Role of GI-endoscopy for the screening of digestive tract cancers in Europe.
European Society of Gastrointestinal Endoscopy (ESGE) **Position Statement**

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Summary of sentences

- *In Europe, both currently and in 2040, 1 of 3 cancer-related deaths are expected to occur due to digestive cancer. Endoscopic technologies enable at a relatively low invasiveness to diagnose precancerous conditions and early cancers, improving patients survival. Overall, endoscopy capacity must be adjusted to facilitate effective screening programs and rigorous control of quality assurance and surveillance programs required.*

- *For **average-risk population**, ESGE recommends the implementation of organized population-based programs for **colorectal cancer** screening based on faecal immunochemical test (FIT) targeting individuals, irrespective of gender, aged between 50 and 74 years. Depending on local factors, namely adherence of target population and endoscopy services, primary screening by colonoscopy (or sigmoidoscopy) may also be recommendable. For **gastric cancer**, endoscopic screening should only be considered in **high-risk areas**, for individuals with more than 40 years, while its use in **countries / regions at intermediate risk** should be based on local setting and availability of endoscopic resources.*

- *Endoscopic screening for **esophageal cancers or pancreatic cancer must only be considered in high-risk individuals or patients (opportunistic):** for squamous-cell carcinoma, in those with personal history of head-neck cancer, achalasia or previous caustic injury; for Barrett's associated adenocarcinoma for those with longstanding GERD symptoms (i. e. > 5 years) and multiple risk factors (age ≥ 50 years, white race, male sex, obesity, first-degree relative with BE or EAC.); and for pancreatic cancer screening, EUS may be used in those with a history of familial pancreatic cancer (with an affected first degree-relative) and inherited genetic syndromes.*

Introduction

Mostly due to an aging population and environmental risk-factors, gastrointestinal (GI) cancers represent a significant burden for Europen citizens with one fourth of all the malignancies diagnosed in Europe. It may be estimated that 600,000 cases of GI-cancer and 360,000 related deaths per year occur in European Union (1). Moreover, when diagnosed in a symptomatic phase, most GI-cancers are still associated with dismal prognosis. Five-year survival, as estimated in 2000-2007, was 41% overall, varying according to site of diagnosis: 12% for esophagus, 24% for stomach, 48% for colorectum, and 6% for pancreas (1). In addition, late-stage cancers represent an economic and financial burden due to palliative treatment and new biological treatment for advanced disease.

A better understanding on the natural history of GI-cancers showed that most of them are preceded by slowly progressing precancerous conditions or lesions, as well as by early invasive stages, leading to the opportunity for effective interventions. Beyond the classic adenoma-carcinoma sequence for colorectal carcinogenesis, similar pathways based on metaplasia-dysplasia-cancer progression have been shown for upper-GI as well as pancreatic-cancer. In addition, advances in genetic factors led to the identification of the pathogenetic mutations responsible for familial GI-cancer syndromes.

Within this scope, endoscopic techniques applied to the GI tract, ie, gastrointestinal endoscopy, represent a set of unique technologies for cancer early detection and potential intervention in precancerous conditions/lesions. In fact, whenever possible, endoscopic resection of precancerous and early invasive lesions have been associated with incidence prevention and very high 5-year survival rates, being less invasive, usually preferred by patients and less costly than surgical treatments Moreover, endoscopic and histological diagnosis of precancerous conditions leads to an effective risk stratification of the endoscopic population, appropriately adjusting surveillance protocols to those high-risk patients that may benefit the most.

With the current position statement, ESGE board wishes to summarize its position regarding the current role of endoscopy in the screening of the diverse gastrointestinal neoplasms and to support the role of digestive endoscopy in cancer incidence and mortality reduction. Outside the scope of this will be the discussion of organization of screening programs as also other alternatives to endoscopy will be discussed in brief. In fact, even though substantial development in our own field and significant and relevant evidence to show the impact of endoscopy as briefly stated above, the awareness by other stakeholders may lead to underuse or poor allocation of resources to health facilities involved in providing screening services, thus affecting patients' benefits that could be achieved.

