even high in the presence of gastric atrophy, dependent on the distribution of the atrophy (corpus predominant or both antrum and corpus are involved) and the residual function of antrum. Hence, there are few studies that report the role of G-17 on screening or early detection of gastric cancer. In a recent Chinese study of 12,112 participants with prospective follow up, it was found that both low and high levels of G-17 were associated with higher risk of gastric cancer development, suggesting a J-shaped association[2]. Instead of using G17 alone, it is frequently incorporated with serum pepsinogen assay as a panel of assay (e.g. GastroPanel®) for assessment of gastric cancer risk.

Serum pepsinogen assay

Serum pepsinogen assay measures serum pepsinogen (PG) I and the PG I/PG II ratio. Development of atrophic gastritis would lead to reduced production of serum PG from the normal stomach, particularly PG I. PG II, however, would remain relatively constant. Hence, a low PG I or PG I/PG II ratio would be indicative of the presence of gastric atrophy and risk of future development of gastric cancer.

Although both values are continuous variables, specific cut-off values have been proposed including a PG I <=70 and a PG I/PG II ratio <=3. In a recent meta-analysis using these cut-off values, the sensitivity and specificity for diagnosis of gastric cancer was 59% and 73%, respectively[3]. On the other hand, the respective sensitivity and specificity for diagnosis of chronic atrophic gastritis was 59% and 89%.

Serum pepsinogen assay is frequently combined with *H. pylori* serology for prediction of gastric cancer risk. Patients can be stratified into four groups according to the *H. pylori* infection statuses (positive or negative) and the PG I level or PG I/PG II ratio (low or normal) (Table 1) as in the ABC Method. It has been shown that patients with low PG I (or PG I/PG II ratio) and negative *H. pylori* infection status (Group D) would have the highest risk of gastric cancer due to the presence of severe gastric atrophy that lead to negative *H. pylori* status. In contrast, those with negative *H. pylori* serology and normal PG I (or PG I/PG II ratio) (Group A) are at very low risk of gastric cancer. In a prospective study of 9,293 participants from Japan, it was shown that the annual incidence of gastric cancer in group A was 0.04% and those in group D was 0.6%, respectively[4]. Apart from serum PG levels, age and sex were the other important risk factors for gastric cancer progression in that study.

Anti-parietal cell antibodies

Anti-parietal cell antibodies (APCA) target the gastric parietal cells and are frequently found in patients with autoimmune gastritis or pernicious anemia. Intuitively, APCA would lead to atrophic gastritis and hence higher risk of gastric cancer. The risk appears to be particularly high among those with negative *H. pylori* infection statues. However, in a recent nested case-control study from China, it was found that APCA seropositivity was negatively associated with gastric cardia cancer (Odds ratio 0.42) but not non-cardia gastric cancer[5]. The usefulness of APCA for gastric cancer detection remains to be determined.

Molecular tumor markers

Conventional tumor markers such as serum carcinoembryonic acid (CEA), carbohydrate antigen (CA) 19-9 and CA72-4 lack sensitivity and specificity for gastric cancer diagnosis. Hence, efforts have been directed to identify other potential gastric cancer-specific molecular markers on protein-coding genes, microRNAs, long noncoding RNAs, methylated gene promoter, circulating tumor cells and DNA. These markers, when over-expressed or downregulated, are used for diagnosis or early detection of gastric cancer, as well as, prediction of treatment response and prognosis. There is a very long list of potential biomarkers that have been tested in previous trials but none of them has been incorporated into clinical practice[6, 7].

Most of these potential biomarkers are not sensitive enough for detection of early cancer and existing studies are also limited by either small and retrospective in nature or with no proper validation in different patient groups. With advances in molecular detection techniques, the detection of miRNAs and LcRNA appear to be promising candidates of early detection of gastric cancer. Further large-scale prospective studies are needed to characterize the role of molecular markers on early detection of gastric cancer.

Non-endoscopic Diagnosis of Early Gastric Cancer, continued

CONCLUSION

Currently available non-invasive diagnosis of gastric cancer by either radiological examination or blood tests are still far from satisfactory for accurate early diagnosis or screening purposes. They could possibly be used in identifying high risk patients that warrant further endoscopic examination, particularly in high risk populations. However, serological tests are largely developed for the identification of gastric atrophy associated with non-cardia cancer and may not be suitable for the diagnosis of cardia cancer, which is more related to gastroesophageal reflux disease. Endoscopy still remains the gold standard for early diagnosis of gastric cancer.

Table 1: The ABC Method of Assessing Gastric Cancer Risk

		H. pylori antibody titer	
		Negative	Positive
Serum Pepsinogen Index	Normal	Group A	Group B
	Atrophic*	Group D	Group C

*Atrophic was defined when serum pepsinogen I level ⩽70 ng/ml and a pepsinogen I/II ratio ⩽3.0 were simultaneously fulfilled.

Level of grey intensity represents risk of gastric cancer.

References:

1. *Hamashima C. Current issues and future perspectives of gastric cancer screening. World J Gastroenterol 2014;20:13767-13774.*
2. *Tu H, Sun L, Dong X, et al. A serological biopsy using five stomach-specific circulating biomarkers for gastric cancer risk assessment: a multi-phase study. Am J Gastroenterol 2017;115:704-715.*
3. *Bang CS, Lee JJ, Baik GH. Prediction of chronic atrophic gastritis and gastric neoplasms by serum pepsinogen assay: A systematic review and meta-analysis of diagnostic test accuracy. J Clin Med 2019;8:E657*
4. *Watabe H, Mitsushima T, Yamaji Y, et al. Predicting the development of gastric cancer from combing Helicobacter pylori antibodies and serum pepsinogen status: a prospective endoscopic cohort study. Gut 2005;54:764–8.*
5. *Wang SM, Roth MJ, Murphy GA, et al. Serological profile of anti-Parietal cell antibodies, pepsinogens and H. pylori and risk of upper gastrointestinal cancer: A nested case-control study in China. Cancer Epidemiol Biomarkers Prev 2019 Sep 9. pii cebp.0512.2019*
6. *Sawaki K, Kanda M, Kodera Y. Review of recent efforts to discover biomarkers for early detection, monitoring, prognosis, and prediction of treatment responses of patients with gastric cancer. Expert Rev Gastroenterol Hepatol. 2018;12:657-670.*
7. *Necula L, Matei L, Dragu D, et al. Recent advances in gastric cancer early diagnosis. World J Gastroenterol. 2019;25:2029-2044.*

Endoscopic Resection of Early Gastric Cancer

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Principle of endoscopic resection for early gastric cancer

Since lymph node metastasis (LNM) is the most important prognostic factor in gastric cancer, gastrectomy with lymphadenectomy had been the gold standard for treatment in Japan, even for patients with early gastric cancer (EGC). When the prognosis in patients with endoscopic resection (ER) is similar to that in patients with gastrectomy in some categories of EGC, ER is acceptable in these categories. In addition, en bloc resection is demanded because of the precise pathological staging and potential risk of local recurrence.

The 5-year cancer-specific survival (CSS) rates in patients who underwent gastrectomy with lymphadenectomy for gastric cancer confined to the mucosa and submucosa were 99.3% and 96.7%, respectively. Considering the surgical mortality and the 5-year survival rate of 99.3%, ER in the categories of mucosal cancer is assumed to have a prognosis similar to that of surgical resection when the upper limit of the 95% confidence interval (CI) of LNM in the categories are <1%. However, in those categories, it is important to reveal the long-term results in selecting ER similar to those in patients who undergo gastrectomy with lymphadenectomy. Thus, based on the presence/absence of evidence of a favorable long-term outcome in addition to almost no rate of LNM, the indication for ER is divided into absolute and expanded indications: the former with favorable long-term results and the latter without reliable long-term results.

In submucosal cancer, ER is assumed to be similar to surgery if the upper limit of the 95% CI of LNM is <3%.

Endoscopic mucosal resection and Endoscopic submucosal dissection

Endoscopic mucosal resection (EMR) was first reported in 1984, and has been widely accepted as an effective, minimally-invasive treatment for EGC. However, larger-sized lesions cannot be resected completely by EMR at one time and have the potential for a high risk of local recurrence. Piecemeal resections in lesions larger than 2 cm lead to a high-risk for local cancer recurrence and inadequate pathological staging. Endoscopic submucosal dissection (ESD) technique was first published in 2000. ESD enables a higher en bloc and pathologically complete resection rate and lower local recurrence compared to EMR. The ESD has now replaced EMR, occupying over 90% of ER for EGC in 2015.

ESD has higher risk of complications such as severe bleeding or perforation, and still requires high endoscopic skills. Also, ESD using conventional devices has its technical difficulty and requires intensive training under experts. Because these knives lack the ability to grasp the targeting tissue, maneuverability is often difficult under unstable conditions (like single hand surgery). Comparing those devices, Clutch Cutter is technically easier and simpler to perform. (Figure 1). Gastric ESD using Clutch Cutter (DP-2618DT-50-, FUJIFILM Medical Co, Ltd) may be acceptable in the countries with less incidence of EGC. Furthermore, the traction method using dental floss and a hemoclip (DFC, any hemoclip available) for gastric ESD can make submucosal dissection easier and safer because of good visualization and tension whenever we dissect submucosal layer by any ESD devices. It has been now standard in Japan. In order to standardize gastric ESD procedure, simple ESD with Clutch Cutter under the traction method using DFC is demonstrated in this chapter.

Indication of ER

Japanese Gastric Cancer Association (JGCA) guidelines were first published in 2001, for the purpose of 1) showing the appropriate indication of each treatment method for gastric cancer, 2) reducing differences in the therapeutic

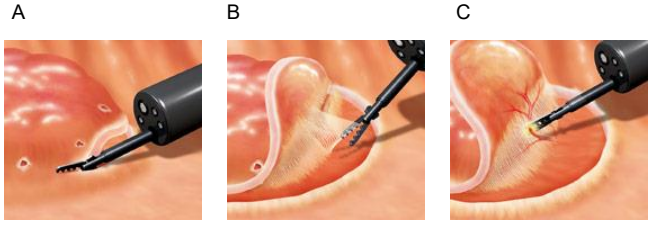

Figure 1: *A, mucosal cutting by Clutch Cutter surrounding marking dots after submucosal injection: B, Submucosal dissection using Clutch Cutter: C, Endoscopic hemostasis for small vessels by using Clutch Cutter*

Endoscopic Resection of Early Gastric Cancer, continued

approach among institutions, 3) improving the safety and outcome of the treatment for gastric cancer, 4) reducing the personnel and economic burden by avoiding unnecessary treatments, and 5) improving a mutual understanding between medical staff and patients. With the accumulation of evidence, the guidelines were updated to ver.5 in 2018. In addition, the Japanese Gastroenterological Endoscopy Society (JGES) guidelines for endoscopic submucosal dissection (ESD)/endoscopic mucosal resection (EMR) of early gastric cancer (EGC) were issued in 2016.

Accepted indications for endoscopic resection (ER) of EGC for small mucosal EGC consisted with intestinal histology type because of technical limitation. Resection of large or ulcerated lesions had not been technically feasible until the development of ESD. With the development and prevalence of ESD, the expanded criteria had been proposed based on the results of two large-scale studies that included patients who underwent gastrectomy for EGC. Gotoda et al. analyzed 5,265 patients who underwent radical surgery with lymph node dissection, in which no lymph node metastasis (LNM) was shown in 1) differentiated, mucosal cancer measuring >2 cm in diameter and without UL and 2) differentiated, mucosal cancer measuring ≤3 cm with ulceration (UL), with the upper limit of 95% CI <1% of LNM. Furthermore, Hirasawa et al. revealed that 3) undifferentiated, mucosal cancer measuring ≤2 cm without UL had no LNMs with the upper limit of 95% CI <1% of LNM. These three categories were regarded as expanded indications for ESD.

Recently, a multicenter single-arm confirmatory clinical trial (JCOG0607) that included patients meeting the categories 1) and 2) in the above criteria was conducted. In this trial, the threshold 5-year overall survival (OS) was set at a value 5% lower than the expected 5-year OS (91.1%), which was calculated based on the actual age and sex distribution of the enrolled patients. In the results, the 5-year OS rate in the enrolled patients was 97.0% (95% CI, 95.0%–98.2%) and the lower 95% CI of the 5-year OS (95.0%) was higher than the threshold 5-year OS (86.1%). Based on this favorable result, these two categories were promoted to an absolute indication for ESD in the JGCA guidelines ver. 5 (Table 1).

Curability of ER

For curability of ER, en bloc resection with no lymphovascular invasion and a negative surgical margin is essentially required. When the lesion does not meet the curative criteria including lateral/vertical margins, histological type, size of tumor and depth of tumor, it was referred to as "non-curative resection" which means that surgical resection with lymphadenectomy is requested as standard treatment option.

With the update to the JGCA guidelines ver. 5, the technical terms related to the curability for ER of EGC were updated: eCura A to C-2 (Table 2), eCura is an LNM risk scoring system. In the JGCA guidelines ver. 5, curative resection and expanded curative resection were changed into eCura A and B, respectively. Based on the results by Hasuike et al., the categories of the differentiated-type mucosal cancer in the expanded curative resection were promoted to eCura A in the JGCA guidelines ver. 5. In addition, non-curative resection was divided into eCura C-1 and C-2: eCura C-1 corresponds to cases with the only unsatisfactory curative factor of piecemeal resection or resection en bloc with a positive horizontal margin and eCura C-2 corresponds to the others.

Tumor depth	UL	Differentiated		Undifferentiated	
		≤2 cm	>2 cm	≤2 cm	>2 cm
cT1a(M)	Negative				
	Positive	≤3 cm	>3 cm		
cT1b(SM)		≤3 cm	>3 cm		

White, light gray, dark gray, and black areas correspond to absolute indication of EMR/ESD, absolute indication of ESD, expanded indication of ESD, and relative indication, respectively.

Table 1: *The criteria of the indication for ER of EGC in the JGCA guidelines ver. 5.*

Tumor depth	UL	Differentiated		Undifferentiated	
		≤2 cm	>2 cm	≤2 cm	>2 cm
pT1a(M)	Negative				
	Positive	≤3 cm	>3 cm		
pT1b(SM1)		≤3 cm‡	>3 cm		
pT1b(SM2)					

† White, dark gray, and black areas correspond to eCura A§*, eCura B§*, and eCura C-2, respectively.
‡ A lesion with a submucosal undifferentiated component is regarded as eCura C-2.
§ Confined to negative horizontal and vertical margins without lymphovascular invasion
* Piecemeal resection or positive horizontal margin is regarded as eCura C-1.
ER, endoscopic resection; EGC, early gastric cancer; JGCA, Japanese Gastric Cancer Association; UL, ulceration; M, cancers confined to mucosa; SM, cancers invading into submucosa; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; SM1, submucosal invasion depth of <500 μm; SM2, submucosal invasion depth of ≥500 μm.

Table 2: *The criteria of the curability for ER of EGC in the JGCA guidelines ver. 5.*

Endoscopic Resection of Early Gastric Cancer, continued

Management after ER

In patients with eCura A after ER for EGC, follow up with esophagogastroduodenoscopy (EGD) at intervals of 6–12 months was recommended (Figure 2), with the main aim of detecting metachronous gastric cancers. In those with eCura B, follow up with EGD, as well as ultrasonography or computed tomography (CT) scan for the detection of metastases, is desirable at intervals of 6–12 months. However, it should be noted that 14.7% of these curabilities was changed into eCura C-2 in re-evaluating the pathology using additional deeper sections.

Since patients with eCura C-1 carry a very low risk for harboring LNM, nonsurgical treatments such as repeated ESD, diathermy, or careful follow-up in the expectation of a burn effect from the initial ESD could be proposed as alternatives and provided upon the patient's informed consent. In cases with no additional treatment, careful follow up with EGD is desirable at intervals of 6 months.

In this category, additional surgery was basically recommended for all patients due to the potential risk of LNM until the JGCA guidelines ver. 4. However, the rate of LNM in such patients who underwent gastrectomy with lymphadenectomy after ER was only 5.2%–11.0%. Thus, this recommendation may have been excessive. In the JGCA guidelines ver. 5, the statement for the management of eCura C-2 was changed as follows: additional surgery is the standard treatment method, but clinicians should decide considering the patient's physical condition. In clinical practice, about 80% of patients aged ≥80 years selected no additional treatment after ESD with eCura C-2. In such situation, the use of a risk-scoring system (eCura system) is recommended for evaluating the risk of LNM.

Some clinicians have been confused in the use of the term "eCura" because this term had already been used in the eCura system and the concept of "eCura" is different between the eCura system and eCura A to C-2 in the JGCA guidelines ver. 5.

A risk-scoring system for predicting the risk of LNM (eCura system)

In a large-scale multicenter study, the 5-year CSS rates in patients with additional surgery and those with no additional treatment after ESD with eCura C-2 for EGC were 98.8% and 97.5%, respectively. However, propensity-score matching analysis showed that, in such patients, gastric cancer-related death reduced to about one-third by receiving additional surgery. For further risk stratification of patients with eCura C-2, a scoring system for predicting the risk of LNM (eCura system) was established (Table 3). In this system, weighted points were assigned for pathological factors: 3 points for

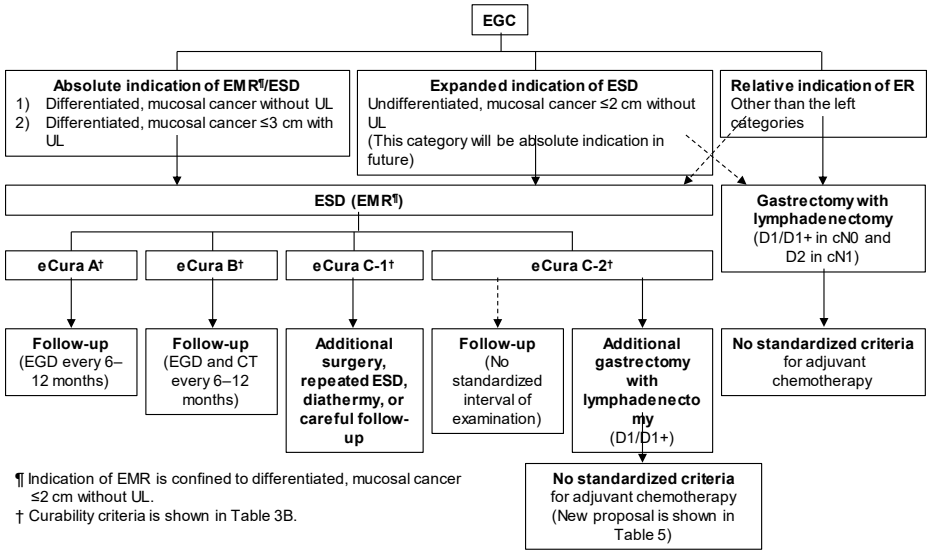

Figure 2: *The flowchart of follow-up after gastric ESD/EMR*

Endoscopic Resection of Early Gastric Cancer, continued

lymphatic invasion and 1 point each for tumor size >30 mm, positive vertical margin, SM2, and vascular invasion. This system consists of 7 points with three risk classifications. The rates of LNM in the low- (0–1 point), intermediate- (2–4 points), and high-risk (5–7 points) categories were 2.5%, 6.7%, and 22.7%, respectively. In patients without additional treatment after ESD with eCura C-2, the 5-year CSSs in each risk category were 99.6%, 96.0%, and 90.1%, respectively. However, since this was a retrospective single-center study, it is difficult to reach the conclusion that the eCura system was externally validated. A prospective, multicenter study with large cohort should be employed for highly reliable external validation of this system.

7-point scoring		Three risk classification		
Total points¶	LNM risk by point (%)	Risk category	LNM risk by category (%)	The 5-year CSS in patients with no additional treatment (%)
0	1.6	Low	2.5	99.6
1	2.6			
2	4.9	Intermediate	6.7	96.1
3	7.4			
4	8.3	High	22.7	90.1
5	19.9			
6	27.3			
7	26.7			

3 points for lymphatic invasion; 1 point each for tumor size >30 mm, positive vertical margin, SM2, and vascular invasion; 0 points each for undifferentiated-type and UL.
LNM, lymph node metastasis; ER, endoscopic resection; EGC, early gastric cancer; CSS, cancer-specific survival; SM2, submucosal invasion depth of ≥500 μm; UL, ulceration.

Table 3: *"eCura system" for predicting LNM in patients with eCura C-2 after ER for EGC.*

References

1. *Japanese Gastric Cancer Association. Gastric cancer treatment guideline. 5th ed. (in Japanese). Tokyo: Kanehara; 2018.*
2. *Ono H, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. Dig Endosc. 2016; 28: 3-15.*
3. *Gotoda T, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer. 2000; 3: 219-25.*
4. *Hirasawa T, et al. Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer. Gastric Cancer. 2009; 12: 148-52.*
5. *Hasuike N, et al. A non-randomized confirmatory trial of an expanded indication for endoscopic submucosal dissection for intestinal-type gastric cancer (cT1a): the Japan Clinical Oncology Group study (JCOG0607). Gastric Cancer. 2018; 21: 114-23.*
6. *Sano T, et al. Recurrence of early gastric cancer. Follow-up of 1475 patients and review of the Japanese literature. Cancer. 1993; 72: 3174-8.*
7. *Fujishiro M, et al. Updated evidence on endoscopic resection of early gastric cancer from Japan. Gastric Cancer. 2017; 20: 39-44.*
8. *Ono H, et al: Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001;48:225-9*
9. *Suzuki S, et al. Usefulness of a traction method using dental floss and a hemoclip for gastric endoscopic submucosal dissection: a propensity score matchng analysis (with videos). Gastrointest Endosc. 2016;83:337-46.*
10. *Hatta W, et al. A Scoring System to Stratify Curability after Endoscopic Submucosal Dissection for Early Gastric Cancer: "eCura system". Am J Gastroenterol. 2017; 112: 874-81.*

Contemporary Management of Advanced Gastric Cancer

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This brief review will discuss contemporary management of gastric adenocarcinoma which accounts for greater than 90% of all gastric malignancies. Endoscopic treatment of early gastric cancer (Tis or Stage I) has previously been discussed. Intermediate stages of gastric cancer (Stages II and III) are treated with multimodality therapies, while treatment of unresectable stage IV cancer is considered palliative. In Western countries approximately half of patients present with locally advanced or metastatic gastric cancer at diagnosis, and an additional 40% to 60% of those undergoing resection of gastric adenocarcinoma relapse after surgery. The most common metastatic sites include the liver, peritoneal surfaces, and non-regional/distant lymph nodes.

Appropriate treatment has been aided by addition of clinical staging groups (cTNM) which are different from stage groupings used for pathological (pTNM) or postneoadjuvent (ypTNM) therapy as defined by the 8th edition of the American Joint Committee on Cancer (AJCC, 2017) Cancer Staging Manual (Table 1). Clinical stage groups are based on two data sets, the US National Cancer Data Base (NCDB) and the Shizuoka Cancer Center data set from Japan representing aggregate data from over 4,000 patients. Prognosis is highly dependent on the stage of cancer at diagnosis (Figure 1). A better understanding of the molecular profiling of tumors and biomarker testing has also guided clinical decision making. While systemic therapies for advanced esophageal, esophagogastric junction and gastric adenocarcinomas (intestinal type cancers of the distal stomach and diffuse type cancers of the proximal stomach) are often used interchangeably, this chapter will emphasize treatment of gastric adenocarcinomas which include Siewert type III cancers (subcardial cancer with the tumor center between 2 and 5 cm below the esophagogastric junction) and more distal cancers.

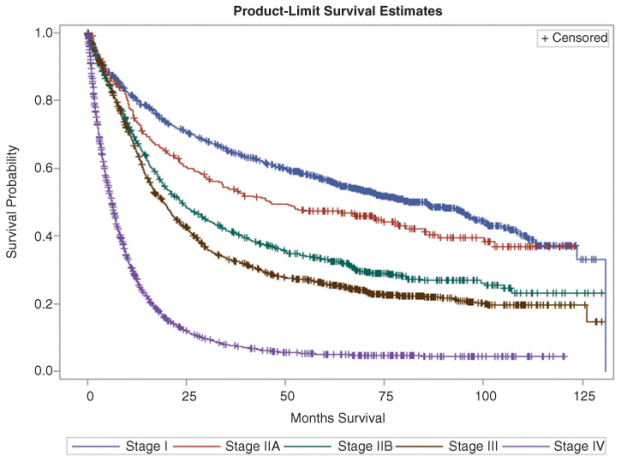

Figure 1. *Clinical stage (cTNM) and overall survival in patients diagnosed with gastric cancer, stratified by clinical stage groupings, based on NCDB data. Reproduced with permission from Ajani JA, Haejin I, Sano T et al. American Joint Committee on Cancer. Chapter 17: Stomach. In: AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.*

Recent Advances in the Molecular Biology of Advanced Gastric Cancer

Molecular Classification of Gastric Cancer

A detailed review of genetic risk assessment for gastric cancer is beyond the scope of this review. Hereditary cancer syndromes associated with a substantial risk for gastric cancer include the autosomal dominant hereditary diffuse gastric cancer syndrome (prophylactic gastrectomy is recommended between the ages of 18 and 40 for *CDH1* mutation carriers), Lynch Syndrome associated with mismatch repair deficiency (*EPCAM, MLH1, MSH2, MSH6, PMS2*), juvenile polyposis syndrome (*SMAD4, BMPR1A*), and Peutz-Jeghers syndrome (*STK11*). There is no clear-cut evidence to support gastric cancer screening in patients with familial adenomatous polyposis (FAP or AFAP), but given the high risk of ampullary carcinoma in these patients endoscopy with a side-viewing scope is recommended at age 25-30 years with visualization of the stomach. Other hereditary syndromes which predispose to gastric cancer, but with insufficient evidence to recommend routine screening include ataxia telangiectasia (*ATM*), Bloom syndrome (*BLM/RECQL3*), hereditary breast and ovarian cancer syndrome (*BRCA1, BRCA2*), Li-Fraumeni syndrome (*TP53*), xeroderma pigmentosum (7 different genes), and Cowden syndrome (*PTEN*).

Contemporary Management of Advanced Gastric Cancer, continued

Biomarkers that are Commonly Used To Guide Treatment of Advanced Gastric Cancer

Several validated biomarkers are currently being used in clinical practice for guiding drug therapy for patients with advanced gastric cancer, and molecular testing for HER2 status, microsatellite instability and programmed cell death ligand 1 (PD-L1) expression are routinely used in management of metastatic gastric cancer. A growing body of literature using molecular profiling and profiling using next generation-sequencing will likely yield additional avenues for guiding treatment in the future.

Overexpression or amplification of the HER2 gene and its protein product is associated with the development of gastric adenocarcinoma, and the addition of HER2 monoclonal antibodies in the form of trastuzumab (or an FDA-approved biosimilar) to chemotherapy is recommended HER2 overexpressing metastatic adenocarcinoma (see below). HER2 testing is recommended for all gastric cancer patients at the time metastatic disease is documented.

Microsatellite instability (MSI) has been discussed in relation to colorectal cancer (Section 3.0) as a hallmark of DNA mismatch repair deficient (dMMR) tumors. Pembrolizumab is a highly selective humanized monoclonal IgG4 antibody directed against the PD-1 receptor on the cell surface. The drug blocks the PD-1 receptor, preventing binding and activation of PD-L1 and PD-L2. In a remarkable example of bed-to-bedside translation the U.S. Food and Drug administration approved the immune checkpoint PDL-1 inhibitor pembrolizumab for the treatment of unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors as second-line or subsequent therapy. This site-agnostic approval includes treatment of MSI-H/dMMR gastric adenocarcinomas. MSI/dMMR status should therefore be assessed in all patients with documented or suspected metastatic gastric cancer. Additionally, pembrolizumab was granted FDA approval as a third or subsequent-line treatment option in patient with locally advanced or metastatic disease whose tumors express PDL-1, and PDL-1 testing is recommended for ad-

Table 1. *American Joint Committee on Cancer (AJCC) TNM Staging Classification for Carcinoma of the Stomach* [1]

Table 1. American Joint Committee on Cancer (AJCC) TNM Staging Classification for Carcinoma of the Sto

	Clinical Staging (cTNM)			Pathological Staging (pTNM)			
	cT	cN	M		pT	pN	M
Stage 0	Tis	NO	MO	**Stage 0**	Tis	NO	MO
Stage I	T1	NO	MO	**Stage I**	T1	NO	MO
	T2	NO	MO	**Stage IB**	T1	N1	MO
Stage IIA	T1	N1,N2,N3	MO	**Stage IIA**	T1	N2	MO
	T2	N1,N2,N3	MO		T2	N1	MO
Stage IIB	T3	NO	MO		T3	NO	MO
	T4a	NO	MO	**Stage IIB**	T1	N3a	MO
	T3	N1,N2,N3	MO		T2	N2	MO
	T4a		MO		T3	N1	MO
Stage III	T3	N1,N2,N3	MO	**Stage IIIA**	T2	N3a	MO
	T4a	N1,N2,N3	MO		T3	N2	MO
Stage IVA	T4b	Any N	MO		T4a	N1 or N2	MO
Stage IVB	Any T	Any N	M1		T4b	NO	MO
				Stage IIIB	T1	N3b	MO
					T2	N3b	MO
					T3	N3a	MO
					T4a	N3a	MO
					T4b	N1 or N2	MO
				Stage IIIC	T3	N3b	MO
					T4a	N3b	MO
					T4b	N3a or N3b	MO
				Stage IV	Any T	Any N	M1

1 Based on the American Joint Committee on Cancer TNM Staging classification for carcinoma of the stom
See this publication for definitions of T, N and M.

vanced stage patients. Since Epstein-Barr virus (EBV)-positive gastric cancers (8% to 10% of gastric cancers often of diffuse histology and located in the proximal stomach) often have elevated PDL-1 expression, it has been suggested that immune checkpoint inhibitor therapy may be beneficial in these patients, although more data is needed.

New molecular classifications based on the molecular profiling of tumors, sub-type classifications and immune profiling are establishing the foundation for future clinical trials with novel targeted agents and immunotherapy.

Approach to the Management of Gastric Adenocarcinoma. Treatment of Surgically Resectable and Locoregional Disease

Endoscopic treatment of early gastric cancer (Tis or Stage I) has been discussed in the previous chapter. Baseline clinical stage based on endoscopic ultrasound, CT, 18-fluorodeoxyglucose (FDG) PET/CT, and laparoscopy allows decisions on initial and subsequent treatment options including multi-modality therapy. Surgery is the primary treatment option for patients with localized gastric cancer with the goal of complete resection with negative margins (R0 resection). Microscopic (R1) or macroscopic (R2) residual disease in the absence of distant metastasis dictate further treatment. D2 lymph node dissection (D1 removal of the greater and lesser omenta and associated lymph nodes plus removal of all lymph nodes along the left gastric artery, common hepatic artery, celiac artery, splenic hilum, and splenic artery) is standard in some Asian countries, while a more limited lymph node dissection (D1 resection) is often performed in Western countries.

Combined modality therapy increases survival in medically fit patients with locoregional disease. Perioperative chemotherapy is preferred for localized resectable disease (T2 or higher or any N), while postoperative chemoradiation is used for those with T3-T4, any N or node-positive T1-T2 tumors with more limited D1 lymph node dissection. Preferred regimens for perioperative chemotherapy (cT2 or higher disease or any N) (Table 2) include fluoropyrimidine and oxaliplatin or fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT). Preoperative chemoradiation is also an option for these patients. Patients who have not received preoperative chemotherapy or chemoradiation and have pathological stage pT3, pT4, Any N or Any pT, N+ disease or those with less than D2 lymph node dissection should receive postoperative chemoradiation which includes fluo-

Table 2. *Principles of Systemic Therapy for Advanced Gastric Cancer*

TREATMENT OF SURGICALLY RESECTABLE AND LOCOREGIONAL DISEASE

Perioperative Chemotherapy (preferred)
Preferred Regimens
Fluoropyrimidine and oxaliplatin
Fluorouracil, leucovorin, oxalipaltin and docetaxel (FLOT)
Other Recommended Regimens
Fluorouracil and cisplatin

Preoperative Chemoradiation
Preferred Regimens
Fluorouracil (or capcitabine) and oxaliplatin
Fluorouracil (or capcitabine) and cisplatin
Fluoropyrimidine (fluorouracil or capcitabine) and paclitaxel
Other Recommended Regimens
Paclitaxel and carboplatin

Postoperative Chemoradiation
(For patients who receive less than D2 lymph node dissection)
Fluoropyrimidine (infusional fluorouracil or capcitabine) before and after fluoropyrimidine-based chemoradiation

Postoperative Chemotherapy
(For patients who have undergone primary D2 lymph node dissection)
Capcitabine and oxaliplatin

TREATMENT OF UNRESECTABLE DISEASE

First-Line Therapy (trastuzimab should be added to first-line therapy for HER2 overexpressing metastatic tumors. Not recommended for use with anthracyclines)
Preferred Regimens
Fluoropyrimidine (fluorouracil or capcitabine) and oxaliplatin
Fluoropyrimidine (fluorouracil or capcitabine) and cisplatin
Other Recommended Regimens
Fluorouracil and irinotecan
Paclitaxel and cisplatin or carboplatin
Docetaxel with cisplatin
Fluoropyrimidine (fluorouracil or capcitabine)
Docetaxel
Paclitaxel
DCF (docetaxel, carboplatin, fluorouracil) modifications
ECF (epirubicin, cisplatin, fluorouracil)
ECF modifications

Preferred Second-Line Therapy (Dependent on prior therapy and performance status)
Ramucirumab and paclitaxel
Docetaxel
Paclitaxel
Irinotecan
Trifluridine and tipracil
Pembrolizumab (for MSI-H or dMMR tumors)

Third-Line or Subsequent Therapy
Fluorouracil and irinotecan
Pembrolizumab for gastric adenocarcinoma with PD-L1 expression

ropyrimidine (infusional fluorouracil or capecitabine) before and after fluoropyrimidine-based chemoradiation.

Contemporary Management of Metastatic and Recurrent Gastric Cancer

Gastric adenocarcinomas are considered inoperable if there is evidence of locally advanced (N3 or N4 lymph node involvement or invasion/encasement of major vascular structure, excluding splenic vessels) disease, distant metastases, or peritoneal involvement (including positive cytology). Systemic therapy, however, can improve survival and provide palliation of symptoms in these patients. There is agreement based on several studies that patients who receive chemotherapy live for several months longer than patients who receive supportive care alone. While a variety of chemotherapeutic options exist, first-line therapy with two cytotoxic drug regimens is recommended for most patients, reserving 3-drug regimens for those with good performance status.

Preferred first line regimens include a fluropyrimidine such as fluorouracil or capcitabine combined with either oxaliplatin or cisplatin (Table 2). A phase III randomized trial suggested that FOLFOX (containing oxaliplatin) is associated with less toxicity with similar or improved efficacy (in older adults) compared to fluorouracil plus cisplatin. Based on the ToGA trial, addition of trastuzimab to first-line therapy is recommended for those whose tumors are HER-2 positive (based on immunohistochemistry or *in situ* hybridization). Other drug combinations with evidence for use as first line regimens include fluorouracil and irinotecan, paclitaxel with cisplatin or carboplatin, docetaxel and cisplatin, DCF (docetaxel, carboplatin, fluorouracil) modifications, and ECF (epirubicin, cisplatin, and fluorouracil) modifications.

Preferred second line therapies (dependent upon prior therapy and performance status) include ramucirumab (a fully humanized monoclonal antibody directed against vascular endothelial growth factor receptor-2 or VEGFR-2) and paclitaxel, single agent docetaxel, paclitaxel, or irinotecan, and trifluridine and tipiricil. Pembrolizumab is recommended for second-line or subsequent therapy for MSI-H or dMMR tumors. Pembrolizumab is also recommended for third-line or subsequent therepy for gastric adenocarcinoma with PD-L1 expression (as determined by an FDA-approved companion diagnostic test). Other third-line therapies include ramucirumab, irinotecan and cisplatin, and docetaxel and irinotecan. The PD-1 inhibitor Nivolumab has been approved by the Japanese Ministry of Health, Labor and Welfare for treatment of advanced gastric cancer that has progressed on previously received chemotherapy.

Palliative Care

The goal of palliative care in patients with advanced or metastatic gastric cancer is to improve quality of life and is best accomplished through an interdisciplinary approach. Common complications which require attention include bleeding, obstruction and pain.

Bleeding is common in patients with gastric cancer and has treatment approaches include endoscopic approaches, interventional radiology approaches and external beam radiation. Endoscopic therapy including injection therapy with epinephrine, ablative therapy with argon plasma coagulation, and mechanical clip placement maybe transiently effective but results are often short-lived. A new approach using Hemospray® an inert mineral powder has been shown to successfully stop acute bleeding from gastrointestinal neoplasms. The powder absorbs water at the bleeding site and acts to form a mechanical barrier over the bleeding site. None of these modalities, however, provide a long-term solution to chronic tumor-related bleeding. Angiographic embolization with gel foams or metal coils is also an option for acute bleeding. External beam radiation therapy may be effective in managing chronic tumor-associated bleeding.

Gastric outlet obstruction from distal gastric cancer results in nausea, vomiting, abdominal discomfort and reduced oral intake. While surgical bypass is an option, alternate approaches are preferable as palliation. Endoscopic placement of self-expanding metal stents is a non-surgical option for palliation of tumor-associated gastric outlet obstruction which carries a high rate of success in selected patients. When these modalities are not possible and the goal is relief of obstructive symptoms of abdominal distension with associated discomfort, nausea and vomiting placement of a percutaneous venting gastrostomy is an option.

Tumor-related pain is best approached with the assistance of palliative care experts on a multidisciplinary team.

Contemporary Management of Advanced Gastric Cancer, continued

References

1. *Ajani JA, Haejin I, Sano T et al. American Joint Committee on Cancer. Chapter 17: Stomach. In: AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.*
2. *Bang YJ, Van Cutsem E, Feyereislova A et al. Trastuzimab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-esophageal junction cancer (TOGA):a phase 3 open-label, randomized controlled trial. Lancet 2010;3 76:687-697.*
3. *Biagioni A, Skalamera I, Peri S et al. Update on gastric cancer treatments and gene therapies. Cancer Metastasis Rev 2019; Epub ahead of print Sept 5.*
4. *Cheng J, Cai M, Shuai X et al. Systemic therapy for previously treated advanced gastric cancer: A systematic review and meta-analysis. Crit Rev in Oncol/Hematol 2019;143:27-45.*
5. *Marabelle A, Le DT, Ascierto PA wet al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: Results from the phase II KEYNOTE-158 study. J Clin Oncol 2019; 37: Epub ahead of print November 4.*
6. *National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Gastric cancer. Version 3.2019. Available at www.NCCN.org.*
7. *PDQ Adult Treatment Editorial Board. Gastric Cancer Treatment (PDQ®): Health professionals Version. PDQ cancer information summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2019.*
8. *Wang R, Song S, Harada K eta l. Multiplex profiling of peritoneal metastases from gastric adenocarcinoma identified novel targets and molecular subtypes that predict response. Gut 2019; Epub ahead of print June.*
9. *Wing-Lok C, Lam K, So T et al. Third-line systemic treatment in advanced/metastatic gastric cancer: a comprehensive review. Ther Adv Med Oncol 2019;11:1-11.*

Epidemiology and Global Impact: Is Esophageal Cancer on the Rise?

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Incidence of Esophageal Cancer

Esophageal cancer is the seventh most commonly diagnosed cancer and the sixth leading cause of cancer-related mortality worldwide, with 572,000 new cases and over 500,000 deaths from esophageal cancer in 2018 (Figure 1).[1-6] The highest age-standardized incidence rates of esophageal cancer have been reported in eastern Asia and eastern Africa (12.3 per 100,000 and 8.3 per 100,000, respectively). However, considerable differences exist in geographic patterns, secular trends, and risk factor profiles for the two main histological subtypes, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC).