Methods

In 2017, the European Society of Gastrointestinal Endoscopy (ESGE) governing board established a task force (Public Affairs Working Group led by AS) to assemble a position statement concerning the value of endoscopy for screening purposes in GI cancers. The most prevalent digestive cancers (esophageal squamous cell carcinoma, esophageal adenocarcinoma, gastric carcinoma, colorectal cancer and pancreatic cancer) were considered.

Using a structured PICO framework, detailed literature searches were performed by an expert task force and yielded results, through a modified Delphi process, summarized in recommendations / statements. The PICOs were defined regarding the role in terms of prevention, survival and cost-effectiveness (O) when using digestive endoscopy technologies (upper gastrointestinal endoscopy, colonoscopy and EUS) (IC) in two different settings (P) - for the average risk population versus high-risk groups or settings defined as geography, ethnicity, individual exposures or family history, except for specific management of individuals with known hereditary colorectal cancer syndromes or precancerous gastric lesions.(2,3)

Epidemiological data were taken from online databases available from international studies. European incidence and mortality data in 2018 are pooled national estimates provided by Joint Research Center and European Network of cancer registries (4). Incidence time trends in 2004-2010 are based on observed rates from a pool of population-based cancer registries and available from the same database. Histotype-specific data for esophageal cancer were available from the RARECARENet database on incidence and survival of rare tumors in Europe (5). Survival data were download from the EUROCARE-5 project database (6).

Role of digestive endoscopy for average risk population: colon and gastric cancer

1. ***For average-risk population, irrespective of gender, ESGE recommends the implementation of organized population-based programs for colorectal cancer screening based on faecal immunochemical test (FIT) targeting individuals aged between 50 and 74 years. Depending on local factors, namely adherence of target population and endoscopy services, primary screening by colonoscopy may also be recommendable.***

Frequency and pathogenesis
Colorectal cancer (CRC) represents the second cause of morbidity and mortality in Europe with an estimated number of 380,000 and 175,000 new cases and related deaths in 2018 (7). CRC is uniquely suited for screening programs as compared to other GI-cancer because it detects precursor lesions that can be resected (adenomatous polyps) thus decreasing the incidence and prevalence of CRC, with a consequent reduction in the mortality rate.

Target-population
Most of the screening programs include the population between 50 and 74 years. Such range may vary according to availability of resources. In the US, the target group has expanded to individuals aged 45 and above, due to the increased incidence of CRC in young adults. Same trend is seen in Europe over the last 25 years (8).

Role of endoscopy (sigmoidoscopy and colonoscopy)
Screening of average-risk subjects by fecal occult blood tests (followed by colonoscopy for positive cases) and primary lower-GI endoscopy (either colonoscopy or sigmoidoscopy) can reduce CRC-related incidence and/or mortality significantly (9,10). This is the result of two effects, namely down-staging of already prevalent CRC by anticipation of diagnosis, and prevention of the development of CRC by removal of precancerous polyps.
For guaiac FOBT the evidence is based on 4 RCTs showed an overall 24% reduction in CRC mortality among subjects undergoing screening (10). As FIT has a 2-3 fold higher sensitivity for detecting advanced neoplasia than the guaiac-based test, a greater effect of FIT-based screening is expected (11). The efficacy of a primary sigmoidoscopy screening is supported by four RCTs showing an overall 21% and 28% reduction in CRC incidence and mortality for those undergoing screening [the protective effect ranging between 38% and 43% for mortality and between 31% and 33% for incidence (12,13)].
The efficacy of colonoscopy screening is long-lasting (14) and the test may be performed once-in-a-life time (15,16). However, the long-term efficacy in preventing CRC has been associated with its quality, as reported in the dedicated ESGE document (17). To assess colonoscopy screening, only observational studies are available, estimating a reduction in CRC incidence and mortality of 69% and 68%, respectively(9). Moreover, for opportunistic screening, population coverage for CRC screening remains disappointingly low. Recently, it was estimated that only a small minority (0.4-4%) of the European population underwent a colonoscopy in the last 10 years, as compared with over 60% in the United States (18). This is likely to be related with multifactorial barriers, including personal beliefs (e.g. lack of awareness or fear of the screening