Esophageal Squamous Cell Carcinoma

Approximately 87% of esophageal cancers globally are ESCC.[7] Incidence rates for ESCC range from 1.2 per 100,000 in northern America to 8.8 per 100,000 in eastern and southeastern Asia.[7] Incidence rates of ESCC have declined

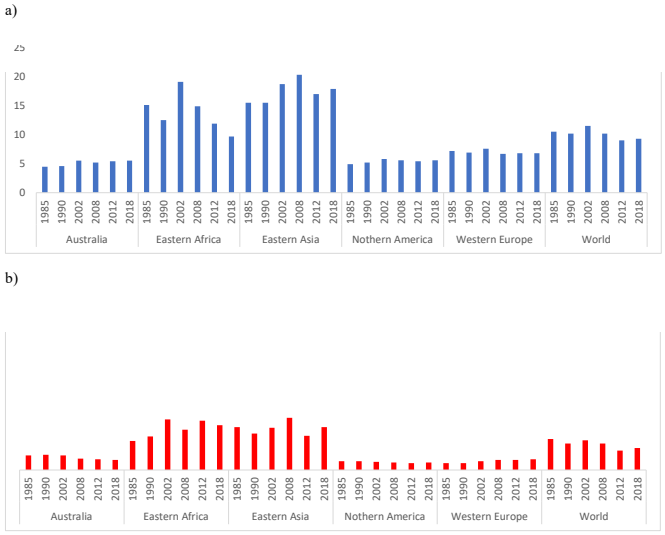

Figure 1: *Age-standardized incidence rates for selected regions over time in a) men and b) women*

in most Western populations from 1970 to 2015 but have remained stable or slightly increased in less developed regions. For example, there has been a sharp decline in men in France (from 28.6 per 100,000 in 1979 to 6.4 per 100,000 in 2013) and Hong Kong, China (from 10.1 per 100,000 in 1994 to 5.0 per 100,000 in 2013).[8] ESCC incidence rates are projected to continue to decline through 2030 in developed countries, including France, the United Kingdom, and the United States.[9] In 2012, 80% of ESCC cases worldwide occurred in central and southeastern Asia, which corresponds to approximately 315,000 new cases annually, more than 50% of which were diagnosed in China (4.9 per 100,000 in Hong Kong).[7, 8, 10] There are two geographic "esophageal cancer belts," one extending from northern China to northern Iran (8.8 per 100,000) and another stretching from eastern to southern Africa (5.1 per 100,000).[7] However, it is difficult to draw conclusions regarding secular trends in these areas, because they have limited data availability and lack population-based cancer registries.[11]

Esophageal Adenocarcinoma

EAC incidence has been increasing since the 1970s. In Europe, North America, and Australia, incidence has increased at a rate of 3.5–8.0% per year.[12] The global incidence of EAC was 0.7 per 100,000 in 2012 with the highest incidence in North America and northern/western Europe (1.9 per

100,000) and lowest incidence in sub-Saharan Africa (0.3 per 100,000).[7] Highest rates for EAC in 2012 were observed in the United Kingdom (7.2 per 100,000 in men) and the Netherlands (7.1 per 100,000 in men).[7] By 2030, rates are projected to rise to 7.8 and 8.7 per 100,000 in men in these two countries.[9]

Risk Factors for Esophageal Cancer

Esophageal Squamous Cell Carcinoma

ESCC is more common in men than women (69% vs. 31%, respectively); however, the magnitude of the ratio of males to females varies from 4:1 in the United States to 1:1 in China and Iran.[8, 13] This difference is likely due to lifestyle factors associated with ESCC, such as tobacco and alcohol use which are more prevalent among men than women in some countries. In other countries, such as Iran, alcohol is rarely consumed and is not a strong risk factor for ESCC.

One of the most consistent independent risk factors for ESCC is low socioeconomic status, defined based on income, job type, or education. This risk remains meaningful after comprehensive adjustment for other potential risk factors,[13] even in countries where social status is compressed, such as China and India.[14, 15]

In developed countries, tobacco use is a strong risk factor for ESCC (relative risk [RR] ranging from 3 to 9 in current vs. non-smokers).[13, 16] Given the high prevalence, tobacco use contributes to a large proportion of population attributable risk. In developing countries, tobacco use appears to have a weaker association with ESCC risk with a RR of approximately 1.5.[17, 18] A duration effect has been observed with respect to smoking tobacco and ESCC risk. One study showed that fewer cigarettes per day for longer duration was more harmful than more cigarettes per day for shorter duration for equivalent pack-years of smoking.[19]

Alcohol use has been found to be an ESCC risk factor in both developing and developed countries, with a three-fold increase in Asia, Africa, and South America, six-fold increase in Europe, and nine-fold increase in North America.[20] The population attributable risk for alcohol varies between countries (e.g., 72.4% of ESCC cases are attributed to excess alcohol use in the United States vs. 10.9% in China).[16, 21] The combined use of alcohol and tobacco appears to have a multiplicative, rather than additive, effect on ESCC risk.[22]

Several studies investigated the association between infectious agents, such as *Helicobacter pylori* and human papillomavirus (HPV), and ESCC risk. A meta-analysis of 2,124 cases and 5,588 controls from 19 studies found no association with *H. pylori* overall (pooled odds ratio, OR: 1.16; 95% confidence interval, CI: 0.57, 0.97) or CagA-positive *H. pylori* strains (pooled OR: 0.97; 95% CI: 0.79, 1.19).[23] However, a stratified analysis of Asian vs. non-Asian study locations found CagA-positive *H. pylori* infection was associated with increased risk of ESCC in non-Asian countries (pooled OR, 1.41; 95% CI: 1.02,1.94) but decreased risk in Asian countries (pooled OR: 0.74; 95% CI: 0.57, 0.97).[23] Regarding HPV, an international consortium assessed cancer samples using antibodies directed toward the major HPV capsid protein (L1) or the early proteins (E6 or E7) of eight high-risk, two low-risk, and four cutaneous HPV types. Only 0.3% of cancer samples were positive.[24] A follow up study showed that the presence of HPV DNA, HPV mRNA or p16(INK4a) upregulation was not consistently found in tumor tissue samples.[25] If any ESCC cases were caused by HPV, the rate was very low, meaning HPV is unlikely to be a main cause of ESCC.

Other factors that have consistently been found to increase ESCC risk include chewing betel quid (RR, 2.2–5.6), consumption of vegetables pickled without the use of vinegar (traditional Chinese method; RR, 2.0), thermal injury from foods >70°C, history of achalasia (RR, 28), and genetic diseases, such as tylosis from the *RHBDF2* gene mutation at 17q25 (estimated penetrance, 90%)[26] and Fanconi anemia.[13, 27]

Esophageal Adenocarcinoma

Barrett's esophagus (BE) is a condition in which the normal esophageal squamous epithelium lining the lower esophagus is replaced with columnar intestinal epithelium.[28] BE is the only known precursor to EAC.[28] In Europe and North America, 1–2% of the general adult population have BE.[29, 30] The risk of EAC in patients with BE is 30- to 125-fold greater than in the general population; however the annual progression risk of BE is low (0.1–0.5% per year).[31] Risk factors for BE include male gender (male:female ratio 2:1), non-Hispanic white race, obesity (particularly abdominal obesity),[32] and gastroesophageal reflux disease (GERD; BE prevalence 5–15% in GERD patients). *H. pylori* infection is associated with lower risk of BE (OR, 0.42), possibly due to decreased acid production in persons with *H. pylori* infection.[33] However, > 90% of patients newly diagnosed with EAC do not

have an existing BE diagnosis.[34] Currently, it is unclear if this observation is due to underutilized screening for BE, or if EAC could arise without BE.[35]

EAC incidence increases with age and is more common among recent birth cohorts.[36] The mean age at diagnosis is 67 years in men and 72 years in women.[37] The sex distribution of EAC varies by country. The male-to-female ratio of EAC is higher in developed areas (7.6 in North America, 6.0 in Europe) and lower in developing countries (3.9 in Latin America, 1.0 in Africa).[38] With regard to race/ethnicity, EAC incidence is much higher in non-Hispanic whites compared with Africans and Asians in the United States and the United Kingdom.[39, 40] In the United States, Hispanics have been found to have an intermediate risk of EAC compared with non-Hispanic Whites. The reason for these racial/ethnic differences is not apparent and could be mediated partly by lifestyle and genetic factors.[41]

Up to one-third of EAC cases could be hereditary and attributable to germline genetic susceptibility.[42] A meta-analysis of four genome-wide association studies of 6,167 BE patients, 4,112 patients with EAC, and 17,159 controls confirmed associations for eight previously identified single nucleotide polymorphisms located at or near the *MHC* region and the *FOXF1, GDF7, TBX5, FOXP1, CRTC1, BARX1,* and *ALDHIA2* genes. Further, eight new risk loci, including one variant (rs9823696, near *ABCC5* and *HTR3C*), were associated with EAC risk independent of BE.[43]

GERD is the strongest risk factor for EAC.[44] A meta-analysis of five studies with 2,357 EAC cases and 4,057 controls found that increasing duration of GERD symptoms was associated with increased risk of EAC at <10 years (OR, 2.80; 95% CI: 1.60,4.91), 10 to <20 years (OR, 3.85; 95% CI: 2.93, 5.07), and ≥20 years (OR, 6.24; 95% CI: 3.37, 11.55).[45] A meta-analysis of six studies showed proton-pump inhibitor therapy was associated with a 71% lower risk of neoplastic progression in patients with BE (adjusted OR, 0.29; 95% CI: 012, 0.79).[46] However, studies of the protective effect of antireflux surgery have had inconsistent results, as EAC incidence was not different in antireflux surgery compared to medical GERD treatment (pooled incidence rate ratio, IRR, 0.76; 95% CI: 0.42, 1.39), and EAC risk remained elevated in patients after antireflux surgery compared with the general population (pooled IRR, 10.78; 95% CI: 8.48, 13.71).[47]

Obesity has been associated with EAC. Risk of EAC increases in a linear exposure-response pattern with body mass index (BMI).[48] Further, in a meta-analysis of three case-control and three cohort studies, central adiposity, measured by waist-to-hip ratio, waist circumference, or visceral fat on abdominal computed tomography, was associated with EAC independent of BMI (adjusted OR, 2.51; 95% CI: 156, 4.04).[49] Two mechanisms have been proposed for the association of obesity and EAC. One hypothesis is mechanical; gastric compression from excess abdominal adipose tissue increases intra-gastric pressure and the incidence of GERD.[50] The second hypothesis is that obesity, a pro-inflammatory state, leads to increased levels of EAC-associated adipokines, such as serum leptin and insulin, and increased EAC risk.[51] While increasing prevalence of obesity in Western populations could contribute to the increased incidence of EAC, the extent of obesity's contribution to the increase in EAC incidence is still debatable.[52]

Tobacco smoking is a moderately strong risk factor for EAC, increasing the odds by two-fold, but weaker than that for ESCC.[53] A pooled analysis of 12 studies from the International Barrett's and Esophageal Adenocarcinoma Consortium found a dose-response relationship with a 2.7-fold increased risk for those with ≥45 smoking pack-years. This risk seems to persist for a long time after smoking cessation. A meta-analysis of 23 studies found only a small difference in risk of EAC between current and former smokers. The reduced risk was mostly among those who ceased smoking for ≥20 years (risk ratio, 0.72; 95% CI: 0.52, 1.01).[54] Proposed mechanisms for the increased risk include DNA hypermethylation damage due to tobacco carcinogens[55] and increased acid reflux exposure due to relaxation of the lower esophageal sphincter by nicotine.[56]

H. pylori infection has been associated with a 40–60% reduced risk of EAC in several meta-analyses.[23,57] This protective effect could be due to atrophic gastritis and reduced acid in gastric fluid. Studies have not shown a consistent protective effect of *H. pylori* infection and GERD.[58, 59] However, a meta-analysis of six case-control studies with 1308 BE cases and 1388 population-based controls found that *H. pylori* infection was inversely associated with BE risk (adjusted OR, 0.44; 95% CI: 0.36, 0.55).[60] Accordingly, eradication of *H. pylori* infection in developed and Western regions has been proposed as a cause of increased EAC incidence rates. Non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, and statins have been implicated in chemoprevention of EAC.[48] A pooled analysis of five case-control and one cohort study found a 32% reduced risk of EAC with NSAID

use.[61] Another pooled analysis of eight randomized clinic trials found a strongly reduced 20-year EAC mortality risk among daily aspirin users (hazard ratio, 0.36; 95% CI: 0.21, 0.63).[62] However, the benefit of EAC risk reduction via NSAID use may not outweigh the risks from their side effect profile. A meta-analysis of three cohort and two case-control studies with 312 EAC cases and 2125 BE controls found that statins were associated with a 41% reduction in EAC risk (adjusted OR, 0.59; 95% CI: 0.45, 0.78).[63] However, large, randomized controlled trials are needed to confirm the chemoprotective effect of statin use in EAC.

Conclusions

The incidence of esophageal cancer overall has remained stable; however, ESCC incidence is declining, whereas EAC incidence is increasing worldwide. This trend is mostly due to changes in ESCC and EAC incidences in developed and Western regions of the world, such as North America and western Europe; these incidences remain relatively stable in developing regions. ESCC and EAC have common risk factors such as age, sex, and smoking; however, this trend in developed countries is likely due to decreases in ESCC-specific risk factors (e.g., low socioeconomic status, alcohol consumption, pickling methods) and increases in EAC risk factors (e.g., GERD, abdominal obesity, decline of *H. pylori* infection).

References

1. *Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.*
2. *Parkin DM, Pisani P, Ferlay J. Estimates of the worlwide incidence of eighteen major cancer in 1985. Int J Cancer 1993;54:594-606.*
3. *Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. Int J Cancer 1999;80:827-41.*
4. *Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.*
5. *Ferlay J, Shin H-R, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893-917.*
6. *Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136.*
7. *Arnold M, Soerjomataram I, Ferlay J, et al. Global incidence of oesophageal cancer by histological subtype in 2012. Gut 2015;64:381-7.*
8. *Wang Q-L, Xie S-H, Wahlin K, et al. Global time trends in the incidence of esophageal squamous cell carcinoma. Clin Epidemiol 2018;19:717-28.*
9. *Arnold M, Laversanne M, Brown LM, et al. Predicting the future burden of esophageal cancer by histological subtype: international trends in incidence up to 2030. Am J Gastroenterol 2017;112:1247-55.*
10. *Ferlay J, Soerjomataram I, Ervik M. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France, 2013.*
11. *Klingelhofer D, Zhu Y, Braun M, et al. A world map of eosphagus cancer research: a critical accounting. J Transl Med 2019;17:150.*
12. *Edgren G, Adami H-O, Widerpass E, et al. A global assessment of the oesophageal adenocarcinoma epidemic. Gut 2013;62:1406-14.*
13. *Abnet CC, Arnold M, Wei W-Q. Epidemiology of esophageal squamous cell caricnoma. Gastroenterology 2018;154:360-73.*
14. *Wei W-Q, Abnet CC, Lu N, et al. Risk factors for oesophageal squamous dysplasia in adult inhabitants of a high risk region of China. Gut 2005;54:759-63.*
15. *Dar NA, Shah IA, Bhat GA, et al. Socioeconomic status and esophageal squamous cell carcinoma risk in Kashmir, India. Cancer Sci 2013;104:1231-6.*
16. *Engel LS, Chow W-H, Vaughan TL, et al. Population attributable risks of esophageal and gastric cancers. J Natl Cancer Inst 2003;95:1404-13.*
17. *Nasrollahzadeh D, Kamangar F, Aghcheli K, et al. Opium, tobacco, and alcohol use in relation to oesophageal squamous cell caricnoma in a high-risk area of Iran. BR J Cancer 2008;98:1857-63.*
18. *Okello S, Churchill C, Owori R, et al. Population attributative fraction of esophageal squamous cell carcinoma due to smoking and alcohol in Uganda. BMC Cancer 2016;16:446.*

Epidemiology and Global Impact: Is Esophageal Cancer on the Rise?, continued

19. *Lubin JH, Cook MB, Pandeya N, et al. The importance of exposure rate on odds ratios by cigarette smoking and alcohol consumption for esophageal adenocarcinoma and squamous cell carcinoma in the Barrett's Esophagus and Esophageal Adenocarcinoma Consortium. Cancer Epidemiol 2012;36:306-16.*
20. *Volume 100E: Personal Habits and Indoor Combustions. Lyon, France: International Agency for Research on Cancer, 2012.*
21. *Wang J-B, Fan J-H, Liang H, et al. Attribuative causes of esophageal cancer incidence and mortality in China. PLoS One 2012;7:e42281.*
22. *Prabhu A, Obi KO, Rubenstein JH. The syngergistic effects of alcohol and tobacco consumption on the risk of esophageal squamous cell carcinoma: a meta-analysis. Am J Gastroenterol 2014;109:822-7.*
23. *Nie S, Chen T, Yang X, et al. Association of Helicobacter pylori infection with esophageal adenocarcinom and squamous cell carcinoma: a meta-analysis. Dis Esophagus 2014;27:645-53.*
24. *Sitas F, Egger S, Urban MI, et al. InterSCOPE Study: associations between esophageal squamous cell carcinoma and human papillomavirus serological markers. J Natl Cancer Inst 2012;104:147-58.*
25. *Halec G, Schmitt M, Egger S, et al. Mucosal alpha-papillomaviruses are not associated with esophageal squamous cell carcinomas: lack of mechanistic evidence from South Africa, China, and Iran and from a world-wide meta-analysis. Int J Cancer 2015;139:85-98.*
26. *Blaydon DC, Etheridge SL, Risk JM, et al. RHBDF mutations are associated with Tylosis, a familial esophageal cancer syndrome. Am J Hum Genet 2012;90:340-6.*
27. *Rosenberg PS, Alter BP, Ebell W. Cancer risks in Fanconi anemia: findings from the German Fanconi Anemia Registry. Haematologica 2008;93:511-7.*
28. *Spechler SJ. Barrett's esophagus and esophageal adenocarcinoma: pathogenesis, diagnosis, and therapy. Med Clin North Am 2002;86:1423-45.*
29. *Cameron AJ, Zinsmeister AR, Ballard DJ, et al. Prevalence of columnar-lined (Barrett's) esophagus: comparison of population-based clinical and autopsy findings. Gastroenterology 1990;99:918-22.*
30. *Shaheen NJ, Richter JE. Barrett's oesophagus. Lancet 2009;373:850-61.*
31. *Hvid-Jensen F, Pedersen L, Drewes AM, et al. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med 2011;365:1375-83.*
32. *Kramer JR, Fischbach LA, Richardson P, et al. Waist-to-hip ratio, but not body mass index, is associated with an increased risk of Barrett's esophagus in white men. Clin Gastroenterol Hepatol 2013;11:373-381.*
33. *Runge TM, Abrams JA, Shaheen NJ. Epidemiology of Barrett's esophagus and esophageal adenocarcinoma. Gastroenterol Clin North Am 2015;44:203-31.*
34. *Bhat SK, McManus DT, Coleman HG, et al. Oesophageal adenocarcinoma and prior diagnosis of Barrett's oesophagus: a population-based study. Gut 2015;64:20-5.*
35. *Sawas T, Killcoyne S, Iyer PG, et al. Identification of prognostic phenotypes of esophageal adenocarcinoma in 2 independent cohorts. Gastroenterology 2018;155:1720-8.*
36. *Thrift AP, Whiteman DC. The incidence of esophageal adenocarcinoma continues to rise: analysis of period and birth cohort effects on recent trends. Ann Oncol 2012;23:3155-61.*
37. *Rutegard M, Shore R, Lu Y, et al. Sex differences in the incidence of gastrointestinal adenocarcinoma in Sweden 1970-2006. Eur J Cancer 2010;46:1093-100.*
38. *Xie S-H, Lagergren J. A global assessment of the male predominance in esophageal adenocarcinoma. Oncotarget 2016;7:38876-83.*
39. *Ali R, Barnes I, Cairns BJ, et al. Incidence of gastrointestinal cancers by ethnic group in England, 2001-2007. Gut 2013;62:1692-703.*
40. *Kubo A, Corley DA. Marked multi-ethnic variation of esophageal and gastric cardia carcinomas within the United States. Am J Gastroenterol 2004;99:582-88.*
41. *El-Serag HB, Peterson NJ, Carter J, et al. Gastroesophageal reflux among different racial groups in the United States. Gastroenterology 2004;126:1692-9.*
42. *Ek WE, Levine DM, D'Amato M, et al. Germline genetic contributions to risk for esophageal adenocarcinoma, Barrett's esophagus, and gastroesophageal reflux. J Natl Cancer Inst 2013;105:1711-8.*

Epidemiology and Global Impact: Is Esophageal Cancer on the Rise?, continued

43. *Gharahkhani P, Fitzgerald RC, Vaughan TL, et al. Genome-wide association studies in oesophageal adenocaricnoma and Barrett's oesophagus: a large-scale meta-analysis. Lancet Oncol 2016;17:1363-73.*
44. *Lagergren J, Bergstrom R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999;340:825-31.*
45. *Cook MB, Corley DA, Murray LJ, et al. Gastroesophageal reflux in relation to adenocarcinomas of the esophagus: a pooled analysis fro mthe Barrett's and esophageal adenocarcinoma consortium (BEACON). PLoS One 2014;9:e103508.*
46. *Singh S, Garg SK, Singh PP, et al. Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis. Gut 2014;63.*
47. *Maret-Ouda J, Konings P, Lagergren J, et al. Antireflux surgery and risk of esophageal adenocarcinoma: a systematic review and meta-analysis. Ann Surg 2016;263:251-7.*
48. *Coleman HG, Xie S-H, Lagergren J. The epidemiology of esophageal adenocarcinoma. Gastroenterology 2018;154:390-405.*
49. *Singh S, Sharma AN, Murad MH, et al. Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. Clin Gastroenterology Hepatol 2013;11:1399-1412.*
50. *Chandar AK, Iyer PG. Role of obesity in the pathogenesis and progression of Barrett's esophagus. Gastroenterol Clin North Am 2015;44.*
51. *Duggan C, Onstad L, Hardikar S, et al. Association between markers of obesity and progression from Barrett's esophagus to esophageal adenocarcinoma. Clin Gastroenterol Hepatol 2013;11.*
52. *Kong CY, Nattinger KJ, Hayeck TJ, et al. The impact of obesity o nthe rise in esophageal adenocarcinoma incidence: esitmates fro ma disease simulation model. Cancer Epidemiol Biomarkers Prev 2011;20:2450-6.*
53. *Cook MB, Kamangar F, Whiteman DC, et al. Cigarette smoking and adenocaricnomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. J Natl Cancer Inst 2010;102:1344-53.*
54. *Wang Q-L, Xie S-H, Li W-T, et al. Smoking cessation and risk of esophageal cancer by histological type: systematic review and meta-analysis. J Natl Cancer Inst 2017;109.*
55. *Kaz AM, Wong CJ, Varadan V, et al. Global DNA methylation patterns in Barrett's esohpagus, dysplastic Barrett's, and esophageal adenocarcinoma are associated with BMI, gender, and tobacco use. Clin Epigenetics 2016;8:111.*
56. *Kadakia SC, De La Baume HR, Shaffer RT. Effects of transdermal nicotine on lower eosphageal sphincter and esophageal motility. Dig Dis Sci 1996;41:2130-4.*
57. *Xie F-J, Zhang Y-P, Zheng QQ, et al. Helicobacter pylori infection and esophageal cancer risk: an updated meta-analysis. World J Gastroenterol 2013;19:2098-107.*
58. *Yaghoobi M, Farrokhyar F, Yuan Y, et al. Is there an increased risk of GERD after Helicobacter pylori eradication?: a meta-analysis. Am J Gastroenterol 2010;105:1007-13.*
59. *Tan J, Wang YC, Sun X, et al. The effect of Helicobacter pylori eradication therapy on the development of gastroesophageal disease. Am J Med Sci 2015;349:364-71.*
60. *Wang Z, Shaheen NJ, Whiteman DC, et al. Helicobacter pylori infection is associated with reduced risk of Barrett's esophagus: an analysis of the Barrett's and esophageal adenocarcinoma consortium. Am J Gastroenterology 2018;113:1148-55.*
61. *Liao LM, Vaughan TL, Corley DA, et al. Nonsteroidal anti-inflammatory drug use reduces risk of adenocarcinomas of the esophagus and esophagogastric junciton in a pooled analysis. Gastroenterology 2012;142:442-52.*
62. *Rothwell PM, Fowkes FG, Belch JF, et al. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet 2011;377:31-41.*
63. *Singh S, Singh AG, Singh PP, et al. Statins are associated with reduced risk of esophageal cancer, particularly in patients with Barrett's esophagus: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2013;11:620-9.*

Esophageal cancer screening: who, when and how?

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Introduction

Esophageal cancer is the sixth leading cause of cancer death in the world among men. In the last 40 years, the incidence has multiplied in countries such as the United States, where it rose from 0.4/100,000 in 1975 to 2.6/100,000 in 2009. The incidence of adenocarcinoma in western countries is rising due to an increase in gastroesophageal reflux disease. Although the incidence of squamous cell carcinoma is declining, it is still the most frequent esophageal carcinoma. As both have well-identified risk factors, efforts should focus on designing accurate, safe and cost-effective prevention strategies, since most of the time the diagnosis is made when the disease is at advanced stage and has become symptomatic and highly fatal.[1-3]

Adenocarcinoma

Adenocarcinoma has a clear relationship with Barrett's esophagus, a complication of gastroesophageal reflux disease that can only be diagnosed by endoscopy and biopsies. The main risk factors are reflux disease, central abdominal obesity, male gender, tobacco consumption, Caucasian race, older age, a high-fat diet and the presence of dysplasia in the biopsy. In patients with no dysplasia, the risk is 0.12–0.50% to 0.33–0.70% per year, but it could be even lower according to recent data. The natural history of low-grade dysplasia has not been elucidated. Although the precise diagnosis of Barrett's with low or no dysplasia seems to have a minimal impact on overall survival, most cases cannot be timely diagnosed yet, so the allocation of resources for detection seems to be a good option.[1]

Who to screen?

A screening endoscopy is not recommended for the general population. Both, the American Gastroenterology Association and the European Society for Gastrointestinal Endoscopy, suggest that screening can be considered in individuals with several risk factors. The British Society of Gastroenterology guideline recommends screening in patients with at least 3 of the following phenotypes: male, over 50, Caucasian and obese. The American College of Physicians recommends screening men over 50 with a history of at least 5 years of reflux and who have some additional risk factors: hiatal hernia, nocturnal symptoms of reflux, obesity, and smoking. Fewer criteria are required for the screening if there is a family history of Barrett's or cancer. The sensitivity and specificity of the different risk factor combinations have not been demonstrated. On the other hand, many patients with esophageal cancer deny a history of reflux symptoms, so recommendations should not focus only on the clinical presentation.[4-6]

There are some models, such as "M-BERET", which are considered as Barrett's predictors; they use variables such as age, abdominal circumference or body mass index, presence of symptoms in the previous week or use of antacid medication. The usefulness of such models lies in reserving the endoscopic resource for those who could theoretically provide better yields, but more validation is needed.[7]

When to screen?

The moment to start screening is when enough risk factors have been detected. If no Barrett's is found, no further screening is necessary. If Barrett's is diagnosed and no dysplasia is detected, surveillance endoscopy should be performed every 3 to 5 years. If low-grade dysplasia is found, endoscopy should be performed at 6 to 12 months, and then every year if no high-grade dysplasia is detected, until 2 consecutive endoscopies show no dysplasia. The endoscopy should be repeated three months after the diagnosis of a high-grade condition, although treatment is strongly recommended.[1, 5, 8]

How to surveil?

A surveillance plan should be proposed based on the probability of the patient's progression to cancer and his/her acceptance to comply with a periodic endoscopic control. The classification recommended for Barrett's is Prague's. If an erosive esophagitis is detected, another endoscopy should be performed after treating it, to rule out Barrett's.[9] The preferred strategy is to take a biopsy every 2 cm from each quadrant, and to biopsy any visible lesions. Chromoendoscopy is not preferred over white light for routine use. Surveillance is not recommended in patients with irregular Z lines or cardial intestinal metaplasia. In patients with Barrett's shorter than 3 cm without dysplasia or metaplasia, an endoscopy should be performed every 5 years. No further surveillance is required if no Barrett's is found. If there is metaplasia, the endoscopy should be repeated within 3 to 5 years, and if it is a long Barrett's it should be done every 2 or 3 years.[1, 5, 8]

Squamous cell carcinoma

Who to screen?

Age is the single most significant risk factor for squamous cell carcinoma. Non-modifiable factors such as being male, black race, genetic predisposition, association with achalasia, otolaryngologic squamous cell tumors, systemic sclerosis, Plummer Vinson syndrome, and tylosis are also associated with squamous cell carcinoma. Modifiable factors include alcoholism, smoking, the intake of caustic or high-temperature substances, chest radiotherapy, and rare conditions such as esophageal papilloma. Smoking causes a 5-fold risk of developing squamous cell carcinoma, but this may vary due to the geographic distribution and other cofactors. Being tobacco a known carcinogen, smoking cessation can also prevent other malignancies, including esophageal adenocarcinoma. Alcoholism is a dose-dependent risk factor, so withdrawal is an anti-carcinogenic strategy. The link with tea, coffee or mate consumption is not well understood, so there is no evidence to warrant any preventive recommendations against their consumption; however, people should be reminded they need to avoid drinking anything at a high temperature.[10, 11]

In endemic areas, screening is recommended over a certain age and should also be considered in high-risk groups such as head and neck cancer patients, tylosis or history of caustic ingestion. Screening is not routinely recommended in the presence of smoking or alcoholism, unless other risk factors are present. In non-endemic areas, screening is suggested in patients with a history of head and neck cancer.[10]

When to screen?

No cost-effective screening plans have been established for patients at risk of developing squamous cell carcinoma. Nor are there any recommendations about the best age to start screening in high-risk groups or how frequently to screen them. In the unusual case of tylosis, annual surveillance programs could be of benefit.[10, 11]

How to screen?

Conventional white-light endoscopy lacks the sensitivity required for detecting esophageal squamous dysplasia, and the role of high resolution has not been formally evaluated for this purpose. Lugol chromoendoscopy is the most effective method to detect abnormal areas suggesting squamous dysplasia. Sensitivity is better using FICE. Using a validated specific narrow-band endoscopy, dysplasia can be seen as brownish areas. Although endocytoscopy can diagnose dysplasia without the need for a biopsy, its role has not been validated yet. Other less invasive methods available to study cytology, such as inflatable balls and sponges have high specificity but very low diagnostic sensitivity, both for dysplasia and for cancer.[10, 11]

Conclusions

To prevent adenocarcinoma, it is crucial to diagnose Barrett's disease early. Endoscopic surveillance is not justified for patients with isolated reflux, except in the context of at least three of the following risk factors: men, over 50, Caucasian, obese. Those risk factors are not required if there is a family history of Barrett's disease or adenocarcinoma. For the squamous variant, modifying risk factors is crucial; if the factors cannot be modified, the patient will probably need a well-programmed follow-up including endoscopy with biopsies. Even considering the subgroup of patients with risk factors associated with reflux symptoms, the population to be screened is too large; consequently, the clinical criteria remain essential when deciding how to allocate resources, to make sure they are used on those who need it most, analysing the patients case by case.

Esophageal cancer screening: who, when and how?, continued

References

1. *Sharma P, et al Espophageal cancer and Barrett´s esophagus. Whiley-Blakwell, 2015: 1-23; 35-43; 88-95.*
2. *Domper Arnal MJ, et al. Esophageal cancer: Risk factors, screening and endoscopic treatment in Western and Eastern countries. World J Gastroenterol 2015; 21(26): 7933-43.*
3. *Yousefi MS, et al. Esophageal cancer in the world: incidence, mortality and risk factors. Biomed. Res. Ther. 2018; 5 (7): 2504-17.*
4. *Fitzgerald R, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut. 2014; 63(1): 7-42.*
5. *Spechler SJ, et al. American Gastroenterological Association Medical Position Statement on the Management of Barrett's Esophagus. Gastroenterol. 2011; 140: 1084 –91.*
6. *Shaheen NJ, et al. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol. 2016; 111(1): 30-50.*
7. *Thrift AP, et al. External Validation of the Michigan Barrett's Esophagus Prediction Tool. Clin Gastroenterol Hepatol. 2017; 15(7): 1124–6.*
8. *Weusten B, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy. 2017; 49(2): 191-8.*
9. *Hunt R, et al. World Gastroenterology Organisation Global Guidelines: GERD Global Perspective on Gastroesophageal Reflux Disease. J Clin Gastroenterol. 2017; 51(6): 467-78.*
10. *Codipilly DC, et al. Screening for esophageal squamous cell carcinoma: recent advances. Gastrointest Endosc, 2018; 88(3): 413-26.*
11. *He Z, et al. Efficacy of endoscopic screening for esophageal cancer in China (ESECC): design and preliminary results of a population-based randomised controlled trial. Gut. 2019; 68(2): 198-206.*

Prevention of Esophageal Cancer: Diet, Lifestyle and Gastro-Esophageal Reflux.

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INTRODUCTION

Esophageal cancer is the 8th most common malignancy in the world and the 6th leading cause of cancer-related death, with a survival rate of less than 20% at 5 years. Poor survival rate is mainly related to a late diagnosis due to a lack of early symptoms.

Two epidemiologically and biologically distinct subtypes must be considered in this disease. Squamous Cell Carcinoma (SCC) accounts for over 90% of esophageal neoplasms and occurs in countries located in the "esophageal cancer belt", which stretches from the Caspian Sea through Central Asia to the Western Pacific. Esophageal Adenocarcinoma (EAC) is the most common subtype in the West and its incidence rates have increased by about 500% in the last four decades. Other histological subtypes, such as sarcomas and small cell carcinomas, comprise less than 2% of cases.

SQUAMOUS CELL CARCINOMA

Risk Factors

Genetics

Complete genome analysis and exome sequencing have shown TP53 mutations in 83%, and mutations in cell cycle genes as well as in differentiation genes in 2-10% of patients. GWAS, performed mainly in Asia, have identified risk variations in the PLCE gene, regions of the TP53 gene and HLA class II genes. In addition, 9 susceptibility loci have been identified in ALDH2 and ADH1B significant only with alcohol consumption (Figure 1)

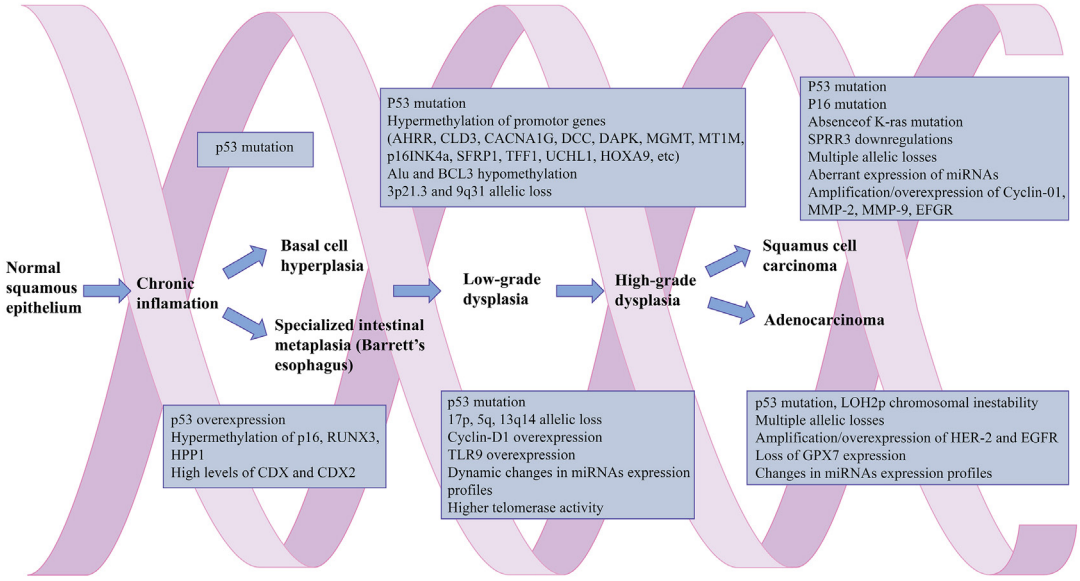

Figure 1: *Carcinogenesis of the esophageal cancer: Processes in Eastern and Western. Adapted from Chung C-S, et al. Prevention strategies for esophageal cancer: Perspectives of the East vs. West. Best Pract Res Clin Gastroenterol. 2015;29: 869–883*

Prevention of Esophageal Cancer: Diet, Lifestyle and Gastro-Esophageal Reflux, continued

Figure 2: *Primary prevention in esophageal cancer. An imbalance in favor of alcohol, tobacco and processed animal products over the consumption of vegetables represents a greater risk in this neoplasm.*

Demographic factors

Low socioeconomic status has been recognized as independent risk factor for SCC, even after adjusting risk to other variables such as tobacco and alcohol, in both developing and developed countries.

Diet

People with higher consumption of fruits and vegetables have a lower risk of SCC. Red and processed meat consumption may lead to an increased risk of SCC possibly through hyper-methylation of p16 gene promoter. Hot drinks are also associated with an increased risk of SCC. Chronic thermal injury generates higher rates of G>A somatic transitions in p53 gene CpG dinucleotides and lower epithelial barrier function. Deficiencies of micronutrients, such as vitamins A and E, and intake of flavonoids may contribute to augment the risk of SCC. Green tea and coffee but not black tea consumption would have protective effects (Figure 2)

Lifestyle: tobacco and alcohol

In western countries, smokers have a five-fold increased risk of SCC compared to non-smokers, while in Asia and South America a three-fold increased risk is observed. Stop smoking decreases the risk of SCC, particularly in western populations. On the other hand, excessive alcohol consumption is associated with an increase of over 6 times the risk in Europe and 9 times in the United States, while in Asian populations a range of relative risk of 1.6 to 5.3 is observed. There is a synergistic effect of alcohol and tobacco consumption, with simultaneous exposure increasing the risk 12 and 19 times in men and women, respectively. The increased risk of alcohol-related esophageal cancer is reversible after drinking cessation; it has been estimated that it takes 16 years to reverse the cumulative risk.

Oral health

Studies suggest that tooth loss significantly increases the risk of SCC in Asia, and daily toothbrushing decreases the risk.

Caustic Injury

Absolute risk in patients with caustic injury ranges from 2-16%. The time to develop cancer varies significantly from 10 to 40 years after the incident in most cases.

Head and Neck Cancer

A relationship has been established between SCC and the history of squamous cell head and neck cancers (HNSCC). The excess risk in these patients is estimated with a standardized incidence index of 21.8. Secondary SCC have a poor prognosis and is considered the most fatal of all secondary cancers among patients with previous HNSCC.

Associated Syndromes

SCC has been clearly associated with tylosis, a rare autosomal dominant disease characterized by palmoplantar keratoderma and 90% of EC risk by the age of 70. The risk of SCC is up to 50 times greater in patients with achalasia, often detected 10 to 15 years after the initial diagnosis.

Prevention strategies

As a primary prevention strategy, to avoid alcohol consumption, tobacco and betel quid chewing is recommended. Reduction of meat and hot drinks consumption increasing fruits and vegetables intake, maintaining adequate oral hygiene is proposed to reduce SCC (Table 1 and Figure 2).

The strongest evidence to support SCC screening comes from studies conducted in high-incidence regions in China. In particular, the low incidence of SCC has prevented the establishment of screening guidelines in the West. In the opinion of experts, screening should be considered under pre-existing conditions associated with a very high risk or poor prognosis, such as previous HNSCC, tylosis, achalasia and caustic ingestion.

Endoscopic surveillance programs have been shown to be feasible and effective in identifying precursor lesions in

Table 1. *Preventive strategies for esophageal cancers in Western and Eastern countries.*

	Western countries	Eastern countries
Histology subtype	Adenocarcinoma	Squamous cell carcinoma
Precursors	Barrett's esophagus	Basal cell hyperplasia and squamous hyperplasia
Primary prevention	Avoidance of meat, processed food intake, LES-relaxing drugs High fruits/vegetables intake Maintenance of ideal BW Lifestyle modification for GERD	Abstinence from alcohol consumption, cigarette smoking, betel quid chewing Avoidance of meat, processed food intake, hot beverages High fruits/vegetables intake Adequate oral hygiene
Secondary prevention	Endoscopic screening white men aged over 50 with long term (5 years) GERD symptoms PPI therapy for GERD, Barrett's esophagus	Endoscopic screening high risk population with alcohol consumption, cigarette smoking, betel quid chewing, history of head-and-neck cancers
Tertiary prevention	Regular endoscopic surveillance for Barrett's esophagus Endoscopic treatment of HGIN/CIS	Endoscopic treatment of HGIN/CIS

Abbreviation: LES, lower esophageal sphincter sphincter; BW, body weight; GERD, gastroesophageal reflux disease; HGIN, high-grade intraepithelial neoplasia; CIS, carcinoma in situ. Adapted from: Chung et al 2015.

patients with previous head and neck cancers as a tertiary prevention strategy. Similarly, there are expert recommendations for esophagogastroduodenoscopy (EGD) every 1 to 3 years in patients with tylosis, chronic achalasia (>10-15 years), or a history of caustic ingestion (>10 to 20 years). Endoscopic resection of high-grade intraepithelial neoplasia and carcinoma *in situ* is proposed as tertiary prophylaxis.

ESOPHAGEAL ADENOCARCINOMA (EAC)

Risk Factors

Genetics

GWAS have identified susceptibility loci in genes involving esophageal embryonic development (TBX1, FOXP1, FOXF1, BARX1), immune response (HLA locus) and cell proliferation (CRTC1). Authors have pointed out the aggregation of Barrett and EAC in families (Familial Barrett's Esophagus) where the mutation of the VSIG10L gene would play a role. Finally, there are two syndromes with genomic instability associated with EAC: Bloom syndrome and Fanconi anemia (Figure 1)

Demographic factors

The risk of EA increases by 3 times in patients over 50 years-old. The male sex confers a risk 7 times greater than that of women. In the United States, the rate of EAC also shows a predilection in non-Hispanic white people.