test), organizational issues (e.g. lack of recommendation by primary care physicians), and financial barriers (19).
In Europe, most countries have in fact implemented organized invitational screening programs basedon fecal occult blood tests (20). The main advantages of organized versus opportunistic screening are represented by active invitation of all eligible subjects and the implementation of quality assurance programmes. Besides, there is a potential to send reminders to increase participation and to proactively remove any organizational barrier for patients to navigate throughout all the screening process. When compared to non-organised settings, organized programs have also been shown to result in a high compliance with follow-up of those with a positive primary screening and high adherence in subsequent screening rounds of those with a negative test(21). Organized screening programs require however several resources. One of the most challenging aspects of an organized program is the heavy burden on the available endoscopic capacity and the high costs. The most reasonable solution for this problem would be to proportionally increase the number of endoscopists in order to match the additional burden of colonoscopies for the screening program, including surveillance thereafter (22,23). Besides, to prevent unnecessary extra colonoscopies due to inappropriate indications, surveillance guidelines should be strictly followed (24). As mentioned above, organized programs require complex organizational activities that, when considering the large variability in the structure of the different health systems, are not necessarily available in all European countries. Indeed, some regions or countries in the EU have not yet implemented screening programs (25). In these countries, average-risk patients may exceptionally apply for a case-by-case or 'opportunistic' non-organized screening method for CRC prevention. Although having implemented CRC screening, the actual coverage of the target population by invitation showed a wide variability across the member states, ranging between 1.5% and 100%. Equally, participation rates vary widely across EU countries, resulting in an actual screening coverage of 19.8% for the entire 50 to 74 target age range in population based programs, and 25.1% in the age range targeted by the programs (26). Although underestimated (as several programs could not provide adequate data about opportunistic screening activities), the corresponding figure for non-population based programs was as low as 4.2% (9).

Cost-effectiveness
Convenience of population-based CRC screening has been shown in several simulation models. In particular, such screening has been demonstrated to be cost-saving, or cost-neutral, due to the substantial decrease in the expenditure for CRC treatment, including biological therapy, achieved by CRC incidence prevention and down-staging of already prevalent cancers (27).

Surveillance for subjects at increased risk of CRC due to personal or family CRC history has been addressed in previous ESGE guidelines.

2. ***Annual or biannual endoscopic screening for gastric cancer should be considered only in high-risk areas, while its use in those at intermediate risk should be based on local setting and availability of endoscopic resources.***

Epidemiology
Gastric cancer is the 5th most common malignancy and the 3rd leading cause of cancer death worldwide (28). Gastric cancer is decreasing in developed countries, but it is still responsible of

about 80,000 new cases per year in EU, with an incidence rate of 16x100,000 per year. Even though gastric cancer can be early recognized and treated, most of the cancers are still being late diagnosed, with an overall 5-years' survival of 24%; nevertheless, mortality might be improved in around 40% with early detection by means of screening (29,30).
Gastric cancer screening is intended for the intestinal type of gastric cancer, that represents more than 95% of all gastric cancers, as it is the final stage of the sequence inflammation–metaplasia–dysplasia–carcinoma (known as the Correa cascade) (30). The diffuse type of gastric cancer has a different carcinogenesis sequence; as so, screening is not indicated. Nowadays, screening for the intestinal type of gastric cancer is only being performed in countries with a high disease incidence (defined as an age-standardized rate ≥20 per 100,000), such as Japan or South Korea (29.9 and 41.3, respectively) (31,32). Screening enables to detect gastric cancer at earlier stages, eventually even as early gastric cancer, defined as carcinomas limited to the mucosa or submucosa, regardless of lymph node involvement; thus, lesions amenable to curative endoscopic treatment, such as endoscopic submucosal dissection (33,34).

Target population
All screening studies are from Asia and most used the range from 40 to 80 years-old since most gastric adenocarcinomas are diagnosed after the age of 40 years. This is similar (although wider) to the 50 to 75 years-old range of the European colorectal cancer screening recommendation(29,35).
Family history, pernicious anaemia, previous partial gastrectomy or other subgroups of patients are out of the scope of the present statement and shoud follow specific recommendations.