Diet

Studies have estimated that 20% of EAC is related to lower fruit and vegetable intake.

Fibers, folic acid, vitamin A/C/E, ß-carotene and selenium may be the underlying protective mechanism. Dietary fiber action mechanism include modification of gastroesophageal reflux and/or weight control. In contrast, high levels of fat, nitrites/nitrates, salts and polycyclic aromatic compounds, which are commonly used in processed meat, would be carcinogenic. A positive association was observed between total meat intake - especially red and processed meat - and the risk of EA. (Table 1 and Figure 2)

Lifestyle: Obesity, sedentary lifestyle, tobacco and alcohol

Obesity, both in terms of increased body mass index (BMI) and central adiposity (independently), has been consistently associated with the risk of EAC. Several meta-analyses have shown a dose-response effect of increased BMI on the risk of EAC, as well as a lower risk of EAC in more physically active individuals. In a stratified analysis, this protective effect was stronger for overweight and obese individuals than for healthy weight individuals. Unlike the SCC, the association between tobacco and EAC is moderate. There is no evidence that alcohol consumption is a risk factor for EAC, even for individuals consuming seven or more drinks a day. (Table 1 and Figure 2)

Gastroesophageal Reflux (GERD) and Barrett's Esophagus (BE)

GERD is the most significant and well-characterized risk factor for EAC. The mechanism of progression would be determined through replacement of the esophageal lining by columnar epithelium - Barrett's esophagus (BE) - and its progression to dysplasia and neoplasia. Therefore, patients with BE dysplasia have an increased risk of progression to EAC, with a risk 30-125 times greater than general population. However, the absolute annual risk of EA in patients with EAC remains low, and most patients with BE will not develop EAC. Meta-analyses have intended to stratify BE by identifying reflux duration, length >3 cm and degree of dysplasia as predictive factors for progression to EAC. The latter is used to define surveillance algorithms based on estimations of the annual risk of EAC: 0.33% in BE without dysplasia, 0.54% in low-grade lesions, and 7% in high-grade lesions.

Helicobacter pylori (H. pylori)

Observational studies have reported a 40%- 60% reduction in the risk of EAC associated with *H. pylori* infection. The prevalence of *H. pylori* infection has declined in Western populations since the mid-20th century, which was earlier than the onset of the increasing incidence of EAC. *H. pylori* eradication should be performed following the International Consensus recommendations, and particularly caution in patients with BE and countries with high prevalence of EAC and low prevalence of gastric cancer.

Hormonal and Reproductive Factors

Studies found a reduction in the risk of EAC in postmenopausal women using menopausal hormone therapy compared to non-users and a significant decrease in the risk associated with the use of oral contraceptives. Continued research efforts are needed to establish the role of sex hormone exposure in the EAC etiology.

Prevention strategies

As primary prevention measures it is proposed to promote the consumption of fruits and vegetables and to reduce processed fruits and vegetables, especially meat products; and to avoid overweight and lifestyle modifications to reduce GERD.

As a secondary prevention, BE screening leads to earlier detection of EAC and better outcomes, with an increase in 5-year survival from 17% to 74% in prospective series. The American College of Gastroenterology identifies the following risk factors: age > 50 years, chronic GERD (>5 years) or frequent symptoms (at least weekly), white race, male, central obesity (waist circumference >102 cm or waist-hip ratio >0.9), smoking (current or past), and a first-degree relative with BE or EAC. The current recommendation for detection of EAC in established BE is EGD with protocolized biopsies. If the endoscopic evaluation is positive for BE, as tertiary prevention measures, it is the level of dysplasia that guides the behavior.

Regarding chemoprophylaxis, recent studies have raised a chemopreventive role for aspirin and high-dose of proton pump inhibitor therapy in patients with BE. This combination reduced BE progression to high-grade dysplasia, adenocarcinoma, or death.

Observational studies would show that statins protect against esophageal cancer reducing the risk of EAC in patients with BE.

There are strong inverse associations between the use of NSAIDs and the risk of EAC. However, their use requires careful considerations of the absolute risk of EAC in individual patients and the negative effects of these drugs.

NEW SCREENING TECHNIQUES

The main barrier in expanding the detection criteria relies in the cost-effectiveness of the EGD diagnosis and management. Improving EAC detection requires inexpensive, widely available and accurate techniques. The other significant challenge with screening endoscopies is the difficulty of early endoscopic identification. Lugol chromoendoscopy has been adopted as the gold standard for EAC. For EAC, chromoendoscopy with various substances and electronic chromoendoscopy have been studied with promising results.

Data with biomarkers and non-endoscopic approaches are still insufficient to replace endoscopy. Large scale trials have shown promising data with Cytosponge with TFF3 or EndoCDx© system.

DISCUSSION

To reduce the burden of esophageal cancers, a multidisciplinary approach should be considered. From the perspective of clinicians and gastroenterologists, the identification and elimination of risk factors is an important first step for primary prevention, which may include precipitating factors of gastroesophageal reflux disease and dietary modifica-

tions. In order to achieve this goal, primary care intervention and education play a key role in public health policies. Secondary prevention includes identification of precancerous lesions and cancer at early stages of the disease when endoscopic treatment is possible. For tertiary prevention, endoscopic surveillance for the detection of metachronous neoplasms. Preventive strategies for esophageal cancers in western (EAC) and eastern (SCC) countries are summarized in Table 1.

It has been difficult to develop standardized screening recommendations due to the significant heterogeneity in population incidence and risk factors for esophageal cancer. We can only achieve this by detecting larger populations of people at risk for this cancer, but we are currently limited by the cost and accuracy of standard endoscopy. With continued advances in new screening techniques, this may change soon, allowing for more rigorous screening and, hopefully, better survival outcomes.

REFERENCES

1. *Bornschein J, et al. The Rationale and Efficacy of Primary and Secondary Prevention in Adenocarcinomas of the Upper Gastrointestinal Tract. Dig Dis. 2019;37: 381–393.*
2. *Chung C-S, et al. Prevention strategies for esophageal cancer: Perspectives of the East vs. West. Best Pract Res Clin Gastroenterol. 2015;29: 869–883.*
3. *Coleman HG, Xie S-H, Lagergren J. The Epidemiology of Esophageal Adenocarcinoma. Gastroenterology. 2018;154: 390–405.*
4. *Jankowski J, et al. Chemoprevention of esophageal cancer with esomeprazole and aspirin therapy: Efficacy and safety in the phase III randomized factorial ASPECT trial [Internet]. Journal of Clinical Oncology. 2018. pp. LBA4008–LBA4008.*
5. *Jarl J, et al. Time pattern of reduction in risk of oesophageal cancer following alcohol cessation--a meta-analysis. Addiction. 2012;107: 1234–1243.*
6. *Lam AK-Y. Cellular and Molecular Biology of Esophageal Cancer [Internet]. Esophageal Cancer. 2015. pp. 25–40.*
7. *Pandey G, et al. Systematic review and meta-analysis of the effectiveness of radiofrequency ablation in low grade dysplastic Barrett's esophagus. Endoscopy. 2018;50: 953–960.*
8. *Sardana RK, et al. Dietary impact on esophageal cancer in humans: a review. Food Funct. 2018;9: 1967–1977.*
9. *Thrumurthy SG, et al. Oesophageal cancer: risks, prevention, and diagnosis [Internet]. BMJ. 2019. p. l4373.*
10. *Wang Q-L, et al. Smoking Cessation and Risk of Esophageal Cancer by Histological Type: Systematic Review and Meta-analysis. J Natl Cancer Inst. 2017;109.*

Surveillance of Barrett's Oesophagus

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Basic Definitions

Barrett's oesophagus is metaplastic condition in the distal oesophagus where the physiological multi-layered squamous surface epithelium is replaced by a single-layered columnar epithelium. This surface lining usually spreads continuously from the gastro-oesophageal junction (with the stomach also being lined with a single layer of columnar cells). The gastro-oesophageal junction (GOJ) is defined by the proximal end of the gastric folds, a position that – in patients without Barrett's oesophagus - is usually also indicated by the sharp demarcation line (so-called "Z-line" due to its of jagged appearance) that marks the transition between oesophageal squamous epithelium and gastric columnar epithelium. In patients with Barrett's oesophagus, this epithelial squamo-columnar junction is positioned more proximally above the anatomical GOJ in the oesophagus, with the segment of metaplastic lining (epithelium) being either of a circumferential or a tongue-shaped (or mixed) appearance which can stretch over several cm. Disjunct islands of columnar lined oesophagus can also occur above that line. Further characteristics are explained in the paragraphs below.

Rationale for Surveillance of Barrett's Oesophagus

It is the current understanding that endoscopic surveillance of patients with Barrett's oesophagus is the best available tool to improve outcome. The actual risk of progression towards oesophageal adenocarcinoma (OAC) is with 0.2-0.7% per patient per year much lower than initially estimated (de Jonge *et al.*, 2010; Bhat *et al.*, 2011; Hvid-Jensen *et al.*, 2011) population-based, cohort study involving all patients with Barrett's esophagus in Denmark during the period from 1992 through 2009, using data from the Danish Pathology Registry and the Danish Cancer Registry. We determined the incidence rates (numbers of cases per 1000 person-years, but endoscopic surveillance at regular intervals enables the detection of neoplastic changes at a much earlier stage compared to targeted diagnostic tests when the patient already presents with symptoms (Kastelein *et al.*, 2016).

Endoscopic treatment of early neoplastic lesions such as high-grade dysplasia (HGD) and intramucosal cancer (IMC)

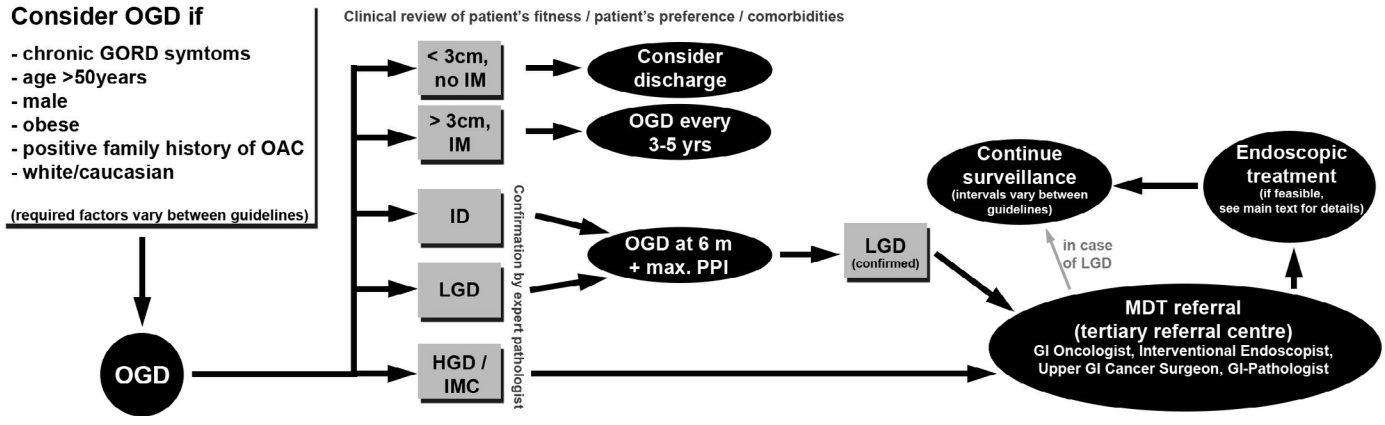

Figure 1: *Key features of algorithms for Surveillance of Barrett's Oesophagus.*

Please see main text for details. Abbreviations: GORD: gastro-oesophageal reflux disease, HGD: high-grade dysplasia, IM: intestinal metaplasia, IMC: intramucosal cancer, LGD: low grade dysplasia, MDT: multidisciplinary team meeting, OAC: oesophageal adenocarcinoma, OGD: oesophago-gastro-duodenoscopy, PPI: proton pump inhibitor.

results in excellent prognostic outcome comparable to Barrett's patients under surveillance who do not show progression. A meta-analysis of 51 studies including more than 11,000 patients, demonstrated that endoscopic surveillance of patients with non-dysplastic Barrett's oesophagus reduces OAC mortality by more than 61% (mortality risk 0.386; 95% CI: 0.242-0.617)(Qiao *et al.*, 2015). This was confirmed in a recent meta-analysis, which also reported that not only OAC-related, but also all-cause mortality is significantly better in surveillance patients compared to those in whom diagnostic test were undertaken due to symptoms (Hazard ratio [HR] 0.59; 95% Confidence Interval [CI]: 0.45-0.76) (Codipilly *et al.*, 2018). Post-treatent quality of life is also more likely to be preserved after endoscopic than radical surgical treatment.

There are obviously also studies not confirming these results, which is one of the reasons why National and International guidelines show a certain variation regarding the recommendations for inclusion criteria and surveillance strategies.

Current Guidelines on Surveillance of Barrett's Oesophagus

Key recommendations

In the following, I will refer primarily to the recommendations of the *European Society of Gastrointestinal Endoscopy* (ESGE) which were published in 2017 (Weusten *et al.*, 2017). Other guidelines that have been published before and after show minor deviations in the suggested algorithm, mainly with respect to some core issues that remain under lively debate and which are discussed further below.

A gastroscopy for endoscopic assessment is recommended every five years for patients with a maximum length of their Barrett's oesophagus of 1-3cm, and every three years for patients with metaplastic segments of 3-10cm. Patients with a segment of columnar-lined epithelium shorter than 1cm should not undergo surveillance (Weusten *et al.*, 2017). Patients with Barrett's oesophagus that extends more than 10cm should be referred to a specialized centre. A tertiary referral should also be made when endoscopic treatment is required. These specialized tertiary centres are defined by an annual case load of more than 10 new patients requiring endoscopic treatment of HGD and early OAC, a number of 30 supervised (by an established expert interventional endoscopist) endoscopic resections per year, established Barrett's MDTs and a prospective case database. Endoscopists and histopathologists should have undergone specific training (Weusten *et al.*, 2017).

A biopsy that has been classified as dysplastic requires assessment by a second expert pathologist. This applies not only to low-grade (LGD) and high-grade dysplasia, but also for confirmation of cases classified as "indefinite for dysplasia" (ID). Patients with ID should also receive maximum acid suppressive treatment before being re-assessed after 6 months. A follow-up gastroscopy with biopsy sampling is also recommended in presence of (confirmed) LGD. If dysplasia is subsequently not confirmed a second follow-up should be scheduled after 12 months before these patients will then be considered again as "non-dysplastic Barrett's oesophagus". If LGD persists, then discussion in a multi-disciplinary team meeting (MDT) is required to determine if endoscopic treatment should be offered. Any case of HGD dysplasia should be referred directly to an expert centre for discussion in the MDT and – in most cases - further endoscopic treatment. Treatment consists of endoscopic resection of any visible lesion followed by radiofrequency ablation (RFA) of the remainder of the metaplastic segment. Endoscopic resection can also be considered as a diagnostic tool to complete staging of a visible lesion, since it is also first choice for stage T1a cancers and a proportion of T1b tumours (no further surgery required for well or moderately differentiated tumours when invasion depth <500µm, deep margins tumour-free, no lymphatic or vascular invasion). If there is no visible lesion, then quadrantic biopsies should be taken every 1cm and the patient been brought back for further assessment after 3 months.

There is a high risk of sampling error which is why the so-called "Seattle" protocol should be followed strictly for biopsy sampling (Levine *et al.*, 2000). In addition to targeted biopsies from visible lesions, "random" quadrantic biopsies are to be taken every 2cm of the Barrett's segment starting from just above the gastro-oesophageal junction (GOJ) indicated by the top end of the gastric folds. Islands above the squamo-columnar junction must be sampled separately. Visible lesions should be classified according to the Paris classification and adequate photo documentation should be provided.

Discrepancies between different guidelines

There is still some incongruence regarding the actual definition of Barrett's oesophagus. While most expert panels

agree that a minimum segment length of 1cm is required, the presence of intestinal metaplasia (IM) is necessary for a diagnosis of Barrett's oesophagus according to the American and recent European guidelines (Sharma *et al.*, 2015; Weusten *et al.*, 2017), but not required as such in the British and Asian Pacific guidelines (Fitzgerald *et al.*, 2014; Fock *et al.*, 2016)screening and diagnosis, surveillance, pathological grading for dysplasia, management of dysplasia, and early cancer including training requirements. The rigour and quality of the studies was evaluated using the SIGN checklist system. Recommendations on each topic were scored by each author using a five-tier system (A+, strong agreement, to D+, strongly disagree. In line with these definitions, most guidelines advise not to take any biopsies from a "normal" squamo-columnar junction (or changes of <1cm). Otherwise, the Seattle protocol, should be followed, although biopsies can be taken "every 1-2cm" in the United States (Sharma *et al.*, 2015). In addition to strict recommendation to follow the Prague classification for stratification of the actual Barrett's segment by stating the length of the circumferential (C) and the maximum (M) length of the metaplastic tongues (see definitions above), both the British and the Americans suggest certain quality indicators for endoscopic reporting. These can in minor variations also be found in other national guidelines and include reporting on presence of a hiatus hernia, distance of the squamo-columnar junction, the GOJ and the diaphragmatic pinch (among other factors).

Whilst most guidelines agree that screening of the general population for Barrett's oesophagus is not cost-effective, most guidelines define a set of risk indicators that allow selection of individuals who should be considered to undergo endoscopic assessment (e.g. age >50 years, male sex, white ethnicity, obesity, chronic reflux symptoms, and a positive family history of OAC). However, recommendations vary between guidelines how many of these risk factors need to be present to qualify a patient for further investigations.

Issues under Debate

Surveillance of non-dysplastic Barrett's oesophagus

The positive correlation of the length of Barrett's oesophagus with its risk of progression has been demonstrated in numerous studies. Data from 1175 patients that were followed-up at five tertiary centres in the U.S. confirmed a risk increase of 28% per each additional cm of Barrett's length (Anaparthy *et al.*, 2013). Pohl *et al.* reported transition rates towards more advanced lesions in 0.22% of patients with segments >3cm, 0.03% in patients with segments >1cm and <3cm, and 0.01% if the metaplastic segment was <1cm (Pohl *et al.*, 2016). This resulted in a calculated number-needed-to survey of 450 to detect early neoplasia in segments >3cm, 3,440 between 1-3cm and 12,364 if the area was <1cm. Due to the low progression risk for patients with short segments, there is ongoing debate if segments <3cm require surveillance at all in view of cost-effectiveness. Among others, the British guidelines therefore suggest that consideration should be given to discharging these patients from surveillance, if there has been no progression of the histopathological findings at the first follow-up gastroscopy (Fitzgerald *et al.*, 2014)screening and diagnosis, surveillance, pathological grading for dysplasia, management of dysplasia, and early cancer including training requirements. The rigour and quality of the studies was evaluated using the SIGN checklist system. Recommendations on each topic were scored by each author using a five-tier system (A+, strong agreement, to D+, strongly disagree. In 2012, the *American Society of Gastrointestinal Endoscopy* (ASGE) even suggested no surveillance for cases of non-dysplastic Barretts's oesophagus (Evans *et al.*, 2012). It has been suggested that biomarkers could facilitate a better risk stratification but there is currently no candidate available that would be feasible for routine clinical use due to a lack of sufficient proof of clinical benefit (Gordon *et al.*, 2014).

Algorithm for low grade dysplasia (LGD)

A hot topic is the algorithm for patients with confirmed LGD. The European consensus is rather pro-active. Although endoscopic treatment is not the definite first choice, it should be offered to the patient once feasibility has been discussed at the local Barrett's MDT (Weusten *et al.*, 2017; di Pietro, Fitzgerald and BSG Barrett's guidelines working group, 2018).

In contrast, the recommendations of various U.S. bodies favour continued surveillance of LGD (Evans *et al.*, 2012; Shaheen *et al.*, 2016). Interestingly, most of these statements are based on data from the period prior to widespread application of RFA. A recent study, published in 2018, concluded that there was no significant difference in the progression rates towards HGD and OAC between patients undergoing either further surveillance or endoscopic intervention, but this was based on single-centre data from

Surveillance of Barrett's Oesophagus continued

patients seen between 1991 and 2014 (Kahn *et al.*, 2018) with endoscopic surveillance considered a reasonable alternative. Few studies have directly compared outcomes of radiofrequency ablation to surveillance and those that have are limited by short duration of follow-up. This study aims to compare the long-term effectiveness of radiofrequency ablation versus endoscopic surveillance in a large, longitudinal cohort of patients with Barrett's esophagus, and low-grade dysplasia.We conducted a retrospective analysis of patients with confirmed low-grade dysplasia at a single academic medical center from 1991 to 2014. Patients progressing to high-grade dysplasia or esophageal adenocarcinoma within one year of index LGD endoscopy were defined as missed dysplasia and excluded. Risk factors for progression were assessed via Cox proportional hazards model. Comparison of progression risk was conducted using a Kaplan-Meier analysis. Subset analyses were conducted to examine the effect of reintroducing early progressors and excluding patients diagnosed prior to the advent of ablative therapy. Of 173 total patients, 79 (45.7%. The authors tried to correct for bias by excluding patients that were seen prior to the introduction of RFA and reported similar results, but there has been a boost of the quality standards for RFA treatment during the last five years, so that older data, prior to this period, always needs to be interpreted with care.

A more recent update by the *American Gastroenterology Association* (AGA) asks for a repeat assessment of LGD after 8-12 weeks (compared to the 6 months suggested in Europe) (Wani *et al.*, 2016)including systematic reviews and expert opinion (when applicable. Ablation should be performed if LGD still persists. If a decision is made in favour of surveillance, then further follow-up gastroscopies should be undertaken after six and twelve months, and then yearly until "conversion into non-dysplastic Barrett's oesophagus".

It has also been suggested that expert pathologists audit their number of LGD cases among Barrett's surveillance patients and document the rate of patients with neoplastic progression.

Surveillance after endoscopic treatment of Barrett's oesophagus

Ablative treatment should always aim for complete eradication of the Barrett's segment. There remains the risk for recurrence of both columnar metaplasia in the treated segment and (rarely) dysplastic foci. These can either be overt or can occur in so-called "buried glands" underneath the neo-squamous epithelium. Hence, there is general consensus that endoscopic surveillance after ablative treatment is useful with biopsies being taken from the area that previously defined the Barrett's segment (Reed and Shaheen, 2019)reduces the risk of esophageal adenocarcinoma (EAC. As phrased in an U.S. statement, the evidence for this approach is weak, but algorithms should follow a "pragmatic framework" (Shaheen *et al.*, 2016).

The recommended intervals for further surveillance vary between guidelines but are generally shorter when compared to those for non-dysplastic Barrett's oesophagus. Quite tight surveillance schedules are usually suggested for the first 2-3 years, with intervals then being stretched if no recurrence or progression is documented. Intervals obviously depend on the success rate of endoscopic treatment. In cases of complete eradication of the Barrett's segment, the AGA suggests endoscopic assessment after 12 and 24 months, then every three years, whereas follow-ups should be performed after 6, 12, 24, and 36 months in cases of incomplete eradication before intervals are prolonged (Wani *et al.*, 2016)including systematic reviews and expert opinion (when applicable.

An expert opinion-based model analysis of data of the U.S. and UK RFA registries states that the most severe histology grade before treatment is the main factor influencing the risk of recurrence (Cotton *et al.*, 2018)so surveillance endoscopy is recommended after complete eradication of intestinal metaplasia (CEIM. There, it is suggested that patients with LGD prior to treatment should be seen after 12 and 36 months whereas patients with HGD or IMC should be assessed after 3, 6 and 12 months.

Relevance of advanced endoscopic imaging modalities and molecular markers

There are obvious limitations regarding the diagnostic yield of random biopsies taken according to the Seattle protocol, since only a minute area of the metaplastic segment can be assessed with these small tissue samples. The use of more sophisticated endoscopic techniques for the assessment of the Barrett's mucosa is discussed in each guideline. These include narrow band imaging (NBI) or similar "virtual chromoendoscopy" techniques such as flexible spectral imaging colour enhancement (FICE) or iScan. There are also ongoing efforts to improve risk stratification by established standard methods of chromoendoscopy and magnifying endoscopy (Goda *et al.*, 2018). Initial studies were promising

demonstrating improved dysplasia detection rates when these techniques were compared with traditional white light endoscopy (Qumseya *et al.*, 2013). However, most guidelines abstain now from too high praise of a specific advanced endoscopic imaging technique. While high-definition white light endoscopy (ideally with magnification) is recommended, virtual chromoendoscopy is not generally supported despite acknowledgements of its potential merits (Fitzgerald *et al.*, 2014; Shaheen e*et al.*, 2016; Beg *et al.*, 2017; Weusten *et al.*, 2017). Beg *et al.* reported that adequate use of the available endoscopy modalities in the hands of a trained endoscopist can reduce the number of biopsies needed for Barrett's assessment and has therefore an impact on costs (Beg *et al.*, 2018).

No role outside clinical studies is attributed to confocal laser endomicroscopy (CLE) which allows the real-time detection of intestinalised epithelium and even dysplastic changes. This technique can be combined with tissue-based biomarkers showing promising performance compared to standard histopathology (Tofteland *et al.*, 2014; Ross-Innes *et al.*, 2015)(ii. An alternative approach is the application of molecular surface probes that can be viewed during endoscopy in real-time (Bird-Lieberman *et al.*, 2012). However, these techniques are not yet ready for routine clinical practice and are mainly explored at academic centres.

Among other candidates (e.g. p16, cyclin A and altered ploidy) only immunohistochemical assessment of p53 has been established as biomarker for HGD and its use for histopathology assessment has been recommended in the British guideline (Fitzgerald *et al.*, 2014)screening and diagnosis, surveillance, pathological grading for dysplasia, management of dysplasia, and early cancer including training requirements. The rigour and quality of the studies was evaluated using the SIGN checklist system. Recommendations on each topic were scored by each author using a five-tier system (A+, strong agreement, to D+, strongly disagree.

Summary and Conclusion

Leaving considerations of cost-effectiveness aside, it is generally accepted that surveillance of patients with Barrett's oesophagus improves the patient's outcome due to a higher rate of neoplastic lesions being detected at early stage when curatively intended, endoscopic treatment can be offered. Guidelines will need to remain "fluid" and in constant update regarding the patient stratification for appropriate surveillance intervals. Endoscopic imaging modalities are further improving and there is high research interest in the establishment of both endoscopic and tissue-based biomarkers for individual risk stratification.

The standards required for diagnostic assessment, endoscopic treatment and patient follow-up are higher than ever which does not only further improve the patients' prognosis but facilitates cross-study data comparison. But every guideline is only as good as adherence to its recommendation by the end-user. While the establishment of dedicated Barrett's surveillance endoscopy sessions has been shown to raise local dysplasia detection rates (Ooi *et al.*, 2017), adherence to the diagnostic standards in the community and during "*ad hoc*" lists is often very poor in view of both endoscopic reporting and biopsy sampling standards (Vogt *et al.*, 2018). This leaves definitively room for improvement. In particular since education of the general population on Barrett's oesophagus has been thus successful that 94% of participants in a recently published survey believe in the benefits of endoscopic surveillance (Stier *et al.*, 2018).

References

1. *Anaparthy, R. et al. (2013) 'Association Between Length of Barrett's Esophagus and Risk of High-grade Dysplasia or Adenocarcinoma in Patients Without Dysplasia', Clinical Gastroenterology and Hepatology, 11(11), pp. 1430–1436. doi: 10.1016/j.cgh.2013.05.007.*
2. *Beg, S. et al. (2017) 'Quality standards in upper gastrointestinal endoscopy: a position statement of the British Society of Gastroenterology (BSG) and Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS).', Gut, 66(11), pp. 1886–1899. doi: 10.1136/gutjnl-2017-314109.*
3. *Beg, S. et al. (2018) 'Impact of advanced endoscopic imaging on Barrett's esophagus in daily clinical practice', Gastrointestinal Endoscopy, 87(5), pp. 1189–1194. doi: 10.1016/j.gie.2017.09.012.*
4. *Bhat, S. et al. (2011) 'Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study.', Journal of the National Cancer Institute, 103(13), pp. 1049–57. doi: 10.1093/jnci/djr203.*

Surveillance of Barrett's Oesophagus continued

5. *Codipilly, D. C. et al. (2018) 'The Effect of Endoscopic Surveillance in Patients With Barrett's Esophagus: A Systematic Review and Meta-analysis', Gastroenterology, 154(8), pp. 2068-2086.e5. doi: 10.1053/j.gastro.2018.02.022.*
6. *Cotton, C. C. et al. (2018) 'Development of Evidence-Based Surveillance Intervals After Radiofrequency Ablation of Barrett's Esophagus.', Gastroenterology, 155(2), pp. 316-326.e6. doi: 10.1053/j.gastro.2018.04.011.*
7. *Evans, J. A. et al. (2012) 'The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus', Gastrointestinal Endoscopy, 76(6), pp. 1087–1094. doi: 10.1016/j.gie.2012.08.004.*
8. *Fitzgerald, R. C. et al. (2014) 'British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus', Gut, 63(1), pp. 7–42. doi: 10.1136/gutjnl-2013-305372.*
9. *Fock, K. M. et al. (2016) 'Asia-Pacific consensus on the management of gastro-oesophageal reflux disease: an update focusing on refractory reflux disease and Barrett's oesophagus', Gut, 65(9), pp. 1402–1415. doi: 10.1136/gutjnl-2016-311715.*
10. *Goda, K. et al. (2018) 'Newly developed magnifying endoscopic classification of the Japan Esophageal Society to identify superficial Barrett's esophagus-related neoplasms.', Esophagus : official journal of the Japan Esophageal Society, 15(3), pp. 153–159. doi: 10.1007/s10388-018-0623-y.*
11. *Gordon, L. G. et al. (2014) 'Cost-effectiveness of endoscopic surveillance of non-dysplastic Barrett's esophagus', Gastrointestinal Endoscopy, 79(2), pp. 242-256.e6. doi: 10.1016/j.gie.2013.07.046.*
12. *Hvid-Jensen, F. et al. (2011) 'Incidence of adenocarcinoma among patients with Barrett's esophagus.', The New England journal of medicine, 365(15), pp. 1375–83. doi: 10.1056/NEJMoa1103042.*
13. *de Jonge, P. J. F. et al. (2010) 'Risk of malignant progression in patients with Barrett's oesophagus: a Dutch nationwide cohort study.', Gut, 59(8), pp. 1030–6. doi: 10.1136/gut.2009.176701.*
14. *Kahn, A. et al. (2018) 'Longitudinal outcomes of radiofrequency ablation versus surveillance endoscopy for Barrett's esophagus with low-grade dysplasia.', Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus, 31(4). doi: 10.1093/dote/dox120.*
15. *Kastelein, F. et al. (2016) 'Impact of surveillance for Barrett's oesophagus on tumour stage and survival of patients with neoplastic progression.', Gut, 65(4), pp. 548–54. doi: 10.1136/gutjnl-2014-308802.*
16. *Levine, D. S. et al. (2000) 'Safety of a systematic endoscopic biopsy protocol in patients with Barrett's esophagus.', The American journal of gastroenterology, 95(5), pp. 1152–7. doi: 10.1111/j.1572-0241.2000.02002.x.*
17. *Ooi, J. et al. (2017) 'Dedicated Barrett's surveillance sessions managed by trained endoscopists improve dysplasia detection rate', Endoscopy, 49(06), pp. 524–528. doi: 10.1055/s-0043-103410.*
18. *di Pietro, M., Fitzgerald, R. C. and BSG Barrett's guidelines working group (2018) 'Revised British Society of Gastroenterology recommendation on the diagnosis and management of Barrett's oesophagus with low-grade dysplasia.', Gut, 67(2), pp. 392–393. doi: 10.1136/gutjnl-2017-314135.*
19. *Pohl, H. et al. (2016) 'Length of Barrett's oesophagus and cancer risk: implications from a large sample of patients with early oesophageal adenocarcinoma', Gut, 65(2), pp. 196–201. doi: 10.1136/gutjnl-2015-309220.*
20. *Qiao, Y. et al. (2015) 'Surveillance in Patients With Barrett's Esophagus for Early Detection of Esophageal Adenocarcinoma: A Systematic Review and Meta-Analysis.', Clinical and translational gastroenterology, 6(12), p. e131. doi: 10.1038/ctg.2015.58.*
21. *Qumseya, B. J. et al. (2013) 'Advanced Imaging Technologies Increase Detection of Dysplasia and Neoplasia in Patients With Barrett's Esophagus: A Meta-analysis and Systematic Review', Clinical Gastroenterology and Hepatology, 11(12), pp. 1562-1570.e2. doi: 10.1016/j.cgh.2013.06.017.*
22. *Reed, C. C. and Shaheen, N. J. (2019) 'Management of Barrett Esophagus Following Radiofrequency Ablation.', Gastroenterology & hepatology, 15(7), pp. 377–386. Available at: http://www.ncbi.nlm.nih.gov/pubmed/31391808 (Accessed: 9 October 2019).*

Surveillance of Barrett's Oesophagus continued

23. *Ross-Innes, C. S. et al. (2015) 'Evaluation of a Minimally Invasive Cell Sampling Device Coupled with Assessment of Trefoil Factor 3 Expression for Diagnosing Barrett's Esophagus: A Multi-Center Case–Control Study', PLOS Medicine. Edited by E. L. Franco, 12(1), p. e1001780. doi: 10.1371/journal.pmed.1001780.*
24. *Shaheen, N. J. et al. (2016) 'ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus', American Journal of Gastroenterology, 111(1), pp. 30–50. doi: 10.1038/ajg.2015.322.*
25. *Sharma, P. et al. (2015) 'Quality Indicators for the Management of Barrett's Esophagus, Dysplasia, and Esophageal Adenocarcinoma: International Consensus Recommendations from the American Gastroenterological Association Symposium', Gastroenterology, 149(6), pp. 1599–1606. doi: 10.1053/j.gastro.2015.08.007.*
26. *Stier, M. W. et al. (2018) 'Perceptions of risk and therapy among patients with Barrett's esophagus: a patient survey study.', Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus, 31(4). doi: 10.1093/dote/dox109.*
27. *Tofteland, N. et al. (2014) 'Evaluation of the updated confocal laser endomicroscopy criteria for Barrett's esophagus among gastrointestinal pathologists.', Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus, 27(7), pp. 623–9. doi: 10.1111/dote.12121.*
28. *Vogt, J. S. et al. (2018) 'Quality of endoscopic surveillance of Barrett's esophagus', Scandinavian Journal of Gastroenterology, 53(3), pp. 256–259. doi: 10.1080/00365521.2018.1430251.*
29. *Wani, S. et al. (2016) 'Diagnosis and Management of Low-Grade Dysplasia in Barrett's Esophagus: Expert Review From the Clinical Practice Updates Committee of the American Gastroenterological Association.', Gastroenterology, 151(5), pp. 822–835. doi: 10.1053/j.gastro.2016.09.040.*
30. *Weusten, B. et al. (2017) 'Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement', Endoscopy, 49(02), pp. 191–198. doi: 10.1055/s-0042-122140.*

Treatment of Early Esophageal Cancer

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Introduction

Management of esophageal carcinoma can be challenging for practitioners and is mainly based on the stage of the disease and overall condition of the patient. Early esophageal cancer is traditionally defined as a disease limited to submucosa without any evidence of further local or distant invasion (T1N0M0 based on TNM system). Although most patients with esophageal cancer present late in the course of the disease, surveillance programs for Barrett's esophagus as well as growing number of advanced endoscopic techniques such as high definition endoscopy or narrow band imaging have relatively increased the number of early esophageal cancers specially in communities where surveillance programs have been implemented. Early disease can be treated and even cured using mucosal resection by endoscopic or surgical modalities while more advanced lesions may require chemotherapy, radiation, more invasive surgery, or even palliative management. Early esophageal carcinoma can be an incidental finding in a diagnostic test performed for an unrelated reason or pathology report of the carcinoma in an endoscopically resected lesion, however, other patients might experience symptoms such as dysphagia, weight loss or upper gastrointestinal bleeding. Endoscopic therapy has been shown to be equivalent of esophagectomy in early esophageal adenocarcinoma and majority of small recurrences are treated endoscopically (Ramay 2019).

Staging

An upper endoscopy and biopsy is crucial to confirm the diagnosis if this was not done before staging. Staging of a newly diagnosed esophageal cancer is necessary in determining the appropriate management strategy. TNM system is the most widely used staging system, based on which, T1N0M0 disease is considered superficial or early esophageal cancer. Any tumor more advanced than T2N0M0 is considered locally advanced and should not be treated with local resection while there is controversy regarding treatment of T2N0M0 disease. Endoscopic Ultrasound (EUS) and cross sectional imaging such as CT scan are essential in staging esophageal cancer. EUS is more accurate in early disease as well as T and N staging but is of limited use in cases where the tumor causes obstruction in the lumen. EUS is shown to provide sensitivity, specificity, and positive and negative likelihood ratio of 0.85 (95% CI, 0.82-0.88), 0.87 (95% CI, 0.84-0.90), 6.62 (95% CI, 3.61-12.12), and 0.20 (95% CI, 0.14-0.30), respectively in staging T1a lesions and 0.86 (95% CI, 0.82-0.89), 0.86 (95% CI, 0.83-0.89), 5.13 (95% CI, 3.36-7.82), and 0.17 (95% CI, 0.09-0.30), respectively for T1b lesions. (Thosani et al) The accuracy of EUS in N staging is enhanced from 80% to more than 92% by adding fine needle aspiration (FNA) of suspected lymph nodes while it is decreased in post-radiation staging. With the advancement of endoscopic resection techniques, T1a stage has been subdivided to M1 (limited to epithelial layer), M2 (limited to lamina propria) and M3 (limited to muscularis mucosa) and T1b has been subdivided to SM1 (limited to 1/3 of submucosa), SM2 (limited to 2/3 of submucosa) and SM3 (limited to submucosa but passed the 2/3) to further elaborate on lesions that might require adjuvant treatment in addition to local resection and hence the use of EUS is increasing in staging early esophageal cancer. The role of positron emission tomography (PET), laparoscopy and thoracoscopy in staging of the esophageal cancer is controversial although PET is recommended in improving M staging in patients who may be a candidate for curative therapy (Wong 2012).

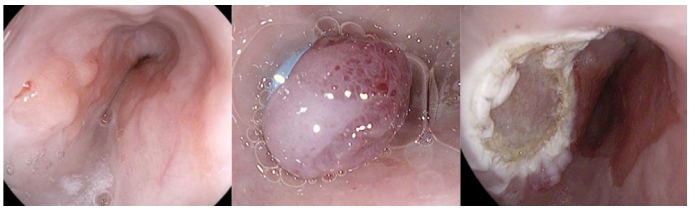

Figure 1: *Esophageal intramucosal carcinoma presenting as nodularity in Barrett's esophagus (left) treated with cap-assisted band EMR (middle) and immediate post-EMR appearance (right).*

The role of radiotherapy or chemoradiotherapy in the treatment of early esophageal cancer is not well defined and current evidence does not support routine use of these modalities. Their use in specific cases, such as contraindication to endoscopic or surgical treatments, should be discussed

on an individual basis among a panel of experts/tumor boards. There is also insufficient evidence on the role of brachytherapy in the treatment of early esophageal cancer.

Endoscopic treatment

Any tumor that is confined to the mucosa (T1a) is associated with a low risk of lymph node invasion and could be considered for endoscopic therapy while more advanced diseases are associated with higher rate of metastasis and therefore endoscopic therapy alone is likely insufficient. For instance, the risk of lymph node involvement is zero with disease limited to lamina propria but increases to around 5% with overall T1a disease and more than 16% with T1b disease. Most experts recommend endoscopic treatment for M1 and M2 disease as well as well-differentiated M3 cases without lymphovascular invasion. Esophagectomy is the treatment of choice for more advanced resectable esophageal cancer cases. Three main types of endoscopic therapy include endoscopic ablation therapy (EAT), endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). The advantage of EMR and ESD over EAT is to provide reasonable specimen for pathological evaluation and staging. Although esophagectomy provides more definitive pathological assessment and eliminates the need for surveillance, it is associated with significant morbidity and mortality and should be avoided for early stage cancers. Patients should be referred to a therapeutic endoscopist with proper training and experience in endoscopic treatment of Barrett's and early esophageal cancer. In the absence of large randomized trials, there is low to moderate level of evidence supporting that endoscopic treatment is associated with higher local recurrence, which has mostly been treated endoscopically while adverse events were higher in patients undergoing esophagectomy.

Most contemporary guidelines recommend endoscopic resection of visible lesions in patients with Barrett's and dysplasia or intra-mucosal carcinoma (IMC) followed by endoscopic ablation of remaining of the Barrett's. The American Society for Gastrointestinal Endoscopy (ASGE) recommends endoscopic treatment over esophagectomy for the treatment of HGD or IMC in patients with Barrett's. The 5-year survival has been shown to be similar in patients with HGD or IMC treated with endoscopic treatment or esophagectomy. EMR of visible lesions upgrades the pathology in approximately 40% of patients. Surveillance should be continued after complete ablation of Barrett's. Surgical management of early esophageal cancer is discussed in the next chapter.

Endoscopic ablation therapy

Commonly used endoscopic ablation therapy includes Radiofrequency ablation (RFA), photodynamic therapy (PDT), endoscopic cryotherapy (EC), and Argon Plasma Coagulation (APC). These techniques are especially helpful in the context of high-grade dysplasia (HGD) or early esophageal cancer in the area of Barrett's esophagus and are often used in addition to endoscopic resection of the primary high-grade lesion to ablate the remaining Barrett's. RFA is currently the preferred method mainly due to the risk of stricture formation after PDT. EC is using liquid nitrogen to induce apoptosis and is predominantly used in the treatment of Barrett's with HGD or cancer. Studies on the effectiveness of EC are currently ongoing. APC is not the method of choice if other modalities are available due to lack of evidence on its effectiveness. None of these techniques are recommended in the management of a primary esophageal cancer and therefore further discussion of these methods would be outside of the spectrum of this manuscript.

Endoscopic Mucosal Resection (EMR)

EMR is the appropriate management for T1a lesions but should be avoided in any lesions invading to submucosa due to higher risk of local and distant recurrence in more advanced tumors. It can provide en-bloc resection for lesions under 1.5-2 cm however larger lesions may requires piecemeal resection using injection and lifting prior to resection by snare. EMR requires further training and special equipment in most cases. The rate of adverse events with EMR is relatively low and includes immediate and post-procedural bleeding in less than 10%, perforation in less than 3%, stricture in one third of the cases, which could be treated with endoscopic dilation in most cases. There are two main types of EMR techniques for esophageal lesions; conventional method and cap-assisted EMR. The area next to the edge of the lesion primarily marked using a cautery device to later recognize the resection margin in case of distortion by using snare cautery. Use of narrow band imaging or chromoendoscopy will enhance detection of the edges. In conventional method the lesion is lifted using injection of a liquid into submucosa followed by resection by cautery snare technique. In cap-assisted EMR method, after lifting the lesion, it is suctioned into an EMR cap attached to the tip of the endoscope and an elastic band is released to grasp the base

of this lesion. A snare cautery method is then used to resect this part. Routine antibiotic prophylaxis is not necessary but the author recommends enhanced acid suppression with PPI +/- sucralfate for 10-14 days after the procedure. Patients should be warned for the signs of complications before being discharged.

Endoscopic Submucosal Dissection (ESD)

ESD is used to remove lesions that invade up to submucosa. It allows for en-bloc resection, even of large lesions. Similar to EMR the area close to the margin of the lesion is first marked using a cautery device. In this method, a tunnel is created proximal to and going underneath the lesion into the submucosa using a needle knife and the lesion is then cut in a stepwise method until it is completely separated form submucosa and removed en-bloc. It is crucial to keep the tunnel in submucosa and not involve deeper or more superficial layers in the cut. The en-bloc resection is higher with ESD as compared to EMR however, the procedure time is significantly longer and the rate of complications is higher as compared to EMR. A randomized clinical trial in 40 patients with HGD or early esophageal carcinoma showed a more radical resection with ESD but mean follow-up of 23 months revealed no difference in the recurrence rate (*Terheggen et al*).

Conclusions

Management of early esophageal cancer is different from more advanced disease. Lesions can be curatively treated endoscopically without the need for esophagectomy. Multidisciplinary care and accurate imaging and pathological staging is crucial before planning management and therefore the patients are better investigated and managed in an expert centre where experienced pathologists, therapeutic endoscopists, thoracic surgeons as well as medical and radiation oncologists are available. EMR and ESD can provide complete resection of early esophageal cancer with comparable results. Other endoscopic ablation methods such as RFA should then be used to ablate the remaining Barrett's tissue if the high-risk lesion is found in the background of Barrett's esophagus.

References

1. *Evans JA Early DS Chandraskhara V Chathadi KV Fanelli RD Fisher DA et al. The role of endoscopy in the assessment and treatment of esophageal cancer . Gastrointest Endosc 2013 ; 77 : 328 – 34 .*
2. *K Muro, F Lordick, T Tsushima, G Pentheroudakis, E Baba, Z Lu, B C Cho, I M Nor, M Ng, L -T Chen, K Kato, J Li, M -H Ryu, W I Wan Zamaniah, W -P Yong, K -H Yeh, T E Nakajima, K Shitara, H Kawakami, Y Narita, T Yoshino, E Van Cutsem, E Martinelli, E C Smyth, D Arnold, H Minami, J Tabernero, J -Y Douillard, Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic oesophageal cancer: a JSMO–ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS, Annals of Oncology, Volume 30, Issue 1, January 2019, Pages 34–43.*
3. *Merkow RP, Bilimoria KY, Keswani RN, Chung J, Sherman KL, Knab LM, Posner MC, Bentrem DJ. Treatment trends, risk of lymph node metastasis, and outcomes for localized esophageal cancer. J Natl Cancer Inst. 2014 Jul 16;106(7).*
4. *Ramay FH, Vareedayah AA, Visrodia K, Iyer PG, Wang KK, Eluri S, Shaheen NJ, Reddy R, Martin LW, Greenwald BD, Edwards MA. What Constitutes Optimal Management of T1N0 Esophageal Adenocarcinoma? Ann Surg Oncol. 2019 Mar;26(3):714-731.*
5. *Terheggen G, Horn EM, Vieth M, et al. A randomised trial of endoscopic submucosal dissection versus endoscopic mucosal resection for early Barrett's neoplasia. Gut 2017; 66:783.*
6. *Thosani N, Singh H, Kapadia A, Ochi N, Lee JH, Ajani J, Swisher SG, HofstetterWL, Guha S, Bhutani MS. Diagnostic accuracy of EUS in differentiating mucosal versus submucosal invasion of superficial esophageal cancers: a systematic review and meta-analysis. Gastrointest Endosc. 2012 Feb;75(2):242-53.*
7. *Wong R, Walker-Dilks C, Raifu A. Evidence-based guideline recommendations on the use of positron emission tomography imaging in oesophageal cancer. Clin Oncol (R Coll Radiol). 2012 Mar;24(2):86-104.*

Treatment of Advanced Esophageal Cancer

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Introduction

The majority of patients with esophageal cancer already at presentation is found to have incurable disease. Reasons include the presence of metastases, locally irresectable cancer or a poor medical condition.

In general, for these patients, a variety of palliative treatment modalities are available depending on tumor stage, extent of the tumor and clinical condition of the patient.

Chemotherapy (with or without radiotherapy)

Patients with lymph node metastases not located in the resection plane and in a reasonable to good clinical condition can be treated with palliative chemotherapy with or without radiotherapy for local tumor control and improvement of dysphagia.

Although worldwide no consensus exists with regard to type of chemotherapy, first-line treatment usually consists of schedules including fluoropyrimidine and platinum-containing chemotherapy, for example capecitabine met oxaliplatin. Median survival of patients treated with these schedules is approximately 11 months, while the median survival of patients with supportive treatment usually is less than 6 months. Meta-analyses have shown that addition of a third chemotherapeutic agent only gives limited additional survival benefit. Something similar can be seen with second-line treatment: treatment with chemotherapy – mostly monotherapy with taxane, or irinotecan – offers a surviving advantage (median approximately 5-7 months versus 3.5 months with only supportive care) but treatment with two chemotherapeutic agents does not improve survival. By the end of 2018 it was demonstrated that – in case of disease progression after first-line and second-line therapy – patients still can be treated with third-line chemotherapy – in this case trifluridine/tipiracil – with a median survival of 5.7 months versus 3.6 months with only supportive treatment.

In order to improve systemic treatment options, current research focusses on target directed treatment. Drugs in this category bind selectively to certain proteins that are overexpressed on cancer cells, causing the cancer cell to stop growing. When administered as monotherapy these agents have a limited activity, but in combination with chemotherapy they significantly improve survival of patients. An example includes first-line treatment with trastuzumab combined with fluoropyrimidine and platinum containing chemotherapy. Trastuzumab binds to the human epidermal growth factor-2 (HER-2) receptor and should be administered to patients with a tumor that overexpresses the HER-2 receptor. The advantage of adding trastuzumab is most optimal in patients with in whom the tumor highly expresses HER2 (which means HER2 3+ or HER2 2+ and FISH positive): median survival of this group was 16.0 months versus 11.8 months for patients not treated with trastuzumab. For second-line treatment also a targeted agent is registered, in particular ramucirumab binding to the vascular endothelial growth factor receptor-2 (VEGF-R2), which in combination with paclitaxel results in a significant improvement in survival (median survival 9.6 months versus 7.4 months). Unfortunately, no biomarker is available that differentiates between patients that may have benefit of adding ramucirumab to the chemotherapeutic regiment.

For patients with esophageal squamous cell cancer often similar regimens are administered compared to patients with esophageal adenocarcinoma because no randomized controlled trials (RCTs) have been performed. Therefore, for both patient groups usually the same regimens are chosen for treatment. A recent development in this group of patients is that checkpoint-inhibitors – a type of immunotherapy – seems effective when the tumor overexpresses the receptor PDL-1. The exact role of checkpoint-inhibition in the treatment of esophageal cancer needs however to be established.

Palliation of malignant dysphagia

As said above, the survival of patients that cannot be treated with palliative systemic treatment is usually approximately 6 months; it is important in this period to guarantee that the patient does not develop dysphagia and if so, that it is treated.

In current practice, multiple therapeutic options are available for palliation of dysphagia due to esophageal cancer.

Treatment of Advanced Esophageal Cancer, continued

The European Society of Gastrointestinal Endoscopy (ESGE) guidelines state that patients should undergo either stent placement or intra-luminal brachytherapy (ILBT), depending on predicted life expectancy. Nowadays, ILBT is often replaced by external-beam radiotherapy (EBRT).

In our own experience, decision making in the selection of the optimal palliative strategy remains challenging, as esophageal stenting and palliative ILBT or EBRT might be most effective in resolving dysphagia in selected groups of patients.

Esophageal stent placement

Currently available stents vary in the way they are braided or laser-cut, but they all have a cover that protects the stent against tissue or tumor ingrowth (Figure 1). Based on the earlier studies, esophageal stenting is the preferred therapeutic option in patients that have a poor predicted prognosis, because of faster relief of dysphagia due to the instant therapeutic effect of a stent compared to ILBT.

Nonetheless, a well-known relative contra-indication for palliative radiotherapy and thus indication for stent placement is a malignant esophageal fistula, as experts believe that application of radiotherapy might lead to further enlargement of the fistula. Placement of a covered stent may successfully seal off the luminal defect to prevent further contamination of the mediastinum and aspiration pneumonia.

Complications of stent placement may seriously impair remaining quality of life of patients. Remarkably, stent-related complications appear to have increased in recent years, possibly related to the increased use of chemoradiotherapy prior to stent placement. Pooled data analysis from the ESGE guidelines showed early complications to include reflux (9%), severe pain (9%), hemorrhage (8%), pneumonia (4%), and perforation (3%) [4]. Late complications include reflux (15%), severe pain (15%), hemorrhage (11%), pneumonia (10%), and fistula (5%). An overview of stent-related complications is shown in Table 1.

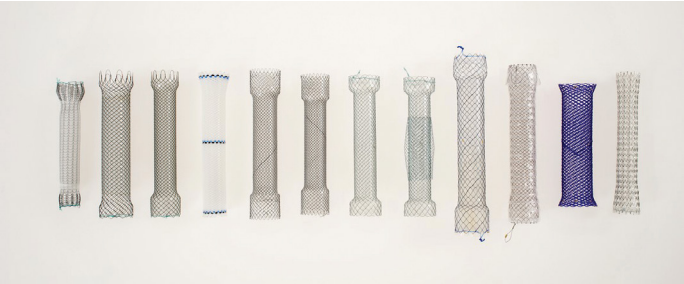

Figure 1 – *Different types of esophageal stents*

Table 1 - *Overview of complication rates related to stents, ILBT and EBRT*

	Stents	ILBT	EBRT
Early complications (%)			
Severe pain	8.7	0.2*	-
Haemorrhage	7.6	0.8*	-
Migration	6.6	-	-
Perforation	3.3	0.8*	-
Pneumonia	3.5	0.2*	21.2
Reflux	9.3	-	-
Anaemia	-	-	42.3
Oesophagitis	-	-	44.2
Nausea and vomiting	-	-	58.7
Radiation dermatitis	-	-	41.3
Late complications (%)			
Severe pain	15	0.2*	-
Haemorrhage	11.3	0.8*	-
Migration	11	-	-
Perforation	4.5	0.8*	-
Ingrowth/overgrowth	14	-	-
Obstruction	9	-	-
Reflux	15	-	-
Pneumonia	10.3	-	-
Fistula	5	8.3*	-
Stricture	-	12.2*	-

- indicates study report did not include specific outcome.
* indicates early/late complication rates were not reported separately.
Abbreviations: ILBT, intra-luminal brachytherapy; EBRT, external beam radiotherapy

An interesting subject of recent research is the development of radioactive esophageal stents. A phase 3 RCT compared radioactive stents loaded with ^{125}Iodine seeds with conventional stents in patients with incurable esophageal cancer.

Treatment of Advanced Esophageal Cancer, continued

The radioactive stent prolonged survival (177 versus 147 days) and gave better relief of dysphagia with mean dysphagia scores remaining significantly lower from one month after stent placement to the last follow-up visit. Remarkably, major complications including fistula formation were not different between both groups. For implementation in daily practice, additional high-quality evidence from large comparative studies in different parts of the world should confirm these promising findings.

Besides radioactive stents, drug-eluting stents with chemotherapeutic agents have been developed and investigated as well. The chemotherapeutic agent is delivered locally at the esophageal wall and thereby potentially cause less systemic toxicity. However, this type of stent loaded with paclitaxel or 5-fluorouracil, has only been tested in animal models without esophageal malignant strictures. Further studies in animal models are needed before this application is ready to be tested in human subjects.

Radiotherapy

Intra-luminal brachytherapy

ILBT is recommended in patients with a relatively good prognosis given its sustained palliation of dysphagia and low complication rate. For ILBT, an applicator delivers intraluminal radiation at the tumor site (Figure 2). Currently applied ILBT doses are reported to range from 12 Gray (Gy) up to 21 Gy delivered in one to three fractions. The best radiation dose to be applied for palliation of dysphagia remains however uncertain.

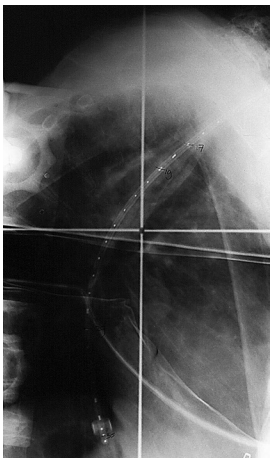

Figure 2– *X-ray showing applicator for intra-luminal brachytherapy in the esophagus*

With regard to the safety profile of ILBT, A pooled data analysis showed major complications in 23% of patients, mainly involving ILBT related stenosis (12%) and fistula formation (8%). Less frequently reported major complications include perforation (1%) and hemorrhage (1%). Complication rates seem not to be different for administered ILBT doses. An overview of reported complications is presented in Table 1.

Even though ILBT has been widely recommended in patients with an expected long-term survival, its use in current clinical practice has reduced. Main limitations of ILBT were reported to be lack of experience and complexity of the procedure. Despite the proven efficacy of ILBT for palliation of dysphagia, these results show a need for more accessible therapeutic alternatives in palliative patients with an expected longer survival.

External beam radiation therapy

A frequently used alternative to ILBT is (fractionated) EBRT. Most commonly used palliative radiation schemes include 20 Gy in five fractions or 30 Gy in ten fractions, delivered with opposing fields in an anterior-posterior direction. Typically, EBRT leads to an initial increase of dysphagia symptoms due to radiation induced swelling, followed by a long-term relief of dysphagia a few weeks after completion of EBRT.

Although fractionated EBRT is widely used for palliation of dysphagia, data on its efficacy is scarce. One series reported a reduction of dysphagia symptoms in 104 of 138 (75%) patients experiencing dysphagia prior to EBRT. Additional therapy for palliation of dysphagia was required in 42 patients (30%).

With regard to toxicity, EBRT was well tolerated and premature discontinuation of EBRT was reported in only two patients (1%), rehospitalization in five patients (3%), and no EBRT related deaths were noted.

In conclusion, based on the current evidence, EBRT might be an effective and safe therapeutic alternative to ILBT for palliation of dysphagia.

Combined therapies

Few studies have assessed the efficacy and safety of a combination of ILBT and EBRT. These studies reported contrasting results, and only one study showed a statistically

significant difference between treatment arms, in favor of patients undergoing ILBT in combination with EBRT. Complication rates were not increased with combination treatment. It remains however uncertain if addition of EBRT to ILBT is beneficial for the palliation of dysphagia.

Summary

In patients with metastases not located in the resection plane and in a reasonable to good clinical condition, palliative chemotherapy with or without radiotherapy for local tumor control and improvement of dysphagia should be considered.

Nonetheless, in the majority of palliative patients, treatment of dysphagia is most important. Esophageal stent placement continues to be the most favorable option in patients with a poor predicted prognosis, given its rapid relief of dysphagia. Due to ongoing developments for patients with incurable esophageal cancer, palliative care is improving and therefore patients' life-expectancy is increasing, resulting in a decreased number of stent placements over the past years and concurrent changes in patient characteristics.

Although ILBT remains a recommended first-line palliative option, EBRT has emerged as a potential and interesting alternative. However, data on its efficacy and safety in palliation of dysphagia is limited and EBRT needs to be compared with ILBT in an RCT to evaluate possible implementation in clinical practice.

Finally, It is important to stress the need for more guidance to reduce the known variation between hospitals in first-line palliative management strategies for esophageal cancer. A preferably simple prognostic prediction tool could aid in identifying patients for the best palliative strategy and prognostic prediction tools should be developed to guide treatment allocation for palliative options to improve the care of patients.

Conflicts of interest

The author has received research grants related to some part of this review from Boston Scientific, Cook Medical, Ella-CS and MI-Tech.

References for further reading:

Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D, Committee EG. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016; 27: v50-v7.

Smyth EC, Lagergren J, Fitzgerald RC, Lordick F, Shah MA, Lagergren P, Cunningham D. Oesophageal cancer. Nat Rev Dis Primers 2017; 3: 17048.

Janmaat VT, Steyerberg EW, van der Gaast A, Mathijssen RH, Bruno MJ, Peppelenbosch MP, et al. Palliative chemotherapy and targeted therapies for esophageal and gastro-esophageal junction cancer. Cochrane Database Syst Rev. 2017;11:CD004063.

van den Ende T, Smyth E, Hulshof MCCM, van Laarhoven HWM. Chemotherapy and novel targeted therapies for operable esophageal and gastroesophageal junctional cancer. Best Pract Res Clin Gastroenterol 2018; 36-37: 45-52.

Homs MY, Steyerberg EW, Eijkenboom WM, Tilanus HW, Stalpers LJ, Bartelsman JF, et al. Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial. Lancet 2004; 364: 1497-504.

Spaander MC, Baron TH, Siersema PD, Fuccio L, Schumacher B, Escorsell A, et al. Esophageal stenting for benign and malignant disease: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2016; 48: 939-48.

Zhu H-D, Guo J-H, Mao A-W, Lv W-F, Ji J-S, Wang W-H, et al. Conventional stents versus stents loaded with 125iodine seeds for the treatment of unresectable oesophageal cancer: a multicentre, randomised phase 3 trial. Lancet Oncology 2014; 15: 612-9.

Fuccio L, Mandolesi D, Farioli A, Hassan C, Frazzoni L, Guido A, et al. Brachytherapy for the palliation of dysphagia owing to esophageal cancer: A systematic review and meta-analysis of prospective studies. Radiother Oncol. 2017; 122: 332-97.

The Rise and Fall of Colorectal Cancer

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Colorectal Cancer is the third most common cancer in men (after lung cancer and prostate cancer) and second most common cancer in women (after breast cancer) worldwide. Based on the figure from GLOBOCAN, there was an estimated 1,006,000 new cases of colorectal cancer in men and 795,000 in women in the year 2018, constituting 10% of global cancer burden. Despite its high incidence, the mortality of CRC is relatively low. The age-standardized mortality rate (ASMR) was 10.6 per 100,000 in men and 7.0 per 100,000 in women [1]. This is much lower than the other gastrointestinal cancers such as gastric cancer, pancreatic cancer and liver cancer.

As in many other cancers, the incidence and mortality of CRC increase markedly with age, and most cases of CRC and deaths occur in people older than 50 years. However, there is a recent trend of increasing young CRC (below the age of 50 year) as described below.

There is a wide variation in CRC incidence around the World, with the highest rate from Australia and New Zealand (Age-standardized incidence rate 40.6 per 100,000 in men and 30.5 per 100,000 in women) and Europe, rising incidence in East Asia (Japan, Korea and China) and a high but reducing incidence in the United State. The lowest rate of CRC is in South to Central Asia (ASIR 5.6 per 100,000 in men and 3.5 per 100,000 in women).

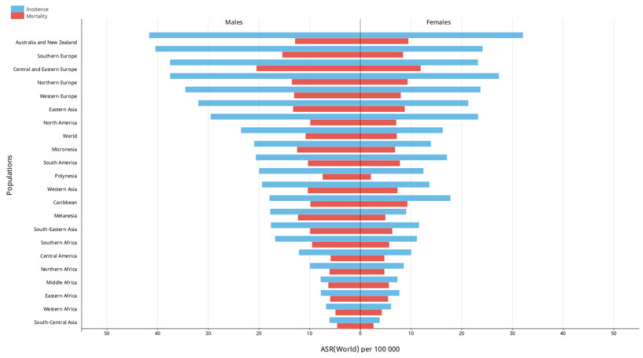
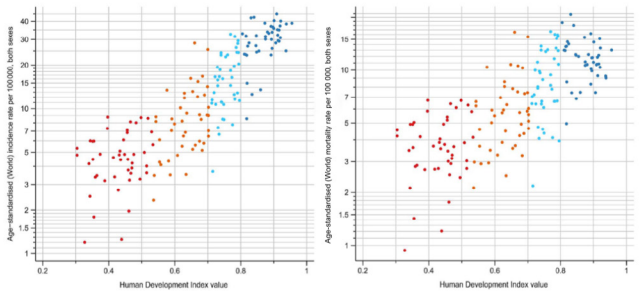


Fig 1. *Global estimated age-standardize incidence (A) and mortality (B) rate per 100,000 of colorectal cancer according to GLOBOCAN 2018.*

CRC incidence rates across the world varies up to 10-fold worldwide. The recently published data from IARC [2] suggest a strong positive gradient with the level of economic growth. There is a distinct gradient across human development index (HDI is a statistic composit0e index which include life expectancy, education and per capita income indicators) with CRC incidence (Fig 2). [3] Rapid increases in both incidence and mortality of CRC are now observed in many medium-to-high HDI particularly in Eastern Europe, Asia and South America. In contrast, CRC incidence and mortality rate are stabilizing or declining in a number of high HDI countries such as the USA, Australia, New Zealand and Western European countries.



Adapted by permission from BMJ Publishing Group Limited. *Gut*, Arnold M, Sierra M, Laversanne M, Soerjomataram I, Jemal A, Bray F, volume 66, issue 4, 683–691, © 2017. (Arnold et al., 2017). From Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. (2013). GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer. Available from: http://globocan.iarc.fr, accessed on 10 July 2017.

Based on temporal changes in incidence and mortality of CRC of 37 countries, the International Agency for Research

on Cancer in Lyon France and the American Cancer Society have identified three groups of countries/regions of the world. Group 1: Increasing incidence and mortality over the past 10 years (Eastern European countries, Latin America and Asia); Group 2: Increasing incidence and decreasing mortality (Several European countries such as Netherlands, Denmark, Sweden, Norway, Finland, UK, Italy, and Singapore) and Group 3: Decreasing incidence and mortality (US, Australia, New Zealand, Austria, France, Japan and Israel).

The rationale behind these rises and falls in incidence and mortality are not entirely clear but it is likely to be related to societal and economic development, improvement in treatment options and accessibility, particularly in low-income and middle-income countries that faces increasing burden of CRC. Two important factors that impact on the global increasing incidence of CRC are 1. Ageing population, 2. Obesity and diabetes. As CRC is largely a disease of the population above the age of 50, the worldwide increasing proportion of population in this age group will inevitably witness increasing incidence of CRC. In countries with remarked longevity and large population, such as China [4] and Latin America, the impact on healthcare system can be huge. There is also ample evidence to suggest that obesity and type 2 diabetes mellitus is associated with rise in CRC incidence. BMI $\geq$ 28 in the West and BMI $\geq$ 24 in the East have been demonstrated to increase risk of the condition. Blood sugar level has also been demonstrated to increase in many cancers including CRC [5].

Prioritization of primary prevention and early detection by screening plays a key role in the improvement of outcome of CRC. The extent to which screening programs in decreasing incidence rates of CRC through detection and removal of adenomatous polyps is difficult to assess at this moment. But opportunistic screening programs in the USA, Japan and Israel lend support to the effectiveness of this strategy. In the US, simulation modelling studies have suggested that a larger contribution from screening and a smaller but demonstrable impact of reduction in exposure to risk factors and improvements in treatment.

In the past few years, new biomarkers, endoscopic device and screening strategies have been described which may enhance early diagnosis of CRC. However, many of these technologies are expensive and may not be cost-effective for population-wide implementation. Strategies need to be established in countries of different ethnical background and economical situation to enhance prevention and early diagnosis of colorectal cancer. The following chapters will elaborate on the various dimension of colorectal cancer prevention, screening and treatment.

References

1. *Ferlay J , Colombet M, Bray F. Cancer incidence in Five Continents, C15plus: IARC CancerBase No. 9 Lyon, France 2018*
2. *IARC Handbooks of Cancer Prevention IARC Volume 17: Colorectal Cancer Screening. Lyon France. 2019*
3. *Arnold M, Sierra MS, Laversanne M et al. Global patterns and trends in colorectal cancer incidence and mortality. GUT 2017; 66:683-91*
4. *Tsoi KK, Hirai HW, Chan FC et al. Cancer burden with ageing population in urban regions in China: projection on cancer registry data from World Health Organizatio. Br Med Bull 2017; 12:83-94.*
5. *Lauby-Secretan B, Scoccianti C, Loomis D et al. Body fatness and cancer- viewpoint of the IARC Working Group. N Engl J Med 2016; 375: 794-8*

Colorectal Cancer Screening from a Global Perspective

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Burden of Disease

Colorectal cancer (CRC) - a global public health issue - is covered in the Chapter by Sung (*The Rise and Fall of Colorectal Cancer,* pages 60-61). A few key points here will suffice to set the context for this chapter on CRC screening. In 2018, the International Agency for Research on cancer (IARC) estimated that there were 1.8 million new CRC cases and 881,000 deaths from the disease worldwide[1]. Globally, colorectal cancer accounts for 9.2% of all cancer deaths, and is second only to lung cancer as a cause of cancer deaths. CRC incidence, which rises in parallel with economic transition, reflects a progressive "westernization" of lifestyle. Most of the increase in CRC burden in the next 25 years is expected in less developed countries because of economic transition and the adoption of western life-style patterns. By 2040, IARC estimates that there will be 3.1 million new cases and 1,564,000 CRC deaths worldwide. Primary prevention, which focuses on interventions to change "westernized" life-style behaviours will be important to address the anticipated rise in CRC burden, and is covered in the chapter by Young (*Diet and Lifestyle for Prevention of Colorectal Cancer*, pages 79-83). A combined approach that encompasses primary prevention and CRC screening is needed. The focus in this chapter is on CRC screening.

Approach to CRC Screening: Organized vs Opportunistic

CRC screening is a major public health intervention, and the approach to screening varies greatly across jurisdictions. Determinants, facilitators and barriers to participation occur at the policy, organization, provider and patient levels[2]. The health policy in a country is a key determinant of the approach to CRC screening. In countries that adopt a public health policy, cancer screening is publicly-funded by a single-payor universal access insurance system. In these settings (e.g., Canada, Netherlands, England, Australia, New Zealand, Italy, Taiwan) cancer screening is delivered in an organized, population-based approach. Organized cancer screening, as defined by IARC, includes: (1) an explicit policy with specified age categories, method and interval for screening; (2) a defined target population; (3) a management team responsible for implementation; (4) a health care team for decisions and care; (5) a quality assurance structure; and (6) a method for identifying cancer occurrence in the population. To fulfill these criteria requires an investment in program infrastructure, including an IT system dedicated to screening. The ability to collect and link data (including cancer registry data) across all the steps in the screening process is key to operate, monitor and report on the performance and impact of the screening program.

In contrast, opportunistic screening occurs outside of an organized screening program. In these settings (e.g., the US) screening is often delivered through fee-for-service reimbursement of physicians by payors. Compared with opportunistic screening, organized screening focuses much greater attention on the quality of each step in the screening process, from identifying and inviting the target population to follow-up of participants, and monitors and reports publicly on the performance of the program. Thus, a key advantage of organized screening is that it provides greater protection against the harms of screening, including over-screening, poor quality and complications of screening, and poor follow-up of those who test positive.

Organized, population-based screening is clearly a major public health intervention that requires both public support and a substantial funding commitment from government. In 1968 Wilson and Jungner set forth 10 principles of screening. Recently, Dobrow et al conducted a systematic review of subsequent work on population-based screening decisions to examine how these principles have evolved[3]. This review showed a shift in screening principles with an increasing focus on infrastructure requirements and resource or system capacity. The authors identified 12 principles, 3 focused on the disease (e.g., epidemiology, natural history), 3 focused on the screening test (e.g., test characteristics) and 6 focused on the program/system (e.g., infrastructure, benefits and harms, economic evaluation). Today, decision making regarding organized, population-based cancer screening requires careful consideration of this broader set of principles. Organized, population-based cancer screening programs involve considerable initial "up-front" investment of public funds with benefits that accrue much later. However,

given the rising costs of treatment, CRC screening programs can show favorable cost-effectiveness over a relative short period of time. In making the case to governments for public investment in organized CRC screening, economic evaluation is important.

Early Detection Programs

In many countries, there is both insufficient capacity in terms of health human resources (endoscopists, pathologists, surgeons, oncologists) and access to high quality treatment. In such situations, building capacity in health care infrastructure and resources is a needed first step. The World Health Organization (WHO) recommends strengthening diagnostic and treatment capacity and quality first. Coupled with this is raising public awareness of the need to seek medical attention and diagnostic work-up in the event of large bowel symptoms[4]. Taken together, these aspects - raising awareness of the importance of large bowel symptoms and making high quality colonoscopy and treatment readily available - comprise an Early Detection Program. In essence, it does not make sense to attempt to implement CRC screening when the necessary capacity for prompt diagnosis and high quality treatment are not available.

CRC Screening Strategies Used Around the World

In the past 20 years, there has been remarkable progress in CRC screening efforts, globally[5,6]. IARC recently completed a review of the published evidence for CRC screening modalities, and concluded there is sufficient evidence that the use of stool-based tests (guaiac testing and FIT) and lower endoscopy (sigmoidoscopy and colonoscopy) reduces the risk of death from CRC and that the benefits outweigh the harms. Evidence from comparative effectiveness studies to evaluate one test over another was inconclusive[2].

United States and Canada

In the US, at the health policy level, insurance status is the most important determinant of CRC screening, and mostly the approach is with opportunistic colonoscopy. The best US example of organized CRC screening is in the Kaiser Permanente Northern California (KPNC) integrated health system. In that system, which serves approximately 4 million members, prior to 2006, CRC screening was opportunistic, predominantly using sigmoidoscopy and gFOBT. Starting in 2007, screening transitioned to mailed FIT outreach to individuals who were not up-to-date. Opportunistic colonoscopy was an option throughout. Thus, KPNC transitioned from opportunistic to organized CRC screening with the launch of FIT[7].

In Canada, in 2008, Ontario, which has a population of 14.4 million, was the first Canadian province to launch an organized, population-based CRC screening program[8], based on gFOBT for those age 50 to 74 years at average risk and colonoscopy for those at increased risk, defined by a family history of one or more first degree relatives with the disease. The program replaced the gFOBT with FIT in 2019. Six of the other 9 Canadian provinces have launched organized CRC screening programs, using FIT (in 5 provinces) or Hemoccult II Sensa (in 1 province). Three provinces and all 3 territories have yet to implement organized CRC screening programs.

Latin America

Uruguay has the highest CRC incidence among Latin American countries (CRC incidence 35.0/100,000). In 1996, Uruguay began a FIT pilot, and in 2017, the transition to an organized, population-based program began. Several FIT pilots are underway in Latin America, including those in Brazil, Chile and Argentina.

European Union

In 2003, the EU Council called for the introduction of evidence-based screening, adopting a population-based approach. The EU quality assurance guidelines[9] evaluated the evidence for CRC screening, and provided recommendations on the quality assurance of each step in the screening process. By 2018, population-based programmes with active invitation at regular intervals of the entire target population, identified through screening registries, had been established, or piloted, in 22 of 28 EU member states and in 7 of 19 non EU countries, with three EU member states having approved plans for introducing a population based program in the near future[6].

Colonoscopy capacity influences screening program design. The majority of population-based programs have adopted or are planning to adopt biennial FIT[10] and about half of them are targeting older age groups, starting at age 55 or 60 years, and stopping at age 69 or 74. Only Poland has implemented colonoscopy screening, offered once in the lifetime, within an organised program, while the Luxembourg and Swiss programs are offering a choice of colonoscopy or FIT. Sigmoidoscopy (FS) screening, offered once in the lifetime, has been adopted in one region in Italy (Piedmont), with

FIT offered as an alternative test for those refusing FS. In England, the Bowel Cancer Screening Program, which was launched in 2006, is based on gFOBT. FIT was introduced in 2018. Following the full roll-out of FIT over the age range 50 to 74, it is anticipated that FS will be maintained as an alternative option in England.

Asia-Pacific

Currently there are six countries in the region, including Australia, Japan, Korea, New Zealand, Singapore, and Taiwan, with nationwide screening programs funded (total or partial) by governments. Most programs provide screening starting at age 50 years except for Japan, which starts at age 40. Only Australia and Taiwan have an upper age limit (74 years)[6]. All six programs use FIT as the initial screening test with diagnostic colonoscopy offered to those with a positive FIT. Pilot programs are underway in Hong Kong and Thailand.

What is the Performance of CRC Screening?

Information about the performance and impact of CRC screening is limited. Available data mainly pertain to organized, population-based programs, given that monitoring and reporting are key elements of these programs.

United States and Canada

In opportunistic screening, there is generally no performance monitoring and reporting on a jurisdiction-wide basis. Based on survey at CDC in 2018, 68.8% of US adults 50-75 years reported being up to date with CRC screening.

In contrast, for organized cancer screening there is detailed information from performance monitoring. For example, in 2017 in Ontario, Canada 62.5% were up-to-date with CRC screening. In 201680% had a colonoscopy within 6 months following a positive gFOBT and the cancer detection rate for those screened with gFOBT was 1.4/1000.

European Union

A recent report compared the performance of CRC screening programs in the EU member states using key quality indicators11. For those countries that have implemented organized, population-based screening programs, wide variation exists. For example, for those countries/regions using FIT, participation rates range from 22.8 to 71.3%, and compliance with referral for colonoscopy following a positive-FIT ranges from 64 to 92%.

Asia-Pacific

In general, for those Asian countries with organized, population-based screening programs, participation and follow-up colonoscopy among those with a positive stool test are low[12]. A recent report from Australia documents the progress of the National Bowel Cancer Screening Program, which was launched in 2006 based on the FIT, with complete roll-out to the full target age group anticipated by the end of 2020[13]. The participation rate in 2015-16 was 41%, with a favorable stage-shift among participants, although only 68% of those with a positive FIT has having undergone a follow-up colonoscopy.

What is the Impact of Screening on CRC Incidence and Mortality?

In the US, a recent study from KPNC reported an increase in the proportion of individuals who were up-to-date with CRC screening associated with implementing organized FIT screening in the context of pre-existing opportunistic colonoscopy in average risk persons[7]. The increased participation was accompanied by a 25.5% reduction in CRC incidence and 52.4% reduction in CRC mortality.

In Europe, preliminary reports of CRC incidence and CRC mortality following the introduction of population-based programs show a beneficial impact of screening on CRC burden at the population level. For example, in the Veneto region of Italy, biennial FIT screening was associated with a reduction in CRC mortality based on a comparison between early and late screening areas[14].

In Taiwan, the effectiveness of FIT screening in reducing CRC mortality has been reported. In the initial five years of this program (2004-09), FIT screening was associated with a 10% reduction in CRC mortality when comparing those who did and did not participate in screening[15].

Figure 1. *CanScreen5 data collection and submission platform.*

Canscreen5

One of the challenges in CRC screening globally, has been the lack of a standardized approach to program evaluation that would facilitate international comparisons and the identification of performance gaps. In 2019, IARC launched CanScreen5, which is intended to address this gap (https://canscreen5.iarc.fr/index.php). CanScreen5 provides a platform for data collection and comparative evaluation of screening performance indicators around the world, following the experience of the EU screening report[10]. All countries/regions should seriously consider contributing their data to CanScreen5 [Figure 1].

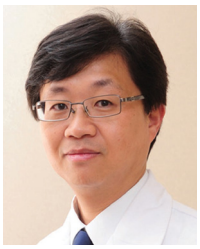
Conclusion

CRC is a major global public health problem, and the forecast increase in the burden of disease related to economic transition, may be accompanied by widening disparities among and within countries. This may be exacerbated by disparity in the availability of and access to health care resources observed across countries. CRC screening may mitigate these trends, if effective policies are established to ensure sustainability over time and equity of access. Raising participation in hard-to-reach populations is challenging but is a key accountability for those who lead CRC screening programs. In the US, most CRC screening is opportunistic, with colonoscopy the dominant screening method for those at average risk. In most other countries, organized, population-based screening is being implemented, with FIT as the dominant screening method. Early results indicate a reduction in CRC mortality associated with implementation of organized, population-based CRC screening. However, variability in the performance of screening programs underscores the need to improve participation and strengthen quality for all the steps in the screening process. CanScreen5 is an important platform to facilitate and support consistent performance reporting from CRC screening programs, to identify gaps and conduct comparisons globally.

References

1. *Bray F et al. Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 Countries. CA Cancer J Clin. 2018;68(6):394-424.*
2. *IARC (2019). Colorectal cancer screening. IARC Handb Cancer Prev. 17:1–300. Available from: http://publications.iarc. fr/573.*
3. *Dobrow MJ et al. Consolidated principles for screening based on a systematic review and consensus process. CMAJ 2018;190:E422-9.*
4. *Guide to Early Cancer Diagnosis. Geneva: World Health Organization; 2017.*
5. *Young GP et al. The global paradigm shift in screening for colorectal cancer. Gastroenterology 2019;156(4):843-51.*
6. *Rabeneck L et al. International perspective on the burden of colorectal cancer and public health impact. Gastroenterology 2020; in press.*
7. *Levin TR, Corley DA, Jensen CD, et al. Effects of organized colorectal cancer screening on cancer incidence and mortality in a large community-based population. Gastroenterol 2018;155(5):1383-91.*
8. *Rabeneck L, Tinmouth JM, Paszat LF, et al. Ontario's ColonCancerCheck: Results from Canada's first province-wide colorectal cancer screening program. Cancer Epidemiol Biomarkers Prev 2014;23(3):508-15.*
9. *Segnan N et al (2010). European Guidelines for Quality Assurance in Colorectal Cancer Screening Report on the Implementation of the Council Recommendation on Cancer Screening (First Report). Luxembourg: Publications Office of the European Union.*
10. *Ponti A et al (2017). Against Cancer. Cancer Screening in the European Union. Report on the implementation of the Council Recommendation on cancer screening. European Commission. Brussels.*
11. *Senore C et al. Performance of colorectal cancer screening in the European Union member states: Data from the second European screening report. Gut 2019;68:1232-44.*
12. *Chiu H-M et al. Colorectal cancer screening in Asia. Curr Gastroenterol Rep 2017;19:47.*
13. *Ee HC et al. The National Bowel Cancer Screening Program: Time to achieve its potential to save lives. Public Health Res Pract 2019;29(2):e2921915.*
14. *Zorzi M, Fedeli U, Schievano E, et al. Impact on colorectal cancer mortality of screening programmes based on the faecal immunochemical test. Gut 2015;64(5):784-90.*
15. *Chiu HM, Li-Sheng Chen S, Ming-Fang Yen A, et al. Effectiveness of fecal immunochemical testing in reducing colorectal cancer mortality from the one million Taiwanese Screening Program. Cancer 2015;121:3221-9.*

Stratified Screening Approach in Resource-Limited Country/Region



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How to select screening modality in resource-limited country/region

Screening for colorectal cancer (CRC) is concerned with many aspects of demands, including manpower demand such as public health workers, healthcare professionals, and laboratory staffs; clinical infrastructures such as endoscopy service and medical management of screening-detected neoplasms; and sustained administrative and funding support. Currently, colonoscopy is deemed as the most accurate examination in detecting colorectal neoplasms, which has sensitivity of higher than 95% for detecting both advanced adenoma and invasive cancers. It also has the advantage of being able to resect neoplastic lesions that detected during examination thus it is nowadays not only used as a diagnostic exam but also as a screening tool.[1] Its effectiveness in reducing CRC mortality and incidence has been demonstrated in cohort studies.[2] Nevertheless, if we consider the prevalence of neoplasm (0.2-0.3% for invasive cancer, 5 to 10% for advanced adenoma and 30-40% for adenoma) in the general population of screening age (i.e. 50 to 75 years in most of the screening programs), nearly 60 to 70% of the exams would be negative for neoplasm if colonoscopy is used as a primary screening tool for the targeted screening population. Adding to the fact that not all adenoma (especially diminutive or small ones) would eventually progress into invasive cancer, and the high invasiveness and high-cost characteristics of colonoscopy, it would be most ideal if we can select subjects at higher risk of advanced neoplasm from a large population by using a triage test.[3, 4] Such a triage test should have the characteristics of low-cost, high accuracy, and high acceptance by the public. Currently, stool-based test, either guaiac occult blood test (gFOBT) or fecal immunochemical test (FIT), fit the above-mentioned characteristics and its effectiveness in reducing CRC mortality by screening has been proven in previous randomized controlled trials (gFOBT) or cohort studies (gFOBT and FIT). [5-7] Collectively, in resource-limited regions, population mass screening with colonoscopy may not be practical, and strategies using non-invasive triage test to select high-risk population should be considered.