Role of endoscopy (upper GI endoscopy)
In high-risk areas (defined as having an age-standardized rate ≥20 per 100,000), endoscopy has a clear role for primary screening. The interval between negative exams varies among studies but most reported annual or biennial endoscopies(29). Also in these regions, either serologic screening based on pepsinogen testing was promoted and its effectiveness demonstrated(36–38).
For the regions with an age-standardized mortality rate for gastric cancer <10 per 100,000, endoscopic screening is not recommended for the entire population (39).
For the intermediate risk regions, between 10 and 20 per 100,000, endoscopy may have a role for primary screening if the cost-effectiveness is proven in the respective country. The interval between negative exams might be every 5 years(40).

Cost-effectiveness
Several studies concluded that endoscopic screening is cost-effective in high incidence regions (41–45). Indeed, the two most recent studies, both for the Korean population, concluded that endoscopic screening is cost-effective. Studies indicated that either annual screening for male and biennial for female, for a population aged 50 to 80 years-old, as well as annual screening in patients aged above 40 years-old (44–46).
In Europe, one study compared 3 screening strategies: stand-alone upper endoscopy; endoscopy combined with a colorectal cancer screening colonoscopy after a positive faecal occult blood test; or pepsinogens serologic screening. It concluded that an endoscopic gastric cancer screening every 5 years was cost-effective only if combined with a screening colonoscopy (40). This means that in Europe, if a colorectal cancer screening programme is already in place (by means of faecal occult blood or stand-alone colonoscopy), all countries with an intermediate incidence

rate of gastric cancer such as Albania, Belarus, Macedonia, Russia, Latvia, Ukraine, Estonia, Lithuania, Portugal, Moldova, Romania, Slovenia, Bulgaria and Croatia (presented according to their ASR, from 20.1 to 10.3) might benefit by providing their populations a screening upper endoscopy in conjunction with colonoscopy. Although prospective studies on the use of pepsinogen as a screening method are ongoing in some European countries, its high cost and limited availability outside Asia are the main limitations from a cost-effectiveness and practical perspective; as so, they cannot be recommended at the moment (3,37).
In the East, three other studies concluded that an endoscopic mass screening every 2 years was only cost-effective in high risk subjects aged 50-70 years, with an odds ratio for cancer > 3.9, but not for the entire population(45,47,48).
Only two studies in low risk scenarios (America) were published and concluded that gastric cancer incidence would have to increase by 337% to become cost-effective (49,50).

Surveillance for subjects at increased risk of gastric cancer due to personal history of precancerous conditions or lesions has been addressed in previous ESGE guidelines.

Role of digestive endoscopy in high-risk settings

3. ***Endoscopic screening for squamous-cell carcinoma may be considered only in individuals at increased risk, such as those with head-neck cancer, achalasia or previous caustic injury or those with longstanding GERD symptoms (i. e. > 5 years)***

Epidemiology
Esophageal cancer is the 7th most commonly occurring cancer in men and 13th most common in women (51). Globally, SCC accounts for the majority of the cases of esophageal cancer although its ratio with adenocarcinoma varies country by country, being on average approximately one in EU. About 19,200 new SCC diagnoses per year were estimated in EU as of 2013. Over the past three decades, a consistent decline in the rates of esophageal SCC have been observed in Western Europe with a stable or slower decline in central European countries. On the other hand, an increase in SCC incidence has been reported in Eastern European countries. The decline in SCC incidence in Western Europe has been mainly attributed to the reduction in alcohol consumption and smoking habit. SCC survival is low, being 38% at 1 year and 12% at 5 years after diagnosis (5).