Non-invasive screening test as a primary screening tool for mass screening

Using the non-invasive test as the primary screening tool to select subjects at risk of significant colorectal neoplasm can increase the likelihood of detecting significant neoplasm at colonoscopy. (Figure 1) It can therefore remarkably reduce the colonoscopy demand thereby improve the efficiency of screening and reduce colonoscopy-related cost and unnecessary complications. Whilst selecting a primary screening test, several issues need to be carefully considered:

Sensitivity: High sensitivity enables better detection of advanced neoplasm (advanced adenoma and cancer) and reduces missed lesions, leading to a higher screening effectiveness.

Specificity: High specificity can reduce the number of false-positive test hence reduce the likelihood of negative finding at diagnostic exam (i.e. colonoscopy) thereby improves the efficiency and the cost pertaining to diagnostic exam.

Positivity rate: Positivity rate is not only associated with sensitivity and specificity of the test but is also affected by disease prevalence. High positivity rate is associated with increased diagnostic exam workload and its related cost and affects screening efficiency as well.

Cost: Cost is another important consideration and may affect screening-related finance. This is extraordinarily important when funding is constrained.

Public acceptance: High screening test performance is not a guarantee of high compliance by the public. Only if uptake of the CRC screening test is high then we can achieve a high detection rate for advanced neoplasms.

Stool-based screening tests, including guaiac fecal occult blood test (gFOBT) or fecal immunochemical test (FIT), are currently the most popular primary screening test especially in government-funded programs because they can significantly constrain the demand for colonoscopy.[8] Though only gFOBT was proven to be effective in reducing CRC mortality by randomized trials, FIT has superior screening uptake, higher sensitivity to early CRC and advanced adenoma, and higher specificity as compared with gFOBT.

Stratified Screening Approach in Resource-Limited Country/Region, continued

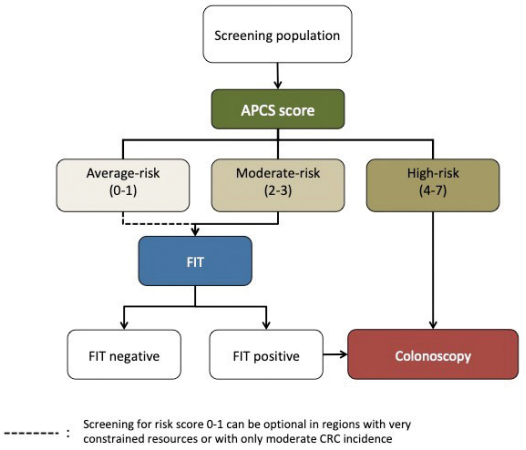

Figure 1 *Risk stratified two-tier screening approach for CRC: FIT as an example*

FIT is gradually replacing gFOBT as the primary screening test.[5] FIT is less likely affected by diet because it is an immunoassay specific for human hemoglobin whereas gFOBT detects the heme moiety of hemoglobin, which is also present in animal food products (e.g., beef, pork, lamb, and processed foods containing these meats). Typically, only one or two stool samples are required and dietary restriction is obviated for FIT testing, and adding the user-friendly design of spatula and stool sample collection tube, its acceptance by the public is much higher than gFOBT thereby contributing to higher neoplasm detection.[9, 10] Quantitative FIT, for which positive cutoff is adjustable, can help the screening organizer to determine the optimal cutoff of FIT based on the regional colonoscopy capacity, prevalence of advanced colorectal neoplasm (CRC and advanced adenoma) and healthcare cost.[11]

The positivity rate of FIT in population screening, the major determinant for colonoscopy demand, usually ranges from 4 to 10%.[6, 7, 10] This means colonoscopy capacity that required in FIT screening program is much lower than that in the colonoscopy-based screening settings. Its sensitivity for invasive CRC is around 80% and advanced adenoma around 30%, both are much lower than colonoscopy. Therefore repeat FIT at fixed intervals is required to detect neoplasm missed at previous screening round or newly developed neoplasms.[12] One or two years are the most widely applied screening intervals for FIT, which is based on the sojourn time for an advanced adenoma to progress into invasive cancer (estimated to be around 3 years). Several programs have reported the effectiveness of FIT screening in reducing CRC mortality or even CRC incidence.[6, 7, 13, 14] FITs are similar in effectiveness to colonoscopy when used in a consistent, programmatic way to screen for CRC. Its cost-effectiveness, based on the modeling study by the United States Preventive Services Task Force (USPSTF), is close to that of colonoscopy-based screening if adherence to FIT screening over time is good.[15]

Stratified screening approach in regions with multiple ethnicities

The risk of CRC may differ according to geographic variations and ethnicity.[16] Launching a nationwide population-based program in such region may encounter some barriers especially when an ethnic majority is not at the highest risk of CRC and resources are constrained. In Malaysia, where Malay comprises 67% of the entire population, Chinese has CRC incidence of 27.35/10^5, which is much higher than that in Malay (18.95/10^5) and Indian (17.55 per 10^5) populations.[17] In China, where the east coast presented a higher mortality rate (>15 and 10–14.9 per 10^5 in men and women) than central and west China (5–14.9 and 5–9.9 per 10^5), significant discrepancy also exists between rural and urban regions.[18] As such, risk score-based approach may be helpful to select high-risk subjects for diagnostic examination. In the Asia-Pacific region, a risk score system using simple demographic and lifestyle features (gender, age, family history, and smoking) has been developed and validated to select high-risk Asian subjects for priority of CRC

Table 1. *Asia-Pacific Colorectal Screening Score*[19]

Risk factor	Criteria	Score
Age, year	<50	0
	50-69	2
	≥70	3
Gender	Female	0
	Male	1
Family history of CRC in first-degree relatives	Absent	0
	Present	2
Smoking	Never	0
	Current or past	1

Stratified Screening Approach in Resource-Limited Country/Region, continued

screening. (Fig 2) Studies have demonstrated that it had a good discriminatory power in differentiating subjects with various risk profile for advanced neoplasm (advanced adenoma and invasive cancer) and could reduce the colonoscopy workload.[19, 20] In multi-ethnic region where nationwide screening program is not in place, primary care physicians can select high-risk subjects for colonoscopy using this triage tool. Further study of comparing its performance with FIT or whether the risk score can enhance the awareness of the public is mandatory.

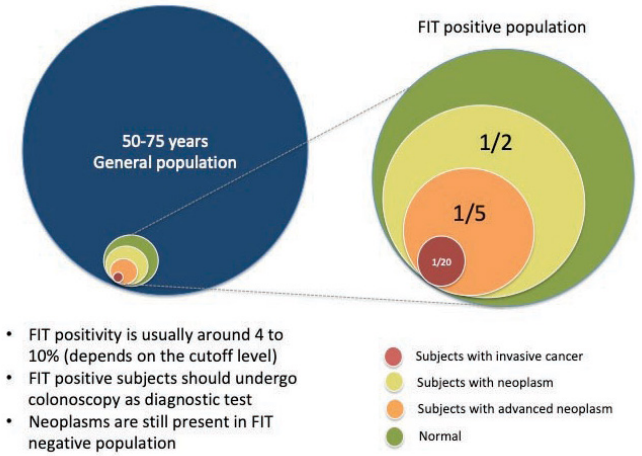

Figure 2. *Using a clinical scoring system to triage patients for screening colonoscopy*

Emerging non-invasive tests

In addition to gFOBT or FIT, some other non-invasive tests were developed for CRC screening. Multi-target stool DNA test identifies 10 biomarkers known to be associated with CRC and precancerous lesion, including altered human DNA and hemoglobin. The sensitivity of Multi-target stool DNA test for the detection of both invasive cancers (92.3%) and advanced precancerous lesions (42.4%) exceeded that of FIT by an absolute difference of nearly 20%.[21] The 2015 USPSTF recommendations include this test as an "alternative" screening test that "may be useful in select clinical circumstances" and American Cancer Society guidelines also recommend its use in 3-year interval in parallel with annual FIT or gFOBT.[22] Even though, the barrier of adopting its use in large-scale organized screening program is its high cost (USD 500 or more), which is higher than the cost of colonoscopy in some countries. Moreover, its unclear public acceptance and lacking evidence on its effectiveness also limited its use as a triage test. Septin-9 is a blood-based test listed as an alternative test. However, due to the insufficient sensitivity, it is no longer listed by the USPSTF as a primary screening test.

Summary

In resource-limited regions, making efficient use of clinical resources and funding by selecting people who are at higher risk for CRC is most crucial. Risk-stratification using non-invasive test or applying risk score system are some of the viable options.

References

1. *Lieberman DA, Weiss DG, Bond JH, et al. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. N Engl J Med 2000;343:162-8.*
2. *Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med 2013;369:1095-105.*
3. *Inadomi JM, Vijan S, Janz NK, et al. Adherence to colorectal cancer screening: a randomized clinical trial of competing strategies. Arch Intern Med 2012;172:575-82.*
4. *Quintero E, Castells A, Bujanda L, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012;366:697-706.*
5. *Hewitson P, Glasziou P, Watson E, et al. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. The American journal of gastroenterology 2008;103:1541.*
6. *Chiu HM, Chen SL, Yen AM, et al. Effectiveness of fecal immunochemical testing in reducing colorectal cancer mortality from the One Million Taiwanese Screening Program. Cancer 2015;121:3221-9.*
7. *Zorzi M, Fedeli U, Schievano E, et al. Impact on colorectal cancer mortality of screening programmes based on the faecal immunochemical test. Gut 2015;64:784-90.*
8. *Schreuders EH, Ruco A, Rabeneck L, et al. Colorectal cancer screening: a global overview of existing programmes. Gut 2015;64:1637-49.*

Stratified Screening Approach in Resource-Limited Country/Region, continued

9. *van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology 2008;135:82-90.*
10. *Moss S, Mathews C, Day TJ, et al. Increased uptake and improved outcomes of bowel cancer screening with a faecal immunochemical test: results from a pilot study within the national screening programme in England. Gut 2017;66:1631-1644.*
11. *Giorgi Rossi P, Vicentini M, Sacchettini C, et al. Impact of Screening Program on Incidence of Colorectal Cancer: A Cohort Study in Italy. Am J Gastroenterol 2015;110:1359-66.*
12. *Levin TR, Corley DA, Jensen CD, et al. Effects of Organized Colorectal Cancer Screening on Cancer Incidence and Mortality in a Large Community-Based Population. Gastroenterology 2018;155:1383-1391 e5.*
13. *Chen LS, Liao CS, Chang SH, et al. Cost-effectiveness analysis for determining optimal cut-off of immunochemical faecal occult blood test for population-based colorectal cancer screening (KCIS 16). J Med Screen 2007;14:191-9.*
14. *Lee JK, Liles EG, Bent S, et al. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. Ann Intern Med 2014;160:171.*
15. *Arnold M, Sierra MS, Laversanne M, et al. Global patterns and trends in colorectal cancer incidence and mortality. Gut 2017;66:683-691.*
16. *Abu Hassan MR, Ismail I, Mohd Suan MA, et al. Incidence and mortality rates of colorectal cancer in Malaysia. Epidemiol Health 2016;38:e2016007.*
17. *Zhu J, Tan Z, Hollis-Hansen K, et al. Epidemiological Trends in Colorectal Cancer in China: An Ecological Study. Dig Dis Sci 2017;62:235-243.*
18. *Yeoh KG, Ho KY, Chiu HM, et al. The Asia-Pacific Colorectal Screening score: a validated tool that stratifies risk for colorectal advanced neoplasia in asymptomatic Asian subjects. Gut 2011;60:1236-41.*
19. *Chiu HM, Ching JY, Wu KC, et al. A Risk-Scoring System Combined With a Fecal Immunochemical Test Is Effective in Screening High-Risk Subjects for Early Colonoscopy to Detect Advanced Colorectal Neoplasms. Gastroenterology 2016;150:617-625 e3.*
20. *Imperiale TF, Ransohoff DF, Itzkowitz SH. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014;371:187-8.*

Novel Devices for Screening of Colorectal Cancer

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Colorectal cancer (CRC) is one of the most common cancers in western countries[1]. Conventional colonoscopy remains the undeniable reference standard for CRC screening and diagnosis

of colonic pathology; however, few new alternatives have been proposed. These novel tools may increase the accuracy of lesion detection, ease procedure-related discomfort and/or minimize the risk of colonoscopy-related complications. With novel endoscopic devices, it has been assumed that patient acceptance/compliance with the procedure could be increased significantly. Also the new artificial intelligence (AI) software could aid in the process of decision making and increase the adenoma detection rate (ADR). Most of these devices are still under investigation and lack the evaluation seal of high-quality clinical studies. Therefore, their wide use in CRC screening is yet an unmet global need.

Endoscopic alternatives to CRC screening

Mini-robotic and capsule devices for CRC screening

Several flexible mini-robotics systems for colon inspection have been deviced[2]. These devices are either wireless (capsule endoscopy) or tethered with various rolling propulsion mechanisms. For example: i) devices tracked by a wheel advancing steadily through the colon; ii) legged devices, which grip the colonic mucosa or use vacuum to move forward in a cyclic way; iii) devices, which electrically stimulates the colonic muscle layers to contract and push the device forward by forced peristalsis; iv) devices, which use magnets or electromagnets or external magnetic resonance (MRI) field to advance in the colon[2]. A detailed presentation is provided in Table 1.

Table 1. *Functionality of mini-robotic and capsule devices for CRC screeing*

Functionality					
Challenge	Image	Steering + control	Loco-motion	Working Channel	Therapy
PillCam	+	-	+	-	-
Invendoscope	+	+	+	+	+
Endotics	+	+	+	-	-
Colonosight	+	+	+	+	+
Aeroscope	+	+	+	-	-
Neoguide	+	+	-	+	+

Colon capsule endoscopy (CCE)

Colon capsule endoscopy (CCE) or simply capsule colonoscopy (CC) was first introduced in 2006 as a minimally-invasive and discomfort-free endoscopic alternative. Major key quality indicators are caecal intubation rate and adenoma detection rate (ADR). However, despite promising feasibility studies, the first clinical iteration of colon capsule (CCE1) prove to be suboptimal in terms of both completion rates and overall sensitivity for detection not only of colorectal polyps/advanced adenomas but cancers as well[3].

Therefore, a second generation (CCE2) (Medtronic, USA) Figure 1 was realised and approved. CCE2 is equipped with a battery lasting about 10 hours and 2 optical domes at either end of the capsule with an angle of view of 172° degrees for each camera to enable fuller visualisation of the relatively wider lumen structure in the colon. CCE 2 is provided with an AFR (Automated Frame Rate) system: the CCE 2 communicates in real time with the Data Recorder 3 (DR3) and captures up to 35 frames per second when in motion, while only 4 frames per second when virtually stationary[3]. A large meta-analysis of 14 studies with 2420 patients showed that CCE II had a sensitivity of 86% for detection of polyps > 6 mm and 87% for polyps > 10 mm (87%), in comparison with 58% and 54% with CCE I, respectively[4]. The European Society of Gastrointestinal Endoscopy

(ESGE) guidelines endorsed CCE for the use in average risk patients, in patients with a previous incomplete colonoscopy, in patients unwilling to perform a conventional colonoscopy or in those for whom colonoscopy is not possible or contra-indicated[5]. Furthermore, both Japan's Pharmaceuticals and Medical Devices Agency (JPMDA) and the US Food and Drug Administration (FDA) have approved CCE for the diagnosis of colonic disease when colonoscopy is required but difficult to conduct and in patients unwilling or unable to undergo colonoscopy but have not approved CCE for the purpose of bowel screening[6]. As reading the CCE videos quickly and accurately remains challenging, the capsule can be en-rich with various software algorithms to allow for a quick review of CCE videos with a high polyp detection rate for experienced CCE readers[7]. The device also holds CE mark in Europe.

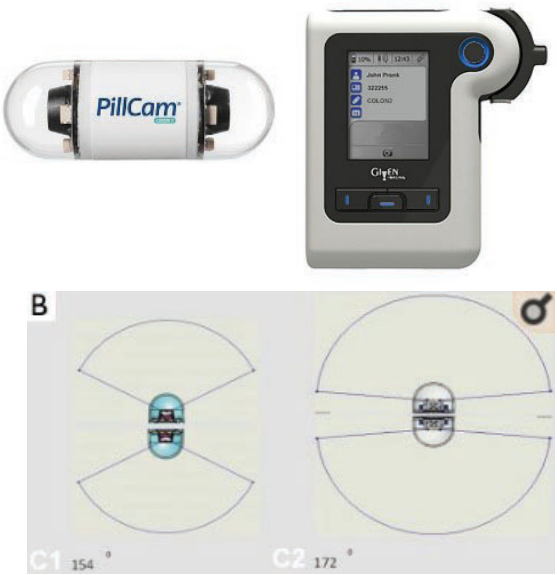

Figure 1. *(Capsule colonoscope and reader) and B) difference in view fields between CCE1 and CCE2 (source: www.medtronic.com, ref. 7)*

Aeroscope

The Aer-O-scope (GI View Ltd, Ramat Gan, Israel) Figure 2 is a unique optical system, constructed to allow 360° panoramic viewing the side colonic walls, allowing full inspection

of haustral folds. The system is based on two balloons being inflated with CO2 at a time of insertion in order to airtight the colon. Forward traction is possible by pressurising the colon segments between the balloons. Aer-O-Scope has been reported as a safe device to effectively screen the entire colon to the cecum within 30-60 min[8] The Aer-O-Scope has recently received clearance from FDA 510(k) for therapeutic intervention during colorectal cancer screening, however the full implementation into real world clinical practice of this device is still pending.

Figure 2. *The Aer-O-Scope Disposable Scanner (source: www.giview.com)*

Invendoscope

The Invendoscope (Invendo Medical GmbH, Kissing, Germany) Figure 3 is a single use colonoscope developed with an aim to minimize the risk of cross contamination from inadequate sterilization of colonoscopes. It allows retrograde viewing and navigation as equipped with a robotic hydraulically articulated tip. It advances through the colon thanks to innovative solution utilizing an air-filled inverted sleeve that cushions the colonic lumen as the device moves forward. It allows for a relatively quick colon inspection, however with relatively high level of discomfort[2]. The device is available on the market, holds CE mark and FDA approval and is no longer self-driven scope but operates similarly to standard colonoscope[9].

Novel Devices for Screening of Colorectal Cancer, continued

Figure 3. *Invendoscope (source: www.medgadget.com)*

Endotics

This robotic colonoscopy (Endotics) system (Era Endoscopy S.R.L. Italy) Figure 4 is composed of flexible body and tail with steerable tip and assisted with water jet air. It allows full control of the disposable probe by hand-operated console to achieve real time images. The following functions are available: i) manipulating robotic colonoscope in every direction, ii) elongating the body of the devise in every direction to follow the colonic flexures, rinsing the field and insuflate or deflete the colon. The devise has been reported as safe and painless. Endotics holds CE mark.

Figure 4. *Endotics system (source: vitramed.com)*

As screening test should be considered effective not only when it has a high accuracy for the detection of early cancers and preferably polyps as well, but also when it is well accepted by the general population and fit the different resources and budgets of national healthcare systems worldwide. Currently due to overall costs, the CEE and other robotic procedures might be viewed as an optional or accessory procedures in well-organized screening programs in selected patients.

C-scan

CheckCap comes with a brave new solution of prep-less checkup. Check-Cap is a clinical-stage medical diagnostics company developing C-Scan® Figure 5, the first capsule-based system for preparation-free, colorectal cancer screening and hope to increase compliance. The capsule system includes a short-lived radioisotope within a collimator housing that emits three X-ray beams in all directions, by way of a rotating miniature electric motor as the capsule scans the length of the GI tract.

Figure 5. *C-scan system (source: www.check-cap.com)*

A small volume of ingested radiopaque contrast agent increases the contrast of the colon's walls and differentiates them from stool content. The capsule also includes a microprocessor and RF communication to transmit data to the C-Scan® Track, as well as transmitting electromagnetic signals that allow the C-Scan Track to track the 3D position and orientation of the capsule within the body.[10] The C-Scan® Track is a tracking control and data collection unit comprising three external patches that are worn on the patient›s back during C-Scan®Cap passage. It consists of an integrated positioning, control, and recording system that continuously tracks the capsule's position and orientation along the colon, activates the capsule's scanning function during movement in the colon, and records and stores the capsule's information (https://www.check-cap.com/). At present the system is undergoing further clinical evaluation since its FDA approval earlier in 2019.

Next generation endoscopy systems and novel endoscopic devices

G-eye system

The G-EYE™ HD+ system (Pentax Medical) has been invented for the purpose of optical endoscopic visualization, diagnosis and treatment of lesions in the GI tract Figure 6A. The system enables easy endoscope positioning in the GI tract and combines three types of endoscopes (G-EYE34-i10L/F; G-EYE38-i10L/F; G-EYE38-i10F2) with various insertion tube and distal end diameters and working lengths parameters offering similar angle views (140^0). The G-EYE endoscopes could be adjusted with disposable advancing balloon (AB) placed over the instrument channel for the purpose of performing double balloon colonoscopy. The whole system (G-EYE + AB) are simultaneously controlled by the NaviAid SPARK2C inflation system Figure 6B.

Figure 6A *The G-EYE™ HD+ system (source: https://www.pentaxmedical.com)*

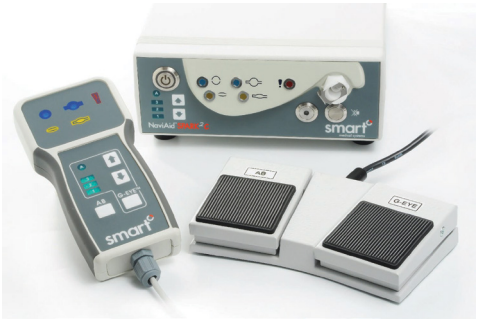

Figure 6B *NaviAid SPARK2C inflation system (source: https://www.pentaxmedical.com)*

It has been documented that balloon-assisted colonoscopy provided better ADR (48.0%) in comparison to ADR (37.5%) in standard colonoscopy group. Moreover balloon assisted colonoscopy provided better detection of advanced flat adenomas and sessile serrated adenomas over standard colonoscopy[11]. These observations were based on the results of recently conducted randomized, controlled, international, multicenter trial with enrollment of one thousand patients[11]. G-EYE™ HD+ system is available in European countries, holds CE mark. FDA approval is not yet available.

G-EYE™ colonoscopy has recently been tested with GI Genius AI module (Medtronic) for polyp detection.The GI Genius is designed to use AI to increase detection of pre-cancerous lesions in the colonic mucosa with a visual marker with a purpose of increasing ADR. GI Genius holds CE mark and FDA approval is pending.

FUSE

It is known that traditional, forward-viewing (TFV) colonoscopes with170°field of view (FoV), even in the most experienced hands, may miss polyps or other colonic pathology. Fuse Full Spectrum Endoscopy (FUSE®) (EndoChoice / Boston Scientific) is a novel colonoscopy platform and it is revolutionary in its ability to provide a full 330° FoV, achieved by three imagers and LED groups positioned one at the front and two at each side of the scope's distal tip. By giving endoscopists the ability to see more of the mucosa, theoretically provides the ability to detect more pre-cancerous polyps Figure 7.

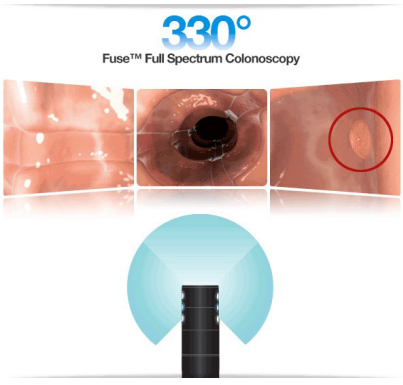

Figure 7 *FUSE (Full Spectrum Endoscopy) (source: http://www.fusecolonoscopy.org)*

The ability of Fuse system to improve colonoscopy outcomes has been further evaluated with a systematic review and meta-analysis of randomized tandem studies evaluating add-on devices on colonoscopes and the FUSE scope showed statistically significantly lower lesions miss rates with these devices/scope compared with CC, in the whole colon, with a clinically high effect size[12].

Novel Devices for Screening of Colorectal Cancer, continued

Of other studies to mention, Gralnek et al conducted an international, multicentre, randomised trial in 185 patients referred for colorectal cancer screening, polyp surveillance and diagnostic assessment with back-to-back tandem colonoscopy with standard forward-viewing and FUSE colonoscope. The authors reported that FUSE endoscopy as technology advancement for colonoscopy, which could improve the efficacy of CRC and surveillance[13].

Endocup and Endocuff

The (endo)cap is a single-use colorless and transparent material to facilitate observation of GI mucosa in a clear, unclouded field of view and designed to maintain a convenient distance between the camera scope and lumen to maintain a clear endoscopic view (Figure 8).

Figure 8 *The transparent endoscopic cup (source: https://medical.olympusamerica.com)*

The cap was originally launched by Olympus (Olympus America Inc, Center Valley, PA, US) in 1993 and then followed by first generation Endocuff (Arc Medical Design, Leeds, United Kingdom), launched in 2012. Endocuff is a single-use soft, radiopaque device that consists

of a cylindrical polypropylene core and 2 rows of flexible thermoplastic elastomer-made projections. It is available in 4 different color-coded sizes to fit all scopes and its technical characteristics. The device not only stabilizes the scope in the middle of the lumen allowing traction against sudden slippage around flexures but also achieves wider mucosal coverage as well as the projections, which move independently from another in a passive way, flatten the folds and allow more accurate colonic inspection[14]. Despite its revolutionary design, Endocuff was associated with a couple of drawbacks (mucosal erosions and difficulties in terminal ileum intubation) that paved to way for its descendant, namely Endocuff Vision (Norgine Pharmaceuticals Ltd, Uxbridge, United Kingdom). Made of a polypropylene cylinder and a single row of 8-longer than in the first generation Endocuff-thermoplastic elastomer-made projections (Figure 9).

Figure 9 *Endocuffs (Norgine Pharmaceuticals Ltd) (source: https://medical.olympusamerica.com)*

Other add-on device, which was launched in 2015 was endorings (EndoAid, Caesarea, Israel) – single use device composed of 2 layers of flexible, silicone circular rings placed on a cuff aimed at reducing loop formation, slippage and stretching out the folds to improve polyp detection during colonoscope withdrawal[14]. All these devices may increase the yield and compliance of CRC screening. The studies evaluating their practical utility are ongoing.

References

1. *Bray F et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.* ***CA Cancer J Clin.*** *2018; 68(6):394-424*
2. *Tapia-Siles SC et al. Current state of micro-robots/devices as substitutes for screening colonoscopy: assessment based on technology readiness levels. Surg Endosc 2016; 30 (2): 404-413*
3. *Pasha S. Applications of Colon Capsule Endoscopy. Curr Gastroenterol Rep. 2018 Apr 12;20(5):22. doi: 10.1007/s11894-018-0628-7. Review.*
4. *Spada C et al. Accuracy of first- and second-generation colon capsules in endoscopic detection of colorectal polyps: A systematic review and meta-analysis. Clin Gastroenterol Hepatol, 2016; 14(11): 1533-1543*
5. *Spada C et al. Colon capsule endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2012, 44(5): 527-36*

Novel Devices for Screening of Colorectal Cancer, continued

6. *Miluzzo SM et al, Colon capsule endoscopy and its effectiveness in the diagnosis and management of colorectal neoplastic lesions. Expert Rev Anticancer Ther 2019; 19(1):71-80*
7. *Yung DE, et al. Review: capsule colonoscopy-a concise clinical overview of current status. Ann Transl Med. 2016 Oct;4(20):398. Review. PubMed PMID: 27867950; PubMed Central PMCID: PMC5107393.*
8. *Gluck N et al. A novel self-propelled disposable colonoscope is effective for colonoscopy in humans (with video). Gastrointest Endosc 2016; 83(5): 998-1004.*
9. *Boškoski I et al. Endoscopy robotics: Current and future applications. Dig Endosc 2019; 31(2): 119-124*
10. *Gluck N, Half EE, Bieber V, Schwartz D, Ron Y, Gralnek I, Klein A, Lachter J, Levy MS, Moshkowitz M, Arber N. Novel prep-less X-ray imaging capsule for colon cancer screening: a feasibility study. Gut. 2019 May;68(5):774-775. doi: 10.1136/gutjnl-2018-316127. Epub 2018 May 21. PubMed PMID: 29785966.*
11. *Shirin H et al. G-EYE colonoscopy is superior to standard colonoscopy for increasing adenoma detection rate: an international randomized controlled trial (with videos). Gastrointest Endosc. 2019 Mar;89(3):545-553*
12. *Gkolfakis P et al. Meta-analysis indicates that add-on devices and new endoscopes reduce colonoscopy adenoma miss rate. Eur J Gastroenterol Hepatol. 2018; 30(12):1482-1490.*
13. *Gralnek IM et al. Standard forward-viewing colonoscopy versus full-spectrum endoscopy: an international, multicentre, randomised, tandem colonoscopy trial. Lancet Oncology 2014; 15(3): P353-360*
14. *Gkolfakis P et al. Colonoscopy attachments for the detection of precancerous lesions during colonoscopy: A review of the literature. World J Gastroenterol 2018; 24 (37): 4243-4253*

Colorectal Cancer in the Young

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Colorectal cancer is the third most common cancer worldwide with an estimated 1.8 million new cases and accounting for more than 800,000 deaths in 2018 [1]. In recent years, evidence suggests that there is a rising trend of colorectal cancer among younger adults in the United States [2], as well as other Western countries such as Australia [3] and Canada [4]. Similar trends of rising young-onset colorectal cancer have also been reported in Asia. Using the population-based national registry of Taiwan, Korea, Japan and Hong Kong, there is a confirmed rising trend of young-onset colorectal cancer in the past 10 years from mid 90s to mid 2000 [5]. Therefore, the increasing trend in young-onset CRC is not limited to the Western world.

Using the IARC data, a recent study followed the colorectal cancer incidence of selected jurisdictions for roughly 20 years from 1988 through 2007 [6]. Younger adults in this study were defined as those ages under 50 years of age because most colorectal cancer screening programs around the world use this age cut-off for the initiation of screening for the average risk individual. The investigators selected representative jurisdictions based on the following criteria: (i) industrialized city/prefecture/province/state/country and (ii) having data with high completeness and validity from the CI5plus database, that is, data sets spanning the entirety from 1988 to 2007. Countries/jurisdictions included in this study are Australia, Brazil, Canada, China (Hong Kong and Shanghai), Germany, Italy, Japan, the Netherlands, Sweden, the United Kingdom, and the United States.

Overall, the Annual Percentage Change (APC) of colorectal cancer for those ages <50 years was noted to be increasing at a faster rate as compared with those ages ≥50 years in many regions. This include Australia (+1.10% vs. −0.35%), Brazil (+9.20% vs. +5.72%), Canada (+2.60% vs. −0.91%), China–Hong Kong (+1.82% vs. −0.10%), China–Shanghai (+1.13% vs. −2.68%), Japan (+2.63% vs. +0.90%), United Kingdom (+3.33% vs. +0.77%), and the United States of America (+1.98% vs. −2.88%). The percentage changes rate between these age groups show differences reaching statistical significance.

Furthermore, rectal cancers do appear to increase more rapidly compared to colonic cancer. The APC for individuals <50 years in rectal cancer was also shown to be increasing at a faster rate as compared with those ages ≥50 years in Germany (+2.71% vs. −4.90%), Sweden (+1.17% vs. +0.64%), and the Netherlands (+2.12% vs. +0.88%). It is worth to note that all these countries/regions that show increase in young-onset CRC are industrialized and belong to economically developed countries/ regions.

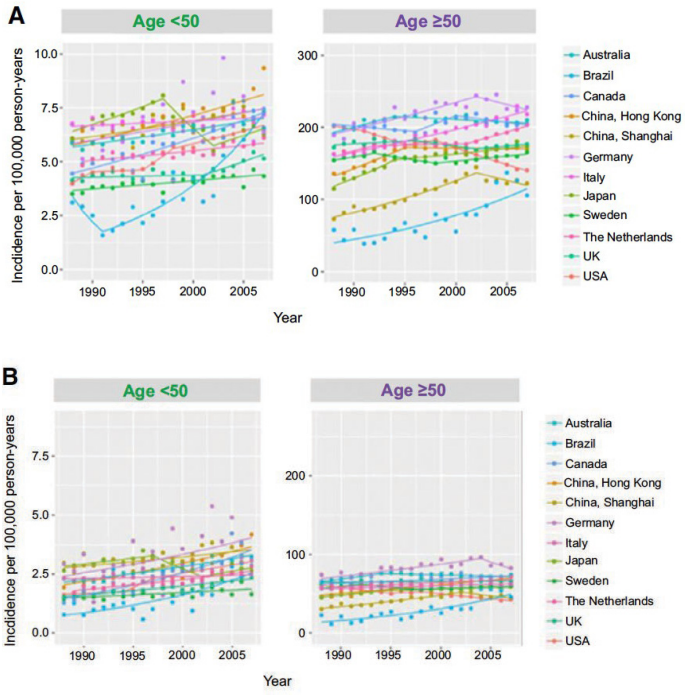

Fig 1. *Incidence of colonic (A) and rectal cancer (B) among populations in 12 regions/countries in the Five Continents of the World. (From Lui RN et al [6])*

Although some of the young CRC cases may be inherited, the majority appear to arise sporadically [7]. Identifying these patients poses a difficult challenge to healthcare systems [8]. Small case series have suggested that young-onset colorectal cancers are more likely distributed distally in the colon and rectum, with a higher proportion of patients developing synchronous and metachronous tumours [9], present with a more advanced tumour stage, exhibiting a mucinous and signet ring histologic subtype, and be poorly differentiated.

The reasons for this have yet to be fully elucidated, but a low awareness of colorectal cancer for both patients and physicians, with an underestimation of symptoms, leading to delays in diagnosis and management is a possible contributing factor. Although, still uncommon in terms of the scale, the societal impact of young-onset CRC cannot be understated.

There are at least two possible explanations of rising incidence of young-onset CRC. The application of screening strategies and colonoscopic polypectomy have reduced CRC incidence and mortality in the West. Nevertheless, since CRC screening is usually recommended to those aged 50 years or above, the impact of screening towards the current younger age groups would be smaller than that towards the older generations.

The alternative explanation is related to lifestyle (to becoming more of sedentary living and consuming more meat than vegetables) and the increasing problem of obesity that might be contributing factors to this change in epidemiology. Westernized lifestyle factors (including low fruit and vegetable intake, high-fat diet, tobacco and alcohol consumption) are well-established risk factors of CRC. The differential observation between the Western and the Asian populations may imply that despite continuous socio-economic development to adopt more western-like lifestyles, there may still be deep-rooted traditions among these Asian populations that protect them against CRC, especially for those generations who still grew up in a macro-environment that largely consumed traditional non-Western diet. Further analytical epidemiological studies are needed to clarify the specific dietary habits that contribute to this effect.

With this observation of rising incidence of young-onset CRC, the American Cancer Society has updated their guidelines providing a qualified recommendation to lower the age of screening for average risk adults to 45 years of age from 50 years [10]. This change in screening policy is debatable as it will inevitably shift resources to screening a younger population, while the majority of patients are still those above the age of 50 years and much more likely to benefit from screening. However, the fact that screening colonoscopy and polypectomy for premalignant lesions can effectively disrupt the adenoma-carcinoma sequence, and will likely to save cost in the long run cannot be overstated. With a predilection of these lesions in the distal colon and rectum, the efficacy and cost effectiveness of performing flexible sigmoidoscopy should be an idea worth visiting. Immunochemical-based stool tests could also be a viable entry test as a more economic and safer alternative for younger adults.

Ultimately, the choice of age criterion and screening modalities will need to be region/population-specific, and will be dependent on local incidence rates of young-onset colorectal cancer. Individual governments' resource prioritization policy is also important as adopting a screening program will incur potential opportunity costs. Although it would be premature at this juncture to advocate for earlier screening in individuals with average risk around the world, raising awareness and conducting cost-effective analyses in the future would be a way forward to address this problem.

References

1. *Bray F, Ferlay J, Soerjomataraml, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.*
2. *Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, Rosenberg PS, et al. Colorectal cancer incidence patterns in the United States, 1974–2013.J Natl Cancer Inst 2017;109:27–32*
3. *Young JP, Win AK, Rosty C, Flight I, Roder D, Young GP, et al. Rising incidence of early-onset colorectal cancer in Australia over two decades: report and review. J Gastroenterol Hepatol 2015;30:6–13.*
4. *Patel P, De P. Trends in colorectal cancer incidence and related lifestyle risk factors in 15–49-year-olds in Canada, 1969–2010. Cancer Epidemiol 2016;42:90–10*
5. *Sung JJY, Chiu HM, Jung KW, Jun JK, Sekiguchi M, Matsuda, Kyaw MH. Increasing trend in young-onset colorectal cancer in Asia: more cancers in men and more rectal cancers. Am J Gastroenterol 2019; 114:322-9*
6. *Lui RN, Tsoi KKF, Ho JMW, Lo CM, Chan FCH, Kyaw MH, Sung JJY. Global increasing incidence of young-onset colorectal cancer across 5 continents: a joinpoint regression analysis of 1,922,167 cases. Cancer Epi Biomarker Prev 2019 DOI 10.1158/1055-9965 EPI-18-111.*

Colorectal Cancer in the Young, continued

7. *Chang DT, Pai RK, Rybicki LA, Dimaio MA, Limaye M, Jayachandran P, et al. Clinicopathologic and molecular features of sporadic early-onset colorectal adenocarcinoma: an adenocarcinoma with frequent signet ring cell differentiation, rectal and sigmoid involvement, and adverse morphologic features. Mod Pathol 2012;25:1128–39*
8. *Campos FG. Colorectal cancer in young adults: a difficult challenge. World J Gastroenterol 2017;23:5041–4.*
9. *Liang JT, Huang KC, Cheng AL, Jeng YM, Wu MS, Wang SM. Clinicopathological and molecular biological features of colorectal cancer in patients less than 40 years of age. Br J Surg 2003;90:205–14.*
10. *Wolf AMD, Fontham ETH, Church TR, Flowers CR, Guerra CE, LaMonte SJ, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin 2018; 68:250–81*

Diet and Lifestyle for Prevention of Colorectal Cancer

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Introduction

There is no doubt that diet and lifestyle are associated with risk for colorectal cancer (CRC) and that modification of these influences provides options for its prevention.

Colorectal cancer develops slowly, taking over a decade in most cases to progress from a normal cell through dysplasia to invasive cancer. Cancer development (or oncogenesis) involves several stages (see Figure), each characterized by increasing genomic instability and progressively disordered phenotype. This process of oncogenesis can be well advanced before we become aware from symptoms that something might be wrong.

Epidemiological studies provide the evidence that risk for CRC is unquestionably associated with the nature of the diet and lifestyle since people moving from relatively low incidence to higher incidence areas who adopt the new lifestyle, show an increased risk within their own lifetime as well as their offspring. Historically it has been shown that migrants from certain eastern Europe and Asian countries to countries with a more affluent western lifestyle (like Australia and the USA) repeatedly show this. Furthermore, as the diet "westernizes" in non-western countries such as Japan, Hong Kong, China and Singapore, we see major changes in the risk for CRC. High-risk regions are characteristically more affluent, people are physically less active lifestyle and food availability very different.

A body of evidence indicates that a combination of inappropriate food and nutrition, physical inactivity, and overweight and obesity – simply our diet and lifestyle – causes roughly one third of the world's cancer burden. The impact of diet varies between different organ types of cancer but it contributes as much as 75% to risk for CRC. There are over 2 million new cases of CRC each year.

The associations of diet and lifestyle with altered chance of getting CRC, point to the opportunity created by following a healthy diet and keeping our weight under control, to prevent many thousands of people getting cancer each year. Given what we know about the scientific mechanisms by which dietary factors might influence risk, it is apparent that changing our lifestyle has the capacity not just to reduce the chance that oncogenesis is initiated but also to block or slow the process once it has begun (see Figure). Of course,

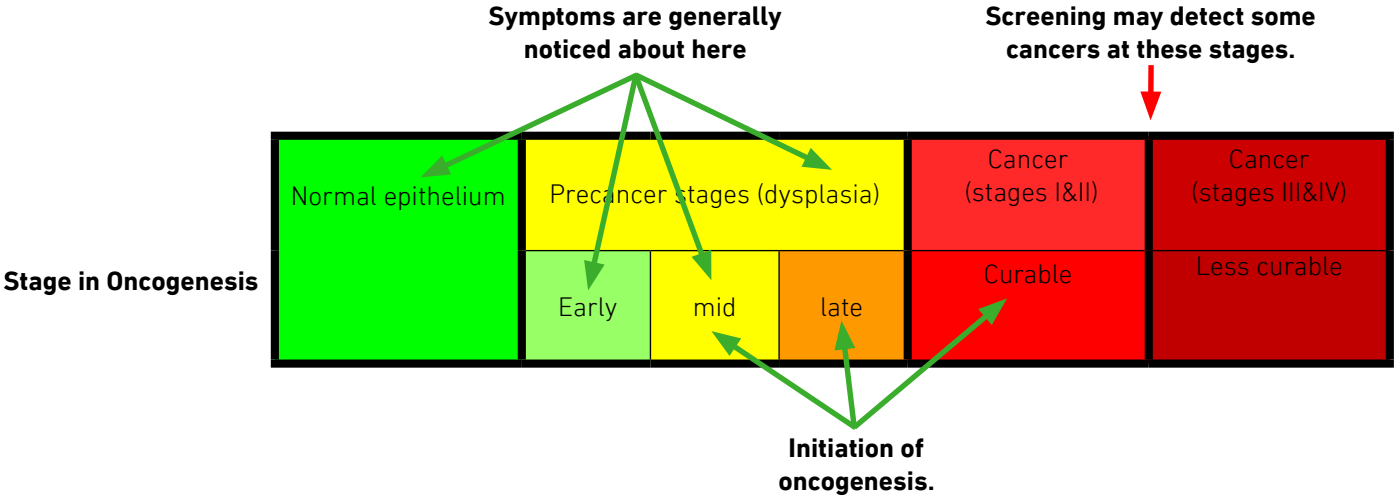

Figure: *Diagrammatic representation of process of cancer development and the stages at which diet/lifestyle, screening and symptom identification might act to regulate risk. The colour changes with progression. The process of oncogenesis is characterised by increasing instability of the cell's genome (i.e. its DNA). Clearly, diet and screening work at different stages.*

Diet and Lifestyle for Prevention of Colorectal Cancer, continued

Table 1: *Summary of factors where evidence is strong or suggestive for increased or reduced risk for colorectal cancer. (Derived and simplified from the WCRF report).*

Evidence direction and strength	Dietary/lifestyle factor
Strong – decrease in risk	• Physical activity • Wholegrains • Dietary fibre (especially insoluble fibres such as wheat bran) • Dairy products • Calcium supplements
Strong – increase in risk	• Red meat (dose related; also other haem-containing foods) • Processed meat (no safe threshold) • Alcohol (>2 drinks per day) • Overweight or obese
Suggestive – decrease in risk	• Vitamin C-containing foods. • Fish consumption • Vitamin D • Multivitamin supplements
Suggestive – increase in risk	• Low consumption of non-starchy vegetables • Low consumption of fruit

the converse can apply – certain lifestyles might accelerate cancer development.

Two key strategies underpin prevention by diet and lifestyle

1. The overall balance of what we eat that is important.

Our diet must be balanced. Eating a lot or too little of any particular food will not compensate for getting the balance right and it can result in a boring and unattractive diet. Our diet should comprise a broad range of different foodstuffs. Vary the diet as much as one can, ensure that plant-foods are included and minimise foods that increase risk. Remember that drinks are part of the diet. Broad-based balance focussing on healthy foods compensates to a degree for occasional modest intake of "risky" foods.

B. An imbalance between food intake and physical activity is bad for us.

We must maintain a healthy weight: if overweight or obese, one is either eating too much, undertaking too little physical activity, or both. Admittedly, losing weight is easier for some than others but this rule still applies.

Key recommendations and strategies

The recommendations and strategies provided below are drawn from the excellent Third Expert Report from World Cancer Research Fund (WCRF) and the American Institute of Cancer Research, and are based on the generic diet and lifestyle recommendations aimed at helping "people to reduce their risk of developing cancer". Their ten recommendations are pruned to eight of specific relevance to CRC. A few comments specific to CRC are added where appropriate and summarised for CRC in Table 1.

1. Be a Healthy Weight

The WCRF considers that greater body fatness is convincingly causal for CRC and this evidence has strengthened over the last decade.

It recommends to keep as lean as possible within the normal range of body weight (BMI < 25) and avoid weight gain in adult life. It suggests that this is best achieved by:

- "being physically active
- "eating a diet rich in wholegrains, vegetables, fruit and pulses such as beans
- "limiting 'fast foods' and other processed foods high in fat, starches or sugars
- "limiting sugar sweetened drinks"

2. Be Physically Active

The WCRF considers that there is strong evidence that this protects against CRC and reduces risk of weight gain.

It recommends that some form of activity be undertaken each day and that we sit less. it suggests:

- energetic walking for at least 30 minutes every day (150 minutes minimum per week).
- as fitness improves (and subject to physical constraints with ageing), aim for more vigorous activity. there are many ways to achieve this apart from visiting the gym.
- limit sedentary habits such as watching television. the latter is particularly important because of exposure to food advertising.

3. Eat Wholegrains, Vegetables, Fruit, & Beans

the rationale behind this recommendation is that most diets that are protective against crc are comprised mainly of foods of plant origin.

recommendation: make wholegrains, vegetables, fruit, and pulses (legumes) such as beans and lentils a major part of the usual daily diet.

the wcrf considers that there is strong evidence that eating wholegrains protects against crc, and that eating foods containing dietary fibre protects against crc, weight gain, overweight and obesity. while evidence for protection by non-starchy vegetables or fruit is limited, the overall association and direction of effect are consistent with a protective benefit. animal models and mechanistic studies on bioactive components of foods further support the credibility of a protective effect. such components can influence activation and inactivation of dietary carcinogens. some studies indicate that insoluble fibres such as wheat bran are more effective than soluble fibres in prevention of crc.

The recommended dietary goals are:

- "consume a diet that provides at least 30g per day of fibre from food.
- "include foods containing wholegrains, non-starchy vegetables, fruit and pulses (legumes) such as beans and lentils in most meals
- "eat a diet high in all types of plant foods including at least five portions (one portion is 80g) or servings (at least 400g or 13oz in total) of a variety of non-starchy vegetables and fruit every day
- "when eating starchy roots and tubers as staple foods, eat non-starchy vegetables, fruit and pulses (legumes) regularly too if possible"

4. Limit "Fast Foods" & Processed Foods

The evidence is strong that such foods cause weight gain and so lead to overweight and obesity, being energy-dense and low in micronutrients. "Fast foods" and other pre-prepared (ready for consumption) and processed foods are high in fat, sugars and sometimes preservatives.

Fast foods include hamburgers, fried chicken, fried potato chips (French fries) and high-calorie drinks (containing sugars). But also beware of products that are made from white flour such as bread, pasta, pastries, cakes and biscuits (cookies). Be aware that processed low-fat foods (including even products such as yoghurt) tend to be high in sugars and so remain energy dense and possibly worse than the original product.

WCRF recommends that we:

- Limit consumption of processed foods high in fat, starches or sugars – including 'fast foods'; many pre-prepared dishes, snacks, bakery foods and desserts; and confectionery (candy).

5. Limit Red & Processed Meat

It is considered that the evidence that processed meat increases CRC risk is clear-cut. Any level of intake is clearly associated with increased risk for CRC. Some studies have also shown that "well-done" red meat when directly exposed to flame, results in generation of carcinogens such that consumers of such meat may have a substantially increased risk.

Red meat can be defined as all types of mammalian muscle meat including beef, veal, pork, lamb, mutton, horse and goat. These meats increase risk for CRC in a dose-dependent fashion with studies suggesting that risk is increased more than 50% when consumption exceeds 100g/day. It is not recommended to completely exclude red meat from the diet as it is an excellent source of high quality protein, iron, zinc and vitamin B12. Nonetheless, alternative muscle foods from chicken and fish are good sources of some of these and a well-chosen vegetarian diet can avoid deficiencies in these nutrients. Consumption of fish is shown to be protective for CRC in many studies

The recommendations are:

- Limit consumption of red meat to no more than about three portions per week. Three portions is equivalent to about 350–500g (about 12–18oz) cooked weight (raw meat is about 40% heavier).

Diet and Lifestyle for Prevention of Colorectal Cancer, continued

- Consume very little, if any, processed meat.
- Consume very little, if any, red meat cooked in a direct flame especially if well-done (heavily burnt on the surface).
- Substitute red meats with fish especially, and chicken.

6. Limit Sugary Drinks

The evidence is strong that consumption of sugar sweetened drinks causes weight gain and hence overweight and obesity, especially when consumed frequently or in large amounts. Sugar-rich drinks are high in simple sugars (such as fructose, glucose, sucrose) and these are energy dense (as are high sugar processed foods). Fruit juices are also energy-dense and best consumed as the fruit from which they were made.

The recommendations are:

- Do not consume sugar sweetened drinks.
- Eat, rather than drink, fruits.
- When adding sugar to tea or coffee, keep it to a total of 5-10g (1-2 teaspoons) per day.

7. Limit Alcohol Intake

There are a number of reasons apart from increasing risk of CRC, to limit alcohol consumption. Nonetheless, it is both a somewhat confusing and sometimes controversial area. It can be confusing because of the evidence that red wine (1-2 glasses per day and not the alcohol in it but chemicals arising from red grapes and fermentation) reduces risk of heart disease. Similar benefit for the heart can be had from other plant-based foods.

WCRF concludes that the evidence that alcoholic drinks increases risk for CRC is strong. It is dose-dependent without an obvious safe threshold but might, as with red meat consumption, be mitigated to some degree by an otherwise healthy diet. All alcoholic drinks carry risk and it must be noted that alcohol increases risk for most alimentary tract cancers and breast cancer. As a consequence, in recent years recommendations have become very restrictive.

Recommendations are:

- For cancer prevention, it's best not to drink alcohol.
- When consuming alcoholic drinks, do not exceed national guidelines, i.e. no more than two standard drinks a day for men and one a day for women.

8. Supplements Are Of Limited Value

Purification of certain bioactive micronutrients including selenium, vitamin D, Vitamin A, antioxidants, polyphenols and a range of other micronutrients characteristic of healthy foods, and inclusion in pills or powders has often been proposed and marketed and sometimes tested. In fact, the WCRF considers that the only micronutrient supported by strong evidence to be protective for CRC is calcium while vitamin D and multivitamin tablets have some supporting evidence.

The results of randomised controlled trials are not consistent and it is considered that because adequate levels of protective bioactive substances in food are inherent in a healthy balanced diet, supplements are not recommended.

The recommendation is:

- Do not expect high-dose dietary supplements to provide CRC prevention
- Aim to meet nutritional needs through diet alone
- Consider calcium supplements when safe and particularly in individuals at high risk.
- Vitamin D and multivitamins might be of benefit.

Is there a specific diet for CRC?

There are nuances in diet that apply to CRC and not necessarily in the same way to other cancers although recommendations for CRC (Table 1) are not inconsistent with the broad generic advice for cancer in general.

Individual studies quantify risk for CRC in relation to individual dietary components but results vary widely and generalisations become problematic. Individual components such as physical activity and obesity increase risk by up to 50% as a generalisation while diets high in fibre, whole grains or fruit/vegetables seem to reduce risk by 5-50%. But none of these elements exists in isolation of others and combinations are not necessarily additive and might interact.

It is most chastening to recognise that an early study showed that the risk for CRC varied in excess of ten-fold between the best and worst extremes.

How do dietary factors alter risk?

This is complex area is well summarised in the WCRF report. There are many studies on mechanisms of dietary interactions that provide scientific credibility to support observational and pragmatic interventional studies. For

instance, consumption of dietary fibre increases generation of short chain fatty acids in the colon. These in turn have major benefits for health of normal epithelium and control of genomic instability as the genome becomes disordered. Studies have shown that carcinogens are produced in red meat exposed to hot flames and that bacteria in the colon generate mutagenic compounds.

Is there a role for the microbiome?

In reality we have known for decades that metabolic activity of colonic microflora are important. Examples include fermentative production of short chain fatty acids and generation of mutagens from dietary protein. Assignment of these and other benefits to microbial species, and how we might modulate microbial diversity so as to reduce risk, is currently under exploration.

The challenge in changing diet

Food is not just an exercise in filling up the tank, it is often a key part of day-to-day social interactions. Some foods are expensive and some have little control over what food is presented to us to eat. Others are not accessible for some for reasons other than personal economics. Nonetheless, consuming a broad range of available foods in moderation and controlling weight remain crucial for prevention of cancer in general and CRC specifically. The WCRF recognises this and emphasises that any improvement has a worthwhile effect. Furthermore, gradual change towards a healthier lifestyle is more likely to be sustainable and so achieve long-lasting benefit.

Bibliography

World Cancer Research Fund / American Institute for Cancer Research. Diet, Nutrition, Physical Activity and Cancer. A Global Perspective. Continuous Update Project Expert Report, 2018. Available at http://dietandcancerreport.org/

- This substantial resource of many hundreds of pages covers all aspects of cancer prevention by diet and lifestyle. The following papers serve to demonstrate some of the additional points made in this piece.

Le Leu RK, Winter JM, Christophersen CT, Young GP, Humphreys KJ, Hu Y, Gratz SW, Miller RB, Topping DL, Bird AR, Conlon MA. Butyrylated starch intake can prevent red meat-induced O6-methyl-2-deoxyguanosine adducts in human rectal tissue: a randomised clinical trial. British Journal of Nutrition 2015; 114: 220–230

Bradbury KE, Appleby PN, Key TJ. Fruit, vegetable, and fiber intake in relation to cancer risk: findings from the European Prospective Investigation into Cancer and Nutrition (EPIC). Am J Clin Nutr. 2014 Jul;100 Suppl 1:394S-8S. doi: 10.3945/ajcn.113.071357. Epub 2014 Jun 11. Review.

McCredie M, Williams S, Coates M. Cancer mortality in migrants from the British Isles and continental Europe to New South Wales, Australia, 1975-1995. Int J Cancer. 1999 Oct 8;83(2):179-85.

Fung KY, Cosgrove L, Lockett T, Head R, Topping DL. A review of the potential mechanisms for the lowering of colorectal oncogenesis by butyrate. Br J Nutr. 2012 Sep;108(5):820-31. doi: 10.1017/S0007114512001948. Epub 2012 Jun 7.

Kune S, Kune GA, Watson LF. Case-control study of dietary etiological factors: the Melbourne Colorectal Cancer Study. Nutr Cancer. 1987;9(1):21-42.

Endoscopic Polypectomy

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Introduction

Colorectal cancer is a preventable disease [1]. Whilst modification to diet and exercise and avoiding known carcinogens such as smoking can have an impact by avoiding the formation of polyps, the single most effective mechanism to prevent colorectal cancer is to remove the precursor lesion: colonic adenoma. Colorectal cancer is an ideal disease to apply screening to as it is a serious common condition, it has a long detectable preclinical phase as a colorectal polyp, treatment by polypectomy is much cheaper and less invasive than treatment for cancer, and the prevalence of polyps is relatively high in the population. We have a number of good screening tests which are relatively inexpensive and straightforward to administer, which can detect polyps. Less invasive and cheaper tests such as Faecal Immunochemical Testing (FIT), with or without stool DNA tests, detect polyps, but do so less effectively than more invasive tests such as flexible sigmoidoscopy or colonoscopy. CT colonography can also detect larger polyps effectively but like FIT then requires a colonoscopy to confirm and resect the lesions which is required in up to 30% of cases after CT colonography. Colorectal cancer screening is estimated to have accounted for over half the reduction in deaths from colorectal cancer seen between 1975 and 2000[2].

The "adenoma-carcinoma sequence", described by Muto and Morsen in the 1970s, envisaged cancers developing from adenomatous polyp in the colon which develop slowly and become increasingly pathologically abnormal, before invading the bowel wall to become a cancer. Removing this abnormal tissue and its associated genetically mutated cells completely stops progression of carcinogenesis. Flexible endoscopy with polypectomy is therefore the final common pathway to detect and resect colorectal polyps, interrupting the adenoma-carcinoma sequence, and preventing colorectal cancer.

Polypectomy and prevention

The efficacy of colonoscopic screening is perhaps best known from the results of the National Polyp Study in the United States of America. Originally reported in 1993, this showed that patients who underwent colonoscopy and had an adenoma removed had a 76-90% lower risk for developing future colorectal cancer compared to three reference populations at 6 years [3]. A follow up study for this cohort to a median of 15 years showed that the risk of death from colorectal cancer was reduced by 53% and that the protective effect of polypectomy lasted out to 10 years. This is consistent with the concept that colorectal polyps have a long dwell time of more than 10 years before they grow to become an invasive cancer, and that by interrupting the adenoma-carcinoma sequence colorectal cancer can be prevented. The National Polyp Study data were a major driver for the widespread adoption of screening colonoscopy in the United States; however this was a cohort study and therefore subject to a range of bias and confounders. In order to demonstrate a causal link between polypectomy and cancer prevention a randomized trial was needed.

A number of groups worldwide developed population-based trials of flexible sigmoidoscopy around the age of 55 to 74, to target the left colon and rectum where adenomas develop roughly ten years before the rise in left sided colorectal cancer in the population. A study in the United Kingdom randomized 170,000 people to a one off flexible sigmoidoscopy (57,000) or usual care. At 11 years follow up, this showed a 23% decrease in the development of colorectal cancer anywhere in the colon and a 31% decrease in death due to colorectal cancer. When the analysis was restricted to just the distal colon and rectum (the areas covered by flexible sigmoidoscopy) the decrease in cancer incidence was 50% [4]. A subsequent analysis after 17 years showed that the risk of colorectal cancer and colorectal cancer related death, continued to be suppressed in the flexible sigmoidoscopy group suggesting a very long term protective effect and that polypectomy was the causative mechanism. Three other large trials of flexible sigmoidoscopy screening also reported around this time ((US Prostate, Lung, Colorectal and Ovarian cancer screening trial (PLCO), the Italian Screening for Colon and Rectum trial (SCORE), and the Norwegian Colorectal Cancer Prevention trial (NORCCAP)) and a combined analysis showed a similar level of reduction in colorectal cancer incidence and mortality, with a greater effect in men than in women. [5]

Endoscopic Polypectomy, continued

In order to perform polypectomy, adenomas need to be detected comprehensively. Failure to detect adenomas is linked with a higher rate of cancer occurring after colonoscopy. In a large Californian study of 314,000 colonoscopies, and 132 endoscopists, those endoscopists in the lowest quintile of detection (adenoma detection rate 7-19%) had a rate of cancer after colonoscopy that was 52% higher, and a rate of colorectal cancer related death occurring after colonoscopy that was almost three times higher, than those in the top quintile of adenoma detection (adenoma detection rate 34-55%). A 1 percent absolute increase in the adenoma detection rate was associated with a 3% relative decrease in the rate of cancer occurring after colonoscopy [6]. A large Polish study of endoscopists who through feedback were able to improve their adenoma detection rate showed a reduction in their cancer rate after colonoscopy. Therefore the preventative effect of polypectomy is in part dependent on the skill of the colonoscopists in finding target lesions.

There is no randomized trial of colonoscopy against no screening yet available, but numerous large cohort studies demonstrate a constant and large effect on reductions in left sided colorectal cancer, consistent with the flexible sigmoidoscopy data; however some studies show a much less profound or even no cancer protective effect in the right colon. This was something of a paradox, in part explained by data showing that incomplete colonoscopies, which by definition did not find and remove pre-malignant lesions from the right side (proximal) colon, had a much higher rate of post colonoscopy colorectal cancer. However even when the colonoscopy was complete, the protective effect seemed much less than when adenomas were removed from the left colon. Two potential mechanisms may account for this. Adenomas have different shapes depending on where they occur in the colon. In the left colon they commonly appear as "mushrooms" with an adenomatous head and a stalk of normal mucosa. These often reddish lesions are straightforward to detect and by transecting the stalk of normal mucosa can be easily removed completely "en bloc" with clear margins (Figure 1). However in the right colon adenomas are more commonly "flat" with minimal elevation from the surface of the colon, making them both more difficult to detect and more difficult to resect comprehensively. There is therefore a higher risk in the right colon that an adenoma might remain in situ to develop into a cancer in the future.

Serrated pathway to colorectal cancer

A second mechanism may relate to the fact that historically adenomas had been thought to be the only polyps that developed into colorectal cancer. Another type of colonic polyp, the hyperplastic or "serrated" polyp which are commonly seen in the rectum were not thought develop into cancer, nor did they predict future colorectal cancer risk; however in the last decade it has become clear that a subset of serrated polyps, especially if they are larger and in the right colon, do have pre-malignant risk. They are termed sessile serrated adenomas / polyps (SSA/Ps) or sessile serrated lesions (SSLs). This "serrated pathway", which is molecular-genetically different from the adenoma-carcinoma sequence, may account for 15-30% of colorectal cancers.

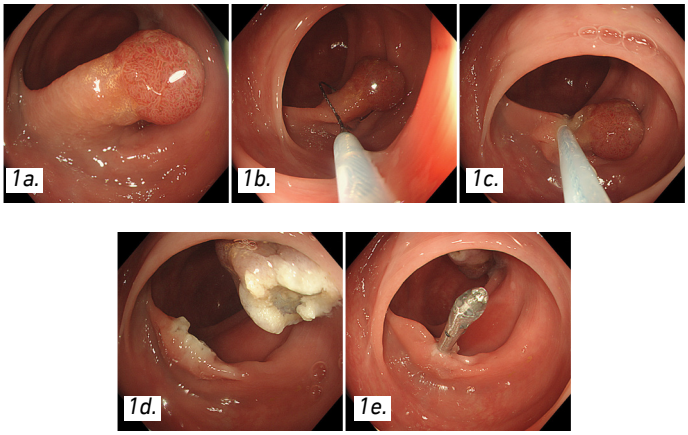

Figure 1: *1a. 10mm pedunculated "stalked" adenomatous polyp in sigmoid colon. 1b. Electrocautery snare around polyp stalk. 1c. Snare closed tightly on stalk. Note normal mucosa on stalk. 1d. Stalk transected with diathermy (white areas). 1e. Endoscopic clip applied to polyp base to reduce bleeding risk.*

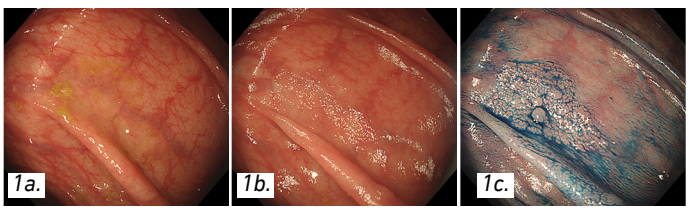

Figure 2: *2a. 20mm Sessile Serrated Lesion ascending colon, note subtle blurring of blood vessel pattern and adherent bile stained mucus. 2b. After washing the polyp becomes almost invisible. 2c. After application of blue dye (chromoendoscopy) to the bowel lining the serrated lesion is much clearer.*

Endoscopic Polypectomy, continued

The molecular -genetic "finger print" of interval cancers in the right colon is consistent with an origin from sessile serrated lesions, suggesting they have been missed or ignored [7]. Serrated polyps differ in appearance from adenomas being very flat in shape and almost transparent, making them very difficult to detect even with modern high definition colonoscopes. (Figure 2) However subtle clues such as a mucus cap, changes in vascular pattern, or colonic fold shape can all signal their presence. Colonoscopists have had to learn to recognize these new lesions and detection rates have been rising rapidly, with more modern data suggesting that cancer prevention rates in the right colon are improving. Therefore the failure of colonoscopy to prevent colorectal cancer in the right colon may reflect a historic failure to recognize and remove an important subset of pre-malignant polyps. [8]

Patients with multiple serrated polyps, either more than 20 in total with more than 5 above the rectum, or with five serrated polyps above the rectum with two of these being large (≥10mm in size) meet the WHO 2019 criteria for having Serrated Polyposis Syndrome. Such patients, as with other adenomatous colonic polyposis syndromes, have a substantially increased risk of colorectal cancer, perhaps as much as 7% at 5 years; however with intensive colonoscopy screening and polypectomy every 1-2 years this rate can be reduced to close to the population risk, suggestive that resection of serrated polyps and interrupting the serrated pathway may also be protective against colorectal cancer.

Effective polypectomy

In order to be effective, polypectomy has to completely remove the pre-malignant tissue. It had been assumed that the use of snaring with diathermy (electrical heating of the snare wire) was very effective for this. However in 2013, a large US study that took biopsies from the edge of polypectomy sites after the polyp was thought to be completely removed showed residual polyp tissue in 10% of cases. Strikingly, the rate of residual polyp tissue was 4 times higher for serrated polyps compared to adenomatous polyps, suggesting that their flat shape and subtle appearance was making comprehensive resection harder. [9]

The need to resect polyps comprehensively has led to changes in polypectomy technique. The use of snares alone to resect pedunculated polyps which have a stalk of normal mucosa have needed to be adapted for sessile and flat

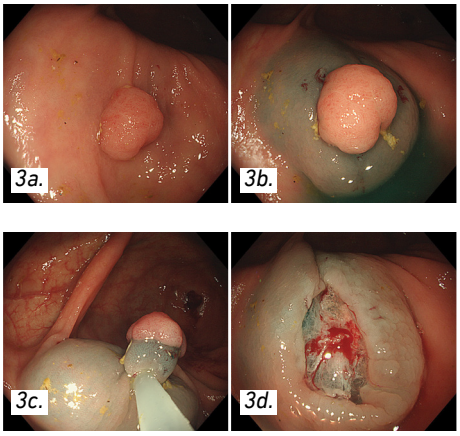

Figure 3: *3a. 8mm sessile adenoma in caecum. 3b Polyp after injection of saline with blue dye under the polyp to lift it from the bowel wall and enhance grip. 3c. Polyp gripped by snare. Note "pseudostalk" of normal mucosa. 3d. After resection. Note clean edges with no residual polyp.*

lesions. Injection of a cushion of fluid underneath the polyp often with a coloring agent to highlight to polyp edges has become common prior to snare resection, termed Endoscopic Mucosal Resection (EMR). The fluid cushion allows easier grasping of a rim of normal tissue around sessile or flat polyps forming a pseudo stalk and aiding complete resection (Figure 3).

Recently an emphasis on removing lesions as a single piece to reduce recurrence risk and improve histological specimen has been made. Even very large lesions can now be removed in a single piece using Endoscopic Submucosal Dissection (ESD). However en bloc resection may increase the risk of bleeding or bowel wall damage, including perforation. Therefore effectiveness in cancer prevention needs to be balanced against the complications of the polypectomy.

For small and diminutive sessile colorectal polyps which have a relatively low risk of developing into colorectal cancer, cold snaring has become popular, where the polyp tissue is transected without the use of diathermy, often using specially designed thin wire snares. While the risk of immediate bleeding is slightly higher, the more serious risk of delayed bleeding or perforation is reduced.

Improvements in the rate of adenoma detection through better instrument and techniques, better polypectomy

Endoscopic Polypectomy, continued

techniques, and quality assurance programs in endoscopy have combined to reduce the number of colonoscopies that are incomplete or where polyp are missed or incompletely resected. This has led to a steady decline in the number of cancers that occur after a "clear" colonoscopy, so called "post-colonoscopy colorectal cancers". In the UK the number of such cancers as a proportion of all colorectal cancers detected has fallen from 10.6 to 7.3% over the period 2001 to 2007 and is likely to fall further[10].

Conclusions

Flexible endoscopy, especially colonoscopy with polypectomy, is the most powerful tool to prevent the development of colorectal cancer. The ability to prevent one of the world's leading cancer killers has been a major success story for the gastroenterological community over the last three decades. Further understanding of the molecular-genetic basis of colorectal cancer development via the serrated pathway, and optimization of detection and comprehensive resection of colorectal polyps, has led declining rates of colorectal cancer. We should look forward to a future where colonoscopy with polypectomy remains the criterion standard for colorectal cancer prevention, with ultra-low rates of colorectal cancer for at least a decade post-procedure for those screened effectively.

Funding

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In memoriam

This article is dedicated to the memory the late Prof. Wendy Atkin who was a pioneer of the concept that endoscopic polypectomy could prevent colorectal cancer.

References

1. *Lauby-Secretan B,et al. The IARC Perspective on Colorectal Cancer Screening. N Engl J Med. 2018;378:1734-1740*
2. *Edwards BK et al. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer. 2010;116:544-73.*
3. *Winawer SJ et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med. 1993;329:1977-81*
4. *Atkin WS et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet. 2010;375:1624-33*
5. *Holme Ø et al. Effectiveness of flexible sigmoidoscopy screening in men and women and different age groups: pooled analysis of randomised trials. BMJ. 2017;356:i6673. doi: 10.1136/bmj.i6673.*
6. *Corley DA et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med. 2014;370:1298-306.*
7. *Nishihara R et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med. 2013;369:1095-105*
8. *East JE et al. Serrated lesions in colorectal cancer screening: detection, resection, pathology and surveillance. Gut. 2015;64:991-1000*
9. *Pohl H et al. Incomplete polyp resection during colonoscopy-results of the complete adenoma resection (CARE) study. Gastroenterology. 2013;144:74-80.*
10. *Morris EJ et al. Post-colonoscopy colorectal cancer (PCCRC) rates vary considerably depending on the method used to calculate them: a retrospective observational population-based study of PCCRC in the English National Health Service. Gut. 2015;64:1248-56*

Treatment of Early Colorectal Cancer

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Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the fourth leading cause of cancer-related death in the world. Therefore, timely detection and appropriate treatment in the early stages of the disease is important. By endoscopy we can identify its location: colon cancer (above 15cm from the anal margin) or rectal cancer (within 15cm from the anal margin). Early stage colon cancer is confined to the mucosa or submucosa that does not invade the muscularis propria as shown in figure 1. These cancers can be completely resected with no subsequent evidence of involvement of adjacent organs, lymph nodes or distant sites. When colorectal cancer is found early, it can often be cured. The 5-year survival rate of localized (Stage I or II diseases) colon cancer is 90% and 89% for rectal cancer. About 39% of CRC are diagnosed at this early stage. When cancer has spread outside the colon or rectum, survival rates are lower. The five-year survival rate for cancer that has spread to nearby lymph nodes is 71.1%.

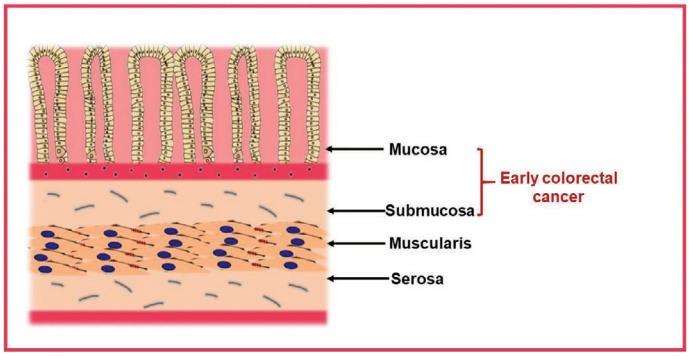

Figure 1. *Colon layers involved in the early cancer*

Treatment of early colon cancer

Early treatment for colon cancer is mainly based on less invasive techniques and preserving as much of the colon as possible. For stage 0 the treatment options are: local excision or simple polypectomy and segmentary en-bloc resection for a larger lesion not amenable to local excision. The main tool for diagnosis and for early treatment is either sigmoidoscopy or a total colonoscopy. Colonoscopy allows us to determine the exact localization and biopsy of the lesion, detection of precancerous or cancerous lesions and removal of the lesions. Complete endoscopic resection should be carried out whenever the morphological structure of the polyp permits. Protruded lesions can usually be treated with conventional mucosectomy. If the colonoscopic findings suggest that the lesion invades the submucosa (e.g., hard appearance, polyp-on polyp configuration, or existence of nonstructural pits), surgery should be considered. Depressant lesions are found during endoscopy and these lesions rapidly invade the submucosal layer. Those confined to the mucosa or that only minimally invade the submucosa can be completely removed with the Endoscopic Mucosal Resection (EMR) or Endoscopic Submucosal Dissection (ESD), with 5-year survival rate greater than 90%. Table 1 summarizes the clinical outcomes of the different treatment options in early stage of CCR.

Localized disease

For Stage I and II, wide-margin surgical resection and anastomosis is recommended. The goal of surgery is a wide resection of the involved segment of bowel together with the removal of its lymphatic drainage. Primary colon cancers without systemic disease are treated mainly by surgery with

complete meso-colic excision (CME) with arteries and veins ligated as close as possible to the main vascular trunk to have lower local recurrence rate and improved survival. The concept of CME is similar to the total meso-rectal excision (TME) for rectal cancer and allows an excellent oncological outcome with a 5-year cancer specific survival rate of 93% in stage I and 91.4% in stage II. The extent of the colonic resection is determined by the blood supply and distribution of regional lymph nodes. The resection should include a segment of colon of at least 5 cm on either side of the tumor, although wider margins are often included because of obligatory ligation of the arterial blood supply. To clearly define stage II versus III a more advanced stage, and to identify and eradicate potential lymph node metastases, at least 12 lymph nodes must be resected. Colonic segmental resection is performed according to the site of the tumor; right hemicolectomy transverse colectomy, left hemicolectomy or total colectomy are the most common surgical procedures and it is always indicated in absence of metastases, preserving most of the colon cancer free.

Laparoscopic Colectomy

In recent years the efficacy of colectomy has been evaluated by laparoscopic surgery or by conventional open technique. The long-term oncological results of laparoscopic colectomy are similar to those of the conventional approach as shown in Table 1. Contraindications to laparoscopy may include whether a patient has a distended bowel; advanced disease; if the procedure cannot achieve an R0 resection; and/or an inability to tolerate pneumoperitoneum. It is important that if this technique is chosen it must be performed by a surgeon who is skilled in the technique and has experience in the oncological area. Table 2 shows the advantages of open and laparoscopic colectomy.

Adjuvant chemotherapy

Adjuvant chemotherapy is not indicated in the early stages of the disease, it is only reserved for a more advanced colon cancer with metastasis to lymph nodules and nearby organs, or with clinical presentations of perforation or obstruction. Previous studies have showed that the use of chemotherapy in early stages does not have any benefit for the patient, so it must be initiated with endoscopic therapy or local resection of the lesion.

Treatment of rectal cancer

As happens in colon cancer, the first therapeutic measure when finding a lesion is to perform endoscopic resection with timely histological staging. In the past the gold standard of treatment for all low rectal cancers was anterior resection with colo-anal or low rectal anastomosis and abdominal-perineal resection. These procedures led to good results in terms of local recurrence and 5-year survival rate. Unfortunately, resection of the rectum is a major surgery procedure associated with significant morbidity (7–68%), mortality (0– 6.5%), and sometimes distressing functional consequences for the patient. Recently. Studies reported in literature considers local excision as curative surgery in most of the patients with a primary tumor which is limited to the mucosa and submucosa (early stages) and does not present cytological or histological high-risk features (poorly differentiated cells, vascular and neural invasion, presence of mucinous histology and tumor ulceration). In these patients, local excision of rectal tumors preserves anal continence, bladder and sexual functions and achieves the same oncological results. In T1 patients, local excision is feasible

Table 1. *Treatment options in early stage colorectal cancer*

	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 colectomy	94.2%	16% 3-year	< 1% 30-day	19%
Open Colectomy	89.17 %	18% 3-year	1% 30-day	19%
Total meso- rectal excision	91.4%	7.3% 5-year	0.8% 30-day	15-20%

Treatment of Early Colorectal Cancer, continued

Table 2. *Advantages for Complete Mesocolic Excision (CME) by open technique and Laparoscopic Colectomy*

Laparoscopic Colectomy	**CME by open technique**
Decreased length of hospital stays	Gold standard
Smaller incisions	Lower cost
Less narcotic usage	No limitations regarding surgical extent, number of organs and quadrants
Less blood loss	Fallback option for all situations
Lower transfusion rates	Method of choice for dense adhesions
Improved pulmonary function after surgery	Method of choice for complex rearrangement/rerouting of structures
Decreased number of morbidities	Full tactile ability
Perioperative recovery was faster	Shorter surgery time
Earlier recovery of bowel function	Dissection in the mesocolic plane produces an intact fascial-lined specimen, which contains all the blood vessels and lymphatics through which the tumor may disseminate
Lower abdominal wall adhesions	Less intestinal and pelvic adhesions

because the curative rate is high (90-95%) and the risk of recurrence is low (5-10%) as reported in the literature. TME (Total Meso-rectal Excision) permits more accurate en bloc, full-thickness local excision of rectal tumors than local excision, without compromising anorectal function. Criteria for local treatment include well to moderately differentiated T1 cancer, the absence of lympho-vascular or perineural invasion, and tumors less than 3 cm in diameter occupying less than one-third of the circumference of the bowel lumen. An important aspect of the management of rectal cancer is to limit the risk of local-regional recurrence in the pelvis. For laparoscopic surgery there is much less evidence than in colon cancer, so its use as a first option is not recommended.

Chemotherapy and radiation

In early disease local radiotherapy can be used as an alternative to local surgery in patients who refused radical surgery. Once the tumor invades the muscularis propria (T2), preoperative radio-chemotherapy is strongly recommended because local excision alone has a high percentage of recurrence associated with significantly worse intestinal and sexual functions. For patients with tumors at increased risk of local regional recurrence in the pelvis, preoperative chemotherapy with radiation is recommended.

Conclusions

In recent years, the screening and early detection programs have expanded an early stage detection of the disease which allows performing early and timely treatment. This advancement has led to significantly improved patient survival. The early treatment of the disease is based on endoscopic treatment. Endoscopy can, in many cases, help to identify the stage of the disease and offer curative treatment without the need for any adjuvant therapy. In cases where the pathology is showing data of probable risk of recurrence, radical surgery to remove the tumor, nodules and mesentries decrease long term recurrence rates. Chemotherapy and radiotherapy are not indicated in patients with early stage colon cancer, but their beneficial use, can be evaluated in early stages of rectal cancer.

References:

1. *Buccafusca AG, Ilaria P, Sebastiano RG, Paolo T. Early colorectal cancer: diagnosis, treatment and survivorship care. Crit Rev Oncol / Hematol. 2019;136:20-3.*
2. *Cervantes A, Arnold D. Rectal cancer : ESMO Clinical Practice Guidelines for diagnosis , treatment and follow-up. 2017;28:22-40.*

Treatment of Early Colorectal Cancer, continued

3. *Costas-Chavarri A, Nandakumar G, Temin S, Lopes G. Treatment of Patients With Early-Stage Colorectal Cancer : ASCO Resource-Stratified Guideline: 2019;5:1-19*
4. *Dimitriou N, Griniatsos J. Complete mesocolic excision : Techniques and outcomes. World J Gastrointest Oncol. 2015;7:383-388.*
5. *Freeman HJ. Early stage colon cancer. World J Gastroenterol. 2013;19:8468-8473.*
6. *Labianca R, Nordlinger B, Beretta GD, Mosconi S, Cervantes A, Arnold D. Clinical practice guidelines Early colon cancer : ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up clinical practice guidelines. 2013;24:64-72. doi: 10.1093/annonc/mdt354.*
7. *Lezoche E, Sanctis A De. Early Rectal Cancer : Definition and management. Dig Dis. 2007;25:76-9*
8. *Nelson H, Sargent DJ, Wieand HS, Fleshman J, Anvari M, Stryker SJ, Beart RW Jr, Hellinger M, Flanagan R Jr, Peters W OD. A Comparison of Laparoscopically Assisted and Open Colectomy for Colon Cancer. N Engl J Med. 2004: 350:2050-9.*

Endoscopic Management for Early Colorectal Cancer

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Introduction

Since colorectal Tis cancer (mucosal: M), by definition, has not metastasized, a complete cure is possible with complete local resection.1) On the other hand, in pT1 (submucosal: SM) cancer, lymph node metastasis occurs in approximately 10% of the cases. Additional treatment for certain cases may be required after endoscopic treatment.1) Based on the Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines for the Treatment of Colorectal Cancer 2019, we have outlined a strategy for management of early colorectal cancer (Tis and T1 cancer) (Fig 1).[1)]

Current additional surgical resection criteria for endoscopic resected colorectal pT1 (SM) cancer

The recommendation level and evidence level of the JSCCR Guidelines for the Treatment of Colorectal Cancer 2019 was determined based on the GRADE system.[1)] In the guidelines, the indications of additional treatment for T1 colorectal cancer after endoscopic resection was described. Concretely, if the vertical tumour cut margin is positive, additional surgical resection is preferred (recommendation level/evidence level 1C). If one or more of the below findings is noted in the histological examination of the resected specimen, additional surgery with lymph node dissection should be considered: (1) SM invasion depth ≥1000μm, (2) vascular invasion, (3) presence of poorly differentiated adenocarcinoma, signet-ring cell carcinoma, mucinous carcinoma, (4) budding grade (BD) at the deepest portion of the invasive front - Grade 2/3 (Fig 2).