Target population
In moderate and lower risk Western countries, the most important risk factors are the combination of tobacco smoking and excessive alcohol consumption (52). Unlike adenocarcinoma, esophageal SCC is 3 to 5 times as likely among people who consume alcohol (3 or more drinks daily), and the risk increases synergistically with tobacco smoking. SCC screening in moderate and lower risk countries would include a too large population at risk and seems therefore impractical. Screening is therefore usually proposed to small subgroups of patients at very high risk, such as those with previous or concomitant diagnosis of head and neck

squamous cell carcinoma(53), achalasia (up to 10 times risk)(54), previous radiotherapy for breast cancer, history of head and neck cancer, previous caustic injury to the esophagus, and tylosis (55). There is no specific recommendation on the best timing to start screening for SCC. For high risk diseases, achalasia is a good example of absence of consensus, although the absolute risk increase for SCC was 308.1 per 100,000 patients per year, suggesting a strict endoscopic surveillance for these patients. But in practice, no consensus is reached between world experts on timing, with practices still varied with screening commencing at or within 1 year of diagnosis compared with 5 and 10 years. Surveillance intervals also varied, performed every 2-5 years(56).

Role of endoscopy

Precancerous dysplastic lesions are detectable using endoscopy and non-invasive screening methods, however routine screening is currently not recommended outside high risk areas or for low risk individuals **(57)**. Endoscopy remains the gold standard for diagnosis of dysplasia and early SCC but it is invasive and expensive, and therefore alternative approaches to broaden the test-population are of interest. Since serologic tests are not clinically available yet, other invasive but less costly tests are needed to diagnose SCC or premalignant lesions, such as exfoliative cytology **(58)**.

Cost-effectiveness

There are very few studies about cost-effectiveness of SCC screening, compared with Barrett's esophagus screening and surveillance. A cost-benefit analysis studied standard endoscopic screening strategies of esophageal cancer in high-risk areas of China. The authors found that, compared with no screening, all screening strategies with varying screening age, frequencies, and follow-up intervals could save more life years(59). A recent study used a decision-analytic Markov model to study the cost-effectiveness of incorporating high-resolution microendoscopy into an SCC screening program in China, with results showing that it could be cost-effective(60). There are no European studies suggesting that endoscopic screening for SCC is either necessary or cost-effective. The low incidence of SCC in the European population and the predominance of public health systems might be some of the main reasons why screening of this condition is not an option even in individuals with risk factors. Interestingly, if screening for SCC in the Western world was extended to Barrett's cancer, and gastric cancer combined, by performing a single upper endoscopy at the time of screening colonoscopy, it might be a cost-effective method to screen for multiple cancers simultaneously, with an incremental cost-effectiveness ratio comparing favorably with commonly performed screening strategies for other cancers(49).

4. Endoscopic screening for BE-AdCa may be considered only in individuals at increased risk, such as those longstanding GERD symptoms (i. e. > 5 years) and multiple risk factors (age ≥ 50 years, white race, male sex, obesity, first-degree relative with BE or EAC.), respectively.

Epidemiology

Esophageal cancer has a poor five-year survival of less than 15% (61,62). Moreover, there has been a striking increase in the incidence of esophageal adenocarcinoma (EAC) and associated death in most Western countries over the past thirty years(63,64). Barrett esophagus (BE) is a premalignant condition for the development of EAC, characterised by the replacement of the

normal squamous epithelium above the gastroesophageal junction with columnar epithelium (65,66). The prevalence of BE in general population has been estimated to be 1% to 2% (67,68). The annual risk of BE converting to EAC, after excluding the cases diagnosed during the first year, is 0.12% to 0.50% (69,70). Because of this pre-existing condition, EAC can potentially be prevented by screening for this precursor lesion.

Target population

Screening for BE or EAC by endoscopic and non-endoscopic methods is not recommended for the general population, because of the relatively low risk. The screening population needs to be enriched by high-risk individuals in order to be cost-effective **(71)**. Epidemiological studies have identified risk factors for BE and EAC. The main risk factors for BE are gastro-esophageal reflux disease (GERD), obesity, male sex, age and cigarette smoking **(64)**. GERD is the strongest established risk factor for BE and EAC, especially symptoms that are present for ten years are associated with development of EAC **(63,72)**. BE is more common in men than in women and among patients with BE, there is a 2-3 times higher transformation to EAC in men than women **(63)**. BE increases with age, and the risk becomes substantial in men after the age of 60 years who have GERD symptoms **(73)**. The presence of intestinal metaplasia (i.e. goblet cells) is a risk factor for evolution to neoplasia **(65)**, and a requirement to fulfill the ESGE definition of BE. Other risk factors for conversion from BE to EAC are the presence of dysplasia or long-segment Barrett **(65)**.

Screening age

In view of the abovementioned established risk factors, ESGE recommends endoscopic screening after the age of 50-60 years (according to local availability) for patients who have chronic GERD symptoms for more than 5-10 years**(74)**. The reason why screening high risk individuals might be beneficial lies in the epidemiological finding that the majority of esophageal cancers are detected at an advanced stage and that patients under surveillance for BE are detected at an earlier stage with better outcome in comparison to patients who were not under surveillance. Therefore, once the diagnosis of BE is confirmed, patients should be surveilled according to the existing guidelines until the age of 75, if no dysplasia is found, as reported in ESGE guideline.

Role of endoscopy

Although endoscopy might be the gold standard, it is invasive and requires staff and expensive equipment (75). Alternatively, ultrathin nasal endoscopy has been proposed as an alternative, with a good accuracy and patient's tolerance. It has been shown to be more cost-effective and to have a comparable sensitivity and specificity % for the endoscopic diagnosis of BE versus standard endoscopy (62,76–78). Video-capsules, specifically designed to allow imaging of the esophagus are available. They have a potential advantage over standard endoscopy in terms of tolerance, acceptability and need for sedation. However, they are quite expensive and studies showed unfavourable diagnostic characteristics with a sensitivity of 60-67% and specificity of 84-100% in detection of BE (68).

Cytosponge is the best studied non-endoscopic screening device to detect BE and allows risk stratification of patients in combination with biomarkers like p53. A soluble capsule, encasing a little sponge, is swallowed. After entering the stomach, the capsule is dissolved and the sponge is

recovered by an attached string. The cytology retrieved by Cytosponge is then immunostained for TFF3 (Trefoil factor 3), a protein coding gene(79). A trial of 1000 patients (BEST2) demonstrated a specificity of 92.4% and a sensitivity of 80% that increased to 87% for Barrett segments of ≥3 cm circumference. This is an accuracy comparable to current screening test for colorectal and cervical cancer (79). Although it is a safe method, given the lower sensitivity and specificity of non-endoscopic screening methods it is not indicated in screening yet and more studies are on the way to further validate it in a primary care setting.

Cost-effectiveness

Because of the low risk and incidence of EAC, screening of all individuals is not cost-effective. Even the cost-effectiveness of surveillance of BE is often questioned, since it largely depends on the incidence of neoplasia development in BE (80). Based upon a cancer incidence of 0.5% (70), surveillance is cost-effective every 5 years for nondysplastic BE and every 3 years for LGD in long-segment BE (81). In regions where the cancer incidence is lower, the usefulness of surveillance is questioned(62,69). One of the problems that compromises the cost-effectiveness of surveillance is the fact that most of the cancers are not detected during surveillance but at the time or within a year of the index endoscopy (69,70). A cost analysis using a micro-simulation model for the Cytosponge suggested that in comparison to endoscopy, it had an equal gain in quality of life years, but with a higher cost-effectiveness. When combined with endoscopic therapy, it was suggested that Cytosponge is cost effective in reducing EAC mortality (82).

Pancreatic cancer

> ***5. For pancreatic cancer screening, EUS may be used in high-risk patients such as those with a history of familial pancreatic cancer (with an affected first degree-relative) and inherited genetic syndromes.***

Epidemiology

Pancreatic cancer (PC) ranks amongst the most aggressive cancers and has a mortality rate that nearly equals the incidence rate (83). About 100,000 new cases of pancreatic cancer and 95,000 related deaths have been estimated in Europe as of 2018. There have been only small improvements in the 5-year survival rate over the last two decades, which still remains well below 10%.The poor prognosis of the disease is attributed to the aggressive biology, ineffective therapies, and advanced stages at the time of diagnosis (84,85). Thus, detection of precursor lesions or early-stage PC may be an effective approach to improve survival (86).