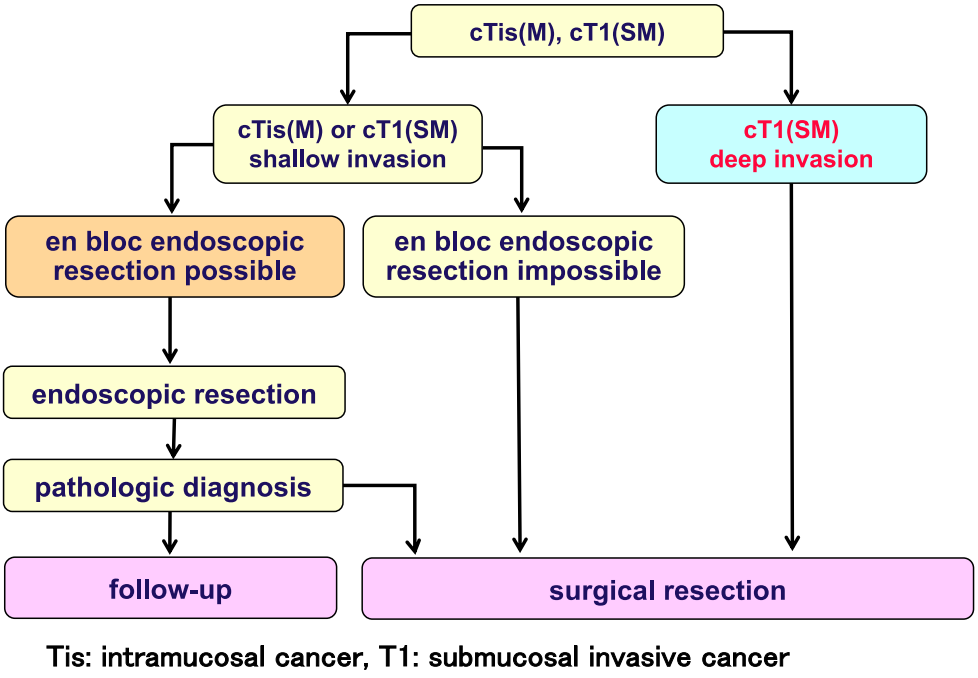

Figure 1.*cTis(M)cancer or cT1 (SM)colorectal cancer treatment strategy based on the JSCCR Guidelines for the Treatment of Colorectal Cancer 2019*

Endoscopic Management for Early Colorectal Cancer, continued

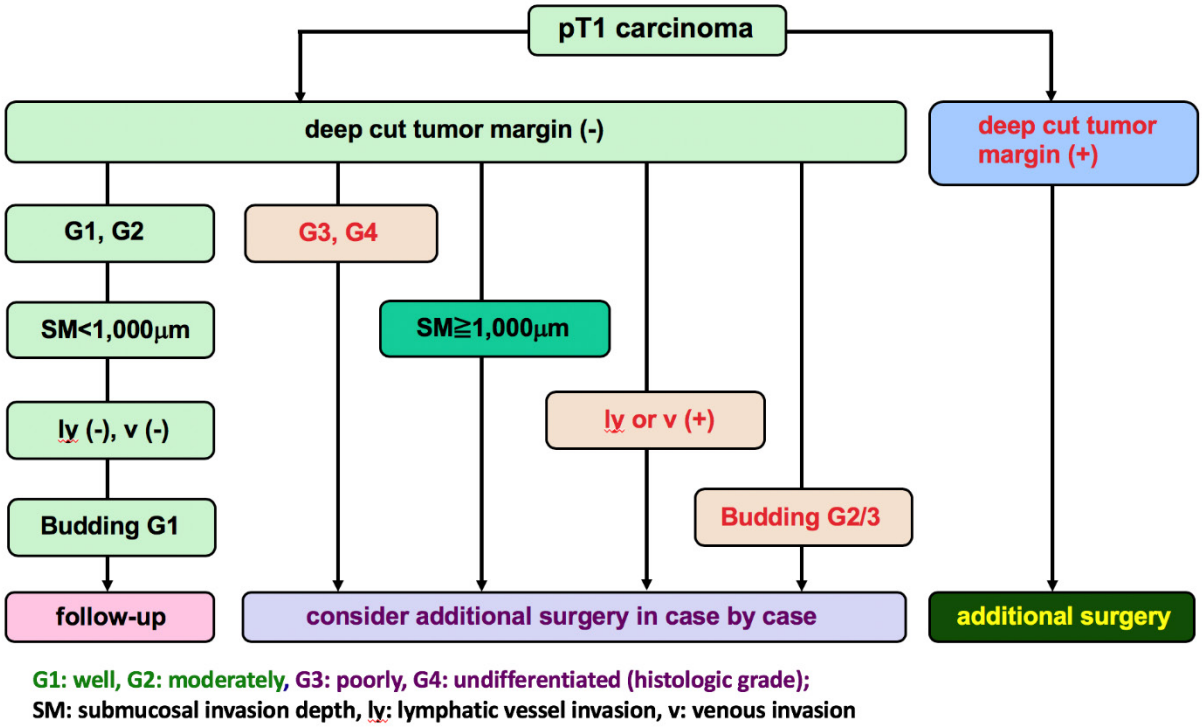

Figure 2.*Therapeutic strategy for submucosal (T1) colorectal cancer resected endoscopically based on the JSCCR Guidelines for the Treatment of Colorectal Cancer 2019*

The method to determine the submucosal invasion depth was explained in the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma 2019.[2] Additional surgery with lymph node dissection should be considered with various conditions in addition to pathologic findings. This include the curability of colorectal cancer based on concrete percentage metastatic risks predicted by analysing various risk factors for lymph node metastasis, patient conditions (age, level of physical activity, complications, postoperative quality of life, etc.) and whether informed consent is obtained.[1]

Recent knowledge for management of colorectal T1 cancer

It has been clarified that additional surgery with lymph node dissection is not always necessary even if endoscopic resected lesion reveal a pT1b (SM invasion depth is ≥1000μm) cancer. Nakadoi et al reported a 1.2% of lymph node metastatic risk of T1 colorectal cancer, irrespective of the degree of SM invasion, in the absence of: (1) vascular invasion; (2) unfavourable histologic; and (3) BD - Grade 2/3.[3] Yoshii et al.[4] investigated the prognosis of T1b cancer after endoscopic resection and reported that in the absence of unfavourable histology, vascular invasion, and high degree of BD, the recurrent rate with endoscopic resection alone was 3.4% and that with endoscopic resection plus additional surgery was 2.3%. The rates were low in both groups with no significant difference. In addition, the JSCCR clarified that even in cases with T1b cancer, when no other metastatic risk factors besides SM deep invasion (i.e., unfavourable histology components, vascular invasion, and high degree of BD grade) were detected, the rate of lymph node metastasis was very low.

On the other hand, in a multi-center study, Kobayashi et al.[5] reported that case in 798 patients with colorectal T1 cancer that was surgically resected with lymph node dissection without preceding endoscopic treatment, there was 2.3% of overall postoperative recurrence rate. Furthermore, according to a survey by the Japanese Society of Gastroenterolog-

ical Surgery,[6] the nationwide incidence of operational death during colorectal surgery is 0.24%–0.7. Also, it has been clarified that the pre-surgical endoscopic treatment for cases with T1 colorectal cancer never have significant effect on the oncologic behaviour after additional surgery.[7]

Management (endoscopic treatment) for colorectal T1 cancer in near future

With the current aging society, many factors such as the patient's age, underlying disease, level of physical activity, patients' will, and possibility of a colostomy (Miles' operation) should be considered in order to determine whether a patient should undergo surgery. In particular, the postoperative quality of life after Miles' surgical procedure for lower rectal cancer may lead to sexual and excretory dysfunction. Importantly, the patient must decide whether he/she will undergo the surgery after enough understanding of disease and discussion with doctor.

In the near future, it is highly likely that colorectal cancer treatment will move towards a strategy of evaluating the risk of lymph node metastasis using completely resected colorectal T1b cancer. After en bloc endoscopic resection for colorectal T1 cancer, necessity of the additional surgery can be considered. To proceed this ideas, there are several issues to be solved as follows; 1. standardization and quality control of precise invasion depth diagnosis prior to endoscopic resection (en bloc complete resection is possible or not), 2. endoscopic resection technique such as endoscopic mucosal resection, endoscopic submucosal dissection or full thickness resection, and 3. precise pathologic diagnosis with adequate specimen handling.[8] Furthermore, introduction of biomarkers or other factors which may predict curative conditions without metastasis will significantly benefit patients with CRC.

References

1. *Hashiguchi Y, Muro K, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol 2019 (in press)*
2. *Japanese Society for Cancer of the Colon and Rectum: Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma. Third English Edition, p39-40, Knahara & Co Ltd, Tokyo, 2019*
3. *Nakadoi K, Tanaka S, Kanao H, et al. Management of T1 colorectal carcinoma with special reference to criteria for curative endoscopic resection. J Gastroenterol Hepatol 2011 ; 27: 1057-62*
4. *Yoshii S, Nojima M, Nosho K, et al. Factors associated with risk for colorectal cancer recurrence after endoscopic resection of T1 tumors. Clin Gastroenterol Hepatol 2014; 12: 292-302*
5. *Kobayashi H, Mochizuki H, Morita T, et al. Characteristics of recurrence after curative resection for T1 colorectal cancer: Japanese multicenter study. J Gastroenterol 2011; 46: 203-11*
6. *Report of survey in 2009. The database committee of the Japanese Society of Gastroenterological Surgery (in Japansese: https://www.jsgs.or.jp/modules/oshirase/index.php?content_id=212).*
7. *Tamaru Y, Oka S, Tanaka S, et al. Long-term outcomes after treatment for T1 colorectal carcinoma: a multicenter retrospective cohort study of Hiroshima GI Endoscopy Research Group. J Gastroenterol 2017; 52: 1169-1179.*
8. *Tanaka S, Asayama N, Shigita K, et al. Towards safer and appropriate application of endoscopic submucosal dissection for T1 colorectal carcinoma as total excisional biopsy: Future perspective. Dig Endosc 2015; 27: 216-22*
9. *Tanaka S, Oka S, Tamura T, et al. Molecular pathologic application as a predictor of lymph node metastasis in submucosal colorectal carcinoma: Implication of immunohistochemical alteration as the deepest invasive margin. Muto T, Mochizuki H, Masaki T Edt. Tumor budding in colorectal cancer: Recent progress in colorectal cancer research. p171-180, NOVA, Hauppauge NY, 2006*

Contemporary Management of Advanced Colorectal Cancer

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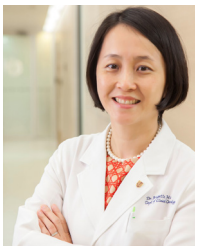

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Over the past decades, a deeper understanding of colorectal cancer (CRC) biology together with a paradigm shift in the management of advanced disease has led to unprecedented improvement in the clinical outcome of patients with metastatic CRC (mCRC). This article will highlight these key developments and touch upon the future directions for clinical research.

1. Recent Advances in the Molecular Biology of Metastatic Colorectal Cancer

1.1 Molecular Classification of Colorectal Cancer

In recent years, advancements in genome sequencing and bioinformatics have enabled an in-depth characterization of the genomic heterogeneity and molecular aberrations in CRC. The comprehensive genomic sequencing of CRC through the efforts of The Cancer Genome Atlas (TCGA) project and others have laid the foundation for the molecular classification of CRC. The Consensus Molecular Subtypes (CMS) Consortium describes four CMS groups: CMS1 (MSI [microsatellite instability] immune), CMS2 (canonical), CMS3 (metabolic) and CMS4 (mesenchymal), with an indeterminate group possibly representing a transition phenotype [1] The utility of this framework in providing a molecular basis for personalized oncological therapy is currently under investigation.

1.2 Biomarkers that are Commonly Used in Current Oncological Practice

Several validated biomarkers are currently being used in clinical practice for guiding drug therapy for patients with mCRC. Activating mutations of *KRAS* and *NRAS* confer innate resistance to epidermal growth factor receptor (EGFR) antibodies such as cetuximab and panitumumab. Activating mutations in *BRAF* (majority are V600E hotspot mutations) are mutually exclusive from the presence of *KRAS* mutations. Patients with *BRAF*-mutant mCRC have poorer prognosis than those with *BRAF* wild-type (WT) tumors when treated with EGFR antibodies and chemotherapy. The National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) guidelines suggest that both extended *RAS* (*KRAS* and *NRAS*) and *BRAF* mutation should be tested before starting EGFR antibodies, and that EGFR antibodies should be used only in *RAS*-WT mCRC [2,3]. The optimal treatment of patients with *RAS* or *BRAF*-mutant mCRC is currently under active investigation.

Primary tumor location (left *versus* right-sided) has been recently recognized to be an important predictive and prognostic factor in mCRC. Patients with mCRC and left-sided primaries have higher response rate and longer survival than those with right-sided primaries, following treatment with chemotherapy plus EGFR antibody in randomized trials. The biological basis of this difference is likely to be multi-factorial and may include genomic, embryological and environmental factors [4]. Patients with left-sided primaries should preferably receive a combination of chemotherapy and EGFR antibodies in the initial treatment of mCRC if they are medically fit [2,3]. Patients with right-sided primaries maybe treated with chemotherapy in combination with a vascular endothelial growth factor (VEGF) antibody in the first-line setting in mCRC, as they are less likely to benefit from EGFR antibody therapy compared with those with left-sided primaries.

Microsatellite instability (MSI) is a hallmark of deficient DNA mismatch repair (dMMR) and is one of the leading causes of genetic hypermutability in cancers. This phenomenon can be identified using immunohistochemistry to detect the loss of the four MMR proteins, namely MLH1, MSH2, MSH6 and PMS2, or with molecular tests such as polymerase chain reaction (PCR) and next-generation sequencing (NGS).

Current recommendations for MSI testing include its use for the diagnosis of hereditary non-polyposis colorectal cancer (HNPCC) and to aid clinical decision on the use of adjuvant chemotherapy in stage II colon cancer [3]. Recent studies have shown that MSI-H/dMMR mCRC are more likely to respond to inhibitors targeting the immune-checkpoint proteins such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), than microsatellite stable (MSS) tumors [2,3]. Therefore, MSI-dMMR testing should be done before making clinical decisions on immunotherapy for patients with mCRC.

Genetic polymorphism of genes encoding drug-metabolizing enzymes such as uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) and dihydropyrimidine dehydrogenase (DPD), have been associated with increased toxicity to irinotecan and fluoropyrimidines, respectively. Population-based differences in the prevalence of UGT1A1 polymorphisms have been well described [5], and some guidelines have recommended UGT1A1 phenotyping especially in Asian patients if there is a clinical suspicion of UGT1A1 deficiency and when using an irinotecan dose of over 180 mg/m^2 per administration [6]. Routine testing of DPD phenotyping before starting fluoropyrimidines is currently not recommended [6].

1.3 Less Common and Potentially Actionable Molecular Subtypes of Metastatic Colorectal Cancer Under Clinical Evaluation

Some emerging biomarkers are currently under investigation for their predictive and prognostic potential. HER2 (ERBB2) overexpression in RAS WT and BRAF WT mCRC has been shown to be a negative predictor of response to EGFR antibodies [7]. It has also become a promising therapeutic target as shown in phase II studies of dual HER2-targeted therapy in heavily pretreated HER2-ampified mCRC patients. Anaplastic lymphoma kinase (ALK) fusions and neurotrophic tropomyosin receptor tyrosine kinase (NTRK) fusions are found in around 1% of mCRC. Patients with tumors harboring such fusion genes may respond to kinase inhibitors that specifically target these alterations [8]. Most of the drugs targeting these molecular targets remain experimental and formal regulatory approval is pending.

2. Contemporary Approach to the Management of Recurrent or Metastatic Colorectal Cancer

Approximately 25-35% of CRC patients present with metastatic disease. Pooled analyses of clinical trials in the first-line treatment of mCRC suggest that the median overall survival (OS) of certain patient subgroups may reach up to 40 months [9], compared to only around 12 months when 5-fluorouracil (5FU) was the only cytotoxic drug available. The reason for this improvement is multifactorial and may include the multidisciplinary approach towards the treatment of oligo-metastatic disease (OMD), advances in systemic therapy and the implementation of a personalized approach to treatment.

2.1 Multidisciplinary Approach Towards the Treatment of Oligo-metastatic Disease

The practice of surgical resection and local ablation of colorectal liver metastases (CRLMs) has contributed to a significant improvement in survival for patients with mCRC. The broadening feasibility of surgical and ablative techniques has also re-defined the meaning of resectability of OMD. In general, OMD may be characterised by the presence of metastases at 2 (or sometimes 3) visceral sites, and a maximum total of 5 (sometimes more) lesions [2]. Patients with OMD should be managed under a multidisciplinary team (MDT) consisting of oncologists, surgeons, interventional radiologists and pathologists, which review and individualize the management of each patient during the evolving course of his or her treatment. For patients with unresectable metastases, conversion chemotherapy may render some of these lesions resectable. In the 8th edition of the American Joint Committee on Cancer (AJCC) staging manual, the 'M' (metastasis) category has been expanded in part to reflect this change in the therapeutic paradigm. M1a denotes metastases confined to one distant site (can be treated more aggressively especially for liver-limited disease), M1b denotes metastases to more than one site, and M1c denotes peritoneal metastases (as these patients generally fare worse than those with visceral organ metastases) [10].

2.2 Advances in Systemic Therapy

The armamentarium of the oncologist has greatly expanded in the past decades. The fluoropyrimidines have been the chemotherapy backbone before the 1990s, and a myriad of regimens have since become available with the introduction of oxaliplatin and irinotecan. Subsequent phase III studies in the first and subsequent-line setting have confirmed the benefit of VEGF and EGFR antibodies, as well as multi-kinase inhibitors against VEGF-receptor in refractory mCRC.

At present, there are at least nine classes of anti-neoplastic agents for mCRC [Table 1]. Traditionally, systemic therapies are usually administered as sequential 'lines' of therapy. However, with the advent of other approaches such as maintenance therapy, continuation of VEGF antibodies beyond clinical progression and also immunotherapy, the optimal sequencing of drug regimens is still evolving. Despite these changes, it has been consistently shown that patients who have access to most of the known anti-neoplastic agents at some point during the course of their illness tend to live longer than those who do not, regardless of the drug sequencing [11]. Some of the commonly used drug regimens in the initial treatment of mCRC are summarized in Table 2 [3]. A comprehensive discussion is beyond the scope of this article, but in general, infusional chemotherapeutic 'doublets' (FOLFOX, FOLFIRI, XELOX/CAPOX) or 'triplet' (FOLFOXIRI) can be used alone or in combination with targeted therapies such as VEGF or EGFR antibodies. The partnering of EGFR antibodies with oral fluoropyrimidines is not preferred due to the overlapping gastrointestinal toxicity which may undermine clinical efficacy. The combination of EGFR and VEGF antibodies must also be avoided due to toxicity concerns. For patients who have failed prior lines of fluoropyrimidine-based chemotherapy regimens, drugs which have been approved for refractory mCRC may include trifluridine/tipiracil (TAS-102) and regorafenib [2,3]. These agents have been shown to improve survival in randomized studies when compared with placebo in patients with mCRC who were refractory to standard chemotherapy[2,3].

For specific molecular subgroups such as MSI-H/dMMR mCRC, PD-1 inhibitors such as nivolumab and pembrolizumab have also been recently approved for patients who have chemotherapy-refractory mCRC [12]. Of the 8-10% of mCRC which harbor BRAF mutations, subgroup analysis from phase III studies have shown that such patients have the worst prognosis compared with RAS-WT and RAS-mutant subgroups even following intensive treatment with a 4-drug regimen [13]. The use of BRAF inhibitors either in combination with irinotecan and cetuximab, or in a chemotherapy-free combination with cetuximab and a MEK inhibitor are currently being evaluated in phase III setting. The role of dual HER2-targeted therapy for HER2-amplified mCRC is also being investigated in clinical trials.

2.3 Overview on the Management of Toxicities associated with Systemic Therapies in the Treatment of Metastatic Colorectal Cancer

One of the aims of palliative therapy is to alleviate cancer-related symptoms without undue worsening of quality of life in cancer patients, therefore judicious management of drug-related toxicities is an integral part of managing mCRC. The systemic agents that are used in routine practice can be broadly categorized into different classes (Table 1) that are associated with unique toxicities: cytotoxic chemotherapy, VEGF and/or receptor (VEGFR) inhibitors (anti-angiogenic agents), EGFR antibodies and immune-checkpoint inhibitors (PD-1 and CTLA-4 inhibitors). In general, nearly all cytotoxic agents could exert both acute toxicity on normal tissues with high cellular turnover such as the bone marrow, skin and gastrointestinal (GI) mucosa. This could increase the risk of infection, bleeding, oral mucositis and diarrhoea. Some cytotoxic agents are associated with more subacute and cumulative toxicities, such as sensory neuropathy with oxaliplatin and hand-foot-syndrome (or known as palmar-plantar erythrodysesthesia) with infusional and oral 5FU. These risks could be higher in multi-drug regimens than in monotherapy. In regions where hepatitis B is endemic, routine testing of hepatitis B (HBV) surface antigen status is recommended before treatment. If a patient is a HBV carrier, prophylactic anti-viral therapy should be started before treatment for the prevention of HBV reactivation during chemotherapy.

For VEGF/VEGFR inhibitors, hypertension and proteinuria are known class-effects common to nearly all anti-angiogenic agents. Uncommonly, VEGF/ VEGFR inhibitors maybe associated with an increased risk of GI perforations and bleeding, as well as arterial and/or venous thromboembolism. Some multi-kinase VEGFR inhibitors such as regorafenib may have a higher risk of hand-foot-syndrome and hepatotoxicity. VEGF/VEGFR inhibitors will need to be withheld well in advance before any major surgical procedures as they may increase the risk of bleeding. For EGFR antibodies, the more common side effects include skin rash (acneiform, dryness), diarrhoea and hypomagnesemia. The risk of infusion-related hypersensitivity for the different types of monoclonal antibodies is generally uncommon, but the incidence maybe slightly higher for antibody that is chimeric in origin compared with antibodies that are humanized/ fully human.

Contemporary Management of Advanced Colorectal Cancer, continued

Table 1. *Classes of anti-neoplastic agents that maybe used in the treatment of colorectal cancer outside clinical trials**

*The approval status/drug labelling of these agents may differ between regulatory authorities in different countries/regions. Most of these agents listed below are approved for the treatment of colon and/or rectal cancer by the United States Food and Drug Administration as of September 2019 (https://www.cancer.gov/about-cancer/treatment/drugs/colorectal). The exceptions are UFT and TS-1 which are approved in parts of Asia and Europe.

Drug Name	**Mechanism**	**Biomarkers Recommended for testing by the ESMO and/or NCCN or ESMO (Pan-Asian Adapted) Guidelines 2,3,6**
Fluoropyrimidine-based • 5FU • Capecitabine • UFT • TS-1 • TAS-102	Anti-metabolite UFT: 1:4 molar combinations of tegafur with uracil TS-1: Tegafur, gimeracil and oteracil TAS-102: Trifluridine and tipiracil hydrochloride	-
Oxaliplatin	Platinum analogue	-
Irinotecan	Topoisomerase I inhibitor	UGT1A1 polymorphism (see text above for indication)
VEGF/VEGFR antibodies: • Bevacizumab • Ramucirumab • Aflibercept	• Bevacizumab: Anti-VEGF-A antibody • Ramicirumab: Predominantly anti-VEGFR-2 antibody • Aflibercept: Recombinant fusion protein that functions as a decoy receptor to prevent VEGF-A, VEGF-B, and PGF from binding to their receptors	-
EGFR antibodies: • Cetuximab • Panitumumab	• Chimeric (mouse/human) EGFR antibody • Fully humanized EGFR antibody	Extended RAS mutation testing BRAF mutation testing
Immune-checkpoint inhibitors: • Pembrolizumab/Nivolumab • Nivolumab and Ipilimumab	• Pembrolizumab/nivolumab: PD-1 antibodies • Ipilimumab: CTLA-4 antibody	MSI-H/dMMR
Regorafenib	Multi-kinase inhibitor with anti-angiogenesis effects	-

Legend: ESMO = European Society of Medical Oncology; NCCN = National Comprehensive Cancer Network; 5FU = 5-fluorouracil; UGT1A1 = uridine diphosphate glucuronosyl transferase 1A1; VEGF/R = vascular endothelial growth factor/receptor; PGF = placental growth factor; EGFR = epidermal growth factor receptor; PD-1 = programmed cell death protein 1; CTLA-4 = cytotoxic T-lymphocyte–associated antigen 4; MSI = microsatellite instability; dMMR = deficient mismatch repair; 5FU = 5-fluorouracil.

Contemporary Management of Advanced Colorectal Cancer, continued

Table 2. *Some commonly used chemotherapy combinations in the initial treatment of metastatic colorectal cancer**
**This table is not exhaustive and only selected regimens are listed. The details on schedule and dosages of these regimens can be found in the ESMO, NCCN and ESMO (Pan-Asian Adapted) guidelines 2,3,6*

Name of Regimen	Constituents	Preferred Choices of Antibodies for combination
Infusional 5FU backbone: FOLFOX FOLFIRI FOLFOXIRI	 Oxaliplatin, leucovorin, 5FU Irinotecan, leucovorin, 5FU Oxaliplatin, irinotecan, leucovorin, 5FU	 Bevacizumab, cetuximab or panitumumab Bevacizumab, cetuximab or panitumumab Bevacizumab
Oral fluoropyrimidine backbone: XELOX/ CAPOX XELIRI SOX	 Capecitabine, oxaliplatin Capecitabine, irinotecan TS-1, oxaliplatin	 Bevacizumab Bevacizumab
Bolus 5FU backbone: 5FU/LV	 5FU, leucovorin	 Bevacizumab

The antibodies against immune checkpoint proteins such as PD-1 and CTLA-4 can be associated with autoimmune toxicities which are generally mild and uncommon with PD-1 inhibitors when used as monotherapy, but may be more prevalent and severe when PD-1 and CTLA-4 inhibitors are used in combination. In principle, autoimmune toxicities may potentially affect any tissues in the body which contain T-cell infiltrates. These may include the skin, glandular tissues with endocrine function (resulting in endocrinopathy involving the thyroid, pituitary and adrenal glands), GI tract, some neural tissues and visceral organs. Serious to potentially fatal autoimmune toxicities are rare and may include colitis, fulminant hepatitis, pneumonitis, Steven-Johnson syndrome, nephritis and myocarditis.

In summary, the management of toxicities associated with the systemic agents as mentioned can be guided by several key principles: (1) Careful and regular monitoring of patients for toxicities before and during treatment; (2) prompt dose interruption/ modification and institution of appropriate supportive treatment; (3) early reporting of toxicity by increasing patient's vigilance through counselling; (4) and where indicated, prophylactic therapy for reducing the risk of certain toxicities – such as HBV reactivation during chemotherapy, should be started before treatment. Details on the management of toxicities associated with individuals agents can be found in the manufacturer's drug insert. Oncological societies such as the ESMO and the American Society of Clinical Oncology (ASCO) have also published some online practice guidelines on this topic that are relevant to the management of mCRC [16,17].

2.4 Prognostic Stratification and Personalized Model of Management

Decision-making in the management of mCRC should be based on prognostic factors related to the patient's medical fitness, the clinical extent and molecular characteristics of the cancer. Patients should be stratified according to their performance status and medical co-morbidities, sidedness of the primary tumor, disease extent, organ function and molecular factors (KRAS, NRAS, BRAF mutation and dMMR-MSI status). The treatment paradigm of mCRC has evolved over time, and the traditional model of a 'one-size-fits-all', sequential approach to different 'lines' of drug therapy has gradually been superseded by a more personalized model [2,3]. Drugs can sometimes be re-introduced if they have demonstrated durable activity previously during the course of a patient's treatment. Other approaches such as the use of maintenance chemotherapy with or without concomitant bevacizumab, chemotherapy 'holidays' as well as the continuation of bevacizumab beyond clinical progression have all been gradually incorporated into routine oncological practice. Medically fit patients with potentially resectable liver-limited or OMD maybe candidates for more aggressive (and relatively more toxic) 3-drug or 4-drug regimens in order to achieve a higher chance of tumor shrinkage and subsequent R0 resection. For the majority of patients with unresectable metastases, the overall treatment goal would be palliative with the aim of prolonging overall survival and maintaining quality of life with acceptable toxicities. For patients who are elderly, frail and with multiple comorbidities, a more conservative approach by starting chemotherapy as

monotherapy or at lower doses with gradual dose-titration if the general condition improves can be considered safely without jeopardizing survival significantly.

3. Contemporary Management of High-Risk Locoregionally Advanced Rectal Cancer

The contemporary treatment of rectal cancer is fundamentally based on a risk-adapted approach as assessed by a MDT. High-risk rectal cancer is generally defined as the presence of T3/T4 disease and/or nodal metastases, in which there may be threatened circumferential margins or involvement of the levator ani [14]. One of the notable achievements in the early 2000s is the introduction of neoadjuvant (pre-operative) radiotherapy (RT) with or without concurrent chemotherapy for patients with high-risk rectal cancer. At present, neoadjuvant short-course pelvic RT (25 Gray [Gy] total dose at 5 Gy/fraction) or concurrent chemotherapy with long-course pelvic RT (45–50 Gy in 25–28 fractions) are regarded as standard therapeutic options for high-risk rectal cancer [14,15]. Traditionally, 5FU has been the agent of choice given as a radio-sensitizer during pelvic RT and randomized studies have found that oral capecitabine is an effective alternative to infusional 5FU, but the addition of other cytotoxic agents such as oxaliplatin to 5FU during concurrent RT did not significantly improve survival. Other approaches of systemic intensification, or sometimes called 'total neoadjuvant therapy' include the administration of additional chemotherapy prior to starting concurrent chemotherapy-RT (CRT), the use of 'consolidation chemotherapy' following CRT and prior to surgery, and also chemotherapy alone without RT prior to surgery. The feasibility of adding targeted therapy or immune-checkpoint inhibitors to neoadjuvant therapy have been investigated in phase I to II clinical trials. Ongoing phase III studies are addressing the question of whether such strategies may improve treatment outcome or not for patients with high-risk rectal cancers. In some patients who achieved complete response following neoadjuvant RT, some retrospective studies have suggested a watch-and-wait approach, especially for patients who are frail, at high surgical risk or those that refuse operation [14].

Summary and Future Directions

Developments in recent years have significantly altered how patients with advanced CRC are managed leading to improvement in survival and quality of life. In the near future, the priority areas of research are to optimize the practice of precision oncology by identifying new therapies for potentially druggable targets in molecular subgroups, to elucidate the clinical utility of CMS in individualizing drug therapy, and to investigate how novel agents such as immune-checkpoint inhibitors can be optimally incorporated into standard therapies for the treatment of advanced CRC.

References

1 *Guinney J, et al. The consensus molecular subtypes of colorectal cancer. Nat Med 2015; 21: 1350–1356.*

2 *Van Cutsem E, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016; 27: 1386–1422.*

3 *Benson AB, et al. NCCN Guidelines for Colon Cancer. Version 2.2019. NCCN.org (accessed 6 September 2019).*

4 *Arnold D, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Ann Oncol 2017; 28: 1713–1729.*

5 *Ma BB, et al. Population-based differences in treatment outcome following anticancer drug therapies. Lancet Oncol 2010; 11: 75–84.*

6 *Yoshino T, et al. Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO–ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. Ann Oncol 2018; 29: 44–70.*

7 *Raghav K, et al. Validation of HER2 amplification as a predictive biomarker for anti–epidermal growth factor receptor antibody therapy in metastatic colorectal cancer. JCO Precis Oncol 2019.*

8 *Dienstmann R, et al. Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. Nat Rev Cancer 2017; 17: 79–92.*

9 *Lenz HJ, et al. Impact of consensus molecular subtype on survival in patients with metastatic colorectal cancer: results from CALGB/SWOG 80405 (Alliance). J Clin Oncol 2019; 37: 1876–1885.*

10 *Amin MB, et al. (Eds.). AJCC Cancer Staging Manual (8th edition). Springer International Publishing: American Joint Commission on Cancer; 2017*

Contemporary Management of Advanced Colorectal Cancer, continued

11 *Grothey A, et al. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol 2004; 22: 1209–1214.*

12 *Luchini C, et al. ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, and its relationship with PD-1/PD-L1 expression and tumour mutational burden: a systematic review-based approach. Ann Oncol 2019 May 6. pii: mdz116. doi: 10.1093/annonc/mdz116. [Epub ahead of print]*

13 *Cremolini C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. Lancet Oncol 2015; 16: 1306–1315.*

14 *Glynne-Jones R, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28: iv22–iv40.*

15 *Benson AB, et al. Rectal Cancer, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Cancer Netw 2018; 16: 874–901.*

16. *American Society of Clinical Oncology, Online Practice Guidelines, titled: 'Supportive Care and Treatment Related Issues': https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/supportive-care-and-treatment-related-issues*

17. *European Society of Medical Oncology, Online Practice guidelines, titled: 'Supportive and Palliative Care https://www.esmo.org/Guidelines/Supportive-and-Palliative-Care*

Genetic Testing and Management of Syndromic and Familial Gastrointestinal Cancers

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Introduction

The attributable risk that genetic and familial factors make to gastrointestinal cancer, especially colorectal cancer, is estimated to be 30%. From high penetrant mutations in high penetrant genes, to genes with moderate penetrance through to polygenic risk SNPs and then to family history statistically related but as yet genomically uncharacterized, there is ample opportunity to introduce tailored surveillance and other preventative measures (Table 1). The capacity to identify these genetic and genomic characteristics is at the heart of new concepts of precision prevention using tailored strategies based on risk and an understanding of the velocity of the natural history of gastrointestinal neoplasia. Carrier frequency in populations is surprisingly common. According to estimation, 1:275 people carries a Lynch Syndrome pathogenic mutation and the estimates may increase as more widespread genomic testing is done in populations unaffected with cancer. Reciprocally penetrance may decline as testing is done more broadly with weaker phenotypes (Figure 1)

For in depth review of this topic readers are referred to US, European and Australian guidelines [1,2,3,4,5,6,7].

Genetic Testing:

1. Which patients and families to test?

   Gastroenterologists should be alert to the possibility of syndromic GI cancer at all times through consideration of the family phenotype.

   The horizon for identifying high penetrant genes such as carriers of pathogenic variants in the Lynch Syndrome mismatch repair genes has quickly changed from restricting genetic testing to families with a strong history of colorectal (and some other) cancers (the Amsterdam criteria – Table 2), to identifying individuals with family or personal characteristics that would suggest a germline predisposition (Bethesda criteria – Table 3), to universal testing of all colorectal cancers either age restricted (the Melbourne criteria) or unrestricted (Ohio State Colorectal Cancer Initiative). The Amsterdam and Bethesda criteria are manageably specific (meaning the false positive rate is low with a relatively high positive predictive value for the effort) but sensitivity is low – (many Lynch Syndrome carriers are missed). Countries contemplating engaging in identifying familial cancer might consider this progression in the course of their early experience and

Table 1 – *Syndromic colorectal cancer: syndromes, phenotypes, genes, age of onset.*

Syndrome	Mode	Polyps?	Gene(s)	Age of onset	Features
Lynch Syndrome (due to mismatch repair gene mutations) Muir Torre Syndrome	AD	Few	MLH1, MSH2, MSH6, PMS2 EPCAM deletion	Adult	Colorectal, endometrial cancers principally but others Skin tumours Microsatellite unstable Gene and gender specific penetrance
Familial adenomatous polyposis and Attenuated FAP	AD	100s to 1000s	APC	Adolescence to adulthood	Evolving density of adenomas Duodenal adenomas Desmoid Disease Osteomas, thyroid, brain, adrenal and other tumors
Peutz Jeghers Syndrome	AD	3 or more PJ polyps in GI tract	STK11	Childhood to adult	PJ polyps Lip pigmentation Breast, hepatobiliary, lung cancer Testicular and cervix
Juvenile Polyposis	AD	Juvenile and mixed in GI tract	SMAD4 BMPR1A	Childhood to adult	No extra GI tumours Hereditary Haemorrhagic Telangiectasia (SMAD4)
Hereditary Mixed Polyposis	AD	Mixed polyps	Grem1	Variable	Rare Due to amplification
MUTYH associated polyposis	AR	Adenomas and mixed None to 100s	MUTYH	Adolescence to adult	Similar phenotype to attenuated APC
NTHL1 associated polyposis	AR	Attenuated FAP	NTHL1	Adult	Attenuated polyposis
POLE, POLD1	AD	Attenuated FAP	POLE, POLD1	Adult	Adenomatous polyposis Colorectal Cancer (MSI H or MSS) Endometrial (POLD1)
Serrated Polyposis Syndrome	N/K	WHO criteria	N/K RNF43 or MUTYH (rare)	Adult	Multiple serrated polyps evenly spread in colon or 2 of 5+···>10mm proximally

where resources are constrained. Careful family histories are imperative for this approach.

2. Phenotype ascertainment

With the advent of cancer gene panel testing, defining the phenotype (Table 1) has become less important, but is still important where variants in multiple genes are identified and there is uncertainty as to which might be responsible. The key differentiating clinical information to be ascertained is whether the presentation across a family involves multiple polyps if present (or not), their type, number and location and what cancers are occurring across the family pedigree together with their age of onset. Family history should be a routine (but often overlooked) part of clinical assessment. The clinical management is informed not only by the genetic predisposition once identified, but the phenotype. Penetrance plays into clinical decision making as well.

Probands presenting without a family history are more challenging: young age should always be an alert to the possibility of a genetic predisposition. This is easily tested by tumor testing (microsatellite instability or immunohistochemistry testing for loss of mismatch repair protein expression) with respect to Lynch Syndrome (Figure 2). Note that such testing is not genetic testing – it is characterizing the phenotype and does not require the consent processes required for germline testing. Studies suggest that IHC on colonoscopic biopsies may be more informative than surgically resected specimens where

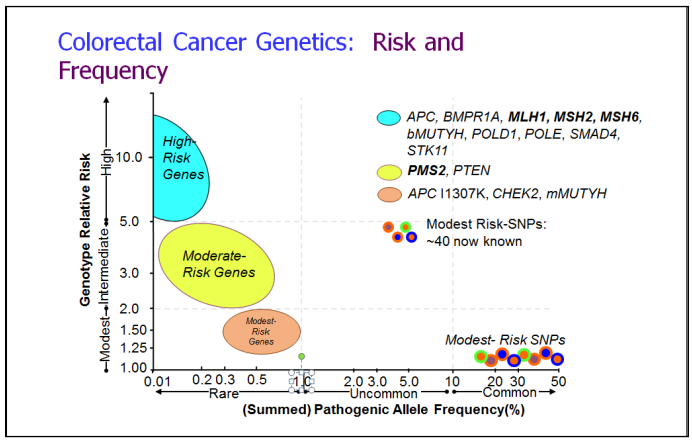

Figure 1 - *Genetic risk for colorectal cancer: relative risk against gene allele frequency. Courtesy: Prof Mark Jenkins, University of Melbourne*

Table 2 – *Amsterdam criteria for Lynch Syndrome.*

Amsterdam "criteria": 3: 2: 1 rule

- At least three relatives with a LS cancer
  - one related to the other two in first degree
  - over two successive generations
  - one diagnosed before age 50 years
- FAP excluded
- Tumour verified
  - Colorectal, endometrium, small bowel, ureter, renal pelvis

The Royal Melbourne Hospital

fixation may be compromised due to limited penetration into the surgical specimen. Patterns of MMR protein loss are very helpful to identify the gene involved: typically loss of MLH1and PMS2 is due to an MLH1 mutation (where there is no methylation of the MLH1 gene), loss of MSH2 and MSH6 is due to a MSH2 mutation, and isolated MSH6 or PMS2 is due to MSH6 and PMS2 respectively. Double hits in the tumor account for most loss where there is no germline mutation or MLH1 methylation.