Target population

Given the overall low incidence of pancreatic cancer (lifetime risk 1.3%), it is not cost-effective to screen the general population (84)**. However, selective screening of high-risk individuals is considered beneficial. According to the International Cancer of the Pancreas Screening Consortium (CAPS), to be a candidate for screening, an individual should have a lifetime risk of > 5% for pancreatic cancer** (87)**. These worldwide experts published consensus criteria for screening individuals based upon their genetic susceptibility or family history. These criteria take into consideration the specific genetic mutations and the degree/ number of relatives affected to determine the need for screening. Recent studies suggest that patients with new-onset diabetes without traditional risk factors for diabetes**

(e.g., metabolic syndrome) are also at increased risk for PC, and could potentially benefit from screening (88–90).There is still a need for consensus on many issues, including when to start screening, the ideal method and interval of follow-up, and the optimal time to consider surgery.

Role of endoscopy

The development of a sensitive and specific screening test is crucial for decreasing mortality from PC. Unfortunately, none of the current diagnostic modalities have all the attributes of an effective screening tool with acceptable sensitivity, specificity, invasiveness, and cost effectiveness. Endoscopic ultrasound (EUS) has a greater sensitivity for detection of small pancreatic tumors compared to CT and MRI/MRCP and is therefore the preferred diagnostic modality to screen for PC. Unfortunately, the high resolution must be balanced with the need for sedation, cost, and invasiveness of the test.

The only endoscopic method that is clinically used for pancreatic cancer screening is endoscopic ultrasound (EUS). EUS has the ability to detect small pancreatic lesions and it offers the possibility of tissue sampling, being the most accepted screening method for early PC detection (87,91,92).

A number of studies have looked at the efficacy of EUS for the early detection of pancreatic dysplasia and other precursor lesions in high-risk individuals (HRIs) (92–108). Nevertheless, the diagnostic yield of EUS varies widely. According to a recent meta-analysis (109), EUS detected more high-risk lesions (1.07 [0.05–2.09] per 100 patient-years) than MRI (0.41 [0.05–0.78]), without reaching statistical difference. Furthermore, EUS detected more cases with chronic pancreatitis. Regarding routine follow-up after baseline screening, most published studies used the same imaging tests(87).

Few studies have compared the diagnostic yield of imaging tests for high-risk individuals in screening, and most comparisons have not been performed in a blinded, randomized fashion. The prospective CAPS3 study (105) performed blinded comparisons of CT, MRI/MRCP, and EUS for one-time screening. It showed that EUS and MRI are better than CT for the detection of small, predominantly cystic, pancreatic lesions, with good concordance of lesion number, size, and location between EUS and MRI/MRCP. However, it has been shown that EUS was particularly sensitive for the early detection of small solid lesions, while MRI was very sensitive for the detection of (small) cystic lesions (108). Consequently, they suggested that within a screening setting, in order to maximize the detection rate of clinically relevant lesions, both EUS and MRI should be considered.

The risk of incorrect diagnosis and overtreatment of the lesions identified by EUS remains a significant concern. EUS is an operator-dependent test with only modest interobserver agreement (110). Furthermore, the role of EUS-guided fine needle aspiration to evaluate pancreatic lesions in high-risk individuals is not well established. It proved to be very accurate (sensitivity 85%–89% and specificity 96%–99%) in diagnosing solid pancreatic lesions (111). However, there is a risk of false-positive cytology from small lesions that can lead to unnecessary surgery (87). Moreover, in cystic lesions the cytology has low accuracy, and often the volume of cyst fluid aspirated from small cysts is low (112).

Cost-effectiveness

According to CAPS (87), "successful" screening refers to detecting those high-risk lesions that benefit from surgery: high-grade dysplasia, high-grade PanIN, or T1N0M0 margin-negative PC.

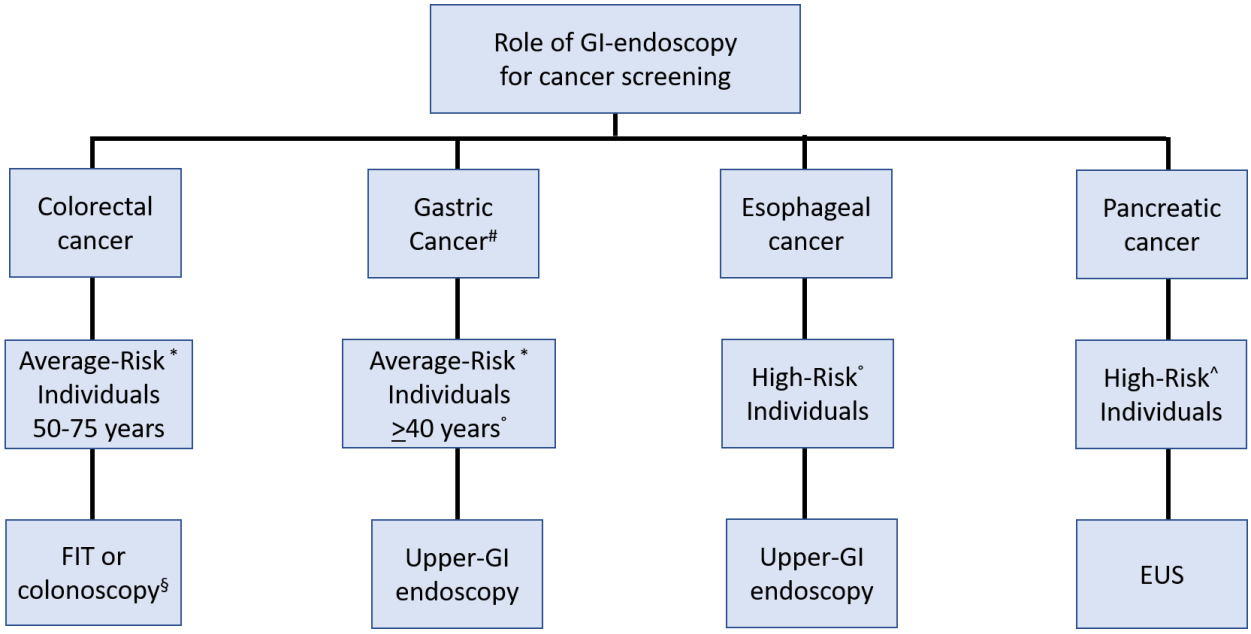
A recent meta-analysis (109) showed that EUS can detect a large number of pancreatic lesions, but only a small subgroup represents high-risk lesions. Accordingly, there is a risk of overtreatment for pancreatic screening that is magnified by the risks of morbidity and mortality (∼1–2%) of pancreatic surgery. However, perioperative mortality has significantly declined from 15% in 1970s, to 4% in modern series, and < 2% in high-volume centers (113–115).

Another approach to evaluate the benefits of the pancreatic screening would be to consider its impact on the quality of life of the individuals who are at risk for developing cancer. A recent systematic review showed that high-risk individuals have positive psychological outcomes from participating in PC screening programs. Although screening might not always be reassuring, it may improve individuals' quality of life, and this should be an important aspect when considering PC screening.

Conclusions

When applied to GI-cancer prevention, the impact of GI-endoscopy is substantial, and it is strictly related with three main variables, namely the absolute burden of each cancer according to country-specific disease incidence, the risk attributable to the target population, and the expected efficacy of screening prevention. Consequently, we stratified the opportunity of endoscopic screening in two main categories according to whether it should apply to average-risk subjects or only high-risk subjects (Figure 1). When coupling the high accuracy of endoscopy-related GI-cancer prevention with the availability of non-surgical endoscopic treatment of precancerous and early-invasive lesions, this represents an unique opportunity to eradicate GI-cancer in an acceptable and efficient manner.

Figure 1. Role of GI-endoscopy in the screening for GI-cancer.



#Only for regions at intermediate-/high risk.

*For subjects at increased risk of CRC or gastric cancer, see corresponding ESGE Guidelines.

§Sigmoidoscopy is also an acceptable alternative.

°For SCC: personal history of head-neck cancer, achalasia or previous caustic injury ; for BE-EAC: longstanding GERD symptoms (i. e. > 5 years) and multiple risk factors (age ≥ 50 years, white race, male sex, obesity, first-degree relative with BE or EAC.

^ history of familial pancreatic cancer (with an affected first degree-relative) and inherited genetic syndromes.

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