Multiple polyps should alert to one of the polyposis syndromes, such as familial adenomatous polyposis. MUTYH-associated polyposis can be challenging as a third of people presenting with cancer with bi-allelic MUTYH mutations may have no synchronous adenomas, and polyps can also be serrated.
Polyposis may present de novo without a family history in a quarter of individuals but de novo presentation is rare with Lynch Syndrome.

Screening endometrial cancers (and endometrioid ovarian cancers) universally with IHC is gaining acceptance, at least under 60 years of age or those with LS features in their family history. MLH1 methylation in these tumors is common. BRAF testing is not helpful so a reflex to methylation testing of the MLH1 promotor is needed and often proves the case.

Urinary tract epithelial cancers are amongst the commonest non-colon, non-gynecological cancers in Lynch Syndrome. Comprehensive urinary tract screening in Denmark proved ineffective (sensitivity low, specificity low) but targeting screening to subpopulations (eg males with MSH2 or MSH6 mutations and with a family history of urinary tract cancer) may be a useful strategy.

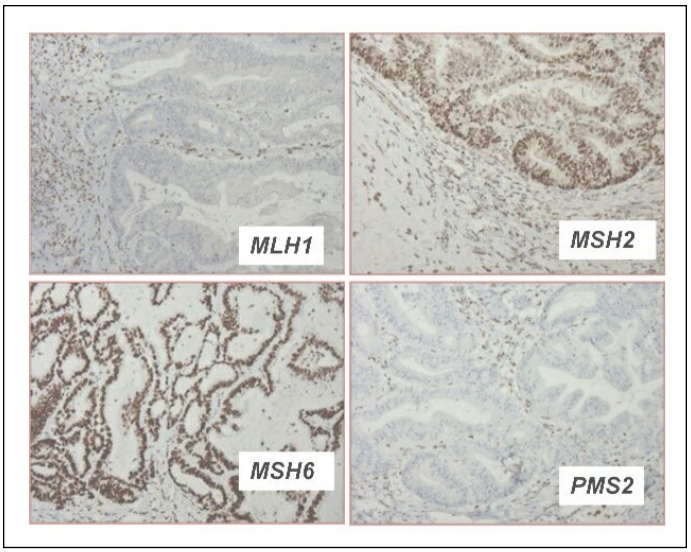

Figure 2 – *Immunohistochemistry stain for MMR protein loss of expression: In this case, MLH1 & PMS2 is lost.*

3. Genetic testing

With the introduction of next gen sequencing, there has been a rapid evolution of testing strategies across all genomics, and, as a consequence, an exponential fall in the cost of testing. This means the "net" of gene testing can be spread wider, addressing less convincing phenotypes (e.g. smaller adenoma numbers, older age groups). With this comes surprises which challenge clinical interpretation in the family context on the one hand, and progressively widens our understanding of genotype-phenotype correlations. A largely agnostic approach to gene selection and broad phenotype presentations leads to identification of actionable genes responsible for the cancers (at least in part) and opportunities for cascade testing (predictive DNA testing) across the family [8].

There is little evidence to suggest that familial syndromes are ethnically restricted so all countries should be alert to their presence. However, there are differences in the variants within the genes which are ethnically determined.

Detailed cost benefit studies have supported LS screening using tumor testing (IHC, MSI, BRAFV600E mutation detection or MLH1 promotor methylation studies). [9]. Whether this meets a willingness-to-pay threshold depends on competing needs and is geo-economically sensitive and entirely understandable. Lynch Syndrome screening is well within reach of most countries.

4. Variant interpretation

There is substantial agreement internationally about the genes that are responsible for GI cancer predispositions including the mismatch repair genes (Figure 3). However, interpreting whether individual variants are pathogenic or not continues to be challenging. Some are straightforward: those that truncate the protein perhaps through nonsense mediated decay of the gene product or encompass deletion or insertions likely to disrupt gene function, can be confidently assigned as pathogenic. However, many variants, especially if involving a change in a single nucleotide, are much more problematic. Indeed, the application of genomics to medicine is often held up at the bottleneck of such interpretation. Critical to the tasks of interpreting variants of uncertain significance is access to the widest range of data and experience from pedigree/segregation analyses, multiple tumor signature observations associated with the variants, evolutionary conservation analysis, physico-chemical analyses of the translated protein (Grantham score), understanding of the allele frequency in unselected populations and where available RNA or other functional studies of the consequence of the variant in the gene (Figure 4).

Table 3 – *Revised Bethesda Guidelines for tumour testing (MSI or ICH) for Lynch Syndrome.*

Revised Bethesda Guidelines for tumour testing (MSI or IHC) for Lynch Syndrome
• Colorectal cancer diagnosed in a patient who is <50 years of age
• Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumours,* regardless of age.
• Colorectal cancer with the MSI-H† histology‡ diagnosed in a patient who is <60 years of age.§
• Colorectal cancer diagnosed in one or more first-degree relatives with a HNPCC-related tumour, with one of the cancers being diagnosed <50 years of age.
• Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumours, regardless of age.
The Royal Melbourne Hospital

Genetic Testing and Management of Syndromic and Familial Gastrointestinal Cancers, continued

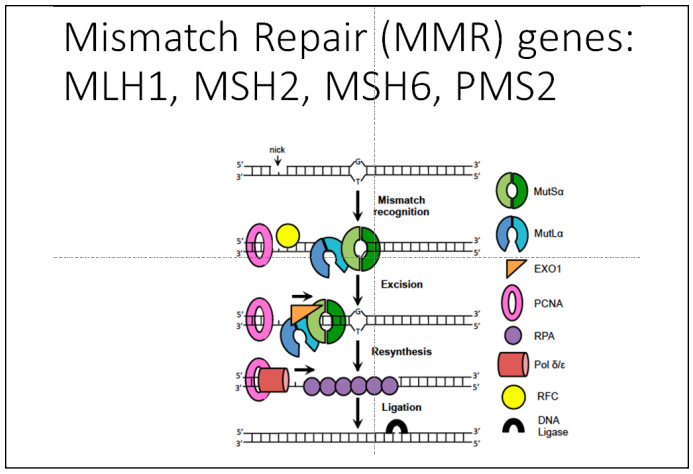

Figure 3 – *Mismatch repair. In humans, MutSα includes MSH2 and MSH6, , and MutLα includes MLH1 and PMS2.*

Table 4 – *Penetrance estimates for cancer in Lynch Syndrome Reference: www.eviq.org.au.*

Cancer	MLH1 to age 70 yrs[1, 2, 3]	MSH2 to age 70 yrs[1, 2, 3]	MSH6 to age 70 yrs[2, 4]	PMS2 to age 70 yrs[3]	Lynch syndrome to age 70 yrs*	General population to age 70 yrs
Colorectal (male)	34%	47%	22%	20%	38%	3.1%**
Colorectal (female)	36%	37%	10%	15%	31%	2.2%**
Endometrial	18%	30%	26%	15%	33%	1.3%**
Gastric	6%	0.2%	Insufficient data	-	6%	0.38%**
Ovarian	11%	15%	Low	-	9%	0.57%**
Urothelial	0.2%	2.2%	0.7%	-	<3%	0.33%**
Small bowel	0.4%	1.1%	Insufficient data	-	<3%	0.12%#

*This data does not take into account the impact of surveillance.
**Source: Australian Institute of Health and Welfare (AIHW) 2016. Australian Cancer Incidence and Mortality (ACIM) books. 2015 data.
#Source: NSW Cancer Registry. Annual NSW cancer incidence and mortality data set, 2014.

Management of Syndromic Gastrointestinal Cancer:

Whereas panel genetic testing has required less syndromic definition, management still is determined by syndromic understanding informed by the genotype.

1. Lynch Syndrome

   Recommendations for management of Lynch Syndrome carriers have long been standardized to annual or biennial colonoscopy to carriers commencing at age of 25 or 5 years earlier than the youngest onset in the family. They are founded on risk (Penetrance) estimates, feasibility and accuracy and utility of screening tests. (Table 4). This however is changing as more refined information is published which defines gene and gender specific risks (penetrance) by age (www.plsd.eu) and from international comparative studies where national protocols vary from annual to every 3 years, but benefits of more frequent colonoscopy have not been realized (Figure 5). Start times can be delayed for MSH6 and PMS2 carriers: PMS2 in particular has come under scrutiny for its lower penetrance (and thus cancer risk). This is likely to lead to a relaxation of frequency recommendations and weakening of gynaecological recommendations for risk reducing surgery for PMS2 carriers which, for the other genes, prescribe hysterectomy and bilateral oophorectomy at conclusion of family planning (10). LS carriers affected with their first cancer increasingly survive due to inherently better prognoses than their sporadic counterparts (less likely to metastasize), but continue to be at risk for metachronous cancer from the many Lynch Syndromic sites (www.plsd.eu). (11)

   Surgery is needed if cancer develops. Few would advocate prophylactic colectomy. The extent of surgery, once cancer develops, is controversial. Colectomy eliminates the risk (otherwise 60% at 40 years) of metachronous colon cancer and is generally the favored option. However, the decision needs to be individualized taking into account patient age, background bowel habit and sphincter integrity. A strong case can be made for a more extensive operation in young patients with a mismatch deficient tumor, even if the germline findings are not yet known at the time of surgery.

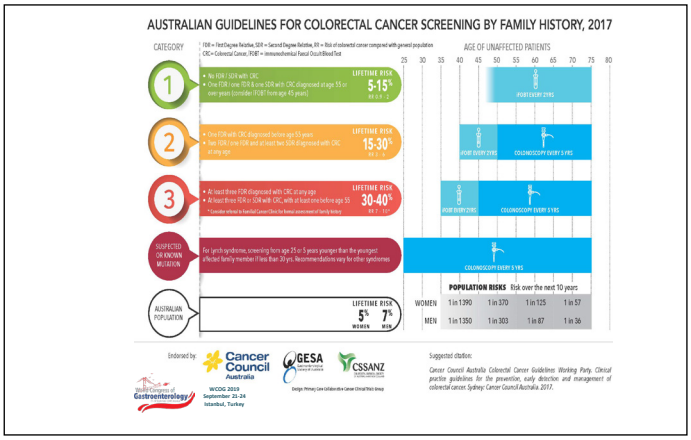

Figure 5 – *Penetrance for any cancer in Lynch Syndrome pathogenic MMR gene carriers with on line calculator given organ, current age, gender and gene. – Prospective Lynch Syndrome Database.*

Reference: www.lscarisk.org. The risks change on the site, as more data is entered.

Genetic Testing and Management of Syndromic and Familial Gastrointestinal Cancers, continued

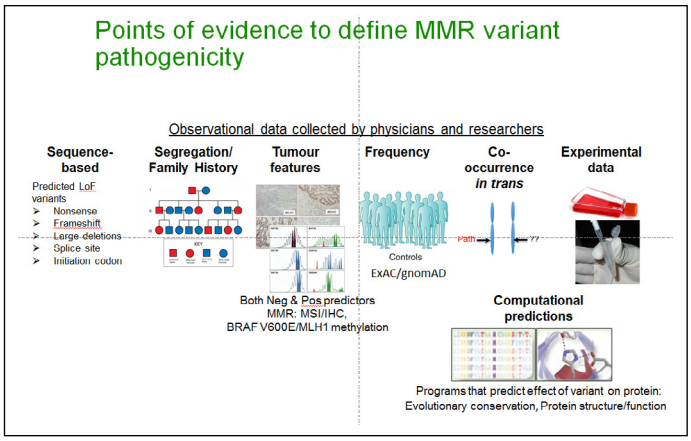

Figure 4 – *Evidence assembled through multifactorial Baysian analysis for mismatch repair variants.*

Prostate cancer risks have now been pinpointed, elevating the approach to prostate screening beyond the controversial average risk/PSA debate.

Aspirin chemoprevention in Lynch Syndrome is standard of care. The dose is still uncertain. Currently, 100mg daily is advised from the timing of colonoscopy initiation.

2. Polyposis syndromes

The high penetrance for cancer in FAP has for a century dictated prescriptions for colectomy in FAP. However, there is variation in advice relating to the age at which this should be done, the density of polyps that might trigger surgery, and the preference for proctocolectomy with ileo-anal pouch construction or colectomy with ileo rectal anastomosis (IRA). There are pros and cons for each approach. Advice to undergo ileo-anal pouch construction, once considered the answer to the threat of cancer in FAP, has been tempered by the later follow-up of patients and their pouches showing 30% or more develop adenomas in the pouch by 7 years, and even cancer. The pelvic surgery required to achieve proctectomy carries a risk to fertility, and pouch function is rarely comparable to a retained rectum. But rectal cancer remains the threat, so monitoring of the rectum at least annually is mandatory if it is left in situ with an IRA. High grade dysplasia, large rectal polyps or an uncontrollable rectal polyp burden are best addressed with proctectomy as would the development of a cancer.

MUTYH-associated polyposis , though attenuated in phenotype, is usually managed along the same lines as attenuated FAP . There is room for expectant management with regular surveillance in patients who are invested in their health and compliant to follow up.

Peutz Jeghers Syndrome. Capsule endoscopy has aided the surveillance in PJS immeasurably. Polyps are reliably identified and good estimates of their location found by noting the timing of polyp detection as a proportion of total small bowel transit time. This dictates whether an antegrade or retrograde double balloon enteroscopy is best deployed for their removal. CT or MR enterography also has proved valuable in small bowel polyp screening. Scoping of upper and lower tracts should be at least every 3 years. Mammography, preferably by MRI and or ultrasound to address the breast cancer risk, should be instituted in the fourth decade. Pancreatic and biliary screening, though not evidence based, is logical given the established risks for these cancers in PJS. Smoking should be stopped in view of the lung cancer risk.

Juvenile Polyposis Syndrome requires 3 yearly upper and lower GI surveillance. Small bowel capsule surveillance is justifiable in SMAD4 carriers.

Surveillance scheduling in the rarer syndromes (NAP (NTHL1), MSH3 recessive polyposis), mixed polyposis syndrome (Grem1), POLE and POLD1) is simply an extrapolation from attenuated FAP with little gene specific

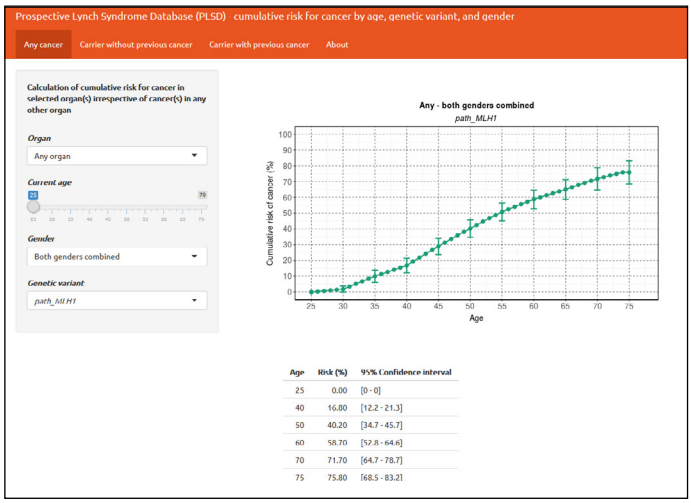

Figure 6 – *Screening of average, moderate and high risk groups for colorectal cancer.*

evidence for guidance. Experience with serrated polyposis syndrome is emerging. A reasonable strategy is one to three colonoscopies in a year to clear serrated polyps and then biennially; first degree relatives should have colonoscopy from mid 30s every 5 years.

3. Non syndromic familial colorectal cancer risk

These families fall into a moderate risk category, statistically substantiated but largely biologically not understood. Polygenic Risk Scores are making inroads into understanding the germline biology of this risk. We are likely to see such scoring systems separate those within the group with a risk readily accepted for colonoscopy screening, versus others whose surveillance can be downgraded or even obviated.

Until empirical data from screening emerges to support the molecular information, screening can be recommended to match risk determined epidemiologically or from a simple family history. Moderate risk colonoscopy guidelines derived on this principle are shown in Figure 6 from the Australian Guidelines. Emerging data suggests that advanced adenomas in the family carry a familial risk similar to an established cancer.

References

1. *Vasen HFA, Bianco I, Aktan-Collan et al. Revised guidelines for the clinical management of Lynch Syndrome (HNPCC): Recommendations by a group of European experts. Gut 2013;62(6)812-23*
2. *Ladabaum U, Ford JM, Martel M, Barkun AN. American Gastroenterological Association technical review on diagnosis and management of Lynch Syndrome. Gastroenterology 2015; 149: 783-813.*
3. *Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW. ACG Clinical Guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. American J of Gastroenterology 2015;110(2): 223-263*
4. *Giardiello FM, Allen JI, Axilbund JE et al. Guidelines on the genetic evaluation and management of Lynch Syndrome: a consensus by the US Multi-Society Task Force on colorectal cancer. Gastroenterology 2014; 147: 502-526.*
5. *Van Leerdam ME,RoosVH, van Hooft JE et al. Endoscopic management of polyposis syndromes: European Society of Gastrointestinal Endoscopy guideline. Endoscopy 2019; 51: 877-895*
6. *New South Wales Cancer Institute. eviQ Guidelines. www.eviQ.org.au*
7. *www.nice.org.uk/guidance/dg27*
8. *Yurgelun MB, Allen B, Kaldate RR et al. Identification of a variety of mutations in cancer predisposition genes in patients with suspected Lynch Syndrome. Gastroenterology 2015; 149: 604-13.*
9. *Snowsill T, Coelho H, Huxley N, Jones-Hughes T, Briscoe S, Frayling I et al. Molecular testing for Lynch Syndrome in people with colorectal cancer systematic reviews and economic evaluation. Health Technol Assess. 2017; 21(51): 1-238*
10. *Broeke ten SW, Brohet RM, Tops CM, van der Klift HM, Velthuizen ME, Bernstein I et al. Lynch Syndrome caused by germline PMS2 mutations :delineating the cancer risk. Journal of Clinical oncology 2015;33(4): 319-25.*
11. *Dominguez-Valentin M, Sampson JR, Seppala TT et al. Cancer risks by gene, age and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genetics in Medicine 2019 https://doi.org/10.1038/s41436-019-0596-9.*
12. *Van der post RS, Vogelaar IP, Cairneiro F et al. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 carriers. J Med Genetic 2015; 52: 361-74*

How Should We Monitor Patients with Adenoma?

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Introduction

There is compelling evidence that screening for colorectal cancer (CRC) can reduce both CRC incidence and mortality. Detection and removal of adenomas can reduce CRC mortality and as some patients with adenomas are at risk for subsequent CRC, adenoma surveillance after polypectomy is recommended (1).

The primary aim of surveillance after polypectomy is to prevent incidence and mortality from CRC in an individual who, by virtue of having adenoma(s), may have a higher than average risk of CRC. The evidence that we achieve these aims with surveillance after high-quality screening remains uncertain. Much of the benefit of colonoscopy either as a primary screening test or after a positive FIT, may be due to detection and removal of neoplasia at the baseline examination. The additional benefit of surveillance is not certain. Nevertheless, as more screening occurs, more patients with adenomas are identified, and these individuals become candidates for surveillance. Currently, about 25% of colonoscopies in the United States are performed for polyp surveillance.

Most surveillance recommendations have been based largely on studies which assessed the risk of developing high-risk adenomas (HRA), defined as adenomas >10mm, or with villous histology or high-grade dysplasia. New evidence of the risk of CRC after colonoscopy and polypectomy is now available which provides a more compelling rationale for risk stratification of patients with adenomas, with the aim of preventing post-colonoscopy CRC (PC-CRC). Surveillance recommendations were updated by the Multi-society task force on CRC (MSTF) in 2019 (2).

Why do patients develop colorectal cancer after colonoscopy?

Surveillance is driven by concern for development of CRC after colonoscopy and polypectomy. We have assumed that individuals with adenomas may have genetic predisposition and/or contributing life-style risk factors for CRC, which lead to development of adenomas, and such individuals may develop neoplasia again. This hypothesis formed the basis for initiating intensive, frequent surveillance back in the 1970's. We now understand that risk of CRC after colonoscopy may be due to several factors, and that many patients do not need frequent follow-up. The first, and perhaps most important factor, is the quality of the baseline examination, which includes the completeness of the exam and the quality of the bowel prep. One key metric of colonoscopy quality is the adenoma detection rate (ADR). There is an inverse relationship between the ADR and the risk of PC-CRC (3). There is further evidence that improvement in ADR results in reduction in PC-CRC (4). Failure to detect and/or failure to completely remove adenomas may be associated with higher risk of PC-CRC, and likely accounts for more than 50% of PC-CRC. A second factor in PC-CRC is the biology of the lesion. Patients who harbor HRA are more likely to develop new advanced lesions in a short time period, compared to those who have a negative exam or low risk adenomas (LRA) defined as 1-2 tubular adenomas less than 10mm. Therefore, rational surveillance should be based both on the quality of the baseline exam and the biology of the baseline findings.

Recommendations for Adenoma Surveillance (Table 1)

The cornerstone of the recommendations is the performance of a high-quality baseline colonoscopy, defined as:

1. Complete exam to cecum with documentation
2. Adequate bowel prep to detect lesions >5mm
3. High-quality endoscopist meeting or exceeding ADR benchmarks for screening exams (age greater than 50 years) of 20% for women and 30% for men
4. Complete polyp resection with documentation of polyp size.

Ideally, surveillance intervals should be based on the risk and timing of developing CRC after baseline colonoscopy. We now have strong evidence with CRC outcomes to inform some of our recommendations (2).

How Should We Monitor Patients with Adenoma?, continued

1. No adenoma at baseline:
   Two recent studies show that individuals with no adenomas at baseline, enjoy a reduced risk of CRC (by 45-56%) compared to an unscreened population, which is durable for at least 15 years (5,6). This forms the basis for recommending a 10 year interval after a high-quality baseline exam.
2. Low-risk adenomas (LRA) at baseline (defined as 1-2 tubular adenomas less than 10mm):
   A Norwegian cohort study (7) and three large American studies (8-10) find that the risk of CRC after removal of LRA is low, and statistically similar to the risk in patients with no adenoma. These data form the basis for recommending follow-up at 7-10 years after the baseline exam.
3. High-risk adenomas (HRA) at baseline (defined as adenoma(s) greater than or equal to 10mm, or adenoma (s) with villous histology or high-grade dysplasia):
   Several new studies (7-10) demonstrate that individuals with HRA have a higher risk of CRC during follow-up (compared to those with no adenoma or LRA). The odds ratios for incident CRC vary from 1.7 to 5.2 across several studies. In one study (8), the risk of fatal CRC was higher in patients with baseline HRA. Among patients with baseline HRA, there is a higher risk of CRC within 5-10 years after baseline colonoscopy (9), and a higher risk of incident recurrent HRA within 3-5 years of a baseline exam with HRA. These studies are consistent, and provide the strongest evidence to date, to justify

Table 1: *Summary of 2019 Surveillance Recommendations*

Conventional Adenomas

Most significant Baseline Colonoscopy Finding	2019 recommendation for next exam	Strength of new evidence compared to 2012
No adenoma	10 years	Stronger
1-2 tubular adenomas <10mm	7 to 10 years*	Stronger
3-4 tubular adenomas <10mm	3 to 5 years*	Stronger
5-10 adenomas	3 years	Strong, Similar
10+ adenomas	1 year	Weak, similar
Tubular adenoma ≥10mm	3 years	Stronger
Adenoma with villous histology	3 years	Stronger
Adenoma with HGD	3 years	Stronger
CRC	1 year	Strong, Similar

* Change from 2012 recommendation

Sessile Serrated Polyps (SSP)

Baseline Finding	2019 recommended interval	Evidence is similar to 2012
Hyperplastic polyps in rectum or sigmoid colon <10mm	10 Years	Moderate, no new evidence
Hyperplastic polyps proximal to the sigmoid colon < 10mm	10 years	Weak
1-2 SSP <10mm with no dysplasia	5 to 10 years*	Weak
3-4 SSP <10mm	3 to5 years*	Weak
5-10 SSP <10mm	3 years	Weak
Serrated polyp >10mm or with dysplasia or Traditional serrated adenoma	3 years	Weak
Serrated Polyposis	1 year	Strong
Classic Hyperplastic polyp >10mm	3 to 5 years	Weak

intensive early surveillance at 3 years after baseline, when detection and removal of HRA may prevent the development of CRC. A study from the UK demonstrated better outcomes (cancer mortality) in patients with HRA who had surveillance, compared to a cohort without surveillance (11). This is one of the first studies to demonstrate that surveillance actually improves patient outcomes.

Other recommendations are based on moderate or weak evidence, and summarized in Table 1.

1. Polyp multiplicity
   Prior work has shown that individuals with 3 or more adenomas had an increased risk of developing HRA during surveillance, which was the basis for recommending a 3 year interval for repeat colonoscopy. There is some evidence now (2,8), that the finding or 3 or 4 small (<10mm) tubular adenomas may not be associated with greater risk than finding 1 or 2 adenomas. It is quite possible that with high-definition endoscopy and higher quality colonoscopy, more patients with multiple small polyps are now detected, who may not be at high risk.

2. Serrated Polyps
   Few studies have evaluated the natural history of patients with serrated polyps. Several patterns are emerging, but evidence is still weak. Patients who develop PC-CRC are more likely to have CRC in the proximal colon, with characteristics of the serrated polyp pathway (CPG island methylation, microsatellite instability). These findings in PC-CRC have raised two concerns. The serrated pathway may be associated with silencing of a mis-match repair gene (MLH-1), raising concern that progression from polyp to cancer might be accelerated, as it is in Lynch syndrome. The second concern is that serrated polyps are notoriously difficult to detect at colonoscopy, and missed lesions might explain some of the PC-CRCs. Small (<10mm) serrated polyps without dysplasia are probably low-risk lesions, whereas those with large (>10mm) serrated polyps, serrated polyps with dysplasia or traditional serrated adenomas have a higher risk of developing HRA or CRC during surveillance (9). There is some debate about the risk associated with "hyperplastic" polyps >10mm. One concern is that these polyps are part of the serrated polyp family, and could be misclassified by pathologists. Lacking

Table 2: *Timing of 2nd Surveillance Exam*

Baseline Finding	**Recommended interval for 1st Surveillance Exam**	**Finding on 1st surveillance exam**	**Recommended interval for 2nd surveillance exam**
1-2 TA <10mm	7 to10 years	Normal exam**	10 years
		1-2 TA <10mm	7 to 10 years
		3-4 TA	3 to5 years
		HRA***	3 years
3-4 tubular adenomas <10mm	3 to 5 years	Normal exam	10 years
		1-2 TA <10mm	7 to 10 years
		3-4 TA <10mm	3 to 5 years
		HRA	3 years
HRA***	3 years	Normal exam	5 years
		1-2 TA <10mm	5 years
		3-4 TA <10mm	3 to5 years
		HRA	3 years

* TA = Tubular adenoma
** defined as absence of adenoma, SSP or CRC
*** defined as adenoma >10mm or with villous histology or high-grade dysplasia

good studies of natural history, the recommendations for surveillance of serrated polyps are cautious because of the concerns about PC-CRC, but are based on weak evidence.

3. Piecemeal resection of polyps >20mm.
   There is moderate evidence that supports repeating the exam at short (<1 year) interval to assure that resection was complete.

Surveillance after the baseline exam and first surveillance exam has been studied, and recommendations are summarized in Table 2. It must be noted that the existing recommendations are based on the risk of HRA, not CRC after the first surveillance exam. The key principle emerging from multiple studies is that the finding of a HRA at any point along the screening-surveillance continuum, is associated with a higher risk of developing subsequent HRA (2). Therefore an individual with a HRA at baseline, and a negative exam at 3 years, should have follow-up every 5 years thereafter, which is similar to recommendations for patients with prior CRC.

Areas for further study

There are many areas of uncertainty in the management of patients after detection of adenomas that require further study.

1. Importance of colonoscopy quality.
   As colonoscopy quality improves, intensity of surveillance might be modified. For example, if a "high-detector" with excellent ADR detects 5 small tubular adenomas, it is quite possible that that patient may be a low-risk patient. As more endoscopists measure and improve their quality, it is quite possible that rates of missed lesions or incompletely removed lesions will decline and that intervals can be safely extended.
2. Risk factors for CRC
   At this time, the most significant risk factors for PC-CRC are colonoscopy quality and the biology of the baseline polyp(s). Other factors such as smoking, BMI, NSAID use or family history of adenoma could mitigate risk during surveillance, and have not been carefully studied.
3. Family history of CRC or advanced polyps
   It is not clear if individuals with a family history of CRC, who are themselves found to have adenomas, need more intensive surveillance because of the family history. Currently, no guidelines recommend this, but further study would help clarify this question.
4. Role of intermediate testing
   PC-CRC which occurs in the first few years after baseline colonoscopy is most likely related to the quality of the baseline exam. Colonoscopy is an imperfect test even in expert hands. It is possible that supplementation of colonoscopy with an intermediate non-invasive test such as FIT or multi-targeted stool DNA could improve outcomes. This hypothesis has not yet been tested.
5. Recommendations for surveillance are often not followed. Future study should determine if adherence to recommended surveillance intervals does reduce incidence and mortality of CRC.

Summary

There is now strong evidence for risk stratification of patients with adenomas, based on the likelihood that such patients will subsequently develop CRC. Individuals with HRA should have intensive surveillance, whereas those with LRA need infrequent surveillance. The foundation of any surveillance program is the performance of a high-quality baseline colonoscopy by endoscopists who accurately detect and completely remove adenomas. As colonoscopy quality continues to improve, it is quite possible that individuals with only LRA will require little or no surveillance.

References

1. *Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for colonoscopy surveillance after screening and polypectomy: A consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2012; 143: 844-857*

2. *Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kalternbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK.* **Recommendations for follow-up after colonoscopy and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2019 in press. https://doi.org/10.1053/j.gastro.2019.10.026**

3. *Corley DA, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med 2014;370:1298-306.*

4. *Kaminski MF, Wieszczy P, Rupinski M, et al. Increased Rate of Adenoma Detection Associates With Reduced Risk of Colorectal Cancer and Death. Gastroenterology 2017;153:98-105.*

How Should We Monitor Patients with Adenoma?, continued

5. *Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med 2013;369:1095-105.*
6. *Lee JK, Jensen CD, Levin TR, et al. Long-term Risk of Colorectal Cancer and Related Deaths After a Colonoscopy With Normal Findings. JAMA Intern Med. doi:10:1001/jamainternmed.2018.5565. Published online December 17, 2018*
7. *Løberg M, Kalager M, Holme Ø, et al. Long-term colorectal-cancer mortality after adenoma removal. N Engl J Med 2014;371:799-807.*
8. *Click B, Pinsky PF, Hickey T, et al. Association of Colonoscopy Adenoma Findings With Long-term Colorectal Cancer Incidence. Jama 2018;319:2021-2031.*
9. *He X, et al. Long-term risk of colorectal cancer after removal of conventional adenomas and serrated polyps. Gastroenterology 2019; doi.https://doi.org/10.1053/j.gastro.2019.06.039*
10. *Lieberman et al; Baseline colonoscopy findings associated with 10 year outcomes ina screening cohort undergoing colonoscopy surveillance. Gastroenterology 2019; doi: https://doi.org/10.1053/j.gastro.2019.07.052*
11. *Atkin W, Wooldrage K, Brenner A, et al. Adenoma surveillance and colorectal cancer incidence: a retrospective, multicentre, cohort study. Lancet Oncol 2017;18:823-834.*

How Should We Monitor Patients with Inflammatory Bowel Diseases?

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Chronic inflammatory bowel diseases (IBD) have been linked to increased colorectal cancer risk. In a recent meta-analysis including 54.478 patients with ulcerative colitis from 116 studies, the overall prevalence of CRC was reported to be 3.7% (1). The cumulative incidence of developing CRC increased from 2% by 10 years, to 8% and 18% by 20 and 30 years, respectively. However there are conflicting reports with regard to cancer risk. Accordingly, a study from Denmark with more than 2000 patients with ulcerative colitis or Crohn's disease showed no increased cancer risk in ulcerative colitis patients. In contrast patients with Crohn's disease had an overall 55 % increased risk of cancer, with a 15-fold risk for small bowel cancer and 3.4-fold increased risk for colorectal cancer (2).

There is considerable discussion whether this risk has decreased over time. The improved treatment modalities and increasing surveillance strategies may contribute to a decreasing incidence overall. In a recent meta-analysis with 5 studies and 7199 patients the odds of colon cancer development were reduced by 42% and the odds of death associated with colon cancer was reduced by 64% in patients undergoing surveillance versus patients without surveillance pointing to a beneficial effect of surveillance endoscopy (3).

While the overall risk seems low and probably declining in the last decades, there are a number of risk factors which are clearly linked to an increased cancer risk in this population. Young age at onset of IBD, duration of active disease, the degree of inflammation and presence of dysplasia and/or strictures, family history of cancer and the coexistence of primary sclerosing cholangitis (PSC) have been linked to an increased cancer risk (Table 1).

Albeit there are no randomized trials demonstrating the benefit, and a 2006 Cochrane review fail to demonstrate that surveillance endoscopy improves survival in patients with extensive colitis, it is generally accepted that surveillance endoscopy should be offered to IBD patients. Accordingly, the American Gastroenterological Association, the American Society of Gastrointestinal Endoscopy, the German and British Societies of Gastroenterology and the European Society of Gastrointestinal Endoscopy all endorse surveillance endoscopy in patients with IBD. The European's Crohn's and Colitis Organisation (ECCO) also concludes that the risk of colorectal cancer in ulcerative colitis is increased compared

Table 1. *Definition and follow up intervals of risk groups with IBD*

Risk Groups	Definition	Follow-Up
Low risk	• extensive but quiescent ulcerative colitis ***or*** • extensive but quiescent Crohn's colitis ***or*** • left-sided ulcerative colitis (but not proctitis alone) ***or*** Crohn's colitis of a similar extent.	5 years
Intermediate risk	• extensive ulcerative or Crohn's colitis with mild active inflammation that confirmed endoscopically / histologically or • post-inflammatory polyps or • family history of colorectal cancer in a first-degree • relative < 50-year of age	3 years
High risk	• extensive ulcerative or Crohn's colitis with moderate • or severe active inflammation confirmed endoscopically/histologically or • primary sclerosing cholangitis (including after liver transplant) or • colonic stricture in the past 5 years or • any grade of dysplasia in the past 5 years or • family history of colorectal cancer in a first-degree relative < 50-year of age	1 year

with the general population and surveillance endoscopies are recommended (4). All organisations confirm that the risk is especially increased in patients with longer disease duration, larger extent of disease and increased inflammatory activity. Furthermore, the presence of PSC and family history of colorectal cancer confer additional risks.

However, there is considerable debate over the timing and frequency of surveillance endoscopy, whether it should be offered to all IBD patients, or whether surveillance should be based on risk assessment. Based on the risk factors a stratified surveillance programme for these patients seems feasible and has been recommended by the British Society of Gastroenterology and the European's Crohn's and Colitis Organisation (ECCO) (4).

In general, the guidelines recommend surveillance via colonoscopy to all patients with ulcerative colitis (pancolitis/ left-sided colitis) and Crohn's colitis (involving > one-third of colon) 10 years after onset of symptoms. In accordance with this guideline, ECCO concludes that these patients should be screened, however, in patients with rectal involvement a regular surveillance programme is not necessary. Accordingly, ECCO recommends screening colonoscopy in all patients (except those with rectal involvement only) 8 years following onset of symptoms to assess disease extent and exclude dysplasia.

Furthermore, in all patients with concomitant PSC annually surveillance is recommended starting from the time PSC has been diagnosed. Subsequent surveillance colonoscopies are recommended based on risk stratification, with intervals of 5 years (low risk), 3 years (intermediate risk) and 1 year (high risk) (Table 1). The risk groups are defined as follows: a) Low Risk: extensive but quiescent ulcerative colitis or Crohn's colitis or left sided ulcerative colitis (not proctitis alone) or Crohn's colitis at similar extent; b) Intermediate Risk: extensive ulcerative or Crohn's colitis with mild active inflammation (confirmed endoscopically or histologically), post-inflammatory polyps, family history of colorectal cancer in a first-degree relative 50 years or over; c) High Risk: extensive ulcerative or Crohn's colitis with moderate or severe active inflammation that has been confirmed endoscopically or histologically, presence of primary sclerosing cholangitis (including after liver transplant), colonic stricture in the past 5 years, any grade of dysplasia in the 5 past years or family history of colorectal cancer in a first-degree under 50 years (5,6).

Surveillance endoscopies should only be performed during clinical remission and after extensive bowel preparation. Regarding the technique of surveillance endoscopy there are two options that have been recommended. Traditional white light endoscopy may still be used with 2-4 random biopsies taken every 10 cm. While this technique is time consuming and laborious, international guidelines still advocate for this surveillance technique. Recent guidelines strongly recommend using chromoendoscopy (using either a non-absorptive blue contrast agent or an absorptive stain i.e. methylene blue or indigo-carmine) with targeted biopsies. So far there is convincing evidence that this targeted approach in combination with chromoendoscopy increases the detection rate of dysplastic lesions up to 4.5-fold. A recent meta-analysis combined the findings from 6 studies with more than 1200 patients demonstrated that the detection rate of dysplasia in chromoendoscopy versus white light endoscopy was 7% improvement (number needed to treat (NNT) was 14.3). The absolute difference in lesions detected by targeted biopsies was 44%, and flat lesions was 27%, both in favour of chromoendoscopy (7). Differentiating chronic inflammatory changes from early dysplastic lesions remains a challenge. The disadvantage of chromoendoscopy with targeted biopsies are the increased time needed for the procedure, additional costs for consumables and experience in detecting suspicious mucosal lesions. So far there is no convincing evidence that narrow-band imaging enhances the rate of detection of dysplastic lesions in patients with chronic inflammatory bowel disease. Other options, such as confocal laser endomicroscopy, are attractive options, however, to date have not been recommended for routine purposes. Accordingly, the SCENIC International Consensus Group recommend performing surveillance colonoscopy with chromoendoscopy and not using narrow-band imaging for surveillance (8). For the management of large lesions, non-polypoid lesions and endoscopically invisible dysplasia, referral to experienced tertiary centers is recommended.

Conclusion

Overall the risk of colorectal cancer increases after 8-10 years of active disease in patients with ulcerative colitis and Crohn's disease. The need for surveillance is agreed upon all major gastroenterological societies, despite a lack of randomized controlled trials demonstrating superiority of surveillance endoscopy versus observation. Nonetheless patients are recommended to undergo surveillance colonos-

copy 8-10 years after onset of symptoms. Most guidelines recommend to stratify follow-up exams according to risk factors with follow-up intervals at 1, 3 or 5 years respectively. The recommended surveillance technique is chromoendoscopy with targeted biopsies. White light endoscopy with random biopsy is still allowed when chromoendoscopy is not available.

References

1 *Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001;48:526-35.*

2 *Ibraheim H, Dhillon AS, Koumoutsos I, Gulati S, Hayee B. Curriculum review: colorectal cancer surveillance and management of dysplasia in IBD. Frontline Gastroenterol 2018;9:271-277.*

3 *Bye WA, Nguyen TM, Parker CE, Jairath V, East JE. Strategies for detecting colon cancer in patients with inflammatory bowel disease. Cochrane Database Syst Rev 2017;9:CD000279.*

4 *Magro F, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, Burisch J, Gecse KB, Hart AL, Hindryckx P, Langner C, Limdi JK, Pellino G, Zagórowicz E, Raine T, Harbord M, Rieder F; European Crohn's and Colitis Organisation [ECCO]. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. J Crohns Colitis 2017;11:649-670.*

5 *Boland BS, Shergill A, Kaltenbach T. Endoscopic Surveillance in Long-standing Colitis. Curr Treat Options Gastroenterol 2017;15:429-439.*

6 *Abraham BP. Cancer surveillance in ulcerative colitis and Crohn's disease: new strategies. Curr Opin Gastroenterol 2016;32:32-7.*

7 *Subramanian V, Mannath J, Ragunath K, Hawkey CJ. Meta-analysis: the diagnostic yield of chromoendoscopy for detecting dysplasia in patients with colonic inflammatory bowel disease.* Aliment Pharmacol Ther *2011;***33***:304–12.*

8 *Laine L, Kaltenbach T, Barkun A, McQuaid KR, Subramanian V, Soetikno R; SCENIC Guideline Development Panel. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. Gastroenterology 2015;148:639-651.*

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Early Diagnosis and Treatment of GI Cancer

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